COVID-19-associated pulmonary aspergillosis (CAPA) in Iranian patients admitted with severe COVID-19 pneumonia

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Abstract

Purpose Bacterial or virus co-infections with SARS-CoV-2 have been reported in many studies; however, the knowledge on Aspergillus co-infection among patients with COVID-19 was limited. This study was conducted to identify and isolate fungal agents and to evaluate the prevalence of pulmonary aspergillosis (CAPA) as well as antifungal susceptibility patterns of Aspergillus species in patients with COVID-19 admitted to Shahid Beheshti Hospital, Kashan, Iran.

Methods The study involved 119 patients with severe COVID-19 pneumonia referred to the Shahid Beheshti Hospital, Kashan, Iran. A total of 17 Aspergillus spp. that were isolated from COVID-19 patients suspected of CAPA were enrolled in the study. CAPA was defined using ECMM/ISHAM consensus criteria. The PCR amplification of the β-tubulin gene was used to identify the species. The antifungal activities of fluconazole, itraconazole, voriconazole, amphotericin B against Aspergillus spp. were evaluated according to the Clinical and Laboratory Standards Institute manual (M38-A3).

Results From the 119 patients with severe COVID-19 pneumonia, CAPA was confirmed in 17 cases (14.3%). Of these, 12 (70.6%) were males and 5 (29.4%) were females; the mean age at presentation was 73.8 years (range: 45–88 years; median = 77; IQR = 18). Aspergillus fumigatus (9/17; 52.9%), Aspergillus flavus (5/17; 29.4%), Aspergillus oryzae (3/17, 17.6%), were identified as etiologic agents of CAPA, using the molecular techniques. Voriconazole and amphotericin B showed more activity against all isolates. Moreover, the MIC of fluconazole, itraconazole varied with the tested isolates. For 3 clinical isolates of A. fumigatus, 2 isolate of A. flavus and 3 A. oryzae, the MIC of fluconazole and itraconazole were ≥ 16 µg/mL.

Conclusions We observed a high incidence (14.3%) of probable aspergillosis in 119 patients with COVID-19, which might indicate the risk for developing IPA in COVID-19 patients. When comparing patients with and without CAPA regarding baseline characteristics, CAPA patients were older (p = 0.024), had received more frequent systemic corticosteroids (p = 0.024), and had a higher mortality rate (p = 0.018). The outcome of CAPA is usually poor, thus emphasis shall be given to screening and/or prophylaxis in COVID-19 patients with any risk of developing CAPA.

Keywords Pulmonary aspergillosis · COVID-19 · Azole · Antifungal drug resistance
Affect the susceptibility to fungal infections, such as the to aggravate COVID-19?” Or, conversely, “Can COVID-19 issue might have raised the question: “Can fungi underlie the emergence of COVID-19 disease, there were several reports on the isolation of fungi in affected patients. This results of studies conducted worldwide, few months into the emergence of COVID-19 disease, there were several reports on the isolation of fungi in affected patients. This issue might have raised the question: “Can fungi underlie to aggravate COVID-19?” Or, conversely, “Can COVID-19 affect the susceptibility to fungal infections, such as the influenza virus that has been investigated and proven by numerous studies?”.

Aspergillus species cause various pulmonary infections including invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis, fungal asthma, and Aspergillus bronchitis [5–10]. Usually, insufficient attention to timely diagnosis and treatment of this disease leads to the patient’s death. Opportunistic fungi, which are usually harmless, are among the major causes of pulmonary fungal infections that become pathogenic in abnormal and susceptible hosts. As reported in Salmanton-Garcia et al.; cases of pulmonary aspergillosis associated with COVID-19 (CAPA) have been documented by researchers since August 2020 [11]. Since then, varying reports on cumulative incidences of CAPA, including rates of 0.7–7.7% among COVID-19 cases [12, 13], 1–39.1% among COVID-19 patients admitted in ICU [12, 14, 15], and 3.2–29.6% among COVID-19 patients who received mechanical ventilation [12, 16]. Similar to influenza-associated pulmonary aspergillosis, CAPA develops few days following ICU admission. The establishment of pulmonary aspergillosis superinfection in COVID-19 and influenza patients follows exposure to common risk factors [17].

Thus, it is important to investigate the occurrence of such infections among patients with severe COVID-19 disease, in terms of nosocomial infections, especially those admitted to intensive care units and might require a long hospital stay. Therefore, this study was conducted to identify and isolate fungal agents and evaluate the prevalence of systemic fungal infections among patients with COVID-19 disease admitted to Shahid Beheshti Hospital, Kashan, Iran.

