

The Association Between COVID-19 and Invasive Pulmonary Aspergillosis: A Challenge for Health Care System

Ali Arianezhad¹, Behnam Azizolahi², Reza Ghaffaripour²

¹ School of Medicine, Dezful University of Medical Sciences, Dezful, Iran

² Department of Medical Laboratory Sciences, School of Paramedicine, Dezful University of Medical Sciences, Dezful, Iran

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Abstract- The emerging disease of COVID-19 was announced as a pandemic in 2020, with wide prevalence worldwide. After the duration of the pandemic of the disease, reports based on the invasion of *Aspergillus* into patients' lungs with COVID-19 and their hospitalization in ICU were published by the researchers, which attracted the attention of other researchers to perform such studies. In this review, PubMed, ScienceDirect, Scopus, Springer, Wiley, ProQuest, Sid, Cochrane, and the search engine Google Scholar were searched for publications by the keywords include COVID-19, *Aspergillus*, SARS-CoV-2, Invasive pulmonary aspergillosis, fungal and viral co-infection or a combination of them. The data were extracted and descriptively discussed. Not many studies have been performed on the association between aspergillosis and COVID-19. However, although the results of the studies suggest some possible causes of these concomitant infections like underlying diseases and prolonged mechanical ventilation, they also recommend further studies. Since the diagnosis of common fungal and viral infections is difficult, the concurrent incidence of these two infections in patients becomes a therapeutic challenge. Accordingly, this issue increased the mortality rate in this group of patients, especially in those hospitalized in ICU. According to the recently performed studies, various problems, including underlying diseases and difficult diagnostic methods of some dangerous diseases like invasive aspergillosis, are discussed in patients with COVID-19.

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Introduction

Inhalation of fungal spores placed in the respiratory pathway is with induction or aggregation of respiratory diseases such as asthma, allergic rhinitis, sinusitis, and pneumonitis (1-4). *Aspergillus* is one of the fatal fungal species (5,6), which besides growing in respiratory pathways, has the ability to produce allergen. So, by fragmentation of fungal hyphae, it plays an important role in establishing allergic reactions (7,8) and annually threatens millions of humans' lives (9). Toxin secretion from fungi is another harmful process during fungal respiratory involvements. All these processes become more important when the patient develops immune system compromising, which can even lead to death (10).

In this regard, some reports indicated a high mortality rate in individuals with immune system weakness and with fungal pathogens, especially *Aspergillus* (11-13). Numerous studies have been done on immune response against fungal proliferation in airways and lungs, in which giant cells play a role as the first cells of the defense line against inhaled fungi (14). Accordingly, through this work, the resistance of the immune system increases against the invasion of inhaled fungi (15). Spores that are not phagocytosed and allowed to grow are responsible for performing allergic reactions (16,17).

Thereafter, the lymphatic immune system initiates to work, and in its glands, dendritic cells induce a specific immune pathway through both providing antigens to T lymphocyte cells and signaling produced by T-helper (18-

Corresponding Author: R. Ghaffaripour

Department of Medical Laboratory Sciences, School of Paramedicine, Dezful University of Medical Sciences, Dezful, Iran
Tel: +98 6142429531, Fax: +98 6142429730, E-mail address: ghaffaripour.r@dums.ac.ir

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20). Other members of the immune system also play a role in the process of defeating fungal pathogens, including interleukin 1, interleukin 2, and interferon-gamma (21). Despite a clear role of the above-mentioned factors in inducing an allergic response to fungal pathogens, a distinct mechanism in this regard is not thoroughly identified yet (22-24). Besides genetic factors, environmental factors are also effective in the growth of fungal pathogens. So, it can be said that infection, lifestyle, elimination of normal flora of the respiratory system following the use of antibiotics, and change in dietary regimen can be effective in this process (25-27).

Previously, studies have been done on the incidence of invasive aspergillosis in patients with HIV, the results of which indicated the ability to defeat of immune system of the individual with HIV against the growth of *Aspergillus* fungi (28). Therefore, it can be said that each viral infection that has the ability of the body's immune system to weaken could inevitably provide an environment for the growth of opportunistic fungal pathogens like *Aspergillus*. Accordingly, one of these viral infections is COVID-19 (29). This virus was observed for the first time in Wuhan, China, in December 2019, and after spreading globally, it became a pandemic (30). Consequently, the World Health Organization introduced this virus as a health emergency internationally (31). Notably, this virus provides the environment for the growth of other infections by invading to respiratory system besides direct damaging the respiratory system by weakening the immune system. In addition, after the invasion of the virus into the respiratory system, in cytokine rate increases in tissue, which causes pulmonary fibrosis in patients with COVID-19 (32). Clinical symptoms of the disease of COVID-19 are fever, coughing, fatigue, myalgia, and in some cases, emerging gastrointestinal symptoms (33,34). In the pandemic of COVID-19, the invasion of *Aspergillus* fungi to patients' lungs is considered a new challenge, which should be properly managed by health authorities (35,36). In the current review study, we investigated the prevalence and diagnostic methods of invasive pulmonary aspergillosis in patients with COVID-19.

