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The Association Between Mucormycosis and COVID-19: A Literature Review

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Abstract
Objectives: the objective of the present paper is to note possible associations between the occurrence of mucormycosis and the COVID-19. **Materials and Methods:** a literature review was carried out on the databases of Pubmed, Web Of Science and Medline, being a search strategy consisting of the following combined keywords: "fungal infections AND COVID-19", "fungal co-infection AND COVID-19" e "mucormycosis AND COVID-19". Analyzes were performed using Excel software regarding location, patient profile and pre-existing comorbidities. **Results:** From a total of 1.847 articles, 66 were included in the literature review after it had been applied evaluation criteria on whether the studies had met said criteria or not. Regarding the place of origin of the studies, the one that appeared most frequently was India. In addition, 26 studies in which 48 reports of mucormycosis cases associated with COVID-19 had been stated were found. And, regarding patients, the most common comorbidities were diabetes mellitus, arterial hypertension, and heart diseases with an average age of 51,9 years and higher prevalence in the male gender. Rhino-orbital cases were most frequent. **Conclusion:** An increase in the number of cases of mucormycosis associated with COVID-19 has been demonstrated in several countries. This association between diseases causes an increase in mortality rates, which highlights the importance of correct diagnostic and therapeutic management.

Keywords
mucormycosis, COVID-19, SARS-CoV-2, *Mucor* spp.

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INTRODUCTION
In December of 2019, an outbreak of an infection characteristically similar to pneumonia occurred in the Chinese city of Wuhan. Rapidly, the infection spread around the world. After the sequencing of the genome, both the disease and its etiological agent were identified. It was a beta-coronavirus whose pathogen was identified as SARS-CoV-2. Thus, in February of 2020, the World Health Organization (WHO) named the disease as coronavirus 2019, popularly known as COVID-19 [1,2,3]. The coronavirus 2019 transmission happened at such a rapid pace that, in March of 2020, WHO officially acknowledged COVID-19 as a pandemic [1].

The most serious form of COVID-19 causes a differentiation in the expression of pro-inflammatory markers, for the release of IL-1, IL-2, IL-4, IL-6, IL-10, and TNF-alpha cytokines is increased, while the expression of IFN-gamma, CD4 and CD8 cells is decreased. The occurrence of said different inflammatory response caused by the viral infection can enhance patients' susceptibility to fungal and bacterial infections as well [1,4]. Besides, the disease caused by SARS-CoV-2 damages lung tissue, which increases COVID-19 patients' susceptibility to

invasive fungal infections, especially those airborne transmitted, such as mucormycosis, for example [1]. The mucormycosis is an invasive and opportunistic infection, and those patients affected by COVID-19 and with pre-existing comorbidities are more susceptible to the development of this mycosis, since infection by SARS-CoV-2 can cause lung damage that favor fungal invasion through the respiratory tract [5,6,7,8]. Furthermore, several studies demonstrate the occurrence of this co-infection associated with COVID-19. Among them, it is possible to mention Pakdel *et al*. (2021) who carried out a study with 58 patients suspected of mucormycosis and, among these, 15 individuals were affected by mycosis and positive for COVID-19 (25.8%) [9].

In general, co-infections are responsible for inhibiting significantly the hosts' immune system, as well as increasing resistance to antimicrobial treatment and damaging disease prognostics. Additionally, there are reports of increasement in mortality rates of patients affected by invasive fungal infections (IFIs) and COVID-19. Therefore, the mucormycosis and other fungal and bacterial co-infections are considered significant concerns due to its occurrence on vulnerable patients, which stresses the need brought by the COVID-19 pandemic of establishing monitoring and preventive programs concerning nosocomial infections, excessive usage of and resistance to antimicrobials [10,11].

MATERIALS AND METHODS

The literature review was carried out with the objective of verifying the existent associations between mucormycosis and COVID-19. For this purpose, databases from Pubmed, Web Of Science, and Medline were analyzed. The search terms consisted of these key-words combined: "fungal infections AND COVID-19", "fungal coinfection AND COVID-19", and "mucormycosis AND COVID-19".

