Fungal Infections in COVID-19 Patients

Subjects: Microbiology

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Patients with severe COVID-19, such as individuals in intensive care units (ICU), are exceptionally susceptible to bacterial and fungal infections. The most prevalent fungal infections are aspergillosis and candidemia. Nonetheless, other fungal species (for instance, Histoplasma spp., Rhizopus spp., Mucor spp., Cryptococcus spp.) have recently been increasingly linked to opportunistic fungal diseases in COVID-19 patients. These fungal co-infections are described with rising incidence, severe illness, and death that is associated with host immune response. Awareness of the high risks of the occurrence of fungal co-infections is crucial to downgrade any arrear in diagnosis and treatment to support the prevention of severe illness and death directly related to these infections.

Keywords: fungal infection ; COVID-19 ; SARS-CoV-2 ; Candida ; Aspergillus ; Mucor ; immune response ; microbiome

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), has infected millions of patients worldwide, and placed an unprecedented stress on healthcare systems [1][2][3][4]. This disease has predisposed a relatively high number of patients to acute respiratory distress syndrome, and co-infections are a frequent complication [5][6], especially with prolonged hospital stays [7]. Changes in humans' microbiota have been recently observed in COVID-19 patients [1], with patients often being colonized or infected by microorganisms responsible for secondary infections (co-infections or superinfections), often caused by bacteria and fungal pathogens [5][7][8][9]. Indeed, several opportunistic infections following severe respiratory viral infections have been recognized in COVID-19 patients [2]—particularly, a higher incidence of fungal co-infections (**Figure 1**) [10][11][12]. For example, in Spain, the incidence of candidemia cases was higher in the first and second waves and lower during the third wave, also with a prevalence of invasive pulmonary aspergillosis (IPA) cases [11]. Moreover, the coronavirus-associated pulmonary aspergillosis (CAPA) showed to affect up to 30% of ventilated patients with COVID-19 admitted in intensive care units (ICU) [13], and, in a hospital in Pisa (Italy), 21.9% of 315 hospitalized patients with COVID-19 had a superinfection [14].

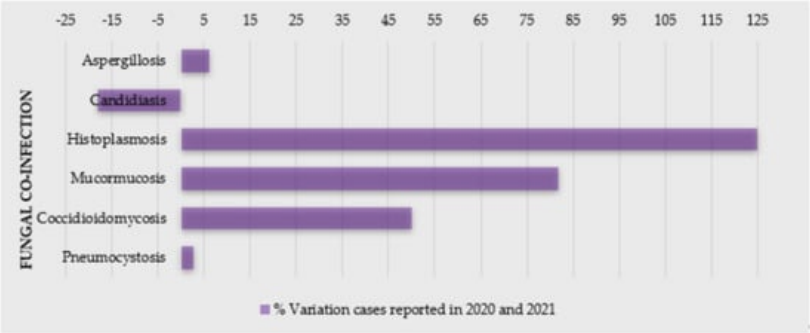

Figure 1. Percentage of variation of cases of COVID-19 patients with fungal co-infections reported in 2020 and 2021 (source: PubMed).

The main pathogens related to co-infections are reported to be Enterobacterales (44.9%), non-fermenting Gram-negative bacilli (15.6%), Gram-positive bacteria (15.6%), and fungi (5.5%) [14]. In COVID-19 patients, the most fungi related to co-infections are *Aspergillus* spp., *Candida albicans, Candida glabrata*, *Candida dubliniensis*, *Candida parapsilosis sensu stricto*, *Candida tropicalis*, and *Candida krusei (Pichia kudriavzevii)* [8]. Moreover, these cases have been indicated as mainly primary and catheter-related infections [15].

There is still lack of information regarding the long-term impact of secondary infections on the outcome of hospitalized COVID-19 patients [9][16]. Patients with co-infection undergoing invasive mechanical ventilation showed to be 3.8 times more likely to die than those without positive cultures [9]. In order to perform an efficient treatment and reduce mortality, it is important to make an accurate early identification [12]; however, these co-infections raise difficulties on diagnosis,

treatment (including broad-spectrum antimicrobial drugs, mechanical ventilation, extracorporeal membrane oxygenation), prognosis, and even increase the disease the symptoms and mortality of COVID-19 [8][12][15][17][18][19].

