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Comparison of Oral Manifestations in Hospitalized COVID-19 Positive Patients and COVID-19 Negative Dental Outpatients. A Case Series Study and Literature Review

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Abstract

Background: The Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease, also named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which can cause various systemic manifestations that pose a threat to human life. Oral lesions in patients with COVID-19 may appear during or after the illness and may or may not be a consequence of the viral infection. **Objective:** In this case series we compare the oral manifestations in hospitalized COVID-19 positive patients and COVID-19 negative dental outpatients. **Methods:** 60 hospitalized COVID-19 patients and 41 control patients, were examined for oral signs and symptoms. The controls were dental patients who visited the hospital for dental care without complaining of any problems related to the oral cavity itself. **Results:** We have observed a strong association between certain clinical findings and COVID-19, including alterations in taste (ageusia, dysgeusia, and hypogeusia), anosmia, hairy tongue, tongue imprints, red tongue, erythematous candidiasis, pseudomembranous candidiasis, and exfoliative cheilitis. A trend but not statistically significant association at the level of 5% was also noted for colored tongue, linea alba, and pale mucosa. On the contrary, fissured tongue and oral mucosa pigmentation were more frequent in the controls, statistically significant at the level of 5%. **Conclusion:** COVID-19 has been found to impact the oral cavity, resulting in various oral lesions that can be attributed to either the direct action of the virus or the patient's immune response.

Keywords

Case Series, COVID-19, SARS-CoV-2, Oral Lesions/Manifestations,

Hospitalized Patients, Control/Dental Patients

1. Introduction

Since 2019, scientists worldwide have tried to study the relationship between the coronavirus and various clinical manifestations. The virus responsible for the COVID-19 disease was named severe acute respiratory virus syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. As of 28 August 2022, more than 598 million confirmed cases and more than 6.4 million deaths have been reported globally.

Various signs and symptoms have been reported, including taste alterations like hypogeusia, dysgeusia, and ageusia. Some studies have even shown a strong relationship between taste loss and COVID-19. Other notable clinical features include mucosal lesions such as red macules, erosive lesions, plaque-like lesions, bullae and/or vesicles, hemorrhagic crusts, and erythema. Petechiae in the oropharynx, oral aphthae, and primary/secondary herpes infection were also related to PCR positivity while cheilitis or angular cheilitis were the only oral signs associated with lung involvement in patients with PCR positivity. Xerostomia, burning mouth syndrome, and candidiasis have also been reported. Other reported oral lesions in COVID-19 patients were herpetiform erosions or ulcers, erythema multiforme-like erosions or ulcers, and maculae [1]-[11].

Specifically, studies indicate that around two-thirds of COVID-19 patients experience at least one oral symptom, with approximately one-third presenting dysgeusia as the earliest manifestation of COVID-19. Although less common than dysgeusia and xerostomia, oral mucosal lesions were detected in approximately 20.5% of COVID-19 cases [12]. These lesions typically develop within 10 days of infection. Recent studies indicate that among these lesions, aphthous-like lesions were the most frequent Notably, patients with oral lesions resembling Kawasaki disease are at a higher risk of developing severe COVID-19 symptoms or requiring hospitalization [13].

While certain authors suggest that loss of smell, loss of taste, and xerostomia can be prodromal signs of COVID-19, potentially predicting both the onset and severity of the disease [14], others propose that these manifestations should be considered only suggestive, and not conclusive indicators [15].

However, there is currently no concrete evidence regarding the pathophysiologic origin of these symptoms. They may be caused directly by the viral infection, or alternatively, they may be linked to patient comorbidities, iatrogenic factors, medication-related issues, or stress. Additionally, the factors contributing to oral mucosal lesions may include local immune responses within the oral cavity, fungal infections, injuries from medical devices, vasculitis, and issues with microcirculation.

Studies have found that SARS-CoV-2 affects microvessels, causing endothelii-

tis, microthrombosis, and capillary congestion. Damage to the microcirculatory system leads to hypoxia and triggers an inflammatory response, which accelerates tissue damage [16].

One possible pathophysiologic mechanism is linked to the high levels of angiotensin-converting enzyme (ACE-2), which is a component of the renin-angiotensin system, in the epithelial cells of the tongue and the salivary glands. It is believed that the virus attacks these enzymes causing taste alterations like dysgeusia and mucocutaneous oral lesions in patients with COVID-19 [5]. Recent research showed that the levels of ACE-2 expression are higher in the tongue compared to buccal and gingival tissues [7] [17].

SARS-CoV-2 infects the oral cavity through the surface ACE-2 receptors and transmembrane protease, serine 2 (TMPRSS2) which are present in the cells of the oral mucosa and salivary glands. Furthermore, multi-omics analysis has revealed that the virus deregulates the immune system mainly by decreasing the expression of interferon-1 and increasing cytokines levels [7] [18].

Moreover, in a recent study, it is supported that oral lesions in COVID-19 patients were caused by the virus itself rather than the drugs used for their treatment as it was found that adjunctive treatments with methylprednisolone (alone or in combination with TMZ) did not affect the oral lesions [19].

Our aim was to compare the oral manifestations in hospitalized patients who tested positive for COVID-19 to the oral manifestations in dental outpatients who tested negative for COVID-19, and also to estimate the statistical strength of the relationship between oral manifestations and COVID-19, and to report the most frequent lesions. To our knowledge, no similar studies have been conducted in Greece or Cyprus to date.

2. Materials and Methods

In this case series, a total of 60 patients were examined along with 41 controls, who were matched based on sex and age. Data about COVID-19 patients was gathered between May 2021 and July 2021, while data for the control group was acquired from January 2022 through September 2022. The average age of both patients and controls was about 55 years. The patients included in the study tested positive for COVID-19 and were hospitalized at the "Asklepieion Voulas' General Hospital", Greece but they were not admitted to the intensive care unit. On the other hand, the control group consisted of dental patients who visited the Hospital for dental care and tested negative for COVID-19. These control patients were randomly selected during their hospital visit, which required a COVID-19 test prior to entry following the Hospital's policy. Prior to their clinical examination, they reported no other problems related to the oral cavity. The study excluded the pediatric population and patients with systemic conditions that could affect the oral mucosa. The oral cavity was systematically examined.

