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Oral manifestations associated with COVID-19 disease: An observational cross sectional study☆

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A R T I C L E I N F O

Keywords:
COVID-19 disease
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RT-PCR
SARS-CoV-2
Xerostomia
Stomatopyrosis

A B S T R A C T

Objectives: The aim of present study was to investigate oral manifestations associated with COVID-19 disease.
Materials and methods: This cross-sectional study comprised 367 suspects with mild/moderate COVID-19 symptoms who reported to a tertiary care hospital's screening OPD. An in-depth case history was taken, and an oral cavity examination was performed to detect any oral findings. All participants were tested for SARS-CoV-2 using a naso-pharyngeal swab and reverse transcription polymerase chain reaction.
Oral manifestations and the results of RT-PCR testing were correlated. Statistical analyses were performed using Epi Info and R software. To estimate the prevalence of oral symptoms, the Pearson chi-square test was used.
Results: Oral manifestations were found in 58% of the study population. The difference in the prevalence of oral manifestations between RT-PCR positive COVID-19 patients versus RT-PCR negative suspects was statistically significant ($p = 0.007$) with xerostomia and dysgeusia being significantly higher in positive patients ($p = 0.036$ and $p = 0.044$ respectively) while the prevalence of stomatopyrosis and other intraoral signs was insignificant.
Conclusion: Xerostomia and dysgeusia are the common oral manifestations of COVID-19.

1. Introduction

COVID-19 disease was first detected in Wuhan, China in December 2019, and the disease's global spread prompted WHO to designate it as a global pandemic on March 11, 2020. This disease is caused by the enveloped RNA beta corona virus named Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). The SARS-CoV-2 virus disease, which began as a pneumonia outbreak in China, has now spread rapidly throughout the globe. As of April 1, 2021, there are around 128,540,982 cases globally with roughly 2,808,308 recorded deaths, and India is one of the most affected nations, with approximately 12 million cases.[1]

The SARS-CoV-2 virus encodes four major structural proteins namely the spike protein, the membrane protein, the envelope protein, and the nucleocapsid protein. The spike protein protruding from the surface of SARS-CoV-2 is a Type I glycoprotein that binds to specific host cell receptors (metallopeptidase named Angiotensin-Converting Enzyme 2) via a receptor-binding domain facilitating its entry into the target cells. A positive correlation between ACE-2 and CoV-1 has been observed. Genomic and structural studies have shown that the receptor-binding domain of SARS-CoV-2 exhibits similar molecular characteristics as that of SARS-CoV-1.[2] COVID-19 disease may be asymptomatic or may present itself with mild and common symptoms like fever, dry cough, altered taste and smell sensation to severe symptoms like difficulty in breathing, chest pain, etc. A flurry of studies have reported oral manifestations such as oral ulcers, vesiculobullous lesions, erythematous macules, papules, dysgeusia, and xerostomia.[3–6] Oral mucosa may be the first area to get infected with SARS-CoV 2 virus. Thus, oral manifestations could be suggestive of COVID-19 and may help us in early identification and management. Scientific data search mostly led us to cross-sectional studies that have either been questionnaire-based or

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have included patients who are already on COVID-19 treatment or had no comparison group.[7–9] The present cross-sectional study was designed to estimate the prevalence of oral manifestations amongst COVID-19 suspects and compare the same between RT-PCR positive COVID-19 patients and RT-PCR negative COVID-19 suspects.

2. Materials and methods

This observational cross-sectional study was conducted in suspected COVID-19 patients[10] reporting to the Out Patient Department of the tertiary care hospital between September and December 2020. Patients with preexisting complaints of xerostomia and stomatopyrosis (of the duration ≥2 weeks prior to their hospital visit) and those requiring supplemental oxygen therapy were excluded from the study. The study was approved by the Institutional Ethics Committee in compliance with the Helsinki declaration and written informed consent was obtained from each participant. A case report from Israel concluded that 56.3% of COVID-19 patients showed oral manifestations.[4] Considering this prevalence with 5% absolute precision and 95% confidence level, the sample size was calculated to be 367 using OpenEpi version 3.01 software.

