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ORIGINAL ARTICLE

Mucormycosis in Mainland China: A Systematic Review of Case Reports

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Abstract

Background Mucormycosis is a lethal fungal infection with increasing incidence. The epidemiology of mucormycosis in current mainland China has not been fully elucidated.

Objectives To investigate the epidemiology, risk factors, manifestations, diagnosis, treatment and prognosis of mucormycosis in mainland China.

Methods We searched for published mucormycosis case reports/series in mainland China in the PubMed, WanFang and China National Knowledge Infrastructure databases from January 2001 to July 2020. Cases of proven/probable mucormycosis were included.

Results A total of 390 cases were included in this review. Most of the patients were male (61.3%), and diabetes was the most common predisposing factor (37.2%). Pulmonary mucormycosis (42.1%) was the most common form followed by cutaneous infection (21.0%). Of 390 patients, 24 died before therapy. Among the remaining 366 patients, 208 (56.8%) received antifungal drugs alone, 16 (4.4%) received surgery alone, and 142 (38.8%) received a combination of drugs and surgery, the mortality of the last group is much lower (34/142, 23.9%). The overall mortality was 37.2%. A multivariate analysis indicated that factors associated with increased mortality included corticosteroid use alone as immunosuppressive therapy, rhino-orbito-cerebral or disseminated mucormycosis (compared with pulmonary mucormycosis), and drug administration other than amphotericin B (AmB), posaconazole (POS) and itraconazole (ITR) (compared with the use of conventional AmB), while factors associated with decreased mortality included cutaneous mucormycosis and surgical therapy. Combination or sequential antifungal therapy of AmB and POS or ITR did not reduce mortality compared with conventional AmB monotherapy.

Conclusion In mainland China, mucormycosis is a serious fungal infection with high mortality.

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Corticosteroid use, rhino-orbito-cerebral and disseminated mucormycosis were adverse prognostic factors. Antifungal therapy combined with surgery could improve the prognosis.

Keywords Mucormycosis · Epidemiology · Treatment · Systematic review · Mainland China

Introduction

Mucormycosis is a life-threatening invasive infection caused by fungi of the order Mucorales. The mobility of mucormycosis has been rising in recent years, mainly in diabetic and immunocompromised patients, such as hematological malignancies patients and hematopoietic stem cell transplant recipients, solid organ transplant recipients, and surgical, burn and trauma patients [1–6]. Mucorales can cause infection in various forms, including cutaneous and soft tissue, rhino-orbito-cerebral, pulmonary, gastrointestinal, disseminated and other uncommon forms. Diagnosis relies on the recovery of characteristic broad hyphae in tissue or positive mycological findings. Delayed initiation of therapy is associated with increased mortality [1, 7, 8]. Lipid formulations of amphotericin B (AmB) are considered the drug of choice for mucormycosis [9, 10]. However, with fewer adverse reactions, newer triazoles, such as posaconazole (POS) and isavuconazole, have emerged as therapeutic options [9, 10].

A recent systematic review and meta-analysis by Jeong et al. [10, 11] presented the global epidemiology, diagnoses, treatments and outcomes of mucormycosis; however, this review only included publications in English. A large population and a substantial number of cases of mucormycosis are observed in China, and the epidemiology and treatment methods may be different from those in other regions. The epidemiology and treatment experience of mainland China should be taken as a reference. Therefore, we performed this systematic review covering English and Chinese publications to explore the epidemiology, risk factors, manifestations, diagnoses and treatments of mucormycosis in mainland China.

Methods

Literature Search

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), WanFang (http://www.wanfangdata.com.cn/), and China National Knowledge Infrastructure (CNKI) (http://www.cnki.net/) for articles published related to mucormycosis in mainland China between January 2001 and July 2020. The key words included mucormycosis, zygomycos*, mucor*, Mucorales, Zygomycet*, *Mucor*, *Rhizopus*, *Rhizomucor*, *Absidia*, *Lichtheimia*, *Apophysomyces*, *Cokeromyces*, *Cunninghamella*, *Saksenaea*, *Syncephalastrum* and China. The references were limited to English language and human subjects when searching PubMed and limited to Chinese language and human subjects when searching the WanFang and CNKI databases.

Eligibility Criteria

Case reports/series of proven/probable mucormycosis in mainland China were included according to European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [12]. The cases must have the following documentations: (1) age and sex of the patient; (2) site(s) of infection; (3) method(s) of diagnosis; (4) specific treatment strategies; and (5) patient outcomes. Repeated cases and those with amphibolous information were excluded.

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports was applied to evaluate the articles [13]. Two authors (LWW and PQZ) independently scored as yes, no, unclear, and not applicable for each of the checklist's questions and decided whether to include each article. The disagreement was resolved by consensus or a third author (XQC) decision.

Data Extraction and Definition

Extracted data included the publication year, patient demographics, predisposing factors, body sites of infection, methods of diagnosis, causative pathogens, treatment details and clinical outcomes.

The sites of infection were defined as the involved sites at the time of diagnosis. Disseminated infection was defined as infection at two or more noncontiguous

sites, while disseminated cutaneous infection in burn or trauma patients was defined as cutaneous mucormycosis. In addition, chronic cutaneous infection on the central face caused by *Mucor irregularis* with sinus involvement was defined as cutaneous infection rather than rhino-orbito-cerebral because this fungus seldom invades deep tissues [14]. Seven major clinical forms of mucormycosis infection were included in this study: (1) pulmonary, (2) rhino-orbito-cerebral, (3) cutaneous, (4) gastrointestinal, (5) renal, (6) disseminated, and (7) other uncommon sites.

