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CLINICAL MICROBIOLOGY - REVIEW

# An overview of COVID-19 related to fungal infections: what do we know after the first year of pandemic?

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## Abstract

In 2019, severe acute respiratory syndrome caused by CoV-2 virus became a pandemic worldwide, being the fast spread of the disease due to the movement of infected people from one country to another, from one continent to another, or within the same country. Associated comorbidities are important factors that predispose to any fungal coinfections. Because of the importance of fungal infections in COVID-19 patients, the aim of this work was to collect data of the more encountered mycoses related to patients undergoing this disease. Aspergillosis was the first COVID-19-related fungal infection reported, being *A. fumigatus* the most frequent species for CAPA. Other fungal infections related include mainly candidiasis and mucormycosis, being *Rhizopus* spp. the more prevalent species found. Influenza-associated pulmonary aspergillosis is well documented; thus, similar complications are expected in severe forms of COVID-19 pneumonia. Therefore, in patients with COVID-19, it is important to take special attention to the surveillance and suspicion of fungal coinfections that might worsen the patient's prognosis.

**Keywords** Associated pulmonary aspergillosis (CAPA) · *Aspergillus* · *Candida* · Non-*Candida* yeasts · Mucormycosis · Pneumonia

## Introduction

In 2019 in Wuhan, China, cases of unexpected pneumonia have emerged. The etiological agent of the disease that causes severe acute respiratory syndrome (SARS) is a virus belonging to Coronaviridae family, named coronavirus (CoV-2) [1]. The first was reported in 2002 (SARS-CoV) in China and in the Middle East, Saudi Arabia in 2012, (MERS)-CoV. Thus far, SARS-CoV-2 has become a pandemic worldwide, and until now (June 23rd 2021) over 179 million of infected people and over 3 million deaths have been reported representing an obit percentage of 2.1% [2]. The rapid spread of coronavirus disease was largely due to the movement by traveling of infected people from one country to another, from one continent to another, or within the same country.

Overall, the disease pattern ranged from asymptomatic, mild flu-like to severe respiratory distress. Associated comorbidities such diabetes, chronic obstructive pulmonary disease, immunocompromised conditions like corticosteroid, interleukin inhibitors or broad-spectrum antibiotic therapy, mechanical ventilation, long-term stay in intensive care unit stay, severe lung tissue damage, acute respiratory distress

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syndrome, use of catheters, immunological dysfunction, immune dysregulation characterized by decreased T cells including CD4 and CD8 cells, alveolar macrophages activity disturbed, cytokine storm, and lymphocytopenia are often seen [3–6]. Tomography findings are in mainly consisting of ground-glass opacities, nodular infiltrates and consolidations, bullous emphysema, interstitial change, halo sign, and reverse halo sign similar to what we see in patients with mucormycosis [7–9]. Clinical symptoms including cough, fever, dyspnea, and/or respiratory insufficiency are observed among many others [10].

These are indeed predisposing for any fungal coinfection, such as invasive aspergillosis (IA), disseminated candidiasis, endemic mycoses, phaeohyphomycosis, mucormycosis, or fusariosis, among others, even in the absence of classical well-defined host factors [6, 10, 11]. Prolonged use of corticosteroids is considered a risk factor for invasive fungal diseases [12]. The relation between COVID-19 and aspergillosis is known as CAPA (COVID-19-associated pulmonary aspergillosis). The criteria to classify patients with CAPA vary from those with risk factors for an IPA (invasive pulmonary aspergillosis), as considered by the EORTC [13], or those with other factors such as diabetes, obesity, or hypertension. Criteria based on AspICU algorithm [14] were also applied. Recently, a case definition for IAPA (influenza-associated pulmonary aspergillosis) was proposed by an expert panel to classify patients with CAPA, classified as putative aspergillosis rather than probable or proven [6]. In the IAPA case definition, host factors are not used because IAPA may develop in any patient with severe influenza. The European Society for Clinical Microbiology and International Society of Human and Animal Mycology recently published guidance to identify proven, probable, and possible CAPA [15]. Regardless of the definition, it is difficult to distinguish between infection and colonization.

It was reported that 14–30% of hospitalized patients diagnosed with COVID-19 develop a severe respiratory failure requiring intensive care admission. Invasive aspergillosis appeared at a range from 11 to 21 days after the onset of COVID-19 and affected up to 30% of intubated patients [16–18]. Some authors pointed to a mortality rate ranging from 15 to 30%, with less survival in patients with CAPA, compared with those without [1, 19–24]. The same trend has been previously observed for influenza-related aspergillosis [25].

In general serum galactomannan (GM) is negative, whereas bronchoalveolar lavage (BAL) GM antigen is reported positive at a percentage of 77.8, being hypothesized that patients have an airway invasive infection rather blood vessels invasion to cause release of galactomannan. Thus, wherever possible BAL GM should be performed, since it is more sensitive than in serum. However, due the high aerosolized risk, this procedure is avoided in COVID-19 patients, and tracheal secretions, for instance, are preferred [6, 15, 20, 26]. In one study, it was observed that *Aspergillus* tests from COVID-19 patients were similar to those with pneumococcal pneumonia but lower than those with influenza. Thus, it was concluded that in ICU, the specificity of tests is low and tests like pan-fungal B-D glucan should not be used, advising that a positive test for *Aspergillus* in COVID-19 should be interpreted with caution [27].

COVID-19-associated mucormycosis will be further discussed. This is an infection that is worldwide distributed and has no predilection for a particular country. The large number of reported cases from India is link to possess a high burden with 77 million people with diabetes and another 36.5 million with prediabetes which are a high-risk condition, worsen, if is being uncontrolled, for suffering, particularly, rhino-orbital-cerebral mucormycosis [28, 29].

Treatment with interleukin inhibitors or tocilizumab (monoclonal antibody), which was used as therapy in COVID patients [30, 31], could also potentially increase the risk of other fungal infections, such those, among others, caused by *Candida* spp., *Histoplasma* spp., or *Pneumocystis jirovecii* [32]. Candidemia has been reported in 2.5–6.9% of COVID-19 patients in the ICU, mainly catheter-related infections and often with unfavorable outcomes [33, 34].

Considering all, the objective of this work was to collect data on the more encountered mycoses related to patients undergoing COVID-19. Although there are reviews related to this topic, all are, in general, treated separately. Thus, an updated data considering this information altogether can be found in this single review.

