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Review article

Infections caused by *Candida* spp. in patients with COVID-19: A literature review

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Abstract

Objectives: This review aimed to evaluate the frequency of infections caused by yeasts of *Candida* spp. in patients affected with COVID-19. **Materials and methods**: A literature review was carried out in the Pubmed, Medline and Scielo databases, using the following keywords: *Candida* spp." AND "COVID 19" AND "Candidiasis" AND "Candida". The selected studies present data about the types of infection, fungal isolates and the treatment employed. **Results:** There is an increase in mortality rates in individuals co-infected with COVID-19 and *Candida* spp., especially in those with associated risk factors. The most frequent species were *Candida albicans*, *C. glabrata*, *C. tropicalis* and *C. auris*. Furthermore, candidemia and oropharyngeal candidiasis were the clinical forms mentioned in association with COVID-19. Management is also dependent on the clinical form and the classes of antifungal agents recommended and/or tested in these studies are azoles, echinocandins and polyenes. **Conclusion:** Co-infection by *Candida* spp. and COVID-19 leads to a worrying scenario in which the number of cases has increased around the world, causing higher mortality rates in these patients. This increase was evident throughout the study, as well as emphasizyng the importance of correct identification and management of these infections.

Introduction

The spread of the coronavirus disease 2019 (COVID-19) has occurred rapidly across mainland China and has become a global threat [1]. The agent responsible for the infection, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2], can cause acute respiratory distress syndrome (ARDS) [3]. Patients with ARDS in critical condition have a deregulated activation of the immune system, causing a high increase of pro-inflammatory cytokines, interleukins (IL-1β, IL-2, IL-6, TNF-α), anti-inflammatory cytokines (IL-4, IL-10) as well as the decrease of TCD4+ and TCD8+ cells [4, 5]. Immunological complications resulting from this syndrome can contribute to the development of superinfections [6].

The SARS-CoV-2 virus has its entry into the body facilitated by the mediation of the angiotensin II-converting enzyme (ACE2). The ACE2 protein is expressed in several cells, such as: pulmonary alveolar cells, small intestine enterocytes, endothelial cells, which justifies the systemic impairment caused by COVID-19. Virus infection induces changes in the immune system, which range from a rapid immune response, as in mild cases, to an exacerbated response, causing an extensive inflammatory response that is associated with higher mortality. Among the numerous changes caused in the immune system by infection with the virus that causes COVID-19 is lymphopenia, where there is an abrupt decrease in lymphocyte counts, presenting itself as a common feature in critically ill patients, but not in patients who present mild cases of infection [7].

In addition, SARS-CoV-2 has a certain pattern in the production of antibodies, where the humoral response is initially mediated by class M immunoglobulins (IgM) and later by class G (IgG). However, Brito *et al.* (2020) suggest a causal relationship between the severity of the disease caused by COVID-19 and the humoral immune response, therefore, those patients who have high titers of acute-phase

antibodies tend to have a poor clinical prognosis compared to others [8].

Because it presents changes in inflammatory markers, COVID-19 represents a challenge for the diagnosis of other co-infections, considering the similarity of symptoms. Consequently, critically ill patients undergo antibacterial therapy. Hospitalization of the patient in the intensive care unit (ICU) concomitant with the prolonged use of antibiotics leads to exposure to the risk of infections [9]. Critically ill patients, especially those admitted to the ICU and requiring mechanical ventilation or longer hospital stays, are more likely to develop fungal co-infections [10]. Thus, they have a greater tendency to be treated with broad-spectrum antibacterials, perform more invasive tests, require parenteral nutrition and use a central venous catheter, which are predisposing factors for the development of an opportunistic infection. Therefore, the presence of this immunocompromise significantly increases the risk of infection by *Candida* species [4][11].

Fungal infections are caused by opportunistic pathogenic fungi and their diagnosis is a challenge in low-resource settings. *Candida* spp. is one of the most commonly isolated pathogens in ICUs, affecting 6-10% of patients. The mortality rate reaches 70% in these patients [12]. Candidemia has shown a higher incidence after the dissemination of COVID-19, and according to some studies, these fungal infections are also responsible for the increase in the mortality rates due to the disease [13,14,15,16].

Regarding the high mortality rates, a study by Silva *et al.* (2021), which had 212 samples, corroborates the data cited, as their results show a significant higher risk of death in co-infected patients when compared to individuals without co-infection. Among the fungal agents responsible for this increase were some species of the genus *Candida*, the majority being represented by Non-albicans *Candida* spp., followed by *C. albicans* [17]. Supporting these data, Arastehfar *et al.* (2021) revealed a high mortality rate among patients with COVID-19-Associated Candidiasis (CAC), which was approximately 83%, despite treatment with antifungal agents [13].