A thorough case history was obtained from each patient including their demographic details, tobacco usage, and comorbidities like diabetes mellitus, hypertension, etc. Details about symptoms of viral respiratory infection such as cough, fever, myalgia, sore throat, nasal congestion, running nose, etc. were elicited from all the participants. Patients were also enquired about oral symptoms such as altered taste sensation (dysgeusia), feeling of dry mouth (xerostomia) and burning sensation in the oral cavity (stomatopyrosis) using standardized questionnaires.[11,12] Following this all patients underwent thorough intraoral examination, following proper biosafety guidelines, by the authors to detect the presence of intraoral signs like ulcers, erythema, macules, papules, etc. All the details were recorded in a case history sheet. After examination patients were tested for SARS CoV-2 with RT-PCR using nasopharyngeal swabs. RNA was extracted from the clinical samples with a QIAamp viral RNA mini kit (QIAGEN, Hilden, Germany) following the manufacturer's instructions at the COVID-19 virus research diagnostic laboratory of the institute. Depending upon the results of RT-PCR, the participants were divided into two study groups i.e., RT-PCR positive COVID-19 patients (SG-1) and RT-PCR negative COVID-19 suspects (SG-2). Results of RT-PCR tests and oral findings were further correlated.

Data entry was done in Microsoft Excel spreadsheet and analysis was done using Epi info and R software. Categorical variables like prevalence of oral manifestations, results of RT-PCR tests, comorbidities, etc. were summarized as frequency and percentage. For subgroup analysis of categorical variables, chi-square test was used. Logistic regression was used for estimating the adjusted odds ratio (OR) with 95% confidence interval. The 95% confidence interval (CI) and p-value for each OR were tabulated. $p < 0.05$ was considered statistically significant.

3. Results

Amongst 367 COVID-19 suspects included in the study, 60% (n = 217) of the study participants were RT-PCR positive COVID-19 patients (Table 1). More than half of the participants were less than 50 years of age and 70% of the study participants were males. One in every four of the study participants had a history of at least one comorbidity like hypertension, coronary artery disease, diabetes mellitus, bronchial asthma and the same distribution was found in each of the two study groups. 6% of study participants had a history of tobacco smoking and 2% were users of smokeless tobacco.

The clinical features of study participants have been represented in Table 2. Out of 176 study participants who had fever, 121 (55.8%) were RT-PCR positive, and 55 (36.7%) were RT-PCR negative, this difference is statistically significant (p-value= <0.001). 30% of all the participants had cough, 20% had sore throat, 7% had shortness of breath and 11% had other symptoms like running nose, headache, and myalgia. 58% of the study population had oral manifestations such as xerostomia, dysgeusia, stomatopyrosis, intraoral signs like ulcers, erythema, etc. The prevalence of any one of the oral manifestations amongst RT-PCR positive patients (64%) and RT-PCR negative suspects (50%) had a statistically significant difference. Xerostomia (38%) was the most common oral manifestation followed by dysgeusia (32%). There was a statistically significant difference in the prevalence of xerostomia (SG1-42.9%; SG2-32%) and dysgeusia (SG1-35.9%; SG2 26%) between the two study groups. Amongst the participants, 18% had stomatopyrosis, 13% had intraoral signs like macula, whitish patch, vesicle, erythema, and 3.7% had oral ulcers, the prevalence of these findings did not have a statistically significant difference (Table 3).

Table 4 presents the univariate and multivariate regression analysis and risk estimation of clinical symptoms for COVID-19 infection amongst the study participants. The clinical features like fever (OR 2.2), oral manifestations (OR 1.7), and other symptoms (OR 2.2) like running

Table 2
Clinical features of study participants.

