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REVIEW

Epidemiological Characteristics, Pathogenesis and Clinical Implications of Sinusitis in the Era of COVID-19: A Narrative Review

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Abstract: Sinusitis is a common condition with various forms and different etiologies. In the era of COVID-19, a large number of studies covered the association between sinusitis and COVID-19, while others reported the impact of COVID-19 on the development of acute invasive fungal rhinosinusitis (AIFR), together with the most commonly associated predisposing factors. Fungal sinusitis, particularly AIFR, can be life-threatening. It is important to dissect this association and improve current evidence and management. Therefore, we conducted this literature review to highlight the association between COVID-19 and sinusitis based on evidence from the available studies in the literature. Evidence shows that chronic sinusitis might have a negative impact on COVID-19 outcomes. However, current results are conflicting, and further studies are needed. On the other hand, COVID-19 can also cause olfactory dysfunction, which is usually temporary. In addition, we found several studies that indicated the association between COVID-19 and AIFR. The condition is usually associated with severe morbidities, as affected patients are usually immunocompromised, including those with uncontrolled diabetes, malignancy, immunosuppression, AIDS, the administration of chemotherapy and other immunosuppressive drugs, and COVID-19.

Keywords: COVID-19, severe acute respiratory syndrome coronavirus-2, sinusitis, fungal rhinosinusitis, pathogenesis

Introduction

Since the severe acute respiratory syndrome (ARDS) coronavirus 2 (SARS-CoV-2) emerged and caused coronavirus disease 2019 (COVID-19), different reports have indicated the global burden the pandemic caused on the different aspects of the communities and their populations.[1,2] In addition, the disease has been associated with not only the development of ARDS but other conditions and complications that might even be life-threatening. In addition, it has been evidenced that COVID-19 can significantly decrease $CD8^+$T and $CD4^+$T cells leading to a remarkable reduction in the immune response and producing a state of immunosuppression.[3] Such events can lead to serious conditions, including bacterial and fungal infections. These infections can emerge as hospital-acquired infections or are associated with other pre-existing morbidities, including lung diseases and diabetes.[1–3]

Epidemiological evidence shows that 5–98% of COVID-19 patients usually suffer from gustatory and olfactory dysfunction.[4–8] This might not be very pleasant but is not potentially life-threatening. On the other hand, fungal sinusitis, particularly acute invasive fungal rhinosinusitis (AIFR), can be life-threatening. Furthermore, the condition is usually associated with severe morbidities, as affected patients are usually immunocompromised. Evidence among studies in the literature shows that affected patients with AIFR usually include patients with uncontrolled diabetes, malignancy, immunosuppression, AIDS, the administration of chemotherapy and other immunosuppressive drugs, and COVID-19.[9,10]

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There is an emerging burden of chronic sinusitis during the COVID-19 era, mainly as it can be found in different forms. Therefore, it is essential to study the association between COVID-19 and sinusitis to provide healthcare authorities with a better understanding of these events and establish the best management practice. For that, we conducted this narrative literature review to highlight the association between COVID-19 and sinusitis based on evidence from the available studies in the literature.

Methods

We conducted a thorough literature search to curate all the relevant articles and formulate the best evidence. We searched different databases, including Scopus, PubMed, and Google Scholar. In addition, a manual search was also conducted to find all potentially related articles that could help us formulate our evidence. First, the research team prepared the keywords according to the medical subject headings (MeSH). Then, we searched the articles using the keywords separately and with combinations. The keywords used in the present review article to explore the works of literature were "sinusitis", "invasive", "COVID-19", "risk factors", "fungal", "rhinosinusitis", and "pathogenesis." The present literature review included only published English-language articles with access to full texts. We excluded the research articles other than in the English language and the published articles without the peer review process. Initially, we searched using keywords and retrieved 285 articles. However, after applying the inclusion and exclusion criteria, the present study used 96 papers for the review related to epidemiological characteristics, pathogenesis, and the association between sinusitis and COVID-19.

COVID-19 and Chronic Sinusitis

Association Between Both Conditions

We presented the summary of studies that demonstrated the association between chronic rhinosinusitis (CRS) and COVID – 19 in Table 1.

