Azole Resistance and CYP51A/B Mutations in *Aspergillus* Clinical Isolates Before and During the COVID-19 Pandemic: A Molecular Surveillance Study

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Abstract- We conducted a cross-sectional study to (I) determine the relative frequency of antifungal-resistant *Aspergillus* clinical isolates, (II) address changes in susceptibility to available antifungals in patients infected with *Aspergillus spp*. with COVID-19, and (III) determine mutations in the *CYP*51A and *CYP*51B genes of *Aspergillus spp*. Isolated from the clinical specimens. A total of 30 fungal species were enrolled in the study. The antifungal activities of itraconazole and voriconazole were assessed using azole-containing agar media in Petri dishes. After identifying resistance in the isolates, the *CYP*51A and *CYP*51B gene regions were sequenced using the designed primers, and mutations were identified. To amplify *CYP*51A and *CYP*51B, primers with the specified sequences were used. Genomic DNA from 22 azole-resistant *Aspergillus* isolates was amplified using the *CYP*51-A and *CYP*51-B gene primers. 12/22 (54.54%) azole-resistant *A. flavus* isolates with the Tandem Repeat (TR34)/L98H (leucine-to-histidine substitution) mutation, MICs above the CLSI Epidemiological Cutoff Value. One carried the F46Y /TR34. 5/22 azole non-WT *A. fumigatus* isolates, *CYP*51-A analysis revealed that M220I, S297T/ TR34/L98H mutations, 4 *A.orezea* isolates had C498T/TR34 at a *CYP*51-B gene. Antifungal susceptibility testing should be performed when possible, and efficient systems must be implemented to monitor the evolution of newly introduced azole-resistant *Aspergillus* spp. In addition, these data are useful for clinicians to understand the incidence of azole resistance, enabling optimal management of affected patients and helping choose the right solution for infection management.

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Introduction

The increasing incidence of fungal diseases has become a challenge in the world, with more than one billion people suffering from fungal infections, and about 1·6 million people are estimated to die of fungal diseases annually. *Aspergillus* is among the most common causes of fatal fungal infections (1). The COVID-19 pandemic,

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caused by the SARS-COV-2 virus, led to a large number of cases of Acute Respiratory Distress Syndrome (ARDS), many of whom required hospitalization and admission to the Intensive Care Unit (ICU). Among these critically ill patients, superinfections—particularly bacterial and fungal—were prevalent and played a key role in increasing morbidity and mortality. Contributing factors included excessive corticosteroid administration, prolonged use of broad-spectrum antibiotics, intravascular catheter placement, mechanical ventilation, and hemodialysis. These conditions created an environment where infections like mucormycosis, aspergillosis, and candidiasis could thrive. Nine cohort studies show that 8% of COVID-19 patients had bacterial-fungal coinfections (2). Invasive pulmonary aspergillosis (IPA) has been increasingly reported in these patients, as observed during past influenza pandemics, though precise incidence rates have not yet been determined (3-11). *Aspergillus* species can cause a spectrum of disease, ranging from mild allergic reactions to severe invasive infections, depending on the patient's immune status and exposure to fungal spores. *Aspergillus fumigatus* accounts for most human infections, but other species, such as *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*, can also be involved (12,13).

Amphotericin B and azoles are the main treatments for aspergillosis, with voriconazole being the first-line therapy. Azoles, including itraconazole, isavuconazole, and posaconazole, inhibit lanosterol 14α-demethylase, an enzyme crucial for ergosterol biosynthesis (14-16). *Aspergillus* species have two isozymes, *CYP51A* and *CYP51*B; while neither is individually essential for growth, both must be inactivated to halt growth completely (18-20). The rise of azole-resistant *Aspergillus* spp. since the COVID-19 pandemic has led to increased global efforts, including in Iran, to monitor and assess the spread of these resistant strains.

