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Evaluation of epidemiological characteristics and risk factors affecting mortality in patients with candidemia

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Background/aim: The aim of this study was to determine epidemiologic characters of patients with candidemia and to evaluate risk factors that can affect mortality rates among these patients.

Materials and methods: Patients admitted to the İstanbul Medeniyet University Göztepe Training Hospital between 2009 and 2011 who had a positive blood culture for *Candida* spp. during hospitalization were studied retrospectively for demographic characteristics and risk factors. Statistical comparisons were estimated with the Stata 12 package. Independent variables associated with mortality were estimated by Cox regression analyses.

Results: A total of 89 patients were identified with a positive blood culture. Of the isolates, 72% (64/89) were *C. albicans* and 10% (9/89) were non-*albicans Candida*, while 18% (16/89) were unidentified. *C. parapsilosis* was the most frequently isolated species among non-*albicans Candida*. The crude mortality rate among candidemia cases was 30% (27/89). By univariate analysis, being in the ICU and age (≥50 or ≥60) were found to be statistically significant, whereas by multivariate analysis only age of ≥50 years was independently more associated with mortality (OR, 2.7; CI, 1.05–6.73).

Conclusion: Candidemia is associated with high mortality rates. Patients older than 50 years are found to be at considerable risk in terms of adverse outcomes.

Key words: Candidemia, epidemiology, risk factors, mortality

1. Introduction

Candidemia is the most prevalent clinical invasive candida infection. Although it usually occurs in neutropenic patients, it has begun to be encountered in various patient groups in recent years and is at the forefront as a cause of nosocomial infections. In a study from the United States, fungi ranked fourth among the causes of circulatory infections (1). Candidemia is associated with high morbidity and mortality rates in patients that stay in the hospital for the long term. Candidemia-associated mortality rate ranges between 10% and 49% (2).

Candida reaches the blood circulation via three different routes: the gastrointestinal system, the urinary system, and intravascular catheters (3). There are certain risk factors that facilitate the development of candidemia. These include gastrointestinal surgical intervention, presence of a central venous catheter, mechanical ventilation, total parenteral nutrition, burns, malignancy, hemodialysis, long-term intensive care unit stay, broad-spectrum antibiotics, corticosteroid use, and *Candida* colonization in the oral mucosa (4–6).

In the present study, we aimed to retrospectively evaluate mortality-associated risk factors in candidemia cases developed in our hospital.

2. Materials and methods

2.1. Patients and variables

Files of the patients whose blood cultures revealed *Candida* growth in the microbiology laboratory between 1 January 2009 and 31 December 2011 at the İstanbul Medeniyet University Göztepe Training and Research Hospital were retrospectively reviewed. Patient age and sex, reason for hospitalization, the clinic at which the patient stayed, underlying disease, history of past surgical intervention, duration of hospital stay, time to *Candida* growth in

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blood culture, use of antifungal agent, and prognosis were derived from the patient files and recorded.

For isolation and identification of *Candida* from blood culture, cultures that gave a positive signal in the automatized blood culture system (BacT/Alert 3D 120, BioMerieux, France) were transferred onto blood agar and Endo agar. The agars on which transfer was performed were incubated at 37 °C for 24–48 h. The samples that showed growth were examined by Gram staining and typing was performed using a fungi identification kit (Candifast Es Twin, ELITech Microbio, France) for the samples that revealed yeast.

2.2. Statistics

Statistical analyses were done with the Stata 12 (StataCorp, USA) statistical package. Categorical variables were analyzed by chi-square test or Fisher's exact test as necessary. Comparisons were done using 2 × 3 tables and the Fisher–Freeman–Halton test. Continuous variables were generally analyzed by Student's t-test. Independent risk factors were modeled by Cox regression analysis. Backward elimination was used for Cox regression analysis. Variables were tested in terms of collinearity and thereafter they were separately included into and excluded from the model and the final model was formed. Proportionality of variables and suitability of the final model were tested. Kaplan–Meier survival graphics were drawn and difference in survival function was assessed by log-rank test. Statistical significance was evaluated at $P < 0.05$ as two-sided.

3. Results

Positive blood culture was detected in a total of 89 cases over the course of study period. While *C. albicans* was identified in 72% (64/89) and non-*albicans Candida* species were identified in 10% (9/89) of these cases, typing failed in 18% (16/89). *C. parapsilosis* was the most frequently isolated species among non-*albicans Candida* species. Solid organ tumors were present in six of the cases and none of these patients had been using chemotherapeutic agents at the time that candidemia was detected. Four patients were followed at the Department of Pediatric Hematology for febrile neutropenic episodes. No data were obtained from the records involving long-term use of agents that suppress the immune system, such as corticosteroids or tumor necrosis factor alpha inhibitors. Table 1 illustrates the distribution of candidemia cases among clinics and Table 2 illustrates characteristics of living and dead patients.

