



A Systematic Review of the Potential Implication of Salivary Secretions in Covid-19 Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review

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ABSTRACT

As reported on 23rd May 2021, there are a total of 167,313,629 confirmed cases of Covid-19 all across the world with a mortality of about 3,473,851 whereas in Saudi Arabia 439,847 were registered cases of covid-19 and 7,237 deaths. According to the World Health Organization (WHO) a total of 12,244,264 people were vaccinated with Covid-19 vaccination. Covid-19 is a respiratory infectious disease. More recent researches on SARS-COV-2 suggests the entry of the virus into the host cell using the host entry factors like TMPRSS-2, TMPRSS-4 and ACE-2 in the oral tissues.

The spike proteins of the SARS COV-2 attaches to the ACE-2 and TMPRSS2 of the salivary gland. Saliva provides the lubrication of the oral cavity, initiation of digestion and provides immunity in host. A complete research of all the articles was done using databases like: SCOPUS, PUBMED, EMBASE and WEB OF SCIENCE. In case of SARS CoV-2, the salivary glands act as reservoir for the virus. Intake of these viruses present in infectious saliva droplets found in the air would lead to the transmission of infection to an individual. Saliva is more efficient when compared to the blood as it doesn't clot. A reduced secretion of saliva is observed in patients post the covid 19 disease.

Keywords: Covid-19; salivary secretions; saliva; salivary glands; SARS CoV-2; ACE-2; TMPRSS; oral cavity.

1. INTRODUCTION

COVID-19, that stands for the corona virus disease 2019, is a highly infectious disease that is caused by SARS-COV-2 (Severe Acute Respiratory Syndrome Corona Virus 2). The first case infected with Covid-19 was identified in December, 2019. Later the disease spread globally to various parts of the world, leading to WHO declaring it as a pandemic. The signs and symptoms of Covid-19 are variable but mostly it includes fever, headache, dry cough, fatigue, breathing difficulties, and significant loss in taste and smell. Among all the cases of Covid-19 registered, 81% had developed mild to moderate symptoms, 14% developed severe symptoms and 5% suffered with critical symptoms. Usually it was reported that the old aged patients are at a higher risk of mortality due to Covid-19 disease. Damage to organs is observed in few people who experience long COVID. Many studies are under process to investigate more about the long term effects of Covid-19 [1].

As reported in January 2021, 3 new variants of Covid -19 was discovered in London, South Africa and Brazil. While studying the new UK variant using epidemiology, genome sequencing and modelling; it was reported that this strain transmits easily when compared to the other strains. Mostly the upper respiratory tract and the lower respiratory tract are effected by Covid -19 especially the lungs. The virus acts by accessing the host cells through the Angiotensin converting enzyme 2 (ACE - 2), found abundantly in type II alveolar cells. The corona virus uses spike glycoproteins to enter the host cell. If the Alveolar cells are severely affected it may eventually lead to death. The corona virus transmits from human to human by direct or contact transmission. Cough, nasal droplets and sneeze can cause direct transmission, while the mucus membrane of nose and eyes, ocular contact and saliva can cause contact transmission. In a dental clinic, the

chance of transmission of SARS-COV-2 through saliva is inevitable.

For safety of the dental doctors and patients, inside the dental clinics, the study of role of saliva in transmitting the virus is significant. As mentioned earlier about the crucial role of Angiotensin converting enzyme 2 (ACE-2) in invasion of SARS-COV-2 inside the cell, we need to analyze the Saliva of Covid-19 patients to explain the pathogenesis of SARS-COV-2 in the oral cavity of the patient. To keep a track of the present day COVID-19 pandemic, we need to carry out a quick and efficient diagnosis of it. Most commonly used upper respiratory tract specimen to diagnose Covid-19 are nasopharyngeal and oro-pharyngeal swabs. These 2 diagnosis specimens are painful and may even lead to nose bleed in thrombocytopenia patients. More recent researches on SARS-COV-2 suggests the entry of the virus into the host cell using the host entry factors like TMPRSS-2, TMPRSS-4 and ACE-2 in the oral tissues. In the oral cavity, the Salivary Glands and the barrier mucous acts like potential gate ways for transmission of the viral infection and also its replication [2].

