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## Oral Manifestations in Mild to Moderate Cases of COVID-19 Infection in the Adult Patient

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### ABSTRACT

Coronavirus disease 2019 (COVID-19) is a serious illness with a wide range of symptoms. The all effects of this rising number of atypical infection on the oral cavity are not completely known. The aim of the present study was to investigate the oral manifestation which could be observed in mild to moderate cases of COVID-19. This questionnaire survey includes 289 adult patients with who were confirmed COVID-19 positive based on the polymerase chain reaction (PCR) and followed at home by the Canik district health directorate between January 2021 and June 2021. After applying the exclusion criteria cases with mild to moderate patients were included in the study. A 4-part questionnaire was applied to the patients for evaluation. The first part of the questionnaire included demographic characteristics, smoking, general health status and oral hygiene habits; the second part includes xerostomia findings; the third part includes the determination of gingival changes and mouth sore. Fourth part includes the evaluation of taste-smell alteration and trigeminal neuropathic pain. The effects of the variables collected in the first part of the survey were statistically evaluated on finding of xerostomia, gingival changes, taste-smell alteration, mouth sore and neuropathic pain. Class comparisons were made using Wilcoxon and Kruskal-Wallis tests, multiple comparison were made using Mann-Whitney test, the relationship between the categorical variables were examined with  $\chi^2$  test. The highest prevalence symptom was xerostomia (69%) and patients over 65 years of age were more symptomatic ( $P=0.015$ ). There is a statistical difference in dry mouth between patients who smoked more than 20 cigarettes a day and those who did not smoke ( $P=0.002$ ). There is no statistical difference between the oral hygiene habits of the patients and the symptoms of COVID-19 ( $P=0.33$ ). A statistical difference is found between patients without chronic disease and patients with one or more chronic diseases in terms of xerostomia, taste-smell changes, gingival changes and neuralgia form pain ( $P=0.01$ ). The highest incidence of mouth sores was 35% in patients with more than one chronic disease. this is followed by type II diabetes (21%), hypertension (18%) and patients without chronic disease (7%), respectively. Xerostomia was more common in COVID-19 infected patients over 65 years of age. Smoking and comorbidities increased the prevalence of oral symptoms of COVID-19 infected patient. COVID-19 may cause neuralgia form pain at lips and tongue hypoesthesia as well as olfactory and gustator dysfunctions.

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### INTRODUCTION

The novel Coronavirus Disease-19 (COVID-19) epidemic continues around the world with profound social and economic impacts. More than two hundred and fifty million infections and more than five million deaths have been reported since its first appearance (1).

Patients affected by COVID-19 typically develop a mild flu-like condition that begins 2-14 days after exposure. It can occur with a variety of conditions ranging from life-threatening multi-organ failure, and the mortality rate is significantly higher in those with co-morbidities, the elderly, and those requiring hospitalization and ventilation support in intensive care units (2).

**Table 1.** Questionnaire for investigating the oral manifestations of coronavirus disease 19 (COVID-19).

Questions	Answers				
Dou you agree to participate in this study?	Yes	No			
1 <sup>st</sup> section: demographic data, oral hygiene status and smoking					
Gender	Female	Male			
Age					
1. Dou you have the habit of brushing your teeth regularly?	No	2-3 times a week	1 time per day	2 times a day	3 times a day
2. Dou you have a habit of using mouth wash regularly?	No	2-3 times a week	1 time per day	2 times a day	3 times a day
3. Do you smoke	No	5 a day	10 a day	20 per day	30-40 per day
4. Do you have one of the following chronic diseases and do you use medication?	Heart disease	Diabetes	Hypertension	Liver kidney failure	
	<i>Auto-immune diseases:</i>	Sjogren's syndrome	Lupus erythematosus	Pemphigus	
	Mucous membrane pemphigoid	Erythema multiforme	Lichen planus	Behcet's disease	
Medication name:					
2 <sup>nd</sup> section: xerostomia alteration data					
Have your following symptoms change after your COVID-19 symptoms started?					
1. Bad odor in my breath increased during the day	Almost	Never	Very little	A little much	Too much
2. The feeling of dryness in my throat increased during the day	Almost	Never	Very little	A little much	Too much
3. My thirst increased during the day	Almost	Never	Very little	A little much	Too much
4. I have difficulty swallowing and speaking	Almost	Never	Very little	A little much	Too much
5. I have difficulty using dentures (dentures)	Almost	Never	Very little	A little much	Too much
6. I feel burning in my tongue and mouth while eating	Almost	Never	Very little	A little much	Too much
3 <sup>rd</sup> section: gingival changes and mouth sore data					
1. My gums bleed more when brushing teeth	Almost	Never	Very little	A little much	Too much
2. I have swelling in my gums	Almost	Never	Very little	A little much	Too much
3. Increased redness in my gums	Almost	Never	Very little	A little much	Too much
4. I have sores in my mouth	Yes (tongue/ lip/gum/palate)	No			

