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Literature Review

The Impact of Complication of COVID-19 - Associated Pulmonary Aspergillosis

Ahmad Aliyu*

Department of Microbiology, Ibrahim Badamasi Babangida University, Lapai, Niger State, Nigeria

***Corresponding Author:** Ahmad Aliyu, Department of Microbiology, Ibrahim Badamasi Babangida University, Lapai, Niger State, Nigeria.

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Abstract

Background: Invasive Pulmonary Aspergillosis (IPA) is a secondary fungal infection that increasing the mortality rate and enhanced the concerns due to its detrimental effect among COVID-19 patients. Direct impairment to the airway epithelium is facilitated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which allow the invasion of Aspergillus species.

Aim: The study aimed to evaluate the diagnostic criteria, incidence, risk factors and mortality rate that leads to the complication of COVID-19-associated pulmonary aspergillosis (CAPA) from the available data in the studies.

Method: A systemic literature review was carried out to evaluate all current epidemiology that reports the incidence of CAPA from relevant published articles.

Results: In critical ill COVID-19 patients, sputum and tracheal aspirate are usually positive but can represent upper airway colonization. Bronchoscopy with bronchoalveolar lavage is insignificant due to the risk of infection and nosocomial transmission among health care workers. Alternatively, CT-guide biopsies post mortem have been used more than autopsy and non-bronchoscopic lavage is usually preferred method for CAPA diagnosis when compared to bronchoalveolar lavage. The mortality rate is about 52/90 (58%) approximately and common comorbidities include diabetes mellitus, obesity, arterial hypertension, chronic respiratory failure, chronic obstructive pulmonary disease, chronic renal failure, bronchial asthma and cerebrovascular disease. Aspergillus fumigatus is a common causative agents of CAPA. Italy and UK had the highest mortality rate of 25.0% followed by Spain with 15.4% when compared to other locations.

Conclusion: Respiratory specimen is the most preferred invasive pulmonary aspergillosis (IPA) sample for fungal diagnostic examination. The detection of galactomannan does not prove tissue invasion and infection. The results of serum galactomannan is usually low in CAPA. Further studies on CAPA are needed urgently to differentiate between pulmonary and tracheobronchitis phenotypes of aspergillosis, immunological defense and host factors and to address the therapeutic options and appropriate diagnostic criteria of the infection.

Keywords: *Invasive Pulmonary Aspergillosis; COVID-19; SARS-CoV-2; Aspergillus fumigatus; Galactomannan*

Introduction

In December, 2019, COVID-19 was emanated from Wuhan, China and became widespread across the globe [1]. Invasive pulmonary aspergillosis (IPA), fungal and bacterial infections are usually transmitted due to the susceptibility of patients infected with viral pneumonia

