Coinfection of fungi with SARS-CoV-2 is a detrimental health risk for COVID-19 patients

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Abstract

Background: Notable fungal coinfections with SARS-CoV-2 in COVID-19 patients have been reported worldwide in an alarming way. Mucor spp. and Rhizopus spp. were commonly known as black fungi, whereas Aspergillus spp. and Candida spp. were designated as white fungi implicated in those infections. In this review, we focused on the global outbreaks of fungal coinfection with SARS-CoV-2, the role of the human immune system, and a detailed understanding of those fungi to delineate the contribution of such coinfections in deteriorating the health conditions of COVID-19 patients based on current knowledge.

Main body: Impaired CD4+ T cell response due to SARS-CoV-2 infection creates an opportunity for fungi to take over the host cells and, consequently, cause severe fungal coinfections, including candidiasis and candidemia, mucormycosis, invasive pulmonary aspergillosis (IPA), and COVID-19-associated pulmonary aspergillosis (CAPA). Among them, mucormycosis and CAPA have been reported with a mortality rate of 66% in India and 60% in Colombia. Moreover, IPA has been reported in Belgium, Netherlands, France, and Germany with a morbidity rate of 20.6%, 19.6%, 33.3%, and 26%, respectively. Several antifungal drugs have been applied to combat fungal coinfection in COVID-19 patients, including Voriconazole, Isavuconazole, and Echinocandins.

Conclusion: SARS-CoV-2 deteriorates the immune system so that several fungi could take that opportunity and cause life-threatening health situations. To reduce the mortality and morbidity of fungal coinfections, it needs immunity boosting, proper hygiene and sanitation, and appropriate medication based on the diagnosis.

Keywords: COVID-19, SARS-CoV-2, Fungal coinfection, Mucormycosis, IPA, CAPA

1 Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which is spread by human-to-human close contact, especially through respiratory droplets [1]. COVID-19 is a flu-like disease, bearing no symptoms in most infected individuals, but may develop signs and cause acute respiratory distress syndrome (ARDS), pneumonia, and even death [2]. Moreover, it is not only limited to respiratory illness but also has consequences for renal, hematological, and central nervous system (CNS) and develops a severe disease in older individuals and those with underlying medical conditions, including obesity [3], hypertension [4], rheumatic diseases [5], and diabetes mellitus [6, 7]. The intensity of mutation in spike proteins results in more powerful variants of SARS-CoV-2 such as B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta) [8], B.1.621 (Mu) [9], and B.1.1.529 (Omicron) [10] which could weaken the human immune system robustly. According to a retrospective cohort study, the individuals infected with alpha, beta, gamma, and delta variants have an elevated hospitalization risk compared to those infected with progenitor SARS-CoV-2 variants [11]. Because of prolonged hospitalization, the weakened immune system unleashes pathogens, mainly opportunistic fungi, which leads to the impairment of organs and even death [12].

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However, there are tens of thousands of recognized fungi in nature, and among them, over 300 fungal species have been identified as human pathogens. Most fungal infections are caused by opportunistic fungi such as *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis* [13]. In the case of COVID-19, patients with ARDS, hospitalized in intensive care units (ICU), receiving broad-spectrum antibiotics, going through invasive or noninvasive ventilation, and undergoing immunosuppressive or corticosteroid therapies are at the highest risk of getting opportunistic fungal infections [14]. Fungi responsible for these emerging coinfections, including *Mucor* spp. and *Rhizopus* spp., are named black fungi, whereas *Aspergillus* spp. and *Candida* spp. are called white fungi [15].

Furthermore, such fungal attacks caused reducing the number of CD4+ and CD8+ T cells resulting in disruption of the adaptive immune system in individuals infected with SARS-CoV-2 [12]. Basically, fungi are destroyed by CD4+ T cell-mediated adaptive immune responses, which protect cells from fungal attack through the action of IFN-γ from T helper cell 1 (Th1) or Interleukin-17 (IL-17) from Th17 cell. As the SARS-CoV-2 infected individuals have disrupted adaptive immune responses, the fungal infection takes over without any interference [16]. Moreover, the innate immune system also gets hampered by the “cytokine storm” due to ARDS and fails to give protection against the fungal pathogen [17].