Table 1 Summary of Studies That Demonstrated the Association Between Chronic Rhinosinusitis (CRS) and COVID – 19

Authors	Study Design	Sample Size	Findings
Lee SW et al[11]	Nested case-control study	Matched (both groups) – 12,217	SARS- CoV- 2 infections were significantly higher among CRS patients [Adjusted odds ratio (AOR) = 1.22 and 95% confidence interval (CI) = 1.04–1.42] COVID-19 patients with CRS had more negative outcomes [AOR = 1.71, 95% of CI = 1.09–2.71]
Wang H et al[12]	Cohort study	1172 hospitalized COVID – 19 patients	COVID – 19 patients with CRS did not significantly develop severe illness. However, this study had several limitations, such as assessing the CRS through self-reported telephonic interviews and excluding the fatal cases.
Sbeih F et al[13]	Retrospective cohort study	COVID – 19 positive patients = 998 COVID – 19 Negative patients – 996	COVID – 19 positive patients with CRS had significantly more risk of hospitalization than those without CRS (AOR = 3.19, 95% CI = 1.12–10.68)
Workman AD et al[14]	Matched cohort	CRS Patients – 12,000 Controls – 12, 000	No statistical significance in contracting COVID – 19 infections among the patients with and without CRS
Miller LE et al[15]	Historical cohort	1707 CRS patients (197 – Received oral corticosteroids 1510 – Did not receive oral corticosteroids)	There was no statistically significant difference in COVID – 19 positive results between the CRS patients who received oral corticosteroids with the CRS patients who did not receive them.

Note: Data presented in this table is authors, study design, sample size, and important findings with the level of evidence.

Many previous studies have investigated the association between COVID-19 and chronic rhinosinusitis. For instance, a nested case-control study conducted in Korea by Lee et al[11] demonstrated that the rate of COVID-19 infections was higher among patients with chronic rhinosinusitis than among others without it. Lee et al reported that SARS- CoV- 2 infections were significantly higher among CRS patients [Adjusted odds ratio (AOR) = 1.22 and 95% confidence interval (CI) = 1.04–1.42] and COVID-19 patients with CRS had more severe outcomes [AOR = 1.71, 95% of CI = 1.09–2.71] Moreover, the rate of severe COVID-19 outcomes was higher among patients with chronic rhinosinusitis than others (21% versus 13.3%). On the other hand, a cohort study by Wang et al[12] reported that the risk of developing severe COVID-19 was not associated with chronic rhinosinusitis. However, it should be noted that the authors mentioned that deceased patients with chronic rhinosinusitis were excluded from the study. These patients could have been patients with severe COVID-19. Therefore, their data might not have been adequately represented. A retrospective study conducted by Sbeih et al[13] showed that chronic rhinosinusitis was significantly associated with an increased risk of hospital admission in COVID-19 patients (AOR = 3.19, 95% CI = 1.12–10.68). However, they also reported that this risk was not associated with an increased risk of mortality, mechanical ventilation, or admission to the ICU. The risk of hospitalization in COVID-19 patients with chronic rhinosinusitis is 3.46 times higher than in patients without rhinosinusitis. A more recent case-control study by Workman et al[14] showed that the risk of COVID-19 is not associated with having chronic rhinosinusitis. Miller et al[15] further demonstrated that the risk of COVID-19 is not associated with the administration of steroid therapy in patients with chronic rhinosinusitis. There have been some concerns regarding the negative impact of steroid therapy on the immune response in patients with chronic rhinosinusitis. However, current evidence does not support these concerns, which need further evaluation in future investigations.

Pathogenesis

Evidence shows that chronic rhinosinusitis is significantly associated with increasing the risk of sepsis, pneumonia, and mortality. This might be attributed to the fact that the presence of sinusitis might lead to a significant reduction in nitric oxide production and can provide a viral or bacterial reservoir, increasing the susceptibility to developing a secondary infection and reducing the functions of the host immune response.[16,17] Previous studies also showed different modalities of immune dysfunction with chronic rhinosinusitis, including specific antibody deficiency and epithelial barrier dysfunction.[18–20] This can significantly increase the risk of COVID-19 and induce a severe disease.

