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Comparison of *Candida* colonization in intensive care unit patients with and without COVID-19: First prospective cohort study from Turkey

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Abstract

Candida species are the primary cause of fungal infections in intensive care units (ICUs). Despite the increasing prevalence of *Candida*-related infections, monitoring the progression of these infections from colonization in COVID-19 ICU patients lacks sufficient information. This study aims prospectively to compare 62 COVID-19 and 60 non-COVID-19 ICU patients from admission to discharge in terms of colonization development, rates, isolated *Candida* species, risk factors, and *Candida* infections during hospitalization. A total of 1464 samples were collected at specific time intervals from various body sites [mouth, skin (axilla), rectal, and urine]. All samples were inoculated onto CHROMagar Candida and CHROMagar Candida Plus media, and isolates identified using MALDI-TOF MS. COVID-19 patients exhibited significantly higher colonization rates in oral, rectal, and urine samples compared to non-COVID-19 patients, ($p < 0.05$). Among the *Candida* species, non-albicans *Candida* was more frequently detected in COVID-19 patients, particularly in oral (75.8%–25%; $p < 0.001$) and rectal regions (74.19% – 46.66%; $p < 0.05$). Colonization with mixed *Candida* species was also more prevalent in the oropharyngeal region ($p < 0.05$). Mechanical ventilation and corticosteroid use emerged as elevated risk factors among COVID-19 patients ($p < 0.05$). Despite the colonization prevalence, both COVID-19-positive and negative patients exhibited low incidences of *Candida* infections, with rates of 9.67% (n = 6/62) and 6.67% (n = 3/60), respectively. Consequently, although *Candida* colonization rates were higher in COVID-19 ICU patients, there was no significant difference in *Candida* infection development compared to the non-COVID-19 group. However, the elevated rate of non-albicans *Candida* isolates highlights potential future infections, particularly given their intrinsic resistance in prophylactic or empirical treatments if needed. Additionally, the high rate of mixed colonization emphasizes the importance of using chromogenic media for routine evaluation.

Lay summary

This is the first prospective cohort study comparing *Candida* colonization features including species and body sites from the time of admission to the externalization in intensive care unit patients with and without COVID-19. It provides key points that can be referenced for fungal approaches in future disasters.

Key words: COVID-19, *Candida*, colonization, CHROMagar Candida Plus, intensive care unit.

Introduction

Invasive *Candida* infections, especially in patients already colonized, are becoming a leading cause of mortality.[1] The rate of colonization rises with prolonged intensive care unit (ICU) stays, medication, and exposure to catheters. Additionally, the location of colonization and colonization in multiple body regions are critical factors influencing the development and prevalence of infections. Furthermore, the extensive use of antibiotics and corticosteroids, along with damage from SARS-CoV-2, may facilitate the deep invasion of commensal yeasts into organs, leading to invasive infections.[2]

Candida species, including the multi-resistant *Candida auris*, have been responsible for ICU outbreaks during the COVID-19 pandemic, requiring colonization screening. However, the impact and cost-effectiveness of colonization follow-up through surveillance cultures for early detection of *Candida* infections in ICU patients are currently under investigation.[3] Additionally, there is an increase in the literature on infections caused by non-albicans *Candida* species, with their intrinsic resistance profiles posing challenges to effective prophylaxis and treatment strategies. Since colonization can serve as a precursor to future infections, the presence and accurate identification of non-albicans *Candida* species are crucial, particularly in specific patient groups.

