Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2022; 61 (4): 616-625

Distribution of *candida* species and risk factors for invasive candidiasis

Candida türlerinin dağılımı ve invaziv kandidiyazis için risk faktörleri

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ABSTRACT

Aim: The aim of this study was to investigate the *Candida* species isolated from the clinical samples of patients in the pediatric intensive care unit and to determine the risk factors for invasive candidiasis.

Materials and Methods: Patients with *Candida* species detected in clinical samples between January 2013 and December 2018 were included in this study. The demographic characteristics of the patients, the use of broad-spectrum antibiotics and immunosuppressive drugs, underlying diseases, blood transfusions, history of surgical operations, whether there is bacterial growth with *Candida* species in the same clinical sample, parenteral nutrition and invasive interventions were retrospectively analyzed and their relationship with invasive candidiasis was investigated.

Results: A total of 91 patients were included in the study. The mean age was 72.3 ± 70.1 months. Among the patients 48.4% had *Candida albicans* while 51.6% had non-albicans *Candida. Candida parapsilosis* (n = 18, 19.8%) and *Candida tropicalis* (n = 14, 15.4%) were the most common non-albicans *Candida* species. The most common antifungal treatment was fluconazole (n = 34, 59.6%). There was no statistically significant relationship between invasive candidiasis and the underlying disease, central venous and / or urinary catheter, broad-spectrum antibiotic, corticosteroid, gender and surgical operation (p> 0.05). On the other hand, there was a statistically significant relationship between invasive candidiasis and parenteral nutrition, blood transfusion and bacterial growth with *Candida* species in the same clinical sample (p <0.05).

Conclusions: Non-albicans *Candida* species are more common than *Candida albicans* in the pediatric intensive care units. *Candida parapsilosis* is the most common among non-albicans *Candida* species. Parenteral nutrition, blood transfusion and bacterial growth with *Candida* species in the same clinical sample increased the risk of invasive candidiasis.

Keywords: Pediatric intensive care unit, invasive candidiasis, *candida* species, contamination.

This article was presented as a poster presentation at the 16th Pediatric Emergency Medicine and Intensive Care Congress-12th Pediatric Emergency Medicine and Intensive Care Nursing Congress (2-5 October 2019 Antalya).

ÖZ

Amaç: *Bu çalışmada, çocuk yoğun bakım ünitesinde yatan hastaların klinik örneklerden izole edilen Candida türlerinin araştırılması ve invaziv kandidiyazis için risk faktörlerinin belirlenmesi amaçlanmıştır.*

Gereç ve Yöntem: *Bu çalışmaya Ocak 2013 ile Aralık 2018 tarihleri arasında klinik örneklerde Candida türleri tespit edilmiş hastalar alınmıştır.*

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Application date: 05.08.2021 Accepted: 01.07.2022

Hastaların demografik özellikleri, geniş spektrumlu antibiyotik ve immunsupresif ilaç kullanımı, altta yatan hastalıkları, kan transfüzyonu, cerrahi operasyon öyküsü, aynı klinik örnekte Candida türleri ile birlikte bakteri üremesi olup olmadığı, parenteral beslenme ve invaziv girişimler retrospektif olarak incelenmiş ve invaziv kandidiyazis ile ilişkisi retrospektif olarak araştırılmıştır.

Bulgular: *Çalışmaya toplam 91 hasta dahil edilmiştir. Ortalama yaş 72,3 ± 70,1 ay bulunmuştur. Hastaların %48,4'ü Candida albicans iken, %51,6'sı da non-albicans Candida vardı. Candida parapsilosis (n = 18, %19,8) ve Candida tropicalis (n = 14, %15,4) en yaygın albicans dışı Candida türleri olarak tespit edilmiştir. En yaygın verilen antifungal tedavi flukonazoldü (n = 34, %59,6). Altta yatan hastalık, santral venöz ve/veya üriner kateter, geniş spektrumlu antibiyotik, kortikosteroid, cinsiyet, cerrahi operasyon ile invaziv kandidiyazis arasında istatistiksel olarak anlamlı ilişki bulunmamıştır (p> 0,05). Öte yandan, aynı klinik örnekte Candida türleri ile birlikte bakteri üremesi, parenteral beslenme ve kan transfüzyonu ile invaziv kandidiyazis arasında istatistiksel olarak anlamlı ilişki bulunmuştur (p<0,05).*

