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ORIGINAL RESEARCH

Comparative Prognosis of Fungal Balls Versus Invasive Pulmonary Mucormycosis

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Background: Pulmonary mucormycosis is recognized as a highly fatal invasive fungal infection. However, clinical observations have demonstrated unexpectedly favorable outcomes in some patients. This study aimed to compare the clinical presentation, management, and prognosis between patients with fungal balls and invasive pulmonary mucormycosis.

Methods: This observational study included patients diagnosed with pulmonary mucormycosis at the Second Xiangya Hospital of Central South University between 2007 and 2023. Based on imaging characteristics, the patients were divided into invasive pulmonary mucormycosis and fungal balls groups, and the underlying diseases, clinical manifestations, diagnostic method, treatment, and prognosis were analyzed.

Results: Compared to invasive pulmonary mucormycosis patients, pulmonary mucormycosis patients with fungal balls had fewer systemic underlying diseases, such as diabetes, immunosuppression, and more pre-existing lung diseases like bronchiectasis (82.4%) and tuberculosis (64.7%). They exhibited milder symptoms, mainly cough and sputum, with lower CRP and ESR levels. Pulmonary mucormycosis patients with fungal balls typically involved a single upper lobe, while invasive pulmonary mucormycosis patients often had bilateral lung involvement. Ten pulmonary mucormycosis patients with fungal balls treated surgically without antifungal therapy still had favorable prognoses than those with invasive disease.

Conclusion: Compared to invasive pulmonary mucormycosis patients, pulmonary mucormycosis patients with fungal balls exhibit milder clinical symptoms and more favorable prognosis. Surgical intervention might play a critical role in the management of pulmonary mucormycosis patients.

Keywords: pulmonary mucormycosis, fungal balls, infection, favorable prognosis

Introduction

Mucor spp. are conditionally pathogenic fungi widely found in air, soil, and rotten food. Its spores can infect the human body through inhalation, ingestion, or trauma, causing mucormycosis.[1] Mucormycosis is a rare invasive fungal disease caused by *Mucorales* fungal infection, with rapid disease progress and a high mortality rate of 40%-80%. The order *Mucorales* includes fungi from the family *Mucoraceae*, among which *Rhizopus* spp. are the most common causative agents of mucormycosis, followed by *Mucor* spp. and *Lichtheimia* spp.[2,3] In patients with diabetes, hematologic malignancies, organ transplantation and other underlying diseases, *Mucor* spp. is the second most common pathogen after *Aspergillus* spp.[4] Depending on the site of infection, mucormycosis can be classified into rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated type. Pulmonary type is the second most common manifestation after rhinocerebral type.[5] The clinical and radiological features of pulmonary mucormycosis lack specificity, often making it difficult to distinguish from other invasive pulmonary mycoses such as invasive pulmonary aspergillosis.[1] Notably, some patients with pulmonary mucormycosis exhibit imaging features of fungal balls that closely resemble the characteristic appearance of aspergilloma caused by *Aspergillus* spp. Both entities typically develop within pre-existing pulmonary

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cavities and share clinical manifestations such as hemoptysis. This radiographic and clinical similarity often leads to delayed diagnosis or misdiagnosis.[6]

In 2022, the Chinese expert consensus on the diagnosis and treatment of mucormycosis proposes that the diagnosis of mucormycosis mainly relies on identification of the pathogen and histological examination. At the same time, surgical treatment for mucormycosis should be initiated as soon as feasible. Moreover, systemic antifungal drug therapy is also necessary, including liposomal amphotericin B, isavuconazole and posaconazole.[1] In our cohort, we identified a significant number of patients who presented with fungal balls, a non-invasive form of the disease. While invasive pulmonary mucormycosis is associated with high mortality, the clinical course and outcomes of mucormycosis presenting as fungal balls remain poorly characterized. Direct comparisons of prognosis, treatment strategies, and outcomes between these two forms are limited but critically needed to guide clinical management. To systematically compare the clinical presentation, management, and prognosis of these patients with those having invasive pulmonary mucormycosis, we collected clinical data of 42 patients with pulmonary mucormycosis, including the diagnostic method, clinical features, imaging findings, treatment, prognosis, and follow-up data.

