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

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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.
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 underetermined, 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 BactAlert 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 Biotype 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, MICw, MICm, 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 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, MDRI, SAPT2, SAPT4, XYR1, and ZWF1α) as described previously by Tavanti et al [29].

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 and S154F 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
| Variable                                      | COVID-19 With Candidemia | COVID-19 Without Candidemia | P Value | Adjusted OR (95% CI)  |
|------------------------------------------------|--------------------------|-----------------------------|---------|-----------------------|
| Median age (years)                              | 66.5 (35–98)             | 69 years (IQR, 25–98)       | <.001   | 2.057 (1.026–4.113)   |
| Gender                                         | Male 24 (73%)            | 14 (86%)                    | .01     | 2.519 (1.026–6.813)   |
| Duration of hospital stay (days)                | 9 (27.3%)                | 24 (82.7%)                  | <.001   | 0.026 (0.010–0.109)   |
| Presence of Indwelling Device                  | Central venous catheter  | 23 (70%)                    | <.001   | 4.7 (1/02–11.655)     |
|                                                   | Mechanical ventilation   | 21 (64%)                    | <.001   | 3.591 (1.44–9.795)    |
|                                                   | Urinary catheter         | 14 (41%)                    | <.001   | 3.686 (0.92–26.203)   |
| Biochemical Markers (Reference Range)           | Ferritin (11–306.8 ng/mL)| High/Low 27 (82%)/6 (18%)  | <.001   | 13.402 (3.62–48.509)  |
| Species spectrum of Candida                      | candida auris            | (n = 14)                    | <.001   | 4.7 (1/02–11.655)     |
|                                                   | candida tropicalis       | (n = 7)                     | <.001   | 3.591 (1.44–9.795)    |
|                                                   | candida albicans         | (n = 6)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida glabrata         | (n = 3)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida parapsilosis     | (n = 1)                     | <.001   | 3.686 (0.92–26.203)   |
| Gender                                         | Male 24 (73%)            | 14 (86%)                    | .01     | 2.519 (1.026–6.813)   |
| Duration of hospital stay (days)                | 9 (27.3%)                | 24 (82.7%)                  | <.001   | 0.026 (0.010–0.109)   |
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|                                                   | candida glabrata         | (n = 3)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida parapsilosis     | (n = 1)                     | <.001   | 3.686 (0.92–26.203)   |
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|                                                   | candida tropicalis       | (n = 7)                     | <.001   | 3.591 (1.44–9.795)    |
|                                                   | candida albicans         | (n = 6)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida glabrata         | (n = 3)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida parapsilosis     | (n = 1)                     | <.001   | 3.686 (0.92–26.203)   |
| Gender                                         | Male 24 (73%)            | 14 (86%)                    | .01     | 2.519 (1.026–6.813)   |
| Duration of hospital stay (days)                | 9 (27.3%)                | 24 (82.7%)                  | <.001   | 0.026 (0.010–0.109)   |
| Presence of Indwelling Device                  | Central venous catheter  | 23 (70%)                    | <.001   | 4.7 (1/02–11.655)     |
|                                                   | Mechanical ventilation   | 21 (64%)                    | <.001   | 3.591 (1.44–9.795)    |
|                                                   | Urinary catheter         | 14 (41%)                    | <.001   | 3.686 (0.92–26.203)   |
| Biochemical Markers (Reference Range)           | Ferritin (11–306.8 ng/mL)| High/Low 27 (82%)/6 (18%)  | <.001   | 13.402 (3.62–48.509)  |
| Species spectrum of Candida                      | candida auris            | (n = 14)                    | <.001   | 4.7 (1/02–11.655)     |
|                                                   | candida tropicalis       | (n = 7)                     | <.001   | 3.591 (1.44–9.795)    |
|                                                   | candida albicans         | (n = 6)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida glabrata         | (n = 3)                     | <.001   | 3.686 (0.92–26.203)   |
|                                                   | candida parapsilosis     | (n = 1)                     | <.001   | 3.686 (0.92–26.203)   |

**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.

*aTotal 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 | 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<sub>50</sub> | 64 | 0.125 | 0.5 | 0.06 | 0.125 | 1 | 0.125 | 0.5 | 16 |
| MIC<sub>90</sub> | 140.8 | 0.17 | 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 | <0.015 | <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 | <0.015–0.03 | <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 krusei* (1) MIC | 8 | 0.25 | 0.125 | 0.06 | 0.25 | 0.125 | 0.25 | 0.125 | 8 |

