Fungal coinfections in COVID-19 patients – Current evidence and future directions

Gouthami Jajapuram*, Subhadra Polisetti, Venugopal Madhusudhana, Vinay Kumar Pandey

Jajapuram G, Polisetti S, Madhusudhana V, et al. Fungal coinfections in COVID-19 patients – current evidence and future directions. J Exp Clin Microbiol. 2022;6(3): 52-57.

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for the ongoing pandemic named Coronavirus Disease (COVID-19). COVID-19 patients, especially those who are severely ill or immunosuppressed, are more prone to invasive fungal infections. Early detection is mandatory in COVID-19 patients with invasive mycoses, which can be done through comprehensive diagnostic intervention to ensure effective treatment.

In this review, we have discussed the importance of evaluating coinfections associated with COVID 19, the types of invasive mycoses, different methods of diagnosis, clinical settings, and the importance of standard treatment in patients with COVID-19. The current article aims to help clinicians manage aspergillosis, candidiasis, mucormycosis, and cryptococcosis in patients with COVID-19.

Key Words: *Fungal coinfection; Aspergillosis; Candidiasis; Mucormycosis; COVID-19; SARS-CoV-2*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for the ongoing pandemic named Coronavirus Disease (COVID-19) [1]. SARS-CoV-2 is a single-stranded Ribose Nucleic Acid (RNA) virus that infects the lower respiratory tract and even has the ability to cause severe or sometimes fatal Novel Corona Virus-Infected Pneumonia (NCIP) [2]. SARS-CoV-2 virus supposedly originated from bats and later spread to humans via an intermediate animal, which has spread globally after the Wuhan epidemic (China) [3]. Globally, it has spread to more than 223 countries, confirmed more than 178 million cases, and reported more than 3.8 million deaths [4]. India is the second most impacted country in the world, next to the United States, with approximately 33 million confirmed COVID-19 cases and 4.4 lakh deaths as of September 2021 [5]. COVID-19 is transmitted not only due to large droplets produced at the time of coughing and sneezing by the symptomatic patients but can also transmit from asymptomatic patients prior to the onset of symptoms. Coronavirus has undergone several mutations that have increased its virulence [6].

Several studies have demonstrated that the nasal cavity had greater viral loads than the throat, without any difference in viral burden between the symptomatic and asymptomatic patients. Patients continue to be infectious until the symptoms persist and even after clinical recovery [7].

People across all age groups are at risk of this virus. Clinical presentations can vary among individuals ranging from symptomless to Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction. The most common clinical manifestations include fever, cold, cough, sore throat, headache, fatigue, loss of taste and smell, diarrhea, breathing difficulty, and myalgia, along with conjunctivitis (as reported in some patients). The average time from the onset of symptoms to breathing difficulty is 5 days, hospitalization is 7 days, and acute respiratory distress is 8 days. The average duration of hospitalization is ten days, as the recovery of patients is generally seen from the second to the third week. Other complications include Acute Respiratory Distress Syndrome (ARDS), acute lung injury, acute kidney injury, and shock [8].

In patients under COVID treatment, respiratory tract infections, especially fungal infections, have become a life-threatening concern. Many bacteria have been reported as possible co-pathogens like *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophilia*, and similarly many viruses, like the influenza virus, non-SARS-CoV-2 coronavirus, rhinovirus/enterovirus, parainfluenza, respiratory syncytial virus, and meta pneumo virus, have been found as co-pathogens in COVID-19 patients. The fungal coinfection is mainly caused by Candida, *Aspergillus*, *Cryptococcus*, and Mucorales [9].

The fungal coinfections were primarily observed in the critical COVID 19 patients treated in the Intensive Care Unit (ICU) with obligatory mechanical ventilation or prolonged hospital stays [10]. Therefore, it is essential to note that patients with COVID-19 can progress to further fungal infections during the advanced stages of the disease, especially steroid-induced immunosuppression. COVID-19 patients reported damaged alveoli with severe inflammatory exudation, along with immunosuppression with decreased CD4 + T and CD8 + T cells [11].

Aspergillus and Candida are the primary pathogens for fungal coinfections in severe COVID-19 patients. Mucor and *Cryptococcus* are other infrequent opportunistic fungal pathogens that cause upper respiratory tract infections in these patients [11].

Covid 19 associated candidiasis (both superficial and invasive) varies by country and region. Studies from Spain, India, Iran, Italy, the UK, and China have reported rates of 0.7% (7/989), 2.5% (15/596), 5% (53/1059), 8% (3/43), 12.6% (17/135), and 23.5% (4/17), respectively [12].

The prevalence of mucormycosis varied from 0.005 million to 1.7 per million population globally, while in India, its prevalence is nearly (0.14 cases per 1000 population), which is 80 times higher than in developed countries from 2019 to 2020. 50 % of non-surviving COVID-19 patients are diagnosed with Secondary infection [13].

