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Evaluation of patients with candida infections in a tertiary care hospital's general intensive care unit in Turkey.

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ABSTRACT

INTRODUCTION: Studies indicate that approximately 90% of the patients followed in the ICU have *Candida* spp colonization. In this study we aimed to elucidate the epidemiology, characteristics, management and outcomes of patients with candidemia in the intensive care unit of a training and research hospital.

MATERIAL AND METHODS: All patients over the age of 18 who were hospitalized in general intensive care unit more than 24 hours between 2013 and 2019 were included in the this retrospective study.

RESULTS: A total of 43 critically ill patients with blood cultures positive for *Candida* spp. have been enrolled in this retrospective analysis. The duration of stay in the intensive care unit of the survivors was approximately 53 days, while the average length of stay in the intensive care unit of the non survivors was 16 days, and this difference was statistically significant ($p < 0.05$), 89.7% of septic patients with candidemia died the intensive care unit. There was a statistically significant difference between the two groups in terms of platelets, urea and systolic blood pressure ($p < 0.05$), the mean platelet and systolic blood pressure values of the surviving patients were higher than the deceased individuals, while the urea value was lower. The average fungal growth time of the surviving individuals was 17 days, while this period was 1 day in the non-survivor patients.

CONCLUSIONS: The mortality rate was higher in patients with sepsis and concomitant candida infection at very soon days of ICU hospitalization. Early administration of empirical antifungal therapy with coverage of non-albicans should be considered for septic patients.

KEY WORDS: Candidemia, sepsis, non-albicans, intensive care unit, candida species.

INTRODUCTION

The number of fungal infections observed in hospitalized patients has been increasing in recent years [1]. Among the factors that pave the way for this situation are the increase in the number of patients in advanced age, the widespread use of invasive devices, broad-spectrum and/or long-term antibiotics and immunosuppressive drugs, and the increase in the number of patients whose immune system is suppressed due to their primary disease [2-4]. Most of the hospital-acquired fungal infections are blood stream infections due to *Candida* species [5]. *Candida* species mostly affect mucous membranes and skin; however, they can lead to many different clinical conditions, from candiduria to endocarditis [6]. Invasive candidiasis may occur with the spread of the agent into the blood stream, liver, spleen, brain, heart and eyes. Organs and cavities can be affected by direct spread, such as the thorax in esophageal perforation and the peritoneum in intestinal perforation [7]. In recent years, in parallel with the developments in the field of diagnosis and treatment, an increase has been observed in the incidence of fungal infections and the number of patients at risk for opportunistic fungal infections [8,9].

Among opportunistic fungi, *Candida* species are the most common, with *C. albicans* being the first species, but an increase is also observed in non-*albicans* [10]. The group with the highest risk for fungal infections are intensive care unit (ICU) patients whose general condition is poor, who are treated with long-term broad-spectrum antibiotics and who are treated with corticosteroids/cytotoxic agents [11]. The integrity of the skin and mucosa of the patients hospitalized in the ICU may be impaired due to surgical operation, wounds, intubation or vascular catheter. At the same time, colonization with *Candida* occurs on the mucousa and skin surfaces following the alteration of the endogenous flora due to the use of broad-spectrum antibiotics [12]. Fungal infections are a serious problem with an increasing frequency in critically ill patients. The majority of these infections are due to *Candida* species. The frequency and survival rates of invasive candidiasis vary [12]. In this study we aimed to elucidate the epidemiology, characteristics, management and outcomes of patients with candidemia in the intensive care unit of a training and research hospital.

MATERIAL AND METHODS

This study was conducted on patients aged 18 years and older who were hospitalized in the general intensive care unit (17 bed capacity) of TC SBU Bursa Yüksek İhtisas Training and Research Hospital between 1 January 2013 and 31 December 2019. The ethics committee approval has been granted at 08.09.2021 and protocol number: 2011-KAEK-25 2021/09-01. Demographic data of the patients, duration of stay in the intensive care unit, comorbidities, causes of hospitalization, mortality, intensive care disease severity score (APACHE 2) and candida score, microbiological culture growths, treatments were collected from the hospital records. Candida score is a four-item clinical score and includes the components "severe sepsis", "total parenteral nutrition", "surgery", and "multifocal *Candida* colonization". Two points for severe sepsis and one point is added for each other component resulting in a maximum score of 5.

