Pulmonary Mucormycosis as the Leading Clinical Type of Mucormycosis in Western China

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The aim was to better understand the clinical characteristics of patients with mucormycosis in western China. We retrospectively investigated the clinical, laboratory, radiological and treatment profiles of mucormycosis patients during a 10-year period (2010–2019). As a result, 59 proven mucormycosis were enrolled in this study. It was found that 52.5% of patients had worse clinical outcomes. Pulmonary mucormycosis (PM) was the most common clinical manifestation. The most frequent risk factor was diabetes mellitus (38, 64.4%) for mucormycosis patients. Cough (43, 93.5%), fever (24, 52.2%) and hemoptysis/bloody phlegm (21, 45.7%) were the most common manifestations of PM. There were no differences in clinical manifestations, risk factors and laboratory tests between different clinical outcome groups (P>0.05). Lymph node enlargement (30, 65.2%), patchy shadows (28, 60.9%), cavitation (25, 53.3%) and bilateral lobe involvement (39, 84.8%) were the most common on chest CT. Nodule was more common in good outcome group (P <0.05). A total of 48 cases (81.4%) were confirmed by histopathological examination, 22 cases (37.3%) were confirmed by direct microscopy. PM patients were treated with amphotericin B/amphotericin B liposome or posaconazole had better clinical outcomes (P <0.05). In conclusion, PM was the most common clinical type of mucormycosis in China. Diabetes mellitus was the most common risk factor. PM has diverse imaging manifestations and was prone to bilateral lobes involvement. Early diagnosis and effective anti-mucor treatment contribute to successful treatment.

Keywords: mucormycosis, pulmonary mucormycosis, diabetes, clinical analysis, clinical outcome

INTRODUCTION

Mucormycosis is a rare, emerging and opportunistic fungal infection with high morbidity and mortality caused by filamentous fungi of the Mucoraceae family, order Mucorales. Mucorales fungi are ubiquitous in nature. Humans are infected mainly by inhaling sporangiospores, occasionally through the ingestion of contaminated food or traumatic inoculation (Prakash and Chakrabarti, 2019; Shariati et al., 2020). The prevalence of mucormycosis varies between developing and developed countries, ranging from 0.01 to 14 per 100 000 population in Europe and India (Bitar et al., 2009; Chakrabarti and Singh, 2014; Ruhnke et al., 2015). With the growth of the number of
immunocompromised patients, increased awareness and development of diagnostic techniques, the incidence of mucormycosis is rising (Prakash et al., 2019). According to clinical presentations, mucormycosis is mainly classified as rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated types (Skiada et al., 2020). The common risk factors of mucormycosis are diabetes, hematological malignancy, use of corticosteroids or immunosuppressants, and trauma (Petrikkos et al., 2014; Jeong et al., 2019). However, the main cause of mucormycosis also varies in different countries. Hematological malignancies are the main cause in countries with high income, while diabetes mellitus (DM) or trauma are the main cause in developing countries (Chakrabarti and Singh, 2014). Diagnosis of mucormycosis is challenging because of the low sensitivity and specificity of clinical diagnostic methods (Skiada et al., 2018).

The mortality of mucormycosis remains high, it may be related to delayed diagnosis, high cost of managing mucormycosis and limited treatment options (Skiada et al., 2018). Previous studies on the characteristics of mucormycosis have been conducted mainly in America, Europe and India (Prakash and Chakrabarti, 2019). Data about mucormycosis from China is sparse. The causative agents of mucormycosis vary with different geographical locations (Prakash and Chakrabarti, 2019), and the epidemiology, the clinical disease pattern of mucormycosis vary from country to country.

To better understand the clinical characteristics of patients with mucormycosis in China, in this retrospective study, we compared the demographic features, clinical presentations, laboratory data, radiographic findings and therapeutic strategies in mucormycosis patients with different clinical outcomes who were admitted to a university hospital from Jan 2010 to Dec 2019 in western China.

MATERIALS AND METHODS

Patients

From Jan 2010 to Dec 2019, the patients with a diagnosis of mucormycosis at hospital discharge were retrospectively reviewed in West China Hospital, Sichuan University, a 4,300-bed academic tertiary hospital in Chengdu, China. According to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria and previous references (De Pauw et al., 2008; Petrikkos et al., 2014; Skiada et al., 2018), inclusion in the final study group required the diagnosis of proven mucormycosis as defined as follows: (1) age ≥ 14 years; (2) clinical manifestations and radiographic findings consistent with mucormycosis; and (3) histological presence of mucormycosis in tissue specimens, and/or broad-based, ribbon-like, non-septate hyphae with right-angle branching filamentous fungi on direct microscopy of clinical specimens, and/or Mucorales species cultured from clinical specimens. Based on clinical presentation and the involvement of the body sites, rhino-orbital-cerebral, pulmonary, cutaneous and disseminated mucormycosis were classified (Jeong et al., 2019). The following data of demographic information, underlying diseases, use of corticosteroid or immunosuppressive agent, clinical manifestations, laboratory data, radiologic findings, diagnostic procedures, therapeutic strategies and clinical outcomes at 90 days were collected.

