












Results from a national survey on COVID-19-associated mucormycosis in Germany: 13 patients from six tertiary hospitals

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Abstract

Background: Most COVID-19-associated mucormycosis (CAM) cases are reported from India and neighbouring countries. Anecdotally cases from Europe have been presented.

Objective: To estimate the disease burden and describe the clinical presentation of CAM in Germany.

Methods: We identified cases through German mycology networks and scientific societies, and collected anonymised clinical information via FungiScope®.

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Results: We identified 13 CAM cases from six tertiary referral hospitals diagnosed between March 2020 and June 2021. Twelve patients had severe or critical COVID-19, eleven were mechanically ventilated for a median of 8 days (range 1-27 days) before diagnosis of CAM. Eleven patients received systemic corticosteroids. Additional underlying medical conditions were reported for all but one patient, five were immunocompromised because of malignancy or organ transplantation, three were diabetic. Eleven patients developed pneumonia. Mortality was 53.8% with a median time from diagnosis of mucormycosis to death of 9 days (range 0-214 days) despite treatment with liposomal amphotericin B and/or isavuconazole in 10 of 13 cases. CAM prevalence amongst hospitalised COVID-19 patients overall (0.67% and 0.58% in two centres) and those admitted to the intensive care unit (ICU) (1.47%, 1.78% and 0.15% in three centres) was significantly higher compared to non-COVID-19 patients ($P < .001$ for respective comparisons).

Conclusion: COVID-19-associated mucormycosis is rare in Germany, mostly reported in patients with comorbidities and impaired immune system and severe COVID-19 treated in the ICU with high mortality compared to mainly rhino-orbito-cerebral CAM in patients with mild COVID-19 in India. Risk for CAM is higher in hospitalised COVID-19 patients than in other patients.

KEYWORDS

amphotericin B, COVID-19, COVID-19 vaccination, fungal infection, isavuconazole, mortality, mucormycosis, prevalence

1 | INTRODUCTION

Background: Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its treatment alter metabolism and immune system in several ways, promoting the development of fungal infections.¹ Early on during the pandemic, the awareness for COVID-19-associated aspergillosis was high due to the already known association of aspergillosis and severe influenza.^{2,3} COVID-19-associated mucormycosis (CAM) gained worldwide attention in early 2021, during the second wave of the COVID-19 pandemic in India, where high number of COVID-19 cases, overuse of corticosteroids for treatment even of mild COVID-19, high incidence of diabetes without glycaemic control, and an overall high count of Mucorales spores indoors and outdoors have been proposed to be main drivers.⁴⁻⁶ The unprecedented surge of cases with CAM became a major healthcare issue with strongly increased prevalence over months.⁷ Of course, this put also infectious diseases physicians in other regions on alert.

Mucormycosis usually is rare with an estimated average incidence per 100,000 persons of 0.2 cases, and a maximum of up to 14 in India and Pakistan.⁸ In the context of COVID-19, rhino-orbitocerebral mucormycosis is the most common clinical presentation reported to date, primarily associated with uncontrolled diabetes or corticosteroid exposure.⁶ Pulmonary CAM has been rarely described, mostly in immunocompromised patients with malignancy or transplant recipients.^{4,9} The underlying immunological mechanisms that promote

development of fungal infections in patients with COVID-19 are not fully understood. It has been shown that SARS-CoV-2 can functionally alter β -cells in the pancreas resulting in impaired insulin secretion thereby promoting diabetes and may also cause damage to the airway epithelium after a cytokine storm and lymphocyte depletion compromising the immune response.^{10,11}

In Europe, anecdotally CAM cases have been reported from the Czech Republic, France, Germany, Italy, the Netherlands and the United Kingdom.¹²⁻¹⁷ Rhino-orbitocerebral mucormycosis was less frequent, most patients had pulmonary or disseminated disease.¹²⁻¹⁷

For Germany, numbers and the epidemiology of CAM cases are unknown to date. There is a lack of systematic surveillance programmes for fungal infections, therefore, a national survey was compiled to identify CAM cases in German hospitals and to obtain clinical data of respective cases diagnosed between March 2020 and June 2021 in six German tertiary hospitals.