Symptoms	COVID Positive (n = 217)	COVID Negative (n = 150)	Total (n = 367)	p-value
Fever	121 (55.8)	55 (36.7)	176 (48.0)	<0.001*
Cough	67 (30.9)	45 (30.0)	112 (30.5)	0.858
Sore throat	33 (15.2)	41 (27.3)	74 (20.2)	0.004*
Shortness of Breath	316 (7.4)	15 (10.0)	16 (7.4)	0.374
Other Symptoms like running nose, cold, headache.	32 (14.7)	11 (7.3)	43 (11.7)	0.030*
Oral Manifestations	139 (64.1)	75 (50.0)	214 (58.3)	0.007*

Table 1
Demographic and Risk factor profile of study participants.

Item	Sub-group	COVID Positive (n = 217)	COVID Negative (n = 150)	Total (n = 367)	p-value
Age Group	18–49 years	112 (51.6)	89 (59.3)	201 (54.8)	0.341
	50–60 years	80 (36.9)	47 (31.3)	127 (34.6)	
	60-years	25 (11.5)	14 (9.3)	39 (10.6)	
Gender	Male	155 (71.4)	102 (68.0)	257 (70)	0.481
	Female	62 (28.6)	48 (32.0)	110 (30)	
Medical Comorbidities	Yes	57 (26.3)	35 (23.3)	92 (25.1)	0.524
	No	160 (73.7)	115 (76.7)	275 (74.9)	
Smoking	Yes	11 (5.1)	11 (7.3)	22 (6.0)	0.369
	No	206 (94.9)	139 (92.7)	345 (94.0)	
Smokeless Tobacco Use	Yes	6 (2.8)	2 (1.3)	8 (2.2)	0.356
	No	211 (97.2)	148 (98.7)	359 (97.8)	
Total		**217(59.1)**	**150(40.9))**	**367(100)**	

Table 3
Oral manifestations among the study participants.

Symptoms	COVID-19 RT-PCR Positive (n = 217)	COVID-19 RT-PCR Negative (n = 150)	Total (n = 367)	p-value
Xerostomia	93 (42.9)	48 (32.0)	141 (38.4)	0.036*
Dysgeusia	78 (35.9)	39 (26.0)	117 (31.9)	0.044*
Stomatopyrosis	44 (20.3)	22 (14.7)	66 (18.0)	0.169
Signs In Oral Cavity	37 (17.0)	23 (15.3)	60 (16.3)	0.747

nose, headache, and body ache were found to have a significant positive association with COVID-19 infection. Multivariate regression analysis shows fever (Odds Ratio 2.2), oral manifestations (OR 1.6) and other symptoms (OR 2.7) were associated with COVID-19 infection independently. The odds of RT-PCR positive cases having fever was 2.2 (1.4–3.3) times higher than the RT-PCR negative suspects. The odds ratio increased to 2.3 when the participant had fever and anyone of the oral manifestations. Similarly, the odds ratio for cough (1.1) and sore throat (0.4) increased to 1.6 and 0.6 respectively. Table No 5 summarizes the distribution of intraoral signs amongst study participants.

4. Discussion

COVID-19 is provisionally diagnosed based on clinical findings ranging from fever, cough, cold, loss of smell, to acute respiratory distress syndrome. As there is a global surge in the individuals suspected of having COVID-19, signs and symptoms that are strongly linked to the disease would aid in early diagnosis. The present study assessed oral manifestations found in the suspects of COVID-19 disease.

Out of 367 study participants, 217 were RT-PCR positive, and 139 of them had at least one of the oral manifestations such as xerostomia, dysgeusia, stomatopyrosis, or intraoral signs such as oral ulcers, erythema, macule, or papule. The most common oral symptom was xerostomia, followed by dysgeusia. Erythema was the most common intraoral sign in 37 patients, followed by ulcers and a whitish patch.

