ORIGINAL ARTICLE

Journal of Research in Dental and Maxillofacial Sciences
DOI: 10.52547/jrdms.7.3.155

Oral Symptoms and Factors Associated with COVID-19: A Case-Control Study

Farzin Sarkarat [1], Alireza Tootoonchian [1], Seyed Hosein Mirpour [1], Morteza Moogahi Nezhad [1], Seyed Hesam Aldin Haeri Araghi [1], Vahid Rakhshan [2]

[1] Oral and Maxillofacial Surgery Department, Craniomaxillofacial Research Center, Tehran Islamic Azad University of Medical Sciences, Farhikhtegan Hospital, Dental Branch, Tehran, Iran
[2] Private Dentistry Practice, Tehran, Iran

Corresponding author:
Alireza Tootoonchian, Oral and Maxillofacial Surgery Department, Craniomaxillofacial Research Center, Tehran Islamic Azad University of Medical Sciences, Farhikhtegan Hospital, Dental Branch, Tehran, Iran

drtootoonchian@yahoo.com

Article History
Received: Jun 25, 2021
Accepted: September 17, 2021

Abstract

Background and Aim: Coronavirus disease-2019 (COVID-19) is a serious pandemic situation. Assessment of associated factors contributing to its severity is of clinical significance. This study assessed the factors associated with COVID-19 and its severity.

Materials and Methods: In this case-control study, we assessed self-reports of 93 COVID-19 patients and 50 healthy controls regarding demographics, smoking habit, sinusitis, rhinoplasty or tonsillectomy history, xerostomia, dysosmia, dysgeusia, taste disturbances (metallic taste and foul taste), and bleeding or inflammation in the oral cavity. Further admission to ICU or death were recorded later. We also assessed the patients' laboratory tests including WBC, neutrophils, lymphocytes, basophils, eosinophils, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) at the time of admission. Diagnosis of patients was based on clinical assessments, Reverse transcriptase polymerase chain reaction (RT-PCR) and chest computed tomography (CT) scan results. Healthy controls had no flu like signs and symptoms in the past 1 month prior to the study. Associations between the abovementioned factors and disease, and disease severity were analyzed by the Chi-square test, independent-sample t-test, one-sample t-test, and Spearman's correlation coefficient (α=0.05).

Results: Variables with statistically significant associations with COVID-19 included smoking (P=0.004), xerostomia (P=0.000), dysgeusia (P=0.000), dysosmia (P=0.000), and taste disturbances (P=0.000). CRP (P=0.000), ESR (P=0.000), and neutrophil percentage (P=0.000) were also elevated in patients. Eosinophil (P=0.000) and basophil percentages (P=0.016) were lower than normal range in patients. Age was associated with death (P=0.010) and ICU admission (P=0.009).

Conclusion: Xerostomia, dysgeusia, dysosmia, and taste disturbances can be early markers of COVID-19. Older ages are prone to more severe forms of disease.

Key Words: COVID-19; Dysgeusia; Olfaction Disorders; SARS-CoV-2; Taste Disorders; Xerostomia

Cite this article as: Sarkarat F, Tootoonchian A, Mirpour SH, Moogahi Nezhad M, Haeri Araghi H, Rakhshan V. Oral Symptoms and Factors Associated with COVID-19: A Case-Control Study.
J Res Dent Maxillofac Sci. 2022; 7(3):155-161.

Introduction

Respiratory diseases caused by viral agents are one of the most critical problems in public health, as they are responsible for high rates of morbidity and mortality, mainly in young children, the elderly and immunocompromised

individuals. The most common respiratory viruses that affect the susceptible population are human orthopneumovirus (previously known as human respiratory syncytial virus), influenza virus, coronavirus, and human metapneumovirus. The transmission of these viruses is mainly by contact with fomites or suspension droplets [1]. Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome with a helical symmetry nucleocapsid of about 26-32 kilobases in size, making it the largest investigated genome among the RNA viruses [2,3]. Since Dec 8, 2019, several cases of pneumonia of unknown etiology have been reported in Wuhan, Hubei Province, China. Most patients worked at or lived around the local Huanan seafood wholesale market, where live animals were also on sale. In the early stages of this pneumonia, severe acute respiratory infection symptoms occur, with some patients rapidly developing acute respiratory distress syndrome, acute respiratory failure, and other serious complications [4].

