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Risk Factors and Clinical Outcomes of Candidemia Associated With Severe COVID-19

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IMPORTANCE: COVID-19 can cause serious illness requiring multimodal treatment and is associated with secondary infections. Studies have suggested an increased risk of fungal infections, including candidemia following severe COVID-19 though understanding of risk factors and clinical outcomes remains unclear.

OBJECTIVES: To describe clinical characteristics, outcomes and risk factors of candidemia among patients hospitalized with severe COVID-19.

DESIGN, SETTING, AND PARTICIPANTS: A multicenter, case-control study of patients with severe COVID-19 was conducted to evaluate risk factors and clinical outcomes in patients who developed candidemia between August 2020 and August 2021.

MAIN OUTCOMES AND MEASURES: Chart review evaluating institutional and patient demographics, clinical and mycological characteristics, concomitant interventions (antibiotics, immunosuppressive agents, parenteral nutrition, degree of oxygen support, mechanical ventilation, surgery), treatment regimens, and outcomes (length of stay and discharge disposition)

RESULTS: A total of 275 patients were enrolled in the study, including 91 patients with severe COVID-19 and subsequent candidemia and 184 with severe COVID-19 without candidemia. Most patients received antibiotics prior to candidemia episode (93%), while approximately one-quarter of patients received biologic for COVID-19. In-hospital mortality was significantly higher in the cases compared with the controls (68% vs 40%; $p < 0.01$). *Candida albicans* was the most common (53%), followed by *C. glabrata* (19%). Use of central lines, biologic, and paralytics were independent risk factors for candidemia.

CONCLUSIONS AND RELEVANCE: Candidemia following COVID-19 infection is a concern that requires clinical consideration and patient monitoring. Risk factors for the development of candidemia in the setting of COVID-19 infection are largely consistent with traditional risk factors for candidemia in hospitalized patients.

KEY WORDS: candidemia; co-infection; COVID-19; severe acute respiratory syndrome coronavirus 2 infection

Since its declaration as a pandemic by the World Health Organization in March 2020, COVID-19 has surpassed over 444 million cases and resulted in over 5.9 million deaths as of early March 2022 (1). While strides have been made in preventative and therapeutic interventions, including vaccines, antivirals, and anti-inflammatory medications (2), there is much to be understood about managing patients with COVID-19.

Secondary infections present a serious concern in patients with prolonged illness. Research regarding secondary infections in COVID-19 initially focused on bacterial infections (3–6), but attention on the relevance of secondary fungal infection in COVID-19 management is growing. Candidemia in patients with COVID-19 has been reported in variable rates, ranging from 0.8% to 14%,

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which is three to eight times that reported in historical, non-COVID-19 populations (7). Furthermore, in COVID-19 patients with secondary candidemia, the mortality rates range from 40% to 70%, underlining the urgency for a better understanding of the relationship between these infections.

Early recognition of candidemia has long been identified as key to minimizing morbidity and mortality (8). Therefore, it is essential to understand the unique characteristics, prevalence and risk factors for fungal co-infection among patients with COVID-19. Many traditional risk factors for candidemia are present among patients with severe and critical COVID-19 including prolonged hospital length of stay, critical illness, immunosuppressive treatment, and presence of central venous catheters (9); however, whether unique risk factors exist for fungal co-infections among patients with COVID-19 is unclear. The study aims to describe clinical characteristics, outcomes and risk factors of candidemia among patients hospitalized with severe COVID-19.

MATERIALS AND METHODS

Study Design and Setting

This multicenter, retrospective, case-control study included patients with severe COVID-19 who were also diagnosed with secondary candidemia from eight academic medical centers between August 2020 and August 2021. Participating centers were in New York/New Jersey, United States. All study sites received approval for conduct of this study with waivers of informed consent from their Institutional Review Boards (IRBs). Each site was listed within the IRB approval from Robert Wood Johnson University Hospital Office for Human Subject Protection (STUDY ID Pro2021000676), which functioned as the coordinating site. All procedures were in accordance with the ethical standards of the institutional IRB and with the Helsinki Declaration of 1975. The study was approved on May 18, 2021. The guidelines for reporting observational studies with the Strengthening the Reporting of Observational Studies in Epidemiology checklist was used to strengthen the reporting of our findings.

