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# Effects of fungal infections associated with COVID-19 in pandemic era

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**Abstract**

Fungal infections such as endemic mycoses, pneumocystosis, candidiasis, aspergillosis, mucormycosis and cryptococcosis associated with COVID-19 are becoming complicated in management and diagnosis of critical ill COVID-19 patients. However, mortality rates due to fungal infections are significantly high. The purpose of this study is to evaluate the effect of fungal infections associated with COVID-19 during the pandemic era. A systemic literature review was carried out to evaluate the effect of fungal infections associated with COVID-19 incidence from relevant published articles. Invasive Fungal Infections (IFIs) had the highest incidence of 26.7% from 137 intensive care unit patients screened for IFIs in 2020. Currently, drugs that are commonly used in the treatment of COVID-19 patients such as casirivimab and imdevimab, bamlanivimab and etesevimab, sotrovimab, and remdesivir had no any effects on fungal infections. In India, 53% of mortality rate which caused by 60% of *Candida auris* and in Brazil, 72.7% following corticosteroids use were reported. Recently, no any reports related to mortality rate due to *Candida* infections associated with COVID-19 in Spain and USA. Numerous current advances in management and diagnosis of these fungal infections associated with COVID-19 have not been much potentially significant. It is predicted and possible that the development of new and potent antifungal drugs, antimicrobial peptides and nanotechnology based approaches for drug delivery would help to reduce or eliminate these fungal infections associated with COVID-19 and restraint its spread across the globe.

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## 1.0 Introduction

In March, 2020, World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) as a pandemic disease, and was first examined in December 2019 in Wuhan, China (Basile *et al*., 2022). In December, Vaccinations began with emergency use of the COVID-19 mRNA BNT162b2 vaccine authorized by Pfizer–BioNTech (The World Health Organization, 2020). Even with the rapid development of pathogen-specific therapies, there is serious ongoing transmission of SARS-CoV-2 globally. And generated an increased risks to public health, intensified by the emergence of WHO labelled variants of concern strains (Basile *et al*., 2022). COVID-19 clinical spectrum is ranging from asymptomatic infection to multi-organ impairments, severe respiratory ailments including extra-pulmonary disease (Huang *et al*., 2020). Currently, invasive aspergillosis (IA) are frequently reported as a fungal co-infection in COVID-19 patients which is uncommonly reported in the early pandemic (Basile *et al*., 2022). It is not uncommon for opportunistic invasive fungal disease (IFD) to take place in the context of severe respiratory viral infections such as para-influenza, respiratory syncytial virus infections, influenza and recently COVID-19 (Garcia-Vidal *et al*., 2020). However, increase in fungal co-infections due to non-*Aspergillus* filamentous fungi and yeasts are

also reported. The first invasive fungal disease to be reported is COVID-19 associated pulmonary aspergillosis (CAPA) (Mouren *et al*., 2021). COVID-19 associated candidiasis (CAC) is frequently observed as candidaemia, with *Candida glabrata* and *Candida albicans* being the most common etiological agents. Candidemia in COVID-19 patients has being increasingly reported in many current studies. It was reported in US that almost 9% of COVID-19 patients in intensive care unit (ICU) developed candidaemia infections (Bishburg *et al*., 2021). Multidrug resistant outbreak of *Candida auris* have also been noted in some studies (Prestel *et al*., 2021). It was also reported that almost 26% of positive SARS-CoV-2 in 251 patients infected with candidemia (Seagle *et al*., 2021). Pneumocystis and COVID-19 share related overlapping features, such as laboratory, radiological and clinical examinations as a results of frequent misdiagnosis (Choy *et al*., 2020). In some studies, specimens was examined from 108 HIV negative COVID-19 patients and found that *P. jirovencii* was positive in 9.3% and explored the incidence of Pneumocystis in pulmonary samples obtained from critical ill COVID-19 patients and found it around 1.4% (Rovina *et al*., 2022). The prompt recognition and therapy of the invasive fungal diseases is paramount, as antifungal drug options varies from those for aspergillosis. The accurate and rapid identification of the fungal pathogens via mycological examination and reported common symptoms such as cough, fever and dyspnea, and radiological investigation such as ground glass opacities in COVID-19 associated pulmonary aspergillosis (CAPA) and non-CAPA invasive fungal diseases (IFDs) (Basile *et al*., 2022). Laboratory diagnosis is burdensome in processing the procedures of bronchoscopies and impelled sputum collection to prevent the COVID-19 nosocomial transmission. Even with the advancements in the understanding of management, diagnosis and prevention of COVID-19 associated fungal infections, the challenging is still remain. There is a sudden rise of rare molds infection called mucormycosis during the COVID-19 pandemic and has been reported globally as one of the COVID-19 associated comorbidities. Mucormycosis, commonly known as "black fungus" and the spot of the infection by the fungus appears black in pigmentation. The most frequently targeted organs of this molds include eyes, kidney, brain, lungs, Gastrointestinal (GI) tract, nose, skin and sinuses. Recognizable symptoms of this mold infections include facial swelling, runny nose, swollen eyes and blurred vision (Dogra *et al*., 2022). The noticeable signs of this molds infection include tissue necrosis, which is usually lead to vascular thrombosis. The molds is mainly responsible for Rhizopus and Mucor infections including *Lichtheimia* species, *Cokeromyces* species, *Rhizomucor* species, *Cunninghamella* species, *Apophysomyces* species and *Saksenaea* species (Dogra *et al*., 2022). The fungal spores can be deftly spread across via inhalation of droplets and disseminated in the surrounding air (Richardson, 2009). Basically, the mortality rate of mucormycosis incidence is statistically estimated as 46% across the globe (Werthman-Ehrenreich, 2021). These molds are the second most prevalent following *Aspergillus* species as an opportunistic secondary pathogen (Slavin *et al*., 2015). In India, the prevalence of mucormycosis infections is 140 per million in the population according to WHO (Chakrabarti and Dhaliwal, 2013). The predispose factors of mucormycosis infections include uptake of corticosteroids, COVID-19, diabetes, hospital acquired infections, surgeries and hematological malignancies (Dogra *et al*., 2022). Complications related to this molds infection include thrombosis and blindness. Adequate maintenance of good personal hygiene is the most proper preventive measures to reduce disease occurrence. Diagnosis require the use of conventional and new methods for examination such as PCR based methods, biopsy and computer tomography scans. The available treatment options are usually ineffective due to similarity of the drug targets in the pathogen with the host but the surgical removal of the affected spot and use of antifungal agents are recommended (Riley *et al*., 2016).