During the pandemic, the intensive care demands of COVID-19 patients were notably high. Additionally, many of these patients exhibited characteristics such as the need for mechanical ventilation, corticosteroid administration, and prolonged hospitalization, making them more prone to fungal colonization and subsequent infections, as highlighted in existing literature. Despite the significant challenges associated with conducting research during a pandemic, this study is

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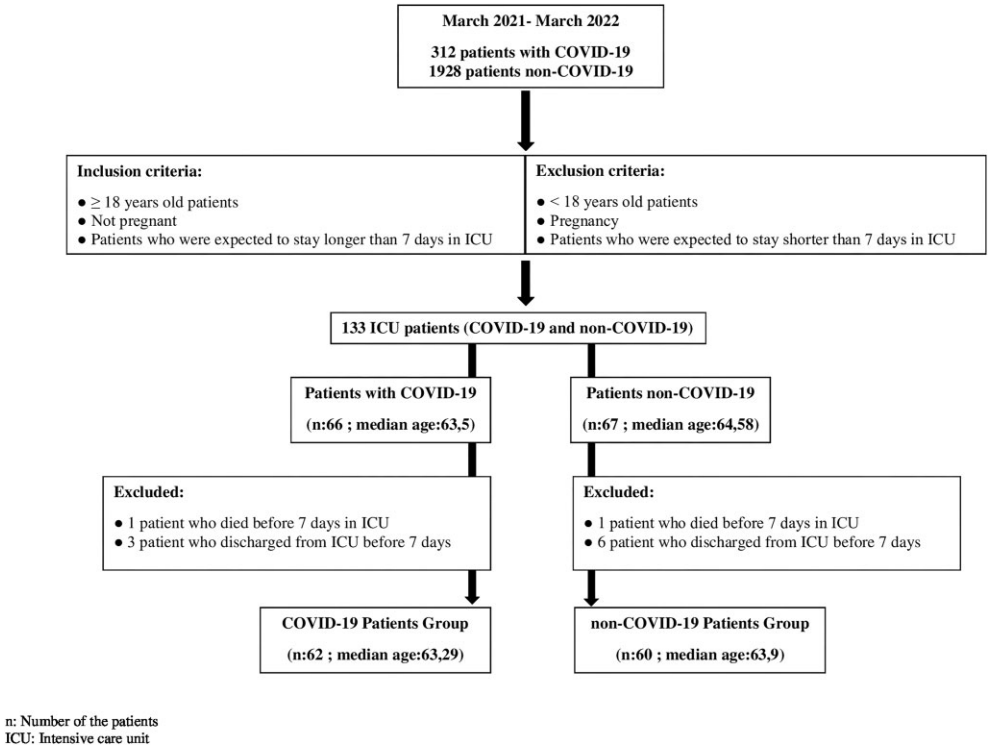

Figure 1. Flowchart of the study

crucial for providing previously unexplored information on *Candida* colonization in this patient population. It offers valuable insights into potential threats and facilitates the implementation of preventive measures for future pandemics, that may increase the need for intensive care, mechanical ventilation, and use of corticosteroid.

Currently, there is a lack of prospective studies examining *Candida* colonization rates, species epidemiology, and predisposing factors in the COVID-19-positive population. The objective of this study was to compare the dynamic colonization characteristics of *Candida* species over time in ICU patients with and without COVID-19. In addition, a new medium, CHROMagar Candida Plus was evaluated for its performance in clinical samples.

Materials and methods

Patient groups

In this prospective cohort study, changes in *Candida* colonization rates across different body regions during hospitalization were compared between COVID-19-positive and negative patients. All patients were admitted to the ICUs of Istanbul University, Istanbul Faculty of Medicine between March 2021 and March 2022. The inclusion criteria were defined as being ≥ 18 years old, not pregnant, and expected to stay in the ICU for more than seven days. Patients who died or were discharged within seven days of ICU admission were excluded from the study (Fig. 1).

The minimum required number of patients was calculated using the G - Power Software (version 3.1.9.7; Heinrich–Heine-Universitat Düsseldorf, Düsseldorf, Germany). *Candida* infection and colonization were defined according to clinical symptoms, and biochemical and microbiological findings.[4]

Sample collection

Samples were taken at certain time intervals from four different body parts of the patients [mouth, skin (axilla), rectal, and urinary region] and evaluated at the Mycology Laboratory of Istanbul University, Istanbul Faculty of Medicine, Department of Medical Microbiology.

