

# Putative invasive pulmonary aspergillosis in critically ill patients with COVID-19: An observational study from New York City

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## Abstract

**Background:** Critically ill patients with coronavirus disease-2019 (COVID-19) are at the theoretical risk of invasive pulmonary aspergillosis (IPA) due to known risk factors.

**Patients/Methods:** We aimed to describe the clinical features of COVID-19-associated pulmonary aspergillosis at a single centre in New York City. We performed a retrospective chart review of all patients with COVID-19 with *Aspergillus* isolated from respiratory cultures.

**Results:** A total of seven patients with COVID-19 who had one or more positive respiratory cultures for *Aspergillus fumigatus* were identified, all of whom were mechanically ventilated in the ICU. Four patients were classified as putative IPA. The median age was 79 years, and all patients were male. The patients had been mechanically ventilated for a mean of 6.8 days (range: 1-14 days) before *Aspergillus* isolation. Serum galactomannan level was positive for only one patient. The majority of our cases received much higher doses of glucocorticoids than the dosage with a proven mortality benefit. All four patients died.

**Conclusions:** Vigilance for secondary fungal infections will be needed to reduce adverse outcomes in critically ill patients with COVID-19.

## KEYWORDS

acute respiratory distress syndrome, COVID-19, pulmonary aspergillosis, SARS-CoV-2

## 1 | INTRODUCTION

Invasive pulmonary aspergillosis (IPA) has been reported in critically ill patients in the ICU.<sup>1,2</sup> Patients with coronavirus disease-2019 (COVID-19) may develop acute hypoxemic respiratory failure and are at high risk of requiring mechanical ventilation with prolonged ICU stays. Further, patients with severe COVID-19 may be administered high-dose glucocorticoids. Hence, there is a theoretical risk of IPA in patients with COVID-19 due to combined known risk factors. However, there are scant data on aspergillosis in patients with COVID-19.<sup>3-6</sup> The aim of the study was to describe the clinical features of critically ill COVID-19-infected patients with pulmonary aspergillosis at a New York City hospital.

## 2 | PATIENTS AND METHODS

We performed a retrospective chart review of all COVID-19-infected patients with *Aspergillus* isolates in respiratory samples during 21 March and 22 April 2020 at Mount Sinai Beth Israel, an acute care hospital in New York City. We collected longitudinal clinical data, including fraction of inspired oxygen (FiO<sub>2</sub>) and vital signs, laboratory and microbiology data, treatment, and outcomes. Serial chest radiographs and computed tomography (CT) scans were reviewed. Glucocorticoid dose was converted into an equivalent dose of prednisone. Fever was defined as a temperature of  $\geq 100.4$  Fahrenheit. We used the clinical algorithm for ICU patients to classify pulmonary aspergillosis as either putative IPA or colonisation (*Asp*ICU

algorithm).<sup>7</sup> As per the clinical algorithm, persistent fever was defined as fever persisting despite at least 3 days of antibiotic therapy or recrudescence of fever while on antibiotics without other apparent cause. Worsening respiratory status was defined by an increase in  $\text{FiO}_2$  requirement on mechanical ventilation, or worsening respiratory failure led to invasive mechanical ventilation. Study approval was obtained from the institutional review board of the Icahn School of Medicine at Mount Sinai.

