Open Forum Infectious Diseases

MAJOR ARTICLE

A High Frequency of *Candida auris* Blood Stream Infections in Coronavirus Disease 2019 Patients Admitted to Intensive Care Units, Northwestern India: A Case Control Study

Ekadashi Rajni,[1] Ashutosh Singh,[2] Bansidhar Tarai,[3] Kusum Jain,[2,4] Ravi Shankar,[5] Kalpana Pawar,[2] Vedprakash Mamoria,[1] and Anuradha Chowdhary[2]

[1]Department of Microbiology, Mahatma Gandhi University of Medical Science & Technology, Jaipur, Rajasthan, India, [2]Medical Mycology Unit, Department of Microbiology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India, [3]Department of Microbiology, Max Hospital, New Delhi, India, [4]Department of Zoology, Ramjas College, University of Delhi, Delhi, India, [5]Department of Biostatistics, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

Background. The ongoing pandemic of coronavirus disease 2019 (COVID-19) has overwhelmed healthcare facilities and raises an important novel concern of nosocomial transmission of *Candida* species in the intensive care units (ICUs).

Methods. We evaluated the incidence and risk factors for development of candidemia in 2384 COVID-19 patients admitted during August 2020–January 2021 in ICUs of 2 hospitals (Delhi and Jaipur) in India. A 1:2 case-control matching was used to identify COVID-19 patients who did not develop candidemia as controls.

Results. A total of 33 patients developed candidemia and accounted for an overall incidence of 1.4% over a median ICU stay of 24 days. A 2-fold increase in the incidence of candidemia in COVID-19 versus non-COVID-19 patients was observed with an incidence rate of 14 and 15/1000 admissions in 2 ICUs. *Candida auris* was the predominant species (42%) followed by *Candida tropicalis*. Multivariable regression analysis revealed the use of tocilizumab, duration of ICU stay (24 vs 14 days), and raised ferritin level as an independent predictor for the development of candidemia. Azole resistance was observed in *C auris* and *C tropicalis* harboring mutations in the azole target *ERG11* gene. Multilocus sequence typing (MLST) identified identical genotypes of *C tropicalis* in COVID-19 patients, raising concern for nosocomial transmission of resistant strains.

Conclusions. Secondary bacterial infections have been a concern with the use of tocilizumab. In this cohort of critically ill COVID-19 patients, tocilizumab was associated with the development of candidemia. Surveillance of antifungal resistance is warranted to prevent transmission of multidrug-resistant strains of nosocomial yeasts in COVID-19 hospitalized patients.

Keywords. *Candida auris*; *Candida tropicalis*; COVID-19; nosocomial infections; tocilizumab.

Invasive fungal infection has been increasingly highlighted as a serious concern in critically ill patients with coronavirus disease 2019 (COVID-19) in several countries of South America, Middle East, Europe, Asia, and the United States [1–13]. Patients with severe COVID-19 disease who are hospitalized in intensive care units (ICUs) for prolonged periods of time often require multiple courses of broad-spectrum antibiotics, mechanical ventilation, and other invasive devices, which results in increasing exposure to, and risk of, acquiring nosocomial blood stream infections (BSIs) due to *Candida* species (spp) [2, 3, 14, 15]. Recent studies originating from the United States, Italy, Spain, and Brazil emphasized a significant, 3- to 10-fold increase in incidence of ICU candidemia among COVID-19 patients compared to a non-COVID-19 cohort [2–4, 9, 16–20]. These increasing reports about secondary fungal infections as complications of severe COVID-19 raises a parallel concern regarding the emergence and transmission of multidrug-resistant (MDR) nosocomial *Candida* spp in COVID-19 ICUs [10, 21, 22]. A recent report of secondary healthcare-associated infections (HAIs) in COVID-19 patients from a quaternary care hospital in New York City, USA showed that a relatively large proportion of fungal infections (15%) were primarily due to hospital-associated *Candida* spp [15].

In the beginning of the COVID-19 pandemic in April–July 2020, we apprised a series of candidemia cases due to nosocomial MDR yeast *Candida auris* in critically ill COVID-19 patients hospitalized in a single center in Delhi. It is notable that, in the series, 70% of *C auris* isolates were multidrug-resistant, including 30% that were resistant to 3 classes of antifungal drugs [10]. Several recent studies on *Candida* BSIs

Received 16 June 2021; editorial decision 25 August 2021; accepted 6 September 2021.

Correspondence: Prof. A. Chowdhary, MD, PhD, FRC Path, FIDSA, FAAM, Medical Mycology Unit, Department of Microbiology, V. P. Chest Institute, University of Delhi, Delhi-110007, India (chowdhary.anuradha@gmail.com).

Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab452

lack information on the species identification and antifungal susceptibilities pattern, thus they underestimate the burden of antifungal resistance in COVID-19 settings. Furthermore, the impact of immunomodulatory agents, such as corticosteroids and interleukin (IL)-6 receptor blockers, on the incidence of *Candida* BSIs is largely undetermined, despite the widespread use of these agents to manage inflammatory complications of COVID-19. To obtain better insight into the development of candidemia and associated risk factors in COVID-19 patients, we retrospectively analyzed a large set of 2384 COVID-19 patients hospitalized in the ICUs of 2 hospitals in Northwestern India (ie, Delhi and Jaipur, Rajasthan) for 6 months from August 2020 to January 2021. We evaluated the incidence and risk factors for development of candidemia in COVID-19 patients compared to the matched control group of COVID-19 patients without candidemia.

MATERIAL AND METHODS

Study Design and Data Collection

This case-control study was conducted in COVID-19 ICUs of 2 multispecialty hospitals (hospital A with 50 ICU beds and hospital B with 80 ICU beds) of Northwestern India. The study included COVID-19-positive adults over age 17, admitted in the COVID-19 ICUs, who developed candidemia from August 1, 2020 to January 31, 2021, and were followed up for a period of 30 days. The present study is a retrospective review of candidemia in adult patients (>17 years) with polymerase chain reaction (PCR)-proven COVID-19 across COVID-19 ICUs in 2 hospitals. Candidemia was defined as the growth of *Candida* spp on 1 or more blood culture, and the date of the first positive fungal blood culture was used for calculation of all durations. Candidemia patients were identified starting from the laboratory databases of the participating hospitals and subsequent review of clinical records. Data concerning demographics (age, gender), comorbidities, laboratory tests, Sequential Organ Failure Assessment (SOFA) score at ICU admission, treatment, and outcomes (ICU admission, length of hospital stay, and mortality) were collected directly from electronic health records. All patients had a diagnosis of COVID-19 confirmed by real-time reverse-transcription PCR testing performed on nasopharyngeal throat swab specimens. The ICU database was screened to include a control group of 70 COVID-19 (1:2 case-control matching) hospitalized patients without candidemia admitted during the same time period as cases and matched based on age (±5) and the SOFA scores available at the time of their admission to the ICUs. No sample size calculations were performed a priori for this exploratory study.

