Iranian Journal of Microbiology
Volume 16 Number 2 (April 2024) 236-242

ORIGINAL ARTICLE

Risk analysis of candidemia and its effect on mortality in COVID 19 and non COVID 19 patients

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Received: December 2023**, Accepted:** February 2024

ABSTRACT

Background and Objectives: Candidemia is the most common serious fungal infection in critically ill patients in intensive care units (ICU). It series fourth among bloodstream infectious agents. In this study, candidemia risk analysis was examined in COVID 19 and non-COVID 19 patients during the pandemic period.
Materials and Methods: COVID 19 and non-COVID 19 cases who were followed up with candidemia in the ICU of our hospital were retrospectively screened. Demographic data, intubation, central venous catheter (CVC), medications, and total parenteral nutrition (TPN) status were evaluated in terms of risk between the two groups. Isolated *Candida species* and susceptibilty were evaluated.
Results: When age, gender, medication, intubation, TPN and CVC were evaluated, no difference was seen in terms of risk. Differences were detected in terms of comorbidities. While the most frequently identified *Candida* species was *C. albicans*, the most frequently detected species in the COVID19 patient group was *C. parapsilosis.*
Conclusion: There was no difference in candidemia incidence and risk factors between the two groups. Since candidemias were evaluated in terms of comorbidities, it was determined that Diabetes Mellitus (DM) and chronic obstructive pulmoner disease (COPD) were more common in patients with COVID 19 and less common in coronary artery disease (CAD) and malignancy.

Keywords: Bloodstream infections; Candidemia; COVID 19

INTRODUCTION

The COVID 19 pandemic, which started in Wuhan, China and affected the whole world, has caused an increase in the number of patients in ICUs in our country. As a result of the patients staying in intensive care for a long time, severe clinical conditions developed with additional infections. This situation also affected bloodstream infections due to the increased risk of infection in the ICU. Candidemia is one of the most common bloodstream infections that frequently affects patients in intensive care (1). It is an important health care-related infection with high mortality and morbidity (2). In the general patient population, prolonged hospital stay, neutropenia, hemodialysis, TPN, mechanical ventilation and CVC use are known risk factors. COVID-19 patients may develop Acute Respiratory Distress Syndrome (ARDS). They may undergo mechanical ventilation and high-dose steroid therapy for weeks due to re-

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spiratory distress. These factors may cause a potential increase in the risk of candidemia (3). It is also affected by many co-morbidities such as old age, diabetes, cirrhosis, cancer and malnutrition. It is reported that 20% of patients required hospitalization during the pandemic period, and 1/4 of this patient group required intensive care (4). Although ICU admission, mechanical ventilation and mortality rates vary, similar reports are published in many countries around the world (5). It is reported that factors that predispose to fungal diseases, such as lymphopenia (35-63%), leukopenia (9-25%) and T cell dysfunction, are frequently seen in symptomatic patients with COVID 19 disease (6).

The aim of our study is to investigate the candidemia risk analysis of COVID 19 patients followed during the pandemic period.

MATERIALS AND METHODS

Samples. The data of adult patients hospitalized in the ICU during the pandemic period in our hospital were reviewed retrospectively. In the study, demographic, clinical and laboratory data of patients with *Candida* growth in blood culture hospitalized in the adult ICU, COVID 19 and non COVID19 patients (control group) were compared. The patients have additional diseases such as cancer, diabetes, hypertension, renal disease, neurological disease, CAD, liver disease, COPD, immunodeficiency and surgical operation history, antibiotic, antiviral, steroid, immunomodulator use history, mechanical ventilation use, CVC. The need for parenteral nutrition was recorded. Isolated *Candida* spp. from the blood culture and their antifungal susceptibility were investigated. The patient's hemogram, procalcitonin, CRP, Ferritin, Interleukin6 (IL6), WBC (white blood cell), Neutrophil count, Lymphocyte count, Neutrophil/Lymphocyte ratio, D dimer, Fibrinogen values were recorded. The study was planned in accordance with the helsinki declaration. Training and Research hospital ethics committee decision (23.06.2022, number:141).

