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Original Article

Oral Manifestations of COVID-19 Correlated to Medical and Drug History. A Survey on Infected Medical Doctors

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Abstract

Objective: Reporting the oral symptoms of COVID-19 and correlate the occurrence of these symptoms with various possible etiologic factors.

Methods: A cross-sectional web-based survey targeted medical doctors infected with COVID-19. The survey questioned the diagnosis of the disease, the severity of the disease symptoms, the oral symptoms along with drug and medical history. A total sample of 312 response were analyzed and correlated with various factors including the patients' age, sex, medical history, drug history, hospitalization, and severity of COVID-19 symptoms.

Results: Oral manifestations were reported in 72.5% of the participants. The most common oral manifestations were dysgeusia in 76% of patients which was partial in 64% of the participants. Xerostomia was reported in 41.6% of cases. Aphthous stomatitis and recurrent herpetic infections were also reported.

Conclusion: The most common oral manifestations of COVID-19 are dysgeusia and xerostomia followed by oral ulcers. The occurrence of oral manifestations is increased by 4.7 folds among patients with underlying systemic diseases.

Key words: COVID-19, Oral symptoms, Dysgeusia, Xerostomia, Aphthous stomatitis

Introduction:

Late in the year 2019, Doctors at Wuhan hospitals received for the first-time cases with unusual viral pneumonia. Clusters of patients with viral pneumonia and acute respiratory distress syndrome (ARDS) were falling every day in China. The symptoms of the disease were quite variant between infected persons and the course of the disease was unclear. The unknown virus was discovered. Corona virus-19. A member of the Corona viruses that has never caused infection in Human before. The structural homology between the new virus and the severe

acute respiratory syndrome (SARS) orm CoV-SARS-1 has given it the name CoV-SARS-2 [1].

In no time the disease was all-over the world. This event was the most fetal pandemic crisis since the influenza outbreak in 1918. The number of patients around the world was tremendously increasing. In many countries, the medical condition was fearful and seemed to be out of control [2]. Doctors were facing an unknown enemy. In 2020 The world health organization (WHO) declared a pandemic disease [3].

Scientist all over the world were working day and night to record, observe and analyze each symptom of the disease, as well as recognizing the mutated versions and structure of the virus. Although, in absence of clear pathogenesis this was impossible. In 2019 Chen and colleagues published the structural analysis of receptor binding illustrating the binding of the viral spike to Angiotensin convertase enzyme-2 (ACE-2) [4]. In 2020 Walls and his coresearchers introduced the antigenicity of SARS-CoV-2 spike glycoprotein and confirming the binding to the ACE-2 [5]. Although the ACE-2 receptor expression is higher in the lung tissue being the major target of the disease, and despite that the expression in many other tissues such as renal tissues and gastro-intestinal mucosa and oral mucosa may justify the wide array of symptoms in different individuals, the answer to the question why certain people show symptoms that are not evident for all others is unknown [6-7].

The suggestion of oral manifestations of the disease was introduced and with viral outbreak the demand of oral specialist aid was increasing [8-9]. The oral manifestations of COVID-19 were discussed in many articles representing different researches, most of them are case-reports and retrospective studies.

Trials have been made to answer the question whether these symptoms were due to Co-infections [7] or due to direct infection with the virus [10]. The presence of the virus in the salivary secretions raised many questions whether if the oral mucosa is a target of the virus [11].

As many questions were raised, COVID-19 became a hot topic for publication. The race to introduce new information affected both, the quality of the studies and the publication process as well. Contradiction was present between many of the published articles [12-13]. Many articles were withdrawn after publication due to methodological errors.

What are the oral signs and symptoms that a patient is having during the disease and how to manage these manifestations, these questions must have an accurate answer. With unclear prognostic factors and death rate of 4 to 5% the development of prospective oral screening studies to find out the nature of these symptoms was almost impossible [14-15].

Designing proper research in short time was a challenge. Surveys have been developed with different designs to investigate the nature of oral signs and symptoms avoiding direct contact with the patient during active infection [16]. Patient shaping of their symptoms was extremely variable [17]. Selection of COVID-19 patients of certain population with fair knowledge about the oral lesions, signs and symptoms of specific oral infections was a possible option. Based on the previous observation this survey study targeted doctors who were infected with COVID-19 to investigate the nature of oral manifestations of the disease.

