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ORAL MANIFESTATIONS OF COVID-19:

Systematic review

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ABBREVIATIONS

PCR: Polymerase Chain Reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Covid-19: Coronavirus disease 2019

CS: Cross sectional study

CaS: Case Series

STD: Taste or Smell Disorders

V.A.S: Visual analog scale

NC: Non-communicated

TMJ: Temporo-mandibular joint

DM: Diabetes Mellitus

COPD: Chronic bronchopulmonary disease

CRP: C-reactive protein

LDH: Lactate dehydrogenase

MIS-C: Multi-inflammatory syndrome in children

ENT: Ears-Nose-Throat

ABSTRACT

Introduction: COVID-19 is a viral disease caused by SARS-CoV-2. It was reported among humans for the first time in December 2019, at Wuhan, China. Its general manifestations include fever, asthenia, dry couch, shortness of breath and pneumoniae. Several oral manifestations have been described among positive Covid-19 patients such as macular erythematous lesion, anosmia, dysosmia, ageusia or dysgeusia. However, the origin of the oral mucosa lesions and the causality of Covid-19 is yet to be proven. The aim of this systematic review is to analyze the oral manifestations among Covid-19 positive patients. **Material and methods**: A comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials was conducted from December 2021 to March 2022. **Results:** 11 studies were included among which there were 5 cross-sectional studies, 1 case serie, 3 prospective cohort studies and 2 observational studies. A total of 40 oral manifestations and 15 different locations were reported. The most frequent manifestations were in order ageusia, tongue alteration, anosmia and ulcerative lesions. **Conclusion**: The onset of the oral manifestations occurred at the same time than the systemic ones or developed less than a week after the appearance of the systemic ones. The majority of the patients were aware of the oral lesions. The severity of SARS-CoV-2 infection seemed to be inversely proportional to the appearance of oral manifestations and increase with the age of the patients. The severity of the Covid-19 infection seemed to be related with the gender of the patients, with higher frequency of manifestation in women. Covid-19's severity didn't seem to be associated with the recovery.

KEYWORDS

COVID-19;

Coronavirus; SARS-2; oral;

Mouth;

Oral manifestations;

Oral lesions;

Dysgeusia;

Anosmia;

Ageusia;

Dysosmia;

Oral mucosal lesions.

1. INTRODUCTION

1.1. Genesis of COVID-19

Severe acute respiratory syndrome coronavirus-2 SARS-CoV-2 has been identified as the causative agent for COVID-19, named after Coronavirus disease-2019. [1,2]

The first cases appeared as viral pneumonia from of unknown origin in December 2019, Wuhan, in the province of Hubei, China.[3, 2, 4]

The city of Wuhan is well famous for its developed local fish and wildlife market, the Huanan Seafood Wholesale Market, localized downtown to the city and selling live animals including poultry and wildlife as well. The emergence of the first cases were strongly related to the market making first scientists to think of an infection transmitted through bats. [3, 4]

Early reports suggested that SARS-CoV-2 infected bats through the animal reservoir transmission, being similar in that way to SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (middle east respiratory syndrome coronavirus).

An important fraction of positive cases was obtained from the Western part of the Huanan Seafood Market, location of the animal facilities.[5]

The first known case of a viral pneumonia from unknown etiology was reported on the 8th of December 2019 in Wuhan. The Wuhan Health Commission publically revealed the existence and spread of a viral pneumonia outbreak off unknown etiology on the 31st of December 2019, affecting by this time 27 people mostly related to the Huanan Seafood Wholesale Market, notifying the World Health Organization WHO in the meantime.[3]

On the 8th of December 2019, the onset of the first pneumonia-like syndrome off unknown etiology was recorded in Wuhan, China. [1, 3]

The 31st of December saw the report of the first 27 cases suffering from unknown etiology pneumonia-like syndrome in Wuhan, China.[3]

On 9th of January 2019, the Chinese Center for Disease Control and Prevention announced the identification of a novel coronavirus from admitted patients presenting the pneumonia-like symptoms, being the causative agent responsible for the viral pneumonia-like outbreak. China also confirmed the first case of death by SARS-CoV-2.[1, 3]

The first cases outside of China happened to be confirmed in Thailand on the 13th of January 2020 and Japan on the 16th of January 2020 from travelers that happened to be in Wuhan, Hubei, China during the onset of the outbreak.[4]

On the 20th of January 2020, WHO reported 282 laboratory-confirmed cases as well as 6 deaths in their SITUATION REPORT-1. 1, confirming in the meantime a human-to-human transmission.[3]

On the 30th of January 2020, the SARS-CoV-2 outbreak has been declared as a global public health emergency of international concern PHEIC.

The first case of death abroad China was reported in Philippines on the 2nd of February 2020.[1]

The disease generated by SARS-CoV-2 has been named COVID-19 standing for Coronavirus disease-2019 on the 11th of February 2020 by the International Committee on Taxonomy of Viruses (ICTV).[3]

A few days later, on the 19th of February 2020, WHO made public its SITUATION REPORT-59 with evidence of confirmed cases number exceeding 200,000. Other data were focused on the time required for the SARS-CoV-2 to cause Covid-19 in 100,000 persons. According to the report, it needed a period of time long of 3 months to reach to first 100,000 confirmed Covid-19 cases when it only took 12 days to reach the next 100,000 confirmed cases of Covid-19.

WHO redefined the global status of Covid-19 as a pandemic on the 11th of March 2020, leading a certain amount of protective measures such as social distancing and community or country lockdowns.[1,3, 6]

The SITUATION REPORT-209 issued by WHO on the 16th of August 2020 globally confirmed 21,294,845 cases of Covid-19 accounting for 761,779 deaths, reaching 216 countries and regions from all the six continents with the United States of America, Brazil and India as the largest cumulative number of confirmed cases.[1, 3]

1.2. Genetics of COVID-19

SARS-CoV-2 virus is made out of a single stranded, non-segmented, positive-sense RNA envelope exhibiting a diameter of 50 to 200 nm and a size ranging from 27 to 32 kB, being one of the largest RNA-virus's genomes. The virus anatomical structure is organized thanks to a double lipid layer which includes Spike glycoprotein, an envelope protein, a glycoprotein membrane and a nucleocapsid protein. [2, 6]

Coronaviruses were named after the crown-shaped spikes proteins expressed on the surface.[1]

The anatomy of the outer shell of SARS-Cov-2 given by the spikes proteins resembles protrusions or Peplomers giving a crown-like appearance, "Corona" meaning "crown" in Latin. 3 segments form the Spike protein: the large ectodomain, a transmembrane domain and intracellular trail. Receptor-binding units S1 and S2 belong to the ectodomain area.[2]

The first human discovered coronaviruses happened to be HCoV-229E and HCoV-OC43. Their identification happened in the 1960's and until then it wasn't known that coronaviruses were capable of developing a zoonotic infection. HCoV-229E belongs to the Alpha-coronavirus lineage when HCoV-OC43 belongs to the Beta-coronavirus lineage. [1, 7, 8]

The International Committee on Taxonomy of Viruses realized a taxonomic study of Coronaviridae. SARS-CoV-2 virus belong to the Nidovirales order, the Coronaviridae family which is divided into the four-different genus Alpha-Coronavirus, Beta-Coronavirus, Gamma-Coronavirus and Delta-Coronavirus.

Beta-Coronavirus is further divided into 3 different Lineage. The A lineage comprises the Human Coronavirus-OC43 and Human Coronavirus-HKU1. The lineage B is made of SARS-CoV and SARS-CoV-2. The C lineage is represented by the Middle East Respiratory Syndrome-Cov (MERS-CoV). [1]

Both Alpha and Beta-Coronaviruses are able to infect mammals. Furthermore, human found viruses' express genetic similarities with the Betacoronavirus genus.

During the past 2 decades, betacoronavirus have emerged as risk of global outbreak with three highly pathogenic agents being SARS-CoV, MERS-CoV and SARS-CoV-2.[2]

So far, there have been 7 human-affecting coronaviruses identified, SARS-CoV-2 being the last one. Those human-affecting coronaviruses can be divided into 2 distinct groups according to the pathogenic ability. The group of highly-pathogenic comprises SARS-CoV, MERS-CoV and SARS-CoV-2 while the group of low-pathogenic human-affecting coronaviruses is made of HCoV 229E, NL63, OC43 and HKU1.

MERS-CoV and SARS-CoV were zoonotic infections, passing from the animal range to the humans thanks to mutations. Evidences demonstrated that bats and other species such as rodents caused the infections.[1]

SARS-CoV-2 being third zoonotic infection of the 21st century.[9]

The S protein sequences of SARS-CoV and SARS-CoV2 show 87,2% similarity, 76,2% identity and 2% gaps, with the S protein sequence from SARS-CoV 2 being longer than the one of bat-SARS like coronavirus and SARS-CoV.[7]

The Receptor Binding Domain (RBD) of SARS-CoV and SARS-CoV-2 present about 76 to 78% of similarities. This amount of similarities between the sequences of Spike proteins from SARS-CoV and SARS-CoV-2 might be the reason why both target the same receptor within the host cell which is the Angiotensin Converting Enzyme 2 or ACE2. [2]

The lying down conformation of SARS-Cov-2 has been identified thanks to cryon-electron microscopy. This lying down state provides better immune system evasion but is not helpful regarding receptor binding.[3]

SARS-CoV2 is a novel coronavirus, encountered for the first time in 2019 whose whole genomic sequence accounts for 96% of similarities in its sequence with bat-SARS like coronavirus BatCoV-RaTG13 and 79% with SARS-CoV and 50% with MERS-CoV.[2, 3]

Thus, the strain of SARS-CoV-2 can be coming from bat naturally, being the evolved version of the BatCoV-RaTG13.[5, 9]

The amino acid residues from SARS-CoV and SARS-CoV-2 is approximately of 72%. One of the major genomic singularity of SARS-CoV-2 is the insertion at the junction between subunits S1 and S2 from Spike protein of 4 amino acid residues: V483A, L455I, F456V and G476S or PRRA near the binding interface in the RBD.

The accessory gene *orf8,* responsible for encoding a protein ORF8 which triggers the intracellular stress pathway, suffers a deletion of 382 nucleotides in the sequence of SARS-CoV-2 from the sequence of SARS-CoV. This deletion of ORF8 might be in favor of a human adaptation from a zoonotic infection after cross-species transmission from a host-animal.

This modification in the amino acid sequence enables the cleavage of Spike protein via furin and proteases by creating a polybasic cleavage site RRRA.[3]

By the time of the SARS-CoV pandemic in China, 2003, the rate of infection that can be defined as the average number of people infected by an individual, named R0, reached 2.75. The sixth discovered coronavirus MERS-CoV, encountered in Saudi Arabia, had a rate of infection around 1. In the meantime, R0 ranks from 1.5 to 3.5.[2, 10]

SARS-CoV-2 divergence for its neutral site when compared to other viruses reaches 17% off a study over the coding sequences. The values of synonymous substitution per substitution sites or DS that the Spike Gene displays are higher than other viruses DS, either involving a higher mutation rate or by natural selection leading to an acceleration of synonymous substitutions.[3, 9]

Analyzing the coding sequences of SARS-CoV-2, researchers encountered 103 SARS-CoV-2 genomes or strains. Out of those 103 SARS-CoV-2 strains, 149 mutations have been identified as well as the possibility to classify the strains according to 2 types. 101 of 103 SARS-CoV-2 strains displays linkage between the two single nucleotide polypeptides or SNP. The 2 SNP locate at sites 8,782 and 28,144. There are 2 major distinct types of SARS-CoV-2 being the L-type, accounting for 70% of the 103 SARS-CoV-2 genomes and S-type, representing 30% of the total strains. While the L-type has a higher prevalence than the S-type, the late S-type corresponds to an older version or strain of SARS-CoV-2.

Those mutations taking place in the Spike protein domain have been identified as accounting for 13. The mutations spike protein undergoes gives rise to other strains with different abilities.

The Spike D614G mutation was introduced to Europe in March 2020. The mutated strain soon replaced the original SARS-CoV-2. The mutation in the Spike protein appears to increase infectivity, displaying less shedding the original strain, being more stable and increasing the transduction of multiple human cell types.