Materials and methods

Study design

This descriptive study was performed on COVID-19 patients, diagnosed using clinical, radiological, and molecular tests, and admitted to Shahid Beheshti Hospital, Kashan, Iran within a period of 11 months; August 2020–June 2021. Shahid Beheshti hospital (latitude 33°00′46″ N, longitude 51°24′24″ E) with an area of about 40,000 m² and 400 beds is located at 5 km of Kashan–Ravand road as the only general hospital in Kashan, a city in the center of Iran, that provides services to about 300,000 population. This hospital became one of the most important referral centers for the management of COVID-19 patients during the COVID-19 pandemic. The samples for mycological examination including the broncho-alveolar lavage, and sputum were collected and processed based on clinical symptoms. The study was approved by the joint Ethical Committees of Tehran University of Medical Sciences, with ethic number IR.TUMS.SPH.REC.1399.329. The study included adult immunosuppressed patients with COVID-19 pneumonia admitted to ICU who used invasive MV for more than 4 days. We defined a “Probable CAPA” in patients with at least one of the following conditions: The presence of new cavitary lung lesion(s) at chest computed tomography without alternative explanation, positive serum GM EIA index ≥ 0.5, positive BAL GM index ≥ 1.0, or a positive culture/PCR for Aspergillus species in BAL sample [18].

Diagnosis of probable CAPA tracheobronchitis requires observation of tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar, alone or in combination, on bronchoscopic analysis and mycological evidence. Definitions for ‘probable’ CAPA have been proposed by ECMM/ISHAM consensus criteria for research and clinical guidelines in which a positive galactomannan (GM) in serum or bronchoalveolar lavage (BAL), recovery of Aspergillus species in BAL culture, positive polymerase chain reaction (PCR) for Aspergillus species in BAL or blood, or chest
imaging consistent with a fungal infection suffices the diagnosis [18, 19]. Refer to Table 1

Sample collection and preparation

The study was conducted on 119 specimens. We collected 114 broncho-alveolar lavage (BAL) samples and 5 sputum samples from hospitalized patients.

Initial examination

The collected specimens were initially examined under the microscope using 10% KOH solution for the detection of fungal hyphae. Parts of specimens were subcultured on Sabouraud Dextrose Agar (SDA) 2% (Merck, Denmark) and incubated at 35°C for 7 days. A few of the colonies grown on SDA were also mixed with sterile saline and 3% glycerol in a 0.5 ml microtube and stored at -70°C.

DNA extraction and PCR amplification of ITS region

The genomic DNA was directly isolated from BAL specimens using the high pure PCR template purification kit (Roche, Germany) based on the manufacture’s guide. The PCR amplification was performed using the 3 μL of test sample as a template, in a total volume of 25 μL (1 μL of each of forward and reverse primers, 10 μL of PCR Master Mix (Amplicon, Denmark), and 9 μL of deionized distilled water. The amplification was achieved using the β-tubulin primers (BT-forward: 5’-GGTAACCAATCGGAGT GCTTTC-3’), and reverse (BT-reverse: 5’-ACCCTCAGT GTAGTGACC CTTGGC-3’) [20, 21] using the following program: Initial denaturation of DNA at 95°C for 2 min, 35 cycles consisted of a denaturation step at 94°C for 45 s, an annealing step at 58°C for 60 s, and an extension step at 72°C for 60 s, with a final extension at 72°C for 15 min following the last cycle. The PCR products were examined by staining with a DNA-safe stain and electrophoresis on 1.5% agarose gel. The PCR products were subjected to sequencing and analyzed using the MEGA7.0.21 software.

Antifungal susceptibility test

The minimum inhibitory concentrations (MIC) of fluconazole, itraconazole, voriconazole, amphotericin B were assessed according to the Clinical and Laboratory Standards Institute (CLSI) M38-A3 guidelines [22]. After preparation of antifungal serial dilutions, the 96-well microtitre plates were inoculated with the spore suspensions to obtain 5 × 10^5 cells/mL in every well. The microplates were incubated at 35°C for 48 h. All tests were carried out in duplicate. The standard strain of Candida parapsilosis ATCC 22,019 and Aspergillus fumigatus ATCC®MYA-3627™ were used for quality control. The MIC cutoff values for antifungals were concluded according to the CLSI M38-A3 guideline [22].

Statistical analysis

Statistical analysis was performed using SPSS software (version 16.0). The MICs range of all antifungals were calculated. We used the Mann–Whitney U test or Fisher’s exact test to compare differences between patients with and without CAPA when appropriate.

