Proven *Aspergillus flavus* pulmonary aspergillosis in a COVID-19 patient: A case report and review of the literature

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Abstract
Severe COVID-19 patients complicated with aspergillosis are increasingly reported. We present a histopathological proven case of fatal COVID-19–associated pulmonary aspergillosis (CAPA), due to *Aspergillus flavus*. This report and existing published literature indicate diagnostic challenges and poor outcomes of CAPA in ICU patients.

KEYWORDS
Aspergillosis, COVID-19, Immunocompetent

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been sweeping across the globe. Like severe influenza pneumonia, COVID-19 is associated with acute respiratory distress syndrome (ARDS), which might be considered a risk of fungal colonisation and infection of the respiratory tract.¹,² Mortality in severe COVID-19 cases is significant compared with non-severe infection cases due to the higher co-infection rate.³ Unlike bacterial co-infections, the risk of fungal co-infections, including oropharyngeal candidiasis, invasive aspergillosis (IA), endemic mycoses, mucormycosis and fusariosis is notable in patients with severe COVID-19, despite the absence of classical well-defined host factors.⁴⁻¹² Possible explanations for the development of fungal co-infections include immune paralysis caused by COVID-19 infection–induced ARDS, diffuse alveolar damage with severe inflammatory exudation and lymphopenia.¹³,¹⁴ Preliminary reports showed 19-33% of severe COVID-19–associated pulmonary aspergillosis (CAPA) in ICU patients.¹⁵,¹⁶ Research findings strongly suggest that mechanically ventilated COVID-19 patients with longer duration of hospital admission should be systematically screened for *Aspergillus* infections.¹⁵ Here, we describe CAPA in an immunocompetent patient and review the available literature on the subject.

2 | CASE REPORT

A 70-year-old man with a history of recent hospital admission due to SARS-CoV-2 infection with the diagnosis of exacerbation of viral pneumonia that was had been referred to Imam Khomeini Hospital complex Tehran, Iran. Imam Khomeini Hospital complex is the largest referral centre in the country, admitted 25,410 patients in 2020 alone. Time course of the patient is detailed in Figure 1. In
the previous hospitalisation, COVID-19 infection was confirmed by positive nasopharyngeal PCR and with more than 50% field involvement of both lungs on chest CT scan. At the first admission, he had received hydroxychloroquine 200 mg/PO/BID for 5 days, interferon beta-1 A/SC/every other day for 5 doses and dexamethasone 8 mg/IV/ daily according to the country guideline and had been discharged from the hospital after 12 days with a partial clinical recovery. However, after 3 days he was re-admitted with exacerbation of respiratory symptoms. On admission, his respiratory rate was 28/min and SpO2 in room air was 80%. The patient’s laboratory data showed lymphopenia (216/mL) and elevated inflammatory markers (ESR: 30 mm/1hr, CRP: 40 mg/L, ferritin: 3,000 ng/mL, lactic acid dehydrogenase: 440 U/L and marked elevated D-dimer: 2,572 ng/mL). Other laboratory results included WBC: 7,200/mL, PMN: 95.5%, Hb: 16 gr/dL, PLT: 176,000/mL and creatinine: 1.1 mg/dL. SARS-CoV-2 PCR test was still positive at the time of his re-admission. Chest CT scan (Figure 2A) revealed multi-lobar peripheral ground-glass opacities compatible with COVID-19 pneumonia (>50% involvement). Evaluation for heart diseases was negative (normal echocardiography). According to the progression
of lung involvement due to the SARS-CoV-2 infection, the patient was treated with high-dose methylprednisolone 250 mg/daily/IV for 3 days followed by dexamethasone 4 mg/IV/TID, atazanavir/ritonavir/PO/daily and supportive care. With the start of treatment, the patient’s condition slightly improved, respiratory distress decreased and SpO2 reached 88% in room air, but in the second week of hospitalisation, the recovery process was not significant. In the third week of hospitalisation due to not achieving the desired therapeutic result, especially in the respiratory symptoms and persistence of high inflammatory markers, the patient underwent a new diagnostic evaluation. SARS-CoV-2 PCR test was reported positive again. A second CT scan showed reduction in ground-glass opacities and three new foci of peripheral wedge-shaped air-space opacities with reverse halo in the right middle lobe (Figure 2B). Sputum samples for acid-fast bacilli were negative. Because of likely/plausible fungal infection, voriconazole (6 mg/kg/BID day one followed by 4 mg/kg/ BID) was started and the corticosteroid dose (dexamethasone 4 mg/ IV/ daily) was reduced. Tissue obtained through CT-guided biopsy of a peripheral lung lesion showed septate hyphae consistent with Aspergillus. Culture of the biopsy samples showed growth of green, powdery surface colonies suspected for Aspergillus spp. (Figure 3). Molecular identification was performed based on beta-tubulin gene sequence and identified as Aspergillus flavus. Despite antifungal therapy for 5 days, respiratory failure progressed and he went on non-invasive ventilation support. Follow-up CT scan showed that the opacities had evolved into irregular cavities, one of which contained sloughed debris mimicking a fungus ball and two cavities connected with bronchial lumen via bronchial wall defects (Figure 2C). After 48 hours, the patient was intubated on mechanical ventilation due to progressive respiratory failure, while continuing dexamethasone, voriconazole, sofosbuvir/daclatasvir and meropenem therapy. Unfortunately, the patient died after 12 hours with cardiac arrest. An autopsy was not performed.

