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Clinical and microbiological features and outcomes of mucormycosis in critically ill patients

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ABSTRACT

Introduction: Mucormycosis is a rare invasive fungal infection with high mortality in patients with severe underlying predisposing factors causing immunosuppression. The exact incidence of mucormycosis and the optimal therapeutic approach is difficult to determine, especially in severe cases, due to the rarity of the disease. The new second-generation triazole isavuconazole provides an alternative treatment option which may represent a potential benefit in severe cases.

Materials and methods: A retrospective case series was conducted of patients with a positive laboratory culture for Mucorales and consistent clinical findings who required intensive care treatment. Patient characteristics including demographics, comorbidities, microbiological analysis, specific antifungal therapy and clinical outcome were analysed.

Results: Fifteen critically ill patients with Mucorales detected between 2016 and 2019 were included in this study; the crude mortality rate was 100%. At the time of diagnosis of mucormycosis, 80% of subjects had relevant medical immunosuppression and 53.3% of subjects had neutropenia. Manifestation of mucormycosis was pulmonary in 53.3% of subjects, rhino-orbital in 20% of subjects and disseminated in 26.7% of subjects. Notably, 40% of all patients had received antifungal prophylaxis prior to mucormycosis, mainly with posaconazole due to underlying haematological malignancy, thus possibly representing break-through infections. Antifungal therapy for invasive mucormycosis was administered in 80% of subjects for a median duration of 16 days.

Conclusion: In this retrospective cohort analysis of intensive care patients, the prognosis of mucormycosis was extremely poor. An aggressive strategy for diagnosis and treatment is essential for intensive care patients with mucormycosis. There is a need for further research to determine if combination therapy in higher dosages or prompt surgery is beneficial in severe critically ill patients.

Introduction

Mucormycosis is a rare invasive fungal infection associated with high mortality rates. The causative pathogens are fungi of the order Mucorales, mainly *Rhizopus* spp., *Mucor* spp. and *Lichtheimia* spp., which are typically found on decaying organic material and soils (Binder et al., 2014; Cornely et al., 2014). Severe immunosuppression and diabetes mellitus are the most important predisposing factors for invasive mucormycosis. In particular, haematological malignancy is associated with increased risk of disseminated mucormycosis (Jeong et al., 2019). Mucormycosis is associated with mortality rates of up to 80%, especially in patients with haematological malignancy and in cases with affection of the central ner-

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vous system (Sipsa and Kontoyiannis, 2012; Cornely et al., 2019). There seems to have been an increase in the incidence of mucormycosis in recent years, but the exact incidence is difficult to determine due to the rarity of the disease and difficulty in establishing the diagnosis. Mucorales account for up to 10% of invasive mould diseases in patients after solid organ transplant and allogeneic haematopoietic stem cell transplantation (allo-HSCT) (Petrikkos and Skiada, 2014; Guinea et al., 2017; Cornely et al., 2019). The most common manifestations of mucormycosis are pulmonary and rhino-orbital (Binder et al., 2014). Pulmonary mucormycosis often presents with unspecific clinical signs; therefore, a high index of clinical suspicion and rapid diagnostic measures leading to timely initiation of aggressive antifungal treatment are key aspects of a favourable outcome (Lin et al., 2017).

Due to the severity of mucormycosis and the underlying predisposing comorbidities, a relevant proportion of cases are treated in intensive care units (ICUs), but epidemiological data on mucormycosis in severely ill patients are sparse apart from small cohorts (Machicado et al., 2014; Bassetti et al., 2018; Maleitzke et al., 2019; Claustre et al., 2020). Mortality of mucormycosis is very high in ICU patients despite intensified antifungal therapy and surgical intervention. In these cases, organ failure and organ replacement procedures further complicate antifungal therapy, and drug-related toxicity can occur as defining the correct dose can be challenging. Therefore, salvage therapy with the new triazole isavuconazole as a single agent or as combination therapy with liposomal amphotericin B may represent a beneficial new treatment option for ICU patients. Due to the rarity of the disease, therapeutic experience in patients with mucormycosis requiring intensive care is limited. As such, the aim of this study was to analyse the clinical course of patients with mucormycosis requiring ICU therapy, with special regard to antifungal treatment regimens.