Data were collected for demographics, risk factors for candidemia, utilization of tocilizumab, and use of steroids. For anti-inflammatory treatments for COVID-19, data were analyzed based on anti-inflammatory treatment used or not, that is, steroid treatment and intravenous tocilizumab (8 mg/kg single administration or repeated once). Demographic and clinical characteristics of patients are presented with number and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. The processes and practices undertaken in both the hospitals are listed in the Supplementary Data.

Statistical Analysis

Factors affecting the occurrence of candidemia among the COVID-19 patients were determined by binary logistic regression analysis. The dependent variable for the logistic regression analysis was presence or absence of candidemia. Multivariable logistic regression analysis was performed between the dependent variable and all the independent variables that were found to be significant in univariate logistic regression ($P < .1$). Adjusted odds ratio (OR) in multivariable and unadjusted OR in univariate logistic regression analysis with 95% confidence intervals (CIs) are reported. Logistic regression was performed in EZR (Easy R, version 1.54) statistical software, which is based on R and R commander [23]. Variance inflation factor (VIF) was computed to determine the presence of multicollinearity among the independent variables in STATA software using the package "collin", which is meant for determining the multicollinearity among the categorical variables. A VIF <5 confirmed the absence of multicollinearity.

Mycological Investigations

Blood Culture Specimen Collection and Processing

Blood samples were obtained by using aseptic precautions. Before collecting the blood sample, the skin was disinfected with 0.5% chlorhexidine in 70% isopropyl alcohol. The antecubital fossa was the preferred sampling site, and samples from central vein catheters were obtained from needleless caps that were disinfected with 0.5% chlorhexidine in 70% isopropyl alcohol. Two automated blood culture systems were used during the study period: BactecTM FX (Becton Dickinson, Sparks, MD) and Bact/Alert 3D (bioMérieux, Marcy l'Etoile, France). Blood cultures were incubated in the instrument for up to 5 days. Bottles that were flagged as positive were streaked onto blood and Sabouraud agar plates. Blood culture bottles that did not show visible microorganism were also subcultured after 5 days. After incubation at 37°C for up to 48 hours, yeast were identified to the species level.

Yeast Identification

Candida species isolated from blood cultures were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry ([MALDI-TOF] Bruker Biotyper OC version 3.1; Daltonics, Bremen, Germany, https://www.bruker.com) using the ethanol-formic acid extraction protocol [24]. In addition, *C auris* species identification was confirmed by amplification

and sequencing of the internal transcribed spacer region of ribosomal deoxyribonucleic acid (DNA) and of the D1/D2 domain of the large subunit ribosomal DNA as described previously [25].

Antifungal Susceptibility Testing and Azole Target *ERG 11* Gene Analysis

Antifungal susceptibility testing was performed by using the Clinical and Laboratory Standards Institute broth microdilution method M27-A3/S4 [26, 27]. Antifungals tested were fluconazole ([FLU] Sigma, St. Louis, MO), itraconazole ([ITC] Lee Pharma, Hyderabad, India), voriconazole ([VRC] Pfizer, Groton, CT), posaconazole (POS, Merck, Whitehouse Station, NJ), isavuconazole ([ISA] Basilea Pharmaceutical, Basel, Switzerland), 5-flucytosine ([5-FC] Sigma), micafungin ([MFG] Astellas, Toyama, Japan), anidulafungin ([AFG] Pfizer), and amphotericin B ([AMB] Sigma). *Candida krusei* ATCC 6258 and *Candida parapsilosis* American Type Culture Collection (ATCC) 22019 were used as quality control strains. The geometric mean minimum inhibitory concentrations (MICs) with 95% CIs, MIC_{50}, MIC_{90}, medians, and ranges were calculated using Prism version 6.00 (GraphPad Software). Furthermore, all azole-resistant yeast isolates obtained from candidemia were subjected to azole target *ERG 11* gene sequencing as detailed previously [28]. To determine the genotypes of *Candida tropicalis* prevalent in COVID-19 ICUs, we performed MLST using 6 housekeeping genes: *ICL1*, *MDR1*, *SAPT2*, *SAPT4*, *XYR1*, and *ZWF1α* as described previously by Tavanti et al [29]. Allelic profiles and the diploid sequence type (DSTs) of the 6 gene sequences were obtained from the *C tropicalis* MLST sequence-type database (http://pubmlst.org/ctropicalis/). Phylogenetic analysis of the isolates was determined by constructing an unrooted neighbor-joining tree based on concatenated sequences of all 6 genes (*ICL1*, *MDR1*, *SAPT2*, *SAPT4*, *XYR1*, and *ZWF1α*) by using MEGA 5.2 version.

Patient Consent Statement

The study was granted ethical approval under File Number MGMCH/IEC/JPR/2020/181 by Mahatma Gandhi University of Medical Science & Technology, Jaipur, Rajasthan, India. The committee waived the need for patient consent because the study was retrospective data collection with no intervention.

RESULTS

Study Population

A total of 2384 confirmed COVID-19 patients were admitted in the 2 ICUs during the 6-month span of the study period. Overall, 33 patients with candidemia were identified, accounting for an incidence of 1.4% over a median ICU stay of 24 days. There were 22 candidemia patients in hospital A and 11 candidemia patients in hospital B, and a corresponding incidence rate of 15/1000 and 14/1000 admissions, respectively, was recorded. The demographic and clinical characteristics of the study population are summarized in Table 1. The median age of candidemia patients was 66.5 years and 73% of them were males. The median onset of candidemia on day 12 of ICU stay (IQR, 5–42 days) was noted.

Risk Factors for Candidemia

Univariate and multivariable analyses of factors potentially associated with the development of candidemia are shown in Table 1. In univariate comparison (non-candidemia vs candidemia patients), the following variables were associated with the development of candidemia: longer stay in the ICU (6 vs 24 days), raised ferritin levels (26% vs 82%), patients supported with mechanical ventilation (33% vs 64%), and central venous catheter (33% vs 70%); patients with underlying hypertension (20% vs 64%), diabetes (10% vs 58%), and lung disease (4% vs 15%); and administration of tocilizumab (20% vs 67%). Multivariable logistic regression analysis showed that candidemia was associated with the use of tocilizumab (OR = 11.952; 95% CI, 1.431–99.808; P = .022), prolong duration of ICU stay (OR = 0.041; 95% CI, 0.005–0.358; P = .004), and raised ferritin level (OR = 8.905; 95% CI, 1.241–63.904; P = .03). The mean VIF for all the variables included in multiple logistic regression was 1.29 (<5), confirming the absence of multicollinearity among the variables tested. Overall, in-hospital mortality after 30 days was 64% in candidemia patients compared to 36% in the control group without candidemia.