## Methods

We searched in Pub Med and Google Scholar database for eligible studies published until May 31th 2021 for COVID-19-related fungal infections, using the key words "COVID-19" AND, "CAPA," "COVID-19" AND "fungal infections," "COVID-19 pneumonia," "COVID-19" AND "*Candida*" OR candidiasis, "COVID-19" AND "*Aspergillus*" OR aspergillosis, "COVID-19" AND "Mucormycosis" OR Post "COVID-19" fungal infections, "COVID-19" AND "*Cryptococcus*," "COVID-19" AND "*Pneumocystis*," "COVID-19" AND "*Histoplasma*" OR Histoplasmosis OR endemic mycosis. A total of 160 articles were identified through the initial database search. We excluded 32 articles including four reviews, two research letters, and the remain ones for lack of the information we needed or publications that did not report primary data. After the removal of duplicated items and screening based on title and abstract, 134 articles were assessed for eligibility. Sixty-three were related to COVID-19 and invasive pulmonary aspergillosis and definitions of probable, proven, or putative according with

the author definition criteria selection, including 36 articles of clinical case description of CAPA related. Thirty-seven publications were related to cases of mucormycosis and twenty-six to other fungal infections, including candidiasis, yeast non-*Candida* infections, pneumocystosis, and endemic mycosis. We collected data on epidemiology (age, gender, comorbidities), diagnostic methods, fungi isolated, antifungal indicated therapy, and clinical outcomes that are presented in the corresponding tables. We restricted our search to works published in the English language.

## Results

Overall, 178 cases of CAPA were published. Mortality was reported in 88 cases; survivors in 80 and 10 were not specified. The main comorbidities reported were DBT, ATH, obesity, and COPD. A total of 163 *Aspergillus* species were recovered distributed as follows: *A. fumigatus* (130), following by *A. flavus* (15), *A. niger* (5), *A. terreus* (4), *A. nidulans* (2,) and one strain of *A. ochraceus*, *A. calidoustus*, *A. awamorii*, *A. citrinoterreus*, and *A. penicilloides*. *A. fumigatus* was generally susceptible to all drugs, except in 3 reports in which the TR34L98H resistance mutation in the cyp51A gene was found, associated with azole resistant [35–37]. Voriconazole was the drug most used, following by amphotericin. All data is detailed in Table 1.

Mucormycosis reported cases were 158, mainly related to uncontrolled diabetes. The isolation from different samples includes *Mucor* spp. (4), *Rhizopus* spp. (16), *R. oryzae* (4), *R. azygosporus* (1), *R. arrhizus* (1), *R. microsporus* (4) *Lichtheimia* spp. (2), and *L. ramosa* (1). In cases diagnosed by histology only or those from which no isolation from culture was available, it was named as mucormycosis or Mucorales (125). Forty-eight deaths and eighty-two survivors were reported. Amphotericin liposomal formulation and deoxycholate were the most antifungal drugs used. All data is detailed in Table 2.

Fungemia due to *Candida* species was reported in 149 cases. The mortality was high, but not accurate percentage could be calculated, due non-reported data in 17 cases. Forty-four patients died and 23 survived. The most frequent species isolated from blood cultures were *C. albicans* (64), *C. auris* (51), *C. glabrata* (17), *C. tropicalis* (9), *C. parapsilosis* (6), *C. dubliniensis* (6), *C. orthopsilosis* (1), and *C. krusei* (renamed as *Pichia kudriavzevii*) (2). Non-*Candida* yeasts seen were *Trichosporon asahii* (6), *Saccharomyces cerevisiae* (2), *Rhodotorula mucilaginosa* (1), and *C. neoformans* (2). Histoplasmosis, coccidioidomycosis and paracoccidioidomycosis cases were 4, 2, and, 1, respectively. *P. jirovecii* was reported in two cases. All data is detailed in Table 3.

Only one case of pulmonary fusariosis classified as putative, due by *F. proliferatum* in an immunocompetent patient, was reported [112]. There are six reports in which mix isolations were described. One describes a pulmonary mucormycosis diagnosed by biopsy, in which from bronchoalveolar lavage *A. flavus*, *A. niger*, *C. albicans*, *C. glabrata*, and *C. krusei* were found [113]. In another study, *R. arrhizus* plus *A. fumigatus* were isolated from a lung of a patient suffering from COVID-19 [114]. In a patient with a history of pulmonary embolism treated with corticosteroids, *R. microsporus* plus *A. fumigatus* were found [42]. In one patient with lymphoma, *R. microsporus* plus *A. fumigatus* were isolated from bronchoalveolar lavage [115]. Other report showed in a patient with diabetes and leukemia, *A. fumigatus* isolated from BAL, and after some days, isolation of *R. microsporus* was detected, and in other patient with no underlying disease, treated with corticosteroids, *A. fumigatus* was first isolated and days after *L. ramosa* [81]. Other report of fatal COVID-19-associated pulmonary aspergillosis described a mix fungi isolation from respiratory tract secretions. *A. niger* plus *C. albicans* were isolated from a patient with diabetes, hepatitis B, and hypertension, whereas *A. terreus* plus *C. albicans* were isolated from an otherwise healthy patient [116].

## Discussion

The use of steroids, such as dexamethasone to modulate immune-mediated organ damage, interleukin inhibitors, and broad-spectrum antibiotics for the management of COVID-19, could exacerbate preexisting comorbidities and enhance the chances of new onset of fungal infections as was above discussed. Due to the high incidence of influenza-associated pulmonary aspergillosis, it seems natural to expect similar complications in severe forms of COVID-19 pneumonia. The incidence of fungal infections in SARS 2003 was 14.8–33% and the mortality rate 25–73.7% [117]. Besides, reports of severe influenza pneumonia complicated by fungal infections were published [118].

It is important to mention that the development of any fungal coinfection is highly expected in colonized patients, given the characteristics of the coronavirus disease. Therefore, taking into consideration, previous risk factors seem necessary, indicating whether coinfections might worsen the patient's prognostic values. Mortality in patients with COVID-19 and CAPA has been seen to increase compared to COVID-19 patients without CAPA [19]. The high mortality in CAPA patients could be related with critically ill COVID-19 individuals that require mechanical ventilation, who were mostly elderly and had significant co-existing chronic comorbidities [116].

