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Review Article

COVID-19 associated with pulmonary aspergillosis: A literature review

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Abstract Bacterial or virus co-infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported in many studies, however, the knowledge on *Aspergillus* co-infection among patients with coronavirus disease 2019 (COVID-19) was limited. This literature review aims to explore and describe the updated information about COVID-19 associated with pulmonary aspergillosis. We found that *Aspergillus* spp. can cause co-infections in patients with COVID-19, especially in severe/critical illness. The incidence of IPA in COVID-19 ranged from 19.6% to 33.3%. Acute respiratory distress syndrome requiring mechanical ventilation was the common complications, and the overall mortality was high, which could be up to 64.7% ($n = 22$) in the pooled analysis of 34 reported cases. The conventional risk factors of invasive aspergillosis were not common among these specific populations. Fungus culture and galactomannan test, especially from respiratory specimens could help early diagnosis. *Aspergillus fumigatus* was the most common species causing co-infection in COVID-19 patients, followed by *Aspergillus flavus*. Although voriconazole is the recommended anti-*Aspergillus* agent and also the most commonly used antifungal agent, aspergillosis caused by azole-resistant *Aspergillus* is also possible. Additionally, voriconazole should be used carefully in the concern of complicated drug–drug interaction and enhancing cardiovascular toxicity on anti-SARS-CoV-2 agents. Finally, this review suggests that clinicians should keep alerting the possible occurrence of pulmonary aspergillosis in severe/critical COVID-19 patients, and aggressively microbiologic study in addition to SARS-CoV-2 via respiratory specimens should be indicated.

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Introduction

Since the first recognition of novel pneumonia in Wuhan, China at the end of 2019, its causative pathogen - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been detected soon and its associated infection - coronavirus disease 2019 (COVID-19) has rapidly developed worldwide.[1–3] As of August 2, 2020, a total of 17,660,523 patients had been infected by SARS-CoV-2 and the overall fatality rate was 3.9% (n = 680,894).[1] Although the whole world work hard to understand and manage SARS-CoV-2 infections, a lot of issues, including how to prevent its spread, the appropriate treatment and vaccination remains unclear in this COVID-19 pandemic.

In addition, coinfection between SARS-CoV-2 and other respiratory pathogens have become another serious concern in the treatment of patients with COVID-19.[4–9] Many bacteria, such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophilia*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and many viruses, such as influenza virus, rhinovirus/enterovirus, non-SARS-CoV-2 coronavirus, respiratory syncytial virus, parainfluenza, and metapneumovirus, have been reported as possible co-pathogens among COVID-19 patients.[4–11] Rarely, co-fungal infections with COVID-19 were also reported and the reported pathogens included *Candida*, *Cryptococcus*, Mucorales and *Aspergillus* spp.[2,4,9,12]

Among these possible co-pathogens in COVID-19 patients, we should pay more attention to *Aspergillus* because invasive pulmonary aspergillosis (IPA) is difficult to diagnosis and can be associated with high morbidity and mortality.[13–15] Co-infection of IPA in the severe influenza patients has been recently reported in the Netherland, Belgium, Taiwan, and China.[16] Based on the experience about severe influenza-associated IPA, IPA might comprise up to 17—29% of severe influenza patients and contributed to a high mortality rate of up to 67%.[17] The IPA following respiratory viral infections has not only limited to influenza virus, but may also follow respiratory syncytial virus or parainfluenza virus, SARS, human herpesvirus 6, and adenovirus.[18–21] However, the studies and knowledge about the association of COVID-19 with pulmonary aspergillosis have been limited. Therefore, we did a comprehensive review of literature reporting co-pulmonary aspergillosis in patients with COVID-19 to provide updated information.