Methods

Study Design and Patients

The study collected a total of 42 patients diagnosed with pulmonary mucormycosis at the Second Xiangya Hospital of Central South University in Changsha, Hunan Province from 2012 to 2023. The study protocol was reviewed and approved by the Hospital's Institutional Review Board (IRB) (Approval No: LYF20240004). All patients provided voluntary informed consent to participate in this study.

Patients were included if they met the following criteria: 1) diagnosed pulmonary mucormycosis according to the 2023 Global Guideline for the Diagnosis and Management of Mucormycosis[3] and the Expert Consensus on Clinical Diagnosis and Treatment of Mucormycosis in China (2022);[1] 2) availability of complete clinical and radiological data. Exclusion criteria were: 1) extrapulmonary mucormycosis without lung involvement; 2) insufficient clinical information for analysis. Confirmed diagnosis included: (1) histopathological examination of tissue biopsy specimens showed *Mucor* spp. hyphae or (2) positive culture of tissue or sterile body fluids or (3) detection of *Mucor* spp. by mNGS. Clinical diagnosis included: possession of host factors, clinical manifestations, and microbiological evidence.

Based on imaging characteristics, patients were classified into two groups: those with fungal balls (n=17), and those with invasive pulmonary mucormycosis (n=24).

Clinical and Sociodemographic Data Collection

We collected comprehensive clinical data through a standardized case report form. Variables included demographic characteristics (age, gender), underlying diseases (hematological malignancies, diabetes mellitus, etc)., clinical manifestations, laboratory parameters, imaging features, bronchoscopy findings, diagnostic method, treatment regimens (surgical and antifungal therapy), and prognostic outcomes. Follow-up information was obtained via telephone interview from 2015 to 2024, with the endpoint set in October 2023.

Mucorales Identification

Histopathological examination: Tissue samples were stained with hematoxylin and eosin (H&E) and Grocott's methenamine silver (GMS). The presence of broad, pauci-septate hyphae with right-angled branching was considered indicative of *Mucorales* infection.

Fungal culture: Samples from sterile sites (eg, lung tissue, bronchoalveolar lavage fluid) were cultured on appropriate media. Fungal identification was based on macroscopic and microscopic morphological characteristics.

Metagenomic Next-Generation Sequencing (mNGS): For cases where conventional methods were inconclusive, mNGS was performed on clinical samples to detect and identify *Mucorales* pathogens through genomic sequence alignment.

Statistical Analysis

Data analysis was performed using IBM SPSS 26.0. Descriptive statistics were used to summarize patient demographic characteristics, clinical manifestations, treatment, and prognosis. Quantitative data were expressed as medians with quartiles or means, while qualitative data were expressed as frequency and percentage. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate, and a P-value < 0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

Among the 17 patients with fungal balls, defined as fungal masses forming within pre-existing pulmonary cavities or cystic spaces,[7,8] 6 (35.3%) were male, with a mean age of 50.88 years. Underlying conditions included bronchiectasis (14 cases, 82.4%), pulmonary tuberculosis (11 cases, 64.7%), hypertension (4 cases, 23.5%), and diabetes (2 cases, 11.8%). Other comorbidities consisted of systemic lupus erythematosus (1 case), history of hormone therapy (1 case), and history of abortion (1 case); one patient had no documented comorbidities. In contrast, patients in the invasive pulmonary mucormycosis group (n=24) exhibited a higher prevalence of systemic immunosuppressive conditions, including diabetes (13 cases, 54.2%) and hematologic malignancies (5 cases, 20.8%), but lower rates of structural lung diseases such as bronchiectasis (6 cases, 25.0%) and pulmonary tuberculosis (2 cases, 8.3%). The differences in the prevalence of bronchiectasis and tuberculosis between the two groups were statistically significant ($p < 0.05$, Table 1).

Table 1 Demographic and Base Line Characteristics of 42 Patients with Pulmonary Mucormycosis