A study by Cultrera *et al.* (2021) reinforces this increasing incidence of candidemia, since they compared the microbial isolations found in COVID-19 patients hospitalized in an intensive care unit (ICU) with those in a non-COVID-19 ICU, those in the period before the pandemic. Among the most isolated microorganisms among the ICU-COVID were the agents *C. albicans* (n=29) and *C. parapsilosis* (n=13), in addition, in a smaller number, there was the appearance of *C. lusitaniae* (n= 2) and *C. glabrata* (n=4) [18]. Chen *et al.* (2020) also demonstrates the high incidence of the *Candida* genus in patients infected with the virus, in a study with 99 patients affected by COVID-19 were 4 (4%) had fungal infections, most of them by *C. albicans* (n=3) and *C. glabrata* (n=4) [19].

Candida spp. yeasts are commensals, but also considered part of the human microbiota, being found in the skin, mucosa, gastrointestinal, urinary and genital tracts. Candida species are opportunistic in situations of immunodeficiency and can cause superficial infections such as oropharyngeal candidiasis and vulvovaginitis even invasive forms such as candidemia [13].

Invasive candidiasis is one of the main causes of mortality related to infections, therefore diagnosis and treatment are extremely important for clinical success. The literature describes that invasive infections caused by fungi present a higher mortality in patients with COVID-19 who had not received treatment with antifungal agents compared to those who did. Still, the literature emphasizes the importance of early diagnosis so that antifungal treatment can be carried out immediately in order to achieve success in treatment and reduce mortality [13]. Song *et al.* (2020) present in their research that the SARS epidemic that took place in 2003 presented an incidence of fungal infections of 18.8-27% and was one of the main causes of death for patients with the virus, accentuating the importance of the probability of co-fungal infections [20].

Knowing the importance of diagnosis, treatment and exposure of patients to factors predisposing to fungal infection, this study aimed to review the literature relating infections caused by yeasts of the *Candida* spp. in patients diagnosed with COVID-19.

Materials and methods

A literature review was carried in *Pubmed*, *Medline* and *Scielo* databases, by combining the terms "*Candida* spp." AND "COVID 19" AND "Candidiasis" AND "*Candida*".

The selection of articles was made based on the analysis of the title, abstract and, when necessary, the full text was read. The keywords followed the search criteria of the databases and quotes were used to have a better selection of the analyzed term, plus the Boolean operator (AND). No filters were used. Articles where there was no specific approach to the subject and case reports were excluded. Articles in duplicates from the searched databases were manually excluded.

After selecting the articles, the full text was read and the items relevant to the study were selected, including the year of publication, the country and the fungal isolates found. The data relevant to the research were added to an Excel program for data extraction.Where the presence of candidemias in patients with COVID-19 was analyzed and, through the compilation of some data in graphs, it was possible to detect the *Candida* spp. species that most affected patients co-infected with COVID-19.

Results

A total of 180 articles were found in the search through the Pubmed, Medline and Scielo databases. After the first analysis, 51 articles that were in duplicate were excluded, leaving 129 articles. After reading the title and abstract, 97

articles were excluded for approaching case reports or diverted from the topic in question. Thus, 32 articles remained, 29 of which were extracted from the Pubmed database and 3 from the Medline database. The search on the Scielo platform resulted in zero articles with the keywords already mentioned (*see Materials and Methods section*). Selected articles were read in full and included in the review.

Among the most common themes found in the reviewed articles are: information regarding fungal and COVID-19 co-infections, oral manifestations by *Candida* spp. in patients affected by the virus, invasive candidiasis related to COVID-19, among others. In addition, results were found on the increased incidence of COVID-19-Associated Candidiasis (CAC), management of infections, and information over the growth in mortality data from these co-infections.The flowchart of the selection of articles is shown in Figure 1.

We analyzed the number of citations of the *Candida* spp. species that most affected patients positive for COVID-19. The species mentioned were *C. albicans* (n=22), *C. auris* (n=15), *C. glabrata* (n=15), *C. parapsilosis* (n=12), *C. tropicalis* (n=12), *C. Krusei* (n=12), *C. stellatoidea* (n=1), *C. Guilliermondii* (n=1), *C. lusitaniae* (n=1) and *C. orthopsilosis* (n=1). In most of the studies, more than one species was cited. Figure 2 represents the relation of the number of citations by species of the genus *Candida* spp.

