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ORIGINAL ARTICLE

Impact on the clinical evolution of patients with COVID-19 from an Intensive Care Unit with isolation of *Candida* spp. in respiratory samples

Impacto na evolução clínica de pacientes com COVID-19 de uma Unidade de Terapia Intensiva com isolamento de Candida spp. em amostras respiratórias

Impacto en la evolución clínica de pacientes con COVID-19 de una Unidad de Cuidados Intensivos con aislamiento de Candida spp. en muestras respiratorias

Mariangela Cauz[1] ORCID 0000-0002-6930-7313

Luzia Neri Cosmo Machado[1] ORCID 0000-0001-9863-7349

Nereida Mello da Rosa Gioppo[1] ORCID 0000-0001-6169-0832

Suelem Bassan Brandt[2] ORCID 0000-0003-1745-7261

Edcarlos Augusto Caloi[2] ORCID 0000-0001-8737-2779

Lilian Cristiane Baeza[1] ORCID 0000-0003-4119-9573

[1]*Universidade Estadual do Oeste do Paraná*.

[2]*Hospital Universitário do Oeste do Paraná*.

Email: lilianbaeza@gmail.com.

Address: Universidade Estadual do Oeste do Paraná, Rua Universitária, 1619 - Universitário, Cascavel – PR – Brazil.

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ABSTRACT

Background and Objectives: several patients with COVID-19 require hospital admission due to severe respiratory complications and undergo intensive care with mechanical ventilation (MV) support. Associated with this situation, there is an increase in fungal co-infections, which has a negative impact on the outcome of COVID-19. In this regard, this study intended to compare *Candida* spp. incidence in the respiratory tract of patients admitted in the COVID and General Intensive Care Units (ICU) at a teaching hospital in 2021. **Methods:** the results of protected tracheal aspirate samples from 556 patients admitted to the COVID ICU and 260 to General ICU as well as the respective records. **Results:** of the patients analyzed, 38 revealed a positive sample for *Candida* in the COVID ICU and 10 in the General ICU, with an incidence of 68.3/1000 and

38.5/1000, respectively. Males were predominant in both wards. The most affected age group was the population over 60 years old, and the average hospital admission for the COVID ICU was 22.1 years, and for the General ICU, 24.2. **Conclusion:** *Candida albicans* was the most frequently isolated species, and the mortality rate in patients positive for *Candida* was higher in patients with COVID-19 compared to patients in the General ICU, suggesting that patients infected with SARS-CoV-2, admitted to the ICU under MV, are more predisposed to colonization by *Candida* spp., which can have a fatal outcome in these patients.

Keywords: *COVID-19. SARS-CoV-2. Coinfection. Candida. Mechanical Ventilation.*

RESUMO

Justificativa e objetivos: muitos pacientes com COVID-19 necessitam de hospitalização devido às complicações respiratórias graves, e são submetidos a cuidados intensivos com suporte de ventilação mecânica (VM). Associado a esse quadro, verifica-se o aumento de coinfecções fúngicas, que tem impacto negativo no desfecho da COVID-19. Nesse sentido, este estudo pretendeu comparar a incidência de *Candida* spp. no trato respiratório de pacientes internados nas Unidades de Terapia Intensiva (UTI) COVID e Geral em um hospital escola em 2021. **Métodos:** foram avaliados os resultados de amostras de aspirado traqueal protegido provenientes de 556 pacientes internados na UTI COVID e 260 na UTI Geral, bem como os respectivos prontuários. **Resultados:** dos pacientes analisados, 38 revelaram amostra positiva para *Candida* na UTI COVID e 10 na UTI Geral, com incidência de 68,3/1000 e 38,5/1000, respectivamente. O sexo masculino foi predominante em ambas as alas. A faixa etária mais acometida foi a população acima de 60 anos, e a média de internação para a UTI COVID foi de 22,1 anos, e para a UTI Geral, 24,2. **Conclusão***: Candida albicans* foi a espécie isolada com maior frequência, e a taxa de mortalidade em pacientes com positivos para *Candida* foi maior em pacientes com COVID-19 em relação aos pacientes da UTI Geral, sugerindo que pacientes infectados com SARS-CoV-2, internados em UTI sob VM, são mais predispostos à colonização por *Candida* spp., que pode ter um desfecho fatal nesses pacientes.

