

Epidemiological profile of patients with oral alterations during the COVID-19 infection – an integrative review

Perfil epidemiológico de pacientes com alterações orais durante a infecção por COVID-19 – uma revisão integrativa

Perfil epidemiológico de pacientes con alteraciones orales durante la infección por COVID-19 – una revisión integrativa

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Abstract

COVID-19, first identified in Wuhan, China, in December 2019, rapidly escalated into a global pandemic, causing significant health and economic crises. In addition to systemic symptoms, several oral manifestations have been reported in infected patients, given the high presence of the SARS-CoV-2 receptor (ACE-2) in oral tissues. This study aimed to conduct an integrative literature review to analyze oral alterations associated with COVID-19, compiling cases from the PubMed database up to February 26, 2021. A total of 19 studies encompassing 266 patients were included. The most common oral manifestations were dysgeusia, ageusia, hypogeusia, aphthous and hemorrhagic ulcers, burning sensation, and xerostomia. Oral co-infections, such as herpes simplex and candidiasis, were also observed. Results indicate that patients with systemic conditions (e.g., hypertension, diabetes, obesity) tend to develop more severe symptoms and require hospitalization, particularly individuals over 60 years old. The study highlights the importance of dental professionals in the multidisciplinary management of COVID-19 patients, as oral symptoms may serve as early indicators of infection. Standardization of data reporting in future studies is essential to enhance the understanding of oral involvement in COVID-19.

Keywords: COVID-19; Pandemics; Antibody testing, COVID-19; Oral manifestations.

Resumo

A COVID-19, identificada pela primeira vez em Wuhan, China, em dezembro de 2019, rapidamente evoluiu para uma pandemia global, causando crises econômicas e de saúde significativas. Além dos sintomas sistêmicos, várias manifestações orais foram relatadas em pacientes infectados, devido à alta presença do receptor do SARS-CoV-2 (ACE-2) nos tecidos orais. Este estudo objetivou conduzir uma revisão integrativa da literatura para analisar as alterações orais associadas à COVID-19, compilando casos da base de dados PubMed até 26 de fevereiro de 2021. Um total de 19 estudos envolvendo 266 pacientes foram incluídos. As manifestações orais mais comuns foram disgeusia, ageusia, hipogeusia, úlceras aftosas e hemorrágicas, sensação de queimação e xerostomia. Co-infecções orais, como herpes simples e candidíase, também foram observadas. Os resultados indicam que pacientes com condições sistêmicas (como hipertensão, diabetes e obesidade) tendem a desenvolver sintomas mais graves e necessitam de hospitalização, particularmente indivíduos com mais de 60 anos. O estudo destaca a importância dos profissionais de odontologia no manejo multidisciplinar de pacientes com COVID-19, pois os sintomas podem servir como indicadores precoces de infecção. A padronização na descrição dos relatos de casos em estudos futuros é essencial para melhorar a compreensão do envolvimento oral na COVID-19.

Palavras-chave: COVID-19; Pandemias; Sorodiagnóstico da COVID-19; Manifestações orais.

Resumen

La COVID-19, identificada por primera vez en Wuhan, China, en diciembre de 2019, escaló rápidamente a una pandemia global, causando importantes crisis sanitarias y económicas. Además de los síntomas sistémicos, se han reportado diversas manifestaciones orales en pacientes infectados, dada la alta presencia del receptor del SARS-CoV-2 (ACE-2) en los tejidos orales. Este estudio tuvo como objetivo realizar una revisión integradora de la literatura para analizar las alteraciones orales asociadas con la COVID-19, recopilando casos de la base de datos PubMed hasta el 26 de febrero de 2021. Se incluyeron un total de 19 estudios que abarcaron 266 pacientes. Las manifestaciones orales más comunes fueron disgeusia, ageusia, hipogeusia, úlceras aftosas y hemorrágicas, sensación de ardor y xerostomía. También se observaron coinfecciones orales, como herpes simple y candidiasis. Los resultados indican que los pacientes con condiciones sistémicas (por ejemplo, hipertensión, diabetes, obesidad) tienden a desarrollar síntomas más graves y requieren hospitalización, particularmente las personas mayores de 60 años. El estudio resalta la importancia de los profesionales dentales en el manejo multidisciplinario de pacientes con COVID-19, ya que los síntomas orales pueden servir como indicadores tempranos de infección. La estandarización de la información en futuros estudios es esencial para mejorar la comprensión de la implicación oral en la COVID-19.