All oral signs were recorded. Also, there were reported taste alterations including ageusia, dysgeusia, and hypogeusia as well as anosmia. The examination

of one patient (patient 23) focused solely on clinical findings, as the individual could not communicate and was unable to report taste and smell disorders. This was considered, and we adjusted our sample size accordingly when calculating the relative frequencies of the respective manifestations.

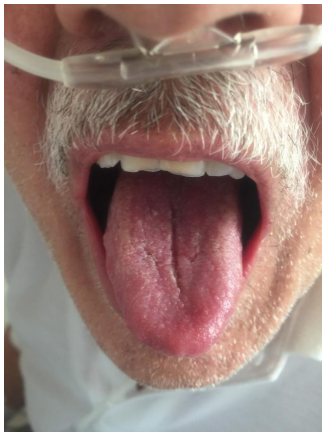
The data were analyzed using IBM SPSS Statistics, USA (Version 27.0.0). The statistical tests used for the comparison of the frequency of clinical findings in patients and controls were Pearson's Chi-square test of Independence and Fisher's Exact Test of Independence 2-tailed.

3. Results

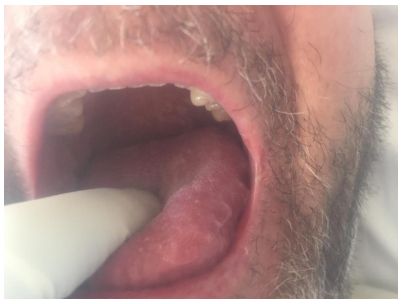
A total of 60 patients were examined along with sex and age matched 41 controls.

The main clinical findings we detected in patients and controls were hairy tongue, tongue invaginations/imprints, red tongue, exfoliative cheilitis, linea alba, candidiasis (pseudomembranous, erythematous, median rhomboid glossitis), hemorrhagic lesions, fissured tongue, leukoplakia, melanotic or pigmented lesions, herpes labialis, syncheilitis/angular cheilitis, atrophic glossitis, hyperplastic fungal papillae, pale mucosa, and ulcers/erosions along with taste alterations and anosmia. (Picture 1-5)

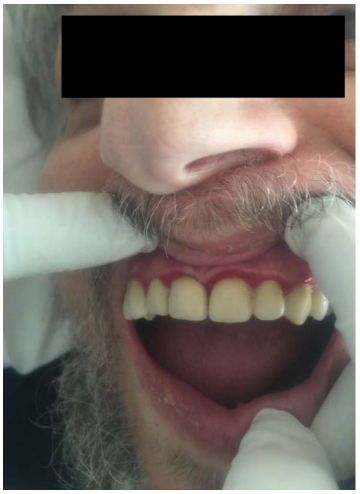
These oral manifestations are presented for COVID-19 patients in Table 1 and for controls in Table 2.



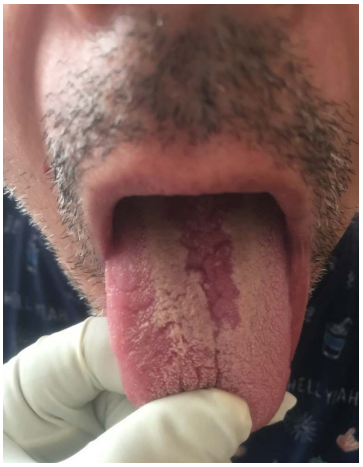
Picture 1. COVID-19 patient. Fissured tongue.



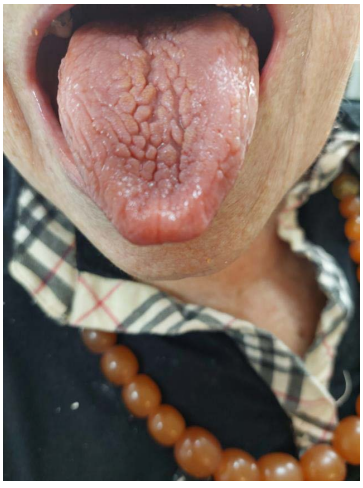
Picture 2. COVID-19 patient. Tongue imprints.



Picture 3. COVID-19 patient. Free gingival margin gingivitis, exfoliative cheilitis.



Picture 4. COVID-19 patient. Median rhomboid glossitis, hairy and fissured tongue.



Picture 5. Dental/Control patient. Fissured and atrophic glossitis.

Table 1. COVID-19 patients and oral manifestations at Asklepieion Voulas' General Hospital-2021.

No	Sex	Age	Oral manifestations
1	M	68	fissured tongue, hairy tongue, exfoliative cheilitis
2	F	60	dysgeusia, linea alba, hairy tongue
3	M	50	linea alba, fissured tongue, hairy tongue, red tongue, tongue imprints, erythematous candidiasis
4	M	16	linea alba, fissured tongue, hairy tongue, tongue imprints
5	F	46	hairy tongue, red tongue, pale mucosa
6	F	59	fissured tongue, syncheilitis, melanotic macules (dark skinned)
7	F	55	linea alba, fissured tongue, hairy tongue, tongue imprints, mucosal pigmentations
8	M	54	fissured tongue, hairy tongue
9	M	55	linea alba, hairy tongue, colored tongue, tongue imprints, melanotic macules
10	F	38	ageusia, anosmia, linea alba, herpes labialis, hairy tongue, pale mucosa
11	M	42	linea alba, hairy tongue, red tongue, mucosal pigmentations
12	M	65	hairy tongue, hematic lesion, mucosal pigmentations
13	M	39	linea alba, hairy tongue, fissured tongue, tongue imprints, pseudomembranous candidiasis, leukoplakia, mucosal pigmentations
14	M	39	linea alba, fissured tongue, hairy tongue, red tongue, tongue imprints
15	F	58	ageusia, anosmia, fissured tongue, hairy tongue, red tongue, tongue imprints
16	F	42	ageusia, anosmia, hairy tongue, mucosal pigmentations (dark skinned)
17	F	67	anosmia, hairy tongue
18	M	41	hairy tongue (dark skinned)
19	M	54	partially hairy tongue, partially atrophic glossitis, red tongue, pseudomembranous candidiasis, leukoplakia
20	M	57	hairy tongue, erythematous candidiasis, mucosal pigmentations

