Fungal Co-Infections in COVID-19 Patients

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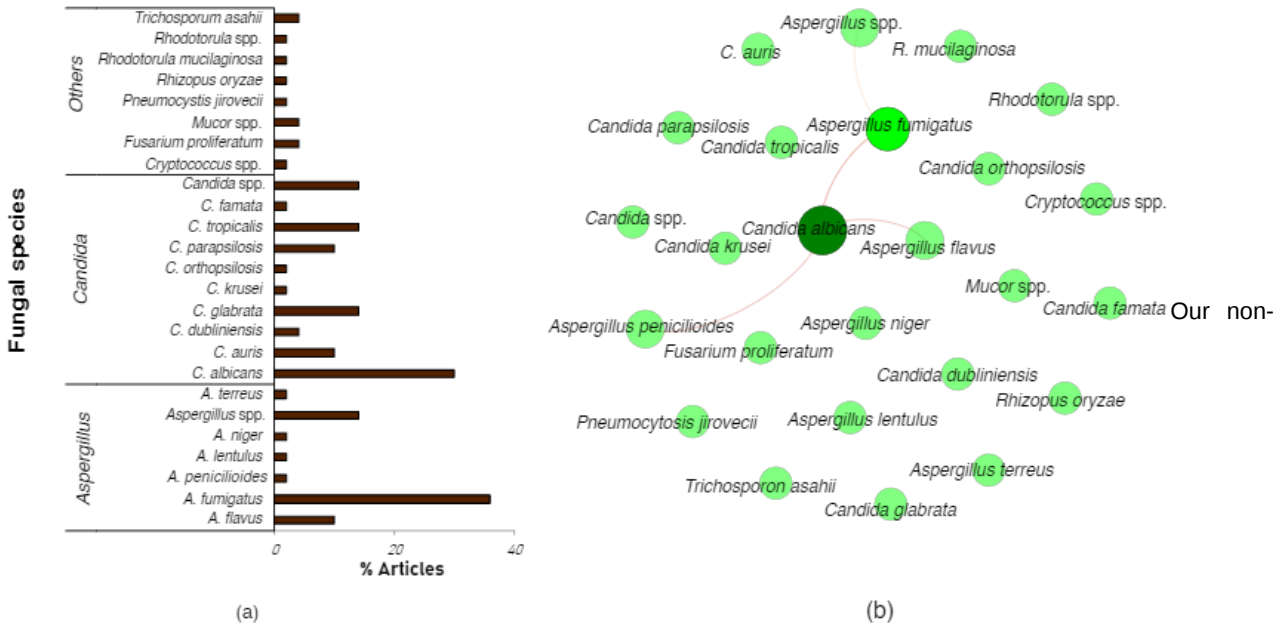
Fungal co-infections are reported in severely ill COVID-19 patients admitted to the ICU, with a higher rate of incidence for aspergillosis followed by candidemia, as observed from our literature analysis. Fungal co-infections may increase disease severity and lead to more severe outcomes.

Keywords: COVID-19 ; fungal co-infections ; corticosteroid treatment ; COVID-19-associated candidiasis ; COVID-19-associated pulmonary aspergillosis ; mucormycosis

Incidence and prevalence

Hospitalized COVID-19 patients in the ICU may encounter other complications such as secondary microbial infections due to pathogenic molds and yeasts. In multiple centers across Wales, an incidence of 14.1% and 12.6% for aspergillosis and yeast infections, respectively, were observed amongst critically ill COVID-19 patients.[1] An analysis of clinical data from several countries revealed that the aggregate incidence of COVID-19-associated pulmonary aspergillosis (CAPA) was found to be between 1% and 39.1%[2]. Whereas, for candidemia (blood infections of *Candida* spp.), up to 12% were reported for a health center[3] and between 1.54% and 7.54% for a center in Brazil [4]. In order to elucidate the diversity and co-occurrence of fungal co-infections in COVID-19 patients, we summarized several randomly selected reports on fungal co-infections in COVID-19 patients (**Figure 1**).



Our non-exhaustive summary of the literature reports revealed at least twenty different fungal species in hospitalized COVID-19 patients. Most of the fungal co-infections are due to *Aspergillus fumigatus* (common etiological agent of COVID-19 associated pulmonary aspergillosis (CAPA)), followed by *Candida albicans* (common etiological agent of candidiasis or candidemia) (**Figure 1a**). Significant co-occurrence between *Candida albicans* and *Aspergillus fumigatus*, *A.flavus,* or *A.penicillioides* was mostly reported (**Figure 1b**).