A score ≥ 3 is considered as an accurate discriminative value to select patients with *Candida* colonization requiring antifungal treatment. Patients with growth other than blood culture were considered multifocal colonization. Survival data at 28th day were obtained from medical records. All patients over the age of 18 who were hospitalized in two general intensive care units more than 24 hours, between 1 January 2013 and 31 December 2019 have been enrolled in the study. Patients under 18 years of age, hospitalized for less than 24 hours, and without candidemia were excluded from the study.

Statistical methods

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage were given for categorical data, and median, minimum and maximum descriptive values for continuous data. "Mann Whitney-U Test" was used for comparisons between groups, and "Pearson Chi-square or Fisher's Exact Test" was used for comparison of categorical variables. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

A total of 1337 patients had admitted to our ICU in this 7 year period. A total of 43 critically ill patients with blood cultures positive for *Candida* spp. have been enrolled in this retrospective analysis. The results of the evaluation of whether there was a significant difference or relationship between demographic and clinical findings according to the survival status of the cases within the scope of the study were given in Table 1-2. When the table is examined, 89.7% (n=26) of 29 individuals lost their lives in the intensive care unit. The prolongation of the stay in the intensive care unit affects the survival of the cases. The length of stay in the intensive care unit of the survived individuals was approximately 53 days, while the average length of stay in the intensive care unit of the deceased was 16 days, and this difference was statistically significant ($p < 0.05$).

The presence of ankylosing spondylitis, aplastic anemia, hepatitis, congestive heart failure, muscular dystrophy, Parkinson's disease, rheumatoid arthritis and Wilson's disease did not differ significantly between the alive and deceased individuals. When the laboratory results and vital signs of the cases were analyzed according to the survival status, it was seen that there was a statistically significant difference between the two groups in terms of platelets, urea and systolic blood pressure ($p < 0.05$). It was determined that the mean platelet and systolic blood pressure values of the surviving individuals were higher than the deceased individuals, while the urea value was lower.

Table 3 shows the treatment agents used by the patients according to their survival status and the distribution of growth in their cultures. There was a statistically significant difference between the two groups in terms of fungal growth time ($p < 0.05$). In the cultures of the surviving individuals, the average fungal growth time was 17 days, while this period was found to be 1 day in the deceased patients. Figure 1 shows the changing distribution of *Candida* species in years.

Table 1. Distribution of demographic data of patients.