Strategically, the specific search for mucormycosis, which is caused by the *Mucor* spp. genera, also known as "black fungus", is due to the recent increase in this particular mycosis case numbers in patients infected with COVID-19 in many countries, mostly in India [12]. Besides, it is an invasive airborne fungal infection, which causes a noticeable increase of this co-infection susceptibility in COVID-19 patients, for the disease damages lung tissue [1].

The boolean operator "AND" was used as a way of restricting the search findings, for the main objective was to find possible associations between the terms. The first article selection was made through the analysis of titles and summaries; no filters were applied. Regarding the criteria used, the articles repeated among the three databases used were analyzed, and those studies that did not mention mucormycosis as a fungal co-infection associated with COVID-19 were excluded. After selection, the articles included in this review were read in full and analyzed in terms of place of origin, patient profile and pre-existing comorbidities. For the compilation of these analyzes and better visualization of the information, tables and graphs were made in Excel software.

RESULTS

The review of the literature consisted in articles found in the databases of *Pubmed, Web Of Science*, and *Medline*; 1.837 articles were found in total. Then, selection criteria was applied after title and summaries analysis had been carried out, which identified the same 664 articles in all three databases. This left 1.173 articles to be analyzed next; from these studies, 1.106 were excluded from the analysis, for they had no relation with mucormycosis and COVID-19. Thereby, 67 articles were thoroughly read and included in this review. The flowchart which explains the selection of articles used in this paper is illustrated in Figure 1.

Regarding the places of origin of the study, those that appeared more frequently were India (n=40), United States (n = 8), performed in more than one place (n = 6), Iran (n = 2) and , less frequently, China (n = 2), Egypt (n = 1), Brazil (n = 1), Italy (n = 1), Netherlands (n = 1), Spain (n = 1), Turkey (n = 1) and Mexico (n = 1). These data demonstrate the relevance and distribution of studies that associate mucormycosis infections with the COVID-19 virus. Figure 2 represents the number of studies performed in different locations.

Due to the rising global increase of cases and the great number of report case studies (n=27) of COVID-19 associated with mucormycosis (CAM) found in the databases analyzed in this research, these patients' profiles also have been analyzed according to age/gender, pre-existing conditions, mucormycosis clinical form, and outcome. The 27 studies comprised, 49 case reports in total. The results found are illustrated in Table 1.

Diabetes mellitus was the comorbidity mentioned the most (63%), followed by arterial hypertension (24%), kidney diseases (12%), heart diseases (10%), organ transplants (6%), obesity, asthma, hypothyroidism, leukemias and pneumonia (4%), urinary tract infection, cryptococcosis, hyperlipidemia and sepsis (2%). In most cases, patients had more than one pre-existing condition, though approximately 10% of them had no underlying diseases, and 6% of studies did not

mention pre-existing conditions at all [7,13-37]. These data are represented in Figure 3.

From reports analysis, it was determined patients had an average age of 52,3 years. Also, a higher prevalence of CAM in the male gender was noticed. Said data supports the study of Pakdel *et al*. (2021), in which the authors noted patients had an average age of 52 years, and most of them were men (71,4%) [9]. Regarding clinical forms of mucormycosis, the rhino-orbital form of the disease was the most prevalent (76%), followed by, pulmonary form (10%), gastrointestinal form (4%), disseminated form (4%), and cutaneal form (4%); in 2% of reports, no information regarding the topic was mentioned. According to reports outcomes, it was established a mortality rate of 37%.