Materials and methods

This retrospective analysis was conducted between February 2016 and February 2019 at a university hospital in Munich, Germany. Patients were identified from the Institute for Microbiology's database using the HyBase analysis system (epiNet AG, Bochum, Germany). Inclusion criteria were: positive laboratory culture for Mucorales with consistent clinical presentation, intensive care treatment, and age >18 years. Cases of proven or probable mucormycosis, as defined according to the European Organisation for Research and Treatment of Cancer/ National Institute of Allergy and Infectious Diseases Mycoses Study Group definitions for invasive fungal diseases, were included (De Pauw et al., 2008). Proven mucormycosis was based on histopathological findings. As well as typical staining, polymerase chain reaction and molecular techniques were used for fungal identification. Pulmonary mucormycosis was classified as probable as the diagnosis was mainly based on bronchoalveolar lavage (BAL) when patients did not undergo surgery. Medical records including clinical charts and nursing records were reviewed. Data collection included patient demographics, comorbidities, clinical parameters, laboratory findings, microbiological analysis, hospital stay, outcome, and antifungal and antibiotic therapy. Data extraction was performed according to published methods (Gilbert et al., 1996; Worster et al., 2005). Relevant variables were defined, documented in an abstraction form, and extracted by a clinical microbiologist, an intensive care physician and a haematologist. The Ethics Committee of the Technical University of Munich approved the protocol of this retrospective study, and waived the need to obtain consent for the collection, analysis and publication of the data (Approval No. 806/20 S-EB).

All samples were collected using aseptic techniques. Primary microbiological cultures were performed on Columbia agar, Schaedler agar, chocolate agar (prepared culture media, Becton Dickinson, Sparks, MD, USA) and thioglycolate broth (Oxoid Thermo Fisher Scientific, Waltham, MA, USA). Colonies of Mucorales were subcultured on Sabouraud dextrose agar (Oxoid Thermo Fisher Scientific, Waltham, MA, USA) for macroscopic, microscopic and matrix-assisted laser desorption/ionization-time of flight (Bruker Daltronics GmbH, Leipzig, Germany) species identification. Moreover, molecular species identification via 28s rDNA polymerase chain reaction and sequencing was performed. Galactomanan detection (Platelia Aspergillus Ag, Bio-Rad Laboratories, Munich, Germany) was performed using BAL and serum samples. Results were reported as optical density index with a cut-off of 0.5 (Ullmann et al., 2018).

Statistical analyses were performed using Excel 2013 (Microsoft Corp, Redmond, WA, USA). Continuous data are described as median (range) and categorical data are described as absolute and relative frequencies.

Results

During the study period, 16 ICU patients with detection of Mucorales were identified. One case with pulmonary detection of Mucorales was a drowning victim, admitted to the ICU with ventricular fibrillation and cardiogenic shock after successful resuscitation. Molecular species identification showed rhizopus microspores, but no antifungal therapy was initiated. The patient survived the incident and was discharged from the ICU after 9 days. The authors believe that this case represents pulmonary colonization rather than invasive mucormycosis, and therefore this patient was excluded from further analyses.

The median age of subjects was 54 (range 31–80) years, and 10 patients (66.7%) were male. Patients were mainly admitted to the ICU because of sepsis and respiratory failure. All patients required invasive mechanical ventilation and were treated with broad-spectrum antibiotics (Table 1). Six cases of pulmonary mucormycosis were classified as probable as the diagnosis was based on BAL; all remaining cases were classified as proven mucormycosis.

Invasive pulmonary mucormycosis was present in eight cases: four had received allo-HSCT, two had child C liver cirrhosis, one patient had undergone treatment for diffuse large B-cell lymphoma (DLBCL) and one patient had undergone treatment for multiple myeloma (MM). Three of these patients died before the initiation of antifungal therapy. Among three cases with rhino-orbital mucormycosis, two patients had received allo-HSCT and one had acute lymphoblastic leukaemia. In two of these patients, histological proof of mucormycosis could be assessed and one patient had cerebral mucor invasion. Four cases with disseminated mucormycosis were identified; all four had pulmonary involvement, one had additional intra-abdominal detection of Mucorales, one initially had soft tissue manifestation and two had cerebral mucormycosis. Underlying comorbidities were receipt of allo-HSCT, haemophagocytosis, acute myeloid leukaemia and diabetes mellitus. Median time interval from ICU admission to detection of Mucorales by culture was 19 days, indicative of the advanced condition of the predisposing comorbidities.