Characteristics	Total (n=43) n (%) or Median (Min – Max)	Alive (n=14) n (%) or Median (Min – Max)	Deceased (n=29) n (%) or Median (Min – Max)	p value
Age, years	57 (14-88)	65 (32-77)	55 (14-88)	0.299
Gender				0.826
Male	21 (48.8)	6 (42.9)	15 (51.7)	
Female	22 (51.2)	8 (57.1)	14 (48.3)	
Comorbid Diseases	28 (65.1)	7 (50)	21 (72.4)	0.184
Diabetes Mellitus	10 (23.3)	3 (21.4)	7 (24.1)	1.000
Hypertension	3 (7)	1 (7.1)	2 (6.9)	1.000
Cancer	5 (11.6)	0 (0)	5 (17.2)	0.156
CAD	6 (14)	4 (28.6)	2 (6.9)	0.077
COPD	3 (7)	0 (0)	3 (10.3)	0.539
Candida Species				1.000
Non-Albicans	22 (51.2)	7 (50)	15 (51.7)	
Albicans	21 (48.8)	7 (50)	14 (48.3)	
Candida Type				0.058
Albicans	21 (48.8)	7 (50)	14 (48.3)	
Cruseii	2 (4.6)	0 (0)	2 (6.8)	
Glabrata	6 (14)	0 (0)	6 (20.7)	
Parapsilosis	10 (23.3)	7 (50)	3 (10.3)	
Tropicalis	4 (9.3)	0 (0)	4 (13.7)	
APACHE2 score	20(5-54)	16(7-40)	25(5-54)	0.078
Length of stay at ICU, days	26(1-206)	52.5(20-166)	16(1-206)	<0.001
Reason of stay at ICU				0.559
Lower Respiratory Tract Infection	6 (14)	2 (14.3)	4 (13.8)	
Other	7 (16.3)	2 (14.3)	5 (17.2)	
CPR	2 (4.7)	1 (7.1)	1 (3.4)	
Pnemoni	14 (32.6)	3 (21.4)	11 (37.9)	
Postoperative	2 (4.7)	1 (7.1)	1 (3.4)	
Sepsis	8 (18.6)	2 (14.3)	6 (20.7)	
Trauma	4 (9.3)	3 (21.4)	1 (3.4)	
Abdominal Surgery	7 (16.3)	2 (14.3)	5 (17.2)	1.000
Candidemia (ICU admission blood culture)	40 (93)	12 (85.7)	28 (96.6)	0.243
The time of pulling the catheter, day (if catheter was inserted)	3(1-6)	3(2-5)	4(1-6)	0.942
Candida Score				0.497
0	8 (18.6)	2 (14.3)	6 (20.7)	
1	15 (34.9)	6 (42.9)	9 (31)	
2	6 (14)	3 (21.4)	3 (10.3)	
3	10 (23.3)	3 (21.4)	7 (24.1)	
4	4 (9.3)	0 (0)	4 (13.8)	

Table 2. Distribution of laboratory findings and clinical findings of patients.

Laboratory and clinical findings	Total (n=43)	Alive (n=14)	Deceased (n=29)	p value
	n (%) or Median (Min – Max)	n (%) or Median (Min – Max)	n (%) or Median (Min – Max)	
WBC (/mcl)	10900(1640-115000)	12100(5900-18600)	8700(1640-115000)	0.826
Hb (g/dl)	9.1(6.5-13)	9.2(8.1-13)	9.1(6.5-11)	0.751
Plt (10 ³ /mcl)	167(18-695)	230.5(125-695)	98(18-538)	0.004
ALT (U/L)	38(8-12000)	38(8-198)	38(10-12000)	0.452
AST (U/L)	44(14-3713)	31.5(23-3713)	46.5(14-1860)	0.197
Urea (mg/dl)	87.5(0-275)	46.5(0.4-137)	112.5(0-275)	0.003
Creatinine (mg/dl)	1(0-69)	0.7(0.5-69)	1.3(0-6.7)	0.080
HeartRate/minute	119(60-175)	120(86-145)	118(60-175)	0.919
SBP, mmHg	95(60-160)	110(80-140)	90(60-160)	0.041
DBP, mmHg	50(30-70)	50(40-70)	50(30-70)	0.199
Fever (°Celcius)	38(35-39.6)	38.1(35.6-39.4)	37.8(35 – 39.6)	0.378

WBC: White blood cell; Hb: Haemoglobin; Plt: Platelet; ALT Alanine aminotransferase; AST: Aspartate aminotransferase; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 3. Distribution of treatment agents of patients and growth in their cultures.

