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BASIC RESEARCH:

Clinical, Epidemiological, and Oral-Related Factors in Post-COVID-19 Mucormycosis Patients: A Systematic Review of Case Reports

Factores clínicos, epidemiológicos y orales relacionados en pacientes con mucormicosis post-COVID-19: una revisión sistemática de reportes de casos

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ABSTRACT: Oral mucormycosis has become a significant concern due to increased cases during the COVID-19 pandemic, potentially linked to corticosteroid-induced immune suppression. This study reviews case reports to identify and describe the clinical and epidemiological factors associated with post-COVID-19 mucormycosis from a dental perspective. A comprehensive search of PubMed, Google Scholar, DOAJ, and NIH Library databases yielded 32 relevant case reports from an initial 180. The average age of patients was 53 years, with 21.9% having a confirmed COVID-19 diagnosis one month prior to mucormycosis diagnosis. Corticosteroid use was reported in 65.6% of cases. Common symptoms included pain (65.6%), swelling (21.9%), and ocular pain (12.5%), with Amphotericin B being the predominant treatment (59.4%). Oral manifestations such as maxillary bone exposure (21.9%) and dental abscesses (31.3%) were noted. This study highlights a potential link between corticosteroids and mucormycosis, despite limitations in report consistency and follow-up data, offering valuable insights for clinical management of post-COVID-19 mucormycosis.

KEYWORDS: Mucormycosis; Case reports; COVID 19; Oral medicine; Systematic review; Oral health.

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RESUMEN: La mucormicosis oral se ha convertido en un problema relevante debido al aumento de casos durante la pandemia de COVID-19, posiblemente asociado a la inmunosupresión inducida por corticosteroides. Este estudio revisa reportes de casos con el objetivo de identificar y describir los factores clínicos y epidemiológicos asociados a la mucormicosis post-COVID-19 desde una perspectiva odontológica. Se realizó una búsqueda exhaustiva en las bases de datos PubMed, Google Scholar, DOAJ y NIH Library, obteniéndose 32 reportes de casos relevantes a partir de un total inicial de 180. La edad promedio de los pacientes fue de 53 años, y el 21.9% presentó un diagnóstico confirmado de COVID-19 un mes antes de la detección de mucormicosis. El uso de corticosteroides se reportó en el 65.6% de los casos. Los síntomas más frecuentes fueron dolor (65.6%), tumefacción (21.9%) y dolor ocular (12.5%), siendo la anfotericina B el tratamiento más utilizado (59.4%). Se observaron manifestaciones orales como exposición del hueso maxilar (21.9%) y abscesos dentales (31.3%). Este estudio resalta una posible relación entre el uso de corticosteroides y la mucormicosis, a pesar de las limitaciones en la consistencia de los reportes y la escasa información de seguimiento, proporcionando información valiosa para el manejo clínico de la mucormicosis post-COVID-19.

PALABRAS CLAVE: Mucormicosis; Reportes de casos; COVID-19; Medicina oral; Revisión sistemática; Salud bucal.

INTRODUCTION

In March 2020, the World Health Organization (WHO) issued a global health alert due to the rapid spread of COVID-19, a novel coronavirus of the severe acute respiratory syndrome type 2 (SARS-CoV-2) (1). This virus significantly impacted global survival rates and quality of life due to its high mortality rate. The effects of this disease, whether immediate or long-term, have been linked to adverse immune responses, exacerbation of pre-existing cognitive deficits, or the induction of new pathologies. One such outcome is mucormycosis, also known as "black fungus," a rare but severe opportunistic fungal infection (2).

The emergence of mucormycosis has become a concern among patients recovering from COVID-19, with its increasing incidence and association with a high risk of morbidity and mortality, raising questions about its pathogenesis and related factors in this specific patient group (3). Although there are no comprehensive data on the prevalence of mucormycosis, as of November 8, 2023, the WHO has reported 771,820,937 confirmed cases of COVID-19, including 6,978,175 deaths (4).