[2]. Apparently, COVID-19 patients are immunocompetent, mostly of advanced age with comorbidities such as renal disease, hypertension, chronic heart and diabetes [3]. Eventually, the patients will develop severe infections with cytokine storm, respiratory failure, and complex immune disorder that demand urgent hospitalization in the intensive care unit (ICU) [4]. Some studies have reported that the CAPA has raised a concern about the infection as an additional contributing factor for the increase of mortality rate [2]. The complication of influenza-associated pulmonary aspergillosis (IAPA) has leads to acute respiratory distress syndrome (ARDS) to numerous critical ill patients [2]. Studies reported 108 critical ill patients with ARDS and increased mortality rate was observed in patients with CAPA when compared to the patients without aspergillosis [6]. Viral respiratory agents cause direct damage to the airway epithelium and facilitates *Aspergillus* species to propagate and invade the tissue [7]. Viral infection inhibits ciliary clearance and leads to systematic impairment of immune system [8]. Mycological examination of airway invasive aspergillosis in COVID-19 patients, is usually difficult to carry out due to low sensitivity of detection of circulating galactomannan in serum and decrease use of diagnostic bronchoscopy [2]. Mycological examination of *Aspergillus* species in specimens of the upper respiratory tract such as tracheal aspirate or sputum usually does not make different between invasive disease and *Aspergillus* colonization. However, the first case of secondary aspergillosis infection was reported in China. Studies have reported that immune-modulatory therapy and steroid, facilitate an increased risk of severe COVID-19 which is referred as COVID-19 associated pulmonary aspergillosis (CAPA). Studies reported that about 9% of mechanically ventilated patients were diagnosed with either putative, proven or probable of CAPA [10]. In invasive pulmonary aspergillosis (IPA), the classical host factors are uncommonly reported in patients with CAPA. Diffuse pulmonary micro thrombi and direct epithelial injury in addition with immunosuppressive treatment, immune system impairment and hyper inflammatory response may be compromised [10]. Significant differences between tracheobronchial and parenchymal classes of CAPA is needed, and radiological signs of IPA are not clearly seen in severe COVID-19 patients with pneumonia. *Aspergillus fumigatus* is the common clinical isolate in respiratory cultures investigation [2]. β-d-glucan, bronchoalveolar lavage, polymerase chain reaction, serum galactomannan and *Aspergillus*-specific lateral-flow device test can be incorporated in the diagnostic criteria. These methods are often shows low sensitivity and appropriate treatment of CAPA is required. Therapeutic options include voriconazole, liposomal amphotericin B and isavuconazole. Administration of prophylactic treatment is currently debated due to incidence of high mortality rate among patients with *Aspergillus* infection [2].

Methodology

Data collection

A literature search for publications that comprises aspergillosis, fungal species, COVID-19, *Aspergillus* species and SARS-CoV-2 from 2020 to 2021 was conducted in databases that include indexed journals and journals that publish related articles. The studies cited in each of the articles selected for this study was also searched again. In the search for data collection, only English keywords were used. The databases evaluated include Google Scholar, Scopus, World Health Organization publications, Pubmed website, Science Direct, Web of Science, Scielo, Medline, African Journals Online databases and grey literature to evaluate all published papers reporting COVID-19 associated pulmonary aspergillosis. The Boolean operator (AND) was used to narrow and combine the literature searches. During this study, abstracts were reviewed and the relevant full text articles were selected. In the article search, the following keywords were used: aspergillosis AND invasive OR case OR patient OR infection OR report, COVID-19 OR coronavirus AND SARS-CoV-2 AND aspergillosis, and aspergillosis AND guideline OR treatment OR therapy OR diagnosis OR therapeutic drug monitoring.

Study design

Population based including COVID-19 patients in intensive care unit and hospital, and results were reviewed and evaluated. The terminology used as mentioned above and diagnostic criteria for invasive pulmonary aspergillosis with emphasis on serious fungal infections especially COVID-19 associated pulmonary aspergillosis were evaluated in calculating the frequency percentage estimates of mortality rate in different locations.

Statistical analysis

Descriptive statistics (Frequency and percentage) of clinical isolates and mortality rate due to the complication of CAPA were enumerated and subjected to graphic profile using IBM® SPSS® Statistics version 25.0 (IBM® Corp., Armonk, NY, USA).

Results

Table 1 revealed the diagnostic criteria and their specimens in COVID-19 patients. The result shows that sputum in critical ill COVID-19 patients is usually positive but can represent upper airway colonization. The use of bronchoscopy with bronchoalveolar lavage is decreasing due to the risk of infection and nosocomial transmission among health care workers. Serum is predominantly negative in CAPA and reported studies. Tracheal aspirate shows positive in critical ill COVID-19 patients and can represent upper airway colonization. Alternatively, CT-guided biopsies post mortem have been used more than autopsy. Non-bronchoscopic lavage is alternative method of CAPA diagnosis to bronchoalveolar lavage. Table 2 shows the incidence and risk factor for CAPA in some developed countries from 2020 to 2021. The result shows high mortality rate about 52/60 (58%) approximately and common comorbidities include diabetes mellitus, obesity, arterial hypertension, chronic respiratory failure, chronic obstructive pulmonary disease, chronic renal failure and many others. Figure 1 is a graphic representation of the clinical isolates of *Aspergillus* species from reported studies. The result shows that *Aspergillus fumigatus* is the most predominant fungal species. Figure 2 is a graphic representation of the mortality rate due to the complication of CAPA from different locations. The result showed that Italy and UK had the highest mortality rate of 25.0% followed by Spain with 15.4% when compared to other locations.