Given the emphasis on the detrimental effects of fungal coinfections with SARS-CoV-2 in COVID-19 patients, this review study gathers facts and findings to delineate the worldwide notable fungal coinfections; roles of the immune system in the infections; morphological features, pathogenesis, clinical results, and laboratory diagnosis; and control and prevention of those fungi to deliver a comprehensive overview.

2 Main text
2.1 Fungi involved in creating coinfection with SARS-CoV-2
Several fungal diseases have been documented with SARS-CoV-2 infections, including mucormycosis, COVID-19-associated invasive pulmonary aspergillosis (CAPA), invasive candidiasis, and pneumocystis pneumonia [18–21]. The etiologic agents of mucormycosis are *Rhizopus arrhizus*, *Rhizomucor pusillus*, *Apophysomyces variabilis*, and *Lichtheimia corymbifera* [22], whereas *Aspergillus fumigatus* and *Aspergillus flavus* were predominant in CAPA [18, 23–25]. Besides, several *Candida* spp. such as *C. albicans*, *C. tropicalis*, and *C. parapsilosis* have been reported in invasive candidiasis [18]. Contrarily, pneumocystis pneumonia caused by *Pneumocystis jirovecii* has been documented in rare occurrences [18, 26]. Understanding the structure, pathogenicity, clinical sign symptoms, and laboratory diagnosis of those fungi would be helpful to outline their contribution to worsening the health conditions of COVID-19 patients (Table 1). There are many symptoms shared by *Mucor* and *Rhizopus* infections, such as chest pain, dyspnea, fever, headaches, tiredness, coughing, blisters on the skin, and a stomach-ache. The diagnosis varies, except for the similarity in a computed tomography scan’s result [27]. The morphologic features of *Mucor* and *Rhizopus* are also similar in several characteristics. They are saprophytic colonizers, filamentous, and have a stiff cell wall but vary in possessing sporangiospores and a stolon [28]. Also, *Aspergillus* and *Candida* have almost identical morphological features but distinct pathways for causing illness. *Aspergillus spp.* infects respiratory and nasal tissues, whereas *Candida spp.* attacks mainly endothelium and epithelial cells. The symptoms are significantly different in this situation because *Aspergillus spp.* has the most substantial match with the SARS-CoV-2 pathways and remarkably impacted the health of COVID-19 patients [29, 30].

