Oral Complications arising after treatment in patients infected with SARS-COV-2 virus - A Systematic Review

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Abstract

Background: The global COVID-19 pandemic has brought forth numerous medical challenges, including the emergence of secondary infections, particularly fungal infections in patients recovering from SARS-CoV-2. There is a growing concern about the oral complications and fungal manifestations in such patients. Currently, most literature on this subject is limited to case reports or case series, with little long-term data available. This review aims to highlight the occurrence of oral fungal infections, particularly mucormycosis, and their clinical presentations, diagnostic methods, and therapeutic interventions in COVID-19 patients. Early diagnosis and timely treatment are critical for improving outcomes in affected individuals.

Methods: A systematic search was conducted in PubMed, Scopus, and Science Direct using the keywords “oral diseases,” “oral manifestations,” and “COVID-19.” Inclusion criteria focused on studies examining oral manifestations in confirmed COVID-19 patients. Clinical cases, case series, and retrospective or prospective studies were included, while other study types, including non-COVID oral infections, were excluded.

Results: COVID-19 patients are at an increased risk of developing fungal infections such as mucormycosis, candidiasis, and aspergillosis, primarily due to immunosuppression and the use of medications like corticosteroids (e.g., dexamethasone). These infections manifest in the oral cavity, often affecting the palatal and alveolar bone. Maxillectomy and debridement are commonly required to manage these conditions.

Conclusion: Recurrent oral infections post-COVID-19 recovery should be a cause of concern for both patients and healthcare providers. Identifying early mucosal changes and maintaining oral hygiene are crucial for preventing severe complications. Intensive care and follow-up are necessary for managing fungal infections in COVID-19 survivors.

Introduction

The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, has led to unprecedented challenges in modern healthcare. Since its initial identification in December 2019 in Wuhan, China, the virus has rapidly spread worldwide, affecting millions of people and placing immense strain on healthcare systems [1]. As of today, the ongoing impact of the pandemic continues to evolve, bringing forth not only the direct consequences of the viral infection but also a myriad of secondary complications that pose significant threats to patients ’ health. SARS-CoV-2 primarily spreads through respiratory droplets, direct contact, and aerosols, making it highly contagious [2]. The virus predominantly affects the respiratory system, causing symptoms ranging from mild cold-like presentations to severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-

organ failure [3]. However, COVID-19 is now recognized as a multisystem disease, with the potential to cause complications beyond the respiratory tract. Emerging evidence suggests that the oral cavity can also serve as a reservoir and a site for various complications, including viral manifestations, secondary bacterial infections, and, importantly, fungal infections [4].

Historically, coronaviruses such as SARS-CoV (responsible for the 2003 SARS outbreak) and MERS-CoV (Middle East Respiratory Syndrome) have been associated with significant viral pathogenicity. Both viruses belong to the same family as SARS-CoV-2 and share some biological and clinical features [5]. However, SARS-CoV-2 has demonstrated a far greater ability to spread, largely due to its efficient transmission mechanisms and its affinity for the human ACE2 (angiotensin-converting enzyme 2) receptor, which is expressed in various tissues, including the lungs, heart, and oral mucosa. This widespread distribution of ACE2 receptors provides a basis for the virus's ability to affect multiple organ systems, including the oral cavity [6].

While the direct impact of COVID-19 on the respiratory system has been extensively studied, the secondary complications arising in patients during and after infection are equally concerning. In particular, co-infections and secondary microbial invasions have garnered attention due to their role in exacerbating disease outcomes [7]. Studies from the early phases of the pandemic indicated that bacterial infections were a major cause of death in COVID-19 patients, especially those in critical care [8]. More recently, fungal infections have emerged as a significant complication in COVID-19 patients, particularly in those with compromised immune systems [9].

