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Clinical characteristics and mortality of mucormycosis in hematological malignancies: a retrospective study in Eastern China

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Abstract

Background Mucormycosis is a significant cause of morbidity and mortality in patients with hematological malignancies, but its characteristics are not fully understood. This study aimed to gain a better understanding of the clinical features of mucormycosis in patients with hematological malignancies in eastern China.

Methods A single-center retrospective analysis was conducted on the demographic profile, microbiology, management, and 90-day mortality of mucormycosis patients with hematological malignancies between 2018 and 2023.

Results A total of 50 cases were included in the study, consisting of 11 proven and 39 probable cases of mucormycosis. The median age of the patients was 39.98 ± 18.52 years, with 52% being male. Among the cases, 46% had acute myeloid leukemia (AML), 16% had acute lymphoblastic leukemia (ALL), and 16% had myelodysplastic syndrome. The most common manifestations of mucormycosis were pulmonary (80%), disseminated (16%), and rhinocerebral (4%). The diagnosis was confirmed through histology, culture, microscopy, and molecular diagnostic techniques. The most commonly identified fungal species were Cunninghamella (40%), Rhizopus (26%), and Rhizomucor (22%). Treatment involved antifungals in 84% of cases and surgery in 10% of cases. The 90-day mortality rate was 76%. Logistic regression analysis revealed that treatment with amphotericin B and surgery was associated with improved survival, while neutropenia and administration of voriconazole prior to diagnosis was associated with higher mortality.

Conclusions Mucormycosis continues to have a high mortality rate in patients with hematological malignancies. Early diagnosis using various techniques, including molecular biology, along with the appropriate use of amphotericin B and surgery when possible, is vital for the successful treatment of mucormycosis.

Keywords Mucormycosis, Hematological malignancies, Diagnosis, Treatment

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Background

Mucormycosis is an infrequent but serious fungal infection caused by filamentous fungi of the Mucorales order, which are commonly found in the environment. The infection is mainly acquired through inhalation of sporangiospores, although it can also occur due to ingesting contaminated food or traumatic inoculation [1]. The incidence of mucormycosis varies between developed and developing countries, with rates ranging from 0.12 to 14 cases per 100,000 people in Europe and India [2, 3]. Factors such as an increasing immunocompromised population, improved awareness, and advancements in diagnostic technology have contributed to the rising incidence [4]. Mucormycosis can present in different forms, including rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated types [5]. Common risk factors for developing mucormycosis include diabetes mellitus, hematological malignancies, use of glucocorticoids or immunosuppressants, trauma and COVID-19 infection [1, 6, 7]. However, the primary causes may vary between countries, with hematological malignancies being the predominant cause in high-income countries, while diabetes mellitus or trauma are more prevalent causes in developing countries [1, 8]. Diagnosing mucormycosis is challenging due to the low sensitivity and specificity of clinical tests, which can lead to delays in diagnosis. This, along with the high cost of managing mucormycosis and limited treatment options, contributes to the high mortality rate of 45–90% observed in low and middle-income countries like India [9]. Research on the characteristics of mucormycosis, particularly in individuals with hematological malignancies, has been predominantly conducted in the United States and Europe. However, there is a scarcity of data on the combination of hematological malignancies and mucormycosis in China and other regions. To gain a deeper understanding of the clinical characteristics of patients with hematological malignancies and mucormycosis in China's eastern region, we conducted a retrospective analysis of demographic characteristics, clinical manifestations, laboratory tests, pathogens, treatment strategies, and prognosis. The analysis was based on patients admitted to a university-affiliated hospital in eastern China between January 2018 and March 2023.

Materials and methods

Data source and patient population

From January 2018 to March 2023, this study included patients with hematologic malignancy diagnosed with mucormycosis at The First Affiliated Hospital of USTC, University of Science and Technology of China (a 5000-bed academic tertiary hospital in Anhui, Eastern China). In order to be included in the study, patients had to meet the criteria set by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) and the global guideline for the diagnosis and management of mucormycosis [4, 10].