Results

From a total of 119 patients with severe COVID-19 pneumonia, CAPA was confirmed in 17 cases (14.3%). Of these, 12 (70.6%) patients were males and 5 (29.4%) were females; the mean age at presentation was 73.8 years (range: 45–88 years; median = 77; IQR = 18). Aspergillus fumigatus (9/17; 52.9%), Aspergillus flavus (5/17; 29.4%), Aspergillus oryzae (3/17, 17.6%), were identified as etiologic agents of CAPA, using the molecular techniques.

The predominant underlying diseases among patients with CAPA included diabetes (12 cases), kidney disorder (6

Table 1 Defining and diagnosing CAPA according to the 2020 ECMM/ISHAM consensus criteria

| Proven CAPA (Microbiology) | Probable CAPA (Clinical factors) |
|----------------------------|----------------------------------|
| SARS-CoV-2 + ARDS + ICU patients | SARS-CoV-2 + ARDS + ICU patients |
| Tracheal biopsy (Histology) | BAL + Microscopy / Aspergillus (positive) |
| Invasive growth (Microscopy) + | BAL + Culture/PCR Aspergillus (positive) |
| Culture/Aspergillus (positive) + | Serum + GM / Lateral flow assay (index > 0.5) |
| PCR/Aspergillus (positive) + | BAL + GM / Lateral flow assay (index ≥ 1.0) |
| Or a combination | Or a combination |
| | Eschar or a combination |

CAPA COVID-19-associated aspergillosis, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, ARDS acute respiratory distress syndrome, ICU intensive care unit, BAL bronchoalveolar lavage, GM enzyme immunoassay for galactomannan
cases), heart failure (5 cases), liver transplantation (3 cases), AML (2 cases), ALL (1 case), and CML (1 case). Whereas patients with CAPA had diabetes (70.6%) and kidney disorder (35.3%) as their main underlying diseases, diabetes and malignancy were seen in patients with non-CAPA at the rate of 21.6 and 13.7%, respectively.

Dyspnea (100%), myalgia (100%), headache (88.2%), fever (76.5%), arthralgia (70.6%), and gastrointestinal symptoms (53%) were the most frequent symptoms at presentation of the patients (Table 2).

We compared baseline characteristics of patients with and without CAPA (Table 3); we found that CAPA patients were older \( (p = 0.024) \). On management and development of complication among the studied patients, we observed that CAPA patients had received more frequent systemic corticosteroid \( (p = 0.024) \), and had a higher mortality rate \( (p = 0.018) \).

The clinical course and disease outcome of patients with and without CAPA is been demonstrated in Table 3.

MICs range of all antifungals are shown in Table 4. Voriconazole and amphotericin B showed more activity against all isolates. The MIC of fluconazole, itraconazole varied with the tested isolates. For the clinical isolates of \( A. fumigatus \) (three isolates), \( A. flavus \) (two isolates), and \( A. oryzae \) (three isolates), the MIC of fluconazole and itraconazole were \( \geq 16 \mu g/mL \). The remaining isolates showed sensitivity to antifungal drugs used.

The antifungal treatment, length of stay, and outcome in presumed CAPA cases is shown in Table 5

**Discussion**

Since COVID-19 is similar to influenza regarding clinical symptoms and characteristic host’s immune response to the viral agent, it is expected that COVID-19 can favor the development of opportunistic fungal infections. The available reports in this regard can be good evidence of the importance of fungal diseases in these patients. On the other hand, in trying to control bacterial superinfection, physicians dealing with patients with COVID-19 tend to be non-restrictive and tend to over-prescribe broad-spectrum antibiotics, which may increase patients’ susceptibility to fungal infections. Systemic fungal superinfections can negatively impact the prognosis and subsequently increase the mortality rate among patients with