Methods:

This is a survey study that was designed to investigate the oral symptoms of SARS-CoV-2 at a sample of infected medical doctors. The survey was designed as a google form published among communities of medical personals through the internet.

A survey was conducted between December 2020 and August 2022.

Target population*:*

All medical doctors with previous infection with CoV-19. All responses were considered regardless of sex, age, if the survey questions are fully reported.

The questionnaire was distributed among all medical doctors' communities. The survey was sent through direct email, WhatsApp, and face book groups along with personal distribution through different healthcare units. Appendix 1

Ethical approval:

This is a survey study that was designed to investigate the oral symptoms of SARS-CoV-2 at a sample of infected medical doctors personals. The study was approved by the Faculty of Dentistry Beni-Suef University Research Ethical Committee: #FDBSUREC/10092020/ME. The survey was designed as anonymous google form published among communities of medical personals through the internet. The approval consent for all participants was a part of this survey.

Sample size calculation:

Using the most recent WHO records for doctors 445,000 physicians were registered in Egypt [18]. Based on these records, the sample describing population for this survey was calculated using Gill et al. 2010 sample size table with Confidence level 95%. The calculated sample equivalent to this population size was 384 Johnson and Gill, 2010 [19].

The survey comprised a total of 3 main sections. The first section included demographic data and diagnostic method for COVID-19 infection. The second section included question about duration of the disease, the general manifestations of the disease, the previous medical history. History of smoking, severity of COVID-19 infection and history of hospitalization. Drug history and treatments for COVID-19. Presence of blood discrepancies during COVID-19 infection. The third section targeted detailed oral manifestations of the disease and questions about the oral hygiene and presence of previous oral lesions.

The questions about oral manifestations were designed based on a systematic search through the current literature, dated between 2019 and January 2020. The authors reviewed the most reported oral manifestations to estimate the valuable questions to design the survey.

Statistical analysis:

Qualitative data were presented as frequencies and percentages. Quantitative data were presented as mean and standard deviation (SD) values. Binary logistic regression analysis was used to determine significant predictors of oral manifestations of COVID-19. Model fit was tested using -2 Log Likelihood test and Pseudo r2 tests and the model was fit to describe the relations between the independent and the dependent variables. The regression coefficient (β), standard error (SE), Odds Ratio (OR) and 95% confidence interval (95% CI) were calculated. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

Response rate and baseline characteristics

According to the calculated sample size, 384 subjects were targeted however to ensure this number is met, we increased the sample size to this number was increased by 50% to be 576 according to Kotrlik and Higgins in 2001[20] to compensate for non-responsive subjects. the collected responses were 312 questionnaires giving a response rate of 54%. Base line characteristics are presented in Table 1.

Table 1. Frequencies (n), percentages (%), mean, and standard deviation (SD) values for base line characteristics of the study sample

Base line characteristic (n = 312)	
Age [Mean (SD)]	38.3 (6.2)
Gender [n (%)]	
Male	126(40.3%)
Female	186(59.7%)
Smoking [n (%)]	22 (7.1%)

Medical history

Less than half of participants had previous medical history prior to COVID-19 infection. Medical history findings are presented in Table 2. The most prevalent disease was gastro-intestinal diseases followed by cardiovascular diseases while the least prevalent diseases were musculo-skeletal and immunological diseases.

Drug history

Almost one third of participants reported regular intake of drugs prior to COVID-19 infection. Drug history findings are presented in Table 3. The most prevalent drugs were anti-hypertensive drugs followed by oral hypoglycemics while the least prevalent drugs were anxiolytics and anti-epileptics

Table 2. Frequencies (n) and percentages (%) for medical history among study participants

Medical history (n = 312)	n (%)
Diabetes Mellitus	50 (15%)
Bronchial asthma	38 (12%)
Gastro-esophageal reflux disease (GERD)	36 (11.5%)
Hypertension	34 (11%)
Rheumatic arthritis	14 (4%)
Anemia	6 (2%)
Medically-free	182 (58.3%)

Table 3. Frequencies (n) and percentages (%) for drug history among study participants