## 2.0 Materials and Methods

### 2.1 Data Collection

Eighty nine (89) published articles were evaluated that comprises fungal species or/and fungal infections associated with COVID-19 and SARS-CoV-2 from 2019 to 2022. The search were conducted in databases that include indexed journals and journals that publish related articles. Prospective and retrospectives studies, randomized controlled trials, case-control studies, cohort studies and randomized studies were searched. Only English keywords were used in the search for data collection. The databases evaluated include Web of Science, World Health Organization publications, Medline, Google Scholar, Scopus, PubMed, Science Direct, Scielo and African Journals Online databases to evaluate all published articles reporting fungal infections associated with COVID-19. The Boolean operator (AND) was used to combine and narrow the studies search. In the published article search, the following keywords were used: endemic mycosis AND COVID-19, pneumocystosis AND COVID-19, Candidiasis AND COVID-19, Aspergillosis AND COVID-19, mucormycosis AND COVID-19, cryptococcosis AND COVID-19, fungal infections AND SARS-CoV-2, fungal species AND COVID-19 and fungal infection AND therapeutic drugs.

**3.0 Results**

Table 1 is the prevalence of invasive fungal infections (IFIs) in critical ill COVID-19 patients. The result shows that the invasive fungal infections (IFIs) had the highest incidence of 26.7% from 137 intensive care unit patients screened for IFIs in 2020 using multicenter and prospective studies. Table 2 is the summary of the therapies used for COVID-19. The results shows that the drugs such as casirivimab and imdevimab, bamlanivimab and etesevimab, sotrovimab, and remdesivir had no effect on fungal infections. Table 3 is the synopsis of steroids used in the treatment of COVID-19 patients infected with *Candida* species. The result shows that no any reports based on mortality rate due to *Candida* infections associated with COVID-19 in Spain and USA. In India, 53% cases of mortality rate which caused by 60% of *Candida auris* and in Brazil, 72.7% following corticosteroids use were reported. Table 4 is the case reports on invasive aspergillosis in COVID-19 patients. The result shows that Italy and USA had no mortality cases and 57.9% mortality rate in UK is due to COVID-19 associated pulmonary aspergillosis.

**Table 1. Synopsis of the occurrence of Invasive Fungal Infections (IFIs) in severe COVID-19 patients**

| S/N | Trial Design | Population | Type of IFIs | Frequency Percentage | References |
|---|---|---|---|---|---|
| 1. | Polymerase Chain Reaction (PCR) analyses on critical ill COVID-19 patients | Severe COVID-19 patients | *Pneumocystis jirovecii* Pneumonia | 1.4% | (Blaize *et al*., 2020) |
| 2. | Retrospective and Single Center analyses on critical ill COVID-19 patients | 89 COVID-19 Intensive Care Unit Patients (ICU) | COVID-19 Associated Candidemia | 8.9% | (Bishburg *et al*., 2021) |
| 3. | Surveillance Data analyses on critical ill COVID-19 patients | 251 Candidemia patients | Candidemia | 25.5% were SARS-CoV-2 patients | (Seagle *et al*., 2021) |
| 4. | Single Center analyses on critical ill COVID-19 patients | Not Mentioned | COVID-19 Associated Candidemia | ×5 multiple compared to pre-pandemic | (Nucci *et al*., 2020) |
| 5. | Single Center and Retrospective analyses on critical ill COVID-19 patients | 145 COVID-19 ICU Mechanical Ventilated patients evaluated for fungal super-infection and 54% on Extracorporeal membrane oxygenated | Putative/probable Invasive Fungal Infection with 1 *Fusarium* species reported | 4.8% | (Fekkar *et al*., 2021) |
| 6. | Observational analyses on critical ill COVID-19 patients | 108 severe COVID-19 patients | *Pneumocystis jirovecii* Pneumonia | 9.3% | (Alanio *et al*., 2020) |
| 7. | Multicenter, Prospective and Observational analyses on critical ill COVID-19 patients | Not Mentioned | COVID-19 Associated Mucormycosis | 1.8% | (Selarka *et al*., 2021) |
| 8. | Cross-sectional study analyses on critical ill COVID-19 patients | 197 severe mechanical ventilated COVID-19 patients | Fungal Ventilator Associated Pneumonia | 8.2% Mucor 16.4% Aspergillus | (Meawed *et al*., 2021) |
| 9. | Metanalysis on critical ill COVID-19 patients | 118 studies | Fungal super- and co-infections | 8% and 4% respectively | (Musuuza *et al*., 2021) |

