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Challenges of the Global COVID-19 Pandemic and Invasive Fungal Pathogens in SARS-COV-2 Associations: A Dangerous Relationship

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Abstract

Background: COVID-19 is a rapidly transmissible pneumonia-like illness caused by SARS-CoV-2 that out broke in China in 2019 and is currently circulating worldwide. In the current context of the SARS-CoV-2 pandemic, complications are observed in clinical settings for the treatment of severe COVID-19 disease in nosocomial settings, due to cases of fungal co-infections. **Objective:** To carry out a review on fungal infections associated with respiratory infections caused by COVID-19 (Sars-Cov-2) and their aggravation. **Methodology:** The purpose of this study is to inform the reader about the characteristics of SARS-CoV-2 and the main fungal species that are affecting patients undergoing treatment for severe COVID-19, provoking discussion of the importance of the proposed topic, in relation to co-infections by different fungal microorganisms. **Result:** 80 scientific studies were selected, resulting from patients with COVID-19 and most commonly observed in patients with a history of comorbidities such as *diabetes mellitus*, hypertension, kidney disease, severe liver disease, oncological diseases, obesity and with severe COVID-19. These data do not represent the total number of records of the disease in the world, but cases reported by researchers in their series, showing the overlapping of fungal co-infection through the compromised immune status due to the use of therapeutic drugs, dysregulation of the microbiota,

age of patients and the severity itself of the severe inflammation caused by COVID-19. **Conclusion:** The immunosuppression caused by the infection of COVID-19 concomitant with its therapy through corticosteroid therapy and comorbidities of the patients made fungal infections more susceptible, and these interfere in the evolution of the case and in the treatment of COVID-19, being relevant to distinguish secondary infections to therapy and the best possible reconstitution of the clinical picture.

Keywords

Fungal Coinfections, COVID-19, Coronavirus, Systematic Review

1. Introduction

COVID-19 is a rapidly transmissible pneumonia-like illness caused by SARS-CoV-2 that out broke in the city of Wuhan in China in December 2019 and is currently circulating across the planet. In 2021, it already accounted for millions of people infected with the severe acute respiratory syndrome virus (SARS-CoV-2) [1]. As the COVID-19 pandemic has evolved, increasing concerns have been reported about invasive fungal infections, particularly with the use of potent immunosuppressive drugs to treat immune storms in patients with severe illness from this infection [2].

Fungal infections have been reported as a complication of severe COVID-19, impairing the clinical course of patients hospitalized in hospital intensive care settings [3]. Fungal nosocomial infections are being related due to the permanence of hospitalized patients, causing concern due to the experience of the pandemic caused by the COVID-19 disease, having relevance in critically ill patients affected by the disease [4].

In the context of a severe acute respiratory syndrome, in patients infected with SARS-COV-2 (COVID-19), patients may require intensive care, using for prolonged periods, these devices and broad-spectrum medications, increase the risk of fungal infections secondary.

The current pandemic, known as SARS-CoV-2 (COVID-19) which causes Severe Acute Respiratory Syndrome, according to WHO (World Health Organization) panel records, the disease has already affected more than 635,000 people with cases confirmed, resulting in more than 6 million deaths worldwide. Brazil ranks fifth among countries in number of cases of the disease (35 million), behind the United States (97 million), India (44.6 million) and France (36.3 million). In addition, the number of deaths in Brazil (more than 688,000) is the second highest in the world ranking, after the USA [5].

The enveloped RNA virus (SARS-CoV-2) is genetically different from known coronaviruses such as SARS-CoV-1 (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome). According to the International Committee on Taxonomy of Viruses (ICTV), this virus is classified in the su-

per-kingdom Riboviria, order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae and genus Betacoronavirus (β-CoV), which then contains the species SARS-CoV-2. Based on genetic properties, the Coronaviridae family is further composed of the genera Alphacoronavirus (α-CoV), Gammacoronavirus (γ-CoV) and Deltacorovirus (δ-CoV). Among these genera, the only ones capable of producing infection in humans and animals, causing respiratory, gastrointestinal, hepatic and neurological symptoms, are Betacoronavirus (β-CoV) and Alphacoronavirus (α-CoV) [6].

Six CoVs are known to infect humans, but two of them are capable of causing respiratory syndrome: SARS-CoV and MERS-CoV, however other species of CoVs cause mild respiratory disease in humans (HCoV-HKV1, HCoV-OC43, HCoV-NL63 and HCoV-229E).

The rapidly changing virus. The first variant of Sars-CoV-2, called D614G, was identified in early 2020, and is considered the most infectious genotype in humans. In December, the English strain B.1.1.7 (Alpha) was identified, which is more contagious than the original strain identified in Wuhan. Then came the strains B.1.351 (Beta), from South Africa, the one from Manaus/Brazil, called P.1 (Gamma) and then B.1.617.2 (Delta) in India. Later, the variant B.1.525 (Eta) appeared, already identified in several countries, such as Nigeria, United Kingdom and Denmark; B.1526 (Iota) identified in the USA, B.1.617.1 (Kappa) isolated in India, C.37 (Lambda) isolated in Peru and finally B.1.621/B.1.621.1 (Mu) isolated in Colombia, then B.1.1.529 (Ômicron), isolated in South Africa and its various lineages [7] [8].

SARS-CoV-2, after activating the immune system, triggers an excessive and unregulated immune response, causing what is called a cytokine storm, promoting cell damage in the patient, causing this excessive inflammatory process to cause Respiratory Distress Syndrome (SDRG) or Severe Acute Respiratory Syndrome (SARS) [9].

