

## **Analysis of oral changes in hospitalized patients with Covid-19: a retrospective cohort study**

**Análise de alterações bucais em pacientes com Covid-19 hospitalizados: um estudo de coorte retrospectivo**

**Análisis de los cambios orales en pacientes hospitalizados por Covid-19: un estudio de cohorte retrospectivo**

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### **Abstract**

The outbreak of a new coronavirus was identified in Wuhan, China in late 2019. SARS-CoV-2, spreads through salivary droplets from a carrier causing a respiratory illness. Its clinical behavior is variable and manifests itself with mild symptoms, moderate or developing a severe respiratory infection. The oral cavity was identified as a gateway for the virus and evaluating its possible role as an aggravating factor in the infectivity and progression of the infection was the objective of this study. A retrospective cohort study was performed with data from 274 medical records of patients with COVID-19. They were collected at the patient's admission, with seven and fourteen days to analyze the occurrence of oral alterations and relate them to the severity of the infection. In total, 154 patients had oral alterations. The most frequent oral alteration was the presence of ulcerations in the mucosa at the three collection times (T0, T1 and T2). Complementary tests were red blood cells, platelets, leukocytes, bleeding time, TGP, TGO, albumin, creatinine, CRP, urea, d-dimer and leukocyte-lymphocyte ratio. No predictors were observed for the development of oral changes in patients with COVID-19. Changes in the oral mucosa were observed in most of the patients analyzed. An association between diabetic patients and the presence of oral lesions was observed in the evaluated patients, after 7 and 14 days. The study revealed that patients with changes in the oral mucosa had a more severe evolution of COVID-19, including death, indicating that the presence of oral changes may be related to an unfavorable prognosis of the infection.

**Keywords:** Coronavirus infections; Oral manifestations; Hospital assistance.

### **Resumo**

O surto de um novo coronavírus foi identificado em Wuhan, na China no final de 2019. O SARS-CoV-2, se propaga através de gotículas salivares de um portador causando uma doença respiratória. Seu comportamento clínico é variável e manifesta-se com sintomas leves, moderado ou desenvolver uma infecção respiratória grave. A cavidade bucal foi identificada como porta de entrada para o vírus e avaliar seu possível papel como agravante na infectividade e progressão da infecção foi objetivo desse estudo. Realizou-se um estudo de coorte retrospectivo com dados de 274 prontuários de pacientes com COVID-19. Foram coletados na admissão do paciente, com sete e quatorze dias para analisar a ocorrência de alterações bucais e relacioná-las com a severidade da infecção. No total, 154 pacientes apresentaram alteração bucal. A alteração bucal mais frequente foi a presença de ulcerações em mucosa nos três

tempos de coleta (T0, T1 e T2). Os exames complementares foram as hemácias, plaquetas, leucócitos, tempo de sangramento, TGP, TGO, albumina, creatinina, PCR, ureia, d-dímero e razão leucócito-linfócito. Não foram observados fatores preditores para o desenvolvimento de alterações bucais em pacientes com COVID-19. As alterações em mucosa oral foram observadas na maioria dos pacientes analisados. Foi observada associação de pacientes diabéticos e a presença de lesões bucais nos pacientes avaliados, após 7 e 14 dias. O estudo revelou que os pacientes com alterações em mucosa bucal, apresentaram evolução mais severa da COVID-19, incluindo o óbito, sinalizando que a presença das alterações bucais pode estar relacionada a um prognóstico desfavorável da infecção.