2.2 The global fungal outbreaks in COVID-19 patients
Although fungal disease outbreaks are rare, opportunistic fungi take advantage of the weakened immune system of COVID-19 patients [15, 31]. Geological differences have influenced the occurrences of fungal coinfection. Peng et al. [18] reported that the fungal coinfection rate was significantly higher in patients from Asia than non-Asian patients. With the uprising second wave of COVID-19, a rare fungal disease mucormycosis caused by *Mucor spp.* happened in India with a high mortality rate [32]. Though India dealt with the severity, other regions, including the USA, the UK, Australia, France, Brazil, and Mexico, also reported having black fungus cases [33]. On May 25, 2021, two black fungus cases in Dhaka, Bangladesh, were found in individuals recovered from COVID-19. In July and August 2021, another two patients aged 40 to 60 were also diagnosed with black fungus. They were at their post-recovery stage of COVID-19, and their second COVID-19 tests were also negative. Interestingly, one of them even received two doses of the COVID-19 vaccine [34]. Moreover, John et al. [31] have reviewed 41 case reports of COVID-19 and mucormycosis, where 29 were recorded from India. Until July 21, 2021, over 45,374 mucormycosis cases have been reported in India, whereas 4,322 have died [32, 35]. Symptoms of mucormycosis developed between 6 and 24 days from the onset of disease, and a six-day delay of treatment could lead to mortality up to 66% [36, 37]. Nevertheless, some individuals who did not have diabetes and took steroids
| Name of fungi | Morphology | Pathogenicity | Clinical manifestation | Symptoms                         | Diagnosis                        | References |
|--------------|------------|--------------|------------------------|----------------------------------|----------------------------------|------------|
| Black Fungi  | Mucor spp. | Saprophytic colonizers | Infection is assumed to spread by | 1. Pulmonary mucormycosis | 1. Chest discomfort | [56]       |
|              |            | Involves filamentous mycelium or budding yeast cells that are spherical | 1. Inhalation, traumatic inoculation or ingestion | 2. Rhinocerebral mucormycosis | 2. Dyspnea | 2. Fluorescent in situ hybridization |
|              |            | Contain branched sporangiospores | 2. Invasion of blood vessels, which results in tissue infarction, necrosis, and thrombosis | 3. Subcutaneous mucormycosis | 3. Fever | 3. Gomori methenamine silver stain |
|              |            | Contain rigid cell walls with the presence of cellulose or chitin | 4. Intravascular mucormycosis | 4. Maxillofacial mucormycosis | 4. Headache | 4. Immunohistochemistry analysis |
|              |            | Cell wall consists of lipids, proteins, phosphates, amino sugars, Phosphorus, Magnesium, and Calcium | 5. Gastrointestinal mucormycosis | 5. Fatigue | 5. Periodic acid–Schiff stain |
|              |            | 6. Cough | 7. Mucosal necrosis | 8. Ophthalmologic abnormalities such as proptosis, ptosis, aphasia, and visual alterations | 6. Wet mount | 7. Conventional PCR |
|              |            | 9. Nasal bridge or upper inside of black mouth lesions that rapidly worsen | 10. Breathing problems | 11. Infected skin might develop blisters or ulcers, and the region may turn black | 9. Real-time PCR | 8. DNA sequencing |
|              |            | 12. Discomfort, warmth or redness or swelling surrounding the affected area | 12. Stomachache | 13. Bleeding in the digestive tract | 10. Restriction fragment length polymorphism | 11. APHID32C and APHID50C |
|              |            | 14. Stomachache | 15. Ophthalmologic abnormalities such as proptosis, ptosis, aphasia, and visual alterations | 16. Computed tomography (CT) scan | 12. ELIspot | 13. Computed tomography (CT) scan |
| Name of fungi | Morphology | Pathogenicity | Clinical manifestation | Symptoms | Diagnosis | References |
|--------------|------------|--------------|------------------------|----------|-----------|------------|
| **Rhizopus spp.** | Differ with *Mucor* spp. in having unbranched sporangiospores and having stolon | Infection is assumed to spread by | Involved in creating infections to immunocompromised patients such as | *Rhizopus* spp. also cause *Mucormycosis*; thus, the symptoms are the same | Diagnosis is carried out by: | [57, 58] |
| | | 1. Inhalation, traumatic inoculation or ingestion | 1. Pulmonary mucormycosis | 1. Chest discomfort | 1. Computed tomography (CT) scan |
| | | 2. Invasion of blood vessels, which results in tissue infarction, necrosis and thrombosis | 2. Rhinocerebral mucormycosis | 2. Dyspnea |
| | | 3. Subcutaneous mucormycosis | 3. Fever |
| | | 4. Maxillofacial mucormycosis | 4. Headache |
| | | 5. Gastrointestinal mucormycosis | 5. Fatigue |
| | | 6. Cough |
| | | 7. Skin blisters |
| | | 8. Stomach pain |
| **White Fungi Aspergillus spp.** | 1. Appear in velvety yellow to green or blue or brown mold | Infection routes are | Clinical significances are | Clinical signs and symptoms are | Diagnostic procedures are | [59] |
| | | 1. Respiratory route | 1. Chronic cavitary pulmonary aspergillosis and aspergilloma | 1. Anorexia | 1. Wet mount |
| | | 2. In tissue where hyphal growth forms | 2. Allergic bronchopulmonary aspergillosis | 2. Weight loss | 2. Gomori’s methenamine silver stain (GMS) |
| | | 3. Dissemination in extrapulmonary tissues | 3. Allergic fungal sinusitis | 3. Malaise | 3. Periodic acid–Schiff (PAS) |
| | | 4. Paranasal sinuses | 4. Rhinosinusitis | 4. Sweating | 4. Galactomannan (GM) detection in fluids |
| | | 5. Fungal colonization in the gastrointestinal tract at the sites of the cornea | 5. Cutaneous infection | 5. Fever | 5. Early bronchoalveolar lavage (BAL) |
| | | 6. Central nervous system infection | 6. Persistent productive cough | 6. CT scan |
| | | 7. Dyspnea |
| | | 8. Chest pain | 7. Thin-section chest computed tomography |
| | | | 8. Multidetector computed tomography (MDCT) |
Table 1 (continued)