2 | METHODS

A survey on patients with laboratory confirmed COVID-19 with mycological evidence of mucormycosis was conducted in collaboration with partners of the FungiScope® network¹⁸ and the German Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) covering the University Hospitals in Germany and more than 50

other hospitals across the country. Partners were invited via email. Announcements were posted on Twitter to increase visibility. Furthermore, the National Reference Center for Invasive Fungal Infections (NRZMyk) searched its database for eligible cases and if the provider of the fungal isolate gave her or his consent to be contacted for epidemiological studies, we reached out for an anonymised follow-up. In addition, we conducted a literature search using PubMed (<https://pubmed.ncbi.nlm.nih.gov>, search string ((COVID-19 OR corona OR SARS-CoV-2) AND (mucormycosis OR mucorales OR fungal infection) AND Germany))) and contacted authors for further information and additional CAM cases at their centre. Centres interested to join the study provided data on demographics, underlying conditions, COVID-19 severity and associated treatment, intensive care unit (ICU) treatment, diagnosis of mucormycosis and antifungal therapy, response to antifungal treatment and outcome, which was collected in the FungiScope registry.¹⁸ Cases were classified according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) criteria.¹⁹ Inclusion criteria were extended by underlying conditions or host factors not listed in the EORTC/MSG criteria, which included COVID-19 and diabetes. Furthermore, cases were included, if diagnosis was based on mycological evidence from non-sterile body sites only, without radiological assessment or confirmative radiological findings and those cases that were identified through sequencing efforts. Correlations were tested using the Fisher's exact or Chi-square test. Odds ratios (OR) for occurrence of mucormycosis in hospitalised COVID-19 patients and non-COVID-19 patients overall and in the ICU were provided with 95% confidence intervals (95% CI) and *P*-values. *P*-value below 0.5 was considered significant. The study was approved by the local ethics committee of the University of Cologne, Germany (study ID 05-102).¹⁸

3 | RESULTS

Thirteen unvaccinated patients with COVID-19 and subsequent (2) or concurrent (11) mucormycosis were reported from six tertiary hospitals in Germany, ranging from one to four cases per centre (Figure 1). Two cases were published in a recent study on autopsy findings in COVID-19 patients (case 09, case 10).¹⁴ Eight patients were male (61.5%), and median age was 57 years (range 30–75 years). Eleven patients were tested SARS-CoV-2 PCR-positive upon admission to the hospital and two patients one and two months prior. Severe or critical COVID-19 was reported for twelve patients, of whom 11 required intensive care involving mechanical ventilation in median for 8 days (range 1–51 days) before diagnosis of mucormycosis. Underlying medical conditions in addition to COVID-19 were reported for all but one patient, five were immunocompromised due to treatment of leukaemia or after organ transplantation, three had diabetes. Haemodialysis was required in one patient with diabetic nephropathy (case 04), in another blood sugar levels were elevated during glucocorticosteroid use that normalised upon discontinuation



FIGURE 1 Distribution of German sites reporting CAM cases and per cent population per state tested positive for SARS-CoV-2 and reported to the Robert Koch Institute between February 2020 and June 2021 (Data sources: population per German state on December 31, 2020 through Statistisches Bundesamt (www.destatis.de) accessed on July 3, 2021 and total number of COVID-19 cases (tested positive for SARS-CoV-2 and reported to the Robert Koch-Institute) per state through www.rki.de on June 30, 2021)

(case 12). In a third case, diabetes was poorly controlled with varying blood sugar levels during hospital stay (case 06).

Eleven patients (84.6%) received systemic glucocorticoids for treatment of COVID-19 symptoms for 7 days (median, range 1–10 days) with dexamethasone ($n = 6$) and hydrocortisone ($n = 4$) being the most common steroids, one only after the diagnosis of mucormycosis (case 06). Hydrocortisone (240 mg per day) was used between two and ten days to treat severe to critical COVID-19 only during the first wave in Germany (before June 2020). Dexamethasone was administered in the dosage of 6 mg per day for seven or ten days in all but one case, where a corticosteroid boost was administered once (case 04).