Samples were collected on the 1st and 7th days following admission to the ICU, as well as on the day of discharge. For patients with ICU stays exceeding one month, a fourth sample was collected on the 28th day. Changes in colonization profiles from the initial day of hospitalization until the patient's discharge from the ICU were analyzed. Additional samples taken in the case of suspected infections were sent to the Department of Infectious Diseases and Clinical Microbiology of Istanbul University, Istanbul Faculty of Medicine, and/or Mycology Laboratory of Istanbul University, Department of Medical Microbiology, Istanbul Faculty of Medicine.

Culture and identification procedures

All specimens were inoculated on CHROMagar Candida media (CHROMagar, France) to detect mixed growth, and CHROMagar Candida Plus media (CHROMagar, France) to avoid missing *C. auris*. Cultures were incubated for 48 h at 35 ± 2°C under aerobic conditions and were evaluated at 24 and 48 h. All phenotypically different colonies on both media were subcultured on Sabouraud dextrose agar. The microscopic morphology of all isolates was evaluated on corn meal Tween-80 agar with the Dalmau Plate

Table 1. Distribution of patients sample counts according to body regions and time zone.

COVID-19 (n)	Region (sample type)	Time intervals					Total (n)
		1[a]	2[b]	3[c]	4[d]	5[e]	
(+) (62)	Oral (swab/tracheal aspirate)	62 (17/45)	62 (14/48)	60 (8/52)	4 (1/3)	1 (0/1)	189 (40/149)
	Axillary (swab)	62	62	60	4	1	189
	Rectal (swab)	62	62	60	4	1	189
	Urinary (urine)	62	62	60	4	1	189
(-) (60)	Oral (swab/tracheal aspirate)	60 (14/46)	60 (10/50)	56 (0/56)	1 (0/1)	0 (0/0)	177 (24/153)
	Axillary (swab)	60	60	56	1	0	177
	Rectal (swab)	60	60	56	1	0	177
	Urinary (urine)	60	60	56	1	0	177
Total (n)		488	488	464	20	4	**1464**

n: Number of the patients.
[a]1st day of hospitalization in ICU.
[b]One week after ICU admission.
[c]Discharge day from the ICU (<30 days of stay in the ICU).
[d]Discharge day from the ICU (>30 days of stay in the ICU).
[e]Discharge day from the ICU (>40 days of stay in the ICU).

Method[5] and all isolates were identified to the species level using MALDI-TOF MS (Version 4.1.80; Biotyper Bruker, Germany).

Calculation of *Candida* colonization index (CI)

The colonization index of all patients was calculated by dividing the number of culture-positive (colonized) regions by the total number of cultured regions.[6]

Statistical analyses

The IBM SPSS Statistics program (28.0 version, 2021) was used for statistical analysis and the Kolmogorov-Smirnov test was used to determine the normal distribution of the data. A comparison of *Candida* CIs between two patient groups was made using the Independent Samples *t* test. The change of colonization indices according to time was evaluated with the Paired Samples *t* test. The Chi-square (χ^2) or Fisher's Exact tests were used to compare the ratios of the variables, and values '< 0.05' were considered significant.

Results

Distribution of samples and patients' characteristics

In this study, among a total of 2240 patients (312 with COVID-19 and 1928 non-COVID-19) hospitalized in the ICU of Istanbul Medical Faculty Hospital between March 2021 and March 2022, 133 patients (67 hospitalized in the COVID-19 ICU and 66 hospitalized in other ICUs) were prospectively examined. From these 133 patients, a total of 11 patients were excluded based on the exclusion criteria and as a result, 62 COVID-19 and 60 non-COVID-19 ICU patients participated in the study (Fig. 1).

A total of 1464 samples (756 from COVID-19 patients and 708 from non-COVID-19 patients) were collected during the study from various body sites and at different times for comparison. The distribution of samples according to patient groups, body regions, and time is shown in Table 1.

