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Candida spp. infection frequency and risk factors in malignant critical care patients

Burcu İleri Fikri[1], Alev Öztaş[1], Hazal Özsağıroğlu[2], Güldem Turan[1]

[1]Department of Intensive Care Unit, Başakşehir Çam and Sakura City Hospital, University of Health Sciences, İstanbul, Turkey
[2]Department of Anaesthesiology and Reanimation, Başakşehir Çam and Sakura City Hospital, University of Health Sciences, İstanbul, Turkey

ABSTRACT

Aims: *Candida* spp. can cause fatal infections in the person in case of immunosuppression such as malignancy. The aim of our study is to examine the frequency, prognosis and risk factors of *Candida*-related infections in our patients with malignancies followed in our intensive care unit (ICU).

Methods: ICU patients with malignancy with fungal infection accepted as the case group and the patients without *Candida* were considered as the control. Demographic characteristics, risk factors and *Candida* risk scores were recorded and compared in both groups.

Results: *Candida* spp. reproduction was observed at a very high rate with 24%. However, there was no difference in mortality between the two groups with and without *Candida* infection. In our study; *Candida* risk score, presence and duration of central venous catheter, antibiotic and steroid use in the last 1 month were found to be the factors determining the risk of *Candida* infection.

Conclusion: The contribution of the presence of fungal infection to mortality in our cancer patients does not seem different from others. However, in this patient group, it is difficult to distinguish colonization from invasive fungal infections. At this stage, the use of treatment decisions using risk factors and risk scoring comes to the fore.

Keywords: ICU, malignancy, *Candida* spp., mortality.

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INTRODUCTION

Infections due to *Candida* spp. cause severe problems associated with increased morbidity and mortality in ICUs.[1,2] Candidemia constitutes 10% of nosocomial infections and is associated with mortality defined as high as 40%.[3] The number of patients followed in ICUs with the diagnosis of malignancy is relatively high, and these patients have risks for *Candida* infection due to their immunosuppressed status. Except for mortality, *Candida* infections remain serious with increasing duration of stay and cost, and there may still be different approaches among clinicians in both diagnosis and treatment phases. It usually delays the diagnosis of *Candida* spp. infections as a result of the time required to obtain a positive blood culture, and this delay may cause mortality in our malignant patients. To start an effective early treatment, the diagnosis of *Candida* infections must be made quickly. Evaluation of risk factors is important for clinical guidance so that the patient to be treated can be determined as soon as possible.

The primary aim of our study was to evaluate whether there was a difference in mortality between the two groups in the ICU, and secondarily, it was aimed to reveal the difference in *Candida* risk factors statistically.

METHODS

Our study was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital, with the decree dated 13/01/2022 and numbered 2022.01.13. All patients with malignancy were reached by retrospectively scanning through the hospital registry system among all patients hospitalized in the Level 3 ICU between 01/01/2021-30/11/2021. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criteria

- ICU patients over the age of 18 with a diagnosis of malignancy.
- Patients with ongoing malignancy (chemotherapy, radiotherapy processes).
- All patients who will undergo or have undergone surgery for their active malignancy.

Exclusion Criteria of the Study

- Patients in remission whose malignancy has been treated more than 1 year after the remission period.
- Patients with a duration of stay in ICU less than 24 hours.

Corresponding Author: Burcu İleri Fikri, drburcuileri@hotmail.com

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These patients were divided into 2 groups patients with fungal reproduction in at least one of the culture samples taken during ICU admission and patients with no reproduction at all. Demographic characteristics of these 2 groups, which organ malignancy they have, APACHE-II, Sofa scores, ICU length of stay, first month and 3rd-month mortality, discharge data, fungal growth in which culture, whether they received treatment, if any, which antifungal agent was given, and risk factors were examined. *Candida* Risk Score Criteria (total parenteral nutrition (TPN) given, undergone surgery, presence of severe sepsis and multiple colonization), presence and duration of central venous chateter (CVC), long duration of stay in ICU, antibiotics, steroids, or other immunosuppressive treatments (chemotherapy) in the last 1 month agents) were investigated in our study as risk factors.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quartile, third quartile, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Independent groups t-test was used for comparisons between two groups of normally distributed quantitative variables, and the Mann-Whitney U test was used for comparisons between two groups of non-normally distributed quantitative variables. Pearson chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

