

Prevalence of Oral Lesions in COVID-19 Egyptian Patients

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ABSTRACT

Objectives: The aim of this article is to detect whether oral lesions affect the tongue mainly due to higher cells expressing angiotensin-converting enzyme 2 (ACE2) than in other oral sites in COVID-19 patients. Moreover, the etiology of oral lesions was evaluated either resulting from SARS-CoV-2 sequelae or from adverse effects of drugs used for COVID-19 treatment. **Materials and Methods:** One hundred and twenty-four patients were admitted to the study. All patients' data were obtained including age and gender, laboratory testing, drug administration, respiratory and systemic conditions, signs and symptoms, and oral manifestations. **Results:** Oral manifestations were seen in 112 (90.3%) of all patients. Oral ulcers represented the most prevalent lesions in the oral cavity in 104 patients (92.8%). Lip, tongue, and labial mucosa showed the most common sites for oral lesions. Most of oral lesions were displayed in the tongue in 96 patients (85.7%). Various medications were used in the treatment of patients. **Conclusion:** The tongue represented the most common site of oral lesions in COVID-19 patients followed by the labial mucosa. No correlation was found between the oral lesions and the drugs used for the treatment of SARS-CoV-2 infection. The systemic health and the severity of the disease were not related to the spread of the oral lesions.

KEYWORDS: Angiotensin-converting enzyme 2, coronavirus, oral lesions

INTRODUCTION

In the recent couple of years, a new coronavirus disease (COVID-19) has emerged, causing an exceptional pandemic that is being treated as an urgent threat by health authorities around the world.^[1] The coronavirus-caused condition is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a zoonotic respiratory virus with bats and pangolins as the most likely source and transitional hosts.^[2] COVID-19 is hypothesized to be transmitted by close person-to-person contact (approximately 2 m), a distance at which respiratory droplets from an infected person during coughing, sneezing, or speaking might spread to others who do not have appropriate barriers. Additional routes of transmission emerge when spit droplets fall on other surfaces, such as the ground, and persons come into touch with them,^[3] with catastrophic consequences not only in medically compromised

individuals, but even in otherwise healthy young people with a healthy immune system.^[4]

Viral replication takes place in the upper respiratory system and subsequently disseminates throughout the body, causing serious complications.^[5] Fever, shortness of breath, cough, runny nose, sputum production, muscle discomfort, headache, weariness, arthralgia, diarrhea, and conjunctivitis are some of the symptoms.^[6] The average incubation time ranges from 7 to 14 days. Many patients develop mild-to-moderate diseases with upper and lower respiratory tract involvement; others have a serious disease or even have critical conditions such as respiratory failure, septic shock, or multiple organ failure.^[7] After recuperation, the contagiousness

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can last for up to 2 or 3 weeks.^[8] Susceptibility, genetics, systemic disorders, population, gender, and age are all important factors to consider when it comes to the initiation and course of viral infection. Patients with asthma or pulmonary edema are at a significant risk of death.^[9]

The active receptor for SARS-CoV-2 is a metalloproteinase called angiotensin-converting enzyme 2 (ACE2), which was detected in COVID-19 patients.^[10] ACE2 has been discovered in a variety of organs and tissues including type I and type II alveolar epithelial cells in nasal and oral mucosal tissues, nasopharynx, smooth muscle cells, and endothelial cells of skin and stomach vessels, obviously in the basal cell layer of epidermis and non-keratinizing squamous epithelium.^[11] The levels of ACE2 in each population may also differ. As a result, the start and progress of the disease might range from subclinical signs to acute and violent consequences.^[8] Because ACE2 is involved in cellular entrance, ACE2-expressing cells may act as target cells, making them vulnerable to SARS-CoV-2 infection.^[12] It was discovered that mice infected with SARS-CoV-2 had lung failure as a result of ACE2 downregulation. Thus, the oral mucosa and pulmonary epithelial cells are engaged in the entry of virus, allowing it to replicate and trigger an inflammatory response.^[13]

Although oral symptoms of SARS-CoV-2 infection were rare, the presence of ACE2 in the oral cavity showed that an oral infection route for SARS-CoV-2 could not be ruled out.^[14] The ACE2-positive cells were found to be abundant in epithelial cells.^[12] The oral tissues, based on these findings, should be considered a high-risk location for SARS-CoV-2 infection. The tongue had stronger ACE2 expression than the buccal or gingival mucosa.^[14] The interaction of SARS-CoV-2 with ACE2 receptors may reduce taste bud sensitivity, resulting in defective gustatory responses.^[15] Oral symptoms, on the contrary, have been postulated as a possible drug reaction that can occur during the latency phase.^[16]