Between the two groups of patients, there were no differences in terms of age, gender, sociodemographic data, and underlying diseases other than COVID-19 ($p > 0.05$) (Table 2). The average hospitalization period for patients with and without COVID-19 was 15.33 days (range: 7–42 days) and 11.90 days (range: 7–28 days), respectively. These parameters were intentionally grouped similarly to enable more accurate comparison.

During the study time bloodstream infections due to *Candida* developed in only two patients (one with COVID-19 and one without COVID-19), urinary tract infections in seven patients (five with COVID-19 and two without COVID-19), and wound infection in one COVID-19-positive patient. Details regarding the risk factors, antifungal therapies, colonization features, and infections are provided in Tables 3 and 4.

In patients with COVID-19, mechanical ventilation and corticosteroid use were significantly more prevalent risk factors ($p < 0.001$), whereas in the non-COVID-19 group, the frequency of abdominal surgery was significantly higher ($p = 0.002$).

Distribution of *Candida* species detected in cultures according to the patient groups and colonized regions

A total of 1464 samples were examined, and 471 fungal isolates were detected from the mycological cultures. During the time in the ICU, patients with COVID-19 (91.23%, 57/62) were found significantly higher colonized compared to non-COVID-19 patients (68.33%, 41/60) ($p < 0.05$). When examined separately by region, patients with COVID-19 were found to be more commonly colonized in the oropharyngeal region (64.51%, 40/62 and 30%, 18/60; $p < 0.001$), urinary tract (66.13%, 41/62 and 25%, 15/60; $p < 0.001$), and rectal region (75.8%, 47/62 and 53.33%, 32/60; $p = 0.009$) compared to non-COVID-19 patients. *Candida* colonization was not detected in the axillary region in either group.

According to *Candida* species isolated from the colonization regions were evaluated, *Candida albicans* was determined to be the most frequently detected species in all regions in both groups (42.25%, 199/471), and no difference was observed between the two groups. Additionally, non-albicans *Candida* isolates were notably more commonly found in the oropharyngeal and rectal regions of COVID-19 patients. According to examination of non-albicans *Candida* species, *C. glabrata* was the most frequently isolated species in both groups (24.2%, 114/471), followed by *C. kefyr* (11.8%, 56/471), *C. tropicalis* (11.25% 53/471), *C. krusei* (2.76%, 13/471), *C. lusitaniae* (2.12%, 10/471), and *C. parapsilosis* (1.27%, 6/471). The distribution of *Candida* species colo-

Table 2. Distribution of sociodemographic data, underlying diseases, and risk factors for *Candida* colonization in patients with and without COVID-19.

Patient characteristics	COVID-19 (n:62)	Non-COVID-19 (n:60)	p-values
Male/female (%)	37/25 (59.7/40.3)	36/24 (60/40)	0.96
Median age (min–max)	63.29 (23–94)	63.9 (22–93)	0.82
Smoking n (%)	54 (87.1)	42 (70)	0.33
Average days of hospitalization in the intensive care unit (min–max)	15.33 (7–42)	11.90 (7–28)	0.08
Mortality rate (%)	32.25	30.26	0.99
Underlying diseases n (%)			
• Pulmonary disease (except COVID-19)	19 (30.6)	23 (38.3)	0.37
• Cardiovascular disease	48 (77.4)	40 (66.6)	0.18
• Kidney failure	11 (17.7)	17 (28.3)	0.16
• Liver failure	3 (4.8)	5 (8.3)	0.48
• Trauma	0	1 (1.6)	0.49
• Burn	0	0	–
• Diabetes mellitus	28 (45.1)	19 (31.6)	0.12
• Malignancies	9 (14.5)	15 (25)	0.14
Solid organ	5 (8)	12 (20)	0 .06
Hematological	4 (6.4)	3 (5)	0.51
• Transplantation	1 (1.6)	0	0.50
Bone marrow transplantation	0	0	–
Solid organ transplantation	1 (1.6)	0	0.50
• Abdominal surgery	2 (3.2)	13 (21.6)	**0.002**
Risk factors for *Candida* colonization n (%)			
• Presence of peripheral venous catheter	62 (100)	60 (100)	–
• Presence of central venous catheter	43 (69.3)	32 (53.3)	0.06
• Presence of surgical drain	2 (3.2)	14 (23.3)	**0.001**
• ECMO*	5 (8)	0	0.06
• Mechanical ventilation	55 (88.7)	26 (43.3)	**<0.001**
• Enteral nutrition (Nasogastric tube)	62 (100)	56 (93.3)	0.06
• Total parenteral nutrition	0	4 (6.6)	0.06
• Use of broad-spectrum antibiotics	62 (100)	59 (98.3)	0.49
• Antifungal use	8 (12.9)	15 (25)	0.44
• Corticosteroid use	56 (90.3)	10 (16.6)	**<0.001**