**Table 1** *Aspergillus* species infections associated with COVID-19. According with the report, CAPA was defined as proven, probable, or putative

| Species (n° isolates) | Age range | Diagnosis | UD reported | Country | ATFT | Patient (n) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| *A. flavus* (1) | 85 | TS culture +. Serum GM 1.4 | ATH | Argentina | AND, VCZ | 1 M | Died | 38 |
| *A. flavus* (1) | 80 | TS culture + | Thyroid cancer removed | France | VCZ, ISA | 1 M | Died | 39 |
| *A. flavus* (1) | 70 | LB culture + | None | Iran | VCZ | 1 M | Died | 40 |
| *A. fumigatus* (3) | 23–69 | Serum GM 0.9–2.1 (5/5). TS culture + (2/5). Sputum culture + (1/5). TS GM 0.2–4.2 (3/5). Serum ALFD + (2/5) | AML, ATH (1)<br>DBT (2) | Argentina | AMB 1/5<br>VCZ 4/5 | 4 M/1 F | Died 1/5<br>Alive 4/5 | 41 |
| *A. fumigatus* (1) | 73 | Serum GM and LF: +<br>Nested PCR + | PE. Thrombo phlebitis | Argentina | AMB<br>VCZ | 1 M | Alive | 42 |
| *A. fumigatus* (1) | 66 | TS culture + | None | Australia | VCZ | 1 F | Alive | 26 |
| *A. fumigatus* (1) | 70 | TS culture +<br>ALFD TS +. Serum GM: NG<br>BG: NG | COPD. DBT. CKD. ATH. Obesity | Austria | VCZ | 1 M | Died | 43 |
| *A. fumigatus* (5)<br>*A. flavus* (1) | 56–77 | BAL and ETA culture +. GM 0.6–2.6. Serum GM: 0.1–0.8 | CD. CT. HIV. AML. ATH. CKD | Belgium | VCZ<br>ISA | 7 M | Died 4/7<br>Alive 3/7 | 44 |
| *A. fumigatus* (8) | 53–73 | BAL culture + (4/8)<br>Sputum culture + (4/8) | Obesity. ATH (7). DBT (2). COPD (2). CKD (2) | China | NR | 8 M | NR | 1 |
| *A. fumigatus* (1) | 46 | Sputum culture + | DBT. ATH | China | VCZ | 1 M | Alive | 45 |
| *A. fumigatus* (2) | 53–63 | Culture TS +. Serum GM 0.1–1.1. BAL GM 8.2. TS GM 2.2 | ATH. Asthma | Denmark | VCZ | 2 F | Died 2/2 | 46 |
| *A. fumigatus* (7) | 43–77 | BAL culture + (7/9). BAL GM 0.03–3.9. Serum GM 0.03–0.51 | ATH (7). IHD (2). DBT (1). Obesity (3). Asthma (1). None (1) | France | VCZ 1<br>CAS 1<br>None 7/9 | 5 M/4 F | Died 4/9 Alive 5/9 | 47 |
| *A. fumigatus* (1) | 74 | TS culture +<br>Serum GM and BG: NG | MS. ATH | France | None | 1 M | Died | 48 |
| *A. fumigatus* (15)<br>*A. niger* (1)<br>*A. calidoustus* (1) | 44–86 | BAL culture +<br>BAL GM 0.07–3.4 (8/19) | ATH (7). COPD (4). DBT (7). Asthma (4). HIV (1). None (1). TB (2) | France | VCZ 9 | 15 M/4 F | Died 7/19<br>Alive 12/19 | 49 |
| *A. fumigatus* (1) (azoles R) | 56 | TS culture +<br>Serum GM and BG: NG | Obesity. DBT. ATH | France | None | 1 M | Died | 37 |
| *A. fumigatus* (2) | 70–80 | BAL culture +. GM BAL GM 6.1–6.3<br>Serum: ≤ 0.50–1.5 | Pulmonary fibrosis. None | Germany | AMBL | 2 M | Died 2/2 | 50 |
| *A. fumigatus* (3) | 54–62 | BAL culture + (1/5). TS culture + (2/5). BAL GM > 2.5 (3/5) | COPD (2). ATH (3)<br>Corticosteroid therapy (3). Emphysema (1). None (2) | Germany | VCZ 2<br>CAS 2<br>ISA 1 | 3 M/2 F | Died 3/5<br>Alive 2/5 | 17 |

**Table 1** (continued)

| Species (n° isolates) | Age range | Diagnosis | UD reported | Country | ATFT | Patient (n) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| *A. fumigatus* (1) (azoles R) | 66 | TS culture + . Serum GM 1.1 Serum BG: 202 pg/ml | Obesity. DBT. ATH | Ireland | AMB | 1 M | Died | 35 |
| *A. fumigatus* (1) | 73 | BAL culture + . Serum GM 8.6 | ATH. DBT. HT. Obesity | Italy | AMBL | 1 M | Died | 33 |
| *A. fumigatus* (15)<br>*A. flavus* (3)<br>*A. niger* (1) | 57–70 | BAL culture + (19/30). BAL GM > 1 (30/30). Serum GM + (1/30) | Obesity (10). ATH (16). DBT (5). SOT (1). COPD (6) | Italy | VCZ 16/30 | 23 M/7 F | Died 10/30<br>Alive 20/30 | 19 |
| *A. fumigatus* (6) | 43–83 | TS culture + (2/6). BAL culture + (3/6), sputum culture + (1/6). BAL GM 1.6–4 (2/6). Serum GM 0.1–0.4 (3/6) | CODP (2). CT (3). Asthma (1). None (2) | Netherlands | VCZ + AND 5<br>AMBL 1 | 6 M | Died 4<br>Alive 2 | 21 |
| *A. fumigatus* (1) (azoles R) | 74 | TS culture +<br>TS GM: > 3. Serum BG: 1590 pg/mL | None | Netherlands | VCZ, AMBL | 1 F | Died | 36 |
| *A. fumigatus* (5)<br>*A. flavus* (1)<br>*A. terreus* (1) | 39–76 | Nondirected BAL culture + and GM 1.1 to > 4 (9/9) | Obesity (6). Asthma, COPD (2). ATH (3). RT (1) | Netherlands | AMB, VCZ | 6 M/3 F | Died 2/9<br>Alive 7/9 | 51 |
| *A. fumigatus* (26)<br>*A. niger* (1)<br>*A. flavus* (1) | 59–72 | TS and BAL culture + . BAL GM + (9/19). Serum GM NG | COPD, asthma (7). DBT (5) | Netherlands | NR | 14 M/5 F | Died 10/19<br>Alive 9/19 | 24 |
| *A. fumigatus* (2)<br>*A. flavus* (6)<br>*A. niger* (2) | 46–85 | Culture + . Serum GM 0.1–0.3 (9/9) | ATH (4). DBT (8). Stroke (1) | Pakistan | AMB 2/9<br>VCZ 3/9<br>None 4/9 | 7 M/2 F | Died 4/9<br>Alive 5/9 | 52 |
| *A. fumigatus* (2)<br>*A. nidulans* (1) | 78–83 | Culture BAS + . BAL GM + | ATH. IHD. CKD None | Spain | AMB | 2 M | Alive 2/2 | 7 |
| *A. fumigatus* (9)<br>*A. nidulans* (1) | 51–72 | BAS culture + (8/10). BAL culture (1/10). Sputum culture + (1/10). Serum GM 0.2–1.) and BAL GM 1.1–3.8 (2/10) | COPD (4)<br>Obesity (2)<br>DBT (5). MS, HIV, HT and IHD (1) | Spain | VCZ 4<br>AMB 5<br>CAS, MCF and AND 1<br>ISA 2<br>None 2 | 8 M/2 F | Died 7/10<br>Alive 1/10<br>NR 2/10 | 53 |
| *A. fumigatus* (3) | 67–73 | BAL culture + . Serum GM 1.4–1.5 (3/1). One NG | None (3). Lung cancer (1) | Spain | AMB, ISA, AND | 2 M/2 F | Died 1/4<br>Alive 3/4 | 54 |
| *A. fumigatus* (6)<br>*A. lentulus* (1)<br>*A. terreus* (1)<br>*A. awamori* (1)<br>*A. citrinoterreus* (1) | NR | TS culture + (1/8). BAL culture (2/8)<br>BAS culture (7/8). BAL GM > 7 (1/8). Serum GM 0.1–1.9 (8/8). BG: 2.6–17.8 (8/8) | Obesity (4). ATH (7). COPD, SOT, CLL (1). Asthma (2) | Spain | VCZ 2/8 AMBL 2/8 ISA 4/8<br>None 3/8 | 6 M/2 F | Died 8/8 | 20 |
| *A. fumigatus* (3) | 55–66 | BAS culture +<br>Serum GM 0.7 (1/3) | ATH, obesity (2)<br>DBT, asthma (1) | Switzerland | VCZ 3/3 | 3 M | Died 1/3<br>Alive 2/3 | 55 |