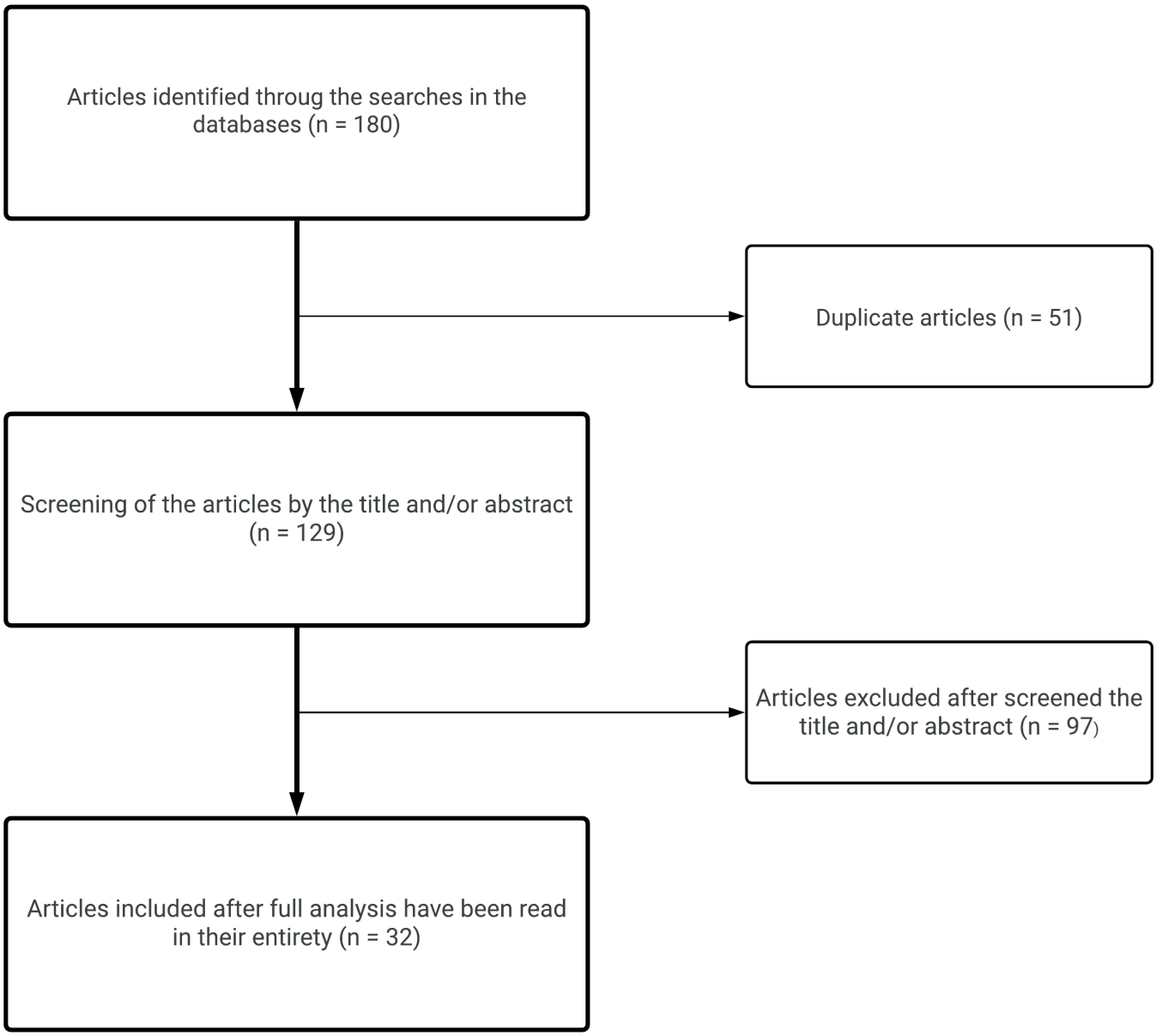

Figure 1. Study review flowchart.

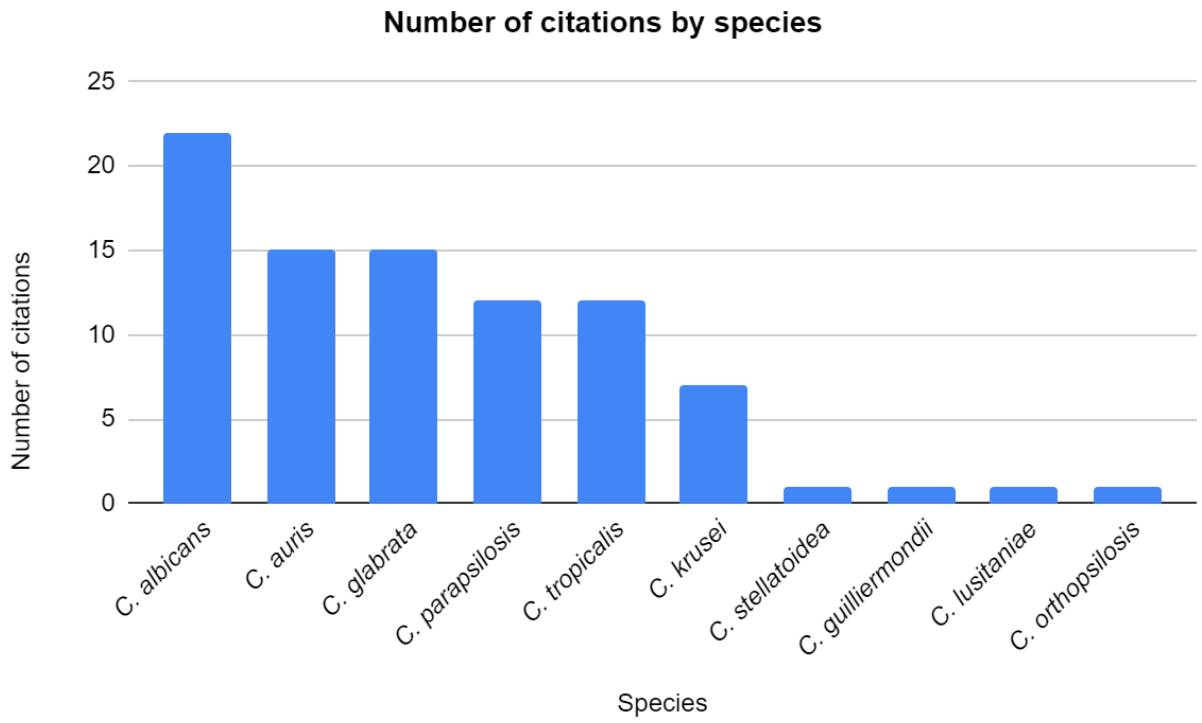

Figure 2. Graph relating the number of citations in studies by species.