Continued

21	M	60	hairy tongue, erythematous candidiasis
22	M	50	fissured tongue, hairy tongue, tongue imprints
23	F	45	linea alba, fissured tongue, hairy tongue, hematic lesions
24	F	42	fissured tongue, hairy tongue, tongue imprints, mucosal pigmentations (dark skinned)
25	F	63	fissured tongue, hairy tongue, exfoliative cheilitis, melanotic macules (dark skinned)
26	F	54	ageusia, anosmia, fissured tongue, hairy tongue, tongue imprints, mucosal pigmentations (dark skinned)
27	F	58	dysgeusia, hairy tongue, red tongue, red mucosa (dark skinned)
28	F	64	ageusia, anosmia, fissured tongue, erythematous candidiasis, ulcer, melanotic macules
29	M	77	no answer about taste and smell, fissured tongue, pseudomembranous candidiasis
30	F	44	linea alba, fissured tongue, hairy tongue, tongue imprints
31	M	43	linea alba, hairy tongue, colored tongue, tongue imprints, pseudomembranous candidiasis, exfoliative cheilitis (dark skinned)
32	M	51	dysgeusia, linea alba, fissured tongue, hairy tongue
33	M	70	linea alba, fissured tongue, hairy tongue, tongue imprints, pseudomembranous candidiasis, erythematous candidiasis
34	F	46	dysgeusia, hairy tongue, exfoliative cheilitis, leukoplakia, erythematous candidiasis
35	M	56	fissured tongue, hairy tongue
36	M	65	dysgeusia, fissured tongue, hairy tongue, exfoliative cheilitis, hemangioma, pseudomembranous candidiasis, melanotic macules
37	M	31	linea alba, hairy tongue, tongue imprints, colored tongue, exfoliative cheilitis
38	M	74	linea alba, tongue imprints, atrophic glossitis, exfoliative cheilitis, pseudomembranous candidiasis, erythematous candidiasis, leukoplakia
39	F	69	hairy tongue, erythematous candidiasis, hematic macule
40	F	42	hairy tongue, tongue imprints

Continued

41	M	49	ageusia, hairy tongue, tongue imprints
42	M	82	fissured tongue, atrophic glossitis, red tongue, petechiae, atrophy of the surface of the vermillion border of the lower lip
43	F	57	fissured tongue, hairy tongue, colored tongue, exfoliative cheilitis
44	F	80	dysgeusia, fissured tongue, hairy tongue, colored tongue, mucosal pigmentations (dark skinned)
45	F	54	anosmia, dysgeusia, hairy tongue, colored tongue, tongue imprints, exfoliative cheilitis, erythematous candidiasis
46	F	54	fissured tongue, tongue imprints, hyperplastic fungal papillae, exfoliative cheilitis
47	F	67	hypogeusia, linea alba, hairy tongue, colored tongue, exfoliative cheilitis
48	F	60	linea alba, hairy tongue, tongue imprints, mucosal pigmentations (dark skinned)
49	M	44	hairy tongue, pseudomembranous candidiasis, erythematous candidiasis
50	M	65	linea alba, fissured tongue
51	M	43	no manifestations
52	M	60	hairy tongue, erythematous candidiasis
53	M	44	linea alba, hairy tongue, tongue imprints, red tongue, exfoliative cheilitis, mucosal pigmentations (dark skinned)
54	F	42	linea alba, hairy tongue, exfoliative cheilitis
55	F	58	dysgeusia, anosmia, hairy tongue, tongue imprints, exfoliative cheilitis
56	F	44	exfoliative cheilitis
57	F	76	hypogeusia, pseudomembranous candidiasis, erythematous candidiasis, exfoliative cheilitis
58	M	61	dysgeusia, linea alba, fissured tongue, hairy tongue, colored tongue, tongue imprints
59	M	55	fissured tongue, hyperplastic fungal papillae, atrophic glossitis, exfoliative cheilitis, ulcer, leukoplakia
60	M	53	dysgeusia, linea alba, fissured tongue, hairy tongue, tongue imprints, pseudomembranous candidiasis, red mucosa, mucosal pigmentations (dark skinned)

Table 2. Controls-Dental patients and oral manifestations at Asklepieion Voulas' General Hospital-2022.

No	Sex	Age	Oral manifestations
1	M	49	fissured tongue, syncheilitis, red mucosa, mucosal pigmentations (dark skinned)
2	M	87	fissured tongue, atrophy of the surface of the vermillion border of the lower lip, imprints of the inner surface of the lower lip
3	F	48	linea alba, small tumor of the mucosa of the upper lip
4	F	38	linea alba, hairy tongue, colored tongue, tongue imprints (dark skinned)
5	F	24	mucosal pigmentations, hairy tongue (dark skinned)
6	M	18	fissured tongue, hairy tongue, leukoplakia
7	F	87	fissured tongue, atrophic glossitis, erythematous candidiasis, ulcer, small tumor of the mucosa of the cheek
8	F	48	fissured tongue
9	F	72	fissured tongue, hairy tongue, atrophic glossitis, erythematous candidiasis
10	F	41	fissured tongue, hairy tongue, mucosal pigmentations (dark skinned)
11	F	72	fissured tongue, atrophic glossitis, ulcer, leukoplakia, melanotic macules
12	M	40	herpes labialis, leukoplakia, mucosal pigmentations (dark skinned)
13	F	71	fissured tongue
14	F	75	fissured tongue
15	F	44	fissured tongue
16	M	74	linea alba, fissured tongue, hairy tongue
17	F	22	fissured tongue
18	M	51	linea alba, fissured tongue, hairy tongue, hemangioma
19	F	41	linea alba, fissured tongue
20	M	55	fissured tongue, hairy tongue, leukoplakia
21	F	83	fissured tongue, melanotic macules
22	F	66	fissured tongue, atrophic glossitis, exfoliative cheilitis, mucosal pigmentations (dark skinned)
23	M	42	linea alba, fissured tongue, hairy tongue, red mucosa, mucosal pigmentations (dark skinned)