Drug history (n = 98)	n (%)
Anti-hypertensive drugs	38 (38.8%)
Oral hypoglycemics	26 (26.5%)
Insulin	22 (22.4%)
Proton pump inhibitor	18 (18.4%)
Antibiotics	18 (18.4%)
Anti-acids	16 (16.3%)
Systemic steroids	12 (12.2%)
Anti-depressants	8 (8.2%)
Immuno-modulators	6 (6.1%)
Diuretics	6 (6.1%)
Anxiolytics	2 (2%)
Anti-epileptics	2 (2%)

COVID-19 symptoms and hospitalization

All participants reported symptoms of COVID-19 which are presented in Table 4. The most prevalent symptoms were body aches followed by headache, fever and loss of smell while the least prevalent symptoms were runny nose and vertigo.

The most common diagnostic method was clinical signs and symptoms (Table 5). The most common duration of symptoms was one week.

Only fourteen subjects (9%) were hospitalized, one third of these subjects reported ICU admission and two thirds of participants reported being under non-invasive ventilation (CPAP).

COVID-19 diagnosis and duration of symptoms

Table 4. Frequencies (n) and percentages (%) for COVID-19 symptoms

COVID-19 symptoms (n = 312)	n (%)
Body aches	216 (69.2%)
Headache	204 (65.4%)
Fever	198 (63.5%)
Anosmia (Loss of smell)	194 (62.2%)
Total loss of smell	152/194 (78.4%)
Partial loss of smell	42/194 (21.6%)
Cough	180 (57.7%)
Ageusia (Loss of taste)	172 (55.1%)
Sore throat	158 (50.6%)
Myalgia	156 (50%)
Diarrhea	142 (45.5%)
Shortness of breath	116 (37.2%)
Chest Pain	102 (32.7%)
Runny nose	86 (27.6%)
Vertigo	82 (26.3%)

COVID-19 related drugs

The most common drugs were Vitamin C and Zinc while the least commonly used drug was Tocilizumab (Table 6).

Table 5. Frequencies (n) and percentages (%) for COVID-19 diagnosis and duration of symptoms

COVID-19 diagnosis and duration of symptoms (n = 312)	n (%)
Diagnosis	
Clinical signs and symptoms	210 (67.3%)
PCR test	152 (48.7%)
Suspicious lab findings	120 (38.5%)
Chest CT	78 (25%)
Blood chemistry	4 (1.3%)
Duration of symptoms	
Less than one week	4 (1.3%)
One week	78 (25%)
Two weeks	50 (16%)
More than two weeks	58 (17.9%)
No answer	124 (39.7%)

Table 6. Frequencies (n) and percentages (%) for COVID-19 related drugs

COVID-19 related drugs (n = 312)	n (%)
Vitamin C	288 (92.3%)
Zinc	258 (82.7%)
Azithromycin	232 (74.4%)
Steroids	132 (42.3%)
Lactoferrin	106 (34%)
Hydroxychloroquine	48 (15.4%)
Cephalosporin	40 (12.8%)
Remdesivir	22 (7.1%)
Oseltamivir (Tamiflu)	12 (3.8%)
Antifungals	16 (5.1%)
Doxycycline (Vibramycin)	10 (3.2%)
Acyclovir	10 (3.2%)
Linezolid	8 (2.6%)
Meropenem	6 (1.9%)
Tocilizumab (Actemra)	2 (0.6%)

Oral manifestations of COVID-19

Oral manifestations of COVID-19 are presented in Table 7. Oral manifestations were reported by 72.5% of subjects. The most common oral manifestation was loss of taste in approximately three quarters of participants.

Total loss of taste was more prevalent than partial loss. When subjects were asked about the duration of loss of taste; 1.2% reported loss of taste for less than one week, 37% for one week, 33.7% for two weeks and 22.1% reported loss of taste for more than two weeks. As regards oral ulcers; multiple and mild painful ulcers were the most common types with a prevalence of 29.2% for each type, respectively. The least common type of ulcer was severe painful ulcers in 8.3% of subjects who suffered oral ulcers. Ten subjects reported previous experience with these oral manifestations.