Study patients were adults (≥ 18 yr) with blood cultures drawn during the study period and had severe COVID-19, defined as individuals with respiratory rate greater than 30, oxygen saturation less than 94% on room air or the need for supplemental oxygen, Pao_2/Fio_2 less than 300 or more than 50% lung involvement on imaging with confirmed diagnosis of COVID-19 by a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test via a nasopharyngeal swab. The control group consisted of patients with severe COVID-19 without candidemia, and case patients were those with severe COVID-19 with confirmed candidemia. An episode of candidemia was defined as a positive blood culture for any *Candida* species identified by the microbiology laboratory. Controls were randomly selected from the same day of admission as cases in a 2:1 ratio.

Patient demographics, clinical and mycological characteristics, as well as comorbidities, concomitant interventions (antibiotics, immunosuppressive agents, parenteral nutrition, degree of oxygen support, mechanical ventilation, surgery), treatment regimens, and outcomes (length of stay and discharge disposition) were extracted retrospectively from each institution's electronic medical record and entered into a single Research Electronic Data Capture database. We sought to compare characteristics and outcomes among cases and controls and describe management of candidemia among cases.

Data Collection

Data on baseline, infection and demographic characteristics were assessed from the time of the COVID-19 diagnosis. The U.S. Centers for Disease Control and Prevention criteria to define infections were used to identify appropriate study patients by individual investigators; these determinations were then reviewed by the primary investigators to validate selection (10). Bloodstream infections was defined as fungal infection identified on blood cultures. Blood cultures were performed using BACTEC FX (Becton, Dickinson and Co., Franklin Lakes, NJ) Blood Culture Systems. Scores for several clinical indices were calculated, including the Charlson Comorbidity Index (CCI) for the degree of comorbid illness, Sequential Organ Failure Assessment (SOFA) scores for the severity of failed organs, and the respiratory rate oxygenation (ROX) index for the risk of intubation. The CCI and ROX scores were calculated for all study patients at the time of hospital admission. The SOFA score was calculated within 24 hours of ICU admission for patients admitted to the ICU only.

Statistical Analysis

All study measures and outcomes were first summarized overall and by case-control groups using range, median with interquartile range (IQR) for continuous measures, or frequency with percentage for categorical measures. Ordinal measures were summarized using median with IQR or frequency with percentage. The number of cases with missing data for each measure was tracked where applicable. Bivariate analyses using independent *t* tests or Wilcoxon rank-sum tests (depending on the result of Shapiro-Wilk normality testing) for continuous measures, Pearson chi-square or Fisher exact tests for categorical measures, and Wilcoxon rank-sum tests for ordinal measures were completed prior to any multivariable analyses. A multivariable logistic regression model with Akaike information criterion-based stepwise selection was then used to evaluate the development of candidemia in addition to COVID-19. Predictors included study site, patient demographics and prior medical history and clinical and pharmacotherapies received while hospitalized.

Statistical analyses were performed using R Version 4.1.1 (11), including the "MatchIt," "survival," and "DescTools" packages, and all two-sided *p* values of less than 0.05 were considered statistically significant (12–14).

RESULTS

A total of 275 patients were included in the study—184 control patients with severe COVID-19 and 91 case patients with severe COVID-19 and candidemia. Three of the eight hospital sites accounted for more than 50% of the study population. Baseline characteristics including demographics and comorbidities are summarized in **Table 1**. Most patients were male (61%) and median age was 65 years (IQR, 57–75 yr). The median CCI score was higher in COVID-19 patients without candidemia as compared with those with candidemia (4 vs 3; $p = 0.02$). Rates of individual comorbidities were similar between groups, except for a higher incidence of coronary artery disease in the control group of study patients without candidemia. Diabetes mellitus was present in approximately 40% of study patients, although other immunocompromising conditions such as malignancy, transplantation, and chronic corticosteroid use were less common.

Patients reported symptoms consistent with SARS-CoV-2 infection for a median of 6 days prior to hospital admission. Median ROX index score on hospital admission was 10.3 (IQR, 5.4–17.8 ROX index) in the control group (without candidemia) and 6.2 (IQR, 3.9–15 ROX index) in the cases with candidemia ($p = 0.01$). Patients with candidemia were more likely to require nonrebreather, high-flow nasal cannula, or mechanical ventilation at time of admission (**Table 2**). Case patients with candidemia also had a higher incidence of admission to the ICU (87.9% vs 58.2%; $p < 0.01$) and prolonged ICU length of stay (21 vs 10 d; $p < 0.01$) as compared with those without candidemia. Of the patients admitted to the ICU, median SOFA score at the time of ICU admission was 8 (IQR, 4–10) and comparable between groups.

