

The Oral Lesion in the COVID-19 Patient: Is It True Oral Manifestation or Not?

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Objective: Many previously reported publications mentioned that oral lesion in COVID-19 patients was varied. The term oral manifestations refer to pathognomonic features that are found consistently with a specific cause and effect. In this context, the oral manifestation of COVID-19 was inconclusive. This systematic review aimed to analyse previously reported publications related to oral lesions in COVID-19 patients to define as oral manifestations or not. The PRISMA guidelines were implemented in this review.

Methods: All umbrella reviews, systematic reviews, systematic reviews and meta-analyses, comprehensive reviews, and original and non-original studies were included. Twenty-one of systematic review, 32 original studies and 68 non-original studies reported the oral lesion in COVID-19 patients.

Results: Most of the publications mentioned that ulcers, macular, pseudomembranes and crusts were frequent oral lesions. The reported oral lesions in COVID-19 patients did not show any pathognomonic features and might be unrelated directly to COVID-19 infections, however, more likely due to gender, age, underlying diseases, and medication.

Conclusion: The oral lesions found in previous studies do not have pathognomonic features and are inconsistent. Therefore, the reported oral lesion, in present time, cannot be defined as an oral manifestation.

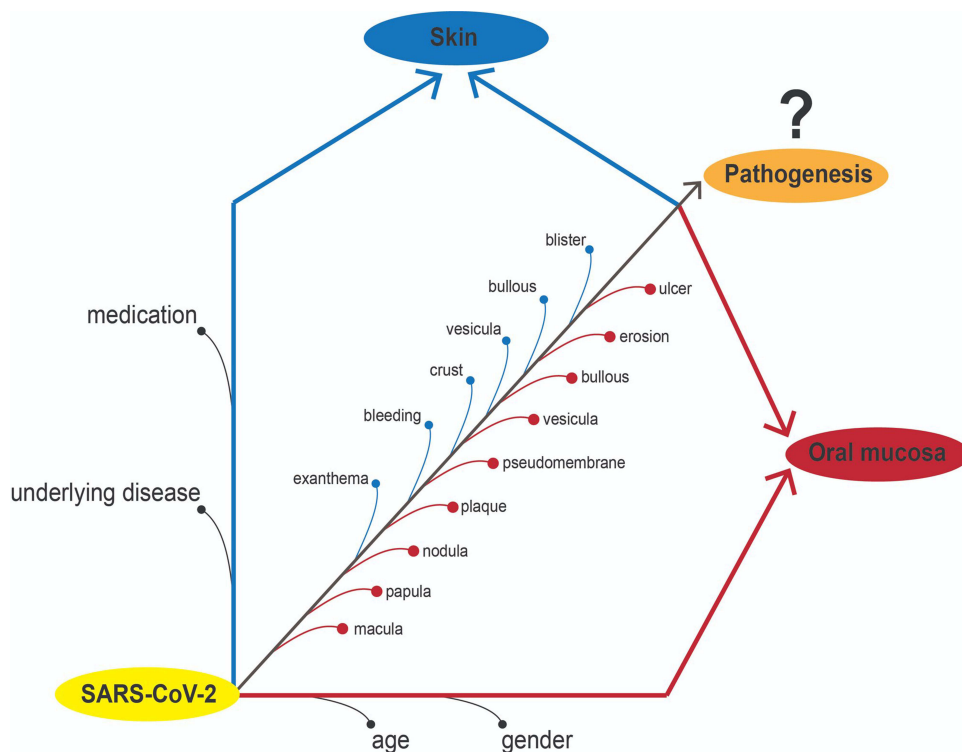
Keywords: oral lesion, oral manifestation, underlying disease, medication, COVID-19

Introduction

Some viruses have a specific manifestation in the oral mucosa or pathognomonic features that can lead a dentist, oral pathologist, or oral medicine specialist to lead to clinical diagnosis. The herpes simplex virus is the cause of primary herpes infection in children. The pathognomonic feature is oral ulceration in the entire mucosa and gingiva,¹ and it is called primary gingiva stomatitis.² The secondary infection presents a specific ulceration in the vermilion of the lips called herpes labialis.³ In other virus infections, like a varicella-zoster infection, the pathognomonic feature was segmental oral ulceration in oral mucosa⁴ and facial area.⁵ The measles infection also has pathognomonic features in the oral mucosa called Koplik's spot and cannot be found in other virus infections.⁶

Coronavirus infectious disease (COVID-19) is a disease that has been haunting the world for nearly three years. The disease is caused by a viral named SARS-CoV-2.⁷ The main symptoms are fever, cough, dyspnea, malaise and fatigue, while more serious conditions like respiratory failure and pneumonia could lead to mortality.^{8,9} SARS-CoV-2 infection, like other viral infections described in a recent report, considered has pathognomonic features in the oral mucosa called COVID tongue.¹⁰⁻¹³ Further, this condition is known as benign migratory glossitis¹¹⁻¹³ and is unable to be considered an oral manifestation. Many kinds of literature have described the oral manifestation or pathognomonic features of COVID-19. But until today, none have concluded the pathognomonic features of COVID-19 because various oral lesion was found in the patient, both hospitalized¹⁴ and non-hospitalized, like a casualty.¹⁵ The most common oral symptom was dysgeusia¹⁶ and

Graphical Abstract



xerostomia,¹⁷ while the oral lesion was an oral ulcer.¹⁶ Further, other oral lesions, vesiculobullous, blisters, and pseudomembranes (*Candida albicans* infections)¹⁴ were reported and more frequent in hospitalized patients.¹⁵ The oral lesion looks not specific; in the pediatric patient, the maculopapular (erythematous lesions), ulcers, desquamations (dry and cracked lips), and depapilation lesion (strawberry tongue) were found.¹⁸ The doubt of oral manifestation of pathognomonic features arises when accompanied by skin lesions. Most patients have skin lesions similar to herpes simplex virus infection or autoimmune diseases.¹⁹ This finding also created doubtfully regarding oral lesions whether is a causality of SARS-CoV-2 (pathognomonic features) or just the casualty.

The oral ulcers, as the common oral lesion found in COVID-19 patients, are mentioned as causality (oral manifestations or pathognomonic features) because of the presence of angiotensin-converting enzyme 2 (ACE-2) in the oral epithelial tissue. It is suspected to be the first receptor for developing oral lesions in SARS-CoV-2-infected patients.²⁰ However, until today, the pathogenesis and interaction between the ACE-2 and SARS-CoV-2 in the oral mucosa has not been able to explain.^{21,22} The development of various oral lesions in COVID-19 patients looks like a casualty, because it is influenced by various factors such as underlying disease,^{23,24} immunological and psycho-social factors,²⁵ medication,^{26–28} and age and gender.²⁹ Nevertheless, various literature has referred to the lesions found as causality, oral manifestation, or pathognomonic features of COVID-19.^{15–17,19,22,24,26–28} For this reason, this systematic review was composed of various reports regarding oral lesions in COVID-19 and whether the reported lesions can be referred to as oral manifestations or pathognomonic features or not.

Materials and Methods

Search Strategy

In this report, PRISMA guidelines for systematic reviews were implemented. The PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Science Direct (<https://www.sciencedirect.com>), and Scopus documents (<https://www.scopus.com/search/form.uri?display=basic#basic>) were searched up to December 22, 2022. All databases were searched using the following terms: (“COVID-19” [All Fields] OR “Sars-Cov-2” [All Fields]) AND “oral manifestation” [All Fields] OR “oral lesion” [All Fields]).

The researchers implemented language restrictions when assessing the records, and only the full-text articles in English were finally qualified for further evaluation. Additionally, a manual search of the bibliographies and the publications identified from a database search for potentially eligible references was performed. In order to identify missing information or data, we attempted to contact the authors of the relevant studies.

Study Assessment and Analysis

All types of articles, including umbrella reviews, systematic reviews, systematic review and meta-analysis and comprehensive review, were included to collect all the evidence. Initially, the records were assessed by two independent authors according to the relevance of the title and/or abstract (A.S and M.D.C.S). At this stage, the full reports were validated independently by another author (D.A), especially in doubtful cases. Studies considered potentially eligible by at least one of the authors in the initial search were then verified in their entirety by all authors.

The umbrella, systematic, systematic, meta-analysis, and comprehensive reviews have analyzed the description and collected the conclusion. The comprehensive review must follow the PRISMA guideline while collecting the data. While the original (pilot, cohort, observational, prospective, retrospective and cross-sectional) and non-original (case reports, case series, letters to the editor, correspondences and clinical images) studies analysed the patient demographic and related like gender, age, underlying disease, history of medication, oral lesion and skin lesion were listed as a primary outcome. Any disagreements between authors (A.S and M.D.C.S) were resolved after consultation with the third author (D.A).

Results

The 21 reviews (umbrella review, systematic review, meta-analysis and comprehensive review) discussed the oral lesion of COVID-19 patients. While the 32 original studies (pilot, cohort, observational, prospective, retrospective and cross-sectional) and 68 non-original studies (case reports, case series, letters to the editor, correspondences and clinical images) reported the oral lesion found in COVID-19 patients with the demographic data like ages, gender, underlying disease, medication and skin lesions (Figure 1).