Recent studies suggest that the pathogenesis of mucormycosis in post-COVID-19 patients is significantly influenced by immunosuppression and the use of corticosteroids in treating COVID-19 (5). Immune system dysfunction and altered microflora may predispose patients to colonization by fungi of the genus Mucorales, the primary causative agents of mucormycosis (6). Moreover, the literature indicates that mucormycosis often presents its initial signs and symptoms in the oral cavity, commonly associated with poor oral health. This underscores the importance of studying oral-related factors in this context.

The role of diabetes in the pathogenesis of post-COVID-19 mucormycosis has also been emphasized (7), as it may create an environment conducive to invasive fungal growth (8, 9). Given this, it is crucial to study the pathogenesis and oral-related factors to better understand

this disease's impact on healthcare professionals, particularly in dentistry, since they play a critical role in early identification and management of oral complications in post-COVID-19 patients.

The objective of this systematic review is to identify and describe the clinical and epidemiological factors associated with post-COVID-19 mucormycosis from a dental perspective, aiming to support early diagnosis and treatment planning.

METHODS

PROTOCOL AND REGISTRATION

The research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data PRISMA-IPD Statement (10). An a priori protocol for this systematic review was developed and registered in the PROSPERO portal (11) with registration number CRD42023476051. The full record can be accessed at the following URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=476051

FOCUSED QUESTION

What are the pathogenetic mechanisms and oral-related factors contributing to the development of mucormycosis in post-COVID-19 patients?

ELIGIBILITY CRITERIA AND DATA ITEMS

Eligibility criteria were determined according to the PICOTS framework (12). Data items are presented based on the assumptions made by the authors. Detailed information can be found in Table 1.

INFORMATION SOURCES, SELECTION PROCESS, AND SEARCH STRATEGY

The databases PubMed, Google Scholar, DOAJ, and the NIH Library were searched from June to September 2023. Manuscripts from PubMed and Google Scholar were independently selected by G.C.V. and M.A.G.R., while G.M.N.R. and M.N.A.O. reviewed DOAJ and the NIH Library. The selection process involved an initial filter for title relevance, followed by an abstract analysis based on key terms, and ultimately a full-text review. In cases where the inclusion was uncertain, consensus was reached among J.A.H.M. and M.L.C.L. by employing the JBI Critical Appraisal Checklist for Case Reports (13). There was no restriction on the age of publications included in the search. The search strategy incorporated the AND and OR Boolean operators, with keyword-based delimitation. Mendeley (14) was used as the reference management software. Specific search strategies for each database are outlined in Table 2.

Study Risk of Bias and Certainty Assessment

The risk of bias was assessed using the ROBINS-E tool (15), and results were provided for individual manuscripts and overall analysis. Certainty of evidence was evaluated using the GRADE framework (16). In cases of high or very high risk of bias, or low certainty, manuscript inclusion was discussed among the authors. These procedures were performed independently by M.A.G.R. and M.L.C.L., with G.C.V. and G.M.N.R. consulted in case of doubts.

HETEROGENEITY ASSESSMENT

Clinical heterogeneity was assessed by examining the timing of COVID-19 diagnosis and

treatment, patient comorbidities, and mucormycosis treatment. This assessment was conducted independently by J.A.H.M. and M.L.C.L., with the remaining authors serving as impartial evaluators.

DATA COLLECTION PROCESS AND SYNTHESIS METHODS

Data from the included manuscripts were 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 dental relevance. Synthesis Without Meta-analysis (SWiM) (17) reporting guideline was used as a guide in the synthesis of results because conducting a meta-analysis was not feasible. A narrative synthesis was then conducted, grouping data by sociodemographic profile, medical and family history, diagnostic and treatment methods, and dental relevance. Data collection was carried out G.C.V. and M.N.A.O. with verification by a researcher external to the project.

In all cases, descriptive statistics were used to calculate averages and standard deviations for age and sex, while percentages were used for other factors. For quantitative results, percentages were calculated, with frequencies presented as a percentage of the total. All statistical analyses were conducted using SPSS version 24.

Table 1. Eligibility criteria and data items.

