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Systematic Review

Pathogenesis and Oral-Related Factors in Post-COVID-19 Mucormycosis Patients: A Protocol for a Systematic Review of Case Reports

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Abstract

During the COVID-19 pandemic, there was a notable increase in cases of oral mucormycosis, with some researchers linking corticosteroid treatment to immune suppression, potentially increasing susceptibility to this fungal infection. Early oral manifestations may serve as indicators for timely diagnosis. This protocol for a systematic review aims to elucidate the pathogenesis and related factors of post-COVID-19 mucormycosis through the analysis of case reports. We will conduct a comprehensive search of relevant articles, excluding review articles and case series. Bias risk will be assessed using the ROBINS-E tool, and certainty of evidence will be evaluated using the GRADE framework. A narrative synthesis of the data will be performed, focusing on sociodemographic profiles, medical and family histories, diagnostic methods, treatment approaches, and dental relevance.

Keywords: *Oral mucormycosis, COVID-19, Corticosteroids, Pathogenesis, Case reports.*

Introduction

In March 2020, the World Health Organization (WHO) issued a global health alert due to the rapid spread of COVID-19, an emerging coronavirus of the severe acute respiratory syndrome type 2 (SARS-CoV-2). This virus had a profound impact on global mortality rates and quality of life due to its elevated fatality rate. The consequences of this illness, whether immediate or prolonged, were associated with adverse immune reactions, exacerbation of pre-existing cognitive impairments, or the onset of novel pathologies. One such consequence was mucormycosis, also recognized as "black fungus," an infrequent yet severe opportunistic fungal infection.[1-3]

The appearance of mucormycosis became worrisome among individuals recovering from COVID-19, given its escalating occurrence and connection with heightened risks of morbidity and mortality, prompting inquiries into its pathogenesis and related factors within this particular patient cohort. Although comprehensive data regarding the prevalence of mucormycosis were lacking, as of November 8, 2023, the WHO had documented 771,820,937 confirmed COVID-19 cases, including 6,978,175 fatalities.[3-4]

Recent investigations have indicated that the pathogenesis of mucormycosis in post-COVID-19 patients is substantially influenced by immunosuppression and the administration of corticosteroids for treating COVID-19. Dysfunction of the immune system and alterations in microflora may render patients susceptible to colonization by fungi belonging to the Mucorales genus, the principal causative agents of mucormycosis. Furthermore, literature has suggested that mucormycosis often manifests its initial signs and symptoms within the oral cavity, frequently associated with suboptimal oral hygiene. This underscores the significance of exploring oral-related factors in this context.[4-7]

The role of diabetes in the pathogenesis of post-COVID-19 mucormycosis has also been underscored, as it may foster an environment conducive to invasive fungal proliferation. Consequently, investigating the pathogenesis and oral-related factors is imperative to gain a better understanding of this disease's impact on healthcare providers, especially within dentistry, as they will play a pivotal role in promptly identifying and managing oral complications in post-COVID-19 patients.[7-8]

The purpose of this protocol will be to describe the methods of a systematic review that will be used to analyze the pathogenesis and related factors in post-COVID-19 mucormycosis patients from a dental perspective, aiming to provide insights for the development of guidelines facilitating early detection and effective treatment strategies.

Methods

The study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) Statement.[9] A predefined procedure for this systematic review has been developed and registered in the PROSPERO portal under registration number CRD42023476051. The complete record will be accessible at the following URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=476051.

Focused question

What will be the underlying mechanisms and factors in the mouth contributing to the development of mucormycosis in individuals recovering from COVID-19?

Inclusion Criteria and Data Elements

Criteria for inclusion will be determined according to the PICOTS framework.[10] Data elements will be presented based on the assumptions made by the authors. The inclusion criteria will be as follows, population pertain to individuals of any gender and age seeking healthcare services, while groups seeking care are excluded. Regarding intervention, it involves individuals diagnosed with both COVID-19 and mucormycosis, excluding healthy patients. Comparison involves healthy individuals, with no specified exclusions. Outcome criteria cover pathogenesis, related factors, and dental perspectives, excluding unspecified dental aspects. There are no limitations on publication age (time). The study design includes individual case reports, with case series being excluded (study design).

Table 1. Search strategy.

Database	Search strategy
PubMed	("case reports"[Publication Type] OR "case report"[All Fields]) AND (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("mucormycosis"[MeSH Terms] OR "mucormycosis"[All Fields] OR "mucormycoses"[All Fields])) AND ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "covid" [All Fields] OR "covid 19" [MeSH Terms] OR "covid 19" [All Fields])
Google Scholar	"Case report" AND "oral mucormycosis" AND "covid".
DOAJ	(Case report) AND (oral mucormycosis) AND (covid)
NIH Library	"Case report" AND "oral mucormycosis" AND "covid".