Faced with this pandemic scenario, some fungi were highlighted due to their opportunism and ability to adapt to infections as secondary sources. Aspergillus, commonly found in soil, plants, decomposed organic matter, air, water, food, and dust, and when inhaling the spores of species causing human infection, immunocompromised patients may experience invasive infection of the lungs and sinuses and invasive systemic spread, known as aspergillosis, whereas for immunocompetent individuals, localized infection of the lungs and sinuses and allergic symptoms may occur due to non-infectious mechanisms [10].

The main infectious agent, when it comes to opportunistic infections associated with co-infections, is *Aspergillus fumigatus*, a filamentous fungus, which causes several forms of the disease, however, the most serious is the invasive pulmonary one; evolving to fatal pneumonia if not treated [11]. Aspergillosis can also be caused by the following agents: *A. flavus*, *A. terreus* and *A. niger*. Chong [12], define COVID-19-associated pulmonary aspergillosis (CAPA) as the most common infection of the symptoms of invasive pulmonary aspergillosis. The

symptoms are fever resistant to antibiotic therapy, pleural pain and cough, however, the symptomatology can be nonspecific [9].

As the world struggles to cope with the deadly effects of COVID-19, a new threat known as "black fungus" has appeared around the world. The disease is rare but can be serious worldwide, with a high incidence of damage reported in India. Fungi of the order Mucorales, can be acquired by sporongiodosporic inhalation due to food contamination or traumatic inoculation, their agents belong to the genera *Rhizopus*, *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor*, *Cunninghamella* and *Syncephalastrum* [13].

According to Prakash and Chakrabarti [14], patients with uncontrolled *diabetes mellitus* are associated with the onset of mucormycosis, in patients with hematological malignancy, organ transplant recipients, iron overload and large skin lesions, among others. This infection can still affect the rhino-orbito-cerebral region (ROC), pulmonary, cutaneous, gastrointestinal region, and may be disseminated, with the most frequent clinical manifestations, the ROC and pulmonary forms [15].

Another group of extreme importance is the yeasts of the genus Candida. These fungi are part of the microbiota of humans and animals, and when immunity deficiency occurs these organisms proliferate developing the fungal infection candidiasis that can cause infections in the bloodstream (Candidemia). The most infectious species to humans are: *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* and more currently the emerging species in certain parts of the world: *Candida auris*, informs us the CDC [16].

The risk factors for an invasive infection in the bloodstream, both for yeast species of the genus Candida, are similar: use of broad-spectrum antibiotics, diabetes, prolonged use of venous catheters, breathing tubes, long stay in intensive care and invasive procedures all make Candida spp. and other fungi, with high rates of morbidity and mortality, further worsening the situation of individuals who are immunosuppressed [16] [17].

2. Methodology

About 102 articles were initially selected for the description of this review. Data were collected using PUBMED, SCIELO, GOOGLE ACADÊMICO, BIRREME, SCIENCE DIRECT and SPRINGER LINK databases from 2021 to 2022, using the terms: Co-infections, COVID-19, Aspergillosis, Candida, Mucormycosis, Fungal infections, Coronavirus and SARS-CoV-2, with articles that provided information that correlated fungal infections with COVID-19 disease.

A total of 80 articles were identified through the initial database search. We excluded articles due to lack of information or publications that did not report primary data. For the selection of articles, we related COVID-19 and invasive pulmonary aspergillosis, systemic infections by yeasts of the genus *Candida*, *Cryptococcus*, *Trichosporon*, in addition to information related to cases of mucormycosis and black fungi, as well as other systemic and endemic fungal infec-

tions such as *Paracoccidioides* and *Cococcidioides*.

After removing duplicate items and sorting based on title and abstract, 37 publications were selected to compose the table with the respective fungal species and co-infections with COVID-19.

Also for composing this table, we collected data on epidemiology, age, sex, clinical site of infection and isolated fungal species, indicating the current situation and clinical outcomes in which cases involving these associations of different microbiological species presented in the corresponding table are found.

3. Results

In the search in order to answer the questions, through the descriptors, 37 articles were identified, of which they were selected in the year 2020 (7, 18.92%) and in the years 2021 and 2022 (15, 40.54%) respectively. The results reported in this study are associated with factors and hospitalized patients who developed fungal diseases after and during COVID-19.

According to the records presented in our series, in Table 1, infections by the yeast genera *Candida*, *Trichosporon and Cryptococcus* (17, 45.9%) were the ones that occurred most frequently in patients with COVID-19, followed by filamentous fungi of the genus *Aspergillus*, *Rhizopus* and *Coccidioides* (12, 32.43%) that had risk factors comparable to the findings observed in patients with COVID-19.

Cases involving SARS-CoV-2 and fungal infections have been reported by several countries such as Germany, Brazil, USA, India, China, France, Colombia, Argentina, Spain, Austria and Qatar. In our sample, case records were most reported in the USA (11, 29.7%), followed by Brazil (10, 27%) and then India (4, 10.8%).

We investigated that relative to host age; fungal infections associated with SARS-CoV-2 were shown to have a more pronounced effect in the older age group. The incidence of co-infections according to the authors' reports, the ages reported were between 1 year (younger age) and 88 years (older age). Most cases involved male patients, females ranked second (Table 1).

The elderly, mostly male, aged between 55 and 77 years, were diagnosed with more comorbidities, including neutropenia, *diabetes mellitus*, structural lung disease and/or using mechanical ventilation, corticosteroids or immunomodulators for the treatment of COVID-19. Reports of pulmonary and respiratory infections (11, 29.7%) were the most common, followed by cases of pneumonia (8, 21.6%) and then blood infections (7, 18.9%) (Table 1).

It was possible to see that hospitalized patients with COVID-19 affected by fungal co-infections have a higher risk of mortality, even more so if they have complicated underlying diseases such as *diabetes mellitus*, hypertension, oncological diseases, heart, kidney and liver diseases and, even age, correlating with the treatment system using mechanical ventilatory support and drug therapy, becomes relevant in COVID-19.