The original infectious strain of SARS-CoV-2 contained D614 in its S1 subunit. Since March 2020, a variant strain of SARS-CoV-2 appeared exhibiting as main difference a mutated G614 spike protein instead of the original D614 variant. This strain variation lead to a higher infection rate exhibiting higher viral loads of SARS-CoV-2 without correlation with the severity of the disease. Thus, the variation of D614 Spike protein into G614 Spike protein increased the infectious potential of SARS-CoV-2, making its spread easier among population.[3, 5, 9]

1.3. Etiopathogenesis of COVID-19

SARS-CoV-2 has a double lipid layer membrane which comprises a viral Spike glycoprotein. To interact with the cell receptors of the host, the viral Spike glycoprotein has a receptor binding domain. The assembly of viral particles is realized through the membrane glycoprotein.[1, 3]

The spatial organization of coronaviruses comprises 4 structural proteins. The helical capsid is formed by the Nucleocapsid protein and manages its genome. A lipidic envelope made of Spike proteins, Envelope and Membrane proteins, encircles the virus. The virus assembly is ensured by the membrane and envelope proteins while Spike proteins will interact within the process of host cell recognition and virus entry.[9]

The main process of entry of the virus into a host cell is performed through receptor-mediated endocytosis. SARS-CoV-2 targets the receptors of Angiotensin Converting Enzyme 2 ACE2 as entry-receptors the same way SARS-CoV processes.[11]

Six crucial amino acid residues are involved in the Receptor Binding Domain RBD. SARS-CoV and SARS-CoV-2 differ of 5 amino acid residues out of the 6 critical ones.[1]

Tridimensional analysis of both structures of SARS-CoV and SARS-CoV-2 revealed a greater binding affinity towards ACE2 for SARS-CoV-2.[7]

S1 and S2 receptor-binding subunits from the ectodomain region interfere in the virus entry process. The S1 subunit binds to the host receptor during the infection of SARS-Cov-2. The S2 subunit mediates the process of endocytosis by fusing the viral membrane with the host cell, releasing into the cell the viral genome of SARS-CoV-2.[2]

The Spike protein is about 1300 amino acid residues and is a clove-shaped trimer made of 3 S1 heads and a trimeric S2 stalk.[9]

For the infection to be generated, SARS-CoV-2 needs to entry the host cell. This interaction is mediated by Spike protein. Spike get cleaved into Receptor Binding Subunit S1 and Membrane Fusion S2 by host proteases. The process of cell entry takes place with the direct binding of the S1 subunit to the sugar receptors and ACE2 from the cell's surface while dimensional modifications occur in the S2 subunit leading to a post-fusion state in which the 3 pairs of heptad region HR-N and HR-C will form a 6-helix bundle structure. The hydrophobic fusion peptides of the helix will then insert into the host cell through the cell transmembrane

anchors. The host membrane and the viral membrane fuse because of the ended-position of the fusion peptides and the transmembrane anchors. Receptor binding, low pH and the amount of energy generated during this process make the membranes fusing faster, accelerating the virus entry. [2, 9, 12]

SARS-CoV-2 uses sugar receptors as entry mechanism, especially since it displays a high affinity to bind human ACE2, which is higher than the one of SARS-CoV strain. The spike protein from the ectodomain binds to ACE2's peptidase domain and is primed by transmembrane protease serine 2 TMPRSS2. SARS-CoV-2 strain enter the host cell thanks to endocytosis and the exposed spike protein is processed by Cathepsin L and Cathepsin B lysosomal proteases as well as furin. [1,3, 11]

TMPRSS2 is expressed together with ACE2 in nasal epithelial cells, lungs and brunches. Thus, SARS-CoV-2 displays a high tropism for the respiratory tract epithelial tissues. TMPRSS2 and Cathepsin L perform a simulative effect on furin's efficacy leading to the entry of the virus into the host cell.[2, 3]

SARS-Cov-2 is made of 4 structural proteins and 16 non-structural proteins nsp1-nsp16. The non-structural proteins participate in virus entry into the cell and pathogenesis. [2, 8, 9]

The RNA processing as well as RNA replication is performed via Nsp1. Nsp1 acts through the binding to 18S ribosomal RNA to interfere with mRNA translation in the mRNA entry channel of ribosome. The survival signaling pathway of host cell is modulated by Nsp2. Nsp3 separates the translated protein. The transmembrane Domain 2 TM2 is contained in the Nsp4 and has a modification activity towards the membrane. The process of polyprotein is performed through Nsp5 during replication. Nsp6 is a transmembrane domain. Nsp7 and Nsp8 increase Nsp12 and template-primer RNA combination. Nsp9 plays a role of single stranded RNA-Binding protein. The cap methylation of viral mRNAs is obtained through Nsp10. The process of viral replication and transcription needs a critical enzyme which is RNA-dependent RNA polymerase contained in the Nsp12. This process of viral replication and transcription is also performed through the binding of Nsp13 with Adenosine Tri-Phosphate ATP and zinc-

binding domain. Nsp14 has an exoribonuclease domain while Nsp15 displays an endoribonuclease domain and Nsp16 has a 2'-O-ribose methyltransferase. The non-structural proteins of SARS-CoV-2 play key role in splicing, translation and protein trafficking in order to inhibit the defenses of the host.[9]

To suppress the mechanism of mRNA splicing, Nsp16 binds subunit 1 and subunit 2 at the mRNA recognition domain.

1.4. Transmission of COVID-19

It was generally thought at the early stages of the outbreak of Covid-19 that the main transmission mechanisms involved animal to human transmission or zoonotic infections. The comparison with previous MERS-CoV and SARS-CoV mislead the opinion of scientist and epidemiologist during the first weeks Covid-19 appeared.[1]

However, the emergence of a case of five patients in a family cluster brought the evidence of person-to-person transmission. The health Chinese authorities confirmed the person-to-person transmission identifying a chain of 4 generations. That means that a patient contracted the virus from a zoonotic source which is non-human, infected another patient who passed the disease to another individual who finally contaminated another distinct individual.

Respiratory droplets represent the main source of transmission, which is also possible through aerosol droplets and contact droplets.[10]

The entry of the SARS-CoV-2 virus is then produced through the interaction with angiotensin converting enzyme 2 (ACE2) receptors. ACE2 receptors being highly expressed in the oral mucosa, the epithelial linings of the salivary ducts, the tongue with its taste buds, salivary glands may represent entry points for SARS-CoV-2 virus.[13]

1.5. General symptoms of COVID-19

The secretion of cytokines and chemokines conditioned by the entry of SARS-CoV-2 virus gives the intensity of the inflammatory response.[12]

The early systemic symptoms of Covid-19 share a lot of similarities in common with other known infectious diseases. The clinical manifestations of Covid-19 can be classified into mild and severe clinical features. The respiratory system contains several angiotensin converting enzyme 2 (ACE2) receptors especially throughout the epithelial linings, thus it represents the main target for the SARS-CoV-2 virus.[12, 13]

The most common and mild clinical manifestations displayed by Covid-19 include fever, asthenia, dry couch and shortness of breath.

The more severe clinical features of Covid-19 regarding the respiratory system include acute respiratory distress syndrome, pneumonia, trouble in breathing, permanent chest pressure or pain, productive cough with sputum.[4]

The pneumonia is characterized by the presence of fever, mucus production, dry couch, shortness of breath.

The acute respiratory distress syndrome displays tissue damage and destruction due to severe hypoxemia and necrosis.[14]

The worst cases of pulmonary infection resulted in respiratory failure.[12]

Covid-19's tropism for respiratory system cells is also able to cause lesions in other systems, ACE2 receptors being also expressed in the tissues previously presented. Thus, the more severe clinical features also include symptoms such as confusion, myalgia, diarrhea, ageusia and dysgeusia as well as anosmia and dysosmia, abdominal pain, nausea, vomiting, chest tightness, palpitations, upper airways alterations, sore throat, headache, difficulty waking up, bluish lips and face, hemoptysis, septic shock, metabolic acidosis and coagulation dysfunction.[4]

ACE-2 receptors are expressed in the same way independently from the gender. The only sex-based difference in expression of ACE-2 receptors

resides in the kidneys, male having a higher number of ACE-2 receptors. Thus, the SARS-Cov-2 virus displays a higher probability of causing kidney disorders in infected males rather than females.[12]

The high levels of proteinuria, hematuria, blood urea nitrogen, serum creatinine, uric acid, creatine kinase, lactate dehydrogenase and D-dimers reflect the affectation of the kidneys among chronic kidney disease patients which severity and mortality rates increase.

The intensity of the immune response is determined by inflammatory cytokines and chemokines, both able to speed up cytokines reproduction after an infection. Giving the intensity of the cytokines secretion, the so called “cytokine storm” can cause an acute respiratory distress as well as multiple organ failure, causing to patient to go from mild symptoms to severe manifestations and organ failures. The cytokine storm has been identified as containing Interleukins Il-12, IL-15, IL-6, IL-17A, IL-18, TNF-alpha, IFN-beta, IFN-alpha, IFN-beta.

The cytokine storm, along with the lungs hypoxia created by the acute respiratory distress syndrome lead to cardiovascular complications such as arrhythmias, myocarditis, acute coronary syndrome, heart failure and cardiogenic shock.[14]

Furthermore, it has been reported that the viral infection of SARS-CoV-2 was more prone to lead to severe clinical features such as acute respiratory failure and multiple organ failure when it was associated with the presence of systemic comorbidities such as diabetes, hypertension or renal failure.[12]

1.6. Oral Manifestations of COVID-19

The first study[4] about presence of oral lesion in positive Covid-19 patients happened to take place in Spain in April 2020 when authors tried to assess the patterns of the lesion in the oral mucosa of the palate and of gingival margins. The lesion described were enanthems.

The first case of positive Covid-19 patient presenting oral lesion was described in May 2020 and displayed a macular erythematous lesion on the dorsal side of the tongue followed by a tongue ulceration.[4]

Ever since, several oral manifestations have been reported among positive Covid-19 patients. Anosmia or dysosmia and ageusia or dysgeusia that seem to be the most prevalent symptom with a prevalence of 45% in assessed patients in UK. [13] Thus, the United Kingdom National Health Service considers acute or altered sense of taste and smell as the most suspicious criteria to suspect Covid-19 infection.

The second most prevalent site for oral mucosal changes happens to be the tongue displayed several affectations such as strawberry tongue, geographic tongue, fissured tongue and macroglosia. Cases of “Covid tongue”, newly invented to describe the set of tongue manifestations, affect about 25% of patients.[13]

The other oral mucosal lesions encountered in Covid-19 patients include erythematous plaques, blisters and ulcerations, bullae, petechiae as well as mucositis and desquamative gingivitis, including necrotizing gingivitis.[4]

2. RATIONALE, HYPOTHESIS, OBJECTIVES

2.1. Rationale

The origin of the oral mucosa lesions and the causality of Covid-19 is yet to be proven. It is unknown whether the clinical features in the mouth are due to Covid-19 itself in its physiopathological process or if they are resulting from the immunosuppression caused by SARS-CoV-2 (virus lead to a leucopenia) of treatment side effects. In order to identify the origin of the clinical oral manifestations in patients positive with Covid-19, it will be needed to assess the frequency of oral lesions in Covid-19 positive patients as well as their clinical features and all other characteristics that could help identify Covid-19 related lesion and assess the oral cavity of patients infected with Covid-19 in its early stage right after the diagnosis to treat and prevent the evolution of these oral mucosal lesions. [4, 13]

2.2. Hypothesis

Covid-19 patients confirmed with polymerase chain reaction (PCR) display specific oral manifestations.

2.3. Objectives

The main objective of this systematic review is to analyze the oral manifestations among Covid-19 positive patients.

This systematic review has three specific objectives:

-Describe the most frequent oral manifestations of Covid-19 and their characteristics in terms of awareness of the patients and recovery

-Correlate the oral symptomatology with the systemic manifestations of Covid-19.

-Establish the links between severity of SARS-CoV-2 infection and the appearance and characteristics of oral manifestations in Covid-19 patients.

3. MATERIAL AND METHODS

3.1. Protocol

This systematic review was performed through the Preferred Reporting Items for the Prisma Extension Statement for reporting of Systemic Reviews Incorporating Network Meta-Analysis of Health Care Interventions (PRISMA-P checklist).[15]

3.2. Search strategy

Three different databases Medline, Cochrane Central Registry of Controlled Trials and Scopus were used to screen all the pertinent Randomized Controlled Trials (RCTs), Observational Studies, Multicenter Studies, Controlled Clinical Trials, Comparative Studies, Case series, Clinical Trials and Clinical Studies in English through a comprehensive research performed from December 2021 to March 2022.

The key words used: (((COVID-19) OR (Coronavirus) OR (SARS-2)) AND (((oral) OR (dental) OR (buccal)) OR (mouth)) AND ((manifestations) OR (lesions)) OR (dysgeusia) OR (anosmia) OR (ageusia) OR (dysosmia) OR (oral mucosal lesions))).