Descritores: *COVID-19. SARS-CoV-2. Coinfecção. Candida. Ventilação Mecânica.*

RESUMEN

Justificación y objetivos: muchos pacientes con COVID-19 requieren hospitalización debido a complicaciones respiratorias graves y se someten a cuidados intensivos con soporte de ventilación mecánica (VM). Asociado a esta situación, hay un aumento de las coinfecciones fúngicas, lo que repercute negativamente en el desenlace de la COVID-19. En este sentido, este estudio pretendió comparar la incidencia de *Candida* spp. en el tracto respiratorio de pacientes ingresados en las Unidades de Cuidados Intensivos (UCI) COVID y General de un hospital escuela en 2021. **Métodos:** los resultados de muestras de aspirado traqueal protegidas de 556 pacientes ingresados en la UCI COVID y 260 en el UCI General, así como los respectivos registros. **Resultados:** de los pacientes analizados, 38 presentaron muestra positiva a *Candida* en UCI COVID y 10 en UCI General, con una incidencia de 68,3/1000 y 38,5/1000, respectivamente. Los machos predominaban en ambas alas. El grupo de edad más afectado fue la población mayor de 60 años, y la hospitalización promedio en la UCI COVID fue de 22,1 años, y en la UCI General, de 24,2. **Conclusiones:** *Candida albicans* fue la especie aislada con mayor frecuencia, y la tasa de mortalidad en pacientes positivos para Candida fue mayor en

pacientes con COVID-19 en comparación con los pacientes en la UCI General, lo que sugiere que los pacientes infectados con SARS-CoV-2, ingresados en la UCI bajo VM, están más predispuestos a la colonización por *Candida* spp., lo que puede tener un desenlace fatal en estos pacientes.

Palavras-chave: *COVID-19. SARS-CoV-2. Coinfección. Candida. Ventilacion Mecanica.*

INTRODUCTION

COVID-19 (Coronavirus Disease-2019) is characterized by mild to moderate respiratory illness, with symptoms such as fever, cough, fatigue and breathing difficulties, and, in severe cases, results in Acute Respiratory Distress Syndrome (ARDS). In addition to the harmful effects caused by the virus itself, such as alteration of the immune response and direct damage to pulmonary and extrapulmonary tissues, may be accompanied by infections caused by other microorganisms.[1] The high prevalence of morbidity and mortality in patients with COVID-19 is associated with fungal and bacterial co-infection, especially among those suffering from ARDS.[2]

Often, critically ill patients with COVID-19 who develop ARDS are admitted to Intensive Care Units (ICUs), where invasive monitoring, such as using mechanical ventilators and intravenous catheters, can allow the entry of opportunistic pathogens.[3] Furthermore, the widespread use of immunosuppressive medications, such as systemic corticosteroids, and the prolonged use of broad-spectrum antibiotics, together with the tissue damage caused by SARS-CoV-2 (Coronavirus Severe Acute Respiratory Syndrome-2), increase susceptibility. of these patients to invasion by commensal yeasts, causing deep invasive fungal infections. [4]

According to studies, invasive fungal infection (IFI) associated with COVID-19 had an incidence that varied between 4 and 27.7%, with a higher occurrence in cases admitted to ICUs, candidiasis was one of the most commonly reported IFI, representing an associated mortality rate of 40%. [1, 5, 6]