The major salivary glands (parotid, sublingual and sub mandibular) along with the minor salivary glands secrete the saliva in the mouth. Saliva provides the lubrication of the oral cavity, initiation of digestion and provides immunity in host. Saliva is a biological fluid that contains proteins like mucins, that have high sialic acid content along with water and ions. A wide variety of diseases have their biomarkers found in the salivary sections. Very less information was available about the involvement of the oral cavity in the infections related to SARS-COV-2.

According to few research articles, the scientist suggests that the upper respiratory tract and the lower respiratory tract are the main sites for SARS COV-2 infections. Many scientist claimed

the presence of virus in the saliva of patients with nasal secretions and phlegm present in lungs; but unable to explain the presence of the virus in the Saliva of patients with no respiratory symptoms. Later a doctor from the American Dental Association reported the presence of virus in saliva of the patient from infected tissues of their oral cavity based on data from laboratories. The research team of the American Dental Association studied the dead bodies infected with Covid-19, and found the presence of SARS-COV-2 in the salivary glands of the dead.

The spike proteins of the SARS COV-2 attaches to the ACE-2 and TMPRSS2 of the salivary gland. All the SARS COV-2 replicates and secretes virus in the Saliva and can be detected in the saliva by the RT-PCR and immunoglobulin or antigen detection. Saliva based biomarkers can be used for Covid-19 monitoring and also patient stratification used in immunoglobulin detection and salivaomics [3].

Many researchers reported various oral manifestations that were commonly found in 83.9% survivors especially the ectasia of the salivary gland. The hyper inflammatory response of the SARS-COV-2 caused ectasia of salivary glands. Various prospective and retrospective charts studies were carried out on Covid-19 patients that showed preferential target of virus on the oral cavity. A few studies also reported the transmission of SARS-COV-2 virus to the digestive system and lungs via saliva along with few oral symptoms like dry mouth, loss of taste and blistering. It was also studied that ACE-2 and TMPRSS protease that is used by the SARS-COV-2 to infect the human cells, is also expressed by the gingival cell, and salivary gland ductal cells. Additional to this, the saliva of symptomatic Covid patients was studied and found that there is a possibility of transmission of infection by them. Parotitis that leads to the lack of saliva is associated with the loss of taste and sticky saliva [4].

2. METHODOLOGY

2.1 Study Design

A systematic review of literature related to the saliva content found in the patients suffering with Covid-19. This study was conducted following the guidelines of PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis). A complete research of all the articles was done using databases like: SCOPUS, PUBMED, EMBASE and WEB OF SCIENCE. The MESH

terms (General controlled vocabulary) and keywords to be used were selected.

2.2 Eligibility Criteria

All the original articles related to the content of the saliva in the Covid 19 patients were included, along with peer reviewed articles. Studies like abstracts from the conferences and abstracts written in non-Latin language were excluded. Any consensus between the authors were resolved using the eligibility criteria. All the references of the selected articles were analyzed manually, to account the exempted articles from the electronic databases.

2.3 Extraction of Data

All the main findings of articles related to the study of saliva of Covid 19 patients were analyzed and critically reviewed by the authors. It included name of the authors, year of publication, sample type, Country of Research, Journal's name, methodology used to diagnose and the results.

2.4 Selection of Articles

The literature search using Scopus, PubMed, EMBASE and Web of Science electronic databases was done using PRISMA. About 636 articles related to content of saliva in the Covid 19 patients were identified by the authors manually. 345 articles remained after removing the duplicate copies of articles. After studying all the articles completely, it was found that only 43 articles were relevant to our subject by the co-investigators. A complete systematic review of all the 43 potentially relevant articles was done, and incomplete articles with only abstracts were removed from the systematic review. After exclusion of 16 articles, only 27 remained for the II phase of article selection. In the end, only 17 articles remained for complete analysis after exclusion of articles by mutual consent.

