Original Investigation / *Özgün Araştırma*

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Evaluation of Risk Factors in Invasive *Candida* Infections in Children

Çocuklarda İnvaziv Kandida Enfeksiyonlarında Risk Faktörlerinin Değerlendirilmesi

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Abstract

Objective: The aim of this study was to determine the distribution of *Candida* species isolated from children with *Candida* spp. growth in sterile body site cultures, the risk factors for invasive candidiasis, and the factors affecting mortality.

Material and Methods: Patients with *Candida* spp. growth in sterile body region cultures in Clinic of Child Health and Diseases, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul Medeniyet University, pediatrics inpatient services and intensive care units between January 2017 and December 2018 were identified from mycology laboratory records, and patient information and epicrisis files were retrospectively analyzed. Demographic, microbiological and clinical data of the patients were recorded from mycology laboratory records and files.

Results: In 63 (%55.5) patients *C. albicans,* in 15 (%13.27) patients *C. glabrata* and *C. parapsilosis,* in 14 (%12.39) patients *C. tropicalis*, in seven (%6.19) patients *C. kefyr,* in three (%2.15) patients *C. krusei* and (%0.88) *C. guillermondii, C. lipolytica, C. lusitanie* were found in one patient each. Of the patients, 91.1% had at least one risk factor. Length of hospitalization, underlying malignancy and immunodeficiency, cardiac failure, use of indwelling urinary and central venous catheters, total parenteral nutrition and nutrition, and dialysis were factors associated with mortality. It was observed that the use of antifungal treatment had a positive effect on survival. It was found that in those with *C. parapsilosis* growth, the age group was younger, the duration of hospitalization, staying on mechanical ventilator, using broad-spectrum antibiotics was longer, and receiving antifungal treatment for a longer period of time, and it was found to be statistically significant. It was observed that *C. albicans* was higher in patients hospitalized in the pediatric intensive care unit, and *C. parapsilosis* was higher in patients hospitalized in the neonatal intensive care unit.

Öz

Giriş: Bu çalışmanın amacı steril vücut bölge kültürlerinde *Candida* spp. üremesi olan çocuklardan izole edilen *Candida* türlerinin dağılımı, invaziv kandidiyazis için risk föktörlerinin ve mortalite üzerinde etkili olan faktörlerin belirlenmesidir.

Gereç ve Yöntemler: İstanbul Medeniyet Üniversitesi Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi pediyatrik yataklı servisleri ve yoğun bakımlarında Ocak 2017-Aralık 2018 tarihleri arasında steril vücut bölge kültürlerinde *Candida* spp. üremesi saptanan hastalar mikoloji laboratuvar kayıtlarından tespit edilip hasta bilgileri ve epikriz dosyaları retrospektif olarak incelendi. Hastaların demografik, mikrobiyolojik ve klinik verileri mikoloji laboratuvar kayıtlarından ve dosyalarından kaydedildi.

Bulgular: Altmış üç hastada (%55.75) *C. albicans*, 15 (%13.27)'er hastada *C. glabrata* ve *C. parapsilosis*, 14 (%12.39) hastada *C. tropicalis*, yedi (%6.19) hastada *C. kefyr*, üç hastada (%2.65) *C. krusei* ve birer hastada (%0.88) *C. guilliermondii*, *C. lipolytica*, *C. lusitaniae* olduğu görülmüştür. Hastaların %91.1'inde en az bir risk faktörü mevcuttu. Hastanede yatış süresinin uzunluğu, altta yatan malignite ve immün yetmezlik, kardiyak yetmezlik, kalıcı üriner kateter ve santral venöz kateter kullanımı, total parenteral nütrisyonla beslenme ve diyaliz mortaliteyle ilişkili faktörlerdi. Antifungal tedavi kullanımının sağkalıma etkisinin olumlu olduğu görüldü. *C. parapsilosis* üremesi olanlarda yaş grubunun daha küçük, yatış, mekanik ventilatörde kalma, geniş spektrumlu antibiyotik kullanma süresinin daha uzun olduğu ve yine daha uzun süre antifungal tedavi aldığı görüldü ve istatistiksel olarak anlamlı saptandı. *C.albicans*'ın çocuk yoğun bakım ünitesinde yatan hastalarda, *C. parapsilosis*'in ise yenidoğan yoğun bakım ünitesinde yatan hastalarda daha yüksek olduğu görüldü. Risk faktörleri açısından *C. albicans* immün yetmezlik ve geniş spektrumlu antibiyotik kullanımıyla ilişkili iken, *C. parapsilosis* cerrahi

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In terms of risk factors, *C. albicans* was associated with immunodeficiency and the use of broad-spectrum antibiotics, while *C. parapsilosis* was associated with the presence of surgical intervention, *Candida* colonization, chronic lung disease, permanent urinary and central venous catheter use, and lack of enteral nutrition. The relation between both species and mortality was not statistically significant.