| Name of fungi | Morphology | Pathogenicity | Clinical manifestation | Symptoms | Diagnosis | References |
|---------------|------------|---------------|------------------------|----------|-----------|------------|
| Candida spp.  | 1. Diploid | Causing candidiasis by | Clinical symptoms are | All candidiasis disease signs include | Diagnosis could be made by | [60] |
|               | 2. Acquire dimorphism characteristic | 1. Adhering to epithelial cells | 1. Vulvovaginal candidiasis | 1. Discharge from the uterus | 1. Wet Mount |
|               | 3. Comprise filamentous hyphae | 2. Forming colonization | 2. Onychomycosis | 2. Irritation in the vaginal region | 2. PCR |
|               | 4. Secrets toxin | 3. Penetrating epithelia or invading hyphae | 3. Candidemia | 3. Burning sensation in the vagina | 3. Nucleic acid amplification tests (NAATs) |
|               | | 4. Disseminating vascular tissue | 4. Intra-abdominal candidiasis | 4. Dyspareunia | 4. Mass spectrometry |
|               | | 5. Colonizing endothelia | 5. Peritonitis | 5. Dysuria | 5. 1,3-1β D glucan |
|               | | | 6. Biliary candidiasis | 6. White patches emerge that resemble curd in the mouth, throat, tongue, and gum linings | 6. Mannan–antimannan |
|               | | | 7. Candida endophthalmitis | 7. White lesions on the retinal surface | |
| Name of fungi | Morphology | Pathogenicity | Clinical manifestation | Symptoms                                                                                   | Diagnosis                                                                                     | References |
|--------------|------------|---------------|------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------|
|              |            |               |                        | 8. Loss of vision, which may be gradual or occur suddenly                                   |                                                                                               |            |
|              |            |               |                        | 9. Edema of the retina opapillary                                                           |                                                                                               |            |
|              |            |               |                        | 10. Inflammation and stricture development in both intrahepatic and extrahepatic biliary systems |                                                                                               |            |
|              |            |               |                        | 11. Vascular choroid                                                                        |                                                                                               |            |
|              |            |               |                        | 12. Eyestrain, headaches, and floaters                                                        |                                                                                               |            |
were also diagnosed with mucormycosis, indicating that COVID-19 is a risk factor for mucormycosis [38].

Fungal coinfections, including 40 Candida auris-infected cases in the USA, Candida glabrata- and Candida albicans-associated cases in China, Aspergillus flavus- and Aspergillus fumigatus-related infections have also been documented in Europe [39]. In addition, between January and March 2020, 8 out of 104 COVID-19 patients infected with IPA have been found in China [40]. According to some other reports, the morbidity rate for IPA coinfection with COVID-19 patients was 20.6% in Belgium, 19.6% in the Netherlands, 33.3% in France, and 26% in Germany [41, 42]. A study found that when candidemia occurs with SARS-CoV-2, the mortality rate was 83.3%, even though the proper antifungal treatment was given to the patients [43]. In another study conducted in Colombia, 20 cases with around 30 days of observation while receiving antifungal therapy before achieving fungemia and taking up steroids due to COVID-19 came up with a 60% mortality rate [44]. Bekik et al. conducted a study among 2723 hospitalized COVID-19 patients, whereas eight were positive for CAPA, while the morbidity rate was 0.03% for hospitalized individuals and 3.3% for ICU patients. Shockingly, all eight patients with CAPA were died [41]. Furthermore, an observational study on CAPA conducted by Nasir et al. in Pakistan found that the mortality rate was 44% [42].