PICO element	Inclusion and exclusion criteria	Data item
P Population	Inclusion: Men or women of all ages. Exclusion: Groups of men or women.	User who comes to the health service with a request for care
I Intervention	Inclusion: Have a confirmed diagnosis of COVID-19 and mucormycosis. Exclusion: Healthy patients.	Confirmed diagnosis of COVID-19 by PCR or any other method and confirmed diagnosis of mucormycosis by histopathological, radiographic or any other method.
C Comparison	Inclusion: Healthy patients. Exclusion: None.	Users who do not seek health services and do not have a demand for care.
O Outcome	Inclusion: Pathogenesis, related fac-tors and dental perspective. Exclusion: Pathogenesis, related fac-tors and unstated dental perspective.	Timing of COVID-19 diagnosis and treatment, patient comorbidities, surgical and pharmacological treatment, diagnostic methods and dental relationship of the disease.
T Time	Inclusion: No age limitation of publication. Exclusion: None.	Considered age of publications included
S Study design	Inclusion: Individual case report. Exclusion: Case series.	Type of scientific publication included

Table 2. Search strategy.

Database	Search strategy	Articles retrieved
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 "mu-cormycosis"[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]).	53
Google Scholar	"case report" AND "oral mucormycosis" AND "covid".	111
DOAJ	"(case report) AND (oral mucormycosis) AND (covid)".	13
NIH Library	"case report" AND "oral mucormycosis" AND "covid".	3

RESULTS

STUDY SELECTION

The literature search yielded 180 manuscripts. After eliminating duplicates, 155 articles remained. Subsequent exclusions were based on title and abstract relevance, yielding 83 excluded articles. An additional 19 were excluded during the full-text analysis for not presenting post-COVID-19 mucormycosis cases. Finally, 53 articles were analyzed for eligibility, of which 32 were included in the final synthesis of results (18-43). Detailed information on the selection process is shown in Figure 1.

RESULTS OF INDIVIDUAL STUDIES

Of the 32 case reports included, 31 were sourced from PubMed, with the remainder from Google Scholar. Geographically, 22 studies were conducted in India (18, 20-21, 25-28, 30-34, 38-44), five in the USA (19-20, 29), two in Iran (36, 38), and one each in Pakistan (23), Greece (24), and Korea (35). The earliest study was from 2021, with the most recent from 2023. All were published in English. The synthesis of results is presented below, with detailed information in Table 3.

SOCIODEMOGRAPHIC PROFILE OF THE POPULATION AND FAMILY HISTORY

The average age of participants was 53 years (SD=13.7). The predominant sex was male, accounting for 80.6% (26/32) of the cases (18-25, 28-34, 37-41, 43). Only one case report (3.12%) involved a deceased patient (39). Regarding family history, 25% (8/32) of the cases reported diabetes (19, 23-27, 29-33, 35, 39, 41-43), while 15.6% (5/32) reported hypertension (20, 23, 30, 35, 40). These were the only comorbidities noted among the participants.

COVID-19 TREATMENT AND DIAGNOSIS DATE

Of the total manuscripts, 21.9% (7/32) had a confirmed diagnosis of COVID-19 one month prior to medical consultation (18, 31, 33, 36), 18.8% (6/32) at the time of consultation (19, 21, 29, 34, 38, 44), and another 18.8% (6/32) had been diagnosed three months prior to consultation (20, 24, 26, 32, 37, 42). Concerning COVID-

19 treatment, 65.6% (21/32) reported the use of corticosteroids like dexamethasone and methylprednisolone (19-24, 26, 29, 31-34, 37-40, 43-44). Other treatments included antiparasitic drugs like ivermectin (33, 45), oxygen therapy (22), and antiviral drugs like remdesivir (38).

MUCORMYCOSIS SIGNS AND SYMPTOMS, DIAGNOSTIC PROCEDURE, AND TREATMENT

Pain was the most common symptom, found in 65.6% (21/32) of the cases (18-20, 22-23, 26, 28, 31, 33-35, 42-44, 46), followed by swelling at 21.9% (7/32) (18, 20, 33-34, 41), cough at 12.5% (4/32) (19, 32, 38, 40), and ocular pain at 12.5% (4/32) (27, 29, 42, 44). In terms of diagnostic procedure, 100% (32/32) of the cases analyzed reported using incisional biopsy, often supplemented with MRI, CBCT, or histopathological analysis. Amphotericin B was the predominant pharmacological treatment, used in 59.4% (19/32) of the cases (18-20, 22, 27-29, 31-40, 44, 45), followed by posaconazole utilized in 12.5% (4/32) (21-22, 30, 33). Additionally, all cases underwent surgical debridement.