In a prospective, multicenter, cohort evaluation of intensive care patients (n=135), White et al [14]. reported an incidence of 26.7% (aspergillosis 14.1%, and yeast 12·6%) invasive fungal disease in patients with COVID-19. The overall mortality rate was 38%. (p = 0.0387); out of which 53% patients were with the fungal disease, and 31% patients were without fungal infection. A higher risk of invasive fungal disease was reported in patients with corticosteroid therapy and a history of chronic pulmonary disease. A retrospective, multicenter cohort study was conducted by Zhou et al. and reported that out of 191 patients, 56 patients did not survive [15].

The current review is aimed to estimate the relation between fungal coinfection and COVID 19. These findings may help understand the steps to be followed in the future management of patients with COVID-19.

Diagnostic approach to fungal coinfections in covid-19

Patients with COVID-19 are considered to have a severe disease if they have oxygen saturation (SpO2) <94% and a respiratory rate >30 breaths/

Department of Medical Affairs THB c/o Sekhmet Technologies Pvt Ltd., Gurugram, Haryana, India

Correspondence: Gouthami Jajapuram, Department of Medical Affairs THB c/o Sekhmet Technologies Pvt Ltd., Gurugram, Haryana, India Email: gouthami@thb.co.in

Received: 28-Apr -2022, Manuscript No. Puljecm-22-4876; Editor assigned: 2-May-2022, PreQC No. Puljecm-22-4876 (PQ); Reviewed: 16-May-2022, QC No. Puljecm-22-4876 (Q); Revised: 18-May- -2022, Manuscript No. Puljecm-22-4876 (R); Published: 25-May-2022, DOI:10.37532/52-59.

to understand the epidemiology of fungal infections. The surveillance includes etiological (direct microscopy and culture, histopathology) and serological examination (serology antigen and antibody, (1,3)-β-D-Glucan (BDG) and Galactomannan (GM) detection by serum) in suspicious patients. At the same time, Tracheal Aspirate (TA) and Bronchoalveolar Lavage Fluid (BALF) sampling (for culture and biomarker testing) should be evaluated under well-protected conditions as there is a significant risk of aerosol spread and infections among health care workers. To identify the pathogens, Polymerase Chain Reaction (PCR)-based methods, real-time polymerase chain reaction techniques, and molecular identification methods can be executed [17].

Recently, High-Resolution Computed Tomography (HRCT) of thorax has gained importance in the early detection of the wide-ranging features of this dreadful condition if a follow-up scan for COVID-19 patients is undertaken in about ten days or as per protocol or HRCT undertaken in patients with a chest infection and breathlessness with pre-existing risk factors and co-morbidities during this pandemic situation.

Invasive Aspergillosis

More attention should be paid to *Aspergillus* among these co-pathogens in patients with COVID-19, as Invasive Pulmonary Aspergillosis (IPA) is challenging to diagnose and can be associated with high morbidity and mortality. Severe influenza patients with co-IPA have been recently reported in Taiwan, Belgium, China, and Netherland [9].

Use of glucocorticoids, Chronic Obstructive Pulmonary Disease (COPD), prolonged neutropenia, Hemopoietic Malignancy (HM), Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT), Cystic Fibrosis (CF), inherited immune deficiencies, Solid Organ Transplant (SOT), etc. are the potential risk factors for the patients [17].

If the weekly serum galactomannan or (1-3)-β-D-glucan is positive, routine periodical sampling is required to investigate clinical deterioration. Antigen or PCR testing on Broncho Alveolar Lavage (BAL) fluid, *Aspergillus* culture to be performed [18].

Chong and Neu (2021) had performed a literature search through various databases on 1421 patients with COVID-19; the overall COVID-19 Associated Pulmonary Aspergillosis (CAPA) was 13.5%. The CAPA mortality rate was high (48.4%) even though antifungal agents were used [19].

Studies reported in a local hospital (Zhu et al.) in China, from 22 January 2020 to 2 February 2020, showed that 23.3% (60/243) of patients with COVID-19 had coinfection with *Aspergillus*. Pulmonary *aspergillosis* was seen in all COVID-19 patients ranging from asymptomatic to critical COVID-19. Two studies were also reported with co-IPA 20.6% (7/34) among patients with COVID-19 requiring ICU admission in Belgium and 19.6% (6/31) in the Netherlands. Alanio et al [20] reported that the incidence of IPA associated with COVID-19 among patients whet o are mechanically ventilated was 33.3% (9/27) in France [20-22].