**Table 1** (continued)

| Species (n° isolates) | Age range | Diagnosis | UD reported | Country | ATFT | Patient (n) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| *A. fumigatus* (1) | 77–82 | Serum GM 0.7 (1/5), NG (2/5) | ATH, DBT, COPD, CVD (1) | USA | VCZ 3/4<br>CAS 1/4 | 5 M | Died 5/5 | 56 |
| *A. fumigatus* (1) | 56 | TS culture + | DBT. AHT | India | VCZ | 1 M | Died | 57 |
| *A. niger* (1) | 73 | Serum GM 4.9. BG: 84 pg/mL<br>TS culture + | DBT. ATH | Italy | VCZ | 1 M | Died | 58 |
| *A. ochraceus* (1) | 35 | Culture BAL +<br>Serum GM BAL GM 2.1 | None | Iran | AMBL | 1 M | Died | 59 |
| *A. penicilloides* (1) | 70 | Autopsy. Histopathological sequencing. Serum GM 4.2 | DBT. ATH. CKD | Brazil | None | 1 M | Died | 60 |
| *A. terreus* (2) | 66 | BAL and Mini BAL culture + | None | Iran | VCZ, CAS | 1 F | Died | 5 |
| **Resume** | | | | | | | | |
| Total: 162<br>*A. flavus* (15)<br>*A. fumigatus* (131)<br>*A. awamori* (1)<br>*A. calidoustus* (1)<br>*A. citrinoterreus* (1)<br>*A. lentulus* (1)<br>*A. niger* (5)<br>*A. nidulans* (1)<br>*A. ochraceus* (1)<br>*A. penicillioides* (1)<br>*A. terreus* (4) | 23–86 | Positive cultures: 162<br>BAL + Mini BAL > TS > BAS<br>GM (BAL + serum): 42<br>ALFD: 3<br>LF: 5<br>PCR: 2 | ATH 71 > DBT 48 > Obesity 35 > COPD 26 ><br>Asthma 19<br>AML 7<br>CKD 6<br>CT 5<br>IHD 4<br>HIV 3<br>CVD, MS, SOT, CD, HT 2<br>Thyroid cancer, thrombophlebitis, lung cancer, emphysema, stroke, HB: 1 | 20 countries | AMBL/AMB 20<br>AND 8<br>CAS 6<br>ISA 10<br>MCF 1<br>NR 2<br>VCZ 62<br>ATFC 6<br>No ATF 19 | 139 M<br>39 F | Died 88/178<br>Alive 80/178<br>NR 10/178 | |

*AHT* arterial hypertension. *ALFD Aspergillus* lateral-flow device. *AMBL* liposomal amphotericin. *AML* acute myeloid leukemia. *AND* anidulafungin. *ATFT* antifungal treatment. *BAL* bronchoalveolar lavage. *BAS* bronchial aspirate. *BDG* 1,3-ß-D-glucan. *BSAT* broad-spectrum antibiotic therapy. *CAPA* COVID-19-associated pulmonary aspergillosis. *CAS* caspofungin. *CD* cardiovascular disease. *CFA* complement fixing antibodies. *CKD* chronic kidney disease. *CLL* chronic lymphocytic leukemia. *COPD* chronic obstructive pulmonary disease. *COVID-19* coronavirus disease 2019. *CT* corticosteroid therapy. *CTS* chest tomography scan. *CVC* central venous catheter. *CVD* cardiovascular disease. *DBT* diabetes. *DVT* deep venous thrombosis. *FI* fungal infection. *GM* galactomannan. *HB* hepatitis B. *HIV* human immunodeficiency virus. *HM* hematological malignances. *HT* hyperthyroidism. *IHD* ischemic heart disease. *ISA* isavuconazole. *MCF* micafungin. *MS* myelodysplastic syndrome. *MS* myelodysplastic syndrome. *NG* negative. *NR* not reported. *NYS* nystatin. *PE* pulmonary embolism. *RF* risk factors. *RT* renal transplant. *SHF* systolic heart failure. *SOT* solid organ transplant. *TB* tuberculosis. *TMS* trimethoprim-sulfamethoxazole. *TS* tracheal secretion. *UD* underlying disease. *VCZ* voriconazole