Sonuç: *Pediyatrik yoğun bakım ünitelerinde non-albicans Candida türleri Candida albicans'a göre daha sık görülmektedir. Candida parapsilosis, albicans olmayan Candida türleri arasında en yaygın olanıdır. Parenteral beslenme, kan transfüzyonu ve aynı klinik örnekte Candida türleri ile birlikte bakteri üremesi, invaziv kandidiyazis riskini artırmıştır.*

Anahtar Sözcükler: *Pediyatrik yoğun bakım ünitesi, invaziv kandidiyazis, candida türleri, kontaminasyon.*

Bu makale, 16. Çocuk Acil Tip ve Yoğun Bakim Kongresi-12. Çocuk Acil Tip ve Yoğun Bakim Hemşireliği Kongresinde (2-5 Ekim 2019 Antalya) poster bildiri olarak sunulmuştur.

INTRODUCTION

Infections caused by *Candida* species, which are normal flora elements of the body, can range from simple mucocutaneous disease to invasive candidiasis (1). *Candida* colonization is considered a risk factor for the development of invasive candidiasis; because colonization also plays an important role in the pathogenesis of patients in intensive care units where physical barriers are mostly broken. As a matter of fact, it has been shown that the invasive *Candida* species are the same as the *Candida* species colonizing the rectum, lung and urinary system (2). *Candida* species found in the normal body flora cause infection by passing through natural barriers with the application of invasive procedures such as catheters and endotracheal tube applied in intensive care patients (3).

Candida albicans (CA) causes 40-60% of invasive Candida infections. However, the number of formerly non-pathogenic species and non-albicans *Candida* species is gradually increasing due to the increase in the susceptible population and the advancement of laboratory techniques, such as the ability to identify new species and the widespread use of fluconazole (4,5). The frequency of invasive fungal infections has increased in recent years and is among the important causes of morbidity and mortality in intensive care patients (6-8). The growth of invasive candidiasis is associated with the presence of risk factors (clinical severity, advanced age or new born, intensification of therapies with corticosteroids and other immunosuppressive drugs, prolonged use of invasive devices, intense and sustained neutropenia, solid organ transplantation or neoplasia, broad-spectrum antibiotics, previous use of antifungals, renal failure, pancreatitis, etc.) (9).

Since most of the studies are conducted on adults, there is limited literature in the field of invasive candidiasis and *Candida* colonization in critically ill children from pediatric intensive care units (PICU). The current study was undertaken to investigate the frequency of CA and non-albicans *Candida* (NAC) strains isolated in culture specimens of the patients in the PICU. Additionally, the study aimed to determine the risk factors of invasive candidiasis, and also to show the importance of fever and hypotension in the early diagnosis of invasive candidiasis PICU. It was also aimed to show the association between admission diagnosis of the patients and invasive candidiasis frequency.

MATERIALS and METHODS

In our study conducted with 91 patients aged 1 month to 18 years, followed up in the PICU between January 2013 and December 2018, the

reproduction of *Candida* species in clinical samples was investigated. Patients' demographic characteristics, hospitalization date, and diagnosis, age distribution, presence of hypotension, and fever were recorded as clinical markers. *Candida* species growing in cultures, the distinction of *Candida* colonization and invasive candidiasis, potential risk factors, and antifungal drug treatments were retrospectively analyzed. If the same species of *Candida* was isolated from the clinical specimens taken from a patient, only one, if different species were isolated, the first *Candida* species was included in the study. And in the case of the growth of multiple species, the first breeding *Candida* species were included in the study.