Table 1. Fungal species associated with COVID-19 infections reported in the researched literature in 2020 and 2022.

Author (s)	Year	Country	Gender	Average/Age	Site/place	Fungal species in Co-infection
1) Koehler *et al.*, [28]	2020	Germany	M*/F	54 - 73	Pulmonary infection	*Aspergillus fumigatus*
2) Macedo *et al.*, [66]	2020	Brazil	M*	19	Lymphnodes	*Paracoccidioides* spp.
3) Mitaka *et al.*, [29]	2020	EUA	M*	79	Respiratory infection	*Aspergillus fumigatus*
4) Santana *et al.*, [30]	2020	Brazil	M*	71	Pulmonary infection	*Aspergillus penicillioides*
5) Chowdhary *et al.*, [45]	2020	India	M*/F	66 - 88	Blood	*Candida auris*; *C. albicans*; *C. tropicalis*; *C. krusei*
6) Lansbury *et al.*, [26]	2020	China	M/F	42 - 69	Pulmonary infection/Blood	*Candida albicans*; *C. glabrata*; *Aspergillus flavus*; *A. fumigatus*
7) Poignon *et al.*, [63]	2020	France	M*	57	Respiratory infection	*Fusarium proliferatum*
8) Rodriguez *et al.*, [48]	2021	Colombia	M*/F	1 - 86	Blood	*Candida auris*; *C. albicans*; *C. tropicalis*; *C. parapsilosis*; *C. orthopsilosis*; *C. glabrata*; *Trichosporon asahii*
9) Bhagali *et al.*, [46]	2021	India	M*	42	Eyes	*Candida albicans*
10) Bonates *et al.*, [41]	2021	Brazil	M*	56	Rhino-orbito-cerebral	*Rhizopus oryzae*
11) Almeida Jr. *et al.*, [44]	2021	Brazil	M/F	59/74	Renal insufficiency	*Candida auris*
12) Fernandez *et al.*, [34]	2021	Argentina	M*	85	Pneumonia	*Aspergillus flavus*
13) Silva *et al.*, [43]	2021	Brazil	M*/F	35 - 75	Trachea, blood e urine	*Candida albicans and Candida não-albicans*; *Aspergillus* spp.
14) Nielsen *et al.*, [70]	2021	EUA	M	52	Pulmonary infection	*Coccidioides posodasi*
15) Cronyn *et al.*, [51]	2021	EUA	M*	73	Urine	*Trichosporon asahii*
16) Ali *et al.*, [2]	2021	Qatar	M*	58	Blood	*Trichosporon asahii*
17) Almeida Jr. *et al.*, [51]	2021	Brazil	M*/F	57 - 75	Blood	*Trichosporon asahii*
18) Segrelles-Calvo *et al.*, [49]	2021	Brazil	M*	58	Pneumonia	*Trichosporon asahii*
19) Alegre-Gonzalez *et al.*, [60]	2021	Spain	M*	78	Pneumonia	*Cryptococcus neoformans*
20) Damani *et al.*, [61]	2021	EUA	M*	57	Pulmonary infection	*Fusarium* spp.
21) Macedo *et al.*, [67]	2021	Brazil	M*	20/32	Pulmonary infection	*Histoplasma capsulatum*
22) Heaney *et al.*, [69]	2021	EUA	M/F	65	Pulmonary infection	*Coccidioides immitis*
23) Benelli *et al.*, [50]	2022	Brazil	F*	58	Blood	*Trichosporon asahii*
24) Regalla *et al.*, [56]	2022	EUA	M*/F	73	Pneumonia	*Cryptococcus* spp.
25) Chastain *et al.*, [57]	2022	EUA	M*/F	56	Pneumonia/HIV	*Cryptococcus* spp.
26) Chan *et al.*, [58]	2022	China	M*/F	60 - 74	Blood	*C. neoformans and C. laurentii*
27) Roesch *et al.*, [59]	2022	EUA	F*	46	Pneumonia	*Cryptococcus* spp.
28) Munhoz *et al.*, [52]	2022	Brazil	M*	67	Rhino-orbito-cerebral	*Rhizopus microsporus* var. *microsporus*

Continued

29) Singh *et al*., [39]	2022	India	M*/F	25 - 75	Sino-nasal-orbital/ necroses	*Mucormycoses* (black fungi)
30) Samaddar *et al*., [53]	2022	India	M*	55	Brain abscess	*Trichosporon dohaense*
31) Barberis *et al*., [65]	2022	Argentina	M*	68	Blood	*Fusarium verticillioides*
32) Toscanini *et al*., [66]	2022	Argentina	M*/F	19 - 77	Pneumonia	*Histoplasma capsulatum*
33) Nogal *et al*., [68]	2022	EUA	M*	61	Pneumonia	*Histoplasma capsulatum*
34) Huff *et al*., [72]	2022	EUA	M*/F	56	Pulmonary infection	*Coiccidioides immitis*
35) Nassif *et al*., [70]	2022	EUA	F*	67	Liposarcoma	*Coccidioides immitis*
36) Lackner *et al*., [33]	2022	Austria	M*/F	39 - 84	Pulmonary infection	*Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. nidulans*
37) Iturrieta-Gonzales *et al*., [31]	2022	Chile	F*	20	Pulmonary infection	*Penicillium digitatum*

*Predominant gender in the series.

4. Discussion

SARS-CoV-2 is, today, a public health obstacle in the world and it is of extreme importance, all attention to the problems that the virus has caused. Based on research, co-infections of the virus with other microorganisms may hinder the clinical practice of patients affected by COVID-19 [18]. Severe illness from COVID-19 is associated with increased pro-inflammatory cytokines, interleukin (IL)-1, IL-6 and tumor necrosis factor alpha, reduced expression of CD4-interferon-gamma, CD4 and CD8 T cells, which increase susceptibility to fungal infections [19].