Steroids, most commonly dexamethasone, were prescribed for almost two-thirds of all study patients with a median duration of 10 days (IQR, 5–13 d) (Table 2). COVID-19 patients with candidemia were significantly more likely to receive biologic therapy than patients without candidemia (44% vs 18.5%; $p < 0.01$), with tocilizumab most prescribed. Approximately one-quarter of the total study population required continuous paralytic therapy, with more frequent use in the cases with candidemia. Similarly, overall antimicrobial exposure was notably higher in study patients with candidemia, as they were more likely to receive antimicrobial therapy, with higher numbers of prescribed medications, and for longer durations. Median hospital length of stay was significantly longer (30 d [IQR, 21.5–57 d] vs 15 d [IQR, 8–26 d]; $p < 0.01$) and in-hospital mortality was higher (68.1% vs 40.2%; $p < 0.01$) in the cases with candidemia.

There were total of 101 unique *Candida* isolates identified in the 91 case patients with candidemia (**Table 3**). Candidemia was diagnosed a median of 18 days (IQR, 11–26 d) after both hospital admission and COVID-19 diagnosis. The rate and duration of central line placement were both significantly higher in case patients with candidemia (Table 2). Less than 10% of the study population received parenteral nutrition, although total parenteral nutrition (TPN) duration was longer in patients with candidemia. Almost half of patients with candidemia received hemodialysis or continuous renal replacement therapy prior to first positive blood culture. Two patients with candidemia received extracorporeal membrane oxygenation

TABLE 1.
Demographics and Baseline Characteristics of Study Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Positive With or Without Candidemia

Demographics	Total (*n* = 275)	Controls (*n* = 184)	Cases (*n* = 91)	*p*
Age (yr)	65 (57–75)	67 (59–76)	62 (54.5–72)	0.01
Gender				0.16
Male	168 (61.1)	107 (58.2)	61 (67.0)	
Female	107 (38.9)	77 (41.8)	30 (33.0)	
Primary race				0.19
Black or African American	126 (45.8)	87 (47.3)	39 (42.9)	
White	64 (23.3)	45 (24.5)	19 (20.9)	
Hispanic or Latino	47 (17.1)	30 (16.3)	17 (18.7)	
Asian	17 (6.2)	12 (6.5)	5 (5.5)	
Native Hawaiian or other Pacific Islander	3 (1.1)	2 (1.1)	1 (1.1)	
Other	5 (1.8)	4 (2.2)	1 (1.1)	
Unknown	13 (4.7)	4 (2.2)	9 (9.9)	
Body mass index	29.1 (26–34)	28.9 (25.6–34.1)	29.8 (27.1–33.8)	0.32
Study site				Not applicable
University hospital	53 (19.3)	35 (19.0)	18 (19.8)	
Robert Wood Johnson University Hospital	50 (18.2)	34 (18.5)	16 (17.6)	
Newark Beth Israel Medical Center	42 (15.3)	28 (15.2)	14 (15.4)	
Saint Barnabas Medical Center	33 (12.0)	22 (12.0)	11 (12.1)	
BronxCare Health System	33 (12.0)	22 (12.0)	11 (12.1)	
Saint Peter's University Hospital	21 (7.6)	14 (7.6)	7 (7.7)	
SUNY Downstate Medical Center	16 (5.8)	11 (6.0)	5 (5.5)	
Jersey Shore Medical Center	27 (9.8)	18 (9.8)	9 (9.9)	
Underlying medical conditions				
Congestive heart failure	41 (14.9)	29 (15.8)	12 (13.2)	0.57
Coronary artery disease	55 (20.0)	45 (24.5)	10 (11.0)	0.01
Diabetes	118 (42.9)	80 (43.5)	38 (41.8)	0.77
End-stage liver disease	4 (1.5)	3 (1.6)	1 (1.1)	1.0
HIV infection	8 (2.9)	5 (2.7)	3 (3.3)	0.72
Hyperlipidemia	91 (33.1)	66 (35.9)	25 (27.5)	0.16
Hypertension	185 (67.3)	127 (69.0)	58 (63.7)	0.41
Lung disease	42 (15.3)	30 (16.3)	12 (13.2)	0.50
Malignancy	27 (9.8)	17 (9.2)	10 (11.0)	0.65
Renal disease				
Acute kidney injury	13 (4.7)	6 (3.3)	7 (7.7)	0.13
Chronic kidney disease	31 (11.3)	23 (12.5)	8 (8.8)	0.36
End-stage renal disease	22 (2.0)	15 (8.2)	7 (7.7)	0.89
Stroke	27 (9.8)	21 (11.4)	6 (6.6)	0.21
Transplantation (solid organ)	7 (2.5)	5 (2.7)	2 (2.2)	1.0
Chronic steroid use	13 (4.7)	10 (5.4)	3 (3.3)	0.55
Immunosuppressant use	9 (3.3)	8 (4.3)	1 (1.1)	0.28
Charlson Comorbidity Index score at admission	4 (2–6)	4 (2–7)	3 (2–5)	0.02