Oral hygiene

Oral hygiene findings are presented in Table 8. More than two thirds of participants regularly brush their teeth. Less than one fifth of participants reported their oral hygiene as excellent, approximately two thirds reported it as good and less than one fifth reported their oral hygiene as fair. Seven participants didn't answer questions related to oral hygiene.

Significant predictors of oral manifestations of COVID-19

Binary logistic regression model was constructed using presence of oral manifestations (Present/absent) as the dependent variable. Gender, age, medical history, drug history, COVID-19 related drugs, hospitalization and oral hygiene were the independent variables. Model fitting was tested by several methods; first is the statistically significant -2 Log Likelihood test (-2 Log Likelihood = 145.3, P-value = 0.011). Secondly; pseudo R-square tests results were as follows: Cox and Snell = 0.369, Negelkerke = 0.246. Values of these tests indicate good model fit.

Results of the regression model presented in table 9 showed that presence of systemic diseases was the only statistically significant predictor of oral manifestations of COVID-19. Subjects with systemic diseases are 4.798 folds prone to oral manifestations of COVID-19 than those who are medically-free.

Table 7. Frequencies (n) and percentages (%) for oral manifestations of COVID-19

Oral manifestations of COVID-19 (n = 226)	n	%
Loss of taste	172/226	76.1%
Total loss of taste	110/172	64%
Partial loss of taste	62/172	36%
Dry mouth	94/226	41.6%
Metallic taste	56/226	24.8%
Oral ulcers	48/226	21.2%
Myofacial pain	38/226	16.8%
Burning mouth	14/226	6.2%
White patches	20/226	8.8%
A lump or vesicular lesion on lips or oral mucosa	12/226	5.3%
Gingival bleeding	12/244	5.3%

Table 8. Frequencies (n) and percentages (%) for oral hygiene of study participants

Oral hygiene (n = 312)	n (%)
Frequency of tooth brushing	
Regular	214 (68.6%)
Irregular	76 (24.4%)
No brushing	8 (2.6%)
No answer	14 (4.5%)
Self-reported oral hygiene	
Excellent	50 (16%)
Good	194 (62.2%)
Fair	54 (17.3%)
No answer	14 (4.5%)

Table 9. Results of binary logistic regression analysis model for predictors of oral manifestations of COVID-19

Variable	Regression coefficient (β)	Standard Error (SE)	P-value	Odds Ratio (OR)	95% CI
Gender	-0.032	0.422	0.940	0.969	0.423 – 2.217
Age	-0.016	0.037	0.662	0.984	0.915 – 1.058
Systemic diseases	1.568	0.602	0.009*	4.798	1.475 – 15.608
Drug history	-0.322	0.599	0.580	0.724	0.224 – 2.342
Hospitalization	1.102	1.101	0.317	3.009	0.348 – 26.032
COVID-19 related drugs					
Vitamin C	2.310	1.295	0.074	1.076	0.796 – 17.566
Zinc	-0.967	0.853	0.257	0.380	0.072 – 2.022
Azithromycin	0.297	0.504	0.555	1.346	0.501 – 3.613
Frequency of tooth brushing	-0.441	0.941	0.639	0.643	0.102 – 4.070
Self-reported oral hygiene	0.281	0.616	0.648	1.325	0.396 – 4.435

*: Significant at $P \leq 0.05$, OR: Odds Ratio

Discussion:

The last few years witnessed the outbreak of COVID-19 with its variant mutations and waves of infection. Dentist as members of the medical team were required to face the disease and deal with wide range of oral manifestations during and post COVID-19 infection. Identifying the oral manifestation of the disease requires clinical oral examination of the patients during the active disease phase. However, it was not possible for the dentist to contact patients with active disease for screening purposes.

The present study reviewed the occurrence of specific oral manifestations during COVID-19 infection in a population of doctors who experienced COVID-19 infection themselves.

Population awareness of the disease and the nature of oral manifestations will enhance their shaping of the symptoms associated with the disease.

The present study demonstrated the occurrence of oral manifestations in 72.5% of the participants. The most common oral manifestations were dysgeusia in 76% of patients which was partial in 64% of the participants. This was followed by was increased among population with previous medical history with no evidence of correlation with any other factors regarding gender, certain medications or oral hygiene.