It is still debatable whether oral lesions could be predictably clinical manifestations rising from the direct SARS-CoV-2 infection or a systemic outcome; the probability of coinfections enhancing the COVID-19 severity, impaired immune system, and adverse reactions of medical treatment are assumed.^[17]

In order to study the various routes of SARS-CoV-2 infection on the oral mucosa, we explored whether oral lesions mainly impact the tongue mucosa due to increased ACE2-expressing cell than in other oral tissues. Furthermore, the emergence of oral lesions

was assessed and analyzed to determine whether it is a result of SARS-CoV-2 infection or a side effect of particular medicines used to treat COVID-19.

MATERIALS AND METHODS

We performed a cross-sectional study. All cases were presented with a confirmation for COVID-19 in El Beheira and Alexandria Governorate Hospitals, Egypt, between September 2, 2020 and June 10, 2021.

INCLUSION CRITERIA

The following are the inclusion criteria:

- Age >18 years;
- Infection with COVID-19 was verified in a laboratory using reverse transcription–polymerase chain reaction or RT–PCR.

EXCLUSION CRITERIA

The exclusion criteria are as follows:

- Patients without a laboratory-confirmed diagnosis of COVID-19 infection were excluded;
- Patients who had olfactory or gustatory impairment prior to infection with COVID-19;
- Those who have malignant neoplasms;
- Patients suffering from neurodegenerative diseases.

One hundred and twenty-four admitted patients met the inclusion criteria and were recruited in the present study. Patients' data were collected at the time of admission and during their stay in the hospital.

Due to the deficiency of the reference time points, the initiation of the oral manifestations varied extensively among the patients. Oral lesions in all patients were reported. The site and the severity of these lesions were detected. Laboratory testing, drug administration, and respiratory and systemic conditions were documented.

Additionally, the patients were divided into not severe and severe based on clinical manifestations and oxygen supplement requirement [Table 1].

Personal protective measures were used for precaution and prevention of disease transmission. These measures included wearing long-sleeved and fluid-resistant gowns, gloves, N95 masks, protective eyewear, and face shields. Sterilization of all used instruments was performed in between the patients.

Statistical descriptive analysis was conducted to determine the overall prevalence of various findings

Table 1: Severity of the disease

Clinical classification severity [n (%)]	
I. Severe	72 (58.1%)
II. Not severe	52 (41.9%)

within the patients. Data were presented as frequencies and percentages. Statistical analysis was performed using the Statistics Package for Social Sciences v21.0TM software (SPSS Inc., USA). Pearson's correlation coefficient was utilized to assess the statistical association between two variables.

RESULTS

One hundred and twenty-four COVID-19 patients [92 men (74.2%) and 32 women (25.8%)] with mean age (50.32 ± 12.47) were recruited in the current study. Table 2 shows associated general symptoms and systemic conditions. The most common symptoms were feeling tired, asthenia, breathing problems, and cough. In all patients, 92 patients (74.2%) lost both taste and smell, whereas 24 patients (19.3%) lost smell only. Additionally, dry mouth affected 104 (about 84%) of all patients.

All medications prescribed to the patients are displayed in Table 3. It represents the treatment guidelines for COVID-19. All patients received zithrocin, iverzine, vitamin C, and zinc. About 90% of the patients received anticoagulant therapy. Prednisolone was required for 76 patients. Antibacterial drugs were needed in about 70% of the patients. Other drugs were used according to the treatment requirements for the patient.

Oral manifestations were seen in 112 (90.3%) of all patients. About 62% of oral manifestations were asymptomatic. The symptomatic oral manifestations were detected whether painful (21.4%) or burning sensation (14.3%).

There were various oral lesions but oral ulcers represented the most prevalent lesions in the oral cavity in 104 patients (92.8%). Most of oral ulcers were aphthous-like ulcers covered with pseudo-membrane.

