


# Incidence and risk factors for COVID-19 associated candidemia (CAC) in ICU patients

Bircan Kayaaslan<sup>1</sup>  | Ayşe Kaya Kalem<sup>1</sup> | Dilek Asilturk<sup>2</sup> | Betül Kaplan<sup>2</sup> |  
 Gülen Dönertas<sup>2</sup> | Imran Hasanoglu<sup>1</sup> | Fatma Eser<sup>1</sup> | Ruveyda Korkmazer<sup>2</sup> |  
 Zeynep Oktay<sup>2</sup> | Isıl Ozkocak Turan<sup>3</sup> | Deniz Erdem<sup>3</sup> | Hesna Bektas<sup>4</sup> | Rahmet Guner<sup>1</sup>

<sup>1</sup>Department of Infectious Disease and Clinical Microbiology, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey

<sup>2</sup>Department of Infectious Disease and Clinical Microbiology, Ankara City Hospital, Ankara, Turkey

<sup>3</sup>Department of Intensive Care Unit, University of Health Sciences Ankara City Hospital, Ankara, Turkey

<sup>4</sup>Department of Neurology, Ankara City Hospital, Ankara Yıldırım Beyazıt University, Ankara, Turkey

## Correspondence

Bircan Kayaaslan, Infectious Disease and Clinical Microbiology, Ankara City Hospital, Ankara Yıldırım Beyazıt University, Bilkent Street no:1, Çankaya/Ankara 06800, Turkey.  
 Email: [drbican@gmail.com](mailto:drbican@gmail.com)

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## Abstract

**Background:** Critically ill COVID-19 patients have a high risk for the development of candidemia due to being exposed to both well-defined classical risk factors and COVID-19-specific risk factors in ICU.

**Objectives:** In this study, we investigated the incidence of candidemia in critically COVID-19 patients, and the independent risk factors for candidemia.

**Patients/methods:** COVID-19 patients hospitalised in ICU during 1-year period (August 2020 to August 2021) were included. Clinical and laboratory characteristics of all COVID-19 patients, applied treatments, and invasive procedures that may predispose to candidemia were recorded.

**Results:** Of 1229 COVID-19 patients, 63 developed candidemia. Candidemia incidence rate was 4.4 episodes per 1000 ICU days. The most common species was *Candida albicans* (52.3%). Only 37 patients (58.7%) received antifungal therapy. The presence of central venous catheter (OR 4.7, 95% CI 1.8–12.2,  $p < .005$ ), multifocal candida colonisation (OR 2.7, 95% CI 1.4–5.2,  $p < .005$ ), a prolonged ICU stay ( $\geq 14$  days) (OR 1.9, 95% CI 1.08–3.37,  $p < .05$ ), the absence of chronic lung disease (OR 0.4, 95% CI 0.1–0.9,  $p < .05$ ) and the absence of corticosteroid use (OR 0.3, 95% CI 0.14–0.52,  $p < .0001$ ) were significantly associated with candidemia.

**Conclusions:** Our study filled the knowledge gap in the literature about the impact of COVID-19-associated risk factors for the development of candidemia. The classical risk factors for candidemia had a significant effect on candidemia, and contrary to expectations, corticosteroids had a protective effect against the development of candidemia. The results of these studies showing interesting effects of corticosteroids in critically ill COVID-19 patients should be confirmed by further studies.

## KEYWORDS

candida, candidemia, COVID-19, COVID-19 associated candidemia, incidence, risk factors

## 1 | INTRODUCTION

Candidemia is one of the most common nosocomial bloodstream infections in critically ill patients, accounting for 7%–15% of the episodes, and is associated with increased mortality, prolonged hospital

stays, and increased cost.<sup>1,2</sup> Non-neutropenic intensive care unit (ICU) patients undergoing multiple invasive procedures, and immunocompromised patients are at high risk for the development of candidemia.<sup>3,4</sup> The COVID-19 pandemic caused an increase in the number of patients who need to be followed up in ICU, creating a

great burden on the capacity of the intensive care bed and health-care services.<sup>3</sup> Approximately 5% of COVID-19 patients experience critical illness requiring follow-up in ICU where the risk of candidemia is high.<sup>3-5</sup> Additionally, ICU patients with COVID-19 have a higher incidence of candidemia resulting in higher mortality rates compared with those without COVID-19.<sup>6</sup> Therefore, considering candidemia in the early period and the initiation of appropriate treatment in patients at high risk for the development of candidemia is crucial to reducing mortality in severe COVID-19 patients.<sup>6-9</sup> In previous studies, some risk factors were defined for the development of candidemia, but almost all were performed in the pre-COVID-19 period.<sup>1,10,11</sup> Since severe COVID-19 is a disease with its different characteristics and treatment options, there may be changing or newly added risk factors for the development of candidemia. In this study, we aimed to describe the clinical characteristics of COVID-19 patients with candidemia and risk factors for the development of candidemia in COVID-19 ICU.

