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Characteristics of candidemia in COVID-19 patients; increased incidence, earlier occurrence and higher mortality rates compared to non-COVID-19 patients

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Abstract

Severe COVID-19 patients in ICU are at high risk for candidemia due to exposure to multiple risk factors for candidemia. We aimed to compare the incidence of candidemia in ICU patients with and without COVID-19, and to investigate epidemiologic and clinical characteristics of candidemia patients and risk factors for mortality in candidemia patients. This retrospective study was conducted in patients followed in the ICUs of Ankara City Hospital for 2 years, divided into pre-pandemic and pandemic periods. The incidence (event per 1000 patient-days) and epidemiology of candidemia, clinical and laboratory characteristics of patients were compared in COVID-19 and non-COVID-19 groups. Candidemia incidence was higher in the COVID-19 group (2.16, 95% CI 1.77–2.60) than the non-COVID-19 group (1.06, 95% CI 0.89–0.125) (p < .001). A total of 236 candidemia episodes (105 in COVID-19 patients and 131 in non-COVID-19 patients) were detected during the study periods. COVID-19 cases had a higher rate of corticosteroid use (63.8% vs. 9.9%, p < .001). Epidemiology of candidemia and antifungal susceptibility were similar. Candidemia developed 2 weeks earlier in COVID-19 groups and resulted in higher mortality (92.5% vs. 79.4%, p .005). One-third of candidemia patients died before receiving any antifungal treatment, and this rate was higher in the COVID-19 group. In multivariate logistic regression analysis, corticosteroid use, presence of sepsis and age older than 65 years were independent risk factors for mortality in candidemia patients. Candidemia with high mortality is a more serious problem for COVID-19 patients due to its increased incidence, earlier occurrence and a higher rate of mortality.

KEYWORDS
antifungal agents, Candida, candidemia, COVID-19, deep fungal infection, epidemiology, incidence, mortality risk factors, Thi steroids, ICU

1 | INTRODUCTION

Candida species are a significant cause of hospital-acquired bloodstream infections and may cause severe infections associated with prolonged hospital stays and high rates of mortality.[1,2] The disease occurs particularly in patients who need intensive care and are immunocompromised. Exposure to broad-spectrum antibiotics and steroids, invasive procedures such as intravascular catheter and mechanical ventilation, haemodialysis, total parenteral nutrition and prior surgery – particularly abdominal surgery – are among high-risk factors for the development of candidemia.[3]

The global COVID-19 pandemic results in severe acute respiratory disease syndrome requiring intensive care unit (ICU) follow-up in some patients and consequently their exposure to various risk factors associated with candidemia.[4] Demonstrating the benefit of corticosteroids in the treatment of severe COVID-19 in randomised controlled trials has resulted in a significant increase in the use of corticosteroids in hospitalised COVID-19 patients, particularly those followed in the ICU.[5–7] Therefore, severe COVID-19 patients are exposed to corticosteroids in addition to many other risk factors for developing candidemia. Recent articles have drawn attention to the development of invasive fungal infections in critically ill COVID-19 patients and reported the increased incidence of candidemia in intensive care units during the pandemic period compared to the period before COVID-19.[8–10] However, relatively few patients have been included in these studies. In the present study, we aimed to compare candidemia incidence rates in patients with and without COVID-19 hospitalised in ICUs during pre-pandemic and pandemic periods in a large patients' series. Secondly, we aimed to evaluate the epidemiologic and clinical characteristics of candidemia patients with and without COVID-19, and to investigate risk factors for mortality.

2 | PATIENTS AND METHOD

This retrospective study was conducted in Ankara City Hospital, the main pandemic centre and a tertiary hospital in the capital. The authors confirm their adherence to the ethical policies of the journal, as noted on the journal's author guidelines page. Ethical approval was obtained from Ankara City Hospital Ethical Committee 1. All patients older than 18 years followed with the diagnosis of candidemia in ICUs located in two buildings (neurology-orthopaedic and cardiovascular surgery) of the hospital with 6 hospital buildings between 1 March 2019 and 1 March 2021 were included in the study. Upon the detection of the first COVID-19 patient in Turkey in mid-March 2020, the hospital administration made a change in the planning of routine workflow and ICU use to meet the increasing COVID-19 patient burden. During the pandemic, some of these units served as the COVID-19 ICU where only COVID-19 patients were followed regardless of their underlying disease and organ-specific complications, while the remaining units continued to care for non-COVID-19 patients.