The molecular mechanisms of azole resistance can be divided into two general categories: *CYP*51-mediated and non-*CYP*51-mediated (21). Studies have revealed that mutations in the *CYP* 51 gene are found in 50% of azole-resistant clinical and environmental isolates of *Aspergillus* spp. (22).

Therefore, we conducted a cross-sectional study to (I) determine the relative frequency of antifungal-resistant *Aspergillus* clinical isolates, (II) address changes in susceptibility to available antifungals in patients infected with *Aspergillus* spp. with COVID-19, and (III) determine mutations in the *CYP*51A and *CYP*51B genes of *Aspergillus* spp. Isolated from the clinical specimens.

Materials and Methods

Study areas

This study was conducted on 50 hospitalized patients at Shahid Rajaee Hospital, Tehran, Iran, and on patients who were referred to the Immunology, Asthma, and Allergy Research Institute, Tehran, Iran, from January 2017 to the end of 2024. The diagnosis of COVID-19 was confirmed using the specific transcriptase-polymerase chain reaction (RT-PCR). Demographic and clinical data, such as initial diagnoses, predisposing factors, comorbidities, and risk factors for fungal infections, were recorded.

Bronchoscopy was used to collect the bronchoalveolar lavage (BAL) specimens. First, the specimens were subjected to direct microscopic examination using the 10% potassium hydroxide. Then they were cultured on 2% dextrose Sabouraud agar (SDA) (Merck, Denmark) and incubated at 35° C for 7 days. To identify the *Aspergillus* spp., DNA was extracted from the isolated colonies using the Roche (Germany) DNA extraction kit. The PCR was performed according to the program previously mentioned (19).

Antifungal susceptibility assay

Screening for drug-resistant clinical isolates was performed using the Antifungal-Containing Agar Medium Method (TCAM). *Aspergillus* isolates were subcultured on Potato Dextrose Agar (PDA) for 7 days at 30° C. In *vitro* susceptibility testing was performed according to the Clinical & Laboratory Standards Institute (CLSI). For all clinical isolates, fungal growth was tested on a Sabouraud Dextrose Agar (SDA) plate containing 0.1 µg/mL of voriconazole and itraconazole, and on a drug-free control SDA plate. Visual investigation of fungal growth was done after 24 hours. Both antifungal agents were obtained from Sigma (USA).

Candida parapsilosis ATCC 22019 was used as quality control (23). All tests were performed twice.

After identifying resistance in the isolates, the *CYP*51A and *CYP*51B gene regions were sequenced using the designed primers, and mutations were identified. To amplify *CYP*51A and *CYP*51B, primers with the specified sequences were used.

Molecular identification of mutations in the *CYP*51A and *CYP*51B genes

Genomic DNA was extracted to discover the underlying mutations of resistance isolates of *Aspergillus spp. CYP*51-A and B, and promoter regions, were amplified using specific primer sets. The sequences of the

relevant gene loci were assembled and edited with a DNA Sequence Assembler (version 5.15), aligned with reference strains, and then compared.

Statistical analysis

Data were analyzed using SPSS software version 29. To compare variables, Fisher's exact tests were applied. The significance level was set at 0.05 or lower. The MICs Value, Minimum Inhibitory Concentrations (MICs) range, and MICs 90 were calculated for all antifungals. The MIC90 was estimated for organisms with at least 9 observations, the minimum number for which extrapolation would not be necessary. The 95% Confidence Intervals (CI) for the MIC90 were estimated as bootstrap percentile confidence intervals in Mathematica 8 (Wolfram, Champaign, IL) for species with at least 9 observations.

Results

Identification and antifungal susceptibility testing

Of 50 enrolled cases, 23 patients (46%) were infected with COVID-19, and 33 were not.

There was a significant difference between the glucocorticoid treatment (P<0.044), broad-spectrum antibiotics therapy (P<0.051), and invasive ventilator (P<0.01) in patients with COVID-19 in comparison to cases without COVID-19.