RT-PCR procedure. Nasopharyngeal samples SARS CoV2 detection was performed by (Bioexen, RTA, Coronex/TURKEY) SARS CoV 2 qPCR assay on BioRad CFX 96 device (California, USA) according to protocols provided by the manufacturer (qPCR kit targets the ORF1ab and N gene of SARS-CoV-2).

Blood culture procedure. In our hospital, blood cultures (BACTEC) are evaluated in quideline with CLSI recommendations. After the yeast colonies grown on Sabouraud dextrose agar (SDA) were identified with the Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF, BioMerieux, France) device, antifungal susceptibility was studied with the VITEK2 COMPACT (BioMerieux, France) device. Evaluated according to (CLSI) documents M27-S4 and M60.

Statistical analysis. Number Cruncher Statistical System (NCSS) (2007, Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods, Student's t-test, Shapiro-Wilk test, Mann-Whitney U-test ,Pearson Chi-Square test, Fisher's Exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Exclusion criteria. In patients with *Candida* isolation in blood culture, recurrent blood culture growths within 30 days after candidemia were considered the same episode and excluded from the study. In the SARS CoV2 PCR negative control group, the patient group with pulmonary involvement and suspected COVID 19 disease was excluded from the study. Children under the age of 18 were excluded from the study.

Ethical approval. This study was prepared in accordance with Helsinki declaration. Consent was obtained from the Ethics Committee of Kanuni Sultan Süleyman Training and Research Hospital (KAEK/2022.06.141).

RESULTS

This Study was selected from the ICU of a tertiary education and research hospital between 01.01.2021 and 06.01.2022. It was performed with *Candida* strains isolated in 98 blood cultures of the patients, 44.9% (n=44) of whom were SARS CoV2 positive and 55.1% (n=54) were SARS CoV2 negative. During this period, 4333 adult patients, 2270 of whom were COVID 19 patients and 2063 non-COVID-19 patients, were hospitalized in the ICU of our hospital. The incidence of candidemia in this period is 2.26%. (Incidence rate per 1000 admissions is 22.6/1000). While the incidence of candidemia was 2.61% (54 patients)

in the non-COVID19 patients group, it was 1.93% (44 patients) in the COVID-19 patients group. Of the cases, 41.8% (n=41) were female and 58.2% (n=57) were male. Their ages ranged from 24 to 96, with an average of 68.09 ± 16.56 years. While the mean age of patients with COVID19 patients is 67 ± 16, the mean age of non COVID 19 patients intensive care patients is 69 ± 17. Demographic data of the patients, clinical features, risk factors for candidemia, distribution of additional diseases, and discharge method are given in Table 1.

In this study, mortality rates were found to be similar in both groups (66%) (p = 0.652). No statistically significant difference was detected between the patient's age and gender distributions. It was observed that there was no statistically significant difference in terms of hypertension, kidney disease, neurological disease, liver disease and immunodeficiency status (p> 0.05). Diabetes (p=0.040) (ODDS:8.231) and COPD (p=0.001) (ODDS:4.208) were found to be higher in COVID-19 patient than in non COVID-19 patient. The rate of malignancy (p=0.028) and CAD (p=0.026) was found to be lower in COVID 19 patient than in non-COVID 19 patient (Tables 1 and 2).

COVID 19 patients do not show a statistically significant difference compared to non patients in terms of intubation, parenteral nutrition and discharge status (p>0.05). Since the number of patients using immunomodulators was low (n=4), it could not be evaluated statistically. No significant difference was detected according to steroid, antiviral use and antibiotic use (p>0.05).

Platelet, procalcitonin, ferritin, IL-6, WBC, neutrophil, lymphocyte, NLR, D dimer and troponin T measurements did not differ statistically between the two groups (p>0.05) (Table 3).

CRP and fibrinogen measurements were found to be significantly higher in the COVID 19 patient group than in the negative patient group (p = 0.002; p = 0.027) (Table 3). While the most frequently identified *Candida* spp. in non-COVID 19 patient groups is *C. albicans*, the most frequently identified species in COVID 19 patient groups is *C. parapsilosis* (Fig. 1).

