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ORIGINAL ARTICLE

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Understanding clinical outcomes and factors influencing mortality in intensive care unit patients with COVID-19-associated candidemia

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Abstract

Background: During the COVID pandemic, research has shown an increase in candidemia cases following severe COVID infection and the identification of risk factors associated with candidemia. However, there is a lack of studies that specifically explore clinical outcomes and mortality rates related to candidemia after COVID infection.

Objectives: The aim of this international study was to evaluate the clinical outcomes and identify factors influencing mortality in patients who developed candidemia during their COVID infection.

Patients/Methods: This study included adult patients (18 years of age or older) admitted to the intensive care unit (ICU) and diagnosed with COVID-associated candidemia (CAC). The research was conducted through ID-IRI network and in collaboration with 34 medical centres across 18 countries retrospectively, spanning from the beginning of the COVID pandemic until December 2021.

Results: A total of 293 patients diagnosed with CAC were included. The median age of the patients was 67, and 63% of them were male. The most common *Candida* species detected was *C. albicans*. The crude 30-day mortality rate was recorded at 62.4%. The

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logistic regression analysis identified several factors significantly impacting mortality, including age (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.07, $p < .0005$), SOFA score (OR 1.307, 95% CI 1.17–1.45, $p < .0005$), invasive mechanical ventilation (OR 7.95, 95% CI 1.44–43.83, $p < .017$) and duration of mechanical ventilation (OR 0.98, 95% CI 0.96–0.99, $p < .020$).

Conclusions: By recognising these prognostic factors, medical professionals can customise their treatment approaches to offer more targeted care, leading to improved patient outcomes and higher survival rates for individuals with COVID-associated candidemia.

KEYWORDS
candidemia, COVID-19, COVID-19-associated candidemia, intensive care unit, mortality

1 | INTRODUCTION

Throughout the pandemic, severe cases of COVID have led to extended hospital stays or admission to intensive care units (ICUs). This circumstance has given rise to secondary nosocomial infections caused by bacteria or fungi, a phenomenon observed in other respiratory viral infections as well.[1–3] It is well established that the risk of bacterial or fungal infection is elevated in patients receiving intensive care, particularly those who require mechanical ventilation or other invasive medical devices.[4] Furthermore, there are reports suggesting that the use of immunomodulators (such as tocilizumab) and corticosteroid drugs in the treatment of COVID can potentially heighten the risk of fungal infection.[5,6]

Candidemia, which exhibited a high mortality rate ranging from 30% to 60% in clinical studies conducted before the COVID pandemic,[7–9] as garnered renewed attention in the context of COVID. There have been reports on the increased incidence of candidemia following COVID, as well as the identification of risk factors associated with candidemia and studies on mortality.[10–12]

In this groundbreaking international study, our primary focus was to comprehensively investigate the clinical outcomes that emerge from the intricate connection between COVID-19 and candidemia. By meticulously analysing this relationship, we aimed to gain deep insights into the factors that actively contribute to mortality, thereby enhancing our understanding of this complex phenomenon.

2 | MATERIALS AND METHODS

2.1 | Study design

Between March 2020 and December 2021, a retrospective cross-sectional multicentre, international study was designed. The study was conducted using the ID-IRI international clinical research platform (https://infectdisiri.com/). ID-IRI is a global organisation with members worldwide who voluntarily participate in ID-IRI research projects. A total of 34 centres from 18 countries took part in this study, including Afghanistan, Bahrain, Bangladesh, Bulgaria, Croatia, Egypt, Hungary, India, Italy, Pakistan, Portugal, Qatar, Romania, Russia, Sarajevo, Turkey, UAE and the USA.