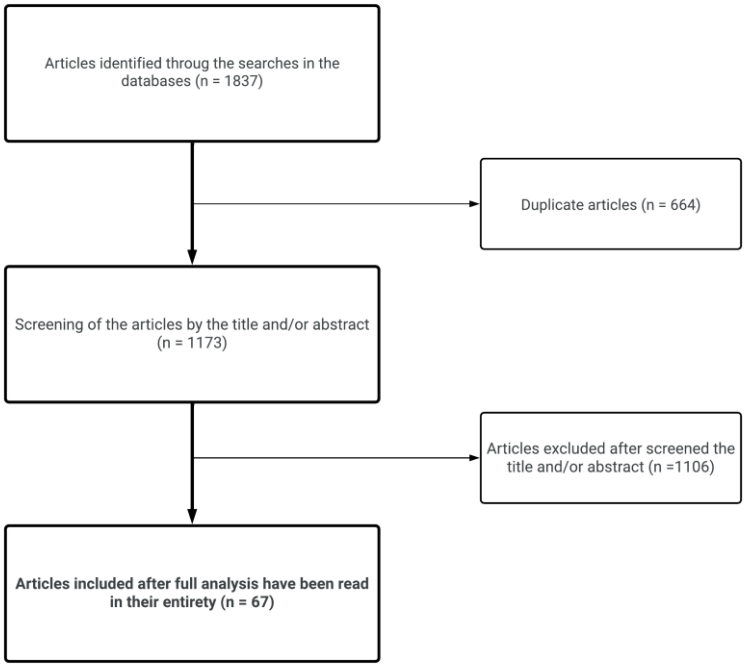

Figure 1: Selection of articles explanatory flowchart

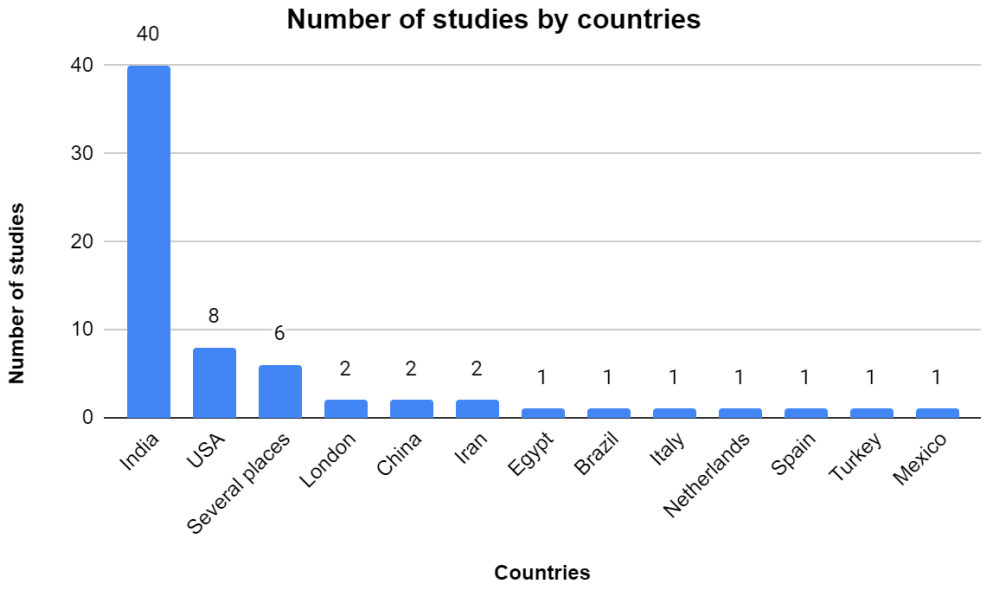

Figure 2: Number of studies citing mucormycosis in association with COVID-19 by different countries.

Table 1: Patients' profile mentioned in case reports of *Mucor* spp. and COVID-19 co-infection

Study	Age and gender	Pre-existing conditions	COVID-19 diagnostic	Mucormycosis diagnostic	Clinical form mucormycosis	Outcome
Mehta *et al.*(2020)	60 years old/Male	Diabetes mellitus	PCR	MR, biopsies e CT	Rhino-orbital	Death
Junior *et al.* (2020)	86 years old/Male	Arterial hypertension	Not mentioned	CT, EGD and pathological exam	Gastrointestinal	Death
Sen *et al.* (2021)	46 years old/Male; 60 years old/Male; 74 years old/Male; 73 years old/Male; 62 years old/Male; 47 years old/Male	Diabetes mellitus; diabetes mellitus and arterial hypertension; diabetes mellitus, arterial hypertension and heart disease; diabetes mellitus; diabetes mellitus and arterial hypertension; diabetes mellitus and heart disease	PCR	MR, CT and arterial hypertension	Rhino-orbital	All patients survived.
Mekonnen *et al.* (2021)	60 years old/Male	Diabetes mellitus, arterial hypertension, asthma and hyperlipidemia	PCR	Angiotomography	Rhino-orbital	Death
Pasero *et al.* (2020)	66 years old/Male	Arterial hypertension and urinary tract infection	PCR	Microscopic exam e TC	Pulmonary	Death
Garg *et al.* (2021)	55 years old/Male	Diabetes mellitus, arterial hypertension and heart disease and renal disease	PCR	Radiography	Pulmonary	Survival
Buil *et al.* (2021)	60 years old/Male; 50 years old/Male; 60 years old/Male; 70 years old/Male	No underlying disease; no underlying disease; diabetes mellitus and obesity; leukemia; diabetes mellitus	PCR	CT and culture; CT and culture; Culture and biopsies; not mentioned	Rhino-orbital; Pulomary; disseminated and rhino-orbital	Survival; death; death and death.
Selarka *et al.* (2021)	42 years old/Male	Diabetes mellitus	PCR	CT and MR	Not mentioned	Survival