Distribution of Species of Candida and Their Antifungal Resistance Patterns

It is interesting to note that, in 42% cases of candidemia, *C auris* was the predominant species followed by *C tropicalis* and *Candida albicans* in 21% and 18% of cases, respectively. Furthermore, a wide spectrum of non-*albicans Candida* species including *C glabrata*, *C krusei*, *C parapsilosis*, and *C gullermondii* were observed as agents of candidemia. In addition, 20 isolates of *Candida* spp cultured from urine of 10 COVID-19 patients were identified (Tables 2 and 3). However, the significance of isolates from urine samples could not be ascertained. Antifungal susceptibility data for *Candida* spp isolated from blood (n = 33) and urine (n = 20) against 9 antifungals are detailed in Tables 2 and 3. Of 14 *C auris* isolates obtained from candidemia, all were resistant to FLU (MIC ≥32 mg/L) and harbored previously known amino acid substitutions Y132F (n = 9) and K143R (n = 5) in ERG11p. In addition, 21% (n = 3) of *C auris* isolates exhibited high MICs of AMB (MIC ≥2 mg/L) and 71% (n = 10) to 5-FC (MIC ≥32 mg/L). A total of 3 *C auris* isolates displayed multiazole resistance. Among 18 *C tropicalis* isolates (blood and urine), a single blood stream isolate showed a high MIC value of 128 mg/L and 2 mg/L against FLU and VRC, respectively, and harbored previously known concurrent amino acid substitutions Y132F and S154F in ERG11p. In addition, a single bloodstream isolate of *C parapsilosis* showed susceptible

Table 1. Characteristics of COVID-19 Patients With and Without Candidemia

	COVID-19 With Candidemia (No. of Patients With Candidemia/Total No. of Patients Admitted to ICU)			COVID-19 Without Candidemia (Control, n = 70)	Univariate Analysis		Multivariable Analysis	
Variable	Total (n = 33/2384[a])	Hospital A (n = 22/1467[a])	Hospital B (n = 11/917[a])	Total (n = 70)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Median age (years)	66.5 (25–86)	66 years (IQR, 25–86)	67 years (IQR, 48–71)	56 (IQR, 27–82)	-	-	-	-
Gender					2.519 (1.026–6.813)			
Male	24 (73%)	14 (64%)	10 (91%)	38 (54%)		.044	5.535 (0.722–42.398)	.1
Female	9 (27%)	8 (36%)	1 (9%)	32 (44%)				
Duration of hospital stay (days)					0.035 (0.011–0.109)	<.001	0.041 (0.005–0.358)	**.004**
<20 days	9 (27.3%)			64 (91%)				
≥20 days	24 (72.7%)			6 (9%)				
Presence of Indwelling Device								
Central venous catheter	23 (70%)	15 (68%)	8 (73%)	23 (33%)	4.7 (1.922–11.495)	.001	3.086 (0.421–22.612)	.267
Mechanical ventilation	21 (64%)	12 (54.5%)	9 (82%)	24 (33%)	3.354 (1.414–7.959)	.006	4.848 (0.802–29.320)	.086
Urinary catheter	14 (27%)	8 (36%)	6 (54.5%)	14 (20%)	-	-	-	-
Dialysis line	3 (9%)	2 (9%)	1 (9%)	2 (3%)	-	-	-	-
Broad-spectrum antibiotics before candidemia	33 (100%)	22 (100%)	11 (100%)	70 (100%)	-	-	-	-
Comorbidities								
Hypertension	21 (64%)	18 (82%)	3 (27%)	14 (20%)	6.875 (2.739–17.260)	<.001	6.203 (0.836–46.035)	.074
Diabetes mellitus	19 (57.5%)	14 (64%)	5 (45%)	7 (10%)	12.214 (4.307–34.635)	<.001	7.726 (0.820–72.813)	.074
Lung disease	5 (15%)	5 (23%)	0	3 (4%)	3.988 (0.892–17.834)	.07	3.958 (0.176–89.109)	.387
Renal disease	3 (9%)	2 (9%)	1 (9%)	2 (3%)	3.4 (0.540–21.409)	.192	-	-
Liver disease	5 (15%)	5 (23%)	0	2 (3%)	-	-	-	-
Malignancy	1 (3%)	0	1 (9%)	1 (1%)	-	-	-	-
Biochemical Markers (Reference Range)								
Ferritin (11–306.8 ng/mL)								
High/Low	27 (82%)/6 (18%)	18 (82%)/4 (18%)	9 (82%)/2 (18%)	18 (26%)/52 (74%)	13 (4.621–36.571)	<.001	8.905 (1.241–63.904)	**.03**
D-dimer (0–243 ng/mL)								
High/low	32 (97)/1 (3%)	22 (100%)	10 (91%)/1 (9%)	22 (31%)/47 (68%)	-	-	-	-
Procalcitonin (>0.5 ng/mL)								
High/low	13 (39%)/20 (61%)	9 (40%)/13 (60%)	4 (36%)/7 (64%)	11 (16%)/56 (84%)	3.486 (1.349–9.012)	.01	1.673 (0.182–15.356)	.649
Species spectrum of *Candida* isolated from BSIs	*Candida auris* (n = 14)	*C auris* (n = 10)	*C auris* (n = 4)	-				
	Candida tropicalis (n = 7)	*C tropicalis* (n = 4)	*C tropicalis* (n = 3)	-				
	Candida albicans (n = 6)	*C albicans* (n = 4)	*C albicans* (n = 2)	-				
	Candida glabrata (n = 3)	*C glabrata* (n = 2)	*C glabrata* (n = 1)	-				
	Candida krusei (n = 1)	*C krusei* (n = 1)	-	-				
	Candida parapsilosis (n = 1)	-	*C parapsilosis* (n = 1)					
	Candida gullermondii (n = 1)	*C gullermondii* (n = 1)	-					
Steroids for Pneumonia	23 (70%)	15 (68%)	8 (73%)	46 (66%)	1.2 (0.492–2.926)	.689		
Tocilizumab	22 (67%)	16 (73%)	6 (54.5%)	14 (20%)	8 (3.153–20.297)	<.001	11.952 (1.431–99.808)	**.022**
Final clinical Outcome								
Deceased	21 (64%)	12 (55%)	9 (82%)	25 (36%)	-	-	-	-
Survived	12 (36%)	10 (45%)	2 (18%)	45 (64%)	-	-	-	-

Boldface highlights the statistically significant *P* values.

Abbreviations: BSI, blood stream infection; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio.

[a]Total number of patients admitted in ICUs during 6-month period from August 2020 to January 2021.