Table 2: General symptoms and systemic conditions

General symptoms [<i>n</i> (%)]	
I. No symptoms	12 (9.7%)
II. Symptomatic:	112 (90.3%)
1. Feeling tired	24 (21.4% of symptomatic patients)
2. Asthenia	84 (75% of symptomatic patients)
3. Breath problems	84 (75% of symptomatic patients)
4. Cough	84 (75% of symptomatic patients)
5. Abdominal symptoms	16 (14.3% of symptomatic patients)
A. Asthenia+ breath difficulty+ cough	56 (50% of symptomatic patients)
B. Asthenia+ breath difficulty+ cough+ abdominal problems	8 (7.1% of symptomatic patients)
C. Felt tired+ asthenia+ breath difficulty+ cough	4 (3.6% of symptomatic patients)
D. Felt tired only	12 (10.7% of symptomatic patients)
E. Felt tired+ abdominal problems	4 (3.6% of symptomatic patients)
F. Asthenia+ breath difficulty	12 (10.7% of symptomatic patients)
G. Felt tired+ asthenia+ breath difficulty+ cough+ abdominal problems	4 (3.6% of symptomatic patients)
H. Cough only	12 (10.7% of symptomatic patients)
Medical condition [<i>n</i> (%)]	
I. Medically free	68 (54.8%)
II. Medically compromised	56 (45.2%)
1. Hypertension	16 (28.5% of medically compromised patients)
2. Diabetic	52 (92.8% of medically compromised patients)
3. Renal disease	4 (7.1% of medically compromised patients)
4. Liver disease	4 (7.1% of medically compromised patients)
5. Cardiac	8 (14.2% of medically compromised patients)
A. Diabetic only	40 (71.4% of medically compromised patients)
B. Hypertensive+ diabetic+ hepatic+ cardiac	4 (7.1% of medically compromised patients)
C. Hypertensive+ cardiac	4 (7.1% of medically compromised patients)
D. Hypertensive+ diabetic+ renal+ cardiac	4 (7.1% of medically compromised patients)
E. Hypertensive+ diabetic	4 (7.1% of medically compromised patients)
Loss of sensation [<i>n</i> (%)]	
I. Loss of taste and smell	92 (74.2%)
II. Loss of smell only	24 (19.3%)
Salivary gland [<i>n</i> (%)]	
I. Dry mouth	104 (83.9%)
II. Not affected	20 (16.1%)

Table 3: Medications prescribed to the patients

Medication [n (%)]	
I.	Zithrocin 124 (100%)
II.	Iverzine 124 (100%)
III.	Zinc, vitamin C 124 (100%)
IV.	Prednisolone 76 (61.3%)
V.	Remdesivir 28 (22.6%)
VI.	Anticoagulant 112 (90.3%)
VII.	Antihypertensive 16 (12.9%)
VIII.	Antibacterial 88 (70.9%)
IX.	Foradil 16 (12.9%)
X.	Colchicine or hydroxychloroquine 16 (12.9%)
XI.	Acetylcysteine 24 (19.3%)
XII.	Silymarin 4 (3.2%)

Lip, tongue, and labial mucosa showed the most common sites for oral ulcers (42.3%, 38.5%, and 34.6%, respectively) [Figure 1]. Regarding lip ulcers, they were hemorrhagic ulcers with crust [Figure 2]. *Candida* infection followed oral ulcers, which represented 42.8% of all oral lesions with 50% displayed in the tongue [Figure 3]. Whole mouth *Candida* and the mucosa represented 25% and 16.7%, respectively, of *Candida* infection. Other lesions were observed as hyperpigmentation (25%) which was shown mostly in the floor of the mouth (57.1%) [Figure 4], tongue coating (10.7%), atrophy of the tongue (17.8%), petechiae (17.8%), herpes (7.14%), and white lesions on the tongue (7.14%). Most of the oral lesions were displayed in the tongue in 96 patients (85.7%) like ulcers only (29.2% of lesions of the tongue), atrophy only (20.8% of lesions of the tongue), or a combination of lesions (12.5% tongue ulcer + tongue *Candida*, 12.5% tongue ulcer + tongue coating) [Figure 5]. This is followed by lesions in the labial mucosa in 76 patients (67.8%) and then the buccal mucosa in 60 patients (53.6%). Moreover, 52 patients (46.4%) suffered from lesions in the lip, whereas 44 patients (39.28%) experienced lesions of the floor of the mouth [Figure 6]. In contrast, lesions of the gingiva represented the least site affected by the oral lesions [Table 4]. Furthermore, there was no significant correlation between oral manifestations and severity or medical conditions. Because all patients received zithrocin, iverzine, vitamin C, and zinc, the correlation between oral manifestations and these drugs cannot be computed. However, there was no significant correlation between oral manifestations and all other drugs taken by the patients [Table 5].