The diagnosis of invasive fungal infection according to revised definition criteria [10] is classified as proven, probable or possible, the last usually less represented. Proven diagnosis is confirmed by histopathology direct microscopy or positive sterile tissue culture showing the presence of Mucor. Probable diagnosis is established when risk factors and clinical features (imaging findings) associated with mucormycosis are present, along with microbiological or molecular biological evidence of Mucor. This evidence can include positive culture or direct microscopy revealing Mucor, or detection of Mucor using metagenomic next-generation sequencing (mNGS) in blood, cerebrospinal fluid, sputum, bronchoalveolar lavage fluid, bronchoalveolar brush, or aspiration fluid. Mucormycosis is categorized into different types based on clinical manifestations and sites of the body involved. These types include rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated mucormycosis. Disseminated mucormycosis refers to infections that involve at least two non-continuous sites.

Demographic data, comorbidities, clinical presentations, laboratory analyses, imaging tests, diagnostic procedures, treatment approaches, and 90-day clinical outcomes were obtained. The all-cause mortality rate was used to define the rate of death within 90 days. According to the patient prognosis, the patients were divided into survival group and death group.

This study was approved by the Ethics Committee of the First Affiliated Hospital of USTC, University of Science and Technology of China (Approval NO:2023-RE-135). Since the data utilized in this study were from retrospective research, the requirement for written informed consent was waived.

Statistical analysis

The statistical analysis of the data was performed using IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables that followed a normal distribution were expressed as mean ± standard deviation and compared using independent sample t-tests. For continuous variables that did not follow a normal distribution, median and interquartile range were used, and comparisons were made using the Mann-Whitney U test. Categorical variables were described using counts and percentages, and comparisons were made using chi-square tests or Fisher's exact tests. A two-tailed P value less than 0.05 was considered statistically significant. Logistic regression analysis was used to determine the relative contribution of various factors to the risk of 3-month mortality.

Results

Underlying conditions

A total of 50 patients were enrolled in this study, comprising 11 proven cases and 39 probable cases. The age range of the patients varied from 6 to 73 years, with a mean age of 39.98±18.52 years. Among the participants, 26 were male, accounting for 52% of the total. Acute leukemia emerged as the most prevalent type of hematological malignancy, with a total of 31 cases (62%). Specifically, there were 23 cases (46%) of acute myeloid leukemia (AML) and 8 cases (16%) of acute lymphoblastic leukemia (ALL). Other diseases observed included myelodysplastic syndrome and aplastic anemia, each with 8 cases (16%), 2 cases (4%) of chronic myeloid leukemia, and 1 case (2%) of primary myelofibrosis. Prior to their diagnosis of mucormycosis, 15 patients (30%) had undergone hematopoietic stem cell transplantation. Additionally, 42 patients (68%) had received antifungal therapy, including 36 cases of voriconazole, 3 cases of caspofungin, 2 cases of fluconazole, and 1 case of amphotericin B liposome. At the time of mucormycosis diagnosis, 38 patients presented with neutropenia (neutrophil count below 1.5×10^9), of which 30 cases had a neutrophil count below 0.5×10^9. The average duration of neutropenia was 17.87±12.91 days.

The survival group consisted of 13 cases and the death group encompassed 37 cases. The proportion of males in the survival group was higher, accounting for 10 out of 13 cases (76.9%). Additionally, the neutrophil count in the survival group before diagnosis was higher compared to the poor prognosis group. However, the use of voriconazole before diagnosis in the survival group was lower than in the death group (38.5% vs. 83.8%, $p<0.05$). There were no significant statistical differences between the two groups in terms of age, basic diagnosis, underlying diseases status, comorbidities, white blood cell count, hemoglobin, proportion and duration of neutrophil count below 0.5×10^9, platelet count, and previous chemotherapy cycles (Table 1).

Sites of infection and diagnostic methods

Table 2 displays the various sites of infection, with pulmonary mucormycosis being the most frequent type (40/50, 80.0%), followed by disseminated mucormycosis