The study was approved by the Ethics Committee of West China Hospital, Sichuan University. Because all the data in this study were routinely obtained, written informed consent was waived.

Laboratory Studies

Laboratory tests including complete blood count, blood biochemistry, procalcitonin (PCT), C-reactive protein, T lymphocyte subset, HIV testing, serum (1,3)-beta-D-glucan test (BDG test), and galactomannan test (GM test) were performed. Clinical samples (including blood, sputum, secretions, urine) were aseptically collected and cultured under aerobic or anaerobic conditions. Bacterial species were isolated and identified using MicroScan WalkAway-96 System (Siemens, USA). Fungal culture was performed on Sabouraud dextrose agar (SDA) and incubated at 30°C. All the items were performed in the Department of Laboratory Medicine of our hospital.

Radiological Assessment

Imaging examinations such as chest computed tomography (CT), abdominal CT, fibroptic bronchoscopy were performed at the discretion of the treating physicians. The CT scans were performed using 64-row multi-slice spiral CT scanner (SOMATOM definition AS+, Siemens) in our hospital. All images were reviewed independently by two experienced radiologists. For patients with PM, chest CT findings including nodule, mass, cavity, patchy consolidation, ground glass opacity, reversed halo sign, lymph node enlargement, pleural effusion and the distribution of the lesion in the lungs were recorded.

Treatment Strategies and Clinical Outcomes

The patients with mucormycosis were treated with amphotericin B (AmB, 0.5-1 mg/kg per day) (North China Pharmaceutical Co., Ltd., China) or amphotericin B liposome (LAmB, 3-6 mg/kg per day) in accordance with the drug instructions, guidelines (Skiada et al., 2013) and patient tolerance. Posaconazole oral suspension (40mg/ml, 10ml, twice daily) (Patheon Inc, Whitby, ON, Canada) was used in patients who have contraindications to amphotericin B or who cannot tolerate the side effects of amphotericin B like reduced kidney function, electrolyte imbalances, nausea and vomiting. The treatment duration was determined by the treating physicians according to the patient’s treatment response and the size of the focus. Management of patients with diabetes included dietary guidance, tight glucose control with insulin and/or hypoglycemic drugs, multiple flash glucose monitoring daily and treatment of complications. A multidisciplinary consulting team, including diabetes, infectious disease, nutrition, wound therapy, surgery, clinical microbiology, and clinical pharmacy, that offered specialist advice, on-going management. Other underlying diseases of these patients such as immune system disease, chronic lung disease were treated normally and systematically. For bacterial
co-infection patients, empirical or targeted antimicrobial therapy were given. Clinical outcomes of patients with mucormycosis were evaluated at 90 days after diagnosis. According to clinical manifestations, laboratory findings and image changes, their clinical outcomes were divided into good and worse outcome. Death or disease progression or persistence were classified as worse outcome. The continuous improvement of clinical symptoms and imaging findings were classified as good outcome.

Statistical Analysis
Statistical analyses were performed using IBM SPSS Statistics for Windows v.26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk normality test was used to test the normality of all quantitative variables. Continuous variables with normal distribution were presented as mean± standard deviation (SD) and compared by Student’s t-test. The relationship between categorical variables was assessed using Chi-square test or Fisher’s exact test. A two-tailed P value lower than 0.05 was considered statistically significant.

RESULTS

Demographic Characteristics and Clinical Outcomes of Mucormycosis Patients
A total of 68 patients with mucormycosis were admitted to our hospital from January 2010 to December 2019, 59 of whom with proven mucormycosis (mean age 54.75 ± 14.72 years; 44 males) were enrolled in this retrospective study. Pulmonary mucormycosis (PM) was the most commonly observed manifestation (46/59, 78.0%), followed by rhino-orbital-cerebral (9/59, 15.3%) and disseminated mucormycosis (3/59, 5.0%). There was only one case of cutaneous mucormycosis. These patients were classified as pulmonary type and other type mucormycosis based on clinical type. The demographic and clinical outcomes of these patients were summarized in Table 1. The ages of patients with PM was higher than that of patients with non-pulmonary mucormycosis (P=0.015). The most frequent underlying disease was diabetes mellitus (38, 64.4%) for mucormycosis patients. More patients with PM had diabetes mellitus than patients with non-pulmonary mucormycosis (P=0.027). A total of 31 mucormycosis patients (52.5%) had worse clinical outcomes, clinical outcome was not obviously different between the two groups (P>0.05).