TABLE 1: Research description by Database

DATABASE	SEARCH	FILTERS	DATE
MEDLINE	(((COVID-19) OR (Coronavirus) OR (SARS-COV-2)) AND (((oral) OR (dental) OR (buccal)) OR (mouth)) AND ((manifestations) OR (lesions)) OR (dysgeusia) OR (anosmia) OR (ageusia) OR (dysosmia) OR (oral mucosal lesions)))	○ Randomized Controlled Trial, ○ Observational study ○ Clinical Study ○ Clinical Trial ○ Multicenter study ○ Controlled Clinical Trial ○ Cases series ○ Comparative Study ○ in the last 5 years, ○ Humans, ○ English ○ MEDLINE.	06/03/2022
SCOPUS	(((COVID-19) OR (Coronavirus) OR (SARS-COV-2)) AND (((oral) OR (dental) OR (buccal)) OR (mouth)) AND ((manifestations) OR (lesions)) OR (dysgeusia) OR (anosmia) OR (ageusia) OR (dysosmia) OR (oral mucosal lesions)))	○ From 2019 to 2022. ○ English. ○ Articles. ○ Subject area: ○ Medical. ○ Dentistry ○ Exact keywords:	06/03/2022

		▪ “Human”. ▪ “Covid-19” ▪ “Coronavirus disease 2019”. ▪ “SARS-CoV-2”. ▪ “Major clinical study”. ▪ "Randomized Controlled Trial". ▪ "Controlled study". ▪ "Retrospective study". ▪ "Cohort analysis". ▪ "Retrospective studies". ▪ "Prospective study". ▪ “Retrospective study”. ▪ "Prospective studies”. ▪ “Observational study" ▪ "Clinical Trial". ▪ “Cross-sectional study” ▪ “Multicenter study”	
COCHRANE	((COVID-19) OR Coronavirus OR (SARS-COV-2)) AND ((oral OR dental OR buccal OR mouth) AND ((manifestations OR lesions) OR dysgeusia OR anosmia OR ageusia OR dysosmia OR (oral mucosal lesions)))	○ Years first published: From 2018 to 2022.	06/03/2022

3.3. Selection Criteria

The PICOS (Patients; Intervention; Comparison; Outcomes; Study Design) process was used to determine the following inclusion criteria: (P) Patients: without limit of age, sex and ethnicity with a diagnosis of Covid-19 confirmed with PCR-test. (I) Intervention: development of oral manifestations. (C) Comparator: Without comparative group. (O) Outcomes: description of the most frequent Covid-19 oral lesions and their characteristics, correlate the oral symptomatology with the systemic manifestations of Covid-19, analyze the links between the severity of the Covid-19 infection and the oral manifestations.

3.4. Inclusion Criteria

The following inclusion criteria were applied: 1) Randomized Control trials (RCTs); 2) Observational studies; 3) Multicenter studies and cases series, 4) Controlled Clinical Trials; 5) Comparative studies; 6) Clinical studies; 7) Clinical trials; 8) English or Spanish; 9) Humans.

3.5. Exclusion Criteria

The following exclusion criteria were applied: 1) Studies in which diagnosis was not confirmed with PCR, 2) Studies that included patients in which the clinical examination was not made by some trained personnel (dentist or physician).

3.6. Data extraction

The following data were obtained from each included study: author, country of origin, study design, number of patients, age of patients, sex of patients, type of oral manifestations, prevalence of the oral manifestations, anatomical

localization of the oral manifestations, duration of the symptoms, covid-19 severity based on the status of hospital admission.

3.7. Quality assessment

A twelve criteria's scale was used to assess the quality of each selected articles: Critical Appraisal Skills Program (CASP)[16] Cohort studies Standard Checklist. The corresponding possible answers were "Yes" or "+", "No" or "-" and "Can't tell" or "?". The sum of the answers was calculated with a maximum of twelve.

4. RESULTS

4.1 Study Selection

An electronic research was performed on 3 different databases (PubMed, Cochrane and Scopus) and resulted in 318 published references. The elimination of the duplicates led to a new total of 280 references. The screening of the titles eliminated 234 articles and made us obtain 46 remaining references. Out of these 46 remaining references, 28 got excluded because of the following criteria: systemic manifestations without oral manifestations (n=15), neurological manifestations without oral manifestations (n=9), unclear object of the study or other criteria evaluated (n=3), subjective assessment and evaluation of the oral lesions (n=1). A total of 18 full-text articles was screened. Out of these 18 full-text articles, 6 got excluded because of the following criteria: absence of Polymerase Chain Reaction diagnosis for Covid-19 (n=5), subjective evaluation of the oral manifestations and only abstract in English (n=1). A final number of 11 studies was included in this systematic review (*annex 1*).

4.2 Study characteristics

The characteristics of the eleven included studies are listed in table 2 (Annex 2).

The study design of this systematic review comprised different type of publications. Out of the 11 selected studies included were 5 cross-sectional studies[17,19,20,23,24], 1 was a case serie[18], 3 of them were prospective cohort studies[21,22,25] and 2 being observational studies[26,27].

A total of 2758 patients were studied in this systematic review. The number of patients of the selected studies ranged from 47[22] to 989[17]. All the participants

turned out to be over 21-year-old except for one study concerning children whose age ranged from 1,3 to 20 years old with a mean age of 9. [22]

The age of the participants of the different studies ranged from 9[22] to 72 years old[19].

The youngest participant was aged of 1,3 years old[22] at the time of the assessment of the lesions when the oldest one was aged of 82 years old. [23]

The male female ration ranged from 15/85%[27] to 75,4/24,6[21].

4.3 Quality assessment

The quality scores obtained from the articles included in this study ranged from 10[19,21] to 12[20-24] out of a total of 12 points. Thanks to the quality assessment, all the articles were identified as cohort studies with a clearly focused question as well as well-defined inclusion and exclusion criteria. The studies used clear objective ways of evaluating and assessing the oral manifestations of the patients suffering from Covid-19.

Out of the 11 selected articles to be part of this systematic review, 100% choose to include patients diagnosed with a confirmed PCR-test and the assessment of the oral lesions was performed through direct examination and/or endoscopy. [17-27]

4.4 Synthesis of results

4.4.1 Frequency of Oral Manifestations of Covid-19 and their characteristics

Frequency of oral manifestations

A total of 40 oral manifestations was found in relation with patients suffering from Covid-19 and that got monitored for these buccal lesions.[17-27]

The most common oral manifestations encountered in the eleven studies revealed to be the ageusia, reported in 7 studies.[17,18,19,21,24,25,27]

The second most prevalent oral manifestations in this systematic review were tongue alterations such as ulcerative lesions, reported in six articles and suffering from different lesions. [18,19,21,22,23,26]

Accounting as the third most common oral lesions, both anosmia[17,18,21,25,27] and ulcerative lesions[19,20,21,24,26] which were reported in 5 different articles.

Xerostomia[18,21,24,26] and tongue color[21,22,23,25] were outcomes appearing 4 times each in the eleven articles.

Other oral manifestations found in this systematic review were facial pain and weakness[18,21,24], masticatory muscles pain and weakness[18,21,22] and alteration of the mucous membranes[21,24,26] reported 3 times.

Six oral manifestations appeared twice in this study, being respectively ageusia along with anosmia[17,25], geographic tongue[19,26], blisters[19,24], cranial nerve palsy and weakness[21,22], rhinorrhea[25,27] and nasal congestion[25,27].

All the other oral manifestations not described previously occurred to appear mentioned once for each. They were 25 oral manifestations appearing only once in the study results. Respecting the order of the encountered articles in this study and their order of appearance, the oral manifestations reported were fissured tongue, papillae hyperplasia, angina bullosa, candidiasis, ulceronecrotic gingivitis, petechiae and spontaneous hemorrhage oral. [19]

Another article[20] noted the presence of aphtous-like ulcer, erythema and lichen planus lesions. [20]

Other reported oral lesions were troubles in the temporo-mandibular joint[21], salivary gland ectasia and trigeminal neuralgia.[21]

Cervical lymphadenopathy, red or swollen lips as well as strawberry tongue were reported in Halepas et al. [22] study.

One article[26] reported bilateral angular cheilitis and herpes labialis.[26]

The oral manifestations of Covid-19 patients have been summarized per article in the Annex 4, Table 3.

Awareness of the oral manifestations

Two studies provided data regarding the patient's consciousness about the presence of oral manifestations in the context of a SARS-Cov-2 infection. [24,25]

84,5% of the patients happened to be aware of the oral manifestations they were experiencing. Among them, 93,9% was facing these symptoms for the first time.[24]

An article referred that out of 10 patients assessed, 40% complained before the assessment when a rate of 60% of oral manifestations presence was found after the objective evaluation. [25]

Recovery period

Data about the recovery period of the oral manifestations resulting from Covid-19 infections were provided in 6 articles among the 11 ones constituting this study.[17,19,21,24,25,27]

The mean period of recovery ranged from 2 days[27] to 3 months[21].

The evaluated symptoms were ageusia[17,19,21,24,25,27], xerostomia and salivary gland ectasia[21], ulcers and erythmas[24], dysosmia[25], and dysgeusia[27].

All of the symptoms were evaluated and documented alone as one only [17,19,21,24,25] except for dysosmia and dysgeusia[27].

Patients recovered from ageusia in less than 2 weeks for one study[17] while when the period of 14 days was exceeded without recovering, the patients were taken to biopsy in another study[19]. Only one study referred an absence of recovery in 54,6% of the patients of its intervention group.[17]

One study[21] displayed an expression of symptoms even further than 3 months in 83,6% of their patients, among which 30% presented xerostomia alone and 12,8% was affected by both xerostomia and salivary gland ectasia.

When all the symptoms evaluated such as ulcers, or erythema, needed a recovery period shorter than 7 days, ageusia happened to be the only symptoms exceeding 10 days before recovery.[24]

Dysosmia disappeared in a range of 8 to 38 days while dysgeusia needed a period from 15 to 38 days.[25]

One study[27] assessed both dysosmia and dysgeusia recovery together, displaying recovery period ranging from 2 to 45 days with an average period of time of 11 days. 26% of the patients of this study expressed symptoms for more than a month.

4.4.2. Correlation of the oral symptomatology with the systemic manifestations of Covid-19

Three studies gave data about the onset of the oral manifestations comparing it to the onset of the general symptoms.[19,24,27]

One article referred that the oral manifestations onset appeared at the mean time than the general symptoms or not further than a week for 92%.[19]

Another study reported the detection of oral symptoms in 81% of the patients between 1 to 4 days after the onset of the general symptoms.[24]

The study of Villareal [27] et al. revealed that 1,3% of its patient was affected by dysgeusia or dysosmia alone without general manifestations of Covid-19 and that these oral manifestations lead the patients to perform a SARS-CoV2 PCR test. The rest of the patients expressed oral symptoms at the same time than the general manifestations.

4.4.3. Severity of SARS-CoV-2 infection

Gherlone[21] et al. reported that 7,3% of their patients manifested with temporo-mandibular joint alterations, among which the mean age was of 48 years old while the group of patients didn't display the jaw alteration was aged of 63,2 years old. The authors described a significant higher prevalence of temporo-mandibular joint alterations for younger patients. These findings join the ones of Favia[19] et al. and Domínguez[17] et al. in the way that the oral manifestations occur in the younger groups of patients displaying less severe forms of Covid-19 infections.

However, the findings of Horzov[23] et al. revealed 91,11% of their patients expressed tongue plaque. All the patients above 40 years old expressed both tongue plaque and more red tongue color. In addition, the tongue plaque had a more yellow and grey coloration which was associated to a more severe manifestation. Thus, the age of the patient of this study conditioned a more severe manifestation of tongue plaque coloration and tongue coloration in contrast to the findings of other studies.

Similar to the results of Horzov[23] et al., Subramaniam[26] et al. reported that 100% of their patients displaying oral manifestations, which accounted for only 1,26% of the total population, were aged of more than 50 years old. This might suggest that the appearance of oral manifestations in the context of Covid-19 infection is conditioned by an elderly age. In addition, the authors declared that 100% of the male group which accounted for 33,3%, had comorbidities and that percentage raised to 66% in the female group accounting for 66,6%. The implication of comorbidities in the development of oral manifestations and a potential influence on their rate is yet to be analyzed.

5. DISCUSSION

Coronavirus disease-2019 is a viral infection caused by the infection of the SARS-CoV-2 virus leading to multiorganic manifestations displaying severity of different intensities.[19] To this day, on the 8th of may 2022, Covid-19 has contaminated 517 millions of people causing the death of 6,25 millions of them.[28] The scientific community, soon after the onset of the pandemic, started realizing and publishing studies over the systemic common signs and symptoms describing fever, cough, headache, sputum production, myalgia, sore throat, diarrhea and dyspnea.[6] The pathogenesis of SARS-Cov-2 is conditioned by the entry of the virus into the host cell, the target cell population being the ACE-2 receptors in the epithelial lining of the respiratory tract and highly expressed in the epithelial cells of the oral mucosa.[6]

5.1 Frequency of the oral manifestations

The main reported oral symptoms to this day were taste and smell alterations. Dos Santos et al.[9] classified the alterations according to their quantitative nature, 24% of their patients experiencing ageusia, or to their qualitative one with 38% of the patients facing dysgeusia and 35% hypoageusia. Dos Santos et al.[9] emphasized on the character of taste alteration which is commonly present in flu-like syndromes but that was absent during the previous SARS-CoV and MERS outbreak, indicating a closer nature of manifestations to the viral ones.

The infections generated by a virus are usually characterized by an abrupt onset of the symptoms cursing together with enanthems, blisters and ulcerations.[6]

Viral infections triggering the appearance of oral lesions are commonly generated by Herpes zoster, Herpes Simplex Virus-1 or mononucleosis or ulcerative disease such as Behçet's disease.[6-13] Thus, the differential diagnosis with other viral infections needs to be performed very carefully putting an emphasis on the complementary tests to support the diagnosis of a new viral lesion instead and exclude other known viral infections.[6]

However, little data about the manifestations of the oral lesions was provided. This systematic review identified a total of 11 scientific publications[17-27] aimed to collect and analyze scientific evidences regarding oral mucosa lesions in patients suffering from Covid-19 infection.