The Systematic Review and Systematic Review and Meta-Analysis Report on Oral Lesions in COVID-19 Patients

Systematic reviews and meta-analysis literature that analysed COVID-19 and its oral manifestation and their conclusions are summarized in Table 1. Among 21 studies published until 2022, three were systematic reviews and meta-analyses, 16 were systematic reviews, one was a systematic review of systematic reviews (umbrella review), and one was a form of a comprehensive review.

Around two reviews concluded on clinical findings in the oral cavity that the most prevalent symptom was dry mouth,²¹ with oral lesions occurring in various sites of the oral mucosa.²⁶ Four studies concluded on data irregularity³³ and also unspecific³⁴ and unclear²⁴ lesions with no clear association with COVID-19.²² Around five studies analysed the potential direct causality of COVID-19 infection to oral lesions and concluded that the lesions are related to the disease,^{14,19} despite not being scientifically proven.^{27,36} Five studies concluded that oral lesions in COVID-19 likely resulted from various external factors (casualty), such as co-infection,³⁵ medical devices and treatments,¹⁵ comorbidities,³² immunosuppression and medications^{28,32} that could mimic other inflammatory diseases.¹⁸ Around

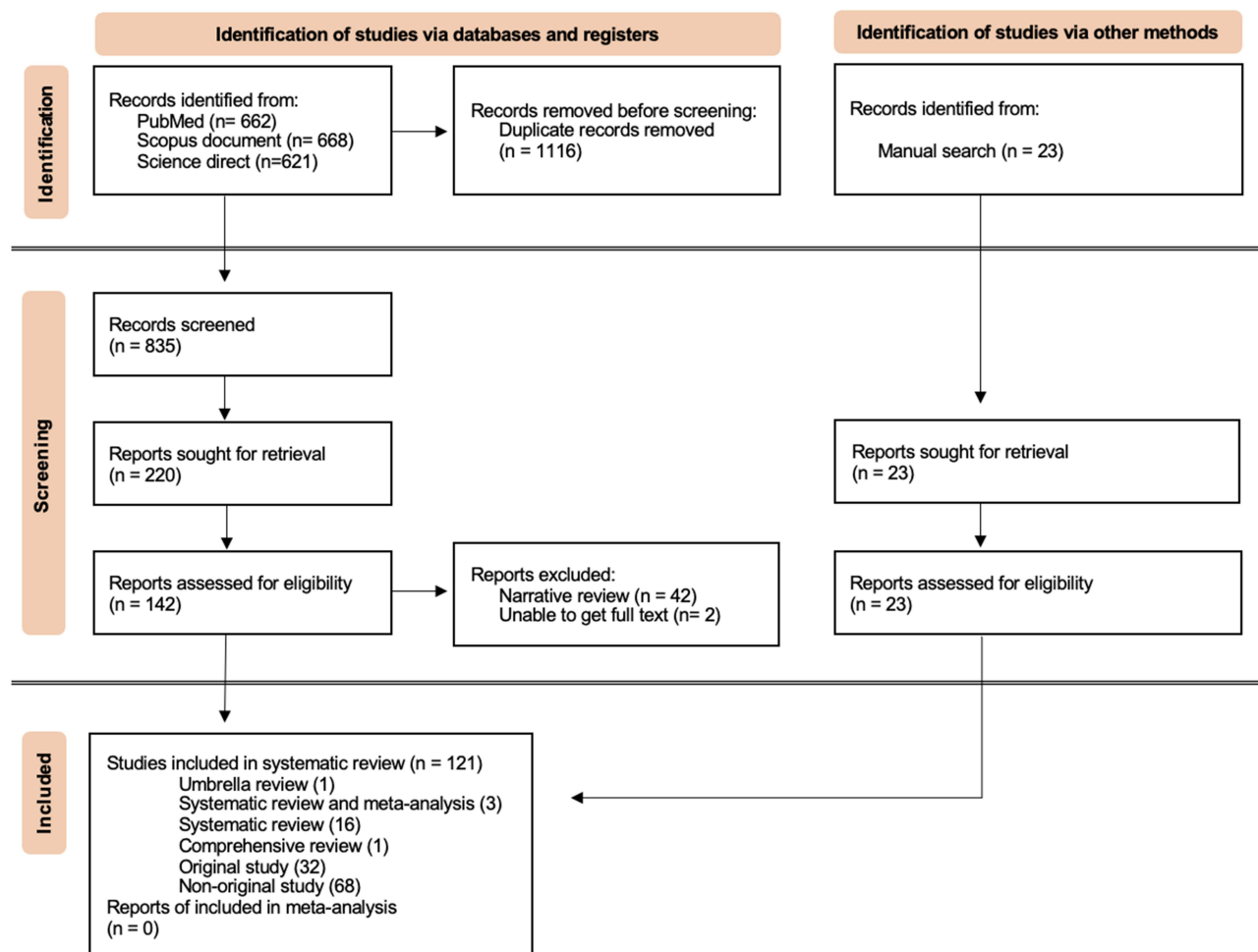


Figure 1 Schematic literature search.

three studies concluded in the urge of further research, including clinical evidence-based research^{30,31} and observational studies¹⁷ to confirm the association between COVID-19 and oral lesions.

The Original Studies Report on Oral Lesions in COVID-19 Patients

Thirty-two original studies include one pilot study, one cohort study, five observational studies, four retrospective studies and fourteen cross-sectional studies (Table 2). The pilot study and cohort study reported all patients with all oral lesions.^{37,38} The observational study reported that the prevalence of oral lesions was 70.34–100% among COVID-19 patients.^{39–44} The prospective study reported oral lesions from all patients.⁴⁵ The retrospective reported 1.70–100% among COVID-19 patients,^{46–50} and the cross-sectional reported 0.67–100% (Figure 2).^{51–68}

The Oral Lesions that Were Found in the Original Studies

Most oral lesions reported in the original study were ulcers.^{37,39,40,42,43,45,48,52,53,60,63,66–68} Some of the cases were found as atrophy,^{42,60} erosion,^{42,48,60} pseudomembrane,^{39,46,59,60,67} vesico-bullous,^{39,43} blister,^{39,67} nodule,⁶⁰ plaque,^{59,60} depapillation,^{39,67,68} macula,^{40,42,45,46,60,67} petechiae,⁴³ ecchymosis,⁴³ fissure,³⁹ hematoma,⁴⁸ swelling and bleeding.⁵⁰ The patient was distributed equally between men and women aged 1–88 (Table 3).

Table 1 A Systematic and Meta-Analysis Result of Correlation Between COVID-19 and Oral Manifestation

Type of Study	Conclusion	Reference
A systematic review of systematic reviews	The presence of oral lesion cannot make an accurate estimation of the prevalence of lesions, the association with COVID-19 severity and occurrence in the natural history of the disease.	[22]
Systematic review and meta-analysis	Dry mouth was the most prevalent oral health condition, followed by oral lesions, orofacial pain, and periodontal symptoms	[21]
Systematic review and meta-analysis	Oral lesions in COVID-19 patients were identified and further observational studies focusing on this issue and on the causal relationships between oral lesions and COVID-19 are needed	[17]
Systematic review and meta-analysis	More studies will be necessary to confirm oral lesion association with direct SARS-CoV-2 infection in the oral cavity.	[30]
Systematic review	The SARS-CoV-2 virus may infect oral mucosa in small numbers of patients with specific oral mucosa findings have been reported.	[19]
Systematic review	It is not clear that oral signs are due to COVID-19 infection itself or are the result of extensive treatment regimen followed.	[27]
Systematic review	Multisystemic inflammatory syndrome in children and Kawasaki disease share the same oral manifestations and their identification may lead to an early diagnosis.	[18]
Systematic review	The ulcerated oral lesions may have relationship with mild to moderate symptoms for COVID-19 or had acute COVID-19.	[29]
Systematic review	The effect on oral mucosa is unclear	[24]
Systematic review	Oral manifestations in SARS-CoV-2 infection cannot be clearly established due to the possible association of other factors, eg, individual or environmental factors.	[16]
Systematic review	A wide variety of orofacial mucocutaneous lesions manifest in COVID-19 likely to be secondary to the disease-associated immune impairment and/or pharmaco-therapy rather than a direct result of SARS-CoV-2 infection	[28]
Systematic review	Clinical evidence-based studies are required to investigate the actual prevalence and possible correlation between COVID-19 and jaw-related disorders.	[31]
Systematic review	SARS-CoV-2 infection-related immunosuppression, steroid therapy, as well as comorbidities such as diabetic hyperglycaemia appear to be the major predisposing factors for the onset of oral and maxillofacial mycoses in patients with COVID-19 across all age groups.	[32]
Systematic review	Very heterogeneous denominations on primary oral lesions emerged from the data extracted	[33]
Systematic review	The development of ulcers are alterations that are related to moderate to severe COVID-19.	[14]
Systematic review	It is important to discriminate between lesions or alterations that actually develop from SARS-CoV2 and the alterations that the patient already had.	[15]
Systematic review	The oral lesion could be related directly to COVID-19, while the latter could be caused by medical devices, treatments, prone position, and immunological impairment.	[15]
Systematic review	The oral mucosal lesions found at various locations within the oral cavity	[26]
Systematic review	Amidst the SARS-CoV-2 pandemic in which many doubts about the disease still remain, caution is needed when evaluating patients and establishing correlations with other diseases that could be associated	[25]
Systematic review	The manifestations of the SARS-CoV-2 infection in the oral cavity are non-specific.	[34]
Systematic review	Oral mucosal lesions are more likely to present as coinfections and secondary manifestations with multiple clinical aspects	[35]
Comprehensive review	Current scientific evidence still could not affirm that most of the oral lesions observed in patients with COVID-19 are related to the virus's direct or indirect action on the oral mucosa	[36]

Underlying Disease and No Medication-Related

Underlying disease, such as diabetes mellitus and hypertension, is reported as a common condition found,^{42,44,45,56,57} followed by hyperthyroidism,⁴² coronary artery disease,^{44,56} bronchial asthma⁵⁶ and myocardial infarct.⁵⁷ While the oral lesions commonly found were ulcers, macula, atrophy,^{42,44,45,49,56,57} erosion and vesicle,^{42,56} crust,⁴² ecchymosis,⁵⁶ nodule⁵⁶ and pseudomembrane.⁴² Three studies did not mentioned details about the underlying disease.^{54,59,64} This condition is found in 18–70 years old patients (Table 4).

