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Original Article

Oral Manifestations of COVID-19 as an Early Diagnostic Aid: An Online Survey of the Egyptian Population

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Abstract

Background: Since the first emergence of COVID-19 infection in December 2019, in Wuhan, China. Many symptoms were recognized including those affecting the oral cavity. Therefore, the study aimed to survey for oral manifestations in suspected and confirmed infected patients and associate them with the demographic data and medical history.
Methods: an online questionnaire was used to collect data and was distributed from May 1 to August 15, 2021. The oral manifestations were divided into four categories: taste-related, salivary glands-related, mucosa-related symptoms, and no oral manifestations.
Results: Participants were 270 from different Governates in Egypt. Oral symptoms were prevalent in 84% of total cases, the most prevalent were taste-related symptoms (73.3%), salivary glands related (51.5%) and mucosa related (17.4%). Also, females showed more salivary gland-related symptoms than males. A significant association was found between patients with a previous history of oral ulcers and mucosa-related manifestations after infection.
Conclusion: Accordingly, COVID-19 infection is heavily prevalent in the oral cavity and its oral manifestations could be used as an early diagnostic aid.
Keywords: COVID19, Ulcers, Ageusia, hyposalivation, oral manifestations.

1. Introduction

1.1.Background

COVID-19 disease is a communicable disease caused by coronavirus 2 that causes severe acute respiratory syndrome (SARSCoV2). The primary known case was identified in Wuhan, China, in December 2019. Since then, the disease has spread around the world, causing a pandemic [1]. This virus is comparable to that which caused the SARS outbreak. Both have this outer proteinous spiky layer giving the pattern of a crown [2]. However, no enough knowledge is yet available about this virus family. The virulence of SARSCoV2 lies in its ability to spread faster than the 2003 SARSCoV1 virus and transmit from person to person, even from asymptomatic carriers [3]. This is because it is air-born, and inhalation risk is most significant especially outdoors. Splashes of contaminated liquids can be transmitted through the eyes, the nose, the mouth and infrequently contaminated surfaces. Humans are contagious for up to twenty days and might be virus carriers without showing symptoms [4]. Various tests are accustomed for diagnosing the disease through the detection of virus supermolecule by real-time reverse transcription polymerase chain reaction, transcription-mediated amplification, or reverse transcription-loop-mediated isothermal amplification of a nasopharyngeal swab [5]. Typical clinical symptoms in COVID19 patients were fever, cough, shortness of breath, and myalgia or weakness with abnormal chest CT. While less common symptoms were sputum formation, headache, hemoptysis, and diarrhea. A change or loss of the feeling of taste and smell was frequently observed. The foremost common symptoms patients reported back to the dental workplace at the diagnostic stage are ageusia (loss of taste), nonspecific dysomy (loss of smell, not associated with rhinitis), and hyposalivation [6].

Besides the unexplained ulcers within the oral cavity, few reported desquamative periodontitis, herpetiform ulcers on the gingiva, blisters/ irregular ulcers on the rear of the tongue, and enlargement of the submandibular salivary glands. These oral manifestations could be associated with an erythrodermic rash on the face [7]. Dysgeusia or ageusia and disomy however are common in patients with COVID-19 [8]

The salivary glands and barrier epithelia of the rima and oropharynx can become infected with SARSCoV2 and contribute to its transmission. The viral load in saliva is correlated to loss of taste and has proven sustained antibody reactions in saliva against the nucleocapsid and SARSCoV2 spike proteins [9].

The rima is believed to be a mirror that reflects underlying health problems. For instance, a significant association between COVID-19 mortality has been reported for diabetic patients who usually suffer from hyposalivation as well as oral ulceration [10]. Therefore, a comprehensive oral examination can help in the early detection of disease with subsequent effective treatment.