All data provided as *n* (%) or median (interquartile range).

TABLE 2.
Hospitalization Details and Outcomes

Outcomes	Total (*n* = 275)	Controls (*n* = 184)	Cases (*n* = 91)	*p*
Duration of COVID symptoms prior to admission (d)	6 (3–7)	5 (3–7)	7 (3–7)	0.74
Acute steroid use[a,b]	196 (71.3)	128 (69.6)	68 (74.7)	NA
Dexamethasone	121 (61.7)	81 (63.3)	40 (58.8)	
Hydrocortisone	36 (18.4)	18 (14.1)	18 (26.5)	
Methylprednisolone	73 (37.2)	48 (37.5)	25 (36.8)	
Prednisone	18 (9.2)	17 (13.3)	1 (1.5)	
Total duration of acute steroids (d)	10 (5–13)	9 (5–12.2)	10 (7–14)	0.06
Biologic use[b]	74 (26.9)	74 (26.9)	40 (44.0)	< 0.01
Infliximab	1 (1.4)	0 (0.0)	1 (2.5)	
Sarilumab	4 (5.4)	4 (11.8)	0 (0.0)	
Siltuximab	1 (1.4)	0 (0.0)	1 (2.5)	
Tocilizumab	66 (89.2)	30 (88.2)	36 (90.0)	
Antimicrobial use[b]	256 (93.1)	165 (89.7)	91 (100.0)	< 0.01
Number of antimicrobials used				< 0.01
Zero	19 (6.9)	19 (10.3)	0 (0.0)	
One	31 (11.3)	30 (16.3)	1 (1.1)	
Two	43 (15.6)	36 (19.6)	7 (7.7)	
Three	43 (15.6)	35 (19.0)	8 (8.8)	
Four	53 (19.3)	31 (16.9)	22 (24.2)	
Five	26 (9.5)	14 (7.6)	12 (13.2)	
Six or more	60 (21.8)	19 (10.3)	41 (45.0)	
Total duration of antimicrobials (d)	12.5 (6–23)	8 (5–15)	20 (14–39)	< 0.01
Total parenteral nutrition given	23 (8.4)	14 (7.6)	9 (9.9)	0.52
Total duration of total parenteral nutrition (d)	11 (6–14.5)	10.5 (6–11)	14 (11–32)	0.048
Central line present[b]	174 (63.3)	88 (47.8)	86 (94.5)	< 0.01
Total duration of central line (d)	14 (8–25)	11 (8–22)	18 (10–28)	0.01
Supplemental oxygen used during COVID admission				
Nasal cannula	185 (67.3)	128 (69.6)	57 (62.6)	0.25
Nonbreather	133 (48.4)	78 (42.4)	55 (60.4)	0.01
High-flow nasal cannula	106 (38.5)	60 (32.6)	46 (50.5)	< 0.01
Bilevel positive airway pressure	64 (23.3)	38 (20.7)	26 (28.6)	0.14
Mechanical ventilation	134 (48.7)	71 (38.6)	63 (69.2)	< 0.01
Respiratory rate oxygenation index at admission	9.1 (4.7–16.8)	10.3 (5.4–17.8)	6.2 (3.9–15)	0.01
Tracheostomy during admission	71 (25.8)	37 (20.1)	34 (37.4)	< 0.01
ICU admission	187 (68.0)	107 (58.2)	80 (87.9)	< 0.01
Sequential Organ Failure Assessment score at time of ICU admission[c]	8 (4–10)	8 (4–10)	7.5 (4–10)	0.79
Continuous paralytic use[a]	65 (23.6)	25 (13.6)	40 (44.0)	NA
Cisatracurium	56 (86.2)	22 (88.0)	34 (85.0)	
Rocuronium	9 (13.8)	3 (12.0)	6 (15.0)	
Vecuronium	5 (7.7)	4 (16.0)	1 (2.5)	
Length of ICU stay (d)	14 (7–26)	10 (6–18)	21 (12–39)	< 0.01
Length of hospital stay (d)	20 (10–35)	15 (8–26)	30 (21.5–57)	< 0.01
In-hospital mortality	136 (49.5)	74 (40.2)	62 (68.1)	< 0.01

NA = not applicable.