Table 2. MIC (mg/L) Distribution of *Candida* spp (n = 22; Blood Stream Isolates) From Hospital A

Candida species (n = Number of Isolates)	Parameters	Drugs								
		FLU	ITC	VRC	ISA	POS	AMB	MFG	AFG	FC
Candida auris (10)	Range	32–256	<0.03–25	0.125–2	0.03–0.125	0.015–0.125	0.5–4	0.015–0.25	0.06–0.5	0.125 to <64
	GM	73.51	0.14	0.5	0.05	0.09	0.93	0.07	0.24	10.76
	MIC_{50}	64	0.125	0.5	0.06	0.125	1	0.125	0.5	16
	MIC_{90}	140.8	0.174	2	0.0125	0.125	4	0.25	0.5	64
Candida albicans (4)	Range	0.25–0.5	<0.03–0.03	0.03–0.06	0.015	0.015–0.125	0.06–0.125	<0.015–0.015	<0.015	<0.125
Candida tropicalis (4)	Range	0.25–1	0.03–0.125	<0.03–0.06	0.015–0.25	<0.015–0.25	0.03–0.5	<0.015–0.03	<0.015–0.3	<0.125
Candida glabrata (2)	Range	<0.25–0.25	0.03	<0.03	<0.015–0.015	<0.015	0.03–0.06	<0.015	<0.015–0.03	<0.125
Candida kruseii (1)	MIC	8	0.25	0.125	0.06	0.25	0.125	0.25	0.125	8
Candida gullermondii (1)	MIC	4	1	0.125	0.5	0.125	0.03	0.125	0.5	<0.125

Abbreviations: AFG, anidulafungin; AMB, amphotericin B; FC, flucytosine; FLC, fluconazole; GM, geometric mean; ISA, isavuconazole; ITC itraconazole; MFG, micafungin; MIC, minimum inhibitory concentration; MIC_{50}, MIC at which 50% of test isolates were inhibited; MIC_{90}, MIC at which 90% of test isolates were inhibited; POS, posaconazole; VRC, voriconazole.

Table 3. MIC (mg/L) Distribution of *Candida* spp (n = 31, n = 11; Bloodstream Isolates, n = 20; Urine Isolates) From Hospital B

Candida Species (n = Bloodstream Isolates) [n = Urine Isolates]	Parameters	Drugs								
		FLU	ITC	VRC	ISA	POSA	AMB	MFG	AFG	FC
Candida tropicalis (3) [11]	Range	<0.25–128	0.03–1	<0.03–2	<0.015–0.25	0.03–0.25	0.03–0.5	<0.015–125	<0.015–0.06	<0.125–0.125
	GM	0.84	0.18	0.08	0.07	0.09	0.15	0.02	0.03	0.12
	MIC_{50}	0.5	0.25	0.06	0.07	0.12	0.12	0.22	0.03	0.125
	MIC_{90}	1.9	0.5	0.6	0.212	0.25	0.5	0.06	0.06	0.125
Candida albicans (2) [5]	Range	<0.25–2	<0.03–0.5	<0.03–0.25	<0.015–0.125	<0.015–0.25	0.03–0.25	<0.015–0.06	<0.015–0.06	<0.125–0.125
Candida auris (4)	Range	64–128	0.125–25	0.5–2	0.125–0.5	<0.015–0.03	0.06–0.25	0.03–0.5	0.06–0.5	32–64
Candida glabrata (1) [2]	Range	0.5–4	0.06–1	0.03–0.125	<0.015–0.05	<0.015–0.5	0.125–0.5	<0.015–0.015	<0.015–0.06	<0.125
Candida parapsilosis (1)	MIC	4	0.5	0.125	<0.015	0.125	0.25	1	1	<0.125
Candida kefyr [1]	MIC	<0.25	0.03	<0.03	<0.015	<0.015	0.125	<0.015	0.06	<0.125
Candida catenulate [1]	MIC	128	0.06	2	0.125	<0.015	0.03	0.03	0.25	<0.125

Abbreviations: AFG, anidulafungin; AMB, amphotericin B; FC, flucytosine; FLC, fluconazole; GM, geometric mean; ISA, isavuconazole; ITC itraconazole; MFG, micafungin; MIC, minimum inhibitory concentration; MIC_{50}, MIC at which 50% of test isolates were inhibited; MIC_{90}, MIC at which 90% of test isolates were inhibited; POS, posaconazole; VRC, voriconazole.

Table 4. Summary of Studies Describing COVID-19-Associated Candidemia

Study (Region/ Country)	Study Period	Number of Candidemia Cases/Total Number of COVID-19 Patients Screened	Prevalence Percentage of Candidemia	Incidence Rate (per 1000 Admissions)		ICU/Ward	Statistically Significant Risk Factors in COVID-19 Candidemia	Percentage Mortality	*Candida* Species Causing Candidemia in COVID-19 Patients
				COVID	Non-COVID				
Nori et al (New York, USA) [1]	March 1– April 18, 2020	3/4267	0.07	NG	NG	ICU and Ward	Not defined for patients with candidemia.	Not specified for candidemia	*Candida* spp (n = 3)
Macauley et al (New York, USA) [2]	May 1, 2014– October 31, 2020[a]	12/236	5.08	51 5-fold increase	11	ICU	Longer ICU stay (19 vs 5 days, $P = .001$), lower SOFA score (5 vs 10, $P = .006$), and longer CVC dwell time (12.5 vs 5.5 days, $P = .022$) in COVID-19 vs non-COVID patients.	Overall, 75%	*Candida albicans* (n = 4) *Candida glabrata* (n = 2) *Candida parapsilosis* (n = 3) *Candida tropicalis* (n = 2) *Candida dubliensis* (n = 1) non-*albicans Candida* spp (n = 1) *C albicans* + non-*albicans Candida* spp (n = 1)
Bishburg et al (New Jersey, USA) [14]	March 10– April 10, 2020	8/89	8.9%	NG	NG	ICU	Multivariable analysis showed only days on MV as an in dependent predictor (OR = 1.07; 95% CI, 1.01–1.15)	38% at day 25	*C tropicalis* (n = 2) *C albicans* (n = 2) *C glabrata* (n = 2) *C parapsilosis* (n = 2)
Kumar et al (Georgia, USA) [16]	March 1– August 5, 2020	11/1565	0.7	NG	NG	ICU	Not specified for candidemia; HAIs were associated with the use of TCZ ($P < .001$), steroids, ($P = .007$), HCQ ($P = .05$), and AKI requiring hemodialysis ($P = .04$).	NG	*C albicans* (n = 6) non-*albicans Candida* spp (n = 5)
Kubin et al (New York, USA) [15]	March 2–May 31, 2020	30/3028	1	NG	NG		Not specified for candidemia. In a multivariable model, ICU stay, IMV, and steroids were associated with HAIs	NG	*Candida* spp (n = 29) Unidentified yeast (n = 1)
Rodriguez et al (Bogota, Colombia) [33]	June–September 2020	20 patients/NG	NG	NG	NG	ICU	ND	60% at day 30	*C auris* (n = 6) *C albicans* (n = 4) *C tropicalis* (n = 4) *C parapsilosis* (n = 3) *Candida orthopsilosis* (n = 1) *C glabrata* (n = 1 *Trichosporon asahii* (n = 1)

