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Call for evidence mapping in accordance with the changing features of invasive pulmonary aspergillosis during the coronavirus disease 2019 pandemic

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I had the opportunity to contribute to an editorial on a recent article regarding the incidence of invasive pulmonary aspergillosis in critically ill patients diagnosed with coronavirus disease 2019 (COVID-19) [1]. While many studies are focused on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection itself, it is important to note that COVID-19 has led to various prognostic changes in many other common diseases. In particular, critically ill patients with COVID-19 have emerged as a group with high risk of invasive aspergillosis. This is considered a novel complication and has been named COVID-19-associated pulmonary aspergillosis (CAPA) [2]. The suggested pathophysiological manifestations of CAPA include destruction of the airway epithelium and suppression of cellular immunity, which is triggered by SARS-CoV-2 infection [3]. Additionally, the poor health condition of intensive care unit (ICU) patients and concomitant therapies for COVID-19 contribute to the deteriorating condition of such patients during co-infection [4]. Patients with CAPA are generally older and more likely to have underlying pulmonary diseases, solid organ transplantation, a hematological or oncological malignancy,

or liver disease.

Recently, Lee et al. [1] reported that the incidence of CAPA in the Republic of Korea (ROK) was 11.2% among ICU patients with COVID-19. These data are comparable with findings from a multicenter retrospective study in the ROK [5]. Since 2020, studies regarding the incidence of CAPA in ICU patients with COVID-19 have revealed diverse prevalence rates (2.5% to 39.0%) [2].

Probable causes of the deviation in CAPA rates among critically ill patients diagnosed with COVID-19 include differences in medical staff awareness of CAPA; variations in the types of clinical specimens used for CAPA diagnosis; differences in the frequency of bronchoscopy to obtain bronchoalveolar lavage fluid; nonspecific radiological findings, poor access to chest imaging or tissue biopsy findings in COVID-19 patients with hemorrhagic tendencies who are on mechanical ventilation; generally low sensitivity of the serum galactomannan assay in non-neutropenic or immunocompetent COVID-19 patients; and the use of diagnostic criteria for pulmonary aspergillosis, which were mainly established for immunocompromised individuals.

It is also challenging to use the diagnostic criteria for CAPA in a clinical setting. For the diagnosis of pulmonary aspergil-

losis before 2020, the clinical research definitions of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSGERC) required the presence of immunocompromising host factors. However, the modified *Asp*ICU algorithm and the 2020 European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) established a consensus regarding the removal of host factors as diagnostic criteria [6]. Of note, the ECMM/ISHAM criteria included the entry criterion of a patient requiring ICU admission for acute respiratory distress syndrome with a polymerase chain reaction (PCR) assay result that confirms the presence of SARS-CoV-2 [6]. It is meaningful that the most recent epidemiological studies of CAPA in the ROK presented objective data based on ECMM/ISHAM criteria [2,5]. Nonetheless, the ECMM/ISHAM consensus criteria have an important limitation in that clinical performance meets expectations only in medical environments where bronchoscopy and quantitative PCR tests for *Aspergillus* species are available. Thus far, most medical institutions in the ROK conduct active surveillance for CAPA that relies on the presence of serum galactomannan or (1,3)-β-D-glucan and the culture of tracheal aspirates. In the ROK, the burden of single-use bronchoscopy and the risk of infection transmission limit the practical use of bronchoscopic lavage procedures. Furthermore, few clinical laboratories perform quantitative PCR tests to detect *Aspergillus*. Therefore, more flexible diagnostic criteria should be considered with particular focus on resource availability. In this context, there is a need to design novel methods for effective collection of respiratory aspirates, then validate those methods via clinical studies. Another important consideration is that patients with CAPA are more likely to be identified by direct microscopic examination, in combination with other diagnostic tools [7]. Notably, periodic screening is important for improving diagnostic sensitivity in clinical settings when host factors mentioned in the EORTC/MSGERC definition are present or the local incidence of CAPA is high. Lee et al. [1] observed that the overall mortality associated with CAPA was 50.0% in ICU patients. This is similar to the findings of a previous study that included patients from the ROK [5]. The French multicenter MYCOVID study, which involved 565 mechanically ventilated patients with COVID-19, found that significant predictors of death included probable or possible CAPA, as well as solid organ transplantation and

age > 62 years [8]. These findings highlight the difficulty of successfully managing CAPA in critically ill patients with COVID-19. High mortality rates might justify the implementation of antifungal prophylaxis as a targeted preventive measure or a preemptive strategy to prevent CAPA-related deaths [4]. However, there is a need to consider the lack of licensed antifungal drugs that could be used as prophylaxis in the ICU, as well as the potential for development of strains that are resistant to antifungal agents.