Mortality was assessed as all-cause mortality during the course of mucormycosis.

Statistical Analysis

Patient characteristics, disease manifestations, causative pathogens and diagnosis methods were summarized descriptively. Categorical variables were assessed by the chi-square test or Fisher's exact test and those with significant or marginal significant correlations ($p < 0.075$) to outcome were included in the multivariate logistic regression analysis to outcome. A 2-tailed p-value of < 0.05 was considered statistically significant.

Results

Using our search strategy, a total of 1183 articles were retrieved in the database, including 157 from PubMed and 1026 from the CNKI and WanFang databases. Abstracts and/or full texts were reviewed by two authors. A total of 857 articles were excluded because of irrelevant articles, duplicates, review articles, incomplete details or amphibolous information, etc. Finally, a total of 326 articles (390 individual patient cases) were included in the analysis. A flowchart showing procedure of screening is shown in Fig. 1. The list of articles included in this study is presented in the Supplementary material (Appendix S1).

Among the 390 cases, 56 were reported from 2001 to 2005, 110 from 2006 to 2010, 117 from 2011 to 2015 and 107 from 2016 to 2020. Although the number of cases in the first five years appears to be the lowest, this is because many of them were eliminated during the screening process due to incomplete information.

Patient Demographics and Predisposing Factors

Of 390 patients, the average age was 44.7 years (range, 2 days–90 years) and the majority were male (61.3%). The majority of cases occurred between the ages of 31 and 70 years (Fig. 2). Significant differences in mortality were not observed for any age group ($p = 0.554$). The predisposing factors of all patients are summarized in Table 1. The most common predisposing factor was diabetes mellitus (37.2%), among which 33.8% were associated with diabetic ketosis. Other major predisposing factors included systemic use of corticosteroids (19.7%) or immunosuppressants (14.4%), solid organ transplantation (11.8%), hematologic malignancy (10.8%) and major trauma (9.0%). Notably, a patient with CARD9 deficiency developed cutaneous mucormycosis [15]. Recently, additional cases of cutaneous mucormycosis in patients with CARD9 deficiency have emerged in China [16].

Clinical Manifestations

Pulmonary mucormycosis (164/390, 42.1%) was the most common clinical form, followed by cutaneous (82/390, 21.0%) and rhino-orbito-cerebral mucormycosis (68/390, 17.4%) (Table 2). Disseminated infection was observed in 9.2% (36/390) of cases. In the 11 cases of gastrointestinal infection, 4 had liver involvement. Disseminated mucormycosis presented the highest mortality (63.9%), followed by rhino-orbito-cerebral mucormycosis (54.4%), while cutaneous mucormycosis presented the lowest mortality (17.1%) ($p < 0.001$) (Table 2).

Associations between patients' predisposing factors and clinical manifestations are summarized in Fig. 3. Notably, diabetes, especially with ketosis, was associated with an increased frequency of rhino-orbito-cerebral infection. Major or minor trauma was associated with cutaneous infection. Renal mucormycosis was mainly observed in patients with solid organ transplantation (13/20).

Diagnostic Methods and Causative Pathogens

Diagnosis mostly relies on conventional phenotypic techniques. A total of 44.9% of the cases (175/390) were diagnosed by histopathology alone, 30.3% (118/390) were diagnosed by mycologic examinations

