IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

OXFORD

Candidemia Among Coronavirus Disease 2019 Patients in Turkey Admitted to Intensive Care Units: A Retrospective Multicenter Study

Amir Arastehfar,[1,a] Nevzat Ünal,[2,a] Tuğrul Hoşbul,[3] Muhammed Alper Özarslan,[4] Ayşe Sultan Karakoyun,[5] Furkan Polat,[4] Diego Fuentes,[6,7] Ramazan Gümral,[3] Tuba Turunç,[8] Farnaz Daneshnia,[1] David S. Perlin,[1] Cornelia Lass-Flörl,[9] Toni Gabaldón,[6,7,10,11] Macit Ilkit[5] and M. Hong Nguyen[12]

[1]Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, New Jersey, USA, [2]University of Health Sciences, Adana City Training and Research Hospital, Laboratory of Medical Microbiology, Adana, Turkey, [3]Department of Microbiology, Gulhane Training and Research Hospital, University of Health Sciences, Ankara, Turkey, [4]Department of Microbiology, Faculty of Medicine, Ege University, Izmir, Turkey, [5]Division of Mycology, Faculty of Medicine, Çukurova University, Adana, Turkey, [6]Life Sciences Programme, Supercomputing Center (BSC-CNS), Barcelona, Spain, [7]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona, Spain, [8]University of Health Sciences, Adana Faculty of Medicine, Adana City Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Adana, Turkey, [9]Division of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria, [10]Catalan Institution for Research and Advanced Studies, Barcelona, Spain, [11]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Barcelona, Spain, [12]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Background. We evaluated the epidemiology of candidemia among coronavirus disease 2019 (COVID-19) patients admitted to intensive care units (ICUs).

Methods. We conducted a retrospective multicenter study in Turkey between April and December 2020.

Results. Twenty-eight of 148 enrolled patients developed candidemia, yielding an incidence of 19% and incidence rate of 14/1000 patient-days. The probability of acquiring candidemia at 10, 20, and 30 days of ICU admission was 6%, 26%, and 50%, respectively. More than 80% of patients received antibiotics, corticosteroid, and mechanical ventilation. Receipt of a carbapenem (odds ratio [OR] = 6.0, 95% confidence interval [CI] = 1.6–22.3, $P = .008$), central venous catheter (OR = 4.3, 95% CI = 1.3–14.2, $P = .02$), and bacteremia preceding candidemia (OR = 6.6, 95% CI = 2.1–20.1, $P = .001$) were independent risk factors for candidemia. The mortality rate did not differ between patients with and without candidemia. Age (OR = 1.05, 95% CI = 1.01–1.09, $P = .02$) and mechanical ventilation (OR = 61, 95% CI = 15.8–234.9, $P < .0001$) were independent risk factors for death. *Candida albicans* was the most prevalent species overall. In Izmir, *Candida parapsilosis* accounted for 50% (2 of 4) of candidemia. Both *C parapsilosis* isolates were fluconazole nonsusceptible, harbored Erg11-Y132F mutation, and were clonal based on whole-genome sequencing. The 2 infected patients resided in ICUs with ongoing outbreaks due to fluconazole-resistant *C parapsilosis*.

Conclusions. Physicians should be aware of the elevated risk for candidemia among patients with COVID-19 who require ICU care. Prolonged ICU exposure and ICU practices rendered to COVID-19 patients are important contributing factors to candidemia. Emphasis should be placed on (1) heightened infection control in the ICU and (2) developing antibiotic stewardship strategies to reduce irrational antimicrobial therapy.

Keywords. bacteremia; candidemia; COVID-19; fluconazole resistance; infection control.

Invasive fungal infections, especially those due to *Candida* spp, are associated with huge economical burdens and high mortality rate [1]. Furthermore, emergence of drug-resistant *Candida* species, such as *Candida auris*, *Candida parapsilosis*, and *Candida glabrata*, imposes a growing threat due to limited options of antifungal therapy [2]. The classic risk factors associated with candidemia include leukopenia, chronic renal failure, abdominal surgery, intensive care unit (ICU) stay, central venous catheters (CVCs), mechanical ventilation, and long-term use of corticosteroids [3]. Most recently, the coronavirus disease 2019 (COVID-19) pandemic has predisposed millions of patients to secondary infections, including fungal infections [4–7]. Indeed, an increased incidence of candidemia associated with COVID-19 and its associated high mortality rate has been reported [8–10]. Recent outbreaks due to multidrug-resistant *C auris* have also been noted in some centers [11, 12]. How COVID-19 patients are at risk for *Candida* infections is not fully understood. The reasons may be multifactorial, including immune dysregulation and organ damage resulting from severe acute respiratory syndrome coronavirus 2, acquired immunodeficiency state stemming from immunomodulatory agents administered to treat severe cases of COVID-19, and breach in standard healthcare practices of infection prevention and antibiotic stewardship [13].