Our study was carried out retrospectively in Başakşehir Çam ve Sakura City Hospital ICU, covering the date range of 01/01/2021-30/11/2021. There were 111 patients in our study, and the group with *Candida* spp. reproduction consisted of 27 patients, and the group without reproduction consisted of 84 patients. The ages of the cases ranged from 18 to 89, with a mean age of 61.32±13.26 years. 47.7% (n=53) of the participants were female and 52.3% (n=58) were male. The APACHE II values of the cases ranged from 2 to 47, and the mean value was 20.07±11.20. Sofa scores range from 0 to 21, with an average sofa score of 7.85±5.60. The duration of ICU hospitalization in the cases ranged from 1 to 155 days, and the mean duration of hospitalization was 14.22±21.12. When ICU discharge routes were examined, it was observed that 64% (n=71) of the cases were dead, 34.2% (n=38) were transferred to the service, 0.9% (n=38) were transferred to palliative, and 0.9% of them (n=1) were transferred to another ICU and left the intensive care unit. Mortality at the end of the first month was observed in 56.8% (n=63) of the participants, and mortality at the end of the third month in 64% (n=71) of the participants. Reproduction was observed in 22.2% (n=6) blood, 18.5% (n=5) urine, 7.4% (n=2) tracheal aspiration sample, 3.7% (n=1) wounds, 48.1% (n=13) multi-areas. When the reproducing fungal species were examined, it was observed that 74.1% (n=20) of those with growth were *C. albicans*, 40.7% (n=11) C. Non-albicans, and 7.4% (n=2) other (rare fungi). Antifungal treatment was started in 81.5% (n=22) of the cases. Azole group was started in 19 of our patients and the echinocandin group was started in 2 patients considering their antifungal resistance. Demographic characteristics, ICU exit patterns and mortality rates according to the groups of the patients are shown in **Table 1**, and reproduction rates and antifungals used in the treatment are shown in **Table 2** and **Figure 1**.