Table 1 Demographic and clinical characteristics of patients with mucormycosis

Variables	All($n=50$) n(%)	Survivors($n=13$) n(%)	Non-survivors($n=37$) n(%)	P value
Age (years)	39.98±18.52	38.46±20.71	40.51±17.97	0.692
Male sex	26(52.0)	10(76.9)	16(43.2)	0.037
Underlying diseases				
Acute myeloid leukaemia	23(46.0)	5(38.5)	18(48.6)	0.526
Acute lymphoblastic leukaemia	8(16.0)	3(23.1)	5(13.5)	0.712
Myelodysplastic syndrome	8(16.0)	0(0.0)	8(21.6)	0.165
Recurrent aplastic anemia	8(16.0)	4(30.8)	4(10.8)	0.212
Chronic myeloid leukemia	2(4.0)	1(7.7)	1(2.7)	0.456
Primary myelofibrosis	1(2.0)	0(0.0)	1(2.7)	1.000
Underlying diseases status[a]	25(50.0)	5(38.5)	20(54.1)	0.333
Comorbidity[b]				
Hypertension	8(16.0)	3(23.1)	5(13.5)	0.712
Cerebral infarction	3(6.0)	0(0.0)	3(8.1)	0.558
Hepatitis B	2(4.0)	1(7.7)	1(2.7)	0.456
Others[c]	3(6.0)	2(15.4)	1(2.7)	0.849
Laboratory data				
White blood cell ($\times 10^9$/L)	1.86±2.35	2.57±2.70	1.61±2.19	0.211
Neutrophil ($\times 10^9$/L)	1.20±1.94	2.15±2.70	0.84±1.47	0.037
Hemoglobin(g/L)	63.94±17.78	62.69±15.39	64.35±18.73	0.776
Blood platelet ($\times 10^{12}$/L)	23.58±17.96	32.62±25.53	20.41±13.48	0.121
Neutrophil count $<0.5\times10^9$/L	30(60.0)	7(53.8)	23(63.2)	0.599
Duration of neutropenia (day)	17.87±12.914	14.36±13.171	18.94±12.828	0.837
Haematopoietic stem cell transplantation	15(30.0)	3(23.1)	12(32.4)	0.778
Prior voriconazole	36(72.0)	5(38.5)	31(83.8)	0.006
Number of chemotherapy	3.38±3.428	2.38±2.755	3.73±3.603	0.397

[a] The number of patiens with active hematological malignancies

[b] A given subject may have had one or more comorbid illnesses

[c] Includes diabetes mellitus(1), pulmonary emphysema(1), syphilis(1)

Table 2 Sites of infection, pathogen genus and co-infecting agent of patients with mucormycosis

	Number of patients (%)	Number of patients who died (%)
Site of infection		
Pulmonary	40(80.0)	28(71.8)
Disseminated	8(16.0)	7(18.9)
Rhinocerebral	2(4.0)	2(5.4)
Pathogen genus		
Cunninghamella species	20(40.0)	16(43.2)
Cunninghamella elegans	9(18.0)	8(21.6)
Cunninghamella bertholletiae	5(10.0)	3(8.1)
Not speciated	6(12.0)	5(13.5)
Rhizopus species	13(26.0)	11(29.7)
Rhizopus microsporus	8(16.0)	7(18.9)
Rhizopus oryzae	3(6.0)	2(5.4)
Rhizopus delemar	2(2.0)	2(5.4)
Rhizomucor species	11(22.0)	6(16.2)
Rhizomucor pusillus	11(22.0)	6(16.2)
Lichtheimia species	4(8.0)	3(8.1)
Lichtheimia ramosa	3(6.0)	2(5.4)
Lichtheimia corymbifera	1(2.0)	1(2.7)
Mucor species	2(4.0)	1(2.7)
Mucor indicus	1(2.0)	1(2.7)
Mucor circinelloides	1(2.0)	0(0.0)
Co-infecting agent		
Bacteria	14(28.0)	11(29.7)
Virus	13(26.0)	8(21.6)
Fungi	9(18.0)	5(13.5)

(8/50, 16.0%), and rhinocerebral mucormycosis (2/50, 4.0%). The studied cases did not present any other forms of mucormycosis.

Among the 50 patients included, a definitive diagnosis was confirmed by histopathological examination in 11 cases. Specifically, 6 cases underwent bronchoscopic biopsy, 2 underwent percutaneous lung puncture biopsy, and 3 underwent received surgical resection with subsequent pathological confirmation. The remaining 39 cases were diagnosed based on microbiological clinical criteria. Out of the 23 patients who underwent bronchoscopy alveolar lavage examination, 13 tested positive for mucormycosis through deep fungal rapid fluorescence staining and direct microscopy of the lavage fluid, and 4 cases had positive fungal cultures. All patients were tested using mNGS, with 23 cases tested on alveolar lavage fluid, 35 cases on blood samples, and additionally, among the 11 patients who underwent histopathological examination, 8 cases were tested on tissue using mNGS. Among these, 12 cases were tested on both alveolar lavage fluid and blood, and 4 cases were tested on both tissue and blood. The mNGS results were positive for mucormycosis in all patients.