Considering ACE-2 as a critical receptor for the SARS CoV-2 virus, ACE-2-expressing epithelial cells in the major and minor salivary glands may prove to be a target for the virus. Since, salivary glands serve as a substantial reservoir for this virus, it can be detected in the saliva even before respiratory symptoms appear.[13] Virus can also be obtained from saliva samples early in the disease and via ductal openings of salivary glands at a later stage.[14] These findings suggest that the oral symptoms may be caused by viral interference with the salivary flow. In our study, 93 (42.9%) RT-PCR positive patients reported xerostomia, compared to 48 (32%) RT-PCR negative patients. Stomatopyrosis, which was found in 20% of confirmed cases and 14.7% of suspects, might be linked to xerostomia. A case series of 140 RT-PCR positive patients, 56% of whom reported xerostomia, yielded similar results.[4] Francesco Freni et al. used the summated Xerostomia Inventory-Dutch Version (SXI-DV) questionnaire to assess xerostomia in 50 RT-PCR positive patients and found dry mouth in 32% of them.[15]

The increasing load of gustatory dysfunction in COVID-19 patients has led to the estimated global pooled prevalence of dysgeusia to 41.47%.[16] Sialic acid is a fundamental component of the salivary mucin and it protects the glycoproteins that convey gustatory molecules inside the taste pores from premature enzymatic degradation. A reduction of sialic acid in the saliva is associated with an increase in the gustatory threshold.[17] Millanetti M et al. has suggested that spike protein of SARS-CoV-2 could also interact with sialic acid receptors, in addition to the known interaction with ACE-2.[18] Thus, it can be hypothesized that dysgeusia may be secondary to accelerated degradation of the gustatory particles.[19] In our study we observed that 117 patients reported dysgeusia out of which 78 were RT-PCR positive.

The presence of vesiculobullous lesions on the skin and mucous membranes of COVID-19 patients have been supported by the immunohistochemical studies suggesting the presence of ACE2 receptors in the skin and mucous membranes including oral mucosa.[20] Data on intraoral signs in COVID-19 patients which have been published till now are limited to case reports and series only.[21] Carmen Martin Carreras Presas et al. reported 3 cases, in which 2 were suspects and one case was confirmed COVID-19 patient. All patients were having pain, oral ulcers, or blisters before seeking medical advice and they suggested that intraoral lesions may often be misdiagnosed due to the lack of intraoral examination.[5] C D Soares et al. also reported a case with vesiculobullous lesions on the lips with erythematous halo and published it as the first report showing the SARS-CoV-2 spike protein, on immunohistochemistry in oral lesions of COVID-19 patients.[22] Favia et al. examined 123 diagnosed and hospitalized moderate to critical COVID-19 cases for oral lesions and categorized them based on when the lesions appeared. Early lesions in the initial stages of Covid-19 before the initiation of treatment were observed in 65.9% of the patients and inferred that the appearance of oral lesions might be an early indication of peripheral thrombosis.[9]

Intraoral signs in COVID-19 may occur as ulcers,[3,22,23] aphthae[24] and maculae. It is still unclear whether the reported cases were related to the COVID 19 infection, unrelated occasional phenomenon or indirectly related occurrence associated with stress, anxiety and co morbidities. Systematic review on oral manifestations in COVID-19 reveals the triad of xerostomia, taste dysfunction, and oral mucosal lesions as prevalent manifestations, with xerostomia being the most common oral symptom and oral lesions having moderate certainty of evidence.[8]

Most of the available literature on oral lesions is published as case reports or series in moderate or severe cases already under COVID-19 treatment. Data for hospitalized patients was collected through medical records rather than directly from the patients, therefore some data may be incomplete. Lesions in some cases may be related to treatment or sequelae of the disease in severe cases. Questionnaire-based research did not include an objective evaluation by a qualified expert which may have led to bias. Since we have examined each patient and have found low prevalence of intraoral signs (13% in SG1; 3.7% SG2) in suspects of COVID -19, we conclude intraoral signs like ulcers, erythema, etc. in COVID-19 disease may be nonspecific and unrelated to disease. If there would have been any association between oral ulcers and infection with SARS CoV-2, it would have been reported by most patients as oral ulcers are usually very painful and interfere with everyday activities. As the patients have reported anosmia and dysgeusia, it seems quite improbable that they would have missed out on reporting painful oral lesions like ulcers.