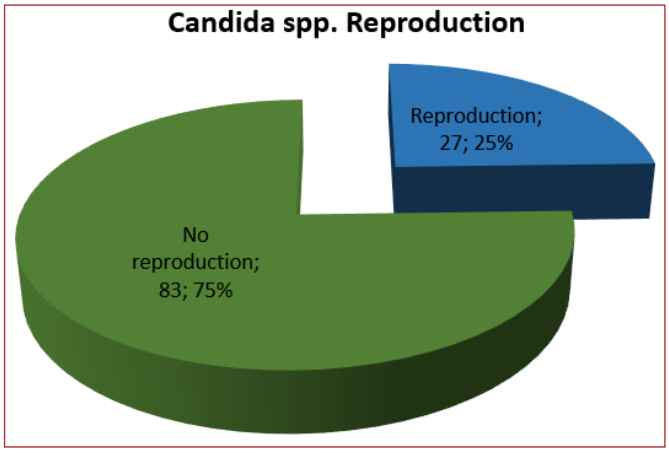

Figure 1: *Candida* reproduction distribution

Table 1: Evaluation of Demographic Characteristics by Groups

	Candida		
	Reproduction (+) (n=27)	Reproduction (-) (n=84)	p
Age			[a]0.688
Mean±SD	62.22±14.85	61.04±12.79	
Median (min-max)	63 (18-87)	61 (25-89)	
Gender			[b]0.624
Female	14 (51.9)	39 (46.4)	
Male	13 (48.1)	45 (53.6)	
Apache score			[c]0.441
Mean±SD	18.11±7.05	20.70±12.21	
Median (min-max)	17 (6-36)	20 (2-47)	
SOFA score			[c]0.441
Mean±SD	7.30±4.03	8.02±6.03	
Median (min-max)	7 (1-17)	8 (0-21)	
Intensive care hospital stay (days)			[c]0.001**
Mean±SD	35.33±32.09	7.43±8.79	
Median (min-max)	27 (1-155)	3 (1-37)	
Mortality at the end of 1st month			[b]0.554
No	13 (48.1)	35 (41.7)	
Yes	14 (51.9)	49 (58.3)	
Mortality at the end of 3rd month			[b]0.086
No	6 (22.2)	34 (40.5)	
Yes	21 (77.8)	50 (59.5)	
ICU discharge route			[d]0.221
Ex	19 (70.4)	52 (61.9)	
Transfer to service	7 (25.9)	31 (36.9)	
Transfer to palliative	1 (3.7)	0 (0)	
Transfer to another intensive care	0 (0)	1 (1.2)	

aStudent t Test, bChi Square Test, cMann Whitney U Test, dFisher Freeman Halton Test, **p<0,01

Table 2: Reproduction Results and Cure Rates

Area, in case of reproduction (n=27)	
Blood	6 (22.2)
Urine	5 (18.5)
Tracheal aspiration	2 (7.4)
Wound	1 (3.7)
Multiple	13 (48.1)
• Reproducing mushroom species (n=27); n(%)	
C. albicans	20 (74.1)
C. Non-albicans	11 (40.7)
Other (rare fungi)	2 (7.4)
Antifungal started? (n=27); n(%)	
Not started	5 (18.5)
Started	22 (81.5)
If started, which (n=22); n(%)	
Azol group	20 (90.9)
Echinocandins	2 (9.0)

•More than one option is marked.

When Risk Factors are examined in detail, 17.1% (n=19) of the cases received total parenteral nutrition (TPN) and 36.9% (n=41) underwent surgery. Multiple fungal colonization was observed in 14.4% (n=16) of the patients, and severe sepsis was observed in 49.5% (n=55) of the patients. The total *Candida* scores of the cases ranged from 0 to 5 and the mean score was determined as 1.66±1.36. 59.1% (n=55) of the participants in the study had CVC, and the mean duration of CVC was 10.85±20.56. 50.5% (n=47) of the cases used antibiotics within the last 1 month, 25.8% (n=24) used steroids within the last 1 month, and 17.2% (n=16) used non-steroidal immunosuppressive therapy (chemotherapy) within the last 1 month. The distribution of Risk Factors is shown in **Table 3**.

Table 3. Distribution of Risk Factors

		n (%)
TPN	Did not receive	92 (82.9)
	Received	19 (17.1)
Surgery	Underwent	70 (63.1)
	Did not undergo	41 (36.9)
Multiple colonization	No	95 (85.6)
	Yes	16 (14.4)
Severe sepsis	No	56 (50.5)
	Yes	55 (49.5)
Total *Candida* score	Mean±SD	1.66±1.36
	Median (min-max)	2 (0-5)
CVC	No	56 (50.5)
	Yes	55 (49.5)
CVC duration	Mean±SD	10.85±20.56
	Median (min-max)	3 (0-150)
Antibiotic use in the last 1 month	No	64 (57.7)
	Yes	47 (42.3)
Steroid use in the last 1 month	No	87 (74.8)
	Yes	24 (21.6)
Immunosuppressive therapy in the last 1 month	No	95 (85.6)
	Yes	16 (14.4)

ICU length of stay in cases with *Candida* reproduction was statistically significantly higher than those without reproduction (p=0.001; p<0.01) **Figure 2**.