Patients were analyzed in two groups based on clinical findings and laboratory results as *Candida* colonization and invasive candidiasis. Colonization was defined as the isolation of a *candida* species from at least one surveillance site. Invasive candidiasis was defined by using the revised and updated consensus definitions of invasive fungal disease, developed by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (10). The presence of at least one type of *Candida* in the culture specimen and the presence of infection markers such as hypothermia, fever, elevation in acute phase reactants, leukocytosis, tachycardia, and hypotension were evaluated as invasive candidiasis. Antifungal therapy was initiated in patients with invasive candidiasis, and colonization was followed without treatment. In addition, patients were divided into two groups as CA and NAC according to the *Candida* species grown in the clinical sample. Broad-spectrum antibiotic and immunosuppressive drug use, underlying disease, blood and blood product transfusion, history of surgical operation, bacterial growth with *Candida* species in the same clinical sample, parenteral nutrition, and invasive interventions (central venous and/or urinary catheter) were considered to be risk factors for patients and investigated.

Yeast strains isolated from patient samples sent to the microbiology laboratory from the PICU were included in the study. From clinical specimens for the first isolation of *Candida* species, the cultures were incubated at 35 C using 5% sheep blood Columbia agar (Merck, Darmstadt, Germany) and eosin methylene blue (EMB) (Merck, Darmstadt, Germany) media and Sabouraud dextrose agar (SDA) (Merck, Darmstadt, Germany) without antibiotics. Blood cultures were monitored in the BACTEC-9120 (Becton Dickinson, Heidelberg Germany) system with a one-week protocol. BACTEC Peds Plus / F blood culture bottles were used as a medium. Since the detection of *Candida* at any concentration in urine samples was thought to reflect renal involvement, it was definitely evaluated together with the species identification (11). In the presence of pure growth in sterile body fluids, microscopic examination and culture results in respiratory tract samples were evaluated together, and dominant growths were considered as factors and were included in the study (12). The strains identified as yeast by gram staining were determined by conventional method and assessed using colony morphology in SDA, chlamydospore, blastospores, true and false hyphae formation in germ-tween 80 gelose and germination test, pigment formation in CHROMagar Candida (Becton Dickinson, UK). The strains not identified by these methods were typed at the species level using commercial API 20 C AUX (bio Mérieux, France) or Vitek 2 (bio-Mérieux, France) systems.

Pearson chi-square and Likelihood Ratio chi-square tests were used for differences between categorical variables. Descriptive statistics are given as numbers and percent values. In addition, binary logistic regression analysis was used to determine the risk factors for invasive candidiasis. Statistical significance was taken as $p < 0.05$. Ethics committee approval was obtained from Mersin University Rectorate Clinical Research Ethics Committee (date: 5 September 2018 and decision no: 2018/355).

RESULTS

The study was conducted with 91 children, 48 (52.7%) of whom were female and 43 (47.3%) were male. The patients were aged between two and 216 months (mean 72.3 ± 70.1 months). Central nervous system diseases (n; 36, 39.6%) ranked first among the causes of hospitalization, followed by malignant diseases (n=13, 14.3%) and metabolic diseases (n=10, 11%), respectively. Of the remaining 32 patients, seven had trauma, seven had a nephrological disease, four had an infectious disease, three had cardiovascular disease, two had the non-malignant hematologic disease, two were in postoperative follow-up and other seven patients had other diseases (immunodeficiency, foreign body aspiration, Prader Willi, bronchopulmonary dysplasia, intoxication).

Table-1. Epidemiological characteristics of the patients with *candida* growth in culture materials.

		Number(n)	Percentage (%)
Gender	Female	48	52.7
	Male	43	47.3
Hospitalization period	2013-2015	22	24.2
	2016-2018	69	75.8
Candida species	*Candida albicans*	44	48.4
	non-albicans *Candida*	47	51.6
	C. parapsilosis	18	19.8
	C. tropicalis	14	15.4
	C. glabrata	7	7.7
	C. kefyr	4	4.4
	C. krusei	4	4.4
Antifungal treatment	No treatment	34	37.4
	Amphotericin-B	9	9.9
	Caspofungin	14	15.4
	Flukonazol	34	37.7
Sample species	Urine	57	62.6
	Peripheral blood	20	22.0
	CVC	8	8.8
	Tracheal aspirate	2	2.2
	Others	4	4.4
Bacterial culture growth	No growth	25	27.5
	Peripheral blood	37	40.7
	Urine	12	13.2
	Tracheal aspirate	8	8.8
	CVC	4	4.4
	Others	5	5.5
Underlying diseases	CNS diseases	36	39.6
	Malignant diseases	13	14.3
	Metabolic diseases	10	11.0
	Nephrological diseases	7	7.7
	Trauma	7	7.7
	Infectious diseases	4	4.4
	Cardiovascular diseases	3	3.3
	Non-malignant hematological diseases	2	2.2
	Hospitalized patients after surgery	2	2.2
	Others*	7	7.7