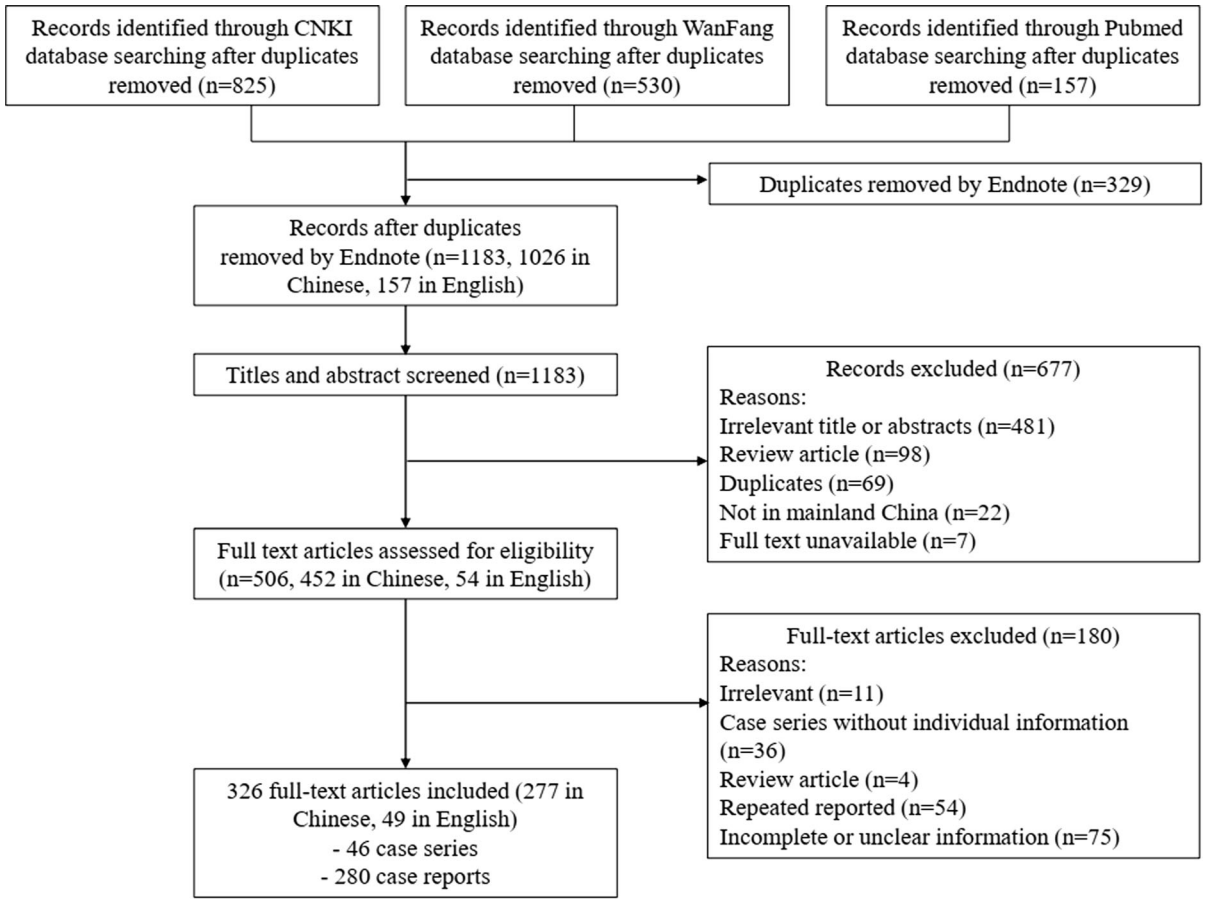

Fig. 1 Flowchart of the study selection. Abbreviations: CNKI, China National Knowledge Infrastructure

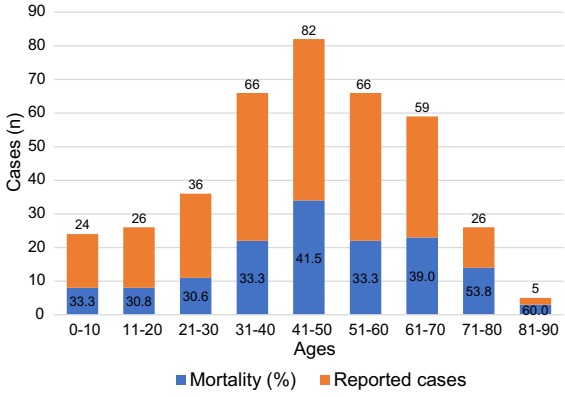

Fig. 2 Number of published cases of mucormycosis in mainland China in each age group and corresponding mortality. Fisher's exact test: $p = 0.544$

(direct microscopy and/or fungal culture) alone, and 24.9% (97/390) were confirmed by both methods. Fungal identification to the genus or species level was performed in 69 cases (Table 3). Pathogens in 33 of the 69 cases were identified by molecular methods, and pathogens in other cases were identified by culture. A total of 6 genera (10 species) of Mucorales were reported, among which *Mucor* and *Rhizopus* were the most commonly involved genera. Notably, 48 of the 69 cases were cutaneous mucormycosis, among which the most commonly reported pathogen was *M. irregularis* (27/48, 56.3%), followed by *Rhizopus arrhizus* (7/48, 14.6%). As only 1 to 8 cases reported pathogenic species in other clinical forms, the dominant pathogenic species of these clinical forms were not clear.

Therapeutic Methods

Of the 390 patients, 24 (6.2%) died before treatment. Among the remaining 366 patients, treatment strategies included antifungal therapy alone (208/366,

Table 1 Sex and predisposing factors of 390 patients with mucormycosis; 145 of these patients died

Characteristics	Number of patients (%)	Mortality (%)
Gender		
Male	239 (61.3)	98/239 (41.0)
Female	151 (38.7)	47/151 (31.1)
Potential risk factors		
Diabetes mellitus	145 (37.2)	60/145 (41.4)
Without ketosis	96 (24.6)	31/96 (32.3)
With ketosis	49 (12.6)	29/49 (59.2)
Hematological malignancy	42 (10.8)	20/42 (47.6)
Hematopoietic stem cell transplant	7 (1.8)	5/7 (71.4)
Solid organ transplantation	46 (11.8)	14/46 (30.4)
Major trauma[a]	35 (9.0)	16/35 (45.7)
Minor trauma[b]	23 (5.9)	6/23 (26.1)
Chemotherapy	33 (8.5)	15/33 (45.5)
Immunosuppressive therapy	85 (21.8)	39/85 (45.9)
Corticosteroid alone	29 (7.4)	16/29 (55.2)
Immunosuppressant alone	8 (2.1)	5/8 (62.5)
Corticosteroid and immunosuppressant	48 (12.3)	18/48 (37.5)
Use of renal replacement therapy	10 (2.6)	4/10 (40.0)
Prior antifungal prophylaxis	14 (3.6)	6/14 (42.9)
Other predisposing factors[c]	9 (2.3)	3/9 (33.3)

[a]Major trauma included traffic accident injuries, major surgery, burns, toxic epidermal necrolysis and other open wound trauma

[b]Minor trauma included cuts, grazes, plant stabs, insect bites, fish bone sticks, local skin erosion or ulceration, venous puncture, dacryocyst irrigation, nasogastric tube incubation, minor surgery and laser therapy for allergic rhinitis