S/N	Specimen	Advantages	Disadvantages	Comments on CAPA	References
1.	Sputum	Easy to obtain from the patients	Not validated for biomarker detection and less representative of lower respiratory tract when compared to bronchoalveolar lavage.	In critical ill COVID-19 patients, it usually shows positive result but can represent upper airway colonization.	Koehler., *et al*. [2]
2.	Bronchoscopy with bronchoalveolar lavage	It is well validated for the diagnosis of invasive pulmonary aspergillosis and influenza associated pulmonary aspergillosis. Validated sample for *Aspergillus* antigen test and it facilitates the visualization of lesions such as plaques.	Easy to be contaminated from the surfaces and can generate aerosol.	It can be used as guidance to know when it is safe to carry out bronchoscopy. And in some regions, utilization is declined due to the risk of SARS-CoV-2 infection among health care workers and nosocomial transmission.	Torrego., *et al*. [11] Wolfel., *et al*. [12] Bullard., *et al*. [13]
3.	Serum	Easy to obtain from the patients, validated sample for (1-3)-β-D-glucan, PCR, galactomannan and lateral flow and highly indicative for invasive pulmonary aspergillosis	Inconsistent performance in non-neutropenic patients and (1-3)-β-D-glucan is not pathogen specific	Consistently negative in CAPA when compared to proven positive results.	Bartoletti., *et al*. [6]

4.	Tracheal aspirate	Easy to obtain from intubated patients.	Not validated for biomarker detection and less representative of lower respiratory tract when compared to bronchoalveolar lavage.	In critical ill COVID-19 patients, it usually shows positive result but can represent upper airway colonization.	Koehler., *et al*. [2]
5.	Lung biopsy	Shows validated proof of invasive pulmonary aspergillosis.	Uncommonly used due to high risk of complications and sampling error.	Alternatively, CT-guided biopsies post mortem have been used more often than autopsy.	Zhang., *et al*. [14]
6.	Non-bronchoscopic lavage	Validated for diagnosis of ventilator associated pneumonia, obtain specimen from lower respiratory tract in a closed-system sampling.	Not validated for *Aspergillus* antigen, invasive pulmonary aspergillosis diagnosis, non-targeted sampling and PCR detection.	Reported as alternative to bronchoalveolar lavage to diagnose CAPA.	White., *et al*. [15]

Table 1: *Diagnostic criteria and their specimens in COVID-19 patients.*

S/N	Country	Environment	Comorbidities	Clinical Isolates	Antifungal drugs	Mortality	References
1.	China	Hospital	Diabetes mellitus, Arterial hypertension, Cardiac disease, Chronic obstructive pulmonary disease, Chronic renal failure	*Aspergillus fumigatus*	Not Available	Not Available	Wang., *et al*. [16]
2.	USA	Intensive care unit	Atrial fibrillation, Chronic obstructive pulmonary disease, Arterial hypertension, Obstructive sleep apnea, Diabetes mellitus, Chronic respiratory failure, Coronary disease, Congenital heart disease, End stage renal disease, Nephrectomy, Vasculitis, Junctional tachycardia, Bipolar disorder, Hypercholesterolemia, Obesity, Hypothyroidism, Gastric ulcer, Atherosclerosis, Sarcopenia.	*Aspergillus fumigatus*	Liposomal amphotericin B, Voriconazole, Voriconazole + Isavuconazole, Caspofungin	4/6	Chauvet., *et al*. [17]
3.	Italy	Intensive care unit	Obesity, Arterial hypertension, Diabetes mellitus, Coronary disease, Chronic obstructive pulmonary disease, Chronic renal failure, Hemodialysis, cerebrovascular disease, Malignancies, Solid organ transplant, Chronic steroid treatment.	*Aspergillus fumigatus* *Aspergillus niger*	Voriconazole	13/30	Bartoletti., *et al*. [6]