Different mechanisms and pathogenetic theories have been proposed to justify the association between severe COVID-19 or increased infectivity of SARS-CoV-2 and chronic rhinosinusitis. For instance, chronic rhinosinusitis is usually caused by a viral infection, which increases the risk of other viral co-infections, including SAR-CoV-2. This has been indicated in a previous investigation that compared viral loads in the nasal mucosa and nasal lavage fluids in patients with and without chronic rhinosinusitis. The authors demonstrated that the risk of having viral co-infection was 2.9 times higher among patients with rhinosinusitis. Moreover, it has been shown that the rate of coronavirus infection was 21.6% in these patients.[21] Another explanation might be the impairment that affects the functions of the sinonasal epithelial barrier, leading to an increased risk of viral invasion in patients with chronic rhinosinusitis. This happens to be a potential impairment in the mucociliary clearance of viral pathogens. In this context, a previous study demonstrated that patients with chronic rhinosinusitis usually have functional and morphologic changes within sinonasal epithelial cells. These changes involve loss of ciliated cells, goblet cell hyperplasia, and basal cell proliferation.[22]

Another factor associated with COVID-19 and severe disease is the increased expression of the transmembrane serine protease 2 (TMPRSS2) and receptor-angiotensin converting enzyme II (ACE2) in the nasal cavities of patients with chronic rhinosinusitis due to their significant reported roles in SARS-CoV-2 transmission and entry. In addition, it is well-known that the nasal epithelium and the sinonasal cavity are regions with the highest rate of ACE2 receptors within the respiratory tract.[23–25] Accordingly, accelerating SARS-CoV-2 entry can occur secondary to viral retention in patients with chronic rhinosinusitis via viral binding receptors to TMPRSS2 and ACE2. Finally, the susceptibility to COVID-19 can be modulated by the local inflammatory response usually encountered in chronic rhinosinusitis. During inflammation, evidence shows that patients with chronic rhinosinusitis usually suffer from impaired innate immune response to potential viral infections.[26]

Furthermore, upregulating the expression of ACE2 might also occur during these inflammatory responses secondary to increased expression of proinflammatory cytokines, including interferons.[27] Therefore, these events can significantly induce SARS-CoV-2 infection in patients with chronic rhinosinusitis.[28] This evidence can be further strengthened by the reports that showed that the severity of COVID-19 in patients with chronic rhinosinusitis could be remarkably reduced by administering an inhibitor of interleukin-13 and 4 (dupilomab).[29,30] Accordingly, these discussed factors in patients with chronic rhinosinusitis can significantly increase the risk of SARS-CoV-2 infection and the severity of a pre-existing COVID-19.

Chronic Rhinosinusitis and COVID-19 Symptoms

Some studies have previously used the Sino-Nasal Outcome Test-22 questionnaire to assess the quality of life and severity of chronic rhinosinusitis-related symptoms in patients suffering from COVID-19.[31] For example, a cross-sectional study by Akhlaghi et al[31] reported no significant differences between patients with and without chronic rhinosinusitis, regarding otologic, nasal, emotional, and sleep domains, according to the Sino-Nasal Outcome Test (SNOT)-22 questionnaire. Therefore, the authors concluded that the presence of COVID-19 in patients with chronic rhinosinusitis does not alter the related manifestations of these patients. Besides, the authors investigated the differences in disease severity among chronic rhinosinusitis patients with and without nasal polyps. It has been shown that no significant differences in COVID-19 severity were noticed between the two groups. However, after one year of the COVID-19 pandemic, the SNOT scores were significantly reduced among the CRS patients (40.1 vs 46.3, $p < 0.01$).[31]

Olfactory Loss in COVID-19

Official epidemiological reports from the World Health Organization show that olfactory dysfunction can occur in 5% to 85% of patients with COVID-19.[5,7,32] In addition, early symptoms of COVID-19 might include sudden olfactory loss with no nasal congestion.[33–36] Accordingly, at the time of outbreaks, different countries have adopted the recommendation that patients with sudden olfactory dysfunction should be isolated for being suspected of COVID-19.[4,36–38] However, it should be noted that this strategy was not reliable in detecting COVID-19 cases, especially as most cases were based on self-reports.[4,39,40]

It should be noted that olfactory loss secondary to COVID-19 is usually reversible, and patients gain partial or normal olfactory functions within the first weeks following the viral infection. On the other hand, it has been shown by de Melo et al in their hospital-based cross-sectional study that olfactory dysfunction might persist in some patients for months after the infection and might be permanent in others.[41] However, it remains controversial why olfactory dysfunction occurs in COVID-19 patients. Accordingly, various investigations have provided some theories regarding the potential pathogenesis of olfactory dysfunction in these patients.[42,43] For example, it might be due to infection of the sustentacular supporting cells and epithelial injury, which is associated with upregulation and overexpression of ACE2 receptors.[44,45] Another factor might be obstruction of the olfactory cleft and epithelial edema.

