INTRODUCTION

Coronavirus Disease-2019 (COVID-19) was announced on November 16, 2019 when the first patient was diagnosed. Subsequently, the World Health Organization declared COVID-19 as a pandemic disease caused by SARS-CoV-2 on March 11, 2020.

A total of 25,051,178 confirmed patients were reported worldwide with 843,586 COVID-19 related deaths by August 31, 2020. The COVID-19 pandemic has caused a serious health crisis worldwide. There were 19,947 confirmed cases and 324 deaths in South Korea, and the trend is increasing rapidly. Approximately 14% of COVID-19 patients have severe symptoms of breathing difficulties and low oxygen saturation, and 5% of patients have respiratory failure, septic shock, and fatal symptoms such as complex organ failure, resulting in death in 2.3% of patients, even though they mostly improved with conservative treatment. The mortality of COVID-19 increases in patients with comorbidities. The fatality rate was 10.5% in patients with cardiovascular disease, 7.3% in people with diabetes, 6.3% in chronic respiratory disease, and 6.0% in hypertension. However, there are still insufficient data on the association between COVID-19 and fungal infection. Therefore, we would like to review patients with fungal infections in the COVID-19 pandemic era.

Key Words: Co-infection, Corona virus, COVID-19, Dermatologic department, Fungus

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-CoV-2)

Coronavirus belongs to the family Coronaviridae which are enveloped and single-stranded RNA viruses. Coronaviruses are classified into 4 groups: α, β, χ, and γ-coronavirus. Severe acute respiratory syndrome (SARS)-CoV-2 belongs to the beta-coronaviruses and is similar to bat CoV and SARS-CoV-1. SARS-CoV-2 has a specific spike glycoprotein that has a strong binding affinity to the angiotensin-converting enzyme 2 (ACE2) receptors, which is approximately 20 times higher than that of SARS-CoV-1. The spike glycoprotein mediates host receptor binding and cell entry, triggering infection of multiple cell types, including respiratory, gastrointestinal, and renal epithelial cells, among others. The virus enters the cell through the endocytic pathway and then replicates in the cytoplasm. The viral genome is then replicated and released into the extracellular space, where it can infect other cells. The virus can also spread from cell to cell through direct contact, leading to the formation of cell-to-cell syncytia.

In addition to the respiratory tract, SARS-CoV-2 infection can involve various organ systems, including the cardiovascular, renal, gastrointestinal, and central nervous systems. The disease can progress to severe respiratory failure, severe pneumonia, shock, and multi-organ failure, which can lead to death. The mortality rate of COVID-19 varies depending on the severity of the disease, with higher mortality rates in patients with pre-existing conditions such as diabetes, hypertension, and chronic respiratory disease. The virus is known to be transmitted through respiratory droplets, and close contact with an infected person can lead to infection. Therefore, it is important to practice good hygiene, social distancing, and the use of personal protective equipment to prevent the spread of the virus.
SARS-CoV-2 is a highly contagious disease transmitted through the respiratory droplets of infected patients, including asymptomatic carriers directly or indirectly. Fever, cough, fatigue, anorexia, myalgia, and diarrhea are the most common symptoms of COVID-19. Severe symptoms are dyspnea, hypoxemia, and rapid progression of respiratory failure. The overall mortality rate is 2.3%.

**CUTANEOUS MANIFESTATIONS IN PATIENTS WITH COVID-19**

A variety of cutaneous manifestations can accompany viral infection. Previous reports showed COVID-19 patients with urticarial rash. Since then, several related symptoms have been reported. Recalcati demonstrated that 20.4% of COVID-19 patients in Italy developed cutaneous manifestations, and the patients had cutaneous manifestations such as erythematous rash, urticaria, and chickenpox-like vesicles. Skin findings, including chilblain-like (40.2%), maculopapular (22.7%), urticarial (8.9%), vesicular (6.4%), livedoid and necrotic (2.8%), and other skin lesions (19.8%), were reviewed by Jia et al. Furthermore, patients may complain of pain, burning, or itching. On the other hand, cutaneous symptoms were subdivided into 6 patterns by Marzano et al., as follows: urticarial rash, confluent erythematous-maculopapular-psoriasiform rash, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis-livedo racemosa-like pattern, and purpuric “vasculitic” pattern. As such, there have been few reports of additional fungal or bacterial infections in patients with COVID-19 who visited a dermatology clinic.

