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ORIGINAL ARTICLE

Clinical characteristics and oral manifestations of COVID-19: a cross-sectional study from Peshawar, Pakistan

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ABSTRACT

OBJECTIVES: To determine the prevalence of oral manifestations among PCR-confirmed COVID-19-positive patients and their potential correlations with age, gender, and systemic manifestations.

METHODS: This cross-sectional study was conducted at Khyber Medical University among 117 randomly selected PCR-confirmed COVID-19-positive patients from October 1, 2020, to January 30, 2021. All the patient records were taken from the Public Health Reference Lab, Peshawar, Pakistan. Telephonic interviews were conducted for data collection using a structured questionnaire. SPSS version 24.0 was used for data analysis. Regression analysis was done to determine the association between dependent variables (oral manifestations) and independent data like age, gender, and systemic features.

RESULTS: Among 117 participants, 56% experienced oral manifestations associated with COVID-19. Taste alterations were experienced by 49.6% (n = 58), xerostomia 34.2% (n = 40), inflammation of the oral cavity 14.5% (n = 17), oral ulcers 10.3% (n = 12), angular cheilitis 6% (n = 7), white lesions 0.9% (n = 1), and bleeding gums 0.9% (n = 1). The average duration for symptoms to last was 10 days. General clinical manifestation of COVID-19 include fever, cough, sore throat, nasal congestion, body aches, diarrhea, difficulty breathing, etc. Oral manifestations had a significant association with gender ($p<0.02$), loss of smell (OR 0.034, 95%CI 0.008-0.153, $p<0.001$) and use of medication (OR 0.051, 95% CI 0.011-0.231, $p<0.001$).

CONCLUSIONS: Oral manifestations were observed in 56% of PCR-confirmed COVID-19-positive patients, with taste alterations being the most common at 49.6%. Significant associations were identified with gender, loss of smell and medication use.

KEYWORDS: COVID-19 (MeSH); Oral Manifestations (MeSH); Dysgeusia (MeSH); Taste Disorders (MeSH); Xerostomia (MeSH); Oral Ulcer (MeSH); Anosmia (MeSH); Fever (MeSH); Fatigue (MeSH); Cough (MeSH).

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INTRODUCTION

The advent of COVID-19 marks a pivotal epoch in global health, enduring as an all-encompassing pandemic that has claimed the lives of 6.3 million individuals to date. This highly contagious disease, propelled by the enveloped RNA beta coronavirus, manifests through a spectrum of clinical symptoms such as fever, flu, sore throat, dry cough, nasal congestion, myalgia, and fatigue. Notably, its repercussions are notably severe for immunocompromised individuals and those with pre-existing comorbidities.[1], The outcomes are even adverse for immunocompromised people and individuals with pre-existing co-morbidities. In regions with constrained resources and lower-middle-income nations, the profound challenges faced by healthcare systems underscore the imperative nature of addressing this monumental health crisis.[2]

The novel coronavirus, notable for both systemic and oral manifestations, is characterized by four structural proteins—spike, membrane, envelope, and nucleocapsid —instigating significant research attention, particularly on the interaction between the spike protein and the ACE-2 receptor.[3,4] This interaction has spurred endeavors in drug and vaccine development, underlining a discernible correlation between COVID-19 and ACE-2.[5] Amidst the surge of COVID-19-related inquiries, reports have emerged detailing oral manifestations, ranging from dysgeusia to vesiculobullous lesions.[1,6] Despite these revelations, a notable dearth of literature exists concerning oral tissue and salivary examination, a critical gap given the virus's heightened transmissibility through saliva. Remarkably, specific oral lesions such as desquamative gingivitis, inexplicit ulceration, petechiae, and candidiasis-like co-infections have been observed in individuals positive for COVID-19.[7]

Additional studies post a plethora of oral manifestations in COVID-19 patients, encompassing taste and smell disorders, inflammation of the oral cavity and tongue papilla, white surface lesions of the tongue, dryness of the mouth, recurrent herpes simplex, geographic tongue, ulcers, candidiasis, and facial and muscle pain during mastication.[8]

The vulnerability of the human oral

Table I: Demographic and clinical characteristics of COVID-19 patients

Patient characteristics		Frequency (n=117)	Percentage
Age (years)	15-29	42	36
	>29-44	52	44.4
	>44-70	23	19.7
Gender	Male	85	72.6
	Female	32	27.4
Clinical Manifestations	Fever and chills	81	69.2
	Fatigue and body aches	66	56.4
	Cough	58	49.6
	Sore throat	39	33.3
	Loss of smell	37	31.6
	Headache	36	31
	Nasal congestion	34	29.1
	Difficulty breathing	27	23.1
	Diarrhea	24	20.5
	Nausea or vomiting	18	15.4
	Dry/itchy eyes	9	7.7