[a]Patients may have received more than one medication listed per category.

[b]Results for case group reflect assessment of outcome prior to diagnosis of candidemia.

[c]Sequential Organ Failure Assessment score calculated for patients requiring ICU admission only.

All data provided as *n* (%) or median (IQR) unless otherwise noted.

TABLE 3.
Candidemia Details for Case Patients

Candidemia Characteristics	Cases ($n = 91$)
Time from COVID diagnosis to candidemia diagnosis (d)	18 (11–26)
Days from candidemia positive to candidemia negative	3.7 (9.7)
Isolated *Candida* species[a]	
Candida albicans	48 (52.7)
C. glabrata	17 (18.7)
C. tropicalis	14 (15.4)
C. parapsilosis	10 (11.0)
C. krusei	2 (2.2)
C. auris	3 (3.3)
Other[b]	7 (7.7)
Suspected source of candidemia	
Central line	57 (62.6)
Intra-abdominal	6 (6.6)
Respiratory	3 (3.3)
Urinary	1 (1.1)
Unknown	20 (22.0)
More than one potential source	13 (4.4)
Renal replacement therapy within 72 hr of candidemia diagnosis	43 (47.3)
Continuous renal replacement therapy	16 (17.6)
Hemodialysis	27 (29.7)
Antifungal therapy used[c]	
Amphotericin	4 (4.4)
Echinocandin	80 (87.9)
Fluconazole	34 (37.4)
Voriconazole	3 (3.3)
Time from candidemia diagnosis to antifungal therapy initiation (hr)	3 (0.8–13.5)
Time from candidemia diagnosis to microbiological clearance (d)	2 (0–4)
Total duration of antifungal therapy (d)	11 (3–15)

[a]Patients may have had more than one *Candida* species isolated from blood cultures.
[b]Other *Candida* species isolated include *C. lusitaniae* (4), *C. dubliniensis* (1), *C. guilliermondii* (1), and *C. nivariensis* (1).
[c]Patients may have received more than one antifungal agent listed.
All data provided as *n* (%) or median (interquartile range) unless otherwise noted.

support. *Candida albicans* was the most frequently isolated pathogen, followed by *C. glabrata* and *C. tropicalis*. Notably, three patients had candidemia due to *C. auris*. Antifungal treatment was initiated a median of 3 hours (IQR, 0.8–13.5 hr) from the time of diagnosis of candidemia. More than half of the patients with candidemia received antifungal therapy within 6 hours of blood culture positivity. The time from candidemia diagnosis to initiation of antifungal therapy was not associated with mortality in the case patients (**Table 4**). Microbiological clearance of *Candida* species was achieved in a median of 2 days (IQR, 0–4 d). Echinocandins and fluconazole were the most prescribed antifungal agents. Five patients did not receive antifungal therapy and died following hospitalization for a length of stay ranging from 7 to 29 days.

Logistic regression models were fit to identify the combination of significant risk factors associated with candidemia. In the final model including 262 study patients, use of central lines (odds ratio [OR], 31.22; 95% CI, 6.58–191.42; $p < 0.001$), biologic therapy (OR, 4.15; 95% CI, 1.74–10.38; $p = 0.002$), and paralytic therapy (OR, 4.48; 95% CI, 1.55–14.29; $p = 0.008$) were significantly associated with increased risk of candidemia. Five of the eight hospital sites were also identified as predictors for candidemia, which may reflect inherent differences in patient population, management, and other site factors. While not statistically significant, the presence of acute kidney injury (AKI) and intubation demonstrated trends toward an increased risk of candidemia. Unexpectedly, ICU admission (OR, 0.14; 95% CI, 0.02–0.74; $p = 0.026$) was associated with a decreased risk of candidemia, which can be possibly explained by survivorship bias since critically ill COVID-19 patients may have died before candidemia episodes could develop and/or optimal infection prevention measures in the ICU wards.