Co-infection by *Candida* spp.

A study by Calderaro *et al.* (2021) in an intensive care unit in Italy included 154 patients who were screened for SARS-CoV-2 and other infectious agents. Of these, 90 patients tested positive for the virus responsible for COVID-19. Among the virus-positive patients, 77 were found to have a bacterial or fungal infection. A total of 75 different etiological agents were found, including 28 bacteria and 47 fungi, with a predominance of the pathogen *C. albicans*, isolated 36 times. In that same study, it was found that SARS-CoV-2 positive patients had higher fungal coinfection (81.4%) than patients who tested negative (53.3%). The study attributed this result to the strong therapeutic pressure [21].

An observational cohort study by Thomsen *et al.* (2021), and conducted in confirmed COVID-19 patients admitted to ICUs at two hospitals in Denmark, evaluated lower respiratory tract specimens that were subjected to routine culture and antimicrobial susceptibility testing. Thirty-four patients were included, of which 12 had co-infection; and, among the pathogens, the *Candida* yeast, which was isolated in 5 endotracheal aspirates, stood out. The most prevalent species was *C. albicans*, identified in 3 aspirates, followed by an isolate of *C. tropicalis* and *C. dubliniensis*. It was observed that all patients who had fungal co-infection had received antimicrobial therapy prior to admission to the ICU [22].

Another study published in 2021, conducted at the University Hospital of Ferrara, located in Italy, aimed to compare microbial cultures performed in COVID-19 positive patients with cultures performed in non-COVID patients in the same period of the previous year, before propagation of pandemic. Antibiotic use during the same periods was also analyzed. An increase in fungal infections was observed in patients positive for COVID-19. The prevalent species was *C. albicans* with 29 isolates, followed by 13 isolates of *C. parapsilosis*, 4 of *C. glabrata* and 2 of *C. lusitaniae*. A significant increase in the consumption of antimicrobials has also been detected [18].

Candidemia associated with Sars-CoV-2 infection

Candidemia, an important infection caused by *Candida* spp., is described as a severe opportunistic fungal infection associated with high mortality in patients hospitalized in ICUs [23]. There are many risk factors for the development of candidemia and they coincide with the factors identified for the development of COVID-19, including advanced age, use of antimicrobials, mechanical ventilation, use of catheters and parenteral nutrition [24]. Arastehfar *et al.* (2021) conducted a retrospective study in Iran that included 1988 COVID-19-positive patients in serious condition, among them 7 patients had fungemia. 9 isolates were obtained. The main species causing the infection was *C. albicans*, representing 55.5% of the isolates, followed by *C. glabrata* 39.3% and *Rhodotorula mucilaginosa* 11.2% [25].

Macauley (2021) conducted a study at a third sector in the United States that included 50 people with candidemia, among them 38 were non-COVID and 12 were COVID positive. Thirty-nine isolates were obtained from the non-COVID group, the prevalent species was *C. glabrata* 30.76%, followed by *C. albicans* 28.21%, *C. parapsilosis* 17.94%, *C. tropicalis* 12.82%, *C. dubliniensis* 7.69 and *C.*

krusei 2.56%. In the Covid group, 13 isolates were obtained, the prevalent species was *C. albicans* 30.76%, followed by *C. parapsilosis* 23.07%, *C. glabrata* and *C. tropicalis* 15,38 and *C. dubliniensis* and other non-albicans 7 .69%. This study detected an almost 5-fold higher incidence of candidemia in the ICU among patients with COVID-19 compared to patients without COVID-19 [23]. Clinical trials described in the literature suggest that the use of corticosteroids for the treatment of patients with COVID-19. However, the use of steroids can lead to an increased risk of developing serious fungal infections such as candidemia. Riche *et al.* investigated the use of corticosteroids in patients with COVID-19, in two medical centers in Brazil, and detected a tenfold increase in the frequency of candidemia in positive patients using the steroid [26].

Data obtained by Kayaaslan *et al.* (2021) corroborate with this information. In a similar study carried out in the ICUs of a hospital in the city of Ankara, Turkey, 2,487 patients with COVID-19 and 27,750 patients without COVID-19 were analyzed. Between them, 105 patients with coronavirus and 131 negative for the virus had an episode of candidemia. Among the risk factors, a greater use of corticosteroids was detected in the COVID-19 group compared to the non-COVID group. The study found a twofold increase in the incidence of candidemia compared to the two groups [24].