**Palavras-chave:** Infecções por coronavírus; Manifestações bucais; Assistência hospitalar.

### Resumen

El brote de un nuevo coronavirus se identificó en Wuhan, China, a fines de 2019. El SARS-CoV-2 se propaga a través de las gotas salivales de un portador y causa una enfermedad respiratoria. Su comportamiento clínico es variable y se manifiesta con síntomas leves, moderados o desarrollando una infección respiratoria grave. La cavidad oral fue identificada como puerta de entrada del virus y evaluar su posible papel como factor agravante en la infectividad y progresión de la infección fue el objetivo de este estudio. Se realizó un estudio de cohortes retrospectivo con datos de 274 historias clínicas de pacientes con COVID-19. Fueron recolectados al ingreso del paciente, con siete y catorce días para analizar la ocurrencia de alteraciones bucales e informar sobre la gravedad de la infección. En total, 154 pacientes presentaban alteraciones orales. La alteración bucal más frecuente fue la presencia de ulceraciones en la mucosa en los tres tiempos de recolección (T0, T1 y T2). Los exámenes complementarios fueron glóbulos rojos, plaquetas, leucocitos, tiempo de sangría, TGP, TGO, albúmina, creatinina, PCR, urea, dímero D y relación leucocito-linfócito. No se observaron predictores para el desarrollo de cambios orales en pacientes con COVID-19. Se observaron cambios en la mucosa oral en la mayoría de los pacientes analizados. Se observó asociación entre los pacientes diabéticos y la presencia de lesiones orales en los pacientes evaluados, a los 7 y 14 días. El estudio reveló que los pacientes con cambios en la mucosa oral tuvieron una evolución más severa de la COVID-19, incluida la muerte, lo que indica que la presencia de cambios en la boca puede estar relacionada con un pronóstico desfavorable de la infección.

**Palabras clave:** Infecciones por coronavirus; Manifestaciones orales; Asistencia hospitalaria.

## 1. Introduction

In December 2019, the outbreak of a new coronavirus called SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2), of unknown origin, began in the province of Wuhan, China. By August 2021, 202 cases had been registered worldwide, with 4,286,932 deaths. In Brazil, 20,151,779 people have been infected and 562,752 deaths have already been reported (Bulletin Epidemiologic Special 75, 2021).

Infection with SARS-Cov-2 has a clinical behavior that varies, from asymptomatic cases or with mild flu-like symptoms, to more severe cases with the development of a severe acute respiratory syndrome. Because it is a new type of coronavirus, many studies are still needed to understand the pathogenesis of the disease in the human body, however, it is known that some risk factors, such as advanced age, obesity and the presence of comorbidities, may be associated with more severe cases. (Machhi et al., 2020).

The main form of transmission of SARS-Cov-2 occurs through the inhalation of respiratory droplets from an infected person, however, the introduction of the virus through touching the mouth, eyes and nose, are also possible forms of contamination. Once in the human body, the virus penetrates into cells that express the ACE-2 receptor (Angiotensin-Converting Enzyme -2), to start its replication cycle. Many human cells have this receptor on their surface, especially the epithelial cells of the lungs, which represent the target organ of infection by SARSCov-2. Epithelial cells of the oral mucosa and salivary glands express ECA-2 and SARSCov-2 on their surface, which has been identified in oral tissues (Brandão et al.; Dietz et al.; 2020; Xu et al., 2020).

In the literature, there are reports of patients with COVID-19 who developed lesions in the oral mucosa, however, it is still unknown whether such lesions represented aspects of the SARS-CoV-2 infection itself or if they resulted from the patient's general clinical condition. Likewise, it is still not possible to state whether the occurrences of these lesions in the mouth are

related to cases with more severe evolution of COVID-19 (Chaux-Bodard et al., 2020; de Maria et al., 2020; Baeder et al., 2021).

In this sense, this research aimed to investigate oral alterations in patients with COVID-19, the possible factors associated with the development of these lesions, and whether the appearance of these oral lesions is related to the most severe form of the disease.

## 2. Methodology

Before data collection, this study was submitted to the approval of the Ethics Committee in Research Central of UFRN (CEP/UFRN), with registration CAAEE 43484821.1.0000.5537, following resolution n° 466/12 of the National Health Council (CNS) being approved in accordance with the consolidated opinion number 4,604,796.

A documentary retrospective cohort study was carried out, using the medical records of patients with COVID-19 as a source of analysis. This research was developed at Hospital Metropolitano Dom José Maria Pires (HMDJMP), in Santa Rita, a reference hospital for COVID-19 in the State of Paraíba.

To obtain the population for this research, the medical records of patients diagnosed with COVID-19 and who were hospitalized in the COVID-19 Wards at HMDJMP, from July to December 2020, were analyzed.