DISCUSSION

This case-control study demonstrated that hospitalized COVID-19 patients that developed candidemia as a complication of SARS-CoV-2 infection experienced worse outcomes, specifically length of stay and survival, as compared with COVID-19 patients without candidemia, with risk factors for candidemia generally consistent with prior literature in non-COVID-19 patients. To our knowledge, this is the largest multicenter case-control study to date that identifies risk factors for the development of candidemia and demonstrates substantially higher in-hospital mortality

TABLE 4.
Time to Antifungal Therapy in Cases (Cases: COVID + Fungemia), Blood Culture & Candidemia Information

Study Measures	Total Sample ($n = 91$)	Final Disposition: Discharged ($n = 29$)	Final Disposition: Deceased ($n = 62$)	p
Hours from candidemia diagnosis to fungal therapy				0.74
Range	−144 to 428.5	0–71	−144 to 428.5	
Median (Q1–Q3)	3 (0.8–13.5)	2 (2–7)	4 (0–22)	
Hours from candidemia diagnosis to fungal therapy–categorized, *n* (%)				0.40
Pre-diagnosis administration (< 0 hr)	4 (4.4)	0 (0.0)	4 (6.5)	
Shortly after diagnosis (0–6 hr)	47 (51.6)	17 (58.6)	30 (48.4)	
Longer after diagnosis (6+ hr)	40 (44.0)	12 (41.4)	28 (45.2)	
Total duration of fungal therapy (d)				< 0.01
Range	0–34	3–34	0–16	
Median (Q1–Q3)	11 (3–15)	16 (14–20)	4 (2–13.5)	

among those with COVID-19 and secondary candidemia compared with those without candidemia.

COVID-19 may increase the risk for candidemia because of its effect on the immune system and the immunosuppressive therapy (steroids and biologics) that patients may receive during treatment, which can weaken the immune system against *Candida* (1, 2). Known risk factors for candidemia in the general inpatient population include an extended length of stay, broad-spectrum antibiotic use, neutropenia, TPN, mechanical ventilation, hemodialysis, and central venous catheter use (9, 15). Identification of risk factors for candidemia is imperative, as laboratory diagnostic methodologies such as the beta-D-glucan assay are associated with high false-positive rates, and polymerase chain reaction assays have limited availability in clinical practice (15, 16). Positive culture or histologic evidence remains the standard for definitive diagnosis of fungal infections (15, 16).

Candidemia is a reported complication of COVID-19 critical illness (17) and is associated with increased morbidity and mortality (18). COVID-19 can cause acute respiratory distress syndrome, which typically requires weeks of mechanical ventilation and often requires the initiation of high-dose steroid therapy. These factors potentially increase the risk of candidemia (19–21). However, our study did not demonstrate mechanical ventilation or corticosteroids as risk factors for candidemia among patients with COVID-19. Additionally, it is reported that candidemia is seen earlier (within 2 wk) during hospital stay among COVID-19 patients compared with patients without COVID-19 (21, 22). We observed a median of 18 days (IQR, 11–26 d) for the development of candidemia. The reasons for this finding are uncertain other than the additive impact of risk factors (higher and earlier use of steroids in other reports [21, 22] and disease severity).

In previous studies, in-hospital mortality in patients with candidemia ranged from 25% to 40% (22, 23), whereas our study found a higher mortality rate of 68% in patients with candidemia and COVID-19, which was also significantly higher than the mortality rate of COVID-19 patients without candidemia ($p < 0.01$). Patients with candidemia were more likely to be admitted to the ICU or require oxygen at admission. Independent risk factors for candidemia identified in our study were the use of central lines, tocilizumab, and paralytic therapy, while AKI and intubation trended toward significance. Interestingly, our study demonstrated that use of paralytic therapy was associated with candidemia, which had not been previously described. The explanation for this is unclear other than many of these patients concomitantly had central lines for continuous paralytic infusions to aid in ventilator synchrony. Despite similar SOFA scores at ICU admission between cases and controls, more than half of the candidemia patients were on renal replacement therapy, and almost half received continuous paralytic infusions. These variables may

serve as surrogates for organ failure, highlighting the impact severity of illness may have on the development of candidemia.

Like previous studies, our study observed an increased use of broad-spectrum antibiotics and longer duration in patients that developed candidemia. (19, 20) The median duration of antibiotics was 8 days for controls and 20 days for cases with documented candidemia ($p < 0.01$). Since secondary bacterial co-infections was a feared complication during the surge of COVID-19 cases, clinicians may have felt compelled to treat with antibiotics despite a clear indication. The evidence on true bacterial co-infection is conflictive and estimates range from 3.6% to 37% (24–26). This should drive clinicians to question whether prolonged utilization of broad-spectrum antibiotics in this population negatively influences mortality by increasing the risk of candidemia.