Table 2 The Original Study of a Reported Oral Lesion in a COVID-19 Patient

Number of Samples	Number of Patients with Oral Lesion	Original Paper Type	Reference
58	58	Pilot study	[37]
154	154	Cohort study	[38]
123	123	Observational study	[39]
74	58	Observational study	[40]
38	16	Observational study	[41]
713	9	Observational study	[42]
14	14	Observational study	[43]
58	42	Observational study	[44]
338	338	Prospective study	[45]
27	27	Retrospective study	[46]
472	332	Retrospective study	[47]
332	242	Retrospective study	[48]
69	5	Retrospective study	[50]
89	18	Retrospective study	[49]
21	6	Cross-sectional study	[51]
573	117	Cross-sectional study	[52]
895	6	Cross-sectional study	[53]
2870	29	Cross-sectional study	[54]
55	22	Cross-sectional study	[55]
217	139	Cross-sectional study	[56]
100	100	Cross-sectional study	[57]
204	165	Cross-sectional study	[58]
434	40	Cross-sectional study	[59]
500	77	Cross-sectional study	[60]
195	57	Cross-sectional study	[61]
124	112	Cross-sectional study	[62]
1856	470	Cross-sectional study	[63]
402	63	Cross-sectional study	[64]
46	10	Cross-sectional study	[65]
380	12	Cross-sectional study	[66]
109	58	Cross-sectional study	[67]
666	78	Cross-sectional study	[68]

The cohort study showed that the oral lesion found in underlying diseases like hypertension, diabetes mellitus, obesity, pulmonary diseases, hypothyroidism, AIDS, and dyslipidemia was ulcers, pseudomembranous, depapilation, erosions and crusts.³⁸

The Medication-Related

The medication-related to oral lesions reported was anti-viral, anti-malaria (hydroxychloroquine), antibiotic and corticosteroid. The skin lesion was found as exanthema, and the oral lesion was anathema (macula and petechiae)⁵¹ (Table 5).

One report mentioned that a skin dan oral lesion was found in the patient without any underlying disease or medication-related. The oral lesions were ulcers, depapilation, crust, pseudomembrane and macula, while the skin lesion was exanthema⁶⁵ (Table 6).

Underlying Disease and Medication-Related

Related to underlying diseases, diabetes mellitus is reported as a common condition found,^{41,58,61,62} and hypertension,^{41,55,58,61,62} cardiovascular disease,^{41,58,62} asthma,^{55,58,61} obesity^{41,58} and renal disease.^{41,62} The medication-

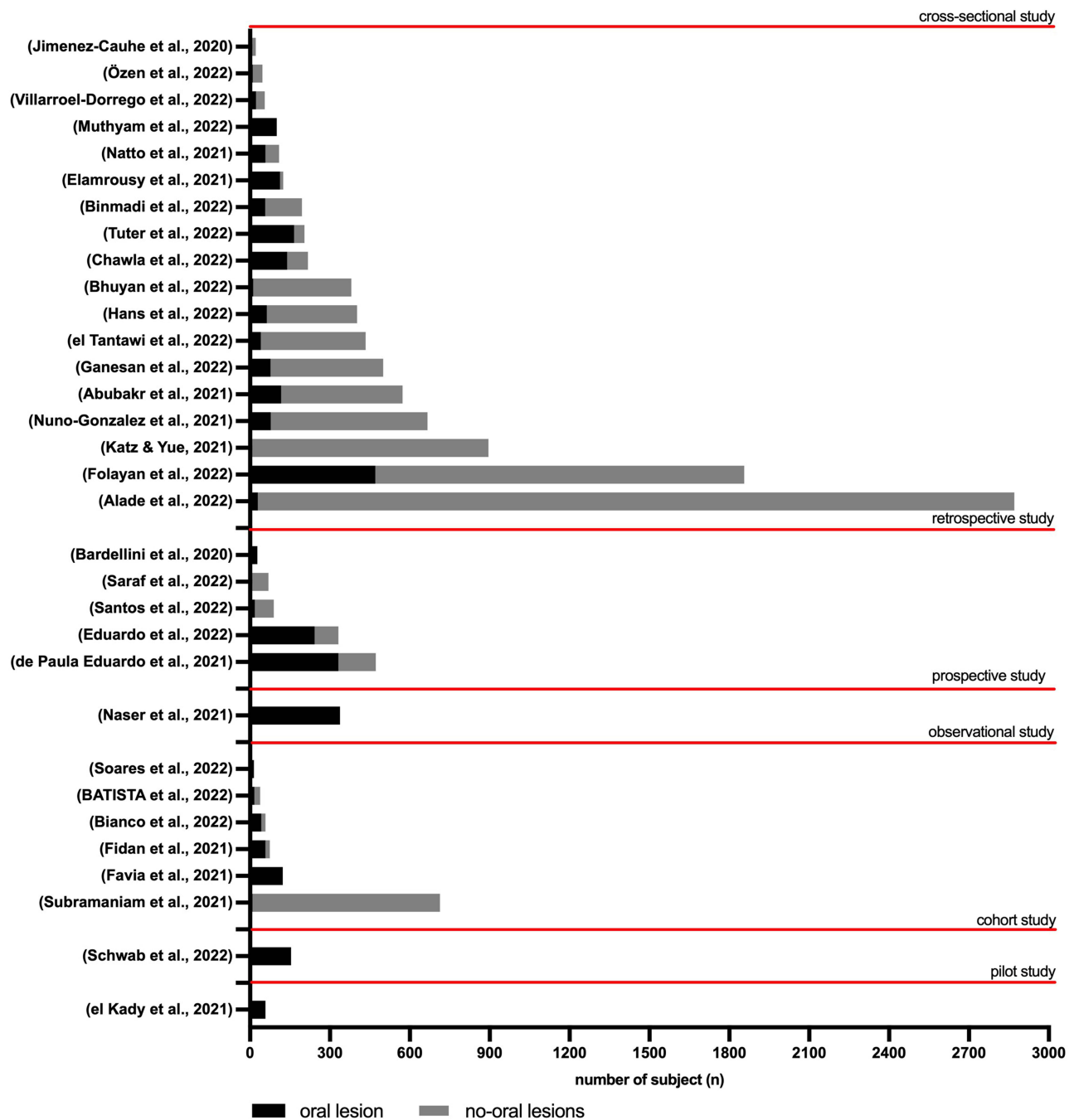


Figure 2 The large-scale study reported the number of cases of COVID-19 and those with oral lesions.

related to the oral lesion was antibiotic,^{41,62} anticoagulant,^{41,62} antimalarial,^{58,62} antiviral,^{55,58,62} and corticosteroids.^{41,55,62} Other underlying diseases and medications are listed in Table 7.

The oral lesion was found as an ulcer,^{41,55,58,61,62} atrophy, pseudomembrane,^{55,61,62} erosion,^{41,55,61} macula,^{55,62} petechiae^{61,62} vesico-bullous,^{61,62} crust, depapilation, ecchymosis, and⁴¹ papule.⁵⁵

The Non-Original Studies Report on Oral Lesions in COVID-19 Patients

The non-original research was 39 case reports (70 cases),^{10,69–106} 6 case series (64 cases),^{107–112} 18 letters to the editor (23 cases),^{113–130} 2 correspondences (2 cases)^{131,132} and 3 clinical images (3 cases)^{133–135} (Table 8).

Table 3 The Original Study of an Oral Lesion in a COVID-19 Patient without Underlying Disease and Mediation Related

Gender (n or %)	Ages	Oral Lesions	Reference
M (31) F (27)	≤30	Ulcers Macule Bleeding	[39]
	>30	Ulcers Macule Bleeding	
M (70) F (53)	63–81	Ulcers Pseudomembrane Petechiae Depapilation Blisters Bullous Fissure	[39]
M (38) F (20)	52.8	Ulcer Macula	[40]
F	60	Ulcers	[42]
	65	Erythema Atrophy Erosion	
M (10) F (4)	23–88	Ulcers Petechiae Vesicobullae Ecchymosis	[43]
M	42.1	Ulcer	[45]
F		Macula Vesicobullae	
M (9) F (8)	4.2	Pseudomembrane Macula	[46]
M (64.5%) F (35.5%)		Ulcers Erosion Hematoma Petechiae	[48]
M	1–12	NS	[49]
F			
M	18–24	Swelling	[50]
F		Bleeding	
F (408) M (165)	36.19	Ulcers	[52]
F	10–17	Ulcers	[53]
	18 – 34		
M (367) F (133)	53	Ulcers Macules Erosion Pseudomembrane Plaque Nodule Atrophy	[60]
M (37%) F (62.3%)	34	Ulcers	[63]

(Continued)

Table 3 (Continued).

