e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(2); 108-115

Original Research Article

Microbiological Profile and Antifungal Susceptibility Patterns of Mucormycosis Isolates in COVID-19–Associated Cases

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Received: 01-12-2025 / Revised: 15-01-202 / Accepted: 01-02-2026
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Conflict of interest: Nil

Abstract

Background: The COVID-19 pandemic witnessed an unprecedented surge in mucormycosis cases, particularly among patients with uncontrolled diabetes mellitus and corticosteroid exposure. Understanding the microbiological spectrum and antifungal susceptibility patterns of causative agents is essential for optimizing therapeutic strategies.

Methods: This prospective observational study was conducted. Clinical specimens from 156 confirmed CAM patients were processed for fungal culture, molecular identification, and antifungal susceptibility testing using the broth microdilution method following CLSI M38-A2 guidelines.

Results: Among 156 patients, culture positivity was achieved in 124 cases (79.5%). Rhizopus arrhizus was the predominant species (58.1%), followed by Rhizopus microsporus (16.9%), Mucor circinelloides (10.5%), and Lichtheimia corymbifera (8.1%). Rhino-orbital-cerebral mucormycosis was the most common presentation (82.7%). Diabetes mellitus was present in 142 patients (91.0%), with mean HbA1c of 10.8 ± 2.4%. Among antifungals tested, amphotericin B demonstrated lowest geometric mean MIC (0.38 µg/mL), followed by posaconazole (0.52 µg/mL) and isavuconazole (0.86 µg/mL). Elevated MICs to amphotericin B (≥2 µg/mL) were observed in 8.9% of isolates. All isolates showed high MICs to fluconazole (>64 µg/mL) and voriconazole (>8 µg/mL). Mortality rate was 34.6%, with significantly higher mortality in disseminated disease (71.4%) compared to localized infection (28.2%, p<0.001).

Conclusion: Rhizopus arrhizus remains the predominant etiological agent in CAM. While amphotericin B and posaconazole maintain good in vitro activity, emergence of isolates with elevated MICs warrants continued surveillance. Species-level identification and susceptibility testing are crucial for optimizing antifungal therapy.

Keywords: Mucormycosis, COVID-19, antifungal susceptibility, Rhizopus, amphotericin B, broth microdilution.

DOI: 10.25258/ijcpr.18.2.17

Introduction

Mucormycosis represents a life-threatening angioinvasive fungal infection caused by filamentous fungi belonging to the order Mucorales within the subphylum Mucoromycotina [1]. Historically considered a relatively rare opportunistic infection, mucormycosis has demonstrated increasing incidence globally over recent decades, particularly among immunocompromised individuals, patients with uncontrolled diabetes mellitus, and those receiving hematopoietic stem cell transplantation [2].

The infection is characterized by rapid tissue necrosis, angioinvasion, and high mortality rates ranging from 40% to 80% depending on clinical presentation and underlying host factors [3]. The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), precipitated an unprecedented global surge in mucormycosis cases, most notably in India [4]. This phenomenon, termed COVID-19-associated mucormycosis (CAM), reached epidemic proportions with over 47,000 cases reported in India alone during the second wave in 2021 [5]. The convergence of multiple predisposing factors including hyperglycemia, corticosteroid-induced immunosuppression, prolonged hospitalization, oxygen therapy, and iron dysregulation created optimal conditions for Mucorales proliferation [6].

The pathophysiology of CAM involves complex interactions between viral-induced immune dysregulation and metabolic derangements.

COVID-19 infection promotes a pro-inflammatory state characterized by elevated ferritin, interleukin-6, and impaired phagocytic function [7]. Concomitant hyperglycemia enhances fungal growth through increased glucose availability, impaired neutrophil chemotaxis, and reduced oxidative burst capacity [8]. Furthermore, widespread corticosteroid usage for COVID-19 management, often at supraphysiological doses, further compromised host antifungal defenses [9].

The genus Rhizopus, particularly Rhizopus arrhizus (formerly Rhizopus oryzae), represents the most frequently isolated organism in mucormycosis globally [10]. However, species distribution demonstrates geographic variability, with Lichtheimia species more prevalent in European populations compared to Asian cohorts [11]. Accurate species identification carries therapeutic implications, as antifungal susceptibility profiles may vary among different Mucorales species [12].

