

# Examining The Clinical Symptoms Of The Oral Cavity And Its Severity In Patients With COVID-19 Referred To Imam Reza Hospital In 2019

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## Abstract

**Introduction:** COVID-19 is a viral infection caused by the acute respiratory syndrome virus (SARS-CoV-2), which clinically affects several human body organs. The present study aims to investigate the clinical symptoms of the oral cavity and its severity in patients with COVID-19 referred to Imam Reza Hospital in Tabriz in 1401.

**Materials and methods:** In this descriptive cross-sectional study, 89 patients with COVID-19 positive PCR tests and 89 healthy individuals who met the conditions for inclusion were examined. Patient demographic information, including age, gender, history of underlying diseases, and use of toothbrushes, was recorded. Then the patients were examined by a dentist, and various oral lesions were recorded. Saliva flow rate, lesion intensity, and gingival inflammation rate (based on BOP) were recorded. The results were analyzed by SPSS24 statistical analysis software and the Marie Chi-square test.

**Results:** Oral lesions, including painful and non-painful ulcers in the mucosa, small blisters in the oral mucosa, the presence of petechiae, and the amount of taste disorder in patients with COVID-19 were significantly higher than in healthy individuals. The severity of gingivitis in patients with COVID-19 was significantly higher than in healthy people. The difference in the frequency of oral lesions was observed in both the sick and healthy groups in both men and women and different age groups.

**Conclusion:** COVID-19 can cause aggravation of oral lesions.

**Keywords:** COVID-19, oral lesions

## Introduction

The clinical course of SARS-CoV-2 infection is extensive and includes asymptomatic infection, upper respiratory system discomfort, and in some cases, acute and severe fatal infections (1 and 2). Common symptoms of infection with SARS-CoV-2 include respiratory symptoms, fever, dry cough, fatigue, and dyspnea (3), while the clinical course of this disease varies from asymptomatic to severe pneumonia (4). However, designing and manufacturing a safe vaccine is the best way to control the pandemic. A definitive drug treatment or an approved vaccine with complete efficacy and safety for COVID-19 has yet to be introduced (5).

The most common clinical symptoms observed in patients with COVID-19 include fever, headache, sore throat, dyspnea, dry cough, abdominal pain, vomiting, and diarrhea. The primary receptors of this virus include ACE2

(angiotensin-converting enzyme 2), which can be found in the lung, liver, kidneys, secretory glands, and endothelial vessels (6). Many skin lesions of COVID-19 have been reported in recent studies, including varicelliform, pseudo chilblain (sudden redness of the fingers), urticarial, maculopapular, petechiae, and purpura, mottling, and lesions suspected of erythema multiforme and Livedo reticularis (7).

Recently, this virus was found in the saliva by RT-PCR. The sensitivity of this test is also higher compared to throat and nasopharynx swabs. In addition, the ACE2 receptor has been found in the oral mucus, especially with high density in the back of the tongue and salivary glands. On the other hand, it has been mentioned that taste disorder in patients with COVID-19 was one of the most common manifestations, with a frequency of 38% in different populations with mild to moderate disease severity (6). The oral lesions observed in COVID-19 are of low severity in young people and high severity in older people.

The SARS-CoV-2 virus enters cells through its spike proteins, which are ACE2. Spike proteins can identify ACE2 on the surface of host cells, and the extent of ACE2 release in the body shows different effects depending on the cell it enters. (8). The creation of oral lesions, including oral ulcers, can also be caused by the pathogenesis of COVID-19. Because the mouth epithelium has ACE2 receptors, damage can occur following the entry of viruses into the cell and its destruction (9). Furthermore, the increase of cytokines following the infection of COVID-19, including interleukin six and ten, can lead to the chemotaxis of lymphocytes and neutrophils to the lesions. These neutrophils show the entry of CD3 and CD8 lymphocytes into the lesion (10). Inflammation in this process also leads to necrotic lesions and ulcers s. On the other hand, dry mouth, which is observed along with COVID-19, also increases the severity of these lesions.

A review study by Iranmanesh et al. in 2020 showed that oral manifestations of COVID-19 include aphthous-like lesions, herpes form, candidiasis, and oral lesions similar to Kawasaki involvement (11). The study of Sofi-Mahmudi in 2021 also showed the most common oral manifestations in dry mouth, taste disorder, and evidence of fungal pseudomembranous disease (12).