The study period was determined as 2 years, between 1 March 2019 and 1 March 2021, and divided into two periods. Between 1 March 2019 and 1 March 2021 was defined as the pre-pandemic period, and between 1 March 2020 and 1 March 2021 as the pandemic period. Patients followed-up in ICUs were divided into two groups as COVID-19 and non-COVID-19. The COVID-19 group included the patients followed in COVID-19 ICUs during the pandemic period with COVID-19 diagnosis, while non-COVID-19 group included those followed in ICUs during pre-pandemic and pandemic periods for reasons other than COVID-19. Total numbers of patient groups hospitalised in COVID-19 and non-COVID-19 ICUs in the defined periods and total patient-days were evaluated to calculate the incidence rates of candidemia. All patients with candidemia followed-up in COVID-19 and non-COVID-19 ICUs were retrospectively screened by using the hospital automation database system, and their data collected in a standardised patient form using medical records. Demographic and clinical characteristics including admission diagnoses, underlying medical conditions, comorbidities, risk factors for candidemia (concomitant bacteraemia, sepsis, central venous catheter, parenteral nutrition, gastrointestinal instrumentation/surgery, mechanical ventilation, prior antibiotic and corticosteroid uses), *Candida* colonisation index and Candida score were recorded in patients' form.

The diagnosis of COVID-19 was made with polymerase chain reaction (PCR) for SARS-CoV-2 and/or the presence of typical findings for COVID-19 on computed tomography with a positive antibody test. Candidemia was identified as the detection of one or more *Candida* species in at least one blood culture in patients who have findings compatible with infection. Each patient was included only once in the study. BacT/Alert (bioMerieux) automated blood culture system was used for monitoring blood culture bottles. Yeasts were identified at species level by using VitekMS (bioMerieux) device and MALDI-TOF MS method. Sensitivity tests were evaluated with Vitek2 (bioMerieux) automated system. Candida colonisation index was calculated as the ratio of the number of distinct body sites colonised with *Candida* strain over the total number of distinct body sites cultures tested (threshold 0.5).[11] Candida score was calculated as follows: multifocal *Candida* species colonisation (1 point), surgery (1 point), total parenteral nutrition (1 point), sepsis (2 points). Variables were encoded as 0 if it was absent and as valid points if it was present. The threshold was 2.5 points for high risk for candidemia. [12]

In order to evaluate whether there is a change in the incidence of candidemia during the pandemic period, we compared COVID-19 patients followed up in a one-year period (pandemic period) and non-COVID-19 patients followed up in two-year period (pre-pandemic and pandemic periods) in terms of candidemia incidence rate (candidemia episode per 1000 patient-days) and the percentages of candidemia (episode per 100 patients). We also compared candidemia cases with and without COVID-19 in terms of clinical characteristics, risk factors for candidemia, candidemia colonisation index, candidemia score, laboratory parameters on the day of

TABLE 1 Data on patients followed in COVID-19 and non-COVID-19 ICUs during the study period

	All patients (Pre-pandemic[a] and pandemic periods[b])	COVID-19 (Pandemic period)	Non-COVID-19 (Pre-pandemic and pandemic periods)	*p*-value
Total patient numbers followed in ICU[c] in defined periods, n	30.307	5.542	24.765	<.001
Total patient-days in ICU in defined periods	172.654	48.653	124.001	
Average ICU stay per one patient, days (IQR[d])	2 (1–7)	7 (3–12)	2 (1–5)	<.001
Candidemia number in defined period, n	236	105	131	<.001
Candidemia rate (episode number per 100 patients), %	0.8	1.9	0.5	<.001
Candidemia incidence rate (event per 1000 patients-day)	1.37 (1.20–1.55)	2.16 (1.77–2.60)	1.06 (0.89–0.125)	<.001

[a]Pre-pandemic period: Time between 1 March 2019 and 1 March 2020.
[b]Pandemic period: between 1 March 2019 and 1 March 2020.
[c]ICU, Intensive care unit.
[d]IQR, Interquartile range.

candidemia, *Candida* species, and antifungal susceptibilities, antifungal treatments and patients' outcomes including duration of ICU stay and mortality. Risk factors for mortality in patients with candidemia were investigated.