Table II: Oral manifestations of COVID-19 among study participants

Oral manifestations	Frequency (n=117)	Percentages (%)
Taste alterations/loss of taste	58	49.6
Xerostomia	40	34.2
Redness/soreness of the mouth	17	14.5
Oral ulcers	12	10.3
Blister/ vesicle on lips or on corners of the mouth	7	6
White lesions in the mouth	1	0.9
Bleeding gums	1	0.9

Table III: Association of baseline patient characteristics with oral manifestations

Parameters		Oral Manifestations		P-value
		No (n=52)	Yes (n=65)	
Gender	Female (n=32)	9 (28.1%)	23 (71.9%)	0.029
	Male (n=85)	43 (50.6%)	42 (49.4%)	
Systemic manifestation	No (n=20)	20 (100%)	0	0.001
	Yes (n= 97)	32 (33%)	65 (67%)	
Co-Morbidities	No (n= 95)	45 (47.4%)	50 (52.6%)	0.186
	Yes (n=22)	7 (31.8%)	15 (68.2%)	
Diabetes	No (n=109)	48 (44%)	61 (56%)	0.743
	Yes (n=8)	4 (50%)	4 (50%)	
Hypertension	No (n=105)	49 (46.7%)	56 (53.3%)	0.152
	Yes (n=12)	3 (25%)	9 (75%)	
Use of medications	No (n=22)	20 (90.9%)	2 (9.1%)	<0.001
	Yes (n= 95)	32 (33.7%)	63 (66.3%)	

cavity's soft tissues and salivary glands to viral infections is accentuated by their composition, with viruses like the herpes simplex virus (HSV) and human papillomavirus (HPV) commonly implicated in oral diseases.[9] Furthermore, immune suppression often sets the stage for opportunistic pathological processes of viral, bacterial, or fungal origin within the oral cavity.[10] The intricate viral entry dance unfolds as SARS-CoV-2 exploits the ACE-2 receptor, prevalent in nasal and oral epithelia, especially on the dorsal surface of the tongue, and localized in the taste cells of fungiform papillae, alongside the co-occurrence of Transmembrane protease, serine 2 (TMPRSS2)[9,11]

A number of studies have reported mouth ulcers, dysgeusia, and xerstomia as manifestations of COVID-19. Oral and nasal mucosa are the initial areas to get early infection. Thus, oral signs and symptoms play a vital role in COVID-19 identification and early management. Increasing evidence also confirms the effects of COVID-19 on the sense of smell, suggesting potential mechanisms such as swelling in the olfactory cleft and damage to both the olfactory bulb and epithelium.[12] In light of this multidimensional oral manifestation panorama, this study aims to thoroughly explore the comprehensive impact of COVID-19 on oral health in Khyber Pakhtunkhwa. Specifically, the study endeavors to elucidate the prevalence of oral manifestations and their potential correlations with age, gender, and systemic manifestations, providing valuable insights into the evolving understanding of COVID-19 pathology in the Khyber Pakhtunkhwa province of Pakistan.

METHODS

This cross-sectional study was conducted at Khyber Medical University, Peshawar, Pakistan. Among the PCR-confirmed COVID-19-positive patients in Khyber Pakhtunkhwa from October 1, 2020, to January 30, 2021. Patient records were collected from the Public Health Reference Lab (PHRL) in Khyber Medical University, Peshawar, which is the leading reference labaratory of Khyber Pakhtunkhwa for the diagnosis and investigations regarding infectious diseases and COVID-19.

A total of 117 confirmed cases of COVID-19 were included in this study using a simple random sampling technique. A confirmed case of COVID-19 was defined as any individual who had a positive result on PCR nasal swab specimens. The sample size was calculated using openepi at 95% confidence level, 8% absolute precision, and based on 25.8% proportions of combined taste and smell dysfunction in COVID-19-positive patient.[8]

Only the PHRL-confirmed cases of

Table IV: Association of Xerostomia with study variables

Variables		Xerostomia		P-value
		No (n=77)	Yes (n=40)	
Inflammation of the oral mucosa	No (n= 100)	72	28	<0.001
	Yes (n=17)	5	12	
Taste Disorder	No (n= 59)	54	5	<0.001
	Yes (n= 58)	23	35	
Gender	Male (n= 85)	61	24	0.029
	Female (n=32)	16	16	
Oral Ulcers	No (n= 105)	73	32	<0.01
	Yes (n= 12)	4	8	

Table V: Logistic regression analysis for association of oral manifestation with different variables