Histopathological work-up was initiated in seven of 15 (46.7%) cases; of these seven cases, fungal aetiology was revealed in five cases. Hyphae were detected in two cases of rhino-orbital mucormycosis and three cases of disseminated mucormycosis (see Table 2). Specimens collected for microbiological work-up were mainly respiratory specimens, but also tissue cultures from deep tissue microbiological swabs. Molecular species identification was performed for 13 of 15 (86.7%) cultures, but susceptibility testing was not performed routinely as this method was not available locally and isolates had to be sent to the German national reference laboratory for invasive fungal infections for susceptibility test-

Table 1
Baseline characteristics

Baseline characteristics(total cohort n=15)	
Median age (range), years	54 (31–80)
Male sex	10/15 (66.7%)
Median duration of hospital stay (range), days	29 (0–126)
Median duration of ICU stay (range), days	18 (0–51)
Mortality on ICU	15/15 (100%)
Predisposing comorbidities	
Haematological disease	12/15 (80%)
Haemophagocytosis (n=1)	7/15 (46.7%)
Diffuse large B-cell lymphoma (n=1)	3/15 (20%)
Myelodysplastic syndrome (n=2)	
Chronic lymphocytic leukaemia (n=1)	
Acute lymphoblastic leukaemia (n=2)	
Multiple myeloma (n=3)	
Acute myeloid leukaemia (n=2)	
Allogeneic haematopoietic stem cell transplantation	
Other predisposing comorbidity	
Child C liver cirrhosis (n=2)	
Diabetes and trauma (n=1)	
Current med. immunosuppression (more than one possible)	12/15 (80%)
Steroid (n=7)	
Other than steroid (n=6)	
Active chemotherapy within 3 months (n=8)	
Neutropenia at diagnosis[a]	8/15 (53.3%)
Severe (<500/µL)	6/8 (75%)
Moderate (500–1000/µL)	2/8 (25%)
Reason for ICU admission	
Sepsis	7/15 (46.7%)
Respiratory failure	6/15 (40%)
Other (bleeding oesophageal varices, acute abdomen)	2/15 (13.3%)
Median interval to ICU admission after hospital admission (range)	6 (0–92) days
Median SOFA score at ICU admission (range)	10 (8–20)
Need for catecholamine therapy at ICU admission	13/15 (86.7%)
Invasive mechanical ventilation	15/15 (100%)
Median duration of invasive ventilation (range)	16 (1–50) days
ECMO	1/15 (6.7%)
Renal replacement therapy on ICU	12/15 (80%)
Other medication parallel to antifungal therapy (more than one possible)	
G-CSF	10/15 (66.7%)
Broad-spectrum antibiotic therapy	15/15 (100%)
Antiviral therapy	11/15 (73.3%)

ICU, intensive care unit; SOFA, sequential organ failure assessment; ECMO, extracorporeal membrane oxygenation; G-CSF, granulocyte colony-stimulating factor.
[a] Severe neutropenia was defined as absolute neutrophil count <0.5 × 10^9/L (<500/μL), and moderate neutropenia was defined as absolute neutrophil count of 0.5–1 × 10^9/L (500–1000/μL).

ing. *Rhizopus microsporus* was isolated in nine of 15 (60%) cases, *Lichtheimia corymbifera* in four of 15 (26.7%) cases and *Rhizopus arrhizus* in two of 15 (13.3%) cases. Galactomanan antigen testing (serum and BAL) was performed regularly to identify a differential diagnosis or mixed invasive fungal infection (13/15, 86.7%), and yielded positive results for two patients, one of whom also had detectable fungal growth of *Aspergillus fumigatus* in two consecutive BAL samples (Table 2).

Antifungal therapy for invasive mucormycosis was administered in 12 of 15 (80%) patients. Three patients did not receive any antifungal therapy, and all three had Mucorales detected by culture from BAL specimens, and presented with respiratory symptoms and 'atypical' pulmonary infiltrates detected by computed tomography (CT) scan. One patient with child C liver cirrhosis was admitted to the ICU with multi-organ failure and respiratory insufficiency. Detection of Mucorales by culture was only available after the patient had died. Another two cases had underlying haematological malignancies (DLBCL and MM) and received immunosuppressive antineoplastic therapy. The patient with DLBCL was neutropenic and died from septic shock directly after hospital admission. The patient with MM was on immunomodulatory drugs and steroids, and died due to respiratory failure; again, detection of Mucorales by culture was only available after the patient had died.