The crude mortality rate among cases was 30% (27/89). Of the patients with candidemia, 42% were over the age of 50 years and 63% were male. Staying in the intensive care unit and age (≥50 or ≥60) were found to be significant for mortality, particularly during univariate comparisons, whereas the multivariate model found that only the age of 50 years and over (OR = 2.7; CI = 1.05–6.73) was a significant risk factor for mortality. Statistical data are demonstrated by Cox regression analysis in Table 3 and by a Kaplan–Meier survival graphic in the Figure.

4. Discussion

Candida species that cause candidemia show variation among countries and regions (7,8). Yapar et al. from Turkey conducted a study on candidemia and found the prevalence of *C. albicans* to be 75.7% and non-*albicans* to be 43.5%, but they reported that *Candida* species have increased in recent years (9). In a study that evaluated 12-year candidemia cases in the Uludağ University Hospital of the Faculty of Medicine, *C. albicans* (45%) was found to be the leading agent, followed by *C. parapsilosis* (26%) (10). A study from Spain reported an increase in non-*albicans Candida* species, although the prevalence of *C. albicans* was found to be 51% and that of non-*albicans* species was found to be 49% (11). Another study reported the most frequently isolated agents to be *C. albicans* (40%), *C. parapsilosis* (23%), *C. glabrata* (15%), *C. tropicalis* (9%), and other species (13%), respectively, from 182 *Candida* attacks in the intensive care unit. The same study emphasized that there is an increase in *Candida*

Table 1. Distribution of the patients with candidemia among clinics.

	Number (%)			
Clinics	Exitus (n = 27)		Survivors (n = 62)	
Adult ICU[µ]	16	(0.59)	11	(0.18)
Internal clinics	4	(0.15)	9	(0.15)
Surgical clinics	3	(0.11)	21	(0.34)
Pediatric diseases	4	(0.15)	11	(0.18)
Newborn ICU	0	(0.00)	10	(0.16)

[µ] : ICU: intensive care unit.

Table 2. Characteristics of deceased and surviving patients.

Variables[x]	Number (%)				P
	Exitus (n = 27)		Survivors (n = 62)		
Age (years)	49.44	(31.06)	27.27	(29.02)	0.003
≥50	16	(59.26)	21	(33.87)	0.025
≥65	12	(44.44)	11	(17.74)	0.008
Male	18	(66.67)	38	(61.29)	0.629
C. albicans	16	(59.26)	48	(77.42)	0.080
Fluconazole	10	(37.04)	18	(29.03)	0.455
CanTime (days)[µ]	16.52	(11.92)	15.32	(16.94)	0.705
Duration of hospital stay (days)	33.96	(28.24)	41.65	(36.28)	0.285
ICU[µ]	6	(0.22)	11	(0.18)	0.001
Diagnosis at the time of hospitalization					
Trauma	5	(18.52)	9	(14.52)	0.753
CNS event	7	(25.93)	19	(30.65)	0.653
GIS surgery	5	(18.52)	15	(24.19)	0.555
Underlying disease[h]					0.461
None	10	(37.04)	25	(40.32)	
Nonfatal	4	(14.81)	3	(4.84)	
Fatal in the near future	9	(33.33)	25	(40.32)	
Rapidly fatal	4	(14.81)	9	(14.52)	

[x]: Continuous variables, age, CanTime, and duration of hospital stay are given as "mean (SD)".
[µ] : CanTime: time from hospitalization to the isolation of *Candida*; ICU: intensive care unit.
[h] : McCabe and Jackson classification.

species, which might have most significantly resulted from intensive use of azole prophylaxis in their unit (12). In the candidemia cases investigated in the present study, the most frequently isolated agent was *C. albicans* (72%), followed by *C. parapsilosis* (9%), whereas *C. krusei* was isolated from a single case. Nevertheless, typing could not be performed for sixteen yeast cells. Our data show similarity to the data from both Turkey and European countries in terms of distribution of the species (8).

Table 3. Hazard ratios and confidence intervals obtained from Cox regression model of variables for outcome.

	Hazard ratio	[95% CI][h]	P-value
C. albicans	0.7	[0.27–1.61]	0.20
Staying in ICU	2.1	[0.85–5.01]	0.06
Age ≥50	2.7	[1.05–6.73]	0.01

[h]: CI: Confidence interval.

