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Orofacial Mycoses in Coronavirus Disease-2019 (COVID-19): A Systematic Review

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ABSTRACT

Objectives: Studies reviewing orofacial mycoses in coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome 2 (SARS-CoV-2) infection are sparse. Here we review the major oral and maxillofacial mycoses of COVID-19, the associated comorbidities, and the probable precipitating factors.

Methods: English-language manuscripts published between March 2020 and October 2021 were searched using PubMed, OVID, SCOPUS, and Web of Science databases, using appropriate keywords.

Results: We identified 30 articles across 14 countries, which met the inclusion criteria of PRISMA guidelines. These yielded a total of 292 patients with laboratory-confirmed COVID-19, 51.4% (n = 150) of whom presented with oral and maxillofacial fungal infections, mainly comprising candidosis, mucormycosis, and aspergillosis. *Candida* infections were the most prevalent, present in 64% (n = 96), followed by mucormycosis, and only a single case of aspergillosis was noted. Oral and maxillofacial mycoses were predominantly seen in those with comorbidities, especially in those with diabetes (52.4%). Oral mucormycosis was noted in 8.6% (n = 13) and mainly manifested on the hard palate. An overall event rate of oral/maxillofacial mucormycosis manifestation in patients with COVID-19 with diabetes mellitus type 1/2 was about 94% (49/52; 95% confidence interval, 0.73%-0.89%), implying a very high association between diabetes mellitus and the latter condition. All fungal infections appeared either concurrently with COVID-19 symptoms or during the immediate recovery period.

Conclusions: SARS-CoV-2 infection–related immunosuppression, steroid therapy, as well as comorbidities such as diabetic hyperglycemia appear to be the major predisposing factors for the onset of oral and maxillofacial mycoses in patients with COVID-19 across all age groups.

Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a wide range of opportunistic bacterial and fungal coinfections.[1] The triad of the most

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common secondary oral fungal coinfections seen in COVID-19 comprises candidosis, mucormycosis, and aspergillosis.[2]

Candida species are generally found as oral commensals in approximately one-half of the general population. They metamorphose into opportunistic pathogens when adverse conditions supervene, as in SARS-CoV-2 infection, causing both localised and systemic infections.[3] COVID-19 itself and/or the associated contributory factors including corticosteroid therapy, lymphocytopenia, mechanical ventilator support, and other localised factors such as poor oral hygiene, xerostomia, and denture-wearing appear to favour *Candida* proliferation in the oral cavity.[4]

On the contrary, mucormycosis (previously called zygomycosis) is an uncommon, angio-invasive disease caused by the fungi belonging to the group of molds called mucormycetes. The most common species that cause mucormycosis are *Mucor* and *Rhizopus* species.[5] They are rarely isolated in health from the oral cavity, and their usual transmission mode is through inhalation of fungal spores common in air and dust.[6] Recent data suggest a number of possible reasons that facilitate germination of mucorales spores in patients with SARS-CoV-2 infection. These include hypoxic conditions, diabetes-related conditions, and/or steroid-induced hyperglycemia and ketoacidosis, immune suppression, and several other risk mediators such as prolonged hospitalisation and mechanical ventilation.[7-9] In addition, numerous reports of oral and maxillofacial mucormycosis in patients with COVID-19, particularly from the Indian subcontinent, with devastating outcomes leading to blindness are now available.[10] Recently, Singh et al[7] in a comprehensive review of oral and maxillofacial mucormycoses reported more than 100 such cases in patients with COVID-19.

The last of the COVID-19–associated triad of common oral and maxillofacial mycoses is aspergillosis. Some studies note that as many as 15% of patients with COVID-19 hospitalised in an intensive care unit experience *aspergillus* infection.[11] For instance, a German report observed COVID-19–associated invasive pulmonary *aspergillosis* in 5 of 19 (26.3%) patients with moderate to severe acute respiratory distress syndrome.[12]

Despite the relative commonality of oral and maxillofacial mycoses in COVID-19, there are no systematic reviews, to our knowledge, that specifically address the prevalence or aetiopathogenesis of these diseases, and there is a need for clinically relevant information. Therefore, the aim of this systematic review was to identify the prevalence, aetiopathogenesis, oral and maxillofacial manifestations, and management these infections either directly linked to COVID-19 per se or secondary to their treatment protocols.

Methods

Data sources

Three reviewers (L.P.S., K.S.F., and H.C.N.) executed an electronic data search using PubMed via OVID, SCOPUS, and Web of Science databases for the English-language manuscripts. Published reports were accessed between March 1, 2020, and October 1, 2021, to identify case series, observational studies, or case reports.

Study selection

Inclusion criteria

a. *Study design*: Case series, case reports, observational studies
b. *Population:* Laboratory-confirmed cases with asymptomatic, mild, moderate, or severe SARS-CoV-2 infection
c. *Setting*: Any health care setting (hospitals, dental clinics) that provides consultation or treatment for SARS-CoV-2 infection
d. Date or country enforced no limitations

Exclusion criteria

a. Review articles
b. Reports that present incomplete outcome details
c. Studies evaluating systemic fungal coinfection without data on oral or maxillofacial yeast manifestation
d. Studies that do not meet the set study objectives, grey literature, abstract only

Search terms

A particular search string was set up for each of the databases, which included the following search terms: COVID-19 OR coronavirus 19 OR novel coronavirus disease 19 OR nCoV-19 OR SARS-CoV-2 OR SARS-CoV-2 infection AND oral lesions OR oral manifestations OR oral fungal lesion OR oral yeast presentation OR oral mucormycosis OR oral black fungus OR oral aspergillosis OR orofacial manifestations OR orofacial fungal presentation OR orofacial yeast manifestation OR maxillofacial yeast manifestation AND mucormycosis AND *Candida* infection OR *Candida* infection AND aspergillosis.

Summary measure

The intended outcome was to review the prevalence, clinical presentation, temporality, and the likely etiology of oral and maxillofacial fungal coinfections in patients with COVID-19.