Furthermore, the work published by Nucci *et al.* (2020), which characterized the incidence and epidemiology of candidemia cases in a hospital in Rio de Janeiro for 21 months, observed an increase in the incidence of candidemia cases, coinciding with the beginning of admission of COVID-19 positive patients: diagnosed 41 cases and had 608 hospital admissions of COVID-19 patients in the period. Between January 2019 and February 2020, 16 cases were diagnosed, while from March to September 2020, 25 cases [14].

A total of 20 patients (48.8%) were in the ICU when candidemia was diagnosed, *C. albicans* being the most frequent agent (41.5% of cases). The administered treatment was anidulafungin (n=28) and fluconazole (n=3), ten patients died before diagnosis and treatment. The main outcome analyzed, the 30-day mortality rate, was 66.7% for COVID positive and 59.4% for non-COVID. All COVID-19 patients were under mechanical ventilation [25].

The increase in the incidence of candidemia mentioned in the literature suggests that more studies should be carried out to understand the association of risk factors, since invasive candidiasis has high mortality rates. Early detection using complete diagnostic methods including histopathology, direct examination, culture, and PCR testing is essential to ensure effective treatment [20].

Critically ill patients should be submitted to tests to detect pathogenic fungi. For the detection of *Candida* spp., tests include methods such as direct microscopy and culture; histopathology; serology such as antigen and antibody detection and β-D-Glucan (BDG)[20].

Culture tests are the gold standard for diagnosing *Candida* spp. in the population, but 50% of cases of invasive candidiasis are not identified by blood culture; therefore, tests such as PCR are recommended to improve the result. β-D-Glucan (BDG) is a panfungal marker, being non-specific for invasive candidiasis. Enzyme immunoassay tests such as ELISA to detect Candida mannan are associated with relatively high specificity and sensitivity. It is recommended to combine several techniques to increase the sensitivity of the tests [25].

Regarding the management of invasive *Candida* spp. infections, the first-line antifungal treatment is the echinocandins, and the second line includes fluconazole, liposomal amphotericin B, voriconazole, posaconazole and isavuconazole. Additionally, the removal of central venous catheters is recommended as a way of controlling the disease in these patients [6].

C. auris infection associated with COVID-19

Chowdhary *et al.* (2020) reported bloodstream infections caused by multidrug-resistant *C. auris* in the intensive care unit (ICU) COVID-19 in India. Of the 596 participants, 15 (2.5%) developed candidemia, with *C. auris* being responsible for 10 of these patients (67%). Patients concurrently infected with *C. auris* and COVID-19 tend to have comorbidities and risk factors, therefore, to reduce these complications, mortality rate and long ICU stays, it is necessary to identify and treat *C. auris* infections [27].

C. auris is an emerging fungus, multiresistant, with nosocomial dissemination and responsible for causing invasive infections, which leads this pathogen to be considered a global threat to human health [27, 28]. A study by Villanueva-Lozano *et al.* (2021) had 12 patients admitted to the ICU positive for COVID-19 and, among these, *C. auris* was isolated in the blood of 6 patients (50%), in the urine of 8 (66.6%) and both isolated in 2 patients (16.6%). The mortality rate was 83.3% among patients with candidemia [29].

Themulti-resistance of *C. auris* to conventional antifungals is a major concern for the world. Villanueva-Lozano *et al.* (2021) evaluated the susceptibility profile of *C. auris* against several antifungal agents: amphotericin B, fluconazole, voriconazole, posaconazole, itraconazole, isavuconazole, andilafungin and caspofungin using the M27-A3/S4 microdilution method. The results revealed that the 15 isolates were not susceptible to amphotericin B and fluconazole, which are the main antifungal agents used in hospitals in Mexico (where the study was carried out). Furthermore, 8 isolates were considered multiresistant, that is, resistant to more than one class of antifungal agents [29].

Generally, *C. auris* outbreaks are associated with resistance to fluconazole and with at least more than 10% of the isolates considered resistant to amphotericin B as well [30, 31, 32, 33].

As reported in the study by Almeida *et al.* (2021), bloodstream infections by *C. auris* occurred in those patients

who already had severe predisposing conditions after long periods of hospital stay, exposure to antimicrobials, central venous catheterization and mechanical ventilation [30, 31, 32, 33]. In these cases, the high mortality rates are multifactorial and may not be attributed only to *C. Auris* [34, 35].

Magnasco *et al.* (2021) observed a significant spread of this pathogen in critically ill patients with COVID-19, therefore, it is concluded that strategies are needed to prevent horizontal propagation and adoption of antimicrobial administration programs in care settings for patients with COVID-19 [36].

Oral manifestations by *Candida* spp. associated with COVID-19

Microorganisms are directly related to the development of oral diseases, but can also increase the risk of systemic diseases such as gastrointestinal infection, aspiration pneumonia, endocarditis, among others. The presence of infection in the oral cavity can lead to an inflammatory process at the systemic level and affect several organs, causing different pathologies. In addition, their proliferative capacity is increased by the use of dental prostheses that cause constant friction in the individual's oral mucosa [37].