4.	Germany	Intensive care unit	Arterial hypertension, chronic obstructive pulmonary disease, Diabetes mellitus, Obesity, Obstructive sleep apnea	*Aspergillus fumigatus*	Voriconazole Isavuconazole	3/5	Koehler., *et al*. [18]
5.	Brazil	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic renal failure	*Aspergillus penicillioides*	Not Availaible	1/1	Santana., *et al*. [19]
6.	Netherlands	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic renal failure	Not Available	Not Available	Not Available	Flikweert., *et al*. [20]
7.	France	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic renal failure, Chronic obstructive pulmonary disease, Dialysis, Stroke, Congestive heart failure, Arrhythmiasis	Not Available	Not Available	Not Available	Razazi., *et al*., [21]
8.	Austria	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic obstructive pulmonary disease, Obstructive sleep apnea, Obesity, Cardiac disease	*Aspergillus fumigatus*	Voriconazole	1/1	Prattes., *et al*. [22]
9.	Pakistan	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Atrial myxoma, Recent stroke	Not Available	Liposomal amphotericin B	1/1	Nasir., *et al*. [23]
10.	Ireland	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Hyperlipidaemia, Obesity	*Aspergillus fumigatus*	Liposomal amphotericin B	1/1	Mohamed., *et al*. [24]
11.	Denmark	Intensive care unit	Arterial hypertension, Bronchial asthma	*Aspergillus fumigatus*	Voriconazole	2/2	Helleberg., *et al*. [25]
12.	Spain	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic obstructive pulmonary disease, Bronchial asthma, Obesity, Chronic renal failure, Chronic lymphocytic leukemia, Non-alcoholic fatty liver disease, central nervous system disease.	*Aspergillus fumigatus*	Isavuconazole, Liposomal amphotericin B, Voriconazole	8/8	Machado., *et al*. [26]

13.	UK	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Chronic renal failure, Obesity, Cancer, Chronic respiratory failure malignancy, Hyperlipidaemia, Cardiac and Vascular disease, Auto immune disorders.	*Aspergillus fumigatus* *Aspergillus versicolor*	Liposomal amphotericin B, Voriconazole, Caspofungin + Voriconazole, Liposomal amphotericin B + Anidulafungin	13/25	White., *et al*. [15]
14.	Switzerland	Intensive care unit	Arterial hypertension, Diabetes mellitus, Obesity, Pulmonary fibrosis, Bronchial asthma	*Aspergillus fumigatus*	Voriconazole	1/3	Lamoth., *et al*. [27]
15.	Belgium	Intensive care unit	Arterial hypertension, Chronic renal failure, Hypercholesterinemia, Diabetes mellitus, Obesity, Acute myeloid leukaemia, Human immunodeficiency syndrome	*Aspergillus flavus* *Aspergillus fumigatus*	Voriconazole Isavuconazole	4/7	Rutsaert., *et al*. [28]
Total						52/90 (58%) approximately	