2.1 Literature review

The English literature was reviewed for published CAPA cases using search terms “corona”, “COVID-19”, “aspergillosis”, “CAPA” and “fungal”. A total of 175 CAPA cases were found and details are presented in Table 1. Although variable case definitions were used, only 7 (4%) cases were classified as proven CAPA.

3 DISCUSSION

Although secondary bacterial and viral infections are reported at low frequency in COVID-19 patients, high frequencies of CAPA cases are published in association with COVID-19 in the ICU. Case series from the Netherlands, Germany and France reported CAPA 19%, 26% and 33% of patients with severe COVID-19 pneumonia, respectively. Although lower rates were reported from Switzerland (3.8%) and China (7%). A major challenge remains diagnosing CAPA as the performance of diagnostic Aspergillus biomarkers remains sub-optimal. Serum galactomannan (GM) detection is commonly negative even in patients with proven CAPA. In our reviewed cases, serum GM was performed in 73 of 183 CAPA patients (39.8%), while GM was detected in only 19 (26%) patients (Table 1). Bronchoscopy with bronchoalveolar lavage (BAL) remains the preferred diagnostic procedure to diagnose CAPA, and GM was detected in 83 of 105 (79%) CAPA patients who underwent bronchoscopy. However, bronchoscopy with BAL involves an aerosol-producing procedure.