2.3 An overview of how fungi take the opportunity of the hampered immune system caused by SARS-CoV-2

SARS-CoV-2 anticipates the presence of angiotensin-converting enzyme-2 (ACE-2) receptor in the lung tissue, hence entering the lung cells with the help of furin. This entry site also provides virus stability [12]. The ACE-2 receptor has a downregulated expression in lung cells, leading to renin–angiotensin dysfunction in conjunction with acute lung injury. Followed by vascular leakage, inflammatory programmed cell death called pyroptosis stimulates inflammatory response locally. The result of pyroptosis is the secretion of different cytokines and chemokines in the blood, such as IL-1β, IL-6, IFN-γ, IFN-γ-produced protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP1) [45]. SARS-CoV-2 has six ORFs in common with all coronaviruses, including ORF1a and ORF1b, which span more than two-thirds of the genome [46]. The ORF codes for nonstructural proteins (Nsps), accessory, and structural proteins. The papain-like protease (Nsp3), chymotrypsin-like, 3C-like or main protease (Nsp5), helicase (Nsp13), and RNA-dependent RNA polymerase (Nsp12) are believed to be involved in SARS-CoV-2 transcription and replication. Spike surface glycoprotein (S), membrane nucleocapsid protein (N), an envelope protein (E), and auxiliary proteins expressed by ORFs are four vital structural proteins in addition to Nsps [12]. While infected with SARS-CoV-2, Nsp3 of the virus leads to the cleavage of ISG15 from IRF3, therefore attenuating the type I IFN. Moreover, SARS-CoV-2 Nsp1 proteins suppress IFN responses. Regarding IRF3 nuclear translocation, SARS-CoV-2 ORF3b has a higher inhibitory impact [47].

Furthermore, SARS-CoV-2 ORF6 inhibits and prevents the generation of interferons (IFNs); consequently, the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway becomes shut off [47]. Contrarily, when viral protein interacts with macrophages, it causes the production of cytokines such as IL-6, IL-10, IL-18, IL-12, IL-1, and TNF-α [48]. The antigen-presenting cells (APC) present viral peptides to T-lymphocytes with the help of the MHC II complex (major histocompatibility complex class II), which conducts adaptive immune response by generating compromised T-memory cells and releasing IFN-γ, IL-10, IL-17, and other chemokines subsequently. Survivors of COVID-19 are hence possessed with several cytokines and chemokines during infection called "cytokine storm" by dint of uncontrolled immune defense. Tocilizumab, infliximab, and serine protease inhibitors are applied to block the secretion of IL-6 and TNF-α and NF-κB expression to control hyper inflammation [49]. T cells and macrophages produce a smaller proportion of type II IFNs than natural killer cells. Type II IFNs induce apoptosis in infected cells and activate macrophages, natural killer cells, and T lymphocytes. Both type I and type II IFNs levels are decreased after in vitro stimulation of immune cells from COVID-19 patients is correlated with increasing disease extremity [50].

Fungal spores are first confronted by the first-line defense of the host, which subsequently results in an innate immune response. In conventional cases, fungal spores are engulfed by macrophages, killed by neutrophils, and attached to dendritic cells through receptor decline-1. However, moving to the presentation of the fungal pathogen to APC, they faced IFN-γ or IL-17 (Th17) that clear out them from the host cell. Host cells are embedded with many cytokines, mainly TNF-α, IL-1, and IL-6 [51]. Fungi are prone to be distinguished by the action of IFN-γ or IL-17 provided by T cells. Given impaired T cells and fewer other lymphocytes, fungi could not be eliminated from an immunosuppressed patient, especially if infected with SARS-CoV-2. To this extent, an opportunistic fungal coinfection in immunocompromised SARS-CoV-2 patients may result in short survival or cure [16] (Fig. 1).
2.4 Control and prevention of fungal infections in COVID-19 patients