Conclusion: In conclusion, although *C. albicans* is still the most common cause in children with invasive candidiasis in our hospital, the rate of increase in non-*albicans* species was found to be higher in the two-year period. Length of hospitalization, underlying malignancy and immunodeficiency, cardiac insufficiency, use of indwelling urinary and central venous catheters, total parenteral nutrition (TPN), nutrition and dialysis are factors associated with mortality. Knowledge of local epidemiological data and risk factors in invasive *Candida* infections is very important for empirical treatment.

Keywords: Invasive *Candida* infection, child, risk factors

müdahale varlığı, *Candida* kolonizasyonu, kronik akciğer hastalığı, kalıcı üriner ile santral venöz kateter kullanımı ve enteral beslenme yokluğuyla ilişkili saptandı. Her iki türün de mortalite ile ilişkileri istatistiksel olarak anlamlı saptanmadı.

Sonuç: Sonuç olarak hastanemizde invaziv kandidiyazisli çocuklarda en sık etken hala *C. albicans* olmakla beraber, iki yıllık periyotta non-albicans türlerin artış hızı daha fazla saptanmış, yenidoğan yoğun bakımda ise literatürde belirtilenin aksine *C. parapsilosis* daha baskın suş olarak görülmüştür. Hastanede yatış süresinin uzunluğu, altta yatan malignite ve immün yetmezlik, kardiyak yetmezlik, kalıcı üriner kateter ve santral venöz kateter kullanımı, total parenteral nutrisyon (TPN) ile beslenme ve diyaliz, mortaliteyle ilişkili faktörlerdir. İnvaziv kandida enfeksiyonlarında lokal epidemiyolojik verilerin ve risk faktörlerinin bilinmesi ampirik tedavi için oldukça önemlidir.

Anahtar Kelimeler: İnvaziv *Candida* enfeksiyonu, çocuk, risk faktörleri

Introduction

*Candida*s are the most common infectious fungal pathogens in humans and are extremely common in nature. They are also found in the human body as normal flora members in the skin, mucous membranes and gastrointestinal tract (1). *Candida* can be isolated from many different anatomical sites such as the skin, throat, and vagina. Therefore, *Candida* infections are usually of endogenous origin. *Candida* can cause limited local infections in various tissues and organs, as well as serious invasive and systemic infections (2). *Candida* species are the most common cause of nosocomial fungal infections. Candida species are the fourth most common cause of bloodstream infections in the USA (3,4). It is a more common infection factor in children with prematurity, immunodeficiency, chronic and critical illness. *Candida* spp. is the most common cause of invasive fungal disease in the pediatric patient group in the United States (USA) and is the second most common cause of central catheter-related blood stream infections (CCBSI) (5). Diagnosis and treatment of *Candida* infections are difficult, and their mortality and morbidity are high (6). For this reason, it is very important to follow up hospitalized patients for the development of invasive *Candida* infection, evaluate risk factors, and obtain appropriate samples. Due to the stated conditions, early diagnosis and appropriate treatment are extremely important in terms of survival. Candidemia is a serious cause of mortality in children. It is also a cause that increases prolonged hospitalization and health care costs with high morbidity. It is very important to identify risk factors associated with widespread infection. In this study, it was aimed to determine the distribution of *Candida* species, invasive candidiasis, as well as mortality-related risk factors in children with *Candida* spp. growth in cultures of sterile body parts followed at our hospital between January 2017 and December 2018. At the same time, demographic characteristics, risk factors and mortality rates of children with invasive infections due to *C. albicans* and non-*albicans Candida* strains were compared. The results obtained from this study enabled the identification of risky patients in our hospital in terms of invasive candidiasis and contributed to the determination of prognosis and treatment.