ORAL RELEVANCE

Only 6.25% (2/32) of the case reports mentioned visiting a dentist as the first point of clinical care, with subsequent referral to the appropriate medical service. Among the oral manifestations found in the analyzed cases were maxillary bone exposure in 21.9% (7/32), difficulty in swallowing in 25% (8/32) , dental mobility in 15.6% (5/32) (20-21, 24, 31, 41), dental abscesses in 31.3% (10/32) (18, 20, 24, 26, 27, 29, 37, 43-44), previous endodontic treatment in 6.3% (2/32) (20, 35), epithelial changes in the hard palate in 12.5% (4/32) (19-20, 28, 31), and periodontitis in 9.4% (3/32) (18, 24,31). Only in 6.25% of the cases did the proposed treatment after mucormycosis include dental interventions, such as partial dental prostheses, endodontic treatments, or ocular prostheses (35).

RISK OF BIAS IN STUDIES

Overall analysis of risk of bias revealed that 81.4% (26/32) of manuscripts had low risk, 9.3% (3/32) had some concerns, and 9.3% (3/32) had high risk. Detailed information can be found in supplementary data.

CERTAINTY OF EVIDENCE

Overall certainty of evidence was rated at moderate, indicating a moderate level of evidence that mucormycosis may be a manifestation in post-COVID-19 patients. Further details can be found in the supplementary material.

HETEROGENEITY ASSESSMENT

The authors reported reduced heterogeneity due to the following factors: Out of the total manuscripts, seven did not specify the timing of the COVID-19 diagnosis, and ten did not provide information about the treatment for COVID-19. Regarding comorbidities, eight manuscripts omitted this information, and three case reports did not mention whether oral cavity structures were examined as part of the diagnostic procedure. However, all case reports indicated the treatment used for mucormycosis.

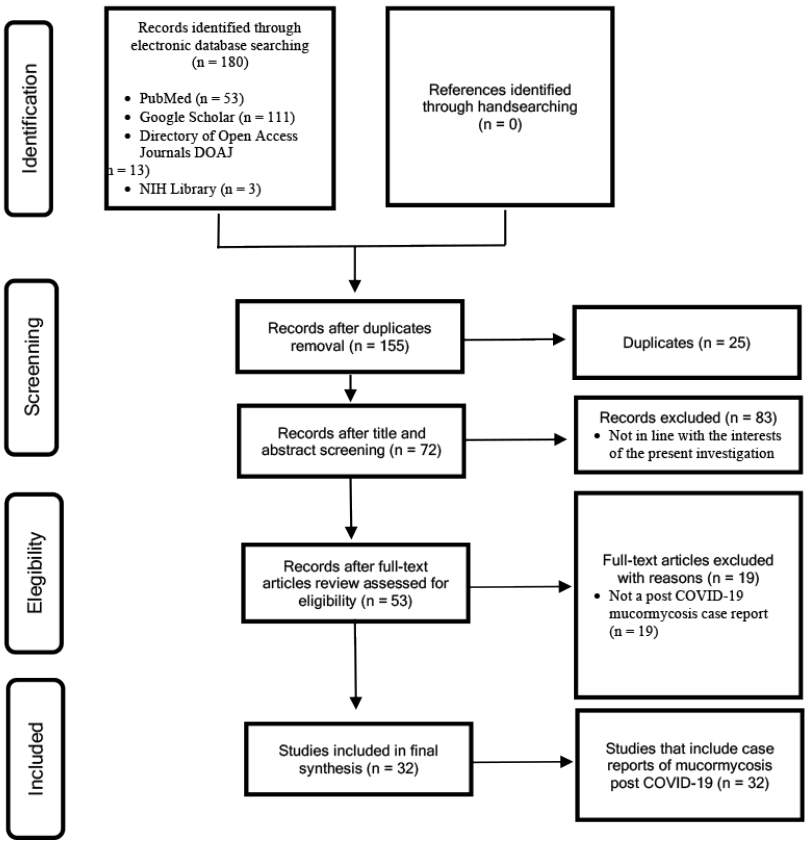

Figure 1. PRISMA selection flowchart.