Krishna *et al*. (2021)	22 years old/Male	Hypothyroidism	PCR	CT and culture	Disseminated	Death
Maini *et al*. (2021)	38 years old/Male	No underlying disease	PCR	CT, biopsies and culture	Rhino-orbital	Survival
Khatri *et al*. (2021)	68 years old/Male	Heart disease and cardiac transplant; diabetes mellitus, arterial hypertension and kidney disease	PCR	CT	Cutaneous	Death
Revannavar *et al*. (2021)	Not cited/Female	Diabetes mellitus	PCR	Radiography and biopsies	Rhino-orbital	Survival
Nehara *et al*. (2021)	59 years old/Female; 52 years old/Male; 62 years old/Female; 70 years old/Female; 68 years /Female	All had diabetes mellitus	PCR	CT, MR and culture; MR, histopathology and culture; MR and culture; MR, PNS and histopathology; MR, histopathology and culture	Rhino-orbital	Death; survival; survival; survival; death
Arana *et al*. (2021)	62 years old/Male; 48 years old/Male	Diabetes mellitus, arterial hypertension, kidney disease, kidney transplant, cryptococcosis and heart disease; arterial hypertension, kidney disease and hypothyroidism	PCR	Culture and CT; Tissue culture	Rhino-orbital; Cutaneal	Survival
Karimi-Galougahi *et al*. (2021)	61 years old/Female	No underlying disease	PCR	Ophthalmological exam, CT e MR	Rhino-orbital	Not mentioned
Zurl *et al*. (2021)	53 years old/Male	Acute myeloid leukemia	PCR	Radiography, microscopic sequencing	Pulmonary	Death
Waizel-Haiat *et al*. (2021)	24 years old/Female	Obesity	PCR	CT	Rhino-orbital	Death

Werthmann-Ehrenreich *et al*. (2020)	33 years old/Female	Arterial hypertension and asthma	Not mentioned	Radiography and CT	Rhino-orbital	Death
Alekseev *et al*. (2021)	41 years old/Male	Diabetes mellitus	PCR	Radiography and CT	Rhino-orbital	Survival
Veisi *et al*. (2021)	40 years old/female; 54 years old/Male	No underlying disease; diabetes mellitus	PCR	CT e MR; CT	Rhino-orbital	Death; survival
Jain *et al*. (2021)	57 years old/Female	Diabetes mellitus	Not mentioned	CT and histopathology	Gastrointestinal	Death
Saldanha *et al*. (2021)	32 years old/Female	Diabetes mellitus	PCR	CT and MR	Rhino-orbital	Survival
Baskar *et al*. (2021)	28 years old/Male	Not mentioned	PCR	Radiography and biopsies	Rhino-orbital	Not mentioned
Saidha *et al*. (2021)	39 years old/Male; 29 years old/Male; 56 years old/Male; 68 years old/Male; 35 years old/Male; 55 years old/Female	Not mentioned; diabetes mellitus; diabetes mellitus; diabetes mellitus, arterial hypertension, hypoalbuminemia, sepsis and kidney disease; not mentioned; diabetes mellitus	The first five used PCR and the last used titles of IgG	Histopathology and Radiography	Rhino-orbital	Not mentioned and one survival
Dallalzadeh *et al*. (2021)	36 years old/Male; 48 years old/Male	Diabetes mellitus	PCR	MR and radiography	Rhino-orbital	Death and survival
Awal *et al*. (2021)	65 years old/Female; 45 years old/Female; 36 years old/Male	Diabetes mellitus; pneumonia; pneumonia	PCR	CT, MR	Rhino-orbital	Not mentioned
Kanwar *et al*. (2020)	56 years/Male	Kidney disease	PCR	Culture, CT and Angio tomography	Pulmonary	Death