2.2 | Case definition

The study included adult patients (≥18 years old) who had been diagnosed with COVID, confirmed by a positive reverse transcription-polymerase chain reaction (RT-PCR) test for acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and were admitted to the ICU and subsequently developed candidemia. The severity of COVID was categorised as mild to severe based on the WHO classification.[13]

2.3 | Data collection

Data of patients with COVID who were monitored in the ICU until discharge or death were collected for this study using Microsoft Forms through a web page link, from December 2021 to April 2022. The collected data encompassed various demographic characteristics and underlying comorbidities of the patients, such as age, gender, obesity (BMI > 35), diabetes mellitus, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, malignancy, solid organ transplantation, hypertension. Additional recorded information included the use of steroid or other immunosuppressive agents in the 3 months prior to the diagnosis of CAC, the utilisation of broad-spectrum antibiotics, the presence of a central venous catheter, total parenteral nutrition, invasive mechanical ventilation, the Sequential Organ Failure Assessment (SOFA) score, absolute lymphocyte count, antiviral treatment for COVID, cytokine releasing syndrome treatment (IL-1 or IL-6 receptor inhibitors), dose and duration of corticosteroid treatment for COVID (with standard guideline recommendation being dexamethasone; 6 mg/day for 10 days, or other options

of corticosteroids), identification of *Candida* species, antifungal susceptibility, antifungal treatment and mortality. Data of patients with COVID who were monitored in the ICU until discharge or death were collected for this study using Microsoft Forms through a web page link, from December 2021 to April 2022. The collected data encompassed various demographic characteristics and underlying comorbidities of the patients, such as age, gender, obesity (BMI > 35), diabetes mellitus, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, malignancy, solid organ transplantation, hypertension. Additional recorded information included the use of steroid or other immunosuppressive agents in the 3 months prior to the diagnosis of CAC, the utilisation of broad-spectrum antibiotics, the presence of a central venous catheter, total parenteral nutrition, invasive mechanical ventilation (IMV), the Sequential Organ Failure Assessment (SOFA) score, absolute lymphocyte count, antiviral treatment for COVID, cytokine releasing syndrome treatment (IL-1 or IL-6 receptor inhibitors), dose and duration of corticosteroid treatment for COVID (with standard guideline recommendation being dexamethasone; 6 mg/day for 10 days, or other options of corticosteroids), identification of candida species, antifungal susceptibility, antifungal treatment and mortality.

The dosage of each type of steroid used for COVID was converted to the equivalent dose of methylprednisolone, and analyses of steroid data were conducted based on the total dose and duration of methylprednisolone. Furthermore, the time intervals (in days) between RT-PCR confirmation of COVID and IMV, between RT-PCR confirmation of COVID and diagnosis of CAC, between hospitalisation and ICU admission, as well as the duration of mechanical ventilation and ICU length of stay, were recorded.

2.4 | Main outcome

Death occurring within 30 days after diagnosis of candidemia was defined as crude mortality. Risk factors for mortality in patients with CAC were investigated.

2.5 | Ethics statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and ethical approval for this study was obtained from the Istanbul Medipol University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (E-10840098-772.02-1631/05.03.2022).

2.6 | Statistics

The statistical analyses were carried out using SPSS software version 22.0. The normal distribution of variables was assessed using the Shapiro–Wilk test. Descriptive analyses were presented as means ± standard deviations for normally distributed variables, and as medians (min–max) for variables that were not normally distributed. Continuous variables were compared using the Mann–Whitney *U*-test due to the violation of parametric test assumptions, while categorical variables were compared using the Chi-square test. To identify independent predictors of mortality in CAC, multivariate logistic regression analysis was performed. All variables that showed significance in the univariate analysis between CAC patients who survived and those who did not survive were included in the multivariate logistic regression models. The performance of the established logistic regression model in predicting mortality was evaluated using ROC Curve analysis, and the sensitivity, specificity, positive predictive value and negative predictive value were reported. A p-value of <.05 was considered statistically significant.

3 | RESULTS

This study examined 293 patients with CAC from 18 participating countries (Turkey [$n = 88$], Qatar [$n = 27$], Afghanistan [$n = 26$], Florida [$n = 24$], Egypt [$n = 24$], Bahrain [$n = 24$], Bulgaria [$n = 20$], Abu Dhabi [$n = 15$], Hungary [$n = 13$], Romania [$n = 10$], India [$n = 7$], Portugal [$n = 5$], Italia [$n = 4$], Russia [$n = 2$], Bangladesh [$n = 1$], Croatia [$n = 1$], Pakistan [$n = 1$] and Sarajevo [$n = 1$]). Table 1 presents the demographic, clinical and microbiologic data of these patients. The median age of the patients was 67 (ranging from 28 to 109), and 63% of them were male.