Moreover, neuropilin-1 receptor (NRP1)-mediated injury to the olfactory sensory mucosa might also represent a significant factor that enhances the pathogenesis of the condition as it enhances binding with the spike protein.[46,47] Although current evidence through a prospective cohort study supports the claims that endothelial injury to the olfactory mucosa is a significant factor for olfactory dysfunction in COVID-19 patients,[48] this mechanism does not adequately represent the characteristics of the phenomenon in these patients. Some of these characteristics include the possible presence of viral particles in olfactory bulbs, neuroimaging changes, the variable duration of olfactory loss in affected patients, and the inverse association between the prevalence of olfactory loss and the severity of COVID-19.

It should be noted that some evidence shows that some of these characteristics can be understood by the potential role of NRP1-mediated viral entry, as the receptor is markedly expressed in neuronal progenitor cells and olfactory neurons.[47] This can facilitate damage and loss of neuronal progenitor cells and olfactory functions following viral entry and damaged olfactory neurons. Moreover, these events will lead to axonal transport to the olfactory bulbs, remarkably delaying the recovery of olfactory dysfunction.

Fungal Sinusitis

Acute Invasive Fungal Rhinosinusitis (AIFR)

AIFR can be defined by acute fungal tissue invasion, with a clinical course that develops within less than four weeks.[49] However, evidence shows that affected patients usually develop the clinical course with days that do not usually exceed a few weeks. Besides, thrombosis and vascular invasion are usually associated.[50] Patients usually present with fever, facial pain, and nasal congestion, with frequent extension into the surrounding structures, like the cranial cavity, orbit, and paranasal soft tissues. Attenuation of vision might occur secondary to orbit invasion. Moreover, neurological impairments and proptosis might occur in intracranial or orbit extensions.[50,51]

It is recommended that the diagnosis and management of AIFR should be conducted urgently as the condition is time-sensitive, might be associated with serious complications, and can even lead to mortality. Furthermore, AIFR represented a major burden even before the COVID-19 era, indicating the present huge burden when many events have been reported in COVID-19 patients. For instance, a 10-year prospective cohort study conducted in Egypt in a pediatric oncology center discovered 45 cases of AIFR. Similar rates were also reported in other countries.[52,53] Another investigation reported that an annual number of 5–7 AIFR cases is usually diagnosed in their center. However, during the COVID-19 pandemic, a substantial increase in AIFR cases was noticed in their center.[54,55]

This has been furtherly indicated in another Egyptian retrospective study, indicating the significant association between COVID-19 and AIFR. However, the authors further demonstrated that the extent of surgical resection and local infection is not associated with COVID-19.[56] Ismaiel et al[57] also conducted a comparative study between COVID-19 and non-COVID-19 patients and found that the rate of AIFR among COVID-19 patients was higher than in the other group. A more recent investigation in India showed the association between COVID-19 and fungal rhinosinusitis as they included a relatively large number of cases in their study.[58] Interestingly, most of the reported cases were of acute onset. On the other hand, a case report by Treviño-Gonzalez et al[59] described a case of chronic granulomatous invasive fungal rhinosinusitis in a COVID-19 patient, which was atypical.

The exact incidence of fungal sinusitis in patients with COVID-19 is still unknown. This is because most of the currently published investigations are limited case reports, reporting the clinical sequence and management approaches of a single or a small number of patients.[60,61] However, a recent systematic review analyzed the findings of 14 reports that reported cases of AIFR in association with COVID-19. The authors reported that 206 cases were retrieved from these articles, mostly found in India, Egypt, and North America.[62] In addition, a large Indian retrospective observational study involving 2826 patients by Sen et al showed that rhino-sinusal mucormycosis (24.6%) was the second most common form of mucormycosis in their COVID-19 patients after rhino-orbital (48.9%).[63] Furthermore, a similar prevalence rate was reported in a review of observational studies by Casalini et al,[64] as the authors reported that the prevalence of fungal sinusitis was 24.6%.

Intracranial involvement was also reported in different investigations. Many previous studies and case reports also showed the involvement of the cavernous sinus by fungal infection associated with COVID-19.[54,65–71] A systematic review of these studies showed a significant association between COVID-19 and the development of these events, with estimated cases of 36/132.[72] Moreover, a prospective longitudinal study by El-Kholy et al[54] estimated that 2.7% of his population (n = 36) had transverse and sigmoid sinus thrombosis.