In healthy individuals, *Candida* species live as commensals, however, in hosts with a weakened immune system, they can cause infections.[7] Bronchial colonization by *Candida* spp. It is prevalent among patients who use mechanical ventilation (MV), being found in approximately 30% of people who use it for more than 48 hours and in 50% of those diagnosed with ventilator-associated pneumonia (VAP). Still in the study by Erami

et al. (2022), the most common comorbidities among patients colonized by *Candida* in the respiratory tract included diabetes, renal disorders, malignancies, and cardiovascular diseases. [2]

Due to the complicated medical situations of COVID-19 patients and inadequate collection of clinical samples, most fungal infections in this group of patients are misidentified. Identification and diagnosis of fungal infections have been a challenge for many researchers; therefore, isolation of *Candida* spp. in the lower airways should be interpreted with caution as causative agents of pulmonary disease. [6]

In this regard, secondary fungal infections can complicate the prognosis of patients with COVID-19. Therefore, it is essential to carry out a specific diagnosis as well as understand the antifungal susceptibility profile of *Candida* spp.. The appreciation of these results, together with patients' clinical condition, must be interpreted by the clinician, aiming for an appropriate treatment for a possible fungal co-infection with SARS-CoV-2. [4,8]

Considering the above, this study aims to compare *Candida* spp. incidence in the respiratory tract of patients admitted to the COVID ICU and General ICU in a teaching hospital in 2021.

METHODS

This is a descriptive, documentary and retrospective study, with a quantitative approach, carried out in a public teaching hospital located in the city of Cascavel, Paraná. This hospital has 298 beds, with 60 General ICU beds, and, during the COVID-19 pandemic, 70 beds allocated to COVID ICU.

The criteria for data collection included analysis of medical records of patients admitted to the COVID ICU (with a positive diagnosis for SARS-CoV-2) and General ICU (with a negative diagnosis for SARS-CoV-2) between January and December 2021, without sex restriction, with age including young people, adults and elderly people, who presented a positive diagnosis for yeast isolation in protected tracheal aspirate samples. Cultures with counts ≥105 CFU/mL, without the isolation of another microorganism, were considered positive. Microorganism identification was carried out by automation using VITEK®2 (BioMérieux, France), in accordance with the manufacturer's recommendations. Data were collected in the Philips Tasy® electronic medical record

system. The variables collected in the system were comorbidities, use of invasive procedures such as MV, MV length, tracheostomy, orotracheal tube, nasoenteral tube (NET), nasogastric tube (NGT), central venous access (CVA), peripheral venous access (PVA), indwelling urinary catheter (IUC), length of admission, use of antimicrobials and corticosteroids, in addition to sex, age, sector of origin of admission, clinical outcome, and species of *Candida*. Patients who did not have a confirmed or negative result by RT-PCR for SARS-CoV-2 were excluded from the research.

Microsoft Office Excel® version 2010 was used to tabulate the data. The incidence of pulmonary candidiasis was calculated using the ratio, in which the numerator was the number of episodes of pulmonary candidiasis during the study period, and the denominator was the number of patients on MV per day in the same period, multiplying the result by 1,000. To assess the association between qualitative variables, the chi-square test was used, considering a significance level of 5%, with $p < 0.05$ being statistically significant. To define the factors associated with the outcome (death), a mathematical model was adjusted using the binary logistic regression method, using the criterion of $p < 0.10$ of the Odds Ratio being statistically equivalent to 1.

Data collection from patient records occurred after the study was approved by the local Ethics Committee, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 65827722.2.0000.0107 and favorable Opinion 5.798.336. The research was conducted in accordance with the required ethical standards (Resolutions 466/2012, 510/2016, 580/2018 of the Ministry of Health).

RESULTS

From January to December 2021, protected tracheal aspirate cultures were performed from 556 patients diagnosed with SARS-CoV-2 admitted to the COVID ICU and from 260 patients admitted to the General ICU (with a negative diagnosis for SARS-CoV-2), as, of these, 38 and 10 had positive cultures for *Candida* spp., respectively. The incidence of pulmonary candidiasis was 68.3/1000 patients per day in the COVID ICU and 38.5/1000 patients per day in the General ICU.