Table 3 Treatment strategies of patients with mucormycosis

Treatment	Number of patients (%)	Number of patients who died (%)
Amphotericin B	23(46.0)	17(45.9)
Amphotericin B + posaconazole	6(12.0)	5(13.5)
Amphotericin B + isavuconazole	2(4.0)	1(2.7)
Amphotericin B + surgery	5(10.0)	1(2.7)
Posaconazole	2(4.0)	1(2.7)
Isavuconazole	4(8.0)	4(10.8)
Untreated	8(16.0)	8(21.6)

Infecting agents

Among the identified species within the Mucoraceae family, Cunninghamella was the most commonly found (40%, 20/50). Within the Cunninghamella genus, Cunninghamella elegans was the predominant species, accounting for 18% (9/50) of the cases, followed by Cunninghamella bertholletiae (10%, 5/50). Other genera within the Mucoraceae family included Rhizopus (26%, 13/50), Rhizomucor (22%, 11/50), Lichtheimia (8%, 4/50), and Mucor (4%, 2/50). Out of the total 50 cases, 52% (26/50) of the patients had concurrent infections involving bacteria, fungi, and/or viruses. Bacterial infections were the most common, affecting 28% (14/50) of the patients, followed by viral infections (26%, 13/50) and fungal infections (18%, 9/50). Specifically, the bacterial infections were as follows: Klebsiella pneumoniae (3/14), Escherichia coli (3/14), Stenotrophomonas maltophilia (2/14), Staphylococcus aureus (2/14), Legionella pneumophila (2/14), Pseudomonas aeruginosa (1/14), Enterobacter cloacae (1/14), and Haemophilus influenzae (1/14). Additionally, one patient had both Klebsiella pneumoniae and Haemophilus influenzae infections simultaneously. Regarding viral infections, cytomegalovirus was detected in 76.9% (10/13) of the cases, followed by adenovirus (2/13) and SARS-CoV-2 (1/13). Concurrent fungal infections included Aspergillus (6/9), Pneumocystis jirovecii (2/9), and Candida (1/9).

Treatment and outcome

In Table 3, we present the treatment protocols and outcomes for 50 individuals who were diagnosed with mucormycosis. Out of these patients, 42 underwent antifungal therapy, resulting in 13 survivors. Among those who received antifungal therapy, 36 were treated with amphotericin B. Specifically, 31 patients (86.1%) received amphotericin B liposome((L-AmB) at a dosage of 3–5 mg/kg/day, while 5 patients (13.9%) received amphotericin B cholesteryl sulfate complex(ABCD) at a dosage of 3–4 mg/kg/day. In addition to antifungal therapy, 8 patients underwent combination therapy, which involved the administration of both amphotericin B and azoles. Specifically, posaconazole was used in 6 cases, while

isavuconazole was used in 2 cases. The average duration of antifungal therapy was 41.68±27.58 days. Surgery was performed in conjunction with antifungal therapy for 5 patients. It is important to mention that 8 critically ill and financially disadvantaged patients did not receive treatment following their diagnosis and unfortunately succumbed to the condition.

The 90-day mortality rate among the patients was found to be 74.0% (37 /50). Table 4 presents the significant risk factors influencing mortality, as determined through logistic regression analysis. Neutropenia (OR: 0.716, $p=0.040$) and prior administration of voriconazole before the diagnosis of mucormycosis (OR: 8.267, $p=0.004$) were identified as risk factors associated with higher mortality. On the other hand, subjects who underwent combined medical and surgical treatment showed a higher survival rate (.OR: 0.08, $p=0.035$).