To provide a further insight into candidemia associated with COVID-19, we conducted a multicenter study in Turkey to assess the incidence rate and cumulative risk of ICU-acquired candidemia, identify factors predisposing to candidemia, and evaluate the risk factors for mortality.

MATERIALS AND METHODS

Patients
This retrospective study was conducted at 3 hospitals in Turkey (Adana City Hospital, Adana; Ege University Medical Faculty Hospital, Izmir; and Gülhane Training and Research Hospital, Ankara). From April through December 2020, all patients with COVID-19 admitted to the participating ICUs were included in the study.

Definitions
Candidemia was defined as positive blood culture for *Candida* species. *Candida* isolates were speciated using matrix-assisted laser desorption ionization-time of flight mass spectrometry at individual centers; however, antifungal susceptibility was not performed as per standard of care. For this study, susceptibility testing was performed in accordance with Clinical and Laboratory Standards Institute (CLSI) M60-A3 [14], and nonsusceptibility to azole agents was defined according to CLSI breakpoints [4, 7, 14, 15]. Immunosuppressed was defined as presence of an active malignancy or immunocompromised state (primary or secondary due to human immunodeficiency virus, hematopoetic stem cell or solid organ transplant, receipt of corticosteroid or other immunosuppressed agents, including biologics). Because steroid was administered to almost all patients in this study, we only included patients receiving steroid (>20 mg prednisone-equivalent daily for >10 days) before COVID-19 diagnosis in the definition.

Data Collection
We reviewed patients' electronic medical records and collected demographic characteristics and underlying medical conditions. Established risk factors for candidemia from published studies were also collected, including the presence CVCs (and their duration), mechanical ventilation, renal replacement therapy, and use of antibacterial agents [3, 16]. Data on bacterial blood stream infections were also included.

ERG11 Sequencing
Fluconazole-resistant *C parapsilosis* isolates were subjected to *ERG11* Sanger sequencing using primers and polymerase chain reaction conditions reported elsewhere [17].

Whole-Genome Sequencing
The genomes of 2 *C parapsilosis* isolates from Izmir Hospital (isolates 35 and 37) underwent Illumina whole genome-sequencing (WGS) using NovaSeq 6000 [18]. Eight previously sequenced *C parapsilosis* isolates, including 2 clonal pairs recovered from the same patient, were included in the analysis of genomic variants for comparison [19, 20]. Single-nucleotide polymorphisms (SNPs) were identified using Freebayes [21] as implemented within the PerSVade version 0.10 pipeline [18]. The genome CDR-317 was used as reference. A multiple correspondence analysis was performed as previously described [19].

Statistical Analysis
Data analyses were conducted using Stata/SE v16.1 (StataCorp LLC, College Station, TX) and GraphPad Prism, version 8.0 (GraphPad Software). Comparisons between 2 groups (candidemia versus no candidemia, and dead versus alive) were performed by Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Variables significant by univariate analysis ($P \le .05$) were entered into a backward elimination in logistic regression model to determine independent risk factors for candidemia or death. Kaplan-Meier curves were used to estimate candidemia-free survival and overall survival, and a log-rank test was used to compare curves between groups. Significance was defined as $P \le .05$ (2-tailed).

Patient Consent Statement
The study protocol was first approved by the Ministry of Health of Turkey and then by the local ethical committees of each center (Adana City Hospital [No. 78/1362], Gülhane Training and Research Hospital [No. 2021/164], and Ege University Hospital [No. 21-6.1T/60]). The study protocol conforms to standards currently applied in Turkey. Due to retrospective nature of the study, it does not include factors necessitating patient consent.

RESULTS

Over the study period, 148 patients were admitted to the ICU (Adana City Hospital, 99 patients; Ege University Hospital, 24 patients; and Gülhane Hospital, 25 patients). Demographics and underlying diseases are presented in Table 1. Twenty-eight COVID-19 patients developed candidemia, yielding a candidemic rate of 19%. This rate was 13-fold higher than the rate of patients without COVID-19 admitted to the ICU in the same study period (1.5%) (Table 2). The probability of acquiring candidemia among COVID-19 patients within 10 days of ICU admission was 6%, but this rate increased to 26% at 20 days and 50% at 30 days (Figure 1). The median duration from hospital admission for COVID-19 to ICU admission was 20 days (interquartile range [IQR], 12–28 days), and from ICU admission to candidemia was 12 days (IQR, 8–18 days) (Figure 1).