**Table 1** (continued)

4 <sup>th</sup> section: taste-smell alteration and neuropathic pain					
<b>1. I can't taste the food I eat</b>	Almost	Never	Very little	A little much	Too much
<b>2. My sense of smell is impaired</b>	Almost	Never	Very little	A little much	Too much
<b>3. I can't smell the food I eat</b>	Almost	Never	Very little	A little much	Too much
<b>4. I have sudden pain in my lips and cheeks with electric shocks</b>	Almost	Never	Very little	A little much	Too much
<b>5. I feel tingling on my lips and cheeks</b>	Almost	Never	Very little	A little much	Too much
<b>6. I feel numbness in my lips and cheeks</b>	Almost	Never	Very little	A little much	Too much

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is detected in the cell membrane of numerous human organs and tissues, including the lungs, kidneys, liver, tongue epithelial cells, and salivary glands (3).

Recent studies have shown that COVID-19 specifically targets ACE2-expressing cells in the olfactory, trigeminal and salivary glands, or dysfunctions occur depending of olfactory and trigeminal bulb invasion due to central nervous system involvement (4-6).

It has been reported that patients diagnosed with COVID 19 have a decrease in salivary gland functions, taste and smell functions, prodromal or with COVID 19 infection. The SARS-CoV-2 virus, known to bind to epithelial and salivary gland cells, is likely to cause changes in the patient's oral cavities (7). In this study, it was aimed to evaluate the oral manifestations that can be reported in mild and moderate cases of COVID-19 patients.

## METHODS

### Study Design

For this study, a survey form was prepared. The survey is consisting of questions asking about the clinical characteristic findings of the known oral findings of COVID-19 and for investigated possible findings.

This study included adult COVID-19 patients ( $\geq 18$ ) who were evaluated Canik district health directorate Samsun, Türkiye between Jan 2021 and Jun 2021 with confirmed SARS-CoV-2 infection. SARS-CoV-2 testing was obtained by sampling both the nasal and oropharyngeal mucosa and analyzed with polymerase chain reaction (PCR). Patients' additional laboratory tests, disease severity, treatment methods (home or hospitalized), whether they received drug treatment and follow-up periods were learned from the electronic patient follow-up system of the Canik district health directorate. The sample size of the study was calculated by power analysis by taking significance level ( $\alpha$ ) 0.05 and statistical power ( $1-\beta$ ) 0.95%. This value was calculated as 111 patient. But for increase the study confident the sample size was kept above this value.

The ethical protocol of this study was obtained from the non-interventional clinical research ethics committee of Samsun

Health Sciences University Training and Research Hospital (GOKA/21/10/19).

The patients included in the study were surveyed over the phone or face-to-face.

### Inclusion criteria

- Patients over 18 years of age
- Patients who volunteer to participate
- Patients who do not normally have symptoms of dry mouth
- ASA I and II patients
- Patients who mild to moderate COVID-19 infection

### Exclusion criteria

- Patients younger than 18 years
- Patients who did not want to participate
- Pregnant patients
- Patients who have had salivary gland disease or have undergone surgery
- Patients with a history of recurrent mouth sores
- Patients with history of oro-facial or neuralgia form pain
- ASA III and IV patients
- Patients with serious COVID-19 infection, who experienced severe respiratory failure (severe pneumonia, severe dyspnea) or patients who required hospitalization.
- Patients that used any other drugs than antiviral drugs (favipiravir and hydroxychloroquine sulphate)

### Survey

Before the questionnaire, the patients were questioned about xerostomia, taste-smell functions, gingival bleeding, and the incidence of mouth sores. A questionnaire consisting of 17 questions and 4 parts was applied (**Table 1**).

The first part of the questionnaire included patients' demographic information (age, gender). The second part (questions 1 and 2) was designed to determine the oral hygiene habits of the patients. The third part (question 3) questioned the smoking habits of the patients, and the fourth part (question 4) questioned the determination of chronic and autoimmune disease of the patients.

