

## Original Article

# Gustatory dysfunction and oral ulceration in COVID-19 patients: A cross sectional study

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## ABSTRACT

**Background:** Over the past year, patients infected by severe acute respiratory syndrome coronavirus-2 presented with severe gustatory dysfunction, the prevalence of which varies among different populations. Furthermore, there have been sporadic reports of oral ulceration observed in coronavirus disease-19 (COVID-19) patients due to varied reasons. The aim of this study was to investigate and characterize the presence of gustatory disorders, oral ulceration, and other oral changes in patients with laboratory-confirmed COVID-19 infection.

**Materials and Methods:** In this cross-sectional observational study, a total of 402 participants who were detected COVID-19 positive by reverse transcription–polymerase chain reaction were included. Their demographic and clinical data were recorded through hospital records. The participants were interviewed either in person or on the telephone to record any change in taste and/or changes within the oral cavity. *t*-test for independent means was used to compare mean age, while other characteristics were compared by Chi-square test and Z-score test. *P* < 0.05 was taken as significant.

**Results:** Out of the total sample of 402 individuals, 262 were male and 140 were female. The prevalence of gustatory dysfunction and oral ulceration was 43.53% and 15.67%, respectively, in the studied sample. Significantly more females had gustatory dysfunction than males and older subjects more commonly than younger. The symptom of loss/change of taste and oral ulceration were more probable to occur together. In addition, the tongue was the most common site for ulceration in our studied sample.

**Conclusion:** Loss of taste is a common symptom of COVID-19 patients, whereas oral ulceration is not so commonly reported. However, the presence of both these symptoms could impair the quality of life of patients and hamper adequate nutritional uptake.

**Key Words:** Ageusia, coronavirus, coronavirus disease-19, oral ulcer, severe acute respiratory syndrome coronavirus-2

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## INTRODUCTION

Coronavirus is a large family of viruses that constitute the major pathogens known to cause acute respiratory infections among humans. Coronaviruses derive their

name from spike-like projections of glycoproteins on its surface giving it a crown-like appearance when seen under an electron microscope.<sup>[1]</sup> These viruses vary from 80 to 200 nm in diameter and

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have single-stranded positive-sense RNA at its nucleus.<sup>[2]</sup> Angiotensin-converting enzyme-2 (ACE-2) seems to be the target host receptor in humans for these viruses.<sup>[3]</sup> Over the years, some of these viruses had a great public impact in their outbreaks such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome-CoV.<sup>[4]</sup> A new and seventh member of this family, SARS-CoV-2, was identified in China in later part of 2019.

The disease caused by SARS-CoV-2 is named coronavirus disease-19 (COVID-19) which has turned into a pandemic in the early part of 2020. Transmitted via droplets as well as through contact with fomites, COVID-19 poses a threat for rapid progression and spread through population.<sup>[5]</sup> Nearly 80% of the affected population are either asymptomatic or have a mild-to-moderate disease. However, the course of illness may be severe in many such as aging or those with comorbidities.<sup>[6,7]</sup> In these vulnerable individuals, there may be hospitalization, requiring intensive care or even mortality.

This disease may present with no symptoms at all to reports of fever, fatigue, dry cough, or dyspnea. Lesser common symptoms include headache, nausea, and vomiting.<sup>[8]</sup> In severe cases, pneumonia develops which could lead to acute respiratory distress syndrome and even death.<sup>[9]</sup> Lately, anosmia (loss of sense of smell) and ageusia (loss of taste) have also been reported as a symptom of this disease.<sup>[10]</sup> A recent meta-analysis conducted to determine the pooled global prevalence of olfactory and gustatory dysfunction in patients with COVID-19 found a prevalence of 52.73% and 43.93%, respectively.<sup>[11]</sup>

Few reports of oral ulceration seen in confirmed and suspect patients of COVID-19 have also emanated.<sup>[12,13]</sup> A case of acute parotitis and even acute necrotizing ulcerative gingivitis has also been reported in confirmed and suspected patients.<sup>[14,15]</sup> In another study, 21 COVID-19 patients who had skin rash also developed enanthem (oral cavity lesions) which were either petechial, macular, macular with petechiae, or erythematovesicular.<sup>[16]</sup> Due to focus on more severe symptoms and lack of direct examination of oral cavity in such patients, gustatory disorders and other oral symptoms are likely to be ignored. Therefore, we estimated the prevalence of gustatory dysfunction, oral ulceration, and other oral symptoms

in laboratory-confirmed cases of COVID-19 in the Indian population.