Electronic data search and analysis

The present review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for a systematic and comprehensive approach. During the first stage of the 3-staged electronic data search and analysis, 2 reviewers (L.P.S. and K.S.F.) examined the titles and abstracts of all published relevant reports that were in line with our set inclusion criteria. Next, a full-text review of all the related articles was performed to explore the data comprehensively during stage 2 of the review process. A detailed analysis of the full text of the selected literature ensured that the eligibility standards were met and the reported outcomes were in accordance with the preset outcome measures. In addition, references of the included reports were examined as a backward search. Finally, the reviewers (L.P.S. and K.S.F.) extracted and assessed the data during stage 2.

Upon completion of the full-text review, specific points linked to the characteristics of each individual included study were mapped and recorded. This assisted in classifying the study design, setting, intervention, and reporting jurisdiction. In addition, the sample size, assessment time, evaluation methods, and study conclusions were systematically analysed. Finally, the third reviewer (H.C.N.) cross-checked the data to validate its accuracy. Relevant reports with case presentations of oral and maxillofacial mucormycosis were evaluated. The frequency of occurrence of the mucormycosis manifestation amongst patients with COVID-19 with and without comorbid diabetic conditions was analysed with random-effects meta-analysis using a comprehensive meta-analysis tool (CMA v.3). The identified manuscripts were listed using a bibliographic software tool, Endnote version 20 (Clarivate Analytics). Summarised characteristics of the included reports are provided in Table 1.

Quality and the overall risk of bias assessment of the included reports

During stage 3 of the systematic assessment of the available records, 2 reviewers (L.P.S. and K.S.F.) independently performed the quality valuation of the eligible studies employing the Joanna Briggs Institute Critical Appraisal Checklist for (i) case reports, (ii) case series, and (iii) analytical cross-sectional studies' critical appraisal checklists.[13] The third and fourth reviewers (Y.Y.L. and M.H.M.N.B.) were referred to in case of any conflict. They evaluated reports were recorded as low-, moderate-, or high-risk, as shown in Table 1. Any case reports or case series with a high risk of bias were omitted from the present review. All the involved reviewers discussed decisions based on the cumulative scores. The report was deemed low-risk when the "yes" score was ≥70%, moderate-risk, when the score was between 50% and 69%, and high-risk when the score was ≤49%.

Results

Of the 108 full texts reviewed, 30 reported cases or case series were included in the present review, and they represented a total of 292 patients with COVID-19, of whom only 150 had fungal manifestations[14-42] (Figure 1). These 30 articles met the PRISMA criteria and encompassed a single descriptive observational study, 6 case series, and 23 case reports.

All 150 patients with confirmed COVID-19 experienced one or more of the following predominant oral fungal infections: candidosis, aspergillosis, or mucormycosis (Table 1). These patients were either asymptomatic or presented with mild, moderate, or severe COVID-19. In addition, a significant age diversity was noted in the cohort, ranging from 3 COVID-19 –positive neonates[15] who experienced oral *Candida* infections to adults older than 75 years old with other mycoses. Interestingly, 3 children aged 11 to 16 years with insulin-dependent type 1 diabetes were noted with rhinocerebral mucormycosis.[35,42]

Of the cohort of patients with fungal infections, 92.6% (139/150) had comorbidities, with only a small minority without recorded comorbidity. The predominant comorbidity noted was diabetes mellitus, reported in 43.3% (65/150)[21,23-33,35-38,40-42] together with or without other comorbidities, such as cardiovascular diseases, renal ailments, and liver diseases. A few other patients exhibited an atopic immune condition,[14] asthma,[26,37] and mild hypothyroidism.[16,38]

Overall, 8.7% of patients with asymptomatic/mild COVID-19 and 91.3% with moderate to severe COVID-19 were affected by candidosis, aspergillosis, or mucormycosis. In addition, none of the patients displayed simultaneous oral coinfection with two different mycoses (Table 1).

In terms of the time of appearance of the fungal infections, 95.8% (92/96) experienced candidosis with their COVID-19 symptoms and 4.2% during the post–COVID-19 recovery period (Table 2). The time span of presentation of candidosis ranged from a few days to 1 month after initial COVID-19 symptom appearance. All patients with candidosis were on either antibiotic, antiviral, and/or steroidal therapy.

As for the sites of candidal manifestations, the tongue was the most common focus of infection, followed by the soft palate, oropharynx, and the buccal/labial mucosa (Figure 2). Finally, all the candidal infections were managed with oral nystatin, miconazole, or systemic fluconazole therapy (Table 2).

As regards oral mucormycosis, we noted 13 cases of the disease predominantly manifesting as pallor or dry palatal mucosa with dry brown secretion to brownish-black ulcerative necrotic lesions, mainly on the hard palate (Table 2). Three patients with mucormycosis presenting with oral lesions were simultaneously diagnosed with COVID-19 symptoms.[25-27] In addition, a number of other cases were fortuitous, incidental findings when examined for moderate/severe SARS-CoV-2 infection.[42-44]

Furthermore, all moderate/severe cases of COVID-19 with the maxillofacial manifestation of mucormycosis were in hospitalised patients, mostly with comorbidities, and all were receiving systemic antibiotics, antiviral, and steroidal therapies for SARS-CoV-2 infection (Table 2). A noteworthy commonality amongst all patients with COVID-19 with oral/maxillofacial mucormycosis was their uncontrolled hyperglycemic condition. Thus, the overall event rate of mucormycosis was 94% (49/52; 95% confidence interval, 0.73%-0.89%) amongst patients with known diabetic type 1/2 conditions (Figure 3). The mucormycosis in the reviewed cohort was essentially managed with liposomal amphotericin B and surgical debridement of the necrotic tissue (Table 2). A single patient[24] who had diabetes and mild COVID-19 presented with a painful deep-ulcerated lesion caused by *Rhizopus* species—belonging to the mucorales group. Additionally, only a single patient presented with histopathologically confirmed oral aspergillosis.

Discussion

Orofacial opportunistic mycotic coinfections are reported with increasing frequency at various stages of COVID-19. To our knowledge, the current review is the first report on the prevalence and aetiopathogenesis of the major opportunistic, mycotic coinfections specific to the orofacial region in laboratory-confirmed COVID-19 cases. The available data clearly

Table 1 – Characteristics of the included studies with risk of bias assessment.