| S/N | Trial Design | Population | Type of IFIs | Frequency Percentage | References |
|---|---|---|---|---|---|
| 10. | Metanalysis and Systemic Review analyses on critical ill COVID-19 patients | 9 studies | Invasive Fungal Infections | 0.12 Overall Pooled Proportion | (Peng *et al.*, 2021) |
| 11. | Single Center, Observational and Retrospective analyses on critical ill COVID-19 patients | 52 Intensive Care Unit patients | Not Mentioned | 5.8% | (Yang *et al.*, 2020) |
| 12. | Review analyses on critical ill COVID-19 patients | 80 COVID-19 Associated Mucormycosis | COVID-19 Associated Mucormycosis | 0.3 – 0.8% occurrence in COVID-19 Intensive Care Unit patients | (Hoenigl *et al.*, 2022) |
| 13. | Prospective and Multicenter analyses on critical ill COVID-19 patients | 137 Intensive Care Unit patients evaluated for invasive fungal infection | Invasive Fungal Infections | 26.7% | (White *et al.*, 2020) |
| 14. | Single Center and Retrospective analyses on critical ill COVID-19 patients | 99 Hospital patients | Secondary Fungal Infection | 5% | (Chen *et al.*, 2020) |
| 15. | Observational and Retrospective analyses on critical ill COVID-19 patients | COVID-19 Intensive Care Unit patient | COVID-19 Associated Pulmonary Aspergillosis | 1.5% | (Gouzien *et al.*, 2021) |
| 16. | Single Center and Retrospective analyses on critical ill COVID-19 patients | 140 Intensive Care Unit patients | Fungal Infection | 15% | (Bardi *et al.*, 2021) |
| 17. | Literature Review analyses on critical ill COVID-19 patients | 21 Care Reports and 28 Observational Studies | Secondary Fungal Infection | 6.4% | (Chong *et al.*, 2021) |

**Table 2. Synopsis of treatments used for COVID-19 patients**

| S/N | Classification of Drugs | Drugs | Mode of Action | Fungal Infection | References |
|---|---|---|---|---|---|
| 1. | Monoclonal Antibodies (mAb) | Imdevimab and Casirivimab | Imdevimab (IgG1λ) and Casirivimab (IgG1k) Recombinant human monoclonal antibodies that bind to the spike protein receptor-binding domain of SARS-CoV-2, which results to the blocking of binding to the human angiotensin-converting enzyme-2 receptor via inhibiting viral attachment to host cells. | Not Reported | (Basile *et al.*, 2022) |

| | | | | | |
|---|---|---|---|---|---|
| | | Tocilizumab | Interleukin-6 antagonist. Sequel in depletion of acute phase reactant production and cytokine | Pneumocystosis, Invasive candidiasis, Cryptococcosis | (Schiff *et al.*, 2011); (Campbell *et al.*, 2011); (Vallabhaneni and Chiller, 2016) |
| | | Etesevimab and Bamlanivimab | Etesevimab (IgG1k) and Bamlanivimab (IgG1k) Recombinant human monoclonal antibodies that bind to the spike protein receptor-binding domain of SARS-CoV-2, which results to the blocking of binding to the human angiotensin-converting enzyme-2 receptor via inhibiting viral attachment to host cells. | Not Reported | (Basile *et al.*, 2022) |
| | | Sarilumab | Interleukin-6 receptor antagonist. Sequel in depletion of acute phase reactant production and cytokine. | Pneumocystis, Candidiasis | (KEVZARA® (Sarilumab), 2022) |
| | | Sotrovimab | Concocted human IgG1 monoclonal antibody that binds to the spike protein receptor binding domain of SARS-CoV-2. | Not Reported | (Basile *et al.*, 2022) |
| 2. | Antiviral Drugs | Remdesivir | Nucleoside anti-proviral drug blocks SARS-CoV-2 replication through RNA-dependent RNA polymerase. | Not Reported | (Basile *et al.*, 2022) |
| 3. | Immune Modulators | Tofacitinib | Janus kinase inhibitors: Bind to janus kinase, which inhibits the activation of the janus kinase signal transducers and activators of transcription signaling pathway, which limits the production of pro-inflammatory cytokines. | Cryptococcosis, Oesophageal candidiasis | (Vallabhaneni and Chiller, 2016); (Cohen *et al.*, 2017); (Kremer *et al.*, 2013) |
| | | Glucocorticoids | Lessen of vasodilation, leukocyte migration, and permeability of capillaries Prevent neutrophil apoptosis and demargination; prevent phospholipase $A_2$ function, and prevent NF-Kappa B and inflammatory transcription factors | Mucormycosis, Candidiasis, Invasive aspergillosis, Pneumocytosis | (Stuck *et al.*, 1989) (Kayaaslan *et al.*, 2021) |