The repercussions of SARS-CoV-2 infections on future global antimicrobial resistance must be explored profoundly [3][16]. In Valencia (Spain), the antifungal consumption increased in 2020 compared to previous year, especially echinocandins, voriconazole, and isavuconazole [11]. Considering that the antimicrobials drugs for COVID-19 patients, both on and during admission, are almost all prescribed uncertainly in clinical settings, there is expected an increase in drug-resistant infections [3].

Lastly, considering the immune response, there has been represented a host dysregulation triggered by SARS-CoV-2 infection, which has been hypothesized as a causal pathway for the increasingly reported mainly fungal (oral) manifestations associated with COVID-19 [20][21]. Additionally, the alteration in human microbiota (due to SARS-CoV-2 infection), which can also indicate the progression of COVID-19, may contribute to bacterial, fungal, or viral infections and affect the immune system [1]. In these patients, this is normally described as an increase in pro-inflammatory markers, such as IL-1, IL-6, and tumor necrosis alpha (TNF-α), less CD4 interferon-gamma expression, and a decreased number of CD4 and CD8 cells, which increase susceptibility to bacterial and fungal infections [12].

2. Fungal Infections as a Co-Morbidity of COVID-19

Fungal co-infections are frequent in the COVID-19 patients; therefore, its awareness is important for proper diagnosis and, subsequently, efficient treatment of the fungal co-infections for reducing morbidity and mortality. Due to a general neglected approach towards fungal tropical diseases, morbidity and mortality is expected to worsen in the context of the COVID-19 pandemic [22]. SARS related to COVID-19 disease is known to increase the risk of invasive fungal infections (IFI) [23][24]. In addition, patients suffering from endemic mycoses and COVID-19 co-infection seem to be an at-risk population and have a poor prognosis. A significant number of cases of COVID-19-associated candidiasis, aspergillosis, mucormycosis, and histoplasmosis have been reported so far from the different region of the world [22][25][26][27]. Some reports even state that COVID-19 increases the mortality rate in the patients having fungal infections, but the case reports suggest that individuals with COVID-19 are more susceptible to a fungal infection mostly because of impaired immune responses, which further increases the awareness of clinicians for more effective diagnosis and treatment [28][29].

2.1. Candidiasis

One of the major complications of severe COVID-19 cases are yeast infections. They are mainly caused primarily by *Candida* spp., which are associated with a high mortality rate, due to a longer ICU stay, catheterization, and broad-spectrum antibiotic use [6] (**Table 1**). Nucci et al. observed stable incidence of candidemia in their hospital during an 18-year period (1.3 episodes per 1000 admissions), but since March 2020, an increase in cases diagnosed with candidemia was noticed [30]. Compared with non-COVID-19 patients, COVID-19 patients with candidemia were more likely to be under mechanical ventilation [30]. Katz et al. evaluated the association between COVID-19 and oral and systemic candidiasis [25]. Generally, candidiasis was significantly associated with increased risk for COVID-19, whereas oral candidiasis showed an insignificant trend [25].

Table 1. Clinical characteristics of COVID-19 patients reported with candidiasis.

Fungal Infection in COVID-19 Infection	Observed Immune Response	Co-Morbidity/ Disease Models	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
Candidemia *Candida duobushaemulonii Candida parapsilosis*, *Candida lusitaniae*	Elevated pro-inflammatory markers (d-dimer, ferritin, CRP, progressive thrombocytosis) and neutrophilia	Acute pulmonary embolism with subarachnoid hemorrhage superimposed bacterial pneumonia	CT scan, Culture, RT-PCR Blood, urine, and DTA	Meropenem, Levofloxacin Trimethoprim/sulfamethoxazole, Amikacin, tigecycline, colistin	Intravenous fluconazole	NR	Dead	[31]