Demographic and Clinical Characteristics in Patients With PM
Demographic and clinical features of PM patients with different clinical outcomes were shown in Table 2. The most common clinical symptoms of PM patients were cough (43, 93.5%), fever (24, 52.2%) and hemoptysis/bloody phlegm (21, 45.7%). Diabetes mellitus (33, 71.7%) was the most frequent underlying disease. There were no significant difference in the gender, age, clinical symptoms and underlying diseases between good and worse outcome group (P>0.05). For laboratory results, there was no significant difference between the two groups (P > 0.05).

Findings of CT Scan in Patients With PM
The chest CT features of patients with PM were diverse, as shown in Figure 1. The detail of chest CT findings in these patients were shown in Table 3. The most common manifestations were lymph node enlargement (30, 65.2%), patchy shadows (28, 60.9%), cavitation (25, 53.3%) and nodules (24, 52.2%). Nodule was more common in good outcome group than in worse outcome group (P <0.05). Lymph node enlargement were more common in patients with worse outcome (P<0.05). Bilateral

**TABLE 1 |** Demographic and clinical outcomes in patients with mucormycosis.

| Variables                              | Clinical type          | P-value  |
|----------------------------------------|------------------------|----------|
|                                        | All (N = 59)           | Pulmonary type (N = 46) | Other type (N = 13) |
| Male                                   | 44 (74.6)              | 35 (76.1) | 9 (69.2) |
| Age (years) (mean ± SD)                | 54.75 ± 14.72          | 57.41 ± 12.40 | 45.31 ± 18.64 |
| Underlying diseases or risk factors    |                        |          |
| Diabetes mellitus                      | 38 (64.4)              | 33 (71.7) | 5 (38.5) |
| Immune system disease                  | 2 (3.4)                | 1 (2.2)   | 1 (7.7)  |
| Corticosteroid medication or immunosuppressive drugs | 4 (6.8)                | 3 (6.5)   | 1 (7.7)  |
| Hematological malignancy               | 3 (5.1)                | 1 (2.2)   | 2 (15.4) |
| Solid tumor                            | 2 (3.4)                | 2 (4.3)   | 0 (0.0)  |
| Chronic kidney diseases                | 3 (5.1)                | 3 (6.5)   | 0 (0.0)  |
| Chronic lung disease                   | 8 (13.6)               | 7 (15.2)  | 1 (7.7)  |
| Chronic liver disease                  | 2 (1.7)                | 1 (2.2)   | 1 (7.7)  |
| Trauma                                 | 2 (3.4)                | 1 (2.2)   | 1 (7.7)  |
| None                                   | 8 (13.6)               | 6 (13.0)  | 2 (15.4) |
| Co-infection of other pathogens        |                        |          |
| Bacteria                               | 42 (71.2)              | 32 (69.6) | 10 (76.9) |
| Other fungi                            | 16 (23.7)              | 14 (30.4) | 2 (15.4) |
| Clinical outcome                       |                        |          |
| Good outcome                           | 28 (47.5)              | 23 (50.0) | 5 (38.5) |
| Worse outcome                          | 31 (52.5)              | 23 (50.0) | 8 (61.5) |

*P < 0.05.
lungs were involved in 84.8% (39/46) of patients, with the left lower lobe (20, 43.5%) and right lower lobe (18, 39.1%) most commonly involved. There was no significant difference in the lobe of lesion distribution between the two groups (P>0.05). There were 13 patients with Mucor and Aspergillus co-infection and 1 patient with lung cancer. Based on imaging findings, 12 patients were suspected to be tumors, and 2 patients were suspected to be aspergillosis in the absence of concomitant Aspergillus.

![Image: Figure 2 showing the changes of chest CT lesions during the follow-up of a patient with pulmonary fungal infection (Mucor with Aspergillus).](image)

**Diagnostic Procedures and Treatment Strategies**

Of the 59 proven patients with mucormycosis, 48 cases (81.4%) were confirmed by histopathological examination, 22 cases (37.3%) were confirmed by direct microscopy. There was no significant difference in the diagnostic procedures between the two groups (P>0.05). A total of 47 patients (79.7%) received treatment. Treatment strategies for these patients with mucormycosis include antifungal drugs, surgery, or both. Most patients (38/59, 64.4%) were treated with amphotericin B/LAmB. More patients with PM were treated with AmB/LAmB (P=0.006) or posaconazole (P=0.004) in good outcome group than in worse outcome group.