**Table 2** COVID-19 related to mucormycosis (CAM)

| Disease or species isolated | Age range | Diagnosis | UD reported | Country | ATFT | Patient (*n*) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| Mucormycosis (*n* = 1) | 33 | Sinus: coenocytic hyphae and culture + . Identification: NR | DBT. AHT. Asthma | USA | NR | 1 F | Died | 61 |
| Mucormycosis (*n* = 1) | 41 | Sinus: coenocytic hyphae and culture + . Identification: NR | DBT | USA | AMB | 1 M | Alive | 62 |
| Mucormycosis (*n* = 1) | 60 | Nasal biopsy: broad aseptate hyphae. Culture + . Identification: NR | DBT | India | AMB | 1 M | Died | 4 |
| Mucormycosis (*n* = 2) | 40–54 | Sinus biopsy: broad aseptate hyphae. Culture + | None. DBT | Iran | AMB PCZ | 1 F/1 M | Died 1/2 Alive 1/2 | 63 |
| Mucormycosis (*n* = 1) | 32 | Paranasal tissue: broad aseptate hyphae. Identification NR | DBT | India | AMB | 1 F | Alive | 64 |
| Mucormycosis (*n* = 1) | 22 | Autopsy. ID: NR | DBT | UK | NR | 1 M | Died | 65 |
| Mucormycosis (*n* = 1) | 86 | Gastric ulcer sample: broad aseptate hyphae. Identification: NR | AHT | Brazil | AMBL | 1 M | Died | 66 |
| Mucormycosis | 20–80 | Nasal endoscopic Debridement: aseptate hyphae | DBT AHT CKD | India | AMBL | 20 M/11 F | Alive 28/31 Died 3/31 | 67 |
| Mucormycosis *Rhizopus/Mucor* (*n* = NR) | 23–67 | TB and nasal swab + | DBT/DKA | India | AMBL | 8 M/2 F | Died 4/10 Alive 6/10 | 68 |
| Mucormycosis | 66 | Nasal swab: aseptate hyphae | DBT | India | AMBL | 1 M | Alive | 69 |
| Mucormycosis | 35–73 | Tissue biopsy: aseptate hyphae. Identification: NR | DBT | India | AMBL | 15 M/3 F | Alive 11/18 Died 7/18 | 28 |
| Mucormycosis (*n* = 1) * | 72 | Guide nodule biopsy: broad aseptate hyphae. Identification: NR | DBT | India | AMBL PCZ | 1 M | Alive | 70 |
| Mucormycosis (*n* = 23) * | NR | Maxillar and ethmoid sinus: aseptate hyphae. Identification: NR | DBT | India | AMB | 15 M/8 F | Alive | 71 |
| Mucormycosis (*n* = 3) * | 39–50 | MRI suspicion of FI (3/3). Sinus tissue: hyphae | DBT | India | AMB | 2 M/1 F | NR | 72 |
| Mucormycosis (*n* = 1) * | 61 | Sinus tissue: broad aseptate hyphae | None | Iran | NR | 1 F | Died | 73 |
| *Mucor* spp. (*n* = 2) | 27–68 | NR | ATH. CVD and DBT. CKD | China | NR | NR | NR | 23 |
| *Rhizopus* spp. (*n* = 1) | 47 | Tissue culture + | AHT. DBT | Argentina | AMBL | 1F | Alive | 74 |
| *Rhizopus* spp. (*n* = 1) | NR | Sinus biopsy: broad aseptate hyphae. Culture + | DBT | India | AMB | 1 F | Alive | 29 |

**Table 2** (continued)

| Disease or species isolated | Age range | Diagnosis | UD reported | Country | ATFT | Patient (*n*) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| *Rhizopus* spp. (*n* = 1) * | 66 | BAL/BAS: aseptate hyphae. Culture + | AHT | Italy | AMBL | 1 M | Died | 75 |
| *Rhizopus* spp. (*n* = 1) | 60 | Sinus tissue: aseptate hyphae. Culture + | DBT/DKA Asthma. AHT | USA | AMBL AMBL + CAS | 1 M | Died | 76 |
| *Rhizopus* spp. (*n* = 1) | 49 | Bronchopleural fistula: aseptate hyphae. Culture + | None | USA | AMB | 1 M | Died | 77 |
| *R. microsporus* (*n* = 1) | 55 | Sputum: aseptate hyphae. Culture + | DBT | India | AMB | 1 M | Alive | 78 |
| *R. microsporus* (*n* = 1) | 53 | Lung tissue post-mortem: hyaline hyphae. Culture + | AML | Austria | VCZ | 1 M | Died | 79 |
| *R. microsporus* (*n* = 1) *R. arrhizus* (*n* = 1) | 60–70 | Orbital pus culture (1/2) and sputum culture (1/2) + | None. DBT | Netherlands | AMBL. ISA + PCZ | 2 M | Died 1/2 Alive 1/2 | 80 |
| *Rhizopus* spp. (*n* = 1) Mucormycosis (*n* = 1) | 36–48 | Sample from eye culture + /Sample: NR | DBT | USA | AMB ISA MCF | 2 M | NR | 81 |
| *R. microsporus* (*n* = 1) * | | Sternal wound cultures + . Serum GM and BG: NG | HTP. AHT. DBT. CKD | USA | AMBL + PCZ | 1 M | Died | 82 |
| *R. oryzae* (*n* = 1) | 38 | Sinus biopsy: broad aseptate hyphae. Culture + | None | India | AMB | 1 M | Alive | 83 |
| *R. oryzae* (*n* = 1) | 62 | Palate biopsy: aseptate hyphae. Culture + | DBT. KTR | Spain | AMB. PCZ | 1 M | Alive | 28 |
| *R. oryzae* (*n* = 1) | 44 | Maxillary sinus biopsy: aseptate hyphae. Culture: NG. Tissue PCR + | DBT | Iran | AMBL PCZ | 1 F | Alive | 84 |
| *R. oryzae* (*n* = 1) * | 50 | Sinus TB: broad aseptate hyphae. Culture + | DBT/AHT | Iran | AMBL | 1 F | Alive | 85 |
| *R. azygosporus* (*n* = 1) | 56 | Sputum and PF: fungal elements. Tissue: broad aseptate hyphae. Culture + | CKD | USA | AMBL | 1 M | Died | 86 |
| *Lichtheimia* spp. (*n* = 1) | 24 | BAL: aseptate hyphae. Culture + | DBT/DKA | Mexico | AMB | 1 F | Died | 87 |
| *Lichtheimia ramosa* (*n* = 1) | 48 | Lower limb biopsy: aseptate hyphae. Culture + | KTR | Spain | AMBL ISA | 1 M | Alive | 88 |
| *Rhizopus* spp. (*n* = 10) *Lichtheimia* spp. (*n* = 1) *Mucor* spp. (*n* = 2) Mucorales, unspecified (*n* = 28) | 46–61 | Tissue culture and tissue PCR | DBT | USA | AMBL | 34 M/7 F | Died 20/41 Others: NR | 89 |