3. RESULTS

The identified genome or RNA sequencing of the virus causing Covid-19 was named as SARS-CoV-2. A study conducted in Taiwan showed a substantial amount of the Virus genome detected in the saliva of the infected patients with Covid-19. The saliva specimen can be used as a diagnostic tool and has less exposure of health care professionals to the infected person as it is

collected easily from the spit of the patient into a sterile bottle. The saliva specimen contains saliva secreted from the salivary gland along with the nasopharyngeal secretions and mucus from the lungs via cilia. The researchers examined the tissues that were mostly infected with covid-19 and found that tongue and tonsils were high carriers of the virus RNA genome. The patient with more virus in the tongue has loss of taste and smell as one of the primary symptom of Covid 19 infection. A doctor from the American

Dental Association Science and Research Institute reported that the mouth of the patient acted as a route of infection and incubator for the SARS-CoV-2 [17]. The oral cells were analyzed against the SARS-COV-2 using the Human cell atlas to check for highly susceptible to covid-19. Other oral symptoms reported were Amblygeusia, Dry mouth, Dryness and inflammation of mouth and enlargement of lymph nodes in the sub-mandibular regions.

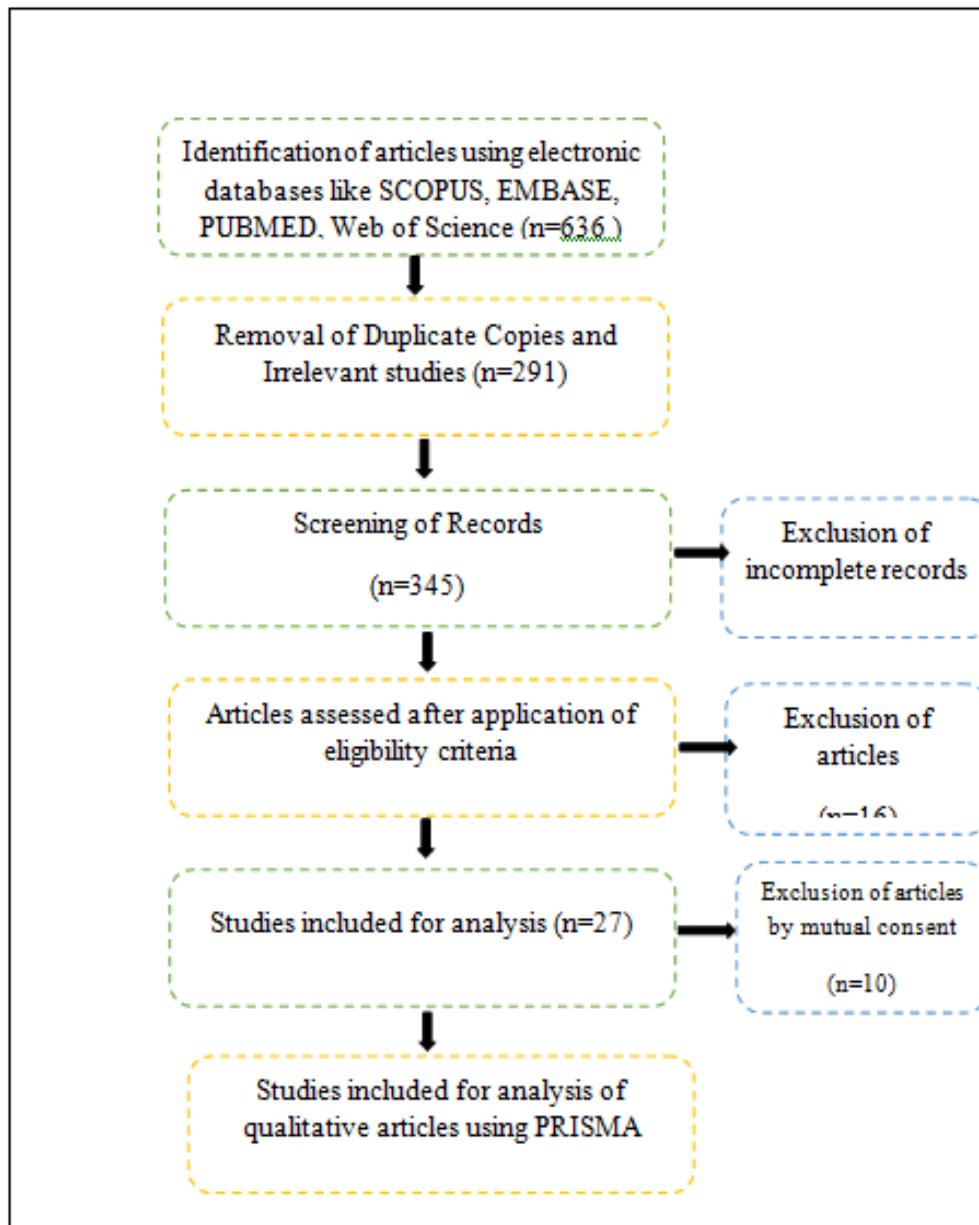


Fig. 1. Flow chart of the systematic review of the literature related to implications of Covid-19 on salivary glands