3.1 | Comorbid conditions

Comorbidities were present in 87% of the patients, with diabetes mellitus 125 (43%) and coronary artery disease 92 (31%) being the most common. Fifty-three patients (18%) had three or more comorbidities, and 85% of them were 65 years or older.

3.2 | Predisposing factors

The main predisposing factors for candidemia included the use of broad-spectrum antibiotics 263 (90%), IMV 262 (89%), the presence of a central venous catheter 211 (72%) and total parenteral nutrition 122 (42%).

3.3 | Microbial identification

A total of 293 *Candida* spp. were isolated from blood cultures, with 250 being identified as specific *Candida* species. The most prevalent species was *C. albicans* 113 (39%), followed by *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. auris* at 46 (16%), 33 (11%), 25 (9%) and 17 (6%), respectively, among the non-albicans species.

TABLE 1 Demographic characteristics of patients with COVID-associated candidemia.

Demographic characteristics	Total $N = 293$
Age median (min–max)	67 (28–109)
Gender	
Female	109 (37)
Male	184 (63)
Comorbidity	254 (87)
DM	125 (43)
Obesity, BMI ≥ 35	42 (14)
Malignancy	29 (9)
Coronary artery disease	92 (31)
Chronic renal failure	48 (16)
Chronic obstructive pulmonary disease	37 (13)
Hypertension	45 (15)
Patients who had three or more comorbidities	53 (18)
Predisposing factors for candidemia	
Use of immunosuppression therapy[a]	29 (10)
Use of long-term steroids[b]	25 (8.5)
Use of broad-spectrum antibiotic	263 (90)
Total parenteral nutrition	122 (42)
Central venous catheter	211 (72)
Use of steroid treatment for COVID median (min–max)	
The total steroid dose (mg)	80 (0–8500)
The total steroid during (days)	10 (0–80)
Antiviral treatments	254 (87)
Remdesevir	85 (33)
Favipiravir	117 (46)
Hydroxychloroquine	35 (13)
Lopinavir-ritonavir	13 (5)
No antiviral treatment	39 (13)
Tocilizumab	53 (18)
Lymphocyte count at diagnosis of CAC median (min–max)	810 (12–14,000)
Renal replacement therapy at diagnosis of CAC	81 (28)
Inotropic therapy at diagnosis of CAC	135 (46)
SOFA score median (min–max)	9 (0–19)
Invasive mechanical ventilation	262 (89)
The total duration of IMV median (min–max)	12 (0–150)
The total ICU length of stay median (min–max)	20 (2–152)
No antifungal treatment	21 (7)
Candida species	
C. albicans	113 (39)
C. glabrata	33 (11)
C. parapsilosis	46 (16)
C. tropicalis	25 (9)
C. auris	17 (6)
C. krusei	6 (2)
Other *Candida* subspecies	10 (3)
Not identified *Candida* spp.	43 (15)
Antifungal resistance[c]	
Azole	22 (15)
Amphotericin B	12 (0.9)
Echinocandin	5 (0.4)
30-day crude mortality	183 (62.4)

Note: Unless stated otherwise, data are presented as numbers (%).

Abbreviations: BMI, Body mass index; CAC, COVID-associated candidemia; DM, Diabetes mellitus; ICU, Intensive care unit; IMV, Invasive mechanic ventilation; RTT, Renal replacement therapy.

[a]Immune suppressive or modulating therapy within 90 days before hospitalisation for COVID.

[b]Long-term steroid use, as defined prednisolone ≥0.3 mg/kg/day ≥3 weeks, in the previous 2 months before the diagnosis of COVID.

[c]Antifungal susceptibility test was performed on 162 of 293 Candida isolates.

3.4 | Antifungal susceptibility testing

Antifungal susceptibility testing was performed on 162 *Candida* spp., revealing resistance rates of 15% to azoles, 0.9% to amphotericin B and 0.5% to echinocandins.

3.5 | Antifungal treatment

Ninety-three per cent of patients received antifungal treatment. The median duration of antifungal therapy in this cohort was 11 days (min–max: 0–55). Of 293 patients, 116 (40%) received an echinocandin, 102 (35%) received an azole as initial therapy and two patients received amphotericin B. In 52 patients (18%), the initial antifungal treatment was switched to another antifungal group. In 36 of these patients (12%), an azole was switched to an echinochandin. Echinocandins were the definitive treatment in 52% of patients. Twenty-one patients (7%) did not receive any antifungal and all of them died. Fifteen of the patients who did not receive antifungal therapy died within the first 72 h. The majority of patients received an echinocandin or azole. Therefore, these two antifungal groups were evaluated in the univariate analysis and no statistically significant results were obtained (p: .075).