Table 4
Risk estimation of clinical symptoms for COVID-19 infection amongst the study participants.

Symptoms	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Odds Ratio (95% CI) of Symptoms combined with Oral Manifestations
Fever	2.2 (1.4–3.3)	2.2 (1.4–3.5)	2.3 (1.4–3.6)
Cough	1.1 (0.6–1.6)	1.2 (0.7–1.9)	1.6 (0.9–2.7)
Sore throat	0.4 (0.3–0.79)	0.4 (0.3–0.8)	0.6 (0.3–1.2)
Breathlessness	0.7 (0.3–1.4)	0.7 (0.3–1.6)	0.6 (0.2–1.4)
Other Symptoms	2.2 (1.1–4.4)	2.7 (1.3–5.9)	1.3 (0.5–3.1)
Oral Manifestations	1.7 (1.2–2.7)	1.6 (1.1–2.5)	

Table 5
Distribution of intraoral signs amongst study participants.

Type of oral lesion	Location of intraoral lesions	Age in years	Extraoral symptoms/comorbidities	Laboratory confirmation of SARS-CoV-2
Erythema	Uvula	27	Fever	RT-PCR Positive
	Floor of mouth and palate	21	Fever	RT-PCR Positive
	Palate and bilateral buccal mucosa	50	Fever, cough and sore throat	RT-PCR Positive
	Soft palate	58	Cough and sore throat with diabetes mellitus and hypertension	RT-PCR Positive
	Hard Palate	33	Loss of smell	RT-PCR Positive
		26	Running nose	RT-PCR Positive
		31	Cough	RT-PCR Positive
		32	Cough and sore throat	RT-PCR Positive
		58	History of close contact with a laboratory RT-PCR Positive COVID-19 patient	RT-PCR Positive
		55	Cough and sore throat with coronary artery disease and hypertension	RT-PCR Positive
		67	History of close contact with a laboratory RT-PCR Positive COVID-19 patient throat with diabetes mellitus and hypertension	RT-PCR Positive
		73	Fever with diabetes mellitus and hypertension	RT-PCR Positive
	Pharynx and tonsillar area	40	Fever	RT-PCR Positive
		42	Fever with history of smokeless tobacco use	RT-PCR Positive
		60	Fever with history of smoking tobacco	RT-PCR Positive
		63	Fever	RT-PCR Positive
	Tongue	55	Fever and cough	RT-PCR Positive
	Corner of mouth	40	Fever and cough	RT-PCR Positive
	Palate	73	Fever with diabetes mellitus and hypertension	RT-PCR Negative
		54	Sore throat	RT-PCR Negative
		25	Difficulty in breathing with history of smoking tobacco	RT-PCR Negative
		40	Fever	RT-PCR Negative
		42	Difficulty in breathing	RT-PCR Negative
		38	Fever	RT-PCR Negative
		30	Fever, cough and sore throat	RT-PCR Negative
		54	Fever. Sore throat, difficulty in breathing, running nose with history of hypertension and bronchial asthma	RT-PCR Negative
		45	Breathing difficulty	RT-PCR Negative
	Pharynx and tonsillar area	27	Cough	RT-PCR Negative
		46	Fever and sore throat	RT-PCR Negative
Ulcer	Palate	59	Fever and headache, hypertension and diabetes mellitus	RT-PCR Positive
		56	Breathing difficulty, hypertension and diabetes mellitus	RT-PCR Positive
		40	Fever	RT-PCR Positive
		68	Fever and breathing difficulty, Coronary artery disease, hypertension and diabetes mellitus	RT-PCR Negative
	Tongue	54	Cough	RT-PCR Positive
		52	Fever and cough, coronary artery disease and diabetes mellitus	RT-PCR Positive
	Buccal mucosa	21	Fever and cough	RT-PCR Positive
		42	Fever and sore throat	RT-PCR Negative
	Lower labial mucosa	41	Fever	RT-PCR Positive
		43	Fever and sore throat	RT-PCR Negative
	Floor of mouth	27	Fever, cough and sore throat	RT-PCR Positive
	Uvula	27	Fever	RT-PCR Positive
		29	Asymptomatic with close contact	RT-PCR Negative
Whitish Patch	Bilateral buccal mucosa	47	Fever with history of smokeless tobacco use	RT-PCR Positive