A retrospective analysis was conducted by using medical data of patients worldwide from Italy, France, Spain, Germany, Netherlands, United Kingdom, Pakistan, Belgium, Mexico, Brazil, Switzerland, Denmark, Qatar, Argentina, Australia, Austria, and Ireland, diagnosed with SARS-CoV-2 from 1 March 2020 to 31 August 2020. Salmanton-García et al [23]. anticipated that treatment of SARS-CoV-2 with tocilizumab or dexamethasone could worsen the immune system. Hence, there was a risk of superinfection of fungus among the patients with COVID-19. They had gathered data from 186 patients who suffered from COVID-19 -Associated Pulmonary Aspergillosis (CAPA) worldwide. Out of which 182 patients were admitted to the Intensive Care Unit (ICU). An average of 10 days after Coronavirus diagnosis, CAPA was identified. Aspergillus fumigatus was identified in 80.3% of patient cultures, out of which 4 were identified as azole resistant. 52.7% of patients received voriconazole at a loading dose of 6 mg/kg for every 12 hours on day one and then at 4 mg/kg for every 12 hours on day two, and then switched to an oral dose of voriconazole at 200 mg twice daily. The number of patients who expired was 52.2% (92), of which 33.0% of deaths were due to CAPA. It was noted that the cumulative incidence of CAPA ranged from 1.0%-39.1% in ICU patients. After a diagnosis of CAPA, patients who survived were treated for an average period of 40 days [23].

A 62-year-old man survived severe COVID-19 pneumonia after receiving supplemental oxygen and methylprednisolone intravenously for 6 days. The patient reported altered behaviour, slurring of speech, and left-side weakness 10 days following the discharge. MRI of the brain revealed a thick-walled peripherally enhancing lesion in the right parietal lobe and was confirmed as a fungal brain abscess. Biopsy from cavitary lung lesion and the purpose culture revealed *Aspergillus* infection. He was started on intravenous antibiotics, vancomycin, voriconazole, and subcutaneous enoxaparin, and finally, craniotomy with excision of the brain abscess was done. The predisposing factors could be suppression of the immune system by COVID-19, comorbidities, steroids, and hospital-acquired infections. However, it is phenomenal to develop fungal brain abscess after COVID-19 without sinonasal and orbital diseases. Various diseases ranging from allergic reactions to invasive lung infections and other organ diseases can be caused by *Aspergillus* depending on the host immune status [24].

Several studies have been carried out on mycological criteria and Galactomannan index positivity in BAL, such as positive *Aspergillus* or positive culture PCR in BAL fluid, as discussed in the mycological studies in the Table 1.

The other studies frequently reported using galactomannan index and culture in BAL samples of COVID-19 patients (Table 1). A high proportion of patients with positive galactomannan and PCR in BAL were reported. The ratio of positive *Aspergillus spp*. (found in culture) was lower than detected using galactomannan [18].

Triazoles (itraconazole, posaconazole, voriconazole, posaconazole), amphotericin B, and its liposomal formulation are the drugs advised for the treatment and prophylaxis of IA. [17]. Echinococcins (carpofenjing or micafungin) can be considered in voriconazole resistant patients [17].

Invasive Candidiasis (IC)

Candida auris is an emergent fungus which can burst severe infections in coronavirus disease. From the beginning of the COVID-19 pandemic, C. auris had been reported in COVID-19 units of acute care hospitals. These changes are mainly due to the sudden changes in infection control procedures, disinfection practices, and inadequate availability of gloves gowns or using them again during the COVID 19 pandemic. An increase in undetected transmission of C. auris cases had been observed without links to known cases in multiple states [30].

Blood cultures and other samples collected under sterile conditions are used to diagnose IC, which is considered hygienic, the gold standard. Diagnostic methods other than culture include mannan and antimannan IgG tests. Recent advances in clinical practice, such as C. *Albicans* Germ Tube Antibody (CAGTA), 1,3-Beta-D-Glucan (BDG), and PCR-based assays, are used as adjuncts to cultures [17].

Nucci et al [31]. (2021) compared the incidence of candidiasis in 2 intervals: from January 2019 to February 2020 (interval 1) and from March 2020 to September 2020 (interval 2) in a tertiary care hospital. They observed that 41 patients were identified with candidiasis, out of

TABLE 1. Mycological studies.

First Author	Number of ICU Patients	Number of Patients BAL Fluid Available (%)	N Patients GM Positive in BAL (%)	N Patients with Culture Positive in BAL (%)	N Patients with PCR Positive in BAL (%)	Reference
Razazi	90	58 (64.4)[b]	not performed	4 (16.7)	16/81 (19.8)[d]	[25]
Fekkar	260	145(55.7)	11/333 (3.3)[a]	255/474 (53.8)[a]	17/449 (3.8)[a]	[26]
Gangneux	45	-	not performed	9 (20)[c]	13/45 (28.8) [c]	[27]
Bartoletti	163	108 (66.3)	30 (27.7)	20 (18.5)	26/67 (38.8)[d]	[28]
Dellière	246	80 (32.5)	8 (10.0)	17 (15.7)[c]	-	[29]

a Instead of the number of patients with BAL, details on the number of positive samples from all respiratory samples were available.

b BAL only in 3 patients, in 55 patient's procedure was through the protected telescope,

c % was calculated among all respiratory samples among BAL samples only,

d % was calculated among performed PCR in BAL samples (since PCR was not performed in all BAL samples).

which 16 were in the first interval and 25 in the second interval. In the second interval, the candidemia incidence was 4.76 (per 1000 admissions), considering only candidemia cases in patients without COVID-19. If they consider only candidemia cases in patients with COVID-19, the incidence was 2.68. If only admissions of patients with COVID-19 were considered, the incidence was 14.80. The most common causative agent of candidiasis was *Candida albicans* (41.5%). The incidence of candidemia in the first and second intervals (per 1000 admissions) was 1.54 and 7.44, respectively (P<.001). Ten patients died before the diagnosis of candidiasis and did not receive treatment. The mortality rate in the whole group was found to be 61.0% (51.6% in patients who received treatment) in the span of 30 days [31].

