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# BIOMARKER LANDSCAPE OF MYCOSIS, WITH SPECIAL EMPHASIS ON MUCORMYCOSIS

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**ABSTRACT:** Systemic fungal infections, including opportunistic and endemic mycoses, pose a significant threat to immunocompromised individuals. Mucormycosis, caused by zygomycetes, is particularly devastating, characterized by tissue necrosis and diverse clinical manifestations. Risk factors such as immunodeficiency and underlying diseases contribute to its incidence. Through a comprehensive literature analysis, this review examines existing data on mucormycosis biomarkers. Treatment typically involves aggressive antifungal therapy and surgical debridement. Promising biomarkers like galactomannan and mannan are identified for early detection and monitoring, crucial for improving diagnostic accuracy and facilitating timely interventions. Pursuing biomarkers for systemic mycoses is crucial for enhancing infection management. Early detection through biomarkers has the potential to decrease morbidity and mortality associated with mucormycosis, ultimately improving outcomes for vulnerable patients.

**INTRODUCTION:** Mycoses are diseases caused by fungi that can affect innumerable tissues and organs in humans. Fungi are ubiquitous microorganisms found in the environment, and while many are harmless, some can cause infections in certain conditions [1]. Every year, environmental or commensal fungi are responsible for approximately 2 million cases of life-threatening opportunistic infections that strike immunocompromised or genetically susceptible hosts [2]. Mycoses can be classified into different types based on the affected body part and the degree of invasiveness [3].

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Superficial mycosis is a localized infection primarily affecting the skin, hair, or nails. Superficial fungal infections can cause discomfort, itching, and other concerns [4]. Typically, superficial mycosis is less severe and is more common among healthy individuals.

However, invasive fungal infections (IFIs), also known as zygomycosis/muromycosis, are severe infections caused by fungi that invade deep in the tissues and organs of the body, often leading to systemic complications. The diseases are caused by zygosporic fungi, also known as zygomycetes, the most common type of filamentous fungi. These infections are particularly problematic in individuals with compromised immune systems [5]. IFIs can manifest in various forms, affecting vital organs such as the lungs, bloodstream, and central nervous system [6]. Delays in identifying and treating systemic fungal illnesses, including endemic mycosis, have been associated with high mortality

rates and account for 1.5 million deaths annually [2]. Immunocompromised patients with IFIs rarely show symptoms. Treatment requires high doses of intravenous antifungal medications and prompt, aggressive surgical debridement. Mucormycosis is classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, and other types. The aim of this review is to investigate the expansion of biomarkers for systemic mycosis.

**Causative Agents of Mucormycosis:** The Mucorales/mucoromycetes are a group of saprophytic fungi that reside in soil and decomposing organic materials. The most common causative agents of mucormycosis are the *Rhizopus, Mucor, Rhizomucor, Lichtheimia (Absidia),* and *Cunninghamella species* [7,9]. Notably, *Rhizopus oryzae (Rhizopus arrhizus*) is predominantly found to be associated with mucormycosis. The prevalence of *Rhizopus microsporus* and *Rhizopus homothallicus* as the causative agent has also increased in recent years [9]. *R. oryzae* causes rhinocerebral and pulmonary mucormycosis. Similarly, Mucor circinelloides, *Rhizomu corpusillus, Lichtheimia corymbifera,* and *Cunninghamella bertholletiae* also play a prominent role in causing mucormycosis. *Apophysomyces variabilis* are the other microorganisms associated with necrotizing fasciitis [8], whereas the Apophysomyces species are associated with cutaneous mucormycosis that cause necrotizing fasciitis. *Lichtheimia ramosa* is the most common causative agent in India [10]. These microorganisms are usually found in soil, decaying vegetation, decaying plant material, and certain environmental niches [11].

**Risk Factors for Mucormycosis:** Mucormycosis poses several risks that contribute to its development. These can be broadly categorized based on medical and environmental conditions. There are some key risk factors, namely, exposure to either environmental or contaminated sources, corticosteroids, malnutrition and respiratory conditions.