One of the most severe fungal complications observed in COVID-19 patients is mucormycosis, commonly referred to as "black fungus." This rare but aggressive fungal infection is caused by fungi from the mucorales order, which can invade the sinuses, brain, and lungs, and, in some cases, the oral cavity [10]. The infection is life-threatening, especially in individuals with weakened immune systems, such as those with uncontrolled diabetes mellitus or those on prolonged corticosteroid therapy, which is often used to treat severe COVID-19. Other fungal infections, such as candidiasis and aspergillosis, have also been reported in COVID-19 patients, contributing to morbidity and mortality [11]. The relationship between SARS-CoV-2 infection and the development of secondary fungal infections can be attributed to several factors. First, the virus itself induces a state of immune dysregulation, characterized by lymphopenia and an excessive inflammatory response, commonly referred to as a "cytokine storm" [12]. This hyper-inflammatory state weakens the body's natural defense mechanisms, making patients more susceptible to opportunistic infections. Second, the use of immunosuppressive therapies, such as corticosteroids (e.g., dexamethasone), while beneficial in controlling the inflammatory damage caused by COVID-19, further predisposes patients to infections by suppressing their immune responses [13]. Third, in critically ill COVID-19 patients, factors such as prolonged hospitalization, mechanical ventilation, and the use of invasive devices increase the risk of nosocomial infections, including fungal colonization of the oral cavity and respiratory tract [14].

The oral cavity, in particular, is a site of interest due to the presence of ACE2 receptors and its direct exposure to the external environment [15]. Fungal infections in the oral cavity can manifest as necrotic ulcers, palatal perforations, and loosening of teeth, often involving both the palatal and alveolar bones. These manifestations not only reflect the severity of the infection but also indicate the potential for systemic spread if not identified and treated promptly. Given the high risk of mortality associated with invasive fungal infections, early diagnosis and aggressive treatment are crucial for improving patient outcomes [16]. Thus, this systematic review aims to consolidate existing knowledge on the prevalence, clinical presentation, diagnostic approaches, and treatment strategies for fungal infections affecting the oral cavity in COVID-19 patients. By doing so, this review seeks to provide insights that can guide clinicians in identifying early signs of fungal involvement and implementing appropriate interventions to prevent severe complications and improve patient outcomes.

Methodology

The systematic review is registered in PROSPERO register no.**CRD42023469323.** The methodology for this systematic review followed a structured approach to identify, select, and analyze relevant studies on fungal

infections in the oral cavity of COVID-19 patients. The review aimed to describe the most prevalent fungal infections, their clinical and radiographic features, and the treatments administered. A comprehensive literature search was conducted across two major databases, PubMed and Scopus, using the search terms "oral diseases," "oral manifestations," and "COVID-19," combined with Boolean operators "AND" and "OR." The inclusion criteria encompassed case reports and case series that documented fungal infections in the oral cavity of patients confirmed to have COVID-19. Studies that focused on other types of oral infections or involved non-COVID-19 patients were excluded. Duplicate studies were removed and the remaining articles underwent title and abstract screening, followed by a full-text review to determine their eligibility based on the above said criteria. The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series [17]. This checklist evaluates factors like patient history, clinical assessments, interventions, and outcomes. The data were synthesized to identify patterns in fungal infection prevalence, clinical presentation, and treatment outcomes, with findings represented in percentages and visually through graphs. The results were then analyzed to provide insights into the association between COVID-19 and secondary fungal infections, particularly in medically compromised patients.

Data extraction and synthesis

Data extraction was performed to gather information on patient demographics, clinical and radiographic characteristics, the site of fungal infection, and treatment modalities. This systematic review included case reports and case series on COVID-19 patients with fungal infections in the oral cavity, as well as case reports on non-COVID patients. Exclusion criteria encompassed other oral infections in COVID-19 patients, clinical trials, in-vitro studies, prospective and retrospective studies, observational studies, randomized controlled trials, and fungal infections in non-COVID-19 patients. The original description of symptoms within the first 14 days of the disease was used to determine the initial oral signs and symptoms. Information was collected at the highest frequency to identify the most prevalent indications or symptoms. Two researchers participated in the study, extracting data from articles that provided details on patient age, gender, medical status, site of infection, clinical features, radiographic findings, and treatments administered. Quality assessment was conducted using the Joanna Briggs Institute Critical Appraisal Tool. To evaluate the evidence for prevalence, diagnostic accuracy, prognosis, therapeutic effects, rare and common harms, and the usefulness of early screening, the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 tool was utilized [18]. The risk of bias was assessed using the JBI Critical Appraisal Checklist for Case Series instrument, which comprised 10 questions covering the patient's description, assessment, interventions, and reporting of negative consequences based on the available data. Each question received a response of yes, no, or ambiguous. Data were synthesized from the collected articles, including details on patient age, gender, medical status, site of infection, clinical features, radiographic features, and treatments administered. The prevalence of fungal infections, the site of infection, their associated clinical and radiological features, and the most common treatments were assessed.