When their antifungal susceptibility is evaluated, in the patient group with COVID 19; fluconazole

Table 1. Distribution of descriptive features

		SARS CoV2		*p*
		Positive (n=44)	**Negative (n=54)**	
Age (year)	Min-Max (Median)	26-92 (67)	24-96 (74,5)	[a]0,407
	Mean ± SD	66,55 ± 15,67	69,35 ± 17,28	
Gender; n (%)	Female	19 (43,2)	22 (40,7)	[b]0,807
	Male	25 (56,8)	32 (59,3)	
▪Comorbidity; n (%)	Malignancy	5 (11,4)	16 (29,6)	[b]0,028*
	DM	22 (50,0)	16 (29,6)	[b]0,040*
	HT	20 (45,5)	26 (48,1)	[b]0,790
	Renal disease	11 (25,0)	13 (24,1)	[b]0,916
	Neurological disease	14 (31,8)	13 (24,1)	[b]0,393
	CAD	8 (18,2)	21 (38,9)	[b]0,026*
	Liver disease	1 (2,3)	7 (13,0)	[c]0,070
	COPD	31 (70,5)	20 (37,0)	[b]0,001**
	Immunodeficiency	22 (50,0)	20 (37,0)	[b]0,197
Intubation n (%)	Yes	34 (77,3)	38 (70,4)	[b]0,441
	No	10 (22,7)	16 (29,6)	
Total parenteral nutrition	Yes	2 (4,5)	5 (9,3)	[c]0,454
n (%)	No	42 (95,5)	49 (90,7)	
Final station;	Discharged	8 (18,2)	15 (27,8)	[d]0,652
n (%)	Inpatient	7 (15.9)	6 (11,2)	
	Exitus	29 (65,9)	33 (61,1)	

[a]Student t Test [b]Pearson Chi-Square Test [c]Fisher's Exact Test [d]Fisher Freeman Halton Test *p<0,05 **p<0,01

Table 2. Demographic data of patients, clinical features, risk factors for candidemia, and distribution statistics of *Candida* spp.

SARS CoV2 RT-PCR TEST[a] positive	B	Std. Error	Wald	df	Sig.	ODDS	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Intercept	19,523	1,570	154,580	1	,000			
Steroid treatment (1)	,786	,822	,914	1	,339	2,194	,438	10,984
Steroid treatment (2)	0[b]	.	.	0	.	.	.	.
C. albicans (1)	,048	1,475	,001	1	,974	1,050	,058	18,905
C. glabrata (2)	,117	1,708	,005	1	,945	1,124	,040	31,950
C. parapsilosis (3)	,954	1,540	,384	1	,535	2,597	,127	53,149
C. tropicalis (4)	,691	1,449	,228	1	,633	1,996	,117	34,154
Others (5)	0[b]	.	.	0	.	.	.	.
Male(1)	-,652	,680	,920	1	,338	,521	,137	1,975
Female(2)	0[b]	.	.	0	.	.	.	.
Malignancy (1)	-,996	,991	1,008	1	,315	,370	,053	2,579
Malignancy (2)	0[b]	.	.	0	.	.	.	.
DM (1)	2,108	,778	7,333	1	,007	8,231	1,790	37,843
DM (2)	0[b]	.	.	0	.	.	.	.
HT (1)	-,441	,801	,304	1	,582	,643	,134	3,091
HT (2)	0[b]	.	.	0	.	.	.	.
Renal disease (1)	,103	,828	,015	1	,901	1,108	,219	5,616
Renal diseases (2)	0[b]	.	.	0	.	.	.	.
Neurological disease (1)	,375	,774	,234	1	,628	1,454	,319	6,633
Neurological disease (2)	0[b]	.	.	0	.	.	.	.
CAD (1)	-1,934	,807	5,740	1	,017	,145	,030	,703
CAD (2)	0[b]	.	.	0	.	.	.	.
Liver diseases (1)	-2,792	1,739	2,576	1	,108	,061	,002	1,854
Liver diseases (2)	0[b]	.	.	0	.	.	.	.
COPD (1)	1,437	,677	4,512	1	,034	4,208	1,117	15,847
COPD (2)	0[b]	.	.	0	.	.	.	.
Immunodeficiency (1)	1,191	,756	2,478	1	,115	3,289	,747	14,480
Immunodeficiency (2)	0[b]	.	.	0	.	.	.	.
Operation history (1)	-2,105	,921	5,221	1	,022	,122	,020	,741
Operation history (2)	0[b]	.	.	0	.	.	.	.
CVC(1)	,538	,681	,624	1	,429	1,713	,451	6,506
CVC (2)	0[b]	.	.	0	.	.	.	.
Intubation (1)	,141	,795	,031	1	,860	1,151	,242	5,467
Intubation (2)	0[b]	.	.	0	.	.	.	.
TPN (1)	-,882	1,581	,311	1	,577	,414	,019	9,172
TPN (2)	0[b]	.	.	0	.	.	.	.