## MATERIALS AND METHODS

### Sample selection

This cross-sectional observational study was conducted from July to September 2020 at ESIC Medical College and Hospital, Faridabad, Haryana, India. The COVID-19-positive patients admitted to our facility during this period were assessed for any oral changes and gustatory dysfunction. The inclusion criteria were reverse transcription–polymerase chain reaction-confirmed cases of COVID-19, those willing to be interviewed, and individuals with ability to understand and respond to questions. Patients with severe symptoms that were unable to interact were excluded from the study. The demographic and clinical data of the patients including the symptoms reported were taken from the hospital records of the patient. The demographic data included age, sex, and smoking status. The clinical records obtained were presence of comorbidities, severity of COVID-19 disease, and symptoms reported by the patient. The categorization of patients into mild/asymptomatic, moderate, and severe was based on the current guidelines given by the Ministry of Health and Family Welfare, Government of India. The patients were then interviewed either in person or through telephone for any changes in oral cavity and change in taste. The respondents were inquired about any change in oral mucosa or appearance of any ulceration within the oral cavity during the clinical course of the disease. The time of appearance of symptoms and location of these changes were also documented. The presence of any gustatory disorder was also recorded. All the participants of the study were provided the details of the study before interviewing them and a verbal or signed consent was obtained. The study was approved by the Institutional Ethics Committee on July 04, 2020, vide letter number 134/A/11/16/Academic/MC/2016/155.

### Statistical analysis

Categorical variables such as demographic and socioclinical characteristics were summarized as counts and percentages. For the purpose of simplifying the results, age was categorized into three groups  $\leq 30$  years, 31–60 years, and  $\leq 61$  years. Oral changes were also succinct into counts and percentages. The socioclinical characteristics were

compared between those with and without gustatory dysfunction and oral ulceration within the total sample. *t*-test for independent means was used for the comparison of the mean age in both the groups. Other characteristics were compared by Chi-square test and Z-score test for two population proportion. All the tests were performed with the use of appropriate statistical software.

## RESULTS

A total of 402 patients that fulfilled the inclusion and exclusion criteria were enrolled in the study. The study population had an age range of 10–78 years with a mean age of  $38.13 \pm 14.41$  years. There were more number of males (65.17%) affected by the disease than females. The smoking status, presence of comorbidities, and severity of disease in COVID-19 patients are summarized in Table 1. The general symptoms reported by the patients are depicted in Figure 1, with fever, dry cough, and sore throat being most common. The prevalence of gustatory dysfunction and oral ulceration was 43.53% and 15.67%, respectively, which were the most frequently reported oral symptoms [Table 2].

The clinical-demographic data of patients with and without gustatory dysfunction are compared in Table 3. There was a significant difference between the mean ages of patients with gustatory dysfunction ( $40.65 \pm 14.95$ ) than without ( $36.18 \pm 13.69$ ). Both the groups had more number of males than females, although significantly more females had gustatory dysfunction than males. Younger age group patients of age  $\leq 30$  years suffered less with respect to change in taste than the older age groups. Within our study population, those with moderate severity of disease suffered more gustatory disturbances and the difference was highly significant ( $P < 0.001$ ). It is also more likely that taste changes occur more frequently in those with comorbidities.