Table 1. Systematic review

Time of publication	Author's name	Country of research	Published in	Title of study	Relation with present study
May 31, 2020	Yuqing Li, Biao Ren, Xian Peng, Tao Hu, Jiyao Li, Tao Gong, Boyu Tang, Xin Xu, Xuedong Zhou.	China	Mol Oral Microbiol.	Saliva is a non-negligible factor in the spread of Covid-19 [5]	SARS-CoV-2 has been detected in saliva samples, making saliva a potential transmission route for COVID-19. saliva-contaminated surfaces could lead to potential cross-infection [5].
May 9, 2020	Pingping Han, Saso Ivanoski	Australia	Diagnostics (Basel)	Saliva- Friend or Foe in the Covid 19 outbreak [6]	This review focuses on the role of saliva as both a foe (a common mode of viral transmission via salivary droplets and potentially aerosols) and a friend (as a non-invasive diagnostic tool for viral detection and immune status surveillance) in combating COVID-19. [6]
Sep16, 2020	LL Fernandez, V B Pacheco, L Borges, H K Athwal, F de Paula Eduardo, L Bezinelli, L correa, M Jimenez, N Dame Teixeira, I M A Lombaert, D Heller.	United States	J Dent Res.	Saliva in the Diagnosis of Covid-19: A Review and New Research Directions. [7]	The utility of saliva as a diagnostic tool opens the possibility of using rapid and less invasive diagnostic strategies by targeting bioanalytes rather than the pathogen. [7]
Nov 19, 2020	Medeiros da Silva RC, Nogueira Marinho LC, de Araújo Silva DN, Costa de Lima K, Pirih FQ, Luz de Aquino Martins AR.	Brazil	Travel Med Infect Dis.	Saliva as a possible tool for the Sars-CoV-2 detection: A review. [8]	Viral nucleic acids found in saliva obtained from the duct of the salivary gland may indicate infection in that gland. Live viruses could be detected in saliva by viral culture. [8]
Sep, 2020	Baghizadeh Fini M.	Iran	Oral Oncol.	Oral saliva and COVID-19.[9]	Saliva offer an ecological niche for the colonization and development of oral microorganisms, but it also prevents the overgrowth of particular pathogens such as viral factors. [9]
Apr,2020	Atukorallaya DS, Ratnayake RK.	Canada	Front Med (Lausanne).	Oral Mucosa, Saliva, and COVID-19 Infection in Oral Health Care. [10]	The high yield of virus in the salivary secretion is a common finding in this infection and ongoing research is focusing on developing saliva as a rapid diagnostic fluid in COVID-19. [10]
May, 2021	Huang N, Pérez P, Kato T, Mikami Y, Okuda K, Gilmore	United Kingdom	Nat Med.	SARS-CoV-2 infection of the oral cavity and saliva. [11]	Saliva from SARS-CoV-2-infected individuals harbored epithelial cells exhibiting ACE2 and