Table 3. Study characteristics.

Author and country	Participants sex and age	COVID-19 (age of diagnosis and treatment)	Signs y symptoms at consultation time	Comorbidities	Diagnosis and diagnostic procedures	Treatments	Intraoral manifestations of the lesion
Agarwal, *et al.* (18) 2023, India	Men 48 years old	Dx: 1-month prior consultation Tx: Not declared	Plaint of pain and swelling in the right maxillary front tooth region	Not declared	Dx: Mucormycosis Netic resonance imaging (MRI).	Amphotericin B	Presemce of periodontal absces in the lesión area
Alekseyev, *et al.* (19) 2021, USA	Men 41 years old	Dx: At the moment of consultation Tx: Steroids and hydroxychloroquine	Loss of taste Cough Deep aching pain in nose that radiated down to the throat	Diabetes mellitus type 1	Dx: Mucormycosis Idement demonstrated evidence of mucormycosis. Subsequently, the patient was imaged with a CT scan and magnetic resonance imaging (MRI)	Amphotericin B	Black eschar in palate
Alramadha, *et al.* (20) 2023, USA	Men 47 years old	Dx: 3 months prior consultation Tx: Systematic corticosteoids	Swelling of the anterior maxilla and tooth mobility of several months dur	Not declared	Dx: Hinocerebral mucormycosi Eam computed tomography systems (CBCT) Incisional biopsy	Pharmacological treatment not declared Surgical debridement	Presence of endodontic treatment in the lesion area
Alramadhan, *et al.* (20) 2023, USA	Men 30 years old	Dx: 4 months prior consultation Tx: Not declared	Chief complaint of significant mobility of several maxillary teeth	Not declared	Dx: Ucormycosis infection Eam computed tomography systems (CBCT) Incisional biopsy	Amphotericin B	Dental mobile Draining fistula
Ambereen, *et al.* (21) 2021, India	Male 39 years old	Dx: At the moment of consultation Tx: Dexamethasone	Complaints of numbness of left side lower lip	None	Dx: mucormycosis Histopathological examination	Posaconazole Minocycline	Dental mobility
Arora, *et al.* (22) 2023, USA	Women 72 years old	Dx: Not declared Tx: Supplementary oxygen, intravenous antibiotics, and corticosteroids	Complaints of pain in the maxilla for 15 days and associated difficulty in swallowing	Not declared	Dx: Gestive of mucormycosis associated with bacterial superinfection Nebeam computed tomography	Amphotericin-B Ceftriaxone Amikacin Repaglinide Posaconazole	Alveolar bone exposure Loss of dental pieces at the site of the lesion
Arshadm, *et al.* (23) 2022, Pakistan	Men 56 years old	Dx: 4 months prior consultation Tx: steroids	Vague Facial pains Discomfort and tooth loosening	Diabetes type not declared and hypertension	Dx: Teomyelitis of maxilla which was later on proved by histopathol-ogy as actinomycotic oste-omyelitis. Clinical discussion: A saprophytic fungus HOPG and a CT scan of hi	Not declared	Multiple tooth extractions involving the superior and inferior alveolar arches.
Artopoulou, *et al.* (24) 2022, Greece	Men 53 years old	Dx: 3 months prior consultation Tx: Corticosteroids	Persistent pain of the maxilla accompanied by teeth loosening	Diabetes type not declared and hyperlipidemia	Dx: Ucormycosis induced osteomielitis Rx and Histopathologic evaluation	Isavuconazole	The presence of generalized periodontitis, severe mobility of dental pieces, and discharge of pus in the gingival sulcus