Taste disturbance, dry mouth (xerostomia), and hyposalivation were reported in oral findings presented during SARS-Cov2 pandemic [11]. Saliva is responsible for protection and lubrication; thus, its loss leads

to local microbial infection and mucosal trauma [12]. Accordingly, xerostomia may be responsible for oral ulceration during infection.

Moreover, understanding the categories of cells that host the Angiotensin-converting enzyme 2 (ACE2) receptor is crucial for determining how susceptible you're to infections throughout your body organs [13-14]. ACE2 expression in salivary glands was demonstrated by RNA-seq profiles and detection confirmation by RT-PCR [15]. Moreover, saliva is more sensitive to SARS-Cov2 detection than nasopharyngeal swabs [16]. Besides, detection of COVID-19 viral load in saliva was confirmed by viral culture [17]. As saliva collection is done without invasive procedures, it is considered an easy and convenient diagnostic aid.

The virus was manifested in Egypt early in 2020 and it is a country that has an average population of 102.2 million and has reported a total confirmed cases of 514,891 and an incidence rate of 16 case/ 100,000/ month since December 2019 and until now according to the WHO [18]. In turn, the present study aimed to measure the prevalence of the COVID19 associated oral manifestations and correlate them to the demographic data as well as patients' health status.

2. Material and Methods

2.1. Eligibility criteria

The following are the inclusion criteria:

- Egyptian Arabic speaking individuals.
- Confirmed COVID-19 case after polymerase chain reaction test (PCR).
- Suspected COVID-9 case after visiting a doctor licensed by the Egyptian ministry of health.

Any incomplete survey was excluded before the analysis.

2.2. Study design

The chosen design is a cross sectional survey-based study. STORBE guidelines for observational studies was followed in reporting our work.

2.3. Setting

The study was conducted from May 1 to August 15, 2021, we collected the data via an online survey (Google form) or structuring face-to-face interviews and entering the answers afterwards to the online form. Convenient sampling was followed as the survey link was shared on social media platforms.

2.4. Ethical consideration

The survey included demographic data and medical history as well. Filling out the form was consent of participation in the study. The case in **Error! Reference source not found.** provided further affirmation about using the image in the study after filling in the form.

2.5. Participants

The patients in the current survey were confirmed COVID-19-positive cases based on the PCR test or diagnosed as a suspected case by a licensed doctor by the Egyptian ministry of health based on the WHO case definition [19-20].

2.6. Variables

The survey included demographic data such as (1) age (2) sex (3) governorate (4) profession. Questions about medical history

were also required: (1) hypertension (2) Diabetes (3) heart disease. Participants were also asked if they had previous oral ulcers before infection. The survey included the oral manifestations expected to relate to COVID-19 infection. We categorized them into four groups: taste-related symptoms (taste sensation impairment), salivary glands-related symptoms (dry mouth and difficult swallowing), mucosa-related symptoms (vesicles, papules, and burning sensation) and the final category including those who did not suffer from any oral manifestations.

Age was presented into three categories. Nominal data was presented as frequencies and percentages to assess the prevalence of each group of oral symptoms. We analyzed demographic data against the reported oral manifestations to investigate any significant associations.

2.7. Statistical methods

Data was analyzed by using SPSS, version 26. Data was be collected by google forums into an excel sheet, translated into English, and cleaned. Descriptive statistics were used to present the demographic characteristics of the sample. Categorical data are represented as n(%) and were analyzed using Chi square test to investigate any associations among the collected oral manifestations and demographic data. Chi square test was also used to investigate the association between each oral manifestation and the suspected and confirmed groups.

2.8. Bias

Since many COVID-19 associated oral symptoms last for days or a week, results may encounter recall bias as participants may be unable to recall which oral symptoms they suffered. Mild oral symptoms may also be ignored or misreported given the patient's and his family's deteriorated psychological state.