2.1 | Statistical analyses

Statistical analyses were performed with IBM SPSS V.20 software version and R Stats Package. We compared incidence rates of candidemia between patients with and without COVID-19 in ICU during the study periods using Poisson regression analysis. Descriptive statistics were presented as frequency and percentages for categorical variables, and medians with quartiles (interquartile range [IQR] 25th–75th percentile) for continuous variables. Categorical variables were compared using Chi-square test in parametric conditions. Student's *t* test and Mann Whitney *U* test were used in the comparison of continuous variables for normally distributed and non-normally distributed data, respectively. Multivariate logistic regression analysis was performed to investigate predictors of high mortality. A *p*-value of less than .05 was considered statistically significant.

3 | RESULTS

During the pandemic period, 2487 COVID-19 patients were followed up in COVID-19 ICUs for a total of 20.909 days. The number of non-COVID-19 patients admitted to ICUs during the pre-pandemic and pandemic period was 27.750 and the patients were followed for a total of 154.466 days. We observed a total of 236 candidemia episodes during the study period, 105 in COVID-19 patients and 131 in non-COVID-19 patients. Candidemia incidence rate was 2.16 (95% confidence interval 1.77–2.60) in COVID-19 group and higher than non-COVID-19 group (1.06, 95% confidence interval 0.89–0.125) ($p < .001$) (Table 1).

Non-COVID-19 patients had been particularly admitted to ICUs with the diagnoses of cardiovascular diseases (37), neurological diseases (32), respiratory system diseases (30), orthopaedic diseases (10), organ transplantation (3) and other varied reasons (19). Baseline demographic and clinical characteristics of candidemia cases with and without COVID-19 and risk factors for the development of candidemia are shown in detail in Table 2. Candidemia patients with COVID-19 had a higher rate of chronic pulmonary disease and a lower rate of heart failure than those without COVID-19 (*p* .09 and .001, respectively). Risk factors for candidemia were similar among candidemia cases with and without COVID-19, except for gastrointestinal instrumentation or surgery, which was higher in non-COVID-19 patients (*p* .02). Corticosteroid use was also detected higher in candidemia cases with COVID-19 (63.8%) compared to non-COVID-19 patients (9.9%) ($p < .001$). Prior or concomitant bacteraemia was detected in a total of 127 patients (53.8%), 35 of them were polymicrobial. The most frequent bacteria were

TABLE 2 Baseline demographic and clinical characteristics of candidemia patients with and without COVID-19 followed in intensive care unit and risk factors for candidemia