Fungal Infection in COVID-19 Infection	Observed Immune Response	Co-Morbidity/ Disease Models	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
Candidemia *(Candida glabrata)*	Leucocytes—normal, C-reactive protein and interleukin 6—altered	Type-2 diabetes ischemic heart disease stadium IV, leg amputation highly suspected bacterial superinfection	Chest X-ray and CT scan, RT-PCR, serology, MALDI-TOF	Darunavir/ritonavir, HCQ, piperacillin/tazobactam, teicoplanin, ertapenem, colistin	Caspofungin	NR	Dead	[32]
Candidemia *Candida auris* (n = 10), *Candida albicans* (n = 3), *Candida tropicalis* (n = 1), *Candida krusei (P. kudriavzevii)* (n = 1)	NA	Underlying chronic conditions (e.g., hypertension, n = 7; DM, n = 6; and chronic kidney and liver disease, n = 2)	MALDI-TOF and molecular identification—sequencing	NR	Micafungin	NR	Dead (n = 8)	[4]
Candidemia *Candida auris* (n = 3)	NA	DM, hypertension, chronic renal failure, coronary artery disease, obesity	Vitek 2 system, MALDI-TOF, sequencing, multiplex PCR	NR	Anidulafungin	NR	Dead	[33]
Candidemia *Candida auris* (n = 12)	NA	DM (n = 6), hypertension (n = 6), multiple myeloma (n = 1), stem-cell transplantation (n = 1), dyslipidemia (n = 1), end-stage renal disease (n = 1), bladder cancer (n = 1), obesity (n = 1), systemic lupus erythematosus (n = 1)	PCR, MALDI-TOF, Vitek2, whole-genome sequencing	Remdesivir (n = 9), HCQ (n = 1),	Amphotericin B n = 10 Micafungin,		Dead (n = 6) Alive (n = 6)	[34]

Both fungi and virus display highly distinctive patterns of sudden emergence, and are based on simple infection-driven, human-to-human transmission [35]. In times of SARS-CoV-2, the vigilance of multidrug-resistant *Candida* spp. (e.g., *Candida auris*, *C. glabrata*, and *Candida duobushaemulonii* [17][31][36]) is extremely important. Data regarding multidrug-resistant *Candida* spp. in COVID-19 patients are scarce [31]. *C. auris*, an emerging pathogen known for a reduced susceptibility to antifungals, is spread across all continents [5], and it is easily transmitted between healthcare professionals. Both *C. auris* and SARS-CoV-2 have been found on hospital surfaces including on bedrails, intravenous (IV) poles, beds, air conditioner ducts, windows, and hospital floors [5]. Hospital-acquired *C. auris* infections in coronavirus disease patients may lead to adverse outcomes and additional strain on healthcare resources [37]. Moreover, the standard COVID-19 critical care of using mechanical ventilation and protracted ventilator-assisted management makes these patients potentially susceptible to colonization and infections by *C. auris* [5]. For example, during April–July 2020 in New Delhi (India), *C. auris* accounted for two-thirds of cases, and the case-fatality rate was very high (60%) [4]. In a phylogenetic molecular clock study (Genoa, Italy), Di Pilato and colleagues showed that all *C. auris* isolates were resistant to amphotericin B, voriconazole, and fluconazole at a high level, owing to mutations in *ERG11* (K143R) and *TACB1* (A640V) genes. Critically, *C. auris* could be easily spread because of the COVID-19 pandemic [38]. After the first *C. auris*-colonized case was diagnosed in a COVID-19 patient in ICU at a hospital in Salvador, Brazil, a multidisciplinary team conducted a local *C. auris* prevalence investigation [33]. Remarkably, findings revealed that among body swabs collected from 47 patients, eight samples from the axillae were positive for *C. auris*. Contaminated axillary monitoring thermometer helped to *C. auris* dissemination. Re-use of these devices must imply a careful disinfection or they should be replaced by other temperature monitoring methods [33]. Moreover, in 2020, the Florida Department of Health was alerted to three *C. auris* bloodstream infections and one urinary tract infection (UTI) in four patients with COVID-19 who had received care in the same COVID-19 ICU ward [39]. A report from in a tertiary academic center (United States, May 2014 to October 2020) showed that in an entire sample (non-COVID-19 and COVID-19 groups), *C. albicans* accounted for a minority of isolates collected [40]. Compared to non-COVID-19 patients with candidemia, COVID-19 patients had lower ICU admission sequential organ failure assessment score, but longer ICU stays and central venous catheter dwell times at candidemia detection [40].

DM: diabetes mellitus, DTA: deep tracheal aspirate, HCQ: Hydroxychloroquine, MALDI-TOF: matrix-assisted laser desorption/ionization time of flight, NA: not applicable/available, NR: not reported, PCR: polymerase chain reaction.