Previous coronaviruses can cause multiple system infections in various animals and mainly respiratory tract infections in humans, such as severe acute respiratory syndrome and Middle East respiratory syndrome; although most patients have mild symptoms and good prognosis. Evidence shows that a new subtype of this family (primarily called nCoV-2019 and then changed to SARS-CoV-2) is responsible for a new disease called coronavirus disease-2019 (COVID-19) by the World Health Organization. So far, about 250 thousands of patients with SARS-CoV-2 have developed severe pneumonia, pulmonary edema, acute respiratory distress syndrome, or multiple organ failure and have died of disease [4].

This virus effectively uses angiotensin converting enzyme 2 receptor for cell invasion [5]. The elderly (> 60 y/o) are at higher risk of showing signs and symptoms. Less than half of the patients have underlying diseases, including diabetes mellitus (20%), hypertension (15%), and cardiovascular diseases (15%). Family cluster was also found. Primary non-specific reported symptoms of SARS-CoV-2 infection at the prodromal phase include malaise, fever, and dry cough. The most commonly reported signs and symptoms are fever (98%), dry cough (76%), and dyspnea (55%). Less common symptoms are sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). About 63% of patients have lymphopenia. Most patients have pneumonia with abnormal findings on chest computed tomography (CT) [3,4,6]. There have also been various studies evaluating the effects of coronavirus on the central nervous system, showing that it may cause dysosmia and dysgeusia. Loss of sense of smell and taste have been reported by individuals residing in Iran as one of the most heavily impacted countries by COVID-19 during the disease outbreak [3].

In this study, we aimed to evaluate the clinical changes and markers of COVID-19 in the maxillofacial region and analyze the correlation between oral symptoms with paraclinical test results and disease severity that may be useful for detection of COVID-19 in early stages of development.

Materials and Methods

This case-control study was conducted on 93 patients and 50 healthy controls. We obtained information from patients with COVID-19, confirmed by clinical, Reverse transcriptase polymerase chain reaction (RT-PCR) and CT findings, who were admitted to two hospitals in Tehran, Iran. The present study was approved ethically by the Research Council, Dental Faculty of Islamic Azad University. The inclusion criterion for healthy controls was not having any cold-like symptoms during the past month. The inclusion criterion for patients was confirmed diagnosis of COVID-19 based on clinical, RT-PCR and CT findings. Information was collected from patients through a short

interview with them, which was done by oral and maxillofacial residents working in Farhikhtegan Hospital and Booali Hospital. Patients were asked questions, and the answers were written by the residents. The questions concerned demographics, smoking habit, sinusitis, rhinoplasty history, tonsillectomy history, xerostomia, dysosmia, dysgeusia, taste disturbances such as metallic taste and foul taste, and bleeding or inflammation in the oral cavity. Further admission to ICU or death were recorded later. We also entered the patients' laboratory test results including, WBC, neutrophils, lymphocytes, basophils, eosinophils, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at the time of admission.

Statistical analysis:

The study population included all available patients and 50 healthy controls during a two months period of the initial coronavirus epidemic due to not performing a similar article previously. Data were statistically analyzed by SPSS version 20. Chi-square test, independent-samples t-test, one-sample t-test, and Spearman's correlation coefficient were applied to find associations between dependent and independent variables. P value < 0.05 was considered statistically significant.

Results

There were 93 COVID-19 patients and 50 controls in this study. Of healthy controls, 19 were females and 31 were males. In the case group, there were 43 females and 50 males. There was no significant association between sex and COVID-19 according to the Chi-square test (P = 0.343). The mean age of healthy controls was 54.54 ± 10.99 years. The mean age was 59.73 ± 15.95 years in patients. There was not a significant difference in the mean age of healthy controls and patients (t-test, P > 0.05).

Of 50 controls, 7 reported mild sinusitis. Of 93 patients, 11 reported mild sinusitis and 5 reported complete sinusitis. This difference was not significant (Chi-square test, P = 0.241). Of healthy controls, 27 were smoker. However, of 93 patients, only 14 were smokers. According to the Chi-square test, the frequency of smoking was significantly lower in patients compared with healthy controls (P = 0.004). Among controls and patients, 3 and 5 reported a history of tonsillectomy, respectively; the difference was not significant between the two groups in this regard (P = 0.877). History of rhinoplasty was reported by 4 controls and 11 patients. The difference was not significant in this respect either (P = 0.476).