Association between COVID-19 and aspergillosis

The role of interleukin-10

Interleukin (IL)-10 has a key function in the regulation of cellular immune responses and is involved in various inflammatory diseases.[22] Highly elevated level of sera IL-6 and IL-10 in pandemic influenza (H1N1) patients may lead to disease progression.[23] A rat model of aspergillosis was significantly associated with increased production of IL-10, which mediate the influx of phagocytic cells and might limit the extent of local tissue destruction of *Aspergillus* infection.[24] However, greater Th2 responses (involving an increase of IL-10) or lesser Th1 responses, might be related to down-regulation of macrophage responses, and increase the host susceptibility to lethal *Aspergillus* infection.[25,26] Collectively, post respiratory viral Th-2 immune response of increasing IL-10 followed by temporary Th1 immune depression predisposes to invasive aspergillosis.

The role of interleukin-6

Proinflammatory cytokines and chemokines, such as TNFα, IL-6, IL-10, interleukin-1β, and monocyte chemoattractant protein-1 were significantly elevated in severe COVID-19 patients.[27,28] The elevated cytokine levels may also contribute to the lethal complications of COVID-19. In severe COVID-19 patients with elevated inflammatory cytokines, postmortem pathology has revealed tissue necrosis and interstitial infiltrations with macrophage and monocyte in the lung, heart and gastrointestinal mucosa. Among the excessive cytokines releasing syndrome (CRS), IL-6 is one of the key cytokines.

IL-6 is a multi-functional cytokine and can play an important role in protective immunity against *Aspergillus* and there is a significant increase in the IL-6 after *Aspergillus fumigatus* infection.[29,30] The patients with IPA may exhibit reduced responsiveness of T cells to IL-6.[31] However, excessive IL-6 signaling in COVID-19 patients with CRS leads to several biological effects such as increasing vessel permeability, acute respiratory distress syndrome (ARDS), cardiac arrhythmia and reducing myocardium contractility. Moreover, the nonimmunocompromised patients with ARDS may become vulnerable to IPA, which prevalence can reach up to 15% of patients.[15]

The immunomodulators may be a beneficial addition to antiviral therapy. IL-6 blockade targeting the host immune system that may be effective for COVID-19. The drug tocilizumab is a recombinant humanized monoclonal anti-IL-6 receptor antibody. Tocilizumab has been approved in patients with COVID-19 pneumonia, ARDS, and elevated IL-6 in China. Early diagnosis of CRS in COVID-19 patients and prompt initiation of immunomodulatory treatment may be beneficial. Timely intervention in patients with elevated serum IL-6 levels may prevent the progression and complications of COVID-19. Nonetheless, IL-6 can be a double-edged sword: tocilizumab can be applied in the treatment of COVID-19 as an anti-IL-6 agent but also can potentially cause *Aspergillus* infection by reducing IL-6 immune response.[32]

Clinical manifestations of COVID-19 with pulmonary aspergillosis

Incidence

Several studies[9,33–41] had reported the occurrence of COVID-19 associated with IPA. The largest series was shown by Zhu et al.[9] in a local hospital in Jiangsu Province, China from January 22 to February 2, 2020, in which 23.3% (60/243) COVID-19 patients had co-infection with *Aspergillus*. Moreover, they found that pulmonary aspergillosis could

develop in patients with asymptomatic, mild, moderate, severe and critical COVID-19. However, no detailed clinical manifestations were described in this report.[9] Additionally, two studies reported the incidence of co-IPA among COVID-19 patients requiring ICU admission was 20.6% (7/34)[35] in Belgium and 19.6% (6/31) in Netherland,[36] respectively. In France, Alanio et al.[34] showed the incidence of COVID-19 associated with IPA was 33.3% (9/27) among mechanically ventilated patients.