**COVID-19 AND FUNGAL INFECTION**

It has been suggested that COVID-19 might increase the risk of co-infection or superinfections. Zhu et al. reported SARS-CoV-2 co-infection with other pathogens in laboratory-confirmed COVID-19 patients, where 94.2% of patients had co-infection with one or more pathogens, with bacterial co-infection being dominant. Furthermore, 31.5% of patients had viral co-infection, 91.8% had a bacterial co-infection such as Streptococcus pneumoniae, Klebsiella pneumoniae, or Haemophilus influenzae, among others, and 23.3% had fungal co-infection. The co-infection fungal pathogens included Aspergillus (23.3%), Mucor (2.5%), Candida (0.8%), and Cryptococcus (0.4%). The rates of viral co-infection (35.3%), fungal co-infection (29.5%), and bacterial-fungal co-infection (29.5%) were the highest in severe COVID-19 patients.

Three cases of Candida albicans, 1 case of Candida glabrata, and 1 case of Aspergillus flavus co-infection among 99 COVID-19 patients were presented by Chen et al. Yang et al. found 3 cases including Aspergillus flavus, Aspergillus fumigatus, and Candida albicans among 52 COVID-19 patients. Zhang et al. also found that co-infections in severe patients with COVID-19 were significantly higher than those in non-severe patients. They suggested that this is due to a decrease in host immune function and the presence of invasive catheters. This may lead to increased susceptibility to secondary infections by multidrug-resistant pathogens. Therefore, clinicians should consider co-infection when diagnosing COVID-19.

Co-infection with COVID-19 and invasive pulmonary aspergillosis was found. It has recently been reported that COVID-19-associated pulmonary aspergillosis (CAPA) causes serious pulmonary abnormalities that require therapy in intensive care unit (ICU) due to its high mortality. CAPA was found in 33% of ICU patients admitted for COVID-19 in France, and 26% in Germany. Severe COVID-19 is associated with impaired immune regulation, affecting both T-helper cell 2 (Th2) and Th1 responses, thus explaining the mechanism behind co-infection. CAPA due to Aspergillus fumigatus requires early diagnosis with the identification of a triazole-resistant isolate. However, exposure to antifungal drugs may reduce sensitivity of the serum galactomannan test and delay the diagnosis.

Meanwhile, it has been reported that co-infection of bacteria or fungi is associated with the use of empirical antimi- crobial agents in patients with coronavirus-related respiratory infections. Approximately 60% of the articles did not mention bacterial/fungal infections. Regarding COVID-19, 8% of patients had bacterial/fungal co-infection during hospitalization. There were not many simultaneous bacterial/fungal infections, as expected, even though patients with coronavirus-related respiratory infections actually use a wide range of empirical antimicrobial agents. Hughes et al. also reported no evidence of risk of concomitant fungal infections in the early stages of COVID-19 in the UK.

**CONCLUSIONS**

The skin provides a shield against external stimuli and is a major part of the immune system. Loss of the skin barrier increases the risk of multiple infections, despite the lack of reports of fungal co-infection in the dermatologic department. More attention should therefore be paid to the COVID-19 pandemic era.
Diagnosis of COVID-19 and fungal co-infection can be delayed, missed, or misdiagnosed. Afterwards, COVID-19 can cause impairment of cellular immune responses and lead to high mortality.

CONFLICT OF INTEREST
In relation to this article, we declare that there is no conflict of interest.

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REFERENCES