Materials and Methods

In this review, PubMed, ScienceDirect, Scopus, Springer, Wiley, ProQuest, Sid, Cochrane, and the search engine Google Scholar were searched for publications by the keywords include COVID-19, *Aspergillus*, SARS-CoV-2, Invasive pulmonary

aspergillosis, fungal and viral co-infection or a combination of them. In these searches, 441 articles were obtained, and after removing duplicate items and based on access to the full text of the articles, 255 articles were selected, which were first reviewed by title and then by abstract by two researchers in the fields of medical mycology and virology. Finally, the results of 21 articles that answered the question of this study were used directly in the present review.

Results

With the occurrence of the pandemic of SARS-CoV-2, a virus of the family Coronaviridae, different studies have been done on the incidence of invasive aspergillosis in patients with COVID-19. Some previous studies have also been done on other diseases caused by other members of this viral family, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The important point that Wang *et al.*, has stated in their case study in 2003 was the invasion of *Aspergillus* to some tissues such as the brain, heart, adrenal glands, kidneys, and lung texture due to consuming high doses of methylprednisolone in 39-year-old patients with SARS. Correspondingly, this led to the patient's death (37).

Prattes *et al.*, in a study in 2020, reported one case of concomitant infection of aspergillosis and COVID-19. The results of this study present the hypothesis of accompanying two diseases of COVID-19 and pulmonary aspergillosis and stated that this concomitant infection could consequently increase the mortality rate in patients (38).

This hypothesis was also stated by Blaize *et al.*, in the assessment of another patient and stated that following an increase in virus proliferation, inflammatory and cytokine responses probably are the other factors of pulmonary invasion of *Aspergillus* (39).

In another study in 2020, Alanio *et al.*, started research on 27 hospitalized patients with COVID-19 in ICU, which despite previous studies claiming consuming antiviral medication of oseltamivir as the reason for pulmonary aspergillosis involvement of patients with influenza, they did not use this medication in the treatment of these patients. In addition, according to a piece of advice by Chinese physicians recorded in previous studies, for all 27 patients, consuming corticosteroids was prescribed (to suppress inflammatory reactions). At the end of the research, due to a high dose of steroids, the incidence of pulmonary aspergillosis was observed in 33% of the studied patients (40).

Van Arkel *et al.*, by considering their study population

consisting of 31 individuals (patients with two diseases of COVID-19 and pulmonary aspergillosis), stated that 19.4% (approximately high rate) of the patients had both viral and fungal infections (24).

Other studies stated similar rates, which can point to the prevalence rate of 33.3% (41) and 35.3% (42) of secondary fungal infections in ICU of hospitals in China.

Rutsaert *et al.*, performed a study to investigate this association in 34 patients with COVID-19 with a mean age of 66 years old who were hospitalized in ICU. As a result, the invasion of *Aspergillus* was confirmed in four patients (43).

Another study aimed to discover the clinical characteristics of patients infected by two diseases of COVID-19 and pulmonary aspergillosis was performed by Wang *et al.*, on 104 patients hospitalized in ICU. This study's design was retrospective case series. Among all the patients, 8 patients (7.7%) were with invasive pulmonary aspergillosis, and all of them was a man with a mean age more than others. In addition, a diagnosis of pulmonary invasion of *Aspergillus* was made on average after almost 19 days, which is a long duration (44).

Four patterns of damage following the *Aspergillus* invasion of the lung in patients with COVID-19 were provided in 2020 by Flilweert *et al.*, which consist of acute fibrinous with organizing pneumonia, diffuse alveolar damage, fibrosis, and organizing pneumonia (45).

Discussion

According to the results of the mentioned studies, different hypotheses have been stated about the causes of co-infection of invasive pulmonary aspergillosis and COVID-19. Also, different diagnostic methods for this fungal disease and the duration of its diagnosis have been discussed.

As previously mentioned about another member of the family, Coronaviridae, in the case study of Wang *et al.*, consuming corticosteroids, although it was prescribed with the aim of resolving the symptoms of SARS disease, causes suppression of the immune system and provides the breeding environment for *Aspergillus* fungi (37).

In this regard, following the study of Blaize *et al.*, the new point mentioned in their study was that since COVID-19 in some individuals rapidly leads to lung failure and death, in case of accompanying another deadly fungal disease such as aspergillosis, the mortality rate severely increases (39). Moreover, delay in the positivity of diagnostic indices of *Aspergillus* fungi (galactomannan index, beta- D glucan, microscopic evidence, and PCR) might be another reason for the increased mortality rate

(39,46).