There was a significant difference in the presence of a Central Venous Catheter (CVC) (P<0.033) and intensive care unit (ICU) duration (P<0.025) between patients with and without COVID-19. There were no differences in gender or risk factors between cases with and without COVID-19 infection.

Using conventional diagnostic methods, 20 samples of *A. flavus* (n:20; 66.66%) were identified, followed by 10 specimens of *A. fumigatus* (n:10; 33.33%) (Table 1).

Table 1. Frequency and distribution of 30 *Aspergillus* isolates from two centers: identification using conventional methods and clinical localization of infection

Identification by sequencing method	ABPA N (%)	Valve N (%)	Pediatric N (%)	Adults N (%)
A. flavus	15(75%)	5(25%)	4(20%)	16 (80%)
A. fumigatus	6(60%)	4(40%)	1(10%)	9(90%)
Total (n=30)	21(70%)	9(30%)	5 (16.6%)	25(83.33%)

This table presents the frequency and distribution of 30 *Aspergillus* isolates obtained from two clinical centers. The table provides a breakdown of the most common *Aspergillus* spp. identified, along with their relative frequencies relative to the total number of isolates from both centers. This distribution is analyzed to identify any notable patterns or trends in the occurrence of *Aspergillus* infections across the two settings.

Preliminary monitoring of the 30 isolates for azole resistance was conducted using the TCAM method. A total of 22 isolates out of 30 (73.33%) grew on the azole-containing Petri dish. Three other resistant isolates to itraconazole (n=2) and voriconazole (n=1) were identified as *A. flavus* according to morphological features (Table 2).

Table 2. Resistance patterns to antifungal agents and molecular characteristics of *Aspergillus* spp. Isolated from patients with and without COVID-19

Identification		Antifungal Susceptibility (95% CI); GM(µg/mL)	MICs90
Classical methods	**Molecular methods**	**Itraconazole**	**Voriconazole**
A. flavus	*A. flavus*	16; 3.48 (N:5)	8;4.75 (N:8)
A. flavus	*A. orizea*	4;4 (N:4)	4,4 (N:2)
A. fumigatus	*A. fumigatus*	4;2.3 (N:3)	4; 3.01 (N:5)

*MIC90 estimated for species with at least 9 isolates, the smallest number where extrapolation would not be necessary
*Estimation of 95% CI only performed for genus or species with at least 9 isolates

Sequencing analysis showed that all these resistant *A. flavus* isolates belonged to the *A. orizea.*

Regarding Table 3. The MICs of the tested antifungals increased 4- to 16-fold for *Aspergillus* strains following

COVID-19 infection.

Regarding the present data, significant differences were observed between increased use of antifungal agents during COVID-19 and the emergence of drug-resistant isolates.

Genomic DNA from 22 azole-resistant *Aspergillus* isolates was amplified using the *CYP*51-A and *CYP*51-B gene primers. 12/22 (54.54%) azole-resistant *A. flavus* isolates with the Tandem Repeat (TR34)/L98H (leucine-to-histidine substitution) mutation, MICs above the CLSI Epidemiological Cutoff Value (CLSI ECV). One carried the F46Y /TR34. 5/22 azole non-WT *A. fumigatus* isolates, *CYP*51-A analysis revealed that M220I, S297T/ TR34/L98H mutations, 4 *A.orezea* isolates had C498T/TR34 at a *CYP*51-B gene.