*Extracorporeal membrane oxygenation.

nization according to regions and patients' COVID-19 status is shown in Table 5.

All of pathogens of *Candida* infections that developed during hospitalization were same species detected from colonization screening cultures. Furthermore, it was noteworthy that, in a patient who developed candidemia due to mixed-type *Candida*, in previous screening samples mixed-type *Candida* of same species had also been isolated (Tables 3 and 4).

During the study, colonization rates and CI values were calculated at least three times, covering the ICU admission days, one week later, and discharge days for patients. Colonization percentages tended to increase in both groups during the hospitalization period but peaked at different times for each group. In COVID-19 patients, colonization rates during hospitalization were found to be 67.74% in the first samples, 79.03% in the second samples, and 75.40% in the third samples. By the way in the non-COVID-19 group, these rates were 40%, 50%, and 77.77%, respectively. While COVID-19 patients reached their highest colonization rate in the second week, non-COVID-19 patients observed their peak in the third week. CI values of these patients were also calculated during same time intervals. CIs were found to be significantly higher at all three sample collection periods in patients with COVID-19 compared to those without COVID-19 [0.24–0.12 ($p < 0.001$), 0.31–0.18 ($p = 0.002$), 0.3–0.17 ($p = 0.004$), respectively]. In all patients from both groups, CIs increased significantly from the first to the seventh day in the ICU ($p < 0.05$). However, after the seventh day, there was no significant difference found until the time of their discharge from the ICU ($p > 0.05$).

Discussion

This study constitutes the first prospective data on *Candida* colonization rates of patients in the COVID-19 ICU obtained by evaluating samples from different body regions at certain time intervals. The main finding of this study was that ICU patients with COVID-19 were found more prone to *Candida* colonization than non-COVID-19 ICU patients. We also observed that non-albicans *Candida* isolates constitute an important part of this colonization. Since there is no prospective study on this subject, these data were compared with findings reported from retrospective studies with COVID-19-positive patients.

In previous studies, the prevalence of *Candida* colonization in ICU patients was reported to be between 20% and 40%.[7] In our study, these rates were found to be 91.23% (57/62) in COVID-19 patients and 68.33% (41/60) in non-COVID-19 patients, which were higher than previous reports. Although the rectal regions were found as the most commonly colonized regions of the body with *Candida* species in both groups, in terms of non-albicans *Candida* presence, COVID-19 patients were more commonly colonized in the oropharyngeal region (75.8%, 47/62), while non-COVID patients were more commonly colonized in the rectal region (46.66%, 28/60). This trend could be associated with the higher frequency of mechanical ventilation and corticosteroid use, which were significantly more common in COVID-19 patients, leading to increased respiratory tract colonization; whereas in non-COVID-19 patients, it could be related to the higher frequency of abdominal surgical procedures. This situation shows that COVID-19 itself may be considered an indirect risk factor,

Table 3. Characteristics of COVID-19 ICU patients with *Candida* infections.