Gender (n or %)	Ages	Oral Lesions	Reference
M	57 –68	Ulcers	[66]
F			
M	39.1	Ulcers	[67]
F		Macules Depapilation Pseudomembrane Blister	
M	55.67	Ulcers	[68]
F		Depapilation	

Abbreviations: NS, not mentioned specifically.

Table 4 The Original Study of an Oral Lesion in a COVID-19 Patient with an Underlying Disease

Gender (n or %)	Ages	Underlying Disease	Medication	Oral Lesions	Reference
M (59.7%) F (40.3%)	20–88	Hypertension Diabetes mellitus Obesity Pulmonary diseases Hypothyroidism AIDS Dyslipidemia	NR	Ulcers Pseudomembranous Depapilation Erosions Crusts	[38]
F	50–70	Hypertension Hyperthyroidism	NR	Ulcers Pseudomembrane Maculae Erosion Crusts	[42]
M	43–69	Diabetes mellitus	NR	Ulcers Atrophy Erosion Vesicle	
M (28) F (20)	63.3	Diabetes mellitus Hypertension Coronary arterial disease Kidney disease Neoplasia Obesity	NR	Ulcers Pseudomembrane Fissure	[44]
M F		Diabetes mellitus Hypertension Respiratory disease Heart disease Liver disease Renal disease Blood disease	NR	Ulcers Macula Vesicobulous	[45]
M F	1–12	Gastrointestinal disease NS	NR	NS	[49]

(Continued)

Table 4 (Continued).

Gender (n or %)	Ages	Underlying Disease	Medication	Oral Lesions	Reference
M (66)	18–23 (138)	NS	NR	Ulcers	[54]
F (104)	15–17 (12)				
	11–14 (20)				
M (71.4%)	18–49 (138)	Hypertension	NR	Ulcers	[56]
F (28.6%)	50–60 (80)	Coronary artery disease		Erythema	
	> 60 (25)	Diabetes mellitus		Macula	
		Bronchial asthma		Erosion	
				Nodule	
				Vesicles	
				Ecchymosis	
				Atrophy	
M (51)	> 35 (54)	Myocardial infarc	NR	Ulcers	[57]
F (49)	< 35 (46)	Diabetes mellitus		Atrophy	
		Hypertension			
M (41.5%)	NR	NS	NR	Ulcers	[59]
F (58.5%)				Pseudomembrane	
				Plaque	
M (55.56%)	47	NS	NR	Ulcers	[64]
F (44.44%)					

Abbreviations: NS, not specified mention; NR, not reported.

Table 5 The Original Study of an Oral and Skin Lesion in a COVID-19 Patient with Medication-Related

Gender (n or %)	Ages	Underlying Disease	Medication	Oral Lesions	Skin Lesion	Reference
NS	40–60	NR	Lopinavir/ritonavir Hydroxychloroquine Azithromycin Tocilizumab Corticosteroids	Macula Petechiae	Exanthema	[51]

Abbreviation: NR, not reported.

Table 6 The Original Study of an Oral and Skin Lesion in a COVID-19 Patient without Underlying Disease and Medication-Related

Gender (n or %)	Ages	Underlying Disease	Medication	Oral Lesions	Skin Lesion	Reference
M (3)	3–8	NR	NR	Ulcers	Exanthema	[65]
F (7)				Depapilation Crust Pseudomembrane Macula		

Abbreviation: NR, not reported.

No Underlying Disease and Medication

The oral lesion in COVID-19 patients without any underlying disease and medication was reported as not different based on age and gender. Demographic analysis shows that the studies involved 30 females and 29 males ranging from 16 to 78 years old. For the female, the youngest patient was reported as 16 years old,¹⁰⁹ and the oldest was 78.¹²⁷ Generally, ulcerations occur most frequently in the oral cavity of COVID-19 patients, whether in single or multiple

Table 7 The Original Study of an Oral Lesion in a COVID-19 Patient with Underlying Disease and Medication-Related

Gender (n or %)	Ages	Underlying Disease	Medication	Oral Lesions	Reference
M (6) F (10)	44–93	Hypertension Diabetes Cerebrovascular disease Renal disease Cardiac disease Obesity	Antibiotic Corticosteroids Anticoagulant	Ulcers Crusts Erosion Depapillation Ecchymosis	[41]
M (54.5%) F (45.5%)	21–89	Hypertension Hypertension and Diabetes Mellitus Asthma	Dexamethasone Remdesivir Lopinavir Ritonavir	Ulcers Erythema Pseudomembrane Erosion Macule Plaques Papule Atrophy Ulcers	[55]
M (76) F (128)	≤ 30 (43) 31–60 (87) > 60 (74)	Hypertension Cardiovascular disease Diabetes mellitus Asthma Rheumatoid arthritis Obesity Thyroid disorders	Favipiravir Hydroxychloroquine Pain killer	Ulcers	[58]
M (48) F (147)	18–24 (64) 25–34 (64) 35–44 (41) 45–54 (13) >55 (13)	Hypertension Allergic Hyperthyroid Diabetes mellitus Asthma Epileptics Depressants Osteoarthritis Benign condition	Antihypertension Antihistamines Thyroid medication Antidiabetics Anti-asthmatics Proton pump inhibitors Nutritional supplements Antiepileptics Antidepressants Osteoarthritis medication Benign prostatic hyperplasia medication Hormone replacements Laxatives	Ulcers Petechiae Pseudomembrane Vesiculobullous Atrophy Erosion	[61]
M (92) F (32)	50.32 ± 12.47	Hypertension Diabetes mellitus Renal disease Liver disease Cardiac	Zithrocin Iverzine Vitamin C Zinc Anticoagulant Prednisolone Antibiotic Remdesivir Foradil Hydroxychloroquine colchicine Acetylcysteine Silymarin	Ulcers Vesicula Pseudomembrane Macule Atrophy Petechiae	[62]

ulcers,^{93,107,109,112,124,127,135} vesiculobullous,¹³¹ edematous,¹¹⁴ necrosis,¹¹⁴ bleeding,^{94,114} depapillation,¹²⁷ macula,¹²⁷ erosion,¹²⁷ pseudomembrane¹²⁷ and non-white specific lesion.¹²⁴ The most common site was the tongue, lips or labial, gingiva, palatal, buccal and commissure of the lips (Table 9).

Table 8 The Individual Case of Oral Lesion in COVID-19 Patient

Number of Patient	Type of Paper	Reference
1	Case report	[69]
1	Case report	[70]
4	Case report	[71]
1	Case report	[72]
1	Case report	[73]
1	Case report	[74]
1	Case report	[75]
1	Case report	[76]
1	Case report	[77]
1	Case report	[78]
1	Case report	[79]
1	Case report	[80]
1	Case report	[81]
1	Case report	[82]
1	Case report	[83]
1	Case report	[84]
1	Case report	[85]
1	Case report	[86]
1	Case report	[87]
1	Case report	[88]
3	Case report	[89]
4	Case report	[90]
3	Case report	[91]
3	Case report	[92]
6	Case report	[93]
6	Case report	[94]
3	Case report	[95]
1	Case report	[96]
1	Case report	[97]
1	Case report	[98]
1	Case report	[99]
4	Case report	[100]
5	Case report	[101]
1	Case report	[102]
1	Case report	[103]
1	Case report	[10]
1	Case report	[104]
1	Case report	[105]
1	Case report	[106]
8	Case series	[107]
4	Case series	[108]
26	Case series	[109]
3	Case series	[110]
2	Case series	[111]
21	Case series	[112]
1	Letter to editor	[113]
1	Letter to editor	[114]
2	Letter to editor	[115]
1	Letter to editor	[116]
2	Letter to editor	[117]

(Continued)

Table 8 (Continued).

Number of Patient	Type of Paper	Reference
1	Letter to editor	[118]
1	Letter to editor	[119]
2	Letter to editor	[120]
1	Letter to editor	[121]
1	Letter to editor	[122]
1	Letter to editor	[123]
1	Letter to editor	[124]
1	Letter to editor	[125]
1	Letter to editor	[126]
3	Letter to editor	[127]
1	Letter to editor	[128]
1	Letter to editor	[129]
1	Letter to editor	[130]
1	Correspondence	[131]
1	Correspondence	[132]
1	Clinical image	[133]
1	Clinical image	[134]
1	Clinical image	[135]

Table 9 The Oral Lesion in COVID-19 Patients without Systematic Condition and Medication

Number	Gender	Ages	Oral Lesions	Location	Reference
1	F	16	Multiple ulcers	Tongue	[109]
1	F	16	Ulcer	Labial	[112]
1	F	17	Ulcer	Buccal	[112]
1	F	19	Multiple ulcers	Tongue	[109]
1	F	19	Multiple ulcers	Tongue	[109]
1	F	19	Multiple ulcers	Tongue	[109]
1	F	20	Ulcer	Buccal	[112]
1	F	21	Multiple ulcers	Tongue	[109]
1	F	23	Vesiculobulous	Lips	[131]
1	F	24	Ulcer	Tongue	[109]
1	F	24	Ulcer	Tongue	[112]
1	F	25	Ulcer	Gingiva	[112]
1	F	25	Multiple ulcers	Tongue	[109]
1	F	26	Ulcer	Buccal	[112]
1	F	27	Ulcer	Labial	[112]
1	F	27	Ulcer	Palate	[112]
1	F	29	Multiple ulcers	Tongue	[109]
1	F	29	Multiple ulcers	Tongue	[109]
1	F	29	Multiple ulcers	Tongue	[109]
1	F	32	Multiple ulcers	Tongue	[109]
1	F	32	Multiple ulcers	Tongue	[107]
1	F	35	Edematous Necrotic Bleeding	Gingiva	[114]
1	F	36	Ulcer	Tongue	[109]
1	F	37	Multiple ulcer	Tongue	[109]

(Continued)

Table 9 (Continued).