Demographic data and comorbidity

Another study in China between January and March 2020 by Wang et al. identified 8 (7.7%) of 104 COVID-19 patients who had IPA at the same time.[33] The mean age of these 8 patients was 73 ± 13 years and all were male. Seven (87.5%) patients had various underlying diseases, including hypertension ($n = 7$), diabetes mellitus ($n = 2$), chronic obstructive pulmonary disease (COPD) ($n = 2$), chronic kidney disease ($n = 2$) and heart disease ($n = 1$). Six patients received corticosteroid treatment but none of them had immunodeficiency or cancer. Additionally, several case series[34–37] or case reports[38–43] including a total of 34 cases provided the detailed clinical characteristics of COVID-19 patients with aspergillosis (Table 1). They were widely reported from France ($n = 11$), Germany ($n = 7$), the Netherland ($n = 7$), Belgium ($n = 7$), Italy ($n = 1$) and Austria ($n = 1$). Their mean age was 66.1 ± 12.3 years and 20 (58.8%) patients were ≥65 years. Man compromised 82.4% ($n = 28$) cases. Hypertension ($n = 15$), diabetes mellitus ($n = 9$), obesity ($n = 7$), COPD ($n = 5$), hypercholesterolemia ($n = 5$), and ischemia heart disease ($n = 3$) were common underlying diseases, but 5 (14.7%) patients did not have any comorbidity. At least one-third of patients had received systemic steroids. However, the European organization for research and treatment of cancer (EORTC) risk host factors for aspergillosis were uncommonly found in 2 of 9 patients in Alanio et al.' study.[34] Moreover, no patient in van Arkel et al.'s study,[36] Koehler et al.'s study,[37] and Lahmer et al.'s report[42] were positive for the EORTC risk host factors.

Radiographic findings

Several studies[33,34,37,38,41] reported the radiographic findings of COVID-19 associated pulmonary aspergillosis. Wang et al.[33] showed that typical IPA presentation including nodules with cavities and dendritic signs could present in the early stage. Additionally, several radiographic findings, such as peripheral nodule, air crescent, reverse halo sign, nodular consolidation, ground-glass opacities, crazy paving pattern, pleural effusion, and pulmonary cysts were reported among patients with COVID-19-associated pulmonary aspergillosis by other reports.[34,37,38,41]

Mycological diagnosis

Several mycological studies, including fungus culture, PCR, galactomannan tests, β-D-glucan test and rarely lateral-flow device were applied to detect the presence of *Aspergillus* spp among these patients. In the review of 34 cases, among 29 patients who had culture-confirmed aspergillosis, *Aspergillus fumigatus* was the most common pathogens (89.7%, $n = 26$), followed by *Aspergillus flavus* (6.9%, $n = 2$). In addition, one case of azole-resistant *A. fumigatus* was reported by Meijer et al.[43] Furthermore, the levels of galactomannan in bronchoalveolar lavage (BAL) fluid were always higher than those in serum.

Therapy

Among the 34 reported cases, the lopinavir-ritonavir combination was the most common anti-SARS-CoV-2 agents, followed by azithromycin and hydroxychloroquine. Voriconazole was the most commonly used antifungal agents, followed by caspofungin, isavuconazole and liposomal amphotericin B, however, 8 patients (23.5%) did not receive any antifungal agent.

Complications and outcome

In the report by Wang et al.,[33] all IPA cases caused by *A. fumigatus* developed in patients with severe/critical COVID-19 after tested negative for SARS-CoV-2. ARDS was the most common complication (50%, $n = 4$), followed by liver damage (12.5%, $n = 1$) and acute kidney injury (12.5%, $n = 1$). All required intensive care unit (ICU) admission, and four required mechanical ventilation (MV). Each one needed continuous renal replacement therapy (CRRT) and extracorporeal membranes oxygenation (ECMO). Further multivariate analysis showed that older age, an initial β-lactamase inhibitor combination, MV and COPD were independent risk factors for IPA among COVID-19 patients.[33] Consistent with Wang et al.'s study in China,[33] the review of other 34 cases showed ARDS ($n = 12$, others had no report), respiratory failure requiring MV support ($n = 28$) and renal failure requiring renal replacement ($n = 11$) were common complications, which indicated that this population should be classified as severe/critical disease of COVID-19. Moreover, there were 22 deaths and the overall case fatality rate was 64.7% among these 34 cases.