Given the lack of field investigation of this issue in our region, this study aimed to investigate the clinical symptoms of head and neck in patients with COVID-19 referred to Imam Reza Hospital in Tabriz in 1401.

## materials and methods

In this descriptive cross-sectional study, patients with COVID-19 were included based on a positive PCR test. Based on the analysis by Santos et al. (7) and the OR parameter equal to 12.68 for taste disorder in patients with COVID-19, using the Power and Sample Size software, considering the power of 90% and the alpha error of 5%, the sample size of at least 89 cases was calculated. Patients with aphthous ulcers, immunodeficiency, mental illnesses, systemic diseases that affect saliva and gingivitis, and the use of drugs that cause ulcers in the mouth were excluded from the study. Patients were studied after partial recovery from the pulmonary involvement of COVID-19 and returning to ordinary life. Patient demographic information, including age, gender, history of underlying diseases, and use of toothbrushes, was recorded. Then the patients were examined by a dentist. In the clinical examination, things such as white plaque, the condition of saliva, painful ulcers s, other ulcers s, small blisters, petechiae, gingivitis, taste disorder, aphthous, and macule were evaluated, and the frequency of the presence or absence of lesions was recorded. The purpose of assessing the saliva condition was to check the examiner in terms of the amount of saliva flow (13). The severity of the lesions was checked and scored by the dentist based on the location, size, number, and pain level. Bleeding on probing (BOP) was used to measure gingival inflammation.

## Results

This study examined 89 patients with COVID-19 and 89 healthy individuals. In the sick group, patients with COVID-19 were 59.6% men and 40.4% women, and in the group of healthy people, 49.4% were men, and 50.6% were women. There was no significant difference in the frequency of men and women in the two groups ( $P=0.114$ ). The average

age in the sick group was 39.49±11.52 years, and in the healthy group was 38.92±12.78 years, and there was no significant difference in the average age of the two groups (P=0.754).

The frequency of systemic disease in patients with COVID (11.2%) is significantly higher than in healthy people (1.1%) (P=0.005). Of the patients with COVID-19, 4.5% had diabetes, 4.5% had anemia, and 2.2% had high blood pressure. In healthy people, 1.1% (1 person) had osteoporosis. None of the patients in the two groups had underlying diseases. Table 1 shows no significant difference in the amount of white plaque inside the mucosa in patients with COVID-19 and healthy people. However, other oral lesions in patients with COVID-19 are significantly more than in healthy people (Table 1). Table 2 shows no significant difference in the viscosity of saliva in patients with COVID-19 and healthy people.

Nevertheless, the severity of gingivitis in patients with COVID-19 is significantly different from that of healthy people (Table 2). Table 3 shows that the frequency of two lesions, white plaque inside the mucosa and small blisters in the oral mucosa, is similar in sick and healthy men. Moreover, there is no significant difference in the frequency of this lesion in sick and healthy women. However, other lesions significantly differ in sick and healthy people by gender (Table 3). The results of Table 4 showed that white plaque lesions inside the mucosa are similar in all age groups in healthy and sick people. However, other oral lesions in different age groups significantly differ between the sick and healthy groups. The taste disorder in all age groups is significantly higher in patients than in healthy people (Table 4). The frequency of oral lesions in age groups and men and women significantly differed (Tables 5 and 6).

Table 1- Comparison of oral lesions types in patients with COVID-19 with healthy people

	Patient		Healthy		P VALUE
	Number	Percent	Number	Percent	
<b>The white plaque inside the mucosa</b>	20	22.47	11	12.35	0.056
<b>Painful ulcer in the mucous</b>	16	17.97	1	1.12	0.003
<b>Non-painful ulcers in the mucosa</b>	17	19.1	0	0	<.001
<b>Small blisters in the oral mucosa</b>	6	6.7	0	0	0.014
<b>The presence of petechiae</b>	17	19.1	0	0	<.001
<b>The degree of taste disorder</b>	46	51.8	1	1.1	<.001