Study(country)	Number of patients	Age/sex	Comorbid conditions	Fungal test	Oral-maxillofacial manifestation Candidosis	Oral-maxillofacial manifestationA spergillosis	Oral -maxillofacial manifestation Mucormycosis	Risk of bias
Asymptomatic/mild COVID-19 cases								
Corchuelo J et al 2020 (Colombia)	1	Female = 40 y	An atopic patient with mostly on analgesics and antibiotics	NM	+	_	_	**L**
Glavina A et al 2020 (Croatia)	1	Female = 40 y	None	NM	+	_	_	**M**
Mirabela D et al (2020) (Romania)	3	Neonates (n = 3) Female (n = 1) Male (n = 2)	None	NM	+	_	_	**L**
Riad A et al (2020) (Czech Republic)	1	Female = 47 y	Mild hypothyroidism and on oral levothyroxine	NM	+	_	_	**L**
Diwakar J et al (2021) (India)	2	Male = 11 y Female = 13 y	Type 1 diabetes mellitus	Fungal culture showing *Rhizopus arrhizus*	_	_	+	**L**
Pauli MA et al (2021) (Brazil)	1	Female = 50 y	Type 2 diabetes	Histopathologic findings confirmed mucormycosis	_	_	+	**L**
Revannavar SM et al (2021) (India)	1	Female (Middle-aged, age not specified)	Uncontrolled type 2 diabetes without ketosis	Fungal culture-confirmed *Rhizopus* species	_	_	+	**M**
Saldanha M et al (2021) (India)	1	Female = 32 y	Uncontrolled type 2 diabetes	Histopathologic examination	_	_	+	**M**
Verma V et al (2021) (India)	2	Female = 44 y Male = 35 y	Healthy patients	NM	+	_	_	**M**
Moderate/severe COVID-19 cases								
Amorim dos Santos et al (2020) (Brazil)	1	Male = 67 y	Type 2 diabetes, hypertensive	Fungal culture	+	_	_	**L**
Baraboutis IG et al (2020) (Greece)	49 patients, 2 of whom experienced a yeast infection	Female (n = 19) Male (n = 30)	NM	NM	+	_	_	**L**
Díaz Rodríguez M et al 2020 (Spain)	1	Female = 78 y	NM	There was a burning mouth sensation and pain	+	_	_	**M**
Salehi et al (2020) (Iran)	53	Sex = NM Age = NM	Cardiovascular diseases (52.83%), and type 2 diabetes (37.7%)	*C albicans* (70.7%); *C glabrata* (10.7%), *C dubliniensis* (9.2%), *C parapsilosis* (4.6%), *C tropicalis* (3%), and *C krusei* (1.5%)	+	_	_	**M**
Alekseyev K et al (2021) (US)	1	Male = 41 y	Type 1 diabetes mellitus	Fungal culture shows *Rhizopus*	_	_	+	**L**
	8				_			**L**

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Table 1 (*Continued*)

Study(country)	Number of patients	Age/sex	Comorbid conditions	Fungal test	Oral-maxillofacial manifestation Candidosis	Oral-maxillofacial manifestationA spergillosis	Oral -maxillofacial manifestation Mucormycosis	Risk of bias
Asymptomatic/mild COVID-19 cases								
Ashour MM et al (2021) (Egypt)		Male (n = 5); ages 42-67 y Female (n = 3); ages 41-65 y	**Cases 1-2; 4, 5, 6, and 8:** Uncontrolled type 2 diabetes mellitus **Case 3**: CRD **Case 7**: Uncontrolled diabetes mellitus, hypertension, and dialysis	Case 1: histopathology and culture revealed invasive *Aspergillus* species Case 2-8: histopathology and culture shows *Rhizopus*		+	+	
Bayram N et al (2021) (Turkey)	11	Female (n = 2) Male (n = 9) Mean age = 73. 1 ± 7.7 y	Eight patients had uncontrolled type 2 diabetes mellitus	NM	_	_	+	**L**
Dallalzadeh LO et al (2021) (US)	2	Male = 36 y Male = 48 y	Type 2 diabetes	Fungal culture shows *Rhizopus*	_	_	+	**L**
Favia G et al 2021 (Italy)	123	Female (n = 53) Male (n = 70) Median age 72 y	NM	Histopathology and culture	+	_	_	**L**
Farid HA et al (2021) (Iraq)	1	Male = 53 y	Uncontrolled type 2 diabetes on oral hypoglycemic Diabetic ketoacidosis at hospital admission	Fungal culture consistent with mucormycosis	_	_	+	**L**
Karimi-Galougahi M et al (2021) (Iran)	1	Female = 61 y	No reported comorbidity	Histopathology and culture	_	_	+	**M**
Mahan KM et al (2021) (US)	1	Male = 13 y	Type 1 diabetes mellitus	NM	_	_	+	**M**
Mehta S et al (2020) (India)	1	Male = 60 y	Diabetic (on oral hypoglycemic)		_	_	+	**M**
Mekonnen ZK et al (2021) (US)	1	Male = 60 y	Uncontrolled insulin-dependent diabetes, asthma, hypertension, hyperlipidaemia	Fungal cultures show *Rhizopus* species	_	_	+	**L**
Mishra N et al (2021) (India)	10	Female (n = 1) Male (n = 9) Age = 55.8 y (range = 37-78 y)	**Case 1-3**: type 2 diabetes mellitus **Case 4**; CKD; **Case 5**: diabetes mellitus, hypertension, and IHD; **Case 6**: diabetes mellitus and CLD; **Case 7**: diabetes mellitus and hypertension; **Case 8**: diabetes mellitus, hypertension,	Fungal culture consistent with mucormycosis	_	_	+	**L**

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Table 1 (*Continued*)