Characteristics	All patients (*n* = 236)	COVID-19 patients with candidemia (*n* = 105)	Non-COVID-19 patients with candidemia (*n* = 131)	*p* value
Age, median (IQR[a])	72 (18–94)	74 (60–81)	69 (58–81)	.36
Gender, male	135 (57.2)	55 (52.4)	80 (61.1)	.18
Any comorbidity	208 (88.1)	94 (89.5)	114 (87.0)	.56
Diabetes	78 (33.1)	38 (36.2)	40 (30.5)	.36
Hypertension	110 (46.6)	52 (49.5)	58 (44.3)	.42
Coronary artery disease	55 (23.3)	29 (27.6)	26 (19.8)	.16
Heart failure	40 (16.9)	13 (12.4)	27 (20.6)	.09
Chronic pulmonary disease	36 (15.3)	23 (22.1)	13 (9.9)	.01
Chronic renal disease	17 (7.2)	10 (9.5)	7 (5.3)	.2
Malignity	27 (11.4)	11 (10.5)	16 (12.2)	.67
Immunosuppression	14 (5.9)	6 (5.7)	8 (6.1)	.89
Cerebrovascular events	19 (8.1)	5 (4.8)	14 (10.7)	.88
Mechanical ventilation	202 (85.6)	92 (87.6)	110 (84.0)	.43
Duration of intubation	5 (1–15)	5 (1–11.5)	5 (1–22)	.27
Sepsis	144 (61.0)	64 (61.0)	80 (61.1)	.98
Central venous catheter	227 (96.2)	103 (98.1)	127 (94.7)	.17
Total parenteral nutrition	73 (30.9)	26 (24.8)	47 (35.9)	.66
Gastrointestinal instrumentation or surgery	23 (9.7)	5 (4.8)	18 (13.7)	.02
Presence of *Candida* spp in urine sample	105 (44.5)	47 (44.8)	58 (44.3)	.94
Presence of *Candida* spp in DTA[b] sample	78 (33.1)	32 (30.5)	46 (35.5)	.45
Multifocal candida colonisation	59 (25.0)	24 (22.9)	35 (26.7)	.49
Candida colonisation index[c]				
≤0.5	111 (47)	50 (47.6)	61 (46.6)	.85
≥0.6	125 (53)	55 (52.4)	70 (53.4)	
Candida score[d]				
≤2 point	152 (64.4)	73 (69.5)	79 (60.3)	.14
≥3 point	84 (35.6)	32 (30.5)	52 (39.7)	
Presence of prior bacteraemia[e]	127 (53.8)	52 (49.5)	75 (57.3)	.38
Prior use of extended spectrum antibiotic	228 (96.6)	99 (94.3)	129 (98.5)	.77
Prior use of corticosteroid	80 (33.9)	67 (63.8)	13 (9.9)	<.001

Note: Data are presented as *n* (%) unless noted otherwise.

[a]IQR, Interquartile range (25% and 75%).

[b]DTA, Deep tracheal aspirate.

[c]Candida colonisation index: Ratio of the number of distinct body sites colonised with Candida strain/the total number of distinct body sites cultures tested. Threshold 0.5.

[d]Candida score: The total score obtained from the following: Multifocal Candida species colonisation (1 point), surgery (1 point), total parenteral nutrition (1 point), sepsis (2 points). Threshold 2.5.

[e]Causative microorganisms in blood cultures (162): Coagulase-negative staphylococci (44), non-fermentative gram-negative bacillus (42), *Klebsiella pneumonia* (26), *Enterococcus spp* (24), *Staphylococcus aureus* (9), *Escherichia coli* (7) and others (10).

non-terminative basils (44) and staphylococci (44), followed by enterococci and *Klebsiella pneumonia*. Bacteraemia rates were similar among candidemia patients with and without COVID-19 patients (*p* .38). There was no difference in candida colonisation index and candida score between candidemia cases with and without COVID-19 (*p* .85 and .14, respectively).

White blood cell count, neutrophil count, urea, creatinine, aspartate aminotransferase, alanine aminotransferase and procalcitonin levels measured on the day of candidemia were detected significantly higher in candidemia patients with COVID-19 than cases without COVID-19. Laboratory parameters of candidemia patients in both groups on the day of candidemia in are shown in detail in Table 3. Duration from ICU admission to candidemia was shorter in COVID-19 patients (13 days [IQR 8–24]) than non-COVID-19 cases (27 days [IQR 13–45]) (p < .001). Antifungal therapy was given to only 63.1% of candidemia patients, and this rate was significantly lower in COVID-19 patients (53.2%) compared to non-COVID-19 patients (71.7%) (p .003), as shown in Table 4.