In the COVID ICU, 23 (60.5%) were male, and 15 (39.5%) were female. The age of these patients ranged from 39 to 83 years, with a median age of 64.5 years. The interaction time ranged from 3 to 55 days (median = 18). Considering the clinical picture evolution,

24 (63.2%) of patients died and 14 (36.8%) were discharged. In the General ICU, 7 (70%) of patients were male, and 3 (30%) were female, aged between 24 and 75 years (median = 65.5 years). The duration of admission ranged from 13 to 48 days (median = 21.5 days). According to the clinical outcome, 6 (60%) of patients were discharged and 4 (40%) died.

The majority of patients had underlying risk factors, 81.6% from COVID ICU and 100% from General ICU. The most prevalent were systemic arterial hypertension and diabetes *mellitus* in both wards analyzed. Other comorbidities that were equally present among patients were alcohol consumption, smoking, dyslipidemia, obesity, among others (Figure 1).

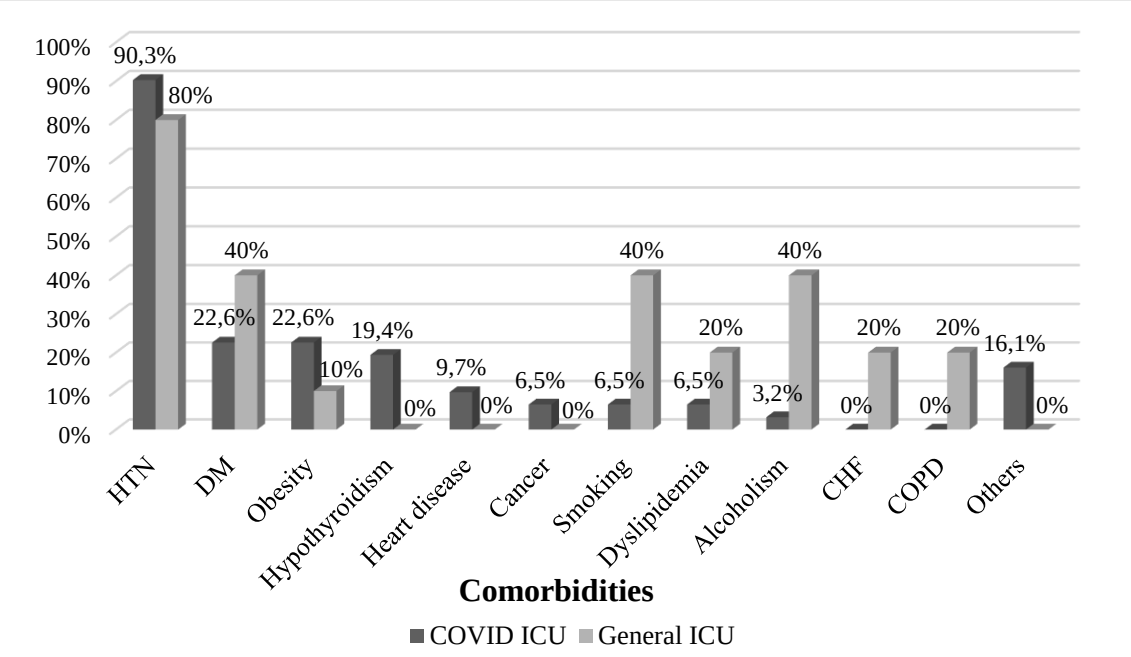

Figure 1. Comorbidities of patients admitted to the COVID ICU and General ICU of a teaching hospital in western Paraná in 2021

Caption: HTN - systemic arterial hypertension; DM – diabetes *mellitus*; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease.

Table 1 describes the invasive procedures to which patients were subjected. It is observed that invasive devices were widely used, resulting in 100% use by patients. The most frequent were orotracheal tube (OTT), NET, CVA, IUC and MV, whose time ranged from 3 to 40 days (median = 15.5) in COVID ICU and from 10 to 29 days in General ICU (median = 18.5).