The association of opportunistic systemic mycoses with COVID-19, reported, can cause relevant damage to the already compromised immune system and aggravate the state of patients who are debilitated, due to comorbidities and the use of corticosteroid therapies in the treatment of the disease, which may lead to risks of an unwanted case evolution [4]. The treatment of these two co-associated infections is complex and requires attention and palliative care. Immunomodulatory drugs, including corticosteroids and cytokine blockers, are options to combat hyperinfection caused by the virus [20] the likely decrease in the immune system and defense cells (lymphocytes) damaged by SARS-CoV-2 seems to be associated with the emergence of co-infections [18]. According to Hoenigl and collaborators [20], these drugs hinder the activation of innate and adaptive antimicrobial responses and exacerbate existing underlying diseases, therefore, they represent important predisposing factors for secondary fungal infections and side effects on susceptibility to fungal infections, because fungi are an extremely neglected public health problem with few treatment options.

Although current studies focus on the intestinal microbiota, signaling the genera *Candida*, *Malassezia*, *Aspergillus*, *Epicocum*, *Sccharomyces*, *Alternaria* and *Cladosporium*, as the most common intestinal fungi in infections [21] [22], however alerts indicate that it is necessary to pay attention to the pulmonary

microbiota in COVID-19.

Reports by Iranian researchers indicate that mortality from COVID-19 is associated with complex mixed bacterial and fungal infections in the lungs and needs monitoring against infections, as populations of certain microbiota species such as *Cutaneotrichosporon*, *Cryptococcus*, *Issatchenkia*, *Wallemia*, *Cladosporium*, *Alternaria*, *Dipodascus*, *Mortierella*, *Aspergillus*, *Naganishia*, *Diutina* and *Candida* can alter the pathogenesis of COVID-19 in patients, needing greater attention [23].

The main fungal pathogens for fungal co-infections in severe COVID-19 patients are *Aspergillus* spp. and *Candida* spp. *Aspergillus fumigatus* and *Candida albicans* are responsible for the majority (85% to 90%) of the different clinical manifestations of fungal infections [24]. Other infrequent opportunistic pathogenic fungi that cause pulmonary infections also need to be considered, such as *Mucor* spp. and *Cryptococcus* spp. [25]. More recently, zygomycetes have emerged as important fungal pathogens, especially in the severely immunocompromised host [24].

Although other yeast-like and filamentous fungal agents have also been reported, in cases with COVID-19 such as *Trichosporon* spp., *Histoplasma* spp., *Coccidioides* spp., *Paracoccidioides* spp., *Fusarium* spp., *Cladosporium* spp., *Alternaria* spp., *Penicillium* spp. at lower frequencies in this pandemic scenario.

British researchers [26], in their studies, demonstrated that *Candida albicans*, *C. glabrata*, *Aspergillus flavus*, *A. fumigatus*, both from respiratory samples, also indicated with probability analysis, that COVID-19 patients-19 with co-infection became more likely to die than those who did not have co-infection, mentioning the growing reports in Europe of pulmonary aspergillosis associated with COVID-19, related to medical treatment, in patients in serious condition and diagnostic difficulties.

Several studies have been warning about the appearance of fungal infections in severe COVID-19 patients, leaving special emphasis on candidemia, invasive aspergillosis and the increasing cases of mucormycosis, popularly known as black fungus; in India, for example, with high rates of this mycosis even before the pandemic and, Paraguay, Uruguay and Brazil, are countries in South America that had records of mucormycosis, however, not as expressive as in India, where high rates of this disease are associated fungus with a large number of cases of diabetes, among other causes [13] [15].

Iranian researchers reported COVID-19 associated fungal infections (CAFIs), in an analysis where they retrieved 22 studies involving 169 patients reporting cases of candidiasis (50.30%), mucormycosis (20.71%), aspergillosis (17.16%), fusariosis (3.55%) and uncharacterized fungal infections (6.51%) and three cases caused by rare pathogens (*Rhodotorula mucilaginosa*, *Sarocladium kiliense* and *Diaporthe foeniculina*) infecting female patients. In this study, 72 (50.35%) patients with CAFIs died [27].

Aspergillosis, caused by *Aspergillus* spp. cause invasive fungal disease with a

high mortality rate, manifesting superficially and profoundly and affecting immunosuppressed patients, given the association of this infection in severe patients of the SARS-CoV-2 pandemic, it was named (CAPA-COVID-19-associated pulmonary aspergillosis). Aspergillosis was the first reported COVID-19-related fungal infection, with *A. fumigatus* being the most frequent species for CAPA.

COVID-19-associated pulmonary aspergillosis (CAPA) is a disease that requires prolonged ICU treatment due to the high mortality rate; records provided by researchers indicate that in France, 33% of patients with COVID-19 in the ICU were affected by CAPA, and in Germany, it affected up to 26% of patients [28].

In the United States, Mitaka and collaborators [29], evaluating respiratory cultures from patients affected by the COVID-19 virus, found *A. fumigatus*, causing pulmonary aspergillosis in patients who received high doses of corticosteroids. *A. penicillioides* is a xerophilous species that occurs in dry habitats and in house dust; is responsible for human and animal allergies. In Brazil, Santana and his collaborators [30] isolated this fungal species, in invasive pulmonary aspergillosis (IPA) in a patient with severe COVID-19.