**Table 2** (continued)

| Disease or species isolated | Age range | Diagnosis | UD reported | Country | ATFT | Patient (*n*) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|
| Total: 158<br>Mucormycosis 97<br>Mucorales 28<br>*Mucor* spp. 4<br>*Rhizopus* spp. 16<br>*R. oryzae* 4<br>*R. microsporus* 4<br>*R. arrhizus* 1<br>*R. azygosporus* 1<br>*Lichtheimia* spp. 2<br>*L. ramosa* 1 | 24–80 | Histology 46<br>Positive cultures 73<br>PCR 1<br>Fungi identified 30<br>Fungi non identified 125 | DBT 62<br>AHT 5<br>KTR 3<br>DKA 2<br>CKD 2<br>AML 1<br>None 4<br>Asthma 1 | 12 countries | AMBL/ AMB 113<br>PCZ 5<br>VCZ 1<br>ISA 2 MCF 1<br>ATFC 2 | 115 M<br>41F<br>NR 2 | Died 48/158<br>Alive 82/158<br>NR 28/158 | |

*AHT* arterial hypertension. *ALFD Aspergillus* lateral-flow device. *AMBL* liposomal amphotericin. *AML* acute myeloid leukemia. *AND* anidulafungin. *ATFT* antifungal treatment. *ATFc* ATF combination. *BAL* bronchoalveolar lavage. *BAS* bronchial aspirate. *BDG* 1,3-ß-D-glucan. *BSAT* broad-spectrum antibiotic therapy. *CAM* COVID-19-associated mucormycosis. *CAS* caspofungin. *CD* cardiovascular disease. *CFA* complement fixing antibodies. *CFS* spinal fluid. *CKD* chronic kidney disease. *CLL* chronic lymphocytic leukemia. *COPD* chronic obstructive pulmonary disease. COVID-19 coronavirus disease 2019. *CT* corticosteroid therapy. *CTS* chest tomography scan. *CVC* central venous catheter. *CVD* cardiovascular disease. *DBT* diabetes. *DKA* diabetic ketoacidosis. *DVT* deep venous thrombosis. *GM* galactomannan. *HIV* human immunodeficiency virus. *HM* hematological malignances. *HT* hyperthyroidism. *HT* hypothyroidism. *HTP* heart transplant patient. *IHD* ischemic heart disease. *ISA* isavuconazole. *KTR* kidney transplant recipient. *MCF* micafungin. *MS* myelodysplastic syndrome. *MS* myelodysplastic syndrome. *NG* negative. *NR* not reported. *NYS* nystatin. *RT* renal transplant. *SHF* systolic heart failure. *SOT* solid organ transplant. *TB* tuberculosis. *TMS* trimethoprim-sulfamethoxazole. *TS* tracheal secretion. *UC* ulcerative colitis. *VCZ* voriconazole. *: CAM post COVID-19

Despite all this, the mortality rate is also high in non-COVID-19 patients at risk such as those with underlying neutropenia with IPA, if treatment is not initiated on time or whether the underlying disease conditions do not improve [119]. Thus, it could be reasonable that an adequate treatment for COVID-19 could have a positive impact on the absence of improvement in the evolution of IPA. Patients with COVID have chronic obstructive pulmonary disease (COPD) for which the association with aspergillosis is well known or asthma/corticoid therapy that are also known risk factors for *Aspergillus* colonization. Thus, COVID-19 might be a risk factor for aspergillosis, and the underlying pulmonary conditions may favor COVID-19-associated aspergillosis [120]. Corticosteroids treatment, as is indicated in severe COVID-19 patients, increases 3 times the risk to develop invasive fungal infections in comparison to other patients who do not receive steroids [121]. Some reports highlight the need to monitor pneumatoceles that might predispose to pneumothorax and/or cavitary lesions that could be complicated with coinfections like aspergillosis, even in the recovery phase of COVID-19 [57, 122].

Other fungal infection such as candidiasis could be expected due the aforementioned conditions that predispose for suffering a fungemia, being an important issue to be considered. Diseases such as diabetes or severe COVID-19 seem to alter the intestinal barrier function that facilitates *Candida* translocation, allowing the gut microbiota like *Candida* species, to reach the bloodstream and then disseminate systemically [123]. The estimated mortality due to invasive candidiasis is 19–40% [124], being even higher among ICU patients, around 70% [125]. Cases of fungemia due to *C. albicans* and non albicans in COVID patients were reported in several publications. The reported cases of *C. auris* sound alarming, due the association of COVID-19 with an emerging pan-resistant yeast [34]. However, its sensitivity to antifungal agents should be studied and suspected according to the epidemiological setting. In Brazil, all *C. auris* were reported as susceptible to azoles, amphotericin, and echinocandins [95]. Some cases have been seen that appeared in colonized patients when they moved from non-COVID-19 rooms to COVID-19 rooms [97]. However, in a report by the CDC evaluating strains originating worldwide, more than 70% of the *C. auris* isolates were resistant to fluconazole. In the USA, resistance of *C. auris* isolates was about 90% for fluconazole, 30% for amphotericin B, and less than 5% for echinocandins. These proportions may include multiple isolates from the same individuals and may change as more isolates are tested [126].

No least is the report of *C. glabrata* pan-echinocandin resistant infection [92]. In Colombia, fungemia due to non-*C. albicans* was 78.94%, including *C. auris* [98]. In India, a high percentage of *C. auris* isolated from blood were resistant to fluconazole, voriconazole, flucytosine, and amphotericin [34]. In a study performed in Minas Gerais, Brazil, from 212 patients, *Candida* species were isolated in 98.2%, mostly from tracheal aspirate. The authors described a mortality rate of 90.5% and 76.3% in cases related to *Candida* non-albicans and *C. albicans*, respectively [91]. *Candida* was also related to oropharyngeal candidiasis (OPC), infecting old people with cardiovascular diseases and diabetes due