Prolonged hospitalization, long-time illness, lack of surveillance and early diagnosis, clinical mismanagement, and antibiotics that suppress the defense system of COVID-19 patients trigger the fungal coinfection [52]. For instance, bronchoscopy performed on COVID-19 patients is an approach of aerosol generation, which could affect immunocompromised patients with fungal spores. The detection of galactomannan (a polysaccharide antigen of Aspergillus spp. cell wall) from bronchoalveolar lavage fluid is quite a functional and prompt method to detect invasive aspergillosis in immunocompromised patients [53]. In addition, PCR tests could also be helpful in early diagnosis other than galactomannan tests [40]. For detection and control of the Candida spp., screening could be performed regularly to determine its risk factors and reevaluate treatment protocol routinely [54]. Voriconazole is considered a preliminary antifungal treatment that works effectively with amphotericin B deoxycholate. Isavuconazole is another antifungal drug that holds the same activity as voriconazole. Echinocandins with azole work rapidly against invasive aspergillosis. Several drugs are still under clinical trials, including the inositol acylase inhibitor fosmanogepix against invasive aspergillosis and oral triterpenoid beta-glucan inhibitor ibrexafungerp against invasive aspergillosis and candidiasis. Although there is no specific time limit for therapy for fungal coinfection, experts suggest taking the drugs for 6 to 12 weeks as a course [55].
3 Conclusions
The severity of SARS-CoV-2 complexities rises with coinfection of fungi during or after SARS-CoV-2 infection. According to the assessment of fatality and number of illnesses, it may not be wrong to say that if pre-diagnosis does not happen or patients remain unchecked for fungal or other coinfection, another threat will emerge in the coming days. It has already been shown that mortality due to fungal coinfection does not change significantly, even if antifungal treatment is taking place to cure the disease. Pre-laboratory diagnosis should be given utmost attention to avoid a worsening condition. Several cautions should be maintained to spread the risk of fungal spores, including wearing masks, sanitizing, and maintaining cleanliness. Changing diet and acquiring the habit of sanitization could help to boost immunity.

Abbreviations
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019; CNS: Central nervous system; ARDS: Acute respiratory distress syndrome; ICU: Intensive care units; Th: T helper cell; IL: Interleukin; CAPA: COVID-19-associated pulmonary aspergillosis; IPA: Invasive pulmonary aspergillosis; ACE-2: Angiotensin-converting enzyme-2; IFN: Interferon; IP-10: IFNγ-produced protein 10; MCP1: Monocyte chemoattractant protein 1; Nsps: Nonstructural proteins; ORF: Open reading frame; IGS15: Interferon-stimulated gene15; IRF3: Interferon regulatory factor 3; TNF: Tumor necrosis factor; APC: Antigen-presenting cells; MHC: Major histocompatibility complex; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