Study(country)	Number of patients	Age/sex	Comorbid conditions	Fungal test	Oral-maxillofacial manifestation Candidosis	Oral-maxillofacial manifestationA spergillosis	Oral -maxillofacial manifestation Mucormycosis	Risk of bias
Asymptomatic/mild COVID-19 cases								
			hypothyroidism, and CKD; **Case 9:** diabetes mellitus and hypothyroidism; **Case 10:** no comorbidity					
Mohammadi F et al (2021) (Iran)	1	Male = 59 y	Healthy	PCR test demonstrated *Rhizopus oryzae*	_	_	+	**M**
Riad A et al (2021a) (Czech Republic)	3	Female (n = 3) **Case 1:** 70 y **Case 2:** 25 y **Case 3:** 56 y	**Case 1:** peripheral neuropathy, urinary incontinence, and vascular disease **Case 2 & 3:** healthy	NM	+	_	_	**L**
Riad A et al (2021b) (Czech Republic)	7	Female (n = 2) Male (n = 5)	**Case 1, 2, and 5:** diabetes mellitus **Case 3, 4, and 6:** diabetes mellitus with hypertension, CVD, stable angina **Case 7:** healthy	RT-PCR	_	_	+	**L**
Veisi A et al (2021) (Iran)	2	Female (n = 1); age 40 y Male (n = 1); age 54 y	**Case 1:** no comorbidity **Case 2:** well-controlled type 2 diabetes mellitus	Histopathology and culture	_	_	+	**L**
Waizel Haiat S et al (2021) (Mexico)	1	Female = 24 y	Uncontrolled diabetes (severe diabetic ketoacidosis)	Direct exam (Sabouraud media isolating *Lichteimia (Absidia) spp*	_	_	+	**L**
Werthman-Ehrenreich A et al (2021) (US)	1	Female = 33 y	Hypertension and asthma	Fungal culture consistent with mucormycosis	_	_	+	**L**

CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic renal disease; CVD, cardiovascular disease; IHD, ischemic heart disease; NM, not mentioned; PCR, polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction.

Joanna Briggs Institute critical appraisal tool for CR (Case Reports): low (L) risk of bias = >70% scores; moderate (M) risk of bias = scores between 50% and 69%; and high (H) risk of bias = scores <49%.

Table 2 – Oral and maxillofacial manifestation of (I) mucormycosis and (II) candidosis and their respective management modalities in the reviewed studies.

I Mucormycosis Study(No. of patients)	Ambulatory/hospitalised patient	Length of stay in the hospital	COVID-19 therapies	Symptoms at the time of presentation	Fungal manifestation (time of onset)	Mucormycosis manifestation	Treatment for fungal infection
Oral mucormycosis in asymptomatic/mild COVID-19 cases							
Pauli MA et al (2021) (n = 1)	Quarantined patient for mild symptoms of SARS-CoV-2 infection	1.5 months for the treatment of fungal infection	Antibiotics, NSAIDs, and tramadol for intense pain	A painful deep ulcerated lesion in the hard palate (near midline)	A week after COVID diagnosis	Mucormycosis in the hard palate	IV amphotericin B and hydrocortisone
Maxillofacial mucormycosis in asymptomatic/mild COVID-19 cases							
Diwakar J et al (2021) (n = 2)	Ambulatory Post-COVID patients with hyperglycemia and diabetic ketoacidosis	None	No exposure to systemic steroids or antibiotics	**Case 1:** pain and swelling of an eye for a week with high-grade fever for 3 days **Case 2:** pain, swelling, and diplopia in the eye	Mucormycosis manifestation at the time of COVID-19 diagnosis	Rhino-orbital-cerebral mucormycosis	Liposomal amphotericin B (LAMB) and systemic antibiotics
Revannavar SM et al (2021) (n = 1)	Ambulatory COVID-positive case with the history of type 2 diabetes	None	No exposure to systemic steroids or antibiotics	Complete ptosis and fever of short duration	Mucormycosis manifestation at the time of COVID-19 diagnosis	Left pansinusitis, ophthalmoplegia, and acute infarct in the left parieto-occipital region	Amphotericin B and antibiotics
Saldanha M et al (2021) (n = 1)	Ambulatory COVID-positive case with uncontrolled diabetes	None	No exposure to systemic steroids or antibiotics	Left eye ptosis and facial pain for 5 days	Mucormycosis manifestation at the time of COVID-19 diagnosis	Nose, paranasal sinus, and orbital apex mucormycosis	Amphotericin B
Oral mucormycosis in moderate/severe COVID-19 cases							
Alekseyev K et al (2021) (n = 1)	Hospitalised	NM	Steroids and hydroxychloroquine IV insulin for diabetic ketoacidosis	Ageusia, dry cough, deep aching pain in the nose radiating down to the throat	With COVID-19 diagnosis	Black eschar on the hard palate	Echinocandins and amphotericin B
Ashour MM et al (2021) (n = 6)	Hospitalised	2 weeks to about a month	NM	Symptoms of SARS-CoV-2 infection	Amongst all cases, invasive fungal disease **within 12–35 days** from initial presentation of COVID-19 infection	In 6 patients, there was hard-palate involvement	**Case 1**: amphotericin B and ambisome **Case 2-8:** amphotericin B
Riad A et al (2021b) (Of n = 7, 1 has palatal mucormycosis involvement)	Hospitalised	NM	NM	A painful lesion in the hard palate for 4 days, also fever and neurological symptoms	After recovery from COVID-19 infection	**Case 1:** ulcerative and necrotic lesion in the left side of the hard palate	Liposomal amphotericin B
Veisi A et al (2021) (n = 2)	Hospitalised	NM	**Case 1 and 2:** Remdesivir and levofloxacin day 1-6 On day 7 IV dexamethasone	Symptoms of SARS-CoV-2 infection	A **week later** of the COVID-19 infection, yeasts manifestation occurred	**Case 1:** black necrotic tissues in hard palate	Systemic amphotericin B
Waizel Haiat S et al (2021) (n = 1)	Hospitalised	NM	Imipenem/linezolid	Pain in the left midface region left lid edema with extension to the upper lip and malar area	With COVID-19 diagnosis	Pallor of hard palate mucosa	Amphotericin B
Werthman-Ehrenreich A et al (2021) (n = 1)	Hospitalised	26 days	No exposure to systemic steroids or antibiotics	Altered mental status, left eye ptosis, afebrile, mild tachycardia, hypertension, and tachypnea	With COVID-19 diagnosis	Dry oral mucosa, with brown, dry secretion on the palate	Vancomycin and piperacillin-tazobactam with amphotericin B
Maxillofacial mucormycosis in moderate/severe COVID-19 cases							
Bayram N et al (2021) (n = 11)	Hospitalised	6 weeks	Broad-spectrum antibiotics and corticosteroids	Symptoms of SARS-CoV-2 infection	The mean time interval between COVID-19 symptom and fungal manifestation was 14.4 ± 4.3 days	7 rhino-orbital and 3 patients of rhino-orbital-cerebral mucormycosis	IV and retrobulbar liposomal amphotericin B
Dallalzadeh LO et al (2021) (n = 2)	Hospitalised	NM	**Case 1:** Antibiotics and corticosteroids **Case 2**: Remdesivir and IV dexamethasone	**Case 1:** Atraumatic left facial swelling and sinusitis **Case 2:** COVID-19 pneumonitis.	**Case 2**: Patient experienced diabetic ketoacidosis after COVID-19 therapy. On day 6, right periorbital edema with purulent discharge	Rhino-orbital-cerebral mucormycosis	**Case 1**: amphotericin, isovuconazole, and micafungin **Case 2**: IV amphotericin B and isovuconazole
Farid HA et al (2021) (n = 1)	Hospitalised	10 days	**Before hospital admission:** Injectable steroids and antibiotics, without medical prescription **At hospital admission:** Favipiravir, anticoagulants, and antibiotics	Symptoms of SARS-CoV-2 infection	**After 2 days of hospital admission**, the patient developed swelling around the right eye with ptosis and right-sided facial palsy	Rhinofacial-orbital-cerebral mucormycosis	Amphotericin B