Materials and Methods

Ethics committee approval was received for our study on 27.02.2019. The study included pediatric patients hospitalized and followed up in Clinic of Child Health and Diseases, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul Medeniyet University, between January 2017 and December 2018 and found to have *Candida* spp. growth in their sterile field body cultures. Patients were identified retrospectively from microbiology laboratory records. *Candida* strain isolated during *Candida* isolation, the area where the *Candida* strain was isolated and the number of growth, length of hospitalization and prognosis of the patient were recorded from the patient files. Invasive *Candida* infection (ICI) was defined as the growth of *Candida* spp. on sterile body sites. Nosocomial infection was defined as the occurrence of ICI within 48 hours of hospitalization. Hospitalization histories of the patients three months before the *Candida* infection were evaluated. The patient's death status was evaluated as dead within 30 days after *Candida* isolation. Prematurity was defined as <37 weeks of gestational age. Candidemia was defined as the isolation of any *Candida* species from blood. Isolation of *Candida* spp. from any blood culture or catheter culture of the patient with central venous catheter and no defined focus of infection was considered as catheter-related candidemia. The total number of days with catheter during positive blood culture was expressed as catheter days. Empirical treatment was defined as starting an antifungal agent before a positive culture result, and antifungal prophylaxis was defined as taking systemic antifungal therapy 24 hours or more before culture was taken. Initial treatment was considered inadequate if more than 72 hours elapsed between the time of culture and the start of antifungal therapy.

Identification of *Candida* Species

Blood and other sterile body fluids (CSF, pleural and peritoneal fluids) taken from the patient were placed in BACT/ALERT FA Plus (Biomerieux, France) bottles and incubated in the BACT/ALERT 3D automated blood culture system. The bottles that the device gave a positive signal were inoculated into bloody, chocolatey and eosin methylene blue media (Biomerioux) and removed to the oven for incubation. During the follow-up, the ones that showed fungal growth in the growth media were sent to the mycology unit of the central laboratory for the identification of the fungus, where it was identified at the species level with Vitek MS (Biomerieux, France). Urine samples were first inoculated on bloody and chromogenic (Biomerieux) media. After 16-24 hours of incubation, the breeding colonies were sent to the central laboratory for identification, and the genus and species were determined by Vitek MS.

Statistical Analysis

SPSS version 15.0 program was used in the analysis of the data. The conformity of the variables to normal distribution was examined with the Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used when presenting descriptive analyzes. Categorical variables were compared with Pearson's chi-square and Fisher's exact tests. The Mann-Whitney U test was used when evaluating non-normally distributed (non-parametric) variables between groups. Kaplan-Meier analysis was used for univariate patient survival. The rate of change in the number of risk factors affecting mortality was analyzed by regression analysis. Cases with a p-value below 0.05 were considered as statistically significant results.

Results

The age of children with *Candida* infection ranged from 0.17 to 218 months, with a median age of 24 months. Of the children, 50.5% are girls and 49.5% are boys. The median value for hospitalization was 29 days (Table 1).

Of the patients, 13.2% were diagnosed with pneumonia, 11.5% with neurological disease, 8.8% with prematurity and 8.8% with abdominal surgical pathology (Table 2).

Table 1. Demographic characteristics of the patients

		n (%)
Median age (month)		24
Min-Max age (month)		0.17-214
Sex	Girl	57 (50.5%)
	Boy	56 (49.5%)
Length of hospitalization (median day)		29

Table 2. Underlying diagnoses of the patients

Underlying disease	n (%)
Pneumonia	15 (13.2%)
Neurological disease	13 (11.5%)
Abdominal surgery pathology	10 (8.8%)
Prematurity	10 (8.8%)
Other*	10 (8.8%)
Hematologic/Oncologic malignancy	9 (7.9%)
Sepsis	9 (7.9%)
Primary immunodeficiency	8 (7%)
Trauma	8 (7%)
Cardiac anomaly	4 (3.5%)
Multiple congenital anomaly	4 (3.5%)
Neurometabolic disease	4 (3.5%)
Renal anomaly	4 (3.5%)
Diabetes mellitus type 1	3 (2.6%)
Nephrotic syndrome	2 (1.8%)
Cystic fibrosis	1 (0.9%)
*Rheumatological disease, ulcerative colitis, urinary system infection.	

Of the patients, 15.04% were treated in the neonatal intensive care unit (NICU), 44.25% in the pediatric intensive care unit (PICU), and 38.9% in the service (Table 3).

There was at least one risk factor in 103 (91.1%) patients. Underlying disease was the most common risk factor in 103 (91.1%) patients. In the follow-up, use of broad-spectrum antibiotics before *Candida* infection 100 (88.5%), indwelling urinary catheter 87 (76.9%), central venous catheter 75 (66.3%), presence of mechanical ventilator 58 (51.3%) and total parenteral nutrition 55 (48.6%) were present in the patient (Table 4).