Results

A total of 188 studies on fungal infections in COVID-19 patients, from which 12 case reports and case series studies met the inclusion criteria after removing duplicates and screening the titles, abstracts, and full texts as shown in **figure 1**. The majority of patients in these case reports were males, with an average age of 50-55 years. The prevalence of fungal infections in COVID-19 patients was strongly associated with underlying health conditions, particularly diabetes mellitus (90% of the cases) as shown in **figure 2A**. This finding correlates with the findings of Tomasz Geca et al in 2022 [19]. Only a small percentage of patients were previously healthy (10%). The most prevalent fungal infection was mucormycosis, accounting for 45% of the cases, followed by candidiasis at 41%, and actinomycosis at 14% as shown in **figure 2B** which is in accordance to Akira A Shishido et al in 2022 [20]. These infections primarily affected the oral cavity, particularly the palatal and alveolar bones, where extensive tissue and bone destruction were observed. Clinical manifestations included exposed necrotic bone (ENB) in 80% of the cases, palatal perforation (PP) in 40% which is in accordance with Amal Suresh et al in 2022 [21] and loosening of teeth, with more severe complications such as loss of vision and extraoral pus discharge occurring in advanced cases as shown in **figure 2C**. The

involvement of both the palatal and alveolar bone regions was more frequent than infections isolated to the palatal bone, leading to significant morbidity in the affected patients as shown in **figure 2D**.

Radiographically, the most common finding was bone destruction, observed in 90% of the cases, particularly in the maxilla, with rarefaction and sequestration being key indicators of fungal invasion as shown in **figure 3A**. Treatment strategies varied based on the severity of the infection, with maxillectomy and resection being the most common surgical interventions performed in 75% of the patients, while debridement and curettage were reserved for less severe cases (25%) which is in accordance with Wael M Said Ahmed et al in 2021 [22] as shown in **figure 3B**. All patients received antifungal therapy, with amphotericin B being the most frequently used drug. Outcomes varied, with better prognosis in patients who received early diagnosis and prompt surgical intervention. However, cases with extensive bone involvement or orbital spread had poorer outcomes, with a few cases resulting in mortality. Further more, the JBI critical appraisal tool was employed to evaluate the risk of bias. Six of the studies demonstrated a medium risk of bias, while one was classified as low risk as shown in **Table 1** and **figure 4**. The Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence provides a hierarchical system for evaluating the strength of evidence in medical research, from Level 1 (highest quality) to Level 5 (lowest quality). According to this tool, case reports and case series fall under Level 4 evidence, which includes studies like case-control studies or those with a “poor or nonindependent reference standard” which falls for the studies included in this systematic review **(Table 2)**.

Discussion

The study highlights the significant impact of secondary fungal infections, particularly in COVID-19 patients, with a focus on mucormycosis, candidiasis, and actinomycosis. These infections are increasingly prevalent in patients with underlying health conditions, especially diabetes mellitus, due to their compromised immune systems [23]. COVID-19 itself, along with the corticosteroids used in treating severe cases, further weakens the body’s defenses, creating an ideal environment for fungal pathogens to thrive. Mucormycosis, which accounted for 45% of the cases in this review, was the most commonly reported fungal infection [24]. The systemic use of corticosteroids, while effective in reducing inflammation and managing severe COVID-19 symptoms, inadvertently increases susceptibility to fungal infections by suppressing immune responses and raising blood glucose levels, which is particularly dangerous in diabetic patients [25]. This combination of factors leads to a high incidence of fungal invasions in the oral cavity, complicating recovery and increasing morbidity.