The mechanism of ulcer formation in the oral mucosa has been studies by S. Erbas[13] et al. The authors explained that the interaction was based on the expression of ACE-2 receptors in the oral mucosa and especially the tongue. The tongue has been identified has the most common location for ulcer in the oral cavity. The onset of the oral mucosal lesion appears at a hyper inflammatory status. The SARS-CoV-2 binding to ACE-2 receptors induce an exaggerative immune response ending up with the liberation of the cytokine storm and the action of T helper 17. This immune reaction can be considered as an immune attack and builds a suitable environment for the development of ulcer. Covid-19 also causes the patients to develop a Covid-19 coagulopathy which is caused by endothelial injuries, immobilization of the patients and increase of prothrombin factors. The association between the immune attack and the Covid-19 coagulopathy provides suitable conditions for necrotic ulcers to develop.

Dos Santos et al.[9] evidenced that it existed different patterns for the oral ulcers to develop: ulcers; blisters; macules; plaques in different locations. However, viruses do not express different pattern of infection. Therefore, the authors emphasized on the coinfection and surinfection theory by bacteria or fungal populations. This explains why Gherlone[21] et al. found that 93,3% of their patients with salivary gland ectasia had antibiotics treatment before the onset of the oral lesions. Hospitalized patients were often treated with antibiotics because of coinfections. In addition, the authors also identified that diabetes mellitus and COPD were associated to dry mouth, COPD being a predictor alone of dry mouth. The authors explained that antibiotic injection, high CRP and LDH serum levels would significantly increase the risk to develop salivary gland ectasia. [21] These findings give strength to the theory of Dos Santos et al.[9]. In addition, Dos Santos et al.[9] concluded that the majority of hospitalized patients presenting oral mucosal injuries had coinfections, treatment adverse reaction and immune system impairment. These findings were supported by Seo[25] et al. who reported

patients with chronic rhinosinusitis and another with allergic rhinitis while 1 patient was suffering from nasal septal perforation and another from deviation.

The SARS-CoV-2 virus targets the ACE-2 receptor cells to entry the host cell and induce viral replication. ACE-2 receptors are highly expressed in epithelial cells lining the oral mucosa, especially on the tongue surface.[13] Dos Santos et al.[9], S. Erbas[13] et al. Triggle et al.[6] developed hypothesis about the pathogenesis mechanisms SARS-CoV-2. Triggle et al.[6] stated that the oral manifestations were whether direct due to the high expression of ACE-2 receptors in the epithelial cells lining the oral mucosa and being a direct target for SARS-CoV-2 or be a consequence of a secondary infection. Indeed, the authors found out that the lesions developed in the oral cavity by their patients were related to multidrug treatments leading to an increase in the expression of erythema multiform among Covid-19 positive patients. Two published articles[9,13] linked multiple etiologies to the development of oral lesions associated with Covid-19, both of them sharing the direct etiology because of the expression of ACE-2 receptors in the oral mucosa. 4 distinct etiologies were identified by S. Erbas[13] et al., being a direct effect of the binding of SARS-CoV-2 to ACE-2 receptors; stress and possible reactivation of herpetic gingivostomatitis due to the Herpes Simplex Virus-1 and candida superinfection due to a dysbiosis caused by drugs of the treatment and the viral infection; drugs used for the treatment of the oral or general symptoms; and a general immunosuppression status caused by prolonged hospitalization and polymedication.

Seo[25] et al. reported that 60% of their patients expressed either only dysgeusia or only dysosmia, having 40% of their studies population expressing both symptoms and thus a reaction off greater intensity. The recovery period ranged from 15 to 38 days for dysgeusia while it started from 8 to 38 days for dysosmia. This results implied that recovering from dysosmia required less time than recovering from dysgeusia, meaning the lesions of the olfactory neuroepithelium would cure faster in the case of dysosmia and need more time for more intense lesions on the tongue.

Dos Santos et al.[9] classified the etiologies according to the two different symptoms of taste alteration and oral ulcers. The taste alteration had 4

different etiologies being a local inflammatory response causing rhinitis and an alteration of the taste bud and then taste; concomitant olfactory alteration leading to an alteration of the taste; drug treatment side effects; and the direct binding of SARS-CoV-2 to ACE-2 receptors in the oral mucosa. However, taste alterations were reported before the appearance of rhinitis in several cases, as well as patients displaying taste alteration without olfactory manifestations and some patients developed the taste alteration while being drug free. Therefore, the authors identified that the interaction between the virus and the oral epithelial cells led to changes in the peripheral nervous system causing taste alteration because of the modifications in the serotonin and dopamine pathways. The mechanism of binding has been studies and revealed that SARS-CoV-2 binds especially to mucins and sialic acid which provides an acceleration to the degradation of taste particles giving an alteration of the taste. The high expression of taste buds on the tongue dorsal surface and the tongue representing one of the main localization for oral manifestations related to Covid-19 is also a logical hypothesis to the authors. In addition, the inhibition of ACE-2 receptors has been proven to be frequently associated with taste alteration with a recovery of a normal taste a few weeks after the inhibition of ACE-2 receptors.

Domínguez[17] et al. declared that there was a higher prevalence of ageusia and anosmia in their non-hospitalized group in comparison to the hospitalized group. The authors reported a significant difference in the sex of the hospitalized patients. The hospitalized group comprised a male/female ratio of 57,6/42,4% when the non-hospitalized group expressed 36,5/63,5%. The hospitalized group was older and more off a male population while the non-hospitalized group which displayed more ageusia and anosmia comprised younger females in comparison. These data could indicate that more severe manifestations occurred in older men when the oral lesions appeared in a higher frequency amongst young females expressing a less severe form of Cvodi-19 infection.

Biadsee[18] et al. published that there was a higher prevalence among women experiencing anosmia and facial pain. However, the authors also published that the olfactory dysfunctions expressed no significant difference between both sexes. These findings tend towards the tendency to develop more lesions for

women. The work of Halepas[22] et al. encountered similar data about the gender distribution and the experienced symptoms, describing a male/female ratio of people manifesting the oral lesions of 42,3/57,7% while the group without oral manifestations expressed a 61,9/38,1% relationship. In addition, Dos Santos et al.[9] found a significant association between taste alteration and Covid-19 in women.

The data providing a higher prevalence of oral manifestations among women tended to be explained by Dos Santos et al.[9]. Indeed, the authors expressed that the female reaction to a viral infection leads to a more important hormonal change giving an alteration of the innate immune response and a higher dysfunction of the organism.

Without regard to the sex and oral manifestations association, Gherlone[21] et al., Horzov[23] et al., and Villarreal[27] et al. reported respectively that there was no significant difference between both sexes in the expression of temporo-mandibular joint alterations, that there were no gender association for both tongue color changes and plaque color changes and finally that there was not any sex dominance for the ears, nose and throat alterations described by Villarreal[27] et al. Those findings counterbalance the previous associations realized by Domínguez[17] et al and Biadsee[18] et al. Dos Santos et al.[9]

5.2 Correlations of the oral manifestations with general symptoms

The course of appearance of the manifestations of Covid-19 seemed to indicate that the oral lesions might occur as the first signs of infection and thus could be useful in the early diagnosis of SARS-CoV-2 infection.[6] Villarreal[27] et al. revealed that 1,3% of the patients suffering from Covid-19 expressed taste or smell alteration only without any other systemic manifestations leading to the performing of a PCR test for Covid-19 which happened to be positive. Villarreal[27] et al. also displayed that oral lesions were expressed either before the onset of the systemic manifestations for 1,3% or at the same time of the appearance of the systemic manifestations for 98,7%, not appearing further than the onset of

general manifestations. Furthermore, Favia[19] et al. expressed that 26,4% of the patient from the moderate group, accounting for 77% of the total population of the study, expressed oral manifestations before the onset of the systemic ones, and that 41% expressed the onset of the oral manifestations in the meantime than the onset of the systemic ones, that 19% of the severe group accounting for 17%, developed oral manifestations before the systemic ones and that 52,4% developed both types of oral and systemic manifestations in the meantime, and finally that 12,5% from the critical group accounting for 8 patients developed oral lesions before the onset of the general ones and that 12,5% expressed both oral and systemic manifestations in the meantime. Therefore, it seemed that the appearance of the oral manifestations could be used as a predictor for Covid-19 infection. However, the data provided by Favia et al. [19] indicated that the oral lesions happened to appear more often at the same time than the onset of the systemic manifestations than before: 41% at the same time against 26,6% for the moderate group, 52,4% against 19 for the severe one and 12,5% against 12,5% for the critical group.

Nevertheless, Natto et al. [24] encountered oral manifestations appearing from 1 to 4 days after the onset of the general symptoms for 81 of the patients. In addition, Favia et al. [19] also reported that 32,6% of their patients from the moderate group developed oral manifestations after the systemic ones, that 28,6% of the patients from the severe group expressed the oral lesions after the systemic ones, and finally that 75% of the critical group displayed the onset of the oral lesions after the onset of the systemic manifestations. The proportion of patients expressed the oral manifestations at the same time or after the onset of the systemic manifestations is more important than the proportion of the groups developing oral lesions before systemic manifestations: the moderate group developed oral lesions in the meantime or after the onset of the systemic ones in 73,6% against 26,4% before, then the severe group displayed 81% against 19% before and finally the critical group expressed 87,5% in the meantime or after against 12,5% before. Thus, it does not seem that the onset of the oral manifestations can used as a predictor for Covid-19 infection. [24,19]

5.3. Severity of the SARS-CoV-2 and oral manifestations

The severity of the infection and immune response is determined by generated by the so called “cytokine storm” which has been proven to be able to cause acute respiratory distress as well as multiple organ failure, leading the patient to go from mild symptoms to severe manifestations and organ failures. The cytokine storm has been identified as containing Interleukins Il-12, IL-15, IL-6, IL-17A, IL-18, TNF-alpha, IFN-beta, IFN-alpha, IFN-beta.[14] The onset of the oral manifestations seemed to appear later according to a gradient severity of the immune response and infection based on Favia[19] et al. findings, reaffirming that the onset the oral symptoms cannot be used as a predictor for SARS-Cov-2 infection. Furthermore, Villarreal[27] et al. reported that 19% of their studied population developed pneumonia among which 18% required hospitalization and developed the oral manifestations at the same time than the rest of the patients not suffering from pneumonia. It does not seem to be an association between the onset of the oral symptoms and the onset of the systemic ones with the severity of the Covid-19 infection. [19,27]

Villarreal[27] et al. also reported that the hospitalized pneumonia group displayed very similar results of taste and smell alterations being respectively 68% and 70% when compared to the non-hospitalized group displaying respectively for taste and smell alterations 70% and 68%. Therefore, the severity of the disease according the Villarreal[27] et al. does not seem to influence neither the onset nor the rate of the oral manifestations.

What’s more is that Horzov et al. [23] published different results according to the severity of SARS-CoV-2 infection. Indeed, the authors classified their population into 3 groups of distinct severity from mild, 10,37%, to moderate for 62,96% of the patients and finally to 26,67% of the patients in the severe group. Lesions were studied on the tongue color changes and classified into pale which would be associated with mild manifestation and red, associated with a more severe lesion. The mild and moderate groups displayed similar results with respectively a pale tongue for 64,29% and 62,35% when expressing red

tongues respectively in 35,71% and 37,5%. Yet severe group expressed an 11,11% of pale tongue and 88,8% of reddish tongue coloration with 41,66% being red and 47,22% being dark red or burgundy according to the authors classifications. Therefore, it seems according to Horzov et al. [23] that the intensity of the oral manifestations is conditioned by the severity of the Covid-19 infection.

However, Domínguez et al.[17] found that among their non-hospitalized patients, there was a significant higher frequency of anosmia and ageusia when compared to the hospitalized group. The authors also reported that the non-hospitalized group had a significant lower rate of recovery from ageusia and anosmia and concluded that there was no significant difference for the recovery status and recovery rate between the intervention and the control group. These results may support the hypothesis that the oral lesions may manifest more when the Covid-19 infection is mild and didn't require hospitalization. When it did require hospitalization, it appeared that the oral manifestations were expressed in a lower frequency. Those results contrasts with the findings of Horzov[23] et al., the links between the severity of the SARS-CoV-2 and the intensity of the oral manifestations remain unclear as Gherlone[21] et al. didn't relate any association between the disease manifestations and severity and the oral manifestations.

Halepas[22] et al. stated a significant association with absence of cough, existence of a systemic rash and presence of conjunctivitis, which would tend to affirm the hypothesis supporting that oral lesions may manifest in mild/moderate forms without pneumonia-like symptoms and further care needed including hospitalization.

Villarreal[27] et al. did declared that 19% of their studied population expressed pneumonia among which 18% required hospitalization. The comparison of the prevalence of taste and smell disorders happened to be in the same range. The severity didn't seem to influence upon the recovery rate from taste and smell disorders which ranged from 2 to 45 days with a mean recovery period of 11 days for both hospitalized and non-hospitalized groups. Out of their total population, Villarreal[27] et al. reported that 26% exceeded one month to experience disappearance of the symptoms.