Table 2: *Incidence and risk factors for CAPA in some developed countries.*

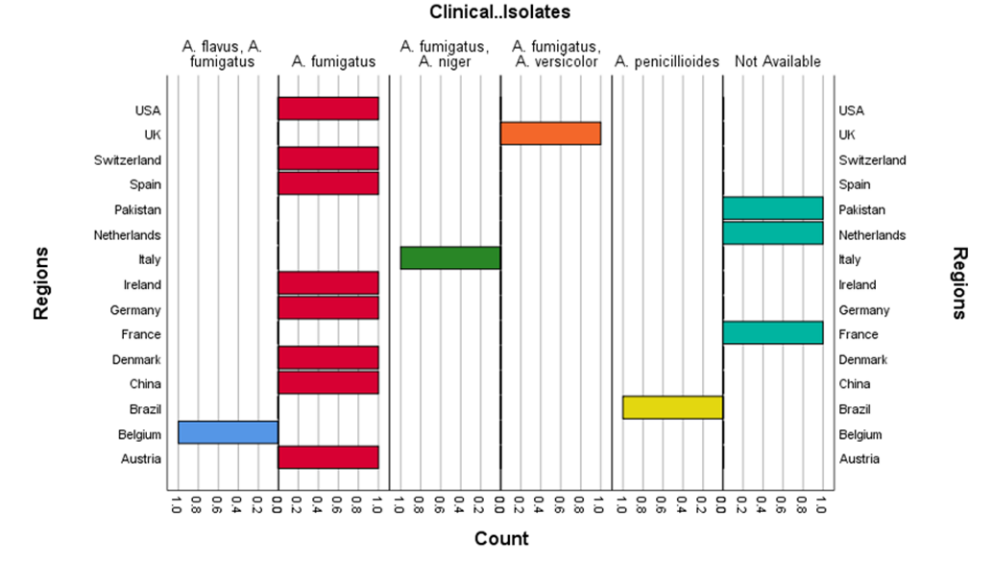

Figure 1: *Incidence of clinical isolates of Aspergillus species in relation to CAPA.*