The sample was obtained through the statistical program Stat Calc of Epi Info 7, where the Fleiss sampling method was considered with correction following the parameters of the 95% confidence interval; the minimum acceptable test power of 80%; as there are generally more unexposed than exposed people in studies, a hypothetical 1.5 was placed. This means that the groups are not equal and that the unexposed group is 50% larger than the exposed group. The number of exposed and unexposed was estimated based on previous studies. With this, an estimated sample number of 322 was generated, but only 274 records were accepted by the inclusion criteria.

The medical records of patients aged 18 years or older, with positive testing (RT-PCR) for COVID-19, clinical and imaging diagnosis compatible with COVID-19, without gender restriction, who presented the medical records with the necessary information for the development of the research. The medical records of patients who did not present the necessary information for the analysis of the study, patients who stayed in the hospital for a period of less than seven days and patients who presented positive laboratory tests for viral infections of the herpes type were excluded from the research.

Initially, the patients were contacted by the researcher in charge, through the telephone number present in the HMDJMP medical record, being invited to participate in the research. Three contact attempts were made, on different days and shifts.

After acceptance, the Informed Consent Form-1 (TCLE-1) was sent via e-mail or Whatsapp to explain how participation would be, as well as the signature of the participants. For cases in which the patient died, authorization was requested from a family member or guardian through the TCLE-2.

The clinical oral examinations of the patients were performed by the researcher and her team of hospital dentists, duly calibrated for this purpose, in accordance with Amib standards (Amib, 2020). The presence of oral alteration was evaluated. In this study, the clinical evolution of the alterations found was not evaluated.

All evaluated patients who presented oral alterations were treated according to the alteration presented with application of antifungals in fungal lesions, scrapings in coated tongues and application of topical corticosteroids in ulcerated lesions.

The collection of data from the medical records was carried out in the Medical File and Statistics Service - SAME of HMDJMP and conducted by the researcher in charge following all protocols for handling and recording information, with the aim of reducing the risk of physical damage to the files as well as the exposure of patient data.

The data collected referred to age, gender, presence of comorbidities, use of medication, presence and type of oral lesions, need for transfer to the ICU, whose information is described in the tables of variables and were transcribed into a clinical form specially developed for this purpose. Subsequently, the data were transferred to a spreadsheet for statistical analysis.

As for the use of systemic drugs, the therapeutic classification categorized by the Who (2020) was used, distributed in alphabetical order according to drug classes: A- Digestive system, B- Blood and hematopoietic organs, C- Cardiovascular system, D- Medicines dermatological, E - Genitourinary system and sex hormones, F - Systemic hormonal preparations, excluding sex hormones and insulins, G - General anti-infectives for systemic use, H - Antineoplastic agents and immunomodulators, I - Musculoskeletal system, J - Nervous system, L - Antiparasitic, insecticide and repellent products, M- Veterinary use, N- Respiratory system, O- Sense organs and P- Miscellaneous.

Data related to the clinical evolution of patients, related to dependent variables, presence of oral and independent changes such as: age, gender, body mass index (BMI), need to transfer the patient from the ward to the ICU, presence and type of underlying disease/comorbidity, use and type of medication used and biochemical changes were categorized and collected taking into account three periods in the clinical evolution of the patient: (T0) date of admission to the hospital, (T1) after 7 days of admission, (T2) after 14 days of hospitalization. These periods correspond, according to the hospital protocol, to the periods for performing the clinical examination in the patients' mouths. The examinations were performed by experienced dentists trained in the evaluation of hospitalized patients.

Categorical data were expressed in absolute and relative frequencies, and for quantitative data median and interquartile range 25-75 were used. For bivariate inferential analysis, Pearson's chi-square test was used. The Prevalence Ratio (PR) was calculated by looking for associations between demographic variables and health status with the outcome at the three follow-up moments. For the survival analysis, the variables that presented  $p < 0.20$  in the bivariate analysis were included in Cox regression models with interval censoring.

Predictive factors for lesion development and remission were presented using the hazard rate with their respective 95% confidence intervals. The statistical software used were IBM SPSS (version 24.0) and Stata (version 17) with  $p < 0.05$  being adopted as statistical significance.

### **3. Results and Discussion**

This study analyzed 274 medical records of patients with COVID-19. It was observed that 55.8% of the patients were male. Most individuals (66.8%) were elderly, that is, they were 60 years old or older at the time of data collection, and virtually all individuals in the sample (99.3%) had some comorbidity, with hypertension arterial the most frequent, present in 66.8% of these (Table 1).