The review found that the oral manifestations of these fungal infections were both severe and rapid in progression, affecting primarily the palatal and alveolar bones. The most common clinical presentations included exposed necrotic bone (ENB), observed in 80% of cases, and palatal perforation (PP), which was noted in 40% of patients. These lesions often began as localized necrosis in the oral cavity but rapidly progressed to more invasive forms involving deep tissues and bones. The involvement of both palatal and alveolar bones in most cases reflects the aggressive nature of these infections. Additionally, complications such as loosening of teeth and, in more advanced cases, loss of vision due to orbital involvement, were noted. These findings underscore the importance of early identification and treatment of oral fungal infections in COVID-19 patients, particularly given the life-threatening potential of mucormycosis if it spreads beyond the oral cavity.

Radiographic imaging, specifically CT scans, played a crucial role in diagnosing these infections, with 90% of cases showing bone destruction. The severity of the radiographic findings often correlated with the extent of clinical damage, including rarefaction and sequestration of the maxillary bones. The review also noted that in several cases, the infection spread beyond the oral cavity to involve the orbit and zygomatic arch, which significantly worsened the prognosis. These findings suggest that once fungal infections reach advanced stages, surgical interventions become more complex and carry higher risks. The spread to vital structures such as the eyes can result in irreversible damage, further emphasizing the need for prompt, aggressive treatment strategies to prevent such complications.

The management of these infections was varied depending on the severity of the cases, with the most common treatments being surgical interventions. Maxillectomy and resection were the preferred methods for 75% of the patients, particularly in cases where the infection had caused significant bone destruction. Debridement and curettage were employed in less severe cases or when the infection was caught early, accounting for 25% of the treatment strategies. The combination of surgery and antifungal therapy, particularly with drugs such as amphotericin B, was shown to be effective in managing the infections, but the outcomes largely depended on the timing of diagnosis and intervention. Patients who were diagnosed early and received prompt surgical treatment had better outcomes, while those with advanced infections, especially with orbital involvement, faced a poorer prognosis, with a few cases resulting in mortality. These findings highlight the urgent need for early detection and timely management of oral fungal infections in COVID-19 patients, particularly those with pre-existing medical conditions, to improve survival rates and reduce complications.

Conclusion

In conclusion, this systematic review reveals the critical prevalence and severe impact of secondary fungal infections in COVID-19 patients, particularly mucormycosis, with candidiasis and actinomycosis also presenting significant risks. These infections most commonly affected the palatal and alveolar bones, often resulting in extensive structural damage and high morbidity. The primary clinical manifestations included exposed necrotic bone (ENB) and palatal perforation (PP), with bone destruction being a significant radiographic finding observed through CT scans. Treatment approaches typically required aggressive surgical interventions, with maxillectomy and resection being the most commonly performed procedures, complemented by antifungal therapy. The findings also demonstrate that medically compromised patients, especially those with underlying conditions like diabetes, are disproportionately affected by these infections. These results emphasize the need for heightened vigilance and proactive management by healthcare providers, particularly in COVID-19 patients with pre-existing health conditions. Early diagnosis and timely intervention, combining surgical and pharmacological treatment, are essential to improving patient outcomes and preventing severe complications. Additionally, these findings underscore the importance of interdisciplinary collaboration between medical and dental professionals in identifying and managing oral fungal infections early to reduce the risk of progression to advanced stages associated with poorer prognosis.

Limitations and future scope

The review was based on a limited number of case reports and case series, which restricts the sample size and may not fully capture the range of fungal infections or variations in clinical presentations across broader populations. Additionally, the review did not include prospective, retrospective, or randomized studies, which may have provided more robust evidence and insights into the prevalence and treatment outcomes of these infections. A lack of long-term follow-up data in most cases further limits our understanding of the progression and recurrence of fungal infections in COVID-19 patients. Furthermore, differences in diagnostic and treatment approaches across studies may introduce variability, making it challenging to standardize findings. Future research should focus on large-scale, multi-center studies to provide a more comprehensive and representative understanding of fungal infections in COVID-19 patients, including variations across demographics and medical conditions. Longitudinal studies with extended follow-up periods would be valuable for examining the recurrence, progression, and long-term outcomes of these infections. Additionally, randomized controlled trials exploring the effectiveness of different antifungal therapies and surgical interventions could provide critical insights into optimal treatment protocols. Research on preventive strategies, particularly for high-risk groups such as diabetic and immunocompromised patients, could aid in reducing infection rates. The development of standardized guidelines for early diagnosis and management of oral fungal infections in COVID-19 patients would further improve patient outcomes. Finally, further investigation into the underlying mechanisms linking COVID-19, immunosuppression, and fungal infections could enhance understanding and enable targeted preventive measures in future healthcare protocols.

