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# The clinical characteristics and outcome of mucormycosis among patients with hematology diseases: a systematic and meta-analysis

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**ADMINISTRATIVE INFORMATION**

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**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2023 and was last updated on 17 July 2023.

## INTRODUCTION

**Review question / Objective** We performed a meta-analysis aimed to pool the mortality and described the clinical characteristics of mucormycosis in hematology patients. What are the main risk factors that affected the outcome: (1)the published year (2)the income of the country (3)underlying diseases (4)gender (5)breakthrough infection (6)surgery (7).

**Condition being studied** Mucormycosis is an angio-invasive fungal infection, caused by saprophytic fungi that belong to the order Mucorales. The fungi under Mucorales are ubiquitous, and morphologically appear as broad, aseptate or sparsely septate ribbon-like hyphae. Humans acquire the infection predominantly by inhalation of sporangiospores, occasionally by ingestion of contaminated food or a variety of percutaneous routes. Mucorale has emerged as an increasingly important pathogen during the past decades. This increasement has been particularly evident in patients with diabetes, malignancy, and solid organ or hematological transplantation, while the prominent increasement was found in India and China among patients with uncontrolled diabetes mellitus. During the period of COVID-19, the pooled occurrences of mucormycosis have increased significantly (seven cases per 1000 patients), 50 times higher than that of the highest prevalence recorded background of mucormycosis (0.14 cases per 1000 patients). Virus-induced endothelial dysfunction, hyper-glycaemia, and immune dysfunction following corticosteroid use increased the risk of mucormycosis infections. The clinical presentation of mucormycosis varies according to the anatomical site of involvement including rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated forms [10]. Mucormycosis is diagnosed based on histologic findings or positive culture from affected lesions owing to the lack of validated serologic biomarkers, which might result in delaying the timely treatment.

The first large review of mucormycosis was made by Roden et al.in 2005, including 929 cases published from 1940 to 2003. The pooled overall mortality was firstly reported 44%. More recently, W. Jeong et al. performed a meta-analysis of mucormycosis published from 2000 to 2017. Diabetes mellitus and hematological malignancy(42% of which had acute myeloid leukemia) were the common underlying diseases. Death was reported in 389/851 (46%) patients. Most published data in hematology patients derive from case series and case reports. However, there is not a meta-analysis that described the mortality of mucormycosis focused on hematology patients, and they are almost impossible to be calculable due to the fact that a tiny fraction of the cases was properly diagnosed and documented. In the era of the increasement of hematological stem cell transplantation, the present of aggressive diagnostic approach and new triazole drugs with a broad spectrum of anti-mold activity against both Aspergillus sp. and mucorales, the clinical characteristics and the mortality of mucormycosis changed over time. Therefore, we performed a meta-analysis aimed to pool the mortality and described the clinical characteristics of mucormycosis in hematology patient from January 2000 to December 2022.

## METHODS

**Participant or population** The trials had to deal with at least 5 cases of mucormycosis in patients diagnosed with hematology diseases.

**Intervention** All the hematologic patients diagnosed with mucormycosis.

**Comparator** Not available.

**Study designs to be included** (1) trials had to deal with at least 5 cases of mucormycosis(proven or probable) in patients diagnosed with hematology diseases; (2) the dead rate, the survival rate, or the population of dead and survival groups were reported; (3) published as a full paper in English. When part or all of the patients were involved in more than one publication, only the most complete or most informative study was included in this analysis.

**Eligibility criteria** Case series with fewer than 5 cases of mucormycosis in hematology patients. The microbiologically or pathologically evidence of mucormycosis result from autopsy were excluded. We also excluded animal studies and those published in languages other than English.

**Information sources** PubMed, Embase and Web of Science were used to search for the original articles analyzing Mucormycosis and Hematologic Diseases, by means of keywords variably combined: 'Mucormycoses', 'Mucormycose', 'Mucorales Infection', 'Mucorales Infections', 'Zygomycoses', 'zygomycosis', 'Hematologic Disease', 'Blood Diseases', 'Blood Disease', 'Hematological Diseases', 'Hematological Disease'. The search was from 2000 to 2022-12-30. We also searched for references from the bibliographies of all eligible studies and relevant systematic reviews.

**Main outcome(s)** The mortality of mucormycosis among patients with hematology diseases.

**Quality assessment / Risk of bias analysis** We used the Newcastlee Ottawa Scale (NOS) to assess the quality of the included studies. The scale enables assessment of the quality of three components, namely study selection (score 0e4), comparability (score 0-2), and outcome (0-3). The overall NOS score can range from 0 to 9 (the higher the score better the study).

**Strategy of data synthesis** For the quantitative aggregation of the survival results, we measured the pooled mortality of mucormycosis infection in hematology diseases by using the random effect model depending on obvious heterogeneity with I2>50%, otherwise, the fixed effect model was used. Differences in mortality in the predefined subgroups were assessed using the X2 test. Assessment of publication bias was performed using a funnel plot with Begger's test and Egger's test. A sensitivity analysis was also conducted to test the impact of the outcomes from these eligible studies. We reported the risk difference (RD) of death with 95%CI among combined medical-surgical therapy versus those who were medically managed, treated with multi-drug versus single-drug, disseminate infection versus single site infection, breakthrough infection versus those who were not breakthrough infection, and under mucor-unactive drugs versus under mucor-active drugs as prophylactic or treatment drug before mucormycosis infection. All statistical tests were two sided and differences at $p< 0.05$ were considered statistically significant. Stata Statistical Software (version 15.0 Stata Corp., College Station, TX, USA) was used for all analyses in our analysis.

**Subgroup analysis** The risk difference between subgroups: 1.male versus female, 2.combined medical surgical therapy versus medical therapy alone, 3.dissemination infection versus isolated

infection, 4.breakthrough infection versus those without breakthrough infection,5. combined multi-drug therapy versus single-drug therapy, 6.mucor-unactive drugs versus under mucor-active drugs as prophylactic or treatment drug before mucormycosis infection.

**Sensitivity analysis** Sensitivity analysis investigates the influence of a single study on the overall meta-analysis estimate, which computes the pooled mortality by omitting one study in each turn. The results of sensitivity analysis show whether the studies are convincing and stable. In our analysis, it demonstrated that all data assessing the mortality of mucormycosis in hematology patients were stable.

**Country(ies) involved** China.

**Keywords** outcome, mucor, hematologic patients.

**Contributions of each author**

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