Patient no.	Antifungal used during the hospitalization in ICU	Reason for antifungal use (agent)	Colonized regions and *Candida* species				Underlying additional diseases	Risk factors for *Candida* colonization
			Oropharyngeal	Rectal	Urinary	Axillary		
1	Fluconazole	Urinary tract infection (***C. albicans***) Colonization index: 0.75	***C. albicans***, *C. kefyr*, *C. inconspicua*	***C. albicans***, *C. kefyr*, *C. lambica*, *C. guilliermondii*	***C. albicans***	–	–	Peripheral venous catheter, Mechanical ventilation, Urinary catheter, Nasogastric tube, Corticosteroid use, Use of broad-spectrum antibiotics
2	Caspofungin	Urinary tract infection (***C. albicans***) Colonization index: 0.75	***C. albicans***, *C. glabrata*	***C. albicans***, *C. glabrata*	***C. albicans***, *C. glabrata*	–	Cardiovascular disease	Peripheral venous catheter, Central venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Nasogastric tube, Mechanical ventilation, Corticosteroid use
3	Fluconazole	Urinary tract infection (***C. albicans***) Colonization index: 0.75	*C. inconspicua*	***C. albicans***, *C. glabrata*	***C. albicans***, *C. inconspicua*	–	Cardiovascular disease, Diabetes mellitus	Peripheral venous catheter, Central venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Corticosteroid use
4	Amphotericin B, fluconazole	Septicemia (***C. glabrata*** and ***C. albicans***) Colonization index: 0.75	***C. glabrata***, ***C. albicans***	***C. glabrata***, ***C. albicans***	***C. glabrata***,***C. albicans***	–	Cardiovascular disease	Peripheral venous catheter, Central venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Corticosteroid use, Nasogastric tube, Abdominal surgery, Surgical drain
5	Caspofungin	Urinary tract infection (***C. albicans***) Colonization index: 0.75	***C. albicans***, *C. glabrata*	***C. albicans***, *C. glabrata* , *C. kefyr*	***C. albicans***, *C. glabrata*	–	Diabetes mellitus, Kidney failure	Peripheral venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Corticosteroid use
6	Caspofungin	Urinary tract infection (***C. albicans***) Colonization index: 0.5	***C. albicans***	–	***C. albicans***	–	Diabetes mellitus	Peripheral venous catheter, Central venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Corticosteroid use

Table 4. Characteristics of non-COVID-19 ICU patients with *Candida* infections.

Patient no.	Antifungal used during the hospitalization in ICU	Reason for antifungal use (Agent)	Colonized regions and *Candida* species				Underlying additional diseases	Risk factors for *Candida* colonization
			Oropharyngeal	Rectal	Urinary	Axillary		
1	Fluconazole, caspofungin	Septicemia after discharge from ICU (***C. albicans***) Colonization index: 0.75	***C. albicans***, *C. kefyr*	***C. albicans***	***C. albicans***	–	Cardiovascular disease	Peripheral venous catheter, Central venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Abdominal surgery, Surgical drain
2	Fluconazole, caspofungin	Wound site infection (***C. albicans***) Colonization index: 0.5	***C. albicans***	***C. albicans***	–	–	Solid organ malignancy, Kidney failure	Peripheral venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Abdominal surgery, Surgical drain
	Caspofungin	Urinary tract infection (***C. albicans***) Colonization index: 0.5	*C. glabrata*	***C. albicans***, *C. glabrata*	–	–	Solid organ malignancy, Diabetes mellitus, Liver failure	Peripheral venous catheter, Use of broad-spectrum antibiotics, Urinary catheter, Mechanical ventilation, Nasogastric tube, Abdominal surgery, Surgical drain

Table 5. Distribution of *Candida* colonization according to regions and patients' COVID-19 status.