Palabras clave: COVID-19; Pandémies; Prueba de anticuerpos COVID-19; Manifestaciones orales.

1. Introduction

The first case of coronavirus identified worldwide was in the city of Wuhan, capital of Hubei Province, China, on December 1, 2019, and was named COVID-19 (Organização Pan-Americana da Saúde, 2021). According to the World Health Organization (2020), COVID-19 was declared a pandemic on March 11, 2020, with 121,241 reported cases of contamination and 4,368 deaths. After five months, on August 11 of the same year, there were 19,959,187 confirmed cases and 382,867 recorded deaths. In October 2021, this figure reached 239,007,759 confirmed cases and 4,871,841 deaths. The pandemic caused countless deaths and a collapse of the health system and the world economy (Organização Mundial de Saúde, 2021).

The main modes of contamination by SARS-CoV-2 are direct contact with salivary droplets (cough, sneeze, and droplets), mucous membranes (nasal, ocular, and oral), and indirect contact with surfaces contaminated by fluids (Taques et al., 2020). Therefore, in addition to the serious consequences inherent in systemic manifestations, such as fever, cough, sore throat, nasal congestion, myalgia, headache, abdominal pain, and even severe acute respiratory syndrome, oral manifestations have also been reported in infected patients, as the mouth is one of the most contaminated anatomical regions (Ho et al., 2020). Among these oral manifestations, vesicular-bullous lesions, painful ulcers, desquamative gingivitis, xerostomia, burning tongue, dysgeusia, and ageusia are the most relevant (Chen et al., 2020). Such manifestations can be explained by the fact that the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE-2) receptor, present in large amounts in the epithelial cells of the oral mucosa as well as the salivary glands (Brandão et al., 2021).

Based on this assumption, the objective of this study was to carry out an integrative literature review regarding the possible oral manifestations caused by the SARS-CoV-2 virus, through a survey of cases reported by the scientific community, published between 2019 and February 26, 2021 (peak of the COVID-19 pandemic), on the PubMed platform. This survey is necessary to help health professionals identify the possible oral manifestations resulting from coronavirus contamination, in order to guide and document the cases already published.

2. Methodology

This scientific research is a study of a quantitative nature regarding the number of selected studies and a qualitative nature in terms of analysis and discussion of results. It is an integrative literature review on oral manifestations observed in patients with COVID-19. The integrative literature review provides a synthesis of knowledge and facilitates its incorporation into clinical practice by applying the results of selected studies (Snyder, 2019).

2.1 Inclusion Criteria

In order to gather evidence of oral alterations in patients with COVID-19, a bibliographic survey of articles containing case reports or patient evaluations was carried out. The following inclusion criteria were established:

1. Patients with a positive real-time polymerase chain reaction (RT-PCR) test;
2. Patients with some oral or facial alteration;
3. Reports that describe, as much as possible, basic epidemiological information about the case, such as age, gender, systemic conditions, site, and type of lesion.

2.2 Exclusion Criteria

The following exclusion criteria were considered:

1. Review articles;
2. Patients without a confirmed RT-PCR test;
3. Articles based on questionnaires without case reports;
4. Articles lacking dental follow-up during the symptomatic period.

2.3 Information Sources and Search Strategies

To retrieve scientific articles, the terms “COVID-19 AND oral alterations” were used as a search strategy in the PubMed database. No restrictions were applied regarding the period of publication or language of the articles. The database search was conducted until February 26, 2021. All articles obtained were imported into the Rayyan QCRI software (Hamad Bin Khalifa University, Qatar).