| Table 2 | Demography and major presenting symptoms of COVID-19 patients with CAPA |
| --- | --- |
| Number of patients | 17 |
| Age at the time of diagnosis-years* | 73.8 (median=77; IQR=18) |
| Sex |  |
| Male | 12 (70.6%) |
| Female | 5 (29.4%) |
| Fungal isolates |  |
| *Aspergillus fumigatus* | 9 (52.9%) |
| *Aspergillus flavus* | 5 (29.4%) |
| *Aspergillus oryzae* | 3 (17.6%) |
| Underlying cause of immunosuppression |  |
| Acute lymphoblastic leukemia | 1 (5.9%) |
| Acute myeloblastic leukemia | 2 (11.7%) |
| Chronic myeloblastic leukemia | 1 (5.9%) |
| Diabetes Mellitus | 12 (70.6%) |
| Liver transplantation | 3 (17.6%) |
| Kidney disorder | 6 (35.3%) |
| Heart failure | 5 (29.4%) |
| Signs and symptoms |  |
| Headache | 15 (88.2%) |
| Fever | 13 (76.5%) |
| Myalgia | 17 (100%) |
| Arthralgia | 12 (70.6%) |
| Gastrointestinal | 9 (53%) |
| Dyspnea | 17 (100%) |
| Extension |  |
| BAL | 17 (100%) |

| Table 3 | Characteristics of patients, clinical course, and outcome in CAPA and non-CAPA cases |
| --- | --- | --- |
| Parameter | Presumed CAPA \( (n = 17) \) | Non-CAPA \( (n = 102) \) | \( p \)Value |
| Age, year, median (range) | 73.8 (45–88) | 61.2 (19–73) | 0.024 |
| Sex, M, \( n \) (%) | 12/17 (70.6) | 65/102 (63.7) | 0.145 |
| Interval from symptom onset to ICU admission, median (range), d | 6 (3–12) | 8 (4–16) | 0.260 |
| Interval from ICU admission to ICU discharge, median (range), d | 10.5 (5–42) | 11.2 (3–40) | 0.425 |
| Interval from symptom onset to death, median (range), d | 16.3 (7–30) | 17.7 (10–39) | 0.371 |
| Systemic corticosteroid use, \( n \) (%) | 6/17 (35.3) | 14/102 (13.7) | 0.031 |
| Mortality, \( n \) (%) | 13/17 (76.5) | 52/102 (50.1) | 0.018 |

CAPA COVID-19-associated pulmonary aspergillosis, COVID-19 coronavirus disease
COVID-19. Certain risk factors ascribed to the development of CAPA, include age, prior respiratory diseases, chronic renal failure, long-term use of corticosteroid, neutropenia, COVID-19 severity, and treatment of COVID-19 patient with corticosteroid or tocilizumab [12, 13, 23, 24]. In the present study, 17 isolates were recovered from cases considered to be CAPA. These isolates were identified using molecular methods to be Aspergillus fumigatus (9/17; 52.9%), Aspergillus flavus (5/17; 29.4%), and Aspergillus oryzae (3/17, 17.6%). In another study from China, 60/257 COVID-19 (23.3%) patients had Aspergillosis [25]. In addition, Koehler et al. showed that 5 (26.3%) out of 19 patients with COVID-19 ARDS were co-infected with Aspergillus [26]. Importantly, three out of the five patients were on steroid therapy but the other two cases had no comorbidity. Moreover, the results of the serum galactomannan antigen test, bronchoalveolar lavage fluid fungal culture, and polymerase chain reaction were positive in two, three, and four of the five patients, respectively. Although the patients received antifungal medication, only two survived [26]. In a study carried out by Rello et al., symptoms of bacterial/fungal infections were compared in COVID-19 patients and H1N1 influenza patients (a 2009 European study performed on influenza patients). The results showed that COVID-19 was associated with Aspergillus flavus (2%), Aspergillus fumigatus (2%), and invasive candidiasis (2%). However, A. flavus was reported in 3.1 of patients with H1N1 [27].

### Table 4

| Fungi Species | MICs Range | Amphotericin B µg/mL | Voriconazole µg/mL | Itraconazole µg/mL | Fluconazole µg/mL |
|---------------|------------|----------------------|-------------------|-------------------|------------------|
| Aspergillus fumigatus (9) | Range MIC90 | 0.125–1 ND | 0.03–1 ND | 0.03–16 ND | 0.125–16 ND |
| Aspergillus flavus (5) | Range MIC90 | 0.25–1 ND | 0.125–1 ND | 0.25–16 ND | 0.125–16 ND |
| Aspergillus oryzae (3) | Range MIC90 | 0.5–2 ND | 0.25–2 ND | ≥ 16 ND | ≥ 16 ND |