3. Results:

3.1. Demographic data

A total of 270 participants completed the online survey. Regarding sex, 75.9 % were females, and 24.1% were males. For age, the minimum age was 15 years, and the maximum age was 75 years. Participants were 30 years old (79.2%), 8.9% were between 30-45, whereas 11.9% were older than 45. Concerning the Governate, participation from Great Cairo region (72.2%) was as follows: Cairo; had 115 Participants, Giza had 79 participants, and from Al Qaliobia there was one participant. Moreover, participants from Delta region were 14.1% and distributed as follows: from Al Sharqia 18, Dakahlia 8 participants, Gharbia; 3 participants, Menofia; 5 participants, Damietta; 4 participants. Furthermore, participation from Upper Egypt region was 8.9%, including participants from Fayoum; 12 Participants, Qena; 6 Participants, Sohag; 3 Participants, Beni-Surf; 2 Participants and Luxor; one Participant. Besides, from Suez Canal region (3.7%) including participants from Ismailia; 7 Participants, Suez; 2 Participants and Port Said; one participant. While from North Coasts, the participants (1.1%) were from Alexandria; with 2 Participants, and North Sinai had one participant.

50.7% of participants were students and 49.3% have other jobs. According to the present findings, 156 (57.8%) cases were COVID-19 confirmed cases and 114 were suspected (42.2%). Participants' medical history was considered: hypertension was the most prevalent and reported by 33 individuals (12.2%), 19 participants were diabetic (7%), 8 participants had cardiovascular diseases (3%) and 210 (77.8%) had no comorbidities (**Table 1**).

Table 1 *characteristics of participants*

Characteristics		Count	N %
Age	<30	213	79.2
	30-45	24	8.9
	>45	32	11.9
Sex	Female	205	75.9
	Male	65	24.1
Region	Great Cairo	194	71.9
	Delta Region	39	14.4
	North Coasts	3	1.1
	Canal Region	10	3.7
	Upper Egypt	24	8.9
Job	Student	137	50.7
	Other	133	49.3
Medical history	Heart Disease	8	3.0
	Blood Pressure	33	12.2
	Diabetes	19	7
	No Comorbidities	229	97.9
COVID status	Confirmed	156	57.8
	Suspected	114	42.2
Ulcers	Yes	26	9.6
	No	244	90.4

3.2. Oral manifestations

Categories were Taste related, Salivary glands-related, Mucosa related, and no oral symptoms. Data was analyzed, taking into consideration patients reported one or more of the symptoms at the same time. The results were as follows:

3.2.1.Taste related oral symptoms.

Taste-related symptoms were the most common(N=198). Participants reported one or more of the following symptoms: altered food taste, loss of salt or sweet taste. Altered food taste was the most prevalent taste-related manifestation, and (46%) was reported either alone, with loss of salt or sweet taste or presented with manifestations from other categories. Whereas 36% of the taste-related reports were loss of salt taste. Loss of sweet taste reports constituted only 18%. Females showed higher taste-related symptoms (N=152, 76.8%) than males (N=46, 23.2%). No significant relations were found between the characteristics of the participants and the taste-related symptoms (P-value> 0.05).

3.2.2.Salivary gland-related symptoms

Salivary gland-related symptoms were the second most prevalent symptoms (N=139). They include dry mouth, difficulty in swallowing, and swelling in the submandibular salivary gland or checks. Participants reported a symptom of this category or more associated with manifestations from other categories. Dry mouth was the most common (59%). Difficulty in swallowing constituted 21%, while swelling of the submandibular salivary gland constituted 13% and swelling in the cheek was the least prevalent (7%).

A significant association was found between sex and salivary-gland-related symptoms as 115 participants were females and 24 were males, with a P-value of 0.01 **(Figure**). No other significant relations were found among salivary-gland-related symptoms and the characteristics of the participants (**Error! Reference source not found.**).