| | | | | | |
|---|---|---|---|---|---|
| | Baricitinib | Aid expression of anti-inflammatory genes such as that for interleukin-10. Janus kinase inhibitors: Bind to janus kinase, which inhibits the activation of the janus kinase signal transducers and activators of transcription signaling pathway, which limits the production of pro-inflammatory cytokines. | Cryptococcosis, Candidiasis, Histoplasmosis, Pneumocystosis | (OLUMIAT (Baricitinib), 2021); (Sanchaz *et al*., 2018) |

**Table 3. Synopsis of steroids used in the treatment of COVID-19 patients infected with *Candida* species**

| S/N | Region | Trial Design | Population | Comorbidities | *Candida* Infection | Mortality | References |
|---|---|---|---|---|---|---|---|
| 1 | **Spain** | Observation and Prospective Studies | 218 Intensive Care Unit (ICU) patients | Malignancies are predominantly seen in COVID-19 patients along with Candida co-infection. Central venous catheters, Length of ICU stay, Total parenteral nutrition | 14.4% with positive *Candida* tests | Not Available | (Segrelles-Calvo *et al*., 2021) |
| 2 | **India** | | 596 COVID-19 ICU patients, 420 Mechanical ventilated, 15 Candida Blood-stream infections | Diabetes mellitus, Hypertension, Length of ICU stay, Chronic kidney disease, Corticosteroids | 2.5% Blood-stream infections | 53% ( 63% for *Candida auris*) | (Chowdhary *et al*., 2020) |
| 3. | **Brazil** | Retrospective studies | Candidemia incidence between Non-COVID-19 and COVID-19 inpatients. | ICU patients (72.7%), High dose, Central venous catheters (90.9%), Corticosteroids. | ×10 increase in candidemia | 72.7% following corticosteroids use | (Riche *et al*., 2020) |
| 4. | **Italy** | | 3/43 Candidemia,43 critical ill COVID-19 patients | Tocilizumab 3/3, Total parenteral nutrition 3/3, Antibiotic 2/3 | 6.9% Blood-stream infection | Still ongoing hospitalization on publication | (Antinori *et al*., 2020) |
| 5. | **USA** | Retrospective studies | 169 without corticosteroids, 226 COVID-19 hospitalized patients, 57 with corticosteroids | Not Mentioned | 7% COVID-19 associated candidemia with corticosteroids and 0% without corticosteroids, 15% COVID-19 | Not Mentioned | (Obata *et al*., 2021) |

| S/N | Region | Trial Design | Population | Comorbidities | *Candida* Infection | Mortality | References |
|---|---|---|---|---|---|---|---|
| | | | | | associated candidemia with tocilizumab and 2.7% without tocilizumab | | |

**Table 4. Synopsis of Invasive Aspergillosis reported in COVID-19 patients**

| S/N | Region | Trial Design | Population | Comorbidities | Mortality | References |
|---|---|---|---|---|---|---|
| 1. | UK | Prospective and Multicenter | 137 Intensive Care Unit (ICU) patients screened for Invasive Fungal Infection | 6/25 Obesity, 12/25 Chronic respiratory disease, 6/25 Diabetes mellitus, 8/25 Hypertension | 57.9% due to COVID-19-associated pulmonary aspergillosis (CAPA) | (White *et al*., 2020) |
| 2. | Argentina | Not Mentioned | 5 ICU patients | 2/5 Diabetes mellitus, 1/5 Hematologic malignancy | 1/5 Died | (Benedetti *et al*., 2020) |
| 3. | Italy | Not Mentioned | 45 COVID-19 autopsies | 3/9 Chronic obstructive pulmonary disease, 7/9 ICU, 7/9 Hypertension | Not Mentioned | (Fortarezza *et al*., 2021) |
| 4. | Netherlands | Prospective and Single center | 1st wave: 33 Mechanically ventilated ICU patients. 2nd wave: 33 Mechanically ventilated ICU patients. | 1/13 Acute renal failure, 2/13 Hypertension, 4/13 Cardiovascular disease, 3/13 Diabetes mellitus, 1/13 Chronic obstructive pulmonary disease. | 40 – 50% in both groups | (Meijer *et al*., 2021) |
| 5. | France | Prospective and Observational | 9/27 COVID-19 associated pulmonary aspergillosis, 27 ICU patients | Home Parenteral Nutrition is predominantly in Invasive Pulmonary Aspergillosis (7/9 vs. 6/18, p = 0.046) | 4/9 | (Alanio *et al*., 2020) |
| 6. | Switzerland | Not Mentioned | 80 ICU Mechanically Ventilated patients | No patient had any predisposing factors | 1/3 | (Lamoth *et al*., 2020) |
| 7. | USA | Retrospective | 226 COVID-19 hospital patients, 57 with corticosteroids, and 169 without corticosteroids | Not Mentioned | Not mentioned | (Obata *et al*., 2021) |