The literature contains numerous studies concerning the risk factors for the development of candidemia. It was demonstrated that long-term hospital stay and presence of a central venous catheter in a patient enhance the risk of developing candidemia (13). Barberino et al. determined the risk factors associated with candidemia to be the presence of a central venous catheter, total parenteral nutrition, broad-spectrum antibiotic use, and chronic renal insufficiency (14). In a study from Thailand, staying in the intensive care unit was emphasized as a risk factor for developing candidemia (15). Das et al. stated that broad-spectrum antibiotic use, presence of intravascular catheter, staying in an intensive care unit, and history of surgical intervention are significant risk factors that influence the development of candidemia. Moreover, the same study determined that the risk of developing candidemia is higher in those having a history of gastrointestinal surgery as compared to other types of surgical interventions (16). In a study carried out in medical and surgical intensive care units, it was emphasized that there was no relation between *Candida* species and risk factors that play a

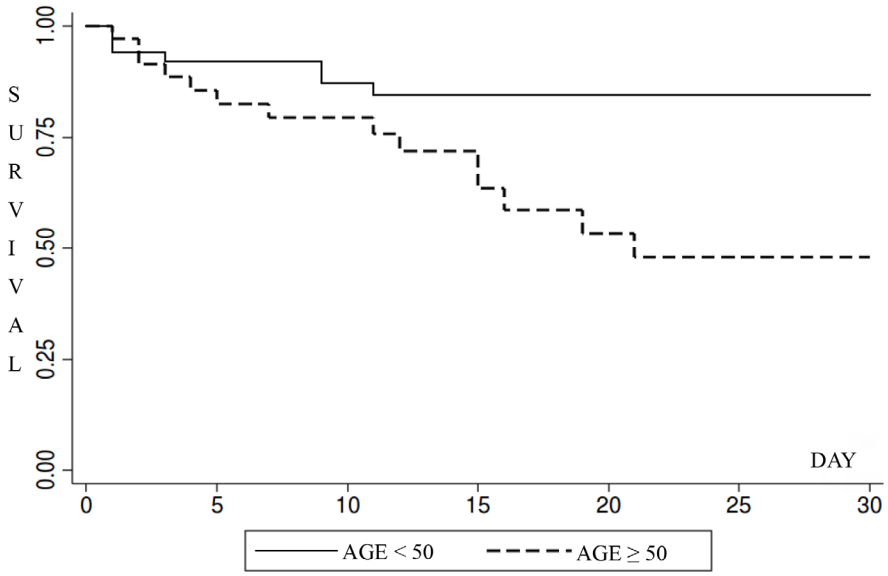

Figure. Kaplan–Meier survival graphic for those aged over 50 years versus under 50 years (log-rank, P = 0.007).

role in the development of candidemia, but that non-*albicans Candida* was the most prevalent agent in those with a history of any surgical intervention, particularly gastrointestinal surgery (17).

Mortality rate shows variations among candidemia cases. Fraser et al. determined the mortality rate to be 57% and demonstrated that severity and prognosis of the underlying disease, duration of candidemia, and APACHE II score are closely associated with mortality (18). It was emphasized that mortality rate is higher in non-*albicans* candidemia as compared to *C. albicans* in immunosuppressed and nonneutropenic patients staying in intensive care units (19). In another study in the literature, it was stated that *Candida* species do not influence mortality (20). In the present study, the most prevalent agent was *C. albicans*, with no statistically significant effect on mortality. It is known that commencing empirical antifungal therapy in the early period favorably influences the mortality rate. However, a study conducted in nonneutropenic patients determined no difference in mortality rate with early antifungal therapy (21). A study from the United Kingdom demonstrated that neither empirical antifungal therapy nor treatment after positive blood culture significantly influenced the mortality rate (16). In the present study, most of the patients did not receive empirical antifungal therapy. Antifungal therapy was commenced after blood culture positivity with no statistically significant difference in mortality rate. Erdem et al. demonstrated that candidemia-associated mortality rate was higher among patients staying in the intensive care unit. In addition, they explained that presence of a central venous catheter or urinary catheter did not influence the mortality rate in candidemia patients because all patients staying in the intensive care unit had invasive catheters (22). In the present study, univariate comparisons revealed that staying in the intensive care unit is a significant factor for mortality, whereas the multivariate model determined no significant relation with mortality and only the age of 50 and over was found to be significantly correlated with mortality.

The most important limitation of this study is that the percentage of nonidentified species of *Candida* is very high and this may have affected the results of logistic regression analysis.