Author and country	Participants sex and age	COVID-19 (age of diagnosis and treatment)	Signs y symptoms at consultation time	Comorbidities	Diagnosis and diagnostic procedures	Treatments	Intraoral manifestations of the lesion
Aswin, *et al.* (25) 2022, India	Men 78 years old	Dx: 5 months prior consultation Tx: not declared	Pain and sensitivity in the upper front and back tooth region Difficulty in speech, mastication	Diabetes type not declared	Dx: Abeculae of necrotic bone with numerous fungal organisms with big nonseptate hyphae branching at obtuse angles Incisional biopsy and histopathological tissue processing	Surgical	Superficie maxilar Rough and sensitive
Bhanumurthy, *et al.* (26) 2021, India	Women 45 years old	Dx: 3 months prior consultation Tx: corticosteroids	Complaint of pain and pus discharge for the past 12 days in the left lower jaw region	Diabetes type not declared	Dx: Egmental osteotomy and surgical debridement of the site. Orthopantomogram Gnetic resonance imaging Hystopathological examination	Pharmacological treatment not declared Segmental osteotomy Surgical debridement of the site	Pain and discharge of pus in the area of the lesion
Bhattacharyya, *et al.* (20) 2023, India	Female 65 years old	Dx: Two months prior consultarion Tx: Meropenem, oseltamivir, Methylprednisolone and Dexamethasone.	Complain of ulceration in her right palate region	Diabetes type not declared and hypertension	Dx: mucormycosis Histopathological examination	Amphotericin B	Need of palate reconstruction
Chakraborty, *et al.* (27) 2022, India	Women 38 years old	Dx: 2 months prior consultation Tx: not declared	Chief complaint of tooth mobility in the upper left posterior region of the jaw with pain in the left eye	Diabetes type not declared	Dx: On-septate hyphae, which are consistent with mucormycosis Blood examination, biopsy, and computed tomography (CT)	Ketoconazole Amphotericin	Multiple irregular ulcers and discharge of pus at the site of the lesion
Dahihandekar, *et al.* (28) 2022, India	Men 60 years old	Dx: 5 months prior consultation Tx: not declared	Chief complaint of loss of esthetics Missing upper teeth	Not declared	Dx: Mucormycosis Not declared	Surgical Amphotericin B	Wide and rigid sur-face on the hard palate
Deek, *et al.* (29) 2022, USA	Men 75 years old	Dx: At the moment of consultation Tx: dexamethasone and daily and convalescent plasma treatment	Left eye conjunctivitis with yellow crusting	Diabetes type II and coronary artery disease	Dx: Mucor infection Cranial CT sca	Surgical Amphotericin B	Abscesses in the area of the lesion
Gb, *et al.* (30) 2023, India	Men 52 years old	Dx: Not declared Tx: not declared	History of fever	Diabetes type not declared and hypertension	Dx: Mucormycosis Incisional biopsy	Posaconazole	Necrosed bone in the upper right alveolar, Loss of dental pieces
Gupta D & Dosi. (31) 2021	Men 58 years old	Dx: 1 month prior consultation Tx: steroids	Pain in the right maxillary quadrant	Diabetes type not declared	Dx: Mucormycosis Cone beam computed tomography (CBCT)	Amphotericin B	Raphe palatal with cardinal signs of inflammation
Gupta D & Dosi. (31) 2021, India	Men 60 years old	Dx: Not declared Tx: oxygen and steroids	Pain and mobility in maxillary	Diabetes type not declared	Dx: Mucormycosis Cone beam computed tomography (CBCT)	Debridement Amphotericin B	Gingival enlargement and dental mobility