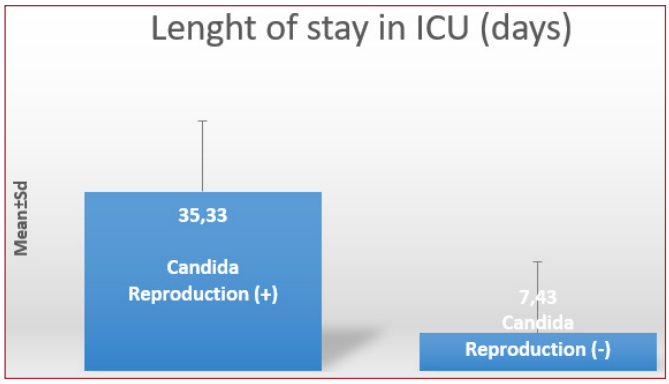

Figure 2: Distribution of intensive care unit stay according to the presence of *Candida* reproduction

Age, gender, APACHE II and Sofa scores of the cases, mortality rates at the end of the 1st and 3rd months, and the route they were discharged from the ICU did not show a statistically significant difference according to the presence of *Candida* reproduction (p>0.05). According to the incidence of *Candida* reproduction, the incidence of TPN and surgery did not show a statistically significant difference (p>0.05). The incidence of multiple sewage in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.001; p<0.01). The incidence of severe sepsis in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.001; p<0.01). The total *Candida* scores of the cases with *Candida* reproduction were found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The incidence of CVCs in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.002; p<0.01). CVC times of cases with *Candida* reproduction were found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The rate of antibiotic use in the last 1 month in those with *Candida* reproduction was found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The rate of steroid use in the last 1 month in those with *Candida* reproduction was found to be statistically significantly higher than those without reproduction (p=0.023; p<0.05). There was no statistically significant difference between the rates of using other immunosuppressive treatments in the last 1 month according to the *Candida* reproduction rate (p>0.05).

DISCUSSION

As ICU physicians, we designed this study based on the question of whether our fungal infections are more common in patients with malignancy among chronic-comorbid diseases such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease and cerebrovascular diseases.

There was a reproduction in the blood culture of 16 of our patients and these patients were referred to as "candidemia". In other words, our candidemia frequency was found to be 15.8% in all patients. Although breeding is considered the gold standard for candidemia, its sensitivity varies between 21-71%.[4] In our study, especially patients with a diagnosis of malignancy hospitalized in the tertiary ICU were selected, and when we looked at our patients' APACHE and SOFA scores, we encountered a patient group with a very low life expectancy. Regardless of the underlying disease in ICUs, the crude mortality rate due to *Candida* infections has been shown in studies to be 30-50%.[5] It was shown in many studies that many more patients with malignancy result in death compared to other chronic diseases.[6,7]

All the patients in our study were patients diagnosed with malignancy, admitted after surgery for malignancy, hospitalized with a complication related to malignancy, or patients whose general condition deteriorated after chemotherapy and indicated for ICU admission. In our patients, the mortality at the end of the 1st month was 56.8% and the mortality at the end of the 3rd month was 64.0%. When we divided all our patients into 2 groups those with and without fungal infection, the mortality at the end of the 1st month was 51.9%, and the mortality at the end of the 3rd month was 59.5% in the group with reproduction. The difficulty in this and similar studies, including ours, is that it is not possible to clearly distinguish whether the patients were lost due to malignancy or due to *Candida* infection.

Fungal infections are opportunistic pathogens which rank 4th among hospital-acquired infections according to studies

in the USA. *Candida* spp, which colonizes the oral cavity and gastrointestinal and genitourinary system in healthy people, can cause fatal infection in immunosuppressed conditions. The main immunosuppression conditions can be listed as chemotherapy and radiotherapy treatments, long-term use of corticosteroids and antibiotics, and the presence of malignancy.[8,9] *Candida* spp. is still the most common in ICU and *C. albicans* comes first.[10] However, some of the increasing non-albicans species have serious consequences due to their resistance to azoles and delays that may occur in reaching echinocandins. In our study, the most common fungal agent was *Candida* spp with *C. albicans* coming first and Fungi other than *Candida* spp. reproduced in 2 cases in our study. Li et al.[11] compared 80 patients diagnosed with a malignancy in tertiary ICU patients with patients without malignancy and found that *Candida* spp. found 30% mortality due to infection and highlighted it as a much higher mortality rate compared to patients without malignancy.