A retrospective analysis of mortality related to bloodstream infection in COVID-19 patients was conducted in Oman by Al-Hatmi AM et al. (2021) [32]. Study reported that 5 patients were diagnosed with invasive candidiasis by the positive blood culture, out of which 4 patients had received antifungal therapy that includes caspofungin [2], caspofungin + amphotericin B [1]. and voriconazole + caspofungin [1]. Despite the antifungal therapy, 3 out of 5 patients did not survive. The study suggested that critically ill patients with COVID-19 are at greater risk of developing coinfection with Candida, increasing the mortality rate. Hence, the need for early diagnosis of candidemia and proper antimycotic therapy is required in severely ill patients with COVID-19 [32].

Echinocandins are considered the first line of drugs for invasive Candida infections, followed by liposomal amphotericin B, fluconazole, and voriconazole, while isavuconazole and posaconazole are considered as the second line alternatives. Triterpenoid ibrexafungerp, rezafungin, fosmanogepix are the novel antifungal drugs that are likely for the treatment of invasive candida infections in the near future [12].

Invasive Mucormycosis

Mucormycosis also known as "Black fungus," is a subacute, chronic, rapidly progressive infection caused by fungi that belongs to the order Mucorales of class Zygomycetes [33]. Pansinusitis, rhino-orbital sinusitis or rhino-cerebral sinusitis, cutaneous, pulmonary, and gastrointestinal are the variable clinical presentations of mucormycosis [34]. This disease mainly affects immunocompromised patients with severe comorbidities like Solid Organ Transplantation (SOT) or Hematopoietic Stem Cell Transplantation (HSCT), hematologic malignancies (HM), severe trauma or burns, and uncontrolled diabetes mellitus [35].

Although it is a less common disease, its consequences are very severe, with a high mortality rate of 20%-50% if localized and 70%-90% in cases of widespread disease [36]. India witnessed an outbreak of this fungal disease in COVID -19 patients who have recovered, especially in patients with uncontrolled diabetes [37]. 'Black fungus' Diabetes patients are not only affected by the long-term use of corticosteroids, but a short course of corticosteroids can also cause several invasive fungal infections, including mucormycosis and aspergillosis [13]. India had reported 82 cases (81.2%) of mucormycosis in COVID-19 patients in a systemic review of literature conducted until May 13,2021 [13].

In an observational, prospective study conducted at a tertiary care center on 23 patients with mucormycosis from August 2020 to December 2020, all associated with COVID 19. Ethmoid sinuses are the most common sinuses affected (100%). An intra-orbital extension was reported in 43.47% of cases, and only 8.69 % of cases had reported the intracranial extension. Most of the cases present are diabetic (21 of 23), and some had uncontrolled glucose levels (12). The study reported that all these patients are treated with steroids during their coronavirus infection treatment [38]. In Surat city (India), 40 cases were reported, out of which eight patients lost their eyesight in 15 days due to mucormycosis [39]. Studies conducted in India in 2020-2021 among patients diagnosed with COVID 19 and mucormycosis, and their clinical characteristics and management are summarised in **Table 2**.

Association of covid-19 and mucormycosis with rapid orbital apex syndrome in a non-ketotic diabetic patient with brain infarction was reported in India, which is very rare. Treatment included an emergency functional endoscopic sinus procedure followed by conventional amphotericin B and antibiotics for one week that showed an improvement in mucosal thickening and sinusitis [40].

Fast and aggressive treatment is needed for mucormycosis. Pharmacological treatment includes amphotericin B and its lipid formulations, posaconazole, isavuconazole, and combination therapy of amphotericin B + echinocandin [36]. Most effective treatment for mucormycosis is the Surgical debridement of necrotic tissues. When compared to antifungal monotherapy, antifungal agents along with surgical debridement had shown a better improvement in the survival of the

TABLE 2

Summary of clinical characteristics and management of sars-cov-2 and mucormycosis coinfection patients in indian studies 2020-2021.