The severity of the general manifestations of Covid-19 seemed to be related with the age of the patient according to Favia[19] et al. Indeed, the age of the different groups classified regarding the severity of the infection increased with the severity of the disease. The moderate form was experienced by 77% of the patients with a mean age of 63 years old, the severe group was filled with 17% of the patients and displayed a mean age of 74 years old, and finally the critical group represented 6% of the patients and was aged of 81 years old. This would suggest an increase in the severity of the manifestations of Covid-19 with an increase age of the patients.

The age and severity relationship was also studied by Domínguez[17] et al. The authors compared the age of the patients according to whether they were part of the hospitalized group or the non-hospitalized group. The hospitalized group displayed a mean age of 60 ±14,6 years old when the non-hospitalized group expressed a mean age of 46,5 ±14,5 years old. This tends to indicate another time than the severity of the manifestations was related to the age of the patients, elderly leading to more severe forms of the Covid-19 infection requiring hospitalization. However, the severity didn't seem to have an influence over the appearance of oral manifestations since the more severe the SARS-CoV-2 infection, the less oral manifestations would appear in comparison to general manifestations.

The tendency to express oral manifestations when the SARS-CoV-2 form is less severe and when patients are younger is also supported by Halepas[22] et al. The authors realized a study over children and sorted out that 55,3% of the patients expressed oral manifestations with a mean age of 7,8 years old (5,8-9,8) meanwhile the patients without oral manifestations represented 44,7% with a mean age of 10,5 years old (8,5-12,5), providing data supporting the previous observation over severity and age.

Furthermore, the relationship between the sex of the patients and severity of the general manifestations and nature of the oral manifestations has been described by 7 articles, comparing different factors.[17-18-21-22-23-26-27]

5.4 Limitations

This systematic review has several limits. It was conducted on the 6th of March 2022 and included English published articles from three different databases being Medline, Cochrane Central Registry of Controlled Trials and Scopus. By the time the research was performed, there were no published articles regarding the SARS-CoV-2 different variants and the oral manifestations of Covid-19. There were no articles regarding the oral manifestations of Covid-19 and the anti-Covid-19 vaccine either. Once again due to a temporal limitation, there were no article available studying the oral manifestations among patients undergoing a second Covid-19 infection.

It would be interesting in the future to develop research about the different SARS-CoV-2 variants that appeared too late to be included in this study and the possible oral manifestations encountered in patients suffering from these new Covid-19 forms.

It would also be interesting to study if the anti-Covid-19 vaccines had an effect on the oral manifestations among vaccinated patients who still expressed symptoms and signs and if there was any difference regarding the appearance of oral manifestations between these patients and unvaccinated Covid-19 positive patients. As anti-Covid-19 vaccines are based on different biological mechanisms, scientists may compare the differences between the oral manifestations when comparing the different vaccines.

The gene polymorphism of the Asian population led to a fewer expression of oral manifestations. Further studies about the differences in expression of ACE-2 receptors in the mouth is needed between both sexes.

CONCLUSION

Coronavirus disease-2019 is a viral disease caused by the infection of the SARS-CoV-2 virus leading to multiorganic manifestations off different intensities. The aim of this systematic review was to analyze the oral manifestations among Covid-19 positive patients.

- The most frequent oral manifestation was ageusia. The second most prevalent oral lesion was tongue ulcers followed by anosmia with an average recovery period of 14 days. The majority of the patients were aware of the lesions they were presenting in the mouth.

- The onset of the oral manifestations occurred at the same time than the systemic ones or developed less than a week after the appearance of the systemic ones. In some cases, the onset of the oral manifestations happened before the development of systemic alterations, leading to a SARS-CoV-2 PCR test without any other alteration than the ones in the oral cavity.

- The severity of SARS-CoV-2 infection seemed to be inversely proportional to the appearance of oral manifestations. The less severe the Covid-19 infection is, the more oral lesions would develop. The more advanced age led to a more severe form of Covid-19 and less oral manifestations.

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https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

ANNEXES

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ANNEX 6: Article version

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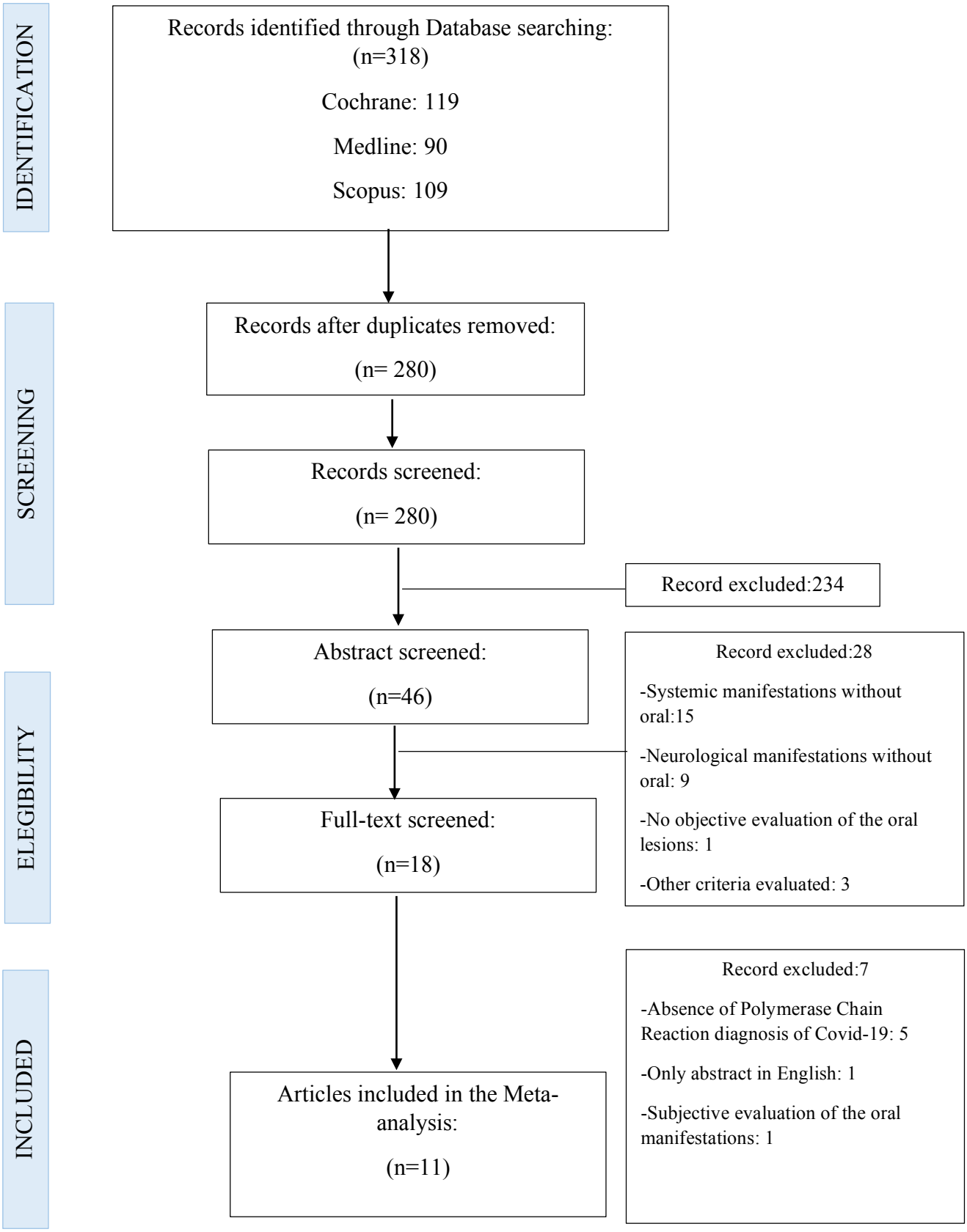

ANNEX 2: Table 1: Quality assessment

	Domínguez[17] et al.	Biadsee[18] et al.	Favia[19] et al.	Fidan[20] et al.	Gherlone[21] et al.	Halepas[22] et al.	Horzov[23] et al.	Natto[24] et al.	Seo[25] et al.	Subramaniam[26] et al.	Villarreal[2] et al.
Clearly focused issue	+	+	+	+	+	+	+	+	+	+	+
Cohort recruited in an acceptable way	+	+	+	+	+	+	+	+	+	+	+
Exposure accurately measure to minimize bias	+	+	+	+	+	+	+	+	+	+	+
Outcomes accurately measure to minimize bias	+	+	+	+	+	+	+	+	+	+	+
Identifications of cofounding factors	+	+	+	+	+	+	+	+	+	+	+
Follow of subjects complete and long enough	+	+	+	+	+	+	+	+	-	+	+
Identification of the results	+	+	+	+	+	+	+	+	+	+	+
Precision of results	+	?	-	+	+	+	+	+	+	+	-
Results believable	+	+	+	+	+	+	+	+	+	+	+
Application of the results to our local population	+	+	+	+	+	+	+	+	+	+	+
Results of this study fits with other available evidence	+	+	+	+	+	+	+	+	+	+	+
Implication of the study for our practice	?	+	?	+	+	+	+	+	?	?	+
SCORE	11	11	10	12	12	12	12	12	11	11	11

ANNEX 3: Table 2: Data extraction

AUTHOR AND YEAR	STUDY DESIGN	NUMBER OF PATIENTS	MEAN AGE	GENDER DISTRIBUTION (%M/F)
Domínguez[17] et al. 2020	CS	Intervention group: n= 846 Control group: n= 143	IG= 56,8± 15,7 CG= 53,5±16,6	IG= 52,7 /47,3% CG= 51/49%
Biadsee[18] et al. 2020	CaS	N=128	36,25 (18-73)	45,3/54,7%
Favia[19] et al. 2021	CS	N=123	72	56,9/43,1%
Fidan[20] et al. 2021	CS	N=74	49,3±7,2	66,2/33,8%
Gherlone[21] et al. 2021	PCS	N=122	66,5 (53,9 -74,1)	75,4/24,6%
Halepas[22] et al. 2021	PCS	N=47	9±5 (1,3-20,0)	51,1/48,9%
Horzov[23] et al. 2021	CS	N=135	48,7±13,2 (18-82)	47,4/52,6%
Natto[24] et al. 2021	CS	N=109	39,3±12,4	53,2/46,8%
Seo[25] et al. 2020	PCS	N=62	33±12 (20-62)	30/70%
Subramaniam[26] et al. 2021	OS	N=713	NC	58,3/41,7%
Villarreal[27] et al. 2020	OS	N=256	43 (18-62)	15/85%

PCR: Polymerase Chain Reaction/ CS: Cross sectional study/ CaS: Case Series/ STD: Taste or Smell Disorders/ VAS: Visual analog scale/ PCS: Prospective cohort study/ OS: Observational study/ NC: Non-communicated

ANNEX 4: Table 3: Outcomes' results

AUTHOR YEAR	COVID-19 ORAL MANIFESTATIONS	ANATOMICAL LOCATIONS OF ORAL MANIFESTATIONS	DURATION AND RECOVERY	SEVERITY BY HOSPITAL ADMISSION STATUS (MEAN AGE & GENDER DISTRIBUTION)
Domínguez[17] et al. 2020	Ageusia: 5,1% Anosmia: 6,5% Association of ageusia along with anosmia: 47,2%	Olfactory neuroepithelium; Tongue papillae.	Recovery ageusia: 45,5% from which 90,6% cured in <2 weeks and 9,4% in >2 weeks.	Hospitalized patients: n=649 (60±14,6 yo; 57,6/42,4%). Non-hospitalized patients: n=197(46,5±14,5 yo; 36,5%/63,5%)
Biadsee[18] et al. 2020	Olfactory dysfunction: 67% (35 males/51 females) no significant difference between both sexes. Anosmia: 19,5% Dysgeusia: 52%. Xerostomia: 52,3% Facial Pain: 26% Masticatory muscle pain: 11% Alteration of the tongue: 15,6%	Olfactory neuroepithelium; Tongue; Forehead; Masticatory muscles (temporal fossa and masseteric insertions on the angle of the mandible areas); Palate; Gums.	NC	NC
Favia[19] et al. 2021	Pain Burning Bleeding Difficulty to chewing & swallowing. Ulcerative lesions: 65-58,2% (Multiple :60%; Simple: 40%)	Tongue; Palate; Lip; Cheek.	Biopsy due to a recovery (n=4) > 14 day. Blisters before the ulcerative lesions (n=7). Oral manifestations:92% at the onset of the general symptoms or not further than a week. Moderate group: Oral manifestations: before the onset of the general symptoms (26,4%), within the week after (41%) the onset of the general	Moderate (77%): mean age of 63yo with Geographic tongue (5%), fissured tongue (4%), Ulcerative lesions (51%), blisters (14%), hyperplasia of papillae (33%), angina bullosa (8%), candidiasis (18%), ulcero-necrotic gingivitis (1%), petechiae (4%), Taste disorders (87%).