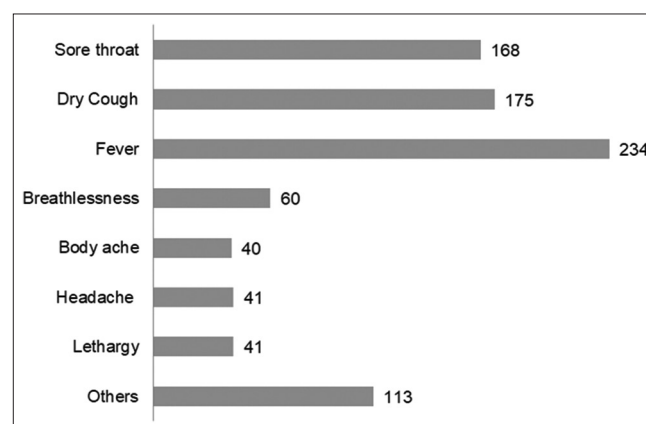
The socioclinical data of patients with and without ulcers are compared in Table 4. There was a significant difference between the mean ages of patients with oral ulceration ( $47.40 \pm 15.29$ ) than without ( $36.40 \pm 13.58$ ). Both the groups had more number of males than females and more nonsmokers than smokers, with insignificant differences in distribution on comparison between them ( $P > 0.05$ ). In patients within the age group

**Table 1: Demographic and socioclinical characteristics of coronavirus disease-19 patients included in the study**

	Frequency (n=402), n (%)
Age groups (years)	
$\leq 30$	152 (37.81)
31-60	217 (53.98)
$\geq 61$	33 (8.20)
Sex	
Males	262 (65.17)
Females	140 (34.82)
Smoking status	
Smokers	92 (22.89)
Nonsmokers	310 (77.11)
Comorbidities	
With comorbidities	90 (22.38)
Without comorbidities	312 (77.61)
Severity of disease	
Asymptomatic/mild	180 (44.78)
Moderate	213 (52.98)
Severe	9 (2.24)

**Table 2: Oral and maxillofacial symptoms reported in coronavirus disease-19 patients included in the study**

Symptom	Frequency (n=402), n (%)
Change in color of oral mucosa	6 (1.49)
Oral ulceration	63 (15.67)
Bleeding gums	13 (3.23)
Change in consistency of saliva	17 (4.22)
Gustatory dysfunction	175 (43.53)
Burning mouth	9 (2.24)
Toothache	8 (1.99)
Extraoral ulceration	9 (2.24)
Loss of smell	83 (20.65)
Other symptoms	10 (2.49)



**Figure 1: General symptoms presented by coronavirus disease-19 patients included in the study.**

of 31–60 years (60.31%) and  $\geq 61$  years (20.63%), ulceration occurred more frequently than the

**Table 3: The relationship between socioclinical characteristics and gustatory dysfunction in patients with coronavirus disease-2019**

Variables	Total study population (n=402), n (%)	with gustatory dysfunction (n=175)	without gustatory dysfunction (n=227)	P
Mean age	38.13±14.41	40.65±14.95	36.18±13.69	<0.001*
Gender				
Males	262 (65.17)	103	159	0.019#
Females	140 (34.83)	72	68	
Age groups (years)				
≤30	152 (37.81)	55	97	0.02#
31-60	217 (53.98)	100	117	
≥61	33 (8.21)	20	13	
Smoking				
Smokers	92 (22.88)	41	51	0.819#
Nonsmokers	310 (77.12)	134	176	
Severity of disease				
Asymptomatic/mild	180 (44.77)	48	132	<0.0001#
Moderate	213 (52.98)	123	90	
Severe	9 (2.23)	4	5	
Comorbidities				
With comorbidities	90 (22.38)	51	39	0.004#
Without comorbidities	312 (77.62)	124	188	

\*Student's *t*-test for independent means  $P < 0.05$  significant, #Chi-square test  $P \leq 0.001$  highly significant

**Table 4: The relationship between socioclinical characteristics and oral ulceration in patients with coronavirus disease-19**