P VALUE: CHI-SQUARE TEST

Table 2- Comparing oral lesions severity in patients with COVID-19 with healthy people

		The viscosity of saliva		The degree of gingivitis	
		Patient	Healthy	Patient	Healthy
<b>Free</b>	Number	66	71	71	61
	Percent	74.16	79.78	79.78	68.54
<b>Very little</b>	Number			1	0
	Percent			1.12	0
<b>Low</b>	Number	12	9	16	17
	Percent	13.48	10.11	17.98	19.10
<b>Medium</b>	Number	6	9	1	10
	Percent	6.74	10.11	1.12	11.24
<b>Intense</b>	Number	5	0	0	1
	Percent	5.62	0.00	0	1.12
<b>P VALUE</b>		.102		.038	

**P VALUE: CHI-SQUARE TEST**

Table 3- Comparison of oral lesions types in patients and healthy people according to gender

		Patient		Healthy		P VALUE
		Number	Percent	Number	Percent	
<b>The white plaque inside the mucosa Painful ulcer in the mucous</b>	Man	11	20.75	5	11.36	0.167
	Woman	9	25.00	6	13.33	0.146
<b>Non-painful ulcers in the mucosa Small blisters in the oral mucosa</b>	Man	6	11.32	0	0	0.023
	Woman	10	27.78	1	2.22	0.001
<b>The presence of petechiae</b>	Man	10	18.87	0	0	0.002
	Woman	7	19.44	0	0	0.002
<b>The white plaque inside the mucosa Painful ulcer in the mucous</b>	Man	4	7.55	0	0	0.085
	Woman	2	5.56	0	0	0.194
<b>Non-painful ulcers in the mucosa Small blisters in the oral mucosa</b>	Man	10	18.87	0	0	0.002
	Woman	7	19.44	0	0	0.002
<b>The presence of petechiae</b>	Man	27	50.94	0	0	<.001
	Woman	19	52.78	1	2.22	<.001

**P VALUE: CHI-SQUARE TEST**

Table 4- Comparison of oral lesions types in patients and healthy people according to age group

	Age group	Patient		Healthy		P VALUE
		Number	Percent	Number	Percent	
<b>The white plaque inside the mucosa</b> <b>Painful ulcer in the mucous</b> <b>Non-painful ulcers in the mucosa</b> <b>Small blisters in the oral mucosa</b>	20-30	6	22.22	4	13.33	0.297
	30-40	2	8.70	2	10.00	0.641
	40-50	8	33.33	3	15.00	0.147
	< 50	4	26.67	2	10.53	0.220
<b>The presence of petechiae</b> <b>The white plaque inside the mucosa</b> <b>Painful ulcer in the mucous</b>	20-30	2	7.41	0	0.00	0.220
	30-40	5	21.74	0	0.00	0.035
	40-50	5	20.83	1	5.00	0.139
	< 50	4	26.67	0	0.00	0.025
<b>Non-painful ulcers in the mucosa</b> <b>Small blisters in the oral mucosa</b> <b>The presence of petechiae</b>	20-30	5	18.52	0	0.00	0.019
	30-40	3	13.04	0	0.00	0.144
	40-50	4	16.67	0	0.00	0.078
	< 50	5	33.33	0	0.00	0.011
<b>The white plaque inside the mucosa</b> <b>Painful ulcer in the mucous</b> <b>Non-painful ulcers in the mucosa</b> <b>Small blisters in the oral mucosa</b>	20-30	1	3.70	0	0.00	0.474
	30-40	3	13.04	0	0.00	0.144
	40-50	1	4.17	0	0.00	0.545
	< 50	1	6.67	0	0.00	0.441
<b>The presence of petechiae</b> <b>The white plaque inside the mucosa</b> <b>Painful ulcer in the mucous</b>	20-30	5	18.52	0	0.00	0.019
	30-40	4	17.39	0	0.00	0.072
	40-50	5	20.83	0	0.00	0.039
	< 50	3	20.00	0	0.00	0.078
<b>Non-painful ulcers in the mucosa</b> <b>Small blisters in the oral mucosa</b>	20-30	14	51.85	0	0.00	0.000
	30-40	15	65.22	0	0.00	0.000
	40-50	11	45.83	1	5.00	0.000
	< 50	6	40.00	0	0.00	0.000