Forty percent of patients had received antifungal prophylaxis prior to mucormycosis. Posaconazole was most frequently used due to underlying haematological malignancy; as such, these cases of mucormycosis may represent breakthrough infections. However, no data on therapeutic drug monitoring or dosage/duration of antifungal prophylaxis were available. Table 3 provides details on antifungal treatment. Four patients in the study cohort received liposomal amphotericin B and isavuconazole combination therapy with a median combination duration of 8.5 (range 5–14) days. Three of these four patients were started with liposomal amphotericin B, and isavuconazole was added after a median of 5 (range 4–15) days due to the persistent severe clinical condition. In the remaining patient, liposomal amphotericin B was added to primary therapy with isavuconazole after 3 days. In three patients on combination therapy who also received continuous dialysis, therapeutic drug monitoring for isavuconazole was performed and this revealed plasma levels between 1.2 and 2.8 µg/mL.

The overall crude mortality rate of mucormycosis was 15 of 15 (100%) in the study cohort. The median survival time from microbiological diagnosis to death was 7 (range 0–40) days. This heterogeneous group of patients with a variety of underlying diseases and manifestations of mucormycosis was studied due to the rarity of the disease and the infrequent use of isavuconazole.

Table 2
Manifestation and diagnosis of mucormycosis.

Manifestation and diagnosis of mucormycosis(total cohort *n*=15)	
Manifestation	
Pulmonary mucormycosis	8/15 (53.3%)
Rhino-orbital mucormycosis (including one case with cerebral affection)	3/15 (20%)
Disseminated mucormycosis (including one case with initial skin/soft tissue infection)	4/15 (26.7%)
Symptoms (more than one possible)	
Fever	5/15 (33.3%)
Pain	2/15 (13.3%)
Sinusitis	3/15 (20%)
Respiratory symptoms	12/15 (80%)
Erythema	1/15 (6.7%)
Imaging	
CT scan (showing pulmonary infiltrates[a] *n*=11, sinusitis *n*=8)	14/15 (93.3%)
Cerebral MRI (showing cerebral invasion in rhino-orbital mucormycosis *n*=1, cerebellar lesions in disseminated mucormycosis *n*=2)	5/15 (33.3%)
Time to detection of Mucorales by culture after admission (range), days	20 (0–125)
Sampling strategy	
Respiratory specimen[b] (TS, BAL)	12/15 (80%)
Tissue culture (in rhino-orbital or disseminated disease)	3/15 (20%)
Detected species	
Rhizopus microsporus	9/15 (60%)
Lichtheimia corymbifera	4/15 (26.7%)
Rhizopus arrhizus	2/15 (13.3%)
Molecular species identification performed	13/15 (86.7%)
Susceptibility testing performed (at German reference laboratory)	2/15 (13.3%)
GM antigen testing performed	13/15 (86.7%)
Positive GM antigen test result	2/13 (15%)
Histopathology performed	7/15 (46.7%)
Intra-abdominal specimens (*n*=2)	5/7 (71%)
Skin biopsy (*n*=1)	
Brain biopsy (*n*=2)	
Biopsy of the paranasal sinuses (*n*=2)	
Histopathology positive for fungi[c]	

CT, computed tomography; MRI, magnetic resonance imaging; BAL, bronchoalveolar lavage; TS, tracheal secretion; GM, galactomanan.
[a] Diffuse or bilateral 'atypical' infiltrates (with ground-glass opacities, nodules or consolidation) in all cases, classical chest CT findings of invasive fungal pneumonia in two cases; bilateral pleural effusion in three cases.
[b] Endobronchial biopsy was (additionally) performed in two cases.
[c] Positive specimens: two cases of rhino-orbital mucormycosis and three cases with disseminated mucormycosis (of those, one skin biopsy, one brain biopsy and one intra-abdominal biopsy).

Table 3
Specific therapy for mucormycosis.

Specific therapy for mucormycosis(total cohort *n*=15)	
Antifungal prophylaxis prior to mucormycosis	6/15 (40%)
Posaconazole	5/6 (83.3%)
Isavuconazole	1/6 (16.7%)
Antifungal therapy for episode of mucormycosis[b]	12/15 (80%)[a]
High-dose liposomal amphotericin B (range 5–10 mg/kg/day)	4/12 (33%)
Isavuconazole (loading dose 200 mg every 8 h for 48 h, maintenance dose	1/12 (8%)
200 mg once daily)	3/12 (25%)
Liposomal amphotericin B and isavuconazole consecutively	4/12 (33%)
Combination therapy liposomal amphotericin B and isavucoanzole	
Median duration of antifungal therapy (range), days	16 (4–40)
Adjunctive surgical therapy	3/15 (20%)
Evacuation of a cerebellar abscess formation (*n*=1)	
Debridement of the paranasal sinuses (*n*=1)	
Laparotomy in peritonitis due to small intestine ischaemia (*n*=1)	

[a] Three patients died before culture results/initiation of therapy.
[b] Empirical antifungal therapy [voriconazole (*n*=1), isavuconazole (*n*=1), high-dose liposomal amphotericin B (*n*=7)] was initiated in nine cases with a median of 8 (range 2–34) days before microbiological diagnosis.