Contribution to Disease Severity, Multidrug-Resistant fungi, and Mucormycosis

Prospective and retrospective data of COVID-19 patients admitted to intensive care units (ICU), especially for a prolonged duration, show that these patients are susceptible to invasive microbial co-infections during hospitalization and that these may lead to more severe outcomes [1][5][6][7]. A prospective cohort study of 135 adults, performed across multiple centers in Wales, showed a significantly higher (up to 25%) mortality rate in COVID-19 patients with fungal infections compared to patients without fungal infections [1]. In particular, a multicenter study of 108 COVID-19 patients admitted to the ICUs in Italy showed a significantly higher 30-day mortality rate for patients with probable COVID-19-associated pulmonary aspergillosis (CAPA) or putative invasive pulmonary aspergillosis, compared to patients without suspected aspergillosis [8]. Similarly, Meijer and co-workers [9] reported mortality between 40% and 50% in patients with CAPA across the first wave (March–April 2020) and second wave (mid-September to mid-December 2020) of the COVID-19 pandemic in Brazil.

With respect to COVID-19-associated candidiasis (CAC), although the incidence rates may be slightly lower than that of CAPA, the mortality rate of COVID-19 patients with candidemia does not appear to differ markedly. Reports from Italy indicate that up to 57.1% and 50% mortality was reported in COVID-19 patients with candidemia [10] and *Candida auris* candidemia [11], respectively. Elsewhere, the mortality rate of COVID-19 patients with candidemia exceeded those of counterparts without candidemia in Iran (100% vs. 22.7%)[7]. Altogether, these observations highlight and re-emphasize the propensity of fungal co-infections to exacerbate disease severity and, consequently, increase the mortality of critically ill patients admitted to the ICUs.

Co-infections by antifungal resistant fungi have also been reported amongst hospitalized COVID-19 patients. Indeed, microbial-resistant pathogens might be consequential for COVID-19 prognosis. In a study[12], the hazard ratio for death within 90 days in critically ill COVID-19 patients was significantly increased by antimicrobial-resistant pathogens. A report[13] from India stated a case-fatality rate of 60% amongst COVID-19 patients with candidemia due to multidrug-resistant *C. auris* infection. Hence, given that antifungal resistance undermines treatment efforts and can escalate treatment costs, reports of fungal species with resistance to multiple antifungals[14][13][11], including echinocandins[15], are worrying. Furthermore, these reports highlight the need to appreciate the global burden of fungal co-infections in the current COVID-19 pandemic and the importance of prompt diagnosis and treatment of fungal pathogens in hospitalized COVID-19 patients.

Furthermore, management of COVID-19 and other underlying host factors have exacerbated the incidence of mucormycosis. Mucormycosis has been reported mostly among COVID-19 survivors (although cases in currently hospitalized COVID-19 patients have also been observed)[16]. *Rhizopus arrhizus* appears to the most common etiological agent of COVID-19-associated mucormycosis (CAM) in India [17]. However, *Rhizopus microsporus*, *Rhizopus homothallicus, Mucor irregulars*, *Saksenaea erythrospora,* and *Apophysomyces variabilis* have also been implicated in mucormycosis cases in India and elsewhere [17][18][19]. A recent systematic review of mucormycosis cases in India and worldwide reported that corticosteroid use was recorded in 76.3% of cases and that 30.7% of mucormycosis cases were fatal [20]. Altogether, the foregoing reports and several other studies suggest that the heightened incidence of mucormycosis in India is related to certain risk factors, including poorly managed diabetes and the prolonged usage of high dosage steroids in treating COVID-19 [21][22][23].

Overview of Risk Factors for Opportunistic Fungal Infections in Critically Ill COVID-19 Patients

Overall, risk factors driving the high incidence of aspergillosis and candidemia in COVID-19 patients are related to invasive procedures (e.g., intubation) predisposing lung tissues to fungal colonization and proliferation [24][25][26], history of chronic pulmonary disease [1], prolonged corticosteroid treatments [1][26], immunological disposition of patients and antimicrobial therapy [15][27]. In one study comparing co-infections in critically ill patients with and without COVID-19, it was observed that the need for invasive assisted respiration was the most decisive factor for co-infections with antifungal-resistant pathogens in patients with severe COVID-19 [24].

Given the high incidence of CAPA and the distinct clinical features of CAPA compared to influenza-associated pulmonary aspergillosis, it has been necessary to establish appropriate case definitions for CAPA in order to facilitate uniformity of reporting across medical practices. To this end, a number of case definitions or guidelines have been proposed for characterizing possible, putative, probable, and proven CAPA cases (See [1][28][29]). According to Koehler and co-workers [28], a proven case of CAPA may be established by direct microscopic and/or histopathological evidence of fungal features that are typical of *Aspergillus* spp. Such evidence includes an observation of invasive growth into tissues with concomitant tissue damage, recovery of *Aspergillus* spp.

SARS-CoV-2 insults in the lungs elicit the release of danger-associated molecular patterns (DAMPs) in severe COVID-19 disease [25]. The release of DAMPs is accompanied by inflammation and extensive damage of lung epithelial tissues, which are enabling risk factors for invasive pulmonary aspergillosis [25]. In severe COVID-19 disease, extensive inflammation and injury to the lungs lead to acute respiratory syndrome (ARDS). ARDS is characterized by difficulty in breathing; hence, assisted ventilation is required for such patients. However, mechanical ventilation and the duration of ventilation is a known risk factor for invasive aspergillosis and CAPA in the ICU [30][31][32].