	Buccal mucosa	33	Fever, cough and sore throat	RT-PCR Positive
	Bilateral retromolar trigone region	61	Fever with hypertension	RT-PCR Positive
	Lower left alveolar ridge	70	Fever with hypertension with history of smokeless tobacco use	RT-PCR Positive
	Right retromolar trigone	60	Breathing difficulty with diabetes mellitus and hypertension with history of smokeless tobacco use	RT-PCR Positive
	Tongue, buccal mucosa	78	Fever with hypertension	RT-PCR Positive
	Floor of mouth	68	Fever and cough with hypertension	RT-PCR Negative
	Buccal mucosa	50	Fever with hypothyroidism	RT-PCR Negative
	Bilateral buccal mucosa	35	Fever, cough and sore throat	RT-PCR Negative
	Ventral surface of tongue	60	Fever, cough and sore throat with hypertension	RT-PCR Negative
Whitish patch with oral submucous fibrosis	Buccal mucosa bilateral	61	Fever with hypertension along with history of smoking and smokeless tobacco use	RT-PCR Positive
Angular cheilitis	Corner of mouth	40	Cough and hypothyroidism	RT-PCR Positive
Inflamed bilateral Stenson's duct	Stenson's duct	54	Fever with hypothyroidism	RT-PCR Positive
Swelling in pharynx	Pharynx	42	Fever, cough and sore throat	RT-PCR Positive
Vesicles	Palate	46	History of close contact with laboratory RT-PCR Positive covid-19 patient	RT-PCR Positive
Bald tongue	Tongue	58	Fever with diabetes mellitus	RT-PCR Negative
Tonsillar hyperplasia	Palate	37	Fever, cough and sore throat	RT-PCR Negative
Bilateral ecchymosis	Palate in greater palatine foramina region	63	Fever with hypertension and bronchial asthma	RT-PCR Negative
Melanin pigmentation	Tongue	30	Breathing difficulty with hypertension and diabetes mellitus	RT-PCR Negative

The incidence of mucormycosis in COVID-19 patients has increased dramatically, particularly during the second wave of the pandemic, which may be associated with aggressive use of corticosteroids and uncontrolled blood sugar levels.[25] We did not come across any patients who had mucormycosis like symptoms may be because, examination was done prior to the initiation of treatment for COVID-19.

The current study's strength is the relatively high number of study participants who were assessed and evaluated for oral symptoms of SARS CoV-2 infection in all suspects, whether symptomatic or asymptomatic. Because this is cross-sectional research, just one point assessment was performed prior to diagnostic confirmation. Furthermore, dysgeusia and xerostomia were assessed subjectively, which adds to the study's limitations. More research is needed to confirm the link between SARS CoV-2 infection and oral symptoms following COVID-19 therapy, as well as objective examination of taste and salivary flow in suspected patients.

5. Conclusion

The results of the study suggest that xerostomia and dysgeusia can be used as indicators for identifying suspects of COVID-19 disease while intraoral signs like ulcers need further evaluation. Along with the various clinical manifestations of the COVID-19 disease consideration should also be given to xerostomia and dysgeusia, which will help in early identification and treatment of the suspects of the disease and thus halting its spread.

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Declaration of competing interest

None.

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