Various studies also reported the frequency of involvement of paranasal sinuses. For instance, Arjun et al[73] reported that the ethmoid sinus was the most commonly involved paranasal sinus in their population (80%). On the other hand, Bayram et al[74] and Nehara et al[70] reported prevalence rates of 90.9% and 100% for the involvement of ethmoid sinuses in their population, respectively. Pansinusitis was also frequently reported in many similar investigations. For instance, Pakdal et al[65] estimated that their study population was commonly affected with pansinusitis. Bayram et al,[74] Sen et al,[71] Nehara et al,[70] and Ravani et al[69] also reported prevalence rates of 90.9%, 100%, 60%, and 77.4%, respectively.

Risk Factors

Diabetes Mellitus (DM)

Many studies have implied the association between different factors that might predispose to the development of AIFR before and during the COVID-19 pandemic. For instance, a non-COVID-19 study by Kursun et al[75] demonstrated that among patients with AIFR, diabetes mellitus (DM) was the commonest comorbidity. Moreover, the authors reported that chronic kidney disease and hematological malignancies were other associated morbidities. Other studies before the COVID-19 pandemic also demonstrated that DM was the most common morbidity in their AIFR populations.[76–81] Furthermore, in 2013, Turner et al[82] showed that in their AIFR population, the prevalence of DM was 47.8%.

Moreover, other factors, such as hematological malignancies and corticosteroids, were prevalent in 39% and 27.6% of their population. DM, highly prevalent in Egypt, is also identified as a risk factor for developing fungal infections in the country.[83] Bakhshaee et al[84] also reported that among patients with AIFR, the commonest associated morbidities were DM and leukemia at 50% and 44.4%. Before the COVID-19 pandemic, evidence from a systematic review demonstrated that the prevalence of DM and hematologic malignancies was 48% and 39% in patients with invasive fungal sinusitis.[82] The association between AIFR and DM might be due to the affinity between fungal infection and high glucose concentrations together with the acidotic environment in these patients. Bala et al[85] showed that the chance of developing mucormycosis is 7.5 times higher in diabetic patients than in healthy individuals.

Studies that included COVID-19 patients also demonstrated that DM was the commonest risk factor for developing AIFR in these patients. For instance, a prospective longitudinal study by El-Kholy et al[54] showed that DM was present in 27.8% of their patients that developed AIFR acutely after COVID-19. This has been furtherly indicated in another Egyptian investigation as the authors showed that COVID-19 is strongly associated with developing DM in previously healthy individuals. DM, in turn, is significantly associated with developing AIFR. Other studies further indicated this. Ismaiel et al[57] showed that DM was the commonest predisposing factor for developing AIFR in their population, followed by renal and liver dysfunction due to the negative impact of these conditions on the immune systems of these patients. A recent systematic review of COVID-19-associated AIFR cases also reported that DM and hypertension were the most common risk factors in the population.[62] The authors reported that DM was prevalent in 73.3% of their population, while hematologic malignancies were found in 1.5%, which was inconsistent with previous pre-COVID-19 studies that indicated that hematologic malignancies were the second commonest morbidities identified in patients with AIFR. Such findings indicate the huge impact of DM on COVID-19 patients in developing AIFR.

Steroids

Steroid therapy might also be a significant risk factor for developing AIFR during COVID-19. This is because many patients have been administered steroid therapy as a management approach for COVID-19 due to the early reports that suggested the administration of steroids for managing COVID-19. This has been further indicated by Donovan et al[62] that steroid use was found in 65% of their COVID-19-associated AIFR population. In addition, in a recent Indian retrospective study by Baghel et al[58] demonstrated that HbA1c levels and duration of steroid use in COVID-19 patients were significantly associated with AIFR.

The association between hyperglycemia and diabetes was also investigated in some studies, which might have induced a larger risk of developing AIFR. Evidence shows that patients might have diabetic ketoacidosis secondary to steroid-induced hyperglycemia, contributing to the risk of AIFR during COVID-19.[86,87] However, it should be noted that steroid dosing was remarkably variable during the COVID-19 pandemic, explaining why some populations might be at more risk of developing secondary infections and adverse events than others.[88,89]

COVID-19-Induced Immunosuppression

Moreover, COVID-19 is a significant risk factor for developing an invasive fungal function. This has been indicated according to evidence from the UK National Mycology Reference Laboratory. COVID-19 might dysregulate the immune functions of affected hosts, leading to an impaired immune response and increased incidence of fungal and bacterial infections. However, it should be noted that Ebeid et al[56] suggested that the association between COVID-19 and AIFR is

not a direct one. In fact, COVID-19 could be responsible for developing other predisposing factors, including DM and impaired immune response, which are usually responsible for the development of AIFR.