Penicillium digitatum and *Penicillium italicum* are mesophilic fungi, found associated with the deterioration and rot of citrus fruits. A study carried out by Chilean researchers [31] described a clinical report of *P. digitatum*, in a patient from a rural area, who developed pneumonia associated with COVID-19 successfully treated with itraconazole. The most extensive work on this fungal genus was carried out by Lyratzopoulos [32], who reviewed 31 cases of invasive pulmonary fungal infection by Penicillium species other than *P. marneffei*, among which they described *P. chrysogenum*, *P. decumbens*, *P. janthinellum*, *P. lilacinum*, *P. purporogenum*, *P. citrinum and P. brevicompactum.*

In a retrospective study, which included 329 ICU patients diagnosed with SARS-Cov-2, 23 of these patients had a positive culture for *Aspergillus* spp. during a hospital stay in Austria. The patients had severe pulmonary disorders and were treated with the antifungal agent's voriconazole, posaconazole, amphotericin B, anidulafungin and caspofungin. The species involved were *A. fumigatus*, *A. flavus*, *A. nidulans* and *A. niger* [33].

Cases of invasive pulmonary aspergillosis by *Aspegillus flavus* were identified in the study by Fernandez and his collaborators [34], through their case report, in Argentina, where they identified similarity with patients who were treated in Europe for COVID-19. After admission to intensive care treatment, patients developed invasive pulmonary aspergillosis, demonstrating that the use of mechanical ventilation support and the use of corticosteroids can lead to cases of fungal co-infections associated with COVID-19.

Argentine researchers [35] reviewed CAPA cases and identified 178 cases. The main comorbidities reported were diabetes, atherosclerotic disease, obesity and chronic obstructive pulmonary disease. The related species were distributed as follows: *A. fumigatus*, followed by *A. flavus*, *A. niger*, *A. terreus*, *A. nidulans*, *A.*

ochraceus, *A. calidoustus*, *A. awamorii*, *A. citrinoterreus* and *A. penicilloides*. *A. fumigatus* was the most commonly reported species and was susceptible to all drugs, associated with azole resistance. Voriconazole was the most used drug, followed by amphotericin B.

Koehler and his collaborators [28] found *A. fumigatus*, causing invasive pulmonary aspergillosis in association with patients infected with SARS-CoV-2 and risk factors for *diabetes mellitus*, arterial hypertension and corticosteroid therapy. Patients were treated with voriconazole and itraconazole. Twenty-nine cases of aspergillosis have been reported among COVID-19 patients from Iran, the majority being male. Pulmonary infection was the most common clinical form of the disease; in addition, disseminated rhinosinusitis has been reported and identified at the species level. *Aspergillus flavus*, the most common etiological agent, followed by *A. fumigatus*, *A. japonicus*, *A. niger*, *A. ochraceus*, *A. terreus* and *A. tubingensis* [27].

The CDC (Centers of Disease Control and Prevention) informs that Aspergillus and mucorales, both are fungal groups that are virtually impossible to avoid contact with, as people inhale their spores, harmful to a weakened immune system, causing infections in the lungs and sinuses nasal passages with chances of spreading to other parts of the body [4].

Tavares [4], emphasize that patients with serious severity of COVID-19 with severe inflammation, dysregulation of the microbiota and treatment with antibiotics, often early, in addition to immunosuppressive drugs, leave the individual prone to mycoses such as *Candida* spp., *Aspergillus* spp. and *Mucorales*; being corroborated by ANVISA's technical note [15] which says there are cases of fungal infections in demand for growth in patients who acquire the severe form of the COVID-19 disease in intensive care, as is the case with invasive aspergillosis and mucormycosis.

We must take into account that in the SARS-CoV-2 pandemic, Severe Acute Respiratory Syndrome; the microbiological co-infection associated with the COVID-19 disease has led individuals to the need for hospitalization and hospital treatment, with opportunistic fungal co-infections. According to Severo [36] mucormycosis is an opportunistic fungal infection that usually does not course with disease in immunocompetent individuals, having clinical manifestations due to the state of the host, associated with diseases and when it appears it usually has a rapid evolution. Mucormycosis is the rarest type of fungal infection in order of importance after candidiasis and aspergillosis.

Mucormycosis depends on some basic conditions of the patient, predominantly in the male population and is associated with diabetes and oncological disease, plus the interaction of steroids, causing greater immunosuppression and the high glycemic rates triggered by *diabetes mellitus*, making these patients even more susceptible patients to the opportunism of zygomycosis [4].

Reports of immunosuppression in cases of SARS-CoV-2 infection associated with uncontrolled glycemia, diabetic conditions can offer an opportunity for the installation of fungal infections. Cases of mucormycosis associated with COVID-19

(CAM: COVID-19 associated mucormycosis) have gained prominence in India, in view of the already existing dissemination of mucormycosis common in that country, as well as the increasing prevalence of *diabetes mellitus* in the Indian population, this being a risk factor for the onset of infection, showing that species of the genus *Rhizopus* were more frequently observed in rhino-orbito-cerebral forms, with 46% of fatal cases [37].

Reports of 35 cases of mucormycosis were described by Nazari [27] that presented rhino-orbito-cerebral manifestations (91.43%) and rhinosinusitis (8.57%) distributed in rhino-sino-orbital infections (48.57%), rhino-orbital (20%), sinus-orbital (14.29%), orbital (5.71%) and rhino-sino-orbital (5.71%) orbital-cerebral involvement (2.86%). Definitive identification of *Rhizopus oryzae* (=*R. arrhizus*).

Research carried out in 2021 [38] showed that the increased use of corticosteroids in diabetic patients undergoing treatment for COVID-19 helps in uncontrolled glucose levels, favoring the appearance of fungi of the order Mucorales, as well as evidenced that in Brazil, patients with diabetes affected by COVID-19 more often needed intensive care units.

In India, cases of mucormycosis, called black fungus, have been associated with a range of pre-existing health conditions, including *diabetes mellitus*, iron overload, cancer, organ transplantation, kidney failure, acquired immunodeficiency syndrome (AIDS) and therapy immunosuppressant [13] [14] [39].