Table 1. Invasive procedures used in patients with positive *Candida* culture admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021

	Admission wards	
	COVID ICU	**General ICU**

Invasive procedures	N (%)	N (%)
Mechanical ventilation	38 (100)	10 (100)
Orotracheal tube	38 (100)	10 (100)
Tracheostomy	13 (34.2)	7 (70)
Nasoenteral tube	38 (100)	9 (90)
Nasogastric tube	8 (21.1)	4 (40)
Central venous access	38 (100)	10 (100)
Peripheral venous access	34 (89.5)	8 (80)
Indwelling bladder catheter	38 (100)	10 (100)
Total	38 (100)	10 (100)

Table 2 demonstrates predictive factors for the outcome of death. The variables considered significant by the logistic regression method were admission days, days of MV and tracheostomy. Among these factors, it was observed that patients with more days on MV were 3.74 times more likely to die (p = 0.007), and patients admitted to the COVID ICU were 38.2 times more likely to die than those admitted to the General ICU.

Table 2. Factors associated with the outcome of death in patients with *Candida* isolated from pulmonary secretions of patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021

Variables	p-value	Odds Ratio [95%CI]
Admission days	0.0124*	0,3811
Mechanical ventilation days	0.0077*	3,7439
General ICU COVID ICU	0.0701	38,2022
Without tracheostomy With tracheostomy	0.0718	0,0010

* Indicate significant differences (p<0.05).

The percentage of deaths comparing the number of positive and negative cases of *Candida* spp. among patients admitted to COVID ICU and General ICU it was 6.83% and 3.46%, respectively, not being statistically significant (p = 0.0540). However, a trend towards significance was observed, with the COVID ICU tending to present more positive cases of *Candida* spp. than the General ICU (Table 3).

Table 3. Absolute (n) and relative frequencies (%) of the number of *Candida* spp. cases in patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021

Tests	COVID ICU		Adult ICU		p-value
	n	%	n	%	
Negative	518	93.17	251	96.54	0.0540
Positive	38	6,83	9	3.46	

Regarding the patients who presented tracheal secretion culture with isolation of *Candida*, all (100%) used antimicrobials. Among the most prescribed were piperacillin/tazobactam, ceftriaxone, azithromycin, meropenem and linezolid (Table 4).

Table 4. List of antimicrobials prescribed to patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021

	Admission wards	
	COVID ICU	General ICU
Antimicrobials	**N (%)**	**N (%)**
Piperacillin/tazobactam	35 (92.1)	9 (90)
Ceftriaxone	30 (78.9)	8 (80)
Azithromycin	27 (71)	-
Meropenem	25 (65.8)	9 (90)
Linezolid	21 (55.3)	5 (50)
Polymyxin B	17 (44.7)	3 (30)
Amikacin	15 (39.5)	1 (10)
Levofloxacin	13 (34.2)	-
Vancomycin	11 (28.9)	4 (40)
Cefepime	6 (15.8)	1 (10)
Teicoplanin	5 (13.2)	1 (10)
Tigecycline	5 (13.2)	-
Moxifloxacin	4 (10.5)	-
Clindamycin	4 (10.5)	3 (30)
Amoxicillin/clavulanic acid	3 (7.9)	-
Imipenem	3 (7.9)	-
Imipenem/cilastatin	3 (7.9)	-
Metronidazole	3 (7.9)	3 (30)
Ampicillin	2 (5.3)	1 (10)
Clarithromycin	2 (5.3)	-
Gentamicin	2 (5.3)	-
Sulfamethoxazole/trimethoprim	1 (2.7)	-
Daptomycin	1 (2.7)	-
Oxacillin	1 (2.7)	-
Ceftazidime	-	2 (20)
Moxifloxacin	-	1 (10)
Total	**38 (100)**	**10 (100)**

Regarding antifungal medications, the frequency of use in COVID ICU patients was 31.6%, with fluconazole being the most prescribed drug, with 91.7%, followed by echinocandins (anidulafungin and micafungin 8.3%, respectively). Meanwhile, in the General ICU, the frequency was 50%, with anidulafungin present in the majority of prescriptions (80%), followed by fluconazole, with 40%.