C. albicans was the most frequently isolated pathogen. In our study, we also reported three episodes of *C. auris* bloodstream infection, two of whom were deceased by the time of this review and one was discharged home alive. In July 2020, the initial three cases of *C. auris*-COVID-19 co-infection were described in Florida, United States (27). Since then, multiple reports from many countries have been documented, including India where 10 patients with *C. auris* candidemia had a mortality of 60% (28). Another report from Mexico, in which *C. auris* was isolated from blood in six patients, identified a mortality rate of 83.3% (29).

While some observations reported that tocilizumab did not influence acquisition of nosocomial infections (30–32), we observed the use of tocilizumab as a strong predictor for candidemia as it was present in 44% of case patients ($p < 0.01$). One hypothesis for this finding is that the interleukin-6 blockade could deter the immune system capacity to overcome candidemia. This has also been reported recently by other investigators where the use of tocilizumab and duration of ICU stay were independent predictors for the development of candidemia (26).

Furthermore, contrary to other analyses, we did not find steroids to be a significant risk factor on logistic regression (20, 21). However, since over two-thirds of all cases in our patient cohort received steroids, the impact of this single factor would be difficult to discern. Additionally, the variability of steroid(s) prescribed and the lack of data collection on steroid doses and durations limited the ability to further assess the relationship between steroid exposure and risk of candidemia. While TPN has been previously identified as a risk factor for candidemia, there were not enough study patients receiving TPN to evaluate this factor as a predictor of candidemia in COVID-19 patients.

While early recognition and treatment of candidemia has been associated with better overall outcomes (8), with continued challenges in timely identification of candidemia, it remains uncertain whether earlier antifungal treatment impacts mortality. In our study, the median time from identification of candidemia to antifungal therapy was 3 hours (IQR, 0.8–13.5 hr). The median time differed between the discharged group (2 hr [IQR, 2–7 hr] vs 4 hr [IQR, 0–22 hr]; $p = 0.74$) and deceased group, respectively. Notably, patients that received antifungal therapy within 6 hours of candidemia diagnosis 17 (59%) were discharged compared with 30 (48%) in the deceased group, although not statistically significant; these findings signal the importance of early antifungal therapy.

While this multicenter study evaluates the largest cohort of patients with COVID-19 and secondary candidemia to date, there are several limitations for consideration. Retrospective design, recall bias, missing information, and lack of follow-up may have affected the robustness of collected data. In addition, absence of standardized management of COVID-19 during the study period led to varied treatment approaches between institutions, potentially impacting patient outcomes. Furthermore, we did not collect data on deep sedation regimens or utilization or lack of ICU liberation bundle, which has been shown to impact outcomes. Last, we do not report *Candida* susceptibilities and the extent of candidemia complications including endophthalmitis and endocarditis, which might have affected outcomes, although these entities are rare.

Timely diagnosis of candidemia remains a challenge with current standard microbiology techniques. In addition to others, our study reports a trend for certain risk factors for candidemia that are more prevalent in critically ill patients. Future research should investigate new modifiable and nonmodifiable risk factors, improved IC surveillance, as well as serology, culture, and rapid diagnostic results to identify appropriate patients who may benefit from empiric antifungal therapy while not unnecessarily increasing the number of patients who receive this therapy. Implications of our study results are unclear due to the evolving nature of COVID-19 management and emerging variant strains.

CONCLUSIONS

Our study demonstrated that COVID-19 can be complicated by candidemia co-infection, leading to higher morbidity and mortality. COVID-19 patients with candidemia required ICU admission and received tocilizumab, antibiotics, paralytic infusions, renal replacement therapy, and central lines more frequently prior to developing candidemia than patients without candidemia. Clinicians should consider implementing protocols for surveillance and prevention of complications associated with infection.