2.4 Selection of Studies

The studies were selected in three phases. In phases 1 and 2, two researchers (A.C.S.G. and K.B.), independently, selected the studies by title and abstract, respectively, from all publications obtained through the search strategy that met the inclusion criteria. Papers that did not meet the eligibility criteria were excluded. In phase 3, among the studies that did not allow identification by title or had incomplete abstracts, the researchers applied the same selection criteria to the full-text reading to determine which ones should be included. Reviewers independently reviewed all full-text articles. In cases of disagreement, discussions were held until a mutual consensus was reached. When mutual consensus was not reached, a third reviewer (J.M.G.) intervened to issue the final decision.

2.5 Data Collection Process

The researchers (A.C.S.G. and K.B.) collected the required information from the selected articles, and a third reviewer (J.M.G.) checked all the information. In cases of disagreement, discussions were held until a mutual agreement was reached among the researchers to determine the final decision.

2.6 Acquired Information

For each study included, the following information was recorded: number of reported cases, sex, age, average time to symptom onset, whether or not there was any systemic alteration, type of lesion and/or oral alteration, and location.

2.7 Measurement of Results

With the results obtained, we evaluated the number of reports available in the literature on oral changes related to COVID-19 infection, the most common lesions and symptoms, the most susceptible sites, and whether there is a relationship between age and gender and the appearance of oral changes.

3. Results

In phase 1, a total of 120 articles were retrieved from the PubMed electronic database. Then, the selection of articles by title and abstract was performed, and 81 articles were excluded, resulting in a total of 39 articles.

Next, the final phase of selection began, in which articles were selected through full-text reading. After reading the 39 articles, 20 were excluded based on the exclusion criteria, and 19 articles were included. A flow diagram of the article search, inclusion, and exclusion process is shown in Figure 1. To evaluate the results obtained from the 19 selected articles, a table was created with data extracted from each article (Table 1), in which each column represents a specific search topic.

The 19 selected articles evaluated oral alterations in a total of 266 patients (including Brandão et al. (2021), Cirillo & Colella (2021), Corchuelo & Ulloa (2020), Dima et al. (2020), Halepas et al. (2021), Hocková et al. (2021), Kitakawa et al. (2021), Maniaci et al. (2020), Mascitti et al. (2020), Ramires et al. (2021), Riad et al. (2021), Riad et al. (2022), Riad et al. (2022), Rodríguez et al. (2022), Santos et al. (2020), Schirinzi et al. (2020), Sinjari et al. (2020), Tapia et al. (2020), and Zarch et al. (2021)). The average age of the evaluated patients was 43.5 years. Among them, 120 (45.1%) were men, 106 (39.8%) were women, and 40 individuals had an unspecified gender (15%).

Among the reported alterations, dysgeusia (n=5), ageusia (n=4), and hypogeusia (n=1) were the main symptoms identified, followed by aphthous and hemorrhagic ulcers (n=7). Some patients also reported a burning sensation (n=3) and xerostomia (n=3). In addition to these manifestations, several patients also had co-infections with herpes simplex (n=4) and candidiasis (n=5). In general, these manifestations were predominantly found on the lips (n=8) and tongue (n=14), with an average duration of 21 days.