First Author,	The duration between diagnosis of SARS-CoV-2 and mucormycosis (days)	Surgical debridement done	Treatment with Antifungal agents	The outcome of the treatment	References
Maini et al.	18	Yes	Amphotericin B, fluconazole	Survived	[41]
Moorthy et al.	NA	Yes (n = 7)	Amphotericin B	Survived (n = 11), died (n = 6), and lost to follow-up (n = 1)	[42]
Rao et al.	NA	Yes	Amphotericin B	Survived	[43]
Saldanha et al.	NA	Yes	Amphotericin B	Survived	[44]
Sarkar et al.	NA	Yes	Amphotericin B	Improved (n = 1), died (n = 4), unchanged (n = 4), exenteration (n = 1)	[45]
Arjun et al.	17.0 ± 3.6	Yes	Amphotericin B deoxycholate and isavuconazole	10% died	[46]
Joshi et al.	Not indicated	Yes, in 10 (45%)	Amphotericin	14 (63%) died	[47]
Garg et al.	17	Scheduled for right upper lobectomy	Amphotericin B	Survived	[48]
Mehta et al.	10	Yes	Amphotericin B	Died	[49]
Singh et al.	19	Yes	Liposomal amphotericin B	Recovered	[50]
Sen et al.	10–15	56% had functional endoscopic sinus surgery (FESS)/paranasal sinus (PNS) debridement, 15% orbital exenteration in 15%, 17% both FESS/PNS debridement and orbital exenteration	Amphotericin B in 73%	Mortality 14%	[51]
Revannavar et al.	NA	Yes	Amphotericin B	Survived	[40]
Baskar et al.	On diagnosis	Yes	Amphotericin	Recovered	[52]
Sharma et al.	NA	Yes	Amphotericin B	Survived (n = 23)	[38]
Sen et al.	Mean ± SD (minimum-maximum), 15.6 ± 9.6 (3–42)	Yes	Amphotericin B, voriconazole/ posaconazole (n = 5)	Survived (n = 5)	[53]
Ravani et al.	NA	Yes (n = 19)	Amphotericin B (n = 19)	Survived (n = 18), died (n = 1)	[54]
Jain et al.	15	Yes	NA	Recovered	[55]
Saidha et al.	NA	Yes	Amphotericin	Recovered	[56]

of the patients.

Hyperbaric Oxygen Pressure (HBO) prevents the growth of the fungus and improves the wound healing rate. Hence, HBO treatment has been suggested as a supportive therapy with and antifungal and surgical therapy for mucormycosis. Diabetic patients with sinusitis or cutaneous mucormycosis are recommended for HBO therapy [36].

A positive case of COVID-19 based on positive RT-PCR and CT of the lungs in a 59-year-old non-diabetic male patient had developed rhino-facial mucormycosis after corticosteroid treatment. Several days after discharge, the patient had a nasal obstruction and left side facial and orbital swelling. A nasal biopsy after the debridement revealed wide hyphae without septa. The sequenced PCR product revealed *Rhizopus oryzae*. Despite all medical and surgical treatment, the patient died [57].

Invasive Cryptococcosis

Cryptococcosis is another opportunistic infection caused by *Cryptococcus neoformans* and *Cryptococcus gattii* [30]. It predominantly presents as meningoencephalitis in COVID-19 patients with comorbidities such as Human Immunodeficiency Virus (HIV) infection (accompanied by CD4+T-lymphocyte count < 200 cells/μL), Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT), and Solid Organ Transplant (SOT), or other immunosuppressive patients who are susceptible to cryptococcosis[17].

Cryptococcosis mainly affects the lungs and central nervous system. A combination of clinical and laboratory confirmation is recommended for the diagnosis of cryptococcosis. Serology, culture, histopathology, direct microscopy, and molecular detection are the different methods used to confirm the Cryptococcosis infection. Molecular detection of *Cryptococcus* comes into action when other diagnostic tools have failed to confirm a diagnosis. The molecular methods included are the pan-fungal polymerase chain reaction (PCR), DNA sequencing for identification, isothermal amplification method, probe-based microarrays, and multiplex PCR. Cerebrospinal fluid (CSF) examination and lumbar puncture are required once a diagnosis of cryptococcosis is made.

A positive case of COVID 19 in ascitic fluid from a patient with a kidney transplant was reported by Passarelli et al [58]. with COVID-19 and decompensated cirrhosis. The patient had developed fungemia due to *Cryptococcus neoformans*. Another case of cryptococcemia was reported by Khatib et al [59]. (2021) in a COVID-19 patient treated with tocilizumab. After analysis, it is concluded that the clinicians should maintain equilibrium between the utilization of tocilizumab and immunosuppressant drugs for COVID-19 patients to avoid the development of infections such as cryptococcemia.

A 76 year old patient survived the respiratory failure (severe COVID-19 pneumonia) after receiving drugs remdesivir, convalescent plasma, corticosteroids, and tocilizumab. The patient reported multifocal ischemic strokes and acute encephalopathy following the discharge. Blood cultures and CSF were positive for Cryptococcus neoformans. Treatment was switched to enteral fluconazole monotherapy after administration of IV amphotericin B and flucytosine for three weeks. Later the CSF fungal culture showed no growth. Cryptococcal meningoencephalitis should be considered in the differential diagnosis of encephalopathy (COVID-19 patients). High-dose steroids with tocilizumab may be predisposing factors [60]. Amphotericin B and its liposomes, 5- flucytosine, and fluconazole are recommended for the treatment and prophylaxis of cryptococcosis [61].