Regarding the use of steroidal anti-inflammatory drugs, 100% of patients admitted to the COVID ICU used these medications. Dexamethasone was prescribed to 100% of patients, followed by hydrocortisone, 10.5%, prednisone, 5.3%, and methylprednisolone, 7.9%. In the Adult ICU, 40% of patients used steroidal anti-inflammatory drugs, with hydrocortisone prescribed in 75% of cases, followed by methylprednisolone and prednisone, with 25% both. Dexamethasone, contrary to what was observed in the COVID ICU, was not prescribed in this unit.

Regarding the isolated yeasts, it was observed that C. *albicans* was the prevalent species in both wards, representing 60.5% in the COVID ICU and 40% in the General ICU. In COVID ICU, there was greater diversity among the isolated species, with five different species, such as *C. tropicalis*, *C. lusitaniae*, *C. dubliniensis* and *C. parapsilosis*. In the Adult ICU, the isolated species were *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. famata* (Table 5).

Table 5. Yeast species isolated from protected tracheal aspirate from patients admitted to the COVID and General ICUs of a teaching hospital in western Paraná in 2021

	Admission wards	
	COVID ICU	**General ICU**
Yeasts	**N (%)**	**N (%)**
Candida albicans	23(60.5)	4 (40)
Candida tropicalis	9 (23.7)	3 (30)
Candida lusitaniae	2 (5.3)	-
Candida dubliniensis	2 (5.3)	-
Candida parapsilosis	1 (2.6)	1 (10)
Candida sp.	1 (2.6)	-
Candida famata		1 (10)
Candida glabrata		1 (10)
Total	**38 (100)**	**10 (100)**

DISCUSSION

Although there are few studies on the lung microbiome, growing evidence indicates that the fungal microbiota is altered in critically ill patients; however, in patients

with COVID-19, lung fungal colonization/infection represents a major concern.[9] Although microbial colonization is an important factor in the development of secondary infections, *Candida* pneumonia is rarely reported in ICUs. In the present study, it was observed an incidence of pulmonary candidiasis of 68.3/1000 patients per day in the COVID ICU and 38.5/1000 patients per day in the Adult ICU.

Some studies have reported that the development of VAP is independent of *Candida* colonization in the airways. Therefore, the meaning of *Candida* colonization in the airways remains controversial, requiring caution when interpreting many clinical conditions. [2]

With regard to gender, there was a higher prevalence of males in admissions, corresponding to 60.5% in the COVID ICU and 70% in the General ICU, corroborating findings from other studies. A study carried out in a university hospital in Italy also showed a predominance of males, compared to females. This occurrence may be related to the greater number of men admitted to hospital in these sectors.[9]

According to patients' age, the median was 64.5 years for COVID ICU patients and 65.5 for General ICU patients, which were close to the study by Viciani *et al*. (2022), demonstrating that the median age was 64 years for patients without COVID-19 and 68 for individuals with COVID-19. [9]

According to Taylor (2021), hospital admission rates for COVID-19 were higher in patients over 65 years of age, requiring ICU admission. This predominance can be justified by the fact that older patients are more vulnerable to complications when subjected to prolonged stays, medical interventions, immune system imbalance, or when they have diseases or comorbidities. As the population ages, the frequency of older patients with health problems requiring treatment in the ICU also increases. [10, 11, 12]

Related to the period of stay in the ICU, it was found that COVID ICU patients had a median stay of 18 days, and General ICU patients had a median of 21.5 days. These data were close to what was presented in a retrospective study, carried out in a tertiary hospital in Spain, where the median length of stay for patients was 20 days.[13] Studies have shown that increased hospital and ICU stays increase the risk of co-infections. The combination of factors associated with treatment, prolonged stays in the ICU, medical interventions, such as the use of MV and intravenous catheters, increase the risk of candidiasis. [7]