DISCUSSION

By the end of 2019, a new coronavirus caused a pneumonia outbreak in Wuhan, China, reinforcing the threat that coronaviruses offer to public health. COVID-19 affects the immune system, generating significant variations in response reactions that might

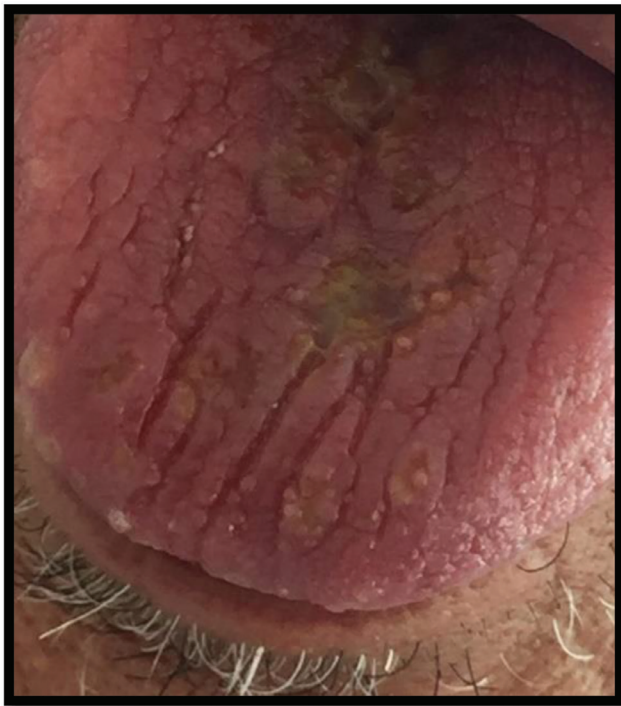


Figure 1: Irregular ulcers covered with pseudo-membrane on the dorsal surface of the tongue



Figure 2: Commissural cheilitis with bleeding, crust, and pus located in the commissure

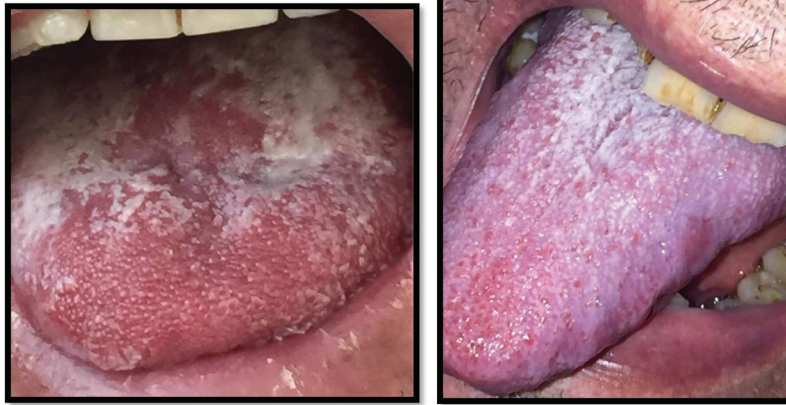


Figure 3: *Candida* infection on the dorsal surface of the tongue



Figure 4: Hyperpigmentation in the floor of the mouth

turn against the host, resulting in autoimmune damage, especially to the connective tissue of the lungs. The infection pathways and pathophysiology of COVID-19, however, are still unknown.^[18]

The present study demonstrated the spread of oral manifestations in 124 COVID-19 patients. About 90% of the patients represented oral lesions, remarkably oral ulcers, despite the severity of the disease. The most common sites of oral lesions were the tongue and the labial mucosa. In addition, dry mouth was observed in most of the patients. This confirms that this could be



Figure 5: Atrophy of the dorsal surface of the tongue with white *Candida* infection distributed mainly on the right lateral side