**FIG. 1: RISK FACTORS FOR MUCORMYCOSIS**

The immunocompromised state is a common risk factor that causes individuals to have a weakened immune system and be susceptible to conditions such as hematologic malignancies (lymphoma), human immunodeficiency virus infection/ acquired immunodeficiency syndrome, organ/cell transplantation, and many others. Poorly managed diabetes mellitus, which is caused by uncontrolled diabetic ketoacidosis [12], use of an immuno-suppressive drug (hematologic malignancies), hematopoietic stem cell transplantation, hematological malignancies with a low level of neutrophils (neutropenia) [13], skin disruption due to trauma or burn that may be susceptible entry point to fungus, conditions leading to elevated iron levels in the body such as hemochromatosis/excessive

iron supplementation, prolonged and high-dose corticosteroid therapy (either for medical conditions [respiratory lung diseases] or as immunosuppressive therapy) [14], hematopoietic stem cell transplantation, solid organ transplantation, chemotherapy, autoimmune or inflammatory disorders, and the use of voriconazole in the past have all been linked to mucormycosis **Fig. 1** [9,15,16,17]. In immunocompetent individuals, mucormycosis is rare but may occur after local cutaneous or soft tissue injuries [16, 17].

**Mucormycosis Prevalence and Incidence in India:** The prevalence of mucormycosis is thought to be 50 times greater in India and other emerging nations than in the developed world as a whole [18]. According to the research by Patruni *et al.* [15], the annual rate of new cases of mucormycosis recorded by a single center increased from 12.9% in 1990–1999 to 50.0% in 2006–2007. There were an average of 89 new cases each year between 2013 and 2015, up from an average of 25 new cases annually between 1990 and 2007 [9]. Between 2005 and 2015, the study found an average annual incidence rate of 18.4 cases in the southern Indian state of Tamil Nadu [7]. However, the average annual number of new cases discovered by Tamil Nadu researchers between 2015 and 2019 was 9.5 [7]. Even though mucormycosis was prominent from the late 80s/early 90s, it gained attention in India particularly during the COVID-19 pandemic, with comorbidities such as diabetes or the use of corticosteroids that has been noted as a contributing factor to the rise in the number of mucormycosis cases [18]. Although invasive aspergillosis (IA) is given a higher priority in intensive care units (ICUs), a multicenter study conducted in Indian ICUs indicated that a substantial (14%) proportion of patients had mucormycosis. Sindhu *et al.* [19] observed that 1 in 10 patients admitted in the ICUs of North Indian hospitals had mucormycosis.

**Mucormycosis Incidence and Epidemiology:** The epidemiology of mucormycosis varies regionally based on population demographics, climate, and environmental conditions [14]. The incidence has historically been low, but the number of reported cases has been on the rise over the last two decades, notably in India, France, Belgium, and Switzerland. In developed countries, 7 of every 8 patients with mucormycosis are immuno-compromised patients [20]. In the period between 2001 and 2010, mucormycosis accounted for 1.5% of the 35,876 cases of IFIs documented in France [20]. The frequency of mucormycosis in Spain increased from 1.2 per 100,000 from 1988 to 2006 to 3.2 per 100,000 in a single-center study conducted between 2007 and 2015 [21]. From 2006 to 2015, 3,374 IFI cases were found among 3,154 people who were treated at hospitals and clinics affiliated with the large US healthcare provider Intermountain Healthcare [21]. During 2005 and 2007, 230 instances of mucormycosis were reported in 13 European countries, according to the European Confederation of Medical Mycology. Another study conducted on more than 560 hospitals in the US between January 2005 and June 2014 indicated that mucormycosis was present in 555 of more than 47 million inpatients [22]. Data from the National Inpatient Sample revealed 5,346 instances of mucormycosis among more than 319 million hospitalizations in the US between 2003 and 2010 [20]. Only eight patients (10.8%) had never been sick before; seven of those had experienced trauma that led to their condition [21].

**Clinical Features of Mucormycosis:** The clinical presentation of mucormycosis is manifested in various forms depending on the site of infection. It is, however, classified into different subgroups based on the organ or system most commonly afflicted by the fungus, such as respiratory (ocular), pulmonary, cutaneous, gastrointestinal, and other systems **Fig. 2** [23, 24].