Predictors	ADJUSTED		UNADJUSTED	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age	0.981 (0.934-1.030)	0.431	1.028 (0.995-1.063)	0.10
Gender	3.701 (1.11-12.26)	0.032	2.616 (1.08-6.30)	0.03
Systemic manifestations	0.000	0.998	0.000	0.99
Co-morbidity	0.730 (0.192-2.786)	0.646	1.929 (0.721-5.156)	0.19
Use of medication for COVID-19	0.300 (0.050-1.795)	0.187	0.051 (0.011-0.231)	<0.001
Fever and chills	0.000	1.000	0.000	1.0
Sore throat	1.453 (.411-5.138)	0.562	0.422 (0.187-0.951)	0.037
Cough	0.339 (0.105-1.100)	0.072	0.243 (0.112-0.530)	<0.001
Loss of smell	0.038 (0.007-0.198)	<0.001	0.034 (0.008-0.153)	<0.001
Headache	0.103 (0.025-0.431)	0.002	0.086 (0.028-0.266)	<0.001

COVID-19, irrespective of gender, aged between 15 to 70 years were included in the study.

Patients with a previous history of oral diseases, having chronic periodontitis, and using dentures or braces were excluded from the study.

Ethical approval for the current study was obtained from the ethics review committee of the Khyber Medical University (Reference # Dir/Ethics/KMU/2020/24). The study was conducted in accordance with the Declaration of Helsinki and consent was obtained from all the study participants entailing their voluntary participation.

Considering the lockdown as per the directives of the Government of Pakistan at the time of data collection, telephonic interviews were conducted with all the consented study participants.

A questionnaire for this study was adopted after a thorough literature search; however, for local settings, content validity was approved by experts in the field and medical education. The main questionnaire comprised four sections, including socio-demographic characteristics (Section 1), information about the clinical features of COVID-19 they experienced (Section 2), information about co-morbidities (Section 3), and details regarding oral manifestation (Section 4).

Statistical analysis was performed using SPSS version 24.0. Mean and standard deviations were calculated for continuous variables. For categorical variables, percentages and frequencies were calculated. The Chi-square test was applied for the assessment of the relationship between categorical variables. $P \leq 0.05$ was taken as a significant marker of association. Regression analysis was done to determine the association between dependent variables (oral manifestations) and independent data like age, gender, and systemic features.

RESULTS

Of the total 117 people interviewed, 72.6% (n = 85) were males and 27.4% (n = 32) were females. The mean age of study participants was 35.29±11.60 years. The duration of COVID-19 symptoms was approximately 10.62±6.19 days.

Among the clinical characteristics, fever and chills were experienced by 69.2% of patients, cough 49.6%, sore throat 33.3%, nasal congestion by 29.1%, difficulty breathing by 23.1%, and loss of smell by 31.6%, as presented in Table I.

Data regarding oral manifestations were recorded, and taste disorders were experienced by 49.6% of participants (n = 58). After taste disorders, xerostomia was the second most frequently occurring oral problem among COVID-19 patients, as reported by 34.2% of participants. Soreness of the mouth, oral ulcer, white lesions, blisters on the corner of the mouth, and bleeding gums were reported by 4.5%, 10.3%, 0.9%, 6%, and 0.9% of study participants, respectively (Table-II).

Upon application of the chi-square test to find the association between the dependent variable (oral manifestation) and independent variables, a statistically significant association between gender ($p < 0.02$) and systemic manifestation ($p < 0.001$) was found with oral manifestations. The use of medication for the treatment of COVID-19 was also found to have a statistically significant association with oral manifestations ($p<0.001$) [Table III].

Table IV presents the data pertaining to the association of xerostomia (dry mouth) with other variables of interest. It is noteworthy that xerostomia had a statistically significant association with inflammation of the oral mucosa ($p<.001$), taste disorder ($p<.001$), and oral ulcers ($p<0.01$).

Both adjusted and unadjusted regression shows a significant association of oral manifestations with gender ($p< 0.032$). Unadjusted regression shows a significant association between oral manifestations and the use of medication for the treatment of COVID-19 (OR 0.051, 95% CI 0.011-0.231 $p <.001$) [Table V).

DISCUSSION

The present study highlights the oral manifestations of COVID-19 among the PCR-confirmed patients. The most common oral manifestation among the study population was taste alteration or taste loss; a finding previously reported among COVID-19-positive patients.[13,14]

The prevalence of taste loss in the current study (49.6%) was quite in line with that of 45% reported in a systematic review and 39.4% in another recently published study.[13,15] Among the COVID-19 positive patients, the literature does indicate not only the gustatory dysfunction but also the global estimated pooled prevalence of taste disorder or dysgeusia as 41.47%.[15,16] Salivary mucin consists of sialic acid which is a key component that protects the glycoprotein which serves to convey gustatory molecules to taste pores. Any imbalance of sialic acid in normal saliva leads to an increased gustatory threshold. Further, it was also hypothesized that SARS-CoV-2 has a spike protein that interacts with both sialic acid and ACE-2.[17]