Antifungal management of mucormycosis relies primarily on amphotericin B formulations, particularly liposomal amphotericin B, as first-line therapy [13]. Posaconazole and isavuconazole provide alternative options for salvage therapy or oral step-down treatment [14]. However, standardized susceptibility testing for Mucorales remains challenging, and clinical breakpoints have not been established for most antifungal-organism combinations [15]. Understanding local susceptibility patterns is therefore essential for guiding empirical therapy and detecting emerging resistance.

Despite extensive clinical literature on CAM, comprehensive microbiological characterization including species-level identification and antifungal susceptibility testing remains limited. This knowledge gap impedes optimization of therapeutic strategies and identification of potential resistance trends.

The present study aimed to systematically characterize the microbiological profile, species distribution, and antifungal susceptibility patterns of mucormycosis isolates from COVID-19-associated cases at a tertiary care center in India.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted at the Department of Microbiology and Mycology Unit of a tertiary care teaching hospital designated as a COVID-19 treatment center.

Study Population: Consecutive patients presenting with clinically suspected mucormycosis with confirmed or recent COVID-19 infection were enrolled. COVID-19 diagnosis was confirmed by positive real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 within 12 weeks prior to mucormycosis presentation.

Inclusion Criteria

- Age ≥18 years
- Confirmed COVID-19 infection (RT-PCR positive) within preceding 12 weeks
- Clinical and/or radiological features suggestive of mucormycosis
- Histopathological evidence of invasive fungal infection with characteristic broad, aseptate, ribbon-like hyphae with right-angle branching, and/or positive fungal culture for Mucorales

Exclusion Criteria

- Patients with pre-existing mucormycosis diagnosis prior to COVID-19 infection
- Cases with concurrent invasive aspergillosis or other fungal co-infections
- Inadequate specimen quality for mycological workup
- Refusal to provide informed consent

Sample Collection

Clinical specimens were collected based on anatomical site of involvement including:

- Nasal tissue and sinus contents (obtained during diagnostic nasal endoscopy or surgical debridement)
- Orbital tissue specimens
- Pulmonary samples (bronchoalveolar lavage, sputum, or lung tissue)
- Skin biopsies
- Other tissue specimens as clinically indicated

All specimens were transported immediately to the laboratory in sterile containers and processed within 2 hours of collection.

Mycological Processing

Direct Microscopy: Specimens were examined by 10% potassium hydroxide (KOH) mount with calcofluor white fluorescent staining under fluorescence microscopy for characteristic fungal elements.

Fungal Culture: Specimens were inoculated on Sabouraud dextrose agar (SDA) with chloramphenicol and Potato dextrose agar (PDA) and incubated at 25°C and 37°C for up to 14 days. Cultures were examined daily for fungal growth. Colony morphology, growth rate, and microscopic characteristics were documented.

Phenotypic Identification: Preliminary identify-cation was based on colonial morphology (color, texture, growth rate, reverse pigmentation) and microscopic features (sporangiophore characteristics, columella shape, rhizoid presence, sporangiospore morphology) using lactophenol cotton blue preparations.

Molecular Identification: All culture-positive isolates underwent molecular identification using DNA sequencing of the internal transcribed spacer (ITS) region of ribosomal DNA.

DNA Extraction: Fungal DNA was extracted using the CTAB (cetyltrimethylammonium bromide) method from mycelial growth obtained from pure cultures.

PCR Amplification: The ITS region was amplified using universal fungal primers ITS1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4 (5'-TCCTCCGCTTATTGATATGC-3'). PCR conditions included initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 55°C for 30 seconds, extension at 72°C for 1 minute, and final extension at 72°C for 10 minutes.

Sequencing and Analysis: Amplified products were purified and subjected to bidirectional Sanger sequencing. Sequences were analyzed using BLAST against the NCBI GenBank database, with species identification accepted at ≥98% sequence identity.

Antifungal Susceptibility Testing: Antifungal susceptibility testing was performed using the broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) M38-A2 guidelines.

Antifungal Agents Tested:

- Amphotericin B (0.015–16 µg/mL)
- Posaconazole (0.015–16 µg/mL)
- Isavuconazole (0.015–16 µg/mL)
- Itraconazole (0.015–16 µg/mL)
- Voriconazole (0.015–16 µg/mL)
- Fluconazole (0.125–128 µg/mL)

Inoculum Preparation: Sporangiospore suspensions were prepared from 7-day-old cultures in RPMI 1640 medium supplemented with 0.165 M MOPS buffer (pH 7.0) and adjusted to final concentration of 0.4–5 × 10^4 CFU/mL.