![Figure 3](image-url)
| Authors/References | Country     | Number of patients | Mean age (SD) | Sex Male (%) | BAL | Serum GM positive/total | Mechanical ventilation (%) | Culture / PCR (%) | Aspergillus species/ Respirator samples (n) | Antifungal therapy (%) | Outcome (mortality) n (%) |
|-------------------|-------------|--------------------|---------------|--------------|-----|------------------------|---------------------------|-------------------|--------------------------------------------|------------------------|----------------------------|
| Bartoletti et al  | Italy       | 30                 | 63            | 24 (80)      | 30/30 (100) | 0/1 (0)                 | 30 (100)                  | 19 (63) / 20 (67) | A fumigatus (15), A niger (3), A flavus (1) / ND | VRC 13 (43)            | 13 (44%)                    |
| White et al       | United Kingdom | 25            | ND            | ND           | 17/19 (89.5) | 1/4 (25)                 | 18 (72)                   | 11 (44) / 16 (64) | A fumigatus (10) / NBL (10)                  | VRC 9 (36), CSP + VRC 2 (8), AMB 2 (12), VRC + AMB 2 (8), FLU 1 (4), VRC + FLU 1 (4), ANI + AMB 1 (4) | 13 (52)                    |
| Marr et al        | USA         | 20                 | 65.5          | 9 (45)       | 1/1 (100) | 4/16 (25)               | ND                        | 17 (85) / ND     | A fumigatus (10), A niger (2), A terreus (1), A fumigatus + A niger (2), Aspergillus spp. (2) / ND | VRC + PSO 1 (5), AMB 1 (5) | 3 (15)                      |
| Dupont et al      | France      | 19                 | 68.4          | 16 (84.2)    | 5/9 (55.6) | ND                      | 18 (94.7)                 | 16 (84.2) / ND   | A fumigatus (14), A calidoustus (1), A niger (1) / BAL (8), TA (4), BA (6) | VRC 8 (42.1) VRC + CSP 1 (5.3) | 7 (36.8)                    |
| Falces-Romero et al | Spain      | 10                | 67.1          | 8 (80)       | 2/2 (100) | 1/2 (50)                | 7 (70)                    | 10 (100) / ND   | A fumigatus (9), A nidulans (1) / BAL(8), TA (4), BA (6) | VRC 2(20), AMB 1(10), VRC + CSP 1(10), AMB + ISA 1(10), AMB + VRC 1(10), AMB + ANI 1(10), MICA + AMB+ISA + VRC 1(10) | 7 (70)                     |
| Alanio et al      | France      | 9                  | 62.8          | 6 (66.7)     | 1/7 (14.3) | 0/8 (0)                 | 9 (100)                   | 7 (77.8) / 4 (44.4) | A fumigatus (7) / BAL (5), TA (2)                                         | VRC 1 (11.1) CSP 1 (11.1) | 4 (44.4)                   |
| Wang et al        | China       | 8                  | 73            | 8 (100)      | ND            | 4 (50)                   | 8 (100) / ND             | A fumigatus (8) / BAL (4), Sputum (4) | ND                                      | ND                                    |
| Rutsaert et al    | Belgium     | 7                  | 66.6          | 7 (100)      | 5/6 (83.3) | 0/6 (0)                 | 7 (100)                   | 6 (85.7) / ND   | A fumigatus (5), A flavus (1) / BAL (6), TA (1)                              | VRC + ISA 2 (28.6), VRC 4 (57.1) | 4 (57.1)                   |
| Flikweert et al   | Netherlands | 7                  | 73            | 5 (71.4)     | 6/7 (85.7) | ND                      | 7 (100)                   | 2 (28.6) / ND   | A fumigatus (2) / BAL (2)                                           | VRC + ANI 6 (85.7)             | 7 (100)                    |
| van Arkel et al   | Netherlands | 6                  | 63.8          | 6 (100)      | 3/3 (100) | 0/3 (0)                 | ND                        | 5 (83.3) / ND   | A fumigatus (4), Aspergillus spp. (1) / TA (2), BAL (3), Sputum (1)          | VRC 5 (83.3), AMB 1 (16.7) | 4 (66.7)                   |
| Koehler et al     | Germany     | 5                  | 62.6          | 3 (60)       | 3/3 (100) | 1/5 (20)                | 5 (100)                   | 4 (80) / 4 (80) | A fumigatus (4) / BAL (2), TA (2)                                        | VRC 2 (28.6), AMB 2 (28.6), CSP 2 (28.6), ISA 1 (14.3) | 3 (60)                     |
| Nasir et al       | Pakistan    | 5                  | 69            | 3 (60)       | ND | 0/5 (0)                | 2 (40)                    | 5 (100) / ND   | A flavus (3), A niger (1), A flavus/A fumigatus (1) / ND                       | VRC 3 (33.3), AMB 2 (22.2) | 3 (60)                     |
| Sarrazyn et al    | Belgium     | 4                  | 75            | 3 (75)       | 4/4 (100) | ND                      | 4 (100)                   | 4 (100) / 2 (50) | Aspergillus spp. (4) / ND                                            | VRC 1 (25), AMB + VRC 2 (50) | ND                         |