Table 3. Distribution of the services where the patients were hospitalized

Inpatient service	n (%)
Pediatric intensive care unit	50 (44.2%)
Newborn intensive care unit	17 (15.0%)
Big child service	16 (14.1%)
Pediatric nephrology service	8 (%7)
Dairy service	7 (6.1%)
Pediatric surgery service	5 (4.4%)
Pediatric infection service	4 (3.5%)
Pediatric hematology-oncology service	3 (2.6%)
Pediatric surgery intensive care unit	2 (1.7%)
Pediatric chest diseases service	1 (0.9%)

Table 4. Distribution of risk factors in culture positive *Candida* infections (n= 113)

Risk factors	n (%)
Underlying disease	103 (91.1%)
Broad spectrum antibiotic	100 (88.5%)
Indwelling urinary catheter	87 (76.9%)
Empirical antifungal use	78 (69.0%)
Central venous catheter	75 (66.3%)
Mechanical ventilation	58 (51.3%)
Total parenteral nutrition	55 (48.6%)
Surgical intervention	49 (43.3%)
Neurological disorder	45 (39.8%)
Corticosteroid use	40 (35.4%)
Multiple hospitalizations	24 (21.2%)
Immunodeficiency	23 (20.3%)
Chronic renal failure	20 (17.7%)
Chronic lung disease	21 (18.5%)
Renal replacement therapy	17 (15.0%)
Heart failure	15 (13.2%)
Candida colonization	12 (10.6%)
Chemotherapy	9 (7.9%)
Hematological malignancy/Solid tumor	9 (7.9%)
Trauma	8 (7%)
Diabetes	5 (4.4%)

When *Candida* species distribution was examined according to intensive care hospitalizations, *C. albicans* was found in five patients, *C. glabrata* in four patients, *C. parapsilosis* in seven patients, and *C. tropicalis* in two patients. In 34 patients with PICU hospitalization, *C. albicans* was the most abundant strain. *C. glabrata* in three patients, *C. parapsilosis* in five patients, *C. tropicalis* in seven patients, *C. kefyr* in two patients and *C. lusitaniae* in one patient were detected. *C. parapsilosis* was detected in one patient and *C. guilliermondii* was detected in one patient with SICU hospitalization (Figure 1).

Mortality was observed in 18 (15.9%) of 113 patients with *Candida* infection. Mortality rates in patients with *C. albicans*, *C. parapsilosis* and non-*albicans* overgrowth were 15.8%, 26% and 9.5%, respectively. While a significant correlation was found between the length of hospitalization and mortality ($p< 0.05$), no significant correlation was found between the length of hospitalization and mortality ($p> 0.05$). The relation between the presence of central venous catheter, urinary catheter, heart failure, haematological/oncologic malignancy and mortality was significant ($p< 0.05$) (Table 5).

TPN duration of patients with *C. albicans* (29.59 ± 48.67) was shorter than non-*albicans* patients (43.04 ± 43.22) (p= 0.036). The duration of antibiotic use in patients with *C. albicans* (33.11 ± 44.56) was shorter than in other patients (46.64 ± 40.67) (p= 0.039) (Table 6).

Patients with *C. parapsilosis* were younger than non-*albicans* species other than *C. parapsilosis* ($p< 0.001$). In addition, the length of hospitalization, mechanical ventilation, antibiotic and antifungal duration was longer ($p< 0.05$) (Table 7).

NICU hospitalization rate (7.94%) was lower in patients with *C. albicans* than in other patients (24%) (p= 0018), while the PICU hospitalization rate (53.97%) was higher than in other patients (32%) (p= 0.020). The NICU hospitalization rate (46.67%) in patients with *C. parapsilosis* was found to be significantly higher than in other patients ($p< 0.001$) (Table 8).