Author and country	Participants sex and age	COVID-19 (age of diagnosis and treatment)	Signs y symptoms at consultation time	Comorbidities	Diagnosis and diagnostic procedures	Treatments	Intraoral manifestations of the lesion
Ingle, *et al.* (32) 2022, India	Men 47 years old	Dx: 3 months prior consultarion Tx: corticosteroids	Fever Cough Shortness of breath Loss of taste Smell sensation	Diabetes type 2	Dx: Invasive sinonasal mucor-mycosis with concomitant plexiform ameloblastoma was made Microscopic examination	Amphotericin B	Palatal erythema, bone defects in the alveolar process
Jawanda, *et al.* (45) 2021, India	Men 70 years old	Dx: 4 months prior consulta-tion Tx: steroids	Chief complaint of pain in the right side maxillary region	Diabetes type 2	Dx: Mucormycosis, actinom-ycosis along with Candi-diasis leading to Maxillary Osteomyelitis Histopathological examination	Posaconazole Clindamycin	Dental loss, denuded mucosa with necrotic bone, oroantral fistula. Superficie rugose
Jawanda, *et al.* (50) 2022, India	Male 70 years old	Dx: Four months prior consultarion Tx: Ivermectin, Remdes-vir, and Tocilizumab	Complaint of pain Noticed denuded bone over the right maxillary alveolar ridge region	Dyabetes type 2	Dx: Osteomyelitis of the maxilla secondary to Mucor-mycosis Histopathological examination	Posaconazole Clindamyn Amphotericin B	Dry mouth or xero-stomia that might predispose the individ-ual to develop various oral infections
Jawanda, *et al.* (33) 2023, India	Men 50 years old	Dx: 1.5 months prior consultation Tx: steroids	Slow-growing swelling Continuous pain on the left side of his face	Diabetes type not declared	Dx: Spergillus along with Mu-cormycosis) Computerised tomography (CT) Scan of para-nasal sinus (PNS) Eviewing clinical, radio-graphic, and histopathologi-cal findings	Oriconazole Posaconazole	Gross facial asymetry
Kanaparti, *et al.* (34) 2022, India	Men 51 years old	Dx: At the moment of consultation Tx: steroids	Pain and swelling on the left side of the face	Not declared	Dx: Mucormycosis Orthopantomogram Nasal endoscopy Mputed tomography scan MRI brain and orbit (T1W-imaging)	Mphotericin B	Pain in dental pieces of the affected region
Kang, *et al.* (35) 2022, Corea	Men 37 years old	Dx: 2 weeks prior consul-tation Tx: not declared	Persistent pain Sudden increase in the mobility of the right second premolar and molar	Diabetes type 2 and hhypertension	Dx: Mu-cormycosis Histopathological examination	Amphotericin B)	Root canal treatment and serial extraction of the right maxillary first premolar and first molar.
Kankam, *et al.* (36) 2022, Iran	Women 58 years old	Dx: 1 month priorcon-sultation Tx: not declared	Week of confusion, dysar-thria, and stupor	Not declared	Dx: Necrotic foci with numerous branching fungal hyphae with acute angle branching Pathological examinatio	Amphotericin B Voriconazole	No declared

Author and country	Participants sex and age	COVID-19 (age of diagnosis and treatment)	Signs y symptoms at consultation time	Comorbidities	Diagnosis and diagnostic procedures	Treatments	Intraoral manifestations of the lesion
Khoshkhou, *et al.* (37) 2023, Iran	Men 37 years old	Dx: 3 months prior consultation Tx: corticosteroids	Complaining about mobility of the upper teeth and purulent discharge within 1 month ago	None	Dx: Mucormycosis Histopathologic analysis	Amphotericin B Levofoxacin Beclomethasone	Periodontal abscess with purulent discharge and necrosis of maxillary bo
Maini, *et al.* (38) 2021, India	Men 38 years old	Dx: At the moment of consultation Tx: Remdesivir, methylprednisolone, dexamethasone	High grade fever Body ache Cough Shortness of Breath	None	Dx: mucormycosis Magnetic Resonance Imaging Functional endoscopic	Remdesivir IV Methylprednisolone Dexamethasone Surgical debridement Amphotericin B	Not declared
Mehta S & Pandey A. (39) 2020, Rhino-India	Men 60 years old Dead reported	Dx: At the moment of consultation Tx: Dexamethasone	Severe breathlessness Pyrexia Tachypnea Generalized malaise	Diabetes type not declared	Dx: Invasive fungal infection likely mucormycosis Clinical picture and MRI	Eropenem Vancomycin Amphotericin B	Not declared
Patil, *et al.* (40) 2022, India	Male 86 years old	Dx: 12 months prior consultation Tx: steroids, methylprednisolone	Cough Shortness Loss of appetite Weight loss Weakness Myalgia	Hypertension	Dx: mucormycosis	Amphotericin B	Dry mouth, breath shortness
R R, *et al.* (44) 2021, India	Men 59 years old	Dx: At the moment of consultation Tx: oxygen, remedisvir and steroids	Pain in the left cheek, eye, and head	Not declared	Dx: Idual rhino-orbital mucormycosis Hystopathological examination	Amphotericin B	Periodontal abscess
Ramani, *et al.* (41) 2022, India	Men 41 years old	Dx: 20 days ago consultation Tx: not declared	Tad facial swelling Blackish green nasal discharge within few days of being hospitalise	Diabetes type 2	Dx: Cronic invasive aspergillosis with fulminant mucormycosis Istopathological examination	Isolation facility	Dental mobility
Sneha, *et al.* (42) 2023, India	Women 50 years old	Dx: 3 months before consultarion Tx: Not declared	Right-sided facial pain	Diabetes type not specified	Dx: Mucormycosis Incisional biopsy	Posaconazole Surgical procedure	Total right maxillectomy treated with rehabilitation using a cast partial denture
Upadhyay, *et al.* (43) 2021, India	Men 39 years old	Dx: Not declared Tx: steroids	Complaining of pain Mobility in the teeth of the upper jaw region	Diabetes type not declared	Dx: Ost-COVID oral mucormycosis The tissues/pus samples from the lesions were analyzed by direct microscopy and culture	Surgical debridement of the left maxilla Bullectomy and left ethmoidectomy	Pus discharge