Candida albicans was the most common species recovered (43%, 12 of 28), followed by *C parapsilosis* (25%, 7 of 28), *C tropicalis* (21%, 6 of 28), and *C glabrata*, *Candida krusei*, and *Candida lusitaniae* (4%, 1 each) (Supplemental Figure 1 and Supplemental Table 1). Forty-three percent (3 of 7) of *C*

Table 1. Demographics, Clinical Characteristics, and Factors Associated With Candidemia Among COVID-19 Patients

Characteristics	All Patients (n = 148)	Candidemia (n = 28)	No Candidemia (n = 120)	Univariate Analysis P Values	Logistic Regression no. 1 — P Values / Odds Ratio (95% CI)	Logistic Regression no. 2 — P Values / Odds Ratio (95% CI)
Demographics and Underlying Diseases						
Age in years, median (IQR)	68 (60–76)	65 (50–73)	70 (60–78)	.13		
Male sex	65% (96)	75% (21)	62% (75)	.77		
Cerebrovascular accident	2% (3)	7% (2)	0.8% (1)	.09		
Cardiovascular disease	19% (28)	18% (5)	19% (23)	1.0		
Chronic lung disease	20% (29)	25% (7)	18% (22)	.32		
Chronic intestinal disease	6% (9)	14% (4)	4% (5)	.07		
Chronic liver disease	2% (3)	0%	3% (3)	1.0		
Chronic kidney disease	19% (28)	14% (4)	20% (24)	.60		
Solid organ malignancy	13% (19)	21% (6)	11% (13)	.20		
Hematologic malignancy	3% (5)	7% (2)	3% (3)	.24		
Immunocompromised status	18% (26)	32% (9)	14% (17)	.049		.75
Hypertension	51% (75)	39% (11)	53% (64)	.21		
Diabetes mellitus	35% (52)	21% (6)	38% (46)	.12		
No known underlying disease	11% (17)	7% (2)	12% (15)	.53		
Events Occurred While Inpatient						
Receipt of any antimicrobial agent	99% (147)	100% (28)	99% (119)	1.0		
Fluoroquinolones	70% (103)	75% (21)	68% (82)	.65		
Carbapenems[a]	68% (100)	86% (24)	63% (76)	.025	.008 / 6.0 (1.61–22.3)	.02 / 6.2 (1.4–28.1)
Anti-pseudomonal agents (β-lactam, monobactam or carbapenem)	78% (114)	67% (18)	80% (96)	.20		
β-lactam agents without anti-pseudomonal coverage	12% (17)	4% (1)	13% (16)	.31		
Glycopeptide/oxazolidinone/cyclic lipopeptide class	49% (72)	54% (14)	48% (58)	.67		
Polymyxin class	22% (32)	31% (8)	20% (24)	.29		
Receipt of corticosteroid	84% (125)	71% (20)	88% (105)	.045		
Presence of central venous catheter.	53% (78)	86% (24)	45% (54)	<.0001	.017 / 4.3 (1.3–14.2)	.11
Duration of central venous catheter, days (median, IQR)	11 days (5–18)	18.5 days (10–25)	8 days (4–15)	.0001		
Requirement for mechanical intubation	84% (125)	89% (25)	83% (100)	.57		
Shock requiring pressor support	70% (104)	75% (21)	69% (83)	.422		
Bacteremia						
Preceding bacteremia[b]	26% (39)	71% (20)	16% (19)	<.0001	.001 / 6.6 (2.1–20.1)	
Preceding bacteremia due to coagulase-negative *Staphylococcus*	15% (24)	50% (14)	9% (11)	0.0001		<.0001 / 13.5 (3.3–55.3)
Preceding bacteremia due to *Acinetobacter baumannii* complex	9% (13)	39% (11)	2% (2)	<.0001		<.0001 / 48.1 (5.9–391.0)

Abbreviations: CI, confidence interval; IQR, interquartile range.

[a]Among patients receiving carbapenem, all received meropenem; 2 patients received both meropenem and ertapenem but at different times.

[b]Please refer to Supplemental Figure 2 for enumeration of specific bacteria responsible for bloodstream infections among patients with and without bacteremia.

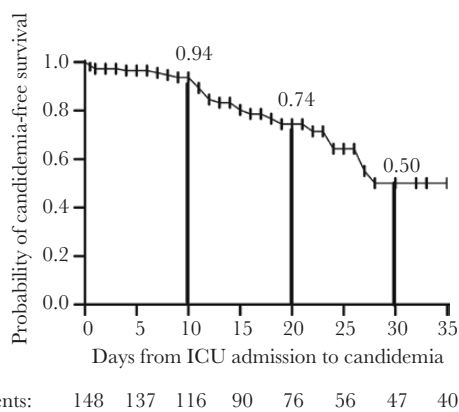**Table 2. Characteristics of Centers Participated in the Current Study**