**Table 2.** Study groups and patient characteristic that collected from the first part of survey.

Patients characteristics	Group Name	Number of patients (n=289) [n(%)]	Number of patients with mouth sore [n (%)]
<b>Age</b>			
18-30	A1	79 (27.3)	4 (0.05)
31-65	A2	196 (67.8)	21 (0.1)
65+	A3	14 (4.8)	2 (0.14)
<b>Gender</b>			
Male	G1	154 (46.7)	12 (0.07)
Female	G2	135 (53.3)	15 (0.1)
<b>Oral hygiene habits</b>			
Poor	O1	76 (26.3)	6 (0.08)
Medium	O2	198 (68.5)	16 (0.08)
Good	O3	15 (5.2)	15 (0.6)
<b>Tobacco Use</b>			
None	S0	200 (0.69)	22 (0.11)
5 per day	S1	20 (0.06)	1 (0.05)
10 per day	S2	33 (0.11)	0 (0)
More than 20 per day	S3	36 (0.12)	4 (0.11)
<b>Comorbidity</b>			
None	C0	207	15 (0.07)
CVD	C1	21	1 (0.04)
Hypertension	C2	14	3 (21)
Diabetes mellitus II	C3	11	2 (18)
More than one chronic disease	C4	17	6 (0.35)
Other	C5	19	0 (0)

CVD: Cardiovascular disease.

After determining the basic habits and characteristics of the patients, xerostomia (questions 1-7), gingival changes (questions 8-10), mouth sores (question 11), loss of taste-smell (question 12-14), and trigeminal neuralgia form pain (questions 15-17) were queried. Patients were asked to choose from a 5-choice scale (from none to too much). The answer to each question was scored from 1 to 5 on a Likert scale. The scores of the questions asked for each finding were summed together. These scores were evaluated statistically. The questionnaires were collected by a single researcher between 1-15 July 2021. Verbal informed consent was obtained during the survey in accordance with the protocol.

The patients were grouped according to the results obtained from the first 4 part (**Table 2**). Patients were divided in to groups according to their age; 18-30 (A1), 31-65 (A2) and over 65 (A3); according to oral hygiene habits; poor (O1), moderate (O2) and good (O3); according to the number of cigarette users; non-smokers (S0), smokers of 5 cigarettes per day (S1), smokers of 10 cigarettes per day (S2), and smokers of 20 and more than 20 per day (S3); according to the comorbidities; those without chronic disease (C0), those with hypertension (C1), those with type two diabetes (C3), those with more than one chronic disease (C4) and those with other diseases (autoimmune etc.) (C5). The oral hygiene habits of the patients were made according to the scoring of the answers to the 1st and 2nd questions; 2-4 points were poor; 5-7 points moderate; a score of 8-10 was accepted as good oral hygiene habit. Each group; xerostomia, gingival changes, gustatory-olfactory changes and trigeminal neuropathic pain were compared with age, gender, smoking and comorbid disease statistically.

### Statistical analysis

Data analysis was done with IBM SPSS 21 (Statistical Package for Social Sciences) program. Summary values of quantitative (numeric) variables were shown as arithmetic mean standard deviation, summary values of qualitative (categorical) variables were shown as frequency and percentage. Class comparisons were made using Wilcoxon and Kruskal-Wallis tests, multiple comparison were made using Mann-Whitney test, the relationship between the categorical variables were examined with  $\chi^2$  test. At the significance level of the obtained values,  $p < 0.05$  was used as a criterion.

**Table 3.** Number of patients with mouth sore and lesion localization and numbers in oral cavity.

Mouth sore	Number of Patients
Lesion localization n=27	
<b>Single localization</b>	
Tongue	7
Lip	5
Gum	2
Palate	5
<b>Multiple localization</b>	
Tongue, Lip	2
Lip, Palate	1
Tongue, Palate	1
Tongue, Gum	1
Lip, Gum	1
Tongue, Lip, Palate, Gum	2

**Table 4.** Patients' oral manifestations and percentages.

Symptoms	Number of patients with symptoms (n=289) [n(%)]
Xerostomia	200 (69)
Gingival changes	90 (32)
Taste-smell changes	177 (61)
Trigeminal neuralgia form pain	58 (20)

## RESULTS

### Statistical results

Internal consistency of the survey was measured with Cronbach's alpha based on standardized items was 0.887 which indicates a high reliability. Item total statistics indicated a consistency within the survey as item-scale correlations were above 0.5.

A total of 346 patient were reached and 289 patients (%53 male and %47 female) between 18 and 81 years old with a mean age of 41.66 were agreed to participate and completed the questionnaire. No significant difference was found between the genders in terms of xerostomia, gingival changes, taste-smell changes and neuralgia form pain (**Table2**).