Number	Gender	Ages	Oral Lesions	Location	Reference
4	F	< 40	Ulcer	Gingiva	[93]
1	F	40	Multiple ulcers	Palatal	[124]
			Non-specific white lesions		
1	F	42	Multiple ulcers	Tongue	[109]
1	F	43	Multiple ulcers	Tongue	[109]
1	F	43	Ulcers	Tongue	[127]
			Depapilation		
1	F	43	Ulcer	Buccal	[71]
1	F	45	Multiple ulcers	Palatal	[135]
1	F	57	Multiple ulcers	Tongue	[109]
1	F	66	Hemorrhagic bleeding	Palatal	[94]
1	F	70	Multiple ulcers	Tongue	[109]
1	F	78	Pseudomembrane	Tongue	[127]
			Macula	Commisure	
			Erosion		
1	M	19	Multiple ulcers	Labial	[71]
1	M	19	Ulcer	Buccal	[112]
1	M	19	Ulcer	Pharynx	[101]
1	M	20	Ulcer	Palate	[112]
1	M	22	Swelling	Tongue	[120]
1	M	25	Ulcer	Tongue	[130]
				Pharynx	
				Palatal	
				Gingival	
1	M	28	Ulcers	Labial	[107]
1	M	29	Multiple ulcers	Tongue	[109]
1	M	30	Petechiae	Tongue	[134]
1	M	31	Multiple ulcers	Tongue	[109]
1	M	31	Ulcer	Labial	[112]
1	M	32	Ulcer	Labial	[101]
1	M	33	Ulcer	Mucogingival junction	[71]
1	M	35	Ulcer	Tonsillar pillar	[107]
1	M	37	Multiple ulcers	Tongue	[71]
1	M	37	Multiple ulcers	Tongue	[109]
1	M	37	Ulcer	Buccal	[112]
1	M	38	Multiple ulcers	Tongue	[109]
2	M	< 40	Ulcer	Gingiva	[93]
1	M	41	Multiple ulcers	Tongue	[109]
1	M	44	Pustule	Gingiva	[102]
				Bone Maxilla	
1	M	47	Multiple ulcers	Tongue	[109]
1	M	48	Petechiae	Palatal	[94]
1	M	50	Multiple ulcers	Tongue	[109]
1	M	51	Macula	Oropharynx	[69]
				Palatal	
1	M	53	Swelling	Tongue	[120]
				Floor of the mouth	
1	M	56	Ulcer	Palatal	[89]

(Continued)

Table 9 (Continued).

Number	Gender	Ages	Oral Lesions	Location	Reference
I	F	58	Ulcer Desquamation Crust Papula	Lip Buccal Tongue	[104]
I	M	68	Multiple ulcers	Tongue	[109]
I	M	69	Multiple ulcers	Tongue	[109]
I	M	NS	Ulcer	Labial Tongue	[106]

Abbreviation: NS, not mentioned specifically.

For the male, the youngest patient was reported as 19 years old,⁷¹ and the oldest was 69 years old.¹⁰⁹ One study did not mention the details of patients' ages.¹⁰⁶ The oral lesion was reported as an oral ulcer as the typical lesion,^{71,89,93,95,101,104,107,109,130} swelling,¹²⁰ petechia,^{94,134} macula,⁶⁹ desquamation, crust and papula¹⁰⁴ and also pustula.¹⁰² The most common site was the tongue, labial mucosa, gingiva, palatal, oropharynx, and floor of the mouth (Table 9).

Oral lesions and skin lesions were also observed in the patient with COVID-19. The oral lesion was ulcer,^{76,98,117,118,122,127} erosion and hemorrhagic crust,⁹⁸ blister,⁹⁸ depapilation,⁷² desquamation¹¹⁷ and erythema^{76,117}—the skin lesion including the erythematous macula, urticaria, exanthema and perioral ulcer (Table 10).

The Medication-Related

The oral lesion of COVID-19 was also related to medication. Antibiotics and analgesics were reported to be the most used drugs for COVID-19 patients. Antibiotics include amoxicillin-clavulanic,¹⁰¹ azithromycin,^{73,77,81,83,101,116,126} moxifloxacin,⁹¹ levofloxacin,⁷⁷ penicillin,⁹⁶ ceftriaxone,⁹⁵ cefixime,¹¹⁰ piperacillin-tazobactam,¹⁰⁰ doxycycline¹⁰⁰ and cefadroxil¹⁰⁵ (Table 11).

The anti-inflammatory and antipyretic drugs include dipyron,^{83,113} acetaminophen,^{90,96,101,119,132} ibuprofen,⁸¹ acetylsalicylic acid,⁷⁷ paracetamol^{73,95,101} Steroids also prescribe dexamethasone,^{77,111,113} prednisone⁷⁷ and methylprednisolone.¹⁰⁰ Other types of drugs include proton pump inhibitors,⁹¹ anti-malaria,^{73,95,116} anti-virus,^{73,100,116}

Table 10 The Oral Lesion with Skin Lesion in COVID-19 Patients without Underlying Disease and Medication

Number	Gender	Ages	Oral Lesions	Location	Skin Lesion	Reference
I	F	30	Erosions & hemorrhagic crusts Ulcers Blisters	Lips Palatal Tongue Buccal Pharynx	Bilateral itchy erythematous macules with rounded erythema	[98]
I	F	30	Depapilation	Tongue	Urticarial rash on her abdomen, legs, and hands	[72]
I	F	31	Multiple ulcers	Tongue Labial	Skin rash	[118]
I	F	46	Ulcer	Tongue	Erythematous in the toe	[122]
I	M	3	Desquamation	Gingiva	Exanthema	[117]
I	M	6	Crust	Lips	Rash of the extremities	[117]
I	M	38	Erythema Ulcer	Tonsillar	Maculopapular rash on trunk	[76]
I	M	53	Ulcer	Commisure	Perioral ulcer	[127]

Table 11 The Oral Lesion in COVID-19 Patients Related to Medication

Gender	Ages	Drug	Oral Lesions	Location	Reference
F	3	Amoxicillin-clavulanic Acetaminophen Ibuprofen Bronchodilator	Depapilation	Tongue	[101]
F	18	Paracetamol Azithromycin Vitamin C Zinc Lactoferrin Dextromethorphan	Depapilation	Tongue	[101]
F	20	Azithromycin Dipyron	Crust	Lip	[83]
F	23	Azithromycin Acetaminophen Vitamin C Zinc	Ulcer	Pharynx	[101]
F	25	Moxifloxacin Pantoprazole Multivitamin	Macula	Tongue	[91]
F	37	Dexamethasone Dipyron	Macula Depapilation	Tongue	[113]
F	41	Acetaminophen Fexofenadine	Bulla	Palatal	[90]
F	55	Acetaminophen	Bulla	Tongue	[90]
F	88	Azithromycin Prednisone Levofloxacin Dexamethasone Acetylsalicylic acid Acetylcysteine Ipratropium bromide	Ulcers Pseudomembrane	Lip all oral mucosa	[77]
M	25	Paracetamol	Bleeding	Gingiva	[95]
M	30	Hydroxychloroquine Ceftriaxone Enoxaparin	Bleeding	Gingiva	[95]
M	33	Ivermectin Azithromycin	Ulcer	Labial Buccal	[126]
M	34	Ivermectin Doxycycline Remdesivir Methylprednisolone Enoxaparin	Ulcer	Tongue	[100]
M	42	Acetaminophen	Macule	Palatal	[90]
M	42	Piperacillin-tazobactam Doxycycline Favipiravir	Ulcers	Palate	[100]
M	43	Steroids	Ulcer	Palatal	[94]
M	44	Vitamin B	Bleeding	Gingiva	[95]

(Continued)

Table 11 (Continued).

Gender	Ages	Drug	Oral Lesions	Location	Reference
M	55	Dexamethasone Colchicine Acetylcysteine Apixaban Omeprazole Mirtazapine Vitamins	Ulcers Pseudomembranous	Labial Palatal Tongue Oropharyngeal	[111]
M	68	Ceftriaxone Remdesivir Methylprednisolone Enoxaparin	Depapilation	Tongue	[100]

antihistamine,⁹⁰ mucolytic,^{77,101,111} anticholinergic,⁷⁷ anti-coagulant,^{95,96,100,111} antiparasitic,¹²⁶ anti-gout,¹¹¹ anti-gerd,¹¹¹ anti-depressant^{110,111} and multivitamin^{73,81,91,95,101,105,111} (Table 11).