Mucormycosis was diagnosed a median 10 days (range 0–62 days) after the first positive SARS-CoV-2 swab (Figure 2). Pulmonary mucormycosis was diagnosed in 11 patients; in two, invasive infection

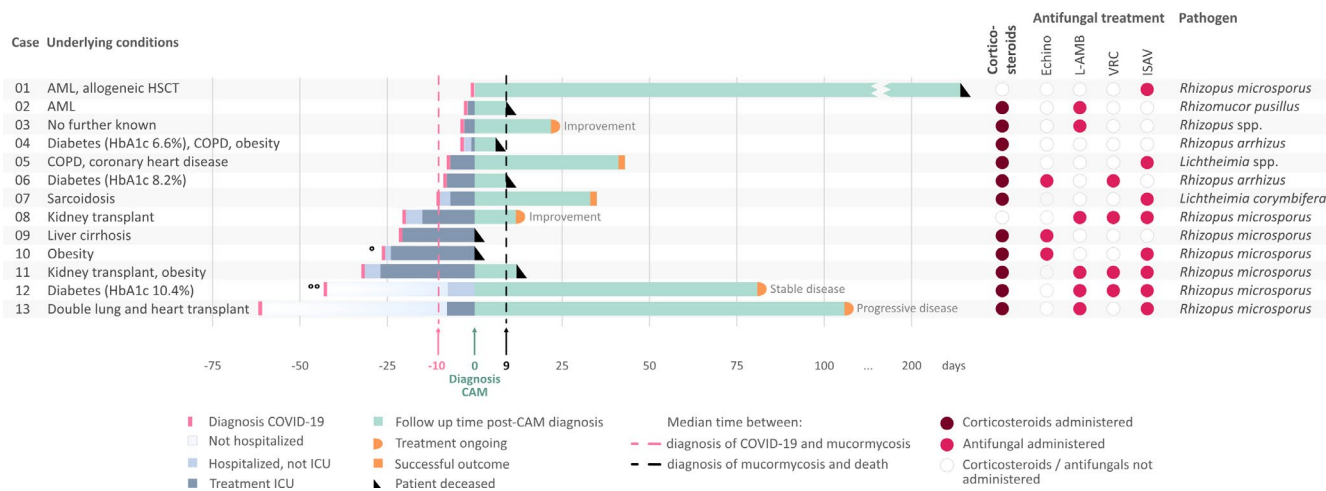


FIGURE 2 Summary of clinical course of 13 patients with CAM reported from six German tertiary hospitals. ° Gastro-intestinal mucormycosis, °° Rhino-orbito-cerebral mucormycosis, others: pulmonary mucormycosis; Abbreviations: AML, acute myeloid leukaemia; CAM, COVID-19-associated mucormycosis; COPD, chronic obstructive pulmonary disease; Echino, echinocandin, HbA1c, haemoglobin A1c; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; ISAV, isavuconazole; L-AMB, liposomal amphotericin B; VRC, voriconazole

was confirmed based on abnormal findings on chest computed tomography (CT) and mycological evidence from lung tissue. In two other cases, the pathogen was identified from tracheobronchial secretions after suggestive findings on the CT. In seven cases diagnosis of lung infection was based on positive culture (5/7, three with suggestive findings on chest CT, one with histology-confirmed brain involvement) or sequencing results (2/7, both without abnormal radiological findings) from bronchoalveolar lavage. Rhino-orbitocerebral and gastrointestinal CAM were both confirmed from respective tissue material, the latter on autopsy.

Pathogen identification to species level was done for eleven cases. Overall, *Rhizopus* spp. was the most prevalent causative pathogen (10/13), *R. microsporus* in seven. *Lichtheimia* and *Rhizomucor* species were identified in two and one cases, respectively. Fungal mixed infection with *Aspergillus* spp. was reported in two cases with pulmonary CAM (case 03, case 06).