No significant difference was found between the oral hygiene habits of the patients (poor, moderate, good) and xerostomia (KW=2.21, P=0.33), gingival changes (KW=2.28; P=0.32), taste-smell changes (KW=0.84; P=0.66) and neuralgia form pain (KW=2.07; P=0.35).

A significant difference was found between age and xerostomia between A1 and A3, A2 and A3 groups ( KW= 6.92; p=0.03 ). Xerostomia symptoms are more frequent in the group of patients over 65 (U= 825; P=0.012 and U= 330 P=0.015). No significant difference was found between age and gingival changes (KW= 2.28; P=0.32), taste-smell changes (KW= 1.145; P=0.5) and neuralgia form pain (KW= 0.88; P=0.64).

While there was no significant difference between smoking and gingival changes (KW=5.61; P=0.13), taste-smell changes (KW=2.47; P=0.48) and neuralgia form pain (KW=3.15; P=0.36), there were only significant statistical results between S0 and S3 groups in terms of xerostomia (KW= 11.68; U=2105; P=0.002).

When the relationship of comorbid chronic diseases with xerostomia was examined, no statistically significant results were found between C0 and C1, C2, C3, C4 groups (KW= 175.4, P<0.001). A significant statistical difference was found between the C1 group and the C2 (U=522 P<0.001), C3 (U=94.5 P<0.001), C4 groups (U=48.5 P< 0.001). Significant statistical difference was found between C2 group and C3 (U=312 P<0.001), C4 groups (U=230 P=0.35). No statistical difference was found between C3 and C4 groups (U=50, P=0.07).

When comparing gingival changes with comorbid chronic diseases; while there was a statistically significant difference

between the C0 group and the C2, C3, C4 groups (KW= 39.87, P<0.001); no statistically significant difference was found between the C0 group and the C1 group (U=2544, P=0.145). Also, no statistical difference was found between C1, C2, C3, C4 groups (P=0.2, P=0.15, P=0.23).

When the taste-smell changes with chronic diseases were evaluated, a statistically significant difference was found between the C0 group and the C2, C3, C4 groups (KW=25.22, P<0.001). A statistically significant difference was found between the C1 group and only the C3 group (U=249.5, P=0.004). There was no significant difference found between the C2, C3, C4 groups in terms of taste-smell changes (P=0.2, P=0.3, P=0.8).

When the effects of chronic diseases on neuralgia form pain were compared, a statistically significant difference was found between the C0 group and the C2, C3, C4 groups (KW=39.87, P<0.001). No statistically significant difference was found between the other groups (P=0.9, P=0.7, P=0.6).

There was no statistically significant result between oral lesion formation and age, gender, oral hygiene habits and smoking (P=0.2). A statistical difference was found between the presence of chronic disease and the formation of oral lesions (P=0.005).

### Patients reported oral symptoms

Patients generally reported that they lost their sense of taste and smell after the appearance of COVID symptoms and continued for 3-10 days (n=272). While 140 patient reported that their sense of smell was lost for only 1-2 hours; 35 patient reported no improvement in their sense of taste and smell for three months. One patient reported that he lost his sense of taste-smell after the COVID symptoms had subsided and recovered after a week.

Patients with mouth sores stated that the lesions were painless, small single or multiple white lesions and healed within 1-2 weeks (n=22). One patient reported that the lesions in his mouth were white, small and painful, and he also experienced neuropathic pain in his lips for one day. One patient reported that the mouth sore on the palate did not heal for 1 month (**Table 3**).

Three patients gave a history of total hypoesthesia of the tongue.

Patients' oral manifestations and percentages are shown on Table 4.

## DISCUSSION

In this study, the relationship between the symptoms with the highest prevalence in covid positive patients and the possible symptoms that may occur in accordance with the character of the SARS-COV-2 virus with age, gender, oral hygiene habits and chronic diseases of the patients was investigated.

The study included 289 patients who were followed up at home and had mild to moderate symptom of covid-19 disease. Xerostomia was observed in 69% of the patients and taste-smell alterations were observed in 61% of the patients. These

symptoms are followed by gingival changes (32%) and neuralgia form pain symptoms (20%). Patients reported that symptoms co-occurred COVID infection.

In our study, no difference was found between gender and xerostomia, gingival changes, taste-smell alterations and neuralgia form pain. In studies investigating taste-smell alterations in covid-positive patients, there are studies showing that women have more olfactory and gustator dysfunction than men. However, our results do not agree with these studies (8-11). It was thought that this result might be due to the fact that the studies were conducted on different races. However, the results of Omezli's study are consistent with our study (12).