According to reports by an Emirati researcher [40]; overuse of steroids for COVID-19 patients has likely been the cause of the rise in the rare fungal disease. The infection stems from reduced immune response and capacity as a result of the steroids used to limit the immune system's overreaction to the infection.

In Brazil, Bonates [41] reported a case of mucormycosis in a male patient from Manaus/Brazil, diabetic, presenting diabetic ketoacidosis and ocular infection, who tested immunoglobulin G (IgG) positive for SARS CoV-2, presenting flu-like symptoms; the patient had necrosis in the region of the nose, orbits and palate and died, and the sequencing test showed 99% similarity with *Rhizopus oryzae*. In Brazil, Munhoz [42], presented a case of rhino-orbito-cerebral mucormycosis in a diabetic patient hospitalized for COVID-19 whose diagnosis was confirmed by identifying the agent *Rhizopus microsporus* var. *microsporus.*

Indian researchers in 2022 [39] reported 102 cases of mucormycosis, being treated for COVID-19. The patients had *diabetes mellitus* and severe diabetic ketoacidosis, favoring fungal opportunism by filamentous zygomycetes in cases of maxillary necrosis, sinus-orbito-nasal involvement and pulmonary infections. Amphotericin-B, posaconazole and isavuconazole are the antifungals used in the treatment of mucormycosis or black fungus.

Silva and researchers [43] correlating co-infections and mortality, the rates found were higher in male patients compared to females, and older age contributed to negative treatment results. Comorbidities such as underlying diseases, cardiovascular diseases and *diabetes mellitus*, obesity, individuals who needed

mechanical ventilation support, entered as risk factors. The vast majority of patients died and most positive cultures for fungi from patients were isolated *Candida* spp. and *Aspergillus* spp. as entities associated with co-morbidities.

A similar situation occurred in Iran. Hypertension, cardiovascular diseases, *diabetes mellitus* and chronic kidney diseases were the underlying diseases reported in cases of co-infections with fungal entities linked to COVID-19. Patients were admitted to the ICU, mechanically ventilated and received antibiotics and corticosteroids. No antifungal was recommended and the patients died [27].

For Chen and associates [18], the intestinal balance can be altered in co-in fection, triggering infection and stimulation of the immune system to a more pronounced inflammation and, if a co-infection increases the level of systemic inflammation, this increases the severity of the disease, reducing the patient's healing time. These researchers, in their sample, highlighted the main fungal species: *Aspergillus* spp, *Candida albicans*, *C. glabrata*, *C. dubliniensis*, *C. parapsilosis* sensu stricto, *C. tropicalis* and *C. krusei*.

Linked to COVID-19, cases of the yeast emerging as one of the most infectious agents, *Candida auris*, are becoming more routine, possibly the pandemic may be favoring the spread of this species of Candida in hospital environments. Almeida-Jr and collaborators [44] presented cases of *C. auris* in Brazil, in the city of Salvador in December 2020, showing that the colonized were in the same intensive care unit to treat COVID-19 and, molecular analyzes showed that the strains found in Brazil they were phylogenetically related to the South Asian clade (Clade 1), considering that the patients had no history of traveling abroad.

Other reported cases occurred in New Delhi, India, 15 cases of COVID-19 associated candidemia (CAC) in ICU patients; *Candida auris*, *C. albicans*, *C. tropicalis* and *C. krusei* were identified; most of those colonized by *Candida auris* were male and aged between 66 - 88 years and had underlying diseases such as hypertension, *diabetes mellitus*, kidney disease and chronic liver disease and half of the patients affected by *C. auris* required mechanical ventilation due to severity of COVID-19 [45].

Another peculiar case reported in India, by Bhagali [46], of a male patient who developed retinitis caused by *Candida albicans* after infection with SARS-CoV-2; this patient was diabetic and hypertensive and needed to use corticosteroids to treat COVID-19. In Brazil, a report of 60 strains of *C. parapsilosis* resistant to the azole fluconazole and tolerant to echinocandins caused an outbreak of candidemia among patients with COVID-19 in a Brazilian ICU; reported and discussed by Daneshia and collaborators [47].

Vitale and researchers [35] listed the yeasts that were associated with co-infections in COVID-19 and found Candida species fungemia reported in 149 cases. The most frequently isolated species from blood cultures were *C. albicans*, *C. auris*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*, *C. orthopsilosis* and *C. krusei* (=*Pichia kudriavzevii*) and also *Trichosporon asahii*, *Saccharomyces cerevisiae*, *Rhodotorula mucilaginosa* and *Cryptococcus neoformans*. Mortality was high, 44 patients died.

In Iran, researchers pointed out those older and female patients were more affected by Candida yeast infections and COVID-19 infections. Cases included oropharyngeal candidiasis (62.35%), pulmonary candidiasis (29.41%), candidemia (7.06%) and endocarditis (1.18%), isolating in these records, *C. albicans*, the most common species, followed by *C. glabrata*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* [27].

Rodriguez and colleagues [48], reported cases of fungemia in inpatients with SARS-CoV-2 at 4 institutions in Colombia in 2020; these patients received therapy with Beta-Lactam antibiotics and steroids, many used a central venous catheter and had a prolonged time in the intensive care unit and developed fungemia due to *Candida auris*, *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. orthopsilosis*, *C. glabrata* and *Trichosporon asahii*.

Incidentally, this last fungal agent, in recent times, has been showing its invasive capacity to cause serious fungal infections. The genus Trichosporon is known for its capacity for superficial colonization; however some species have shown pathogenic potential for systemic infections. This fungal agent has changed from a rare opportunistic pathogen to a group of microorganisms that has been causing alarm and concern worldwide, mainly due to its profile of resistance to antifungal agents.