(1)=Positive (2)=Negative

a. The reference category is: COVID 19 PCR NEGATİF.

b. This parameter is set to zero because it is redundant.

resistance was detected in one *C. albicans* strain (MIC=8). It was determined that 8 of the *C. parapsilosis* strains were resistant to fluconazole (MIC range 8-128), 2 were dose-dependent sensitive (SDD) to fluconazole, and 2 isolates were resistant to caspofungin and micafungin (MIC≥8). Fluconazole resistance was found in 6 of the *C. parapsilosis* strains isolated from the other patient group (MIC range 8-32), fluconazole SDD was found in 3, and caspofungin and micafungin resistance was detected in 1 patient (MIC≥8).

Table 3. Comparison of laboratory results of COVID19 and non- COVID19 patients

		SARS CoV2		*p*
		Positive (n=44)	**Negative (n=54)**	
Platelets	Min-Max (Median)	10-509 (186,5)	5-547 (153)	[e]0,513
	Mean ± SD	195,25 ± 124,48	185,89 ± 133,92	
Procalcitonin	Min-Max (Median)	0,2-100 (2)	0,1-40,2 (1,4)	[e]0,359
	Mean ± SD	7,08 ± 16,49	4,21 ± 7,82	
CRP	Min-Max (Median)	47,8-500 (194,6)	6,8-413 (130,8)	[e]0,002**
	Mean ± SD	212,37 ± 114,14	145,15 ± 93,23	
Ferritin	Min-Max (Median)	354-20000 (1483,5)	18-19357 (685,3)	[e]0,089
	Mean ± SD	2553,81 ± 3712,67	2377,58 ± 4137,53	
IL-6	Min-Max (Median)	30-14975 (227,5)	13,6-52888 (160,9)	[e]0,819
	Mean ± SD	1248,17 ± 3160,66	4372,50 ± 12463,97	
WBC	Min-Max (Median)	4,1-75 (14,6)	1,6-26,8 (12,8)	[e]0,202
	Mean ± SD	17,31 ± 13,12	12,68 ± 6,61	
Neutrophil	Min-Max (Median)	2,6-46,7 (12,3)	0-24,2 (10,3)	[e]0,331
	Mean ± SD	13,73 ± 9,02	11,10 ± 6,01	
Lymphocyte	Min-Max (Median)	0,3-59,9 (1,1)	0,1-7,9 (1,1)	[e]0,172
	Mean ± SD	2,81± 8,93	1,25 ± 1,24	
Neutrophil/ Lymphocyte	Min-Max (Median)	0,2-98,1 (10,6)	0-172,5 (9,1)	[e]0,700
ratio	Mean ± SD	14,56 ± 16,24	18,66 ± 26,93	
D dimer	Min-Max (Median)	1,1-35,2 (5,7)	0,3-35,2 (4,4)	[e]0,275
	Mean ± SD	9,34 ± 9,40	7,23 ± 8,01	
Fibrinogen	Min-Max (Median)	116-1200 (684,5)	106-1200 (490)	[a]0,027*
	Mean ± SD	676,79 ± 245,63	551,14 ± 253,03	
Troponin T	Min-Max (Medyan)	0-402,7 (27,4)	0-265 (0,2)	[e]0,149
	Mean ± SD	76,29 ± 114,60	34,08 ± 73,17	

[a]Student t Test [e]Mann Whitney U Test *p<0,05 **p<0,01

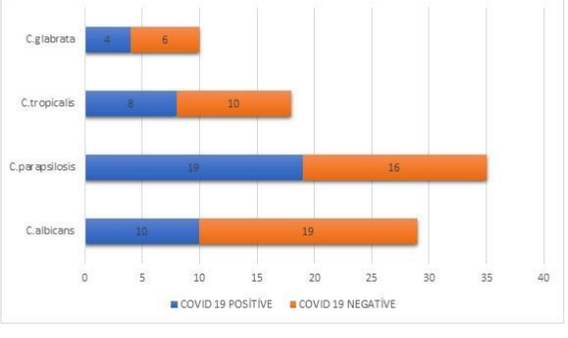

Fig. 1. Distribution of *Candida* spp.