It is known that xerostomia is one of the primary oral symptoms of COVID-19. It is not clear whether the etiology of salivary gland hypofunction is due to peripheral nerve involvement or to ACE-2 receptor inhibition (7,13,14). In our study there was a difference in xerostomia between the >65 age group and 31-65 age and 18-30 age groups in terms of xerostomia. In our literature review, no research on age groups and xerostomia in COVID-positive patients was found. It is known that the prevalence of xerostomia increases with age. In addition, xerostomia prevalence increases in geriatric individuals because of the xenogeneic drugs due to their chronic disease. Our results show that the salivary gland function of individuals over 65 years of age is more affected by the SARS-COV-2 virus.

In this study, we hypothesized that factors such as oral hygiene habits and smoking, which may affect the health of the oral mucosa, may have an effect on the known symptoms of COVID. Our results showed that oral hygiene habits had no effect on xerostomia, gingival changes, taste-smell alterations and neuralgia form pain. however, a difference was found between non-smokers and patients who smoked more than 20 cigarettes a day in terms of xerostomia. Kakoei et al. (15) showed in their studies that daily cigarette use has an effect on xerostomia; however, the effect of the number of cigarettes used per day on hyposalivation was not examined in this study.

It is known that chronic diseases have an effect on salivary gland function (16). In our study, we investigated the effects of different chronic diseases of COVID-positive patients on xerostomia. Our results showed that the presence of concomitant chronic disease increases the xerostomia findings of the patients.

Periodontal diseases in general; they have been associated with oral bacteria, periodontopathogens, respiratory diseases and their adverse consequences. They act in a synergetic mechanism especially with viruses (17). In our study, it was found that covid positive patients with hypertension, type 2 diabetes and more than one chronic disease had more gingival changes.

Similarly, it was found that patients with hypertension, type 2 diabetes and more than one chronic disease had more taste-smell loss and neuralgia form pain compared to healthy individuals. this can be interpreted as the peripheral nerve involvement of SARS-COV-2 increases with the presence of chronic disease.

In this survey, 27 COVID-19 patients reported the appearance of white, painless ulcers in their oral cavities. This is accordance with several report (18-20). It has been shown that stress and anxiety contribute to the formation and progression of oral lesions like aphthous ulcers and this applies to COVID-19 patients. In previous studies, it has been reported that the lesions differ in terms of gender (19,20). However, in our study, it was observed that the distribution of the lesion was not different in terms of gender. In addition, in our study, similar to previous studies, no difference was found between age and oral lesion formation (21). In addition, ACE-2 is detected in the oral cavity and appears in high amounts in tongue, buccal and gingival mucosa epithelial cells. These findings demonstrate that the oral mucosa may be a target for COVID-19 infection.

In this survey, no statistical difference was found between oral hygiene habits and lesion formation and gingival changes. Poor oral hygiene has been proven to increase the oral manifestations of COVID (22,23). Researchers have shown a link between increased bacterial loading and post-viral complications. In our study, the patients were not evaluated clinically. Data are based on patient self-assessment. It was thought that the results of our study were different from other studies.

Five smoking patients reported oral lesion in their mouth. It is known that smoking weakens the health of the oral mucosa and predisposes the oral mucosa to ulceration and inflammation. Although our study sample is small, our study results have been interpreted as smoking has no effect on oral lesion formation and gingival mucosal health in COVID positive patients.

Our study results show that patients with chronic diseases are more prone to oral lesions compared to healthy individuals. Lesions were mostly seen in type 2 diabetes patients with an incidence of 21% and then in hypertension patients with 18%.

There are some limitations in this study. The results may not be generalizable to the entire covid patient population, as our study sample was relatively small and also consisted of only patients with mild-to-moderate disease.

Secondly, the clinical examination of patient cannot be applicable because of most of the dental and university clinics were closed to prevent the spread of the pandemic at the time of the present investigation.

In summary, our study showed that in addition to olfactory and gustator nerve involvement, mild to moderate COVID-19 infected patients may have neuralgia form pain in the lips and cheeks and hypoesthesia in the tongue due to trigeminal nerve involvement. The finding of xerostomia has increased significantly in COVID-positive patients over the age of 65. There is a statistical difference between patients who smoke more than 20 cigarettes a day and non-smokers in the incidence of xerostomia. There is a statistical difference in incidence of xerostomia between patients with chronic diseases and healthy patients. Additionally, oral hygiene level; have no effect on gingival changes and mouth sores.

Further clinical studies are recommended to examine the effects of COVID-19 on salivary gland secretion and nerve involvement to observe long term effects of COVID-19 disease and also maintain oral health.

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## Conflicts of interest

No conflicts of interest between the author and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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