Characteristics	Adana City Hospital	Ege University Medical Faculty Hospital, Izmir	Gulhane Training and Research Hospital, Ankara
Number of hospital beds	1550	1800	1350
Number of ICU beds	310	322	140
Number of candidemia cases before and after COVID-19 periods[a]	135 and 246	131 and 148	75 and 90
Rate of candidemia before and after COVID-19 periods[a]	3.4% and 19.2%	1.1% and 16.7%	1.5% and 17.9%
Mortality rates of patients with candidemia before and after COVID-19 periods[a]	59% and 95%	42% and 50%	49% and 80%

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.
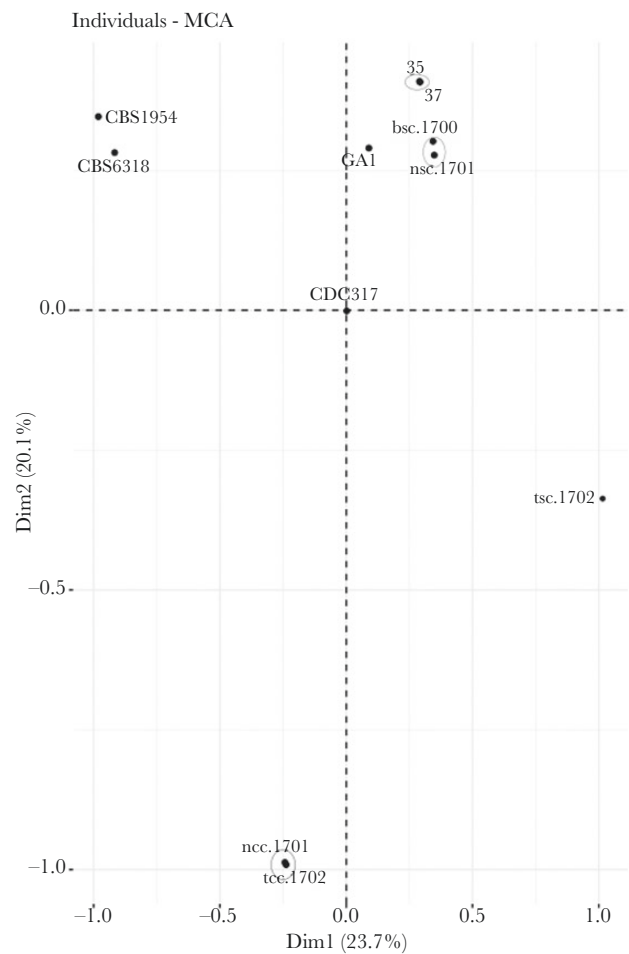
[a]The timeline before COVID-19 period was between January 1, 2019 and December 31, 2019, and during COVID-19 the period was between April 1, 2020 and March 31, 2021.

parapsilosis isolates was nonsusceptible to fluconazole (minimum inhibitory concentration ≥4 µg/mL) (Supplemental Tables 1 and 2). All fluconazole-nonsusceptible *C parapsilosis* isolates harbored Y132F mutation in the 14α-demethylase Erg11p. Of note, both fluconazole nonsusceptible *C parapsilosis* isolates from Izmir (isolates 35 and 37) were recovered from azole-naive patients who resided in units with an ongoing clonal outbreak of fluconazole-resistant *C parapsilosis* that started in 2015 [22]. To evaluate the genetic relatedness of these 2 isolates, we performed Illumina WGS. For comparison, we included WGS data from 8 *C parapsilosis* strains from 2 previous studies: 5 isolates from the same patient (including 2 pairs of clonal isolates) in one study [19], and 3 unrelated strains from clinical and environmental sources in the second study [20]. Our genomic analyses demonstrated that the 2 isolates in this study were closely related. A multidimensional analysis of all 10 isolates showed that the isolates 35 and 37 from the 2 patients in this study were highly related and clustered as close as the 2 known pairs of clonal isolates [19] (Figure 2), suggesting nosocomial transmission. In fact, the isolates 35 and 37 differed by 261 SNPs. This SNP difference is within the range of differences found among clonal pairs of isolates from the same patient in our previous study [19], that is, 115 SNPs in one pair (bsc.1700

and nsc.1701) and 407 SNPs in the second pair (ncc.1701 and tcc.1702). These SNP differences are far lower than the differences found between them and the closest unrelated isolates (ie, 1183 SNPs between 35 and bsc.1700).

Figure 2. Single-nucleotide polymorphisms (SNP)-based multiple correspondence analysis plot showing genetic clusters based on whole-genome SNP analysis. Isolates 35 and 37 were recovered from 2 patients from Izmir hospital with *Candida parapsilosis* fungemia. CBS1954, CBS6318, GA1, and CDC317 represent unrelated clinical and environmental isolates taken from [20]. The remaining 5 isolates correspond to serial isolates from the same patients where 3 distinct clonal complexes were identified [19]. Strains considered from the same clonal complex are circled.