Variables	Total (n=42)	The Fungal Ball (n=17)	Invasion (n=24)	P-value
Male, n (%)	20(47.6)	6(35.3)	14(58.3)	0.146
Age, years, mean ± SD	47.93±16.3	50.88±10.05	45.67±19.77	0.053
BMI, median (IQR)	20.43(15.88,24.31)	23.52(17.58,26.23)	19.63(15.76,22.86)	0.223
Underlying conditions				
Bronchiectasis, n (%)	21(50)	14(82.4)	6(25)	**<0.001**
Tuberculosis, n (%)	14(33.3)	11(64.7)	2(8.3)	**<0.001**
COPD, n (%)	3(7.1)	0(0)	3(12.5)	0.066
Hematological system tumors, n (%)	5(11.9)	0(0)	5(20.8)	**< 0.05**
Bone marrow transplantation, n (%)	2(4.8)	0(0)	2(8.3)	0.137
Aplastic anemia, n (%)	1(2.4)	0(0)	1(4.2)	0.297
Diabetes, n (%)	15(35.7)	2(11.8)	13(54.2)	**< 0.05**
Hypertension, n (%)	7(16.7)	4(23.5)	3(12.5)	0.359
Hepatitis, n (%)	3(7.1)	0(0)	3(12.5)	0.066
Other malignant tumors, n (%)	2(4.8)	0(0)	2(8.3)	0.137
Systemic lupus erythematosus, n (%)	2(4.8)	1(5.9)	1(4.2)	0.803
Chronic renal insufficiency, n (%)	2(4.8)	0(0)	2(8.3)	0.137
Solid organ transplantation, n (%)	1(2.4)	0(0)	1(4.2)	0.297
Syphilis, n (%)	1(2.4)	0(0)	1(4.2)	0.297
Receiving hormone therapy, n (%)	5(11.9)	1(5.9)	4(16.7)	0.279
Receiving broad-spectrum antibiotic treatment, n (%)	1(2.4)	0(0)	1(4.2)	0.297
After abortion operation, n (%)	1(2.4)	1(5.9)	0(0)	0.180
No comorbidities, n (%)	1(2.4)	1(5.9)	0(0)	0.180

Notes: Data are presented as median (interquartile range), mean ± standard deviation, or number (percentage). Bold text indicates a statistically significant P-value (< 0.05).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.

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Clinical Manifestations and Laboratory Parameters

Among the 17 patients with fungal balls, none had the Nutritional Risk Score (NRS) 2002 score ≥3, whereas two patients with invasive pulmonary mucormycosis had scores of ≥3. Additionally, among the patients with fungal balls, two had a SOFA score ≥2 upon admission, and one had a score ≥2 upon discharge. Furthermore, one patient had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of ≥15 upon admission, while none had such a score upon discharge. In this group of patients, cough and expectoration were the most prevalent symptoms, each occurring in 14 cases, accounting for 82.4%. Hemoptysis was observed in 7 cases (41.2%), fever in 4 cases (23.5%), dyspnea in 3 cases (17.6%), and chest pain in 2 cases (11.8%) (Table 2).

Laboratory parameters were compared between patients with fungal balls and those with invasive pulmonary mucormycosis. No significant differences were observed in multiple markers including white blood cell count, neutrophil count, lymphocyte count, procalcitonin (PCT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, total bilirubin (TBL), direct bilirubin (DBL), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and brain natriuretic peptide (BNP) (all $p > 0.05$). Consistent with the diagnostic profile of mucormycosis, neither group showed elevated serum levels of galactomannan or 1-3-β-D-glucan. In contrast, significant differences were identified in mean hemoglobin level, erythrocyte sedimentation rate (ESR), and albumin (all $p < 0.05$). Although C-reactive protein (CRP) levels were markedly higher in the invasive disease group (median 34.70 mg/L vs 6.83 mg/L), this difference showed a trend toward significance but did not reach the statistical threshold ($p = 0.051$) (Table S1).

Imaging Features

The imaging presentation differed substantially between the two groups. Unilateral involvement, particularly in the upper lobe (58.8%), was characteristic of the fungal balls group, whereas multiple lesions in both lungs were significantly more common in invasive disease (37.5% vs 5.9%). The presence of fungal balls and the crescent sign were highly specific to the fungal balls group (100% and 94.1%, respectively), compared to a very low incidence in the invasive group (4.2% for the crescent sign). Invasive pulmonary mucormycosis was associated with a broader spectrum of severe pulmonary abnormalities, including exudation (66.7%), consolidation (58.3%), pleural effusion (37.5%), and nodular opacities (29.2% mass, 20.8% multiple nodules). These findings were infrequent or absent in fungal balls cases. Pleural thickening (35.3%) was the most common ancillary finding in the fungal balls group, with cavities and ground-glass opacity observed in a minority of cases (17.6% and 11.8%, respectively). And 1 case (5.9%) presented with both halo and reverse halo signs (Table S2 and Figure S1).