It should be noted that some relevant studies reported that the above-mentioned risk factors could be combined in patients with COVID-19 and AIFR, representing the most significant risk for health deterioration in affected patients. For example, Pradhan et al[90] reported that DM was present in 96% of their COVID-19 AIFR patients, while a history of using corticosteroids was found in 89% of the total population. This was further indicated in another Indian investigation by Moorthy et al,[91] as the authors reported that almost all of their patients had a history of DM and steroid use. A retrospective study by Moorthy et al[91] reported that uncontrolled diabetes ($p = 0.03$) and patients who received steroids at some point of time during the treatment ($p = 0.0013$) had significantly higher chance of developing the maxillofacial and rhino-cerebro-orbital fungal infections. Similar findings were also reported by other studies and systematic reviews.[72,92]

Serum Ferritin

Even though uncontrolled diabetes mellitus was one of the critical risk factors for developing mucormycosis, the increased level of serum ferritin associated with mucormycosis among COVID-19 patients was demonstrated by some researchers. A study conducted during the second wave of the COVID-19 pandemic in India by Nayak et al identified increased serum ferritin levels with a mean of 662.01 ng/mL and raised levels of D-Dimer as the associated factor for increased risk of developing mucormycosis.[93] A prospective study by Anand et al in 2022 that compared serum ferritin values among COVID-19 and non-COVID patients demonstrated a higher serum ferritin level among COVID-patients, and mucormycosis patients had higher serum ferritin levels, especially among the non-survivors and critically ill patients.[94] Similar findings were observed by Rao et al and Bhadania et al.[95,96]

A summary of studies that demonstrated the risk factors for developing acute invasive fungal rhinosinusitis among COVID – 19 patients are depicted in Table 2.

Table 2 Summary of Studies That Demonstrated the Risk Factors for Developing Acute Invasive Fungal Rhinosinusitis Among COVID – 19 Patients

Authors	Study Design	Sample Size	Findings
Pradhan P et al[90]	Retrospective hospital-based study	46 Covid-associated mucormycosis (CAM) patients	Forty-four patients had diabetes. No significant association between old and newly diagnosed diabetes mellitus for the development of CAM ($P > 0.05$). Patients who were given steroids had a significant factor in the development of CAM.
Moorthy A et al[91]	Retrospective study	18 COVID-19 patients with maxillofacial and rhino-cerebro-orbital fungal infections	Uncontrolled diabetes ($p = 0.03$) and patients who received steroids at some point of time during the treatment ($p = 0.0013$) had significantly higher chance of developing the fungal infections
Singh AK et al[92]	Systematic review	101 CAM cases	Mucormycosis were commonly noted in males (78.9%) and patients with the pre-existing diabetes mellitus (80%)
Nayak PS et al[93]	Case-series	30 CAM patients	Increased serum ferritin levels with a mean (± standard deviation) of 662.01 (±129.2) ng/mL and raised levels of D-Dimer 761.33 (± 151.8) as the associated and interlinked factors along with the diabetes mellitus for increased risk of developing mucormycosis
Rao C et al[95]	Cross-sectional study	75 CAM patients	The most commonly associated comorbidities were diabetes mellitus (60%), elevated mean serum iron level, and total iron binding capacity.

Conclusion

The current literature review discussed the association between COVID-19 and chronic sinusitis and AIFR. Evidence shows that chronic sinusitis might have a negative impact on COVID-19 outcomes. However, current results are conflicting, and further studies are needed. On the other hand, COVID-19 can also lead to olfactory dysfunction, which is usually temporary. In addition, we found several studies that indicated the association between COVID-19 and AIFR. The condition is usually associated with severe morbidities, as affected patients are usually immunocompromised. Evidence among studies in the literature shows that affected patients with AIFR usually include patients with uncontrolled diabetes, malignancy, immunosuppression, AIDS, the administration of chemotherapy and other immunosuppressive drugs, and COVID-19.

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