Figure 1. Time from intensive care unit (ICU) admission to candidemia among patients with COVID-19. The tick marks indicate censored data. The probabilities of candidemia-free survival at 10, 20, and 30 days are presented above the Kaplan-Meier curve.

In the entire patient cohort, 26% (39 of 148) had at least 1 episode of bacteremia. Seventy-one percent (20 of 28) of patients with candidemia and only 16% (19 of 120) of patients without candidemia had bacteremia (*P* = .0001). Furthermore, 31% percent (12 of 39) of patients had more than 1 episode of bacteremia: 6 patients had 2 episodes of bacteremia and 6 had 3 episodes of bacteremia. Altogether, 43% (12 of 28) of patients with candidemia and none of those without candidemia had more than an episode of bacteremia (*P* = .0001). Bacteremia were most commonly caused by Gram-positive bacteria (60%, 34 of 57), especially coagulase-negative *Staphylococcus* (46%, 26 of 57) (Supplemental Figure 2).

Univariate analysis identified immunosuppressed status (*P* = .049), receipt of a carbapenem (*P* = .025), presence of CVC (*P* < .0001), and bacteremia preceding candidemia (*P* ≤ .0001) as risk factors for candidemia (*P* < .0001) (Table 1). The duration of indwelling CVC was significantly longer among patients with candidemia than those without (18.5 versus 8 days, respectively; *P* = .0001). Using logistic regression analysis, receipt of a carbapenem and bacteremia (overall or due to coagulase-negative *Staphylococcus* or *Acinetobacter baumannii* complex) were independent risk factors for candidemia (Table 1).

Information of antifungal therapy was available for 25 patients. Two patients were not treated with antifungals (1 of whom died on the day of candidemia detection). Among the 3 patients infected with fluconazole-resistant *Candida* isolates, 2 were initially treated with fluconazole, which was then transitioned to amphotericin B, and one to an anidulafungin, whereas the other one was azole-naive. Among the 19 patients infected with fluconazole-susceptible isolates, 13 were treated with fluconazole, 2 with an echinocandin, and 4 were initially treated with fluconazole, which was transitioned to amphotericin B (2 patients) or to an echinocandin (2 patients). The overall in-hospital mortality rate was 84% (125 of 148). There was no significant difference in mortality rate between patients with or without

candidemia (86%, 24 of 28 versus 84%, 101 of 120; *P* = 1.0). The median time from candidemia diagnosis to death was 14 days (IQR, 4–23 days). Older age (*P* = .03) and requirement of mechanical ventilation (*P* < .0001) were independent risk factors for death among critically ill COVID-19 patients in ICU (Table 3).

DISCUSSION

This multicenter study of critically ill COVID-19 patients requiring ICU admission identified several important findings. First, 19% of patients developed candidemia, a rate that is higher than previously reported in the literature (range, 2.5% to 14%) [23]. This rate was increased by 13-fold among non-COVID-19 patients admitted to the same hospitals in the same time period. Second, COVID-19 patients with candidemia had prolonged hospital stay, with a median time of 12 days from ICU admission to candidemia diagnosis. Our finding is in line with a recent study by the Center for Disease Control and Prevention, which showed that most candidemia was acquired more than 1 week after COVID-19 [7]. The estimated cumulative risk for candidemia among our patients increased with longer ICU stay, from 6% at day 10 to 26% at day 20 and 50% at day 30 (Figure 1). Third, the majority of patients with candidemia received antibiotics (99%) and corticosteroid therapy (84%) and required mechanical ventilation (84%), all of which are well established risk factors for candidemia. Finally, we identified bacterial bloodstream infection (especially due to coagulase-negative *Staphylococcus* and *A baumannii* complex), receipt of a carbapenem, and presence of CVC as independent risk factors for candidemia. Altogether, our data support the notion that prolonged ICU exposure and healthcare therapeutic interventions of COVID-19 patients were responsible for a higher rate of candidemia observed in our study.

During the COVID-19 pandemic, to limit patient contact, hospitals used mobile and out-of-room monitoring and

Table 3. Factors Associated With Mortality

Factors	Factors Present	Factor Absent	Univariate Analysis *P* Values	Logistic Regression *P* Values	Odds Ratio (95% CI)
Male sex	85% (82/96)	83% (43/52)	.64		
No known underlying diseases	75% (12/16)	86% (113/132)	.28		
Renal disease	96% (27/28)	82% (98/120)	.08		
Hypertension	88% (65/74)	80% (60/74)	.36		
Diabetes	77% (41/53)	88% (84/95)	.10		
Underlying immunosuppression	96% (25/26)	82% (100/122)	.08		
Previous bacteremia	84% (26/31)	85% (99/117)	1.0		
Receipt of steroid	86% (107/125)	78% (18/23)	.36		
Candidemia	86% (24/28)	84% (101/120)	1.0		
Candida albicans	83% (10/12)	88% (14/16)	1.0		
Candida parapsilosis	86% (6/7)	86% (18/21)	1.0		
Requirement of mechanical ventilation	95% (119/125)	26% (6/23)	<.0001	<.0001	61 (15.8–234.9)

Abbreviations: CI, confidence interval; IQR, interquartile range.