**Table 1** - Distribution of sociodemographic and clinical variables in patients with COVID-19 – Santa Rita 2021.

Variable	n (%)
Sex	
Male	153 (55.8)
Feminine	121 (44.2)
age group	
Up to 59 years	91 (33.2)
60 to 79 years old	119 (43.4)
80 years or older	64 (23.4)
high reason for improvement	136 (49.6)
by death	138 (50.4)
BMI	
Low (<18.5)	5 (1.8)
Normal (18.5 to 24.9)	165 (60.2)
Overweight (>25)	104 (38)
Transfer of the ward to the ICU	146 (53.3)
Presence of comorbidity	272 (99.3)
Systemic arterial hypertension	183 (66.8)
Heart disease	105 (38.3)
Diabetes	90 (32.8)
neurological disease	71 (25.9)
chronic lung disease	31 (11.31)
Hepatopathies	30 (10.95)
Dyslipidemia	27 (9.85)
kidney disease	25 (9.12)
Neoplasms	11 (4)
autoimmune diseases	9 (3.28)
Other diseases	22 (8.03)
medication use	272 (99.3)
Digestive system and metabolism	103 (37.6)
Blood and hematopoietic organs	256 (93.4)
cardiovascular system	117 (42.7)
Dermatological	2 (0.7)
Genitourinary system/sex hormones	11 (4)
Systemic hormonal preparations	2 (0.7)
General systemic anti-infectives	273 (99.6)
Antineoplastic agents and immunomodulators	11 (4)
Nervous system	77 (28.1)
Respiratory system	273 (99.6)
Others	274 (100)

Source: Authors.

It was observed that 154 patients (56.2%) had alterations in the mouth upon admission, with ulcers representing the most frequent lesion (43.8%). The same occurred in the analysis of the other evaluation times, seven and fourteen days after the date of admission to the hospital, where ulcers were present in 33.6% and 21.2% of the individuals, respectively (Table 2).

**Table 2** - Oral alterations observed and classified according to elementary lesions described according to the type and period of admission in the 274 patients evaluated - Santa Rita 2021.

Types of oral alteration	admission	7 days	14 days
Ulcer	120 (43.8%)	92 (33.6%)	58 (21.2%)
Spot	50 (18.2%)	38 (13.9%)	25 (9.1%)
Crust	17 (6.2%)	27 (9.9%)	34 (12.4%)
Vesicle	12 (4.4%)	18 (6.6%)	15 (5.5%)
Bubble	7 (2.6%)	3 (1.1%)	0
Board	5 (1.8%)	5 (1.8%)	4 (1.5%)
Nodule	3 (1.1%)	3 (1.1%)	2 (0.7%)
Papule	0	0	1 (0.4%)

Source: Authors.

Remission of the lesions was observed as the patients were treated. Only two patients (11.7%) developed lesions 7 days after admission, which evolved to death; ulcer remission is observed through an increase in the number of crusts, indicating the beginning of their healing process.

The data collected regarding the hematological and biochemical analyzes and their association with alterations in the buccal mucosa showed no statistically significant difference. Data were collected at patient admission, that is, at T0; however, the most prevalent biochemical and hematological alterations among patients were red blood cells, platelets, leukocytes, bleeding time, TGP, TGO, albumin, creatinine, CRP, urea, d-dimer and leukocyte-lymphocyte ratio (Table 3).