Candida albicans was the most common agent of candidemia and detected in 40.0% of COVID-19 and 47.3% of non-COVID-19 patients. No difference was found between COVID-19 and non-COVID-19 groups in terms of candida type and antifungal susceptibilities (Table 4). The antifungal agent to which Candida species were most susceptible was micafungin with a susceptibility rate of 94.1%, followed by amphotericin B (93.3%). Candidemia developed earlier in COVID-19 patients (median 13 days) than non-COVID-19 patients (median 27 days) (p < .001). Only 53.2% of COVID-19 patients with candidemia were able to receive antifungal therapy, and this rate was statistically significantly lower compared to non-COVID-19 group with candidemia (71.7%) (p .003). The most preferred antifungal agent was anidulafungin in both groups. Duration of antifungal treatment was shorter in COVID-19 patients compared to non-COVID-19 patients (p .002).

Duration of ICU stay was significantly shorter in COVID-19 patients (23 days) than non-COVID-19 patients (45 days) (p < .001). Mortality rate was high (85.2%) in all patients with candidemia; it was significantly higher in COVID-19 patients than non-COVID-19 patients (92.5% vs. 79.4%, p .5). In multivariate logistic regression analysis, corticosteroid treatment, presence of sepsis and age older than 65 years were found to be independent risk factors for mortality (Table 5).

4 | DISCUSSION

Patients with severe COVID-19, particularly those followed in the ICU, are at risk for developing candidemia. Most of the risk factors for candidemia such as the use of broad-spectrum antibiotics and corticosteroids, invasive procedures (central venous catheter, mechanical ventilation and haemodialysis), surgical procedures become an inevitable necessity in these patients during the follow-up. Recent studies reported an extra increase in candidemia cases in patients with COVID-19 compared to non-COVID-19 patients; however, the number of patients reported in these studies is relatively small.[8–10] A total of 41 episodes of candidemia were included in the study of Nucci et al, and a total of 72 candidemia episodes in the study of Mastrangelo et al.[8,9]

In this study, we evaluated a large number of patients who were followed up in COVID-19 and non-COVID-19 ICUs for 2 years (pre-pandemic and pandemic periods) and clearly demonstrated an approximately 2-fold increase in the incidence of candidemia in patients with COVID-19 compared to those who did not have COVID-19. Similarly, in the study by Mastrangelo et al,[9] the incidence of candidemia (cases per 10.000 patient-days) in patients with COVID-19 was 10.97 (6.79–16.76), while it was 1.48 (1.10–1.95) in non-COVID-19 historical cohort patients (p < .001). Riche et al[10] also reported a marked increase (10-fold) in the incidence of candidemia in COVID-19 patients compared to those who did not have COVID-19 (1.43 vs. 10.23 in one hospital and 1.15 vs. 11.83 in another hospital per 1000 patient-days, p .001). The incidence of candidemia may differ between centres depending on the characteristics of the centres and patients (eg whether it is a specific branch hospital), the numbers of blood cultures taken from the patients, and laboratory workouts. However, our study and other reports clearly revealed that COVID-19 patients have an additional risk for the development of candidemia compared to patients followed for non-COVID-19 reasons. This increase is, in fact, an expected result due to the increased exposure of COVID-19 patients to risk factors associated with candidemia, such as the need for corticosteroid use in severe disease, the

TABLE 3 Laboratory parameters of candidemia patients with and without COVID-19 on the day of candidemia

Laboratory parameters on the day of candidemia, median (IQR[a])	All patients (n = 236)	COVID-19 patients with candidemia (n = 105)	Non-COVID-19 patients with candidemia (n = 131)	p value
White blood cell, cells ×10^9/L	11.6 (7.9–18.4)	13.5 (8.9–22.9)	11.9 (7.3–15.0)	.001
Neutrophil count, cells ×10^9/L	9.7 (6.4–15.9)	11.8 (8.0–22.0)	8.5 (6.0–11.0)	<.001
Platelet count, cells ×10^9/L	200 (117–301)	196 (102–298)	316 (186–3760)	.23
C-reactive protein, g/L	0.13 (0.064–0.189)	0.126 (0.053–0.199)	0.133 (0.017–0.186)	.78
Procalcitonin, μg/ml	1.0 (0.3–5.1)	1.98 (0.36–7.7)	0.85 (0.14–3.2)	.006
Urea, mg/dl	86.5 (48–157)	122 (56–196)	83 (36–128)	.002
Creatinine, mg/dl	1.1 (0.6–2.5)	1.6 (0.7–3.4)	1.0 (0.5–3.7)	.007
Aspartate transaminase, U/L	47 (28–98)	73 (37–153)	50 (32–90)	.030
Alanine transaminase, U/L	32 (17–59)	44 (26–87)	32 (22–59)	.002
D-dimer, mg/L	4.5 (2.5–10.8)	4.3 (2.2–10.2)	7.0 (3.9–14.0)	.14