Surveillance data assessed differences in candidemia patients with and without a prior COVID-19 diagnosis [28]. COVID-19 patients with candidemia lacked established underlying conditions associated with candidemia but had two times the mortality rate versus candidemia patients without COVID-19 [28]. Over a two-year period, patients followed in the ICU of Ankara City Hospital, Turkey, were divided into pre-pandemic and pandemic periods [29]. In multivariate logistic regression analysis, corticosteroid use, presence of sepsis, and age older than 65 years were independent risk factors for mortality in candidemia patients [29]. Indeed, candidemia with high mortality is reported as a more serious problem for COVID-19 patients due to its increased and earlier incidence, and a higher rate of mortality [28][29].

2.2. Aspergillosis

Aspergillosis is one of the most common opportunistic fungal co-infections caused by some *Aspergillus* spp., which particularly affects immunocompromised persons, such as COVID-19 patients. It critically affects the respiratory system, leading to a mild/serious lung infection, known as pulmonary aspergillosis, a serious form of aspergillosis, which becomes

worse over time and does not have an effective treatment [26][41]. Clinical characteristics of the COVID-19 patients co-infected with aspergillosis can be analyzed in **Table 2**. Based on the available literature, it is suggested to keep a low threshold to investigate for COVID-19 associated pulmonary aspergillosis (CAPA), since an early detection and respective treatment may significantly improve outcomes. Moreover, prolonged courses of steroids should not be given unless further conclusive evidence is available [42], because steroids suppress the immune system, making the patient more susceptible to secondary infections. A rapid and aggressive treatment approach with judicious use of steroids while treating co-infections turns out to be the best possible outcome and solution.

Table 2. Clinical characteristics of COVID-19 patients reported with aspergillosis.

Fungal Infection in COVID-19 Infection	Observed Immune Response	Co-morbidity/ DiseaseModels	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
Aspergillosis *Aspergillus* spp., CAPA	Highly permissive inflammatory response	DM, CVD	CT scan, Culture	HCQ	Azoles, liposomal amphotericin B	NR	Alive	[43]
	Immunocompromised	ARD, HT	CT scan, RT-PCR, Culture, ELISA	NR	Voriconazole	Yes (n = 7)	Some alive and some dead	[44]
	Immunocompromised	DM, HT	CT scan, Culture	NR	Isavuconazole, voriconazole	No	Alive	[42]
		HT, coronary heart disease, obesity	CT scan, RT-PCR, Culture,	HCQ, meropenem, azithromycin	Voriconazole	Yes	Dead	[26]
	Low B-cell and T-cell response	Severe dyspnea, hypertension, DM	CT scan, RT-PCR, Serology	RD, multiple antibiotics	Multiple antifungals	No	Alive	[45]
Aspergillosis *Aspergillus fumigatus, CAPA*	Systemic pro-inflammatory cytokine responses	Asthma, DM, Myeloma	CT scan, RT-PCR, Culture,	NR	Voriconazole, isavuconazole, liposomal amphotericin B, caspofungin, anidulafungin	Yes	Some alive and some dead	[46]
	High inflammatory response and immunosuppression	ALL, AML	RT-PCR, CT scan, Culture, Serology	NR	Caspofungin, fluconazole, liposomal amphotericin B, caspofungin, itraconazole	No	Some alive and some dead	[47]
Aspergillosis *Aspergillus* spp., IA	Acquired immunodeficiency and immunosuppression	ARD	Antigen, CT scan, Culture, Serology	NR	NR	Yes	Death (quick evolution)	[48]
	Strong deregulation of core components of innate immune and inflammatory responses	RHAEM	NA	NA	NA	NA	NR	[49]