Variables	Total Study population (n=402), n (%)	with oral ulceration (n=63), n (%)	without oral ulceration (n=339), n (%)	P
Mean age	38.13±14.41	47.40±15.29	36.40±13.58	<0.001*
Gender				
Males	262 (65.17)	35 (55.56)	227 (66.96)	0.081#
Females	140 (34.83)	28 (44.44)	112 (33.03)	
Age groups (years)				
≤30	152 (37.81)	12 (19.05)	140 (41.29)	<0.001#
31-60	217 (53.98)	38 (60.31)	179 (52.80)	
≥61	33 (8.21)	13 (20.63)	20 (5.89)	
Smoking				
Smokers	92 (22.88)	17 (26.98)	75 (22.12)	0.401#
Nonsmokers	310 (77.12)	46 (73.02)	269 (79.35)	
Severity of disease				
Asymptomatic/mild	180 (44.77)	11 (17.46)	169 (49.85)	<0.001#
Moderate	213 (52.98)	52 (82.54)	161 (47.49)	
Severe	9 (2.23)	0	9 (2.66)	
Comorbidities				
With comorbidities	90 (22.38)	28 (44.44)	62 (18.29)	<0.001#
Without comorbidities	312 (77.62)	35 (55.56)	277 (81.71)	
Presence of Ageusia	175 (43.53)	40 (63.49)	135 (39.82)	<0.0005 <sup>§</sup>

\*Student's *t*-test for independent means,  $P > 0.05$  nonsignificant, #Chi-square test,  $P \leq 0.001$  highly significant, <sup>§</sup>Z-score test for two population proportion

younger age group of  $\leq 30$  years. With respect to the severity of disease and presence of comorbidities between those with and without oral ulceration, the difference was highly significant ( $P < 0.001$ ). While oral ulceration appeared more frequently in patients

with moderate severity of disease, it is also more likely to affect those with comorbidities. Our data also confirmed the greater probability of ageusia and oral ulceration occurring together ( $P < 0.001$ ). Majority of the patients reported their ulcers on

tongue (55%), followed by palate, lower lip, and buccal mucosa.

## DISCUSSION

COVID-19 is a life-threatening infectious disease, especially in elderly and immunocompromised individuals. Clinical signs of COVID-19 disease appear after an incubation period of approximately 5 days and are nonspecific.<sup>[17]</sup> Common symptoms include fever, breathlessness, cough, and fatigue.<sup>[8]</sup> In our study, we found fever, dry cough, and sore throat to be the most prevalent symptoms, with breathlessness, headache, body ache and lethargy being less common.

Due to the high infectivity of this disease and its spread through oro-nasal fluids, the oral cavity is most likely not inspected for any signs. Likewise due to the focus on more life-threatening symptoms, patients and health-care providers overlook oral symptoms. Oral ulceration (15.67%), anosmia (20.65%), and ageusia (43.53%) were the most frequently reported symptoms in the orofacial region. The variations in reporting anosmia range from 31% to as high as 98% in different studies.<sup>[18,19]</sup> Multiple research works have demonstrated very high prevalence of taste dysfunction which are in line with our results.<sup>[20,21]</sup>

Various studies from Europe reported gustatory dysfunction in 70%–90% of patients.<sup>[22]</sup> Tong *et al.* while reviewing gustatory dysfunction in different population reported a prevalence of 5%–24% in Asian cohorts.<sup>[11]</sup> In our studied sample, 43.53% of patients reported gustatory dysfunction. Whereas many previous studies report a higher prevalence of loss of taste in younger population, other studies found no correlation with age.<sup>[23-26]</sup> In our cohort, loss of taste was more prevalent in older age group. In line with our findings, studies across various ethnicity reveal more females to be affected by gustatory dysfunction compared to males.<sup>[22,26,27]</sup> The reason could be more taste responsiveness shown by females on account of having anatomically more fungiform papillae taste buds compared to males.<sup>[28]</sup> While a number of studies found gustatory dysfunction to be a feature in patients with mild disease, we found it to be more prevalent in patients with moderate severity of disease.<sup>[10,29]</sup>

Numerous hypotheses have been offered in an endeavor to describe the manner in which SARS-CoV-2 affects gustatory senses. These include damage to the central nervous system, angiotensin-converting enzyme

2 receptor manifestation, abnormal zinc homeostasis, and increased proinflammatory cytokines among others.<sup>[30-32]</sup> It has been proposed that the virus damages the central nervous system by attaching to the ACE-2 receptors in glial cells and spinal neurons, thus affecting the taste sensation.<sup>[31]</sup> Some authors have suggested that loss of taste might be because of direct infection of the cells in the tongue, whereas other suggest it be due to obstruction of taste cells chemesthesis due to inflammation and damage to cranial nerves VII, IX, and X.<sup>[33]</sup> a similar explanation has been put forth for anosmia in COVID-19 patients, where the virus is believed to enter the central nervous system through the cribriform plate and cause damage to olfactory neurons causing anosmia.<sup>[34]</sup>