3.6 | Outcomes

The crude 30-day mortality rate was 62.4%. Logistic regression analysis identified age, SOFA score, IMV and duration of mechanical ventilation as factors influencing mortality. Table 2 presents the results of both univariate and multivariate analyses of the factors affecting mortality.

TABLE 2 Univariate and multivariate analysis of factors affecting mortality in patients with COVID-associated candidemia.

	Univariant analysis			Multivariant analysis		
	Survival $N = 93$ (%)	Non-survival $N = 200$ (%)	p	Odds	95% CI	p
Age median (min–max)	61 (29–87)	68 (28–109)	**.0005**	**1.046**	**1.020–1.072**	**.0005**
Gender						
Female	26 (28)	83 (41.5)	**.026**			
Male	67 (72)	117 (58.5)				
Comorbidity	74 (71.6)	179 (89.5)	**.021**			
DM	37 (39.8)	88 (44)	.497			
Obesity (BMI ≥ 35)	19 (20.4)	23 (11.5)	**.042**			
Malignancy	4 (4.3)	25 (12.5)	**.034**			
Coronary artery disease	20 (21.5)	72 (36)	**.013**			
Chronic renal failure	9 (9.7)	39 (19.5)	**.034**			
COPD	5 (5.4)	32 (16)	**.011**			
Use of immunosuppression therapy prior to COVID[a]	5 (5.4)	24 (12)	.077			
Use of long-term steroids prior to COVID[b]	8 (8.6)	17 (8.5)	.977			
Use of broad-spectrum antibiotic	83 (89.2)	180 (90)	.843			
Total parenteral nutrition	27 (29)	95 (47.5)	**.003**			
Central venous catheter	49 (52.7)	162 (81)	**.0005**			
The total steroid dose (mg) for COVID	80 (0–8500)	80 (0–6800)	.066			
The total steroid duration (days) for COVID	10 (0–40)	10 (0–80)	.718			
Remdesevir	29 (31.2)	56 (28)	.576			
Tocilizumab	13 (14)	40 (20)	.213			
Echinochandin[c]	57 (53.8)	101 (64.7)	.075			
Lymphocyte count at diagnosis of CAC	900 (12–400)	720 (21–1400)	**.003**			
RRT at diagnosis of CAC	21 (22.5)	60 (30)	.208			
SOFA score	6 (0–13)	9 (0–19)	**.0005**	**1.307**	**1.176–1.453**	**.0005**
Invasive mechanical ventilation	68 (73.1)	193 (96.5)	**.0005**	**7.959**	**1.444–43.863**	**.017**
The total duration of IMV	9.5 (0–150)	13 (0–74)	**.020**	**0.981**	**0.965–0.997**	**.020**
The total ICU length of stay	21.5 (5–152)	20 (2–104)	.117			

Abbreviations: BMI, Body mass index; CAC, COVID-associated candidemia; COPD, Chronic obstructive pulmonary disease; DM, Diabetes mellitus; ICU, Intensive care unit; IMV, Invasive mechanic ventilation; RTT, Renal replacement therapy. Bold values were detected to be statistically significant.

[a]Long-term steroid use, as defined prednisolone ≥0.3 mg/kg/day ≥3 weeks, in the previous 2 months prior to diagnosis of COVID.

[b]Immune suppressive or modulating therapy within 90 days prior to hospitalisation for COVID.

[c]The majority of patients used the echinocandin and azole groups. Univariate analysis was performed for these.

3.7 | The statistical model

Figure 1 displays the area under the ROC curve. The sensitivity, specificity, positive predictive value and negative predictive value of the mortality predictive model are shown in Table 3.