The risk factors that increase the frequency of *Candida* infection in our study overlap with the risk factors that have been revealed in many previous studies.[12] *Candida* Risk Score, presence and duration of the CVC, length of stay in ICU and antibiotic, steroid, and other immunosuppressed treatments in the last 1 month were evaluated. *Candida* Risk Score includes 4 criteria and it is accepted that a value over 2.5 increases the risk. A *Candida* score of >2.5 was found to have 81% sensitivity, 74% specificity, 98% negative predictive value and 16% positive predictive value for invasive candidiasis. In the score, 2 points were given for sepsis and 1 point for other risk factors.[13]

When we compared our patient groups with and without *Candida* reproduction in our study; the incidence of multiple fungal colonization, *Candida* risk score, presence of sepsis, presence and duration of the CVC, antibiotic and steroid use in the last 1 month were found to be the factors determining the risk of *Candida* infection. Although it is known that the use of TPN in groups with and without *Candida* growth, having undergone surgery and receiving immunosuppressive therapy in the last 1 month, increased the risk, they did not make a statistically significant difference. Regarding the use of TPN, we think that we may have obtained clarity by the fact that the standard prepared TPN products in our hospital are transported from the hospital pharmacy to our unit with the cold chain, and that no additions are made to the TPN products, and that they are given in a time not exceeding 24 hours by always paying attention to the extremely sterile conditions with the central catheter.

Another controversial issue in this regard is whether prolonged ICU stays cause an increase in the frequency of *Candida* infection. In the design of many studies in the literature, it is seen that the time to increase the risk of *Candida* is considered to be 30 days or more. In a meta-analysis published by Zhang et al.[9] ICU hospitalization for the risk of *Candida* infection was shown as 25.8 days. In our study, the average duration of stay in ICU was 14.22±21.12 days for all patients. The day of hospitalization in the ICU was 35.33±32.09 days in patients with *Candida* reproduction and 7.43±8.79 days in patients without reproduction, and a significant difference was observed. (p=0.001). What we want to emphasize here, regardless of mortality, is the necessity to ensure the rational use of ICUs and to ensure that patients whose ICU indications disappear should be transferred to the necessary services immediately.

At the beginning of our study, the main issue we wanted to achieve was to examine whether *Candida* infections are mortal in malignant ICU patients. As a result of our study, we did not see a difference in mortality, and this result made us think: Wonder if *Candida* spp. in malignant patients does not cause as many frightening results as we think?

Candida spp. reproduction, especially in blood culture, creates a state of anxiety and alarm, especially in physicians. For these patients, the risk factors that can be corrected are reviewed, and it is decided whether to change the CVC, nasogastric tube and urinary catheter and, if TPN is applied, whether to stop it. In patients with candidemia, an ophthalmology consultation is urgently requested for *Candida* opthalmitis. This examination is done at the bedside, and there may be delays in terms of the need for consultation with other branches. Yet, bedside transthoracic ECHO is performed by the cardiologist for the screening of *Candida* endocarditis in patients with candidemia and transaesophageal ECHO is often recommended to the patients. Since this examination cannot be performed at the bedside, the transport of the patient to another block carries risks for both the physicians and the patient due to possible complications and procedure-specific difficulties associated with the transport. Again, in all patients in whom we detected *Candida* spp. infection, consultation from infectious diseases is requested and opinions are taken for the antifungal agent to be selected, and inevitable treatment delays contribute to the increase in mortality.

The number of the cases was one of the limitations of our study. Furthermore, we need more spesific diagnostic tools for candidemia and colonisation.

CONCLUSION

If we summarize our work, *C. albicans* was the most common pathogen. Candidemia and other *Candida* infections can cause an increase in ICU deaths and ICU costs due to *Candida* infections, as well as the severity of the disease and the complications experienced. As ICU physicians, we see that the number of patients who come to the ICU with the diagnosis of malignancy is quite high. We think that we should keep in mind the predisposing factors and risk scoring for *Candida* spp infections in our cancer patients hospitalized in the ICU.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Başakşehir Çam and Sakura City Hospital, with the decree dated 13/01/2022 and numbered 2022.01.13.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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