Discussion

Invasive mucormycosis is associated with high mortality rates, with worse outcomes in patients with haematological malignancy and ICU patients (Lanternier et al., 2012; Machicado et al., 2014; Bassetti et al., 2018; Maleitzke et al., 2019; Claustre et al., 2020). This may be due to the poor physiological status of these patients, but can also be attributed to distinct diagnostic and therapeutic challenges in ICU patients with mucormycosis. However, data on mucormycosis, particularly in ICU patients, is sparse apart from small cohorts (Machicado et al., 2014; Bassetti et al., 2018; Maleitzke et al., 2019; Claustre et al., 2020).

Establishing a diagnosis of mucormycosis in a timely manner is very important; however, as chest CT scan and respiratory symptoms are often unspecific, and culture growth takes time, this can be challenging and should be addressed using a multi-disciplinary approach with clinical evaluation, imaging, histopathology and fungal culture for genus and species identification, as well as susceptibility testing (Skiada et al., 2020).

It is of utmost importance to identify patients at risk, and this highlights the potential value of rapid detection methods which were not used locally in clinical practice.

Acquisition of biopsy specimens for histopathology and culture is recommended for the diagnosis of mucormycosis (Cornely et al., 2014). As cultures can be false negative, molecular assays of embedded histopathological tissue samples may increase sensitivity (Hammond et al., 2011). In the study cohort, pulmonary mucormycosis was the most common manifestation; however, histopathological work-up of respiratory specimens was not performed routinely, and an endobronchial biopsy was only performed in two cases (see Table 2). Due to the invasiveness of lung biopsy in ventilated high-risk patients, and thrombocytopenia as an additional complicating factor in patients with haematological malignancy, BAL had to be used instead. This highlights the diagnostic challenges in suspected mucormycosis in ICU patients.

Curative surgery for local control of mucormycosis appears to have a beneficial effect (Cornely et al., 2014; Claustre et al., 2020). However, in the study cohort, most cases had pulmonary mucormycosis, and lung resection was not feasible due to the severity of their illness. Surgical debridement was only performed in cases of rhino-orbital and disseminated mucormycosis. Notably, patients died within a median of 7 days of detection of mucormycosis by culture, whereas all patients were admitted to the ICU before the diagnosis of mucormycosis with complications of their underlying diseases. The advanced condition of the predisposing comorbidities and the patient's need for intensive care prior to the diagnosis of mucormycosis may explain the high mortality rate. A prompt initiation of antifungal treatment is very important in the management of mucormycosis. In line with this, medical antifungal treatment was only initiated on the day of culture growth in three patients in the study cohort, but empirical antifungal therapy had already commenced. In the remaining nine patients, antifungal therapy was started a median of 8 (range 2–34) days before the microbiological diagnosis. Therefore, there already seems to be a high index of clinical suspicion in patients at risk, and delayed therapy was not a relevant problem. Interestingly, among the patients in whom antifungal treatment had not been initiated and diagnosis of mucormycosis was established post mortem, two were treated with standard regimens for DLBCL and MM, where invasive mould infection is not usually suspected.

Breakthrough invasive mucormycosis in HSCT patients receiving prophylaxis with posaconazole has been described (Skiada et al., 2020). In 40% of the study cohort, mucormycosis occurred despite antifungal prophylaxis with posaconazole and isavuconazole. All cases with potential breakthrough infection had underlying haematological malignancy. The majority were patients who had undergone allo-HSCT, and neutropenia was present in most cases; this is in line with the association of breakthrough infections with host failure in haematological malignancy, immunosuppression and neutropenia (Lionakis et al., 2018). Nearly two-thirds of the patients received primary antifungal therapy with liposomal amphotericin B, but in the remaining two cases (with previous posaconazole prophylaxis), primary initial therapy with isavuconazole was started. However, a change of antifungal substance class for empirical antifungal therapy should be considered in cases of possible breakthrough infections (Lionakis et al., 2018). Susceptibility testing was not performed routinely in these cases, and no data were available on therapeutic drug monitoring or on dosage/duration of antifungal prophylaxis; as such, it is not possible to draw conclusions on the effect of triazole prophylaxis on breakthrough infections in the study cohort. More data are needed regarding whether inadequate plasma levels of the prophylactic substance contribute to breakthrough infections, or if breakthrough infections after triazole prophylaxis might arise from reduced susceptibility.