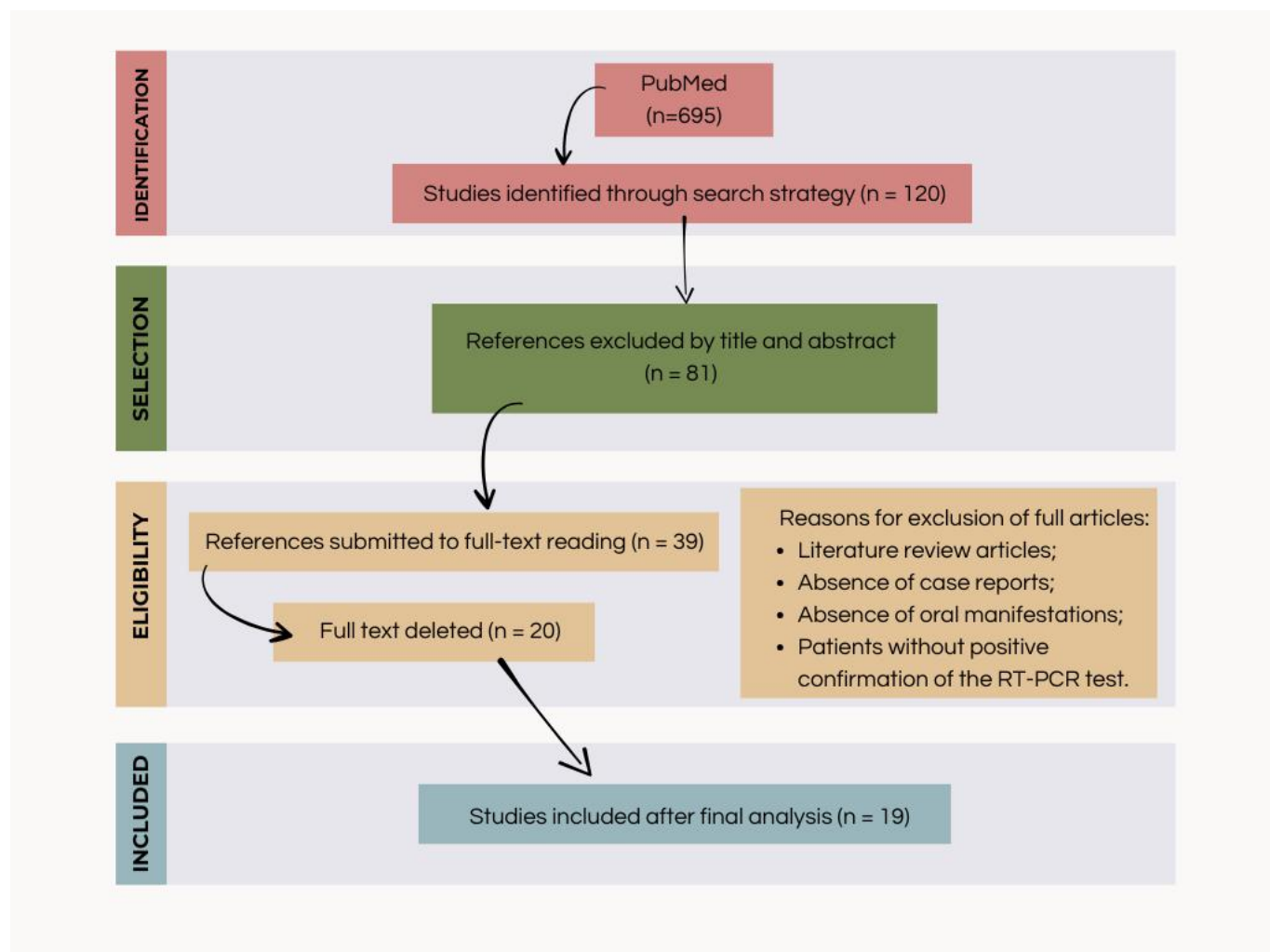
Among the articles that reported systemic conditions, the most common were: hypertension (n=7), diabetes (n=4), obesity (n=4), and thyroid disorders (n=3). On the other hand, in five studies, patients had no comorbidities.

The age of these patients was also evaluated in relation to the type of isolation, considering patients in home isolation as mild, patients hospitalized in a COVID-19 ward as moderate, and patients in the intensive care unit (ICU) as having severe and critical symptoms (Table 2). Only 79 patients had records with clear data on age as well as classification regarding symptoms and type of isolation/hospitalization. Some articles were not considered due to data inconsistency:

- They reported only the mean age of patients, without individualized information;
- They did not specify the type of isolation and/or hospitalization and/or systemic symptoms of SARS-CoV-2 infection;
- They contained subjective data.