Oral candidiasis is a fungal infection that affects users of dental prostheses due to certain factors such as immunosuppression, prolonged use, poor hygiene, among others [37]. About 60% of dental prosthesis users have dental stomatitis caused by *Candida* species, with *C. albicans* being the main responsible for these infections [38, 39

Circumstances such as pre-existing conditions, hospitalization, use of broad-spectrum antibiotics, use of corticosteroids and intubation further compromise those patients affected by SARS-CoV-2 and, therefore, enhance the immunocompromise of this individual. The amount of all these factors makes these patients susceptible to the development of oral and oropharyngeal candidiasis (OPC) [40].

OPC infection begins with *Candida* colonization in the oral mucosa and, most of the time, it is acquired endogenously when the host is immunocompromised [41]. In about 80% of cases, *C. albicans* is the main cause of this infection [38]. Associated symptoms include changes in taste, local discomfort, glossodynia, breathing difficulties and/or dysphagia, among others [41].

It is important to perform the oral cavity exam in those patients with COVID-19 in order to reduce the mortality of opportunistic infections, as in the case of prosthetic candidiasis. In users of dentures, oral anamnesis can be performed before the removal of the prosthesis, in addition to performing a complete examination of the mouth, which includes inspection of the soft and hard palate and oral mucosa [42]. In uncomplicated oral candidiasis, improving hygiene and using topical antifungals are the most indicated treatments [40].

A study by Iranmanesh *et al.* (2020) reported different oral manifestations in patients with COVID-19, which included: ulcer, erosion, blister, vesicle, pustule, fissured or depapillary tongue, macula, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis , petechiae, swelling, erythema and spontaneous bleeding. In 68% of the cases, these lesions were symptomatic and the site of greatest involvement was the tongue (38%). The study also suggests that the diagnoses of these lesions were aphthous-like lesions, herpetiform lesions, ulcers and erosions, white and/or red plaques, lesions similar to angina bullosa hemorrhagica, Kawasaki-like illness, among others [43].

The study reports that the appearance of aphthous lesions may be related to the level of tumor necrosis factor (TNF)-α in patients with COVID-19, which stimulates neutrophil chemotaxis to the oral mucosa and, consequently, the development of these lesions. In addition, factors such as immunosuppression and stress also contribute to such consequences [43].

A study by Salehi *et al.* (2020) demonstrated that patients aged 50 years and older and positive for COVID-19 had a higher risk of developing oropharyngeal candidiasis, which is possibly related to a decreased innate salivary protection activity. This decrease may occur as individuals age [41,44].

In relation to antifungals, the recurrent use of fluconazole to treat oropharyngeal candidiasis (OPC) and the emergence of resistance to azoles led to certain changes in the prevalence profiles of *Candida* species [45]. The azoles, when in prolonged use, can lead to a selection of less sensitive species such as *P. kudriavzevii*, *C. dubliniensis* and *C. glabrata* and, in addition, previously susceptible *Candida* species can develop resistance [46].

Salehi *et al.* (2020) also evaluated the susceptibility profile of these strains (n=53) to different antifungal drugs. In the study, all isolates were susceptible to fluconazole, except for *P. kudriavzevii*, which already has intrinsic resistance, and an isolate of *C. dubliniensis*. Regarding voriconazole, two *C. albicans* isolates were intermediate and the rest were susceptible. The only isolate of *P. kudriavzevii* and one isolate of *C. dubliniensis* were resistant to caspofungin, two isolates of *C. albicans* and all isolates of *C. glabrata* were considered intermediates for this antifungal; therefore, caspofungin was considered to be the least active drug [41].

Also regarding antifungal drugs, Santosh *et al.* (2021) carried out a review article on the management of fungal infections of the oral cavity in association with COVID-19. For the treatment of oral candidiasis, the study reveals that nystatin has favorable results and is usually an oral suspension (100,000 IU/mL and 400,000–600,000 IU/mL), so patients should retain it in the oral cavity before swallow. In addition, treatment with clotrimazole and fluconazole tablets is mentioned, in addition to flucystine oral suspension [47].

According to the review, the species collected from oral candidiasis lesions show that *C. albicans* appears more

frequently, but there may be the appearance of *C. parapsilosis*, *C. krusei*, C. stellatoidea, *C. tropicalis*, *C. glabrata*, *C. guilliermondii* and *C. dubliniensis* [47].

In agreement with the previous study, Jerônimo *et al.* (2021) mentions that the drugs indicated for the treatment of *C. albicans* infections are topical antifungal agents such as nystatin, which can be used in the form of tablets, suspensions or mouthwashes. Nystatin is recommended due to its effectiveness, absence of serious oral side effects, and its low cost when compared to other medications. Regarding systemic therapy, the study reveals that clotrimazole and fluconazole tablets can be used [40].

Data referring to studies and countries carried out, *Candida* species responsible for oropharyngeal candidiasis in COVID-19 positive patients and suggestions for therapy are compiled in Table 1.

Microbiota and COVID-19

The role of a healthy microbiota has been clarified in the literature, and it is known that it plays important roles in the homeostasis of individuals, metabolism and prevention of pathogenic infections. A large number of diseases are related to dysbiosis and fungal infections, including inflammatory bowel disease, colorectal cancer, asthma [48].