(Continues)
| Authors/References | Country | Number of patients | Mean age (SD) | Sex Male (%) | BAL | Serum GM positive/total (%) | Mechanical ventilation (%) | Culture / PCRn (%) | Aspergillus species/ Respirator samples (n) | Antifungal therapy (%n) | Outcome (mortality) %n |
|--------------------|---------|-------------------|-------------|-------------|-----|-----------------------------|---------------------------|-------------------|---------------------------------|------------------------|---------------------|
| Mitaka et al 49    | USA     | 4                 | 78.7        | 4 (100)     | ND  | 1/4 (25)                   | 4 (100) / ND              | A fumigatus (4) / ND     | VRC 3 (75), CSP 1 (25) | 3 (75)                 |
| Lahmer et al 40    | Germany | 2                 | 75          | 2 (100)     | 2/2 (100) | 1/2 (50)                    | 2 (100) / ND              | A fumigatus (2) / BAL (2) | AMB 2 (100)             | 2 (100)               |
| Lescure et al 44   | France  | 1                 | 80          | 1 (100)     | ND   | 1 (100)                    | 1 (100) / ND              | A flavus / TA            | VRC, ISA               | 1 (100)               |
| Blaize et al 42    | France  | 1                 | 74          | 1 (100)     | 0/1 (0) | ND                          | 1 (100) / ND              | A fumigatus / TA         | ND                    | 1 (100)               |
| Antinori et al 43  | Italy   | 1                 | 73          | 1 (100)     | ND   | 1/1 (100)                  | 1 (100) / ND              | A fumigatus / BAL        | AMB                   | 1 (100)               |
| Prattes et al 44   | Austria | 1                 | 70          | 1 (100)     | ND   | 0/1 (0)                    | 1 (100) / ND              | A fumigatus / TA         | VRC                   | 1 (100)               |
| Meijer et al 7     | Netherlands | 1           | 74          | 0 (0)       | 1/1 (100) | 0/1                       | 1 (100) / ND              | A fumigatus / TA         | VRC + CSP             | 1 (100)               |
| Santana et al 45   | Brazil  | 1                 | 71          | 1 (100)     | 0/1 (0) | 1/1 (100)                  | 1 (100) / 1 (100)         | A penicilloides / Autopsy | ND                   | 1 (100)               |
| Sharma et al 46    | Australia | 1           | 66          | 0 (0)       | ND   | 1 (100)                    | 1 (100) / ND              | A fumigatus / TA         | VRC                   | 0 (0)                 |
| Wu et al 47        | China   | 1                 | 46          | 1 (100)     | ND   | ND                         | 1 (100) / ND              | A fumigatus / Sputum     | VRC                   | 0 (0)                 |
| Schein et al 48    | France  | 1                 | 87          | 0 (0)       | 1/1 (100) | 1/1 (100)                 | ND / 1 (100)              | ND                   | VRC                   | 1 (100)               |
| Nasri et al 49     | Iran    | 1                 | 42          | 0 (0)       | ND   | 1/1 (100)                  | 1 (100) / ND              | ND                   | AMB                   | 1 (100)               |
| Mohamed et al 5    | Ireland | 1                 | 66          | 1 (100)     | ND   | 1/1 (100)                  | 1 (100) / ND              | A fumigatus / TA         | AMB                   | 1 (100)               |
| Ghelfenstein et al 50 | France  | 1                 | 56          | 1 (100)     | ND   | 0/1 (0)                    | 1(100) / 1 (100)          | A fumigatus / TA         | ND                    | 1 (100)               |
| Fernandez et al 51 | Argentina | 1           | 85          | 1 (100)     | ND   | 1/1 (100)                  | 1 (100) / ND              | A flavus / TA            | VRC                   | 1 (100)               |
| Machado et al 29   | Spain   | 8                 | 65          | 6 (75)      | 2/8 (25) | 4/8 (50)                   | 8 (100) / 1 (100)         | A fumigatus (5), A fumigatus + A awamori + A terreus(1), A lentulus(1), A citrinoterreus(1) / BA (5), BAL (2), TA (1) | AMB 2 (25), VRC 2 (25), ISA 4 (50) | 8 (100) a |

(Continues)
TABLE 1 (Continued)

| Authors/ References | Country | Number of patients | Mean age (SD) | Sex Malen (%) | BAL | Serum GM positive/total | Mechanical ventilation (%) | Culture / PCR n (%) | Aspergillus species / Respirator samples n (%) | Antifungal theray n (%) | Outcome (mortality) n (%) |
|---------------------|---------|-------------------|--------------|--------------|-----|------------------------|--------------------------|---------------------|-----------------------------------|---------------------------|-------------------------|
| Our study           | Iran    | 1                 | 70           | 1 (100)      | ND  | ND                     | 1 (100)                  | 1 (100) / 1 (100) | A flavus / Biopsy                  | VRC                       | 1 (100)                 |
| Total               | -       | 183               | 68.5 (±9.6)  | 120 (65)     | 83/105 (79) | 19/73 (26)             | 135 (73.7)              | 140 (76.5) / 51 (27.8) | A fumigatus (107), A flavus (8), A niger (7), A nidulans (1), A terreus (1), A penicillioide (1), A calidoustus (1), A lentulus (1), A citiniterreus (1), Aspergillus spp. (7) Mix | VRC (32.7), AMB (16.8), CSP (5.26), FLU (0.5), ISA (2.7), Antifungal combination 24 (13.7) | 93 (50.8)                |

Abbreviations: AMB, amphotericin B; ANI, anidulafungin; BA, bronchial aspirate; BAL, bronchoalveolar lavage; CSP, caspofungin; FLU, fluconazole; GM, galactomannan; ISA, isavuconazole; MICA, micafungin; NBL, non-directed bronchial lavage; ND, not determined; PCR, polymerase chain reaction; PSO, posaconazole; SD, standard deviation; TA, tracheal aspirate; VRC, voriconazole.