CNS; central nervous system CVC; central venous catheter. BPD; bronchopulmonary dysplasia, *Immunodeficiency, foreign body aspiration, Prader Willi, BPD, Intoxication.

Table-2. Comparison of risk factors for *Candida albicans* and Non-albicans *Candida.*

		C. albicans		Non-albicans *Candida*		p
		number	%	number	%	
Central venous catheter		35	79.5	42	89.4	0.314
Urine catheter		44	100	44	93.6	0.242
Number of antibiotics	1	18	41.0	18	38.3	0.795
	2	23	52.2	27	57.4	
	3	3	6.8	2	4.3	
Parenteral nutrition		26	59.1	27	57.4	0.874
Blood transfusion		34	77.3	33	70.2	0.599
Surgery		25	56.8	20	42.6	0.250
Corticosteroid		11	25	7	14.9	0.295
Gender	Female	25	56.8	23	48.9	0.452
	Male	19	43.2	24	51.1	

The distribution of patients was examined from 2013 to 2018. In the first three years, the number of patients who had *Candida* growth was 22 (24. 2% of the patients included in the study) while in the last three years the number of patients who had *Candida* growth constituted 75.8% (n = 66) of the patients included in the study.

CA was produced in 44 (48.4%) patients, while NAC was produced in 47 (51.6%) patients. *Candida parapsilosis* and *Candida tropicalis* were the most isolated species among NAC while *Candida krusei* and *Candida kefyr* were the least isolated (Table-1). *Candida* species were mostly isolated from urine (n= 57, 62.6%) and peripheral blood (n= 20, 22.2%) in clinical samples. The highest bacterial growth rate was observed in peripheral blood samples (n = 37, 40.7%). Based on the assessment of patients according to *Candida* and concomitant bacterial growth, the number of patients who had both pathogen microorganisms (n = 66, 72.5%) was higher than the number of patients without any bacterial growth. (n = 25, 28.5%) (Table-1).

In our study, bacterial growth was investigated as well as *Candida* species in the same clinical samples taken from the patients. The relationship between *Candida* species and the epidemiological parameters of the patients was investigated and descriptive statistics were made. Accordingly, no statistically significant relationship was found between candida species and gender, bacterial growth in culture samples, *Candida* colonization or invasive candidiasis status, corticosteroid, broad-spectrum antibiotic, erythrocyte suspension transfusion, parenteral nutrition, central venous catheter (CVC), urinary catheter, surgical operation and underlying disease(all p values> 0.05) in Table-2.

According to clinical and laboratory results, patients were divided into two groups as invasive candidiasis and colonization. Patients with invasive candidiasis were treated with antifungal medication and patients with *Candida* colonization were not given antifungal therapy. Fluconazole (n = 34, 59.6%) was the most preferred antifungal drug treatment while caspofungin (n = 14, 24.6%) and amphotericin-B (n = 9, 15.8%) were preferred after fluconazole. Patients' invasive candidiasis risk factors were investigated and their descriptive statistics (number and percentage) were given in Table-3. There was no significant difference between CVC, urinary catheter, broad-spectrum antibiotic therapy, immunosuppressive corticosteroid use, surgical operation, gender, bacterıal growth in clinical samples, underlying disease and development of invasive candidiasis (all p values> 0.05) (Table-4) while there was a significant difference between parenteral nutrition, blood transfusion and bacterial growth positivity (p values: 0.001; 0.013 and 0.009, respectively). Blood transfusion history was found positive in 58.8% of patients with colonization and 82.5% of patients with invasive candidiasis. Additionally, invasive candidiasis was observed in 70.1% of patients with blood transfusion while colonization was found in 58.3% of those without. The bacteria growth rate was 55.9% in patients with colonization and 82.5% in patients with invasive candidiasis.