After the taste, xerostomia and smell disorder were the next most commonly manifested symptom associated with COVID-19 infection among this study participants. Around 31.6% of patients experienced a loss of sense of smell. Since the loss of taste is quite possibly one of the most widely recognized symptoms of COVID-19 and generally shows an association with the loss of smell.[18,19] Recent literature focusing on COVID-19 tried to explain the possible relation and mechanism associated with loss of taste and COVID-19 infection.[3,20] One possible explanation suggests that rhinitis triggers the inflammatory response affecting taste buds functioning. Others attributed the loss of taste to the potential side effects of COVID-19 medications.[20] It was reported that smell and taste disorders were the most common symptoms found in the upper respiratory tract of COVID-19 patients in China (Wuhan).[4] Conversely, the percentage of smell and taste disorders found in Europe seemed to be much higher than 70-90%.[21]

In this study and previously, gender had been reported to have a significant association with the oral manifestation of COVID-19, with females found more prone to gustatory dysfunctions. This was supported by the findings of studies conducted in Europe, Italy, South Korea, France, and Turkey, where females had more prevalence of dysgeusia compared to males.[22,23] Conversely, few studies stated that generally, dysgeusia has no association with gender or age in milder cases. No noteworthy association of taste impairment exists with gender or age.[20] Perhaps, the difference in the studies is because of the different strains of coronavirus and the characteristics that each of these strains exhibits. It could also be related to the severity of the disease and genetic disparity. It should also be considered that people belonging to different ethnicities are likely to have a dissimilar reaction to SARS-CoV-2 infection.

Xerostomia was found to be present in 34.2% of patients in this study. A significant association was found between xerostomia and gender. Findings from other studies reported the prevalence of xerostomia among study participants to be 32% and 56% respectively.[8,24] One possible explanation for xerostomia among COVID-19 positive patients is that one major target of CoV-2 virus in both minor and major salivary glands is ACE-2 epithelial cells, for the salivary glands being a major reservoir for SARS CoV-2 virus.[9] This viral overload interferes with the normal saliva flow leading to several oral manifestations among COVID-19-positive patients.[25]

Immunohistochemical studies have supported the presence of vesiculobullous lesions but limited data regarding intraoral signs is available limited to case series reporting oral ulcers and blisters among COVID-19 positive patients.[26] Intraoral lesions as reported by this study included 0.3% oral ulcers, 6% blisters, and 0.9% white lesions. Literature supports that intraoral lesions may arise as ulcers. Furthermore, the possible mechanism causing increased inflammation in related oral tissues including salivary glands and tongue mucosa is ACE-2-related cells acting as host cells for the virus.[10] Nonetheless, oral lesions can be found in other viral infections as well. Fatigue and stress can upsurge the danger of the recurrence of HSV. Oral mucosa damage can occur in patients who are hospitalized due to secondary infections, side effects of medication, and immune impairments.[27]

Based on the findings, a significant association ($p<.001$) was reported between oral manifestation and the use of COVID-19-related medication in the current study. This association is attention-worthy as antiviral drugs have oral implications.[28] Similarly, protease inhibition therapy hurts taste disturbance and parotid functioning and antiviral drugs lead to xerostomia and oral candidiasis, dysgeusia, or ageusia.[28] Pertinent to this, among already immunocompromised covid positive patients having corticosteroid therapy, oral infections were reported requiring meticulous oral health maintenance and management among all such patients.[29]

The oral manifestation of COVID-19 presented in this study are in agreement with the studies conducted previously and highlights the strong association of COVID-19 with taste alterations, loss of smell, xerostomia, and use of medication. This study findings coupled with other such studies lead to the need of having a targeted oral health care package for COVID-19-positive patients to control the adverse oral manifestation.

CONCLUSION

Oral manifestations were evident in 56% of individuals confirmed positive for COVID-19 through PCR testing, with taste alterations prevailing as the most frequent at 49.6%. Notable connections were established with gender, loss of smell, and medication use. In light of this multidimensional oral manifestation landscape, this study endeavored to comprehensively explore the overarching influence of COVID-19 on oral health and its potential association with age, gender, and systemic manifestations. The prevalent occurrence of taste alterations and xerostomia emerged as crucial early indicators for identifying and diagnosing COVID-19. This

underscores the pivotal role of oral health practitioners in comprehending these clinical presentations to enhance patient care and diagnosis.

Limitation of the Study

The cross-sectional study design is a major limitation in establishing temporality.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SH: Acquisition of data, drafting the manuscript, approval of the final version to be published

MR: Study design, drafting the manuscript, approval of the final version to be published

SA: Analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

KR: Analysis and interpretation of data, critical review, approval of the final version to be published

MAK: Study design, acquisition of data, critical review, approval of the final version to be published

SL & NM: Concept and study design, drafting the manuscript, critical review, approval of the final version to be published

MAK: Concept and study design, acquisition of data, drafting the manuscript, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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