Continued

24	F	54	linea alba, fissured tongue, hairy tongue, leukoplakia
25	F	70	fissured tongue, atrophic glossitis, red mucosa
26	F	46	hairy tongue
27	F	57	linea alba, fissured tongue, hairy tongue, leukoplakia
28	M	61	fissured tongue, hairy tongue, syncheilitis, desquamate gingivitis
29	M	68	fissured tongue, tongue imprints
30	F	52	fissured tongue, hairy tongue, exfoliative cheilitis, tongue imprints, white candidiasis, mucosal pigmentations (dark skinned)
31	M	76	fissured tongue, hairy tongue, mucosal pigmentations (dark skinned)
32	M	63	fissured tongue, hairy tongue, tongue imprints, mucosal pigmentations (dark skinned)
33	M	61	fissured tongue, atrophic glossitis, melanotic macule (dark skinned)
34	M	77	fissured tongue, hairy tongue, erythematous candidiasis, hemangioma, melanotic macules (dark skinned)
35	M	34	hairy tongue, melanotic macules (dark skinned)
36	M	33	linea alba, fissured tongue, hairy tongue, melanotic macules (dark skinned)
37	M	30	fissured tongue, hairy tongue, tongue imprints
38	M	57	fissured tongue, hairy tongue, melanotic macules (dark skinned)
39	M	68	fissured tongue, atrophic glossitis, exfoliative cheilitis, melanotic macules (dark skinned)
40	M	56	linea alba, fissured tongue, exfoliative cheilitis, tongue imprints
41	M	46	fissured tongue, hematic macule, melanotic macules (dark skinned)

Statistical Analysis

Based on the frequency of clinical findings while comparing COVID-19 and control patients a hypothesis was made on how strongly related some oral manifestations are to the coronavirus. The strongly related clinical findings are found to be taste alteration (including ageusia, dysgeusia and hypogeusia), anosmia, hairy tongue, tongue imprints, red tongue, erythematous candidiasis,

pseudomembranous candidiasis, and exfoliative cheilitis. A trend but not statistically significant association at the level of 5% was also noted for colored tongue, linea alba, and pale mucosa. Patients compared with controls had similar gender and age distributions.

The statistical analysis produced the following results:

A. Descriptive Statistics:

In relation to the Patients' and Controls' Age, we observe that:

1) The Mean Value is the same (approx. 55 years).

2) The Median is the same (55 years) (Table 3).

Patient Age follows the distribution according to Figure 1:

Control Age follows the distribution according to Figure 2:

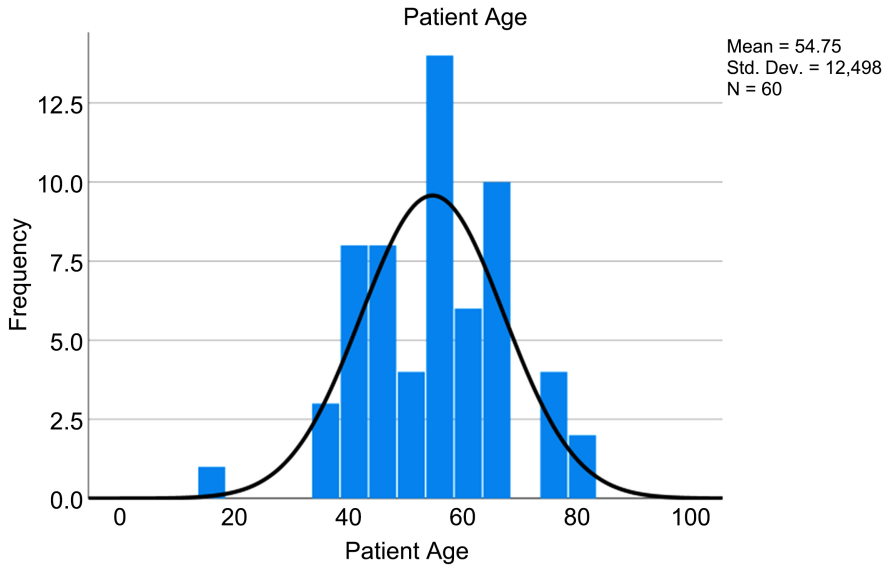


Figure 1. Distribution of patients by age.