Considering the comorbidities presented among patients, systemic arterial hypertension and diabetes *mellitus* were the most prevalent. These data coincide with a cross-sectional study carried out in a tertiary hospital in Egypt, which analyzed patients with COVID-19 under MV admitted to the ICU, which presented hypertension (62.4%) and diabetes *mellitus* (56.3%) as the main underlying diseases. In addition to these, obesity, hypothyroidism, lung disease and heart disease were observed in both the present study and the one mentioned. The presence of cancer/malignancy was also observed in other studies. [7, 14] Patients with underlying chronic diseases and advanced age tend to be more likely to acquire infections due to their weaker immune conditions. [15]

In this study, the invasive devices most used by patients were MV, OTT, CVA, IUC, NET and PVA. Patients admitted to the ICU often require central venous catheterization and parenteral nutrition, while those for whom MV is not necessary receive peripheral venous catheters. In recent decades, urinary catheters have been identified as risk factors for the development of invasive candidiasis.[7,5] These data coincide with those of another study carried out in a university hospital in Spain, where patients positive for *Candida* spp. were admitted to the ICU and required orotracheal intubation. The treatment received was with parenteral nutrition and nasogastric catheters and central and bladder access routes.[3] Using these medical devices provides a direct route into the host by penetrating the skin barrier. *Candida* species can form biofilms on these devices and act as physical barriers to protect antifungal treatment and host immune system defenses, already weakened due to COVID-19. [7]

In our study, patients with more days on MV were 3.74 times more likely to die ($p = 0.007$), and patients admitted to the COVID ICU were 38.2 times more likely to die than those admitted in General ICU. However, this result must be interpreted with caution, as the value obtained for "p" is not significant ($p = 0.07$), but indicates a tendency towards significance. Isolation of *Candida* spp. via the respiratory tract is associated with longer periods of MV and ICU admission, with unfavorable outcomes.[7] As in the present study, Meawed *et al*. (2021) found, in their research, that longer duration of MV proved to be a highly significant risk factor for candidiasis ($p < 0.001$). [14]

In this research, antibiotic therapy was present in 100% of prescriptions in ICUs, with all patients using more than one class of antibiotics. Patients with COVID-19 are more likely to acquire bacterial co-infections, and the most commonly prescribed antibiotics were ceftriaxone and azithromycin, observed in a single-center retrospective

analysis, similar to the current study.[8] In another retrospective observational study, carried out in a tertiary hospital in Spain, ceftriaxone was also the most used antibiotic among patients as well as piperacillin/tazobactam, carbapenems, linezolid and levofloxacin, corroborating the data from this research. [13]

Prolonged use of broad-spectrum antibiotics is associated with microbiota imbalance, creating a favorable environment for the proliferation and transformation of commensal to pathogenic *Candida* morphogenesis.[15] The dysbiosis caused by using these medications allows *Candida* spp. overcome other microorganisms, providing their colonization and dissemination. [7]

Regarding the use of steroidal anti-inflammatory drugs, it was observed that, in COVID ICU, there was 100% use of these medications. Patients with COVID-19 develop a cytokine storm syndrome that is characterized by an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines. In this sense, systemic corticosteroids are frequently used as treatment, such as dexamethasone, which is a well-known medication used to reduce the dysregulation of the inflammatory state.[5]

Although this glucocorticoid reduces the risk of a hyperinflammatory response in patients with COVID-19, its use is a risk factor for the development of opportunistic fungal co-infection, as the hyphae are protected from phagocytic attack. A study demonstrated that treatment with corticosteroids is associated with a 3.33 times greater risk of developing an IFI, when compared to other patients who did not receive this type of medication. [10]