| S/N | Region | Trial Design | Population | Comorbidities | Mortality | References |
|---|---|---|---|---|---|---|
| 8. | Belgium | Not Mentioned | 20 Mechanically ventilated patients | 3/7 Diabetes mellitus, 4/7 dyslipidemia, 3/7 Hypertension, 2/7 Obesity | 4/7 | (Rutsaert *et al*., 2020) |

**4.0 Discussion**

The susceptibility of invasive candidiasis is high especially in COVID-19 patients receiving hemodialysis, parenteral nutrition, anti-bacterial drugs, having central venous catheters and undergoing mechanical ventilation. All these factors are commonly observed in the critical ill COVID-19 patients (Rovina *et al*., 2022) Rubiano *et al*. (2020) reported that patients with underlying conditions such as hematologic malignancy and HIV, have been noted with *Pneumonocystis jirovencii* infections in low numbers which is not consistent with the current study (Table 1). COVID-19 associated mucormycosis (CAM) is another potential complication of COVID-19 usually in geographical locations of higher incidence of the mold species such as Indian and in patients with uncontrolled diabetes mellitus cases (Hoenigl *et al*., 2022). Rovina *et al*. (2022) revealed that patients with cavitary pulmonary mucormycosis or acute invasive fungal rhino-orbital mucormycosis are associated with COVID-19 associated mucormycosis. Monoclonal antibodies such as itolizumab and tocilizumab used for the treatment of COVID-19 can make patients susceptible to these common molds and cause immune impairment while this study shows that the drugs such as casirivimab and imdevimab, bamlanivimab and etesevimab, sotrovimab, and remdesivir had no effect on fungal infections (Table 2). Studies reported that *Mucor* species was isolated in 8.2% of 197 severe ill COVID-19 patients under mechanical ventilation who developed ventilator-associated pneumonia (Meanwed *et al*., 2021). In Indian, almost 2% from the 2,567 COVID-19 patients were diagnosed with mucormycosis in patients with COVID-19 as an epidemic within a pandemic (Selarka *et al*., 2021). However, the first step in managing such condition is to evaluate and examine the high risk of patients for invasive fungal diseases (Basile *et al*., 2022). Non-ventilated COVID-19 patients should also be examined for candidemia and invasive fungal disease especially those in the intensive care unit experiencing sepsis–like syndrome and pulmonary desaturation. Critical ill COVID-19 patients are at high risk who require mechanical ventilation especially for COVID-19 associated pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia and mucormycosis. Nucci *et al*. (2020) reported in Brazil that incidence of candidemia during the pandemic is almost 5 times greater than before the pandemic which is consistent with the current study in Table 3. Rovina *et al*. (2022) revealed that *Aspergillus* species was not reported in any samples by culturing, however the rate of fungal antigenemia was high almost 50% in some retrospective and observational study of critical ill COVID-19 patients while this current study shows that COVID-19 associated pulmonary aspergillosis caused 57.9% mortality rate in UK compared to other endemic locations (Table 4). Predispose factors such as diabetes mellitus in COVID-19 associated mucormycosis is usually reported. The risk of the fungal infection or reactivation of endemic mycosis after or during COVID-19 ailments could be attributed to prior infection or travelling to an endemic locations. In non-COVID-19 patients, diagnostic procedures are related which encompassing laboratory based methods such as nucleic acid amplification techniques based methods, histopathology and culture based in addition with radiology to enhance the diagnostic result. Basile *et al*. (2022) reported that the histopathological analysis of tissue samples is potentially recommended where culture remains a backbone for the diagnosis of numerous invasive fungal diseases. Physical containment level 3 laboratory should be performed with culture of samples in any suspected cases of invasive fungal diseases as the agents of endemic mycoses are risk group 3 pathogens (Basile *et al*., 2022). The diagnosis of histoplasmosis and cryptococcosis should be carried out using serological techniques. The increase availability of nucleic acid amplification techniques for a large range of invasive fungi has been evaluated for good potential for rapid and accurate diagnosis. Studies reported that the first case of Pneumocystis was detected in March, 2021 via autopsy of a male, aged 52 years who was diagnosed with COVID-19 (Jeican *et al*., 2021). Some rare invasive fungal diseases that have been diagnosed and reported in COVID-19 patients include *Trichosporon*, *Rhodotorula fungaemia* and *Fusarium* species (Rovina *et al*., 2022). Cryptococcus should be observed in vulnerable COVID-19 patients. Fungal species such as *Coccidioides*, *Histoplasma* or *Blastomyces* should also be observed in some specific endemic geographical locations. Rovina *et al*. (2022) reported that three (3) patients with co-infection of SARS-CoV-2 and Coccidioides, the infection may be diagnosed and sub-clinical during recovery phase of those COVID-19 patients. Basile *et al*. (2022) has reported that no any dimorphic fungi such as Talaromyces, Paracoccidioides, Blastomyces,