Discussion

Mucormycosis is an aggressive fungal infection with a high fatality rate. The incidence of mucormycosis has been increasing in recent years due to the growing number of individuals with weakened immune systems, improvements in diagnostic technologies, and the COVID-19 pandemic [7]. However, there are differences in the risk factors for mucormycosis between developed and developing countries. In developed countries, hematological malignancies and transplantation are the main risk factors, whereas, in developing countries, mucormycosis primarily affects patients with uncontrolled diabetes mellitus (DM) or trauma [11]. Among various studies, the most common hematological malignancy is AML, with an incidence of 48% in the ECMM study [12], 46% in Italy [13], 34% in France [14], 38% in Lebanon [15], and 42% in a global review by Jeong et al [5]. Other malignancies, such as ALL, non-Hodgkin lymphoma, myelodysplastic syndrome, and rare cancers, also contribute to the risk of mucormycosis. Our study found similar results, with AML being the most common hematological malignancy (46%), followed by ALL, myelodysplastic syndrome, aplastic anemia, chronic myeloid leukemia, and primary myelofibrosis. The COVID-19 pandemic has emerged as a significant contributor to the occurrence of mucormycosis in recent years; however, in our study, the proportion of COVID-19 cases among mucormycosis patients was relatively low (1/50). This may be attributed to several factors, including China's stringent COVID-19 prevention and control measures, the inherently good hygiene practices and public health awareness among patients with hematological malignancies, effective management of chronic conditions such as diabetes, and the availability of adequate medical resources and timely interventions. These factors, when combined, likely contributed to the lower incidence of COVID-19-associated mucormycosis observed in this study. Consistent with previous research [16], our study also revealed that neutropenia increases the risk of mucormycosis infection and worsens the prognosis. Interestingly, the widespread prophylactic use of inactive antifungal drugs, such as voriconazole, has been associated with an increase in mucormycosis cases [17, 18]. Animal studies have even suggested that exposure to voriconazole could enhance the virulence of Mucorales organisms [19]. In our investigation, 36 out of 50 subjects received prior voriconazole prophylaxis or treatment before the diagnosis. Specifically, 17 individuals received prophylaxis due to persistent neutropenia following chemotherapy-induced bone marrow suppression, 4 underwent prophylaxis after stem cell transplantation, and 15 started empirical voriconazole therapy following ineffective broad-spectrum antibacterial treatment for fever. Our findings indicate that prior use of voriconazole has an impact on patient outcomes, leading to a higher mortality rate. Additionally, our study discovered that a higher proportion of male patients survived mucormycosis, suggesting a possible association between biological sex, host sex hormone homeostasis, immune response, and the pathogenesis of the infection [20]. However, further investigations are needed to fully understand this phenomenon. In conclusion, the incidence of mucormycosis is rising globally, and its risk factors differ between developed and developing countries. Hematological malignancies, especially AML, increase the susceptibility to this fungal infection. Neutropenia and prior use of voriconazole are additional factors that worsen the prognosis. The association between biological sex/gender and mucormycosis pathogenesis warrants further exploration.

In both Europe and the United States, mucormycosis infection primarily affects the lungs in patients with

Table 4 Logistic regression analysis to predict factors associated with mortality in patients with mucormycosis

Factors	Univariate analysis			
	Odds ratio	P	95%confidence interval	
Neutropenia	0.716	0.040	0.520	0.987
Prior voriconazole	8.267	0.004	2.001	34.155
Microbiology				
Cunninghamella species[a]				
Rhizopus species	1.375	0.738	0.213	8.858
Rhizomucor species	0.3000	0.144	0.060	1.509
Lichtheimia species	0.750	0.823	0.061	9.270
Mucor species	0.250	0.362	0.013	4.924
Treatment				
Monotherapy[a]				
Combined antifungals therapy	0.955	0.960	0.156	5.846
Medical and surgical treatment	0.080	0.035	0.008	0.835

[a] Reference category

hematological malignancies, with studies reporting a prevalence ranging from 60–71% [21, 22]. Our own findings are consistent with this, as 80% of the cases we examined involved lung involvement. It is crucial to identify mucormycosis promptly in order to improve patient outcomes, as a one-week delay in diagnosis doubles the risk of mortality [4]. However, due to its rarity, mucormycosis is often not considered unless there is a strong clinical suspicion. This poses challenges for its diagnosis. In clinical settings, histopathology, direct microscopy, and culture are commonly used for laboratory diagnosis. However, the culture yield for mucormycosis is only around 50%, and the process is time-consuming [11]. Moreover, the complex clinical presentations and severe conditions associated with hematological malignancies can make it difficult to obtain tissue samples, especially due to low platelet counts and coagulation disorders. As a result, diagnosis is often delayed, and there are missed opportunities for timely treatment.