### 3 | RESULTS

A total of seven patients with COVID-19 who had one or more positive respiratory cultures for *Aspergillus fumigatus* were identified. According to the *AspICU* algorithm,<sup>7</sup> four patients were classified as putative IPA. None of the patients had European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) host factors, including neutropenia and prolonged use of corticosteroids. Only one patient had a pre-existing lung disease (chronic obstructive pulmonary disease in Patient 1). All four patients had compatible signs (fever refractory to at least 3 days of appropriate therapy or worsening respiratory insufficiency despite appropriate antibiotic therapy and ventilatory support), host factor (glucocorticoid treatment with prednisone equivalent > 20 mg/d) and abnormal radiographic findings. Radiographic abnormalities included worsening infiltrates (Patient 1), opacities with dense consolidations (Patient 2), cavitary pneumonia (Patient 3) and diffuse interstitial and patchy hazy opacities (Patient 4). The remaining three patients were classified as having colonisation as they lacked compatible clinical signs. For those three patients, subsequent clinical deterioration was explained by other causes. Clinical characteristics of the patients with putative IPA are shown in Table 1. The median age was 79 years. All experienced worsening respiratory status leading to invasive mechanical ventilation before the isolation of *Aspergillus fumigatus*. The patients had been mechanically ventilated for a mean of 6.8 days (range: 1-14 days) before *Aspergillus* isolation. At *Aspergillus* isolation, fever and leukocytosis were present in one and all four patients, respectively. Serum galactomannan level was positive for only one patient (Patient 2). All patients received concomitant broad-spectrum antibiotic therapy.

All four patients concomitantly received glucocorticoids, with three of which were already given steroids for a mean of 6.6 days (range: 5-8 days) before the isolation of *Aspergillus*. In the remaining one patient (patients 4), glucocorticoid therapy was administered at *Aspergillus* isolation. The overall mean duration of glucocorticoid exposure was 8.5 days (range: 3-11 days) with a mean cumulative prednisone equivalent dose of 722 mg (range: 87-1000 mg). One patient received tocilizumab after *Aspergillus* isolation (Patient 3).

Patient 1 was an 82-year-old man with a history of COPD and pharyngeal cancer who was transferred to the ICU on hospital

day 3 for acute respiratory distress syndrome (ARDS) and septic shock. He was afebrile at *Aspergillus* isolation on hospital day 15, but respiratory status deteriorated with increased  $\text{FiO}_2$  from 50% to 80%. A chest radiograph showed worsening bilateral infiltrates. He was initially treated with cefepime and vancomycin. Voriconazole was added 3 days after the first positive culture for *Aspergillus*. Leukocytosis persisted on broad-spectrum antibiotics and voriconazole. He developed intermittent fever with worsening respiratory status and required continued vasopressor support. The family subsequently requested no further aggressive treatment, and he passed away 17 days after the initiation of antifungal therapy.

Patient 2 was a 79-year-old man with a history of hypertension, coronary artery disease, transient ischaemic attack, and renal cell carcinoma who was transferred to the ICU on hospital day 6 for worsening acute hypoxemic respiratory failure requiring intubation and mechanical ventilation. He was afebrile and had been on non-invasive ventilation (NIV) for 6 days before *Aspergillus* isolation on hospital day 7. Respiratory culture grew *Aspergillus fumigatus* and *Staphylococcus aureus*. A chest CT showed dense bilateral lower lobe consolidations, multifocal ground-glass opacities, pneumomediastinum and pneumopericardium. He was initially treated with cefepime and vancomycin. Voriconazole was started at the second positive culture for *Aspergillus*. A repeat chest CT showed similar findings together with worsening ground-glass opacities. Despite subsequent treatment with meropenem, vancomycin, and voriconazole, he continued to deteriorate with persistent leukocytosis, worsening respiratory status, and multiorgan dysfunction. He expired 13 days after the initiation of antifungal therapy.

Patient 3 was a 77-year-old man with no past medical history who was admitted to the ICU for acute hypoxemic respiratory failure requiring intubation. He developed a fever at *Aspergillus* isolation on hospital day 10. Respiratory status had remained stable. He was initially treated with meropenem and vancomycin. Fever persisted for 4 days, and voriconazole was added. A chest CT showed bilateral patchy ground-glass opacities, bilateral mid to lower lung zone predominant consolidative opacities, bilateral lower lobe cavitary lesions, the largest of which is seen within the right lung base and one of which contains an air-fluid level. He was then treated with voriconazole only. Fever and leukocytosis subsided within 6 days. A repeat chest CT after 2 weeks of voriconazole showed improved bilateral ground-glass opacities, stable to mildly improved cavitary pneumonia within the bilateral lower lobes, and a new cavitary lesion within the subpleural left lower lobe. The subsequent course was complicated by intravenous catheter-related thrombophlebitis with *Staphylococcus epidermidis* bacteremia, which was treated with vancomycin. He had a protracted hospital course with persistent metabolic encephalopathy, chronic respiratory failure required tracheostomy, multiorgan dysfunction and subsequent *Staphylococcus* pneumonia. Due to a lack of improvement, the family requested comfort care, and he expired after 1 month of antifungal therapy.