Time of publication	Author's name	Country of research	Published in	Title of study	Relation with present study
	RC, Conde CD, ..				TMPRSS expression and sustained SARS-CoV-2 infection. Acellular and cellular salivary fractions from asymptomatic individuals were found to transmit SARS-CoV-2 ex vivo. [11]
Apr, 2021	Casillas Santana MA, Dipp Velázquez FA, Sámano Valencia C, Martínez Zumarán A, Zavala Alonso NV, Martínez Rider R, Salas Orozco MF.	Mexico	Medicina (Kaunas).	Saliva: What Dental Practitioners Should Know about the Role of This Biofluid in the Transmission and Diagnostic of SARS-CoV-2. [12]	The authors can mention that information that provides more scientific evidence of the mechanisms of infection of the coronavirus in oral cells and tissues is being published continually. [12]
May, 2020	Yoon JG, Yoon J, Song JY, Yoon SY, Lim CS, Seong H, Noh JY, Cheong HJ, Kim WJ.	Korea	J Korean Med Sci.	Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. [13]	SARS-CoV-2 viral load was consistently high in the saliva; it was relatively higher than that in the oropharynx during the early stage of COVID-19. [13]
June, 2020	Shamsoddin E.	Iran	Evid Based Dent.	Saliva: a diagnostic option and a transmission route for 2019-nCoV. [14]	Given the presence of viral RNA in saliva in the early stages of COVID-19, the recommendations to wear masks to prevent the rapid transmission of infectious droplets into the air, and keep a safe distance from other people are clearly based in evidence. [14]
Dec, 2020	Dave PK, Rojas-Cessa R, Dong Z, Umpaichitra V	United States	Biosensors (Basel).	Survey of Saliva Components and Virus Sensors for Prevention of COVID-19 and Infectious Diseases. [15]	It discusses future research and challenges that must be resolved to realize practical saliva sensors. Such sensors may help minimize the spread of not only COVID-19 but also other infectious diseases. [15]
Nov, 2020	Samavati A, Samavati Z, Velashjerdi M, Fauzi Ismail A, Othman MHD, Eisaabadi B G, Sohaimi Abdullah M, Bolurian M, Bolurian M.	Malaysia	Chem Eng J	Sustainable and fast saliva-based COVID-19 virus diagnosis kit using a novel GO-decorated Au/FBG sensor [16].	The precise and highly sensitive FBG probe proposed in this study was found a reliable tool for quick detection of the COVID-19 virus within 10 s after exposure to patients' saliva in any stage of the disease. [16]
Nov, 2020	Fantozzi PJ, Pampena E, Di Vanna D, Pellegrino E, Corbi D, Mammucari S, Alessi F, Pampena R, Bertazzoni G,	Italy	Epub 2020 Sep 10	Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19.	Xerostomia, gustatory and olfactory dysfunctions may present as a prodromal or as the sole manifestation of COVID-19. Awareness is fundamental to identify COVID-

Time of publication	Author's name	Country of research	Published in	Title of study	Relation with present study
Apr, 2021	Minisola S, Mastroianni CM, Polimeni A, Romeo U, Villa A. Belchior Fontenele MNt, Pedrosa MDS.	Brazil	J. 2021 Apr	Xerostomia and Taste Alterations in COVID-19. Ear Nose Throat	19 patients at an early stage of the disease and limit the spread of the virus. Ear, Nose & Throat Journal called attention to the hypothesis that the xerostomia reported in patients with the Coronavirus Disease 2019 (COVID-19) occurs due to the neuroinvasive and neurotropism potential of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Oct 2020	Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z.	Israel	Otolaryngol Head Neck Surg. 2020	Olfactory and Oral Manifestations of COVID-19: Sex-Related Symptoms-A Potential Pathway to Early Diagnosis.	A considerable number of patients presented with olfactory and oral disorders. Interestingly, women presented with a different cluster of symptoms than men, which may suggest a new clinical approach to diagnosing COVID-19 disease.
March, 2021	Omezli MM, Torul D.	Turkey	Med Oral Patol Oral Cir Bucal.	Evaluation of the xerostomia, taste and smell impairments after Covid-19.	The most frequent finding in patients after the treatment was xerostomia. Taste and smell impairments were more frequently observed in females.
Apr, 2021	Fathi Y, Hoseini EG, Atoof F, Mottaghi R.	Iran	Future Virol. 2021	Xerostomia (dry mouth) in patients with COVID-19: a case series	Xerostomia in COVID-19 could occur before the common symptoms. Therefore, it could be hypothesized that it could be used for early diagnosis, quarantine and treatment. As a result, disease transmission might be prevented and the best treatment outcomes could be achieved.