*Authors indicated CAPA-related mortality.

*Galactomannan values interpreted according to EORTC/MSGERC.52 EORTC/MSGERC denotes European Organization for Research and Treatment of Cancer/ Mycoses Study Group Education and Research Consortium.

When the diagnosis of CAPA is confirmed with contamination risk for healthcare workers. Although bronchoscopy is recommended for diagnostic procedures, and in those who show clinical deterioration or persistent poor respiratory function with or without imaging. Although COVID-19 patients in the ICU who have a positive Aspergillus test performed on upper respiratory tract specimens such as sputum or BAL, bronchoalveolar lavage; CSP, caspofungin; FLU, fluconazole; GM, galactomannan; ISA, isavuconazole; MICA, micafungin; NBL: non-directed bronchial lavage; ND: not determined; PCR, polymerase chain reaction; PSO, posaconazole; SD, standard deviation; TA, tracheal aspirate; VRC, voriconazole.

Our study            | Iran    | 1                 | 70           | 1 (100)      | ND  | ND                     | 1 (100)                  | 1 (100) / 1 (100) | A flavus / Biopsy                  | VRC                       | 1 (100)                 |
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Abbreviations: AMB, amphotericin B; ANI, anidulafungin; BA, bronchial aspirate; BAL, bronchoalveolar lavage; CSP, caspofungin; FLU, fluconazole; GM, galactomannan; ISA, isavuconazole; MICA, micafungin; NBL, non-directed bronchial lavage; ND, not determined; PCR, polymerase chain reaction; PSO, posaconazole; SD, standard deviation; TA, tracheal aspirate; VRC, voriconazole.

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initiation of antifungal therapy should be considered following international treatment guidelines, which recommend triazoles, such as voriconazole or isavuconazole, as first-line treatment.\textsuperscript{23,32} In our case, despite voriconazole therapy, the patient died due to concomitant involvement with coronavirus and failure to antifungal therapy. In \textit{A fumigatus}, triazole resistance should be considered inazole-treatment failure, but in our case, \textit{A flavus} was recovered, which is the predominant \textit{Aspergillus} species causing aspergillosis in Iran.\textsuperscript{17,33,34}

In conclusion, recovery of \textit{Aspergillus} species in a critically-ill COVID-19 patient should not be ignored, but requires a diagnostic workup despite suboptimal performance of relevant biomarkers. The new consensus definitions and reporting of proven CAPA cases will help to further understand the pathophysiology of IA in patients with COVID-19 and help to optimise clinical management.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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sadegh Khodavaisy: Data curation (equal);
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Project administration (equal);
Writing-original draft (equal);
Writing-review & editing (equal).

AUTHOR CONTRIBUTIONS
MRS, NK, FS, HK, AS, SJH, SADM and MK conceived the study, treatment, and discussed the case and the implications; S.KH., MK and BJ diagnosed the case; S.KH., MRS and PEV wrote the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the analysis.