*Rhinoorbitocerebral mucormycosis* (ROCM) had clinical manifestations such as facial pain, headache, nasal congestion, black necrotic eschar in the nasal mucosa, and potential involvement of the eyes and central nervous system. Pulmonary mucormycosis has clinical features such as chest pain, hemoptysis, severe cases of respiratory distress, and radiological findings of nodules or consolidations [25]. Patients with gastrointestinal mucormycosis exhibit the symptoms of abdominal pain, gastrointestinal bleeding, and bowel perforation that affects the entire gastrointestinal tract [26]. However, cutaneous mucormycosis is associated with the symptom of skin lesions, often necrotic or eschar formation [30], and disseminated mucormycosis exhibits malaise, fever, and the involvement of multiple organs [20]. In a study

involving 929 cases of mucormycosis, sinus (39%), lung (24%), disseminated (23%), and skin and soft tissue infections (19%) were the most types [27]. Overall, 62 (60%) of 154 individuals with cancer also had a pulmonary illness, whereas only 6 (4%) had ROCM. Although 145 (33%) patients with diabetes mellitus had ROCM, 222 (66%) had a sinus illness [26]. A total of 101 instances of mucormycosis were identified in France between the years 2005 and 2007, with 28% of the cases being lung infection, 25% being ROCM, 20% being skin and soft tissue infection, and 18% being broad infection [28]. In another study, seven of eight patients who presented with no underlying disease had sustained injuries [23].

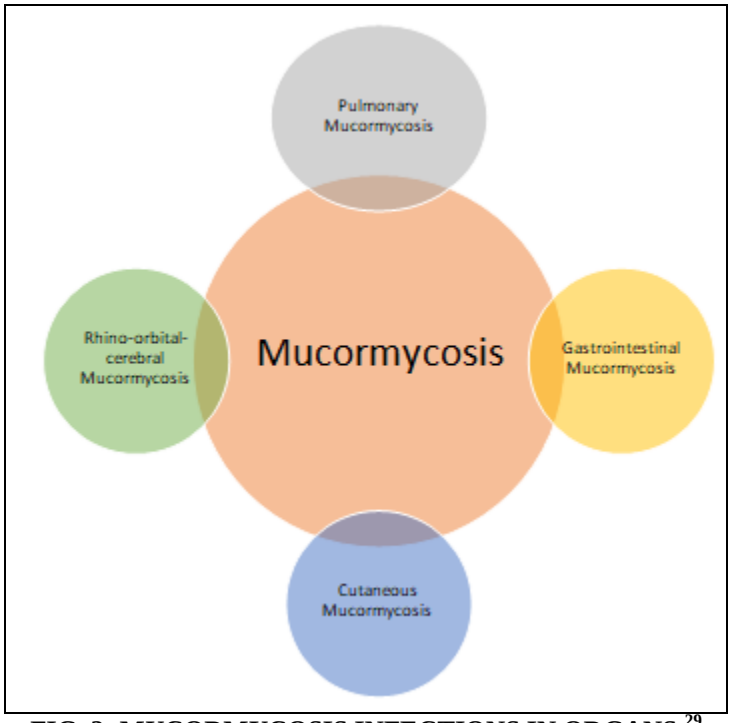


**FIG. 2: MUCORMYCOSIS INFECTIONS IN ORGANS [29]**

**Pathophysiology and Host Defense:** Understanding the pathophysiology of mucormycosis involves the interaction between the host and the fungal pathogen. The host defense mechanism plays a crucial role in preventing the fungal infection. The Defensins, a cationic peptide, and oxidative metabolites are produced by mononuclear and polymorphonuclear phagocytes of normal hosts, which eliminate Mucorales [27].