4. DISCUSSION

The pathogenesis of the epithelial oral cells was explained by the analysis of saliva in covid-19 patients by their expression of ACE 2 receptor. The human saliva plays an important role in preventing viral infections and is considered as one of the first line of Defense responsible for innate immunity. A study reported hypo-salivation in severely infected patients with respiratory infection. If the secretion of the Saliva is low it could interfere with the oral and airway mucosal surface to promote viral colonization and adhesion, thus acting like a physical barrier. The decrease in the production of saliva may inhibit the secretion of antimicrobial peptides. Proteins with anti-viral characteristics found in the saliva like mucin, lysozyme, lactoferrin, salivary agglutinin, beta defensins, Alpha defensins, peroxidases, cystatins and many more. The above mentioned enzymes may hinder the replication of the corona virus in the Saliva. Apart from these enzymes there are few salivary micro-vesicles with minimal 20 microRNA, that may impede the replication of viruses [18].

A study by Liu reported that the salivary gland cells with increased ACE2 expression, where the one that were infected showed the expression of the ACE 2 is more in the the minor salivary glands when compared to the lungs [19]. This indicates that the target for covid-19 virus maybe possibly the salivary glands. In case of SARS CoV 2, the salivary glands act as reservoir for the virus. It was reported that the spread through the asymptomatic patients of covid-19 maybe due to the contaminated saliva. The source of infection maybe the salivary glands in the asymptomatic infection [20].

The transmission of the Saliva droplets depends on their size. The rate of transmission is high in case of small droplets of saliva when compared to the rate of transmission that is slow in case of huge droplets. The droplets of the Saliva from the infected covid-19 patient is produced while sneezing, coughing, speaking and even breathing. The Saliva droplet contains the virus along with moisture. Approximately a cough could produce 3000 saliva droplets during a 5 minute chat; 40000 saliva droplets maybe roughly produced by each sneeze that could travel for several meters in air. The small saliva droplets fly in the air easily and huge saliva drops fall to the ground and settle on the surface. Intake of these viruses present in infectious

saliva droplets found in the air would lead to the transmission of infection to an individual.

In the initial stages, the virus enters into the salivary glands and effects the flow of the saliva and its components. the neuropathic and mucotropic effects of the corona virus alters the functionality of the salivary gland, thus causing xerostomia or hypo-salivation. The administration of various medicines during covid is also known to cause hypo salivation in patients with covid. Rhinorrea and congestion in the patients can also be a risk factor for hypo salivation in covid patients.

Fantozzi et al, conducted a research on the debilitated olfactory and gustatory functions along with xerostomia in patients suffering with Covid 19. They reported that the disability of the gustatory and olfactory systems and xerostomia can be reduced if the doctors are made aware of this malfunctions in the Covid patients. Belchior Fontenele MN et al, studied about the change in the taste during and after Covid 19. Neuroinvasive and neurotropism, related to the Covid 19 virus that can cause the loss of taste and smell in patients suffering with Covid 19. Biadsee A et al, did on research related to the oral and olfactory manifestations in patients suffering with Covid 19 and reported that female showed up a different pattern of symptoms when compared to male. Omezli MM et al, reported about the alterations of taste, smell and xerostomia; they also observed an immense impairment of the taste and smell in female more than male. Fathi Y et al, observed and reported case series of xerostomia in different Covid 19 patients and refers early diagnosis to avoid complications.

In order to minimize the spread of coronavirus; surgical masks, protective eye-wear and face shields are made compulsory for the Healthcare workers. The diagnosis of covid-19 using the Saliva of the infected patient provides many benefits like it is economical, convenient to collectand non invasive. It also minimizes the chances of cross infection.

5. CONCLUSION

Over the other biological Fluids of the body, saliva plays a potential role in diagnosis. Also saliva is more efficient when compared to the blood as it doesn't clot. For the diagnosis of covid-19, the Saliva is collected via; coughing out, saliva swaps, and from the

Duct of salivary glands directly. Before starting any dental emergency treatment inside the clinic the patient need to conduct antibody test, micro fluids RT-PCR test and loop mediated isothermal amplification (LAMP).

Apart from the regular covid-19 testing, chest CT is highly recommended to assess the pulmonary infection associated with signs of covid-19. One among the post Covid symptom was: getting excessive thirst, sore throat and dry mouth (xerostomia). The patients reported minimal saliva secretion from the salivary glands due to which swallowing of the food became much painful. Drinking less water led to brain fog, weakness, anxiety and low blood pressure. Later this resulted in swelling redness and inflammation of the tongue. More research and survey need to be done on the present topic. A survey with the Covid-19 infected patients may add more value to this field.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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