Oral ulcers are a common presenting sign to a wide spectrum of diseases of the oral cavity involving many etiologic factors, including viral infection. A number of viruses such as Herpes Simplex virus, Varicella Zoster virus, and Cytomegalovirus are known to cause oral ulceration.<sup>[35,36]</sup> Herpes virus can easily enter epithelial cells, replicate, and disrupt the integrity of the mucous membrane causing vesicle formation, blistering, and ulceration.<sup>[37]</sup>

Infection with SARS-CoV-2 might cause oral ulceration in a similar manner. ACE2 is the main host cell receptor of this virus and plays a critical role in facilitating the entry of virus into the cells to cause the infection.<sup>[3]</sup> Previous research has demonstrated that the ACE2 receptors are expressed on the mucosa of oral cavity.<sup>[38]</sup> Interestingly, another study documented that epithelial cells of the tongue are highly enriched with these receptors compared to buccal or gingival tissues. The authors suggested that oral cavity could be regarded as potentially high risk for 2019-nCov infectious susceptibility.<sup>[39]</sup> Around 55% of our patients with ulcer located their lesion on tongue which indicates that the reason for oral ulceration; in high probability, a result of SARS-CoV-2 infection. A recent review also found tongue to be the most common site of occurrence for oral ulceration.<sup>[40]</sup>

On comparing the socioclinical characteristics of COVID-19 patients with ulcers to those without, we found that the ulceration of the oral cavity was affecting the older COVID-19 patients more frequently with no significant difference in gender distribution within both groups. Iranmanesh *et al.* also found an equal prevalence of ulceration in both genders, and higher prevalence in older age

groups was found.<sup>[40]</sup> Further in our study, while the asymptomatic or mildly symptomatic patients were spared, it was most commonly seen in those with moderate symptoms. Unfortunately, the patients with severe disease were limited in our sample; therefore, we could not categorically correlate it with increased severity even though it was more prevalent in patients with moderate disease. Our limited data also suggested that those with comorbidities were more affected than those without comorbidities. All these findings suggest that oral ulceration was found more frequently in those that are more susceptible to more severe disease.

As the perception of taste is closely connected with the epithelial lining of tongue, the injury to mucosal epithelial cells of the oral cavity by SARS-CoV-2 might explain ageusia observed in the early stage of disease.<sup>[41]</sup> Since the underlying mechanism for both ageusia and oral ulceration share similarity, the occurrence of these two symptoms together was assessed. The results exhibit that there was a significantly higher probability of ageusia in those with oral ulceration than without.

There are a couple of case reports that discussed the appearance of oral ulceration in suspected and confirmed cases of COVID-19.<sup>[12,13]</sup> Due to the lack of any cross-sectional data with a substantial sample size, the appearance of oral ulcers in these cases was speculated to be due to emotional stress, secondary to medications, or compromised immunity, increasing the susceptibility to opportunistic fungal and viral infections.<sup>[42]</sup>

The drawbacks of our study remain that the data collected were retrospective and through self-reporting. Moreover, our study design being cross-sectional, we could not isolate the cause of ulceration. The ulcers are usually painful, causing unnecessary agony to the patient, and may interfere with their nutritional uptake. Deficiencies of vitamins and/or minerals may further complicate the condition which may result in delayed healing in susceptible individuals.

## CONCLUSION

Gustatory dysfunction is a common symptom of COVID-19 patients, whereas oral ulceration is reported by only a small fraction of patients. However, the presence of both these symptoms could impair the quality of life of patients and

hamper adequate nutritional uptake. To conclude, we recommend a thorough examination of the oral cavity for all COVID-19 patients. To accomplish this, an oral health-care professional should be made a part of the team that provides care to the COVID-19 patients so that none of the signs and symptoms of this disease go undetected and are appropriately managed.

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## Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial, in this article.

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