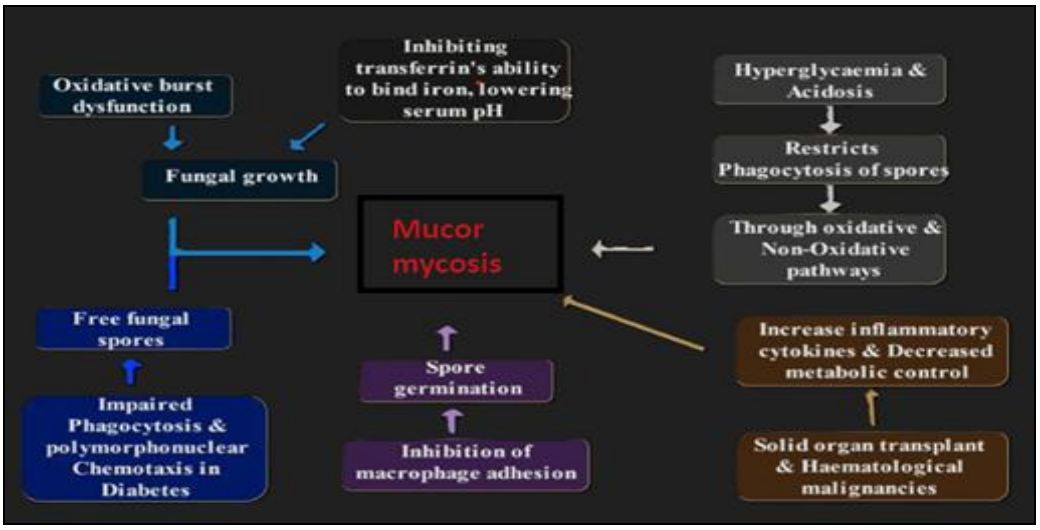


**FIG. 3: PATHOPHYSIOLOGY OF MUCORMYCOSIS 38**

Clinical evidence indicates that these phagocytes are the main host defense mechanism against mucormycosis. Acidosis and hyperglycemia also hamper oxidative and non-oxidative mechanisms of phagocytosis [29]. Patients with neutropenia, for instance, have a higher risk for developing mucormycosis. Furthermore, patients with malfunctioning phagocytes are also at a higher risk for mucormycosis. It is well recognized that both oxidative and nonoxidative processes can hinder the phagocytes' ability to approach and eliminate the organisms in patients with hyperglycemia and acidosis. It is unclear how precisely ketoacidosis, diabetes, or steroid use affects the phagocytes' ability to function. However, in healthy individuals, systemic mucormycosis infections are safeguarded by endothelial cells, circulating neutrophils, tissue macrophages, and specific non-binding proteins [30]. The pathophysiology of mucormycosis is directly or indirectly associated with a condition wherein the host immune system weakens **Fig. 3.**

**Role of Iron in the Pathogenesis:** Patients with elevated accessible serum iron levels have been found to have an increased sensitivity to mucormycosis, a recently discovered essential clinical characteristic. For 20 years, it has been recognized that invasive mucormycosis is significantly more common among patients receiving treatment with the iron chelator deferoxamine. Nevertheless, it is now evident that deferoxamine does not facilitate mucormycosis infections through iron chelation. Although deferoxamine appears to be an iron chelator to the human host, the *Rhizopus* species use deferoxamine as a siderophore to absorb iron that was previously unavailable to the fungus. The quantity of iron that Rhizopus spp. can absorb from deferoxamine is 8–40 times more than that of *Aspergillus fumigatus* and *Candida albicans.*

The increased iron uptake bay Rhizopus spp. is directly connected with a serum iron level increase. Furthermore, iron is extremely necessary for Rhizopus pathogenicity, as evidenced by studies involving animal models, wherein administration of free iron or deferoxamine reduces the survival of mice infected with Rhizopus spp. but not *C. albicans* [49]. Additionally, studies on animals have shown that other iron chelators do not worsen mucormycosis infection because they are not employed by the fungus as siderophores. Patients with diabetic ketoacidosis are at a significantly increased risk for developing rhinocerebral mucormycosis [50].

The finding that patients with systemic acidosis have higher amounts of accessible serum iron is supported by multiple lines of evidence. This is most likely because the presence of acidosis releases iron from binding proteins. For example, sera taken from individuals with diabetic ketoacidosis supported the growth of Rhizopus oryzae in an acidic environment (pH, 6.88–7.30) but not in the an alkaline environment (pH, 7.78–8.38). Higher accessible serum iron levels (69 μg/dL) were noted in acidic sera that promoted *R. oryzae* growth than in sera that did not support the growth of *R. oryzae* (13 μg/dL). Furthermore, sera obtained from normal volunteers showed a decrease in their ability to bind iron under simulated acidotic circumstances, indicating that transferrin's ability to bind iron is momentarily disrupted by acidosis [51]. Thus, an increase in the level of accessible serum iron during diabetic ketoacidosis is probably responsible for at least some of the patients' heightened sensitivity to mucormycosis.

**Diagnostic Methods for Fungal Detection:** Detecting/diagnosing the infection often relies on multiple assessments such as clinical, microbiological, and radiological tests. Microscopy, *in-vitro* fungal culture, histo-pathological examination, radiography, computed tomography, serology, and antigen detection techniques, including the use of lateral flow devices, continue to be heavily relied upon [53].