[c]Other predisposing factors included premature delivery (three patients, one of whom used deferoxamine), intravenous drug abuse (one patient), CARD9 deficiency (one patient), Good's syndrome (one patient), deferoxamine use (two patients, with one case of premature delivery), and external applications of Chinese herbs (two patients)

Table 2 Disease manifestations and mortality for 390 cases of mucormycosis

Disease manifestations	n (%)	Mortality (%)
Pulmonary mucormycosis	164 (42.1)	62/164 (37.8)
Rhino-orbito-cerebral mucormycosis	68 (17.4)	37/68 (54.4)
Cutaneous mucormycosis	82 (21.0)	14/82 (17.1)
Gastrointestinal mucormycosis	11 (2.8)	2/11 (18.2)
Disseminated mucormycosis	36 (9.2)	23/36 (63.9)
Renal mucormycosis	20 (5.1)	7/20 (35.0)
Others[a]	9 (2.3)	0/9 (0.0)
Total	390 (100)	145/390 (37.2)

Fisher's exact test: $p < 0.001$

[a]Others included cornea (two patients), vocal cord (one patient), pulmonary artery (one patient), aortic artery (one patient), mediastinum (two patients), thoracic cavity (one patient) and lumbar intervertebral disc (one patient)

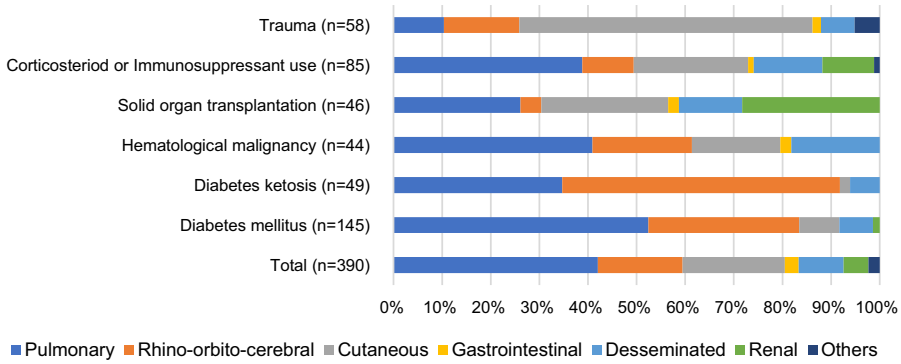

Fig. 3 Associations between predisposing factors and disease manifestations of mucormycosis in mainland China

Table 3 Genera and species of isolated Mucorales in 69 cases and clinical types

Isolated fungi	Clinical types (n)						
	Pulmonary	Rhino-orbito-cerebral	Cutaneous	Disseminated	Renal	Lumber intervertebral disc	Total (n)
Mucor			28	2			30
Mucor irregularis			27	2			29
Mucor indicus			1				1
Rhizopus	3	3	12	4	1	1	24
Rhizopus arrhizus	2	2	7	1	1		13
Rhizopus microspores			3	1		1	5
Unspecified *Rhizopus* spp.	1	1	2	2			6
Lichtheimia	3	1	3				8
Lichtheimia corymbifera	1		2				3
Lichtheimia ramosa	1		1				2
Lichtheimia ornata		1					1
Unspecified *Lichtheimia* spp.	1						1
Synchephalastrum			4				4
Synchephalastrum racemosum			4				4
Rhizomucor	1		1	1			3
Rhizomucor pusillus				1			1
Unspecified *Rhizomucor* spp.	1		1				2
Cunninghamella	1						1
Cunninghamella bertholletiae	1						1
Total	8	4	48	7	1	1	69

56.8%), surgery alone (16/366, 4.4%), and concomitant antifungal therapy and surgery (142/366, 38.8%). From 2001 to 2005, the proportion of patients who received antifungal drugs was lower and the proportion of patients who died before treatment was higher than that in the latter 15 years (Fig. 4). The proportion of patients who received surgery increased

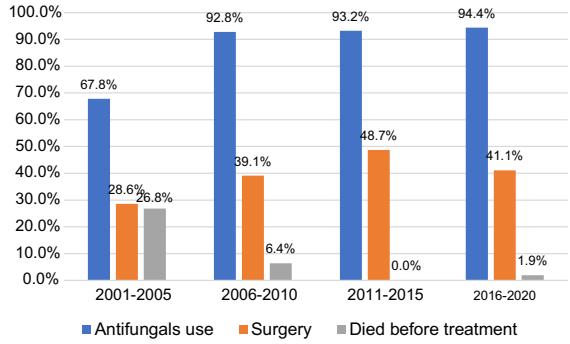

Fig. 4 Percentage of patients with mucormycosis in mainland China who received antifungal therapy and surgery and patients who died before treatment between 2001 and 2020

in the first 15 years but decreased in the last 5 years (Fig. 4).

The mortality of patients who received concomitant antifungal therapy and surgery (34/142, 23.9%) was much lower than those who received either antifungal therapy alone (80/208, 38.5%) or surgery alone (7/16, 43.8%) ($p < 0.001$). However, the situation varies in different clinical types. In pulmonary, rhino-orbito-cerebral and renal mucormycosis, the mortality decreased in concomitant surgical and antifungal therapy compared with antifungals alone (20.8% vs 42.7%, 29.0% vs 66.7%, 12.5% vs 57.1%, respectively), while in cutaneous mucormycosis, the condition was the opposite (23.5% vs 8.9%) (Table 4).