Patient 4 was a 77-year-old man with a history of type 2 diabetes mellitus who was transferred to the ICU on hospital day 8 for

TABLE 1 Clinical characteristics of critically ill COVID-19-infected patients with putative invasive pulmonary aspergillosis

	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	82	79	77	77
Gender	Male	Male	Male	Male
Comorbid conditions				
Hypertension	No	Yes	No	No
Diabetes	No	No	No	Yes
Coronary artery disease	No	Yes	No	No
Chronic obstructive pulmonary disease	Yes	No	No	No
History of cerebrovascular accident	No	Yes	No	No
History of cancer	Yes	Yes	No	No
Dementia	No	No	No	No
Timing of positive culture for <i>Aspergillus fumigatus</i> (hospital day)	Day 15 and 20	Day 7, 10, and 16	Day 10 and 14	Day 10
Clinical features at <i>Aspergillus</i> isolation				
Fever	No	No	Yes	No
Respiratory status at <i>Aspergillus</i> isolation	IMV	IMV	IMV	IMV
New radiographic abnormalities on chest CT or X-ray	Worsening infiltrates	Opacities with dense consolidations	Cavitary pneumonia	Diffuse interstitial and patchy hazy opacities
White blood cell count ( $10^3/\mu\text{L}$ )	32.9	21.1	20.1	20.2
Platelet count ( $10^3/\mu\text{L}$ )	376	146	420	123
Procalcitonin (ng/mL)	0.16	0.30	3.30	9.34
Lactic acid (mmol/L)	1.0	3.6	1.6	3.7
Total bilirubin (mg/dL)	2.4	1.1	1.4	2.9
Serum creatinine (mg/dL)	2.6	3.1	1.5	4.1
Serum galactomannan	NA	0.71	Negative	Negative
Vasopressor support	Yes	Yes	Yes	Yes
Inpatient medications				
Glucocorticoids				
Cumulative dose in prednisone equivalent (mg)	932	1000	870	87
Starting date (hospital day)	Day 8	Day 2	Day 2	Day 10
Duration (d)	10	10	12	3
Tocilizumab	No	Yes	No	No
Antibiotics	Cefepime + Vancomycin	Cefepime + Vancomycin	Meropenem + Vancomycin	Cefepime + Vancomycin
Antifungal therapy	Voriconazole	Voriconazole	Voriconazole	Caspofungin

Abbreviations: IMV, invasive mechanical ventilation; NA, not available.

worsening acute hypoxemic respiratory failure. He had been on NIV for 8 days and on cefepime and vancomycin until respiratory status further deteriorated, which required intubation and transfer to the ICU 2 days before *Aspergillus* isolation. He was afebrile at *Aspergillus*

isolation on hospital day 10. Chest radiographs showed diffuse ground-glass opacities. Caspofungin was started together with meropenem and vancomycin. He continued to deteriorate with multiorgan dysfunction and expired after 3 days of antifungal therapy.

## 4 | DISCUSSION

Reports of pulmonary aspergillosis complicating severe COVID-19 required mechanical ventilation are emerging.<sup>5,6</sup> Most patients did not have underlying immunocompromising conditions, as observed in patients with ARDS due to influenza.<sup>2</sup> Detailed data from patients who presented in the first waves of COVID-19 pandemic are needed to define the incidence and clinical features of COVID-19-associated pulmonary aspergillosis (CAPA).<sup>8</sup> We herein describe the clinical characteristics of four cases of critically ill COVID-19 complicated by putative IPA.