The current literature presented many case reports describing variable clinical presentations of the oral manifestations. In 2022, Cochrane database has published a review identifying the signs and symptoms of COVID-19. The oral manifestations categorized as ageusia alone or in combination with anosmia [21]. Amorim dos Santos et al. in 2021 demonstrated in a systematic review on oral symptoms variant oral manifestations. The symptoms were ageusia whether complete or partial, Anosmia, variant oral mucosal lesion ranging from erythematous to blisters and ulcers. The systematic review included a total number of 40 studies, 33 cross-sectional study and 7 case reports [17]. Few months later the same authors published an update demonstrating the addition of Xerostomia and giving more accurate definition of the oral lesion to be described as aphthous like ulcer, herpes simplex, and Candida. The oral lesions were described by the authors as xerostomia 41.6% of cases. Taste alteration however seemed to be the most common symptom either by partial or complete loss of taste or by metallic taste sensation reported by 24% of the participants. The occurrence of aphthous stomatitis was reported by 21% of the participants while 5% reported herpes simplex lump on their lips and oral mucosa. The occurrence of oral symptoms

miscellaneous and more likely to represent Co-infections [22]. Another systematic review by Orsilsi et al. in 2021 based on multiple case reports, case series, and retrospective studies demonstrated a spectrum of symptoms occurring for non-hospitalized patients mentioning pre-oral ulcers, candidiasis, and macroglossia. For hospitalized patients the authors described increased rates for candida infection [23].

In accordance was the article by Yan et al. in 2020. Authors conducted a cross-sectional survey presenting the data of 59 COVID-19–positive patients who responded to the survey. The authors questioned the chemosensory dysfunction occurring during COVID-19 infections. The results demonstrated strong association between COVID-19 infection and anosmia and dysgeusia [24].

The occurrence of xerostomia was hypothesized to be due to possible neuro-sensory invasion of the SARS-Cov2 [25-26].

In 2020, Lozada-Nur et al. published litter to the editors of Oral surgery, oral medicine, oral

pathology and oral radiology describing the possible causes of dysgeusia symptoms involved in COVID-19 infections. The authors postulated a direct relation was found between the virus and presence of dysgeusia. The researchers hypnotized that change in cellular content of occurs due to the immunologic reaction to the virus and leads to taste alteration or dysgeusia. The authors reported further information were needed to answer certain scientific questions. Among these questions was the correlation between medical and drug history of COVID-19 patients and whether they may affect the severity of dysgeusia.

In agreement with that, the present study demonstrated a positive correlation between oral manifestations including dysgeusia and presence of systemic diseases such as diabetes and hypertension. The results have shown that a total number of 130 (41.7%) patient were complaining from systemic diseases prior to COVID-19 infection. The systemic diseases were subclassified as follow: 38% Diabetes mellitus, 29% with Bronchial asthma, 27% Gastro-esophageal reflux, 26% with hypertension, and 10% with rheumatoid arthritis. In fact, these findings support the postulation that there are no specific oral manifestations for COVID-19. The oral manifestations reported can be justified as a pronunciation of the oral manifestations of underlying systemic diseases and the state of stress created by the novel infection. The limitation of the study: The small sample size must be considered. The major drawback in survey-based studies is that the responses collected may represent a risk of data falsification and miss-understanding of some questions by the reporter. However, the present results within the limitation of the sample study suggests a possible correlation between the medical condition and presence of oral manifestations in COVID-19 patients.

Conclusions:

There is wide array of oral symptoms reported during COVID-19 infection, among which dysgeusia is the most common, followed by xerostomia. Patients with systemic diseases are 4.7 folds more prone to develop oral manifestations during COVID-19 infection.

Statements and Declarations: Ethical approval: This is a survey study that was designed to investigate the oral symptoms of SARS-CoV-2 at a sample of infected medical doctors personals. The study was approved by the Faculty of Dentistry Beni-Suef University Research Ethical Committee: #FDBSUREC/10092020/ME. The survey was designed as anonymous google form published among communities of medical personals through the internet.

Informed consent: The approval consent was a part of this online survey.

Competing interests: All authors declare no finical or personal interest of any nature

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