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REFERENCES
1. Schauwvlieghe AF, Rijnders BJ, Philips N, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. \textit{Lancet Respir Med}. 2018;6(10):782-792.
2. Verweij PE, Gangneux J-P, Bassetti M, et al. Diagnosing COVID-19-associated pulmonary aspergillosis. \textit{Lancet Microbe}. 2020;1(2):e53-e55.
3. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan China. \textit{Clin Infect Dis}. 2020;71:762-768.
4. Dupont D, Menotti J, Turc J, et al. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). \textit{Med Mycol}. 2020;10:myaa078.
5. Nasir N, Farooqi J, Mahmood SF, Jabeen K. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: An observational study from Pakistan. \textit{Mycoses}. 2020;63(8):766-770.
6. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. \textit{Clin Infect Dis}. 2020;ciaa1065.
7. Meijer EF, Dofferhoff AS, Hoiting O, Buil JB, Meis JF. Azole-Resistant COVID-19-associated pulmonary aspergillosis in an immunocompetent host: a case report. \textit{J Fungi (Basel)}. 2020;6(2):79.
8. Salehi M, Ahmadiakia K, Mahmoudi S, et al. Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern. \textit{Mycoses}. 2020;63(8):771-778.
9. Mohamed A, Rogers TR, Talento AF. COVID-19 Associated Invasive Pulmonary Aspergillosis: Diagnostic and Therapeutic Challenges. \textit{J Fungi (Basel)}. 2020;6(3):115.
10. Messina FA, Marin E, Caceres DH, et al. Coronavirus disease 2019 (COVID-19) in a patient with disseminated Histoplasmosis and HIV–A case report from Argentina and literature review. \textit{J Fungi (Basel)}. 2020;6(4):275.
11. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. \textit{Am J Emerg Med}. 2020. (In Press).
12. Poignon C, Blaize M, Vezinet C, Lampros A, Monsel A, Fekkar A. Invasive pulmonary fusariosis in an immunocompetent critically ill patient with severe COVID-19. \textit{Clin Microbiol Infect}. 2020;26(11):1582-1584.
13. Salehi M, Ahmadiakia K, Badali H, Khodavaisy S. Opportunistic Fungal Infections in the Epidemic Area of COVID-19: A Clinical and Diagnostic Perspective from Iran. \textit{Mycopathologia}. 2020;185:607-611.
14. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. \textit{Lancet Respir Med}. 2020;8:e26.
15. Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. High prevalence of putative invasive pulmonary aspergillosis in critically ill COVID-19 patients. \textit{medRxiv}. 2020;8:e48-e49.
16. Koehler P, Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. \textit{Mycooses}. 2020;63(6):528-534.
17. Khodavaisy S, Badali H, Hashemi S, et al. In vitro activities of five antifungal agents against 199 clinical and environmental isolates of \textit{Aspergillus flavus}, an opportunistic fungal pathogen. \textit{J mycol med}. 2016;26(2):116-121.
18. Wang J, Yang Q, Zhang P, Sheng J, Zhou J, Qu T. Clinical characteristics of invasive pulmonary aspergillosis in patients with COVID-19 in Zhejiang, China: a retrospective case series. \textit{Crit Care}. 2020;24(1):1-4.
19. Borman AM, Palmer MD, Fraser M, et al. COVID-19 associated invasive aspergillosis: data from the UK National Mycology Reference Laboratory. J Clin Microbiol. 2020;59(1):e02136–20.

20. Rutsaert L, Steinfort N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. Annals of Intensive Care. 2020;10(1):1-4.

21. Koehler P, Cornely OA, Kochanek M. Bronchoscopy safety precautions for diagnosing COVID-19 associated pulmonary aspergillosis–A simulation study. Mycoses. 2020;64(1):55–59.

22. Wahidi MM, Shojaee S, Lamb CR, et al. The use of bronchoscopy during the COVID-19 pandemic: CHEST/AABIP guideline and expert panel report. Chest. 2020;158:1268-1281.

23. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24:e1-e38.

24. Flikweert AW, Grootenboers MJ, Yick DC, et al. Late histopathological characteristics of critically ill COVID-19 patients: Different phenotypes without evidence of invasive aspergillosis, a case series. J Crit Care. 2020;59:149-155.

25. White L, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Investig Dis. 2020;ciaa1298.

26. Jackson T, Deibert D, Wyatt G, et al. Classification of aerosol-generating procedures: a rapid systematic review. BMJ Open Respir. 2020;7(1):e000730.

27. Verweij PE, Rijnders BJ, Brüggemann RJ, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med. 2020;46(8):1524-1535.

28. Blot SI, Taccone FS, Van den Abeele A-M, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med. 2012;186(1):56–64.

29. Machado M, Valerio M, Álvarez-Uría A, et al. Invasive pulmonary aspergillosis in the COVID-19 era: an expected new entity. Mycoses. 2021;64(2):132-143.

30. Koehler PBM, Chakrabarti A, Chen SCA, et al. Defining and managing COVID-19 associated pulmonary aspergillosis: The 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2020. (In Press).

31. Armstrong-James D, Youngs J, Bicanic T, et al. Confronting and mitigating the risk of COVID-19 associated pulmonary aspergillosis. Eur Respiratory Soc. 2020;56:2002554.