2.3. Histoplasmosis

Histoplasmosis is a systemic mycosis, highly endemic in certain regions of America and Asia, including Brazil and India. It is caused by a dimorphic fungus, *Histoplasma capsulatum,* which predominately occurs in soil containing large amounts of bird or bat droppings. The infection occurs through the inhalation of fungal microconidia after perturbation of these environmental sources [50]. Similarly to aspergillosis, the disease is usually associated with immunosuppressive conditions, clinically presenting severe acute disseminated forms. Underlying lung disorders can predispose individuals to chronic pulmonary histoplasmosis, whereas acute and subacute pulmonary forms mainly occur in healthy individuals after a large fungal inoculum inhalation [50][51]. These clinical forms are less known, often misdiagnosed as bacterial pneumonia and pulmonary tuberculosis (**Table 3**). In the case of this particular fungal disease, it was indicated that most patients who received steroids for COVID-19 treatment developed histoplasmosis (**Table 3**). Histoplasmosis is mainly associated with COVID-19 patients with AIDS, and there are very few studies on the co-infection of *H. capsulatum* and COVID-19 [27][52]. Actually, the important findings were all patients of COVID-19 having co-infection of *H. capsulatum* survived after antifungal treatment with amphotericin B and itraconazole (**Table 3**) [27][52][53][54][55].

ARD: acute respiratory disease/distress, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CAPA: COVID-19-associated pulmonary aspergillosis, CT: computed tomography, CVD: cardiovascular disorder, ELISA: enzyme-linked immunosorbent assay, DM: diabetes mellitus, HIV: human immunodeficiency viruses, HT: hypertension, IA: invasive aspergillosis, NA: not applicable/available, NR: not reported, RHAEM: Reconstituted Human Airway Epithelial Model, RA: Rheumatoid arthritis, HCQ: Hydroxychloroquine, RD: Remdesivir, RT-PCR: real time-polymerase chain reaction.

Table 3. Clinical characteristics of COVID-19 patients reported with histoplasmosis.

Fungal Infection in COVID-19 Infection	Observed Immune Response	Co-morbidity/ Disease Models	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
	Acquired immunodeficiency	HIV	CT-scan, RT-PCR	Tenofovir/lamivudine and atazanavir/ritonavir ceftriaxone, azithromycin	Itraconazole	Yes (dexamethasone)	Alive	[27][52]
Histoplasmosis *Histoplasma capsulatum*	HIV	HIV	CT-scan, RT-PCR	Atazanavir/ritonavir, tenofovir/emtricitabine	Itraconazole, amphotericin B deoxycholate	No	Alive	[27]
	Inflammatory response	NA	CT-scan, RT-PCR	Levofloxacin	Itraconazole	Yes (methylprednisolone)	Alive	[53]
	NA	NA	CT scan, RT-PCR	NA	Itraconazole	No	Alive	[54]
Histoplasmosis *Histoplasma capsulatum*-like intracellular yeasts	Acquired immunodeficiency	HIV	CT-scan, RT-PCR	HCQ, lopinavir/ritonavir, tenofovir disoproxil fumarate/emtricitabine plus dolutegravir	Amphotericin B deoxycholate, itraconazole	No	Lost to follow-up	[55]

ART: antiretroviral therapy; CT: computed tomography; HIV: human immunodeficiency viruses; NA: not applicable/available; HCQ: Hydroxychloroquine; RT-PCR: real time-polymerase chain reaction.

2.4. Mucormycosis

The presence of hyphal infiltration of sinus tissue and a temporal course of less than four weeks defines mucormycosis [56][57]. The most common species related to mucormycosis are *Rhizopus* spp. and *Mucor* spp., but recently, a new *Cunninghamella* species, *Cunninghamella* bigelovii, was described [58]. Clinically, rhino-cerebral mucormycosis (RCM) can have atypical symptoms and signs that are similar to complicated sinusitis, such as crusting, nasal blockage, facial pain, proptosis and chemosis, edema, ptosis, and even ophthalmoplegia, as well as fever and headache and symptoms of intracranial extension [59][60]. A black eschar can be found on the hard palate or in the nasal cavity, but it is not typical [61][62]. Mycotic infiltration of blood vessels, thrombosis with vasculitis, acute neutrophilic infiltrate, bleeding, and tissue infarction are all histological characteristics [63].

Without early treatment and identification, this illness may advance quickly, with reported death rates of 50–80%, due to intra-orbital and cerebral complications. Even with timely treatment of underlying illnesses, diagnosis, and surgical intervention, therapy is frequently ineffective, resulting in infection spread and eventually death [64].

Recently, there has been a shift in the occurrence of sinus mucormycosis infection, and patients have been identified more often. A dramatic increase in cases of invasive fungal sinusitis, especially mucormycosis, has occurred in the past months, with many patients needing drastic surgical operations to treat this illness [65][66]. The use of steroids to control COVID-19 may be directly related to the suppression in immunity; thus, it also allows the colonization of opportunistic fungi, leading to mucormycosis, during any stages of the disease (**Table 4**) [23].

