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Risk factors, clinical characteristics and mortality of candidemia in non-neutropenic, critically ill patients in a tertiary care hospital

Üçüncü basamak bir hastanede nötropenik olmayan yoğun bakım hastalarında kandidemi risk faktörleri, klinik özellikleri ve mortalitesi

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Abstract

Aim: In recent years candida species have emerged as important nosocomial pathogens leading to increased mortality and prolonged hospitalization. In this study, we aimed to determine the distribution of *Candida* species in the intensive care unit (ICU) and to investigate the risk factors and mortality rates in *Candida albicans* (CA) and non-*albicans Candida* infections (NAC).

Methods: This retrospective cohort study was conducted between January 2018 and January 2019. 134 patients hospitalized in the intensive care units with *Candida* reproduction in their blood cultures were included in the study. Blood cultures were processed, and strain distribution was performed according to routine practice using the automated blood culture system BACTEC 9240 (Becton Dickinson, Maryland, USA).

Results: *Candida* growth was detected in the blood culture of 134 patients, among which 54.5% consisted of CA and 45.5% of NAC. NAC was most commonly followed by *C. parapsilosis* (17.2%), and *C. glabrata* (13.4%). Mortality rate of patients aged ≥60 years was significantly higher in all three candida species (*P*=0.003). NAC was seen at an insignificantly higher rate in patients with solid-organ malignancy (*P*=0.09). Although mortality was higher in CA than NAC strain (53.6% and 43.4%, respectively), this was not statistically significant (*P*=0.83).

Conclusion: Although CA is still the most common strain in ICU patients, the incidence of NAC is increasing. Candidemia has high mortality rates in ICU patients. Especially elderly patients with underlying diseases should be followed carefully.

Keywords: Bloodstream infections, Candida albicans, Non-albicans Candida, Risk assessment, Mortality

Öz

Amaç: Son yıllarda kandida türleri mortalitenin artmasına ve hastanede kalış süresinin uzamasına neden olan önemli nozokomiyal patojenler olarak ortaya çıkmıştır. Bu çalışmada yoğun bakım ünitesinde yatan hastalarda Candida türlerinin dağılımını belirlemek ve Candida albicans (CA) ve non-albicans Candida (NAC) risk faktörlerini ve mortalite oranlarını belirlemeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışma, Ocak 2018 ve Aralık 2018 tarihleri arasında gerçekleştirildi. Yoğun bakım ünitelerinde kan kültürlerinde Candida üremesi olan 134 hasta çalışmaya dahil edildi. Kan kültürleri, otomatik kan kültür sistemi BACTEC 9240 (Becton Dickinson, Maryland, ABD) kullanılarak rutin uygulamalara göre işlendi ve tür dağılımı otomatik sistem tarafından gerçekleştirildi.

Bulgular: Toplam 134 hastanın kan kültüründe Candida üremesi saptandı. Bu üremelerin %54,5'i CA ve %45,5'i NAC'den oluşuyordu. NAC'yi en sık %17,2 *C. parapsilosis* ve %13,4 ile *C. glabrata* izledi. Her üç tür için de ≥60 yaş yıllık ölüm oranı anlamlı olarak daha yüksekti (*P*=0,003). Solid organ malignitesi olan hastalarda NAC daha yüksek oranda görüldü, ancak bu istatistiksel olarak anlamlı değildi (*P*=0,09). CA suşunda mortalite NAC suşundan daha yüksek olmasına rağmen (sırasıyla %53,6 ve %43,4), bu istatistiksel olarak anlamlı değildi (*P*=0,83).

Sonuç: YBÜ hastalarında CA hala en sık görülen tür olmasına rağmen, NAC insidansı artmaktadır. Yoğun bakım hastalarında kandidemi yüksek mortalite oranlarına sahiptir. Özellikle altta yatan hastalıkları olan yaşlı hastalar dikkatle takip edilmelidir.