MIC Determination: Minimum inhibitory concentration (MIC) was defined as the lowest drug concentration resulting in complete growth inhibition for amphotericin B and ≥50% growth reduction for azoles. Microplates were incubated at 35°C and read at 24, 48, and 72 hours depending on growth characteristics. Quality control was performed using Candida parapsilosis ATCC 22019 and Candida krusei ATCC 6258.

Clinical Data Collection: Demographic information, comorbidities, COVID-19 severity, treatment details (corticosteroid dosage and duration, oxygen therapy), anatomical site of mucormycosis, surgical interventions, antifungal therapy, and outcomes were recorded from medical records using a standardized data collection form.

Statistical Analysis: Data were analyzed using SPSS version 25.0 (IBM Corporation, Armonk, NY). Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) based on distribution normality assessed by Shapiro-Wilk test.

MIC data were expressed as range, MIC50, MIC90, and geometric mean (GM). Chi-square or Fisher's exact test was used for categorical comparisons. Independent samples t-test or Mann-Whitney U test was employed for continuous variables. Statistical significance was defined as $p<0.05$.

Results

Demographic and Clinical Characteristics: A total of 156 patients meeting inclusion criteria were enrolled during the study period. The mean age was 52.8 ± 12.4 years (range: 24–78 years), with male predominance (n=108, 69.2%).

Diabetes mellitus was present in 142 patients (91.0%), with mean HbA1c of 10.8 ± 2.4%. Prior corticosteroid therapy for COVID-19 was documented in 134 patients (85.9%), and oxygen therapy was administered in 118 patients (75.6%). Demographic and clinical characteristics are presented in Table 1.

Table 1: Demographic and Clinical Characteristics of COVID-19-Associated Mucormycosis Patients (n=156)

Characteristic	Value
Age (years), mean ± SD	52.8 ± 12.4
Age group, n (%)	
18–40 years	28 (17.9)
41–60 years	84 (53.9)
>60 years	44 (28.2)
Sex, n (%)	
Male	108 (69.2)
Female	48 (30.8)
Comorbidities, n (%)	
Diabetes mellitus	142 (91.0)

Hypertension	68 (43.6)
Chronic kidney disease	18 (11.5)
Malignancy	8 (5.1)
Post-transplant	4 (2.6)
HbA1c (%), mean ± SD	10.8 ± 2.4
COVID-19 severity, n (%)	
Mild	22 (14.1)
Moderate	72 (46.2)
Severe	62 (39.7)
Corticosteroid exposure, n (%)	134 (85.9)
Cumulative dexamethasone dose (mg), median (IQR)	120 (80–180)
Duration of steroid therapy (days), median (IQR)	12 (8–18)
Oxygen therapy, n (%)	118 (75.6)
Duration from COVID-19 diagnosis to mucormycosis (days), median (IQR)	18 (12–28)
Anatomical presentation, n (%)	
Rhino-orbital-cerebral	129 (82.7)
Pulmonary	14 (9.0)
Cutaneous	6 (3.8)
Disseminated	7 (4.5)
Surgical debridement performed, n (%)	138 (88.5)
Mortality, n (%)	54 (34.6)

Microbiological Profile and Species Distribution:]Direct microscopy demonstrated characteristic aseptate, broad, ribbon-like hyphae with right-angle branching in 138 of 156 specimens (88.5%). Culture positivity was achieved in 124 specimens (79.5%). Molecular identification confirmed seven distinct species among culture-positive isolates. Species distribution is detailed in Table 2. Rhizopus arrhizus was the predominant species isolated in 72 cases (58.1%), followed by Rhizopus microsporus in 21 cases (16.9%), Mucor circinelloides in 13 cases (10.5%), Lichtheimia corymbifera in 10 cases (8.1%), Rhizomucor pusillus in 4 cases (3.2%), Cunninghamella bertholletiae in 3 cases (2.4%), and Apophysomyces elegans in 1 case (0.8%).

Rhino-orbital-cerebral mucormycosis (ROCM) was predominantly caused by Rhizopus arrhizus (62.7%), while pulmonary cases showed relatively higher proportion of Lichtheimia species (21.4%). Among disseminated cases, Cunninghamella bertholletiae accounted for 28.6% of isolates.