Characteristics	Total (n=43)	Alive (n=14)	Deceased (n=29)	p value
	n (%) or Median (Min – Max)	n (%) or Median (Min – Max)	n (%) or Median (Min – Max)	
Candida Growth, days	8(1-180)	16.5(1-89)	1(1-180)	0.022
Treatment initiation day after sample collection	2.5(1-7)	3(1-7)	2(1-7)	0.336
Fundoscopy				0.013
None	30 (69.8)	6 (42.9)	24 (82.8)	
Normal	13 (30.2)	8 (57.1)	5 (17.2)	
Echocardiography				0,309
No	38 (88,4)	11 (78,6)	27 (93,1)	
Normal	5 (11,6)	3 (21,4)	2 (6,9)	
Treatment Agent				0.140
None	11 (25.6)	1 (7.1)	10 (34.5)	
Amphotericin	1 (2.3)	0 (0)	1 (3.4)	
Anidulafungin	3 (7)	2 (14.3)	1 (3.4)	
Fluconazole	26 (60.5)	11 (78.6)	15 (51.7)	
Caspofungin	2 (4.7)	0 (0)	2 (6.9)	

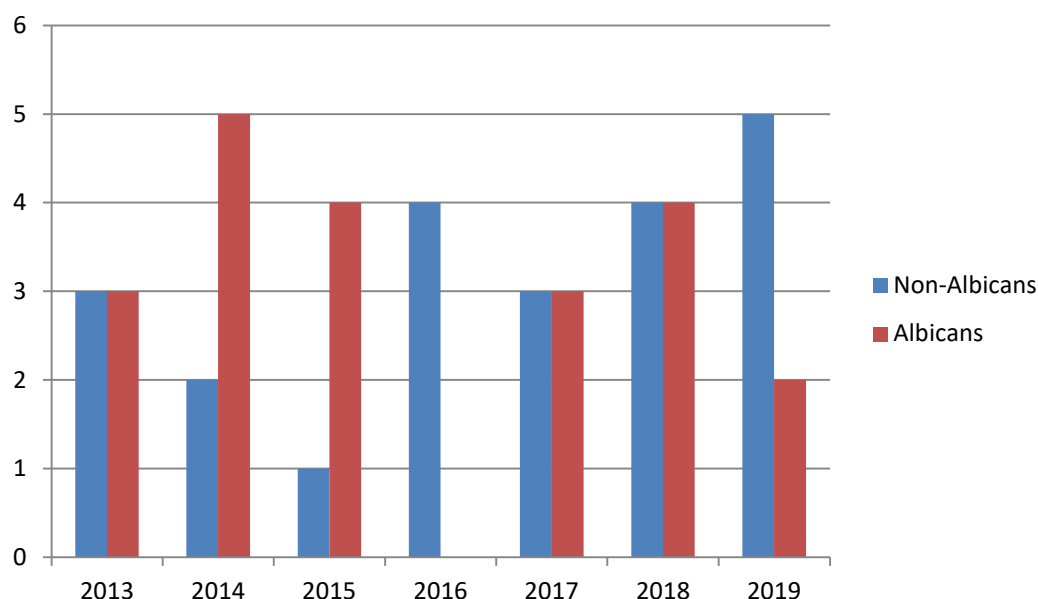


Figure 1. Candida species distribution by years.

DISCUSSION

Health related infections develop in one out of every ten hospitalized patients. It is known that the rate of these infection can be reduced by 30% by taking and implementing effective control measures. In previous literature, it was observed that the mortality ranged between 28.3-30.1% [12–14]. The prevalence of hospital infections is higher in underdeveloped and developing countries than in developed countries [16]. In studies conducted in Turkey, the incidence of candida-related infections varies between 0.8-1.76 per thousand patient days, and between 2.1-4.5 in global literature [16–18].