Anahtar kelimeler: Kan dolaşımı enfeksiyonları, Candida albicans, Non-albicans candida, Risk faktörleri, Mortalite

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Introduction

In the last two decades, the incidence of candidemia has been increasing despite advances in diagnostic methods, the emergence of new antifungal drugs, and the implementation of candida prevention strategies [1]. Candidemia is the 4th most common cause of bloodstream infections in the United States and the 7th most common cause in Europe [2-3]. According to data reported by the European Center for Disease Prevention and Control in 2013, *Candida* spp. is the fifth microorganism causing sepsis in patients admitted to intensive care unit (ICU). Recently, the increase in the incidence of candidemia has been associated with complex medical and surgical procedures that ensure the survival of critical patients [4].

Important risk factors for invasive candidiasis include age, underlying disease, exposure to broad spectrum antibiotics and cancer chemotherapy, advanced care of premature newborns, major abdominal surgery, organ transplantation, prolonged stay in intensive care, vascular catheters, implanted medical devices such as prosthetic heart valves, and parenteral nutrition [5]. While *Candida albicans* (CA) is the most commonly isolated strain from hospitalized patients, non-*albicans Candida* (NAC) strains have been reported with increasing frequency in recent years. *Candida glabrata* strains are found in 15-20% of Candida infections [6]. The mortality of NAC infections is higher than that of CA infections [7-8]. Therefore, early diagnosis of candida infections and early appropriate empirical treatment for CA and NAC species are of immense importance, especially in patients with NAC [6].

The epidemiology of candidemia varies by geographical region. Therefore, surveillance studies are mandatory [4]. In this study, we aimed to investigate the distribution of species, risk factors and mortality rates in candidemia developing in the intensive care unit and thus to make prognosis analysis of CA and NAC infections. This study will guide clinicians in empirical treatment options.

Materials and methods

The hospital in which the study was conducted is a tertiary hospital with 442 beds and receives intensive patients not only from the province it's located in, but also from the surrounding provinces. It is a branch hospital where even specific operations such as lung, kidney, heart, and liver transplantations are performed. 105 of these 442 beds are intensive care beds. This is a retrospective, single-center, observational cohort study. The records of patients between 1 January 2018 and 30 January 2019 in our intensive care unit were reviewed retrospectively. Patients with candida growth in blood culture were included in the study. Candidemia is defined as the detection of a single candida strain in the blood culture. Samples where more than one strain was detected were excluded from the study.

Blood cultures and strain distribution were processed according to routine practice using the automated blood culture system BACTEC 9240 (Becton Dickinson, Maryland, USA). Blood cultures were incubated for 14 days. For isolation of Candida, blood cultures were transferred onto blood and Endo agars, and incubated at 37^0 C for 24-48 hours. Gram staining was performed on the colonies. The germ tube test was performed for those in which yeast cells were detected by microscopy. The positive isolates from the germ tube test were identified as *Candida albicans*. Colonies with negative germ tube test were identified at the species level with identification kits (API 20C AUX; BioMérieux, France).

Following the approval of the study protocol by the local Ethics Committee (SBÜ Ankara Yuksek Ihtisas Training and Research Hospital, approval number:22.10.2018-58/29620911-929), the medical records, clinical features and risk factors of all patients between 1 January 2018 and 30 January 2019 were retrospectively analyzed. Candida growth was detected in blood cultures of 134 patients. The age, gender, previous operation status, presence of solid organ malignancy, antibiotic use, dialysis status, TPN use, ventilator use, breeding candida genus and mortality rates developed within 30 days after reproduction were compared for each patient.

Statistical analysis

Fisher Exact test or Pearson Chi-square tests were used for categorical data analysis by groups. *P*-value of <0.05 was considered statistically significant. Data analysis was performed with SPSS 17.0 (SPSS Ver. 17.0, Chicago IL, USA) program.

Results

Candida growth was detected in the blood culture of 134 patients within the specified period. Among them, 49 were female (36.6%) and 85 were male (63.4%). The patients ranged in age from 1 to 96 years with the mean ages of females and males being 50 (24.3) years and 51 (25.7) years, respectively.