**Table 3** Fungal infections non-CAPA associated to COVID-19

| Strain (*n* isolates) | Fungal co-infection (n cases) | Age range | Diagnosis | UD reported | Country | ATFT | Patient (*n*) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|---|
| *C. albicans* (3), *C. tropicalis* plus *C. albicans* (1), *C. glabrata* (1) | CAC (*n* = 5) | 38–76 | Blood culture + | CVC. BSAT. AHT. Stroke | Oman | CAS MCF VCZ AMB | 5 M | Died 3/5<br>Alive 2/5 | 90 |
| *C. albicans* (3), *C. tropicalis* plus *C. krusei** (1), *C. auris* (12) | CAC (*n* = 15) | 66–88 | Blood culture + (15/15), Urine + (2/15) | CVC. UC. DBT. CKD. AHT | India | MCF | 7 M/3 F** | Died 8/15<br>Alive 7/15 | 34 |
| *C. albicans* (22), *C. tropicalis* (8), *C. glabrata* (3), *C. kefyr* (1) | CAC (*n* = 49) | 35–75 | Blood culture + (3/49), TA (33/49, CVC (3/49), Urine (20/49), Sputum (3/49) | CD. Obesity. DBT | Brazil | MCF<br>FCZ<br>AMB | 22 M/27 F | NR | 91 |
| *C. albicans* (2) | CAC (*n* = 4) | 27–68 | NR | ATH. CVD and DBT. CKD | China | NR | NR | NR | 23 |
| *C. glabrata* (1) | CAC (*n* = 1) | 79 | Blood culture + | DBT. IHD | Italy | CAS | 1 M | Died | 92 |
| *C. albicans* (46), *C. glabrata* (7), *C. dubliniensis* (6), *C. parapsilosis* (3), *C. tropicalis* (2), *C. krusei* * (1) | CAC (*n* = 65) | 27–90 | Oropharyngeal swab culture + | CVD. DBT. HM | Iran | FCZ CAS NYS | NR | NR | 40 |
| *C. glabrata* plus *C. albicans* (1) | CAC (*n* = 1) | 48 | BAL and CVC culture + / Sacroiliac joints biopsy culture + | AHT. Obesity | UK | FCZ | 1 M | Alive | 93 |
| *C. auris* (15) | CAC (*n* = 15) | 36–82 | Blood culture + | CVC. BSA | Lebanon | CAS AND AMBL | 8 M/7 F | NR | 94 |
| *C. auris* (2) | CAC (*n* = 2) | 59–74 | CVC culture (1/2) and blood culture (1/2) + | DVT. CKD. DBT. AHT | Brazil | AND | 1 M/1 F | Alive 2/2 | 95 |
| *C. auris* (4) | CAC (*n* = 4) | NR | Blood (3/4) and urine culture (1/4) + | DBT. CVC. CKD. CVD. None | USA | NR | NR | Died | 96 |
| *C. auris* (12)<br>*C. glabrata* (3) | CAC (*n* = 12) | 36–66 | Blood (6/12), urine (8/12) and both (2/12) cultures + | CVC. UC | Mexico | CAS AND VCZ<br>ISA AMB | 10 M/2 F | Died 8/12<br>Alive 4/12 | 97 |
| *C. auris* (6), *C. albicans* (3), *C. tropicalis* (4), *C. parapsilosis* (3), *C. orthopsilosis* (1), *C. glabrata* (1), *Trichosporon asahii* (1) | CAC/CAY (*n* = 18/1) | 1–88 | Blood culture + | CVC. DBT. CKD. AHT. BSAT. Cancer | Colombia | FCZ. CAS VCZ | NR | Died 12/19<br>Alive 6/19 | 98 |
| *C. albicans* (4)<br>*C. glabrata* (2)<br>*Rhodotorula mucilaginosa* (1) | CAC/CAY (*n* = 6/1) | 25–75 | Blood culture + | Cancer (3). DBT (1). None (4) | Iran | FCZ | NR | Died 6/7<br>Alive 1/7 | 99 |
| *T. asahii* (*n* = 5) | CAY | 57–75 | Blood culture + | DBT (2/5)<br>Others (3/5) | Brazil | VCZ (4/5) | 4 M/1F | Died (4/5) | 100 |
| *Cryptococcus neoformans* | CAY (*n* = 1) | NR | TB culture and CSF +<br>Serum Ag + | Prostate cancer | Italy | AMB + 5FCFCZ | 1 M | Died | 101 |
| *Cryptococcus neoformans* | CAY (*n* = 1) | 78 | BAL culture + | AHT. COPD | USA | AMB. ISA | 1 M | Died | 102 |

**Table 3** (continued)

| Strain (*n* isolates) | Fungal co-infection (n cases) | Age range | Diagnosis | UD reported | Country | ATFT | Patient (*n*) Gender | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|---|
| *Saccharomyces cerevisiae* | CAY (*n* = 1) | 73–76 | Blood culture + | AHT. DBT | Greece | AND FCZ | 2 M | Alive | 103 |
| *Coccidioides immitis* (*n* = 1) | CAE (*n* = 1) | 48 | Serum IgM ID + | SHF | USA | FCZ | 1 F | Alive | 104 |
| *Coccidioides* spp. (*n* = 1) | CAE (*n* = 1) | 48 | Serum CFA: 1/32 | DBT | USA | NR | 1 M | Alive | 105 |
| *Paracoccidioides* spp. (Pb) (*n* = 1) | CAE (*n* = 1) | 19 | Lymph node aspirate: multiple budding cells. Culture + . ID Ab Pb: 1/512 | Malnutrition | Brazil | AMBL | 1 M | NR | 106 |
| *Histoplasma capsulatum* (Hc) (*n* = 1) | CAE (*n* = 1) | 43 | Skin scarification: yeasts compatibles with Hc | HIV | Argentina | AMB ITZ | 1 M | Alive | 107 |
| *H. capsulatum* (*n* = 1) | CAE (*n* = 1) | 43 | Sputum: yeasts compatibles with Hc<br>Urine Gm for Hc: > 2 | HIV | Brazil | ITZ | 1 F | Alive | 108 |
| *H. capsulatum* (*n* = 1) | CAE (*n* = 1) | 36 | Sputum: yeasts compatibles with Hc<br>Urine GM: 24.7 ng/mL and serum GM 5.10 ng/mL | HIV | Argentina | AMB ITZ | 1 F | Alive | 109 |
| *H. capsulatum* (*n* = 1) | CAE (*n* = 1) | 62 | CF and ID: + | DBT. Asthma | USA | AMBL ISA | 1 F | Alive | 102 |
| *Pneumocystis jiroveccii* (Pj) | CAP (*n* = 1) | 52 | BAL: cysts compatible with Pj | HIV | Germany | TMS | 1 M | Alive | 110 |
| *P. jiroveccii* | CAP (*n* = 1) | 83 | TS real time PCR + . BG: 305 pg/ml. Cystic findings on CTS | Asthma. UC. CT | USA | TMS | 1 F | Alive | 111 |