Table 4. Clinical characteristics of COVID-19 patients reported with mucormycosis.

Co-Morbidity/ DiseaseModels	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
Obesity HT	CT-scan, RT-PCR	None mentioned	Linezolid, meropenem	NA	Died	[67]
Asthma HT DM	CT-scan, RT-PCR	Remdesivir	Amphotericin B	NA	Died	[68]
DM Vascular disease	CT-scan, RT-PCR	Tocilizumab, methylprednisolone, dexamethasone	Amphotericin B	Methylprednisolone, dexamethasone	Died	[69]
HT	CT-scan, RT-PCR	Hydrocortisone	Amphotericin B	Hydrocortisone	Died	[70]
NA	CT-scan, RT-PCR	Remdesivir, tocilizumad, dexamethasone	Amphotericin B	Dexamethasone	Died	[71]
Asthma HT DM	CT-scan, RT-PCR	Remdesivir, dexamethasone	Amphotericin B	Dexamethasone	Died	[72]

Co-Morbidity/ DiseaseModels	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
HT	CT-scan, RT-PCR	HCQ, lopinavir–ritonavir	Amphotericin B	NA	Died	[73]
DM ICM RD	CT-scan, RT-PCR	Meropenem	Amphotericin B	Dexamethasone	Alive	[74]
DM	CT-scan, RT-PCR	NA	Amphotericin B	NA	Alive	[75]
HT, DM	CT-scan, RT-PCR	NA	Liposomal amphotericin B, itraconazole	NA	Alive	[76]
NA	RT-PCR CT-scan	Remdesivir, dexamethasone, metformin, glipizide	Amphotericin B, ceftriaxone	Dexamethasone	Live	[77]
DM	CT-scan, RT-PCR	Meropenem, oseltamivir tocilizumab, sitagliptin/metformin	Amphotericin B	Methylprednisolone, dexamethasone	Died	[69]
DM	CT-scan, RT-PCR	Remdesivir, ceftriaxone, azithromycin, dexamethasone	Voriconazole, liposomal amphotericin B	Dexamethasone	Live	[78]
DM (1 patient) No co-morbidity (1 patient)	CT-scan	Remdesivir, convalescent plasma, vancomycin, piperacillin-tazobactam	Amphotericin B	NA	Live (n = 1) Died n = (1)	[68]
Obesity DM	CT-scan, RT-PCR	Amoxicillin-clavulanate, imipenem/linezolid	Amphotericin B	NA	Died	[79]
DM (n = 8) CRF (n = 3)	CT-scan	Broad-spectrum antibiotics	Liposomal amphotericin B	Dexamethasone	Died (n = 7) Alive (n = 4)	[80]
DM HT (all patients)	RT-PCR	HCQ, glucocorticoids	Systemic antifungals	Glucocorticoids	Died (n = 7) Live (n = 8)	[81]
T2DM (4) T2DM with HT (1) HT (1) Kidney Disease (1)	CT-scan, RT-PCR	Tocilizumab, prednisolone, piperacillin/tazobac, linezolid	Voriconazole	Prednisolone	Died (n = 3) Alive (n = 4)	[82]
DM (21-cases) HT (14-cases) Renal failure (1-case)	CT-scan, RT-PCR	HCQ, azithromycin	Caspofungin	Combination of steroids	All Live	[76]
DM (16)	RT-PCR	Corticosteroids	Liposomal amphotericin B, voriconazole, posaconazole	On Steroid	Alive (n = 10) Died n = (6)	[83]
HT, UTI	CT-scan, RT-PCR	Either dexamethasone or methylprednisolone (7 patients); interferon (2 patient); remdesivir (1 patient); flavipiravir and HCQ (1 patient)	Amphotericin B, posaconazole	Dexamethasone or Methylprednisolone (n = 7)	Live	[84]