The use of antifungal therapy was described in 350 cases (Table 5). Voriconazole, fluconazole, ketoconazole, echinocandins, terbinafine, 5-fluorocytosine and potassium iodide do not show effective in vitro activity against Mucorales [17–19] and are not recommended by the global guideline of mucormycosis [9]; thus, we presumed they were ineffective drugs and put them in a single group. Meanwhile, AmB, POS and

Table 5 Antifungal drugs and mortality for 350 patients

Antifungals	n (%)	Mortality (%)
AmB formulations[a]	212/350 (60.6)	66/212 (31.1)
Conventional	123/350 (35.1)	42/123 (34.1)
Lipid-based[b]	89/350 (25.4)	24/89 (27.0)
POS and/or ITR[c]	31/350 (8.9)	7/31 (22.6)
POS alone	9/350 (2.6)	2/9 (22.2)
ITR alone	21/350 (6.0)	5/21 (23.8)
POS and ITR	1/350 (0.3)	0/1 (0.0)
AmB with POS or ITR[d]	66/350 (18.9)	17/66 (25.8)
Other antifungals[e]	37/350 (10.6)	24/37 (64.9)
External use of AmB alone[f]	4/350 (1.1)	0/4 (0.0)

AmB Amphotericin B, *POS* Posaconazole, *ITR* itraconazole

[a]With or without the use of "other antifungals" and without the use of POS or ITR

[b]Of which six patients also applied C-AmB

[c]With or without the use of "other antifungals" and without the use of AmB

[d]AmB combined or sequential with POS or ITR and with or without the use of "other antifungals"

[e]Including voriconazole, fluconazole, ketoconazole, echinocandins, terbinafine, 5-fluorocytosine and potassium iodide, without the use of AmB, POS or ITR

[f]Two of four received surgery

Table 4 Treatment strategies and mortality of different clinical forms of mucormycosis

Clinical forms	Therapy cases (patient deaths, mortality %)			Died before treatment
	Antifungals alone	Surgery alone	Antifungals and surgery	
Pulmonary	103 (44, 42.7)	5 (0, 0.0)	48 (10, 20.8)	8
Rhino-orbito-cerebral	27 (18, 66.7)	2 (2, 100.0)	31 (9, 29.0)	8
Cutaneous	45 (4, 8.9)	3 (2, 66.7)	34 (8, 23.5)	0
Gastrointestinal	3 (0, 0.0)	1 (1, 100.0)	7 (1, 14.3)	0
Disseminated	18 (10, 55.6)	0	10 (5, 50.0)	8
Renal	4 (7, 57.1)	5 (2, 40.0)	8 (1, 12.5)	0
Others[a]	5 (0, 0.0)	0	4 (0, 0.0)	0
Total	208 (80, 38.5)	16 (7, 43.8)	142 (34, 23.9)	25

[a]Others included corneal (two patients), vocal cord (one patient), pulmonary artery (one patient), aortic artery (one patient), mediastinum (two patients), thoracic cavity (one patient) and lumbar intervertebral disc (one patient)

itraconazole (ITR) were considered effective drugs. If the patient took both the effective and ineffective drugs, the latter were ignored for more concise drug classification and statistics. Of the 350 cases, 212 were treated with AmB formulations alone, with the majority (123/212, 58.0%) of these patients receiving conventional (deoxycholate) amphotericin B (C-AmB) and 89 cases receiving lipid-based AmB [15 received Amphotec (amphotericin B colloidal dispersion, ABCD), 5 received Fengkesong (manufactured by pharmaceutical factories in China), and the remaining 69 were not specified]. The mortality of patients who received C-AmB, lipid-based AmB, POS and/or ITR, as well as AmB with POS or ITR was much lower than those who received other antifungal drugs (34.4%, 26.7%, 22.6%, 25.8% vs 64.9%) (Table 5). Between 2001 and 2005, a larger proportion of patients did not receive systemic antifungal drugs or received ineffective drugs; and between 2016 and 2020, AmB in combination or sequential with POS or ITR was more commonly used (Fig. 5).

One hundred cases reported the dosage of C-AmB, and the median [interquartile range (IQR)] dosage of C-AmB was 1 (0.575–1) mg/kg/day (n = 24) or 40 (25–50) mg/day (n = 76) (different forms of dose reporting). The median (IQR) dosage of lipid-based AmB was 2 (1.2–3) mg/kg/day (n = 23) or 70 (50–125) mg/day (n = 49). The median (IQR) course of cure by AmB (C-AmB and/or lipid-based AmB) was 42 (28–63) days (n = 67). The median (IQR) accumulated dose of cure by C-AmB and lipid-based AmB was 1500 (1081.25–2307) mg (n = 42) and 2389 (1100–4462.5) mg (n = 12), respectively.