Similarly, a 76-year- old diabetic male patient tested positive for COVID-19 and survived after receiving antifungal therapy even before evident endoscopic findings appeared. The patient reported mild left-sided cheek swelling and remarkably dropped left angle of mouth 15 days after the discharge. On neurological examination, the left maxillary antrum revealed mild fullness of the pre-maxillary fat planes with mucosal thickening and localized signs of invasive fungal sinusitis without orbital or intracranial complications. He went through endoscopic debridement a few days later, and he had an incredible result with no progressive or critical morbidities [62].

DISCUSSION

COVID-19 patients were reported with reduced lymphocyte count, which consequently affects cell-mediated immune response by decreasing CD4 and CD8 T cells, indicating that SARS CoV-2 consumes immune cells and finally inhibits the cellular immune function. Therefore, susceptibility to coinfections was markedly increased by the immune dysregulation, which was identified in most of the COVID-19 expired patients. The duration of hospital stay was increased significantly because of the presence of coinfections [63]. Haematological and biochemical differences were also caused by coinfections deteriorating the well-being state of the patient. Candida species were observed to be the most prevalent pathogen in critically ill patients. It is hard to differentiate between infection and colonization as it might be a human microbiota [63]. Many interventions that benefit the co-infection are observed in Severe COVID-19 patients (for instance, mechanical ventilation, corticosteroids, broad-spectrum antibacterial, central venous

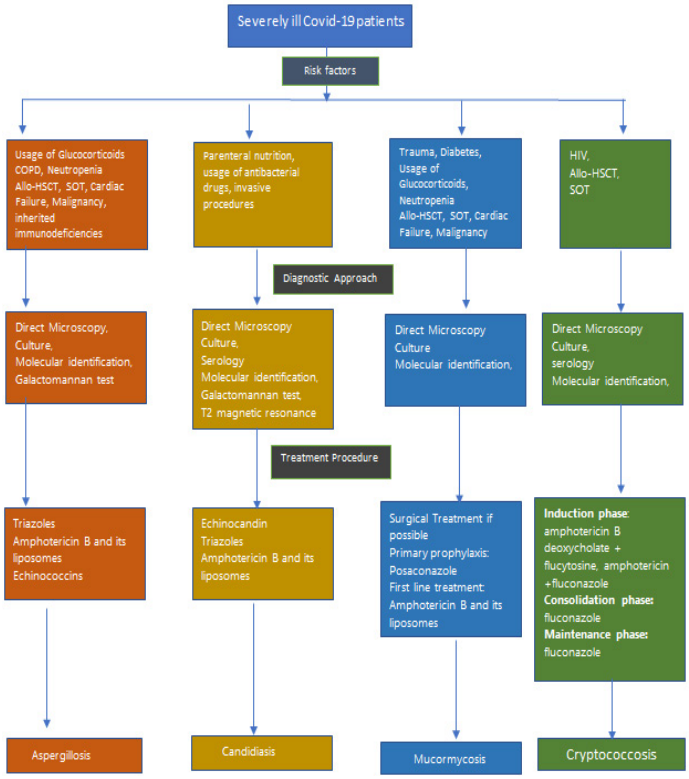

Figure 1: Diagnostic and therapeutic pathway for fungal co-infection with COVID-19.

catheter, and parenteral nutrition) [63]. Additionally, patients with different comorbidities like cardiovascular disease, diabetes, and obesity are at high risk of mortality due to co-infections. Thus, screening for early identification of co-infections in high-risk patients is essential to determine the appropriate interventions to decrease the rate of mortality [63].

These coinfections could be detected by culture from sputum and Bronchoalveolar Lavage (BAL) samples, multiple RT-PCR from the sputum or nasopharyngeal swab samples, or serological fungal antigen tests. For the appropriate treatment of critically ill COVID 19 patients, proper diagnosis and essential tests are mandatory [64].

The below clinical flow chart may assist the clinicians in the treatment of aspergillosis, candidiasis, mucormycosis, or cryptococcosis in patients with COVID-19 by summarizing the risk factors, diagnostic approaches, and their treatments (Figure 1) [17].

CONCLUSION

Fungal coinfection is more prevalent in COVID-19 patients and is accompanied by immunocompromised states, such as uncontrolled diabetes, cardiovascular diseases, and obesity. This review article summarises fungal coinfections associated with COVID-19, clinical settings, latest diagnostic techniques (histopathology, direct microscopic examination, culture, (1,3)-β-D-glucan, galactomannan, PCR-based assays, and standard treatment recommendations. This article aims to assist clinicians in managing diseases caused by aspergillosis, candidiasis, mucormycosis, and cryptococcosis (in COVID-19patients).