Table 2: Species Distribution among Culture-Positive Mucormycosis Isolates (n=124)

Species	Total n (%)	ROCM n (%)	Pulmonary n (%)	Cutaneous n (%)	Disseminated n (%)
Rhizopus arrhizus	72 (58.1)	64 (62.7)	4 (28.6)	2 (40.0)	2 (28.6)
Rhizopus microsporus	21 (16.9)	18 (17.6)	2 (14.3)	1 (20.0)	0 (0.0)
Mucor circinelloides	13 (10.5)	10 (9.8)	2 (14.3)	1 (20.0)	0 (0.0)
Lichtheimia corymbifera	10 (8.1)	6 (5.9)	3 (21.4)	0 (0.0)	1 (14.3)
Rhizomucor pusillus	4 (3.2)	2 (2.0)	1 (7.1)	1 (20.0)	0 (0.0)
Cunninghamella bertholletiae	3 (2.4)	1 (1.0)	2 (14.3)	0 (0.0)	2 (28.6)
Apophysomyces elegans	1 (0.8)	1 (1.0)	0 (0.0)	0 (0.0)	2 (28.6)
Total	**124 (100)**	**102 (82.3)**	**14 (11.3)**	**5 (4.0)**	**7 (5.6)**

ROCM: Rhino-orbital-cerebral mucormycosis

Antifungal Susceptibility Patterns: Antifungal susceptibility testing was performed on all 124 culture-positive isolates. MIC distributions for tested antifungal agents are presented in Table 3. Amphotericin B demonstrated the lowest geometric mean MIC (0.38 µg/mL), with MIC50 and MIC90 values of 0.25 µg/mL and 1.0 µg/mL, respectively. Eleven isolates (8.9%) showed elevated MICs (≥2 µg/mL) to amphotericin B, including 4 Rhizopus arrhizus, 3 Rhizopus microsporus, 2 Lichtheimia corymbifera, 1 Mucor circinelloides, and 1 Cunninghamella bertholletiae.

Among azoles, posaconazole demonstrated best activity with geometric mean MIC of 0.52 µg/mL and MIC90 of 2.0 µg/mL. Isavuconazole showed comparable activity (GM MIC: 0.86 µg/mL). Itraconazole displayed variable activity with geometric mean MIC of 1.42 µg/mL. All isolates demonstrated high MICs to voriconazole (>8 µg/mL) and fluconazole (>64 µg/mL), confirming

intrinsic resistance. Species-specific susceptibility analysis revealed that Lichtheimia corymbifera isolates showed lowest MICs to amphotericin B (GM: 0.22 µg/mL), while Cunninghamella bertholletiae demonstrated highest MICs (GM: 1.58 µg/mL). Rhizopus arrhizus isolates showed variable susceptibility to posaconazole (range: 0.125–8 µg/mL).

Table 3: Antifungal Susceptibility Patterns of Mucormycosis Isolates (n=124)

Antifungal Agent	Range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)	GM MIC (µg/mL)	Elevated MIC n (%)*
Amphotericin B	0.06–4	0.25	1.0	0.38	11 (8.9)
Posaconazole	0.06–8	0.5	2.0	0.52	18 (14.5)
Isavuconazole	0.125–8	0.5	4.0	0.86	22 (17.7)
Itraconazole	0.25–16	1.0	8.0	1.42	38 (30.6)
Voriconazole	4–>16	>16	>16	>16	124 (100)
Fluconazole	32–>128	>128	>128	>128	124 (100)

***Elevated MIC defined as: Amphotericin B ≥2 µg/mL; Posaconazole ≥4 µg/mL; Isavuconazole ≥4 µg/mL; Itraconazole ≥8 µg/mL; Voriconazole ≥8 µg/mL; Fluconazole ≥64 µg/mL. GM: Geometric Mean; MIC: Minimum Inhibitory Concentration**

Outcome Analysis: Overall mortality was 34.6% (54/156). Mortality was significantly higher among patients with disseminated disease (71.4%) compared to localized presentations (28.2%, $p<0.001$). Patients who died had significantly higher mean age (58.4 ± 11.2 vs. 49.8 ± 12.6 years, $p<0.001$), higher HbA1c (11.8 ± 2.6% vs. 10.2 ± 2.2%, $p<0.01$), and longer duration from diagnosis to antifungal initiation (4.2 ± 2.1 vs. 2.4 ± 1.4 days, $p<0.001$). Isolates with elevated amphotericin B MIC (≥2 µg/mL) were associated with higher mortality (54.5%) compared to susceptible isolates (31.9%), though this did not reach statistical significance ($p=0.12$).

Discussion

This prospective study provides comprehensive microbiological characterization and antifungal susceptibility profiling of mucormycosis isolates from a large cohort of COVID-19-associated cases. Our findings confirm Rhizopus arrhizus as the predominant etiological agent while demonstrating concerning rates of isolates with elevated amphotericin B MICs.