The use of medication during COVID-19 treatment also has a side effect on the oral mucosa as oral lesions, observed in male and female patients in diverse age groups. In the female, the oral manifestation was crust,^{83,101} macula,¹¹³ depapilation,^{100,101,113} bullous,⁹⁰ ulcer^{77,101} and pseudomembrane.⁷⁷ In the male, there was depapilation,¹⁰⁰ bleeding,⁹⁵ ulcers,^{94,100,111,126} macula⁹⁰ and pseudomembrane¹¹¹ (Table 11).

Oral lesion-related medication is sometimes also found with a skin lesion. The most common lesion was ulcer,^{73,81,96,105,110,116,119} crust,^{96,105,116,132} macula,¹³⁶ vesicle,¹³² and vesiculobullous,⁹⁶ with skin lesions in the form of petechiae,⁸¹ macula,^{96,110,119} papula,^{96,119,132} exanthem^{73,110} and targetoid lesions.¹¹⁶ The oral lesion mostly affected on lip,^{96,105,116,119,132} while others were on other mucosae⁷³ (Table 12).

Table 12 The Oral and Skin Lesion in COVID-19 Patients Related Medication

Gender	Ages	Drug	Oral Lesions	Location	Skin Lesion	Reference
F	26	Acetaminophen	Ulcer	Lip	Maculopapular rash	[119]
F	32	Cefadroxil Benostamin Etabion Alphamol Vitamin	Ulcer Crust	Labial Lip	Macula	[105]
F	38	Hydroxychloroquine Azithromycin Oseltamivir	Ulcer Crust	Lip Tongue	Erythematous targetoid lesions	[116]
F	40	Ibuprofen Azithromycin Vitamin D2	Petechiae Ulcer Pseudomembranous Macula	Lip Gingiva Tongue	Petechiae	[81]
M	9	Acetaminophen	Vesicles Erosions Crust	Lips Tongue Buccal	Deep red, edematous papules and plaques involving the dorsal hands and feet	[132]

(Continued)

Table 12 (Continued).

Gender	Ages	Drug	Oral Lesions	Location	Skin Lesion	Reference
M	17	Penicillin Acetaminophen Nadroparin calcium	Bullous Erosive Vesicubullous Ulcerations with crusts	Lips Labial	Dark red, purpuric, irregular maculopapular lesions on abdomen	[96]
M	29	Azithromycin Paracetamol Hydroxychloroquine Oseltamivir Vitamin C Vitamin D	Ulcer	Mucosa	Viral Exanthem	[73]
M	64	Tianeptine Trazodone Cefixime	Hemorrhagic ulcers	Lips	Viral exanthem/ macules	[110]

Underlying Disease

Underlying Disease and No Medication-Related

Oral lesions found in the COVID-19 patient with the underlying disease were also reported. Most of the lesion was ulcer,^{42,74,85,89,99,110,123} vesicle,^{42,80} erythema,^{42,80} pseudomembrane,⁴² erosion,^{42,80} crust^{42,111} and atrophy.^{42,94} Other lesions were depapillation,⁷⁴ oedema,⁴² macule,⁴² petechiae⁹⁴ and plaque¹⁰³ (Table 13).

The underlying disease found in men and women was different. Most hypertension,^{42,80,89} diabetes mellitus,^{42,85,89,111} hyperthyroidism,^{42,74} osteoarthritis,⁸⁰ hypothyroidism,¹¹¹ rheumatoid arthritis,⁹⁴ severe dystonia,¹²³ epilepsy,¹²³ arterial hypertension,¹¹⁰ chronic hepatopathy,¹¹⁰ hypercholesterolemia,¹¹⁰ gastroesophageal reflux disease,¹¹⁰ HIV¹⁰³ and asthma⁹⁹ (Table 13).

Table 13 The Oral Lesion Found in COVID-19 Patient with Underlying Disease

Number	Gender	Ages	Underlying Disease	Oral Lesions	Location	Reference
I	F	23	HIV	Plaque	Oral mucosa	[103]
I	F	49	Hypertension Osteoarthritis Maxillary sinusitis	Vesicles Erythema	Palate	[80]
I	F	50	Diabetes mellitus	Ulcers	Palate	[85]
I	F	58	Diabetes mellitus type 2 Hypothyroidism	Hemorrhagic crusts	Tongue Lips	[111]
I	F	59	Rheumatoid arthritis	Atrophy Petechiae	Tongue Whole mouth	[94]
I	M	9	Severe dystonia Epilepsy	Ulcers	Labial	[123]
I	M	24	Hyperthyroidism	Ulcers Depapillation	Labial	[74]
I	M	24	Asthma	Ulcers	Labial Buccal	[99]
I	M	58	Diabetes mellitus Hypertension	Ulcers	Palate	[89]
I	M	68	Arterial hypertension Chronic hepatopathy Hypercholesterolemia Gastroesophageal reflux disease	Hemorrhagic ulcers	Tongue	[110]

One study only reported oral and skin lesions found in COVID-19 patients with underlying disease. The males of 60 and 63 years old with chronic cholecystitis, renal cyst, and inguinal hernia found an erosive and radiating stria in the buccal and tongue. In contrast, the skin lesion was found as a pruritic macule in the arm's skin, arm and flexure surface⁷⁹ (Table 14).

Underlying Disease and Medication-Related

The case presented 13 females with a range of 42–84 years old and 14 males with a range of 46–86 years old. The underlying disease frequently reported was diabetes mellitus,^{84,87,91,92,94,95,107,115,129} hypertension,^{70,82,84,87,90,92,94,95,100,107,108,115} stroke,¹⁰⁰ obesity,^{47,84,92,107} CVD,^{82,121,129} hypothyroidism,^{92,108,129} COPD,^{92,100,107} carcinoma,^{92,107} renal disease^{92,107} and cardiac disease.¹⁰ Other conditions such as rheumatoid arthritis,⁹¹ allergies,⁹⁴ chronic sinusitis,⁷⁰ coronary and peripheral artery disease,⁹² vascular disease,⁹¹ hypercholesterinemia,¹²¹ hyperlipidemia,⁹² pancreatitis,¹⁰⁷ Parkinson's disease,¹⁰⁷ peripheral neuropathy,⁹¹ rectal tumour,¹⁰⁸ HIV,⁷⁸ depression,⁹¹ follicular lymphoma,¹²⁵ kidney transplant⁸² and autosomal dominant polycystic kidney disease⁸² were also reported (Table 15).

Most of the prescribed drug was antibiotics,^{47,70,82,87,90,91,107,108,115,121,125,129} anti-coagulant,^{47,82,91,107} anti-viral,^{78,92,100,115} NSAIDs,^{70,90} steroid,^{47,90,92,100,107,125} anti-diabetic,^{94,95} anti-hypertension,^{94,95} or cardiac drug,¹⁰ anti-malaria,^{82,125} anti-allergic,⁹⁴ and bronchodilator.⁷⁰ Another study only mentions intensive care medicine⁸⁴ and covalent plasma administration.⁹² Azithromycin, Ceftriaxone, dexamethasone and remdesivir are antibiotics, steroids and anti-virals that are frequently prescribed (Table 15).

Table 14 The Oral Lesion Accompanies Skin Lesions Found in COVID-19 Patient with Underlying Disease

Number	Gender	Ages	Underlying Disease	Oral Lesions	Location	Skin Lesion	Reference
I	M	60	Chronic cholecystitis Renal cyst Inguinal hernia	Erosive	Buccal Tongue	Pruritic macule on skin arm	[79]
I	M	63	Chronic cholecystitis Renal cyst Inguinal hernia	Erosive Radiating striae	Buccal Tongue	Brown pruritic macules on the flexure surface of the arm	[79]

Table 15 The Oral Lesion is Found in COVID-19 Patient with Underlying Disease and Medication Related

Number	Gender	Ages	Underlying Disease	Drug	Oral Lesions	Location	Reference
I	F	42	Hypothyroidism CVD Diabetes mellitus	Levothyroxine Azithromycin Linezolid Ceftriaxone	Pseudomembrane White plaques	Tongue Palate	[129]
I	F	50	Obesity Hypertension Diabetes mellitus	Intensive care medication	Crusted	Lip	[84]
I	F	51	Hypertensions	Dexamethasone Azithromycin Indomethacin	Macule Papule-plaque	Palate	[90]
I	F	56	Hypertension Chronic sinusitis	Azithromycin Levofloxacin Montelukast Naproxen Acetaminophen	Vesicles	Lip mucosa	[70]

(Continued)

Table 15 (Continued).