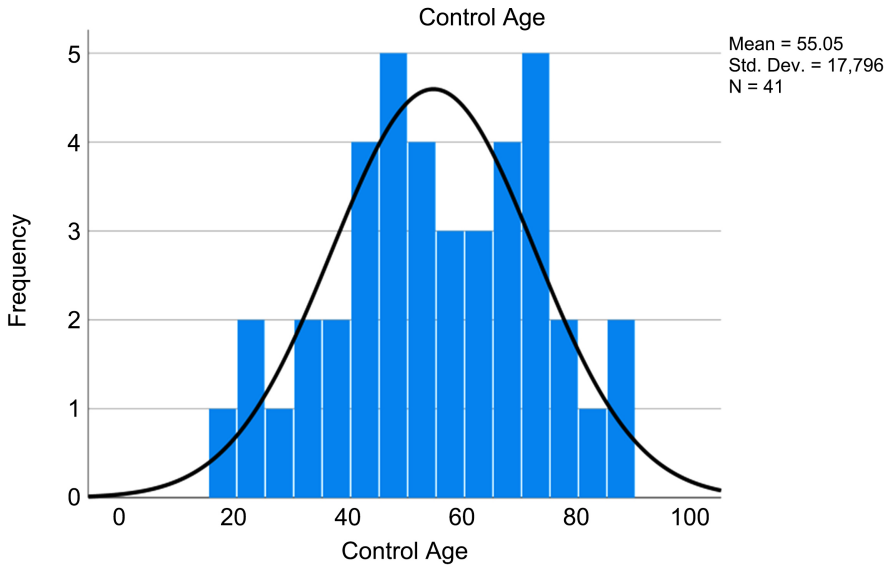


Figure 2. Distribution of controls by age.

Table 3. Patients and controls age mean, median, mode values and standard deviation.

	Patients	Controls
Mean Value	54.75	55.05
Median	55.00	55.00
Mode	54	41
Std. Deviation	12.498	17.796

B. Age and sex matching of controls

We define the binomial variable P_C which takes the values P for patients and C for controls.

We also introduce the interval variable Age_Index, which categorizes the Patients and the Controls into three age groups:

Young: 16 - 39, Middle-aged: 40 - 64, and Old: 65+ years old.

We found no statistically significant relationship between the variables P-C and Age Index at the level of 5% (Fisher-Freeman-Halton Exact Test of Independence: 2-tailed, $p = 0.087$). Therefore, the Patients' and Controls' frequencies in the three Age Groups were similar.

The distribution of Patients and Controls by sex was similar as well. We found no statistically significant relationship between the variables P-C and Sex at the level of 5%. Therefore, the Male and Female frequencies were similar in Patients and Controls (Chi-square test of Independence: $x^2 = 0.044$, $df = 1$, $p = 0.835$).

C. Comparisons of oral manifestations between patients and controls (Patients vs Controls)

Several statistical hypotheses about the independent variables representing the oral manifestations were carried out.

1) It was found that there is a statistically significant difference (at the level of 5%) between the patients' and controls' mean value of the following oral manifestations with these manifestations being more frequent in the patients: taste alteration, anosmia, hairy tongue, tongue imprints, red tongue, erythematous candidiasis, pseudomembranous candidiasis, exfoliative cheilitis (**Table 4**).

On the other hand, we found that there is not a statistically significant difference between the patients' and controls' mean value of the next oral manifestations: colored tongue, linea alba, pale mucosa, hyperplastic fungal papillae, and hemorrhagic lesions. However, colored tongue, linea alba and pale mucosa suggested a valuable trend. (**Table 5**):

2) On the contrary, it was found that there is a statistically significant difference (at the level of 5% between the patients' and controls' mean value of the following oral manifestations with these manifestations being more frequent in the controls: fissured tongue, pigmentation of the oral mucosa (**Table 6**):

On the other hand, we found that there is not a statistically significant difference between the patients' and controls' mean values of the next oral manifestations:

Table 4. Oral manifestations that are more frequent in the patients, statistically significant at the level of 5%.

Oral manifestation	Test	P
Taste alteration (including ageusia, dysgeusia and hypogeusia as a total)	Fisher's Exact Test of Independence, 2-tailed	$p < 0.001$
Anosmia	Fisher's Exact Test of Independence, 2-tailed	$p = 0.02$
Hairy tongue	Fisher's Exact Test of Independence, 2-tailed	$p = 0.004$
Tongue imprints	Pearson's Chi-square test of Independence: $x^2 = 8367$, df = 1, 2-tailed	$p = 0.004$
Red tongue	Fisher's Exact Test of Independence, 2-tailed	$p = 0.02$
Erythematous candidiasis	Fisher's Exact Test of Independence, 2-tailed	$p = 0.008$
Pseudomembranous candidiasis	Fisher's Exact Test of Independence, 2-tailed	$p = 0.035$
Exfoliative cheilitis	Pearson's Chi-square test of Independence: $x^2 = 5104$, df = 1, 2-tailed	$p = 0.024$

Table 5. Oral manifestations that some of them are obviously more frequent in the patients but not statistically significant at the level of 5%.

Oral manifestation	Test	P
Colored tongue	Fisher's Exact Test of Independence, 2-tailed	$p = 0.138$
Linea alba	Pearson's Chi-square test of Independence: $x^2 = 2153$, df = 1, 2-tailed	$p = 0.142$
Pale mucosa	Fisher's Exact Test of Independence, 2-tailed	$p = 0.269$
Hyperplastic fungal papillae	Fisher's Exact Test of Independence, 2-tailed	$p = 0.513$
Hemorrhagic lesions	Pearson's Chi-square test of Independence: $x^2 = 2153$, df = 1, 2-tailed	$p = 1.0$

atrophic glossitis, leukoplakia, syncheilitis, herpes labialis, ulcers, and melanotic macules. However, atrophic glossitis and leukoplakia suggested a valuable trend) (Table 7).

D. Comparisons of oral manifestations between patients

It was studied if there is a relationship between tongue imprints, linea alba and hyperplastic fungal papillae of the patients. The results of these comparisons are that there is a significant relationship between the existence of tongue imprints and linea alba, but not between the existence of tongue imprints and hyperplastic fungal papillae and not between the existence of linea alba and hyperplastic fungal papillae (Table 8).

Table 6. Oral manifestations that are more frequent in the controls, statistically significant at the level of 5%.

Oral manifestation	Test	P
Fissured tongue	Pearson's Chi-square test of Independence: x^2 = 12,420, df = 1, 2-tailed	p = 0.001
Pigmentation of the oral mucosa	Pearson's Chi-square test of Independence: x^2 = 5074, df = 1, 2-tailed	p = 0.034

Table 7. Oral manifestations that some of them are obviously more frequent in the controls.