In recent years, molecular biology techniques, particularly polymerase chain reaction (PCR) and mNGS, have played a significant role in the diagnosis of mucormycosis [4, 23]. PCR provides advantages such as specificity and simplicity, but it also has limitations, such as relying on primer design for specificity and the potential for false positive results due to contamination. However, the introduction of mNGS has addressed these concerns by allowing for the simultaneous detection of almost all DNA or RNA information in a sample, eliminating guesswork and overcoming the limitations of traditional diagnostic methods [24]. Previous studies have shown the effectiveness of mNGS in early mucormycosis diagnosis, especially in cases where patients were unable to obtain pathological samples and routine microbiological tests yielded negative results. Additionally, mNGS has the capability to identify pathogens at the species level, providing valuable guidance for selecting appropriate clinical drugs [25, 26]. In this study, all patients underwent mNGS testing in addition to conventional methods, and the most frequently detected species were Cunninghamella, followed by Rhizopus, while Mucor species had the lowest proportion. This contradicts previous studies that reported Rhizopus as the most common species in cases of hematological malignancies, followed by Mucor [27, 28]. This observation may be attributed to the actual rise of these species, enhanced species identification facilitated by the implementation of mNGS, geographic differences, or reporting bias.

The frequent isolation of Cunninghamella species in our investigation highlights the need for clinical consideration. Previous studies have shown that infections caused by this species have a higher mortality rate compared to other Mucorales species (71% vs. 44%, $p<0.001$). It is important to note that Mucorales cannot be considered a uniform group in terms of antifungal susceptibility, as different species and strains show variations. Pharmacological research has revealed that Cunninghamella exhibits greater resistance to amphotericin B and posaconazole when compared to other Mucorales species [29]. Therefore, we suggest that mNGS could be a valuable supplementary approach for early diagnosis, particularly in patients with hematological malignancies who may not be suitable for tissue pathology or culture. mNGS can also simultaneously detect bacteria and viruses, which allows for timely administration of appropriate antibiotics and ultimately improves patient outcomes.

Currently, the available therapeutic options for managing mucormycosis are limited, as most antifungal agents have proven to be ineffective against mucormycetes. However, some antibiotics, such as amphotericin B, posaconazole, and isavuconazole, have shown promising results in the treatment of mucormycosis [30]. Amphotericin B, particularly its liposomal formulation (L-AmB), is commonly used as the initial treatment. Daily doses ranged from 1 mg/kg per day to 10 mg/kg per day [31]. Recipients of increased doses tended to have increased response rates [31, 32]. Patients receiving 10 mg/kg per day had substantial serum creatinine increases that were mostly reversible [31]. Administering doses exceeding 10 mg/kg per day did not result in higher blood concentrations [33]. In central nervous system (CNS) involvement, animal models and the above observations support use of L-AmB at 10 mg/kg per day [34]. In the absence of CNS involvement, L-AmB 5 mg/kg per day has been used successfully [12, 30, 34]. Consequently, relevant guidelines recommend first-line treatment with L-AmB at a dosage of 5–10 mg/kg/day [4, 14, 30, 35]. Nevertheless, recent findings from a multi-center retrospective clinical study in Japan demonstrated that a dosage of L-AmB exceeding 5 mg/kg/day does not enhance the survival rate among mucormycosis patients compared to those receiving 5 mg/kg/day of L-AmB ($P=0.625$) [36]. Additionally, Chinese patients often struggle to tolerate the high doses recommended in guidelines, and meta-analyses have revealed that lower doses of L-AmB are similarly effective for Chinese patients [37]. Consequently, in our study, the dosage administered to patients was adjusted based on individual tolerance, ranging from 3 to 5 mg/kg/day. Posaconazole is utilized as a supplementary and long-term treatment option when primary medications are ineffective or not tolerated by patients [35]. Recently, isavuconazole has been approved for the treatment of mucormycosis, showing both safety and efficacy comparable to amphotericin B [4]. However, pharmacological studies [38, 39] have revealed varying antifungal susceptibilities among pathogenic Mucor species towards isavuconazole and posaconazole. For instance, Mucor