4 | DISCUSSION

This study involved the analysis of 293 patients with CAC. The median age of the patients pointed an elderly patient population. The most prevalent comorbidities observed were diabetes mellitus and coronary artery disease. In our analysis, a comparison between the data of patients who survived and those who did not survive with CAC revealed that advanced age, SOFA score, invasive mechanical ventilation and the total duration of invasive mechanical ventilation were significant factors. In previous studies, various factors including age, comorbidities and high Charlson comorbidity index scores have been linked to adverse clinical outcomes, and increased mortality in patients with COVID, candidemia and CAC.[12,14–16]

In our study, patients aged 65 years and older accounted for 85% of patients with three or more comorbidities. Age was identified as

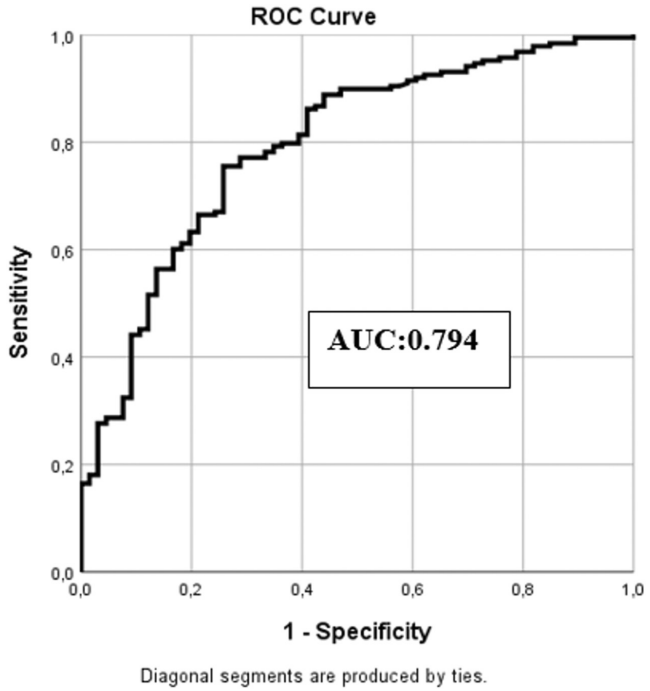

FIGURE 1 Receiver operating characteristic curves of the model to predict mortality.

TABLE 3 The sensitivity, specificity, positive predictive value and negative predictive value of the mortality predictive model.

	Sensitivity	Specificity	PPV	NPV
Mortality model	92.9%	36%	81%	63.8%

Abbreviations: NPV, negative predictive value; PPV, Positive predictive value.

a statistically significant risk factor associated with mortality. There could be several reasons for this. This could be attributed to the diminished B-cell and T-cell function in elderly patients, leading to prolonged inflammatory responses and viral replication persistence.[17] Additionally, the increasing number of comorbidities with age may contribute to poor clinical outcomes.[18,19] Also, diseases that come with old age such as dementia, cardiovascular disease, hypertension and chronic kidney disease have been found to be associated with mortality in the elderly population.[20] Furthermore, the death rate from COVID in individuals aged 65 and over increased exponentially with age.[21,22]

However, the relationship between age and mortality in candidemia is not straightforward. Several studies have reported higher mortality rates in older patients.[8,23,24] In some studies, no significant association was found between age and mortality; these studies were conducted especially in older and elderly patients and the mortality rate was lower than our results.[25–27] There are few studies on mortality in patients with CAC[12,28]; therefore, this topic is not clear in CAC cases. To sum up, the relationship between age and mortality would have been affected by old age-related diseases (e.g. cardiovascular and cerebrovascular) and health care services of the countries. All things considered, age could be a confounding factor.

The SOFA and quick SOFA scores have been recommended by the Third International Consensus Definitions for Sepsis and Septic Shock for screening sepsis and evaluating prognosis.[29] The mean and highest SOFA scores have proven to be the most predictive of mortality in ICU patients.[30] In our study, the median SOFA score was significantly higher in non-survivors. In the context of COVID, an initial Chinese study demonstrated that higher SOFA scores were associated with a higher risk of mortality COVID.[31] Kayaaslan et al. found that the presence of sepsis was associated with mortality, and age and previous steroid use were independent risk factors in COVID, although detailed data on steroid dose and duration were not provided in the article.[12] In our study, the use of long-term steroids before COVID and the total dose and duration of steroids for COVID were not statistically significant factors.