CT: computed tomography; MR: magnectic ressonance; PNS: peripheral neurological exam; EGD: esophagogastroduodenoscopy

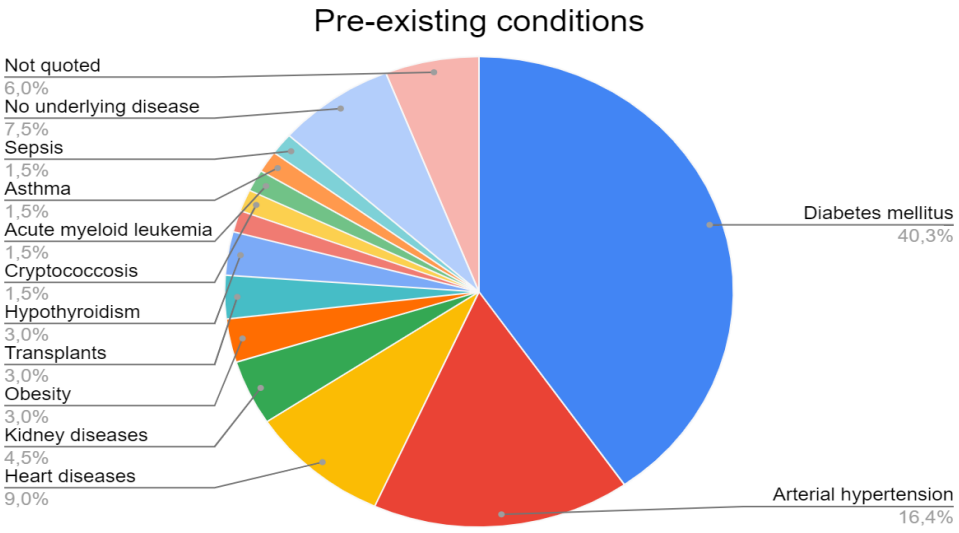

Figure3: Pre-existing conditions present in case reports of individuals affected by mucormycosis and COVID-19.

DISCUSSION

Mucormycosis

Mucormycosis, or black fungus, is an angioinvasive infection caused by filamentous fungi which belong to Zygomycetes class and Mucorales order [38-44]. The term "black fungus" was coined due to the black discoloration of dead and dying tissue the fungus causes [45].

The most common genera found in clinics are *Rhizopus, Lichtheimia* and *Mucor*, the first being the most frequently associated with mucormycosis. *Rhizomucor, Saksnaea, Cunninghamella and Apophysomyces* can also be found, though less frequently [39]. In most cases, mucormycosis transmission happens when the fungal spores found in the air are inhaled, or by direct inoculation of the microorganism in harmed epithelium [46].

Due to its anatomical location, mucormycosis can be classified in different forms: rhino cerebral, pulmonary, cutaneal, gastrointestinal, disseminated; it can also be classified in less usual forms such as osteomyelitis, endocarditis, peritonitis, and renal infection [47]. Rhino cerebral is the most common clinical form of mucormycosis, and it affects mostly individuals with diabetes mellitus [48,49].

There are several predisposing conditions for the development of the different clinical forms of the disease, such as: malignant hematological diseases with or without stem cells transplant, severe or prolonged neutropenia, and poorly controlled diabetes (ketoacidosis present or not present), iron overload, traumas, prolonged use of corticoids, intravenous use of illicit drugs, neonatal prematurity, and/or malnutrition [40,50,51]. Petrikkos *et al*. (2021) stresses the importance of pre-existing diseases clinical management, for the study established a mortality rate of 44% in individuals with diabetes mellitus, 35% in people with no underlying conditions, and 66% in individuals with malignant diseases [52].

Besides, the clinical environment has also been highly related to nosocomial mucormycosis due to heavy loads of fungal exposure in contaminated air conditioning filters, health associated devices such as intravenous catheters, contaminated bandages, etc. [53].

Mucormycosis management entails especially reversing risk factors, chirurgical debridement, and intravenous antifungal therapy such as amphotericin B [54].