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Table 2 (*Continued*)

I Mucormycosis Study(No. of patients)	Ambulatory/hospitalised patient	Length of stay in the hospital	COVID-19 therapies	Symptoms at the time of presentation	Fungal manifestation (time of onset)	Mucormycosis manifestation	Treatment for fungal infection
Karimi-Galougahi M et al (2021) (n = 1)	Hospitalised	2 weeks	Remdesivir, interferon-alpha, and systemic corticosteroid	Symptoms of SARS-CoV-2 infection	Readmitted for fungal infection after 1 week of hospital discharge Black eschar on the skin on the right lateral nasal wall and malar and periorbital regions	Rhino-orbital-cerebral mucormycosis	Insulin (raised blood sugar without ketoacidosis) and systemic antifungals
Mahan KM et al (2021) (n = 1)	Hospitalised	NM	Vancomycin, cefepime, IV insulin, and azithromycin	Disoriented, hypothermic, hypotensive, hyperglycemic, with lips and nares featured dark crusting	Mucormycosis manifestation at the time of COVID-19 diagnosis	Rhinosinusitis, cerebral mucormycosis	Micafungin, isavuconazomiun
Mehta S et al (2020) (n = 1)	Hospitalised	10 days	For COVID-19: IV meropenem and oral oseltamivir with parenteral methylprednisolone	Severe breathlessness, pyrexia, tachypnea, and generalised malaise	On the 10th day of hospitalisation, patient developed sinusitis, bilateral lid edema, and right-eye prominence	Rhinosinusitis, cerebral mucormycosis	Amphotericin B was added
Mekonnen ZK et al (2021) (n = 1)	**Visit 1**: Tested negative for SARS-CoV-2 given antibiotics for bronchitis **At visit 2**: Hospitalised, patient tested positive for SARS-CoV2 at 1 week	31 days	Antibiotic for a week on suspicion of bronchitis After COVID-19 infection confirmation, remdesivir initially. Later, IV vancomycin, cefepime, and dexamethasone	After one week, pt. presented with ARDS and hyperglycemia	1 day after hospitalisation	Rhinosinusitis with orbital involvement	Antifungal (liposomal amphotericin B), caspofungin
Mishra N et al (2021) (n = 10)	Hospitalised	NM	**Cases 4-9:** Steroid treatment **Case 10**: Both remdisivir and tocilizumab **Cases 1, 2, 8 and 9:** remdisivir	Nasal blockage, eye, and facial pain	NM	Rhino-orbital-cerebral mucormycosis	IV amphotericin B
Mohammadi F et al (2021) (n = 1)	**Visit 1**: Hospitalised for SARS-CoV-2 infection	NM	**Visit 1:** Remdesivir and methylprednisolone	**Visit two**: Nasal obstruction and left side facial and orbital swelling	After 10 days of hospital discharge after COVID-19 treatment	Rhino-orbital-cerebral mucormycosis	IV liposomal amphotericin B
Riad A et al (2021b) (Of n = 7, 6 cases had rhinocerebral mucormycosis)	Hospitalised	4-6 weeks	Azithromycin; dexamethosone; salbutamol; enoxaparin sodium; zinc	Symptoms of SARS-CoV-2 infection	From a few days to a month of COVID-19 diagnosis/recovery	Rhino-cerebral mucormycosis	Liposomal amphotericin B
II Candidosis **Study** (No. of patients)	**Ambulatory/hospitalised patient**	**Length of stay in the hospital**	**COVID-19 therapies**	**Fungal manifestation (Time of onset)**	**Oral fungal manifestation**	**Treatment for fungal infection**	
Asymptomatic/mild COVID-19 cases							
Corchuelo J et al 2020 (n = 1)	Ambulatory COVID case	None	Ibuprofen and azithromycin twice for 5 days (1st and 3rd week)	3 weeks post–lab confirmation of COVID-19 infection	Whitish plaque at the back of the tongue and the attached gingiva near the first lower premolar	Nystatin for 2 weeks Use of CHX 0.12%	
Glavina A et al (2020) (n = 1)	Ambulatory COVID case	None	Systemic acyclovir	After a week of COVID-positive symptoms	White lesion on the ventral side of the tongue	Local therapy with nystatin, panthenol, local anesthesia	
Mirabela D et al (2020) (n = 3; neonatal cases)	**Case 1 and 2**: asymptomatic but hospitalised for care **Case 3:** symptomatic and hospitalised	2-3 weeks	**Case 1**: vitamin D **Case 2:** vitamins, eye drops, topical cream for erythema **Case 3:** ampicillin, gentamicin, human immunoglobulins, aminophylline	During hospitalisation	Oral candidosis on the tongue; erythematous lesions	**Case 1 and 2:** topical nystatin **Case 3:** IV fluconazole and topical nystatin	
Riad A et al (2020) (n = 1)	Ambulatory COVID case	None	Azithromycin, linezolid, and ceftriaxone	A few days post-SARS-CoV-2 infection	Multiple pseudo-membranous lesions with white plaques over the dorsal surface of the tongue	NM	
Verma V et al (2021) (n = 2)	**Case 1 and 2:** hospitalised with mild COVID-19 symptoms	A week for fungal infection	**Case 1 and 2:** antiviral therapy	Presented with dysphagia. Upon investigation, SARS-CoV-2 infection was confirmed	**Case 1**: whitish patch on the back and lateral surface of the tongue **Case 1**: whitish patch on	**Case 1**: oral fluconazole and antiviral **Case 2**: oral fluconazole and antiviral (remdesivir)	