[a]IQR, Interquartile range (25% and 75%).

TABLE 4 *Candida* species, antifungal susceptibilities, antifungal treatments and clinical outcomes of candidemia patients with and without COVID-19

Characteristics	All patients (*n* = 236)	COVID-19 (*n* = 105)	Non-COVID-19 (*n* = 131)	*p*-value
Candida species				.71
C. albicans	104 (44.1)	42 (40.0)	62 (47.3)	>.05
C. parapsilosis	58 (24.5)	20 (19.0)	38 (29.0)	>.05
C. glabrata	33 (14.0)	19 (18.1)	14 (10.7)	>.05
C. tropicalis	22 (9.3)	13 (12.4)	9 (6.9)	>.05
Others	19 (8.1)	11 (10.5)	8 (6.1)	>.05
Antifungal susceptibilities				
Fluconazole	161 (68.2)	73 (69.5)	88 (67.2)	.82
Voriconazol	167 (70.8)	75 (71.4)	92 (70.8)	.17
Caspofungin	191 (80.9)	81 (77.1)	110 (84.0)	.37
Micafungin	222 (94.1)	100 (95.2)	122 (93.1)	.14
Flucytosine	220 (93.2)	100 (95.2)	120 (91.6)	.54
Amphotericin B	218 (93.3)	98 (91.6)	120 (92.4)	.62
Time (days) from ICU admission to candidemia, median (IQR[a])	19.5 (9–33)	13 (8–24)	27 (13–45)	<.001
Number of patients received antifungal treatment	149 (63.1)	55 (53.2)	94 (71.7)	.003
Number of patients received antifungal treatment for more than 4 days	125 (53)	43 (41.0)	82 (62.6)	.001
Time (h) from culture positivity to initiation of antifungal treatment, median (IQR)	59 (24–72)	60 (24–72)	58 (24–72)	.10
Duration (days) of antifungal treatment in patients received antifungal treatment, median (IQR)	12 (5–20)	7 (4–18)	16 (7–21)	.002
Antifungal treatment				.052
Anidulafungin	86 (36.6)	31 (29.5)	55 (42.3)	
Caspofungin	6 (2.6)	3 (2.9)	3 (2.3)	
Micafungin	25 (10.6)	7 (6.7)	18 (13.8)	
Fluconazole	23 (9.9)	11 (10.5)	12 (9.2)	
Voriconazole	4 (1.7)	2 (1.9)	2 (1.5)	
Amphotericin B	5 (2.1)	1 (1.0)	4 (3.1)	
No antifungal drug treatment	87 (36.9)	50 (46.8)	37 (28.3)	
Vegetation on echocardiography[b]	5/59 (8.5)	0/9 (0)	5/50 (10.0)	<.001
Endophthalmitis on funduscopic examination[b]	2/20 (10.0)	0/3 (0)	2/17 (11.8)	.019
Abnormal findings on abdominal CT[b,c]	1/20 (5.0)	0/5 (0)	1/15 (6.7)	.16
Duration (days) of ICU stay, median (IQR)	33 (17–55)	23 (12–37)	45 (26–70)	<.001
Death	201 (85.2)	97 (92.5)	104 (79.4)	.005
28-day mortality	179 (75.8)	90 (87.5)	89 (67.9)	.002

Note: Data are presented as *n* (%) unless noted otherwise.

[a]IQR, Interquartile range (25% and 75%).

[b]Echocardiography, funduscopic examination and abdominal CT were performed in 59, 20 and 20 patients respectively.