By univariate analysis, the median age (IQR) of patients who died was higher (70 years [61–78] than the age of patients who survived (60 years [40–72]); *P* = .03).

device controls and extended dwell intravenous catheters [24]. Such approaches could impact infection control practices. Furthermore, the presence of airborne and contact isolation and cumbersome personal protective equipment might have rendered CVC placement more technically difficult. Along the same line, the increase in ICU patient census might have interfered with routine infection control practice such as surveillance and maintenance of CVC devices and favored utilization of these devices for regular blood draws. All of these factors likely adversely increase the risk of catheter contamination and catheter-associated infection. Indeed, 26% (39 of 148) of our patients had at least 1 episode of bacteremia, which were most commonly caused by Gram-positive bacteria, especially coagulase-negative *Staphylococcus*, a finding that echoes published studies [25, 26]. In our study, 71% (20 of 28) of candidemic patients had preceding bacteremia, and bacteremia was an independent risk factor for subsequent candidemia. All the candidemic cases in our study were primary blood stream infection, because there was no apparent infection at another site, and 86% (24 of 28) of these cases was central line-associated bloodstream infections (CLABSIs). Increase in *Candida*-associated CLABSIs among hospitalized COVID-19 patients has been previously reported [27].

More than 80% of our patients received broad spectrum antibiotics, corticosteroid, and mechanical ventilation, which are all classic risk factors for candidemia [3, 16]. Utilization of corticosteroid has significantly improved outcome in severely ill hospitalized patients with COVID-19 [28], and mechanical ventilation is required for patients with COVID-19-associated respiratory failure, thus their use is unlikely to be modifiable. However, the fact that 99% of patients received antibiotics is very concerning. Literature to date showed that bacterial co-infection with COVID-19 occurred in only ~14% of patients in ICU [29], which is less prevalent than in patients with influenza [30]. Nevertheless, empiric antibiotic prescription in COVID-19 patients was widespread [31], and, similar to our finding, >90% of hospitalized COVID-19 patients were noted to receive empirical antibiotics [32]. Because the manifestations of COVID-19 patients with cytokine release syndrome mimic bacterial sepsis, it could be difficult for physicians to withhold antibiotics in this setting.

The association with prolonged ICU acquisition, preceding bacteremia (especially with coagulase-negative *Staphylococcus*), and *Candida* CLABSI suggest that candidemia is linked to infection control issues. Indeed, breach in infection prevention practices has been linked to outbreaks of *C auris* throughout the globe [11, 25, 33]. Furthermore, the high rate of administration of antibacterial agents, especially carbapenem (80%), might impact bacterial flora and promote *Candida* growth [34] and, along with corticosteroid utilization, lead to the selection of *Candida* superinfection in these critically ill and medically complexed COVID-19 patients.

Overall, *C albicans* was the most common species recovered, followed by *C parapsilosis* and *C tropicalis*. Two patients from Izmir were infected with genetically related fluconazole nonsusceptible *C parapsilosis* isolates carrying a Y132F mutation in Erg11p. The clonal outbreaks due to this particular strain of *C parapsilosis* have been reported in numerous countries [35–38] and present a particular challenge as the strains persist, and cause outbreaks despite application of disinfectants [39]. Centers dealing with clonal outbreak due to *C parapsilosis* like ours should closely monitor the emergence of fluconazole resistance, given its association with poorer outcomes [39]. In a recent study, *C parapsilosis* isolates with Erg11-Y132F mutation has also been linked to echinocandin resistance, which further complicates treatment strategy [40]. Because these strains retain susceptibility to amphotericin B [40], and the efficacy of this agent has been shown in in vivo study [41], we recommend amphotericin B as empiric antifungal therapy until susceptibility data are available among centers experiencing problems with fluconazole-resistant *C parapsilosis*.

The mortality rates of COVID-19 in the ICU ranged from 50% to 65%, and the rates were higher among patients requiring mechanical ventilation. Age and need for mechanical ventilation were predictors for mortality among our patients. Unlike previous studies [5, 7, 42], we did not detect a worse outcome among patients with candidemia compared with those without (mortality of 86% vs 84%, respectively). It is possible that, with an overall mortality rate of 84%, it is difficult to distinguish attributable mortality from death caused by candidemia or underlying diseases. Previous studies have suggested that the mortality attributed to candidemia is not significant in a population of patients with high expected mortality [43]. Moreover, in this setting, candidemia might merely be a marker for severity of illness. Along this line, our data showed that the mortality rate for patients with candidemia was ~2-fold higher among patients with COVID-19 than those without (84% versus 50%). This finding suggests that COVID-19 may amplify the risk of death due to candidemia.