Table 2 Clinical Characteristics of 42 Patients with Pulmonary Mucormycosis

Variables	Total (n=42)	The Fungal Ball (n=17)	Invasion (n=24)	P-value
NRS2002≥3, n (%)	2(28.6)	0(0)	2(33.3)	0.390
Admission SOFA score≥2, n (%)	8(47.1)	2(40)	6(50)	0.706
Discharge SOFA score≥2, n (%)	5(71.4)	1(100)	4(66.7)	0.390
Admission APACHE II score≥15, n (%)	2(12.5)	1(20)	1(9.1)	0.554
Discharge APACHE II score≥15, n (%)	1(16.7)	0(0)	1(20)	0.526
Clinical symptoms				
Cough, n (%)	34(81)	14(82.4)	19(79.2)	0.799
Expectoration, n (%)	32(76.2)	14(82.4)	18(75.0)	0.572
Fever, n (%)	21(50)	4(23.5)	17(70.8)	**< 0.05**
Dyspnea, n (%)	15(35.7)	3(17.6)	12(50.0)	**< 0.05**
Hemoptysis, n (%)	12(28.6)	7(41.2)	5(20.8)	0.160
Chest pain, n (%)	8(19)	2(11.8)	6(25.0)	0.280

Notes: Data are presented as number (percentage). Bold text indicates a statistically significant P-value (< 0.05).

Bronchoscopic Manifestations and Microbiological Testing

Bronchoscopy was performed in a subset of patients when the diagnosis remained uncertain or for therapeutic indications such as secretion evacuation (n=26). Bronchoscopy revealed purulent secretions in 5 patients with fungal balls (50.0%), mucosal congestion in 4 patients (40.0%) (Figure 1), hemorrhage in 3 patients (30.0%), and a neoplasm in 1 patient (10.0%). Interestingly, no necrotic material or bronchogenic stenosis was observed in patients with fungal balls, while necrotic material and bronchogenic stenosis was present in 6 and 4 patients with invasive pulmonary mucormycosis (Table S3).

Among the 17 patients with fungal balls, bronchoalveolar lavage fluid (BALF) was collected from 8 patients for relevant tests. Metagenomic next-generation sequencing (mNGS) detected *Cunninghamella bertholletiae* in one BALF sample, but none of the patients had a positive BALF culture result. Sputum samples were collected from 3 patients for relevant tests, mNGS identified *Cunninghamella bertholletiae* in one sample, while the culture results of all patients were negative. Notably, 16 patients underwent tissue pathological examination through surgical or bronchoscopic procedures, and the results indicated the presence of mucormycete hyphae (Table S3 and Figure 1).

In the group of patients with invasive pulmonary mucormycosis, BALF samples were collected from 8 individuals. Among these, *Cunninghamella bertholletiae* was detected by mNGS in 3 cases, and culture results were positive in 2. Sputum samples were obtained from 14 patients, with mNGS identifying the pathogen in 4 cases and culture being positive in 3 (Table S3).