Number	Gender	Ages	Underlying Disease	Drug	Oral Lesions	Location	Reference
1	F	56	Diabetes mellitus Rheumatoid arthritis	Azithromycin	Pseudomembrane	Labial Palate Tongue	[91]
1	F	56	Diabetes mellitus	Remdesivir azithromycin	Ulcers	Palate	[115]
1	F	70	Depression Peripheral neuropathy Vascular disease	Azithromycin Levofloxacin Rivaroxaban Lactoferrin	Pseudomembrane	Tongue Mouth Floor Palate Oropharynx Buccal	[91]
1	F	70	Obese	Remdesivir Dexamethasone Methylprednisolone	Ulcer Pseudomembrane	Tongue Labial	[92]
1	F	71	Hypertension Diabetes mellitus Obesity Renal failure	Azithromycin Ceftriaxone	Hemorrhagic Ulcer	Lip Tongue	[107]
1	F	81	Hypertension COPD	Azithromycin Ceftriaxone	Ulcers Crust	Tongue Lip	[107]
1	F	83	Hypertension Hyperlipidemia Hypothyroidism	Remdesivir Dexamethasone	Ulcer	Tongue	[92]
1	F	83	Obesity Parkinson disease Hypertension Pancreatitis COPD	Piperacillin/ tazobactam Ceftriaxone	Ulcer	Tongue palate	[107]
1	F	84	Hypertension Hypothyroidism Rectal tumor	Piperacillin tazobactam	Ulcer	Lip	[108]
1	M	46	Hypercholesterinaemia CVD	Meropenem azithromycin	Ulcer	NR	[121]
1	M	51	HIV infection	Anti-viral	Ulcer	Gingiva	[78]
1	M	57	Hypertension	Azithromycin Ceftriaxone	Crust	Lip	[108]
1	M	58	Cardiac	Cardiac drug	Depapilation	Tongue	[10]
1	M	62	Diabetes mellitus hypertension	Azithromycin	Ulcer	Tongue	[87]
1	M	67	CVD, Hypertension autosomal dominant polycystic kidney disease kidney transplant	Enoxaparin sodium Hydroxychloroquine sulfate Ceftriaxone sodium Azithromycin Meropeném Sulfamethoxazole Trimethoprim	White plaque Ulcers	Tongue	[82]
1	M	71	Hypertension Diabetes mellitus Allergies	Anti-hypertensive drugs Insulin injections Anti-allergic agents	Erosion Pseudomembrane Ecchymosis	Tongue Palate	[94]

(Continued)

Table 15 (Continued).

Number	Gender	Ages	Underlying Disease	Drug	Oral Lesions	Location	Reference
I	M	72	Diabetes mellitus Hypertension	Piperacillin/ tazobactam	Hemorrhagic	Lips	[107]
I	M	72	Hypertension Diabetes mellitus	Azithromycin Ceftriaxone Anti-hypertensive drugs Anti-diabetic drugs	Hemorrhagic Erosion	Palate Lips	[94]
I	M	75	COPD Coronary and peripheral Artery disease Diabetes mellitus Renal disease Lung carcinoma	Remdesivir Dexamethasone Convalescent plasma	Ulcers	Labial Tongue	[92]
I	M	75	Hypertension	Azithromycin	Ulcers	Tongue	[115]
I	M	78	Follicular Lymphoma	Hydroxychloroquine Steroids Ciprofloxacin tocilizumab.	Ulcer Erosive Plaque	Labial	[125]
I	M	86	Obesity Myeloid sarcoma	Warfarin sodium AAS Axetilcefurs	Ulcers	Lip	[107]
I	M	84	COPD Hypertension Stroke	Meropenem Remdesivir Methylprednisolone Heparin	Ulcer Crust	Lip Labial	[100]

The oral lesion was ulcer,^{47,78,82,87,92,100,107,108,115,121,125} papula-plaque,^{82,90,125,129} pseudomembrane,^{92,94,129} crust,^{84,100,107,108} erosion,^{94,125} hemorrhagic,^{95,107} depapilation,¹⁰ ecchymosis,⁹⁴ macula,⁹⁰ vesicle⁷⁰ and white patches.⁹¹ The location of the lesion dominated in the tongue,^{10,82,87,91,92,94,107,115,129} lip,^{47,70,84,94,100,107,108} palate^{90,91,94,95,129} and labial^{91,92,100,125} (Table 15).

The oral lesion in COVID-19 patients with underlying disease and medication are also found with skin lesions. Six studies reported that the condition consists of three females and two males, ages 41 to 82. The oral lesion found was ulcer,^{86,88,108,110,128} blister and bullae,⁸⁹ crusted,¹⁰⁸ macula¹²⁸ and white patches.¹¹⁰ The skin lesion found as bullae,⁸⁶ rash⁸⁹ and exanthema,¹¹⁰ petechia-like and vesiculobullous.¹²⁸ Other cases reported perioral ulcers⁸⁸ and fungal infection¹⁰⁸ (Table 16).

The underlying disease found was hypertension,^{88,89,108,128} obesity,^{89,110} Hodgkin's lymphoma stage II,⁸⁶ hyperlipidemia,⁸⁸ dyslipidaemia,¹⁰⁸ hypothyroidism,¹⁰⁸ diabetes mellitus,¹²⁸ arterial hypertension,¹¹⁰ myocardial infarction¹¹⁰ and septic shock.¹¹⁰ The medication prescribes like chemotherapy medication,^{86,88} antibiotic,¹⁰⁸ antiviral,^{86,89} antimalarial,⁸⁹ corticosteroid,¹²⁸ anti-vomiting¹²⁸ and anti-hypertension¹¹⁰ (Table 16).

Discussion

COVID-19 patients are reported to suffer from various oral lesions throughout or preceding the disease onset.²⁸ Various questions and hypotheses emerged along with the increasing report of the incidence, especially regarding whether it is a manifestation of the viral infection (causality) or a result of large numbers of unidentified risk factors (casualty). Attempts to analyze the lesions and their correlation to COVID-19 are resulting to thereabouts inconclusive results. Various systematic reviews termed that the lesions are COVID-19 oral manifestations,^{15–17,19,22,24,25,27,28,123} that is also

Table 16 The Oral and Skin Lesion Found in COVID-19 Patient with Underlying Disease and Medication Related

Number	Gender	Ages	Underlying Disease	Drug	Oral Lesions	Location	Skin Lesion	Reference
I	F	43	Hodgkin's lymphoma stage II	Adriamycin Bleomycin Vinblastine Dacarbazine Acyclovir	Ulcers	Oral mucosa	Monomorphic flaccid Bullae over edematous plaques ad erosions on the chest, abdomen, between the scapulas, arms, and thighs	[86]
I	F	65	Obesity Hypertension	Lopinavir Ritonavir Hydroxychloroquine	Blister Bulla	Lip mucosa	Rash under breasts, back, and genital	[89]
I	F	70	Hypertension Dyslipidemia Hypothyroidism	Azithromycin Ceftriaxone	Crust and ulcer	Lip	Fungal infections several areas	[108]
I	F	70	Hypertension Obesity Hypothyroidism	Azithromycin Ivermectin	Crust	Lip	Crust perioral	[108]
I	F	82	Hypertension Hyperlipidemia	NS	Ulcer	Lip	Perioral ulceration	[88]
I	M	42	Diabetes mellitus Hypertension	Dexamethasone Dipyron	Macula Ulcer	Palate Tongue Lip Buccal	Petechiae-like small vesico-bullous	[128]
I	M	61	Obesity Arterial hypertension Myocardial infarction Septic shock	Egiramlon Ebrantil Tenaxum Metoprolol	Hemorrhagic ulcers White patches	Lip Tongue	Viral exanthem on the skin in the form of painless macules	[110]

Abbreviations: NS, not mentioned specifically.

determined by individual and environmental factors,¹⁶ secondary infection and psychosocial factors,^{25,27} immunosuppressive conditions¹⁵ caused by medications^{15,28} and diseases,^{23,24,26,29} or might be as primary direct causality since ACE2 is expressed in the oral cavity.^{15,17,19,22,25–27} We report contradictory findings based on analyses of the patterns of COVID-19 patients with clinical oral lesions and by further breaking down the reported various factors that might be involved. The lesions reported by 70 works of literature were analyzed to see whether they are symptoms or conditions resulting from COVID-19 infection as an oral manifestation or pathognomonic features.

Preceding systematic reviews were summarized to understand the current understanding of oral lesions in COVID-19 patients (Table 1). All systematic reviews give varying conclusion but generally show uncertainty and skepticism towards the concept of oral lesions as COVID-19 manifestation. A meta-analysis also discovered that data on oral lesion prevalence was highly heterogenous, while data on xerostomia show lower heterogeneity,¹⁷ indicating that the most common symptom found on COVID-19 was dry mouth, as also concluded by another review.²¹ A systematic review concludes that oral lesions suffered by COVID-19 patients were very diverse and indistinctive,^{24,34} and mostly unrelated to the SARS-CoV-2 virus.^{17,22,30} The indistinctive lesions would explain the heterogeneity of oral lesion prevalence in COVID-19 patients. Various concepts regarding the correlation between COVID-19 and oral lesions were also stated, such that the virus infected ACE2 receptors in the oral mucosal tissue, thus leading to lesion onset through inflammatory mechanism,^{19,30} and that the lesions might progress along with the disease progression.²⁹ However, despite the statement of direct causality, all these studies mostly concluded the doubt that COVID-19 infection might result in oral manifestations, as no substantial evidence could be found regarding it.¹⁷ These studies suggest that other factors such as

comorbidities,³² medication and immunosuppression^{28,32} are potentially the leading cause of these lesions as various interrelated factors' casualty. This notion led to inconclusive conclusions in these reviews that oral lesions in COVID-19 patients might not be an oral manifestation of the viral infection. Detailed investigation and analysis of these oral lesions and their clinical signs along with COVID-19 patterns is needed to be done on each case published from various case reports, case series, cross-sectional, letters to editors and observational studies to uncover more of the relation between clinical oral lesion with COVID-19 conditions.