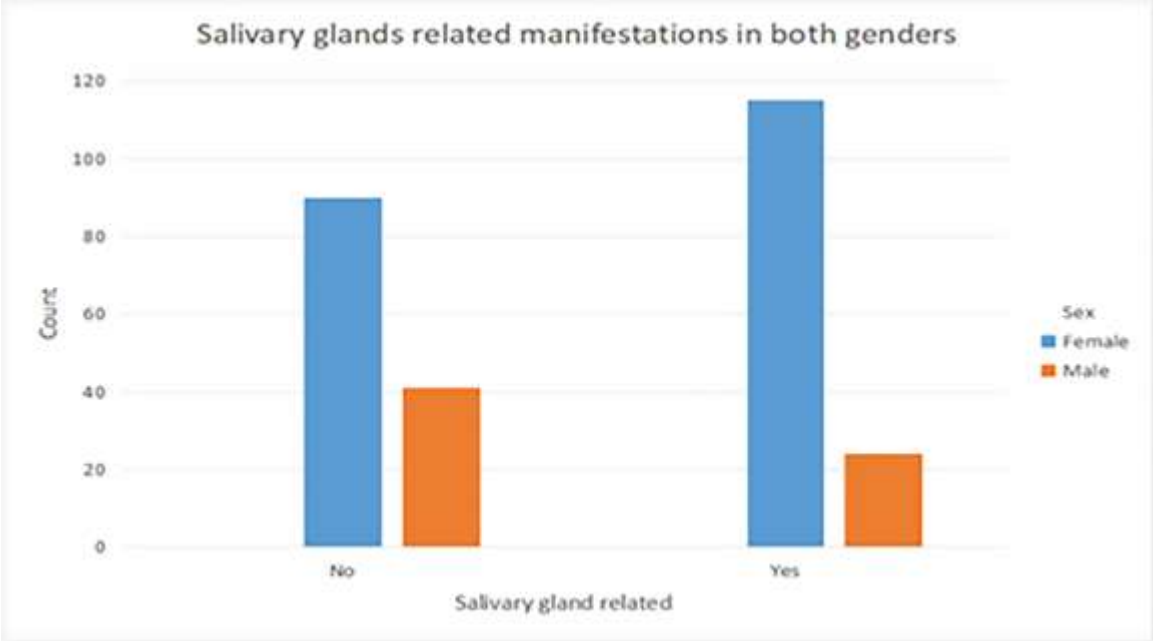

Figure 1 *A bar chart displaying salivary gland-related manifestations in both sexes with females have more salivary gland disfunction than males.*

Table 2: Relations between characteristics and oral

			Count	N % within oral manifestation	P Value
Taste related	Age	<30	155	27.2	0.45
		30-45	20	16.7	
		>45	22	31.3	
	Sex	Female	152	76.8	0.59
		Male	46	23.2	
	Job	Student	99	50.0	0.69
		Other	99	50.0	
	Region	Great Cairo	149	75.3	0.14
		Delta Region	25	12.6	
		North coasts	3	1.5	
		Canal Region	7	3.5	
		Upper Egypt	14	7.1	
	Medical history	Heart diseases	7	3.5	0.69
		Blood Pressure	171	86.4	0.24
		Diabetes	21	10.6	0.21
		No Comorbidities	10	5.1	0.03
	COVID status	Confirmed	120	60.6	0.12
		Suspected	78	39.4	
	Ulcers	already have ulcers before infection	18	9.1	0.62
Salivary gland related	Age	<30	108	77.7	0.28
		30-45	16	11.5	
		>45	15	10.8	
	Sex	Female	115	82.7	0.01
		Male	24	17.3	
	Region	Great Cairo	96	69.1	0.54
		Delta Region	21	15.1	
		North Coasts	3	2.2	
		Canal Region	6	4.3	
		Upper Egypt	13	9.4	
	Job	Student	66	47.5	0.27
		Other	73	52.5	
	Medical history	(Heart diseases	4	2.9	1.00
		Blood Pressure	121	87.1	0.29
		Diabetes	16	11.5	0.71