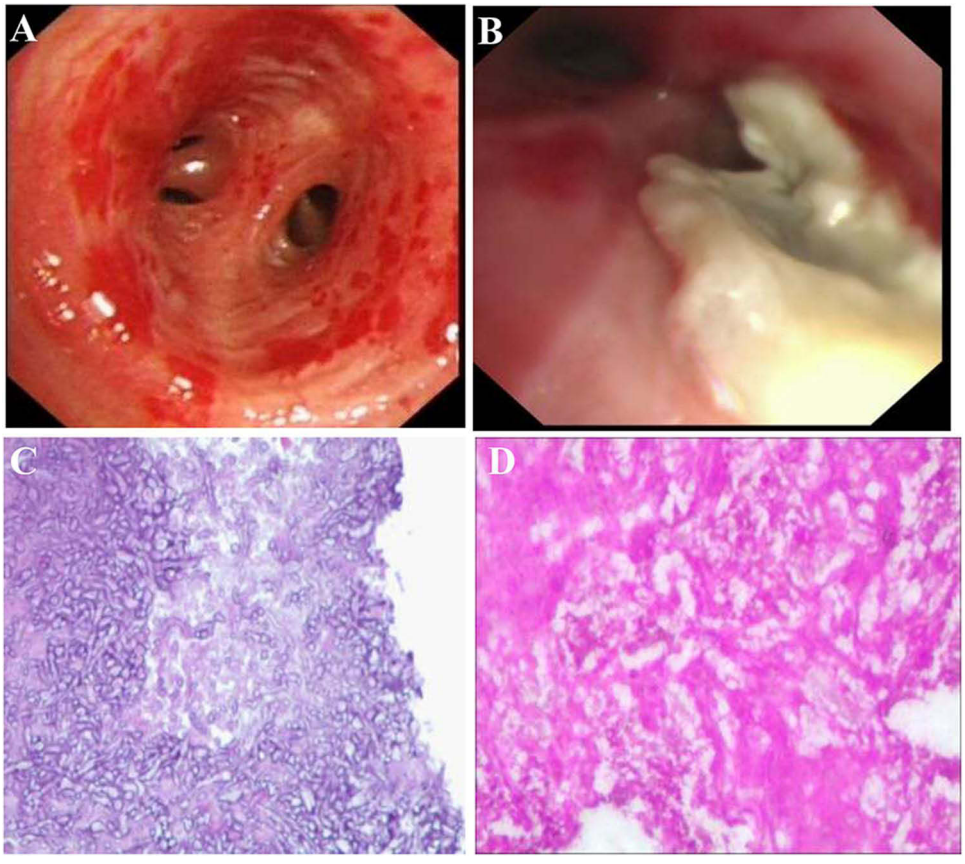

Figure 1 Bronchoscopy and histopathological features of tissues. Bronchoscopic and histopathological findings in patients with fungal balls mucormycosis. (**A**) Bronchoscopic view showing prominent mucosal congestion and edema in a segmental bronchus. (**B**) Bronchoscopic image revealing copious purulent secretions obstructing the airway lumen. (**C**) Histopathological examination of lung tissue (Hematoxylin and Eosin (H&E) stain, 200x magnification) demonstrating broad, ribbon-like, pauciseptate hyphae with right-angled branching, characteristic of *Mucorales* invasion. (**D**) Periodic Acid–Schiff (PAS) stain (400x magnification) providing enhanced visualization of the fungal hyphae morphology, confirming the diagnosis of mucormycosis; although faint, the hyphal structures are consistent with *Mucorales*.

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Table 3 Treatment and Clinical Outcome of 42 Patients with Pulmonary Mucormycosis

Variables	Total (n=42)	The Fungal Ball (n=17)	Invasion (n=24)	P-value
Treatment				
Surgery, n (%)	16(39.0)	13(76.5)	3(12.5)	**<0.001**
Amphotericin B or Amphotericin B lipid formulations, n (%)	22(53.7)	3(17.6)	19(79.2)	**<0.001**
The treatment duration reaches 3 weeks or more, n (%)	10(45.5)	1(33.3)	9(47.4)	0.646
Posaconazole, n (%)	5(12.20)	0(0)	5(20.8)	**< 0.05**
Isavuconazole, n (%)	1(2.44)	1(5.9)	0(0)	0.180
Not receiving antifungal treatment, n (%)	5(12.20)	3(17.6)	2(8.3)	0.373
Clinical outcome				
Improved, n (%)	34(82.9)	15(88.2)	19(79.2)	0.439
Not cured, n (%)	7(17.1)	2(11.8)	5(20.8)	0.439
Death during hospitalization, n (%)	5(12.20)	0(0)	5(20.8)	**< 0.05**
Death after enrollment, n (%)	6(14.63)	1(5.9)	5(20.8)	0.161

Notes: Data are presented as number (percentage). Bold text indicates a statistically significant P-value (< 0.05).

Treatment and Clinical Outcome

Among patients with fungal balls, 13 cases (76.5%) underwent surgical or endoscopic interventions, of which 10 cases did not receive postoperative antifungal drugs active against mucormycetes. Among the patients with fungal balls who received surgical management, the most common underlying conditions were structural lung diseases, particularly bronchiectasis (11/13, 84.6%) and previous pulmonary tuberculosis (8/13, 61.5%). The predominant clinical manifestation was cough and sputum production (11/13, 84.6%). Three cases (17.6%) were treated with amphotericin B or its lipid formulations, and only one of these (33.3%) received treatment for ≥3 weeks. One additional case (5.9%) received isavuconazole. Notably, three patients (17.6%) did not receive any antifungal treatment or surgical intervention due to mild symptoms or patient refusal; during follow-up, they all remained clinically stable (Table 3).