It is important to acknowledge that our study is limited by its retrospective design, and results may have been influenced by practices and patient populations at our hospitals. Experiences at other centers may be different. Furthermore, the number of candidemia among COVID-19 patients was small, and we do not have detailed clinical data associated with non-COVID-19 candidemic patients during the pandemic for comparison. Nevertheless, our study implicates patient management factors that might have elevated the risk for candidemia among COVID-19 patients requiring ICU care.

CONCLUSIONS

Our study underscores that prolonged ICU exposure and ICU practices rendered to COVID-19 patients are important contributing factors to candidemia. Emphasis should be placed on (1) heightened infection control protocols in the ICU as well as

(2) developing hospital antibiotic stewardship strategies to reduce irrational antimicrobial utilization. Given the large heterogeneity among ICU COVID-19 patients, it is difficult to evaluate the impact of candidemia on patient's outcome. Research with larger multicenter studies is needed for matching candidemia and control groups to derive more accurate estimates of mortality attributable to candidemia.

References

1. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med **2012**; 4:165rv13.
2. Arastehfar A, Lass-Florl C, Garcia-Rubio R, et al. The quiet and underappreciated rise of drug-resistant invasive fungal pathogens. J Fungi (Basel) **2020**; 6:138. doi:10.3390/jof6030138.
3. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ. Invasive candidiasis. Nat Rev Dis Primers **2018**; 4:18026.
4. Baddley JW, Thompson GR 3rd, Chen SC, et al. Coronavirus disease 2019-associated invasive fungal infection. Open Forum Infect Dis **2021**; 8:ofab510.
5. 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**; 6:211. doi:10.3390/jof6040211.
6. Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 associated pulmonary aspergillosis (CAPA)-from immunology to treatment. J Fungi (Basel) **2020**; 6:91. doi:10.3390/jof6020091.
7. 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. Online ahead of print.
8. Mastrangelo A, Germinario BN, Ferrante M, et al. Candidemia in coronavirus disease 2019 (COVID-19) patients: incidence and characteristics in a prospective cohort compared with historical non-COVID-19 controls. Clin Infect Dis **2021**; 73:e2838-9.
9. 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**; 64:1083-91.
10. Arastehfar A, Shaban T, Zarrinfar H, et al. Candidemia among Iranian patients with severe COVID-19 admitted to ICUs. J Fungi (Basel) **2021**; 7:280. doi:10.3390/jof7040280.
11. Prestel C, Anderson E, Forsberg K, et al. Candida auris outbreak in a COVID-19 Specialty Care Unit - Florida, July-August 2020. MMWR Morb Mortal Wkly Rep **2021**; 70:56-7.
12. Villanueva-Lozano H, Trevino-Rangel RJ, Gonzalez GM, et al. Outbreak of Candida auris infection in a COVID-19 hospital in Mexico. Clin Microbiol Infect **2021**; 27:813-6.
13. Sopirala MM. Predisposition of COVID-19 patients to secondary infections: set in stone or subject to change? Curr Opin Infect Dis **2021**; 34:357-64.
14. CLSI. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts— Fourth Edition. CLSI Standard M60 CLSI. Wayne, PA; Clinical and Laboratory Standards Institute; **2020**.
15. Pfaller MA, Diekema DJ. Progress in antifungal susceptibility testing of Candida spp. by use of Clinical and Laboratory Standards Institute broth microdilution methods, 2010 to 2012. J Clin Microbiol **2012**; 50:2846-56.
16. Ostrosky-Zeichner L. Clinical prediction rules for invasive candidiasis in the ICU: ready for prime time? Crit Care **2011**; 15:189.
17. Arastehfar A, Daneshnia F, Najafzadeh MJ, et al. Evaluation of molecular epidemiology, clinical characteristics, antifungal susceptibility profiles, and molecular mechanisms of antifungal resistance of Iranian Candida parapsilosis species complex blood isolates. Front Cell Infect Microbiol **2020**; 10:206.
18. Ksiezopolska E, Schikora-Tamarit MA, Beyer R, Nunez-Rodriguez JC, Schuller C, Gabaldon T. Narrow mutational signatures drive acquisition of multidrug resistance in the fungal pathogen Candida glabrata. Curr Biol **2021**; 31:5314-26.e10.
19. Gomez-Molero E, Willis JR, Dudakova A, et al. Phenotypic variability in a coinfection with three independent Candida parapsilosis lineages. Front Microbiol **2020**; 11:1994. doi:10.3389/fmicb.2020.01994.
20. Pryszcz LP, Nemeth T, Gacser A, Gabaldon T. Unexpected genomic variability in clinical and environmental strains of the pathogenic yeast Candida parapsilosis. Genome Biol Evol **2013**; 5:2382-92.
21. Garrison E, Marth G. Haplotype-based variant detection from short-read sequencing. arXiv preprint arXiv:1207.3907 [q-bio.GN] 2012. Available at https://arxiv.org/abs/1207.3907. Accessed 2 March 2022.
22. Arastehfar A, Daneshnia F, Hilmioglu-Polat S, et al. First report of candidemia clonal outbreak caused by emerging fluconazole-resistant Candida parapsilosis isolates harboring Y132F and/or Y132F+K143R in Turkey. Antimicrob Agents Chemother **2020**; 64:e01001-20.
23. 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**; 64:634-40.
24. Bauchner H, Fontanarosa PB, Livingston EH. Conserving supply of personal protective equipment-A call for ideas. JAMA **2020**; 323:1911.
25. Magnasco L, Mikulska M, Giacobbe DR, et al. Spread of carbapenem-resistant Gram-negatives and Candida auris during the COVID-19 pandemic in critically ill patients: one step back in antimicrobial stewardship? Microorganisms **2021**; 9:95.
26. Sepulveda J, Westblade LF, Whittier S, et al. Bacteremia and blood culture utilization during COVID-19 Surge in New York City. J Clin Microbiol **2020**; 58:e00875-20.
27. Fakih MG, Bufalino A, Sturm L, et al. Coronavirus disease 2019 (COVID-19) pandemic, central-line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI): the urgent need to refocus on hard-wiring prevention efforts. Infect Control Hosp Epidemiol **2022**; 43:26-31.
28. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med **2021**; 384:693-704.
29. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect **2020**; 81:266-75.
30. Youngs J, Wyncoll D, Hopkins P, Arnold A, Ball J, Bicanic T. Improving antibiotic stewardship in COVID-19: bacterial co-infection is less common than with influenza. J Infect **2020**; 81:e55-7.
31. Beovic B, Dousak M, Ferreira-Coimbra J, et al. Antibiotic use in patients with COVID-19: a "snapshot" Infectious Diseases International Research Initiative (ID-IRI) survey. *J Antimicrob Chemother* **2020**; 75:3386-90.
32. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* **2020**; 71:2459-68.
33. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant Candida auris infections in critically ill coronavirus disease patients, India, April-July 2020. Emerg Infect Dis **2020**; 26:2694-6.
34. Samonis G, Galanakis E, Ntaoukakis M, et al. Effects of carbapenems and their combination with amikacin on murine gut colonisation by Candida albicans. Mycoses **2013**; 56:105-9.