**Table 3** - Distribution of frequencies referring to biochemical analyzes in patients with COVID-19 and p-value.

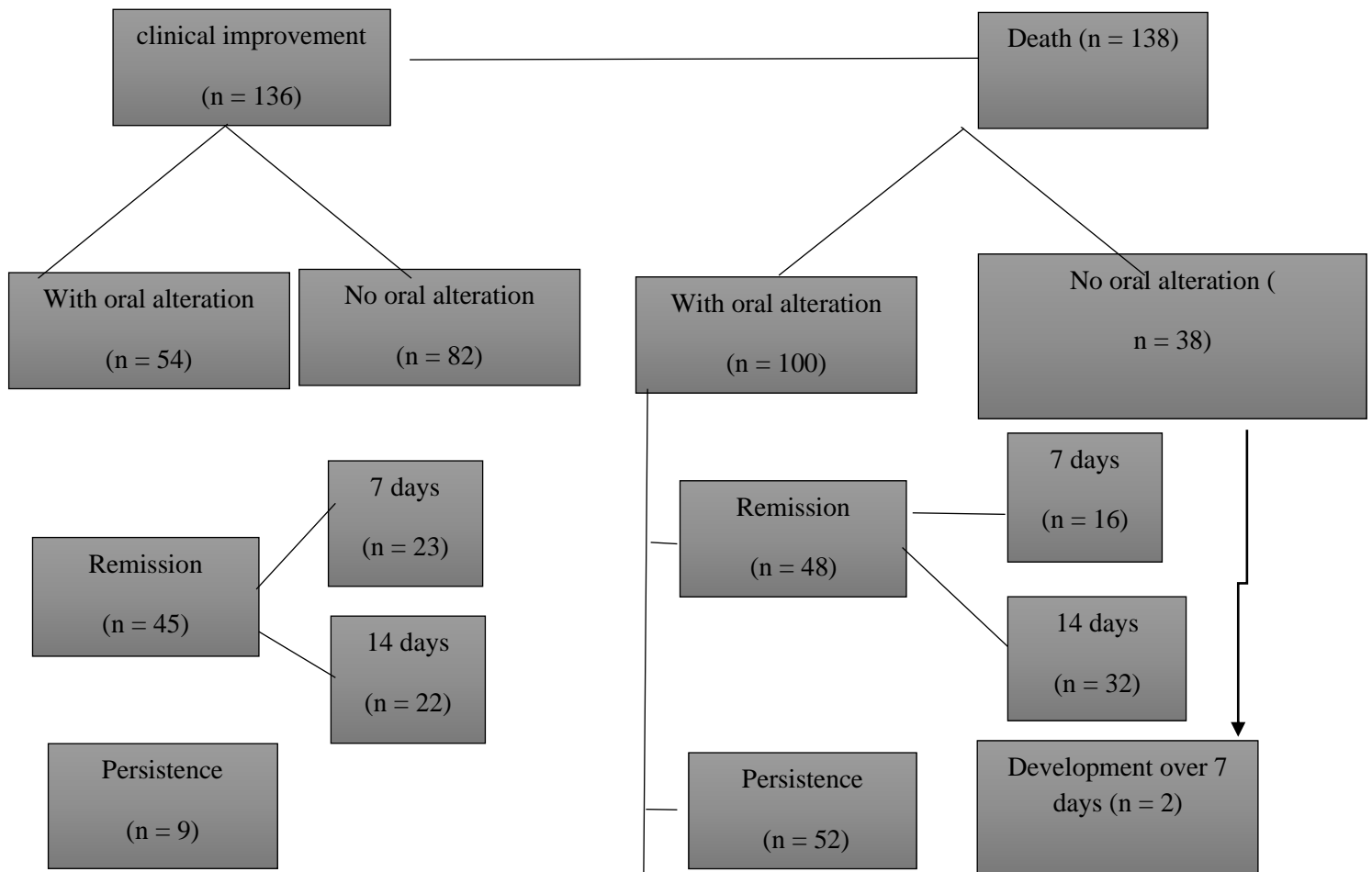
Variable	With oral alteration n (%)	No oral alteration n (%)	p-value
<b>Glycemia</b>			
Normal	111 (40.5)	76 (27.7)	0.184
high changed	43 (15.7)	43 (15.7)	
Changed Decreased	0	1 (0.4)	
<b>glycated hemoglobin</b>			
Normal	112 (40.9)	76 (27.7)	0.154
high changed	43 (15.7)	42 (15.3)	
Changed Decreased	0	1 (0.4)	
<b>Red Cells</b>			
Normal	50 (18.2)	35 (12.8)	0.558
high changed	0	0	
Changed Decreased	104 (38)	85 (31)	
<b>hematocrit</b>			
Normal	86 (31.4)	59 (21.5)	0.272
high changed	0	0	
Changed Decreased	68 (24.8)	61 (22.3)	
<b>Hemoglobin</b>			
Normal	61 (22.3)	38 (13.9)	0.174
high changed	0	0	
Changed Decreased	93 (33.9)	82 (29.9)	
<b>leukocytes</b>			
Normal	47 (17.2)	34 (12.4)	0.684
high changed	106 (38.6)	84 (30.7)	