P VALUE: CHI-SQUARE TEST

Table 5- Comparison of oral lesions severity in patients and healthy people according to gender

		The viscosity of saliva				The degree of gingivitis			
		Patient		Healthy		Patient		Healthy	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
<b>Man</b>	<b>free</b>	41	77.36	33	75.00	41	77.36	28	63.64
	<b>Very little</b>								
	<b>Low</b>	7	13.21	7	15.91	11	20.75	11	25.00
	<b>Medium</b>	3	5.66	4	9.09	1	1.89	4	9.09
	<b>Intense</b>	2	3.77					1	2.27
	<b>P VALUE</b>	<b>0.534</b>				<b>0.217</b>			
<b>Woman</b>	<b>free</b>	25	69.44	38	84.44	30	83.33	33	73.33
	<b>Very little</b>					1	2.78		
	<b>Low</b>	5	13.89	2	4.44	5	13.89	6	13.33
	<b>Medium</b>	3	8.33	5	11.11			6	13.33
	<b>Intense</b>	3	8.33						
	<b>P VALUE</b>	<b>0.088</b>				<b>0.097</b>			

**P VALUE: CHI-SQUARE TEST**

Table 6- Comparison of oral lesions severity in patients and healthy people according to age group

Age group		The viscosity of saliva				The degree of gingivitis			
		Patient	Healthy	Patient		Healthy		Patient	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
<b>20-30</b>	<b>free</b>	23	85.19	24	80.00	22	81.48	22	73.33
	<b>Very little</b>		0.00		0.00	0	0.00	0	0.00
	<b>Low</b>	2	7.41	4	13.33	5	18.52	5	73.33
	<b>Medium</b>	2	7.41	2	6.67	3	11.11	3	10.00
	<b>P VALUE</b>	0.77				0.576			
<b>30-40</b>	<b>free</b>	18	78.26	16	80.00	21	91.30	11	55.00
	<b>Very little</b>	1	4.35	2	10.00	2	8.70	7	35.00

	<b>Low</b>	1	4.35	2	10.00	0	0.00	2	10.00
	<b>Medium</b>	3	13.04	0	0.00		0.00		0.00
	<b>P VALUE</b>	0.309				0.021			
<b>40-50</b>	<b>free</b>	16	66.67	17	85.00	16	66.67	15	75.00
	<b>Very little</b>	5	20.83	2	10.00	8	33.33	4	20.00
	<b>Low</b>	2	8.33	1	5.00	0	0.00	1	5.00
	<b>Medium</b>	1	4.17	0	0.00		0.00		0.00
	<b>P VALUE</b>	0.512				0.364			

## Discussion

In the present study, oral lesions, including painful and non-painful ulcers in the mucosa, small blisters in the oral mucosa, the presence of petechiae, and the amount of taste disorder in patients with COVID-19, were significantly higher than in healthy individuals. However, the frequency of intramucosal white plaque was similar in patients of the two groups. Also, the severity of gingivitis in patients with COVID-19 was significantly higher than that of healthy people, but the viscosity of saliva was similar in both groups.

The oral cavity is the entrance of various microorganisms, including SARS-CoV-2, which can be detected in the saliva of patients with COVID-19 (14). According to the study of BALA et al. (2020), in patients with COVID-19, aphthous ulcers affect the tongue, lips, palate, and oropharynx, and the improvement or evolution of oral lesions corresponds to the resolution of the infection of COVID-19 (15). Malih et al. (2020) reported laryngitis with an aphthous ulcer in the left tonsil, and Kämmerer et al. (2021) reported a patient covered with several gray membranes and an ulcer in the oral cavity (16, 17).

Jimenez-Cauhe et al. (2020) observed COVID-19 patients with macules and petechiae in the palate mucosa along with skin lesions who recovered completely with systemic steroids within two-three

weeks (18). According to Anand et al. (2022), gum bleeding and dental plaque accumulation were more common among COVID-19 patients than among healthy people, and there was a relationship between the severity of periodontitis and COVID-19(19). A review study by Farid et al. (2022) indicated that the reported manifestations included taste disorder, changes in the oral mucosa (patchy, ulcers, plaque-like lesions, geographic tongue, and skin gingivitis), and dry mouth (20).