Patients under 18 years old accounted for 10%. It is noteworthy that the largest number of patients identified belonged to the age group of 19 to 35 years old (n=30) for eight reports. Of these, three babies up to 15 days old were admitted to a neonatal unit with candidia, but none of them required hospital admission. Likewise, patients between 36 and 59 years old (n=28) had little dependence on hospital services (n=3), unlike patients over 60 years old (n=13), who mostly needed hospital care (n=9).

Figure 1 - Article search and selection flowchart.



Source: Authors.

Table 1 – Clinical data described in selected articles.

Authors	No. of patients	Age (average)	Gender (M/F)	Oral manifestations	Site	Onset of symptoms	Systemic diseases
Brandão <i>et al.</i> , 2021	8	53.8	5/3	- Dysgeusia - Aphthous ulcers - Herpes - Ageusia	Lip, tongue, palate, tonsils	4 days	Hypertension, chronic active pulmonary obstruction, diabetes, obesity, renal failure, fibromyalgia, Parkinson's disease, pancreatitis
Cirillo & Colella, 2021	1	36	0/1	- Hypogeusia	Tongue	12 weeks	No comorbidity
Corchuelo & Ulloa, 2020	1	40	0/1	- Petechiae Candidiasis Aphthous ulcers -Melanin pigmentation	Tongue, gum, lip, face	13 days	Not reported
Dima <i>et al.</i> , 2020	3	15 days old	2/1	- Candidiasis	Oral mucosa	Not reported	Not reported

Halepas <i>et al.</i> , 2021	47	9	24/23	- Cranial nerve palsy, - Cervical lymphadenopathy, - Red or swollen lips	Tongue, face, lips	Not reported	Not reported
Hocková <i>et al.</i> , 2021	3	64.3	3/0	Hemorrhagic ulcers	Tongue, lip, face	27 days	Hypertension, liver disease, hypercholesterolemia, reflux, obesity, history of myocardial infarction, septic shock
Kitaka <i>et al.</i> , 2021	1	20	0/1	- Herpes	Lip	14 days	No comorbidity
Maniaci <i>et al.</i> , 2020	1	15	1/0	- Dysgeusia	Tongue	21 days	No comorbidity
Mascitti <i>et al.</i> , 2020	40	57.6	Not reported	-Oral enanthema -Oral lichenoid lesions -Macroglossia - Ageusia -Herpes -Cheilitis	Face, lip, tongue, oral mucosa	Not reported	Not reported
Ramires <i>et al.</i> , 2021	1	50	0/1	- Aphthous ulcers	Lip	24 days	Hypertension, diabetes, obesity
Riad <i>et al.</i> , 2021	18	35.11	4/14	- Halitosis	Oral mucosa	Not reported	No comorbidity
Riad <i>et al.</i> , 2022	1	47	0/1	-Candidiasis	Tongue and palate	Not reported	Thyroid disorders
Riad <i>et al.</i> , 2022	26	36.8	9/17	- Aphthous ulcers - Ageusia	Tongue	4 days	No comorbidity
Rodriguez <i>et al.</i> , 2022	3	58	1/2	- Aphthous ulcers - Burning sensation -Commissural fissure -Candidiasis - Cheilitis - Dysgeusia - Xerostomia	Tongue, oral commissure	42 days	Not reported
Santos <i>et al.</i> , 2020	1	67	1/0	-Geographic tongue -Herpes, -Candidiasis	Tongue	Not reported	Coronary heart disease, hypertension, renal failure
Schirinzi <i>et al.</i> , 2020	86	65	58/28	- Ageusia, - Dysgeusia,	Tongue	4 days	Diabetes, hypertension, respiratory failure, reflux, thyroid disorders
Sinjari <i>et al.</i> , 2020	20	69.2	11/9	- Xerostomia, - Burning sensation, - Difficulty swallowing	Tongue	Not reported	Hypertension, diabetes, obesity, thyroid disorders
Tapia <i>et al.</i> , 2020	4	47.2	1/3	-Hemorrhagic ulcers	Palate and tongue	Not reported	Vasculitis, thrombosis
Zarch & Hosseinzadeh, 2021	1	56	0/1	- Xerostomia - Dysgeusia - Pain - Burning sensation	Lip	2 days	Hypertension and chronic sinusitis