Candida species	Oropharyngeal region			Rectal region			Urinary region		
	COVID-19 (+) (62 patients) n (%)	COVID-19 (-) (60 patients) n (%)	p- values	COVID-19 (+) (62 patients) n (%)	COVID-19 (-) (60 patients) n (%)	p-values	COVID-19 (+) (62 patients) n (%)	COVID-19 (-) (60 patients) n (%)	p-values
C. albicans	17 (27.42)	10 (16.66)	0.153	27 (43.54)	23 (38.33)	0.585	11 (17.74)	11 (18.33)	0.932
Non-albicans *Candida*	47 (75.8)	15 (25)	**< 0.001**	46 (74.19)	28 (46.66)	**0.003**	15 (24.19)	11 (18.33)	0.429
C. glabrata	14 (22.58)	4 (6.66)	0.013	19 (30.64)	14 (23.33)	0.36	7 (11.29)	4 (6.66)	0.53
C. kefyr	11 (17.74)	5 (8.33)	0.124	9 (14.51)	4 (6.66)	0.24	2 (3.22)	0	–
C. tropicalis	6 (9.67)	5 (8.33)	0.796	7 (11.29)	4 (6.66)	0.53	4 (6.45)	1 (1.66)	0.36
C. inconspicua	4 (6.45)	1 (1.66)	0.381	1 (1.61)	0	–	1 (1.61)	0	–
C. lambica	3 (4,83)	0	–	2 (3.22)	0	–	0	2 (3.22)	–
C. guilliermondii	3 (4,83)	0	–	0	1 (1.66)	–	0	1 (1.66)	–
C. krusei	2 (3,22)	0	–	3 (4.83)	2 (3.33)	1	0	1 (1.66)	–
C. lusitaniae	2 (3,22)	0	–	1 (1.61)	2 (3.33)	0.61	0	1 (1.66)	–
C. parapsilosis	1 (1.61)	0	–	3 (4.83)	1 (1.66)	0.62	0	1 (1.66)	–
C. norvegensis	1 (1.61)	0	–	1 (1.61)	0	–	1 (1.61)	0	–

n: Number of colonized patients.

as mechanical ventilation and corticosteroid use, which are consequences of COVID-19 presence, contribute to increased colonization. Previous studies have also indicated that while mechanical ventilation may be one of the causes of colonization in the oropharyngeal region,[8–13] immune dysfunction and lung epithelial cell destruction by COVID-19[14] also make ICU patients more susceptible to fungal colonization and infection. This sheds light on the risk factors that should be focused on the spreading of new possible pathogens that affect the respiratory tract and increase the need for intensive care in the future. On the other hand, the higher frequency of surgical procedures in non-COVID patients may be associated with the observation of a longer-term ICU stay targeted in the study. Since the inclusion criteria of our study required a minimum ICU stay of seven days, this duration of hospitalization could only be achieved with non-COVID patients who had undergone major surgeries.

Despite the presence of high colonization rates and various risk factors, the rate of *Candida* infection development remained low in both groups in our study. Among these infections, candidemia occurred in only one patient each from both groups (1.61% in COVID-19, 1.67% in non-COVID-19). These rates are lower than those reported in different studies (2.5%-14%)[15–19] and even lower than the study conducted in the same ICU in the pre-pandemic period (9%).[20] However, the low infection rates were consistent with the low Cl values observed in the study. The Cl is valuable as it provides preliminary information about patients' future infections. On the other hand, although the CI values were not high enough to warn the development of infection in both groups (<0.5), they were significantly higher in the COVID-19 group at all three calculated periods. Additionally, since the CI values increased with the prolongation of the length of stay in the ICU in both groups, further long-term follow-up of these patients may be beneficial to better understand the impact of significant differences in colonization indices on infection development.