The ability to turn some of these diagnostic techniques into point-of-care tests makes them advantageous in situations where more advanced, specialized mycological expertise like that found in national mycological reference centers is not available. High-tech molecular-based alternative technologies, such as protein fingerprinting using matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry, DNA-sequencing–based techniques, and polymerase chain reaction (PCR), are increasingly being used to supplement these foundation methodologies [54]. The development of multiplex diagnostics, which

do not require fungal culture, is a promising direction. Ideally, these diagnostic methods could also simultaneously analyze other crucial factors such as the fungal pathogen's treatment resistance profile. For a substance to serve as a biomarker, its association with a disease must be stronger than molecular knowledge. Changes in cell wall components can contribute to discrepancies. Quick, culture-independent diagnosis is crucial for deciding antifungal treatment (AFT) initiation or cessation. Biomarker relevance in invasive fungal disease (IFD) diagnosis varies based on factors such as patient characteristics and assay procedures [31]. Biomarkers aid in diagnosing multiple fungal infections, including opportunistic diseases such as aspergillosis. Studies focus on specific antigens or nucleic acids for IFD diagnosis [31]. Antigen detection is useful for diseases such as cryptococcosis and histoplasmosis. Despite clinical value, interpreting biomarker significance can be challenging [33]. Common IFD biomarkers include galactomannan (GM), 1,3-β-D-glucan (BDG), mannan, anti-mannan antibody, and species-specific antigens [33]. Antibodies from previous exposure are common for opportunistic diseases, as indicated in **Table 1.**

**TABLE 1: BIOMARKERS FOR FUNGAL INFECTIONS**

| Infection | Biomarker | Antigen | Antibody | Response to therapy | Reference |
|---|---|---|---|---|---|
| Mucormycosis (GM) | GM | Yes | No | Varies | [42] |
| Mucormycosis (BDG) | BDG | Yes | No | Varies | [44] |
| Candidiasis – *Candida* mannan | *Candida* mannan antigen | Yes | No | Varies | [40] |
| Candidiasis – Anti-mannan | Anti-mannan antibody | No | Yes | Varies | [46] |
| Cryptococcosis – Cryptococcal antigen | Cryptococcal antigen | Yes | No | Limited | [44] |
| Fungal infection – NAA | NAA | Yes | No | Varies | [2] |
| Candidemia – T2 Candida | T2 Candida | Yes | No | Varies | [15] |
| Fungal infection – Next-generation sequencing | Next-generation sequencing | Yes | No | Varies | [54] |
| Mucormycosis in COVID-19 | GM | Yes | No | Not specified | [22] |
| Aspergillosis in COVID-19 – Serum BDG | Serum BDG | Yes | No | Varies | [87] |
| Aspergillosis in COVID-19 – *Aspergillus* PCR | *Aspergillus* PCR | Yes | No | Varies | [93] |
| Aspergillosis in COVID-19 – Anti-mannan | Anti-mannan antibody and antigen | Yes | No | Varies | [46] |
| Aspergillosis in COVID-19 – Mannan | Mannan antigen with anti-mannan antibody | Yes | No | Varies | [45] |

GM, galactomannan; BDG, 1,3-β-D-glucan; PCR, polymerase chain reaction; NAA, N-acetyl aspartate

**Galactomannan (GM):** GM is one of the prominent known biomarkers for detection of Aspergillus. It a 20-kDa soluble polysaccharide antigen detectable in body fluids [34]. GM in bronchoalveolar lavages shows better diagnostic performance than that in serum. Combining GM in bronchoalveolar lavages and serum BDG in people with neutropenia increases the specificity and positive predictive value of each test by as much as 100% (GM enzyme immunoassay and BDG assay) [34, 35]. Platelia GM ELISA™ and BDG assay are used for invasive aspergillosis (IA) detection [35]. Bronchoalveolar lavage fluid GM detection using an OD index cutoff value of 1.5 showed high sensitivity and specificity and proved to be promising against immunosuppression and hematological problems for invasive mycosis detection, particularly invasive pulmonary aspergillosis (IPA) [34]. The galactomannan test is generally thought to exhibit the best sensitivity and specificity when used in conjunction with other tests [55].

**1, 3-β-D-Glucan (BDG):** The most significant and prevalent polysaccharide found in many cell walls is BDG, which is also present in the cell walls of the majority of pathogenic fungi [56, 57]. One of the commercially available assay kits that uses a colorimetric approach to detect and quantify the amount of β-(1-3)-D-glucan in serum and cerebrospinal fluid is called Fungitell®. While it is widely regarded as a sensitive, non-specific pan-fungal test, some fungal species, such as Cryptococcus spp., produce less BDG. The BDG

test identifies a wide variety of fungi, including *Aspergillus, Candida, Pneumocystis, Coccidioides, Histoplasma, Trichosporon, Fusarium,* and *Exserohilum.*

Fungitell™ is a diagnostic test [34], whose positive threshold result value is >80 pg/mL, and a higher threshold improves repeatability. BDG assays, especially Fungitell™, are utilized for early diagnosis of IFD. Assays for BDG also showed improvement after patients receiving AFT were excluded [29].