			symptoms and before specific Covid-19 treatment, one week after (32,6%). Severe group: Oral manifestations occurring before the onset of the general symptoms (19%), within the week after (52,4%) the onset of the general symptoms and before specific Covid-19 treatment, one week after (28,6%).	Severe (17%): mean age of 74yo with Geographic tongue (2%), fissured tongue (1%), Ulcerative lesions (11%), blisters (5%), hyperplasia of papillae (13%), angina bullosa (2%), candidiasis (4%), ulcero-necrotic gingivitis (2%), petechiae (6%), Taste disorders of (88%). Critical (6%): mean age of 81yo with ulcerative lesions (3%), hyperplasia of papillae (2%), angina bullosa (1%), candidiasis (6%), ulcero-necrotic gingivitis (4%), petechiae (4%), spontaneous oral hemorrhage (1%),Taste disorders (83%).
Fidan[20] et al. 2021	Aphtous-like ulcer :46,6% Erythema :32,8% Lichen Planus:20,6%	Tongue (39,7%); Bucal mucosa (34,5%); Gingiva (18,9%); Palate (6,9%).	NC	Patients with: Oral lesions (n=58) and without oral lesions (n=16)
Gherlone[21] et al. 2021	Abnormalities in TMJ:7,3% Masticatory muscle weakness:19% Salivary gland ectasia:38% Xerostomia:24,6% Dysgeusia:17% Anosmia:14% White tongue:28% Oral Ulcers:11% Facial tingling:3% Trigeminal neuralgia:2% Abnormalities of mucous membrane: 1%	TMJ; Buccal mucosa; Olfactory neuroepithelium; Masticatory muscles; Temporal fossa; Mid & lower 1/3 of face.	Up to 3-month follow-up: Oral lesions (86,3%), dry mouth (30%), Dry mouth mouth + Salivary ectasia (12,8%)	DM & COPD significantly associated to dry mouth and COPD was a predictor to dry mouth alone. 93% of patients with salivary gland ectasia received antibiotics. Antibiotics injection, CRP & LDH serums levels increased significantly the risk the develop salivary glands ectasia

				with Antibiotics & LDH levels being predictors alone. No association between was found between the disease manifestations and severity with the oral manifestations.
Halepas[22] et al. 2021	Cervical lymphadenopathy:19,2% Red or swollen lips:48,9% Strawberry tongue:10,6% Cranial nerve palsy:12,8%	Oral mucosa; Cervical lymph nodes; Perioral tissues; Tongue; Facial muscles	NC	Patients with MIS-C (n=47) without sex dominance all above 21 yo (51,1/48,9%). Patients with oral or oropharyngeal manifestations: 55,3% with mean age of 7,8 (5,7 to 9,8) with 42,3/57,7% M/F. Significantly associated with presence of systemic rash, conjunctivitis and absence of cough. Patients without oral or oropharyngeal manifestations: 44,7% with mean age of 10,5 (8,5 to 12,5) with 61,9/38,1%.
Horzov[23] et al. 2021	Tongue coloration (n=134). Pale pink (n=45). Red (n=72). Dark red burgundy (n=17). Tongue plaque (91,11%) - White (n=45). - Grey (n=47). - Yellow(n=31).	Tongue	NC	Mild (10,37%): pale pink tongue coloration (64,29%) and red tongue coloration (35,71%). Moderate (62,96%): pale pink tongue coloration for 62,35% and red coloration of the tongue for 37,5%. Severe (26,67%): pale pink coloration of the tongue (11,11%) and 88,88% of reddish pink coloration among which red (41,66%) and was dark red or burgundy (47,22%).

				Groups > 40 yo always displayed the presence of tongue plaque and more reddish prevalent colour of the tongue.Tongue plaque: present for 91,11% especially in groups > 40 yo. Groups > 40 yo displayed a more prevalent grey and yellow colorations plaque of the tongue. Patients without tongue plaque: 12 (9 from mild group and 3 from the moderate one). No gender association for both manifestations.
Natto[24] et al. 2021	Oral symptoms: 53% Mean age was 39,1±12,2 M/F: 69/31%. Loss of taste: 39,4% Erythema and desquamated:7,3% Coated tongue:7,3% Ulcers and blisters:6,4% Pain and soreness:2,8% Dry mouth:0,9%	Dorsum of the tongue (72,4%); Vestibules (12,1%); Buccal Mucosa, lips & gingiva (8,6%); Ventrum of the tongue (1,7%); Floor of the mouth (1,7%).	Symptoms detected in 1 to 4 days with oral manifestations (81%). Loss of taste as the only symptom persisting further than 10 days. All the others symptoms except from loss of taste: 1 - 7 days. Symptoms experienced for the 1st time for 93,9% of patients with oral manifestations & 84,5% of patients being aware of oral manifestations.	Patients with oral symptoms: 53% Patients without oral symptoms: 47%
Seo[25] et al. 2020	Cough:32,3% Sore throat:30,6% Sputum:14,5% Headache:14,5% Rhinorrhea: 16,1% Nasal congestion:11,2%	Oral mucosa through endoscopy; Nasal mucosa through endoscopy; Tongue.	Evaluation 12±9 days after PCR-confirmed Covid-19 diagnosis. Dysosmia: 8 - 38 days. Dysgeusia: 15 - 38 days.	One symptom being Dysgeusia or Dysosmia (n=6/10) Vs Both (n=4); Chronic rhinosinusitis (n=1); Allergic rhinitis (n=1). Dysgeusia: before objective evaluation:(n=4) Vs after (n=6). None of these patients showed

				oral or tongue alterations during endoscopy.
Subramaniam [26] et al. 2021	Oral manifestations: 1,26% M/F: 33,3/66,6% Comoborbidities:1 00% in male Vs 66% in female. Ulcerations on buccal mucosa: 11,11%. Generalized mucositis: 11,11%. Solitary ulcer on buccal mucosa & geographic tongue & bilateral angular cheilitis: 11,11%. Red & white spots on the palate similar to pseudomembranous candidiasis: 11,11%. Mucositis on upper & lower labial mucosa with geographic tongue & ulcerations: 11,11%. Recurrent herpetic labialis and angular cheilitis: 11,11%. Traumatic ulcer with bloody encrustations: 11,11%. Xerostomia, bilateral angular cheilitis, geographic tongue & glossitis: 11,11%. Mucositis & xerostomia: 11,11%.	Oral mucosa; Tongue; Labial mucosa; Perioral tissues.	NC	NC
Villarreal[27] et al. 2020	ENT: 70% Olfactory alterations:68% Taste alteration: 70% Nasal congestion: 45% Odynophagia: 37% Nasal dryness: 34% Rhinorrhea or mucous discharge: 25% Hearing loss: 8% Tinitus:6%	Olfactory neuroepithelium; Oral mucosa.	Alterations of taste and smell: 2 - 45 days with an average of 11 days recovery. Symptoms for 1 month: 26%.	Taste or olfactory alterations alone leading to a positive-PCR test (1,3%). Oral manifestations at the onset of the general symptoms not further. Pneumonia (19%) among which patients needed hospitalization (18%). Hospitalized patients: alteration of taste (68%) and smell (70%).

PCR= Polymerase Chain Reaction; CS= Cross sectional study; CaS= Case Series; STD= Taste or Smell Disorders ; V.A.S= Visual analog scale; NC= Non-communicated; TMJ= Temporo-mandibular joint; DM= Diabetes Mellitus; COPD= Chronic bronchopulmonary disease; CRP= C-reactive protein; LDH= Lactate dehydrogenase; MIS-C= Multi-inflammatory syndrome in children; ENT= Ears-Nose-Throat.

ANNEX 5: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	20
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	25
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	23-24
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	25
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	25
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	25
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	25
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	26
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention	

Section and Topic	Item #	Checklist item	Location where item is reported
methods		characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	27
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	27
Study characteristics	17	Cite each included study and present its characteristics.	27-28
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	28
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	28-33
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	34-40
	23b	Discuss any limitations of the evidence included in the review.	44
	23c	Discuss any limitations of the review processes used.	44
	23d	Discuss implications of the results for practice, policy, and future research.	45
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

ANNEX 6: Article version

TITLE: « Oral manifestations of Covid-19: Systematic review"

RUNING TITLE: Oral manifestations of Covid-19

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KEYWORDS: COVID-19; Coronavirus; SARS-2; oral; dental; buccal; mouth; manifestations; lesions; dysgeusia; anosmia; ageusia; dysosmia; oral mucosal lesions.

ABSTRACT: **Introduction**: COVID-19 is a viral disease caused by SARS-CoV-2. It was reported among humans for the first time in December 2019, at Wuhan, China. Its general manifestations include fever, asthenia, dry couch, shortness of breath and pneumoniae. Several oral manifestations have been described among positive Covid-19 patients such as macular erythematous lesion, anosmia, dysosmia, ageusia or dysgeusia. However, the origin of the oral mucosa lesions and the causality of Covid-19 is yet to be proven. The aim of this systematic review is to analyze the oral manifestations among Covid-19 positive patients. **Material and methods**: A comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials was conducted from December 2021 to March 2022. **Results:** 11 studies were included among which there were 5 cross-sectional studies, 1 case serie, 3 prospective cohort studies and 2 observational studies. A total of 40 oral manifestations and 15 different locations were reported. **Conclusion**: The onset of the oral manifestations occurred at the same time than the systemic ones or developed less than a week after the appearance of the systemic ones. The majority of the patients were aware of the oral lesions. The severity of SARS-CoV-2 infection seemed to be inversely proportional to the appearance of oral manifestations and increase

with the age of the patients. The severity of the Covid-19 infection seemed to be related with the gender of the patients, with higher frequency of manifestation in women. Covid-19's severity didn't seem to be associated with the recovery.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 SARS-CoV-2 has been identified as the causative agent for COVID-19, named after Coronavirus disease-2019. (1, 2) Early reports suggested that SARS-CoV-2 infected bats through the animal reservoir transmission. The Wuhan Health Commission publicly revealed the existence and spread of a viral pneumonia outbreak off unknown etiology on the 31st of December 2019, affecting by this time 27 people mostly related to the Huanan Seafood Wholesale Market, notifying the World Health Organization WHO in the meantime. (3)

The secretion of cytokines and chemokines conditioned by the entry of SARS-CoV-2 virus gives the intensity of the inflammatory response. (4) The early systemic symptoms of Covid-19 share a lot of similarities in common with other known infectious diseases. The clinical manifestations of Covid-19 can be classified into mild and severe clinical features. (4, 5) The most common and mild clinical manifestations displayed by Covid-19 include fever, asthenia, dry couch and shortness of breath. The more severe clinical features of Covid-19 regarding the respiratory system include acute respiratory distress syndrome, pneumonia, trouble in breathing, permanent chest pressure or pain, productive cough with sputum.

The first reported oral lesion linked to COVID-19 was enanthems in the oral mucosa of the palate and gingival margins. (6) Ever since, several oral manifestations have been reported among positive Covid-19 patients such as macular erythematous lesion, anosmia, dysosmia, ageusia, dysgeusia, ulcerations, blisters and petechiae. (5, 6)

The aim of this systematic review is to analyze the oral manifestations among Covid-19 positive patients.

MATERIAL AND METHODS

Protocol

This systematic review was performed through the Preferred Reporting Items for the Prisma Extension Statement for reporting of Systemic Reviews Incorporating Network Meta-Analysis of Health Care Interventions (PRISMA-P checklist). (7)

Search strategy

Three different databases Medline, Cochrane Central Registry of Controlled Trials and Scopus were used to screen all the pertinent Randomized Controlled Trials (RCTs), Observational Studies, Multicenter Studies, Controlled Clinical Trials, Comparative Studies, Case series, Clinical Trials and Clinical Studies in English through a comprehensive research performed from December 2021 to Mars 2022. The following keywords were used: COVID-19; Coronavirus; SARS-2; oral; dental; buccal; mouth; manifestations; lesions; dysgeusia; anosmia; ageusia; dysosmia; oral mucosal lesions.

Selection criteria

The PICO (Patients; Intervention; Comparison; Outcomes) process was used to determine the following inclusion criteria: (P) Patients: without limit of age, sex and ethnicity with a diagnosis of Covid-19 confirmed with PCR-test. (I) Intervention: development of oral manifestations. (C) Comparator: Without comparative group. (O) Outcomes: description of the most frequent Covid-19 oral lesions and their characteristics, correlate the oral symptomatology with the systemic manifestations of Covid-19, analyze the links between the severity of the Covid-19 infection and the oral manifestations.

Inclusion criteria

The following inclusion criteria were applied: 1) Randomized Control trials (RCTs); 2) Observational studies; 3) Multicenter studies, 4) Controlled Clinical Trials; 5) Comparative studies; 6) Clinical studies; 7) Clinical trials; 8) English or Spanish; 9) Humans.

Exclusion Criteria

The following exclusion criteria were applied: 1) Studies in which diagnosis was not confirmed with PCR, 2) Studies that included patients in which the clinical examination was not made by some trained personnel (dentist or physician).

Data extraction

The following data were obtained from each included study: author, country of origin, study design, number of patients, age of patients, sex of patients, type of oral manifestations, prevalence of the oral manifestations, anatomical localization of the oral manifestations, duration of the symptoms, covid-19 severity based on the status of hospital admission.

Quality assessment

A twelve criteria's scale was used to assess the quality of each selected articles: Critical Appraisal Skills Program (CASP) Cohort studies Standard Checklist (8). The corresponding possible answers were "Yes" or "+", "No" or "-" and "Can't tell" or "?". The sum of the answers was calculated with a maximum of twelve.