DISCUSSION

In our study, when we examined the incidence of candidemia in patients hospitalized in the ICU of our hospital during the pandemic period, we found it to be 2.26% (1.93% in the COVID 19 patient group and 2.61% in the non COVID patient group). Although this rate is seen to be higher than the studies conducted in our country and in the world in the similar period (7-10), higher results were found when only the patient group with COVID 19 was evaluated in different studies (10, 11). In this study, as in similar studies, no significant difference was observed in terms of age and gender (9, 11). Since the immunomodulator or corticosteroid used in patients with COVID19 disease causes immunosuppression, it is known that these patients are a risk factor for candidemia (12, 13). In our study, although the number of patients using immunomodulators could not be evaluated statistically, there was no significant difference in candidemia rates in those using steroids, antiviral and antibacterial agents (p>0.05). The main risk factors in invasive candidiasis involving gastrointestinal *Candida* spp. colonization are impaired intestinal epithelial permeability and immunosuppression (14).

The mortality of candidemia associated with

COVID19 disease has been reported to be between 40-70%. However, mortality caused by candidemia is unknown (14). In our study, mortality in patients with COVID 19 disease was found to be similar (66%), and there was no significant difference in mortality between both candidemia patient group (p=0.652). Intensive use of antibiotics causes deterioration in the intestinal microbiota. However, in this study, no significant difference was detected between the patient groups in terms of antibiotic use (p >0.05).

Although there are studies reporting that CVC is the main source of candidemia (11), no significant difference was found between the two groups in terms of CVC use in the development of candidemia in our study (p=0.429).

Similar to other studies (15, 16), in our study, the risk of candidemia was detected to be significantly higher in patients with diabetes and an additional lung disease with COVID19. The mortality of candidemia associated with COVID19 disease has been reported to be between 40-70%. However, mortality caused by candidemia is unknown (14).

In our study, the most frequently isolated *Candida* spp. in the patient group with COVID19 disease was *C. parapsilosis.* It is known that *C. parapsilosis* is the second or third most frequently isolated isolate from patients (17). *C. parapsilosis* can form a biofilm on CVC and other medically implanted devices and therefore poses a threat to patients undergoing invasive medical interventions. It reproduces rapidly in TPN (17). The risk factors of the patients in our study for *C. parapsilosis*; TPN (n=1), CVC (n=10), intubation (n= 16), dialysis catheter (n=7), nephrostomy (n=1). Although fluconazole and a few isolates echinocandin resistance were observed in the strains, the results of VITEK® 2 COMPACT (BioMerieux, France) antifungal susceptibility used in our study could not be confirmed by broth microdilution tests. In our study, CRP and fibrinogen levels were found to be significantly higher in patients with COVID19 patient group compared to the non COVID19 patient group. Elevated plasma fibrinogen is known to be associated with increased inflammation and disease severity in COVID 19 patients (18, 19).

In this study, we found that *C. parapsilosis* was the most frequently isolated strain in COVID 19 patients. Knowing the local epidemiological trend about *Candida* spp. is important for choosing the treatment option (2). It has been suggested that decreased antifungal susceptibility in non-*C. albicans* species may be associated with routine prophylactic fluconazole use (20, 21). Intrinsic and extrinsic resistance of non *C. albicans* species to azoles also poses a great challenge for prophylactic strategies and empirical therapeutic (22).

CONCLUSION

The risk of candidemia in COVID 19 patients was detected to be significantly higher in patient group with DM and COPD. This rate was detected to be low in patients with malignancy and CAD. When age, gender, medication use, intubation, PTN and CVC were evaluated, no difference was seen in terms of risk.

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