Oral manifestation	Test	P
Atrophic glossitis	Fisher's Exact Test of Independence, 2-tailed	p = 0.094
Leukoplakia	Fisher's Exact Test of Independence, 2-tailed	p = 0.309
Syncheilitis	Fisher's Exact Test of Independence, 2-tailed	p = 0.565
Herpes labialis	Fisher's Exact Test of Independence, 2-tailed	p = 1.0
Ulcers	Fisher's Exact Test of Independence, 2-tailed	p = 0.513
Melanotic macules	Pearson's Chi-square test of Independence: x^2 = 2153, df = 1, 2-tailed	p = 1.0

Table 8. Comparisons of oral manifestations between patients.

Relationship between oral manifestations	Test	P
Tongue imprints and Linea alba	Pearson's Chi-square test of Independence: $x^2 = 8511$, df = 1, 2-tailed	p = 0.004
Tongue imprints and hyperplastic fungal papillae	Fisher's Exact Test of Independence, 2-tailed	p = 1.0
Linea alba and hyperplastic fungal papillae	Fisher's Exact Test of Independence, 2-tailed	p = 0.519

4. Discussion

4.1. Oral Manifestations of COVID-19

Oral manifestations related to COVID-19 cases have been described in the literature. The reported oral signs were quite heterogeneous, varying in the type of lesion, location and incidence when comparing the periods before and during hospital admission. Any oral site can be affected but the most commonly reported sites were tongue and palate, followed by gingiva, lips and labial mucosa [20] [21] [22] [23].

The complications reported in hospitalized COVID-19 patients were: perioral pressure, ulcers, macroglossia, blisters, oral candidiasis, cheilitis, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, anosmia, taste alterations, geographic tongue, macule, papule, plaque, pigmentation, halitosis, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding [20] [21] [22] [23].

In a recent study, it was found that COVID-19 hospitalized patients have a higher prevalence of oral manifestations, which indicates an increased risk of mortality. Furthermore, the authors suggest that dentists should be included in multidisciplinary teams, to facilitate the early detection and treatment of the oral manifestations [24].

Additionally, another study revealed an increased occurrence of xerostomia, mouth ulcers, and taste alterations, among patients with active disease [11].

Some of the hypotheses used in the literature as a potential explanation of the oral lesions were the long-lasting prone position of ICU patients [17] [25], the pressure caused by endotracheal tubes [26] immunosuppression state for a long time [27] [28] and medications [22] [29].

In our study, we demonstrated with statistical significance ($p > 0.05$), that the oral manifestations below were found to be more frequent in COVID-19 patients.

4.1.1. Taste Impairment/Gustatory Dysfunction

The most commonly reported oral symptoms in the literature were dysgeusia

(altered taste), hypogeusia (reduced taste sensation) and ageusia (complete loss of taste) [1] [6] [7] [8] [9] [11] [14] [17] [30] [31]. In our research, 18 out of the 59 patients admitted to the hospital reported experiencing changes in taste.

One of the earliest reported symptoms of SARS-CoV-2 infection is dysgeusia. The prevalence of taste disorders varied widely from 1.0% to 93.0% and their frequency varies geographically, ranging from 14% in Africa to 49% in Europe [6] [32].

Dysgeusia typically appears within five days of a COVID-19 diagnosis, with a duration of two weeks, extending up to four weeks in more severe cases [12].

Studies have revealed a strong association between the severity of COVID-19 and the intensity of dysgeusia, with severe dysgeusia often serving as an early warning sign [12] [33].

The causes of dysgeusia in COVID-19 patients have been extensively investigated. One explanation proposed in published literature is the direct damage to the nasal and oral epithelium, resulting in olfactory and gustatory disorders. Taste alterations happen due to the virus activating the cytokines, which triggers cell apoptosis together and abnormal turnover of the cells, preventing the taste buds on the tongue from differentiating further. It is reported that 95% of the cases of taste impairment are due to olfactory dysfunction. However, there are some reported cases of gustatory dysfunction without any olfactory changes [1]. In our research, there were also cases of patients without coexistence of taste impairment and anosmia.

An Italian objective multicenter study in 2020 suggested two theories regarding dysgeusia and loss of smell. The first theory supports that the virus gains access to the central nervous system by infecting neurons by active transport of cells. The second theory suggests that when the ACE-2 receptor is stopped, these complications happen [34].

Previous research has indicated that taste bud cells express both ACE2 and TMPRSS2, which serve as receptors facilitating the invasion of COVID-19 [35]. It has been discovered that ACE2 receptors are present in human type II taste cells, and evidence suggests that the virus can replicate within these cells, as demonstrated by *in situ* hybridization. So, evidence suggests that COVID-19 can directly affect taste bud cells, leading to dysgeusia. Additionally, there is a possibility that the virus could infect the squamous epithelial cells of the tongue, causing localized inflammation and swelling, thus interfering with the proper functioning of taste buds.

Another possible hypothesis for dysgeusia is the dysfunction of the nervous system. Evidence indicates that SARS-CoV-2 may affect the central nervous system (CNS), as shown by the presence of viral RNA in both the brain and cerebrospinal fluid of COVID-19 patients. Additionally, the detection of ACE2 expression in specific brain regions suggests potential pathways for viral entry and infection. Moreover, due to its neurotropic nature, SARS-CoV-2 has the potential to cause direct damage to the cranial nerves involved in taste (specifically CN

VII, CN IX, and CN X). Additionally, SARS-CoV-2 might inhibit the expression of neurotransmitters, thereby impairing synaptic transmission and contributing to the development of dysgeusia. [13] [35].

4.1.2. Anosmia

Anosmia is defined as the complete or partial loss of the sense of smell. It may be due to various reasons such as head injuries, infections, or nasal blockages. While current literature provides some insight, there is limited understanding of why COVID-19 can lead to this loss of smell. However, similar mechanisms seen in other respiratory viral infections may offer some explanation.