Of the 174 cases in which C-AmB was applied (one case discontinued AmB after only a 5 mg drip due to anaphylaxis and thus was not considered a case of AmB use when summarizing the use of antifungals), 60 cases (34.5%) reported side effects, with 25 reporting hypokalemia, 23 reporting impaired renal function, others reporting nausea/vomit (n = 11), fever (n = 10), chills (n = 5), arrhythmia (n = 5), impaired liver function (n = 5), phlebitis (n = 4), leukopenia or thrombocytopenia (n = 3), hypotension or hypertension (n = 2), rash (n = 2), paresthesia (n = 1), mental disorders (n = 1), etc. Twenty-five of 174 patients (14.4%) discontinued C-AmB use because of side effects. Of the 119 cases that received lipid-based AmB, 33 cases (27.7%) reported side effects, with 14 reporting hypokalemia, 20 reporting impaired renal function, others reporting fever (n = 9), nausea/vomit (n = 6), chills (n = 3), hypotension (n = 2), arrhythmia (n = 3), impaired liver function (n = 3), phlebitis (n = 3), gastrointestinal bleeding (n = 1), anemia (n = 1), leukopenia and thrombocytopenia (n = 1), neural deafness (n = 1), rash (n = 1), etc. Sixteen of 119 patients (13.4%) discontinued lipid-based AmB use due to side effects. The main cause of discontinued drug use was impaired renal function (21/41).

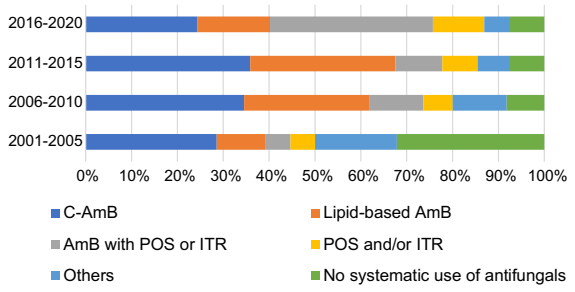

Fig. 5 Proportion of antifungal drugs used in cases of mucormycosis in mainland China between 2001 and 2020

Outcomes

The overall all-cause mortality rate in this study was 37.2% (145/390). Mortality was higher in males than in females (98/239, 41.0% vs 47/151, 31.1%, $p = 0.049$), and much higher mortality was observed between 2001 and 2005 (35/56, 62.5%) than after 2005; moreover, significant variations were not observed in the period after 2005, with a rate of 33.6% (37/110) between 2006 and 2010; 34.2% (40/117) between 2010 and 2015; and 30.8% (33/107) between 2016 and 2020. The median (IQR) follow-up period after treatment of surviving patients was 94 (36.75–243.5) days, as reported in 184/245 cases.

To identify prognostic factors, we compared the distribution of potential factors between survivors and those who died by chi-square test or Fisher's exact test (Table 6). Male, diabetes ketosis, disease manifestations, antifungals and surgery were significantly related to the prognosis ($p < 0.05$). Immunosuppressive therapy was related to the prognosis with marginal significance ($p = 0.070$). Then we put the above variables into multivariate logistic regression to outcome of mucormycosis (Table 7).

Table 6 Comparison of potential factors affecting outcome of mucormycosis between survivors and patients who dead

Factors	Proportion in survivors (%)	Proportion in patients who dead (%)	*p*-value
Male	57.6	67.6	0.049
Diabetes	34.7	41.4	0.187
Diabetes ketosis	8.2	20.0	0.001
Hematological malignancy or HSCT	9.4	13.8	0.179
Solid organ transplantation	13.1	9.7	0.314
Major trauma	7.8	11.0	0.273
Minor trauma	6.9	4.1	0.256
Chemotherapy	7.3	10.3	0.304
Immunosuppressive therapy			0.070
Corticosteroid alone	5.3	11.0	
Immunosuppressant alone	1.2	3.4	
Corticosteroid and immunosuppressant	12.2	12.4	
None	81.2	73.1	
Renal replacement therapy	2.4	2.8	1.000
Disease manifestations			< 0.001
Pulmonary	41.6	42.8	
Rhino-orbito-cerebral	12.7	25.5	
Cutaneous	27.8	9.7	
Disseminated	5.3	15.9	
Others	12.7	6.2	
Antifungals			< 0.001
Conventional AmB[a]	32.7	29.0	
Lipid-based AmB[a,b]	26.9	16.6	
POS and/or ITR[c]	9.8	4.8	
AmB with POS or ITR[d]	20.0	11.7	
Others[e]	5.3	16.6	
External use of AmB alone or none	5.3	21.4	
Surgery	48.6	28.3	< 0.001

ref reference, *HSCT* hematopoietic stem cell transplant, *AmB* amphotericin B, *POS* postaconazole, *ITR* itraconazole

[a]With or without the use of "other antifungals" and without the use of POS or ITR

[b]Of which six patients also applied C-AmB

[c]With or without the use of "other antifungals" and without the use of AmB

[d]AmB combined or sequential with POS or ITR and with or without the use of "other antifungals"

[e]Including voriconazole, fluconazole, ketoconazole, echinocandins, terbinafine, 5-fluorocytosine and potassium iodide, without the use of AmB, POS or ITR

In the multivariate logistic regression, males had a higher mortality than females with marginal significance. Corticosteroid use alone as immunosuppressive therapy significantly increased mortality [odds ratio (OR) = 4.04, 95% confidence interval (CI) 1.64–9.91; $p = 0.002$]. Combination therapy with corticosteroids and immunosuppressants, however, did not significantly affect the prognosis. Immunosuppressants alone also showed significantly increased mortality, but this group contained only eight patients. Disease manifestation was an independent predictor for prognosis. Compared with pulmonary mucormycosis, rhino-orbito-cerebral (OR = 2.31, 95% CI 1.14–4.68; $p = 0.020$) and disseminated infection