Co-Morbidity/ DiseaseModels	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
DM	RT-PCR CT-scan	Remdesivir, levofloxacin, dexamethasone, meropenem, vancomycin, piperacillin/tazobactam	Amphotericin B, posaconazole	Dexamethasone	Live	[85]
No co-morbidity	CT-scan, RT-PCR	HCQ	Amphotericin B	NA	Died	[86]
chronic lymphocytic leukemia DM	RT-PCR	NA	Amphotericin B	NA	Died	[87]
DM HT asthma	RT-PCR	NA	Amphotericin B	No	Died	[88]
AML	CT-scan, RT-PCR	HCQ lopinavir-ritonavir	Amphotericin B	NA	Died	[73]
renal disease	CT-scan, RT-PCR	Remdesivir, vancomycin, cefepime	Liposomal amphotericin B, posaconazole	Dexamethasone	Died	[72]
ICM HF s/p OHT DM HT CKD	RT-PCR	Remdesivir methylprednisolone	Fluconazole	Methylprednisolone, dexamethasone	Died	[89]
No history of any co-morbidity	CT-scan, RT-PCR	Tocilizumab	Liposomal amphotericin B, posaconazole, isavuconazole	Dexamethasone	Live	[90]
DM HT		Piperacillin/tazobactam, HCQ, azithromycinlopin, vir/ritonavir, prednisone Dexamethasone	Liposomal amphotericin B, isavuconazole, posaconazole	Prednisone, Dexamethasone	Live	[91]
HT	RT-PCR	Remdesivir, dexamethasone	Amphotericin B	Dexamethasone	Died	[92]
T2DM (all 6 patients)	CT-scan, RT-PCR	Prednisolone, dexamethasone, methylprednisolone	Amphotericin B, posaconazole	Prednisolone, Dexamethasone, methylprednisolone	All Live	[93]
DM HT	CT-scan, RT-PCR	Remdesivir, interferon-alpha	Systemic antifungals	Systemic corticosteroid	Died	[94]
T2DM, HT (2) T2DM (3)	CT-scan, RT-PCR	Tocilizumab, convalescent plasma, methylprednisolone	Liposomal amphotericin B, posaconazole	Methylprednisolone	Died (n = 2) Alive (n = 3)	[95]
T1DM	CT-scan, RT-PCR	Ceftriaxone, azithromycin, dexamethasone, remdesivir tocilizumab	Amphotericin B	Dexamethasone	Live	[74]
Obesity hypothyroidism	CT-scan, RT-PCR	HCQ, remdesivir, vancomycin, meropenem	Liposomal amphotericin B, posaconazole	Prednisone	Died	[96]
HT Asthma	RT-PCR	Meropenem, remdesivir, dexamethasone	Liposomal amphotericin B	Dexamethasone, prednisolone	Died	[97]

Table 5. Clinical characteristics of COVID-19 patients reported with cryptococcosis and other fungal infections.

2.5. Cryptococcus

Cryptococcus neoformans is also related to a very serious opportunistic infection in immunocompromised patients. It has been reported that *C. neoformans* can infect COVID-19 patients. Mohamad Y et al. described the importance of early suspicion of *C. neoformans* infections in patients with immunocompromised state, considering that Cryptococci patients have a high risk of mortality [98]. In the current perspective, the use of immunosuppressive drugs should be justified and to be alert for infections such as *C. neoformans*, which can cause sepsis and mortality [98]. Studies have shown that almost all patients with COVID-19 having co-infection of *C. neoformans* did not survive, even after treatment with fluconazole and amphotericin B (**Table 5**).

CT: computed tomography; DM: diabetes mellitus; HIV: human immunodeficiency viruses, HT: hypertension; NA: not applicable/available; HCQ: Hydroxychloroquine; RT-PCR: real time-polymerase chain reaction; IHD: ischemic cardiomyopathy.; CKD: chronic kidney disease; AML: acute myeloid leukemia; UTI: urinary tract infections: HF: heart failure; s/p: status post; OHT: orthotopic heart transplant.