COVID-19 associated with mucormycosis (CAM) and patients' background

Invasive mucormycosis is an opportunistic infection, hence why patients with pre-existing conditions (diabetes mellitus, prolonged neutropenia, in graft versus host disease, traumas or use of glucocorticoids, etc.) who tested positive for COVID-19 are more likely to develop mucormycosis. However, factors such as proper management and early diagnosis can improve the chances of survival [5,6].

The disease by COVID-19 can lead to the development of extensive interstitial lung diseases, which means it can predispose fungal invasion through the respiratory system, including lungs and sinuses [7,8]. Recently, many COVID-19 cases

associated with mucormycosis (CAM) have been reported all over the world, mostly in India, which is a country known for its high rates of individuals with poorly controlled diabetes mellitus [55,56].

The incidence of mucormycosis rapidly increased in the second wave of COVID-19, numbering about 14.872 cases in India until May of 2021 which explains why most studies covered in the present paper derived from India. Supportive evidence has been found in the review of literature made by Pat *et al*. (2021), which covered 30 studies and revealed the following results: 71 cases in India (72%), 10 cases in the United States of America (10%), 6 cases in Egypt (6%), 3 cases in Iran (3%), 2 cases in Brazil (2%), and 2 cases in Chile (25). United Kingdom, France, Italy, Austria and Mexico have reported one case each [57,58].

Fouad *et al*. (2021) reported 12 cases of rhino-orbital-cerebral mucormycosis identified from the time period of 6 months (March-September of 2020) in Egypt. It was the largest number of identified cases in the previous 3 years during the same period of time (6 months); 1 case was identified in 2017, 2 in 2018, and 1 in 2019 [59]. Another study reported 23 cases of invasive mucormycosis in the period between August and December of 2020, in contrast to the 20 cases of invasive mucormycosis reported in the time period of 3 years [60,61]. Additionally, Pal *et al.* (2021) shows that the most significant increase of cases happened between 2020 and 2021, for 14% of mucormycosis cases associated with COVID-19 were reported in 2020, while 86% were reported in 2021 [58].

Zhu *et al*. (2020) also identified increased numbers of cases in their study, in which approximately 60 (23,3%) individuals tested RT-PCR positive for COVID-19 and were also co-infected by fungi; 6 (2,5%) of which were infected by *Mucor* spp. [10].

One of the main reasons which may facilitate spores germination of fungi from *Mucorales* genus in patients with COVID-19 is an environment with high rates of glycoses (diseases such as diabetes, corticoids induced hyperglycemia, recent hyperglycemia), hypoxia condition, acid environment (diabetic ketoacidosis, metabolic acidosis), increased ferritin, and decreased phagocytic activity of leukocytes. The latter happens due to the immunosuppression provoked by SARS-CoV-2 joined by other associated risk factors, such as mechanical ventilators or long period hospitalizations [62].

Regarding risk factors, some works support evidence found in the studies covered in this paper concerning diabetes mellitus prevalence in patients with CAM [6,55,58,62,63,64]. For example, Pat *et al*. (2021) found that some of the most common comorbidities in study's participants were diabetes mellitus (85%) and arterial hypertension (58%), while only 4% of patients had no pre-existing conditions [58]. In the retrospective study by Sen *et al*. (2021), 6 patients who had tested positive for COVID-19 developed rhino-orbital mucormycosis, and all of them also had type 2 diabetes mellitus, 5 of which started using insulin during treatment of COVID-19 [6].

Regarding clinical forms found in this review, some studies also supported the evidence of rhino-orbital mucormycosis being the most frequent case, such as Garg *et al*. (2021) whose study found the following clinical forms: rhino-orbital (n=3), pulmonary (n=3), gastrointestinal (n=1), and disseminated (n=1), and Pakdel *et al*. (2021) whose study also found rhino-orbital mucormycosis as the most frequent clinical form of the disease, it being identified in 7 patients (47%) who had tested positive for COVID-19 [9,64]. High mortality rate is a concerning factor as well, for some studies showed death outcomes in more than 37% of cases [9,65]. In relation to the CAM reports analyzed, the present paper found a 37% mortality rate in co-infected patients.