(*continued on next page*)

Table 2 (*Continued*)

I Mucormycosis Study(No. of patients)	Ambulatory/hospitalised patient	Length of stay in the hospital	COVID-19 therapies	Symptoms at the time of presentation	Fungal manifestation (time of onset)	Mucormycosis manifestation	Treatment for fungal infection
					the dorsal surface of the tongue		
Moderate/Severe COVID-19 cases							
Amorim dos Santos et al (2020) (n = 1)	Hospitalised	24 days	Initially: hydroxychloroquine, ceftriaxone, and azithromycin. Later: meropenem, sulfamethoxazole, trimethoprim, immunosuppressants, and anticoagulants	After 24 days of ICU admission, opportunistic fungal infection	The white plaque on the tongue dorsum	Systemic fluconazole and oral nystatin	
Baraboutis IG et al (2020) (n = 2)	Hospitalised	NM	Azithromycin, teicoplanin, dexamethasone	At 7-10 days of hospital admission	Oral candidosis	NM	
Díaz Rodríguez M et al 2020 (n = 1)	Hospitalised	NM	NM	Since hospital admission for SARS-CoV-2 symptoms	Pseudo-membranous candidosis and angular cheilitis	Nystatin for 2 weeks Use of CHX 0.12%	
Salehi et al (2020) (n = 53)	Hospitalised	NM	Antiviral, antibacterial, and corticosteroids	During hospital stay for SARS-CoV-2 infection treatment	Oropharyngeal candidosis	Fluconazole, nystatin, and caspofungin	
Favia G et al 2021 (Italy)	Hospitalised	NM	Antiviral and cortisones	During hospital stay for COVID-19 treatment	**Moderate COVID**: candidosis (18) **Severe COVID**: candidosis (4) **Critical cases**: candidosis (6)	Miconazole nitrate	
Riad A et al (2021) (n = 3)	**Case 1:** hospitalised **Case 2 and 3:** home quarantined	2-3 weeks	**Case 1:** azithromycin, levofloxacin, rivaroxaban, and lactoferrin **Case 2:** moxifloxacin, pantoprazole, and multivitamins **Case 3:** azithromycin	**Case 1:** 3 days after release from the hospital for COVID-19 treatment **Case 2:** 2 weeks **Case 3:** After 2 weeks	**Case 1:** white membranous patches on the tongue dorsum, mouth floor, soft palate, oropharynx region, and buccal mucosa **Case 2:** erythematous candidosis on the tongue dorsum **Case 3:** white membranous patches on labial mucosa, soft palate, and tongue dorsum	**Case 1:** nystatin and 0.2% CHX **Case 2:** topical miconazole **Case 3:** systemic fluconazole and topical miconazole	

ARDS, acute respiratory distress syndrome; CRD, chronic renal disease; CHX, chlorhexidine; ICU, intensive care unit; IV, intravenous; NM, not mentioned; NSAIDs, nonsteroidal anti-inflammatory drugs.