Systemic antifungals were administered in twelve cases, whereby liposomal amphotericin B (L-AMB) and isavuconazole either alone or in combination were most frequently used (10/12) (Figure 2). Echinocandins were used as primary treatment in three patients pre-emptively, in two before promptly switch to isavuconazole or voriconazole and in one with post-mortem diagnosis of mucormycosis. In two patients, brain abscess was surgically removed (case 12, case 13).

All-cause mortality was 53.8% (7/13). Mortality rate at day 14 after diagnosis of CAM was 46.2%, the deceased had severe COVID-19 requiring mechanical ventilation and death occurred within 6 weeks after diagnosis of COVID-19 in all cases. Septic shock and multiorgan failure were the main reported causes of death, mucormycosis-attributable death was reported in two cases.

Two centres reported higher prevalence of CAM amongst hospitalised COVID-19 patients (0.67%, 4/596 and 0.58%, 4/691, $P = 1.0$) between January 2020 and June 2021 compared to prevalence of

mucormycosis not associated with COVID-19 (0.0047%, 2/42,518 and 0.001%, 1/89,048, $P = .51$) overall (centre A: OR = 143.6, 95% CI 26.3–785.7, $P < .001$; centre B: OR = 518.5, 95% CI 57.9–4,644.8, $P < .001$). For ICU patients also similar prevalence was reported in both centres for CAM (1.47%, 4/273 and 1.78%, 3/169, $P = .80$) and for mucormycosis not associated with COVID-19 (0.015%, 1/6,454 and 0.005%, 1/19,636, $P = .99$) (centre A: OR = 96.0, 95% CI: 10.7–861.5, $P < .001$; centre B: OR = 354.8, 95% CI 36.7–3,429.1, $P < .001$). In both centres CAM prevalence was higher overall and in ICU COVID-19 patients compared to mucormycosis prevalence overall and in ICU non-COVID-19 patients ($P < .001$ for all comparisons). In a third hospital, prevalence of CAM in ICU COVID-19 patients was slightly lower (0.15%, 1/647) ($P < .05$ for comparison with the other two centres).

4 | DISCUSSION

Our survey identified 13 cases from six tertiary hospitals mainly in patients with severe or critical COVID-19 requiring invasive mechanical ventilation (Figure 1). An association between high incidence of SARS-CoV-2 positive cases per state and reported CAM cases was not found. Limitations in our study and related underreporting as well as unawareness of rare fungal infections and diagnostic challenges in German centres may or may not be reasons for the given distribution of CAM cases. Despite this, evidence suggests that in Germany CAM is rare.

Rhizopus spp. was the most prevalent causative pathogen (10/13), *Lichtheimia* and *Rhizomucor* were identified in the other cases. This distribution of pathogens is in line with overall agents identified from mucormycosis cases recorded at the NRZMyk in 2020 (50% *Rhizopus* spp., 20% *Lichtheimia* and *Mucor* spp., and 10% *Rhizomucor* spp.).²⁰ No CAM related to *Mucor* spp. was

identified in this survey. For Indian cases, species identification is rarely reported.

Diabetes, one of the main global risk factors for mucormycosis, especially in India, where prevalence is high and disease underdiagnosed and often poorly controlled, is also a relevant risk factor for fungal infections in the European Region, where prevalence is increasing amongst all ages.^{21,22} In Germany, poorly controlled diabetes on admission was the sole reported comorbidity in two patients, of whom one developed rhino-orbito-cerebral CAM during corticosteroid administration, noticeable the only reported rhino-orbito-cerebral CAM case in Germany.

Unregulated use of corticosteroids for treating even mild symptoms of COVID-19 was a major accelerator for mucormycosis during the second COVID-19 wave in India.⁶ Corticosteroids used to suppress inflammation have profound impact on human homeostasis, amongst others stimulating gluconeogenesis leading to increased blood glucose levels, which thereby increase the risk for fungal infections. In Germany, in patients diagnosed with CAM before the WHO provided recommendations on the use of corticosteroids in hospitalised COVID-19 patients, corticosteroids were not administered in all patients but if, doses were higher than later recommended.²³ Blood glucose levels should be monitored continuously to achieve glycaemia control and corticosteroid dosages adapted under consideration of the intended benefits.