| *Candida guillermondii* (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<sub>50</sub>, MIC at which 50% of test isolates were inhibited; MIC<sub>90</sub>, 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 | 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 | <0.015–0.25 | <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 | 1.2 |
| MIC<sub>50</sub> | 0.5 | 0.25 | 0.06 | 0.07 | 0.12 | 0.12 | 0.22 | 0.03 | 0.125 |
| MIC<sub>90</sub> | 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 | 0.03–0.5 | <0.015–0.06 | <0.125–0.125 |
| *Candida auris* (4) | 64–128 | 0.125–25 | 0.5–2 | 0.125–0.5 | <0.015–0.03 | 0.06–25 | 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 | 0.125–0.5 | 0.125–0.5 | <0.015–0.015 | <0.125–0.06 |
| *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<sub>50</sub>, MIC at which 50% of test isolates were inhibited; MIC<sub>90</sub>, MIC at which 90% of test isolates were inhibited; POS, posaconazole; VRC, voriconazole.
| 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) | Statistically Significant Risk Factors in COVID-19 Candidemia | Percentage Mortality | Candida Species Causing Candidemia in COVID-19 Patients |
|------------------------|--------------|------------------------------------------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------------------------------|---------------------|-----------------------------------------------|
| 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. | 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) |
| Macauley et al (New York, USA) [2] | May 1, 2014–October 31, 2020 | 12/236 | 5.08 5% | 11 ICU | | | 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 independent predictor (OR = 1.07; 95% CI, 1.01–1.15) | | 38% at day 25 | Candida 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 | | | | | Candida 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 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). | | | Candida spp (n = 2.9) Unidentified yeast (n = 1) |
| Rodriguez et al (Bogota, Colombia) [33] | June–September 2020 | 20 patients/NG | NG NG ICU ND | | | 60% at day 30 | Candida 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) |
| 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) | Statistically Significant Risk Factors in COVID-19 Candidemia | Percentage Mortality | Candida Species Causing Candidemia in COVID-19 Patients |
|------------------------|--------------|---------------------------------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------------------|-------------------------|---------------------------------------------------------|
| Nucci et al (Rio de Janeiro, Brazil) [3] | March–September 2020 | 9/608 | 1.5 | 2.68 | 3-fold increase | 744 | 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 | 10-fold increase | Hospital 1: 1.43 | ICU | 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 | 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 | Candidemia patients were in ICU | ND | NG | \(C\) albicans \((n = 3)\) |
| White et al (Wales, UK) [7, 31] | March–May 2020 | 22/183 | 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) \(1\) \(C\) 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 | 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 \((n = 4)\) |
| 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) | Statistically Significant Risk Factors in COVID-19 Candidemia | Percentage Mortality | Candida Species Causing Candidemia in COVID-19 Patients |
|------------------------|--------------|---------------------------------------------------------------------|-----------------------------------|---------------------------------------|------------------------------------------------------------|---------------------|-----------------------------------------------------|
| 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 |
| Mastrangelo et al (Milan, Italy) [9] | February 15–June 30, 2020 | 21 patients | NG | 81.68 | 14.46 | 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%; $P = .035$) |
| Antinori et al (Milan, Italy) [47] | March 10–18, 2020 | 3/43 | 6.97 | NG | NG | ICU and ID wards | ND | Overall, 57.1% |
| 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 |
| Cataldo et al (Rome, Italy) [17] | March 1–April 15, 2020 | 5/57 | 8.77 | Not specified for candidemia cases; for bacterial and fungal BSIs, incidence rate was 373 per 10 000 patient-days | NG | ICU | ND | Overall, 32 not specified for candidemia patients |
| Giacobbe et al (Genoa, Italy) [18] | February 20–April 10, 2020 | 3/78 | 3.84 | Not specified for candidemia cases; for bacterial and fungal BSIs, 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 BSIs |
| Morena et al (Milan, Italy) [46] | March 10–23, 2020 | 3/51 | 5.88 | NG | NG | ICU | ND | Not specified for candidemia patients |
| Chowdhary et al (Delhi, India) [10] | April–July 2020 | 15/596 | 0.16 | NG | NG | ICU | ND | Overall, 60% |

Overall, not specified for candidemia patients. Not specified for candidemia patients.
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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 \textit{C auris} being the predominant agent of candidemia (42%). In fact, 64% of candidemia in the present study were due to non-albicans \textit{Candida} spp, ie, \textit{C auris} and \textit{C tropicalis}. In contrast, studies from the USA (Table 4) showed that \textit{C albicans} contributed to 25%–54% of candidemia, whereas 18% of candidemia in the present study was due to \textit{C albicans} [2, 14–16]. In addition, \textit{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 \textit{C auris} has recently been widely recognized in critically ill COVID-19 patients [32–37]. It is interesting to note that COVID-19-associated \textit{C auris} candidemia has been recognized in countries that had not previously recorded this yeast [37]. The first outbreak of \textit{C auris} occurred during a COVID-19 pandemic in a tertiary care center in Lebanon [37]. Similarly, an outbreak of \textit{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 \textit{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 \textit{C auris} outbreak in a COVID-19 specialty care unit in Florida in July–August 2020, 3 \textit{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 \textit{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 \textit{C auris} transmission [38].

To prevent transmission of \textit{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 \textit{C auris} for prolong periods. Thus, screening of patients for \textit{C auris} needs to be undertaken in patients that require repeated admission for long-term sequelae in the post-COVID-19 facilities. A study from Delhi, India undertaking screening of \textit{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, \textit{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 \textit{C tropicalis} genotypes infected the patients in ICUs, which suggests patient-to-patient transmission. Antifungal resistance was observed in both \textit{C auris} and in a single isolate of \textit{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 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 \textit{Candida} BSIs has 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 \textit{Candida} spp were also recorded in the study. Researchers
observed that tocilizumab was associated with increased risk of HAI (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 of 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.

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Potential conflicts of interest.
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