Table 7 Multivariate logistic regression of clinical variables that influence the mortality of mucormycosis

Variables	*p*-value	OR (95% CI)
Male	0.056	1.64 (0.99–2.72)
Diabetes ketosis	0.223	1.63 (0.74–3.55)
Immunosuppressive therapy (ref: none)	0.003	
Corticosteroid alone	0.002	4.04 (1.64–9.91)
Immunosuppressant alone	0.025	6.11 (1.26–29.59)
Corticosteroid and immunosuppressant	0.110	1.82 (0.87–3.80)
Disease manifestation (ref: pulmonary)	< 0.001	
Rhino-orbito-cerebral	0.020	2.31 (1.14–4.68)
Cutaneous	0.010	0.39 (0.19–0.79)
Disseminated	0.046	2.41 (1.01–5.71)
Others	0.297	0.61 (0.25–1.54)
Treatment methods (ref: antifungal therapy alone)		
Surgery alone		
Antifungal therapy and surgery		
Antifungals (ref: Conventional AmB[a])	< 0.001	
Lipid-based AmB[a,b]	0.064	0.53 (0.27–1.04)
POS and/or ITR[c]	0.448	0.67 (0.23–1.90)
AmB with POS or ITR[d]	0.211	0.62 (0.30–1.31)
Others[e]	0.001	4.04 (1.73–9.42)
External use of AmB alone or none	< 0.001	4.89 (2.11–11.32)
Surgery	< 0.001	0.40 (0.24–0.68)

ref reference, *HSCT* hematopoietic stem cell transplant, *AmB* amphotericin B, *POS* postaconazole, *ITR* itraconazole

[a]With or without the use of "other antifungals" and without the use of POS or ITR

[b]Of which six patients also applied C-AmB

[c]With or without the use of "other antifungals" and without the use of AmB

[d]AmB combined or sequential with POS or ITR and with or without the use of "other antifungals"

[e]Including voriconazole, fluconazole, ketoconazole, echinocandins, terbinafine, 5-fluorocytosine and potassium iodide, without the use of AmB, POS or ITR

(OR = 2.41, 95% CI 1.01–5.71; $p = 0.046$) showed significantly increased mortality, while cutaneous infection showed significantly decreased mortality (OR = 0.39, 95% CI 0.19–0.79; $p = 0.010$).

Comparing with C-AmB, treatment with lipid-based AmB, POS and/or ITR, AmB in combination or sequential with POS or ITR did not significantly affect mortality. Treatment with other drugs (OR = 4.04, 95% CI 1.73–9.42; $p = 0.001$) or no systemic antifungal use (OR = 4.89, 95% CI 2.11–11.32; $p < 0.001$) was associated with significantly increased mortality. Surgery significantly reduced the overall mortality rate (OR = 0.40, 95% CI 0.24–0.68; $p < 0.001$).

Discussion

Here, we present a large comprehensive review of published cases of mucormycosis in mainland China, thus providing an update of the unique epidemiology, clinical manifestations and treatment strategies of mucormycosis in this region.

In our review, diabetes mellitus was the most common risk factor for mucormycosis, which was also observed in studies in India [20, 21], South America [22], and the Middle East and North Africa [23, 24] and in a global review [1, 11]. However, in Europe, hematological malignancies were reported as the most common underlying condition [25, 26]. Notably, we found that corticosteroid use alone as

immunosuppressive therapy was an independent risk factor for mortality while combined treatment with corticosteroids and immunosuppressants did not significantly affect the prognosis. This finding led us to speculate that perhaps patients using corticosteroids alone took larger doses of corticosteroids than those who took combined immunosuppressive therapy; however, due to the incomplete information on the cases, this explanation could not be confirmed in this study. Additionally, the effect of immunosuppressant use alone on prognosis is still ambiguous because the sample size was too small (n = 8). Consistent with previous findings [1, 11, 22, 27], we also observed that major/minor trauma was associated with cutaneous mucormycosis.

Our study found that pulmonary mucormycosis was most common in mainland China. Additionally, renal mucormycosis accounted for 5.1% (20/390), which was more than gastrointestinal infections. The majority of renal mucormycosis cases (13/20) developed after renal transplantation, suggesting that surgeons should be cautious of mucormycosis after renal transplantation. The overall mortality and the mortality of each clinical type, except for the rhino-orbito-cerebral type, were lower than that in global terms [10].

In the current review, only 55.1% of cases had positive mycological results and only 69 cases identified the causative pathogens, which was far lower than the proportion in the global reviews [1, 11]. This discrepancy may be due to insufficient awareness of pathogen identification by clinicians as well as inadequate sophistication of reference laboratories and mycology technologists. In addition, most of the 69 cases were cutaneous mucormycosis; therefore, the current statistical results could be different from the actual situation. Notably, *M. irregularis* was the most frequent pathogen reported in cutaneous infection. *M. irregularis* is mainly described in China, Japan and India, and it usually causes chronic, progressive, and destructive cutaneous infection at exposed sites, especially the central face, mostly in immunocompetent patients [14, 28]. Because few cases of other clinical types reported pathogens, we cannot provide a conclusion on the relationship between clinical type and pathogen species. Future case reports should identify the pathogens as accurately as possible to facilitate the improvement of epidemiological data.