AHT arterial hypertension. *ALFD Aspergillus* lateral-flow device. *AMBL* liposomal amphotericin. *AML* acute myeloid leukemia. *AND* anidulafungin. *ATFT* antifungal treatment. *BAL* bronchoalveolar lavage. *BAS* bronchial aspirate. *BDG* 1,3-ß-D-glucan. *BSAT* broad-spectrum antibiotic therapy. *CAC* COVID-19-associated candidiasis. *CAE* COVID-19-associated endemic mycosis. *CAP* COVID-19-associated pneumocystosis. *CAS* caspofungin. *CAY* COVID-19-associated yeasts. *CD* cardiovascular disease. *CFA* complement fixing antibodies. *CFS* spinal fluid. *CKD* chronic kidney disease. *CLL* chronic lymphocytic leukemia. *COPD* chronic obstructive pulmonary disease. *COVID-19* coronavirus disease 2019. *CT* corticosteroid therapy. *CTS* chest tomography scan. *CVC* central venous catheter. *CVD* cardiovascular disease. *DBT* diabetes. *DKA* diabetic ketoacidosis. *DVT* deep venous thrombosis. *GM* galactomannan. *HIV* human immunodeficiency virus. *HM* hematological malignances. *HT* hyperthyroidism. HT hypothyroidism. *HTP* heart transplant patient. *IHD* ischemic heart disease. *ISA* isavuconazole. *MCF* micafungin. *MS* myelodysplastic syndrome. *NG* negative. *NR* not reported. *NYS* nystatin. *RT* renal transplant. *SHF* systolic heart failure. *SOT* solid organ transplant. *TB* tuberculosis. *TMS* trimethoprim-sulfamethoxazole. *TS* tracheal secretion. *UC* ulcerative colitis. *UC* urine catheter. *VCZ* voriconazole. *: renamed *P. kudriavzevii*. **: reported only for *C. auris*

to the weaker immune functions of these patients. CoV-2 as HIV virus produce T lymphocytes consumption [40]. Besides, elderly patients have lower activity levels of protective salivary innate defenses [127]. Fungemia by other yeasts such *Trichosporon* and *Saccharomyces cerevisiae/boulardii* was reported [98, 103]. This last is used in ICU patients as a probiotic for treatment of diarrheal disorders [128].

Moreover, it is not surprising to isolate Mucorales, since many patients with COVID-19 suffer from diabetes mellitus as their underlying disease that alters the body's immunological response enhancing fungal proliferation and diminishing the phagocytic capacity of host immune cells [129]. Besides, corticosteroids have other side effects such as blunting the action of insulin with the increment of blood glucose. This hyperglycemic effect is magnified in diabetic patients and can lead to ketoacidosis [130]. In addition, the ketone reductase enzyme in *Rhizopus* organisms allowing them to thrive in high glucose and acidic conditions, being the reason for the stimulated growth of these organisms in those patients [131]. It is known that in patients with ketoacidosis, rhino-orbital-cerebral mucormycosis can develop, regardless of whether the patient is undergoing a COVID-19 infection. Mucormycosis without concomitant COVID-19 infection has a mortality rate ranging from 40 to 80% [9]. Severe immunocompromised from untreated diabetes made the patients be susceptible to contract both mucormycosis and COVID-19 [4, 61]. In general, uncontrolled diabetes was the main risk factor [67]. The mortality rate appears to reach 100% when both diseases are associated [113]. Besides, it is very important that ophthalmologists suspect the possible orbital infarction syndrome secondary to mucormycosis in these patients [69]. In one report, loss of vision was observed in 66% and orbital exenteration in 38% of the patients analyzed [28].

However, some cases of patients with diabetes without ketosis are reported [29, 70], as well some with non-underlying condition, suggesting a COVID-19 as risk factor due to steroids or interleukin inhibitor therapies [73, 83]. It is important to note that although corticosteroid therapy helps for the treatment of the severe form of COVID, when comorbidities such as diabetes or other immunosuppression factors exit, can be harmful. Steroids can exacerbate hyperglycemia. Therefore, close monitoring hospitalized patients and after discharged should be take into account for possible complications of post-COVID-19 fungal infections such the cases of mucormycosis that have been described [70, 71, 82, 85]. Thus, diagnosis of mucormycosis requires clinical observations, images, histopathologic findings, fungal culture, and surgical debridement which seem to improve patient survival. However, no growth happens very frequently, being important to consider the proper clinical context for suspicion. The risk of *Pneumocystis* pneumonia increases significantly with severe CD4 lymphocytopenia [132]. This is the case of HIV patients, and also this scenario occurs with COVID-19 infection. Thus, patients without other underlying factors might suffer of pneumocystosis as has been reported [111].

SARS-CoV-2 and endemic mycoses have overlapping risk factors. Coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis have been reported. There is a lack of information if severity of COVID and endemic mycosis can be influenced one by the other. It is possible that the fungus stays in a latent stage and be reactivated due to coronavirus disease related to immune dysregulation. In areas where these fungi are endemic, awareness should be taken [102, 104, 107, 108].

The frequency of COVID-19 in AIDS is not higher than the frequency of COVID-19 in the general population [133, 134]. There are reported cases of COF or other infections in HIV/COVID-19-positive patients. However, we do not think it is unexpected, since patients with CD4 < 100 generally present COF to different *Candida* species, endemic diseases, or cryptococcosis. We think that these are HIV-positive patients, with low CD4s susceptible for suffering marker diseases and who were infected with COVID-19. This thought is in agreement with the favorable outcome of HIV/COVID/histoplasmosis case patients in whom not lung damage was observed and no ICU was required [108]. The course and presentation of the reported cases do not vary from those negative COVID-19. Those cases should be taken into account to indicate the appropriate treatment but might not be taken as a separate entity. Nevertheless, the true role of the SARS-CoV-2 virus in HIV patients remains to be fully elucidated.

## Conclusion

This review aimed to summarize all the main published reports of COVID-19-associated fungal infections identified by different methodologies, among which *A. fumigatus* can be considered the most prevalent species reported for CAPA. However, it is difficult to compare the different published studies since not all medical centers use the same criteria to define CAPA, reason for which is needed to find consensus on these definitions. The diagnosis is complicated because serum GM is generally negative, with BAL being the most sensitive sample, but it is difficult to perform due to the risk it represents. Cultures are not very profitable either and PCR is not always useful or available. The suspicion and searching for fungal infections, whether of yeast, hyaline, or pigmented fungi, should be taken into account to indicate the appropriate treatment and improve the patient's prognosis. In addition, it is of paramount importance to make physicians aware of the fact that invasive fungal infections might occur after patients with COVID-19 have been discharged,

particularly those with predisposing conditions, such uncontrolled diabetes related with mucormycosis. This entity has been relevant in recent days, due to the indiscriminate increase in reported cases, especially in India. Therefore, it is mandatory to establish an exhaustive patient follow-up and combine different methodologies of laboratory diagnosis, images, and clinical suspicion related to any fungal infection-COVID-19 related.

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**Availability of data and material** All data is public available.

**Code availability** Not applicable for this section.

## Declarations

**Ethics approval** Not applicable for this section.

**Consent to participate** Not applicable for this section.

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