Clinical significance

Overall, the findings of this review provide several important information. First, in addition to common bacteria and viruses, *Aspergillus* spp. can cause co-infections in patients with COVID-19, especially in severe/critical illness. Most importantly, the outcome of these patients was poor. ARDS requiring MV support was the common complications, and the overall mortality was high. Second, the conventional risk factors of invasive aspergillosis were not common among these specific populations. Therefore, clinicians should keep alert on the possible occurrence of co-infection with *Aspergillus* in COVID-19 patients. Fungus culture and galactomannan test, especially from respiratory specimens could help early diagnosis. Third, *A. fumigatus* was the most common species causing co-infection in COVID-19 patients, followed by *A. flavus*. Although voriconazole is the recommended anti-*Aspergillus* agent and

Table 1 Clinical characteristics of patients co-infected with COVID-19 and pulmonary aspergillosis.

Study/case	Age/ gender	Underlying disease	Systemic steroid	Images		MV	RRT	Anti-COVID-19	Antifungal treatment	Outcome	Culture/PCR (CT)	Galactomannan index	
				ARDS	Cavity							Blood	BAL
Alanio et al. in France[34]													
1	53/M	HTN, obesity, ischemia heart disease	Yes	NR	No	Yes	Yes	LPV-RTV	None	Alive	NG/neg	0.13	0.89
2	59/F	HTN, DM, obesity	No	NR	No	Yes	No	LRV-RTV, AZI	None	Alive	*A. fumigatus*/neg	0.04	0.03
3	69/M	HTN, obesity	Yes	NR	No	Yes	No	LPV-RTV	None	Alive	*A. fumigatus*/23.9	0.03	ND
4	63/F	HTN, DM, ischemia heart disease	Yes	NR	No	Yes	Yes	LPV-RTV	None	Death	NG/neg	0.51	0.15
5	43/M	Asthma	Yes	NR	No	Yes	No	AZI	None	Alive	*A. fumigatus*/neg	0.04	0.12
6	79/M	HTN	Yes	NR	No	Yes	No	LPV-RTV, HCQ, AZI	None	Alive	*A. fumigatus*/34.5	0.02	0.05
7	77/M	HTN, asthma	Yes	NR	No	Yes	Yes	LPV-RTV, HCQ, AZI	VRC	Death	*A. fumigatus*/29.0	0.37	3.91
8	75/F	HTN, DM	Yes	NR	No	Yes	No	LPV-RTV, AZI	CSP	Death	*A. fumigatus*/31.7	0.37	0.36
9	47/M	Myeloma	Yes	NR	No	Yes	No	No	None	Death	*A. fumigatus*/neg	0.09	ND
Rutsaert et al. in Belgium[35]													
10	86/M	Hypercholesterolemia	NR	NR	NR	Yes	NR	NR	None	Death	*A. flavus*/NR	0.10	ND
11	38/M	Obesity, hypercholesterolemia	NR	NR	NR	Yes	NR	NR	VRC, ISA	Alive	*A. fumigatus*/ND	0.30	>2.8
12	62/M	DM	NR	NR	NR	Yes	NR	NR	VRC	Death	*A. fumigatus*/ND	0.20	2.00
13	73/M	DM	NR	NR	NR	Yes	NR	NR	VRC	Alive	*A. fumigatus*/ND	0.10	>2.80
14	77/M	DM, CKD, HTN, pemphigus foliaceus	NR	NR	NR	Yes	NR	NR	VRC	Alive	*A. fumigatus*/ND	0.10	2.79
15	55/M	HIV, HTN, hypercholesterolemia	NR	NR	NR	Yes	NR	NR	VRC, ISA	Death	NG/ND	0.80	0.69
16	75/M	AML, IPA (2012)	NR	NR	NR	Yes	NR	NR	VRC	Death	*A. fumigatus*/ND	ND	2.63
van Arkel et al. in Netherland[36]													
17	83/M	Cardiomyopathy	Yes	NR	NR	NR	NR	LPV-RTV, HCQ	VRC and AFG combination	Death	*A. fumigatus*/ND	0.4	ND
18	67/M	COPD, NSCLC post RT	Yes	NR	NR	NR	NR	LPV-RTV, HCQ	(n = 5),liposomal	Death	*A. fumigatus*/ND	NR	ND
19	75/M	COPD	No	NR	NR	NR	NR	LPV-RTV, HCQ	AMB (n = 1)	Death	*A. fumigatus*/ND	NR	4
20	43/M	None	No	NR	NR	NR	NR	LPV-RTV, HCQ		Alive	NG/ND	0.1	3.8
21	57/M	Asthma	No	NR	NR	NR	NR	LPV-RTV, HCQ		Death	*A. fumigatus*/ND	0.1	1.6
22	58/M	None	No	NR	NR	NR	NR	LPV-RTV, HCQ		Alive	*Aspergillus* spp./ND	NR	ND
Koehler et al. in Germany[37]													
23	62/F	HTN, obesity, hypercholesterolemia, COPD	No	Yes	No	Yes	Yes	Nil	VRC	Death	*A. fumigatus*/pos	Neg	>2.5
24	70/M	Nil	No	Yes	No	Yes	Yes	Nil	ISA	Death	*A. fumigatus*/pos	0.7	>2.5
25	54/M	HTN, DM, aneurysm	Yes	Yes	Yes	Yes	Yes	HCQ, darunavir and cobicistat	CSP	Alive	*A. fumigatus*/pos	Neg	>2.5
26	73/M	HTN, COPD, hepatitis B	No	Yes	No	Yes	Yes	Nil	VRC	Death	*A. fumigatus*/pos	Neg	ND
27	54/F	No	No	Yes	No	Yes	Yes	Ribavirin, LPV-RTV	CSP	Alive	NG/neg	2.7	ND