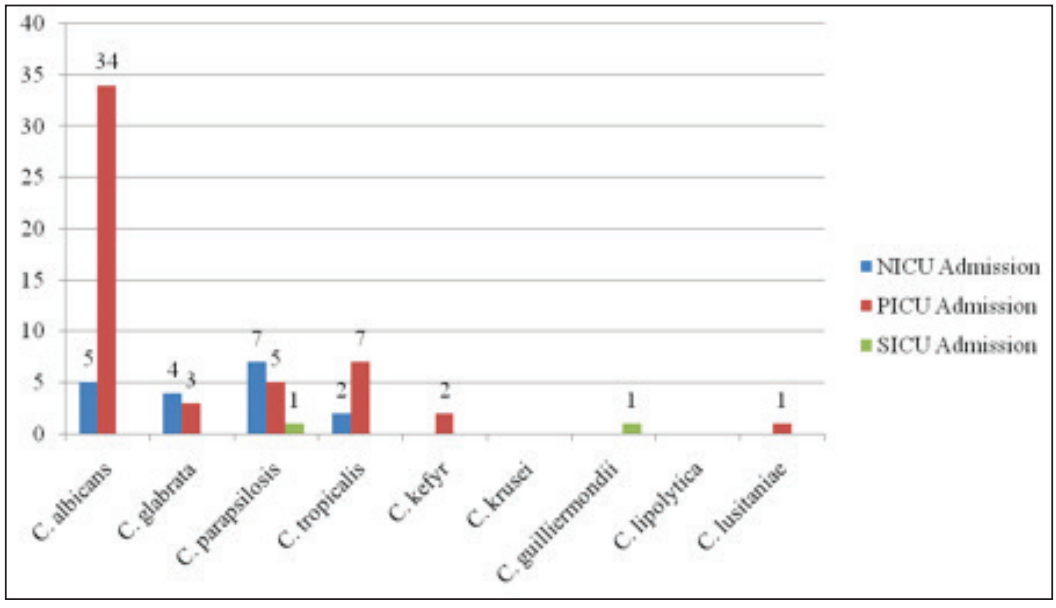

Figure 1. *Candida* species distrubition according to intensive care hospitalizations.

Table 5. Comparison of demographic characteristics and risk factors between the survivors and the deceased

		Alive (n= 95)	Exitus (n= 18)	Total (n= 113)	p
Sex	Girl	49	8	57	0.500
	Boy	46	10	56	
Age (median-month)		33.00	14.00	24.00	0.500
Length of hospitalization (median-day)		28.00	35.50	29.00	**0.035****
Multpl hospitalization		19	5	24	0.450
Prematurity		6	4	10	0.240
Surgical intervention		39	10	49	0.250
Candida colonization		8	4	12	0.080
Immunodeficiency		12	11	23	**<0.001****
Trauma		6	1	7	0.900
Diabetes		6	0	6	0.900
Chronic lung disease		19	2	21	0.370
Heart failure		10	5	15	**0.040****
Chronic renal failure		18	2	20	0.420
Neurological disorder		38	7	45	0.9930
Malignancy		4	5	9	**0.001****
Urinary catheter		69	18	87	**0.011****
Central venous catheter		57	18	75	**0.001****
Mechanical ventilator		46	12	58	0.150
Total parenteral nutrition		38	17	55	**<0.001****
Corticosteroid		30	10	40	0.051
Broad spectrum antibiotic		82	18	100	0.090
Use of antifungal therapy		64	14	78	0.380
Renal replacement therapy (dialysis)		11	6	17	**0.018****
Chemotherapy		5	4	9	**0.015****
Presence of *C. albicans*		53	10	63	0.985
Presence of *C. paraspsilosis*		11	4	15	0.222
Hospitalization in intensive care		56	13	69	0.528

Table 6. Age, duration of hospitalization and risk factors for *C. albicans* and non-*albicans* species

	C. albicans			**Non-*albicans***			
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	**p**
Age (month)	56.97	±65.15	24.00	71.03	±75.59	33.00	0.806
Length of hospitalization (days)	40.79	±47.76	29.00	47.76	±47.42	29.50	0.781
Mechanical ventilator time	28.15	±38.63	17.50	32.00	±28.78	22.50	0.492
TPN duration	29.59	±48.67	15.00	43.04	±43.22	22.50	**0.036****
Corticosteroid duration	18.50	±22.94	10.00	14.43	±13.27	11.50	0.920
Antibiotic use period	33.11	±44.56	21.00	46.64	±40.67	35.00	**0.039****
Antifungal duration	20.07	±30.00	14.00	24.71	±19.90	20.00	0.076
Dialysis time	1.40	±1.26	1.00	1.57	±1.51	1.00	0.793
Chemotherapy duration	35.57	±24.83	30.00	28.00	±9.90	28.00	0.766

Table 7. Age, duration of hospitalization and risk factors for *C. parapsilosis* and non-*C. parapsilosis* non-*albicans* species