There was fever in 54.4% of patients with invasive candidiasis while it was observed in 23.5% of those with colonization. Invasive candidiasis was observed in 19 (73.1%) of 26 patients with hypotension while 38 (58.5%) of 65 normotensive patients had invasive candidiasis. Although there was a significant relationship between fever and invasive candidiasis (p = 0.004), there was no relationship between hypotension and invasive candidiasis (p = 0.193) (Table-3).

Table-3. Comparison of risk factors for invasive candidiasis and colonization.

		Candida colonization (34)		Invasive candidiasis (57)		p
		Number	**%**	**Number**	**%**	
CVC		26	76.5	51	89.5	0.096
Urine catheter		33	97.1	55	96.5	0.882
Fever		8	23.5	31	54.4	**0.004**
Hypotension		7	20.6	19	33.3	0.193
Number of antibiotics	1	16	48.5	19	33.9	0.363
	2	15	45.5	34	60.7	
	3	2	6.1	3	5.4	
Parenteral nutrition		12	35.3	41	71.9	**0.001**
Blood transfusion		20	58.8	47	82.5	**0.013**
Corticosteroid use		6	17.6	12	21.1	0.693
Surgery		14	41.2	31	54.4	0.223
Gender	Female	16	47.1	32	56.1	0.401
	Male	18	52.9	25	43.9	
Bacterıal growth in clinical samples		19	55.9	47	82.5	**0.006**
Sample specıes with bacterıal growth	No growth	15	44.1	10	17.5	0.160
	Urine	4	11.8	8	14.0	
	Peripheral blood	11	32.4	26	45.6	
	Catheter (CVC)	1	2.9	3	5.3	
	Tracheal aspirate	2	5.9	6	10.5	
	Others	1	2.9	4	7.0	
Underlying disease	Malignancy	3	8.8	10	17.5	0.880
	Central nervous system	15	44.1	21	36.8	
	Non-malignant hematological diseases	1	2.9	1	1.8	
	Metabolic	4	11.8	6	10.5	
	Cardiovascular	1	2.9	2	3.5	
	Trauma	2	5.9	5	8.8	
	Infectious	3	8.8	1	1.8	
	Nephrological	2	5.9	5	8.8	
	Post operative	1	2.9	1	1.8	
	Others*	2	5.9	5	8.8	

*Immunodeficiency, foreign body aspiration, Prader Willi, Bronchopulmonary dysplasia, Intoxication, CVC; central venous catheter

Table-4. Risk factors for invasive candidiasis

	B	Wald	OR [95% CI]	p
Parenteral nutrition	1.054	4.134	2.869 [1.039- 7.927]	**0.042**
Blood transfusion	0.653	1.304	1,921 [0.626-5.893]	0.254
Bacterıal growth in clinical samples	0.992	3.360	2,697 [0.934-7.793]	0.067
Fever	1.091	4.369	2,979 [1.070- 8.289]	**0.037**

When all of the risk factors for the invasive candidiasis were included in the model, only parenteral nutrition and fever were found to be significant (p values; 0.042 and 0.037, respectively) (Table-4). Accordingly, those with parenteral nutrition had a 2.869 times higher risk of infection than those without parenteral nutrition and those with fever had a risk of invasive candidiasis 2.979 times more than those without fever.

DISCUSSION

Despite the use of preventive antifungals and appropriate treatment methods, mortality rates can reach 40-50%, especially in newborns and infants (13)**.** Studies and measures taken for the diagnosis, treatment and follow-up of invasive candidiasis affect the morbidity and mortality of, particularly risky patients. Positive advances such as the expansion of intensive care units, the development of technological facilities and the inclusion of new antifungal drugs in the treatment have provided the opportunity to follow the risky patients for a longer time. Therefore, invasive candidiasis infections are becoming a more and more popular topic among physicians. The early culture of patients at risk and measures such as not delaying antifungal therapy and adherence to the rules of asepsis and antisepsis are becoming increasingly important.