For patients with PM, only 3 patients were treated with surgery and LAmB, but there was no statistical difference in clinical outcome (P>0.05). The most common adverse events of AmB/LAmB included renal insufficiency (16/42, 38.1%) and hypokalemia (9/42, 21.4%) in this study. The severity of all adverse events were mild to moderate (grade 1-2) according to the US National Cancer Institute Common Toxicity Criteria (NCI-CTC) (US, National Cancer Institute, 2017). The adverse reaction ratio of AmB/LAmB has not statistical difference between the two groups (P>0.05). As shown in Table 4.

**DISCUSSION**

Mucormycosis is rare, neglected, and associated with high mortality rates. The study found that 52.5% of patients with mucormycosis had poor clinical outcomes. Which is similar to previous research results (Jeong et al., 2019). PM was the most

| TABLE 2 | Demographic and clinical characteristics in patients with pulmonary mucormycosis. |
|----------|---------------------------------|---------------------------------|------------------|-------------------|
| Variables | All (N = 46) (n,%) | Good outcome (N = 23) (n,%) | Worse outcome (N = 23) (n,%) | P-value |
| Male | 36 (76.1) | 5 (21.7) | 6 (26.1) | 0.288 |
| Age | 57.4 ± 12.40 | 56.0 ± 13.44 | 58.8 ± 11.38 | 0.446 |
| Presenting symptoms and signs | | | | |
| Fever | 24 (52.2) | 13 (56.5) | 11 (47.8) | 0.768 |
| Cough | 43 (85.8) | 21 (91.3) | 22 (95.7) | 1.000 |
| Hemoptysis or bloody phlegm | 21 (45.7) | 9 (39.1) | 12 (52.2) | 0.554 |
| Chest pain | 7 (15.2) | 2 (8.7) | 5 (21.7) | 0.414 |
| Shortness of breath | 14 (30.4) | 9 (39.1) | 5 (21.7) | 0.200 |
| Underlying diseases or risk factors | | | | |
| Diabetes mellitus | 33 (71.7) | 16 (69.6) | 17 (73.9) | 1.000 |
| Immune system disease | 1 (2.2) | 0 (0.0) | 1 (4.3) | 1.000 |
| Corticosteroid medication or immunosuppressive drugs | 3 (6.5) | 2 (8.7) | 1 (4.3) | 1.000 |
| Hematological malignancy | 1 (2.2) | 1 (4.3) | 0 (0.0) | 1.000 |
| Solid tumor | 2 (4.3) | 0 (0.0) | 2 (8.7) | 0.489 |
| Chronic kidney diseases | 3 (6.5) | 2 (8.7) | 1 (4.3) | 1.000 |
| Chronic lung disease | 7 (15.2) | 4 (17.4) | 3 (13.0) | 1.000 |
| Chronic liver disease | 1 (2.2) | 1 (4.3) | 0 (0.0) | 1.000 |
| Truma | 1 (2.2) | 1 (4.3) | 0 (0.0) | 1.000 |
| None | 6 (13.0) | 4 (17.4) | 2 (8.7) | 0.655 |
| Laboratory data | | | | |
| White blood cell (× 10^9/L) | 9.13 ± 6.84 | 9.58 ± 9.02 | 8.69 ± 3.76 | 0.665 |
| Neutrophil (%) | 71.96 ± 12.24 | 74.42 ± 12.11 | 69.38 ± 12.10 | 0.170 |
| Lymphocyte (× 10^9/L) | 1.48 ± 0.67 | 1.35 ± 0.60 | 1.62 ± 0.73 | 0.180 |
| Eosinophil (× 10^9/L) | 0.33 ± 1.17 | 0.48 ± 1.46 | 0.19 ± 0.26 | 0.397 |
| Mononuclear cell (× 10^9/L) | 0.49 ± 0.23 | 0.47 ± 0.26 | 0.50 ± 0.20 | 0.539 |
| C-reactive protein (mg/L) | 70.31 ± 87.94 | 66.75 ± 97.40 | 73.17 ± 82.08 | 0.831 |
| Erythrocyte sedimentation rate (mm/h) | 55.23 ± 24.06 | 49.00 ± 24.64 | 40.42 ± 33.31 | 0.278 |
| CD4+ T lymphocyte (%) | 36.94 ± 10.33 | 37.32 ± 8.00 | 36.55 ± 12.54 | 0.771 |
| CD8+ T lymphocyte (%) | 31.61 ± 9.49 | 32.92 ± 8.17 | 30.30 ± 10.80 | 0.475 |
| CD4/CD8 ratio | 1.36 ± 0.77 | 1.23 ± 0.40 | 1.48 ± 1.01 | 0.409 |
| CD4+ T lymphocyte (cells/μL) | 565.45 ± 288.69 | 419.83 ± 92.04 | 740.2 ± 357.47 | 0.062 |
| CD8+ T lymphocyte (cells/μL) | 396.82 ± 176.78 | 338.50 ± 45.12 | 466.80 ± 253.69 | 0.250 |
| Co-infecting agent | | | | |
| Bacteria | 25 (54.3) | 12 (52.2) | 13 (56.5) | 1.000 |
| Virus | 2 (4.3) | 1 (4.3) | 1 (4.3) | 1.000 |
| Fungi | 18 (39.1) | 10 (43.5) | 8 (34.8) | 0.763 |
FIGURE 1 | The findings of chest computed tomography of pulmonary mucormycosis (patients with good outcome: A, B; patients with worse outcome: C–H). (A) Multiple pleomorphic lesions in both lungs; (B) cavity with mural nodule (Mucor co-infecting with Aspergillus); (C) cavity in left lung; (D) thick-walled cavity shadow with gas-fluid level (Mucor co-infecting with Klebsiella pneumoniae); (E) mass shadow in the upper lobe of the left lung; (F) patchy shadow, nodules and consolidation in right lung; (G) cavity and ground-glass opacity; (H) reversed halo sign.
studies have found that neutropenia may be associated with mucormycosis (Patel et al., 2020; Son et al., 2020), and only a few between laboratory results and clinical outcomes in patients with outcomes. Most previous studies have not found a correlation also found that laboratory results were not associated with patient methods (Machouart et al., 2006; Springer et al., 2016). The study also found that Molecular-based assays can help to identify different fungal species which may be the reason for the increase in the incidence of mucormycosis worldwide, especially in China and India (Khan et al., 2020), because the number of diabetes patients in China is much larger than that of hematological malignancies (Liu et al., 2019; Khan et al., 2020), the underlying disease of more mucormycosis patients is diabetes. The high prevalence of diabetes in China and endemic mucor species different from other countries may also be the reasons for the high incidence of PM in diabetic patients in China. More detailed etiological studies of mucormycosis need to be done. We found the incidence of mucormycosis was tended to rise, which may be owing to the improvement of fungal diagnostic technology, health awareness and the visiting rate. In addition, diabetes incidence is on the rise worldwide, especially in China and India (Khan et al., 2020), which may be the reason for the increase in the incidence of mucormycosis in China.