One proposed mechanism suggests that the virus obstructs the nasal epithelium, which can result in the loss of smell, and this effect can persist for weeks to months. Notably, this obstruction tends to resolve after the infection has cleared. Another theory is rooted in neurology. The nasal respiratory epithelium, particularly the ciliated cells, demonstrates a high level of ACE2 expression. Further research is needed to explore these olfactory neurological functions in COVID-19 patients, as they may also be influenced by other neurological conditions like encephalitis, cerebrovascular accidents, and potential long-term neurodegenerative risks [36].

In our research, most of our patients who experienced anosmia also experienced changes in taste. Loss of taste along with anosmia was concurrent and attributed to edema of the respiratory system [17]. This contributes to the theory that olfactory and gustatory dysfunctions are potential indications of COVID-19 [14] [37].

4.1.3. Hairy Tongue

Black hairy tongue (BHT) is quite commonly demonstrated in the COVID-19 case report and literature review. The color may range from yellow-brown to black and usually involves the anterior and middle thirds of the dorsal tongue. This appears to be caused by the accumulation of epithelial squames and the proliferation of chromogenic microorganisms [38]. It appears more frequently in smokers, in people with poor oral hygiene or in those with hyposalivation. However, other underlying conditions have been proposed for causing it including antibiotics, such as bismuth, amoxicillin, tetracycline, linezolid, and psychotropic agents, including olanzapine, phenothiazines, and tricyclic antidepressants, NSAIDs [38] [39].

In our research, 49 out of 60 patients who were hospitalized had hairy tongue. All hospitalized COVID-19 patients received antibiotics and corticosteroids which could influence the results.

4.1.4. Tongue Imprints/Invaginations

Tongue imprints and linea alba are common clinical findings, especially in highly anxious patients with parafunctional habits. In our research, 25 out of the 60 patients who were admitted to the hospital had tongue invaginations and 23

out of 60 had linea alba. There is a strong statistical correlation between tongue imprints and linea alba which may be due to the tongue edema induced by the virus. Stress may also play an essential role in the appearance of these oral conditions [39]. As a result, the teeth imprint their shape on the lateral surface of the tongue bilaterally as well as on the buccal mucosa.

A research conducted in Spain reported that 6.6% of hospitalized patients experienced glossitis with lateral indentations resulting from wearing ventilation masks [11].

4.1.5. Red Tongue

Red tongue found in our study of COVID-19 patients may be due to the inflammation caused by the virus. Based on the literature so far, color changes in the tongue can be due to damage to the microcirculation or even high platelet aggregation [39].

4.1.6. Tongue Alterations: Pseudomembranous Candidiasis, Erythematous Candidiasis

Oral candidiasis infection mainly presents as white or erythematous lesions.

Pseudomembranous candidiasis (white lesions), also known as thrush, is associated with predisposing factors including immune system deprivation. In most patients, thrush is related to hyposalivation, corticosteroid or antibiotic use [38]. Candidiasis resulting from long-term antibiotic therapy, general health deterioration, and poor oral hygiene can be the cause of white patches or plaques on the dorsal surface of the tongue, or lateral border of the tongue or palate or even the buccal mucosa in COVID-19 patients [21].

Erythematous candidiasis appears as a flat red lesion on the dorsal surface of the tongue or on the palate. It is a common oral lesion that can occur during the initial onset of HIV infection appearing as pink or red macular lesions with the same as above predisposing factors and even smoking [38].

It has been found that candidal infection and taste disturbance were the most frequent oral lesions in hospital-admitted COVID-19 patients [9].

Fungal infections can appear simultaneously with coronavirus or during the immediate recovery period [40].

Our results also agree with a case series study, where the most common diagnosis was chronic candidal glossitis in COVID-19 patients, presented in different forms and expansions, and correlated with COVID severity [37].

4.1.7. Exfoliative Cheilitis/Cracked Lips

The causes of exfoliative cheilitis are unknown, but dehydration or delayed hyperactivation response of the immune system have been suggested as some of the possible causes [21].

In our research, 17 out of the 60 patients who were admitted to the hospital had exfoliative cheilitis as a possible result of medications, general symptoms like fever, dehydration, and administration of oxygen.

Exfoliative cheilitis was also frequently observed in children with COVID-19.

This is also a sign of the hyperinflammatory state, as seen in multisystem inflammatory syndrome [41].

As information about cheilitis in the existing COVID-19 literature is limited, further studies are required to investigate this finding.

Other oral manifestations that were observed more frequently in patients with COVID-19, although they were not statistically significant at the 5% level were the following:

4.1.8. Colored Tongue, Linea Alba, and Pale Oral Mucosa

These manifestations appear to be more frequent among hospitalized patients, although this association did not reach statistical significance. On the other hand, we observed no statistically significant difference between hyperplastic fungal papillae and hemorrhagic lesions/petechiae despite their more frequent occurrence in other research studies.

Linea alba is usually associated with parafunctional habits and cheek biting [42]. In our case, stress could be a potential cause or oedema caused by the virus. Also, the hyperplastic fungal papillae could be attributed to inflammation. The pale color of the mucosa might indicate an underlying systemic condition (such as anemia). There are no reported cases of these oral findings in the current literature. Hemorrhagic Lesions/Petechiae can be caused by trauma, infectious diseases, inflammation, viral infections, and other systemic conditions like autoimmune thrombocytopenia. Also, they may be associated with thrombocytopenia induced by SARS-CoV-2 [43] [44].

The presence of a white coating on the tongue could be attributed to poor oral hygiene potentially causing the accumulation of debris, bacteria, and dead cells. Moreover, it may indicate damage to the free oxygen radicals scavenger system, leading to reduced levels of beneficial bacteria like Lactobacillus and Bifidobacterium [11] [45].