In contrast, among patients with invasive pulmonary mucormycosis, only three cases (12.5%) underwent surgical intervention or bronchoscopic procedures. These patients exhibited different characteristics: one had diabetes, one had bronchiectasis, and one had a history of pulmonary tuberculosis, with only one presenting with cough and sputum production. Nineteen cases (79.2%) were treated with amphotericin B or its lipid formulations, of which nine (47.4%) received treatment for three weeks or longer. Five cases (20.8%) received posaconazole. Two patients (8.3%) did not receive any antifungal treatment; both died during hospitalization and are included among the five fatal cases in this group (Table 3).

Regarding clinical outcomes, 15 of the 17 patients (88.2%) with fungal balls improved following treatment. The two patients (11.8%) who failed to recover did not receive any form of treatment, showed neither clinical nor radiological improvement during follow-up; however, neither patient died from mucormycosis. Among those with invasive mucormycosis, five fatalities (20.8%) occurred during hospitalization. Additionally, during follow-up, one patient in the fungal balls group died from causes unrelated to mucormycosis (Table 3).

Discussion

Mucormycosis, previously regarded as a rare invasive fungal disease, is characterized by its ability to invade blood vessels, leading to thrombosis and tissue necrosis.[9] This contributes to a high mortality rate, with one study reporting a mortality rate as high as 46%.[4] Our study affirms this poor prognosis in invasive pulmonary mucormycosis but finds a distinctly different clinical form—pulmonary mucormycosis presenting as fungal balls. We observed that patients with fungal balls exhibited markedly milder symptoms and significantly better outcomes, likely attributable to their overall preserved immune status and the localized rather than invasive nature of infection.

Consistent with established literature, traditional risk factors for invasive mucormycosis include systemic immunocompromise conditions such as diabetes, organ or hematopoietic stem cell transplantation, hematological malignancies,

long-term use of immunosuppressive agents, broad-spectrum antibiotics and so on.[10,11] In our study, half of the patients with invasive pulmonary mucormycosis had diabetes. Research has revealed that diabetes facilitates *Mucorales* proliferation by inducing iron dysregulation and systemic immunosuppression, thereby predisposing patients to invasive pulmonary mucormycosis.[12–14] By contrast, the fungal balls group had a strikingly different comorbidity profile, dominated by underlying structural lung diseases—specifically bronchiectasis (82.4%) and tuberculosis (64.7%), while diabetes was less frequently observed. Although bronchiectasis and tuberculosis are not classic risk factors, both conditions can lead to cavitary lung lesions, which in turn cause localized immune system deficiencies, facilitating fungal colonization without necessitating systemic invasion.[15,16] At the same time, tuberculosis infection can increase the degradation of ferritin, affect the serum iron content, and thus promote the growth of *Mucor* spp.[17] In addition, there was one patient with fungal balls who did not have any underlying diseases. While current research on mucormycosis in immunocompetent hosts remains limited, with most evidence derived from isolated case reports,[18,19] it is clinically crucial to investigate whether these patients harbor subtle immunodeficiencies or immunosuppressive states akin to those seen in other opportunistic fungal infections.

Consistent with findings from other studies, in our research, patients with invasive pulmonary mucormycosis more commonly presented with constitutional symptoms such as fever and dyspnea, reflecting systemic involvement and more extensive parenchymal damage.[1,20] Among the 17 pulmonary mucormycosis patients with fungal balls in our study, 82.4% exhibited cough and sputum production, with significantly lower CRP and ESR levels compared to those with invasive pulmonary mucormycosis, indicating a more contained and chronic infectious process. Because in patients with invasive pulmonary mucormycosis, infection of the lung tissue by *Mucorales* fungi is more extensive, which in turn affects the systemic immune system. Meanwhile, angioinvasion and tissue infarction trigger a robust inflammatory response,[21] all of which contribute to more severe symptoms in these patients. Recent research in aspergillosis, a similarly angioinvasive fungal infection, highlights the critical interplay of cytokines (eg, IL-1β, IL-6, TNF-α) and chemokines in driving disease pathogenesis and shaping the host immune response.[22] While our study did not measure specific cytokine profiles, the clinical marker differences we observed likely reflect this underlying immunologic disparity. Similarly, the observed elevation in hemoglobin levels among patients in the fungal balls group is likely attributable to the lower incidence of hematologic malignancies in this population.[10,11] This interpretation is consistent with our data, which indicate a higher prevalence of hematologic malignancies in the invasive group. Moreover, the etiology of hemoptysis in this cohort may differ from that described in other studies.[23] In many reports, hemoptysis is frequently attributed to mucormycosis-related angioinvasion.[24,25] By contrast, in our study, most patients had pre-existing structural lung abnormalities, such as bronchiectasis or sequelae of pulmonary tuberculosis. These conditions are themselves common causes of hemoptysis and may have contributed to the bleeding independently of fungal vascular invasion. Pulmonary mucormycosis usually affects one side (62–75%), often the upper lobes (40–45%), and occasionally both sides (16–25%).[23,26] In our study, the fungal balls most commonly involved a single upper lobe, with only one case showing bilateral involvement, while invasive cases frequently had bilateral lung involvement.