**Antigens:** The sensitivity and specificity of antigens to be used as biomarkers depend upon the population being tested, types of samples being analyzed, thresholds being used, methodology being applied, and presence or absence of possible fungal case definitions. Rapid innovations in point-of-care diagnostics include the lateral flow device, mannan antigen test, Candida mannan antigen (Mn) and anti-mannan antibody (A-Mn) detection, and cryptococcal antigen test, as indicated in **Table 1.**

**Combination of Biomarkers:** GM significantly enhances the diagnostic performance and accuracy, facilitating early and reliable IPA identification. Although G/GM tests exhibit good specificity and negative predictive value for invasive fungal rhinosinusitis diagnosis, their sensitivity and positive predictive value are low. Measuring BDG levels in at-risk patients proves more valuable for early diagnosis of IPA than serum GM testing, especially in critically immunocompromised patients [36]. Parallel diagnosis increases both sensitivity and diagnostic odds ratio [37]. In individuals without neutropenia, a more accurate diagnosis of IPA may be achieved by combining the GM or BG tests with the IgA/G test. The sensitivity and specificity of various tests are detailed in **Table 2.**

**TABLE 2: SENSITIVITY AND SPECIFICITY OF VARIOUS DIAGNOSTIC TESTS [72, 73]**

| Diagnostic test | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| CrAg LFA | 99.3 | 99.1 | 99.5 | 98.7 |
| CrAg latex (Meridian) | 97.8 | 85.9 | 92.6 | 95.5 |
| CrAg latex (Immy) | 97.0 | 100.0 | 100.0 | 75.8 |
| India ink microscopy | 86.1 | 97.3 | 98.2 | 80.2 |
| CSF culture | 90.0 | 100.0 | 100.0 | 85.3 |
| —100 µL volume | 94.2 | 100.0 | 100.0 | 91.2 |
| —10 µL volume | 82.4 | 100.0 | 100.0 | 75.8 |
| BAL | 77% | 70% | ------- | ------ |

CrAg, cryptococcal antigen; LFA, lateral flow assay; CSF, cerebrospinal fluid; BAL, bronchoalveolar lavage

**Detection and Identification of the Fungi:** The advancements in fungal detection and identification techniques, including microbiological culture, molecular techniques, and imaging studies such as PCR, enzyme-linked immunosorbent assay, Fourier transform infrared spectroscopy (FTIR), MALDI-TOF, and DNA microassay have further enhanced our understanding of the molecular biological components of fungal cells, serving as potential biomarkers [39] **Table 3**. Currently, the "gold standard" for diagnosing a fungal infection is microbial culture, which is widely accepted. Fungal diseases can, however, take days or weeks to grow and be identified. PCR-specific amplification is a quick and efficient way to directly detect DNA and RNA in clinical and environmental samples, allowing for the precise and quantitative attribution of microorganism components. Specific primers are developed for various fungal groups based on the region in the DNA that contains multiple genes encoding different ribosomal RNA molecules. Gene clustering uses multiplex assays enabling the detection of a wide variety of fungi. RNA, serving as the starting point for nucleic acid amplification, has shown a high correlation between nucleic acid sequence-based amplification and the serum BDG test [41]. Next-generation sequencing provides a more precise method for identifying fungi [43], offering a nuanced study of fungal genetic diversity, medication resistance, and epidemic analysis [42]. PCR with electrospray ionization/mass spectrometry is a relatively new technology that can directly detect and identify fungal species from clinical specimens. With quick turnaround times and high throughput, this technique allows for the direct detection and identification of pathogens that cause disease from clinical specimens or mixtures of organisms [60, 61, 62]. With quick turnaround times

and high throughput, this technique allows for the direct detection and identification of pathogens from clinical specimens or mixtures of microorganisms [61, 62]. FTIR is a powerful analytical technique used to study the interaction of molecules with infrared light emerges as a quick and accurate method for microbiological typing, needing no reagents for sample preparation [44]. They can be applied to the analysis of solids, liquids, and gasses. FTIR instruments are now faster and more sensitive than they were in the past since they are digitalized [61]. This utilizes the unique "fingerprint" of microbiological strains by comparing their spectra with pre-existing spectral data. This delves into the cellular biology of fungi by fingerprinting different types of carbohydrates, proteins, and lipids of different fungal spores [44].