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References
1. Saxena SK, Kumar S, Maurya VK, Sharma R, Dandu HR, Bhatt MLB. (2020) Current insight into the novel coronavirus disease 2019 (COVID-19). Coronavirus Disease 2019 (COVID-19)2020. p. 1–8.
2. Sharma Q, Sultan AA, Ding H, Triggle CR (2020) A review of the progress and challenges of developing a vaccine for COVID-19. Front Immunol 11:585354. https://doi.org/10.3389/fimmu.2020.585354
3. Eikz T, Pazarli AC (2020). Relationship between COVID-19 and obesity. Diabet Metab Syndrome:14(5):761–3. https://doi.org/10.1016/j.dxs. 2020.05.047
4. Alpek M (2021) Does COVID-19 cause hypertension? Angiology. https://doi.org/10.1177/00033197211053903
5. Aouissi HA, Belhaoucht I (2021) What about rheumatic diseases and COVID-19? New Microb New Infect 41:100846. https://doi.org/10.1016/j. nmi.2021.100846
6. Bishburg E, Okoh A, Nagararkaris SR, Lindner M, Migliore C, Patel P (2021) Fungemia in COVID-19 ICU patients, a single medical center experience. J Med Virol. 93(5):2810–4. https://doi.org/10.1002/jmv.26633
7. Landstra CP, de Koning EJP (2021) COVID-19 and diabetes: understanding the interrelationship and risks for a severe course. Front Endocrinol. https://doi.org/10.3389/fendo.2021.649525
8. CDC (2021) Emergence of SARS-CoV-2 B.1.1.7 Lineage — United States. https://www.cdc.gov/mmwr/volumes/70/ww/mm/7003e2.htm. Accessed 22 January 2021
9. Chatterjee D, Tazuin A, Laumaea A, Gong SY, Bo Y, Guilbault A et al (2022) Antigenicity of the Mu (B.1.621) and A.2S SARS-CoV-2 Spikes. Viruses. https://doi.org/10.3390/v14101144
10. Aouissi HA (2021) Algeria’s preparedness for Omicron variant and for the fourth wave of COVID-19. Glob Health Med. 3(6):413–4. https://doi. org/10.35772/ghm.2021.01117
11. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R, et al (2022) Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retropsective cohort study. medRev. https://doi.org/10.1101/2021.09.29.21264272
12. Kumar S, Nyoord R, Maurya VK, Saxena SK (2020) 2020 Host immune response and immunobiology of human SARS-CoV-2 infection. In: Saxena SK (ed) Coronavirus disease 2019 (COVID-19): epidemiology, pathogenesis, diagnosis, and therapeutics. Springer Singapore, Singapore, pp 43–53
13. Nargesi S, Bongomin F, Hedayati MT (2021) The impact of COVID-19 pandemic on AIDS-related mycoses and fungal neglected tropical diseases: Why should we worry? PLoS Negl Trop Dis 15(2):e0009092. https://doi. org/10.3389/fimmu.2020.585354
14. Salehi M, Ahmadikia K, Badali H, Khodavaisy S (2020) Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. Mycopathologia 185(4):607–611. https://doi.org/10.1007/s11046-020-00472-7
15. CDC (2021) Fungal diseases and COVID-19. https://www.cdc.gov/fungal/ covid-fungal.html. Accessed 22 March 2022
16. Drummond RA, Franco LM, Lionakis MS (2018) Human CARD9: a critical molecule of fungal immune surveillance. Front Immunol 9:1836. https://doi.org/10.3389/fimmu.2018.01836
17. Nasab MG, Saghazadeh A, Rezaei N (2020) SARS-CoV-2-A tough opponent for the immune system. Arch Med Res 51(6):589–592. https://doi. org/10.1016/j.sard.2020.05.047
18. Peman J, Ruiz-Gaitan A, Garcia-Vidal C, Salavert M, Ramirez P, Puchades F et al (2020) Fungal co-infection in COVID-19 patients: should we be concerned? Revista iberoamericana de micologia. 37(2):41–6. https://doi.org/10.1371/journal.pntd.0009092
19. Saxena SK, Kumar S, Maurya VK, Sharma R, Dandu HR, Bhatt MLB. (2020) Coronavirus Disease 2019 (COVID-19)2020. p. 1–8.
20. Peng J, Wang Q, Mei H, Zheng H, Liang G, She X, et al. (2021). Fungal Fungemia in COVID-19 ICU patients, a single medical center experience. J Med Virol. 93(5):2810–4. https://doi.org/10.1002/jmv.26633
21. Nargesi S, Bongomin F, Hedayati MT (2021) The impact of COVID-19 pandemic on AIDS-related mycoses and fungal neglected tropical diseases: Why should we worry? PLoS Negl Trop Dis 15(2):e0009092. https://doi. org/10.3389/fimmu.2020.585354
22. CDC (2021) Fungal co-infection in COVID-19 patients: evidence from a systematic review and meta-analysis. Aging (Albany NY) 13(6):7745–57. https://doi.org/10.18632/aging.20274
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