Emergomyces, Paracoccidioides and Sporothrix with co-infections of SARS-CoV-2 has being observed but was predicted to occur in the proper clinical settings.

**4.1 Incidence of Invasive Fungal Infections (IFIs) in critical ill COVID-19 Patients**

Currently, the overall incidence of IFIs in critical ill COVID-19 patients ranges from 5% to 27% and 5% in fungal respiratory complications (Rovina *et al*., 2022; Fekkar *et al*., 2021). Some studies reported 6% approximately on secondary pulmonary infections in the literature review of 49 studies and 5% of fungal co-infections in COVID-19 patients (Chong *et al*., 2021; Chen *et al*., 2020). And studies reported 6%, 4% and 8% approximately in the meta-analysis of fungal super- and co-infections (Musuuza *et al*., 2021; Yang *et al*., 2020). In retrospective study of 140 ICU patients, 15% and 27% incidence were reported of invasive fungal infections in critically ill COVID-19 patients (Bardi *et al*., 2021; White *et al*., 2020). Studies reported the overall pooled proportion of fungal co-infection (0.12) in systemic review and metanalysis of 9 studies (Table 1).

**4.2 Risk of Invasive Fungal Diseases (IFDs) and COVID-19 Treatments**

Therapies used to treat COVID-19 patients are categorized into three: [1] monoclonal antibody treatments, [2] antiviral treatments and [3], immune modulators such as janus kinase (JAK) inhibitors and corticosteroids (Table 2). These can inhibit SARS-CoV-2 from entering cells by causing detrimental effects. Corticosteroids are commonly used in the management of COVID-19 patients who are receiving oxygen to modulate the systemic inflammatory response (The recovery collaborative group, 2021). Interleukin-6 inhibitors prevent the janus kinase inhibitors, cascade of cytokine release and inhibit cell signalling mechanisms (Zhang *et al*., 2019). Immunotherapies increase risk of invasive fungal diseases via inhibition of cell signalling, B cells or phagocytes, resultant cytopaenias and inhibition of function of T cells which can result to increased airway colonization of fungal infection (Baddley *et al*., 2021). Close monitoring of COVID-19 patients is needed to examine adverse effects of the drugs used in their treatments including that of subsequent invasive fungal disease since numerous of the new therapies for COVID-19 patients only have emergency use authorization rather than full regulatory approval. The currently available drugs used in the treatment of COVID-19 patients and their references with regards to invasive fungal diseases are summarized in Table 2.

**4.3 Endemic Mycoses**

Mycoses may cause lung infection and co-exist with COVID-19 context, particularly in endemic locations. Other molds and COVID-19 associated pulmonary aspergillosis may be misdiagnosed by given related results. Critical ill COVID-19 patients that are receiving treatment may experience reactivation of past infections or dormant with an endemic fungus. The broad use of interleukin-6 inhibitors or dexamethasone, and other immunosuppressants used in the treatment of critical ill COVID-19 patients may increase the risk of symptomatic endemic mycoses (Segrelles-calvo *et al*., 2020). In chronic lung disease, coccidioidomycosis may increase the risk of critical ill COVID-19 patients. And it was noted that COVID-19 may increase the risk of reactivation of latent infection of Coccidioides. The possible exposure risk factor, demographic and social presentations between COVID-19 and coccidioidomycosis is focusing the role of geographical locations, racial and ethnic minorities (Heaney *et al*., 2020). In South America, SARS-CoV-2 and Histoplasma with four (4) co-infections were reported together with incidence of three (3) infection of HIV (Basile *et al*., 2022). Even if the patients receiving a COVID-19 diagnosis, opportunistic infections such as Pneumocystis pneumonia associated with HIV should be noted in the context of differential diagnosis in patients with suggestive radiological characteristics. When pulmonary imaging triggered SARS-CoV-2 diagnosis, the co-infection in negative HIV patient, the setting of persistent pulmonary histoplasmosis was reported (Stasiak *et al*., 2021).