(*continued on next page*)

Table 1 (*continued*)

Study/case	Age/ gender	Underlying disease	Systemic steroid	Images		MV	RRT	Anti-COVID-19	Antifungal treatment	Outcome	Culture/PCR (CT)	Galactomannan index	
				ARDS	Cavity							Blood	BAL
Lahmer et al. in Germany[42]													
28	80/M	Suspect pulmonary fibrosis	No	Yes	NR	Yes	NR	NR	Liposomal AMB	Death	*A. fumigatus*/ND	1.5	6.3
29	70/M	No	No	Yes	NR	Yes	NR	NR	Liposomal AMB	Death	*A. fumigatus*/ND	<0.5	6.1
Lescure et al. in France[38]													
30	80/M	Thyroid cancer	NR	Yes	No	Yes	Yes	Remdesivir	VRC - > ISA	Death	*A. flavus*/NR	NR	NR
Blaize et al. in France[39]													
31	74/M	Myeldospastic syndrome, Hashimoto's thyroiditis, HTN	No	Yes	NR	Yes	NR	NR	NR	Death	*A. fumigatus*/pos	NR	Neg
Antinori et al. in Italy[40]													
32	73/M	DM, HTN, hyperthyroidism, obesity	No	Yes	No	Yes	Yes	LPV-RTB, HCQ	Liposomal AMB	Death	*A. fumigatus*/NR	8.6	NR
Prattes et al. in Austria[41]													
33	70/M	COPD, sleep apnea, DM, CKD, HTN, ischemia heart disease, obesity	No	Yes	No	Yes	NR	AZI, HCQ	VRC	Death	*A. fumigatus*/NR	Neg	ND
Meijer et a in Netherland[43]													
34	74/F	Polyarthrosis	No	Yes	No	Yes	Yes	HCQ	VRC - > CSP	Death	*A. fumigatus*[a]/NR	Neg	>3.0

[a] Azole-resistant.