For PM, the most common clinical symptoms were cough, fever, and hemoptyis/bloody phlegm. This result was similar to some previous studies. For PM, laboratory results were not associated with patient outcomes. Most previous studies have not found a correlation between laboratory results and clinical outcomes in patients with mucormycosis (Patel et al., 2020; Son et al., 2020), and only a few studies have found that neutropenia may be associated with increased mortality (Spellberg et al., 2012). Neutropenia was not found in our patients with PM, it might not be an important risk factor for mortality in these patients.

The most frequent imaging findings of PM were patchy shadows, cavitation and pulmonary nodules in this study. According to the imaging findings, PM might be misdiagnosed as tumor or pulmonary aspergillosis. Nodule was more common in good outcome group. Lymph node enlargement were more common in patients with worse outcome. Many previous studies have found multiple nodules, reversed halo sign, and cavities associated with PM (McAdams et al., 1997; Marom and Kontoyiannis, 2011). Pulmonary nodules, halo sign and cavitation was also found in patients pulmonary invasive aspergillosis (Althoff Souza et al., 2006; Muldoon et al., 2016). The reversed halo sign has been considered an important clue to the diagnosis of PM, however, it has also been described in other pulmonary diseases, including invasive pulmonary aspergillosis, tuberculosis, organising pneumonia and malignancy (Sullivan and Rana, 2019). Therefore, early biopsy to establish the underlying cause is very important in patients with suspected pulmonary fungal infections.

Diagnosis of mucormycosis is challenging. In clinical practice, laboratory diagnosis of mucormycosis includes histopathology, direct examination and cultures. For PM, the positive rate of Mucorales culture could reach 79% (Prakash and Chakrabarti, 2019). In this study, Mucorales culture positive was found only in 13 patients. It was previously reported that the positive rate of Mucorales culture could reach 79% (Prakash and Chakrabarti, 2019). Which may be related to the low vigilance of doctors to invasive pulmonary mycosis and the absence of fungal culture for puncture specimens. More needs to be done to raise awareness of pulmonary mycosis among doctors. In this study, twelve patients did not receive treatment and left the hospital against medical advice after diagnosis because of their critical condition and financial constraints. PM patients were treated