Among 134 patients, 73 (54.5%) had *C. albicans* and 61 (45.5%) had non-*albicans candida*. Out of the non-*albicans candida*s, there were 23 *C. parapsilosis* (17.2%), 18 *C. glabrata* (13.4%), 7 *C. tropicalis* (5.2%), 3 *C.lusitaniae* (2.2%), 2 *C. lipolytica* (1.5%) and 8 other species (6%). The growth of Candida took between 0-8 days in blood culture samples with an average reproduction time of 2-3 days. *C. albicans*, was the most commonly detected strain with a rate of 54.5%. This was followed by *C. parapsilosis* (17.2%) and *C. glabrata* (13.4%). Malignancy was present in 23.9% of total patients. The rate of surgery among these patients were 71.6%. Around 90.3% of the patients had used antibiotics before the development of candida, and 58.2% had prolonged intubation and 32.8%, chronic renal failure (Table 1). When the 3 most common candida species and mortality rates were analyzed according to age distribution (Table 2), among patients between 0-20 years of age (n=24), 54.2% (n=13) were seen to have CA growth.

While 46.2% (n=6) of these Candidemias were mortal, patients who were ≥60 years of age (n=35) suffered a CA-related mortality rate of 62.9% (n=22) (n=35). *C. parapsilosis* was equally distributed in all age groups, and mortality due to *C. parapsilosis* was 25% between 0-20 years and 60% in ≥ 60 years. *C. glabrata* was not seen in the 0-20 age group, it was similarly detected in other age groups. Total mortality rates of the 3 most common candida species were similar between 0-20 years and 21-59 years of age (29.2% and 30.8%, respectively). The overall mortality rate in the age group of ≥60 years was found to be 56.9%, which was significant (*P*=0.003). No statistically significant difference was found in terms of the

distribution of candida species between the age groups (*P*=0.057), or in terms of mortality (*P*=0.347). When CA and NAC types were compared, there was no statistically significant difference between mortality rates (*P*=0.864). There was no statistically significant difference between the distribution of the three most common candida species (*C.albicans, C.parapsilosis* and *C. glabrata*) (*P*=0.84) according to age groups, and between their mortality rates (*P*=0.989).

Table 1: Characterization of patients with *C.albicans* and non-*albicans Candida* infection

Profile		*C. albicans* (n=73)	Non-*albicans Candida* (n=61)	*P*-value
Age	≥60	34 (57.6%)	25 (42.4%)	0.516
	<60	39 (52%)	36 (48%)	
Gender	Male	52 (61.2%)	33 (38.8%)	0.04
	Female	21 (42.9%)	28 (57.1%)	
Solid tumor	Yes	11 (34.4%)	21 (65.6%)	0.09
	No	62 (60.8%)	40 (39.2%)	
Surgery	Yes	49 (50.5%)	48 (49.5%)	0.136
	No	24 (64.9%)	13 (35.1%)	
Mechanical ventilation	Yes	41 (52.6%)	37 (47.4%)	0.600
	No	32 (57.1%)	24 (42.9%)	
Chronic renal insufficiency	Yes	27 (61.4%)	17 (38.6%)	0.263
	No	46 (51.1%)	44 (48.9%)	
Total parenteral nutrition	Yes	8 (42.1%)	11 (57.9%)	0.242
	No	65 (56.5%)	50 (43.5%)	
Broad spectrum antibiotic exposure	Yes	64 (52.9%)	57 (47.1%)	0.261
	No	9 (69.2%)	4 (30.8%)	
All-cause in- hospital mortality	Yes	37 (53.6%)	32 (46.4%)	0.838
	No	36 (55.4%)	29 (44.6%)	

Table 2: Mortality and age distribution between three most common *Candida* species

Age	C albicans		C.parapsilosis		C. glabrata		Total Ex
	(n) (%)	(ex) (%)	(n) (%)	(ex) (%)	(n) (%)	(ex) (%)	(n) (%)
0-20 (n=24)	13 (54.2)	6 (46.2)	4 (16.7)	1 (25)	0 (0)	0 (0)	7/17 (41.2)
21-59 (n=52)	26 (50)	9 (32.1)	9 (17.3)	3 (33.3)	10 (19.2)	4 (40)	16/45 (35.5)
≥60 (n=58)	34 (58.6)	22 (62.9)	10 (17.2)	6 (60)	8 (13.8)	5 (55.6)	33/52 (63.5)
Mortality	37/73	(50.7)	10/23	(43.5)	9/18	(50)	