**ND** not determined

### Table 5

| Sex/Age Length of stay Fungal species Antifungal treatment | Outcome |
|----------------------------------------------------------|---------|
| M/83 1 week Aspergillus fumigatus Amphotericin B 50 mg/day, Caspofungin | Died |
| M/79 5 days Aspergillus flavus Amphotericin B 50 mg/day, Posaconazole 300 mg/day, Itraconazole | Died |
| M/64 9 days Aspergillus flavus Amphotericin B 250 mg/day, Voriconazole 200 mg/day | Survived |
| F/56 10 days Aspergillus fumigatus Amphotericin B 50 mg/day, Caspofungin | Died |
| M/77 12 days Aspergillus fumigatus Amphotericin B 50 mg/day, Posaconazole 300 mg/day, Itraconazole | Died |
| M/86 2 weeks Aspergillus fumigatus Amphotericin B 50 mg/day, Caspofungin | Died |
| M/59 2 weeks Aspergillus flavus Amphotericin B 300 mg/day, Voriconazole 200 mg/day | Survived |
| M/73 9 days Aspergillus fumigatus Amphotericin B 50 mg/day, Posaconazole 300 mg/day, Nystatin | Survived |
| M/87 2 weeks Aspergillus oryzae Amphotericin B 50 mg/day, Caspofungin | Died |
| F/76 6 weeks Aspergillus flavus Caspofungin, Itraconazole | Died |
| M/78 6 days Aspergillus fumigatus Amphotericin B 50 mg/day, Caspofungin | Died |
| F/69 1 week Aspergillus oryzae Voriconazole 200 mg/day, Caspofungin | Died |
| M/78 1 week Aspergillus fumigatus Voriconazole 200 mg/day, Caspofungin | Died |
| M/88 6 days Aspergillus flavus Amphotericin B 50 mg/day, Posaconazole 300 mg/day | Survived |
| F/45 5 days Aspergillus fumigatus Amphotericin B 50 mg/day, Caspofungin | Died |
| F/86 1 week Aspergillus oryzae Amphotericin B 50 mg/day, Caspofungin | Died |
| M/70 5 days Aspergillus fumigatus Caspofungin | Died |

*F* female, *M* male
of transmission of bronchial fluid samples in patients admitted
to the ICU for mycological diagnostic and galactomannan test
was mentioned as a major diagnostic problem. In addition,
the side effects of antifungal drugs in patients with probable
diseases were discussed and the use of new antifungal drugs
with more promising pharmacokinetic and pharmacodynamic
properties was recommended [17]. In the present study, vori-
conazole and amphoterin B showed more activity against all
isolates. For the 3 clinical isolates of A. fumigatus, 2 isolates
of A. flavus, and 3 A. oryzae (from the present study), the MIC
of fluconazole and itraconazole were ≥ 16 µg/mL. Similarly,
azole-resistant A. fumigatus isolates (resistance to itracona-
zole, voriconazole, and posaconazole with MICs 16, 2, and
0.5 µg/mL, respectively) were reported in a CAPA case from
the Netherlands [32]. Although the survival benefit of anti-
fungal treatment of CAPA is not currently being confirmed,
early diagnosis shall trigger the commencement of antifungal
treatment. Voriconazole remains the recommended first-line
treatment for IPA, except in cases of hematologic malignancies
[33, 34]. However, its tendency for drug–drug interactions,
serious undesirable effects, as well as its narrow therapeutic
window that may require therapeutic drug monitoring limit its
use in the ICU settings [35–37]. In addition, voriconazole may
interfere with experimental COVID-19 therapies, including
hydroxychloroquine, atazanavir, lopinavir/ritonavir, and rem-
desivir [38]. The major alternative for treatment of IPA in the
ICU include the isavuconazole and liposomal amphotericin
B [33]. Isavuconazole shows generally a better pharmacoki-
etic profile, fewer undesirable effects, and a lesser drug–drug
compared to voriconazole [39]. Liposomal amphotericin B
is an effective alternative with broader antifungal activity;
however, renal insufficiency complicates initiation and often
causes withdrawal of this agent particularly in cases of severe
COVID-19 infection that shows tendency for renal tropism
and frequently causes kidney insult [40]. Although itraconazole
is not recommended for treatment of invasive aspergillosis, it
has been shown to exhibit some antiviral activity in a feline
coronavirus model via cholesterol transport inhibition [41].
Thus, it may be an alternative therapy for treating COVID-
19-associated IPA, albeit its problem of drug–drug interac-
tions with other triazoles [41, 42]. Clinical trials shall compare
efficacy and safety profiles of new and established antifungals,
with more promising pharmacokinetic and pharmacodynamic
properties in COVID-19-associated IPA, albeit its problem of drug–drug
interactions in patients with probable COVID-19 pneumonia.
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Declarations

Conflicts of interest The author(s) declare that there are no conflicts
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Ethical approval The Ethical Clearance Committee of the Iran Uni-
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