## 2 | PATIENTS AND METHOD

### 2.1 | Study design and participant

This retrospective study was carried out in COVID-19 ICUs of Ankara City Hospital and approved by Ankara City Hospital Ethical Committee 1. The hospital with a capacity of 3810 beds, 696 of which are intensive care beds, served as the reference pandemic centre in Ankara. We planned to collect the data about clinical characteristics of all confirmed COVID-19 cases with and without candidemia followed up in certain ICUs and to determine the risk factors for candidemia. The three COVID-19 ICUs that were visited daily by infectious disease specialists were chosen for the study. All patients over the age of 18 who were hospitalised with a definitive diagnosis of COVID-19 for 1-year period (August 15, 2020, to August 15, 2021) in the ICUs were included in the study. The definitive diagnosis of SARS-CoV-2 infection was made by reverse transcriptase polymerase chain reaction (RT-PCR), which was performed according to the protocol determined by the World Health Organization (WHO) interim guideline.<sup>12</sup> Patients requiring ICU follow-up were considered as severe COVID-19 infection because they met the criteria for severe illness according to the WHO COVID-19 disease severity classification.<sup>13</sup> In our study, the primary outcome was the development of candidemia. All intensive care patients were divided into two groups based on the presence of candidemia as patients with and without candidemia and were compared of demographic characteristics, comorbidities, and the possible risk factors for candidemia.

### 2.2 | Collecting and processing of data

In routine clinical practice, a standardised patient form is used for the follow-up of COVID-19 patients, and all clinical and laboratory features of patients, and daily changes in their clinical conditions

and administered therapies are prospectively recorded. All patients in ICUs are followed up daily by infectious disease specialists until discharge or death. This standardised patient form includes demographic characteristics (age, gender), and underlying comorbid diseases of the patients (hypertension, diabetes mellitus, coronary artery disease, cardiac failure, chronic renal disease, chronic liver disease, haemodialysis, surgical history, immunosuppression, and other diseases), laboratory and radiological test results. Infection episodes and culture results are closely monitored. Invasive procedures including central venous catheter (CVC), urinary catheter and mechanical ventilation, and their implementation duration and other risk factors for invasive candidiasis are also recorded. Concomitant bacteraemia, sepsis, total parenteral nutrition (TPN), gastrointestinal instrumentation/surgery, the use of prior antibiotics, the use of corticosteroids, and other immunosuppressive drugs are included in the form.

Data were collected retrospectively via special patient forms and the hospital automation system. The treatments given for COVID-19 and other drugs were noted in detail. Antibiotics used before the development of candidemia were recorded. Cephalosporin, piperacillin-tazobactam, anti-pseudomonal carbapenems, colistin, fosfomycin, and tigecycline were categorised as broad-spectrum antibiotics. Vancomycin, teicoplanin, and daptomycin were combined under the heading of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) therapy. Methylprednisolone (MTP) used in the treatment of severe patients was classified as low-dose (40 or 80 mg) and high dose (250–500–1000 mg). Anakinra and tocilizumab combined under the heading of anti-cytokine therapy. Time from ICU admission to documentation of candidemia was noted. The clinical outcomes (discharge or death), and length of ICU stay were also recorded into the patient's forms.

### 2.3 | Definitions

Isolation of one or more *Candida* species from at least one blood culture in a patient with findings consistent with infection was defined as candidemia. Blood culture bottles were monitored by BacT/Alert (bioMérieux) automated blood culture system during the study period. *Candida* species isolated blood culture, urine, deep tracheal aspirate, or other samples were identified at species level using VitekMS (bioMérieux) device and MALDI-TOF MS method. Candidemia incidence was calculated as the number of episodes per 1000 ICU days.

Multifocal candida colonisation, candida colonization index, and candida score were recorded in patients' forms. Detection of candida strains at least two cultures obtained from urine, oropharyngeal mucosa, deep tracheal aspirate, and skin (inguinal and/or axillary sites) were defined as multifocal candida colonisation. Candida colonization index (CCI), candida score, and clinical prediction rule were also calculated for each patient. CCI was calculated by the following formula: the ratio of the number of distinct body sites colonised by candida strains /the total number of distinct body site cultures

tested. The threshold is 0.5.<sup>11</sup> Total candida score was obtained from the following: multifocal candida colonization (1 point), surgery (1 point), TPN (1 point), and sepsis (2 points).<sup>10</sup> Variables were coded as 0 if they did not exist, and as valid points, if they did. A value of 2.5 was the threshold value for high risk for candidemia. We also used the clinical prediction rule to predict nosocomial invasive candidiasis in patients hospitalised in ICUs. The patients were classified as meeting or not meeting the rule.<sup>1</sup> The rule is defined as follows: Any systemic antibiotic (days 1–3) or presence of a CVC (days 1–3) and at least two of the following—TPN (days 1–3), any dialysis (days 1–3), any major surgery (days –7–0), pancreatitis (days –7–0), any use of steroids (days –7–3), or use of other immunosuppressive agents (days –7–0).