Consistent with previous findings [1, 2, 10, 20–22, 24], the current review also indicates that concurrent antifungal and surgical therapy significantly improved the prognosis in the overall cases. However, the condition differed for different clinical types. Pulmonary, rhino-orbito-cerebral and renal mucormycosis benefited from combined antifungals and surgery therapy, while cutaneous mucormycosis presented better survival with antifungals alone. This finding indicated that for cutaneous mucormycosis, which is relatively less severe, antifungal therapy alone can obtain a good effect while surgery can be traumatic and less beneficial.

Intravenous AmB remains the antifungal agent of choice for mucormycosis. C-AmB is the most commonly used formulation in mainland China because it is more economical than lipid-based AmB. The systematic review of mucormycosis in renal transplant patients by Song et al. [2] showed that lipid-based AmB significantly improved survival compared with C-AmB. A global systematic review by Jeong et al. [10] found that although L-AmB did not confer a survival benefit, it led to fewer adverse effects than C-AmB. The global guidelines for mucormycosis recommend L-AmB as a first-line antifungal drug and discouraged C-AmB use whenever alternatives are available because of its substantial toxicity [9]. Our study found that the overall mortality of patients who received lipid-based AmB was lower than that in patients who received C-AmB, although this difference was not significant, while the side effects of lipid-based AmB were slightly fewer than that of C-AmB. However, the percentage of patients who discontinued drug use due to the side effects between C-AmB and lipid-based AmB was similar. Regardless of economic considerations, we recommend the use of lipid-based AmB for the treatment of mucormycosis. The median (IQR) dosage of lipid-based AmB [2 (1.2–3) mg/kg/day] in mainland China was much lower than the dosage reported in the global review [5 (3–5) mg/kg/day] [10] and the review of Europe (5 mg/kg/day) [25] and that recommended in the global guideline (5–10 mg/kg/day) [9]. The dose of C-AmB was also lower [1 (0.575–1) mg/kg/day] than that in the global review [1 (0.7–1) mg/kg/day] [10]. These finding indicated that lower dosages of C-AmB and lipid-based AmB are also effective to Chinese patients; thus, appropriately reduced dose can be

considered when patients show intolerance to a high dose.

With good in vitro activity against Mucorales [17–19, 29, 30], POS has been used successfully in combination or as a monotherapy for mucormycosis and has become an attractive salvage drug choice due to its better tolerance [2, 10, 31]. In our review, 7/9 patients survived with POS monotherapy. Jeong et al. [10] found that only 1/11 patients died after receiving POS oral suspension monotherapy; however, Skiada et al. [25] found that 6/10 patients died with POS monotherapy. The value of POS alone or in combination with AmB needs to be determined by further study. ITR has variable in vitro activity against Mucorales [17–19, 29, 30]. In the current review, ITR monotherapy showed low mortality (23.8%). However, 13 of the 21 cases (61.9%) using ITR alone were cutaneous mucormycosis and 12 of the 13 patients survived. A large proportion of patients with cutaneous mucormycosis in mainland China are caused by *M. irregularis* and had no underlying diseases. For these patients, ITR can be used when AmB is unavailable or intolerant. Jeong et al. [10] also found that ITR capsules in combination with surgical debridement may lead to favorable outcomes in the management of cutaneous disease in immunocompetent patients. Consistent with previous findings [8, 10], our review also found that combined sequential therapy of AmB and POS or ITR did not show an advantage over C-AmB monotherapy.

Recently, mucormycosis cases have been increasingly reported from India during the coronavirus disease 2019 (COVID-19), and such cases were described as COVID-19-associated mucormycosis (CAM) [32]. However, up to now, no such cases have been reported from mainland China. The majority of the CAM were rhino-orbito-cerebral mucormycosis rather than pulmonary type [32], indicating that mucormycosis is not directly related to the pulmonary damage caused by COVID-19 infection. Except for multiple factors including corticosteroid use, worsening of blood glucose control and viral-induced lymphopenia, the contaminated respiratory equipment also plays a big role in the outbreak of CAM in India [32, 33].

We found that there was little change in the overall mortality from 2006 to 2020 despite economic improvements, which may be related to the lack of a significant increase in the rate of effective drug use or surgical intervention over the last 15 years. In future clinical practice, effective drugs should be applied in a timely manner and new antifungal drugs should be explored.

Bias

Certain biases in our systematic review should be addressed. The first is publication bias because the published cases may have a certain specificity and may not fully reflect the true general situation. Second, as patients with certain underlining conditions were more likely to be hospitalized, the proportion of such underlining conditions in mucormycosis could be overestimated. Third, in the process of literature screening, some documents with incomplete information that did not meet the inclusion criteria were screened out. Fourth, despite the inclusion criteria, not all the literature described the basic conditions of patients in detail, thus leading to a statistical bias in the basic conditions. Finally, since this review included case reports only from mainland China, some conclusions may not be fully extrapolated on a broader scale.

Conclusions

This systematic review presented the epidemiology of mucormycosis in mainland China. Diabetes, immunosuppression, transplantation and trauma were the main factors for susceptibility. *M. irregularis* was the major pathogen reported in cutaneous mucormycosis. The outcome of mucormycosis varies as a function of the underlying conditions, infection sites, treatment strategies and antifungal drugs. Concomitant antifungal and surgical interventions significantly improved the prognosis except in cutaneous mucormycosis. Combination or sequential antifungal therapy with AmB and POS or ITR did not show an obvious advantage compared to C-AmB monotherapy.

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Declarations

Conflict of interest None to declare.

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