Candida albicans was the most commonly isolated species in both groups, as a colonizing and infectious agent, in this and other studies.[9,15,20–24] Moreover, there has been an observed increase in the prevalence of non-albicans *Candida* species in recent times, a trend that was also noted in our study.[25–27] The rates of *Candida* infections caused by non-albicans *Candida* species, including *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. dubliniensis*, and *C. auris*, isolated from patients with COVID-19 during the pandemic period vary according to the country and hospital.[25–28] Among non-albicans *Candida* species, *C. glabrata* has been reported more frequently in bloodstream infections.[29,30] Additionally, candidemia data from six different centers in Turkey over six years (2011–2016) showed that, after *C. albicans*, *C. parapsilosis* (29.01%), and *C. glabrata* (10.1%) were the predominant species isolated from ICU patients.[31] Species-level identification is emphasized in many studies to guide antifungal therapy, as non-albicans *Candida* species may exhibit higher resistance to antifungals than *C. albicans*, leading to treatment difficulties and failures.[32] *C. glabrata* (with decreased sensitivity to amphotericin B and azole resistance of 15%–25%), *C. tropicalis* (with increased resistance to azoles ranging from 1% to 20%, and in some regions up to 40%–80%) and *C. parapsilosis* (with increased minimum inhibitory concentrations values for echinocandins, occurring in 10% of frequently isolated cases),[33] which were all mentioned in the last World Health Organization (WHO) fungal priority pathogens list.[34] At this point, special atten-

tion should be paid to *C. auris* due to its high resistance to antifungals, and its ability to cause outbreaks in ICUs.[16] *C. auris* is more commonly colonized in patients' axillary and inguinal regions. Therefore, in this study, samples from axillary regions were included, and additionally, we used the novel chromogenic medium CHROMagar Candida Plus for the first time in Turkey, which is a new selective medium for *C. auris*.[35] However, *C. auris* was not detected in the specimens from both groups.

In this study, in both groups, *C. albicans*–*C. glabrata* and *C. albicans*–*C. krusei* were the most and second most frequently isolated *Candida* species, respectively, in mixed colonizations. In many publications, *C. albicans* and *C. glabrata* were reported to be the two most commonly isolated species in mixed *Candida* infections.[36, 37] There may be a synergy or other interaction between these two *Candida* species, and this issue needs to be clarified with further studies.

The data obtained in these studies will help to reveal new awareness of the treatment approach of these patients in future pandemics likely to occur with mutated isolates. On the other hand, the low rate of candidemia detected in both groups questions the necessity of routine colonization screening, which may cause high costs. In addition, the high colonization rates with mixed *Candida* species necessitate the use of chromogenic media. Early detection and identification of *C. auris* to prevent outbreaks in ICUs is important. However, *C.auris* was not detected in our study indicating that routine screening for this species is not required in our centre.

The low rate of candidemia obtained in our study is pleasing. This situation can be explained by the fact that during the pandemic the number of patients per nurse in our hospital is limited to two and attention is paid to hygiene conditions. However, whether the intense colonization rates detected especially in patients with COVID-19, will lead to additional pathologies in the future, should be determined by long-term studies. There is no prospective study comparing *Candida* colonization of ICU patients with and without COVID-19 during the pandemic period. The reason for this lack may be the fear of disease transmission and the risk of 'cross-contamination' during the collection of patient samples. This study presents the first prospective data on this subject.

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Author contributions

Ilvana Çaklovica Küçükkaya (Data curation, Formal analysis, Methodology, Visualization, Writing – original draft), Günseli Orhun (Data curation, Methodology), Arif Atahan Çağatay (Data curation, Methodology), Sadık Kalaycı (Methodology), Figen Esen (Data curation, Methodology), Fikrettin Şahin (Methodology), Ali Ağaçfidan (Methodology), and Zayre Erturan (Conceptualization, Methodology, Supervision, Writing – original draft)

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Declaration of interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was approved by Istanbul University Istanbul Medical Faculty Ethics Committee on 05.03.2021 and numbered 06 (Number: E-29624016-050.99-149335).

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