Other underlying conditions known to predispose for invasive fungal infections were reported for most German CAM cases. These included immunosuppressive therapy for malignancy or organ transplantation, chronic obstructive pulmonary disease, and liver cirrhosis.²¹ These patients were diagnosed with pulmonary mucormycosis. In Germany, pulmonary CAM was the most common clinical presentation, similar to the reported cases from other European countries,¹²⁻¹⁷ which is in contrast to the large case series reported from India, where the vast majority of cases presented with rhino-orbito-cerebral mucormycosis.^{7,24} This may be explained as on the one hand, in Germany and also in other European countries, patients with CAM were more likely immunocompromised and treated for severe or critical COVID-19 in the ICU, putting them at high risk for pulmonary fungal infection, whereas in India most patients who developed CAM had mild or moderately severe COVID-19 and uncontrolled diabetes, which is associated with rhino-orbitocerebral infection.⁸ On the contrary, diagnosis of pulmonary CAM in general is challenging due to non-specific symptoms and radiological findings, particularly in patients with pneumonia and critically ill patients. The reverse-halo sign shown in the chest CT, which may be suggestive of pulmonary mucormycosis, has also been seen in patients with COVID-19 pneumonia unrelated to mucormycosis.²⁵ In critically ill patients, invasive diagnostic procedures may be contraindicated further reducing diagnostic options in those patients to a minimum. In India, diagnosis might have been hampered by shortage of staff and equipment during peak COVID-19 incidence. Whereby rhino-orbital fungal infections may become apparent by visual inspection early on, diagnosis of pulmonary and also gastrointestinal infections may be delayed or not done at all. Assumed,

sample extraction for diagnostics was successful, culture is frequently negative for Mucorales as sporulation fails under normal laboratory conditions and the fungus often does not to grow in culture media due to lack of viable fungi in the extracted, often necrotic tissue. Differentiation of species based on morphology only is not possible.²⁶ This perpetual dilemma results in underestimation of invasive fungal infections also in non-pandemic times as several autopsy studies have shown.^{14,27}

Time between diagnosis of COVID-19 and mucormycosis was less than two weeks in our study. Similar onset time after COVID-19 diagnosis were reported from other centers.^{2,4,13,24,28,29} Benefits of antifungal prophylaxis in patients with COVID-19 must be further evaluated.³⁰

From our data, it is not evident what impact secondary mucormycosis has on the clinical outcome. Considered separately, invasive mucormycosis, ICU stay, mechanically ventilation and severe COVID-19 are all factors associated with high mortality.^{21,31-33} The complexity and synergy of unfavourable factors in the here presented patient group does not allow for the evaluation of the impact on mortality of one factor or the other.

Public health agencies in most countries conduct little or no mycological surveillance with Germany being no exception. Contagious infections with great significance for the public health are collected centrally by the German Robert Koch-Institute, mycoses are not listed for immediate surveillance. German hospitals report main and secondary diagnoses of patients via International Classification of Diseases (ICD) codes for billing and statistical purposes, which are then made available by the Federal Statistical Office (www.destatis.de) upon request in a summarised and anonymised format with a delay of approximately one calendar year. Patient level clinical information are not available but incidence and prevalence might be extracted. Thus, ad hoc information is not available and epidemiological studies largely depend on collaborative actions within networks and societies. In this national outreach, we contacted German centres already actively involved in national mycological societies and research networks and screened the databases of the NRZMyk, which serves as the national reference laboratory for invasive fungal infections. Despite the efforts, it is reasonable to assume that the thirteen CAM cases reported from six hospitals likely represent only part of the relevant patients. To date, no information on the incidence of CAM in Germany is available, only single centre experiences can be used to estimate the national burden. Mucormycosis had a prevalence of 6 in 1,000 hospitalised patients with COVID-19 treated between January 2020 and June 2021 in two centres. In the ICU population in three centres, prevalence of mucormycosis of 7 in 1,000 COVID-19 patients was only slightly higher compared to overall COVID-19 patients, as the majority of CAM cases were diagnosed in critically ill patients. Prevalence of mucormycosis was higher in COVID-19 patients compared to patients with other disorders overall (2 out of 100,000) and in the ICU setting (8 out of 100,000) in two centres. Awareness for fungal infections was generally high in these hospitals allowing valid comparison of prevalence in patients with COVID-19 and other conditions.