Table 4. Continued

Study (Region/ Country)	Study Period	Number of Candidemia Cases/Total Number of COVID-19 Patients Screened	Prevalence Percentage of Candidemia	Incidence Rate (per 1000 Admissions)		ICU/Ward	Statistically Significant Risk Factors in COVID-19 Candidemia	Percentage Mortality	*Candida* Species Causing Candidemia in COVID-19 Patients
				COVID	Non-COVID				
Nucci et al (Rio de Janeiro, Brazil) [3]	March–September 2020	9/608	1.5	2.68 3-fold increase	7.44	ICU	COVID-19-associated candidemia were under MV compared to non-COVID-19 (100% vs 34.4%, $P < .001$).	66.7% at day 30	*C albicans* (n = 5) *C tropicalis* (n = 2) *C glabrata* (n = 1) *Candida famata* (n = 1)
Riche et al (Porto Alegre, Brazil) [4]	March 16– August 31, 2020	11 patients/NG	NG	Hospital 1: 11.83 Hospital 2: 10.23 10-fold increase	Hospital 1: 1.43 Hospital 2: 1.15	ICU	ND	Overall, 72.7%	*C albicans* (n = 8) *C glabrata* (n = 2) *C tropicalis* (n = 1)
Villanueva-Lozano et al (Nuevo Leon, Mexico) [34]	April–October 2020	12/NG	NG	NG	NG	ICU	ND	Overall, mortality in *C auris* candidemia 83.3%	*C auris* (n = 9). *C auris* + *C glabrata* (n = 3)
Hughes et al (London, UK) [30]	February 20–April 30, 2020	3/836	0.36	NG	NG	Candidemia patients were in ICU	ND	NG	*C albicans* (n = 3)
White et al (Wales, UK) [7, 31]	March–May 2020	22/183[a]	12	12	6.9	ICU	Not determined for candidemia	47.1% at day 30 (ranging from 27.3% in patients on appropriate antifungal therapy to 83.3% in those not receiving appropriate antifungals)	*C albicans* (n = 11) [1 *C albicans* (ascites)] *C albicans* + *C parapsilosis* (n = 1) *C parapsilosis* (n = 1) *Rhodotorula* spp (n = 1) Yeast (no-ID) = 1 (chest drain)
Denny et al (London, UK) [52]	March 1–May 31, 2020	11/NG	NG	NG	NG	ICU	ND	54.4% at day 30	*C albicans* (n = 7) *C parapsilosis* (n = 2) *C glabrata* (n = 1) *Candida dubliniensis* (n = 1)
Agrifoglio et al (Madrid, Spain) [19]	February 28–June 28, 2020	15/139	10.8	NG	1.07–2.19 in non-COVID-19	ICU	ND	Overall, 40%	*C albicans* (n = 9) *C parapsilosis* (n = 4) *C glabrata* (n = 2)
Garcia-Vidal et al (Barcelona, Spain) [8]	February 28–April 22, 2020	Invasive candidiasis developed in 4 of 989 COVID-19 patients. Candidemia occurred in 2 of these patients.	0.4	NG	NG	ICU	ND	Not specified for candidemia patients	*C albicans* (n = 4)

Table 4. Continued

Study (Region/ Country)	Study Period	Number of Candidemia Cases/Total Number of COVID-19 Patients Screened	Prevalence Percentage of Candidemia	Incidence Rate (per 1000 Admissions)		ICU/Ward	Statistically Significant Risk Factors in COVID-19 Candidemia	Percentage Mortality	*Candida* Species Causing Candidemia in COVID-19 Patients
				COVID	Non-COVID				
Bardi et al (Madrid, Spain) [20]	March 1–May 30, 2020	5/140	3.57	NG	NG	ICU	Not specified for candidemia patients. APACHE II score was independently associated with the development of bacterial and fungal infections	Not specified for candidemia patients	*C albicans* (n = 4) *C glabrata* (n = 1)
Mastrangelo et al (Milan, Italy) [9]	February 15–June 30, 2020	21 patients NG	NG	81.68 per 10 000 patient-day follow-up. 6-fold increase	14.46 per 10 000 patient-day follow-up	ICU	COVID-19 patients were more likely to be in the ICU (66.7% vs 29.4%; $P = .003$) and to be treated with immunosuppressive agents (61.1% vs 32.7%; $P = .035$)	Overall, 57.1%	*C albicans* (n = 14) non-*albicans Candida* spp (n = 7)
Antinori et al (Milan, Italy) [47]	March 10–18, 2020	3/43	6.97	NG	NG	ICU and ID wards	ND	NG	*C albicans* (n = 1) *C parapsilosis* (n = 1) *C tropicalis* (n = 1)
Magnasco et al (Genoa, Italy) [35]	February 28–May 31, 2020	4/118	3.39	NG	NG	ICU	ND	50% at day 25 comparable to control group	*C auris* (n = 4)
Cataldo et al (Rome, Italy) [17]	March 1– April 15, 2020	5/57	8.77	Not specified for candidemia cases; for bacterial and fungal BSI, incidence rate was 373 per 10 000 patient-days	NG	ICU	ND	32 not specified for candidemia patients	*C albicans* (n = 2) *C parapsilosis* (n = 2) *C glabrata* + *C parapsilosis* (n = 1)
Giacobbe et al (Genoa, Italy) [18]	February 20–April 10, 2020	3/78	3.84	Not specified for candidemia cases; for bacterial and fungal BSI, incidence rate was 47 episodes/ 1000patients	Not Given	ICU	Not specified for candidemia patients. For bacterial and fungal BSIs in multivariable analysis, anti-inflammatory treatment (TCZ, MPD, MPD+TCZ) was independently associated with the development of BSI	Not specified for candidemia patients	*C albicans* (n = 1) *C tropicalis* (n = 1) *C parapsilosis* (n = 1)
Morena et al (Milan, Italy) [46]	March 10–23, 2020	3/51	5.88	NG	NG	ICU	ND	NG	*Candida spp* (n = 3)
Chowdhary et al (Delhi, India) [10]	April–July 2020	15/596	0.16	NG	NG	ICU	ND	Overall, 60%	*C auris* (n = 10) *C albicans* (n = 3) *C tropicalis* (n = 1) *C krusei* (n = 1)