### Table 3: Chest CT findings of proven patients with pulmonary mucormycosis

| Morphology          | All (N = 46) (n,%) | Good outcome (N = 23) (n,%) | Worse outcome (N = 23) (n,%) | P-value |
|---------------------|--------------------|-----------------------------|-------------------------------|---------|
| Consolidation       | 20 (43.5)          | 9 (39.1)                    | 11 (47.8)                     | 0.767   |
| Nodule              | 24 (52.2)          | 16 (69.6)                   | 8 (34.8)                      | 0.038*  |
| Ground-glass opacity| 7 (15.2)           | 5 (21.7)                    | 2 (8.7)                       | 0.414   |
| Mass                | 15 (32.6)          | 8 (34.8)                    | 7 (30.4)                      | 1.000   |
| Cavitation          | 25 (53.3)          | 10 (43.5)                   | 15 (65.2)                     | 0.139   |
| Patchy shadow       | 28 (60.9)          | 14 (60.9)                   | 14 (60.9)                     | 1.000   |
| Fibrosis            | 17 (37.0)          | 8 (34.8)                    | 9 (39.1)                      | 1.000   |
| Pleural effusion    | 22 (47.8)          | 11 (47.8)                   | 10 (43.5)                     | 1.000   |
| Pleural thickening  | 17 (37.0)          | 6 (26.1)                    | 11 (47.8)                     | 0.221   |
| Lymph node enlargement | 30 (65.2)   | 11 (47.8)                   | 19 (82.6)                     | 0.029*  |
| Reversed halo sign  | 5 (10.9)           | 2 (8.7)                     | 3 (13.0)                      | 1.000   |
| Lobe of lesion distribution |         |                             |                               |         |
| Left upper lobe     | 12 (26.1)          | 5 (21.7)                    | 7 (30.4)                      | 0.738   |
| Left lower lobe     | 20 (43.5)          | 11 (47.8)                   | 9 (39.1)                      | 0.767   |
| Right upper lobe    | 12 (26.1)          | 7 (30.4)                    | 5 (21.7)                      | 0.738   |
| Right middle lobe   | 11 (23.9)          | 8 (34.8)                    | 3 (13.0)                      | 0.165   |
| Right lower lobe    | 18 (39.1)          | 8 (34.8)                    | 10 (43.5)                     | 0.763   |
| Bilateral involvement | 39 (84.8)    | 20 (87.0)                   | 19 (82.6)                     | 1.000   |

*P < 0.05.
with amphotericin B or posaconazole had better clinical outcomes, while untreated patients had poor outcomes. For rhino-orbito-cerebral and disseminated mucormycosis patients, there was no statistically significant difference in clinical outcome between different treatment strategies, which maybe related to the small number of cases. In addition, patients with rhino-orbito-cerebral mucormycosis who underwent surgery and antifungal therapy had better clinical outcomes. At present, treatment options for mucormycosis remain very limited. LAmB combined with surgery are strongly recommend as first-line therapy. Isavuconazole and posaconazole are also options as second-line agents (Cornely et al., 2019). Patients with PM, only 3 patients in this study were received pulmonary lobectomy, so no benefit of antifungal combined surgical treatment over antifungal therapy alone was observed. Bilateral lobe involvement occurred in 84.8% of patients in this study, which was similar to previous studies (Peng et al., 2019). Multifocal involvement limited the surgical options, early and effective antifungal therapy may be more important for patients with PM. The recommended combination of antifungal agents and surgical treatment as a treatment option for mucormycosis may be based on the presence of more rhino-orbito-cerebral mucormycosis in other countries. More researches may be needed to optimize treatment options for different types of mucormycosis. New treatment drugs or methods, such as combination of lipid amphotericin B and caspofungin or posaconazole, VT-1161, deferasirox in combination with a polyene, hyperbaric oxygen and so on, still deserve to be expected to improve clinical outcome (Skiada et al., 2018).

FIGURE 2 | Pulmonary fungal infection (Mucor with Aspergillus) in a 69-year-old man with uncontrolled diabetes, chronic obstructive pulmonary disease and liver cirrhosis. CT imaging showed thick-walled cavity shadow with gas-fluid level in the right upper lobe and left lower lobe of the lung (A). The lesion was significantly reduced after half a month of treatment with posaconazole (B). The lesion continued to shrink after 40 days (C), three months (D), five months (E) and 1 year (F) of treatment.
This study has some limitations. First, it was a retrospective observational study. Only some patients have complete follow-up data in our hospital, especially imaging data, and the follow-up of some patients could only be completed by telephone. Second, the detection rate of tissue culture was low, the pathological diagnosis was determined mainly by morphology and special staining. It is important to raise the awareness of doctors about fungal disease. Third, because mucormycosis is a relatively rare fungal disease in China (Liao et al., 2013), the number of cases in this study was limited. More larger-scale, multicenter studies of mucormycosis in the real world should be done.