35. Choi YJ, Kim YJ, Yong D, et al. Fluconazole-resistant Candida parapsilosis bloodstream isolates with Y132F mutation in ERG11 gene, South Korea. Emerg Infect Dis **2018**; 24:1768–70.

36. Fekkar A, Blaize M, Bougle A, et al. Hospital outbreak of fluconazole-resistant Candida parapsilosis: arguments for clonal transmission and long-term persistence. Antimicrob Agents Chemother **2021**; 65:e02036–20.

37. Magobo RE, Lockhart SR, Govender NP. Fluconazole-resistant Candida parapsilosis strains with a Y132F substitution in the ERG11 gene causing invasive infections in a neonatal unit, South Africa. Mycoses **2020**; 63:471–7.

38. Martini C, Torelli R, de Groot T, et al. Prevalence and clonal distribution of azole-resistant Candida parapsilosis isolates causing bloodstream infections in a large Italian hospital. Front Cell Infect Microbiol **2020**; 10:232.

39. Thomaz DY, deAlmeida JN, Sejas J, et al. Environmental clonal spread of azole-resistant Candida parapsilosis with Erg11-Y132F Mutation causing a large candidemia outbreak in a Brazilian cancer referral center. J Fungi (Basel) **2021**; 7:259. doi:10.3390/jof7040259.

40. Arastehfar A, Daneshnia F, Hilmioglu-Polat S, et al. Genetically related micafungin-resistant Candida parapsilosis blood isolates harbouring novel mutation R658G in hotspot 1 of Fks1p: a new challenge? J Antimicrob Chemother **2021**; 76:418–22.

41. Binder U, Arastehfar A, Schnegg L, et al. Efficacy of LAMB against emerging azole- and multidrug-resistant Candida parapsilosis isolates in the Galleria mellonella model. J Fungi (Basel) **2020**; 6:377. doi:10.3390/jof6040377.

42. Riche CVW, Cassol R, Pasqualotto AC. Is the frequency of Candidemia increasing in COVID-19 patients receiving corticosteroids? J Fungi (Basel) **2020**; 6:286. doi:10.3390/jof6040286.

43. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Effects of nosocomial candidemia on outcomes of critically ill patients. Am J Med **2002**; 113:480–5.