Table 4. Continued

Study (Region/ Country)	Study Period	Number of Candidemia Cases/Total Number of COVID-19 Patients Screened	Prevalence Percentage of Candidemia	Incidence Rate (per 1000 Admissions)		ICU/Ward	Statistically Significant Risk Factors in COVID-19 Candidemia	Percentage Mortality	*Candida* Species Causing Candidemia in COVID-19 Patients
				COVID	Non-COVID				
Arastehfar et al (Mashhad, Iran) [5]	November 2020 to late January 2021	7/1988	0.35	NG	NG	ICU	ND	Overall, 100%	*C albicans* (n = 5) *C glabrata* (n = 3) *Rhodotorula mucilaginosa* (n = 1)

Abbreviations: AKI, acute kidney injury; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; BSI, blood stream infection; CI, confidence interval; COVID-19, coronavirus disease 2019; CVC, central venous catheter; HAIs, healthcare-associated infections; HCQ, hydroxychloroquine; ICU, intensive care unit; ID, infectious disease; IMV, invasive mechanical ventilation; MPD, methylprednisolone; MV, mechanical ventilation; ND, not done; NG, not given; OR, odds ratio; SOFA, sequential organ failure assessment; TCZ, tocilizumab.

[a]COVID-19 patient's admissions were limited to a 5-month period in 2020.

dose-dependent MIC value (4 mg/L) against FLU, and a single *Candida catenulata* strain isolated from the urine displayed a high MIC value of 128 mg/L and 2 mg/L against FLU and VRC, respectively. An echinocandin was commenced for 22 patients pending susceptibility testing, and 4 patients died before blood culture positivity and treatment. Six of 22 patients were switched to fluconazole to complete treatment.

Multilocus Sequence Typing of *Candida tropicalis*

The neighbor-joining phylogenetic tree based on concatenated sequences of the 6 loci (ie, *ICL1*, *MDR1*, *SAPT2*, *SAPT4*, *XYR1*, and *ZWF1α*) of *C tropicalis* isolates demonstrated a heterogeneous population in 2 ICUs. It is interesting to note that of the 4 BSIs with *C tropicalis* in hospital A, 2 patients had identical DST. Similarly, among 3 cases of candidemia due to *C tropicalis* in hospital B, 2 patients had identical DSTs. In addition, urinary and blood stream isolates from a single patient had identical DST.

DISCUSSION

The present study demonstrates a high incidence rate of candidemia, ie, 14 and 15/1000 admissions in critically ill patients with COVID-19 in 2 ICUs in India, which is approximately 2-fold higher than that of the incidence rates of 5–7/1000 ICU admissions observed in non-COVID-19 ICU populations in both the hospitals in 2018–2019. Previously published major worldwide studies reporting candidemia and hospital-associated BSIs due to bacteria or fungi in COVID-19 patients showed a wide prevalence of 0.07%–10.8% of candidemia in COVID-19-hospitalized patients (Table 4). It is interesting to note that, in the 5 studies originating from New York, New Jersey, and Georgia, USA the prevalence of candidemia in COVID-19 patients showed a wide range, ie, 0.07%–8.9% [1, 2, 14, 15, 18]. The high prevalence of 8.9% was observed among 89 COVID-19 adult patients who were admitted to the ICU for worsening disease status [14]. A study investigating the incidence of bacterial and fungal coinfections in 836 hospitalized patients across 2 London hospitals during the first United Kingdom (UK) wave of COVID-19 reported that BSIs due to *Candida* spp presented as late-onset infection, which accounted for 0.4% of secondary infections [30]. In contrast, a national, multicentered study applying an enhanced testing strategy to diagnose invasive fungal disease in COVID-19 intensive care patients in Wales, UK identified 12.6% incidence of invasive yeast infection, mainly (93.8%) due to *Candida* spp [7]. The wide ranges of incidence of candidemia occurring in COVID-19 patients in the above-mentioned studies may be attributed to calculations of incidence based on all patients or extrapolating the incidence to entire populations to determine a total disease burden. This strategy may not accurately identify the burden of BSIs due to *Candida* spp because these infections occur primarily in intensive care settings.

A 3- to 8-fold increase in the incidence of candidemia in COVID-19 patients versus non-COVID-19 patients has been reported in studies originating from New York, USA, Rio de Janeiro and Southern Brazil, Wales, UK, and Milan, Italy [2–4, 9, 31]. It is interesting to note that an 8-fold increase in the incidence of candidemia in COVID-19 patients has been observed in 2 hospitals of Southern Brazil [4]. In the present study, a 2-fold increase in candidemia in 2 hospitals was recorded with *C auris* being the predominant agent of candidemia (42%). In fact, 64% of candidemia in the present study were due to non-*albicans Candida* spp, ie, *C auris* and *C tropicalis*. In contrast, studies from the USA (Table 4) showed that *C albicans* contributed to 25%–54% of candidemia, whereas 18% of candidemia in the present study was due to *C albicans* [2, 14–16]. In addition, *C albicans* was the predominant agent of candidemia in COVID-19 patients in European countries including Italy, Spain, and the UK [7, 9, 17, 19, 20, 30].

As anticipated earlier in the COVID-19 pandemic, BSIs due to *C auris* has recently been widely recognized in critically ill COVID-19 patients [32–37]. It is interesting to note that COVID-19-associated *C auris* candidemia has been recognized in countries that had not previously recorded this yeast [37]. The first outbreak of *C auris* occurred during a COVID-19 pandemic in a tertiary care center in Lebanon [37]. Similarly, an outbreak of *C auris* was recently highlighted in a COVID-19 hospital in Monterrey, Mexico that started in a non-COVID-19 patient, and during the transition from the hospital to the exclusive COVID-19 facility, the infection later spread to 12 patients in the COVID-19 ICU [34]. In addition, increasing reports of transmission of *C auris* among COVID-19 patients has been observed in those geographic regions where this MDR yeast was already prevalent in the hospital environment [32–34, 38]. During a *C auris* outbreak in a COVID-19 specialty care unit in Florida in July–August 2020, 3 *C auris* BSIs and 1 urinary tract infection in 4 patients with COVID-19 were identified. Among 67 patients admitted to the COVID-19 unit, 52% were colonized with *C auris* [38]. Several factors including healthcare personnel using multiple gown and glove layers, extended use of the underlayer of personal protective equipment, and lapses in cleaning and disinfection and adherence to hand hygiene likely contributed to widespread *C auris* transmission [38].