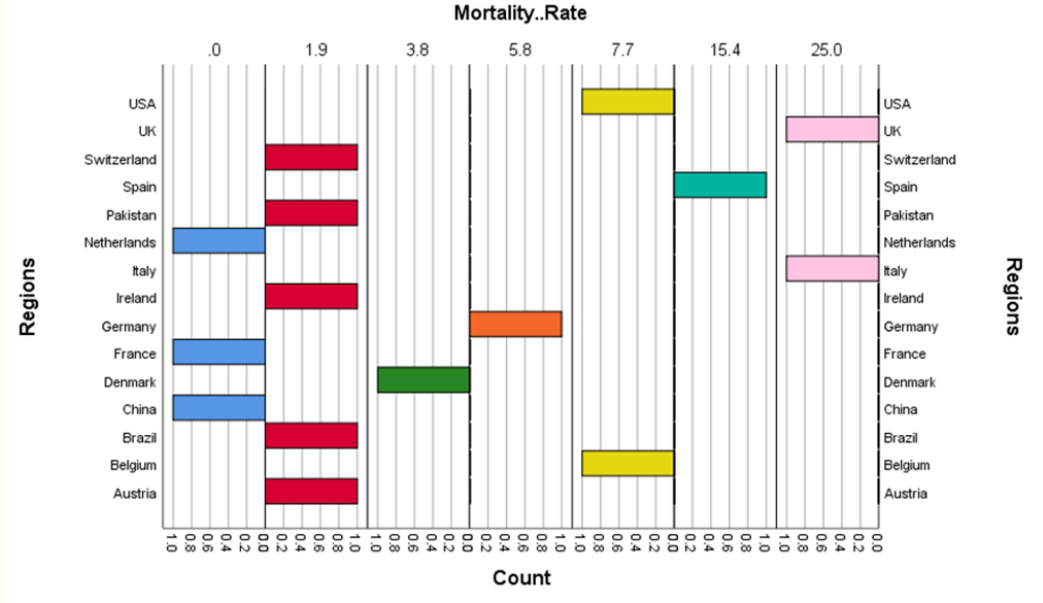

Figure 2: *Mortality rate due to the complication of CAPA.*

Discussion

Wahidi., *et al*. [39], reported that the diagnostic bronchoscopy in COVID-19 patients is complicated due to high risk of viral transmission and nature of aerosol generation. However, Koehler., *et al*. [40], reported that the bronchoscopy allows direct examination of the bronchi and trachea enable to examine *Aspergillus* tracheobronchitis in patients which is consistent to the current study (Table 1). The samples of choice for diagnosis of IPA include lung biopsy specimens and bronchoalveolar lavage fluid (Table 1). Tissue microscopy and culture usually shows the invasive growth of fungal septate and hyphae of primarily sterile samples which represent the diagnostic gold standard for identification of fungal infections. Zhang., *et al*. [14], reported that lung biopsies are usually avoided by many clinicians due to the high risk procedures in the population of COVID-19 patients which is showed in table 1. In bronchoalveolar lavage fluid, the detection of galactomannan is highly indicative of IPA and antigen is released due to active of fungal growth. The main diagnostic methods to confirm severe secondary viral infection of IPA in patients is galactomannan in bronchoalveolar lavage. Use of biomarker such as (1-3)-β-D-glucan rather than galactomannan for serum screening might be significant. Some studies revealed that that two consecutive results serum for (1-3)-β-D-glucan may apparently increase the suspicion of invasive aspergillosis, and reported that (1-3)-β-D-glucan is not specific for aspergillosis [15]. Many years ago, the concept of lateral flow devices (LFDs) or lateral flow assays (LFAs) for the diagnosis of IPA was evaluated and has been used successfully for bronchoalveolar lavage and blood test [2]. The procedures for the detection of IPA has pitch up to be the best when comparing the bronchoalveolar lavage over serum test. Lateral flow testing of bronchoalveolar lavage for IPA shows more reliable. Further studies is needed for lateral flow testing for CAPA but some reports showed that results are similar for galactomannan to the enzyme immunoassay [15]. Bronchoalveolar lavage testing is superior and can increase the sensitivity of PCR due to it is ability to detect *Aspergillus* species that are contaminating or colonizing the airways. And PCR testing of bronchoalveolar lavage shows specificity that is apparently similar to that of galactomannan testing [15]. Depending on the host immune system, *Aspergillus* species was reported to thrive in the environment and inhalation of it is conidia resulted to pulmonary disease and other ailments to COVID-19 patients (Table 2). Koehler., *et al*. [2], reported that *Aspergillus flavus* was the common clinical isolates in respiratory cultures

which is not consistent with the current study. Moreover, a computed tomography is not consistently viable due to the high risk related to the transportation of severe COVID-19 patients. Hoenigl [36] shows that the abnormal expression of anti and pro-inflammatory cytokines accords to a highly permissive inflammatory environment that complements fungal to thrives. With regard to the mycological principle for the diagnosis of COVID-19 associated pulmonary aspergillosis, 52/90 (58%) of mortality rate was reported in this study and *Aspergillus fumigatus* is a common causative agents and Koehler., *et al*. [2], reported 105/190 (55%) mortality rate in their studies and *Aspergillus fumigatus* is a common causative agents. This implies that both studies agreed with each other. Studies have shown that commercial PCR assays and technical standardization provide methodological consistency and quality control include potential ability to identify genetic markers related with antifungal resistance [2]. Koehler., *et al*. [2], also reported that the most commonly antifungal agents used for CAPA patients were voriconazole, isavuconazole and liposomal amphotericin B which agrees to this study (Table 2). In a case of resistance rate that is greater than 5%, the susceptibility test is recommended. Azole failure with a resistance rate greater than 10%, Isavuconazole or voriconazole in combination with liposomal amphotericin B should be administered. Toxicity level may result to neurotoxicity and hepatotoxicity, therefore, therapeutic drug evaluation is needed urgently.