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REFERENCES

1. Johns Hopkins University of Medicine: Coronavirus Resource Center. 2021. Available at: coronavirus.jhu.edu. Accessed March 31, 2022
2. National Institutes of Health: COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed March 20, 2022
3. Russell CD, Fairfield CJ, Drake TM, et al; ISARIC4C investigators: Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: A multicentre, prospective cohort study. *Lancet Microbe* 2021; 2:e354–e365
4. Langford BJ, So M, Raybardhan S, et al: Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clin Microbiol Infect* 2020; 26:1622–1629
5. Goncalves Mendes Neto A, Lo KB, Wattoo A, et al: Bacterial infections and patterns of antibiotic use in patients with COVID-19. *J Med Virol* 2021; 93:1489–1495
6. 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; 27:83–88
7. Baddley JW, Thompson GR 3rd, Chen SC, et al: Coronavirus disease 2019-associated invasive fungal infection. *Open Forum Infect Dis* 2021; 8:ofab510
8. Pappas PG, Kauffman CA, Andes DR, et al: Executive summary: Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 62:409–417
9. Bajwa S, Kulshrestha A: Fungal infections in intensive care unit: Challenges in diagnosis and management. *Ann Med Health Sci Res* 2013; 3:238–244
10. Horan TC, Andrus M, Dudeck MA: CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; 36:309–332
11. R Core Team: R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing, 2021. Available at: https://www.R-project.org/. Accessed April 11, 2022
12. Ho D, Imai K, King G, et al: MatchIt: Nonparametric preprocessing for parametric causal inference. *J Stat Soft* 2011; 42:1–28
13. Therneau T: _A Package for Survival Analysis in R_. R package version 3.2-13. 2021. Available at: https://CRAN.R-project.org/package=survival. Accessed April 11, 2022
14. Andri et mult. al. S: DescTools: Tools for Descriptive Statistics. R package version 0.99.43. 2021. Accessed April 11, 2022
15. Suleyman G, Alangaden GJ: Nosocomial fungal infections: Epidemiology, infection control, and prevention. *Infect Dis Clin North Am* 2016; 30:1023–1052
16. Blumberg HM, Jarvis WR, Soucie JM, et al; National Epidemiology of Mycoses Survey(NEMIS) Study Group: Risk factors for candidal bloodstream infections in surgical intensive care unit patients: The NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis* 2001; 33:177–186
17. Basile K, Halliday C, Kok J, et al: Fungal infections other than invasive aspergillosis in COVID-19 patients. *J Fungi (Basel)* 2022; 8:58
18. Koehler P, Stecher M, Cornely OA, et al: Morbidity and mortality of candidaemia in Europe: An epidemiologic meta-analysis. *Clin Microbiol Infect* 2019; 25:1200–1212
19. Casalini G, Giacomelli A, Ridolfo A, et al: Invasive fungal infections complicating COVID-19: A narrative review. *J Fungi (Basel)* 2021; 7:921
20. Seagle EE, Jackson BR, Lockhart SR, et al: The landscape of candidemia during the coronavirus disease 2019 (COVID-19) pandemic. *Clin Infect Dis* 2022; 74:802–811
21. Kayaaslan B, Eser F, Kaya Kalem A, et al: Characteristics of candidemia in COVID-19 patients; increased incidence, earlier occurrence and higher mortality rates compared to non-COVID-19 patients. *Mycoses* 2021; 64:1083–1091

22. Nucci M, Barreiros G, Guimarães LF, et al: Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. *Mycoses* 2021; 64:152–156
23. Tsay SV, Mu Y, Williams S, et al: Burden of candidemia in the United States, 2017. *Clin Infect Dis* 2020; 71:e449–e453
24. 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; 42:84–88
25. Ripa M, Galli L, Poli A, et al; COVID-BioB study group: Secondary infections in patients hospitalized with COVID-19: Incidence and predictive factors. *Clin Microbiol Infect* 2021; 27:451–457
26. 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
27. Prestel C, Anderson E, Forsberg K, et al: Candida auris outbreak in a COVID-19 specialty care unit - Florida, July-August 2020. *MMWR Morb Mortal Wkly Rep* 2021; 70:56–57
28. Chowdhary A, Tarai B, Singh A, et al: Multidrug-resistant Candida auris infections in critically ill coronavirus disease patients, India, April-July 2020. *Emerg Infect Dis* 2020; 26:2694–2696
29. 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; 27:813–816
30. Meira F, Moreno-García E, Linares L, et al: Impact of inflammatory response modifiers on the incidence of hospital-acquired infections in patients with COVID-19. *Infect Dis Ther* 2021; 10:1407–1418
31. 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
32. Omrani AS, Koleri J, Ben Abid F, et al: Clinical characteristics and risk factors for COVID-19-associated Candidemia. *Med Mycol* 2021; 59:1262–1266