		No comorbidities	7	5	0.19
	COVID status	Confirmed	82	59	0.68
		Suspected	57	41	
	ulcers	already have before infection	17	12.2	0.14
Mucosa related	Age	<30	46	75.4	0.05
		30-45	10	16.4	
		>45	5	8.2	
	Sex	Female	0	47	0.81
		Male	0	14	
	Region	Great Cairo	45	73.8	0.69
		Delta Region	11	18	
		North Coast	0	0	
		Canal Region	1	1.6	
		Upper Egypt	4	6.6	
	Job	Student	26	42.6	0.15
		Other	35	57.4	
	Medical history	Heart diseases	4	6.6	0.08
		Blood Pressure	53	86.9	0.61
		Diabetes	7	11.5	0.84
		No comorbidities	2	3.3	0.26
	COVID status	Confirmed	40	65.6	0.16
		Suspected	21	34.4	
	ulcers	already have before infection	14	23	0.00
No oral symptoms	Age	<30	37	72.5	0.19
		30-45	4	7.8	
		>45	10	19.6	
	Sex	Female	33	64.7	0.04
		Male	18	35.30	
	Region	Great Cairo	33	64.7	0.39
		Delta Region	10	19.6	
		North Coast	0	0	
		Canal Region	1	2	
		Upper Egypt	7	13.7	
	Job	Student	25	49	0.79
		Other	26	51	
		Heart diseases	1	2	1

	Medical history	Blood Pressure	37	72.5	0.01
		Diabetes	12	23.5	0.01
		No Comorbidities	8	15.7	0.01
	COVID status	Confirmed	28	54.9	0.64
		Suspected	23	45.1	
	ulcers	already have before infection	4	7.8	0.8

3.2.1.Mucosa related oral symptoms.

The third prevalent group was mucosa-related (N= 47 participants). It included white patches, oral ulcers, burning sensation, gingival bleeding, vesicles, redness, and pain in the mouth, as well as papules in the gingiva or tongue. Participants reported one manifestation of this category or more or associated with symptoms from other categories. Burning sensation in the mouth or tongue was the most prevalent (26% of mucosa-related reports), while 24% of reports were oral ulcers.

Interestingly, one of the participants -a 25-year-old female with a history of frequent oral ulceration showed severe oral ulceration in the soft palate before confirmation of COVID-19 infection by four days (**Error! Reference source not found.**).

It was found that most of the participants who have a history of previous ulcers suffered from mucosa-related symptoms (

Figure 1). The relation was significant with a P-value equals 0.001 (**Error! Reference source not found.**). Moreover, 21% of reports were pain, and 13% were tongue redness. Bleeding from gingiva constituted 9% of total reports. Additionally, vesicles and papules in the mouth -particularly the gingiva- constituted 7% .

Figure 2 severe oral ulceration in the soft palate of a 25-year-old female. After four days she tested PCR positive. Oral Ulceration was the main symptom beside the recorded fever 38º C. The ulcer resolved after two weeks.