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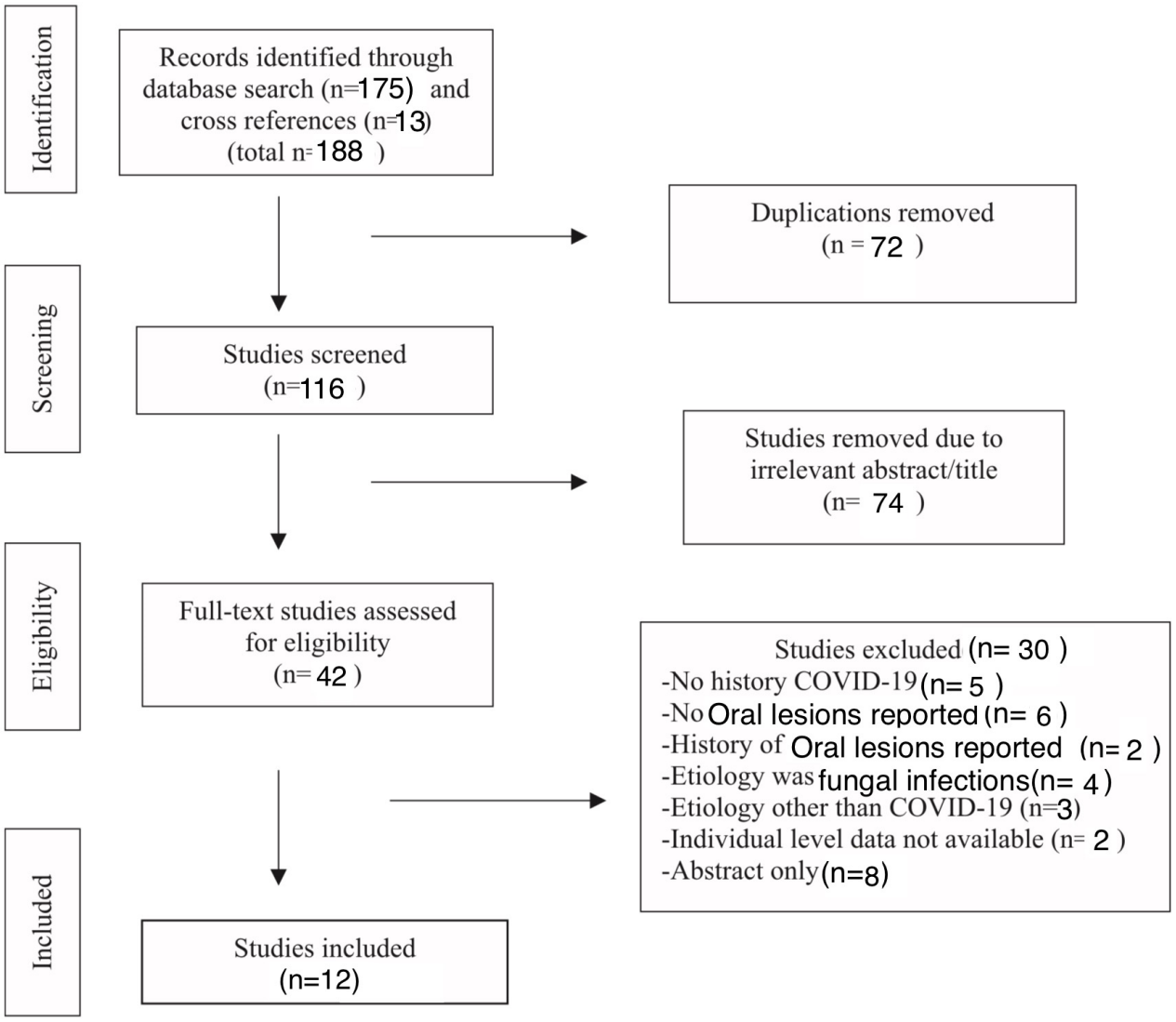
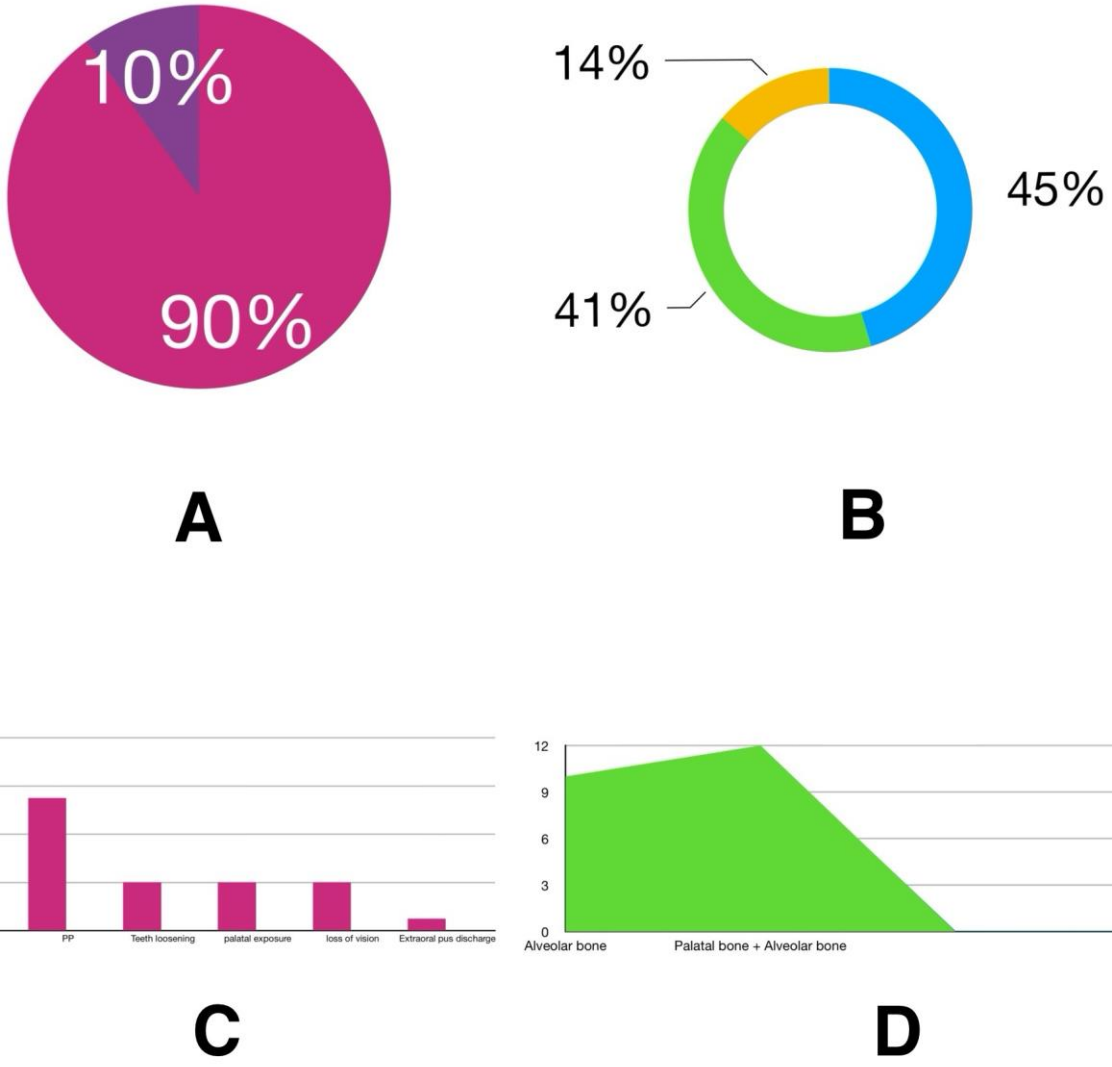