In the study of Zuo *et al.* (2020),Significant changes were observed in the microbiota of patients hospitalized with COVID-19, leading to an increase in opportunistic pathogenic microorganisms and reducing microorganisms that are beneficial to health [49]. In another study, conducted by the same author, the analysis of the fecal microbiota of 30 patients hospitalized with coronaviruses was performed and a change in the fungal microbiota of the patients was demonstrated, with a more heterogeneous configuration when compared to the control group. Samples collected from patients with coronavirus showed an increase in the opportunistic pathogen. *C. albicans* and *C.auris*, yeasts were not detected in healthy controls. The data suggested a change in the fungal microbiota of patients with COVID-19 [50].

Invasive candidiasis associated with COVID-19

According to Arastehfar *et al.* (2020), invasive fungal infections are increasingly recognized as a serious complication of COVID-19. The study suggests that relevant clinical factors such as the long period of hospitalization in the ICU, use of central venous catheters and use of broad-spectrum antibiotics may be responsible for the development of invasive fungal infections in these patients affected by COVID-19 [13]. As for treatment, Arastehfar *et al.* (2020) also emphasizes that echinocandins and azoles are the main antifungal agents used in the treatment of these infections, but therapeutic failures can occur by multiresistant *Candida* species, such as *C. auris* and *C. glabrata*, and, in these cases, the development of new antifungals whose mechanism of action is not yet known [13]. The study in question also reveals that the management of invasive candidiasis in patients with COVID-19 is similar to that of non-COVID-19. Therefore, echinocandins would be the treatment of choice for invasive *Candida* spp. and as alternative second-line therapies, fluconazole, liposomal amphotericin B, voriconazole, posaconazole and isavuconazole could be used [13].

Table 1: Oropharyngeal candidiasis management and species profile in patients with COVID-19.

Study	Country	Present species	Antifungal agents used
Salehi *et al.* (2020)	Iran	*C. albicans* *C. glabrata* *C. dubliniensis* *C. parapsilosis sensu stricto* *C. tropicalis, Pichia kudriavzevii (=C. krusei)*	Susceptibility testing was performed for some classes. All isolates were sensitive to fluconazole, except one isolate of *P. kudriavzevii* and *C. dubliniensis*; Two *C. albicans* isolates intermediate to voriconazole; All *C. glabrata* and two *C. albicans* isolates were intermediates for caspofungin.
Santosh *et al.* (2021)	Jamaica	*C. parapsilosis* *C. krusei* *C. stellatoidea* *C. tropicalis* *C. glabrata* *C. guilliermondii* *C.dubliniensis*	It reviews the use of nystatin, clotrimazole, fluconazole, and flucystine in the management of oropharyngeal candidiasis.
Jerônimo *et. al.* (2021)	Brazil	*C. albicans*	Reviews the use of nystatin, clotrimazole and fluconazole in the management of oropharyngeal candidiasis.

Arastehfar *et al.* (2020) also reviewed some studies carried out in different countries (India, United Kingdom, Italy, Greece and Oman) that reported the association of invasive fungal infections with COVID-19. In the Indian study, 15

patients positive for candidemia in association with COVID-19 were found. Furthermore, 10 of these cases had *C. auris* as the responsible etiologic agent, followed by 3 cases by *C. albicans*, 1 by *C. tropicalis* and 1 by *C. krusei*. For the treatment of these patients amphotericin B and micafungin were used, but only 6 survived [6].

The study carried out in Oman, on the other hand, identified 5 patients with candidemia associated with COVID-19, 3 of which were affected by *C. albicans*, 1 by *C. albicans* and *C. tropicalis* and 1 by *C. glabrata*. In the United Kingdom, 17 patients with the same condition were identified, being 12 cases for *C. albicans*, 1 for *Rhodotorula* spp., 1 for *C. albicans* and *C. parapsilosis* and 2 cases had no identified responsible etiological agents [6].

Two studies carried out in Italy that identified 4 patients with candidemia associated with COVID-19 were cited. Of these cases, 1 was caused by *C. albicans*, 1 by *C. parapsilosis*, 1 by *C. tropicalis* and 1 by *C. krusei*. The study carried out in Greece identified 2 patients who were affected by *S. cerevisae* [6].

Song *et al.* (2020) reinforces the treatment recommendations for invasive candidiasis following the guidelines of the American Society for Infectious Diseases of 2016, as it corroborates the treatment used in previous studies. These guidelines recommend the use of echinocandins (caspofungin, micafungin or andilafungin, azoles (fluconazole, voriconazole, itraconazole) and amphotericin B and their liposomes. Furthermore, it reinforces that therapeutic drug monitoring for azoles should be performed in order to optimize the efficacy and limit toxicity [20].

Péman *et al.* (2020) reviewed eight studies in which participants were affected by COVID-19 and potential invasive candidiasis. Among these 28 patients, 15 cases had *C. albicans* as the responsible etiological agent, 3 were caused by *C. tropicalis*, 4 by *C. parapsilosis*, 4 by *C. auris*, 3 by *C. glabrata*, 1 by *C. lusitaniae*, 1 by *C. guilliermondii* and 1 case had no etiological agent identified. The majority of cases were treated with amphotericin B, andilafungin, fluconazole and isavuconazole [4].