indicus demonstrates high MIC values for both isavuconazole and posaconazole, whereas Mucor amphibiorum and Mucor irregularis exhibit high MICs specifically for isavuconazole. When compared to the genera Rhizopus or Rhizomucor, Mucor species generally display higher MICs against posaconazole and isavuconazole. Consequently, it is recommended to perform molecular identification of Mucor species in conjunction with in vitro susceptibility testing, particularly when considering azole-based therapeutic interventions. Additionally, the use of combination therapy involving multiple antifungal agents is still inconclusive, with contradictory outcomes from different studies. Therefore, current guidelines do not recommend combination therapy as the primary treatment approach. Miller et al. conducted a study that demonstrated a reduced rate of treatment failure when combining amphotericin B with an azole (posaconazole or isavuconazole) for patients with hematological malignancies complicated by mucormycosis [27]. On the other hand, another study involving 106 patients with hematological malignancies and mucormycosis showed that initial combination therapy with two or three antifungal agents did not significantly affect survival rates [40]. In our own study, eight patients initially received combination therapy, but the results did not show significant advantages. Due to the limited number of patients in this study, additional multi-center clinical trials and prospective studies are needed to confirm the potential superiority of combination therapy over monotherapy for patients. The use of both surgical resection and systemic antifungal agents in combination therapy has been shown to improve patient survival rates. According to the ECIL-6 guidelines, surgical debridement is strongly recommended for nasal and cutaneous mucormycosis, while personalized evaluations should be conducted for pulmonary and disseminated mucormycosis to determine the feasibility of surgery [30]. In our study, surgical intervention was performed only on five patients, accounting for 10% of the total study population, and four of them showed favorable prognoses. Univariate analysis indicated that the combination of surgical resection and systemic antifungal medication may increase patient prognostic outcomes. In reality, the proportion of Chinese patients with mucormycosis undergoing surgical intervention is conspicuously low [41, 42]. Objective factors contributing to this trend include severe disease manifestations, the presence of surgical contraindications stemming from comorbidities, infections involving multiple sites or foci, and the inherent complexity of surgical procedures in infected areas. Additionally, subjective factors encompass clinicians' inadequate recognition of the pivotal role of surgery in mucormycosis management, along with heightened concerns regarding surgical complications and a lack of precise assessment of the risk-benefit ratio associated with surgical interventions. Consequently, based on established clinical research and international guidelines, it is crucial for clinicians to reinforce their understanding of the priority accorded to surgical therapy in the comprehensive treatment strategy for mucormycosis. For patients with hematological malignancies complicated by mucormycosis, active interdisciplinary discussions are recommended to assess the potential for surgical interventions in order to maximize patient benefits.

This study has several limitations that need to be addressed. Firstly, it was a retrospective observational study conducted within our hospital, which may have introduced biases and limitations in the data collected. Secondly, there were challenges with regard to bleeding during biopsy procedures, leading to a low inclusion rate of proven mucormycosis patients. This may have resulted in a sample that does not fully represent the entire population of patients with mucormycosis in our hospital. Thirdly, mucormycosis is a rare condition in China, resulting in a limited number of cases included in this study and a small sample size. This may have affected the statistical power and generalizability of the results. To address these limitations, future research should focus on conducting larger-scale, multi-center clinical studies to improve the robustness and reliability of the findings and optimize treatment approaches for this rare but serious condition.

Conclusion

This research presents the latest findings on mucormycosis in individuals with hematological malignancies in eastern China. The study reveals that pulmonary mucormycosis is the most common form of infection in this patient population, particularly among those with AML, a prevalent hematological malignancy. The primary causative agents of mucormycosis are identified as Cunninghamella and Rhizopus species. The study also highlights the significant advantages of molecular biology techniques, particularly mNGS, in diagnosing and managing mucormycosis. However, it should be noted that the mortality rate of mucormycosis in patients with hematological malignancies remains high, underscoring the urgent need to integrate molecular diagnostic techniques for early detection and treatment in the future.

Abbreviations

mNGS	Metagenomic next-generation sequencing
AML	Acute myeloid leukemia
ALL	Acute lymphoblastic leukemia
PCR	Polymerase chain reaction

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Author contributions
All authors contributed to the study conception and design. TS and MX searched the literature, collected and analyzed the clinical data. TS wrote the manuscript. TS and QX revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the First Affiliated Hospital of USTC, University of Science and Technology of China (Approval NO:2023-RE-135). The data utilized in this study were from retrospective research, the requirement for written informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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