According to Xu et al.'s (2020) study, lesions in the form of blisters or painful sores were observed in patients with COVID-19, which can be treated within three to ten days. These authors claimed that ACE2 in the oral cavity is more prominently expressed in epithelial cells of the tongue compared to other sites in the oral cavity, such as the gingival and buccal mucosa, and pain may be caused by the higher **expression** of ACE2 in the surface mucosa cells of the tongue (21).

Recent research has shown that human cells are invaded by the COVID-19 through the angiotensin receptor converting enzyme (ACE2) (22). Thus, cells with ACE2 receptors may become host cells for the virus and trigger an inflammatory response in associated tissues, such as the salivary gland and tongue mucosa. The interaction of SARS-CoV-2 and ACE2 receptors can also weaken taste nerve sensitivity, which may cause taste dysfunction (15). Petrescu et al. (2022) also expressed the initial sensitivity of the oral mucosa, especially the tongue, in SARS-CoV-2 infection due to the high **expression** of angiotensin-converting enzyme (ACE2) in the epithelial cells of the tongue (23).

Salivary glands are potential reservoirs for coronavirus disease 2019 (COVID-19), which could explain asymptomatic infections (24). Ciccarese et al. (2020) reported a 19-year-old woman who complained of fever, sore throat, change in smell, and asymptomatic oral and skin lesions. Physical examination revealed multiple ulcers, blood clots on the lips, and petechiae on the palate and gums. Ten days later, skin and mucosal lesions disappeared (25). According to the study of Riad et al. (2022), the number of ulcers was significantly different among patients, ranging from one to seven per patient, and their size was between 1 and 5 mm. The majority (92.3%) did not bleed, and all (100%) appeared on the back or side of the tongue. All ulcers were painful and interfered with daily activities, and the mean pain intensity score was  $4.65 \pm 1.55$ . None of them had a history of herpes or tongue ulcers. No other ulcers or blisters were observed inside the oral cavity except those surveyed on the tongue (26). According to the study by Marouf et al. (2021), periodontitis, which faced a higher risk of admission to the Intensive Care Unit (ICU) and the need for assisted ventilation, and even led to the death of COVID-19 patients, was associated with increased levels of blood biomarkers and worse disease outcomes. (27). Moreover, studies showed that the healing of mucosal lesions occurred with the removal of SARS-CoV 2 infection, which indicates the relationship between viral infection, oral lesions, and their disappearance (28).

All the above studies confirm the present study's results and the presence of oral lesions in patients. But unlike the above studies, Amorim et al. (2021) concluded in their study that there is no clear evidence of an etiopathological relationship between oral mucosal lesions and SARS-CoV 2.(29). In the present study, the frequency of systemic disease in patients with COVID was significantly higher than in healthy people. None of the patients in the two groups had underlying diseases. In the study of Iranmanesh et al. (2020), underlying diseases (diabetes, immunodeficiency) and vascular disorders are predisposing factors for the development of oral lesions in patients with COVID-19 (11).

In the present study, a frequency difference of oral lesions was observed in both the sick and healthy groups in both men and women. Furthermore, the frequency of oral lesions in different age groups had a significant difference in the two groups. In the study by Iranmanesh et al. (2020), both genders were almost equal in the occurrence of oral mucosal lesions. The recovery time was between three and 28 days after the appearance. Variables such as old age and the severity of COVID-19 are also the most common predictors of the severity of oral lesions in these patients (11).

It should be noted that several variables are involved in causing oral lesions in COVID-19. It should be noted that several variables are involved in causing oral lesions in COVID-19. Stress caused by restrictions on social life during quarantine, oral and dental health issues, herpes simplex virus, glossitis, oral candidiasis, drug reactions, autoimmune disorders, and nutritional deficiencies is among these (30-32).

Oral signs and symptoms presented by patients with COVID-19 can directly result from SARS-CoV-2 infection or secondary disorders caused by systemic damage, changes in the immune system, or adverse effects of treatment.

It is recommended that dentists and health professionals perform a more complete and accurate oral examination with more attention to the type and number of oral manifestations to support the patient and control the pain.

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