Figure 6: Aphthous-like ulcer in the labial mucosa and the floor of the mouth

Table 4: Spread of oral lesions

Oral manifestations [n (%)]	
I. Absence	12 (9.7%)
II. Presence:	112 (90.3%)
a) Asymptomatic	72 (62.3% of the oral manifestation)
b) Painful	24 (21.4% of the oral manifestation)
c) Burning sensation	16 (14.3% of the oral manifestation)
Oral lesions [n (%)], N=112 (100%)	
I. Herpes	8 (7.14%)
II. White lesions	8 (7.14%)
III. Ulcers	104 (92.8%)
a) Perioral ulcers	4 (3.9% of ulcers)
b) Ulcers in whole mouth	12 (11.5% of ulcers)
c) Lip ulcers	44 (42.3% of ulcers)
d) Tongue ulcers	40 (38.5% of ulcers)
e) Labial mucosa ulcers	36 (34.6% of ulcers)
f) Buccal mucosa ulcers	8 (7.7% of ulcers)
g) Gingival ulcer	4 (3.9% of ulcers)
h) Floor of mouth ulcers	8 (7.7% of ulcers)
IV. <i>Candida</i>	48 (42.8%)
a) Whole mouth <i>Candida</i>	12 (25% of <i>Candida</i>)
b) Tongue <i>Candida</i>	24 (50% of <i>Candida</i>)
c) Mucosa <i>Candida</i>	8 (16.7% of <i>Candida</i>)
V. Hyperpigmentation	28 (25%)
a) Tongue hyperpigmentation	4 (14.3% of hyperpigmentation)
b) Floor of mouth hyperpigmentation	16 (57.1% of hyperpigmentation)
c) Lip hyperpigmentation	8 (28.6% of hyperpigmentation)
VI. Tongue coating	12 (10.7%)
VII. Atrophic tongue	20 (17.8%)
VIII. Petechiae	20 (17.8%)
I. Lesions of the tongue	96 (85.7%)
a) Tongue ulcer only	28 (29.2% of lesions of the tongue)
b) Tongue ulcer + tongue <i>Candida</i>	12 (12.5% of lesions of the tongue)
c) Tongue ulcers+ tongue coating	12 (12.5% of lesions of the tongue)
d) Tongue <i>Candida</i> only	12 (12.5% of lesions of the tongue)
e) Atrophic tongue only	20 (20.8% of lesions of the tongue)
f) Tongue hyperpigmentation only	4 (4.1% of lesions of the tongue)
g) White lesion only	8 (8.3% of lesions of the tongue)
II. Lesions of the labial mucosa	76 (67.8%)
a) Petechiae only	12 (15.8% of lesions of the labial mucosa)
b) Ulcer only	32 (42.1% of lesions of the labial mucosa)
c) <i>Candida</i> only	12 (15.8% of lesions of the labial mucosa)
d) Ulcer+ <i>Candida</i>	8 (10.5% of lesions of the labial mucosa)
e) Herpes+ <i>Candida</i>	4 (5.3% of lesions of the labial mucosa)
f) Ulcer+ petechiae	4 (5.3% of lesions of the labial mucosa)
g) Herpes+ ulcer	4 (5.3% of lesions of the labial mucosa)
III. Lesions of the buccal mucosa	60 (53.6%)
a) Petechiae only	20 (33.3% of lesions of the buccal mucosa)
b) Ulcer only	8 (13.3% of lesions of the buccal mucosa)
c) <i>Candida</i> only	16 (26.7% of lesions of the buccal mucosa)
d) White lesion only	8 (13.3% of lesions of the buccal mucosa)
e) Ulcer+ <i>Candida</i>	8 (13.3% of lesions of the buccal mucosa)
IV. Lesions of the gingiva	16 (14.3%)
a) Ulcer only	16 (100% of lesions of the gingiva)
V. Lesions of the floor of mouth	44 (39.28%)
a) Ulcer only	16 (36.3% of lesions of the floor of mouth)
b) <i>Candida</i> only	8 (18.2% of lesions of the floor of mouth)

Table 4: Continued

Oral manifestations [n (%)]	
c) Hyperpigmentation only	12 (27.3.3% of lesions of the floor of mouth)
d) <i>Candida</i> + hyperpigmentation	4 (9.1% of lesions of the floor of mouth)
e) Ulcer+ <i>Candida</i>	4 (9.1% of lesions of the floor of mouth)
VI. Lesions of the lip	52 (46.4%)
a) Ulcer only	36 (69.2% of symptomatic group)
b) Hyperpigmentation only	8 (15.4% of symptomatic group)
c) Herpes+ ulcer	8 (15.4% of symptomatic group)

Table 5: Pearson's correlation coefficient test between oral manifestations and Covid-19 patients

	Pearson's correlation	Sig. (two-tailed)
Oral manifestations	0.38	0.03 (NS)
Severity		
Oral manifestations	0.29	0.10 (NS)
Medical condition		
Oral manifestations	a	a
Xithrone		
Oral manifestations	a	a
Iverzine		
Oral manifestations	a	a
Zinc and Vit C		
Oral manifestations	0.41	0.02 (NS)
Prednisolone		
Oral manifestations	0.17	0.34 (NS)
Remdesivir		
Oral manifestations	0.26	0.15 (NS)
Anticoagulant		
Oral manifestations	0.12	0.49 (NS)
Antihypertensive		
Oral manifestations	0.27	0.14 (NS)
Antibacterial		
Oral manifestations	0.12	0.49 (NS)
Foradil		
Oral manifestations	0.12	0.49 (NS)
Colchicine or hydroxychloroquine		
Oral manifestations	-0.39	0.02 (NS)
Acetylcysteine		
Oral manifestations	0.06	0.74 (NS)
Silymarin		