In severe forms of mucormycosis with refractory or progressive disease, a beneficial outcome was shown for combination therapy of liposomal amphotericin B with posaconazole or echinocandins as an individual treatment strategy (Reed et al., 2008; Pagano et al., 2013; Cornely et al., 2014, 2019; Skiada et al., 2018). However, initial combination therapy of liposomal amphotericin B and posaconazole or echinocandins in a defined patient cohort with haematologic malignancy did not reduce mortality in one study where diagnosis of mucormycosis during ICU stay was an individual risk factor, and isavuconazole was not included in the analysis (Kyvernitakis et al., 2016). Isavuconazole is a second-generation triazole with a favourable drug safety profile and activity against Mucorales (Jenks et al., 2018). Isavuconazole was active as primary or salvage treatment for mucormycosis, with comparable results to amphotericin B. It is approved for the treatment of mucormycosis (Marty et al., 2016; Shirley and Scott, 2016), and can be used in mucormycosis as salvage treatment in cases of refractory disease and drug-related toxicity of first-line regimens (Cornely et al., 2019). In the present study, the antifungal regimens with liposomal amphotericin B and isavuconazole were heterogeneous, and the decision to use combination therapy or monotherapy was at the discretion of the physician in charge. For three patients with combination therapy and simultaneous continuous dialysis, isavuconazole therapeutic drug monitoring was used, as isavuconazole levels can decrease markedly during renal replacement treatment in critically ill patients (Andes et al., 2018; Lahmer et al., 2019). In these three patients, the dose needed to be adjusted to a maintenance dose of 200 mg twice daily to reach plasma concentrations above the therapeutic concentration (>1 μg/mL). The poor physiological status with multi-organ failure and organ replacement procedures in ICU patients complicates antifungal therapy, making drug toxicity management a key element of therapy. Therefore, further studies are needed to evaluate the potential benefit of isavuconazole as monotherapy or combination therapy in light of treatment outcome and drug tolerability profile. More data on therapeutic drug monitoring of isavucoanzole is needed to confirm adequate plasma levels in the case of organ replacement procedures.

In this retrospective cohort analysis of ICU patients, the prognosis of mucormycosis was extremely poor. Due to the lack of a defined antifungal treatment protocol, the small patient number and the high crude mortality rate, no conclusions on the therapeutic outcomes of specific antifungal regimens or manifestations of mucormycosis can be drawn.

In Europe and the USA, mucormycosis is increasing, particularly in patients with haematological malignancy (Cornely et al., 2019). Also, new triazoles offer more (combination) treatment options, and data on mucormycosis specifically for ICU patients are still sparse. Thus, in contrast to other studies (Camara-Lemarroy et al., 2014), this study focused on a highly selected patient cohort representing mucormycosis in a tertiary referral centre in Europe.

The study investigated a heterogeneous patient cohort with complex medical history, highlighting the need for an interdisciplinary approach for diagnosis and treatment of invasive mucormycosis. Although fungal treatment was initiated empirically before the diagnosis of mucormycosis in most cases, survival rates remained low. An aggressive strategy for diagnosis and treatment is essential for ICU patients with mucormycosis. Future studies should investigate whether combination therapy with new triazoles in higher dosages or prompt surgery is beneficial in critically ill patients.

Conflict of interest statement

None declared.

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None.

Ethical approval

The Ethics Committee of the Technical University of Munich approved the protocol of this retrospective study, and waived the need to obtain consent for the collection, analysis and publication of the data (Approval No. 806/20 S-EB).

Author contributions

KR und TL conceived the study. KB, TL, KR contributed to acquisition of the data. KR and KB analysed the data and interpreted the results. KR wrote the manuscript. KB, TL, RO, MH, SR, MV, RMS and DHB revised the manuscript critically. All authors agreed with the article submission. All authors read and approved the final manuscript.

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