A plethora of oral diseases had been found to occur in the oral cavity of patients infected with SARS-CoV-2. We found that oral lesions in COVID-19 are very diverse but mostly in the form of ulcers^{37–43,47,52–57,59–64,71,73,74,76–78,81,82,85–89,92–94,96,98,107–112,115,116,118,119,121–128,131,135} and erosion.^{38,41,42,47,55,56,60,61,80,94,96,98,125,127,132} Some studies also reported an occurrence of recurrent oral lesions, aphthous-like ulcers,⁵³ hemorrhagic ulcers^{38,41,42,83,84,96,107,108,111,116,117,132} and macula (erythema).^{42,55,56,76,80,81,91} While the findings often took place as an ulcer, other oral findings are also found in the form of plaques,^{55,59,60,82,90,125,129} pseudomembrane,^{38,39,42,46,55,59–62,77,81,91,92,94,111,127,129} depapilation,^{38,39,41,72,74,113,127} or bleeding lesion.^{37,94,95,114} Most of these lesions were found in the tongue,^{71,72,79,81,82,87,90–92,94,98,107,109–113,115,116,118,120,122,127–129,132,134} palate,^{80,85,89–91,94,107,112,115,128,129} lip^{70,77,81,83,84,88,89,94,96,98,107,108,110,111,117,119,128,132} and buccal mucosa.^{71,80,98,112,126,128,129,132} In this context, the diversity of types of oral lesions and locations in COVID-19 patients raises a question regarding its causality and casualty. This shows that COVID-19 patients did not show particular clinical patterns and tendencies that could be assumed as pathognomonic lesions of COVID-19.

Unsolved hypotheses of the mechanism of the lesion formation could possibly be solved by analyzing underlying diseases and medications that underwent by COVID-19 patients with oral lesions. Most of these patients have various medical conditions that alter and worsen their immune status to respond to viral infection. We found that most of the patients included in the study suffered from cardiovascular diseases,^{38,41,42,55–58,61,62,70,80,82,84,87–92,94,107,108,110,115,121,128} pulmonary diseases^{38,92} and diabetes,^{38,41,42,55–58,61,62,84,85,87,89,91,92,94,107,111,115,128,129} that could worsen their immune status whether independent or dependent to COVID-19 infection and resulted in the lesion due to wane host defense.¹³⁷ Observations on these patients also show the diversity of the reported underlying diseases that seem to likely be inconsistent and unrelated to the oral lesions. Patients with underlying diseases were separately analysed (Tables 4, 13 and 14) to see whether it could be a key player in the lesion progression, but it was later found that no evident differences in clinical patterns were found in the oral cavity in patients without underlying diseases. This leads to the notion that underlying diseases might not aid the lesion manifesting in COVID-19 patients.

Most patients with underlying diseases received high doses of various medications, like antibiotics,^{41,62} immunosuppressants,^{41,55,62} NSAIDs,⁵⁸ and anti-virals.^{55,58,62} Meanwhile, in patients without underlying diseases who received medications, we found that most of them used antibiotics,^{77,83,91,95,126} NSAIDs,^{83,113} vitamins,^{91,95,111} corticosteroids,^{77,94,111,113} analgesics,^{85,95} and antivirals.⁹⁵ We found that these drugs resulted in mostly ulcers in patients without underlying diseases (Table 11 and Table 15) or with underlying diseases (Table 7), despite the large diversity of the following lesion forms. We also found the same inconclusive lesions in patients without underlying diseases and without medications (Table 4 and Table 9). These drugs may not directly cause the specific manifestation of lesions in COVID-19 patients. Previous systematic reviews stated that steroids could cause immunosuppression that could lead to oral lesion formation.^{15,24,26} Lesions occur in those patients could also occur in non-COVID-19 patients or in patients without steroid prescriptions. This can be inferred that medication is not a plausible factor that could aid COVID-19 manifesting in the oral cavity.

COVID-19 patients often receive multiple medications, which could promote the risk of drug reactions.¹³⁸ Hydroxychloroquine has been used to treat COVID-19 and was reported to be one of the most prevalent erythema multiforme-triggering drugs and various other side effects in patients.^{138–142} The lesion was caused by promoted CD8+ lymphocyte infiltration to the epithelial tissue, thus leading to the necrosis of the cells and subepithelial cleft forming as a hypersensitivity reaction to the drugs consumed.¹⁴⁰ This led to the hypothesis that the crusts suffered by the patients potentially are actually not an oral manifestation of SARS-CoV-2, but probably erythema multiforme, which is the distinct pathognomonic features that also include hemorrhagic crusts along with targetoid lesions on the skin.^{138,142} Our findings highlighted that most of the skin lesion-related medications were exanthema and skin or genital ulceration

(Tables 5, 12 and 16). In contrast, some cases also reported similar skin lesions in the patient without any medication (Tables 6, 10 and 14).

Despite the effort to break down possible influencing factors of oral COVID-19 lesions through underlying diseases and patients' medications, we found no relevance to specific manifestations in the oral tissue. Oral lesions in patients with and without underlying diseases and medications vary with no particular patterns or pathognomonic pattern. The lesions might be resulted from various unidentified interrelated factors with unknown mechanisms, resulting in varying forms of lesions. These lesions are unlikely to be called oral manifestations of COVID-19 since data show clinical signs that are not in accordance with the viral infection itself.

Contrary to previous studies, we also found no correlation between COVID-19 severity and oral lesions.²⁹ Patients with severe COVID-19 symptoms were often to be hospitalized. Oral ulcers in these patients may also occur because of mechanical ventilation and intubation. However, there is no distinguishing oral lesion found in patients with severe COVID-19 symptoms compared to non-hospitalized patients, as both presented with mostly ulcers.⁴¹ This corroborates our statement that oral lesions in COVID-19 patients are not dependent on the viral infection to manifest whether in a mild or advanced stage of the disease. However, despite some studies reported regarding the matter, the number of studies that include the intubation treatment in their reports is limited to make a proper analysis and conclusion to the exact cause of the lesion and how significant the mechanical trauma to the ulcers that reported.

Compared to other diseases with established and distinct oral clinical patterns, such as herpes zoster, primary gingiva stomatitis, and measles, COVID-19 did not show clear and consistent causality to the oral tissue and casualty to form distinct pathognomonic features. Based on the analyses done of the lesions and their clinical patterns, it is difficult and unlikely to conclude that these oral lesions occur as the result of COVID-19 infection, and SARS-CoV-2 does not seem to have any specific manifestations in the oral cavity. We found 121 works of literature (21 reviews, 32 original studies and 68 non-original studies) that could lead to these findings on the inconclusiveness of oral lesions in COVID-19 patients. However, we found irregularity and unclarity in these reports regarding lesion descriptions and terms, such as their type, shape, size, and location. This makes the data heterogeneous and difficult to analyse in a more accurate way. This could be due to the fact that most of the authors who reported the oral lesion in those studies probably were not dentists, let alone oral medicine specialists, thus possibly lead to inaccurate lesion descriptions. The findings of oral lesions in COVID-19 patients has prompted numerous authors to hypothesize that these lesions are attributable to COVID-19 infection itself. Through meticulous analysis on the clinical signs, we found that it is crucial to emphasize that the presence of these lesions does not necessarily establish a causal relationship with COVID-19 infection itself, especially when the clear cause and effect are not found yet. Further comprehensive investigations are imperative to discern potential confounding factors and establish a clearer understanding of the etiology behind these oral lesions in COVID-19 patients. Dentists and oral medicine specialists need an active role in uncovering more about these oral lesions in COVID-19 patients in the future research, especially in its pathogenesis.

On the other hand, it is still debatable whether all reported oral lesions are solely a result of the SARS-CoV-2 infection. One piece of evidence demonstrated that, out of 14 patients, the oral lesions in 13 expressed the spike protein of SARS-CoV-2 and exhibited higher ACE2 expression.⁴³ This indicates the presence of SARS-CoV-2 components in the oral mucosa, but the subsequent processes that occurred have not been determined. Although the study conducted by Soares et al identified the presence of SARS-CoV-2 components within oral lesions, further analyses and investigations involving a larger population of patients and other types of oral lesions are required to comprehensively determine the potential significance and impact of these viral components on oral lesion development. Hence, the direct causality of SARS-CoV-2 in the oral mucosa remains uncertain. Other studies have also corroborated that oral lesions in COVID-19 patients may be secondary lesions associated with trauma events, immune impairment, or adverse reactions to therapeutic interventions.¹⁴³ In the subsequent study, if it can elucidate how the interplay between ACE2, the SARS-CoV-2 spike protein, and the initiation of oral lesions occurs, then the identified lesions can be confidently classified as oral manifestations.

This review has strengths as we conducted comprehensive systematic analyses from various kinds of original and non-original literature. Various types of literature, such as pilot study, cohort, observational, prospective, retrospective, cross-sectional, case reports, case series, and even letters to editor, that report COVID-19 patients with specific oral

lesion conditions were included and analyzed. Through these approaches, detailed analysis and observation on oral lesions on COVID-19 could be done, and a conclusive conclusion could be reached that the lesions that suffered by COVID-19 patients are not oral manifestations of the disease. However, we were unable to determine the bias in this study, as we adhere to descriptive approaches to explain the conformity between oral lesions and COVID-19. Therefore, extensive, and comprehensive research is needed to know the cause of these lesions in COVID-19 patients and discover their pathognomonic features.

Conclusion

Oral lesions in reported studies do not have pathognomonic features and are vary, so in present time they cannot be defined as an oral manifestation. The suspicious factors such as underlying diseases and medications might be classified as predisposing factors. This would arise several possibilities for pathogenesis stacked across one another, making it possible to indirect causality of oral lesion development.

Disclosure

The authors report no conflicts of interest in this work.

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