	C. parapsilosis			**Non-*albicans* other than *C. parapsilosis***			
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	**p**
Age (month)	12.32	±30.39	5.00	70.98	±71.15	43.50	**<0.001****
Length of hospitalization (days)	90.67	±43.08	87.00	36.71	±44.15	23.00	**<0.001****
Mechanical ventilator time	48.78	±31.14	58.00	26.24	±34.43	17.00	**0.032****
TPN duration	52.93	±53.80	27.50	30.15	±42.56	15.00	0.185
Corticosteroid duration	14.43	±12.00	10.00	17.64	±21.42	10.00	0.788
Antibiotic use period	76.47	±43.60	63.00	31.67	±39.96	19.00	**<0.001****
Antifungal duration	33.15	±18.38	28.00	19.95	±26.74	14.00	**<0.001****
Dialysis time	3.00	±2.83	3.00	1.27	±1.03	1.00	0.083
Chemotherapy duration	30.00	±.	30.00	34.38	±23.51	31.50	1.000

Table 8. Comparison of service and intensive care hospitalization for *C. albicans* and *C. parapsilosis*

		C. albicans					***C. parapsilosis***				
		Yes		**No**		**p**	**Yes**		**No**		**p**
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Service hospitalization	Yes	34	(53.97)	29	(58.00)	0.668	6	(40.00)	57	(58.16)	0.187
	No	29	(46.03)	21	(42.00)		9	(60.00)	41	(41.84)	
NICU hospitalization	Yes	5	(7.94)	12	(24.00)	**0.018****	7	(46.67)	10	(10.20)	**<0.001****
	No	58	(92.06)	38	(76.00)		8	(53.33)	88	(89.80)	
PICU hospitalization	Yes	34	(53.97)	16	(32.00)	**0.020****	5	(33.33)	45	(45.92)	0.361
	No	29	(46.03)	34	(68.00)		10	(66.67)	53	(54.08)	
SICU hospitalization	Yes	0	(.00)	2	(4.00)	0.109	1	(6.67)	1	(1.02)	0.122
	No	63	(100.00)	48	(96.00)		14	(93.33)	97	(98.98)	

The rate of immune deficiency (26.98%) was higher in patients with *C. albicans* than in other patients (12.00%) (p= 0.049). Surgical intervention rate (73.3%), *Candida* colonization rate (26.67%), and chronic lung disease rate (40%) were found to be significantly higher in patients with *C. parapsilois* compared to other patients (p< 0.05) (Table 9).

The use of broad-spectrum antibiotics was higher in patients with *C. albicans* than in other patients (p= 0.002). The presence of TPN was higher in patients with *C. parapsilosis* (p< 0.001) (Table 10).

When the mortality rates in *C. albicans* and *C. parapsilosis* were compared, no significant difference was found between them (p> 0.05) (Table 11). An increase in the number of risk factors in all patients was found to increase mortality 0.717-fold (95% CI= 0.583-0.882) (p= 0.002) (Table 12).

Table 9. p values comparison table for underlying disease and catheter use, which are risk factors for *C. albicans* and *C. parapsilolis*

	C. albicans	***C. parapsilosis***
	p	**p**
Surgical intervention	0.903	**0.012****
Candida colonization	0.671	**0.030****
Immunodeficiency	**0.049****	0.468
Trauma	0.939	0.218
Diabetes	0.468	0.371
Chronic lung disease	0.406	**0.022****
Heart failure	0.141	0.994
Chronic renal failure	0.568	0.634
Chronic hepatic failure	0.100	0.072
Neurological disorder	0.973	0.561
Malignancy	0.492	0.842
Presence of urinary catheter	0.261	**0.023****
CVC presence	0.634	**0.003****

Table 10. Comparison table of mechanical ventilator, TPN use and p values of the treatments for *C. albicans* and *C. parapsilolis* risk factors

	C. albicans	*C. parapsilosis*
	p	p
Presence of mechanical ventilator	0.528	0.471
TPN presence	0.528	**<0.001****
Absence of enteral nutrition	0.377	0.831
Presence of corticosteroid	0.143	0.327
Broad spectrum antibiotic use	**0.002****	0.134
Antifungal presence	0.842	0.113
Dialysis presence	0.782	0.842
Chemotherapy presence	0.166	0.842
Multiple hospitalizations	0.774	0.900