To prevent transmission of *C auris* in the COVID-19 care facilities, enhanced vigilance and essential screening of patients is warranted. Furthermore, it is also pertinent to emphasize that patients who have been hospitalized and recover from severe COVID-19 may remain colonized by *C auris* for prolong periods. Thus, screening of patients for *C auris* needs to be undertaken in patients that require repeated admission for long-term sequalae in the post-COVID-19 facilities. A study from Delhi, India undertaking screening of *C auris* colonization among chronic respiratory diseases patients that required repeated admissions in healthcare identified that 9.5% of patients were colonized at the time of admission and 75% remained colonized until discharge [39]. In addition, *C tropicalis* is of particular importance because it is a major cause of nosocomial candidemia, particularly in the Asia-Pacific region [40–44]. In the present study, identical *C tropicalis* genotypes infected the patients in ICUs, which suggests patient-to-patient transmission. Antifungal resistance was observed in both *C auris* and in a single isolate of *C tropicalis*, raising concerns of nosocomial transmission of resistant isolates specifically where hospitals are overwhelmed by patients with COVID-19, resulting in compromised infection prevention practices.

Healthcare practices associated with severe COVID-19 disease and the prolonged critical care have been attributed to the development of candidemia in severely ill COVID-19 patients. In the present study, multivariable logistic regression analysis show that duration of ICU stay (24 vs 14 days), use of tocilizumab (67% vs 20%), and raised ferritin levels (26% vs 82%) are independent predictors of the development of candidemia. Limited studies have analyzed statistically significant risk factors in the development of candidemia in COVID-19 patients (Table 4). A recent case control study from New Jersey, USA identifying the risk factors in the development of candidemia among 89 patients admitted to the ICU for COVID-19 found that candidemia patients had longer median ICU stay than controls (40 vs 10 days, $P = .004$). However, on logistic regression analysis, the authors identified only 2 variables, namely, superimposed infection and days on mechanical ventilation, that were associated with the development of nosocomial candidemia [14]. Similarly, another study from New York, USA showed that the ICU length of stay before the development of candidemia was significantly longer in the COVID-19 group (19 days vs 5 $P = .001$) compared to non-COVID-19 patients who developed candidemia [2].

Although management strategies for COVID-19 have been progressively evolving through the pandemic, therapies with immune-modulating properties, such as IL-6 receptor antagonists and corticosteroids, have been commonly used in severe disease. Tocilizumab, an IL-6 receptor blocker, is used to treat severe, progressive COVID-19 infection. However, secondary infections have been a concern with the use of tocilizumab [16, 45, 46]; however, a clear association with *Candida* BSIs has been not been demonstrated. A study from the United States recently evaluated tocilizumab for treatment of mechanically ventilated patients with COVID-19, and researchers observed increased incidence of secondary bacterial infections among tocilizumab-treated patients (54% vs 26%; $P < .001$), with 39% developing a pneumonia or bacterial BSIs. Kumar et al [16] analyzed predictors and outcomes of HAIs in 1565 COVID-19 patients in Georgia, USA. Tocilizumab was given to 210 patients with severe COVID-19, 42 (20%) of whom primarily developed HAIs bacterial infections. However, 11 cases of BSIs due to *Candidia* spp were also recorded in the study. Researchers

observed that tocilizumab was associated with increased risk of HAIs (OR = 5.04; 95% CI, 2.4–10.6; $P < .001$) [16]. Morena et al [46] studied the clinical characteristics and outcome of 51 patients hospitalized with severe COVID-19 pneumonia treated with tocilizumab; late complications were serious bacterial and fungal infections of the bloodstream in 27% of cases. Further concern of candidemia with use of tocilizumab has been raised in a report from Milan, Italy. Antinori et al [47] observed that during an 11-day period, 43 patients with severe COVID-19 pneumonia were treated with tocilizumab and 3 patients (6.9%) developed candidemia, with 1 patient developing endophthalmitis and endocarditis.

In the present study, receipt of tocilizumab was more likely among the candidemia cohort (67% versus 20% without candidemia), which comprised a high percentage of patients requiring mechanical ventilation (64% vs 34% without candidemia) and significantly raised severity parameters (serum ferritin levels 82% vs 26% without candidemia), suggesting severe immunosuppression. Interleukin-6 is a proinflammatory cytokine involved in the regulation of multiple aspects of innate immune response. Therefore, blockade of IL-6 may impair B-cell proliferation and T-cell differentiation and cytotoxicity, which are essential for immune control of infections [48]. It is interest to note that severe impairment of the macrophage and neutrophil response to *Candida* infection was observed in IL-6-deficient mice. These mice were more susceptible to systemic *C albicans* infection and had a decreased survival and an increased fungal load in their organs compared with IL-6-positive controls [49, 50]. Furthermore, an ex vivo whole blood stimulation assay with *C albicans* lysate revealed an impaired response of COVID-19 patients toward *C albicans*. Patients with COVID-19 showed an attenuated monocyte CD80 upregulation and abrogated release of IL-6, tumor necrosis factor, IL-1a, and IL-1b toward *C albicans*, suggesting an increased susceptibility for *C albicans* infection in critically ill COVID-19 patients [51].

CONCLUSIONS

Finally, it should be considered that our sample size of candidemia patients was limited (n = 33). Other limitations of the present study are its retrospective nature. Moreover, variable infrastructure of healthcare facilities and geographic regions or countries where *C auris* are not endemic may impact generalizability of our results. Further studies with large, controlled data are necessary to evaluate the association of BSIs due to *Candida* spp in patients treated with IL-6 receptor blocker in COVID-19 patients. To reduce unfavorable outcomes in COVID-19 patients, monitoring of invasive fungal infections with emphasis on antifungal resistance is warranted in COVID-19 settings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

This work was funded in part by a research grant from the Indian Council of Medical Research (File No. MYCO/6/2020-ECD-I; to A. C.), Government of India, New Delhi, India and Council of Scientific & Industrial Research (File No. 08/728(0001)/2019-EMR-I; to K. J.), Government of India, New Delhi, India.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Nori P, Cowman K, Chen V, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol **2021**; 42:84–8.
2. 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.
3. Nucci M, Barreiros G, Guimarães LF, et al. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses **2021**; 64:152–6.
4. Riche CVW, Cassol R, Pasqualotto AC. Is the frequency of candidemia increasing in COVID-19 patients receiving corticosteroids? J Fungi (Basel) **2020**; 6:286.
5. 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.
6. Al-Hatmi AMS, Mohsin J, Al-Huraizi A, Khamis F. COVID-19 associated invasive candidiasis. J Infect **2021**; 82:e45–6.
7. White PL, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis **2020**. doi: 10.1093/cid/ciaa1298.
8. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al; COVID-19 Researchers Group. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect **2021**; 27:83–8.
9. 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 **2020**. doi: 10.1093/cid/ciaa1594.
10. 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.
11. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis **2020**. doi: 10.1093/cid/ciaa1065.
12. 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.
13. Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: a literature review. J Microbiol Immunol Infect **2021**; 54:46–53.
14. Bishburg E, Okoh A, Nagarakanti SR, et al. Fungemia in COVID-19 ICU patients, a single medical center experience. J Med Virol **2021**; 93:2810–4.
15. Kubin CJ, McConville TH, Dietz D, et al. Characterization of bacterial and fungal infections in hospitalized patients with COVID-19 and factors associated with healthcare-associated infections. Open Forum Infect Dis **2021**. doi: 10.1093/ofid/ofab201.
16. Kumar G, Adams A, Hererra M, et al. Predictors and outcomes of healthcare-associated infections in COVID-19 patients. Int J Infect Dis **2021**; 104:287–92.
17. Cataldo MA, Tetaj N, Selleri M, et al; INMICOVID-19 Co-infection Group. Incidence of bacterial and fungal bloodstream infections in COVID-19 patients in intensive care: an alarming "collateral effect". J Glob Antimicrob Resist **2020**; 23:290–1.
18. Giacobbe DR, Battaglini D, Ball L, et al. Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest **2020**; 50:e13319.
19. Agrifoglio A, Cachafeiro L, Figueira JC, et al. Critically ill patients with COVID-19 and candidaemia: we must keep this in mind. J Mycol Med **2020**; 30:101012.
20. Bardi T, Pintado V, Gomez-Rojo M, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis **2021**; 40:495–502.
21. Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? Euro Surveill **2020**; 25:2001886.