[c]CT, Computed tomography (infarction in spleen).

characteristic multisystem involvement of the disease and the increased use of broad-spectrum antibiotics in their treatment due to complicated clinical and laboratory conditions. The widespread use of broad-spectrum antibacterial agents in critically ill patients leads to the suppression of normal flora and development of candida colonisation in the gut, and eventually translocation of candida to the bloodstream system.[3,4] Similarly, corticosteroids enhance the adhesion of *Candida* species to the epithelial cells, their growth in the gut, and translocation from the gastrointestinal tract to the bloodstream (shown in vitro studies). In addition, corticosteroids affect negatively almost every cell type in the immune system in many complicated ways and enhance cellular immunodeficiency.[10,13]

TABLE 5 Multivariate logistic regression analysis of the risk factors for mortality

Variables	Candidemia Alive (n = 35)	Candidemia Deceased (n = 201)	p-value	Odds ratio (95% CI[a])	p-value
Age ≥65 years	12 (34.3)	139 (69.2)	<.001	5.6 (2.3–13.4)	<.001
Admission diagnosis, COVID-19	8 (22.9)	97 (48.3)	.005		
Antifungal treatment over than 3 days	27 (77.1)	98 (48.8)	.002		
Prior corticosteroid use	6 (17.5)	77 (36.8)	.023	4.4 (1.5–12.6)	.006
Presence of sepsis	8 (22.9)	136 (67.7)	<.001	7.6 (3.1–19.0)	<.001
Candida species, non-albicans	26 (74.5)	105 (52.2)	.015		

[a]CI, Confidence interval.

Corticosteroids are recommended in the treatment of critically ill patients who need oxygen or ventilation support since a reduced mortality was demonstrated with corticosteroid use compared to standard care or placebo in patients with severe COVID-19 in randomised controlled studies.[5–7,14] However, besides their benefits, it has long been known that the risk of developing candidemia increases with corticosteroid use.[13] In the report by Riche et al,[10] although a small number of patients were included, it was shown that all COVID-19-associated candidemia patients received prior corticosteroid therapy. Similarly, we detected dramatically higher rates of corticosteroid use in candidemia patients with COVID-19 compared to those without COVID-19.

One of the remarkable results of the present study is that candidemia developed in the earlier periods of ICU admission (about 2 weeks) in patients with COVID-19 compared to those without COVID-19. Previous studies did not draw attention to the early development of candidemia in COVID-19 patients.[8–10] Earlier developed candidemia may be due to increased and early use of corticosteroid which is a potential risk factor for candidemia in the patients hospitalised in wards before admission to the ICUs. The similarity of risk factors for the development of candidemia except for corticosteroid use in both groups supports this opinion.

Another notable result of our study is that one-third of all patients with candidemia in the study had died before receiving any antifungal treatment, and this rate was higher in COVID-19 group. Some of the remaining patients with COVID-19 were able to receive antifungal treatment for shorter than proper treatment duration. These results show that candidemia does not come to mind in the early period of infection in ICU patients, especially COVID-19 patients.

Candida types, antifungal susceptibility and treatment choice were not different between COVID-19 and non-COVID-19 groups. *Candida albicans* was the most frequent type in the present study and previous studies.[8,15,16] Mastrangelo et al also reported similar rates of non-albicans candidemia between groups in a total of 72 candidemia patients. Previous other studies had even fewer patients. Majority of the patients were given anidulafungin, micafungin and fluconazole. All organ involvements were in the non-COVID group, but comprehensive diagnostic intervention had been performed on more patients in this group compared to COVID-19 group. Hepatic and renal function tests, and inflammation markers were higher in COVID-19 patients than non-COVID-19 patients. This may be due to the multisystemic characteristic of COVID-19 or the cause of the cytokine storm that requires ICU follow-up, especially in the severe form. Severe COVID-19 and candidemia are both life-threatening infections, with mortality rates reported at over 50% in patients with candidemia and 49% in critical COVID-19.[1,4,17,18] The development of candidemia superinfection or coinfection in COVID-19 patients causes high mortality. In previous studies, overall mortality was 57.1%, 66.7% and 72.7%.[8–10] We detected higher overall mortality (92.5%) in candidemia patients with COVID-19 than those reported in previous COVID-19 studies. This higher mortality may be associated with the differences of study design and populations. While we included only ICU patients in the study, the patients who were not staying in the ICU were also included in other studies. Secondly, high mortality may also be associated with not considering candidemia in the early period of ICU admission and not covering *Candida* species in empirical antimicrobial treatment, or treatment delay.