Trichosporon asahii is a highly resistant emerging pathogen with considerable mortality, particularly in critically ill patients and immunocompromised individuals [2]. Rodriguez in casuistry [48] reported 20 cases of *T. asahii* fungemia in patients with COVID-19, with a reported overall mortality of 60% in this cohort. Segrelles-Calvo and colleagues [49] reported cases of *T. asahii* pneumonia in a patient with COVID-19.

Benelli and researchers [50] reported a case of a patient with bloodstream infection by *T. asahii* in a critically ill patient with COVID-19 associated with *Acinetobacter baumanii*. Almeida-Jr. [51], described 5 critical patients with COVID-19 who developed fungemia by *T. asahii*, who presented risk conditions: central venous catheter, previous exposure to broad-spectrum antibiotics, previous therapy with echinocandin and previous prolonged corticosteroid therapy.

More currently, Cronyn [52] reported urinary infection in a male patient with severe COVID-19, isolating the co-infection agent *T. asahii*, treated with fluconazole and voriconazole, and finally, a case of associated brain abscess to Coronavirus Disease 2019 caused by a rare species of basidiomycete of the genus Trichosporon, *T. dohaense* affecting a diabetic patient who received systemic corticosteroids for the treatment of COVID-19 [53].

Another fungal organism also present in co-infections associated with patients with severe COVID-19 was the genus Cryptococcus. Recently, cryptococcal infections have emerged as a concern after association with COVID-19 infection (CACI), because Cryptococcus spores can remain dormant in human hosts, because cryptococcal infections are considered incurable, their fungal cells can remain dormant for many years and relapse occurs when the host becomes immunocompromised [54], which can lead to invasive cryptococcosis and disse-

mination in contexts of corticosteroid use, immunosuppressive therapy, endocrine and metabolite disorders, and blood and cancerous malignancies [55].

Infection by *Cryptococcus* spp. was reported in severe COVID-19 patients associated with pulmonary infection and followed by cryptococcal meningitis in 13 reports described by Regalla and colleagues [56]. Of 212,479 hospitalized patients with COVID-19; 65 patients were diagnosed with cryptococcosis, with cases of cerebral cryptococcosis, pulmonary cryptococcosis and disseminated cryptococcosis. Twenty-one patients had HIV infection in reports described by US researchers [57]. Chan and reseachers [58] reported 18 cases of COVID-19 infections associated with cryptococcosis, isolating *C. neoformans* and *C. laurentii* in their case series; these researchers, in summary, emphasized that COVID-19-associated cryptococcosis is uncommon; however, it may be underestimated due to underdiagnosis.

In the same year, Roesch and collaborators [59] reported a case of a female patient, where conventional results did not detect the presence of comorbidities. Pathology demonstrated a collection of histiocytes, neutrophils, and necrotic debris, and pathology stains were positive for Cryptococcus fungal organisms, leading to a secondary lung cryptococcal infection. Alegre-Gonzales [60] in Spain, reported disseminated infection by *C. neoformans*, in a male patient with immunosuppression, affected by COVID-19, with fatal outcome.

Still other fungal entities are also involved in cases of patient infections associated with the serious situation involving COVID-19. Fusarium, a plant pathogen, has crossed the species barrier, has become a common pathogen that infects immunocompromised, transplant patients, and rarely infects healthy individuals. A case of fusariosis and COVID-19, associated with pulmonary infection, was reported by Damani [61] in a healthy, non-critical patient.

Fusarium and Scedosporium belong to a heterogeneous group of filamentous fungi defined as infections called hyalohyphomycosis. Cases of severe pulmonary fusariosis associated with the COVID-19 virus have been reported *F. incarnatum*, *F. fujikuroi*, *F. equiseti* and *F. solani* in Iran [62] and a rare case of pulmonary infection due to *Scedosporium* occurred in Chile, described by John and researchers [63].

Another case of this type of infection was reported by Poignon [64] in a case of pulmonary fusariosis described in a diabetic patient with severe COVID-19 due to *F. proliferatum*, in France, and a case of invasive fusariosis, which occurred in Argentina, by *F. verticillioides* in a previously immunocompetent and critically ill patient with severe COVID-19 pneumonia [65].

In a Middle Eastern country, cases of pulmonary fusariosis in two men and four women with positive BAL galactomannan (GM) tests were reported in cases of COVID-19. The causative agents, including *F. incarnatum*, *F. fujikuroi*, *F. equiseti* and *F. solani* detected in bronchoalveolar lavage (BAL) culture [27].

Histoplasmosis is a global systemic mycosis highly endemic in certain regions of the Americas, including Brazil. The acute form of histoplasmosis usually occurs after exposure of more than one individual to a common environmental

source harboring *Histoplasma capsulatum.* One study found that patients with severe COVID-19 in the ICU are at risk of histoplasmosis reactivation when these patients are diagnosed in endemic areas. Toscanini [66] provided this information, when they analyzed serum and urine from patients affected by COVID-19, finding *Histoplasma capsulatum*.

Another study involving *H. capsulatum* was carried out in Rio de Janeiro/Brazil. The researchers found two cases of acute pulmonary histoplasmosis in patients treated at a reference center for infectious diseases in that country, and suggested that COVID-19 may facilitate the development of acute pulmonary histoplasmosis and greater attention in patients from endemic areas with fever and cough after recovery from COVID-19 [67].

Currently, Nogal [68] described a case of a 61-year-old, immunocompetent man admitted to hospital with pneumonia due to COVID-19. Despite adequate therapy, the patient required transfer to the intensive care unit for invasive clinical examinations isolated *H. captulatum*, the patient and mechanical ventilation was treated with Itrazonazole and Amphotericin B.