**4.4 Pneumocystosis**

Co-infections of *Pneumocystis jirovecii* pneumonia was first reported in critical ill dyspnea patient autopsy which was diagnosed by real-time PCR and the case is usually rare in the context of COVID-19 compared to CAPA patients (Jeican *et al*., 2021). COVID-19 and patients with underlying human immunodeficiency virus (HIV) infection are increasingly showing positive results for *Pneumocystis jirovecii* pneumonia via PCR tests (Basile *et al*., 2022). The true incidence of *P. jirovecii* DNA in clinical specimens representing colonization only is yet to be reported, but however PCR results shows that percentage frequencies of positive *Pneumocystis jirovecii* pneumonia ranging from 1.4% to 9.3% as reported currently (Basile *et al*., 2022). Studies reported that twelve (12) COVID-19 and (58.3%) of HIV patients were in receipt of corticosteroids with *Pneumocystis jirovecii* pneumonia found all needed (91.7%) invasive mechanical ventilation (Chong *et al*., 2021). Severe CD4+ lymphopenia is common risk for *Pneumocystis jirovecii* pneumonia, (<1000 cells/$mm^3$) of severe lymphopenia presenting <200 cells/ $mm^3$ of CD4+T cell count (Menon *et al*., 2020). Critical ill COVID-19 patients may activate or re-activate asymptomatic infection of *Pneumocystis jirovecii* pneumonia in colonized patients requiring immunomodulatory therapies or/and adjunctive steroids in the development of lymphopenia (Alanio *et al*., 2021). The diagnosis of *Pneumocystis jirovecii* pneumonia

usually combined the assessment of radiologic findings, clinical features and laboratory tests which is similar to that of negative COVID-19 populations. Diagnosis is usually complicated due to related clinical similarity such as cough and dyspnoea and radiological presentations of COVID-19 and *Pneumocystis jirovecii* pneumonia. Therapy can be initiated before making a definitive diagnosis when there is a high clinical suspicion for *Pneumocystis jirovecii* pneumonia and clinical improvement can be expected within few days. Presently, the use of trimethoprim–sulfamethoxazole has not been reported with any adverse effect (Chon *et al*., 2021).

**4.5 Candidiasis**

The risk factors of *Candida* species associated with COVID-19 are not directly linked to the SARS-CoV-2 infection, however, the association of *Candida* as a fungal co-infection in COVID-19 patients is still under reported currently. The predispose factors such as indwelling central venous catheters, diabetes mellitus, parenteral nutrition, triple lumen catheters, abdominal surgery, multiple antibiotics and renal failure requiring hemodialysis which make the COVID-19 patients on mechanical ventilation and those in intensive care unit more susceptible to develop fungal co-infection (Kundu and Singla, 2022). Another risk factor include severe respiratory failure associated with COVID-19 which require extracorporeal membrane oxygenation (Kundu and Singla, 2022). Currently, studies shows that *Candida* species infection in users of removable dentures can increase the mortality and morbidity rate associated with COVID-19 (Jeronimo *et al*., 2021). Distortion of intestinal mucosal barrier in which SARS-CoV-2 binds enzyme-2 receptor converted by the increased expression of angiotensin generates route for the translocation of *Candida* species to the blood causing candidemia (Nucci *et al*., 2021). In COVID-19, it has been reported that gut mycobiota dysbiosis decrease the relative abundance of the most changed gut fungal taxa and gut fungal α-diversity (Lv *et al*., 2021). The immune dysregulation and complete pathogenesis in COVID-19 patients harboring *Candida* species is still under reported. However, reports on distorted monocyte CD80 up regulation and nullified release of interleukin-6, tumor necrosis factor, interleukin-1a, and interleukin-1b signalling towards increased vulnerability for *Candida albicans* infection (Moser *et al*., 2021). About 6 to 10% cases of the common fungal pathogen reported in this context, *Candida* with approximately 19% to 40% mortality rate with invasive candidiasis is being estimated (Kundu and Singla, 2022). Reported non-*albicans Candida* species including *Candida auris* and *Candida glabrata* either have recently acquire antifungal resistance or inherent resistance to antifungals are the most complicating agents (Arastehfar *et al*., 2020). COVID-19 associated candidiasis can either be invasive or superfcial infection ranging from 0.7% to 23.5% (Kundu and Singla, 2022). *Candida albicans* is the most predominant fungal species among invasive yeast infections in severe COVID-19 patients followed by *Candida tropicalis*, *Candida auris*, *Candida parapsilosis* and *Candida glabrata* (Arastehfar *et al*., 2020). High mortality has been noted with *Candida auris* and *Candida glabrata*. Currently, despite antifungal therapy in patients with COVID-19 pneumonia and candidaemia, 83.3% of mortality rate was reported (Villanueva-Lozano *et al*., 2021).