Source: Authors.

Table 2 - Patients evaluated according to the type of care necessary and age.

Age	Admitted to the ICU (n°)	Admitted to the infirmary hospital (n°)	Home isolation (n°)	Patients who sought care after isolation (n°)	Total of patients reported by age
Up to 18 years old	0	3	3	2	8
Between 19 and 35 years old	0	0	8	22	30
Between 36 and 59 years old	1	2	9	16	28
Between 60 and 79 years old	6	1	0	4	11
80 years old or older	2	0	0	0	2
Total of patients reported according to type of care	9	6	20	44	79

Source: Authors.

4. Discussion

The current scenario of the COVID-19 pandemic has shown a 45% decline in deaths and an average decrease of 65% due to the vaccination process of the population. However, ongoing studies regarding the disease are essential, since oral manifestations can become signs of infection by the virus among patients (Governo Federal do Brasil, 2021).

Regarding oral alterations, the studies summarized in this review reported that ageusia, hypogeusia, and dysgeusia were considered the first symptoms of COVID-19 (Brandão et al., 2021; Cirillo & Colella, 2021; Corchuelo & Ulloa, 2020; Iranmanesh et al., 2021; Maia et al., 2021; Riad et al., 2021; Zarch & Hosseinzadeh, 2021), with the potential to appear before, during, or after the period of disease progression. This information aligns with the work of Amorim dos Santos et al. (2020), which mentioned taste disorders as the initial and prevalent symptoms, mainly in patients with mild and moderate symptoms.

As the disease progresses, several other oral manifestations can be considered both in home isolation and during hospitalization, with ulceration being the most reported (Brandão et al., 2021; Hocková et al., 2021; Iranmanesh et al., 2021; Riad et al., 2021; Santos et al., 2020) in various clinical aspects, such as hemorrhagic, necrotic, and aphthous, and in several regions of the mouth, such as the tongue, palate, and lips. The study conducted by Bemquerer et al. (2021) also indicates that ulceration was the first sign reported, excluding gustatory and olfactory disorders. In addition, the authors mentioned that the most prevalent regions were the tongue, palate, and lips, confirming the data obtained in this research. However, it is suggested that the appearance of ulcers may be related to other factors, such as the use of nonsteroidal anti-inflammatory drugs, vasculitis, or thrombotic vasculitis, preceding COVID-19 infection. Therefore, further studies are needed to confirm this correlation (Iranmanesh et al., 2021).

Furthermore, infectious diseases such as herpes simplex and oral candidiasis had a high prevalence of citations (Brandão et al., 2021; Corchuelo & Ulloa, 2020; Kitakawa et al., 2021; Mascitti et al., 2020). The report of *Candida albicans* was recorded in pediatric patients aged 6 to 15 days who were admitted to a neonatal COVID-19 ward (Dima et al., 2020) and in a 78-year-old patient (Rodríguez et al., 2022). However, both diseases can be considered opportunistic, emerging in situations of immune system suppression or patient stress. In addition, the significant increase in cases of herpes zoster during the COVID-19 pandemic, a disease considered opportunistic, stands out. Thus, the evident relationship between SARS-CoV-2 infection and the diseases that affect patients with low immunity is highlighted (Maia et al., 2021).