<b>Changed Decreased</b>	1 (0.4)	2 (0.7)	
<b>platelets</b>			
Normal	46 (16.8)	32 (11.7)	0.769
high changed	103 (37.6)	85 (31)	
Changed Decreased	5 (1.8)	3 (1.1)	
<b>leukocyte-lymphocyte ratio</b>			
Normal	39 (14.2)	28 (10.2)	0.138
high changed	115 (42)	89 (32.5)	
Changed Decreased	0	3 (1.1)	
<b>bleeding time</b>			
Normal	56 (20.4)	39 (14.2)	0.277
high changed	75 (27.4)	69 (25.2)	
Changed Decreased	23 (8.4)	12 (4.4)	
<b>TGP</b>			
Normal	75 (27.4)	57 (20.8)	0.843
high changed	79 (28.8)	63 (23)	
Changed Decreased	0	0	
<b>TGO</b>			
Normal	76 (27.7)	57 (20.8)	0.761
high changed	78 (28.5)	63 (23)	
Changed Decreased	0	0	
<b>Albumin</b>			
Normal	42 (15.3)	36 (13.1)	0.154
high changed	2 (0.7)	6 (2.2)	
Changed Decreased	110 (40.1)	78 (28.5)	
<b>creatinine</b>			
Normal	54 (19.7)	44 (16.1)	0.784
high changed	100 (36.5)	76 (27.7)	
Changed Decreased	0	0	
<b>ferritin</b>			
Normal	71 (25.9)	57 (20.8)	0.503
high changed	9 (3.3)	11 (4)	
Changed Decreased	74 (27)	52 (19)	
<b>Urea</b>			
Normal	56 (20.4)	47 (17.2)	0.635
high changed	98 (35.8)	73 (26.6)	
Changed Decreased	0	0	
<b>PCR</b>			
Normal	0	0	BR
high changed	153 (56)	120 (44)	
Changed Decreased	0	0	
<b>D-dimer</b>			
Normal	0	0	BR
high changed	154 (56.2)	120 (43.8)	
Changed Decreased	0	0	

Source: Authors.

According to the reason for hospital discharge (because of clinical improvement or death), of the 136 patients (49.6%) who improved, 54 (19.7%) had oral alterations and of the 138 (50.4%) patients who died, 100 (36.5%) presented oral alterations. According to these data, follow the screening flowchart for the evaluation between the reason for discharge and the presence of oral alteration.

**Figure 1** - Flowchart referring to the screening of oral alteration and its evolution in patients with COVID-19 divided according to the reason for hospital discharge: clinical improvement or death.



Source: Authors.

Tables 4, 5 and 6 show the associations of the independent variables and the presence of oral alterations at admission, after 7 days and after 14 days of hospitalization, respectively. Independent variables such as: gender, age, BMI, heart disease, neurological disease, hypertension, neoplasms, use of medication in categories B, D, E, F, G, H, J and N, did not have statistical significance. However, in the outcome after 7 days and 14 days, patients with oral alterations showed statistical significance regarding the reason for discharge (death) and transfer to the ICU.



**Table 4** - Associations between independent variables and outcome on admission – Santa Rita 2021.

Variables	Categories	oral alteration		P*	PR	CI (95%)
		on Admission				
		Yea n (%)	No n (%)			
Diabetes	Yea	47 (52.2)	43 (47.8)	0.044	0.788	0.616 - 1.007
	No	72 (39.3)	111 (60.7)			
A_ digestive/metabolism	No	106 (62.4)	64 (37.6)	0.011	0.747	0.589 – 0.948
	Yea	48 (46.6)	55 (53.4)			
reason for discharge	improvement	58 (43.0)	77 (57.0)	0.836	0.978	0.794- 1.205
	death	77 (55.8)	61 (44.2)			
Transfer_ward to ICU	Yea	80 (54.8)	66 (45.2)	0.564	0.940	0.764-1.158
	No	74 (58.3)	53 (41.7)			

\*Pearson's chi-square test. Source: Authors.