An increase of  $\geq 2$  points in the Sequential Organ Failure Assessment (SOFA) scoring compared to a baseline condition in a patient with suspicious or definite infection was defined as sepsis.<sup>14</sup> The chronic pulmonary disease category includes chronic obstructive disease, asthma, and interstitial lung disease.

## 2.4 | Potential risk factors

In this study, we recorded previously defined risk factors for candidemia, and possible clinical features and treatments of COVID-19 patients that may be associated with candidemia. These factors were chronic renal disease, haemodialysis, the presence of CVC, mechanical ventilation, bacteraemia, sepsis, TPN, immunosuppression, the use of corticosteroids or other immunosuppressive treatment, multifocal candida colonization, previous gastrointestinal instrumentation/surgery. COVID-19 specific factors such as low-dose or high-dose corticosteroid use, anti-cytokine treatment, and extracorporeal membrane oxygenation (ECMO) were also evaluated. Prolonged hospitalisation was considered a potential risk factor for candidemia, and a stay equal to or longer than 14 days in ICU was accepted as a prolonged ICU stay.

## 2.5 | Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics for Windows version 23.0 and R Studio 1.4.1106 and R software 4.0.4. Comparisons of candidemia groups (absent, exist) in terms of numerical variables were made by using the Mann-Whitney U test due to the violation of the parametric test assumptions. The relationship between candidemia and categorical variables was investigated using the Pearson Chi-square test when the test assumptions were satisfied. Otherwise, Fisher's Exact Test was used. Univariable and multivariate logistic regression analyses were applied to estimate the association between demographical and clinical variables and candidemia. Several independent risk factors such as CVC and use of the broad-spectrum antibiotics caused quasi-complete separation problems due to relatively imbalanced sample size (a rare event). Therefore, univariable penalised logistic regression analysis

was applied to those variables. Hence, multiple logistic regression analysis was carried out using penalised maximum likelihood estimation approach with optimal penalisation parameters using the R rms package. A  $p$ -value  $< .05$  is considered statistically significant. All variables which are significant in the univariable logistic regression analysis were considered as candidates for multivariate logistic regression analysis.

## 3 | RESULTS

Of the 1229 COVID-19 patients followed during the study period, 63 developed candidemia. The candidemia incidence rate was 4.4 episodes per 1000 ICU days, and candidemia was detected after a median of 12 days (IQR 3–16) from the first admission to ICU. The most common species were *C. albicans* (52.3%) and *C. tropicalis* (16.9%). Only 37 of candidemia cases (58.7%) had received antifungal therapy. Echinocandins, especially anidulafungin, were the most commonly used antifungal therapy in patients having documented candidemia (Table 1).

There was no difference in terms of age and gender between patients with and without candidemia ( $p > .05$  for both). At least one comorbidity was present in 82.5% of patients with candidemia and 87.1% of patients without candidemia ( $p > .05$ ). The two groups were similar in terms of comorbidities, except hypertension and chronic lung disease, which were detected to be higher in patients without candidemia than in those with candidemia ( $p < .05$  for both). Further details are presented in Table 2.

Compared with the non-candidemia group, invasive procedures were applied at a higher rate in the candidemia group. Mechanical ventilation rate was statistically higher in patients with candidemia (88.9%) than in those without candidemia (48.8%) ( $p < .001$ ). The patients with candidemia needed CVC use more frequently (95.2% vs. 48.6%,  $p < .001$ ). There was no history of gastrointestinal instrumentation/surgery and pancreatitis in both candidemia and non-candidemia cases (Table 2). ECMO was not used in any of the patients followed up.

We obtained the data upon colonization index, candida score, and clinical prediction rule from all of the patients included in the study. In our routine practice, urine, rectal swab, and blood cultures are taken from all patients admitted to the intensive care unit on the day of admission. If the patient is admitted to the ICU as intubated from another unit, deep tracheal aspirate culture is also taken. The multifocal candida colonisation rate was statistically significantly higher in patients with candidemia (52.4%) than in non-candidemia cases (8.5%) ( $p < .001$ ). Although the rate of patients with a candidemia score of 3 and above was quite low in both groups, the rate was statistically lower in the non-candidemia group (20.6% vs 10.8%,  $p < .05$ ). The clinical prediction rule for candidemia was met at a higher rate in candidemia patients ( $p < .05$ ) (Table 2).