Early diagnosis of IPA is critical but challenging in mechanically ventilated patients with COVID-19. Bronchoscopy and transbronchial biopsy are rarely performed given the risk of complications and transmission of the virus. Further, pneumonia due to SARS-CoV-2 may obscure the radiological findings of IPA. Consolidation is commonly seen in both COVID-19 and superimposing pulmonary aspergillosis, and any new radiological signs could be obscured by background bilateral ground-glass opacities. Systemic inflammatory markers are almost always elevated with severe COVID-19, which make them less useful to diagnose secondary fungal infection. While it has been suggested that a low procalcitonin level may indicate a high likelihood for invasive fungal infection in critically ill patients with clinical signs of sepsis,<sup>9</sup> the procalcitonin level was elevated in only two patients with putative IPA.

At our institution, fungal cultures are routinely performed on bronchoscopy specimens and other respiratory specimens as clinically indicated; consequently, it is plausible there were instances of *Aspergillus* respiratory infection that were not identified. *Aspergillus* infection can be seen in construction-related clusters.<sup>10</sup> While there was some construction at our institution during the first wave of COVID-19, it was physically remote from the units where all of the cases were identified. Further, there were no instances of isolating *Aspergillus* from any patients without the diagnosis of COVID-19 within or around the study period.

For research purposes, EORTC/MSG Consensus Group have proposed definitions of proven, probable and possible invasive fungal disease.<sup>11</sup> However, these consensus definitions are much less useful for immunocompetent patients in the ICU, as the diagnosis of probable or possible IPA requires the presence of classic host factors. We used the *AspICU* criteria, which is an algorithm for diagnosing IPA in the ICU patients with positive *Aspergillus* endotracheal aspirate cultures,<sup>7</sup> to distinguish putative IPA from colonisation. However, the performance characteristics of the algorithm for COVID-19 patients have not been validated with autopsy or post-mortem biopsy data.

Serum galactomannan was positive in only one patient in our case series. Serum galactomannan is more specific for invasive aspergillosis than beta-D-glucan but has poor sensitivity in non-neutropenic patients.<sup>12</sup> Combining three case series of CAPA, only three (13%) out of 23 patients had positive serum galactomannan level.<sup>5,6,13</sup> The less frequently elevated serum galactomannan levels might simply reflect colonisation rather than infection or suggest

that angioinvasive pulmonary infection is a rare phenomenon in CAPA. In any case, the diagnostic value of serum galactomannan for CAPA seems less promising.

All the patients with putative IPA died in our consecutive cases, suggesting the grave prognosis of critically ill patients with CAPA. On the other hand, Alanio et al reported no significant difference in mortality between IPA and non-IPA patients in a report of eight COVID-19-infected patients with putative IPA.<sup>6</sup> Further data from multi-institutional series are needed to clearly characterise the potential impact on mortality of CAPA. Although dexamethasone was recently shown to decrease 28-day mortality in mechanically ventilated patients with COVID-19,<sup>14</sup> the majority of our cases received much higher doses of glucocorticoids than what was proven beneficial. Since one of the potential sequelae of COVID-19 is secondary fungal infections as our cases demonstrated, vigilance for secondary infections will be needed to reduce adverse outcomes. Clinicians should have a high index of suspicion for CAPA when a critically ill patient with COVID-19 in the ICU develops further respiratory decompensation, fevers or new or worsening radiographic abnormalities of the lungs, particularly if there is no response to empiric antibacterial therapy. It is important to obtain a respiratory culture for fungal pathogens and a serum galactomannan level in these settings to attempt to identify this ominous complication of COVID-19.

### CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

### AUTHOR CONTRIBUTIONS

**Hayato Mitaka:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); writing-original draft (lead); writing-review and editing (equal). **David C. Perlman:** Conceptualization (equal); methodology (equal); supervision (equal); writing-review and editing (equal). **Waleed Javaid:** Supervision (equal); writing-review and editing (supporting). **Nadim Salomon:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); supervision (equal); writing-original draft (supporting); writing-review and editing (equal).

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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