Fungal Infection in COVID-19 Infection	Observed Immune Response	Underlying Disease Process	Test/Diagnosis Performed	COVID-19 Treatment	Antifungals Used	Steroids?	Outcome after Treatment	References
	High inflammatory response and immunosuppression	HAT, HBV	CT-scan, RT-PCR	meropenem, vancomycin	Fluconazole	Yes (tacrolimus, prednisone)	Death	[99]
	Acquired immunodeficiency and immunosuppression	HIV	CT-scan, RT-PCR	Tenofovir-DF/ Emtricitabine-atazanavir/ritonavir	Amphotericin B deoxycholate plus fluconazole	No	Death	[100]
Cryptococcus neoformans	High inflammatory response and immunosuppression	Stage IV prostate cancer HT, colon-sigma diverticulosis	CT-scan	No	Fluconazole Amphotericin B plus flucytosine	Dexamethasone	Death	[101]
	High inflammatory response and immunosuppression	HT, DM	NA but COVID19 positive mentioned	Tocilizumab and corticosteroids	Anidulafungin, Amphotericin, flucytosine	Methylprednisolone	Death	[98]
Coccidioidomycosis (*Coccidioides immitis, C. posadasii*)	Impaired cytokine signaling from CD4+ Th1 and cytotoxic CD8+ T-cells among patients	No associated respiratory symptoms & disease	CT scan, Culture, Serology	NR	Liposomal Amphotericin B	No	Alive	[102]
Coccidioidomycosis (*Coccidioides immitis)*	Depressed cellular immunity	Progressive respiratory symptoms, hypoxemia	CT scan, Culture,	Remdesivir	Fluconazole	No	Alive	[103]
	Cytokine release storm	RA	CT scan, Culture, Serology	HCQ, Tocilizumab	Caspofungin, ganciclovir, cefoperazone	Glucocorticoids	NR	[104]
	Functional immune suppression related to $CD4^+$ lymphocytopenia	HIV, progressive hypoxemia	RT-PCR, Culture, Serology, CT	NR	Trimethoprim-sulfamethoxazole	NR	NR	[105]
	Immunocompromised	ARD, DM, HT	RT-PCR, Culture, Serology,	HCQ, Lopinavir-ritonavir	Antifungals and antibacterials	Yes	Some alive and some dead	[106]
Pneumocystis jirovecii	Low CD4 count (35.6%)	HIV	CT, RT-PCR, Multiplex PCR	NR	Co-trimoxazole and oral prednisolone	No	Alive	[107]
	Anemia, lymphopenia, raised C-reactive protein, immunosuppression	HIV	CT, RT-PCR	NR	Co-trimoxazole, IV pentamidine	No	Death	[108]
	Severe depletion of $CD4^+$ cells	HIV	RT-PCR, Culture, CT	Emtricitabine, Ritonavir	Trimethoprim-sulfamethoxazole	No	NR	[109]
	Immunocompetent patient	Recovered from COVID-19	RT-PCR, Culture, CT	Enoxaparin, ceftaroline	Trimethoprim-sulfamethoxazole, methylprednisolone	Yes	Alive	[110]
	Immunocompromised patients	HT, hepatic steatosis, massive lung thromboses	RT-PCR, Culture, CT, Histopathology	Remdesivir	Trimethoprim-sulfamethoxazole, prednisone	Yes	Some alive and some dead	[111]
Saccharomyces cerevisiae (boulardii) (n = 2)	Immunosuppression	HT (first) Diabetes (second)	RT-PCR	Oseltamivir HCQ	Anidulafungin, fluconazole	No treated with Ultra-Levure [preparation of *Saccharomyces cerevisiae* (*boulardii*)]	Both live	[112]
Fusarium proliferatum	Immunocompetent diabetic patient	HAT associated hypothyroidism	RT-PCR	No	Amphotericin B caspofungin	No	Alive	[113]

2.6. Other Fungal Infections

Some other types of fungal infections have also been reported along with COVID-19. This is the case of *Coccidioides immitis* and *Pneumocystis jirovecii* (**Table 5**). Although co-infection with *P. jirovecii* is considered life-threatening, according to recent publications, patients improved clinically when treated with common drugs, such as trimethoprim–sulfamethoxazole [109][110]. Similarly to the other cases, during these co-infections, steroids had a negative impact on COVID-19-associated fungal co-infections conditions [110][111].

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ARD: Acute respiratory disease/distress, CT: Computed tomography, DM: Diabetes mellitus; HIV: human immunodeficiency viruses; HT: Hypertension; IA: Invasive aspergillosis; NA: Not applicable/available; NR: Not reported;

RHAEM: Reconstituted Human Airway Epithelial Model; RA: Rheumatoid arthritis; HCQ: Hydroxychloroquine; RD: Remdesivir; RT-PCR: real time polymerase chain reaction; HBV: hepatitis B virus.

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