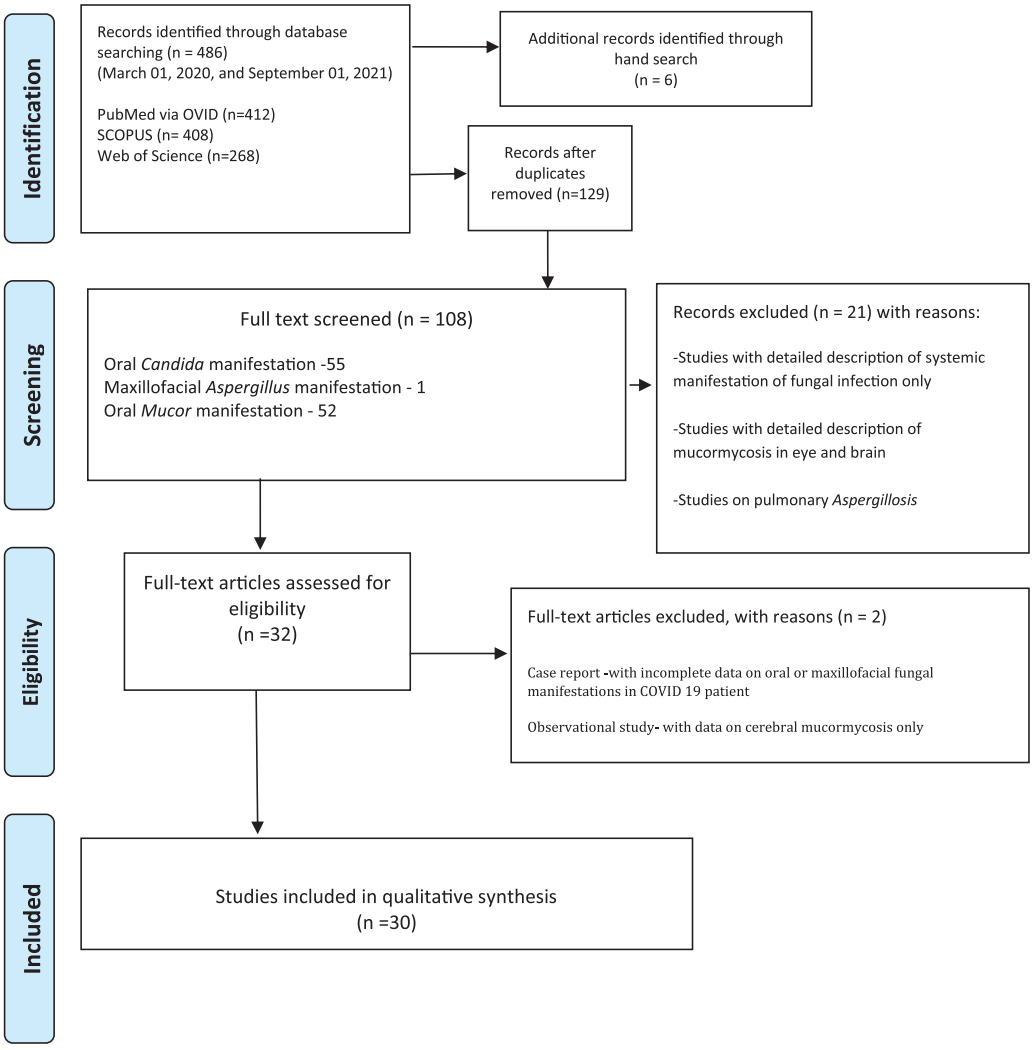

Fig. 1 – PRISMA flowchart of the literature search and study selection.

indicate that such coinfections in COVID-19 are due to 3 major fungal groups, *Candida* spp, *Aspergillus* spp, and mucorales, a group of common zygomycotic fungi. These infections manifest with a spectrum of clinical presentations, ranging from erythematous and edematous mucosae to pseudomembranous lesions and, on occasions, to extensive focal tissue necrosis involving the alveolar bone.

Candidosis

Oral candidosis due to several pathogenic candidal species is perhaps the commonest human fungal infections seen in debilitated individuals.[43,44] *C albicans*, the most common agent of oral candidosis, as well as several non-albicans *Candida* species have been reported in our cohort of COVID-19 cases, especially in hospital-bound patients.[20,23] In general, these manifestations could be explicable in terms of diabetic ketoacidosis that promotes yeast growth and lymphocytopenia, especially the T lymphocytes, due to SARS-CoV-2 infection. Other causative factors include the use of broad-spectrum antibiotics and steroid therapy and neglected and poor oral hygiene.[45]

It is known that oral candidal infections are common amongst the "very young, the very old, and the very sick",[44] and this aphorism has been, once again, proven to be the case in COVID-19. For instance, candidosis was present in 3 full-term neonatal patients with COVID-19 infection, with no history of receiving antibiotics.[15] Characteristically, neonates exhibit immature cellular immune responses, resulting in increased susceptibility to infection,[46] and this, together with the SARS-CoV-2 infection, are the likely causes for such manifestations. Nevertheless, more comprehensive studies are needed to better understand the oral mycoses of COVID-19 in the neonatal population.

Aspergillosis

It is now known that bronchopulmonary aspergillosis is the another common opportunistic systemic infection seen in COVID-19.[47,48] In general, it is frequently seen in those who are immunosuppressed and may lead to life-threatening complications.[49] A solitary case of aspergillosis with maxillary sinus invasion in a patient with uncontrolled diabetes with severe COVID-19 was noted in our review.[29].

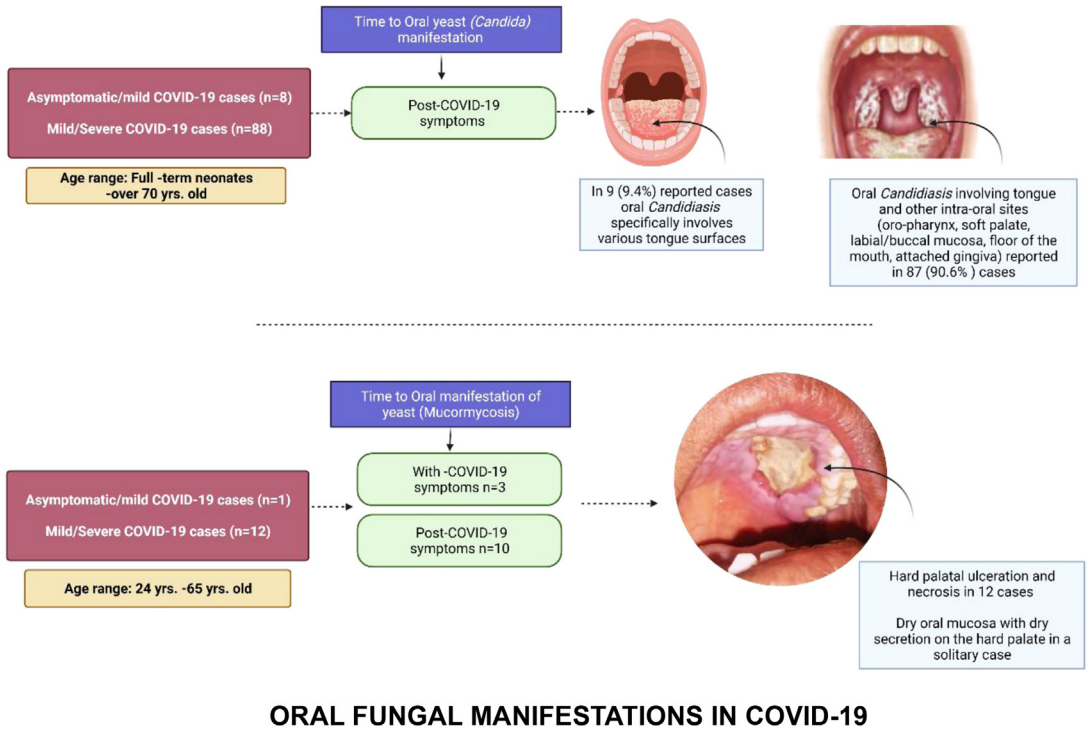

Fig. 2 – Schematic illustration of the reviewed data on oral-fungal manifestations related to COVID-19.