Prior nosocomial infection and bacteraemia were more common in the candidemia cases ( $p < .001$  for all), and nearly all cases in the

**TABLE 1** *Candida* species and antifungal treatments in COVID-19 patients with candidemia

Characteristics	Distribution (n = 63)
<i>Candida</i> species (65 isolates in 63 patients)	
<i>C. albicans</i>	34 (52.3)
<i>C. parapsilosis</i>	8 (12.3)
<i>C. glabrata</i>	9 (13.8)
<i>C. tropicalis</i>	11 (16.9)
<i>C. cefyr</i>	2 (3.1)
<i>C. dubliniensis</i>	1 (1.5)
Time (days) from ICU admission to candidemia, median (IQR <sup>a</sup> )	9 (3–16)
Antifungal treatment in patients with candidemia	
Received	37 (58.7)
Not received	26 (41.3)
Number of patients received antifungal treatment for more than 4 days	25 (39.7)
Duration (days) of antifungal treatment in patients received antifungal treatment, median (IQR)	3 (0–10)
Antifungal treatment (n = 37)	
Anidulafungin	21 (56.7)
Micafungin	4 (10.8)
Caspofungin	1 (2.7)
Fluconazole	10 (27.0)
Amphotericin B	1 (2.7)

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

<sup>a</sup>IQR: Interquartile range (25% and 75%).

candidemia group received antibiotics during their hospitalisation in ICU before the documentation of candidemia (Table 2). The rates of steroid use at any dose and high doses were lower in candidemia patients ( $p < .001$  for both). The median day of ICU stay was statistically longer in the patients with candidemia ( $p < .001$ ). The 28-day mortality and overall mortality rates were statistically higher in the candidemia patients. Forty-nine (77.8%) of 63 patients with candidemia died during ICU follow-up (within the first 28-day), 24 of whom had not received any antifungal treatment yet. These patients could not receive any antifungal treatment because they were diagnosed with candidemia after their death.

In the univariate regression analysis, several variables were detected to be significantly associated with the development of candidemia. However, in multivariate regression analysis, the only presence of CVC, multifocal candida colonisation, the absence of chronic lung disease and absence of corticosteroids (at any dose) or high-dose steroid use, and a prolonged ICU stay were significantly associated with candidemia. The results of univariate and multivariate regression analysis are shown in Table 3.

## 4 | DISCUSSION

Severe COVID-19 patients are at high risk for secondary nosocomial infections including candidemia due to mostly requiring ICU follow-up. Previous studies reported an increased incidence of candidemia in critically ill COVID-19 cases.<sup>6,8,9,15</sup> Current guidelines recommend initiation of empirical antifungal therapy for candida in critically ill patients at high risk of candidemia.<sup>16,17</sup> However, the selection of

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

Characteristics Variables	All patients (n = 1229)	Candidemia		p-value
		Absent (n = 1166)	Present (n = 63)	
Age, median (IQR <sup>a</sup> )	72 (61–81)	72 (62–81)	74 (57–81)	.38
Age, equal and above 65 years	821 (66.8)	780 (66.9)	41 (65.1)	.766
Gender, male	768 (62.5)	731 (62.9)	37 (58.7)	.52
Any comorbidity	1068 (86.9)	1016 (87.1)	52 (82.5)	.29
Diabetes	397 (32.3)	379 (32.5)	18 (28.6)	.52
Hypertension	652 (53.1)	627 (53.8)	25 (39.7)	.03
Coronary artery disease <sup>b</sup>	331 (26.9)	316 (27.1)	15 (23.8)	.57
Heart failure	183 (14.9)	175 (5.0)	8 (12.7)	.62
Chronic pulmonary disease	208 (16.9)	205 (17.6)	3 (4.8)	.008
Chronic renal disease	127 (10.3)	120 (10.3)	7 (11.1)	.83
Haemodialysis	67 (5.5)	65 (5.6)	2 (3.2)	.57
Malignancy	133 (10.8)	126 (10.8)	7 (11.1)	.94
Immunosuppression	69 (5.6)	66 (5.7)	3 (4.8)	1
Cerebrovascular events	102(8.3)	98 (8.4)	4 (6.3)	.56

(continues)

TABLE 2 (Continued)