Infections caused by *Candida* species are increasing in risk group patients. İnvasive candidiasis are among the life-threatening infectious agents in hematology and oncology patients, immunodeficient or immunosuppressive treatment taking patients and especially in patients who were mechanically ventilated for a long time in intensive care units. The incidence of invasive candidiasis at a hospital in Spain was analyzed and reported that 331 *Candida* episodes were detected in 13 years. The highest incidence of invasive candidiasis was observed in intensive care units and especially in PICU (14). The present study found that the distribution of *Candida* isolated over the years to have increased significantly in the last three years. The number of patients in the first three-year period was 22 (24.2%), while the number of patients in the last three-year period was 66 (65.8%), which constituted the majority of the patients. This increase in the distribution of invasive candidiasis in recent years is attributed to the fact that physicians consider invasive candidiasis more in line with the increase in clinical experience, laboratory facilities and various factors such as the use of broad-spectrum antibiotics suppressing normal flora and invasive procedures.

Patients in our study were analyzed in two groups as invasive candidiasis and colonization. Antifungal treatment was not applied to 34 (37.3%) patients defined as colonization. In the study of Acar et al. in the intensive care unit with 48 pediatric and adult patients, the colonization rate was found to be 39.6%, similar to our study (15). It is known that prophylactic antifungal treatments prevent the development of serious complications in patients with a mortal infection such as invasive candidiasis, without waiting for culture results. Therefore, the importance of clinical parameters such as high fever and hypotension was investigated for the initiation of antifungal therapy without waiting for culture results when there was a deterioration in the patients' clinical findings and laboratory results. Invasive candidiasis was observed in 31 (79.5%) of 39 patients with fever and *Candida* colonization was found in eight of them and there was invasive candidiasis in 19 (73.1%) of 26 hypotensive patients whereas colonization was found in seven of them. While there was a statistically significant correlation between high fever and invasive candidiasis ($p<0.05$), it was not found with hypotension ($p>0.05$). Thereby,

fever is an important clinical clue in determining the initiation of pre-culture antifungal therapy in case of the suspicion of invasive candidiasis.

The majority of *NAC* species are less virulent than *CA* species in vitro studies and animal models. However, *NAC* species lead to serious infections in humans and are more difficult to respond to treatment, and are mortal (16, 17). Therefore, the distinction between *CA* and *NAC* is important in patients with invasive candidiasis. The distinction between *NAC* and *CA* is particularly emphasized in numerous *Candida* studies in adult and/or pediatric patients. In one of these studies, Şerefhanoğlu et al. conducted a study with 102 adult patients with chronic renal failure between 2007 and 2010, *CA* was found to be 58.8% and *NAC* was 41.2% (18). In a similar study by Alıskan et al. covering the 2008-2010 period and including 163 children and adult patients, *CA* was 48.5% and *NAC* was 51.5% (19). In the distribution of the species responsible for invasive candidiasis, a transition from *CA* to *NAC* has been described worldwide since 1990 (20). Sütçü et al. reported a *CA* of 50% and *NAC* of 50% in a study conducted with 54 children patients in five years covering the years 2012-2016 (21). Our results were similar to the previous studies in the literature. It can be said that most of the invasive candidiasis and colonizations are due to *NAC* species in PICU.

In recent years, the choice of antifungal drugs and *Candida* species have become very important in the treatment of invasive candidiasis. It has been determined that the *Candida* family develops different resistance to these drugs. Among *Candida* species, primary resistance to azoles and/or echinocandins is most commonly seen in *Candida glabrata* (22). Determination of resistance to antifungal drugs made it necessary to isolate *Candida* species in culture samples. There are many studies to show the distribution of *Candida* species in the literature. In these studies, the most common *Candida* species was *CA*, while the second most common *Candida* species were various. Şerefhanoğlu et al. (18), reported *Candida tropicalis* 14.7%, Alışkan et al. (19) reported *Candida parapsilosis* 32.4%, Sütçü et al. (21) reported *Candida parapsilosis* with 24% as the second most common *Candida* species. In our study, *CA* was in the first place similar to the studies in the literature. *Candida albicans* was followed by 19.8% by *Candida parapsilosis*, *Candida tropicalis* was 15.4% and *Candida glabrata* was 7.7%. In the literature, it was found that *Candida parapsilosis* was the second most common type of *Candida* after *CA* in the pediatric population similar to our study (19, 21).