Systemic diseases may be directly linked to the appearance of oral symptoms in people infected with SARS-CoV-2. Among the studies surveyed, nine described patients with some type of systemic disease (Chen et al., 2020; Brandão et al., 2021;

Hocková et al., 2021; Maniaci et al., 2020; Riad et al., 2021; Santos et al., 2020; Schirinzi et al., 2020; Sinjari et al., 2020; Tapia et al. 2020), with hypertension, diabetes, and obesity being the most frequently cited, corroborating the study by Bemquerer et al. (2021). Studies involving patients without any comorbidity totaled five (Corchuelo & Ulloa, 2020; Kitakawa et al., 2021; Cirillo & Colella, 2021; Maniaci et al., 2020; Iranmanesh et al., 2021), all in home isolation and with mild symptoms. The present study concluded that patients without comorbidities tend to have mild symptoms of COVID-19. However, some studies did not mention the presence or absence of comorbidities among the patients investigated (Dima et al., 2020; Halepas et al., 2021; Mascitti et al., 2020; Rodríguez et al., 2022), which could result in fluctuations in the results.

The relationship between gender and SARS-CoV-2 infection is still contradictory. According to Santos et al. (2020), female patients accounted for 56.41% and male patients for 41.92%, contrary to the results obtained in this study, where men were the majority. However, this finding corroborates the study by Sinjari et al. (2020), which found that female patients represented 45% and male patients 55%. Thus, it is concluded that there is no standard relationship between a patient's gender and SARS-CoV-2 infection.

According to the results of the present study, the timing of the appearance of oral lesions was determined based on the moment of the oral evaluation or on the previous days reported by the patient. In the studies conducted by Hocková et al. (2021), the appearance of the most critical oral symptoms occurred more frequently in patients with a long hospital stay and/or those admitted to the ICU who experienced the most severe course of COVID-19. The latency time between systemic and oral symptoms ranged from four days to 12 weeks (Iranmanesh et al., 2021), corroborating the current study. However, the data may be subjective since the reports provided by the authors do not distinguish the days that followed the appearance of the symptoms, highlighting the need for greater standardization in the data described in each report.

To obtain an overview of the existing relationship between hospitalization, age, and the condition of the investigated patients, the following classification was proposed based on the World Health Organization's indications (Governo Federal do Brasil, 2021): patients with mild symptoms in home isolation, those with moderate symptoms hospitalized, and patients with severe and critical symptoms admitted to the ICU, whether or not requiring oxygen therapy.

Among the 266 patients, only 79 had reported hospitalization/isolation conditions with consistent information on systemic symptoms related to SARS-CoV-2. However, it was possible to confirm that in the first age group, under 18 years old, few patients were hospitalized—only three infants around 15 days old. The other three patients in home isolation had mild symptoms and no comorbidities. Patients between 19 and 59 years old were the most frequently reported, indicating that this is the largest age group infected, but the situation may worsen due to systemic diseases and immunosuppression. Finally, it should be noted that with increasing age, there is, consequently, an increase in the number of patients admitted to the ICU, with a significant worsening of the clinical condition after the age of 60.

5. Conclusion

The lack of standardization in the description of data and case reports was observed, which led to instability in the results obtained. However, some information can be highlighted, such as the propensity for patients with comorbidities to develop more severe symptoms of COVID-19, requiring hospitalization for adequate treatment. In addition, with increasing age, there is, consequently, an increase in the number of patients admitted to the ICU, with a significant worsening of the clinical condition after the age of 60.

The oral symptoms considered typical in patients infected with SARS-CoV-2 include dysgeusia, ageusia, and hypogeusia, followed by aphthous and hemorrhagic ulcers, a burning sensation, and xerostomia. These findings suggest potential signs of COVID-19, as the symptoms tend to appear in the first days of disease progression. A multidisciplinary team

including a dentist is essential for managing oral symptoms, providing comfort and quality of life to patients, since numerous symptomatic oral manifestations are noticeable during the infection's progression.

Conflict of Interest

The authors declare that they have no conflict of interest.

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