Candida species isolated in hospitals may present regional variations. When the distribution of candida species is examined in studies conducted in Turkey: Gultekin et al. [17] identified Candida species in 119 (71 patients) of the 24,709 blood culture samples that came to the laboratory for 7 years, and at 2010 reported that *C. albicans* (49%) was most frequently isolated, followed by *C. parapsilosis* (23%) and *C. tropicalis* (14%) respectively. Yenigun et al. [16], reported at 2011 that *C. albicans* has been isolated in 55.2% of blood culture sample, 50% in urine culture sample, and 43.7% in CVC culture sample. Sav et al. [19] detected Candida species in 1122 (28.7%) of 3095 clinical samples that came to the laboratory for 18 months, and 75.6% were *C. albicans*, 12.8% were *C. glabrata*, and 3.57% *C. parapsilosis* at 2013. Tukenmez et al. [12] found that *C. albicans* (75%) was isolated most frequently in a retrospective study in patients who were hospitalized in the ICU for two years. *C. glabrata* (11%), *C. tropicalis* (8%) and *C. parapsilosis* (6%) species followed, respectively at 2017. After evaluating the data of patients in ICU between 2013 and 2019 in this study we have found an even presence between the non-albicans (51.2%) and albicans (48.8%) cases (no significance). The distribution of the candida species was 48.8% *C. albicans*, 23.3% *C. parapsilosis*, 14% *C. glabrata*, 7% *C. tropicalis*, 4.6% *C. crusei* and 2.3% *C. triospor*.

Regarding these outcomes comparing with the results reported by Tukenmez and friends; we could state that there was a shifting paradigm from the dominant growth of non-albicans species. One should bore this in mind this shift on the selection of appropriate empirical treatment. Within several decades, the epidemiologic attribute of candida colonized infections have shifted from *Candida albicans* to a predominance of non-albicans species [20]. *Candida glabrata* has been the major driver of this paradigm change as accounted for 20% of new candida infections worldwide [12,21]. The increased utilization of azole group agents might be responsible for this species shift [21]. There is an emerging resistance against frequently used anti-fungal agents [13].

Candida presents itself as bloodstream infections, catheter-related infections, intra-abdominal infections and urinary tract infections in the intensive care unit conditions [14-18]. The mortality rate due to candida related infections may rise up to 60% [19]. One other down side of candidaemia can be elaborated as longer administration of mechanical ventilation [22]. This situation also leads to several more undesired coincidences for intensive care patients [23]. During additional diagnostic tool such as fundoscopy and echocardiography no new signs have been detected. The echocardiography revealed no statistical significance between the alive and deceased cases. Most importantly no vegetations have been observed in any of the groups. Similar to these results we did not detect any pathological finding in the study population. These might elaborate the severity of the infections in both groups [24,25].

Empirical treatment is an approach supported by guidelines for antifungal therapy. In empirical treatment, especially in risky patients, treatment is started by considering the possible causative agent and sensitivity in patients who are thought to have developed infection, according to the clinical condition of the patient, signs and symptoms of infection [26]. Empirical treatment comes to the fore in patients with severe sepsis, who are followed up in the ICU, who do not respond to antibiotic therapy for 3-7 days, who are colonized with *Candida* species, who have abdominal surgery, anastomotic leakage, pancreatitis, and who have severe sepsis. The problem here is the possibility of delay in treatment [27,28].

According to the results of this study the mean fungal culture positivity has been reported at first day of the ICU hospitalization for the non survivor group. According to recommendation of empirical antifungal treatment of guidelines of sepsis it takes at least 3-7 days to start the appropriate treatment to this group with candida positive culture results. We consider that the delay of the appropriate antifungal treatment for this group may explain the high mortality of non-survivor group.

Limitations of the study - this was a retro-spective monocentric study with the drawbacks entailed by such design. Due to small sample size and in order to avoid selection bias all 43 consecutive patients diagnosed with candidemia were included. Due to the intervention of the pandemic, cases after 2020 were not taken. As a single centre study the results can not be generalized all centers. Also we were not able to look *Candida* colonization which can effect the results.

CONCLUSIONS

According to the results of our study, it was determined that the mortality rate was higher in patients with sepsis and concomitant candida infection at early days of ICU hospitalization. In addition, mortality was observed in patients with candida growth in their cultures during all the ICU stay. In line with these results, it was concluded that early administration of empirical antifungal therapy should be considered for septic patients and it should be cover for non-albicans species which becoming to be dominant strains.

SUPPLEMENTARY INFORMATION

Funding: This research received no external funding.

Institutional Review Statement: The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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