Discussion

There are many studies evaluating pediatric invasive *Candida* infections. Blyth et al. have found that candidemia was connected to vascular catheters in 58% of newborns and 70% of children in their study (7). In this study, prematurity in newborns and being in the intensive care unit, hematological malignancy and neutropenia in children were the main risk factors. In the study by Zaoutis et al., risk factors for disseminated candidiasis have been determined prospectively in 153 of 168 patients, and prematurity, underlying disease, long-term hospitalization, surgical operation, immunosuppression, bone marrow transplantation, candidemia lasting longer than three days, and the use of broad-spectrum antibiotics have been detected as risk factors (5,8). In the study performed by Conde-Rosa et al. on adult and pediatric populations, cases with candidemia have been evaluated retrospectively, potential risk factors were the presence of CVC (97.8%), indwelling urinary catheter (73.3%), mechanical ventilation (64.4%) and wide spectrum antibiotic therapy (95.6%) (9). Ağın et al. have evaluated risk factors in a case-control study conducted in patients with candidemia hospitalized in the pediatric intensive care unit (10). As a result of the study, underlying disease (92.3%), use of mechanical ventilators (80.8%), presence of CVC (59.6%), TPN (76.9%) and urinary catheter use (45%) were determined as risk factors. In their study, Belet et al. have reported that all patients with invasive candidiasis in children had an underlying disease, and antimicrobial therapy (94%), hospitalization in the intensive care unit (57%) and parenteral nutrition (42%) were the main risk factors (11). In our study, 100 (91.1%) of 113 patients had at least one risk factor. The most common risk factors were underlying disease (91.1%), use of broad-spectrum antibiotics (88.5%), presence of indwelling urinary catheter (76.9%), presence of CVC (66.3%), staying on mechanical ventilator (51.3%) and feeding with TPN (48.6%). The high rate of catheter-associated infection highlights the importance of catheter care and early removal of catheters in patients with candidemia. Zaoutis et al. have found that the most common underlying diseases in children with candidemia were oncological (24%), gastrointestinal (15%) and cardiac pathologies, 53% of the patients were in the intensive care unit, 27% of the patients were in the general pediatric or surgical service and reported that 20% of them were followed in the oncology service (8). In our study, the underlying primary diagnoses were determined as pneumonia, neurological diseases, prematurity and abdominal surgical pathology, in order of frequency. Most of our patients were hospitalized in intensive care units at the time of diagnosis (60.9%). PICU, NICU, and SICU hospitalization rates were 44.2%, 15%, and 1.7%, respectively. Demographic characteristics and risk factors for invasive candidiasis in our study were similar to the literature. These data, which we found in our study, show that invasive *Candida* infections mostly affect patients who use antibiotic therapy, have permanent urinary and central venous catheters, receive total parenteral nutrition, are hospitalized in the intensive care unit, and require mechanical ventilation. The presence of underlying primary diseases and clinical conditions also cause prolonged hospitalization and increased

Table 11. Mortality rates for *C. albicans* and *C. parapsilosis*

	Alive		Exitus		p
	n	R%	n	R%	
C. albicans	10	(15.87)	53	(84.13)	0.616
C. parapsilosis	3	(21.43)	11	(78.57)	

Table 12. The effect of the number of risk factors on mortality in all patients

				95% CI		p
	B	S. E.	Exp (B)	Lower	Upper	
Risk factors	-.333	0.106	0.717	0.583	0.882	**0.002****
Constant	4.521	1.037	91.904			**0.001****

need for these procedures, and the presence of these risk factors increases the risk of *Candida* infection. *C. albicans* is the most common cause of invasive fungal disease in children. Recent changes in the epidemiology of *Candida* show that the rates of non-*albicans* candidemia, especially the incidence of *C. parapsilosis*, have increased. According to recent studies, non-*albicans Candida* species account for more than half of ICI in children (12). The most common *Candida* species isolated from children is *C. albicans*. Roilidies et al. have found *C. albicans* as a factor in 66% of neonatal candidiasis cases in their study (13). *C. parapsilosis* is the second most common strain isolated from children with ICI. Most patients with *C. parapsilosis* have diseases that require an indwelling urinary or central venous catheter and total parenteral nutrition (14). Parenteral nutrition and high glucose concentration promote biofilm development. There is a strong relationship between *C. parapsilosis* fungemia and the use of parenteral nutrition (14).