**TABLE 3: METHODS USED TO DIAGNOSE MYCOSIS**

| Methods | Techniques used | Reference |
|---|---|---|
| Whole blood methods | T2 candida$^{R}$ | [48] |
| Blood culture–based methods | FilmArray | [58] |
| | Direct MALDI-TOF MS | [55] |
| | PNA-FISH$^{TM}$ | [51] |
| Conventional methods | CHROMagar$^{TM}$ | [12] |
| | Auxacolor$^{TM}$ | |
| | Vitek 2 YST ID card | |
| Advanced techniques | FTIR | [38] |
| | PCR | |

PCR, polymerase chain reaction; FTIR, Fourier transform infrared spectroscopy; MALDI-TOF MS, matrix-assisted laser desorption ionization–time of flight mass spectrometry

**Mycosis in Patients with COVID-19 Infection:** The pathophysiology of COVID-19, caused by SARS-CoV-2, is typified by a changed immunological response, a changed oxidant–antioxidant balance, and an increase in the production of reactive oxygen species. Lipid peroxidation, DNA damage, and protein digestion all contribute to cellular damage. Increased cytokine storm and hyperinflammation, linked to increased levels of D-dimers, interleukins, and tumor necrosis factor-alpha, amplify this impact [64].

Damage to the epithelium and endothelium is the consequence of this pathogenic action, which later involves multiple organs. T he most prevalent virulent strain of COVID-19 during the second wave was the Delta variation (B.1.617.2), which was linked to a post-COVID consequence known as "black fungus," a vernacular term for mucormycosis, an opportunistic and severe fungal illness [81]. According to the extant post-COVID literature [66, 67], India is the epicenter of black fungus, especially mucormycosis, as compared to the predominance of aspergillosis in the Western world. The widespread use of steroids and related risk factors, such as diabetes mellitus and environmental variables, are among the causes. The term used to characterize fungal sinusitis brought on by COVID-19 is COVID-associated invasive fungal sinusitis [9]. Jain *et al.* [68] identified distinct histological findings in post–COVID-19 mycoses, which were connected with a poor prognosis. The histopathological features are detailed in **Table 4.** Rhino-orbital mucormycosis was the most common invasive opportunistic fungal infection, outnumbering invasive fungal aspergillosis or candidiasis, among patients with COVID-19.

**TABLE 4: HISTOPATHOLOGICAL FINDINGS IN COVID-19 CASES [84]**

| Histological features | Number of cases with observation | Percentage (%) |
|---|---|---|
| Necrosis | 45 | 100 |
| Vascular proliferation | 37 | 82 |
| Angioinvasion | 26 | 58 |
| Giant cell reaction | 24 | 53 |
| Suppurative inflammation | 21 | 47 |
| Fibrin thrombi | 21 | 47 |
| Septic thrombi | 18 | 40 |
| Angiodestruction | 18 | 40 |
| Granulomas | 16 | 36 |
| Bile pigment | 16 | 36 |
| Fungal osteomyelitis | 15 | 33 |
| Necrotizing granulomas | 14 | 31 |
| Perineurial invasion | 7 | 15 |
| Fat necrosis | 4 | 8 |
| Neural necrosis | 1 | 1 |
| Viable area | 41 | 91 |

**Approaches to Managing Mycosis:** Mucormycosis may be wiped out with a combination of rapid diagnosis, treatment of any underlying predisposing diseases (if feasible),

extensive surgical debridement of diseased tissue, and effective antifungal medications. This is especially true for small, isolated lesions, which, if detected early, may typically be surgically removed before they spread or are involved in essential tissues. Unfortunately, there are currently no rapid diagnostic tests available.

**Role of Surgery:** Mucormycosis is challenging to treat with antifungal medicines alone owing to its rapid progression. There is a significant variation in the susceptibility of the strains that cause mucormycosis to AFT; certain strains may be highly resistant to amphotericin B. Because of the angioinvasion, thrombosis, and tissue necrosis typical of this condition, anti-infectives have a more difficult time reaching the infection site. Infected and necrotic tissue need immediate surgical debridement. In patients with rhino cerebral mucormycosis, early surgical excision of the infected sinuses and sufficient debridement of the retro-orbital region can lead to high cure rates (>85%). Surgery for patients with pulmonary mucormycosis is associated with much better outcomes than antifungal therapy alone [49]. The mortality rate associated with localized (non-disseminated) cutaneous mucormycosis is 10% when treated with strict surgical debridement and additional antifungal medications.