Diagnosis

The diagnosis of CAPA is usually complicated. The parenchymal and tracheobronchial are compose of two distinct forms of variable presentation of CAPA. It is crucial to differentiate between these two forms, as this may influence the therapeutic and diagnostic criteria [2]. However, studies reported that some patients with CAPA survive even without receiving antifungal treatment [2]. This shows a potential distinction between tissue invasion and angio-invasion. To distinguish between colonization and invasive infection is problematic. Host factors that are essentials for the diagnosis of probable invasive pulmonary aspergillosis are not commonly present in patients of intensive care unit [5]. Studies shows that histopathological examination in critically ill patients is complicated either due to the high risk of the infections or coagulation abnormalities caused by mechanical ventilation. Studies are needed to evaluates predispose factors in the development of invasive pulmonary aspergillosis and risk factors of aspergillosis infection with SARS-CoV-2 patients. Based on mycological evidence of host factors and clinical factors, the diagnosis of CAPA are of three different forms which include proven, possible and probable. Proven CAPA is based on histopathological examination or direct microscopic identification of fungal agents morphologically compatible with *Aspergillus* species showing invasive fungal growth into tissues and related tissue disorder [16]. Classification in non-proven CAPA depends on biomarkers confirmation or respiratory cultures. Lateral flow assay and PCR are also significant in the diagnosis of CAPA along with serum and galactomannan [2]. The identification of probable tracheobronchitis depends on the characteristic of lesions examined via positive mycological evidence and bronchoscopy. A standard diagnostic criteria should be evaluated for positive tracheal aspirate culture, worsening hypoxemia, mechanically ventilated COVID-19 patients, clinical deterioration and plaques. Tracheobronchial airways appear as white plaques and biopsy should be carried out for tracheobronchial CAPA to identify *Aspergillus* species as a causative agents [2]. Clinicians should be caution to avoid misdiagnosis of CAPA infection with *Candida* species.

Imaging

Computed tomography imaging may be inappropriate in COVID-19 associated pulmonary aspergillosis cases. It is complicated to examine changes in identification of CAPA in the parenchyma via computed tomography imaging due to difficulty of identification of surrounding halos in the imaging and mechanically ventilated COVID-19 patients especially without invasive aspergillosis having nodular infiltrates. Radiological features of invasive pulmonary aspergillosis such as cavitation, reverse halo sign, multiple pulmonary nodules, air crescent, halo sign and ground-glass opacity may not be definite in critical ill COVID-19 patients which presents in computed tomography scans with bronchovascular thickening, bilateral, crazy-paving pattern, peripheral ground-glass opacities and consolidation [2]. Mechanically ventilated COVID-19 patients whose analysis of computed tomography shown newly form of thin-walled cavitary lesions surrounded by fungal ball-like lesions of bilateral peripheral ground glass infiltrates [29].

Incidence and predispose factors for CAPA

Due to differences in diagnostic criteria, definitions, methods, local practices and treatments, the incidence of CAPA varies. The evaluation of CAPA incidence is complicated due to the restrictions in diagnostic tests and paucity of a gold standard. This perspective gave rise to a wide degree, ranging from 3.8 - 34% of variability in the incidence of CAPA among ICU patients [2]. The diagnosis of CAPA is slow compared to that of IAPA and produce lower incidence of the angio-invasive parenchymal form. Table 2 shows some published studies evaluating the incidence of CAPA and predispose factors in some regions of the world. The majority of the studies reported that CAPA mostly occurs in mechanically ventilated and severely ill COVID-19 patients. Some studies reported an incidence of CAPA ranging from 14 to 20% while other studies reported a lower incidence ranging from 3 to 15% approximately [2].

Mycological criteria

The use of bronchoscopy was not in operation due to insufficient personal protective equipment at the beginning of the COVID-19 epidemic. Studies reported that non-directed bronchoalveolar lavage was carried out. This method is inappropriate and invasive compared to bronchoscopy that posed high risk of specimen contamination by upper respiratory flora [30]. Other mycological techniques that require validation include lateral flow test and polymerase chain reaction (Table 1). The *Aspergillus*-specific lateral-flow device test identify an extracellular glycoprotein antigen secreted by *Aspergillus* species only during active fungal growth. This method has been validated in bronchoalveolar lavage and serum, and showed 85% specificity and 79% sensitivity for proven or probable invasive pulmonary aspergillosis in intensive care unit of non-COVID-19 patients [31]. The lateral-flow device test was used in two cases and is currently being evaluated in patients with COVID-19 invasive pulmonary aspergillosis and influenza [32]. Despite the low sensitivity, serial evaluation of serum galactomannan and serum β-d-glucan in addition to multiple cultures of bronchial aspirate, tracheal aspirate, polymerase chain reaction testing of serum and respiratory samples (Table 1) have been included in the development of new diagnostic device [33]. However, the use of different diagnostic criteria may results to high mortality rates. The mortality rate is higher among critical ill patients with positive cultures compared to probable CAPA confirmed using galactomannan [2]. It was also reported that the mortality rate is higher in patients with multiple positive *Aspergillus* species results compared to a single positive biomarker.