REFERENCES

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
2. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020 Apr;76:71-76.
3. Wang Chen, Horby Peter W, Hayden Frederick G,et al. A novel coronavirus outbreak of global health concern. The Lancet. 2020;395(10223):470-473.
4. Cascella M, Rajnik M, Aleem A, et al. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls. 2022,5 Feb.
5. Available from: https://covid19.who.int/region/searo/country/in
6. Rothe Camilla, Schunk Mirjam, Sothmann Peter, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. New Eng J Med. 2020;382(10):970-971.
7. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;(382):1177-1179.
8. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020 Apr;87(4):281-6.
9. Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: A literature review. J Microbiol Immunol Infect. 2021 Feb;54(1):46-53.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med.2020;8(5):475-81.
11. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19) a multi-center study in Wenzhou city Zhejiang China. J Infect. 2020;80(4):388-393.
12. Arastehfar A, Carvalho A, Nguyen MH, et al. Covid-19-associated candidiasis (CAC): an underestimated complication in the absence of immunological predispositions? Journal of Fungi. 2020 Dec;6(4):211.
13. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021;5(4): 102146.
14. White L, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis. 2020;73(7):1634-1644.
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.The lancet. 2020 Mar 28;395(10229):1054-1062.
16. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Patients%20with%20COVID%2D19%20are,may%20experience%20rapid%20clinical%20deterioration. Accessed on 30/5/19.
17. Song G, Liang G, Liu W. Fungal coinfections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia. 2020 Aug;185(4):599-606.
18. Yusuf E, Seghers L, Hoek RA, et al. *Aspergillus* in Critically Ill COVID-19 Patients: A Scoping Review. Journal of Clinical Medicine. 2021;10(11):2469.
19. Chong WH, Neu KP. The incidence, diagnosis, and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. J Hosp Infect. 2021;113:115-129.
20. Alanio A, Delliere S, Fodil S, et al. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med. 2020;8(6):48-49.
21. Rutsaert L, Steinfort N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. An Intensive Care. 2020;10:71.
22. Van Arkel ALE, Rijpstra TA, Belderbos HNA, et al. COVID-19 associated pulmonary aspergillosis. Am J Respir Crit Care Med. 2020;202(1):132-135.
23. Salmanton-García J, Sprute R, Stemler J, et al. COVID-19–associated pulmonary aspergillosis, March–August 2020. Emerg Infect Dis. 2021;27(4):1077-1086.
24. Gupta V, Singh P, Sukriti K. Fungal brain abscess in a post-COVID-19 patient. BMJ Case Reports CP. 2021;14(9):246319.
25. Razazi K, Arrestier R, Haudebourg AF, et al. Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to Coronavirus 19 disease. Critical Care. 2020;24(1):1-1.
26. Fekkar, A, Lampros A, Mayaux J, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Respir Crit Care Med. 2021;203(3):307-317.
27. Gangneux JP, Reizine F, Guegan H, et al. Is the COVID-19 pandemic a good time to include *Aspergillus* molecular detection to categorize aspergillosis in ICU patients? A monocentric experience. J Fungi. 2020;6(3):105.
28. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis. 2021 Dec 6;73(11):3606-3614.
29. Dellière S, Dudoignon E, Fodil S, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect. 2021 May 1;27(5):790-e1.
30. Available from: https://www.cdc.gov/fungal/covid-fungal.html accessed on 28/5/21.
31. Nucci M, Barreiros G, Guimarães LF, et al. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses. 2021 Feb;64(2):152-156.
32. Al-Hatmi AM, Mohsin J, Al-Huraizi A, et al. COVID-19 associated invasive candidiasis. Journal of Infection. 2021 Feb1;82(2):45-46.
33. Kwon-Chung KJ. Taxonomy of fungi causing mucormycosis and entomophthoramycosis (zygomycosis) and nomenclature of the disease: Molecular mycologic perspectives. Clini Infect Dis. 2012;54(1): S8-S15.
34. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis. 2005,1;41(5):634-653.
35. Legrand M, Gits-Muselli M, Boutin L, et al. Detection of circulating Mucorales DNA in critically ill burn patients: Preliminary report of a screening strategy for early diagnosis and treatment. Clin Infect Dis. 2016 Nov 15;63(10):1312-1317.

36. Sipsas NV, Gamaletsou MN, Anastasopoulou A, et al. Therapy of mucormycosis. J Fungi. 2018 Sep;4(3):90.

37. Explained: 'Black fungus' in Covid-19 patients: https://indianexpress.com/article/explained/mucormycosis-in-covid-patients-fungal-infections-7308721/ Accessed on 10/05/2021.

38. Sharma S, Grover M, Bhargava S, et al. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021 May;135(5):442-447.

39. Dyer O. Covid-19: India sees record deaths as "black fungus" spreads fear. Brit Med J. 2021;(373):1238.

40. Revannavar SM, Supriya PS, Samaga L, et al. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? BMJ Case Reports CP. 2021 Apr1;14(4):e241663.