**Antifungal Therapy:** Clinicians have a difficult time deciding which of the available antifungal drugs is optimal for treating mucormycosis owing to a lack of clinical studies (Supplementary Material). Accurate diagnosis of IA using the EORTC/MSG criteria may be useful in identifying circulating GM and BDG fungal biomarkers using serological tests [47]. There have been several studies assessing how well these two biomarkers perform as diagnostic tools, and the results reveal that they do not have enough sensitivity when used alone to detect IA at an early stage. The current molecular assays are also not consistent with one another. A combination of *Candida* biomarkers, including CAGTA, Mn/A-Mn, and BDG (with varying cut-off values), was studied on 100 patients with bacteremia and candidemia. The negative predictive value of a combination of CAGTA and BDG for IC diagnosis increased to 97%. Patients in the intensive care unit performed optimally on this battery of tests [47].

Multiple types of invasive mucormycosis are more prevalent among individuals with immune system disorders, as seen in **Fig. 2.** IFIs can be diagnosed with the use of several biomarkers that have been discovered **Table 1.**

**Empiric Therapy:** Empiric therapy is an early strategy for treating individuals with febrile neutropenia. In high-risk patients, this usually means initiating or modifying antifungal therapy if the fever is prolonged or recurring even after 4–7 days of antibiotics. Empiric therapy for patients with febrile neutropenia who did not show radiological or microbiological signs of infection-causing bacteria and who did not respond well to at least 3 days of broad-spectrum antibacterial therapy [70].

**Pre-emptive Therapy:** Similar to empirical therapy, pre-emptive therapy has historically been used to treat viral infections, such as cytomegalovirus infections, for which treatment is initiated for signs of infection (viremia) before the onset of symptoms, as determined by tests such as PCR for viral load quantification. However, as there is no preventive test for IFIs, this is not feasible. In other words, no diagnostic test can identify the infection before the disease manifests. Rather, it is predicted on suspicion of an existing IFI, specifically a mold infection [71]. Antimold medicines are started when there are findings suggestive of IFIs, which may include seropositivity for AGM and supportive radiographic evidence in high-risk patients [72].

**Prophylactic Therapy:** In patients undergoing hematopoietic cell transplantation, only prophylaxis with fluconazole has proven a survival benefit. Treating patients undergoing hematopoietic cell transplantation prophylactically against IFIs improves outcomes, such as lowering the incidence of IFIs. Fluconazole has been compared with other antifungal agents; however, none of them have shown to have better survival benefits when used in patients undergoing hematopoietic cell transplantation. Prophylactic therapy with posaconazole has been shown to improve survival outcomes in individuals with neutropenia receiving treatment for myelodysplastic syndrome or acute myelogenous leukemia. The choice of antifungal

agent in general depends on whether one can exclude or confirm the diagnosis of zygomycosis.

**Immunotherapy:** T cell–mediated immunity, more precisely responsive to fungal antigens, and is generally the main defensive strategy against IFIs. T cell–mediated immunity is weakened in the immunocompromised host susceptible to IFIs for several reasons, including corticosteroid therapy. It was initially shown by Cenci et al. that mice might be protected against invasive aspergillosis by passively transferring Th1-committed CD4+ T cells specific to Aspergillus. Aspergillus-specific CD4+ T cells can be found and grown *ex-vivo* to sufficient quantities for patient infusion, as demonstrated by Beck *et al.* [73]. Perruccio *et al.* have recently shown how Aspergillus-specific immunotherapy can be used to promote a quick immunological recovery after hematopoietic cell transplantation.

**CONCLUSIONS:** The biomarker landscape of mucormycosis holds great promise for advancing our understanding of the disease and improving patient outcomes. A rapid and accurate diagnosis of IA continues to be a clinical and diagnostic problem despite continuous research into the use of different combinations of test procedures to improve diagnostic accuracy. The development, validation, and use of biomarkers in particular therapeutic contexts is the basis of preventive personalized medicine. Continued research, innovation, and collaboration are essential to further unravel the intricacies of mucormycosis and translate these findings into clinical practice. As we navigate the challenges posed by IFIs, a comprehensive and dynamic approach to biomarker discovery and application will be instrumental in shaping the future of mucormycosis management.

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