Corticosteroid treatment, presence of sepsis and age older than 65 years were found as independent risk factors for mortality in patients with candidemia. Similar to the present study, previous studies have shown that advanced age is a leading factor for death in candidemia patients.[19–21] Sepsis is a risk factor for both the development of candidemia and poor survival in patients with candidemia.[12,22] This study supported the results of previous studies. We also demonstrated that corticosteroid treatment is a mortality-associated factor in patients with candidemia despite its benefits in severe COVID-19 patients. In a large series with 842 patients with candidemia, corticosteroid use was found to be associated with treatment failure and poor survival.[21] In another large series study, corticosteroid use differed between surviving and deceased patients, but was not an independent risk factor in multivariate analysis.[20] Appropriate and non-delayed antifungal therapy is crucial for the treatment of candidemia.[19] In this study, some of the patients were unable to receive any antifungal agents, and some had received for 3 days or shorter. However, we did not demonstrate an independent association between short treatment duration and mortality in multivariate analysis. Delaying antifungal treatment until the obtainment of positive blood culture was reported as an independent risk factor for high mortality.[23]

There are some limitations in the present study. The conducting of the study in two of the six specified buildings of the hospital (neurology-orthopaedic and cardiovascular surgery buildings) may have led to the selection of a special patient population among non-COVID-19 patients. However, patient selection related to specific branches had to get up during the pandemic periods for COVID-19 and non-COVID-19 patients and had relatively fewer negative effects on patient population. Another important limitation was that we could not investigate specific risk factors for the development of candidemia in COVID-19 patients because of the difficulty of including COVID-19 patients without candidemia. The other limitation is the retrospective character of the study, as data obtained from patient files may be incomplete or incorrect.

In conclusion, we detected an increased incidence of candidemia in COVID-19 patients compared to non-COVID-19 group followed in pre-pandemic and pandemic periods. Clinical characteristics were substantially similar in two groups. The most remarkable difference between groups was prior corticosteroid exposure. While the majority of COVID-19 patients were given corticosteroid therapy, only a small proportion of non-COVID-19 patients received it. The possible collateral damage of corticosteroid therapy, such as severe candida infection, should not be forgotten in the management and treatment selection of ICU patients, especially those diagnosed with COVID-19. Our study showed that candidemia may develop earlier, approximately within 2 weeks, in patients hospitalised in the ICU with COVID-19 compared to those hospitalised for other reasons and cause high mortality with a rate of 92.5%. Corticosteroid use, presence of sepsis and advanced age were independent risk factors for mortality in patients with candidemia. Candidemia with high mortality rates should always be kept in mind during the follow-up of ICU patients, even in the early period.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

Bircan Kayaaslan: Conceptualization (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Writing-original draft (lead); Writing-review & editing (lead). **Fatma Eser:** Formal analysis (supporting). **Ayse Kaya Kalem:** Investigation (supporting); Writing-review & editing (equal). **Zeynep Bilgic:** Investigation (equal). **Dilek Asilturk:** Investigation (equal). **Imran Hasanoglu:** Writing-review & editing (supporting). **Muge Ayhan:** Investigation (lead). **Yasemin Tezer Tekce:** Data curation (supporting). **Deniz Erdem:** Formal analysis (lead). **Sema Turan:** Writing-review & editing (lead). **Ipek Mumcuoglu:** Formal analysis (equal). **Rahmet Guner:** Conceptualization (supporting); Methodology (supporting); Writing-review & editing (supporting).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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