HTN, hypertension; LPV-RTV, lopinavir-ritonavir combination; AZI, azithromycin; HCQ, hydroxychloroquine; DM, diabetes mellitus; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; RRT, renal replacement therapy; VRC, voriconazole; CSP, caspofungin; CKD, chronic kidney disease; AML, acute myeloid leukemia; IPA, invasive pulmonary aspergillosis; ISA, isavuconazole; AFG; anidulafungin; AMB, amphotericin B; NSCLC, non-small cell lung cancer; RT, radiotherapy; PCR, polymerase chain reaction for *Aspergillus*; CT: cycle time values; BAL, bronchoalveolar lavage fluid; NG: no growth; neg: negative; pos: positive; NR, no report; ND, not done.

also the most commonly used antifungal agent, aspergillosis caused by azole-resistant *Aspergillus* is also possible.

The challenge in the management of pulmonary aspergillosis among COVID-19 patients

Adverse effects

Many drugs that have been proposed for treatment of COVID-19 are reported to cause cardiac adverse events. For example, hydroxychloroquine, azithromycin and protease inhibitors such as lopinavir/ritonavir have the potential for unwanted QT-interval prolongation and risk of drug-induced Torsade de Pointes, ventricular arrhythmias, and sudden cardiac death.[44,45] The chloroquine and hydroxychloroquine can cause direct myocardial toxicity. However, in a large cohort of 201 COVID-19 patients in New York, the maximum QTc during treatment was significantly longer in the chloroquine/hydroxychloroquine and azithromycin combination group vs the chloroquine/hydroxychloroquine monotherapy group (470.4 $\pm$ 45.0 ms vs. 453.3 $\pm$ 37.0 ms, $p = 0.004$). Seven patients (3.5%) required discontinuation of these medications due to QTc prolongation.[46] Patients with pre-existing heart disease are especially susceptible to drug-induced arrhythmias.[45] This is important because up to one-third of patients with COVID-19 have cardiac injury or cardiomyopathy, which can further increase the risk of cardiac arrhythmias.[47] Clinical protocols to manage COVID-19 and avoid cardiac adverse effects are recommended. If baseline electrocardiographic testing reveals a moderately prolonged QTc (QTc $\geq$ 480 ms for female, $\geq$ 470 ms for male, but $<$ 500 ms), optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged (QTc $\geq$ 500 ms or increased by $\geq$ 60 ms), the above-mentioned drugs that might further prolong QTc should be avoided.[48]

Drug—drug interaction

Voriconazole is a standard first-line treatment for IPA but intravenous therapy can prolong the QT interval and the potential for drug—drug interactions.[49,50] For COVID-19 patients treated with voriconazole for IPA, another concern would be increased the risk for QTc prolongation for these patients, especially in the presence of baseline QTc $\geq$ 450 ms.[51] Cytochrome P450 (CYP) 3A4 is the most prevalent metabolizing enzyme in the human liver. CYP3A4-mediated drug interactions would be of considerable clinical importance in COVID-19 patients using lopinavir/ritonavir, azithromycin, and voriconazole that are highly dependent on CYP3A for clearance and also are potent inhibitors of CYP3A4 metabolism.[52,53] However, in a randomized study for 30 healthy male volunteers in the UK, coadministration of azithromycin does not affect the steady-state pharmacokinetics of voriconazole.[54] Therefore, further study should investigate the safety of using voriconazole in COVID-19 patients receiving anti-SARS-CoV-2 agents. Additionally, isavuconazole — a new antimold azole, which does not have the side effect of QTc prolongation, may deserve further investigation regarding its potential role in the treatment of COVID-19 complicated IPA.

Conclusions

During this COVID-19 pandemic, aspergillus can cause co-infection with SARS-CoV-2 despite these patients who did not have a traditional risk factor of aspergillus infection. Respiratory specimens for mycologic studies, such as culture, galactomannan tests, and PCR can help early diagnosis. The outcome of COVID-19-associated pulmonary aspergillosis is poor and the recommend antifungal agent — voriconazole should be used carefully in the concern of complicated drug—drug interaction and enhancing cardiovascular toxicity on to anti- SARS-CoV-2 agents.

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