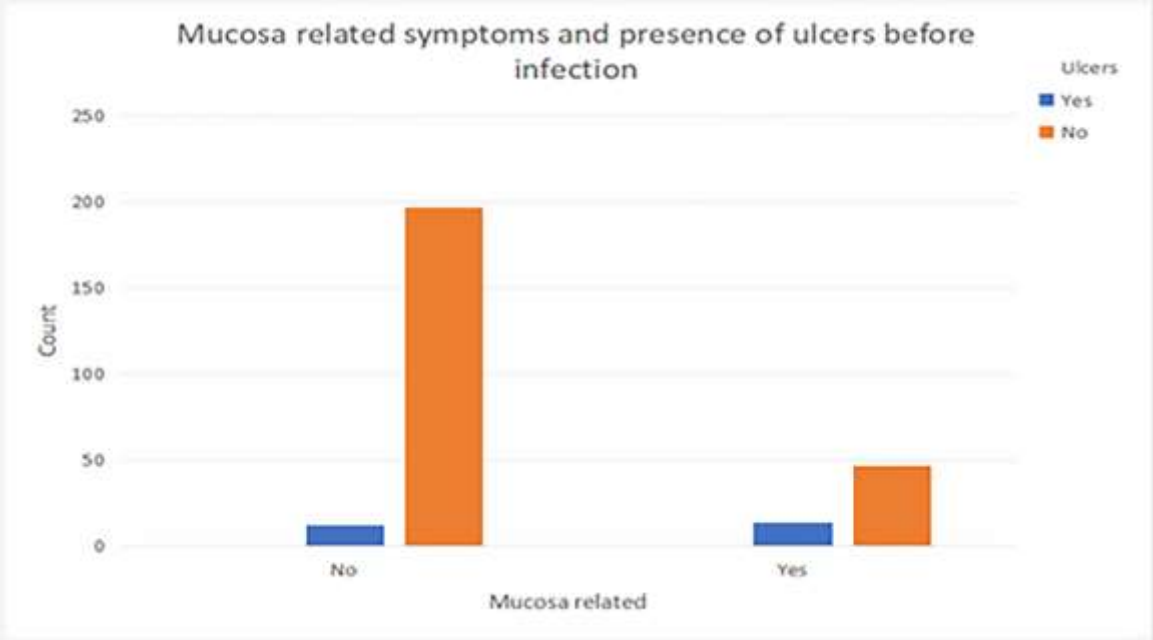

Figure 1 *A bar chart illustrating the relation between mucosal related symptoms and presence of ulcers before and after confirmed infection.*

3.2.1.No related oral symptoms

There were 43 participants (16%) not suffering from any oral manifestations (53% confirmed, 47% suspected). The sex distribution was 26 females (60%) and 17 males (40%). This difference was significant, with a p-value of 0.01.

Regarding the association between the absence of oral symptoms and systemic diseases; from the 43 participants showing no oral symptoms, one had heart disease, 11 were hypertensive (**Figure 2**), and eight were diabetic (**Figure 3**) with a P-value less than 0.05 for both. The rest 23 participants showed no comorbidities **(Error! Reference source not found.**).