Characteristics Variables	All patients (n = 1229)	Candidemia		p-value
		Absent (n = 1166)	Present (n = 63)	
Mechanical ventilation	625 (50.9)	569 (48.8)	56 (88.9)	<.001
Duration of mechanical ventilation, median day (IQR)	5 (3–9)	5 (3–9)	5 (2–9)	.709
Sepsis	532 (43.3)	498 (42.7)	34 (54.0)	.08
Central venous catheter	627 (51.0)	567 (48.6)	60 (95.2)	<.001
Total parenteral nutrition	62 (5.0)	51 (4.4)	11 (17.5)	<.001
Gastrointestinal instrumentation or surgery	–	–	–	
Pancreatitis	–	–	–	
Presence of <i>Candida spp</i> in urine sample	178 (14.5)	153 (13.1)	25 (39.7)	<.001
Presence of <i>Candida spp</i> in DTA sample	139 (11.3)	119 (10.2)	20 (31.7)	<.001
Presence of <i>Candida spp</i> in other samples <sup>c</sup>	33 (2.7)	30 (2.6)	3 (4.8)	.24
Multifocal candida colonisation	114 (9.3)	97 (8.3)	17 (27.0)	<.001
Candida colonization index <sup>d</sup>				
<0.5	1097 (89.3)	1067 (91.5)	30 (47.6)	<.001
≥0.5	132 (10.7)	99 (8.5)	33 (52.4)	
Candida score <sup>e</sup>				
≤2 points	1089 (88.7)	1039 (89.2)	50 (79.4)	.017
≥3 points	139 (11.3)	126 (10.8)	13 (20.6)	
Positive of clinical prediction rule for candidemia <sup>f</sup>	296 (24.1)	274 (23.5)	22 (34.9)	.039
Presence of nosocomial infection	689 (56.1)	637 (54.6)	52 (82.5)	<.001
Presence of prior bacteraemia	273 (22.2)	246 (21.1)	27 (42.9)	<.001
Prior medication				
Any antibiotic	985 (80.1)	923 (79.2)	62 (98.4)	.001
Extended spectrum antibiotic <sup>g</sup>	966 (78.6)	904 (77.5)	62 (98.4)	<.001
Antifungal agent	97 (7.9)	60 (5.1)	37 (58.7)	<.001
Corticosteroid at any dose	805 (65.5)	778 (66.7)	27 (42.9)	<.001
High-doses corticosteroid <sup>h</sup>	288 (23.5)	277 (23.8)	11 (17.5)	.016
Anti-cytokine therapy <sup>i</sup>	116 (9.4)	112 (9.6)	4 (6.3)	.39
Length of stay in ICU	9 (5–14)	9 (5–14)	18 (9–36)	<.001
Overall death	611 (49.7)	565 (48.4)	51 (81.0)	<.001
28-day mortality	598 (48.6)	549 (47.1)	49 (77.8)	<.001

Note: Data are presented as n (%) unless noted otherwise. Bold values were detected to be statistically significant.

Abbreviation: DTA, Deep tracheal aspirate.

<sup>a</sup>IQR: Interquartile range (25% and 75%).

<sup>b</sup>The chronic pulmonary disease category includes chronic obstructive disease, asthma and interstitial lung disease.

<sup>c</sup>Other samples contain cerebrospinal fluid, sputum and pleural fluid.

<sup>d</sup>Candida colonization 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.

<sup>e</sup>Candida score: The total score obtained from the following: Multifocal colonisation with *Candida species* (1 point), surgery (1 point), total parenteral nutrition (1 point), sepsis (2 points). Threshold 2.5.

<sup>f</sup>A positive clinical prediction rule for candidemia: Any systemic antibiotic (days 1–3) or presence of a central venous catheter (days 1–3) and at least two of the following—total parenteral nutrition (days 1–3), any dialysis (days 1–3), any major surgery (days –7–0), pancreatitis (days –7–0), any use of steroids (days –7–3), or use of other immunosuppressive agents (days –7–0).

<sup>g</sup>Extended spectrum antibiotic includes anti-pseudomonal cephalosporins, piperacillin-tazobactam, carbapenems, fosfomycin, colistin and tigecycline.

<sup>h</sup>High-dose corticosteroid: Methylprednisolone doses of 250–500–1000 mg.

<sup>i</sup>Anti-cytokine therapy includes anakinra and tocilizumab.

TABLE 3 Multivariate logistic regression analysis of the risk factors for candidemia in COVID-19 ICU patients