In this study, the mortality rate of patients diagnosed with COVID-19 and admitted to the COVID ICU (63.2% 24/38) was significantly higher than that observed among negative patients admitted to the Adult ICU (40% 4/10), similar to the study by Calderaro *et al*. (2021), who analyzed infectious agents in lower respiratory tract samples from patients positive and negative for SARS-CoV-2 admitted to the ICU of a tertiary hospital located in Parma, Italy. According to study reports, infections caused by *Candida* and other fungal species tend to affect patients with severe viral infections, and may be associated with increased morbidity and mortality. [17,18]

Regarding the yeasts isolated, C. *albicans* was the most frequently isolated species in both wards. *Candida* spp. are recognized as opportunistic microorganisms that cause serious infections in immunocompromised individuals. An important characteristic of

Candida virulence is biofilm formation, which involve the ability to adhere to tissues and surfaces, and are extremely resistant to routine antifungals. Biofilm formation involves the adhesion of yeast cells, which promotes their proliferation, extracellular matrix material accumulation and yeast cell dispersion, which can establish new biofilms.[19] The extracellular matrix assists in fungal colonization and invasion, by acting as a protective barrier, increasing adhesion and production of hyphae; thus, it protects the cell from immune attack by increasing resistance to antifungal agents. [7]

These data corroborate data from the study by Erami *et al*. (2022), in which C. *albicans* was the prevalent species, isolated from bronchoalveolar lavage (BAL) samples from patients with COVID-19 pneumonia who used MV for more than four days, admitted to a hospital in Iran. [2]

The exact pathogenesis of candidiasis associated with COVID-19 is not clear, however several factors have been proposed to explain how patients with COVID-19 are more predisposed to *Candida* infection. SARS-CoV-2 infection can cause a reduction in lymphocytes and, consequently, the impairment of immune defense against fungal agents, including *Candida*. Elevated blood lactate and acidosis is associated with greater severity of COVID-19, allowing restructuring of the yeast cell wall to mask β-glucans and escape host immunological recognition. Additionally, *Candida*'s ability to form biofilms may be triggered through oxidative stress and pH imbalance observed in COVID-19 patients. [1] In our study, although the outcome of death and positive tracheal secretion culture for *Candida* is not statistically significant, the COVID ICU tended to present more positive cases of candidiasis in relation to the General ICU. Delisle *et al*. (2008) showed, based on regression analysis, that there is a significant association between respiratory tract colonization by *Candida* and hospital mortality.[20]

Disseminated candidiasis has become more prevalent as COVID-19 has progressed[2]. However, isolation of *Candida* spp. should be valued in all critical patients, due to the potential virulence factors produced by this microorganism, which corroborate the successful colonization or invasive infection of the host's tissues. [21] As there are controversies regarding the interpretation through the isolation of yeasts in samples from the respiratory tract, since the diagnostic criteria for candidiasis for this site are not well established. [6] Therefore, it is important to question whether it is possible *Candida* pneumonia or just colonization, with more laboratory and clinical interaction studies

needed to determine cut-off points and establish the use of antifungal prophylaxis in a population at risk.

We conclude that patients admitted to the ICU for COVID-19 share some risk factors and underlying diseases, such as chronic respiratory diseases, corticosteroid therapy and invasive devices. To our knowledge, this is the first case series reported of a possible correlation of respiratory tract candidiasis after COVID-19 in critically ill patients. More studies are needed to understand the association between isolation of *Candida* in the respiratory tract and its clinical importance. An accurate and rapid diagnosis of candidiasis will provide adequate treatment for patients, in addition to representing an improvement in the mortality rates resulting from these infections not only in patients with severe COVID-19, the target of this study, but also in other critical patients mainly in ICUs.

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Authors' contributions:

Luzia Neri Cosmo Machado, Nereida Mello da Rosa Gioppo, Suelem Bassan Brandt and **Edcarlos Augusto Caloi** contributed to the laboratory identification of the isolates. **Mariangela Cauz** and **Lilian Cristiane Baeza** contributed to laboratory identification of the isolates, data analysis and interpretation and manuscript writing.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.