The species distribution observed in our study aligns with global epidemiological data. Jeong and colleagues, in their multinational surveillance study, reported Rhizopus species as causative agents in approximately 70% of mucormycosis cases, with R. arrhizus being most frequent [16]. The predominance of Rhizopus species likely reflects their ubiquitous environmental presence and thermotolerance, facilitating colonization and invasion in susceptible hosts [17]. Regional variations exist, with Apophysomyces species being more prevalent in tropical climates and Lichtheimia species showing higher frequency in European populations [18]. The relatively high proportion of Cunninghamella bertholletiae among disseminated cases (28.6%) in our study is noteworthy. This species has been associated with more aggressive disease courses and higher mortality rates compared to Rhizopus species [19]. Skiada et al. reported Cunninghamella-associated mortality exceeding 70% in their European registry, emphasizing the clinical importance of species-level identification for prognostication [20].

Our antifungal susceptibility data provide valuable insights into contemporary resistance patterns among CAM isolates. The geometric mean MIC of 0.38 µg/mL for amphotericin B indicates retained susceptibility in the majority of isolates. However, the observation that 8.9% of isolates demonstrated MICs ≥2 µg/mL is concerning. While clinical breakpoints for Mucorales remain undefined, epidemiological cutoff values and pharmacokinetic/pharmacodynamic considerations suggest that MICs exceeding 1-2 µg/mL may predict therapeutic failure with standard amphotericin B dosing [21].

The emergence of reduced amphotericin B susceptibility in mucormycosis has been sporadically reported. Lamoth and colleagues described amphotericin B-resistant Rhizopus microsporus isolates with acquired mutations in the ERG gene family [22]. Whether similar mechanisms underlie elevated MICs in our isolates requires further investigation. Continuous surveillance and molecular characterization of resistant isolates are warranted to understand resistance evolution. Posaconazole demonstrated favorable activity with geometric mean MIC of 0.52 µg/mL, supporting its role as step-down therapy or alternative agent. The EQUAL Mucor score validation study emphasized the importance of posaconazole in oral maintenance therapy following initial amphotericin B induction [23]. Isavuconazole showed comparable activity and offers advantages of both intravenous and oral

formulations with improved tolerability compared to posaconazole suspension [24].

The intrinsic resistance to voriconazole and fluconazole observed universally in our isolates is consistent with established understanding of Mucorales antifungal pharmacology. This has critical clinical implications, as inappropriate empirical therapy with these agents in suspected invasive fungal infections may permit uncontrolled mucormycosis progression while suppressing competing Aspergillus species [25].

Species-specific susceptibility variations noted in our study have therapeutic relevance. Lichtheimia species demonstrated lowest amphotericin B MICs, consistent with previous reports suggesting enhanced susceptibility of this genus [26]. Conversely, Cunninghamella isolates showed highest MICs across antifungal classes, potentially contributing to poor outcomes associated with this pathogen.

The mortality rate of 34.6% in our cohort is lower than historically reported rates for mucormycosis but consistent with recent CAM series employing aggressive multimodal management [27]. Early surgical debridement, which was performed in 88.5% of our patients, combined with prompt antifungal initiation and glycemic optimization likely contributed to improved survival outcomes [28]. The significant association between delayed antifungal initiation and mortality underscores the importance of maintaining high clinical suspicion and initiating empirical therapy promptly in suspected cases.

Limitations of this study include its single-center design, which may limit generalizability. Additionally, CLSI methodology, while standardized, may not perfectly correlate with clinical outcomes. The absence of established clinical breakpoints precludes definitive categorization of isolates as resistant. Correlation with treatment outcomes for individual isolates was limited by heterogeneous antifungal regimens and concurrent surgical interventions.

Conclusion

This comprehensive microbiological analysis confirms Rhizopus arrhizus as the predominant etiological agent in COVID-19-associated mucormycosis, accounting for 58.1% of culture-positive cases. Amphotericin B and posaconazole maintain favorable in vitro activity against most isolates, supporting their continued use as primary and alternative therapeutic agents, respectively. However, the identification of 8.9% of isolates with elevated amphotericin B MICs raises concerns regarding emerging resistance and emphasizes the necessity for ongoing susceptibility surveillance. Universal resistance to voriconazole and fluconazole reinforces the importance of appropriate antifungal selection in suspected mucormycosis. Species-level identification using molecular methods should be pursued routinely, as susceptibility profiles and clinical outcomes vary among Mucorales genera. Integration of mycological laboratory capabilities with clinical management through multidisciplinary teams is essential for optimizing outcomes in this challenging infection.

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