In a prospective surveillance program involving patients with invasive candidiasis, 2496 *NAC* infection attacks were detected between 2004 and 2008. The most common species identified in these attacks were *Candida glabrata* (46.4%), *Candida parapsilosis* (24.7%) and *Candida tropicalis* (13.9%). Two or more *Candida* species were identified in 4.4% of invasive candidiasis cases (23). In our study, two or more *Candida* species were detected in six patients (6.5%). It must be considered that a patient may be infected by different *Candida* species at the same time.

Patients included in the study were grouped according to their diagnoses at admission to the intensive care unit. Central nervous system diseases were the most common (n = 36, 39.6%), followed by malignant diseases (n = 13, 14.3%) and metabolic diseases (n = 10, 11.0%). The relationship between *Candida* colonization and invasive candidiasis with patient groups was investigated. The fact that each of the patient groups was a risk factor for candida colonization and invasive candidiasis was not found statistically significant ($p > 0.05$). However, invasive candidiasis was found mostly in the patient group with malignant disease (76.9%). Malignant diseases were followed by trauma and nephrology patients (71.4%). Thereby, malignant diseases were the highest group of patients with the highest risk of invasive candidiasis, while infectious diseases were the lowest with 25% (Table-3). Malignant patients were the most susceptible group to invasive candidiasis which may be due to their exposure to various immunosuppression treatments, broad-spectrum antibiotics, and frequently seen neutropenia during their treatment. Especially preventive health care should be given to this patient group with much more carefully.

Although the long-term stay of patients in intensive care units was found to be the most important risk factor for invasive candidiasis there are no standard risk factors in the literature. No statistically significant relationship was found between invasive candidiasis and underlying diseases, CVC, urinary catheter, broad-spectrum antibiotics, immunosuppressive treatments, gender, and surgery in the present study ($p > 0.05$). On the other hand, there was a statistically

significant relationship between parenteral nutrition, blood transfusion and bacterıal growth in clinical samples and invasive candidiasis ($p < 0.05$). Bacteria suppress the immune system of patients and increase the risk of invasive candidiasis. The most significant preventable risk factor for invasive candidiasis was parenteral nutrition. Invasive candidiasis was present in 41 (77.3%) of the 53 patients who were fed parenterally and only 16 (42.1%) of 38 patients who were not fed parenterally. (Table-3). Parenteral nutrition is started in patients who are malnourished, in the post-operative period, and whose vital signs are not suitable for enteral nutrition. Parenteral nutrition increases the risk of mortality and morbidity, especially in critically ill patients. Therefore, enteral nutrition should be preferred as the first choice of nutrition for risky patients. If parenteral nutrition is initiated upon appropriate indications, enteral nutrition should be started as soon as possible.

There are some limitations of this study. First, this is a retrospective study so that the patients whose data could not be obtained from the medical files and records were not included in the study. Second, the study was conducted in a single center and to generalize our findings multicenter studies with a big number of participants are required.

CONCLUSION

In conclusion, *NAC* species are more common than *CA* as a causative agent of invasive candidiasis in the PICU and *Candida parapsilosis* is the most common among *NAC* species. This result should be considered when starting empirical treatment. Although there are a wide variety of risk factors for invasive candidiasis, those that cause a significant increase alter from unit to unit. The presence of parenteral nutrition, blood transfusion and bacterıal growth in clinical samples, increased the risk of invasive candidiasis. Additionally, fever should be considered as a clinical diagnostic criterion for the initiation of prophylactic antifungal therapy in patients at risk for invasive candidiasis

Acknowledgement and Conflict of interest

1-These authors contributed equally to this work

2-No financial support was received for the study.

3-The authors declare no conflict of interest.

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