In this study, we found an association between invasive mechanical ventilation and the duration of invasive mechanical ventilation with mortality. However, previous studies have yielded varied results regarding the impact of length of stay in hospital and ICU, and duration of mechanical ventilation on mortality in candidemia patients with COVID. Kayaaslan et al. compared patients with COVID with and without candidemia and found no significant difference between the groups in terms of mechanical ventilation and duration of intubation. However, the duration of ICU stay was longer in patients with non-COVID candidemia, and this difference was statistically significant. Notably, these factors were not found to be associated with mortality.[12] Boachie et al. reported that candidemia patients with COVID had a higher incidence of in-hospital mortality and longer median ICU length of stay, hospital length of stay and duration of mechanical ventilation.[32] The discrepant findings regarding these factors' impact on mortality may also stem from variations in the quality of healthcare and adherence to infection control measures.

Severe COVID cases during the pandemic necessitated hospitalisation in the ICU and mechanical ventilation support, resulting in increased mortality and morbidity.[14] Consequently, an upsurge in secondary infections, including candidemia, has been reported in hospitalised patients with COVID,[33,34] prompting studies on mortality in patients with CAC.[12] Despite an extensive search on PubMed, we could not find an article encompassing such a large number of cases as in our study, examining the factors influencing mortality in patients with CAC. Previous studies primarily focused on investigating the incidence and risk factors of candidemia in patients with COVID,[6,33–35] while only a few examined mortality in patients with CAC.[12,32] In our international study, the crude 30-day mortality rate in patients with CAC was 62.4%. The mortality rate in patients without CAC has been reported to range from 23% to 54% in the ICU or other hospital wards.[9,36–39] In hospitalised patients with COVID, the mortality rate was almost two times higher in mechanically ventilated patients than in non-mechanically ventilated.[21,40] Studies conducted during the COVID pandemic have indicated a higher risk of mortality in patients with CAC compared to those without.[11,33,41] The reported 30-day crude or all-cause in-hospital mortality rates

ranged from 60% to 90%.[11,12,32] Seagle et al. found that all-cause in-hospital fatality was two times higher among those with COVID compared to those without.[28] However, Mastrangelo et al. reported no statistically significant difference in mortality between COVID and non-COVID candidemia patients.[6] According to data from reported studies, mortality rates in patients with CAC appear to be quite high.

Ninety-three per cent of patients received antifungal treatment. The median duration of antifungal treatment was 11 days (min–max: 0–55). Fifty-two per cent of patients received an echinochandin as definitive treatment. The guideline recommends the use of echinocandins in critical patients in first-line therapy.[42] Clinical and microbiological response rates in efficacy studies with echinocandins are 60%–70%.[43,44] Some studies found that survival and clinic response rates were lower in ICU patients than in non-ICU patients.[44–46] The authors emphasised that this was a reflection of the underlying poor condition of ICU patients (e.g. high APACHE II score) independent of antifungal therapy. Similarly, Suh et al. reported that the low clinical response rate may be related to the advanced age of patients and the high proportion of patients with septic shock.[27] Crude mortality of the patients receiving echinocandins was 64.7% in our study. The high mortality rate may be related to the fact that the study group was ICU population with CAC. The initial antifungal treatment trend of the centres participating in this study is in line with the guideline recommendation.

Our study has several limitations. First, this is a retrospective study; this may result in incomplete or incorrect data entry. Second, there is no control group to determine the additive of COVID or candidemia on mortality. This made it difficult for us to differentiate factors influencing COVID mortality from those influencing CAC mortality. Furthermore, the potential impact of additional bacterial or fungal coinfections on mortality might not have been adequately identified. Finally, the mortality attributed to candidemia is undetermined.

In conclusion, we acknowledge that COVID and candidemia are distinct clinical conditions associated with high mortality rates. However, mortality appears to be further exacerbated in patients with CAC. Our study revealed a remarkably elevated crude mortality rate within 30 days, and this rate escalates with factors such as age, high SOFA score, mechanical ventilation and prolonged duration of mechanical ventilation. These findings hold immense importance as they provide valuable insights for identifying and acknowledging adverse outcomes among patients in the ICU with CAC. By shedding light on these outcomes, the study contributes significantly to enhancing the ability to recognise and understand the potential challenges faced by this specific patient population. Such knowledge can aid in implementing targeted interventions and developing effective strategies to improve patient care and outcomes in the ICU.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon request.

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