**CONCLUSIONS**

The most common clinical type of mucormycosis in China was PM. The most common risk factor was diabetes mellitus. Diabetic patients with clinical manifestations of febrile and
hemoptysis, CT findings of nodules, cavities and bilateral lung involvement should be vigilante against PM. Early diagnosis and effective anti-mucor treatment are very important to improve the prognosis of patients with mucormycosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of West China Hospital, Sichuan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XL and JQ conceived of and designed the study. JQ and XL collected, analysed or interpreted data. JQ wrote the draft. All authors read, revised and approved the final manuscript.

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REFERENCES

Althoff Souza, C., Muller, N. L., Marchiori, E., Escuissato, D. L., and Franquet, T. (2016). Pulmonary Invasive Aspergillosis and Candidiasis in Immunocompromised Patients: A Comparative Study of the High-Resolution CT Findings. J. Thorac. Imaging 21 (3), 184–189. doi: 10.1097/ 01.rti.0000215552.16011.ad

Bitar, D., Van Cauteren, D., Lantermier, F., Dannaoui, E., Che, D., Dromer, F., et al. (2009). Increasing Incidence of Zygomycosis (Mucormycosis), France, 1997-2006. Emerg. Infect. Dis. 15 (9), 1395–1401. doi: 10.3201/eid1509.090334

Chakrabarti, A., and Singh, R. (2014). Mucormycosis in India: Unique Features. J. Fungi (Basel) 5 (Suppl 3), 85–90. doi: 10.1186/myc.12243

Cornely, O. A., Alastruey-Izquierdo, A., Arenz, D., Chen, S. C. A., Dannaoui, E., Hochhegger, B., et al. (2019). Global Guideline for the Diagnosis and Management of Mucormycosis: An Initiative of the European Confederation of Medical Mycology in Cooperation With the Mycoses Study Group Education and Research Consortium. Lancet Infect. Dis. 19 (12), e405–e421. doi: 10.1016/S1473-3099(19)30312-3

De Pauw, B., Walsh, T. J., Donnelly, J. P., Stevens, D. A., Edwards, J. E., Calandra, T., et al. (2008). Revised Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. 46 (12), 1813–1821. doi: 10.1086/588660

Jeong, W., Keighley, C., Wolfe, R., Lee, W. L., Slavin, M. A., Kong, D. C. M., et al. (2013). The Epidemiology and Clinical Manifestations of Mucormycosis: A Systematic Review and Meta-Analysis of Case Reports. Clin. Microbiol. Infect. 25 (1), 26–34. doi: 10.1016/j.cmi.2012.07.011

Khan, M. A. B., Hasham, M. J., King, J. K., Govender, R. D., Mustafa, H., and Al Kaabi, J. (2020). Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J. Epidemiol. Glob Health 10 (1), 107–111. doi: 10.2991/ jegh.k.191028.001

Liao, Y., Chen, M., Hartmann, T., Yang, R. Y., and Liao, W. Q. (2013). Epidemiology of Opportunistic Invasive Fungal Infections in China: Review of Literature. Chin. Med. J. (Engl) 126 (2), 361–368.

Liu, W., Liu, J., Song, Y., Zeng, X., Wang, X., Mi, L., et al. (2019). Burden of Lymphoma in China, 2006–2016: An Analysis of the Global Burden of Disease Study 2016. J. Hematol. Oncol. 12 (1), 115. doi: 10.1186/s13045-019-0785-7

Machouart, M., Larche, J., Burton, K., Collomb, J., Maurer, P., Cintrat, A., et al. (2006). Genetic Identification of the Main Opportunistic Mucorales by PCR-Restriction Fragment Length Polymorphism. J. Clin. Microbiol. 44, 805–810. doi: 10.1128/JCM.44.3.805-810.2006

Marom, E. M., and Kontoyiannis, D. P. (2011). Imaging Studies for Diagnosing Invasive Fungal Pneumonia in Immunocompromised Patients. Curr. Opin. Infect. Dis. 24 (4), 309–314. doi: 10.1097/QCO.0b013e32834bb2e1

McAdams, H. P., Rosado de Christenson, M., Strollo, D. C., and Patz, E. F. Jr. (1997). Pulmonary Mucormycosis: Radiologic Findings in 32 Cases. AJR Am. J. Roentgenol 168 (6), 1541–1548. doi: 10.2214/ajr.168.6.9168721

Muldoon, E. G., Sharman, A., Page, I., Bishop, P., and Denning, D. W. (2016). Aspergillus Nodules; Another Presentation of Chronic Pulmonary Aspergillosis. BMC Pulm Med. 16 (1), 123. doi: 10.1186/s12890-016-0276-3