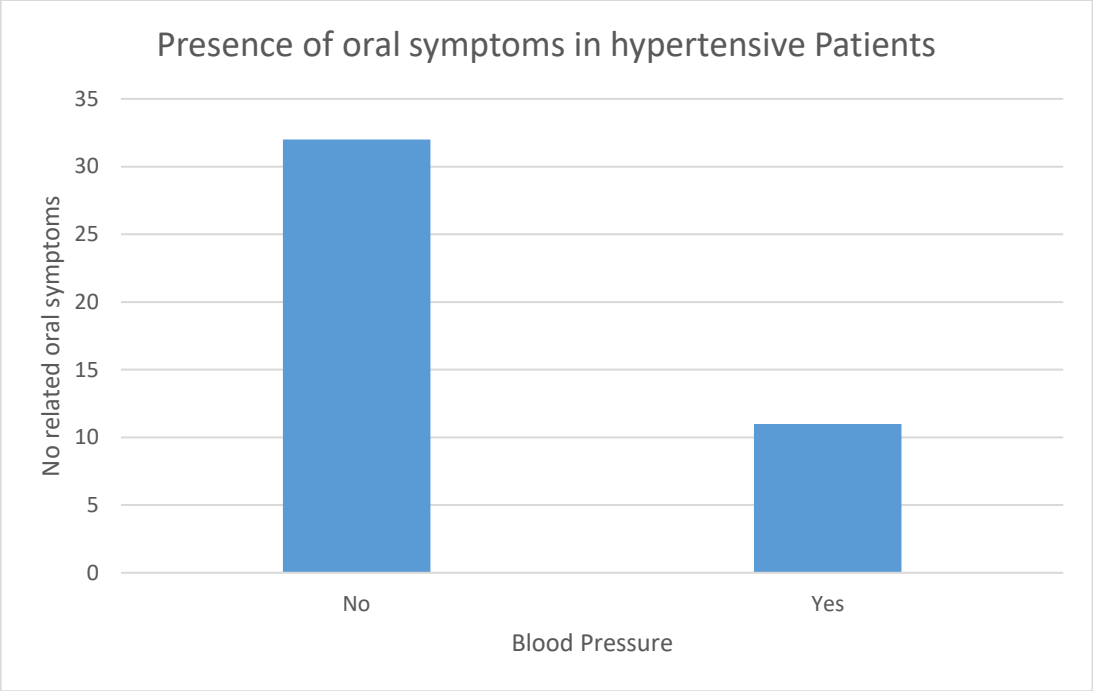

Figure 2 A bar chart showing the relation between the presence of oral symptoms and hypertension.

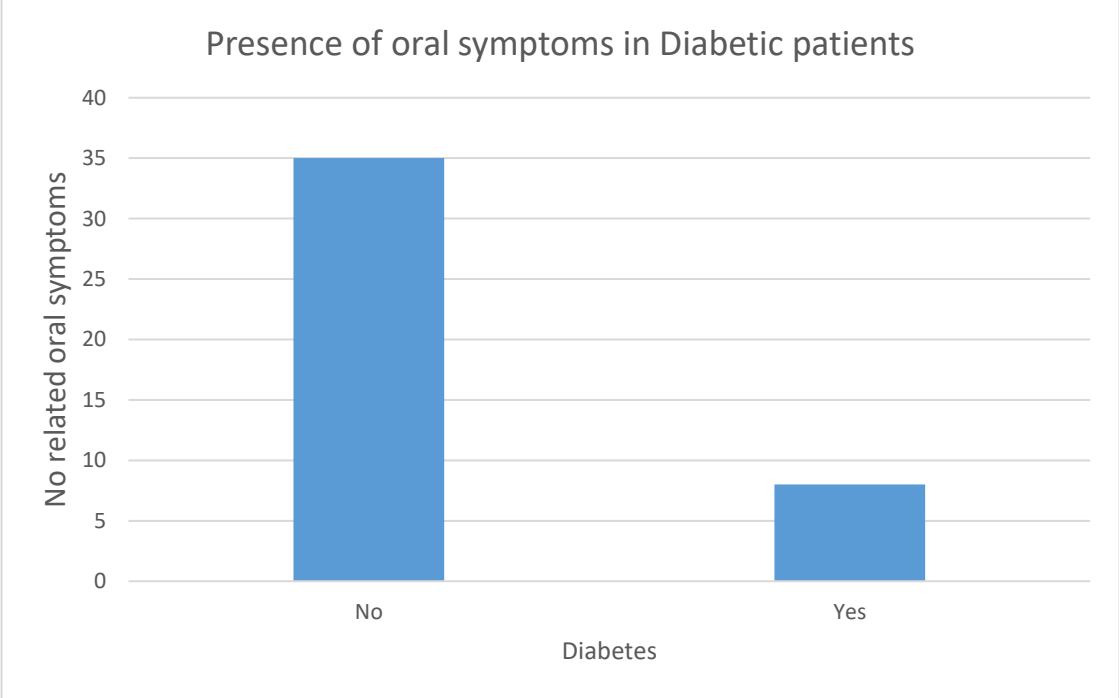

Figure 3 A bar chart representing the relation between absence of oral symptoms and diabetes.

4. Discussion

SARS-COV-2 spreads by binding the spike protein to ACE2 human receptors, which are highly represented in oral mucosal tissues [21]. Therefore, this makes the oral manifestation among the early -if not the earliest- symptoms of infection and important for early diagnosis.