Variable	Univariate				Multivariate			
	OR	95% CI L	95% CI U	p	OR	95% CI L	95% CI U	p
Age	1.0	0.98	1.01	.3791				
Age, (equal or above 65 years)	0.9	0.54	1.57	.7657				
Sex, female	1.2	0.71	1.98	.5273				
Comorbidity, at least one	0.7	0.36	1.37	.2947				
Diabetes mellitus	0.8	0.47	1.45	.5161				
Hypertension	0.6	0.34	0.95	<b>.0309</b>	0.7	0.39	1.14	.1373
Cardiac failure	0.8	0.39	1.76	.6164				
Coronary artery disease	0.8	0.46	1.52	.5666				
Chronic renal disease	1.1	0.49	2.44	.8352				
Haemodialysis	0.6	0.13	2.32	.4203				
Chronic lung disease	0.2	0.07	0.75	<b>.0150</b>	0.4	0.15	0.95	<b>.0393</b>
Malignancy	1.0	0.46	2.31	.9395				
Immunodeficiency	0.8	0.25	2.73	.7632				
History of cerebrovascular event	0.7	0.26	2.08	.5660				
Central venous catheter	19.1	6.38	57.30	<b>&lt;.0001</b>	4.7	1.83	12.17	<b>.0013</b>
Sepsis	1.6	0.95	2.62	.0812				
Total parenteral nutrition	4.6	2.28	9.39	<b>&lt;.0001</b>	1.3	0.62	2.70	.4971
Mechanical ventilation	8.4	3.79	18.57	<b>&lt;.0001</b>	2.1	0.92	4.76	.0790
Duration of mechanical ventilation	1.0	1.02	1.07	<b>.0002</b>				
Multifocal candida colonisation	4.1	2.25	7.38	<b>&lt;.0001</b>	2.7	1.41	5.21	<b>.0027</b>
Prior or concurrent nosocomial infection	3.9	2.03	7.60	<b>&lt;.0001</b>	0.9	0.45	1.95	.8541
Prior bacteraemia	2.8	1.67	4.71	<b>&lt;.0001</b>	1.3	0.70	2.22	.4523
Corticosteroid use at any dose	0.3	0.19	0.63	<b>.0005</b>	0.3	0.14	0.52	<b>&lt;.0001</b>
High-dose corticosteroid use (equal or above 250 mg)	0.4	0.21	0.86	<b>.0163</b>	0.3	0.16	0.66	<b>.0019</b>
Broad-spectrum antibiotic use	13.9	2.59	75.04	<b>.0043</b>	2.1	0.61	6.92	.2453
Narrow-spectrum antibiotic use	1.2	0.62	2.36	.5838				
Anti-cytokine treatment	0.6	0.23	1.79	.3930				
Anti-MRSA treatment	5.1	2.95	8.90	<b>&lt;.0001</b>	1.5	0.84	2.84	.1632
Length of ICU stay	1.1	1.04	1.08	<b>&lt;.0001</b>				
Length of ICU stay (equal or above 14 days)	4.9	2.88	8.23	<b>&lt;.0001</b>	1.9	1.08	3.37	<b>.0260</b>

Abbreviation: OR, Odds ratio. Bold values were detected to be statistically significant.

patients with high risk for candidemia who should be given antifungal treatment is difficult due to the broad application of known risk factors in ICUs. Additionally, considering the complex clinical characteristics of COVID-19, the empirical treatment decision becomes more difficult. There are limited data investigating the effects of classical risk factors and specific risk factors for COVID-19 together on the development of candidemia in COVID-19 patients. In the present study, we investigated the incidence of candidemia and the independent risk factors that are associated with the development of candidemia in critically ill COVID-19 patients.

This study contributes to our limited knowledge on the epidemiology of candidemia in the COVID ICU by adding some new

observational data. Firstly, data of all COVID-19 patients followed in ICU over a 1-year period was included, and the estimated incidence of candidemia was determined. The high incidence of candidemia in our study with 4.4 per 1000 ICU day supported the previous data regarding higher incidence of candidemia reported in COVID-19 studies.<sup>4,6,8,9,15</sup> Omrani et al reported candidemia incidence as 2.34 episodes per 1000 ICU days in COVID-19 patients.<sup>18</sup> Kayaaslan et al reported a 2-fold increase in the episodes of candidemia in patients with COVID-19 followed in the ICU compared to those without COVID-19 (2.16 vs 1.06 per 1000 hospital day,  $p < .001$ ) in the same or near period.<sup>6</sup> The incidence of candidemia may change according to the characteristics of units and patients, blood culture

routines (frequency, number of bottles, etc) and blood culture techniques. Nevertheless, it is clear that COVID-19 patients in ICU at high risk for the development of candidemia. Another important result of the study was that a considerable amount of the patients with candidemia had died before the detection of candidemia and had not been received any antifungal treatment. This result also highlights the need to identify risk factors for the development of candidemia in COVID-19 patients.

During ICU follow-up, COVID-19 patients are frequently exposed to many risk factors for the development of candidemia. However, COVID-19 cases may exhibit differences in risk factors for the development of candidemia compared to patients without COVID-19 due to the unique characteristics of the disease. Some risk factors, such as abdominal surgery, are less common in COVID-19 patients, while others, such as the need for mechanical ventilation and CVC, and corticosteroids use, may be more common.<sup>19</sup> A recent report comparing 64 candidemia cases with a diagnosis of COVID-19 and 187 candidemia cases without COVID-19 found that liver disease, solid organ malignancies, and previous surgery were not as common in patients with COVID-19 as in patients without COVID-19. On the other hand, mechanical ventilation, presence of CVC, corticosteroids and immunosuppressant use were more common in COVID-19 patients compared to non-COVID-19 patients.<sup>19</sup> In this study, none of the COVID-19 patients, with and without candidemia, had recent gastrointestinal surgery and an episode of pancreatitis.