Additionally, particular attention is needed concerning the clinical impact of corticosteroids or immune modulators on the incidence and mortality of CAPA. Lee et al. [1] demonstrated that daily high-dose steroid use (methylprednisolone > 60 mg/day) was an independent predictor of CAPA that led to a significant increase in the 30-day mortality rate. This finding is consistent with the results of previous studies [5,8]. Kim et al. [5] also suggested that patients with COVID-19 receiving high doses of corticosteroids (> 60 mg of dexamethasone equivalent for the first 10 days) might carry a greater risk of CAPA. Such an increased risk can result in adverse outcomes among critically ill patients with COVID-19. Nonetheless, because corticosteroid therapy improves overall mortality in critically ill patients with COVID-19, many experts do not recommend the discontinuation of corticosteroids in patients who have been diagnosed with CAPA. Additional studies concerning the optimal dose and length of corticosteroid use are needed to clearly elucidate the benefits and risks.

Lee et al. [1] reported that the median time to diagnosis after admission was 9.5 days (interquartile range, 7.0 to 12.0). In a previous study, the median interval between admission to the ICU and diagnosis of CAPA was 9 days (interquartile range, 5 to 13). In contrast, another study published in the ROK reported 25 days (range, 2 to 77) as the median interval between symptom onset and CAPA diagnosis [5]. This finding indicates the potential for a delayed diagnosis of CAPA—the medical resources available for diagnosis, as well as the awareness of CAPA by medical staff, may influence the timing of diagnosis in clinical settings. However, several confounding variables (e.g., hospital environment, COVID-19 treatment protocols, and host factors) might have contributed to differences in the timing of CAPA onset.

In the context of the H1N1 influenza pandemic, the occurrence of respiratory virus infection was a significant risk factor for the development of invasive pulmonary asper-

gillosis [9]. Thus far, there are limited data concerning the differences and similarities between influenza-associated pulmonary aspergillosis (IAPA) and CAPA. Although both diseases have similar incidence (10% to 30%) and mortality (approximately 50%) rates, IAPA is more common in immunocompromised patients (25% to 30% in the IAPA group vs. < 10% in the CAPA group) and occurs more rapidly after ICU admission (3 to 7 days vs. 3 to 14 days), compared with CAPA [9]. In particular, the positive rate of serum galactomannan is higher in IAPA patients than in CAPA patients (50% to 70% vs. 10%) [9]. The use of more immunomodulators in patients with COVID-19 than in patients with influenza could also be responsible for the different clinical characteristics of invasive pulmonary aspergillosis.

Because CAPA has a high mortality rate, there is an urgent need to identify and correct problems at each stage of prevention, diagnosis, and treatment. The treatment of patients with severe COVID-19 requires enhanced infection control within the hospital environment, as well as drug interventions related to immunosuppressant agents. For the early diagnosis of CAPA, a higher index of suspicion and greater active surveillance within high-risk groups are needed among immunocompetent, critically ill patients with COVID-19, in addition to the considerations for high-risk patients who exhibit immunosuppression. The gains and losses of antifungal prophylaxis and preemptive strategies should also be validated through clinical trials. According to the optimized clinical algorithm for CAPA diagnosis, active use of clinically validated diagnostic tools is important for the provision of timely optimized treatment that adheres to clinical guidelines. In this context, expansion of insurance coverage for antifungal drugs that have been newly introduced in the ROK (e.g., isavuconazole) may also be considered.

In conclusion, Lee et al. [1] further explored the association of a high prevalence of CAPA with a high mortality rate by evidence mapping analysis. Their study suggested that clinicians should ensure optimal use of corticosteroids by using a risk-benefit analysis approach. Additionally, early identification of CAPA and primed treatment must be prioritized to reduce the mortality associated with CAPA. For optimal antifungal treatment, the development of reasonable diagnostic algorithms that can be implemented in resource-limited settings, with proper administrative support from the insurance system, will contribute to the resolution of problems associated with CAPA.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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