Most of the participants were young individuals aged between 30-45, and most of them were students. The presentation of great Cairo Governorates was higher than the other regions, this may be explained that the inhabitants are of a higher level of education and awareness. In the present study, COVID-19 confirmed cases were included as well as those with a suspected infection before confirmation.

Putting in consecration that every patient who participated in the current study could suffer from one or more symptoms, taste-related was the most common, reported by 198 out of 270 participants (73.3%). It manifests in the form of altered taste or loss of salt or sweet taste. These findings align with recorded findings reported in China and Italy [22-23]. The high prevalence of taste-related symptoms could be explained by the fact that 96% of the ACE2 receptors of the oral cavity lies on the tongue where taste buds are present [21]. Accordingly, this supports the hypothesis that taste-related symptoms demonstrated in COVID-19 infection could be an early diagnostic symptom.

Salivary gland-related symptoms were the second most prevalent, constituting 139 out of 270 participants (51.5%). The two major salivary glands-related symptoms were dry mouth and difficulty in swallowing which is linked to lack of saliva. These observations are matched with the findings of hen and Zhao [9]. These observations support the hypothesis that SARS-COV-2 infects salivary glands [23], causing hyposalivation. This change in the saliva is hypothesized to interrupt neurological transduction causing the detected taste dysfunction [24]. SARS-CoV-2 was detected in saliva in both early and late stages [23-25]. The suggestion of using saliva in diagnosis needs further investigation to control other factors like using a medication, associated temperature and circadian rhythm [26].

The third prevalent symptoms were mucosa related, where 47 out of participants (17.4%) were recognized. The two major mucosa-related symptoms were oral ulcers and burning sensation and some of the participants reported ulcers before getting COVID-19 infection. The present remarks coincide with previously published studies relating oral ulceration to COVID-19 infection with a variety in severity [23-27] not due to drugs or systemic health [25].

Significant association was found between salivary gland related symptoms and sex (p value = 0.01). Females showed more salivary gland related symptoms than males. This predominance is explained by the physiological hormonal differences between female and male [17-29-30].

Furthermore, a significant relationship was predicted between patients with the previous history of ulcers and mucosal-related manifestations after infection. This is supported by the case presented in our study, which manifests severe oral ulceration on the soft palate before the infection is confirmed oral ulceration on the soft palate before the infection confirmation. This could be seconded to viral replication in

cells and the increase in cell permeability of the oral lining mucosa after oral tissue infection leading to the development of ulcers [31]

In this study, the patients suffering from different categories of oral manifestations during or before confirming infection were 227 out of 270 (84%). Female patients accounted for the highest percentage than males. This finding was inconsistent with other studies [14-17]. This could be explained by female participation being higher in our study.

Moreover, a significant association was found between the absence of oral symptoms and hypertension. This observation goes against Mariz's findings [31] who described those hypertensive patients with more oral manifestations than healthy ones. Taking into consideration the small sample in the current study, where only 13% of participants reported to be hypertensive with no oral symptoms; accordingly, the relation between hypertension and oral manifestations in COVID-19 patients' needs further investigation.

Besides, in this study a significant association between the absence of oral symptoms and diabetes was reported, which stands against the supposition that diabetic patients are more susceptible to oral symptoms during COVID-19 [13]. This could be due to the small unrepresentative sample of diabetic patients participating in the study.

Limitations

The study did not include controls free of COVID-19 infection to compare the presentation of the oral manifestations between the two groups. Also, female participants were more than males, which may have affected the representation of oral symptoms, thus needs further investigation.

5. Conclusion

The current study indicates a significant effect of COVID-19 on the oral tissues. Taste- related disorders and salivary gland-related symptoms are of high prevalence in COVID-19 patients. The oral manifestations could be an early diagnostic aid for COVID-19 infected patients.

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Conflict of interest

Authors declared that there is no conflict of interest.

Ethics:

This study protocol was approved by the ethical committee of the faculty of dentistry-Minia university.

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