In conclusion, candidemia is a serious condition with high mortality. The risk of mortality is significantly higher particularly in patients at the age of 50 years and over and those staying in the intensive care unit. Therefore, candidemia should be considered in the differential diagnosis. Moreover, knowing local epidemiological trends of *Candida* species that are isolated from blood cultures would be a guide in choosing empirical antifungal agents.

References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004; 39: 309-317.
2. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007; 20: 133-163.
3. Edwards JE. *Candida* species. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Philadelphia, PA, USA: Churchill Livingstone; 2010. pp. 3225-3240.
4. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. Clin Infect Dis 2001; 33: 177-186.
5. McKinnon PS, Goff DA, Kern JW, Devlin JW, Barletta JF, Sierawski SJ, Mosenthal AC, Gore P, Ambegaonkar AJ, Lubowski TJ. Temporal assessment of *Candida* risk factors in the surgical intensive care unit. Arch Surg 2001; 136: 1401-1408.
6. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk Factors for hospital-acquired candidemia: a matched case-control study. Arch Intern Med 1989; 149: 2349-2353.
7. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans *Candida spp* among candidemia isolates from inpatients in various parts of the world: a systematic review. Int J Infect Dis 2010; 14: 954-966.
8. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RC, Messer SA. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol 2001; 39: 3254-3259.
9. Yapar N, Uysal U, Yucesoy M, Cakir N, Yuce A. Nosocomial bloodstream infections associated with *Candida* species in a Turkish University Hospital. Mycoses 2006; 49: 134-138.
10. Gürcüoğlu E, Ener B, Akalin H, Sinirtaş M, Evci C, Akçağlar S, Yilmaz E, Heper Y. Epidemiology of nosocomial candidaemia in a university hospital: a 12-year study. Epidemiol Infect 2010; 138: 1328-1335.
11. Bouza E, Muñoz P. Epidemiology of candidemia in intensive care units. Int J Antimicrob Agents 2008; 32: 87-91.
12. Bassetti M, Righi E, Costa A, Fasce R, Molinari MP, Rosso R, Pallavicini FB, Viscoli C. Epidemiological trends in nosocomial candidemia in intensive care. BMC Infect Dis 2006; 10: 21-25.
13. Koçak BY, Kuloğlu F, Çelik AD, Akata F. Evaluation of epidemiological characteristics and risk factors of candidemia in adult patients in a tertiary-care hospital. Mikrobiyol Bul 2011; 45: 489-503 (in Turkish with English abstract).
14. Barberino MG, Silva N, Rebouças C, Barreiro K, Alcântara AP, Netto EM, Albuquerque L, Brites C. Evaluation of blood stream infections by *Candida* in three tertiary hospitals in Salvador; Brazil: a case-control study. Braz J Infect Dis 2006; 10: 36-40.
15. Chaiwarith R, Ounbang P, Khamwan C, Nuntachit N, Sirisanthana T, Supparatpinyo K. Epidemiology of adult candidemia at Chiang Mai Universty Hospital. Southeast Asian J Trop Med Public Health 2011; 42: 1505-1514.
16. Das I, Nightingale P, Patel M, Jumaa P. Epidemiology, clinical characteristics and outcome of candidemia: experience in a tertiary referral center in the UK. Int J Inf Dis 2011; 15: 759-763.
17. Chow JK, Golan Y, Ruthazer R, Karchmer AW, Carmeli Y, Lichtenberg DA, Chawla V, Young JA, Hadley S. Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit Care Med 2008; 36: 1993-1998.
18. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992; 15: 414-421.
19. Dimopoulos G, Ntziora F, Rachiotis G, Armaganidis A, Falagas ME. *Candida albicans* versus non-*albicans* intensive care unit-acquired bloodstream infections: differences in risk factors and outcome. Anesth Analg 2008; 106: 523-529.
20. Chi HW, Yang YS, Shang ST,Chen KH, Yeh KM, Chang FY, Lin JC. *Candida albicans* versus non-*albicans* bloodstream infections: the comparison of risk factors and outcome. J Microbiol Immunol Infect 2011; 44: 369-375.
21. Davis SL, Vazquez JA, McKinnon PS. Epidemiology, risk factors and outcomes of *Candida albicans* versus non-*albicans* candidemia in nonneutropenic patients. Ann Pharmacother 2007; 41: 568-573.
22. Erdem I, Oguzoglu N, Ozturk Engin D, Ozgultekin A, Inan AS, Ceran N, Kaya F, Genc I, Goktas P. Incidence, etiology and risk factors associated with mortality of nosocomial candidemia in a tertiary care hospital in Istanbul, Turkey. Med Princ Pract 2010; 19: 463-467.