Of 50 healthy controls, 3 reported having xerostomia while 1 stated that he might have it or may have a mild form of it. Of 93 patients, 46 had definite xerostomia while 5 had a mild form of it. The difference between the two groups was significant (Chi square test, P = 0.000). Dysgeusia (impaired sense of taste) was reported by only 1 healthy control. However, of 93 patients, 29 reported definite dysgeusia and 8 reported a mild form of it. The difference between controls and patients was significant (Chi-square, P = 0.000). Only 1 control reported complete dysosmia, while of 93 patients, 20 had complete dysosmia and 8 had mild dysosmia. This difference was significant (P = 0.000). None of healthy controls reported having taste disturbances (such as metal taste or foul taste); while 32 patients reported complete and 7 reported mild taste disturbances. The difference between the case and control groups was significant (P = 0.000). Both groups had disturbances in the oral cavity (like bleeding or inflammation): 8 controls and 7 patients reported such disturbances; however, the difference in this regard was not significant (Chi-square, P = 0.115).

In patients, the mean CRP was 49.25 ± 41.42. It was significantly higher than the reference value of 5 (one-sample t-test P = 0.0000). The mean ESR was 48.14 ± 26.33 in

patients. It was significantly higher than the maximum normal ESR = 20 (one-sample t-test, P = 0.000). The mean WBC count was 7421.8 ± 4072.3, which was not significantly different from the median of the normal reference value = 7500 (median of 4000 – 1100; P = 0.854). The percentage of neutrophils was 72.68 ± 10.50, which was significantly higher than the maximum normal range (50-60%) (P = 0.000). The lymphocyte percentage was 20.76 ± 10.03, which was not significantly lower than the lowest acceptable norm (20-40%) (P = 0.472). The percentage of eosinophils was 1.56 ± 0.99, which was significantly lower than the lower bound of the acceptable norm (2 – 8%) (P = 0.0003). The basophil percentage was 0.5933 ± 0.57752, which was lower than the lower bound of the acceptable range (1 – 4%) (P = 0.016).

Of 93 patients, only 3 expired. None of the variables were significantly associated with death (*P* > 0.05), except for old age. The mean age of surviving patients was 59.0 ± 15.7 years (range: 18 – 97 years); while the mean age of deceased patients was 80.3 ± 4.0 years (range: 76 – 84 years). The Spearman's correlation coefficient showed a positive correlation between age and death (Rho = 0.264, P = 0.010). Of 93 patients, 16 were admitted to the ICU. Similarly, no variables were significantly associated with ICU admission (P > 0.05), except for old age. The mean age of ward patients was 57.6 ± 15.9 years (range: 18 – 87 years), while the mean age of ICU patients was 70.1 ± 12.3 years (range: 54 – 97 years). The Spearman's correlation coefficient showed a positive correlation between age and death (Rho = 0.269, P = 0.009).

Discussion

The aim of this study was to evaluate certain demographic, clinical, and laboratory factors that can be associated with COVID-19 and its severity. It was found that some factors were more likely to appear in COVID-19 patients compared with healthy controls. These were xerostomia, dysgeusia, dysosmia, and taste disturbances. On the other hand, smoking was less frequent in COVID-19 patients than in healthy participants. In patients, ESR and CPR levels as well as neutrophil percentage were elevated. Instead, the eosinophil percentage and basophil percentage were decreased. Only older age was associated with higher death or ICU admission.

Given the importance of COVID-19, assessing factors that can be associated with COVID-19 disease or its more severe forms is of significant clinical importance. Besides, when the pandemic reaches a plateau and passes a peak, moderate or milder forms of disease will be more important to be attended as soon as possible [7]. Song et al., in a clinical and paraclinical study showed that males were more susceptible to COVID-19 and decrease of white blood cells, lymphocytes, monocytes, and platelets, and increased levels of ESR, CRP, Creatinine, blood urea nitrogen, LDH, and NLR (neutrophil-lymphocyte ratio) were found in COVID-19 patients [8]. Tan et al. showed that the CRP level in the severe group at the initial and advanced stages of disease was higher than that in the mild group. Correlation analysis showed that CRP, ESR, and granulocyte/lymphocyte
ratio were positively associated with the CT severity score. Also, CRP in severe COVID-19 patients increased significantly at the initial stage, before CT findings [9].

Our findings regarding dysosmia were in line with previous studies showing that dysosmia can be much more prevalent in COVID-19 patients than in general population [7,10-16]. Dysosmia and anosmia could be initial symptoms of COVID-19 and a useful early marker for prompt testing of patients [17,18]. Very high rates of dysosmia up to 98% of inpatients have been reported [12], and many of them have complete anosmia [10].