Table 3. Minimum inhibitory concentrations (MICs) of antifungal agents against *Aspergillus* spp. isolated from patients with and without COVID-19

Strains	MIC range Itraconazole in patients without COVID-19 (µg/mL)	MIC range Itraconazole in patients with COVID-19 (µg/mL)	Fold change in MIC
A. flavus	0.03-0.125	0.03-16	1-8
A. orizea	0.03-0.0.6	0.25-4	4-12
A. fumigatus	0.0625-0.125	0.5-4	6-10
Strains	**MIC range of voriconazole in patients without COVID-19**	**MIC range voriconazole in patients with COVID-19 (µg/mL)**	**Fold change in MIC**
A. flavus	0.03-0.5	0.5-4	8-6
A. orizea	0.0625-0.125	0.25-4	2-10
A. fumigatus	0.03-0.5	0.125-4	4-6

This table presents the minimum inhibitory concentrations (MICs) of various antifungal agents. Isolates were obtained from both COVID-19-positive and COVID-19-negative patients. Antifungal susceptibility testing was performed according to CLSI/EUCAST guidelines, and MIC values are reported to indicate the level of antifungal activity required to inhibit the growth of each isolate. The table also highlights potential differences in susceptibility patterns between the two patient groups, contributing to the understanding of resistance trends during the COVID-19 pandemic.

Discussion

Resistance trends pre- and post-COVID

Since the onset of the COVID-19 outbreak, considerable increases in antifungal resistance have been reported, which may be due to increased use of wide-spectrum systemic antifungal agents, but the true relative frequency has not yet been defined. In this cross-sectional study, azole and amphotericin B resistance were recorded in *Aspergillus* spp. The identification of amphotericin B- and itraconazole-resistant isolates after the COVID-19 pandemic has become a concern. Since the treatment of chronic ABPA, as well as *Aspergillus* cardiac infection, requires repeated courses of amphotericin B and itraconazole, this could increase the risk of selecting for resistant species. In addition, as liposomal amphotericin B is no longer commercially available in our region, voriconazole and itraconazole are now considered first-line treatment for invasive aspergillosis. Therefore, we believe there will be greater pressure to use the mentioned azole in the coming years, which implies a high risk of selection for azole-resistant strains worldwide.

Resistance to azoles before the COVID-19 pandemic has also been detected, albeit sporadically, in France, India, Japan, China, Denmark, Switzerland, Norway, Germany, Argentina, with prevalence values ranging from 0% to 8.1% (24-27). The percentage of azole-resistant strains is similar to that reported in other studies during or after the COVID-19 pandemic, with the highest proportion of non-wild-type isolates (19,28-30).

The rapid spread of resistance species highlights the role of antifungal susceptibility testing. In the present study, the TCAM was applied straightforwardly, allowing us to monitor 30 isolates from two different centers. There is a significant correlation between the results obtained with this method and those of the CLSI

reference method, supporting its reliability. However, TCAM is a qualitative technique that does not precisely define susceptibility to antifungal medications.

Mutation patterns

In the present study, the T293A alteration, leading to the amino acid substitution L98H, was found in 12 isolates of *A. flavus*: 8 were voriconazole–resistant, and 5 showed cross-resistance to itraconazole. The TR34 mutation was also reported in 12 isolates, the same mutations reported from the Netherlands, Denmark, and China (31), Brazil (32,33), and Kenya. Literature review showed that the TR34/L98H substitution was the most commonly reported mutation in *A. fumigatus* recovered from clinical samples.

For the first time, we reported (M220I, S297T, F46Y) and C498T/TR34 substitution in clinical samples of *A. fumigatus* isolates and clinical samples of *A.orezea* isolates, respectively.

The pattern of antifungal resistance appears to have evolved during the COVID-19 pandemic. Notably, there has been an increase in the detection of azole-resistant *Aspergillus* isolates in COVID-19 patients. Therefore, it is strongly recommended to perform antifungal susceptibility testing whenever feasible. Additionally, effective surveillance systems should be implemented to monitor the emergence and spread of azole-resistant *Aspergillus* spp. These data are essential for clinicians to understand the current incidence of azole resistance and to optimize the management of affected patients. Furthermore, this information is crucial in selecting the most appropriate antifungal therapy, ensuring more targeted and effective treatment strategies for managing *Aspergillus* infections.

The Ethics Committee of Shahid Rajaee Hospitals, Tehran, Iran, approved this study (ethics code: IR.TUMS.SPH.REC.97000).

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