The disease usually ensues after inhalation of *Aspergillus* spores, and their subsequent germination and proliferation in the bronchopulmonary system.[50] However, on occasions, the infection may manifest in nasal sinuses, the oral cavity, and the eyes.[51] The most common agent of the disease known to cause invasive oral and maxillofacial lesions is *A flavus*.[50] In the absence of a robust immune response, the angioinvasive hyphal elements of *Aspergillus* species usually cause thrombosis, leading to tissue infarction and necrosis. The other virulence traits of the fungus include the production of hemolysins, proteases, phospholipases, and the toxins, aflatoxin and gliotoxin.[52-54]

Mucormycosis

Mucorales that cause mucormycosis are common saprophytic fungi found in air, dust, and wet, organic materials.[6] They cause infection predominantly in patients with poorly controlled diabetes mellitus or those who are immunocompromised due to disease or drugs. Hence, it is not surprising that the prevalence of mucormycosis has increased during the COVID-19 pandemic. Oral mucormycosis was reported in 7 reviewed cases of mild to moderate SARS-CoV-2 infection, and most of them involved patients with either controlled or uncontrolled diabetes.[24-30] Their clinical presentation

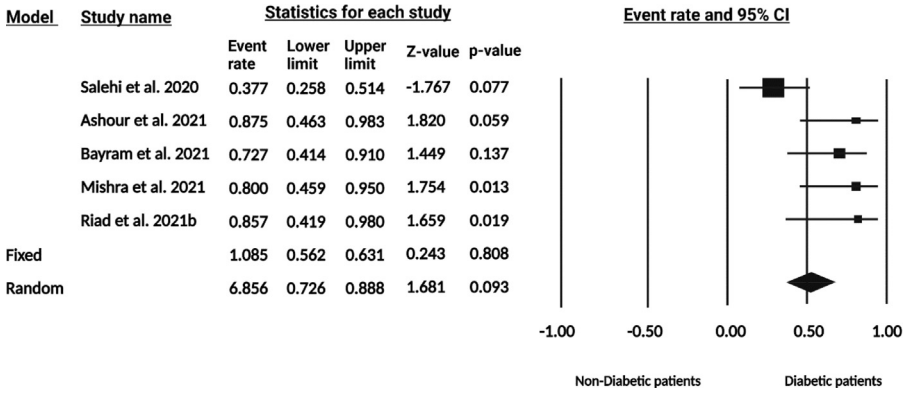

Fig. 3 – Prevalence and a 95% confidence interval of oral-maxillofacial mucormycosis manifestations in patients with/without type 1/2 diabetes comorbid conditions.

included malaise, facial pain, swelling, irregular black eschar, exudation of pus from the eye and nose, and low-grade fever.

As noted above, mucormycosis is the third most reported opportunistic fungal infection in patients with SARS-CoV-2 infection.[55] It has 4 to 5 categories: rhinocerebral, cutaneous, disseminated, gastrointestinal, or pulmonary, depending on the infected tissues.[56] Of these, rhinocerebral mucormycosis is relevant in the current context as it affects the oral cavity, sinuses, nasal passages, and brain. The infection usually begins in the nasal mucosa or palate and spreads via nearby vessels to the paranasal sinuses, often involving the maxillary and ethmoidal sinuses.[57] Previous literature from the pre−COVID-19 era also indicates that rhinocerebral mucormycosis affects patients with poorly controlled diabetes and immunosuppressed patients.[58] Many of the cases in our review had documented mucor invasion of cranial nerves III, IV, and VI, leading to ptosis, pupillary dilatation, proptosis, and vision loss. In addition, hematogenous spread to the cavernous sinus led to fatal cavernous sinus thrombosis in a few cases.[59-61]

In cases in which mucormycosis is suspected, prompt diagnosis and treatment are critical because of the angioinvasive nature of the fungus and its rapid systemic dissemination. A number of recent cases, particularly from the Indian subcontinent, report fungal invasion seeded in the maxillary sinus and progressing into maxillary alveolar bony tissues and then the oral cavity as well as the orbits, with eventual blindness of the individual.[57] Late diagnosis of the disease with orbital invasion needs to be managed by radical surgery of the affected regions and removal of the orbital contents.

Apart from the *Mucor* genus, other disease-causing genera in this group include *Rhizopus* and *Absidia*.[62,63] In the oromaxillofacial region, *Mucor* and *Rhizopus* species account for most of the oral and rhinocerebral mucormycosis in COVID-19 cases. In contrast, a single case from Mexico reported isolating *Absidia (Lichteimia)* spp (belonging to mucorales) from the biopsy of a young female patient with severe diabetic ketoacidosis secondary to steroidal therapy for COVID-19 treatment.[27]

In clinical terms, it should be noted that most oral mycoses in COVID-19 may present as innocuous red patches on the hard palate or the buccal mucosa, as shown by incidental findings in SARS-CoV-2 infection.[42-44] However, as some of these lesions may lead to impairment of vision and/or even removal of the affected bony tissues and eventual disfigurement, all clinicians examining the oral cavity should maintain a high index of suspicion and be cognisant of the oral and maxillofacial mycoses that may pose a threat to the long-term health and the quality of life of these patients, particularly after recovery from SARS-CoV-2 infection. Indeed, oral and maxillofacial mycoses in COVID-19 could be construed as a little-known silent manifestation of the pandemic.

Study limitations

Our review has a few limitations. First is the disparate and heterogeneous nature of the reported cases emanating from various geographic locales, a significant proportion with limited and incomplete data. For instance, only a few case reports or case series included microbiological or histopathologic data of the fungal lesions confirming the diagnoses, and mere clinical observations were reported. In addition, most reports documenting oral candidosis did not elaborate on the species differentiation of *Candida* species. Additionally, it should be noted that the majority of fungal infections reported thus far have been diagnosed in hospitalised patients with severe COVID-19, and the data presented cannot be extrapolated for all patients with COVID-19 who mostly have mild symptoms.

Conclusions

Patients with SARS-CoV-2 infection are susceptible to oral fungal superinfections. The most likely reasons for this could be the impaired immune defenses due to the underlying viral infection, immunosuppressive and steroid therapy for COVID-19, ventilator-associated fungal infection, xerostomic conditions, and/or extant diabetes mellitus. Oral and maxillofacial mycoses, when present, appeared either concurrently with COVID-19 symptoms or during the immediate postrecovery period. Attending clinicians must maintain a high degree of suspicion of the possibility of these mycoses, particularly in patients with underlying comorbidities such as diabetes. A full and complete oral examination of patients with COVID-19 leading to early identification and treatment of secondary oral and maxillofacial mycoses can considerably reduce morbidity and improve their long-term health and quality of life.

Author contributions

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Supplementary materials

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