It is reported that severe infections in the inferior respiratory tract, as it happens in many COVID-19 cases, usually affect older individuals and those individuals with pre-existing conditions such as diabetes mellitus and heart diseases [66]. The average age and prevalence of the male gender in CAM cases found in the reports covered in this paper are also supported by data found by Pakdel *et al*. (2021) whose study established an average age of 52 years old and prevalence of the male gender in patients (66%) [9].

Considering all studies mentioned, it is clear that there is a similar background of the individuals affected by the disease. Besides, the increase in cases of mucormycosis associated with COVID-19 has been a huge concern, which is one of the reasons why the disease should be taken into account in COVID-19 patients' differential co-infection diagnosis. Many cases of CAM have been reported in India, though Nepal, Brazil, Colombia, United States of America, and other nations have been affected as well and therefore should take into account this fungal threat during the pandemic [67,68,69].

Treatments for COVID-19 associated with mucormycosis (CAM)

According to the guidelines of the European Confederation of Medical Mycology (ECMM) and the Mycosis Study Group (MSG), the management of COVID-19 associated with mucormycosis (CAM) is similar to the management of mucormycosis patients who are not infected by COVID-19. The key to management success is to diagnose patients based

on clinical, microbiological, histopathological, or radiological characteristics. It is also important to control or eliminate underlying predisposing factors [1].

Guidelines also state that surgery should be the first procedure to be made, joined by the addition of systemic antifungal as first-line treatment. Also, the use of liposomal amphotericin B associated with doses of intravenous isavuconazole and posaconazole is recommended. Prophylaxis with posaconazole can be performed on high-risk patients [1].

Bhatt *et al*. (2021) describes diagnostic and therapeutic possibilities for patients co-infected by fungi and COVID-19. For patients severely affected by COVID-19 or immunocompromised, the study mentions the following diagnostic steps: direct fluorescent microscopy and histopathology, molecular culture and identification. Regarding microscopy, possible typical findings are non-septate hyphae or pauciseptate hyphae (6-16 µm wide), and, regarding culture, white or grayish cotton wool colonies can be found, the procedure being made in routine media of 30-37ºC. Molecular identification can be based on methods like PCR, HRM, or target genes (18s, ITS, 28s, or rDNA) [1].

Concerning therapeutic possibilities, surgery is recommended as the first option if possible. As primary prophylaxis the use of posaconazole is recommended, and as first-line treatment it presents amphotericin B lipid complex, liposomal amphotericin B, and posaconazole oral suspension [1].

Mrittika *et al*. (2021) conducted a study with 2.826 patients affected by COVID-19 associated with rhino-orbital-cerebral mucormycosis, and liposomal amphotericin B was used in approximately 73% of cases. Besides, it is mentioned in the study that, whenever said resource is not available, amphotericin B deoxycholate or amphotericin B lipid complex can be used. The preference for the liposomal form of this medication is associated with its lower nephrotoxicity compared to other forms. In the study, isavuconazole and posaconazole were considered effective alternatives in patients with impaired kidney function, though amphotericin B can be a treatment option as well [70].

Supporting these guidelines' therapeutic recommendations, Patel *et al*. (2021) conducted a retrospective multicenter study in India with 187 patients affected by CAM, approximately 72% made use of liposomal amphotericin B, followed by posaconazole (39%), amphotericin B deoxycholate (16,6%), and isavuconazole (10,2%) [71].

CONCLUSION

The literature demonstrates that the possible association between SARS-CoV-2 infection and the occurrence of fungal diseases such as mucormycosis can be explained by the dysregulation of the inflammatory response caused by the COVID-19 virus, as it induces an increase in the susceptibility of patients. Thus, through this review, it was found a greater number of studies involving, with pre-existing conditions and simultaneously infected by SARS-CoV-2 and fungi of the genus *Mucor* spp.

The cases of mucormycosis in patients with COVID-19 have been more frequent in the pandemic scenario and can lead to serious consequences for patients, which are reflected in high mortality rates, being considered a worrying scenario. Therefore, the study is extremely relevant as it observes this increase in the number of cases and alerts to the need for agility and precision in diagnosis and treatment. Further studies are included to more precisely understand the elements responsible for the association between mucormycosis and a COVID-19, available diagnostic methods, and possible methods.

Further studies are needed to understand more precisely about the mechanisms responsible for the association between mucormycosis and COVID-19, available diagnostic methods and possible treatments.

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