Discussion

Candida is an important cause of bloodstream infections in critical patients hospitalized in Intensive Care Units [9]. Longer survival of patients with serious and complex problems as a result of advances in medicine has led to a population of individuals susceptible to infection. Candida is the most common fungal pathogen in intensive care patients and its main clinical form is blood circulation infection, followed by peritonitis and other abdominal infections, and endocarditis. There has been a shift in the distribution of agents among candida species reported in many hospitals over the last two decades. While almost all of the candidemia strains reported in the past are CA, increasing candidemia rates have been reported with NAC species in recent years [10]. The incidence of NAC infection varies widely between regions and the reason for this is unclear [11]. This may be due to different patient populations and health care standards [12]. The most commonly reported NAC species were *C.parapsilosis* or *C. glabrata*, followed by *C. tropicalis* and *C. crusei* [10-11]. Although the frequency of detection varies, pathogens have been identified as *C. albicans*, *C. glabrata*, *C. parapsilosis, C. tropicalis* and *C. krusei* in 95% of the infections in the last 20-30 years [13]. Their distribution varies according to the studies conducted in different geographical regions. CA is the most common species, but significant regional differences have been found between the number of cases caused by *C. glabrata* and *C. parapsilosis*. In studies from Northern Europe and the United States, numerous cases of *C. glabrata* have been reported, whereas in Spain and Brazil, the number of cases caused by *C. glabrata* is less and most of the cases are attributed to *C. parapsilosis* [2]. While the incidence of CA decreases globally, *C. glabrata* and *C. krusei* are stable and *C. parapsilosis* and *C. tropicalis* rates have been increasing [1]. In our study, we determined that 54.5% of the cases were CA. The most common causative agent after CA was *C.parapsilosis* with 17.2%. This result was consistent with other studies conducted in Turkey [14-17]. In our study, the third most common strain was *C. glabrata* (13.4%). We could not find any relationship between any candida species and mortality. Some previous studies have reported the association of *C. glabrata* with high age and high mortality rates [18-20]. Again, studies showing a high mortality relationship with CA have been reported [20]. In the study conducted by Das et al. there was no significant relationship between *C. glabrata* and mortality [21]. In another study in the literature, it was reported that candida species do not affect mortality [22]. In our study, no difference was found between CA and NAC in terms of age, gender, underlying disease and mortality rates among patients with candidemia. Although CA mortality rate was higher in our study than NAC (53.6% and 43.4%, respectively), this was not statistically significant. When the three most common types of candida were compared, total mortality among ≥60 years of age was significantly higher in *C. albicans, C. parapsilosis* and *C. glabrata* compared to other age groups (P=0.003). In a study by Karadağ et al. mortality was reported to be significantly higher in patients aged 50 years and older [23]. We did not find any difference between the development of CA and NAC infection with total parenteral nutrition [24] or mechanical ventilation 2 weeks prior to diagnosis, which was reported as a risk factor for NAC infection. Similar results have been reported in the study conducted by Gong et al [6]. In our study, there was no difference between the presence of solid organ malignancy and the development of CA or NAC. This may be due to the lack of neutropenic patients because we don't offer chemotherapy in the hospital. There was no significant correlation between the distribution of candida species among surgical and non-surgical patients. Aliskan et al. reported similar results in their study [14]. Candidemia has been reported to be the cause of mortality at a rate of 30-60% [25,10]. In our study, there was no statistical difference between CA and NAC mortality considering all causes. We found that the crude mortality rate of CA was 53.6% and NAC was 43.4%. In a study conducted in Europe, the 30-day mortality rate in intensive care patients was 53.6% [20]. In another study performed by Marriott et al. in non-neutropenic intensive care patients, they reported a 30-day mortality rate of 56% in patients with Candidemia [26].

Limitations

There were some limitations of this study. Candida index and APACHE II score could not be obtained for each patient due to the retrospective nature of the study. Prospective multi-center studies with large sample sizes should be performed, which could provide more relevant epidemiology information.

Conclusion

Candidemia has high mortality rates, especially in patients in the ICU. CA was found to be the most common pathogen. Especially patients over 60 years of age should be followed up more closely in terms of mortality. Knowledge of local epidemiological trends in candida species will guide clinicians in early diagnosis and therapeutic choices.

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