RESULTS

Trial selection

The electronic research on 3 different databases resulted in 318 published references. The elimination of the duplicates led to a new total of 280 references. The screening of the titles eliminated 234 articles and made us obtain a total of 18 full-text articles was. Out of these 18 full-text articles, 6 got excluded because of the following criteria: absence of Polymerase Chain Reaction diagnosis for Covid-19 (n=5), subjective evaluation of the oral manifestations and only abstract in English (n=1). A final number of 11 studies was included in this systematic review (Scheme 1).

Trial characteristics

A total of 2758 patients were studied in this systematic review. The characteristics of the eleven included studies are listed in table 2 (Table 1).

Quality assessment

The quality scores obtained from the articles included in this study ranged from 10 to 12, showing that they were all high methodological quality (Table 2).

Frequency of oral manifestations of Covid-19

The most common oral manifestation was ageusia. (9, 10, 11, 12, 13, 16, 17, 19). The second ones were tongue alterations. (13, 14, 15, 17). Accounting as the third most common oral lesions, both anosmia (9, 10, 13, 17, 19) and ulcerative lesions (11, 12, 13, 16, 18) got quoted 5 times. Xerostomia (10, 13, 16, 18) and tongue color (13, 14, 15, 17) were outcomes appearing 4 times each. Facial pain and weakness (10, 13, 16), masticatory muscles pain and weakness (10, 13, 14) and alteration of the mucous membranes (13, 16, 18) turned out to be reported 3 times each. Six oral manifestations appeared twice in this study, being respectively ageusia along with anosmia (9, 17), geographic tongue (11, 18), blisters (11, 16), cranial nerve palsy and weakness (13, 14), rhinorrhea and nasal congestion (17, 19). The others oral manifestations in order were fissured tongue, papillae hyperplasia, angina bullosa, candidiasis, ulceronecrotic gingivitis, petechiae and spontaneous hemorrhage oral.

Onset

One article (11) referred that the oral manifestations onset appeared at the mean time than the general symptoms or not further than a week for 92%. Another study (16) reported the detection of oral symptoms in 81% of the patients between 1 to 4 days after the onset of the general symptoms. Another article (27) revealed that 1,3% of its patient was affected by dysgeusia or dysosmia alone without general manifestations of Covid-19 and that these oral manifestations lead the patients to perform a SARS-CoV2 PCR test.

Awareness

In one study (16), 84,5% of the patients were aware of their oral manifestations. Among them, 93,9% was facing these symptoms for the first time. In

another article (17), 40% complained before the assessment when a rate of 60% of oral manifestations presence was found after the objective evaluation.

Recovery period

Patients recovered from ageusia in less than 2 weeks for one study (9) while when the period of 14 days was exceeded without recovering, the patients were taken to biopsy in another study (27). One study (13) displayed an expression of symptoms even further than 3 months in 83,6% of their patients, among which 30% presented xerostomia alone and 12,8% was affected by both xerostomia and salivary gland ectasia. One study (19) assessed both dysosmia and dysgeusia recovery together, displaying recovery period ranging from 2 to 45 days with an average period of time of 11 days. 26% of the patients of this study expressed symptoms for more than a month.

Severity

Gherlone (13) et al. reported that 7,3% of their patients manifested with temporo-mandibular joint alterations, among which the mean age was of 48 years old while the group of patients didn't display the jaw alteration was aged of 63,2 years old. These findings join the ones of Favia (11) et al. and Domínguez (9) et al. in the way that the oral manifestations occur in the younger groups of patients displaying less severe forms of Covid-19 infections. In addition, the tongue plaque had a more yellow and grey coloration which was associated to a more severe manifestation. Similar to the results of Horzov (15) et al., Subramaniam (18) et al. reported that 100% of their patients displaying oral manifestations, which accounted for only 1,26% of the total population, were aged of more than 50 years old. In addition, the authors declared that 100% of the male group which accounted for 33,3%, had comorbidities and that percentage raised to 66% in the female group accounting for 66,6%.

DISCUSSION

Frequency of the oral manifestations

The main reported oral symptoms to this day were taste and smell alterations. Dos Santos et al. (22) classified the alterations according to their quantitative nature, 24% of their patients experiencing ageusia, or to their qualitative one with 38% of the patients facing dysgeusia and 35% hypoageusia. They emphasized on the character of taste alteration which is commonly present in flu-like syndromes but that was absent during the previous SARS-CoV and MERS outbreak, indicating a closer nature of manifestations to the viral ones.

The infections generated by a virus are usually characterized by an abrupt onset of the symptoms cursing together with enanthems, blisters and ulcerations.(20)

Seo (17) et al. reported that 60% of their patients expressed either only dysgeusia or only dysosmia, having 40% of their studies population expressing both symptoms and thus a reaction off greater intensity. The recovery period ranged from 15 to 38 days for dysgeusia while it started from 8 to 38 days for dysosmia. This results implied that recovering from dysosmia required less time than recovering from dysgeusia, meaning the lesions of the olfactory neuroepithelium would cure faster in the case of dysosmia and need more time for more intense lesions on the tongue.

Domínguez (9) et al. declared that there was a higher prevalence of ageusia and anosmia in their non-hospitalized group in comparison to the hospitalized group. The authors reported a significant difference in the sex of the hospitalized patients. The hospitalized group was older and more off a male population while the non-hospitalized group which displayed more ageusia and anosmia comprised younger females in comparison. These data could indicate that more severe manifestations occurred in older men when the oral lesions appeared in a higher frequency amongst young females expressing a less severe form of Covid-19 infection.

Biadsee (10) et al. published that there was a higher prevalence among women experiencing anosmia and facial pain. However, the authors also published that the olfactory dysfunctions expressed no significant difference between both sexes. These findings tend towards the tendency to develop more lesions for women. Halepas (14) et al. encountered similar data about the gender

distribution and the experienced symptoms. In addition, Dos Santos et al. (22) found a significant association between taste alteration and Covid-19 in women.

The data providing a higher prevalence of oral manifestations among women tended to be explained by Dos Santos et al.(22) Indeed, the authors expressed that the female reaction to a viral infection leads to a more important hormonal change giving an alteration of the innate immune response and a higher dysfunction of the organism.

Without regard to the sex and oral manifestations association, Gherlone (13) et al., Horzov (15) et al., and Villarreal (19) et al. reported respectively that there was no significant difference between both sexes in the expression of temporo-mandibular joint alterations, that there were no gender association for both tongue color changes and plaque color changes and finally that there was not any sex dominance for the ears, nose and throat alterations described by Villarreal (19) et al. Those findings counterbalance the previous associations realized by Domínguez (9) et al and Biadsee (10) et al. Dos Santos et al. (22)

Correlations of the oral manifestations with general symptoms

The course of appearance of the manifestations of Covid-19 seemed to indicate that the oral lesions might occur as the first signs of infection and thus could be useful in the early diagnosis of SARS-CoV-2 infection.(20) Villarreal (19) et al. displayed that oral lesions were expressed either before the onset of the systemic manifestations for 1,3% or at the same time of the appearance of the systemic manifestations for 98,7%, not appearing further than the onset of general manifestations. Furthermore, Favia (11) et al. found results that seemed to show that the appearance of the oral manifestations could be used as a predictor for Covid-19 infection. However, their data indicated that the oral lesions happened to appear more often at the same time than the onset of the systemic manifestations than before.

Nevertheless, Natto et al. (16) encountered oral manifestations appearing from 1 to 4 days after the onset of the general symptoms for 81 of the patients. In addition, Favia et al. (11) also reported that 32,6% of their patients from the moderate group developed oral manifestations after the systemic ones, that

28,6% of the patients from the severe group expressed the oral lesions after the systemic ones, and finally that 75% of the critical group displayed the onset of the oral lesions after the onset of the systemic manifestations. The proportion of patients expressing the oral manifestations at the same time or after the onset of the systemic manifestations is more important than the proportion of the groups developing oral lesions before systemic manifestations. Thus, it does not seem that the onset of the oral manifestations can be used as a predictor for Covid-19 infection. (11,16)

Severity of the SARS-CoV-2 and oral manifestations

The severity of the infection and immune response is determined by generated by the so called “cytokine storm” causing acute respiratory distress as well as multiple organ failure. (21) The onset of the oral manifestations seemed to appear later according to a gradient severity of the immune response and infection based on Favia (11) et al. findings. The severity of the disease according the Villarreal (19) et al. does not seem to influence neither the onset nor the rate of the oral manifestations.

However, Domínguez et al. (9) found that there was a significant higher frequency of anosmia and ageusia in the non-hospitalized group, along with a significant lower rate of recovery from ageusia and anosmia and concluded that there was no significant difference for the recovery status and recovery rate between the intervention and the control group. These results may support the hypothesis that the oral lesions may manifest more when the Covid-19 infection is mild. When it was severe, oral manifestations were expressed in a lower frequency.

Halepas (14) et al. stated a significant association with absence of cough, existence of a systemic rash and presence of conjunctivitis, which would tend to affirm the hypothesis supporting that oral lesions may manifest in mild forms without pneumonia-like symptoms.

Villarreal (19) et al. declared that the comparison of the prevalence of taste and smell disorders between hospitalized and non-hospitalized happened to be in the same range. The severity didn’t seem to influence upon the recovery rate from taste and smell disorders.

The severity of the general manifestations of Covid-19 seemed to be related with the age of the patient according to Favia (11) et al.

Domínguez (9) et al compared the age of the patients whether they hospitalized or not. The results tended to indicate another time that the severity of the manifestations was related to the age of the patients, elderly leading to more severe forms of the Covid-19 infection requiring hospitalization. However, the severity didn't seem to have an influence over the appearance of oral manifestations since the more severe the SARS-CoV-2 infection, the less oral manifestations would appear in comparison to general manifestations.

The tendency to express oral manifestations when the SARS-CoV-2 form is less severe and when patients are younger is also supported by Halepas (9) et al.

Limitations

This systematic review has several limits. Due to a temporal limitation, there were no published articles regarding the SARS-CoV-2 different variants and the oral manifestations of Covid-19, nor articles about oral manifestations of Covid-19 and the anti-Covid-19 vaccine either, nor article about oral manifestations among patients undergoing a second Covid-19 infection.

It would be interesting in the future to develop research about the different SARS-CoV-2 variants and the possible oral manifestations encountered in patients suffering from these new Covid-19 forms.

CONCLUSION

The most frequent oral manifestation was ageusia. The second most prevalent oral lesion was tongue ulcers followed by anosmia with an average recovery period of 14 days. The majority of the patients were aware of the lesions they were presenting in the mouth.

The onset of the oral manifestations occurred at the same time than the systemic ones or developed less than a week after the appearance of the

systemic ones. In some cases, the onset of the oral manifestations happened before the development of systemic alterations, leading to a SARS-CoV-2 PCR test without any other alteration than the ones in the oral cavity.

The severity of SARS-CoV-2 infection seemed to be inversely proportional to the appearance of oral manifestations. The less severe the Covid-19 infection is, the more oral lesions would develop. The more advanced age led to a more severe form of Covid-19 and less oral manifestations.

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CONFLICT OF INTEREST

No conflict of interest in this article.

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374 **FIGURE AND TABLE:**

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Figure 1: Search strategy flow chart