In our study, it was observed that *C. albicans* had a significant relationship with the use of TPN and broad-spectrum antibiotics, and even in the use of shorter-term TPN and broad-spectrum antibiotics. In their study, Macdonald et al. have emphasized that the most common type was *C. albicans*, and its emergence was facilitated by the use of TPN and broad-spectrum antibiotics, but they did not report a relationship with duration (15). The use of TPN and CVC is generally needed in patients who are hospitalized in intensive care units or have comorbid diseases. Despite this, there is a study related that feeding with TPN increases *C. parapsilosis* infections even in non-hospital and home environments (16). In our study, *C. parapsilosis* was found to have a significant relationship with both the use of indwelling urinary catheters and CVC ($p< 0.05$), but no significant correlation was found between the use of TPN ($p> 0.05$).

In our study, when we compared the risk factors of *C. parapsilosis* and non-*albicans* strains other than *C. parapsilosis*, a significant correlation was found with younger age group, longer hospitalization, staying on mechanical ventilator, and duration of broad-spectrum antibiotic use ($p< 0.05$). The increase in the possibility of invasive interventions such as the use of TPN and CVC in the presence of prolonged hospitalization, and the prolongation of the duration of stay on mechanical ventilator, also supports the significant relationship of *C. parapsilosis* with these patients. The number of studies evaluating risk factors related to *C. parapsilosis* is not sufficient. Therefore, our study is one of the few studies in terms of evaluating risk factors.

In the current study, it was also found that *C. albicans* was more frequent and significant in patients hospitalized in the PICU, while the frequency of *C. parapsilosis* in patients hospitalized in the NICU was found to be significantly higher. While immunodeficiency and use of broad-spectrum antibiotics were significant in patients with *C. albicans* strain, presence of surgical intervention, *Candida* colonization, chronic lung disease, presence of permanent urinary and central venous catheters, total parenteral nutrition and nutrition were significant in *C. parapsilosis* ($p< 0.05$). Çelebi et al., in their study evaluating pediatric patients with candidemia between January 1997 and December 2005, reported that non-*albicans Candida* species (71.3%) were the most frequently isolated species in patients with malignancy (17). Comparison of *C. albicans* and non-*albicans Candida* strains in terms of demographic and clinical features, determination of risk factors and knowledge of epidemiology are important in terms of guiding the treatment of these patients. Dutta and Palazzi have found no difference between *C. albicans* and non-*albicans* species in terms of demographic data, underlying diagnosis, risk factors, clinical features, dissemination or 30-day mortality in their study conducted in Texas on patients with candidemia aged six months to 18 years (18). Belet et al. have stated that they did not find a statistically significant difference between the two groups in terms of demographic and clinical characteristics in children with invasive candidiasis due to *C. albicans* and non-*albicans Candida* strains (11). In our study, when demographic characteristics, epidemiology and risk factors for *C. albicans* and non *albicans* species of 113 patients with invasive candidiasis were compared, no significant difference was found between them. It is difficult to directly associate *Candida* with mortality. The rates in the publications associated with *Candida* mortality differ according to the type of study. Mortality rates in children with candidemia range from 10% to 26% (12,19-21). In our study, mortality rate was found to be 15.9%. In the evaluation of mortality-related factors, a significant correlation was found between length of hospitalization, immunodeficiency, heart failure, malignancy, presence of indwelling urinary catheter and CVC, nutrition with TPN, and renal replacement therapy (dialysis) and mortality ($p< 0.05$). No significant correlation was found between hospitalization in intensive care units and staying on mechanical ventilator and mortality. The reason for this was thought to be related to the health care given to the patients staying in the intensive care units and receiving mechanical ventilator support.

Conclusion

In conclusion, the determination of the most common risk factors in *Candida* strains, the high rate of ICI in the presence of invasive interventions, the importance of taking infection control measures and careful and careful catheter care. In our study, mortality rate in children with invasive candidiasis was 15.9% and underlying immunodeficiency, heart and chronic liver failure, malignancy, presence of indwelling urinary catheter and central venous catheter, presence and length of TPN, lack of enteral nutrition, presence of dialysis,

prolonged hospitalization, chemotherapy treatment, and duration of broad-spectrum antibiotic therapy were risk factors that increased mortality. These data will enable us to identify patients at risk for invasive candidiasis in our hospital, and will guide the selection of empirical treatment and patient health services. Initiation of appropriate treatment may also contribute to shortening the length of hospitalization and reducing health care costs.

Ethics Committe Approval: The approval for this study was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2019/071 Date: 27.02.2019).

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