Feasible pathophysiologic mechanisms

In tissue invasion by *Aspergillus* species, like in influenza, local immune-paralysis due to influenza-induced hypoxia, suppression of the nicotinamide adenine dinucleotide phosphate oxidase complex, acute respiratory distress syndrome, malfunction of mucociliary clearance with impediment of the lung epithelium and therapy, and corticosteroids usually facilitates the fungal invasion process. About 55% of patients with influenza associated pulmonary aspergillosis has being reported with invasive *Aspergillus* tracheobronchitis cases [2]. The presence of sporulating heads of *Aspergillus* species was reported including pseudo membranes, epithelial plaques and ulceration inside the bronchi through bronchoscopy examination [34]. In severe COVID-19 pneumonia, impairment of the alveolar injury and bronchial mucosa caused by the virus create pleasing environment for fungal growth [35]. This findings revealed that the increased of vascular permeability and pulmonary epithelial aids the invasion of *Aspergillus species* [3]. Severe COVID-19 is commonly associated with impaired immune system, identified by decrease in hyper inflammatory state, function and number of CD4+T and CD8+ T cells. Damage associated molecular patterns that are compromised in the pathogenesis of aspergillosis are usually released during infection with SARS-CoV-2 and leads to an excessive lung injury and inflammatory response [36]. Host factors for CAPA include COVID-19 associated immune impairment and immunosuppressive therapy rather than the pathophysiology of invasive pulmonary aspergillosis. The maturation of phagosomes that inhibit *A. fumigatus* conidia through the process of phagolysosomal fusion is distorted by corticosteroids compromising the host defense mechanisms against the *Aspergillus* species [37].

Possible therapeutic options for CAPA

Isavuconazole or voriconazole have being commonly used as the first-line treatment options for proven, possible and probable CAPA and liposomal amphotericin B as an alternative agent against the infection. Studies reported that the main reason for not administering antifungal agents to COVID-19 patients was early death [2]. The common antifungal agent used are voriconazole, isavuconazole and liposomal amphotericin B. Patients should be examined for feasible drug interactions with cytochrome CYP2C19 and CYP3A due to the hepatically metabolized potential of voriconazole. Isavuconazole can be used in patients for whom liver toxicity is a concern. New antifungal drugs are evaluated in clinical trials. Rezafungin restrain 1, 3-β-d-glucan synthase, showed *in-vitro* activity against *Aspergillus* species and azole resistant of *Aspergillus fumigatus* isolates. Currently, fosmanogepix and olorofim have shown potential activity against *Aspergillus* species [38].

Conclusion

COVID-19-associated pulmonary aspergillosis remains as significant secondary fungal infection in the COVID-19 pandemic era. Isavuconazole or voriconazole should be used for the therapeutic options for CAPA. However the appropriate treatment duration for CAPA is presently under studies. Despite the association between mortality rate and CAPA in developed countries, still the effective diagnosis approach is challenging. Prompt and effective therapeutic option is needed and could be useful in reducing the mortality rate, drug interaction, adverse effects, resistance and angio-invasive disease. This study might be helpful to understand the impact of the complication of CAPA as a driver of mortality in critical ill COVID-19 patients.

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Institutional Review Board Statement

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Informed Consent Statement

Not Applicable.

Conflicts of Interest

Authors declare no conflict of interest.

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Volume 18 Issue 8 August 2022