In addition, pharmaceutical treatments for malignancy and the use of corticosteroids (discussed in a later section) and antibiotics may be risk factors for CAPA [1][33]. For example, in a multicenter study across Wales [1], a significant association was observed between COVID-19 patients with IPA and patients treated for or diagnosed with solid malignancy. Also, treatment with azithromycin for up to 3 days significantly correlated with the incidence of probable invasive pulmonary aspergillosis in COVID-19 patients [33]. Such observation was attributed to the immunomodulatory properties of azithromycin that may weaken the host's immune response and subsequent susceptibility to aspergillosis [34].

COVID-19-associated candidiasis (CAC) refers to the detection of one or more
Candida spp. in the bloodstream or body tissues of COVID-19 patients. Some of the risk factors identified for CAC include prolonged hospital stays, mechanical ventilation, central venous catheters, surgical procedure, and the use of broad-spectrum antibiotics [4][35]. It was observed that COVID-19 patients with candidemia were more likely to be under mechanical ventilation than non-COVID-19 patients [35]. Also, COVID-19 patients with candidemia were more likely to be in the ICU and receiving immunosuppressive agents than patients in the ICU for reasons other than COVID-19 [10].

Immunosuppressants and Fungal co-infections in Critically Ill COVID-19 Patients

Most of the current treatment options for managing patients with severe COVID-19 are immunomodulators [36]. The anti-inflammatory properties of these immunomodulators are important to counteract the heightened and unregulated release of pro-inflammatory cytokines (also known as 'cytokine storm') in the lungs during SARS-CoV-2 infection [37][38]. Thus, immunosuppressants such as dexamethasone, methylprednisolone, prednisone, hydrocortisone, and tocilizumab constitute the most common treatment options for managing severe COVID-19 cases in the ICU [36]. For example, dexamethasone treatment decreased the 28-day mortality in COVID-19 patients on invasive respiratory support or receiving oxygen alone but was not particularly beneficial for COVID-19 patients with less severe disease, suggesting that hyper inflammation mediates the advanced stage of the disease and therefore can be alleviated by immunosuppressants [39][40].

Unfortunately, the immunosuppressants hamper both the individual's innate and adaptive immune responses through sophisticated quantitative and qualitative mechanisms of immune deregulation [33][41][42][43][44], thereby increasing patients' susceptibility to invasive fungal diseases. In particular, steroidal immunosuppressants such as corticosteroids predominantly affect the protective immunity process qualitatively through functional impairment of several effector immune cells, such as monocytes, polymorphonuclear leukocytes, T lymphocytes, and macrophages [42] and is a significant acquired immunological risk factor for pulmonary aspergillosis [45][46]. Thus, corticosteroids such as dexamethasone and methylprednisolone, used for managing critically ill COVID-19 patients, have contraindications, including fostering secondary microbial infections in patients [45][47].

In the present COVID-19 pandemic, questions are being asked regarding the possible relationship between immunosuppressant or corticosteroid use and the incidence of fungal infections in critically ill COVID-19 patients. A number of studies investigating the link between immunosuppressants and fungal co-infections in hospitalized COVID-19 patients are summarised in our review paper (see [48]). In one study [49], a 10-fold increase in candidemia amongst a cohort of critically ill COVID-19 patients receiving high doses of corticosteroids such as prednisone, hydrocortisone, methylprednisolone, and dexamethasone was observed. Similarly, a retrospective study conducted in Chicago and involving 111 COVID-19 patients receiving tocilizumab (a monoclonal antibody that inhibits binding of IL-6 to the membrane and soluble receptors [50]) was significantly linked with the risk of developing fungal pneumonia and sinusitis [51]. However, in a retrospective study involving 4313 COVID-19 patients in New York, corticosteroid use was not associated with increased bacteremia or fungemia compared to non-corticosteroid users when administered within the first seven days of admission [52]. It must, however, be noted that in many of the other reports, mention is made of high doses of corticosteroids often administered for prolonged periods [53], which may explain the high incidence of systemic fungal infections and ultimately negate the lifesaving benefits of these drugs.

It should also be noted that the correlation between corticosteroid use and incidence of fungal infections in hospitalized COVID-19 patients may be masked by other co-founding risk factors for fungal infections, such as the patient's history of pulmonary disease, comorbidities, and mechanical ventilation [1][54]. Apart from corticosteroid use, a history of chronic respiratory disease was linked to a significant increase in the likelihood of aspergillosis [1]. Unfortunately, most of the currently reported investigations on the potential role between immunosuppressants and fungal infections are from a small cohort of patients. Indeed, thorough metanalyses of additional retrospective and randomized control studies will help elucidate the role of immunosuppressants in predisposing COVID-19 patients to fungal co-infections.

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