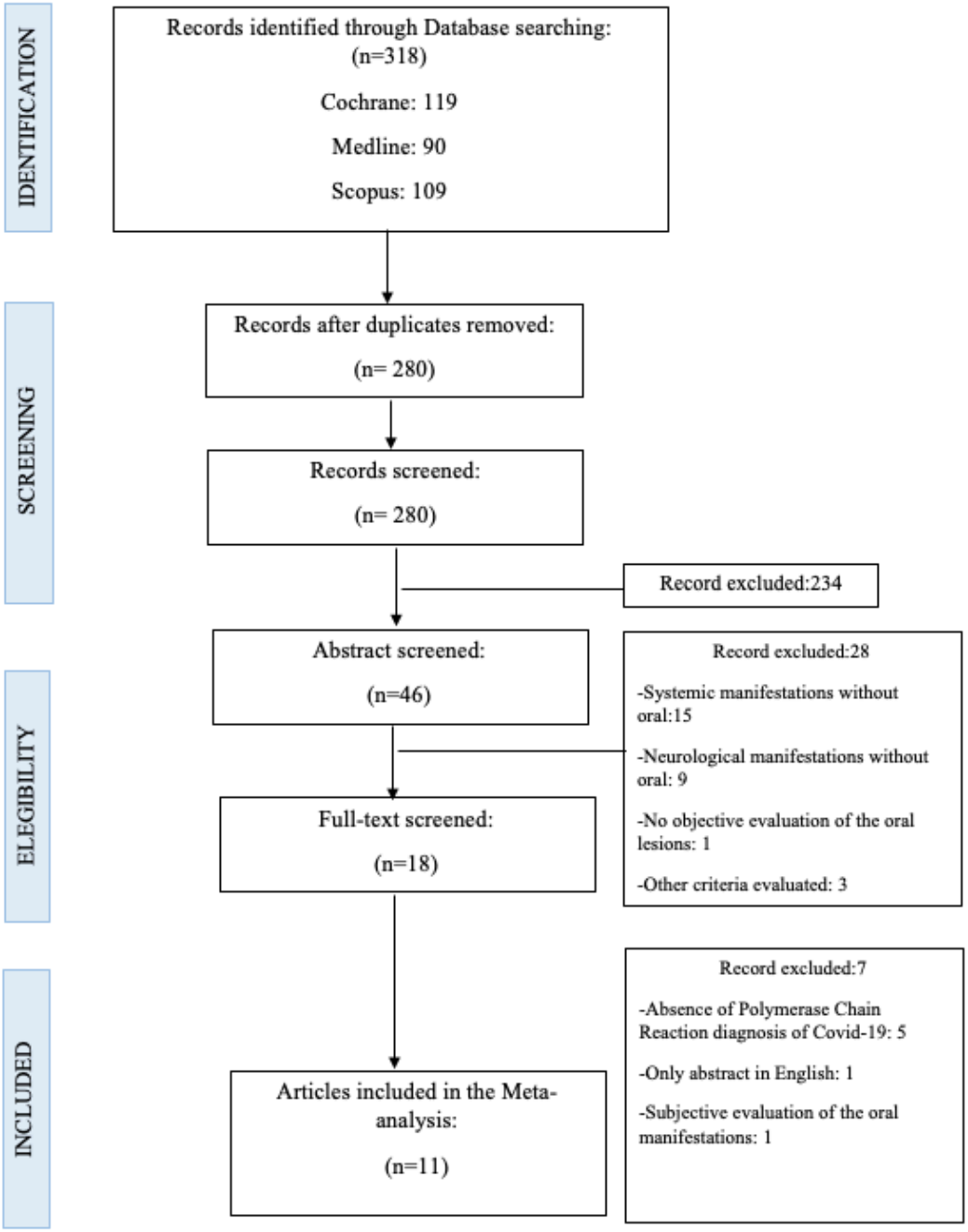

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Table 1: Data extraction

AUTHOR AND YEAR	STUDY DESIGN	NUMBER OF PATIENTS	MEAN AGE	GENDER DISTRIBUTION (%M/F)
Domínguez et al. 2020	CS	Intervention group: n= 846 Control group: n= 143	IG= 56,8± 15,7 CG= 53,5±16,6	IG= 52,7 /47,3% CG= 51/49%
Biadsee et al. 2020	CaS	N=128	36,25 (18-73)	45,3/54,7%
Favia et al. 2021	CS	N=123	72	56,9/43,1%
Fidan et al. 2021	CS	N=74	49,3±7,2	66,2/33,8%
Gherlone et al. 2021	PCS	N=122	66,5 (53,9 -74,1)	75,4/24,6%
Halepas et al. 2021	PCS	N=47	9±5 (1,3-20,0)	51,1/48,9%
Horzov[23] et al. 2021	CS	N=135	48,7±13,2 (18-82)	47,4/52,6%
Natto et al. 2021	CS	N=109	39,3±12,4	53,2/46,8%
Seo et al. 2020	PCS	N=62	33±12 (20-62)	30/70%
Subramaniam et al. 2021	OS	N=713	NC	58,3/41,7%
Villarreal et al. 2020	OS	N=256	43 (18-62)	15/85%

PCR: Polymerase Chain Reaction/ CS: Cross sectional study/ CaS: Case Series/ STD: Taste or Smell Disorders/ VAS: Visual analog scale/ PCS: Prospective cohort study/ OS: Observational study/ NC: Non-communicated

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Table 2: Quality assessment

	Domínguez et al.	Biadsee et al.	Favia et al.	Fidan et al.	Gherlone et al.	Halepas et al.	Horzov et al.	Natto et al.	Seo et al.	Subramaniam et al.	Villarreal et al.
Clearly focused issue	+	+	+	+	+	+	+	+	+	+	+
Cohort recruited in an acceptable way	+	+	+	+	+	+	+	+	+	+	+
Exposure accurately measure to minimize bias	+	+	+	+	+	+	+	+	+	+	+
Outcomes accurately measure to minimize bias	+	+	+	+	+	+	+	+	+	+	+
Identifications of cofounding factors	+	+	+	+	+	+	+	+	+	+	+
Follow of subjects complete and long enough	+	+	+	+	+	+	+	+	-	+	+
Identification of the results	+	+	+	+	+	+	+	+	+	+	+
Precision of results	+	?	-	+	+	+	+	+	+	+	-
Results believable	+	+	+	+	+	+	+	+	+	+	+
Application of the results to our local population	+	+	+	+	+	+	+	+	+	+	+
Results of this study fits with other available evidence	+	+	+	+	+	+	+	+	+	+	+
Implication of the study for our practice	?	+	?	+	+	+	+	+	?	?	+
SCORE	11	11	10	12	12	12	12	12	11	11	11

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Table 3: Outcomes' results

AUTHOR YEAR	COVID-19 ORAL MANIFESTATIONS	ANATOMICAL LOCATIONS OF ORAL MANIFESTATIONS	DURATION AND RECOVERY	SEVERITY BY HOSPITAL ADMISSION STATUS
Domínguez et al. 2020	Ageusia: 5,1%; Anosmia: 6,5%; Ageusia + anosmia: 47,2%	Olfactory neuroepithelium; Tongue papillae.	Recovery ageusia: 45,5% from which 90,6% cured in <2 weeks and 9,4% in >2 weeks.	Hospitalized patients: n=649 (60±14,6 yo;57,6/42,4%). Non-hospitalized: n=197(46,5±14,5 yo; 36,5%/63,5%)
Biadsee et al. 2020	Olfactory dysfunction: 67% (35 males/51 females) no significant difference between both sexes.; Anosmia: 19,5%; Dysgeusia: 52%.; Xerostomia: 52,3%; Facial Pain: 26%; Masticatory muscle pain: 11%; Alteration of the tongue: 15,6%	Olfactory neuroepithelium; Tongue; Forehead; Masticatory muscles; Palate; Gums.	NC	NC
Favia et al. 2021	Pain; Burning; Bleeding; Difficulty to chewing & swallowing.; Ulcerative lesions: 65-58,2%	Tongue; Palate; Lip; Cheek.	Blisters before the ulcerative lesions (n=7). Oral manifestations:92% at the onset of the general symptoms or not further than a week. Moderate group: Oral manifestations: before the onset of the general symptoms (26,4%), within the week after (41%) the onset of the general symptoms and before specific Covid-19 treatment, one week after (32,6%). Severe group: Oral manifestations occurring before the onset of the general symptoms (19%), within the week after (52,4%) the onset of the general symptoms and before specific Covid-19 treatment, one week after (28,6%).	Moderate (77%): mean age of 63yo with Geographic tongue (5%), fissured tongue (4%), Ulcerative lesions (51%), blisters (14%), hyperplasia of papillae (33%), angina bullosa (8%), candidiasis (18%), ulcero-necrotic gingivitis (1%), petechiae (4%), Taste disorders (87%). Severe (17%): mean age of 74yo with Geographic tongue (2%), fissured tongue (1%), Ulcerative lesions (11%), blisters (5%), hyperplasia of papillae (13%), angina bullosa (2%), candidiasis (4%), ulcero-necrotic gingivitis (2%), petechiae (6%), Taste disorders of (88%).
Fidan et al. 2021	Aphtous-like ulcer :46,6%; Erythema :32,8%; Lichen Planus:20,6%	Tongue (39,7%); Bucal mucosa (34,5%); Gingiva (18,9%); Palate (6,9%).	NC	Patients with: Oral lesions (n=58) and without oral lesions (n=16)
Gherlone et al. 2021	Abnormalities in TMJ:7,3%; Masticatory muscle weakness:19%; Salivary gland ectasia:38%; Xerostomia:24,6%; Dysgeusia:17%; Anosmia:14%; White tongue:28%; Oral Ulcers:11%; Facial tingling:3%; Trigeminal neuralgia:2%; Abnormalities of mucous membrane: 1%	TMJ; Buccal mucosa; Olfactory neuroepithelium; Masticatory muscles; Temporal fossa; Mid & lower 1/3 of face.	Up to 3-month follow-up: Oral lesions (86,3%), dry mouth (30%), Dry mouth + Salivary ectasia (12,8%).	DM & COPD significantly associated to dry mouth and COPD was a predictor to dry mouth alone. 93% of patients with salivary gland ectasia received antibiotics. Antibiotics injection, CRP & LDH serums levels increased significantly the risk the develop salivary glands ectasia with Antibiotics & LDH levels being predictors alone. No association between the disease manifestations and severity with the oral manifestations.
Halepaset al. 2021	Cervical lymphadenopathy:19,2%; Red or swollen lips:48,9%; Strawberry tongue:10,6%; Cranial nerve palsy:12,8%	Oral mucosa; Cervical lymph nodes; Perioral tissues; Tongue; Facial muscles	NC	Patients with MIS-C (n=47) without sex dominance all above 21 yo (51,1/48,9%). Patients with oral or oropharyngeal manifestations: 55,3% with mean age of 7,8 (5,7 to 9,8) with 42,3/57,7% M/F. Significantly associated with presence of systemic rash, conjunctivitis and absence of cough. Patients without oral or oropharyngeal manifestations: 44,7% with mean age of 10,5 (8,5 to 12,5) with 61,9/38,1%.
Horzov[23] et al. 2021	Tongue coloration (n=134): Pale pink (n=45), Red (n=72), Dark red burgundy (n=17). Tongue plaque (91,11%): White (n=45), Grey (n=47), Yellow (n=31).	Tongue	NC	Mild (10,37%): pale pink tongue coloration (64,29%) and red tongue coloration (35,71%). Moderate (62,96%): pale pink tongue coloration for 62,35% and red coloration of the tongue for 37,5%. Severe (26,67%): pale pink coloration of the tongue (11,11%) and 88,88% of reddish pink coloration among which red (41,66%) and was dark red or burgundy (47,22%). Groups > 40 yo always displayed the presence of tongue plaque and more reddish prevalent colour of the tongue. Tongue plaque: present for 91,11% especially in groups > 40 yo. Groups > 40 yo displayed a more prevalent grey and yellow colorations plaque of the tongue. No gender association for both manifestations.
Natto et al. 2021	Oral symptoms: 53%; Loss of taste: 39,4%; Erythema and desquamated:7,3%; Coated tongue:7,3%; Ulcers and blisters:6,4%; Pain and soreness:2,8%; Dry mouth:0,9%	Dorsum of the tongue (72,4%); Vestibules (12,1%); Buccal Mucosa, lips & gingiva (8,6%); Ventrum of the tongue (1,7%); Floor of the mouth (1,7%).	Symptoms detected in 1 to 4 days with oral manifestations (81%). Loss of taste as the only symptom persisting further than 10 days. All the others symptoms except from loss of taste: 1 - 7 days. Symptoms experienced for the 1st time for 93,9% of patients with oral manifestations & 84,5% of patients being aware of oral manifestations.	Patients with oral symptoms: 53% Patients without oral symptoms: 47%

Seo et al. **2020**	Cough:32,3%; Sore throat:30,6%; Sputum:14,5%; Headache:14,5%; Rhinorrhea: 16,1%; Nasal congestion:11,2%	Oral mucosa through endoscopy; Nasal mucosa through endoscopy; Tongue.	Evaluation 12±9 days after PCR-confirmed Covid-19 diagnosis. Dysosmia: 8 - 38 days. Dysgeusia: 15 - 38 days.	One symptom being Dysgeusia or Dysosmia (n=6/10) Vs Both (n=4); Chronic rhinosinusitis (n=1); Allergic rhinitis (n=1). Dysgeusia: before objective evaluation:(n=4) Vs after (n=6). None of these patients showed oral or tongue alterations during endoscopy.
Subramaniam **et al.** **2021**	Oral manifestations: 1,26% M/F: 33,3/66,6%. Comoborbidities:1 00% in male Vs 66% in female. Ulcerations on buccal mucosa: 11,11%; Generalized mucositis: 11,11%; Solitary ulcer on buccal mucosa & geographic tongue & bilateral angular cheilitis: 11,11%; Red & white spots on the palate similar to pseudomembranous candidiasis: 11,11%; Mucositis on upper & lower labial mucosa with geographic tongue & ulcerations: 11,11%; Recurrent herpetic labialis and angular cheilitis: 11,11%; Traumatic ulcer with bloody encrustations: 11,11%; Xerostomia, bilateral angular cheilitis, geographic tongue & glossitis: 11,11%; Mucositis & xerostomia: 11,11%.	Oral mucosa; Tongue; Labial mucosa; Perioral tissues.	NC	NC
Villarreal et al. **2020**	ENT: 70%; Olfactory alterations:68%; Taste alteration: 70%; Nasal congestion: 45%; Odynophagia: 37%; Nasal dryness: 34%; Rhinorrhea or mucous discharge: 25%; Hearing loss: 8%; Tinitus:6%	Olfactory neuroepithelium; Oral mucosa.	Alterations of taste and smell: 2 - 45 days with an average of 11 days recovery. Symptoms for 1 month: 26%.	Taste or olfactory alterations alone leading to a positive-PCR test (1,3%). Oral manifestations at the onset of the general symptoms not further. Pneumonia (19%) among which patients needed hospitalization (18%). Hospitalized patients: alteration of taste (68%) and smell (70%).

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