Chowdary *et al.* (2020) conducted a study with 596 patients with COVID-19 admitted to the ICU in New Delhi, India. Among the participants, 15 were diagnosed with candidemia (2.5%), with *C. auris* being the etiologic agent responsible for 67% of cases (n=10), followed by *C. albicans* (n=3), *C. tropicalis* (n=1) and *C. krusei* (n=1). The study also identified that most patients infected with C. auris were elderly and male [25]. In addition, all patients with COVID-19 who developed *C. auris* infections were hospitalized for long periods in the ICU (20-60 days) and also had comorbidities, these being hypertension (n=7), *diabetes mellitus* (n=6), chronic liver and kidney disease (n=2) [27].

This study also performed susceptibility testing to some antifungal drugs such as fluconazole, voriconazole, anudilafungin, amphotericin B, caspofungin, isavuconazole, micafungin, posaconazole and 5-flucytosine. The results demonstrated that all *C. auris* isolates were resistant to fluconazole and 30% were considered not susceptible to voriconazole. Furthermore, 40% were resistant to amphotericin B and 60% resistant to 5-flucytosine; in relation to echinocandins, all isolates were considered susceptible. Therefore, 30% of *C. auris* isolates were considered multiazole (voriconazole and fluconazole) and 70% multiresistant [27].

Arastehfar *et al.* (2021) evaluated the epidemiology of candidiasis associated with COVID-19 (CAC) in the ICUs of two COVID-19 centers in Iran. Of the 1988 study participants, 7 had fungemia (0.03%) and, among them, 6 had CAC. Fungal isolates were collected, and *C. albicans* was the main responsible for CAC cases (57.2%), followed by *C. glabrata* (28.4%) and *R. mucilaginosa* (11.2%). Regarding their profile, the mean age found was 68 years, all of whom were using central venous catheters and therapies with broad-spectrum antibiotics; 43% of patients with fungemia had some comorbidity, while 57% had no underlying disease [13].

In this article, antifungal susceptibility tests were also performed according to the Clinical Laboratory Standards Institute (CLSI) protocol M27-A3; therefore, these isolates were tested against fluconazole, voriconazole, itraconazole, amphotericin B, anidulafungin and caspofungin. The results demonstrated that 2 of the patients infected with *C. albicans* (50%) contained isolates resistant to fluconazole, also resistant to echinocandins; none of the isolates of *C. glabrata* was resistant to the drugs tested and the isolate of *R. mucilaginosa* presented a high minimum inhibitory concentration for all azoles and echinocandins, but low for amphotericin B [13].

In addition, the study revealed high mortality rates among those critically ill patients due to COVID-19 and candidemia, therefore, a rapid diagnosis is essential, followed by the timely initiation of appropriate antifungal therapy [13].

Some studies raise the hypothesis that the disturbance of host defense mechanisms caused by COVID-19, such as the disruption of the epithelial barrier associated with other risk factors, may promote colonization and opportunistic infection by *Candida* spp. existing in the human microbiome. In addition, these studies identified *C. albicans* and *C. glabrata* as the main agents responsible for infections, which may suggest the prevalence of these species in the microbiome of the Iranian population. This fact is corroborated by Arastehfar *et al.* (2021), since *C. albicans* and *C. glabrata* were found to be the main agents responsible for CAC in patients [13].

Considering that candidemia is a common scenario, especially in intensive care units, as is the case with most patients severely affected by COVID-19, the "*Candida* Score" tool helps to identify patients at risk of developing infections by Candida spp. [51]. According to Ahmed et al. (2014), to calculate the *Candida* Score, the following components are considered: parenteral nutrition (sum 1 point), surgeries (sum 1 point), multifocal colonizations

(sum 1 point) and severe sepsis (sum 2 points). Where scores ≥ 3 are considered positive for the risk of developing candidemia [52]. However, a study of 1,699 critically ill patients in the ICU, which used the *Candida* Score tool, showed that scores above 2.5 had 81% sensitivity and 74% specificity in predicting *Candida* spp. infections [53].

Conclusion

After analyzing the articles included in the review, it was possible to see that the most isolated species in infections caused by fungi in patients with COVID-19 were *C. albicans, C. auris, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei* and other species in smaller numbers. *Candida* spp. co-infection, candidemia and oropharyngeal candidiasis are infections mentioned in studies related to COVID-19.

Based on the findings of the researched literature, this relationship between co-infection by COVID-19 and the *Candida* spp. genus can be explained by the immune dysregulation caused by the virus, favoring the appearance of superinfections in these patients.

Candidemia is an infection that has a high mortality rate in patients with COVID-19; therefore, the identification and treatment of candidemia cases is of paramount importance. Patient exposure to antibiotics, corticosteroids, catheterization, mechanical ventilation and advanced age are risk factors for developing this invasive infection.

Susceptibility tests to antifungal drugs are indicated to guarantee a more assertive treatment, especially for systemic infections. Management is carried out with antifungal agents available on the market today and comprises the classes of azoles, polyenes and echinocandins.

Future studies are needed to better clarify the mechanisms of co-infection.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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