Sources of Information, Selection Process, and Search Strategy

The databases PubMed, Google Scholar, DOAJ, and the NIH Library will be searched. Manuscripts from PubMed and Google Scholar will be independently chosen by G.C.V. and M.A.G.R., while G.M.N.R. and M.N.A.O. will review DOAJ and the NIH Library. The selection process will involve an initial filter for relevance of titles, followed by an examination of abstracts based on key terms, and ultimately a review of full-text articles. In cases where inclusion is uncertain, consensus will be reached among Y.L. and K.J.H.R. by using the JBI Critical Appraisal Checklist for Case Reports. There will be no restriction on the age of publications included in the search. The search strategy will incorporate Boolean operators AND and OR, with keyword-based delimitation. Mendeley will serve as the reference management software. Specific search strategies for each database will be outlined in Table 1. We will use the PRISMA 2020 flow diagram for new systematic reviews which include searches of databases and registers only (Figure 1).[11]

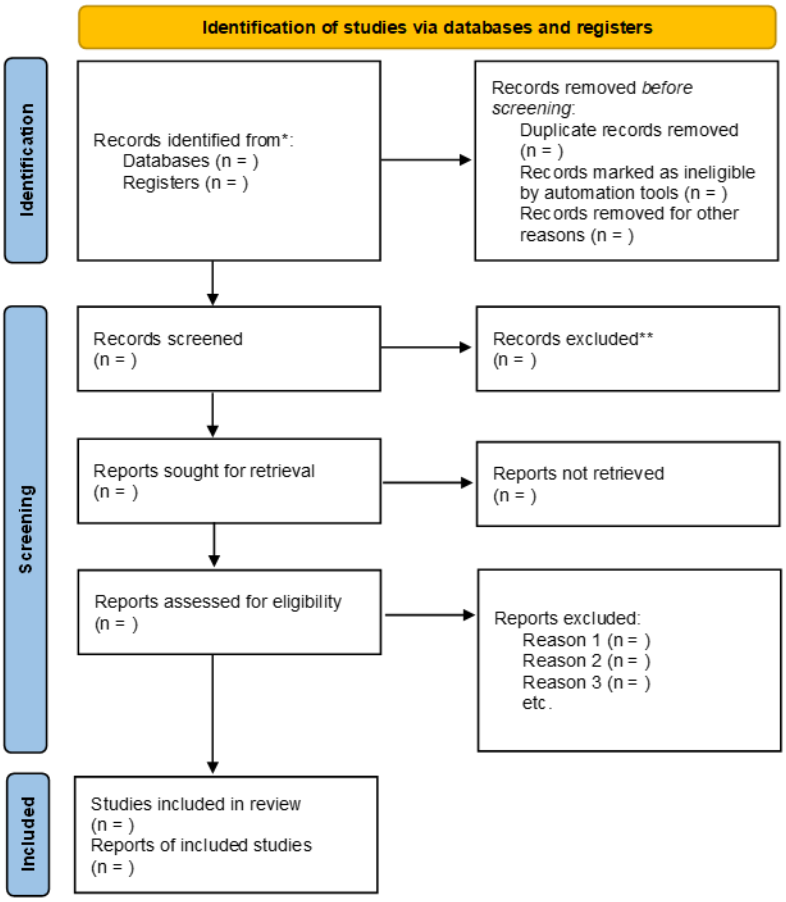

Figure 1. *PRISMA selection flow diagram.*

Assessment of Study Bias and Certainty

The risk of bias will be evaluated using the ROBINS-E tool,[12] and results will be provided for individual manuscripts and overall analysis. Certainty of evidence will be assessed using the GRADE framework.[13] In cases of high or very high risk of bias, or low certainty, inclusion of manuscripts will be discussed among the authors. These procedures will be carried out independently by M.A.G.R. and Y.L., with G.C.V. and G.M.N.R. consulted in case of uncertainties.

Evaluation of Heterogeneity

Clinical variability will be assessed by examining the timing of COVID-19 diagnosis and treatment, patient comorbidities, and mucormycosis treatment. This evaluation will be conducted independently by K.J.H.R. and Y.L., with the remaining authors serving as impartial evaluators.

Data Collection and Synthesis Methods

Data from the included manuscripts will be compiled in an Excel table, detailing author and country, participants' sex and age, COVID-19 diagnosis and treatment, signs and symptoms, comorbidities, diagnostic procedures, treatments, and relevance to dentistry (Table 2). The Synthesis Without Meta-analysis (SWiM) reporting guideline[14] will be used to synthesize the results, as conducting a meta-analysis will not be feasible. A narrative synthesis will then be conducted, categorizing data by sociodemographic profile, medical and family history, diagnostic and treatment methods, and dental relevance. Data collection will be carried out by G.C.V. and M.N.A.O., with verification by an external researcher. Descriptive statistics will be used to calculate averages and standard deviations for age and sex, while percentages will be utilized for other factors. Quantitative results will be presented as percentages, with frequencies expressed as a percentage of the total. All statistical analyses will be performed using SPSS version 24. Ethics approval is not required for this research as it involves analysis of publicly available published documents.

Table 2. Study characteristics table example.

Author and country	Participants sex and age	COVID-19 (age of diagnosis and treatment)	Signs y symptoms at consultation time	Co-morbidities	Diagnosis and diagnostic procedures	Treatments	Intraoral manifestations of the lesion
1st manuscript included							
2nd manuscript included							
3rd manuscript included							
∞ manuscript included							

Conclusions

This systematic review protocol outlines a comprehensive approach to investigate the pathogenesis and oral-related factors contributing to mucormycosis development in post-COVID-19 patients. By analyzing case reports, we aim to provide valuable insights into the mechanisms underlying this fungal infection and its oral manifestations. The synthesis of data from diverse sources will enhance our understanding of the disease progression and inform early detection and treatment strategies, particularly in dental settings. This protocol lays the groundwork for a rigorous and systematic examination of an emerging clinical concern, facilitating evidence-based decision-making in healthcare practice.

Conflict of Interest

Authors declare no conflict of interests.

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