32. Patterson TF, Thompson GR III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;63(4):e1-e60.

33. Zanganeh E, Zarrinfar H, Rezaeitabatabaiefte, et al. Predominance of non-fumigatus Aspergillus species among patients suspected to pulmonary aspergillosis in a tropical and subtropical region of the Middle East. Microb Pathog. 2018;116:296–300.

34. Khodavaisy S, Badali H, Rezaie S, et al. Genotyping of clinical and environmental Aspergillus flavus isolates from Iran using microsatellites. Mycoses. 2016;59(4):220-225.

35. Marr KA, Platt A, Tornheim JA, et al. Aspergillosis complicating severe coronavirus disease. Emerg Infect Dis. 2021;27(1):18–25. https://doi.org/10.3201/eid2701.202896

36. Falces-Romero I, Ruiz-Bastião M, Díaz-Pollán B, Maseda E, García-Rodríguez J, Group SCW. Isolation of Aspergillus spp. in respiratory samples of patients with COVID-19 in a Spanish tertiary care hospital. Mycoses. 2020;63(11):1144-1148.

37. van Arkel AL, Rijppstra TA, Belderbos HN, Van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19–associated pulmonary aspergillosis. Am J Respir Crit Care Med. 2020;202(1):132-135.

38. Sarrazyn C, Dhaese S, Demey B, Vandecasteele S, Reyniers M, Van Praet JT. Incidence, risk factors, timing and outcome of influenza versus COVID-19 associated putative invasive aspergillosis. Infect Control Hosp Epidemiol. 2020;1-7.

39. Mitaka H, Perlman DC, Javaid W, Salomon N. Putative invasive pulmonary aspergillosis in critically ill patients with COVID-19: An observational study from New York City. Mycoses. 2020;63(12):1368-1372.

40. Lahmer T, Rasch S, Spinner C, Geisler F, Schmid RM, Huber W. Invasive pulmonary aspergillosis in severe COVID-19 pneumonia. Clin Microbiol Infect. 2020;26(10):1428-1429.

41. Leschke F-X, Boudalma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis. 2020;20(6):697-706.

42. Blaize M, Mayaux J, Nabet C, et al. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. Emerg Infect Dis. 2020;26(7):1636.

43. Antinori S, Rech R, Galimberti L, et al. Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: A diagnostic challenge. Travel Med Infect Dis. 2020;38:101752.

44. Prattes J, Valentin T, Hoenigl M, Talakic E, Reisinger AC, Eller P. Invasive pulmonary aspergillosis complicating COVID-19 in the ICU–A case report. Med Mycol Case Rep. 2020. https://doi.org/10.1016/j.mmcrc.2020.05.001

45. Santana MF, Pivoto G, Alexandre MAA, et al. Confirmed Invasive Pulmonary Aspergillosis and COVID-19: the value of postmortem findings to support antemortem management. Rev Soc Bras Med Trop. 2020;53:e20200401.

46. Sharma A, Hofmeyr A, Bansal A, et al. COVID-19 associated pulmonary aspergillosis (CAPA): An Australian case report. Med Mycol Case Rep. 2020. https://doi.org/10.1016/j.mmcrc.2020.06.002

47. Wu S, Yang S, Chen R, Chen H, Xu Y, Lin B. Dynamic immune response profiles and recovery of a COVID-19 patient with coinfection of Aspergillus fumigatus and other baseline diseases: a case report. OMICS. 2020;24(10):615–618.

48. Schein F, Munoz-Pons H, Mahinc C, Grange R, Cathébras P, Flori P. Fatal aspergillosis complicating severe SARS-CoV-2 infection: a case report. J Mycol Med. 2020;30(4):101039.

49. Nasri E, Shoaei P, Vakili B, et al. Fatal invasive pulmonary Aspergillosis in COVID-19 patient with Acute Myeloid Leukemia in Iran. Mycopathologia. 2020;185:1077-1084.

50. Ghelfenstein-Ferreira T, Saade A, Alanio A, et al. Recovery of a triazole-resistant Aspergillus fumigatus in respiratory specimen of COVID-19 patient in ICU–A case report. Med Mycol Case Rep. 2020. https://doi.org/10.1016/j.mmcrc.2020.06.006

51. Fernandez NB, Caceres DH, Beer KD, et al. Ventilator-associated pneumonia involving Aspergillus flavus in a patient with coronavirus disease 2019 (COVID-19) from Argentina. Med mycol case rep. (In Press) 2020. https://doi.org/10.1016/j.mmcrc.2020.07.001

52. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367-1376.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting information section.