Figure 1: PRISMA flow chart showing a total of 188 studies on fungal infections in COVID-19 patients, from which 12 case reports and case series studies met the inclusion criteria after removing duplicates and screening the titles, abstracts, and full texts.

Figure 2: (A) Fungal infections in COVID-19 patients were highly prevalent in those with diabetes (90%), with **(B)** mucormycosis (45%) and candidiasis (41%) being most common **(C)** These infections affected the oral cavity,



especially palatal and alveolar bones, causing exposed necrotic bone (80%), palatal perforation (40%), and loosening of teeth. Advanced cases showed severe complications, including vision loss and extraoral pus discharge **(D)** Infections involving both palatal and alveolar bones led to significant morbidity.

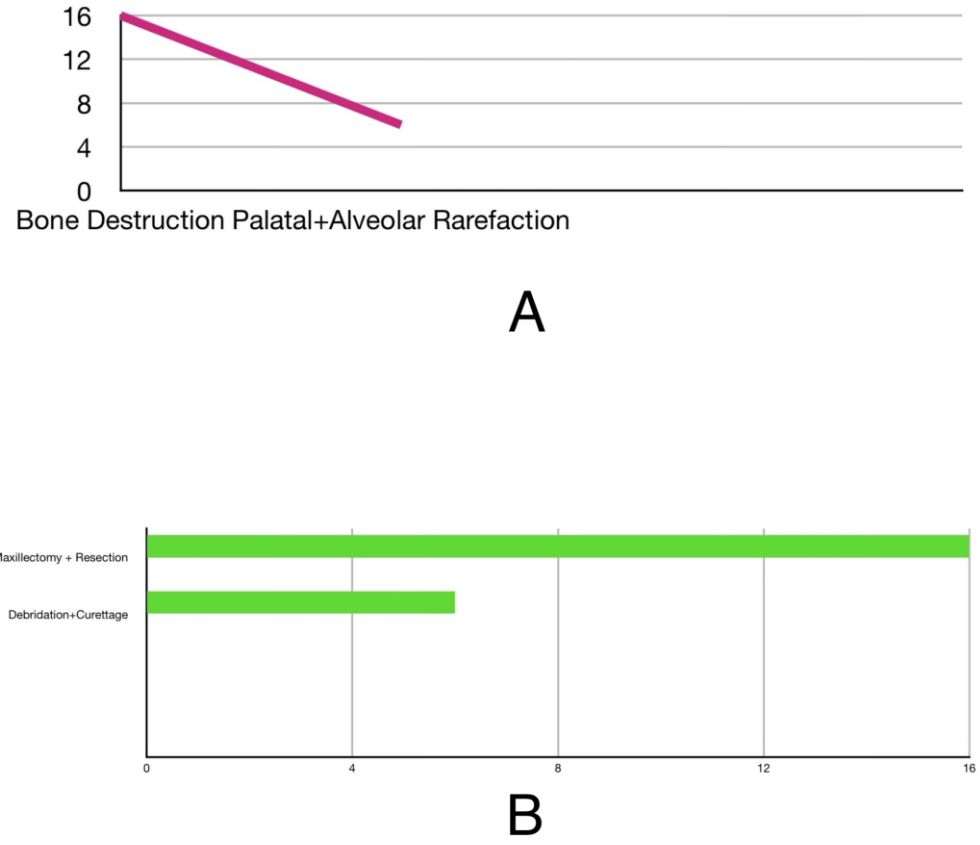


Figure 3: (A) Radiographically, the most common finding was bone destruction, observed in 90% of the cases, particularly in the maxilla, with rarefaction and sequestration being key indicators of fungal invasion **(B)** Treatment strategies varied based on the severity of the infection, with maxillectomy and resection being the most common surgical interventions performed in 75% of the patients, while debridement and curettage were reserved for less severe cases (25%).