It should be noted that self-reports of dysosmia are not exact, but they are 90% accurate [7,19]. Still, future studies should assess dysosmia with objective tests because self-reports can be biased especially if assessed after the patient becomes aware of the COVID-19 diagnosis. Loss of taste was another finding of this study that agreed with previous reports [11,13-15]. Beltrán-Corbellini et al. reported that most COVID-19 patients did not report nasal obstruction and were capable of distinguishing bitterness, saltiness, and sweetness, implying specific affinity of SARS-CoV-2 for the olfactory sensory epithelium [20]. It appears that coronavirus can attack the central and peripheral nervous systems [3,21-23]. Peripheral neurological disturbances should be taken into account while encountering patients with influenza-like signs and symptoms. Xerostomia was more prevalent among patients of this study, compared with healthy controls. However, there is no previous study linking dry mouth to COVID-19. There can be reasons for xerostomia such as nasal congestion disallowing nasal breathing and forcing the patients to breathe through their mouth.

Compared with patients with lower disease severity, patients with more severe forms of disease were older in this study, which was in line with a previous study [14]. Of course, aging weakens of many body systems including the immune system and respiratory function that can make the patients more susceptible to severer forms of disease and lower response to medications [24,25].

Another finding of this study was that the prevalence of smoking was lower in the patient group compared with healthy controls. This contradicts the literature on this subject. Five studies and a systematic review were found in this regard, mostly pointing to adverse effects of smoking on the progression and severity of COVID-19 [4,26-29]. However, in some of them, current and even ex-smoking had a low frequency in patients, which was similar to our findings [30]. The reason for the present findings and those of Zhang et al. [30] is not known, and needs future studies to justify and ravel the underlying mechanisms for the negative association that was observed between smoking and COVID-19.

Conclusion

The present findings indicated that the COVID-19 patients had a much higher prevalence of xerostomia, dysgeusia, dysosmia, and taste disturbances. ESR and CPR were elevated. The percentage of neutrophils was increased while the percentage of eosinophils and basophils decreased. Interestingly, a lower percentage of COVID-19 patients reported to be smokers compared with healthy controls. The Only factor that was associated with higher mortality and ICU admission was older age.

References

1. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. Front Cell Neurosci. 2018 Oct 26;12:386.

2. Gorbalenya A, Baker S, Baric R, de Groot R, Drosten C, Gulyaev A, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol .2020 March;5:536-44.

3. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; a hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg. 2020 Mar 30;42(1):9.

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.

5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang

RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar; 579 (7798):270-3.

6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-13.

7. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. Int Forum Allergy Rhinol. 2020 Jul;10(7):821-31.

8. Song C-Y, Xu J, He J-Q, Lu Y-Q. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. medRxiv 2020.

9. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, Jiang X, Li X. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020 Jul;92(7):856-62.

10. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020 07; 10(7):806-13.

11. Menni C, Valdes AM, Freidin MB, Ganesh S, El-Sayed Moustafa JS, Visconti A, et al. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. medRxiv. 2020:2020.04.05.20048421.

12. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol. 2020 Aug;10(8):944-50.

13. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch torhinolaryngol. 2020 Aug;277 (8):2251-61.

14. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Jun 1;77 (6):683-90.

15. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clin Infect Dis. 2020 Jul 28;71(15):889-90.

16. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol. 2020 Aug;10(8):944-50.

17. Lechien JR, Hopkins C, Saussez S. Sniffing out the evidence; It's now time for public health bodies recognize the link between COVID-19 and smell and taste disturbance. Rhinology. 2020 Aug 1;58(4):402-3.

18. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology. 2020 Jun 1;58(3):295-8.

19. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. Arch Clin Neuropsychol. 2011 Apr;26(3):260-9.

20. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. Eur J Neurol. 2020 Sep; 27(9): 1738-41.

21. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. Nat Rev Microbiol. 2006 Feb;4(2):121-32.

22. Barthold SW, de Souza MS, Smith AL. Susceptibility of laboratory mice to intranasal and contact infection with coronaviruses of other species. Lab Anim Sci. 1990 Sep;40 (5):481-5.

23. Perlman S, Evans G, Afifi A. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. J Exp Med. 1990 Oct 1;172(4):1127-32.

24. Burns EA. Effects of aging on immune function. J Nutr Health Aging. 2004;8(1):9-18.

25. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging. 2006; 1(3):253-60.

26. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. Tob Induc Dis. 2020 Mar 20;18:20.

27. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.

28. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.

29. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, Wei S, Deng Y, Liu J, Liu HG, Yang M, Hu Y. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020 May 5;133(9):1032-8.

30. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Jul; 75(7):1730-41.