41. Maini A, Tomar G, Khanna D, et al. Sino-orbital mucormycosis in a COVID-19 patient: A case report. Int J Surg Case Rep. 2021 May 1;(82):105957.

42. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, Uncontrolled Diabetes and Corticosteroids—An Unholy Trinity in Invasive Fungal Infections of the Maxillofacial Region? A Retrospective, Multi-centric Analysis. J Maxillofac Oral Surg. 2021 Mar;6(20):418-425.

43. Rao R, Shetty AP, Nagesh CP. Orbital infarction syndrome secondary to rhino-orbital mucormycosis in a case of COVID-19: Clinico-radiological features. Indian J. Ophthalmol. 2021 Jun 1;69(6):1627-1630.

44. Saldanha M, Reddy R, Vincent MJ. Paranasal mucormycosis in COVID-19 patient. Indian J Otolaryngol Head Neck Surg. 2021Apr22:1-4.

45. Sarkar S, Gokhale T, Choudhury SS, et al. COVID-19 and orbital mucormycosis. Indian J Ophthalmol. 2021 Apr;69(4):1002.

46. Arjun R, Felix V, Niyas VK, et al. COVID-19-associated rhino-orbital mucormycosis: a single-centre experience of 10 cases. QJM: Intl J Med. 2021;1:4.

47. Joshi AR, Muthe MM, Patankar SH, et al. CT and MRI findings of invasive mucormycosis in the setting of covid-19: experience from a single censer in India. AJR Am J Roentgenol. 2021 Dec;217(6):1431-1432.

48. Garg D, Muthu V, Sehgal IS, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia. 2021 Feb 5:1-0.

49. Mehta H, McLaughlin SK, Lawrence L, et al. Henoch-Schönlein Purpura-Associated Hemorrhagic Shock After Secondary Norovirus Infection. Cureus.2020Nov 23;12(11):11653.

50. Singh RP, Gupta N, Kaur T, et al. Rare case of gastrointestinal mucormycosis with colonic perforation in an immunocompetent patient with COVID-19. BMJ Case Rep. 2021 Jul 2;14(7):244096.

51. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India–Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol. 2021 Jul 1;69(7):1670-1692.

52. Baskar HC, Chandran A, Reddy CS, et al. Rhino-orbital mucormycosis in a COVID-19 patient. BMJ Case Reports. 2021 Jun 1;14(6):244232.

53. Sen M, Lahane S, Lahane TP, et al. Mucor in a viral land: a tale of two pathogens. Indian journal of ophthalmology. 2021 Feb;69(2):244.

54. Ravani SA, Agrawal GA, Leuva PA, et al. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol. 2021 Jun 1;69(6):1563-8.

55. Jain M, Tyagi R, Tyagi R, et al. Post-COVID-19 Gastrointestinal Invasive Mucormycosis. Indian J Surg. 2021 Jun 22:1-3.

56. Saidha PK, Kapoor S, Das P, et al. Mucormycosis of Paranasal Sinuses of Odontogenic Origin Post COVID19 Infection: A Case Series. Indian J Otolaryngol Head Neck Surg. 2021;(17):1-5.

57. Mohammadi F, Badri M, Safari S, et al. A case report of rhino-facial mucormycosis in a non-diabetic patient with COVID-19: a systematic review of the literature and current update. BMC Infect Dis. 2021 Dec;21(1):1-7.

58. Passarelli VC, Petosa AH, de Souza Luna LK, et al. Detected SARS-CoV-2 in ascitic fluid followed by cryptococcemia: a case report. SN Compr Clin Med. 2020 Nov;2(11):2414-2418.

59. Khatib MY, Ahmed AA, Shaat SB, et al. Cryptococcemia in a patient with COVID-19: A case report. Clin Case Rep. 2021 Feb;9(2):853-855.

60. Thota DR, Ray B, Hasan M, et al. Cryptococcal meningoencephalitis during convalescence from severe covid-19 pneumonia. Neurohospitalist. 2022 Jan;12(1):96-99.

61. Spadari CD, Wirth F, Lopes LB, et al. New approaches for Cryptococcosis treatment. Microorganisms. 2020 Apr;8(4):613.

62. Samir A, Abdel-Gawad MS, Elabd AM, et al. Early CT and MRI signs of invasive fungal sinusitis complicating COVID-19 infection: case report. Egypt J Otolaryngol. 2022 Dec;38(1):1-5

63. Silva DL, Lima CM, Magalhães VC, Baltazar LM, Peres NT, Caligiorne RB, et al. Fungal and bacterial coinfections increase mortality of severely ill COVID-19 patients. J Hosp Infect. 2021 Jul;(113):145-154.

64. Yang S, Hua M, Liu X, et al. Bacterial and fungal coinfections among COVID-19 patients in intensive care unit. Microbes Infect. 2021 May-Jun;23(4-5):104806.