The risk factors for the candidemia associated with COVID-19 may be classified as two groups, the well-established classical risk factors, and COVID-19-specific risk factors. Besides classical risk factors, COVID-19 patients are also exposed to specific risk factors such as the use of low-dose or high-dose corticosteroids, anti-cytokine treatment, and ECMO.<sup>20</sup> In this study, we evaluated the risk factors in both groups. In univariate analysis, multiple risk factors were found to be associated with candidemia, but only five of them were found as an independent risk factor in multivariate analysis. Unsurprisingly, our study showed that many of the classic risk factors have a significant effect on the development of candidemia in patients with COVID-19. In support of previous studies, the presence of CVC and multifocal candida colonisation, and prolonged ICU stay were the most significant risk factors for the development of candidemia.<sup>4,21,22</sup> In a recent meta-analysis including 34 studies performed in the pre-COVID-19 period, 29 possible risk factors for invasive *Candida* infection had been evaluated and reported that comorbid conditions and medical interventions had a significant impact in the development of invasive *Candida* infection, while demographical factors did not play a role. Candida colonisation, broad-spectrum antibiotics, CVC, blood transfusion and TPN were reported as the risk factors associated with the highest risk for invasive *Candida* infection.<sup>21</sup> Indeed, CVC is a historically well-established risk factor for candidemia, and are frequently needed in COVID-19 patients followed up in ICU.<sup>4,6,20,22</sup> Therefore, defining CVC as a risk factor is an expected result of the study.

Broad-spectrum antibiotics are frequently added to the treatment of the patients whose clinical worsening continues by the physicians following the patients, although it is well known that bacterial co-infections are rare in SARS-CoV-2 infection and that the virus can cause sepsis without any secondary infectious pathogen.<sup>6,22,23</sup> Before adding antibiotics to the standard therapy in COVID-19 patients, the risk of superinfection with *Candida spp.*, having high mortality, should be kept in the mind. Previous studies pointed out the impact of broad-spectrum antibiotic on candidemia.<sup>20,22</sup> In our study it was a possible risk factor candidemia in univariate analysis, however, it had not been detected as an independent risk factor in univariate analysis. Multifocal candida colonisation provides a strong prediction for the development of invasive candida infection.<sup>10,11,20</sup> Similarly, multifocal candida colonisation was detected as an independent risk factor for candidemia in our study.

Surprisingly, the absence of chronic lung disease and corticosteroid use were the independent risk factors for the candidemia. Previous studies have drawn attention to the beneficial effects of systemic corticosteroid use, as well as its predisposing role in the development of secondary infections such as invasive candidemia.<sup>6,20,24</sup> Kayaaslan et al reported that corticosteroid use was an independent risk factor for the mortality in the patients with candidemia. Corticosteroids were used in 36.8% of patients who died and 17.5% of those who survived.<sup>6</sup> However, the authors emphasised that their study could not investigate the predictive risk factors for the development of candidemia because of the difficulty of including COVID-19 patients without candidemia. In a recent study investigating the risk factors for candidemia associated with COVID-19, it was reported that the use of corticosteroids and tocilizumab was not an independent frequent factor for the development of candidemia.<sup>18</sup> The protective effect of corticosteroids on candidemia may be explained by the fact that their mortality-reducing effect in critically ill COVID-19 patients.<sup>25–28</sup> Corticosteroids have anti-inflammatory and immunosuppressive effect on key cells on the immune system. On the other hand, systemic corticosteroid use results in clinical improvement in critically ill COVID-19 patients, and reduce the length of hospital and ICU stay.<sup>29</sup> The reduced risk of patients' exposure to invasive medical procedures that pose a risk for the development of candidemia may be an acceptable explanation for the protective effect of corticosteroids for candidemia. Similar to the study by Omrani, anti-cytokine treatment was not found as an independent factor for candidemia.<sup>18</sup>

The independent association between the absence of chronic lung disease and candidemia is another unexpected result of our study. Chronic lung disease has been rarely reported as a predisposing factor for candidemia. Omrani et al reported that chronic lung disease was not detected as an independent factor for candidemia in COVID-19 cases.<sup>18</sup> Chronic lung disease has been identified as a predisposing factor for severe COVID-19 causing high mortality.<sup>30,31</sup> This can be explained by the paradoxical situation that COVID-19 patients with chronic lung disease with a high mortality rate do not have enough time for candidemia to occur.

The present study has a number of limitations. Firstly, the study was performed retrospectively. Therefore, we could not fully record some baseline information of the patients such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Second, due to the decision to include COVID-19 patients from the only defined ICUs, a relatively small number of patients who were diagnosed candidemia were included in the study.