**4.6 Aspergillosis**

*Aspergillus* is noted as a common fungus present in the decaying vegetation and soil. The most frequent clinical isolates of *Aspergillus* species causing co-infection in COVID-19 patients is *Aspergillus fumigatus* and *Aspergillus favus* (Lai *et al*., 2021). *Aspergillus* species caused huge spectrum of infections in human beings which includes bronchitis, invasive pulmonary aspergillosis, chronic rhinosinusitis, allergic bronchopulmonary aspergillosis, fungal asthma and chronic pulmonary aspergillosis. In critical ill COVID-19 patients, a cascade of inflammatory reactions and epithelial damage in the lungs are caused by danger associated molecular patterns (Arastehfar *et al*., 2020). Danger associated molecular patterns is reported to be a vital immunomodulatory strategy. *Aspergillus* cleaves fibrinogen and activates Toll-like receptor 4 containing adapter inducing interferon-β which facilitates the activation of overlapping signalling pathways generating cytokines including interleukin-1 and interleukin-6. The predisposing factor for developing COVID-19 associated pulmonary aspergillosis is structural lung damage caused by asthma or chronic obstructive pulmonary disease, broad spectrum of antibiotics in critical ill COVID patients is used besides the corticosteroids (Arastehfar *et al*., 2020). Influenza infection was reported as an independent predisposing factor for invasive pulmonary aspergillosis with a mortality rate of 45% in patients with influenza associated invasive pulmonary aspergillosis (Kundu and Singla, 2022). In Netherlands, a higher percentage of COVID-19 patients were diagnosed with COVID-19 associated pulmonary aspergillosis during the second wave of the pandemic (24.2%) as compared to the first wave (15.2%) (Meijer *et al*., 2021). Radiology is differed showing inconsistence airways to centrilobular nodules to cavitary nodules and consolidation. The radiological features are not significant. Diagnosing COVID-19 associated pulmonary aspergillosis is a remarkable challenge (Marr *et al*., 2021). There is possibility of aerosol generation for galactomannan testing of bronchoalveolar lavage fluids which may not be common in many contexts (Wahidi *et al*., 2020).

Non-bronchoscopic lavage and tracheal aspirates samples from upper respiratory tract can be obtained with ease, but validation of galactomannan testing on these samples is a great challenge (Yusuf *et al*., 2021).

**4.7 Mucormycosis**

In India, Ministry of Health and Family Welfare reported a total number of 20,908 cases of mucormycosis and confirmed 1,376 deaths in July, 2021 (Dogra *et al*., 2022). The epidemic were declared as "black fungus" due to the approximate active cases of more than 28,000 (Singh *et al*., 2021). The incidence of diabetic ketoacidosis and diabetes were reported as 14.9% and 80% respectively. And for COVID-19 disease, 86% of the patients were exposed to corticosteroid therapy (Dogra *et al*., 2022). The mortality rate was reported as 30.7% from 78.9% cases in males, 88.9% cases of COVID-19 associated mucormycosis affects the sinuses, and 56.7% cases of rhino-orbital cerebral region (Singh *et al*., 2021). In COVID-19 patients, complications associated with opacification was reported from computed tomography image showing the mucosal thickening in the sino-maxillary and ethmoid sinus part in a current study (Werthman-Ehrenreich, 2021). COVID-19 associated mucormycosis is ascribed to thermo-tolerant and aseptic properties of the pathogens responsible for causing the infection and can thrives at even relatively high temperatures (Dogra *et al*., 2022). Predisposing factors associated fungal infection to COVID-19 patients include elevated hyperglycemia, endothelial damage, multiplied iron and zinc levels and increased ferritin levels. The emergence of black spots at the affected region, obstruction in nasal region and periorbital or buccal swelling are the reported clinical symptoms of the mucormycosis (Dogra *et al*., 2022).

**4.8 Cryptococcosis**

*Cryptococcus* species and co-infection of SARS-CoV-2 are under reported due to unknown reason. However, clinical symptoms include meningoencephalitis, cryptococcemia, lung infection, and can be transmitted (Basile *et al*., 2022). Cryptococcosis may be present after treatment of COVID-19 patient, even diagnosed post mortem or may occur concurrently (Passarelli *et al*., 2020). Cryptococcosis may affect immunocompetent individuals, underlying immunocompromise or COVID-19 patients receiving corticosteroid therapy (Ghanem and Sivasubramanian, 2021). In non-COVID-19, the lung shows abnormal imaging which ranged from small nodules to large cryptococcomas, non-specific pulmonary infiltrates and it is uncertain that these features may be borne out in the COVID-19 context (Basile *et al*., 2022). Cryptococcal antigen tests is the fundamental molecular analyses in addition to histopathology and culture which are similar to laboratory based diagnostic methods in non-COVID-19 patients. There are paucity of data on the role of the azole in the treatment of patients with cryptococcosis (Cafardi *et al*., 2021).

**5.0 Conclusion**

There are paucity of data regarding the fungal infections associated with COVID-19. However, the effect of fungal infections associated with COVID-19 cannot be disregarded. Non-*Aspergillus* infections are common agents of invasive fungal infections that may exist in patients during or after COVID-19 pandemic era. Complications do exit in relation to management and diagnosis of fungal infections in COVID-19 patients. It must be noted that severe COVID-19 patients have predisposing factors associated with fungal infections. There is need for health care workers to be aware of such complications, to formulate effective practical guidelines and strengthen microbiology and pathology laboratories.

**Declarations**

**Ethics approval and consent to participate**

Not Applicable

**Availability of data and material**

Not Applicable.

**Competing interests**

Author declare no conflict of interest.

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