4.1 | Limitations

A limited set of clinical information was collected for each patient. Several clinical parameters that may be associated with increased risk of mechanical ventilation, developing mucormycosis or worse outcome including baseline laboratory measures, consecutive blood sugar levels during corticosteroid use, ferritin and zinc levels, and respiratory parameters were not requested.^{7,33-35} A control group of patients with severe COVID-19 without developing mucormycosis for comparison of the clinical outcome was not included in this study due to the heterogeneity of underlying conditions. The uncertain diagnosis of invasive mucormycosis based on the EORTC/MSG definitions in several cases, further hampers the ranking of mucormycosis within the list of life-threatening complications in COVID-19 contributing to worse outcome.

5 | CONCLUSIONS

The role of COVID-19 as a predisposing factor for mucormycosis and how mucormycosis impacts the clinical outcome in patients with severe COVID-19 will become evident only in a larger cohort reflecting the diverse patient populations at risk. Single centre evidence leaves us with the assumption that the risk for mucormycosis in the ICU is higher for severe COVID-19 compared to non-COVID-19 severe conditions. Thus, COVID-19 and associated therapy modalities may expand the catalogue of established risk factors not only in low- or middle-income countries necessitating updated guidelines on an interdisciplinary management of mucormycosis.^{6,36} Increase immunity through vaccination in the population would minimise occurrence of severe courses of COVID-19 and associated critical care and thereby reduce potential risk for fungal infections and other superinfections overall.

CONFLICT OF INTEREST

JSt has received lecture honoraria from Gilead and Pfizer, outside of the submitted work.

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Safety Monitoring Board for Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Shionogi. OAC is chair of the Infectious Diseases Working Party (DGHO), Advisory Committee Member (DGI), Educational Officer (ECMM), Treasurer (ISHAM), Bord of Directors Member (MSG-ERC), Editor-in-Chief for Mycoses (Wiley).

Others do not report conflict of interest.

AUTHOR CONTRIBUTION

Danila Seidel: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Michaela Simon:** Writing-original draft (equal); Writing-review & editing (equal). **Rosanne Sprute:** Writing-original draft (equal); Writing-review & editing (equal). **Matthias Lubnow:** Writing-original draft (equal); Writing-review & editing (equal). **Katja Evert:** Writing-original draft (equal); Writing-review & editing (equal). **Claudius Speer:** Writing-original draft (equal); Writing-review & editing (equal). **Jessica Seeßle:** Writing-original draft (equal); Writing-review & editing (equal). **Elham Khatamzas:** Writing-original draft (equal); Writing-review & editing (equal). **Uta Merle:** Writing-original draft (equal); Writing-review & editing (equal). **Christopher Behrens:** Writing-original draft (equal); Writing-review & editing (equal). **Igor Blau:** Writing-original draft (equal); Writing-review & editing (equal). **Philipp Enghard:** Writing-original draft (equal); Writing-review & editing (equal). **Christian S. Haas :** Writing-original draft (equal); Writing-review & editing (equal). **Joerg Steinmann:** Writing-original draft (equal); Writing-review & editing (equal). **Oliver Kurzai:** Writing-original draft (equal); Writing-review & editing (equal). **Oliver A. Cornely:** Conceptualization (equal); Funding acquisition (equal); Resources (equal); Software (equal); Writing-original draft (equal); Writing-review & editing (equal).

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