Incidence of tuberculosis in China is relatively high,[27] and patients with tuberculosis are prone to developing pulmonary cavities and bronchiectasis.[15,16] The pre-existing tuberculous cavities containing necrotic debris and protein-rich exudates create an anaerobic microenvironment conducive to *Mucorales* proliferation and hyphal invasion,[28] and the localized immune dysfunction they induce is inadequate to effectively eradicate pulmonary *Mucorales*.[8,29] *Mucorales* could damage host tissues through the secretion of proteases and toxins, and interfere with immune cell functions to evade host immune clearance.[30] Therefore, our study found a higher proportion of patients also exhibited fungal balls on imaging examinations. Surprisingly, only a minority of patients in the fungal balls group (3/17, 17.6%) presented with a classic radiological cavity. This suggests that fungal balls may form in other pre-existing anatomical spaces, such as dilated airways in bronchiectasis or emphysematous bullae, not solely in post-TB cavities.

Existing research has shown that the combination of surgical intervention and antifungal drugs can improve prognosis.[31] However, there are currently relatively few studies on the use of surgery alone as a treatment. Our data reinforce the critical role of surgery, particularly for the fungal balls form. In our study, a total of 16 patients with pulmonary mucormycosis underwent surgical interventions or endoscopic interventions, including 13 with fungal balls and 3 with invasive disease. Notably, 10 patients with fungal balls did not receive antifungal therapy after surgery, yet

their prognosis remained favorable. This suggests that for localized disease in immunocompetent hosts, surgical eradication alone can be curative, potentially sparing patients the toxicity and complications of prolonged systemic antifungal therapy. In contrast, five patients with invasive pulmonary mucormycosis succumbed to the disease despite receiving guideline-adherent antifungal therapy, highlighting the relentless progression of invasive infection even with standard pharmacologic treatment.

A significant advancement reflected in our study is the utility of mNGS in diagnosing mucormycosis. In cases where conventional culture and histopathology are delayed or negative, mNGS offers a rapid, sensitive, and culture-independent method for identifying *Mucorales* DNA directly from clinical samples such as BALF or sputum. In our cohort, mNGS successfully detected *Cunninghamella bertholletiae* in cases where traditional methods had failed, demonstrating its value as a complementary diagnostic tool capable of guiding timely and targeted intervention, especially in complex or culture-negative scenarios.

Our study has several limitations that must be acknowledged. First, the sample size, though substantial for a rare disease, remains limited (particularly 17 cases in the fungal balls group), which may restrict the statistical power for multivariate analysis and broader generalization of findings. Second, as a single-center, retrospective study, it is subject to potential selection bias and heterogeneity in clinical management over the long study period. Finally, our study has limited exploration of the pharmacological treatment. Future multi-center prospective studies with larger cohorts are needed to validate our observations, refine treatment protocols, and explore molecular host-pathogen interactions in greater depth.

Conclusion

Pulmonary mucormycosis patients with fungal balls, tend to have milder symptoms and a more favorable prognosis compared to invasive pulmonary mucormycosis patients. Surgical intervention or procedures performed via bronchoscopy may be the most promising treatment options for pulmonary mucormycosis patients with fungal balls.

Data Sharing Statement

The data that support the findings of this study are available from the first author, Jiayu Wang, upon reasonable request. (Email: 15047300458@163.com).

Ethics Statement

This clinical study was conducted in accordance with the principles of the Declaration of Helsinki. The clinical study has been reviewed and approved by the Clinical Trials and Ethics Committee of Xiangya Second Hospital, Central South University (registration number: LYF20240004). All patients provided voluntary informed consent to participate in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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