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Quality
Amorim dos Santos et al 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Cantini et al 2020	Y	N	N	N	Y	N	N	N	Y	High
Diaz Rodriguez et al 2020	Y	N	N	Y	Y	Y	Y	N	Y	Moderate
Riad et al 2020	Y	U	N	Y	Y	Y	Y	N	Y	High
Baraboutis et al 2020	Y	Y	Y	N	Y	N	N	U	N	High
Corchuelo et al 2020	N	N	N	N	N	U	U	U	Y	Moderate
Dima et al 2020	Y	Y	Y	U	Y	Y	Y	Y	N	Moderate
Salehi et al 2020	Y	U	U	U	U	U	U	N	U	High
Shishido AA et al 2022	Y	U	U	Y	Y	Y	Y	N	Y	Moderate
A Al Balushi et al 2022	N	Y	Y	U	U	Y	Y	Y	Y	Moderate
R Eghbali Zarch et al 2021	Y	Y	Y	Y	N	Y	Y	Y	Y	High
PS Karthika et al 2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Moderate

Table 1: The risk of bias was assessed using the JBI Critical Appraisal Checklist for Case Series instrument, which comprised 10 questions covering the patient's description, assessment, interventions, and reporting of negative consequences based on the available data.

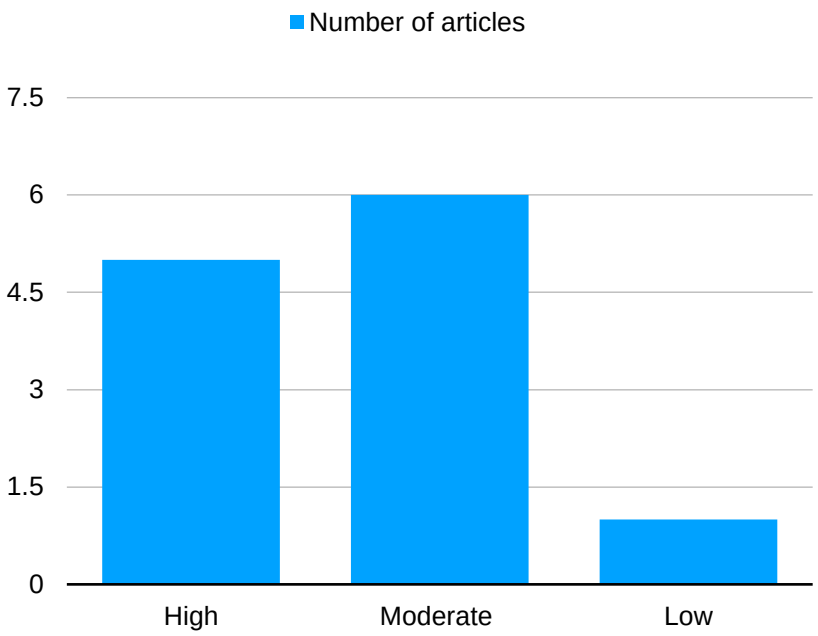


Figure 4: JBI critical appraisal tool was employed to evaluate the risk of bias. Six of the studies demonstrated a medium risk of bias, while one was classified as low risk

sl. no	Author and year	Study design	Level of Evidence
1	Amorim dos Santos et al. 2020	Case Reports	4
2	Cantini et al. 2020	Case Reports	4
3	Díaz Rodríguez et al. 2020	Case Reports	4
4	Riad et al. 2020	Case Reports	4
5	Baraboutis et al. 2020	Case Reports	4
6	Corchuelo et al. 2020	Case Reports	4
7	Dima et al. 2020	Case Reports	4
8	Salehi et al. 2020	Case Series	4
9	Shishido AA et al 2022	Case Reports	4
10	A Al Balushi et al 2022	Case Reports	4
11	R Eghbali Zarch et al 2021	Case Reports	4
12	PS Karthika et al 2021	Case Reports	4

Table 2: The Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence provides a hierarchical system for evaluating the strength of evidence in medical research, from Level 1 (highest quality) to Level 5 (lowest quality). According to this tool, case reports and case series fall under Level 4 evidence, which includes studies like case-control studies or those with a “poor or nonindependent reference standard” which falls for the studies included in this systematic review.