22. Posteraro B, Torelli R, Vella A, et al. Pan-echinocandin-resistant *Candida glabrata* bloodstream infection complicating COVID-19: a fatal case report. J Fungi (Basel) **2020**; 6:163.
23. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **2013**; 48:452–8.
24. van Veen SQ, Claas EC, Kuijper EJ. High-throughput identification of bacteria and yeast by matrix-assisted laser desorption ionization-time of flight mass spectrometry in conventional medical microbiology laboratories. J Clin Microbiol **2010**; 48:900–7.
25. Chowdhary A, Prakash A, Sharma C, et al. A multicentre study of antifungal susceptibility patterns among 350 *Candida auris* isolates (2009-17) in India: role of the *ERG11* and *FKS1* genes in azole and echinocandin resistance. J Antimicrob Chemother **2018**; 73:891–9.
26. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 3rd ed. M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute; **2008**.
27. Clinical and Laboratory Standards Institute. Performance Standards for Antifungal Susceptibility Testing of Yeasts. 2nd ed. CLSI supplement M60. Wayne, PA: Clinical and Laboratory Standards Institute; **2020**.
28. Vandeputte P, Larcher G, Bergès T, et al. Mechanisms of azole resistance in a clinical isolate of *Candida tropicalis*. Antimicrob Agents Chemother **2005**; 49:4608–15.
29. Tavanti A, Davidson AD, Johnson EM, et al. Multilocus sequence typing for differentiation of strains of *Candida tropicalis*. J Clin Microbiol **2005**; 43:5593–600.
30. Hughes S, Troise O, Donaldson H, et al. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect **2020**; 26:1395–9.
31. White PL, Dhillon R, Healy B, et al. Candidaemia in COVID-19, a link to disease pathology or increased clinical pressures? Clin Infect Dis **2020**: ciaa1597.
32. Chowdhary A, Sharma A. The lurking scourge of multidrug resistant *Candida auris* in times of COVID-19 pandemic. J Glob Antimicrob Resist **2020**; 22:175–6.
33. Rodriguez JY, Le Pape P, Lopez O, et al. *Candida auris*: a latent threat to critically ill patients with COVID-19. Clin Infect Dis **2020**: ciaa1595.
34. Villanueva-Lozano H, Treviño-Rangel RJ, González GM, et al. Outbreak of *Candida auris* infection in a COVID-19 hospital in Mexico. Clin Microbiol Infect **2021**; 27:813–6.
35. 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.
36. Di Pilato V, Codda G, Ball L, et al. Molecular epidemiological investigation of a nosocomial cluster of *C. auris*: evidence of recent emergence in Italy and ease of transmission during the COVID-19 pandemic. J Fungi (Basel) **2021**; 7:140.
37. Allaw F, Kara Zahreddine N, Ibrahim A, et al. First *Candida auris* outbreak during a COVID-19 pandemic in a tertiary-care center in Lebanon. Pathogens **2021**; 10:157.
38. Prestel C, Anderson E, Forsberg K, et al. *Candida auris* outbreak in a COVID-19 specialty care unit - Florida, July-August 2020. Morb Mortal Wkly Rep **2021**; 70:56–7.
39. Yadav A, Singh A, Wang Y, et al. Colonisation and transmission dynamics of *Candida auris* among chronic respiratory diseases patients hospitalised in a chest hospital, Delhi, India: a comparative analysis of whole genome sequencing and microsatellite typing. J Fungi (Basel) **2021**; 7:81.
40. Kothavade RJ, Kura MM, Valand AG, Panthaki MH. *Candida tropicalis*: its prevalence, pathogenicity and increasing resistance to fluconazole. J Med Microbiol **2010**; 59:873–80.
41. Negri M, Silva S, Henriques M, Oliveira R. Insights into *Candida tropicalis* nosocomial infections and virulence factors. Eur J Clin Microbiol Infect Dis **2012**; 31:1399–412.
42. Quindós G. Epidemiology of candidaemia and invasive *Candidiasis*. A changing face. Rev Iberoam Micol **2014**; 31:42–8.
43. Motoa G, Muñoz JS, Oñate J, et al. Epidemiology of *Candida* isolates from intensive care units in Colombia from 2010 to 2013. Rev Iberoam Micol **2017**; 34:17–22.
44. Pu S, Niu S, Zhang C, et al. Epidemiology, antifungal susceptibilities, and risk factors for invasive candidiasis from 2011 to 2013 in a teaching hospital in Southwest China. J Microbiol Immunol Infect **2017**; 50:97–103.
45. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis **2020**; 73:e445–54.
46. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med **2020**; 76:36–42.
47. Antinori S, Bonazzetti C, Gubertini G, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun Rev **2020**; 19:102564.
48. Camporeale A, Poli V. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity? Front Biosci (Landmark Ed) **2012**; 17:2306–26.
49. Romani L, Mencacci A, Cenci E, et al. Impaired neutrophil response and CD4+ T helper cell 1 development in interleukin 6-deficient mice infected with *Candida albicans*. J Exp Med **1996**; 183:1345–55.
50. van Enckevort FH, Netea MG, Hermus AR, et al. Increased susceptibility to systemic candidiasis in interleukin-6 deficient mice. Med Mycol **1999**; 37:419–26.
51. Moser D, Biere K, Han B, et al. COVID-19 impairs immune response to *Candida albicans*. Front Immunol **2021**; 12:640644.
52. Denny S, Abdolrasouli A, Elamin T, et al. A retrospective multicenter analysis of candidaemia among COVID-19 patients during the first UK pandemic wave. J Infect **2021**; 82:276–316.