^aCannot be computed because at least one of the variables is constant

NS = non-significant correlation

related to the distribution of ACE2 receptors, which are highly expressed in the salivary glands. Moreover, ACE2-positive cells are enriched in epithelial cells and the oral mucosa, which express the ACE2 higher in tongue than other oral sites. SARS-CoV-2 utilizes ACE2 receptors to access the cells causing inflammatory reactions in related organs and tissues, such as the tongue mucosa and salivary glands, which leads to oral manifestations.^[14]

This affects the functioning of salivary glands, taste/smell sensations, and oral mucosa integrity, interfering with dynamic oral environment also by exerting influence on microbiota balance.^[19,20]

Vardhana and Wolchok^[21] reported that there is a high production of inflammatory cytokines due to SARS-CoV-2 infection, which activates multiple pathways of innate immunity. Raised levels of tumor necrosis factor (TNF) can cause neutrophil chemotaxis to the oral mucosa and the formation of aphthous-like lesions in COVID-19 patients. Stress and immunosuppression as a result of SARS-CoV-2 infection could also be factors in the development of these lesions in COVID-19 patients.^[22] Oral candidiasis was the second most oral manifestation detected. This could be attributed to the drop in the medical condition, long-term

antibiotic therapy, and deterioration in the oral hygiene.^[1,22,23]

Oral hyperpigmentation represented 25% of oral manifestations. This could be related to higher levels of inflammatory cytokines such as interleukin-1 (IL-1), TNF- α , and prostaglandins.^[4,23]

In our study, about 45% of the patients were only systemically compromised. The oral lesions were detected in more than 90% of the patients enrolled in the study no matter what the severity of the disease is. Additionally, not all patients received the same protocol of treatment. This was contradicted by studies which hypothesized that oral lesions are secondary lesions resulting from the worsening of systemic health or due to medications used for treatments for COVID-19.^[24] Besides, Wu *et al.*^[25] found that a lack of mouth care due to external ventilation as in medically compromised and severe cases can result in the deterioration of oral health rapidly. This could be attributed to the course of the SARS-CoV-2 infection, which adversely affects the immune response and leads to high release of inflammatory mediators that are responsible to the development of many oral lesions.

Many approaches to improving immune responses are necessary. COVID-19 patients are treated with a variety of medicines. Instead of fighting the virus directly, they use anti-inflammatories, immuno-modulatory, and/or monoclonal antibodies to regulate the immune response associated with COVID-19 infection, despite the fact that no medications have been proven to be helpful in the treatment of SARS-CoV-2 infection.^[17]

Prednisolone was taken by almost 60% of the patients for modulation of the immune response in the majority of severe inflammatory disorders.^[4] Antiviral treatment using iverzine (ivermectin) was taken which can provide a course of action to decrease the viral load, the severity, and unfavorable clinical outcomes.^[26] It was reported that less than 2% have side effects affecting the oral mucosa from antiviral treatment.^[27] On the contrary, antibiotics significantly affect the microbial balance.^[28] This could be correlated to the *Candida* infection presented in less than 50% of the patients. Remdesivir and chloroquine/hydroxychloroquine were prescribed for a small percentage of the patients for potential treatment of severe COVID-19 complications.^[29,30]

Within the limitation of this study, it was concluded that the tongue represents the most common site of oral lesions in COVID-19 patients due to high expression of ACE2 on the oral mucosa. Oral lesions seemed to be not correlated to the drugs used for the treatment of SARS-CoV-2. Spread of oral lesions in COVID-19

patients is detected despite the systemic health and the severity of the disease.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTIONS

All authors contributed in the study design, data collection and analysis, study writing, and revision process.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

The protocol of the present study was reviewed and approved by the Ethics Committee of Faculty of Dentistry, Kafrelsheikh University (No. DK/04/20) and was registered at ClinicalTrials.gov (NCT04917549). Our study protocol followed the Helsinki Principles Declaration stated in 1975.

PATIENT DECLARATION OF CONSENT

All the patients had signed an informed consent and it is available upon request.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No materials from other sources were used.

CLINICAL TRIAL REGISTRATION

This clinical trial was registered under a clinical trial registration number NCT04917549.

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