DISCUSSION

The objective of this systematic review was to summarize the pathogenetic mechanisms and related factors in post-COVID-19 mucormycosis patients from a dental perspective. Most studies were conducted in India, with male participants predominantly over the age of 50, many of whom had diabetes and hypertension and had suffered from COVID-19 one month prior to consultation. More than half were treated with corticosteroids to combat COVID-19 infection, and the majority were treated with amphotericin B to address mucormycosis. However, the incidence of oral manifestations was relatively low.

These findings align with Al-Tawfiq *et al*. (47), who identified India as having the most literature on mucormycosis and highlighted the role of diabetes and corticosteroid therapy in the pathogenesis of mucormycosis in post-COVID-19 patients. The mean age found in this review is similar to that reported by Selarka *et al*. (48), though it contrasts with the observation that patients in this review were diagnosed with COVID-19, on average, 12 days prior to medical consultation.

Additionally, this review revealed that ocular pain was a common symptom among mucormycosis patients, which contrasts with previous findings by Sen *et al*. (49), who described it as a manifestation of COVID-19. In terms of oral manifestations, literature supports these observations, with other studies emphasizing the role of dentists in identifying such signs (14, 15).

A major strength of this study is that it summarizes the data from a holistic and multidisciplinary perspective, providing insights into a co-infection related to a recently emerged disease. The primary limitations include the scarcity of literature, incomplete reporting of dental treatments, a lack of exploration of oral cavity structures, and a general absence of follow-up data in the analyzed manuscripts. Moreover, given that this is a systematic review of case reports, caution should be exercised when generalizing the findings.

Despite the comprehensive review, this study has limitations. First, the included case reports vary in quality, with a significant proportion of reports being at risk of bias, particularly those with incomplete clinical data. Furthermore, the lack of long-term follow-up data in many cases hinders the ability to draw firm conclusions about the prognosis of mucormycosis in post-COVID-19 patients.

Additionally, the heterogeneity of patient profiles, including differences in comorbidities, treatments, and diagnostic techniques, presents challenges in interpreting the findings. While the synthesis of data using descriptive statistics provided a broad overview, a more robust meta-analysis could have offered a clearer understanding of the associations between treatment variables and clinical outcomes.

The results of this systematic review can guide clinical decision-making in healthcare professionals managing post-COVID-19 mucormycosis patients. Additionally, this underscores the need for further research to address the gaps in long-term follow-up data and investigate the role of other potential risk factors, such as the use of antiviral drugs and oxygen therapy, in the development of mucormycosis. Additionally, clinical trials and cohort studies are needed to validate the findings of this review and establish clearer guidelines for managing mucormycosis in post-COVID-19 patients.

CONCLUSION

With moderate certainty of evidence, this systematic review suggests a potential link between corticosteroid treatment for COVID-19 and an increased risk of developing mucormycosis. The presence of oral manifestations, such

as maxillary bone exposure, dental mobility, and dental abscesses, may serve as early diagnostic indicators, emphasizing the role of dental professionals in early detection and management.

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