In conclusion, candidemia is a highly fatal infection in ICU patients. The higher incidence of candidemia in COVID-19 patients compared to non-COVID-19 patients and the importance of early antifungal treatment in patients with high risk is emphasised from the beginning of the pandemic. However, there is limited data about the determining of independent risk factors for candidemia in this special patient population. In this study, we investigated the incidence of candidemia and the independent risk factors for its development in COVID-19 ICU patients. Our study filled the knowledge gap in the literature, especially about the impact of COVID-19 associated risk factors for the development of candidemia. We showed that the classical risk factors for candidemia such as CVC, multifocal candida colonisation, and broad-spectrum antibiotic have a significant effect on candidemia. On the other hand, contrary to expectations, corticosteroid use was found to have a protective effect against the development of candidemia. The mortality-reducing effect of corticosteroids in critically ill COVID-19 patients and providing of early improvement may result in a decrease in candidemia in COVID-19 patients followed up in ICU. Corticosteroids have highly interesting effects upon COVID-19, a newly emerged disease. The results of these studies should be confirmed by further studies.

#### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

#### AUTHOR CONTRIBUTIONS

**Betul Kaplan:** Data curation (supporting). **Gulen Donertas:** Data curation (supporting). **Ruveyda Korkmaz:** Data curation (supporting). **Zeynep Oktay:** Data curation (supporting). **Isil Ozkocak Turan:** Data curation (supporting). **Hesna Bektas:** Data curation (supporting).

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ORCID

Bircan Kayaaslan  <https://orcid.org/0000-0001-5225-8319>

#### REFERENCES

- Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis.* 2007;26(4):271-276.
- Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis.* 1998;27(4):781-788.
- Epelbaum O, Chasan R. Candidemia in the intensive care unit. *Clin Chest Med.* 2017;38(3):493-509.
- Macauley P, Epelbaum O. Epidemiology and mycology of Candidaemia in non-oncological medical intensive care unit patients in a tertiary center in the United States: overall analysis and comparison between non-COVID-19 and COVID-19 cases. *Mycoses.* 2021;64(6):634-640.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-1242.
- Kayaaslan B, Eser F, Kaya Kalem A, et al. Characteristics of candidemia in COVID-19 patients; increased incidence, earlier occurrence and higher mortality rates compared to non-COVID-19 patients. *Mycoses.* 2021;64(9):1083-1091.
- Bassetti M, Righi E, Ansaldo F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. *Intensive Care Med.* 2014;40(6):839-845.
- Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. *Mycoses.* 2021;64(2):152-156.
- Mastrangelo A, Germinario BN, Ferrante M, et al. Candidemia in COVID-19 patients: incidence and characteristics in a prospective cohort compared to historical non-COVID-19 controls. *Clin Infect Dis.* 2021;73(9):e2838-e2839.
- León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. *Crit Care Med.* 2006;34(3):730-737.
- Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Ann Surg.* 1994;220(6):751-758.
- World Health Organization. *Clinical management of COVID-19. interim guidance, 27 May 2020.* World Health Organization; 2020. <https://www.who.int/publications-detail/clinical-management-of-covid-19>. Licence CC BY-NC-SA 3.0 IGO.
- World Health Organization. Coronavirus disease (COVID-19) technical guidance: laboratory testing for 2019-nCoV in humans. 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance>. Accessed 20 December, 2021.
- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA.* 2016;315(8):801-810.
- Riche CVW, Cassol R, Pasqualotto AC. Is the frequency of candidemia increasing in COVID-19 patients receiving corticosteroids? *J Fungi (Basel).* 2020;6(4):286.
- Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021;47(11):1181-1247.
- Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1-e50.
- Omran AS, Koleri J, Ben Abid F, et al. Clinical characteristics and risk factors for COVID-19-associated Candidemia. *Med Mycol.* 2021;59(12):1262-1266.
- Seagle EE, Jackson BR, Lockhart SR, et al. The landscape of candidemia during the COVID-19 pandemic. *Clin Infect Dis.* 2021:ciab562. doi: 10.1093/cid/ciab562
- Arastehfar A, Carvalho A, Nguyen MH, et al. COVID-19-associated candidiasis (CAC): an underestimated complication in the absence of immunological predispositions? *J Fungi (Basel).* 2020;6(4):211. doi:10.3390/jof6040211



21. Thomas-Rüddel D, Schlattmann P, Pletz M, Kurzai O, Bloos F. Risk factors for invasive candida infection in critically ill patients: a systematic review and meta-analysis. *Chest*. 2021;161:345-355.
22. Guillamet CV, Vazquez R, Micek ST, Ursu O, Kollef M. Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock. *J Crit Care*. 2015;30(4):715-720.
23. McCarty T. Candidemia and severe COVID-19 - which risk factors are modifiable? *Clin Infect Dis*. 2021:ciab635.
24. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet*. 2003;362(9398):1828-1838.
25. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
26. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316.
27. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329.
28. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341.
29. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*. 2017;12(12):CD007720.
30. Güner R, Hasanoğlu İ, Kayaaslan B, et al. COVID-19 experience of the major pandemic response center in the capital: results of the pandemic's first month in Turkey. *Turk J Med Sci*. 2020;50(8):1801-1809.
31. Zheng Z, Peng F, Xu B, Zhao J, Liu H. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25.

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