A research conducted on 1043 COVID-19 patients found that as the disease progressed, a significant portion, up to 62.5%, displayed a yellowish coating on their tongues. This discoloration was linked to factors such as fever and infection. Moreover, a clear association was observed between the severity of lung infection, overall disease severity, and the intensity of the yellow coating on the tongue [11] [45] [46].

Some authors have indicated the presence of tongue coating among patients with COVID-19, although this feature has not been observed by others [40] [47]. Moreover, these authors did not detect significant differences in the occurrence of mouth ulcers, glossitis, and petechiae [11].

The oral manifestations that were more frequent in the controls, statistically significant at the level of 5% are outlined below.

4.1.9. Fissured Tongue

A fissured tongue is a common condition where the dorsal surface is normally papillated but exhibits deep irregular fissures. Fissured tongue was found more

common in controls. Statistical analysis revealed no significant difference at the level of 5% between the controls and the patients. This may be due to better examination conditions. (**Picture 3**, **Picture 4**) or because it is a normal variant seen in up to 20% - 30% of the population [38].

4.1.10. Pigmentation of the Oral Mucosa

This lesion is produced by an increase in melanin deposition and, possibly, a concomitant increase in the number of melanocytes. The exact cause remains unclear [42]. This finding may be due to the increased number of dark-skinned controls (17 out of 41 controls vs 12 out of 60 patients).

On the other hand, we found that there is not a statistically significant difference between the patients' and controls' mean values of the following oral manifestations: atrophic glossitis, leukoplakia, syncheilitis, herpes labialis, ulcers, and melanotic macules, although, atrophic glossitis, and leukoplakia suggested a valuable trend However, in the literature all these manifestations apart from melanotic macules are referred to be more frequent in the patients and this is attributed to a variety of reasons like deficiencies of some major nutrients, immune defect, candida infection in these immunocompromised patients, stress, direct damage to the oral mucosa by the action of virus etc. [21] [30] [38] [41] [43] [48]-[53].

It is important to mention that these findings could potentially be attributed to better examination conditions of the controls.

4.2. Limitations of the Study

We acknowledge certain limitations of our study. Firstly, systemic diseases and various medications taken by the patients could potentially affect the oral cavity. This is because all hospitalized COVID-19 patients received antibiotics and corticosteroids. The limited data on systemic diseases for some patients made it challenging to establish correlations with certainty. Secondly, the examination conditions like room lighting and positioning of the patients were not ideal, and this may have resulted in an underestimation of the prevalence of certain findings among our sample. Moreover, disease severity and duration varied significantly between patients which might cause variations in our results. Finally, we consider that the relatively small sample size is not representative of the general population and represents a barrier to the generalizability of our findings.

The more favorable examination conditions in the control group, namely the optimal positioning and improved lighting, may represent a source of bias. We consider that, although certain associations did not reach statistical significance owing potentially to the limited sample size, they may represent important considerations nonetheless.

4.3. Recommendations for Dental Practitioners and Management of Symptomatology

Dentists play a pivotal role as the first point of contact for patient examinations.

It is crucial to have adequate knowledge of the patterns of presentation, predisposing factors, underlying mechanisms, and the management of COVID-19 oral manifestations. Awareness of these oral manifestations would aid in early diagnosis and intervention, thus facilitating early recovery, reducing morbidity and improving quality of life. Therefore, we consider that the ability to identify such lesions early, is vital in providing high-quality care [30] [33].

It is also suggested that dentists be routinely included in the therapy team. It is advisable to conduct routine oral examinations for hospitalized COVID-19 patients in order to promptly identify and manage any oral lesions. Such a multidisciplinary approach to the management of COVID-19 patients is considered vital to avoid the oral complications of the disease [8] [11] [15].

4.4. Future Implications for Research

Despite significant progress made so far about COVID-19 oral lesions, there are remaining several fields worth exploring.

Future research is needed to determine whether COVID-19 can cause specific lesions in the oral cavity. Several factors need to be considered when investigating the relationship between oral lesions and coronavirus infection. These factors include age, gender, underlying systemic diseases, medications and disease severity. We suggest that, photographic documentation should be used to ensure the accurate comparison of clinical findings and facilitate proper analysis.

It is crucial to thoroughly understand the mechanisms behind oral signs and symptoms, to elucidate their pathophysiology, and to establish definitive causality.

Brzychczy-Sroka *et al.*, proposed a protocol for conducting standardized oral examination and collecting, transporting, and storing biological samples. This protocol aims to minimize technical errors, prevent material contamination, and facilitate analysis through advanced next-generation techniques (NGS). Next-generation sequencing enables the identification of the types of microbes present, and their respective quantities while also categorizing them into specific taxonomic levels. [54]

It's essential to analyze the expression and distribution of SARS-CoV-2 entry receptors in various oral sites. This will help clarify the underlying mechanisms of COVID-19-related oral symptoms and signs.

Further studies are needed to determine if oral mucosal lesions are caused by a direct infection with SARS-CoV-2, and to explore the correlation between the type of oral manifestations and the severity and progression of the disease.

Moreover, it is important to clarify the complex interaction between viruses, bacteria, and host immune responses in order to better understand their role in oral diseases [13] [24] [54].

5. Conclusions

We concluded that the primary factors contributing to the development of oral lesions in COVID-19 patients include poor oral hygiene, opportunistic infec-

tions, stress, immunosuppression, vasculitis, and an exaggerated inflammatory response associated with COVID-19. In our study, we examined 60 COVID-19 patients and identified distinct patterns and characteristics in these oral lesions. More well-structured prospective studies are required to ascertain whether these findings could be classified as oral manifestations of SARS-CoV-2 infection.

COVID-19 infection significantly impacts oral health, with various manifestations observed in affected patients.

Understanding the etiology of COVID-19 oral lesions, exploring future research directions, and recognizing the pivotal role of dentists are critical steps towards mitigating the impact of these manifestations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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