Patel, A., Kaur, H., Xess, I., Michael, J. S., Savio, J., Rudramurthy, S., et al. (2020). A Multicentre Observational Study on the Epidemiology, Risk Factors, Management and Outcomes of Mucormycosis in India. Clin. Microbiol. Infect. 26 (7), 944 e949–944.e915. doi: 10.1016/j.cmi.2019.11.021

Peng, M., Meng, H., Sun, Y., Xiao, Y., Zhang, H., Lv, K., et al. (2019). Clinical Features of Pulmonary Mucormycosis in Patients With Different Immune Status. J. Thorac. Dis. 11 (12), 5042–5052. doi: 10.21037/jtd.2019.12.53

Petrikovs, G., Skaida, A., and Drogari-Apiranthitou, M. (2014). Epidemiology of Mucormycosis in Europe. Clin. Microbiol. Infect. 20 (Suppl 6), 67–73. doi: 10.1111/1469-0691.12563

Prakash, H., and Chakrabarti, A. (2019). Global Epidemiology of Mucormycosis. J. Fungi (Basel) 5 (1), 26. doi: 10.3390/jf5010026

Prakash, H., Ghosh, A. K., Rudramurthy, S. M., Singh, P., Xess, I., Savio, J., et al. (2019). A Prospective Multicenter Study on Mucormycosis in India: Epidemiology, Diagnosis, and Treatment. Med. Mycol 57 (4), 395–402. doi: 10.1093/amycol/myy060

Ruhnke, M., Groll, A. H., Mayser, P., Ullmann, A. J., Mentling, W., Hof, H., et al. (2015). University of Manchester in Association With the Lp: Estimated Burden of Fungal Infections in Germany. Mycoses 58 (Suppl 5), 22–28. doi: 10.1111/ myc.12392

Shariati, A., Moradabadi, A., Chegini, Z., Khoshbayan, A., and Didehdar, M. (2020). An Overview of the Management of the Most Important Invasive Fungal Infections in Patients With Blood Malignancies. Infect. Drug Resist. 13, 2329–2354. doi: 10.2147/IDR.S25478

Skaida, A., Lantermier, F., Groll, A. H., Pagano, L., Zimmerli, S., Herbrecht, R., et al. (2013). Diagnosis and Treatment of Mucormycosis in Patients With Hematological Malignancies: Guidelines From the 3rd European Conference on Infections in Leukaemia (ECIL 3). Haematologica 98 (4), 492–504. doi: 10.3324/haematol.2012.065110

Skaida, A., Lass-Floerl, C., Klimko, N., Ibrahim, A., Roulides, E., and Petrikovs, G. (2018). Challenges in the Diagnosis and Treatment of Mucormycosis. Med. Mycol 56 (suppl_1), 93–101. doi: 10.1093/amycol/myx101

Qu et al. Clinical Analysis of Mucormycosis
Skiada, A., Pagano, L., Groll, A., Zimmerli, S., Dupont, B., Lagrou, K., et al. (2011). Gaustad P et al: Zygomycosis in Europe: Analysis of 230 Cases Accrued by the Registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis Between 2005 and 2007. Clin. Microbiol. Infect. 17 (12), 1859–1867. doi: 10.1111/j.1469-0691.2010.03456.x

Skiada, A., Pavleas, I., and Drogari-Apiranthitou, M. (2020). Epidemiology and Diagnosis of Mucormycosis: An Update. J. Fungi (Basel) 6 (4), 265. doi: 10.3390/jof6040265

Son, H. J., Song, J. S., Choi, S., Jung, J., Kim, M. J., Chong, Y. P., et al. (2020). Risk Factors for Mortality in Patients With Pulmonary Mucormycosis. Mycoses 63 (7), 729–736. doi: 10.1111/myc.13092

Spellberg, B., Kontoyiannis, D. P., Fredricks, D., Morris, M. I., Perfect, J. R., Chin-Hong, P. V., et al. (2012). Risk Factors for Mortality in Patients With Mucormycosis. Med. Mycol 50 (6), 611–618. doi: 10.3109/13693786.2012.669502

Springer, J., Lackner, M., Ensinger, C., Risslegger, B., Morton, C.O., Nachbaur, D., et al. (2016). Clinical Evaluation of a Mucorales-Specific Real-Time PCR Assay in Tissue and Serum Samples. J. Med. Microbiol. 65, 1414–1421. doi: 10.1099/jmm.0.003735

Sullivan, T., and Rana, M. (2019). The Reversed Halo Sign and Mucormycosis. Lancet Infect. Dis. 19 (12), 1379. doi: 10.1016/S1473-3099(19)30548-1

US, National Cancer Institute (2017). Common Terminology Criteria for Adverse Events (CTCAE): Version 5.0. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. (Accessed December 13, 2021).

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