Although some laboratory tests such as galactomannan detection are considered the most sensitive diagnostic tests, since the health care team mostly attempts to perform such tests at the last stages of the disease (Sometimes this is due to the risk of disease transmission during sampling), they lose their opportunity for early diagnosis, which increases mortality rate (39,47,48). Therefore, it seems necessary to perform more studies with large sample sizes to design new protocols (48).

In addition, it is probable that symptoms of invasive pulmonary aspergillosis become emerge after two weeks of being infected with COVID-19 (38).

According to the previous cohort studies performed with the titles of accompanying two diseases of COVID-19 and aspergillosis, new results were achieved, and some of them confirmed previous studies. For instance, Verweij *et al.*, in 2019, after the assessment of statistical data, found that despite using no immunosuppressants (The reason that was identified as the leading cause of providing a growth environment for *Aspergillus*), invasive pulmonary aspergillosis occurs in patients with COVID-19. In addition, due to the similarity of the images resulting from chest imaging of patients with COVID-19 and aspergillosis, it was difficult to distinguish between these two diseases in this way (49).

In some studies, like those performed by Gangeux *et al.*, and Santana *et al.*, some risk factors providing the environment for the invasion of fungal pathogens have been mentioned, including long-term hospitalization in ICU, development of acute respiratory failure syndrome, treatment with high doses of corticosteroids, the occurrence of cytokine storm in body, intubation, and long-term connection to the ventilator (23,50).

All the above-mentioned risk factors are observed in many cases of COVID-19 (33,34,51,52).

Therefore, most of the studies performed by Chinese physicians confirmed the claim that there is a statistical relationship between two diseases of COVID-19 and pulmonary aspergillosis (53,54).

There is no precise awareness of the effect of this fungal pathogen (*Aspergillus*) on the mortality rate of patients with influenza hospitalized in ICU in some studies yet (55,56).

However, according to another study, this background is available that the 90-day mortality rate in patients admitted to the ICU with viral influenza was 51% when accompanied by invasive pulmonary aspergillosis. In contrast, in patients with just influenza, the mortality rate was 28% (57).

Since following disease of COVID-19, almost most

symptomatic patients are hospitalized in ICU under the same conditions, which all were risk factors for infection by fungal-respiratory diseases, so it seems necessary to evaluate patients with COVID-19 regarding the involvement with opportunistic fungal pathogens, especially *Aspergillus* (23,58,59), as well, in case of any infection with fungal disease, process and way of treatment should be changed (60).

Wang *et al.*, in their study, believed that well-timed diagnostic measures, including serology, graphy, and biopsy, should be done for early diagnosis of aspergillosis. Therefore, as it was observed, these diagnostic and therapeutic attempts decrease the number of critically ill patients compared to other research (44,57).

In addition, in some studies, a well-timed diagnosis of pulmonary aspergillosis in patients with COVID-19 has been stated as one of the challenges of treatment in this group of patients (58,61).

One of the main factors of mortality in patients whose immune system is suppressed is invasive aspergillosis (62), which definitely attacks to lungs (63), which is the organ targeted by COVID-19. Some laboratory methods of diagnosis of aspergillosis (such as culture, microscopic assessments, etc.), due to a long time of providing results as well as false-negative results (64,65), are unreliable. In contrast, the test of BAL-GM (which acts based on the presence of galactomannan as a diagnostic index) has a high sensitivity in the diagnosis of invasive aspergillosis (66), So some studies used this method for the final diagnosis of aspergillosis and in some cases to save the patients.

Cytokine storm, which is induced by the immune system against COVID-19, is one of the reasons for the incidence of symptoms of COVID-19 (51). Accordingly, the health care team uses glucocorticoids (GCs) to defeat this phenomenon in order to suppress the immune system. This attempt is known as an underlying factor for the growth of *Aspergillus* fungi in patients with COVID-19 in all studies cited in this research except just one article.

Given the above-mentioned problems regarding this issue, diagnosis of *Aspergillus* fungi and being invasive of the fungal pathogen make difficult the process of decision-making on appropriate diagnostic and therapeutic methods, especially while it is accompanied by a newly emerging disease such as COVID-19, which belongs to respiratory diseases and has a high fatality by itself.

Concomitant infection of these two diseases in one individual severely increases the mortality rate. Although huge information exists in this regard, and some methods are provided for diagnosis, definitely, there are many cases that are not diagnosed or not recorded. Accordingly, this

can be due to a lack of the presence of therapeutic background to exposure to concomitant infection of these two diseases (COVID-19 and aspergillosis).

Finally, further studies are warranted with larger sample sizes in this regard, and making appropriate decisions in health and therapeutic policies considerably helps in decreasing the mortality rate caused by these two diseases.

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COVID-19 and invasive pulmonary aspergillosis

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COVID-19 and invasive pulmonary aspergillosis

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