Another systemic infection agent, case reports of coccidioidomycosis, has also been evidenced in patients with COVID-19. Spores of *Coccidioides* spp. are spread through the air, especially by wind erosion in dusty environments and by dust from activities such as digging or construction and in hot, arid environments. This fungal infection is very common in the US and Mexico, showing infections by two sister species *C. immitis* and *C. posodasi.* In Brazil, this fungal infection is restricted to the arid regions of northeastern Brazil, its incidence is little known and it is a disease that does not have compulsory notification.

In the United States in 2020 [69], described cases of patients involving risks to agricultural and construction workers, firefighters, the elderly, incarcerated people and agricultural workers, migrants may be at greater risk of coccidioidomycosis and COVID-19. Age, diabetes, immunosuppression, smoking and weather conditions were the factors pointed out by the researchers, who also reported that people of black and Latino descent were at greater risk of contracting fungal infections. In Iran, researchers pointed out that for patients with comorbidities, the use of antibiotics (9.52%), corticosteroids (70.44%) and mechanical ventilation (51.16%) were the predisposing factors indicated as the most common in their series, involving these co-infections [27].

In 2021, the female patient, lymphopenic, with sequelae of recent COVID-19 infection developed an atypical disseminated form of coccidioidomycosis in the United States. The patient was treated with fluconazole for coccidioidomycosis and continued under observation for mild liposarcoma progression. Fungal infections may be associated with COVID-19, increasing the risk of atypical forms of infectious diseases in cancer patients [70]. Another case report involved a 52-year-old Hispanic male in the US with obesity and diabetes mellitus, poorly controlled, upon admission, it was positive for severe acute respiratory syndrome (SARS-CoV-2) and collections of tracheal aspirates confirmed secondary

infection by *C. posodasi* [71].

Also in that country, Texas/USA researchers [72] that coincided with the COVID-19 infection identified 60 cases of coccidioidomycosis. The investigators reported that seven of these patients developed clinically progressive coccidioidomycosis, and reported that corticosteroid intakes were considered a risk factor for the development of the fungal disease.

Finally, record of Paracoccidioides mycosis, associated with the case of COVID-19, reported by Macedo and collaborators [73]. PCM is a systemic fungal disease that occurs in Latin America and is most prevalent in South America. Infection begins in the lungs after inhaling active forms of *Paracoccidioides* spp. that affected young patient, male, 19 years old, with weight loss and scattered lymph nodes throughout the body, according to a case report.

COVID-19 still has a high prevalence worldwide. It is important for studies that evaluate the occurrence and frequency of association with and its impact on therapeutic modification and on the respiratory condition [30]. It is clear that fungal co-infections interfere with the systemic inflammation in the course of COVID-19, influencing the treatment, mortality and cure of the disease [9], thus, it becomes relevant for the prognosis and treatment of the patient affected by COVID-19, to know the origin of the secondary infection. For Garcia-Vidal and collaborators [74], co-infections acquired in the community are those that are diagnosed immediately or after the first 24 hours of hospitalization for COVID-19 and co-infections acquired in the hospital are those in which the time diagnosis occurred equal to or after 48 hours of admission for COVID-19.

Immune alterations in patients with SARS, MERS and FLU (influenza), especially alterations in the subsets of peripheral blood T lymphocytes, contribute to the understanding of the characteristics, diagnosis, monitoring, prevention and treatment of the disease [75]. According to Iranian researchers, Almasi and Mohammadipanah [76] there are two factors that address drug discovery to develop a new drug for SARS-CoV-2. Drug retargeting, screening molecular databases using drug modeling tools, and screening compound libraries in antiviral assays are current major approaches to finding potential agents for SARS-CoV-2 therapy. Much progress in understanding SARS-CoV-2 and molecular details of its lifecycle, followed by the identification of new therapeutic targets, is needed to lead to an efficient approach to anti-SARS-CoV-2 drug discovery.

In fact, the association of COVID-19 infection and fungal infections brings great problems to patients affected by these two diseases, depending on the immune capacity of the host; the final outcome can be death. Fungal infection of coronavirus patients can significantly increase mortality rates [77] [78] [79] [80]. Even after curing COVID-19, patients complain of self-reported long-term COVID symptoms, such as persistent fatigue, body pain, mood swings; cognitive problems, ongoing breathing problems after symptomatic SARS-CoV-2 infection [1].

5. Conclusions

This review aims to raise awareness of the importance of early detection and treatment of fungal infections, as mortality rates are high in patients with COVID-19, or even those with other immunosuppression conditions. It is necessary to accurately identify risk factors associated with secondary infections in each diagnosed patient to ensure optimal clinical outcomes.

It is important to keep in mind strategies and protocols to define more efficient and personalized treatments for COVID-19 patients, due to the emergence of fungal coinfections and the complexity that they can cause in the course of the disease, to allow safer interventions for patients, resulting in better treatment results.

It is also worth remembering that the growing cases of co-infections associated with fungi, the cases of mucormycosis that occurred in India, or even the rise of emerging fungi such as *Candida auris*, a multiresistant fungus, presented the SARS-CoV-2, and has shown their multiple abilities to infect and cause clinical emergency damage.

Frequent monitoring of co-infections acquired in the community and in hospital environments should be constant, serving as a surveillance for the scientific and medical community for cases of superinfections, raising awareness about the possibility of fungal co-infections, conscious use of antifungal drugs, which are often scarce in certain places, become essential factors, which aim to reduce delays in diagnosis and treatment, in order to help prevent serious illness and death from these infections.

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Author Contributions

DPLJ is the principal investigator, designed the study, wrote and organized the manuscript. AGM, SMC, BSFM, NCAS, CBA, collected the data, organized the information and wrote the manuscript. All other authors participated, read and conceived the review, organized its structure, assembled the sections, and revised the manuscript, agreeing with the finalized and published version of the manuscript.

Conflicts of Interest

The authors declared that there were no conflicts of interest.

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