**Table 5** - Associations between independent variables and the 7-day outcome.

Variables	Categories	oral alteration		P*	PR	CI (95%)
		With 7 days				
		Yea n (%)	No n (%)			
Diabetes	Yea	62 (68.9)	28 (31.1)	0.007	0.643	0.457- 0.905
	No	89 (48.4)	95 (51.6)			
A_ digestive/metabolism	No	85(49.7)	86 (50.3)	0.003	1.371	1.125-1.670
	Yea	32 (31.1)	71 (68.9)			
reason for discharge	improvement	61 (44.9)	75 (55.1)	<0.001	0.645	0.519-0.801
	death	42 (30.4)	96 (69.6)			
Transfer_ward to ICU	Yea	99 (67.8)	47 (32.2)	<0.001	0.589	0.443- 0.781
	No	58 (45.3)	70 (54.7)			

\*Pearson's chi-square test. Source: Authors.

**Table 6** - Associations between the independent variables and the 14-day outcome.

Variables	Categories	oral alteration With 14 days		P*	PR	CI (95%)
		Yea n (%)	No n (%)			
Diabetes	Yea	79 (87.8)	11 (12.2)	0.003	0.432	0.237-0.788
	No	52 (28.3)	132 (71.7)			
A_ digestive/metabolism	No	121 (70.8)	50 (29.2)	0.002	0.432	0.247- 0.755
	Yea	13 (12.6)	90 (87.4)			
reason for discharge	improvement	63 (46.3)	73 (53.7)	<0.001	0.537	0.459- 0.627
	death	138 (100.0)	0 (0.0)			
Transfer_ward to ICU	Yea	141 (96.62)	5 (3.4)	<0.001	0.076	0.031-0.183
	No	58 (45.3)	70 (54.7)			

\*Pearson's chi-square test. Source: Authors.

A statistically significant association was observed between the presence of oral alterations in diabetic patients only after 7 and 14 days. As for the patients who used drugs for the digestive system, statistical significance was also observed in patients with oral alterations only after 7 and 14 days. At seven and fourteen days it was also found that the patients who were discharged had significantly fewer oral lesions than those who needed to be transferred to the ICU and progressed to death.

Cox's multivariate analysis showed that he did not use medication for the digestive system and metabolism (HR: 2.18; 95%CI: 1.13-4.22) and did not have systemic arterial hypertension (HR: 1.78; 95%CI %: 1.13-2.79) are prognostic factors for remission of oral alterations in patients with COVID-19. However, no risk factors were found for the development of oral alterations.

This study was important because it investigated factors related to the development of changes in the oral mucosa of hospitalized patients with COVID-19, as well as all issues related to their stay and outcomes.

Of a total of 400 records, 274 met the inclusion criteria and were listed for the research. It was observed that most patients were male, aged 60 years or older, with comorbidities, with systemic arterial hypertension (SAH) being the most prevalent (183-66.8%). These findings corroborate the results of recent studies, which demonstrated an association between COVID-19 and chronic diseases, such as cardiovascular disease, arterial hypertension, diabetes mellitus and chronic kidney disease (Carrilo-Largo, 2020; Pedrosa; Nogueira, 2020; Pfutzner et al, 2020).

A relevant finding in the evaluated sample was that more than half of the patients evolved to a severe condition of COVID-19 with transfer to the ICU and subsequently to death. The absence of vaccines during this period may have contributed to this. We consider this mortality rate to be high and believe that the disease follows a more severe course in elderly patients with comorbidities. In the study by Zhou et al. (2020), in which risk factors for mortality in patients with COVID-19 were investigated, it was evidenced that 40% of the patients who died had some type of comorbidity, with arterial hypertension being the most prevalent and diabetes being the third present comorbidity. These data are similar to those observed in this research. In the sample, (66.8%) had SAH and (32.8%) diabetes upon admission.

Hematological and biochemical tests were collected from patients upon admission and showed alterations mainly related to the presence of anemia, leukocytosis, tests related to liver and kidney function, in addition to d-dimer, CRP and leukocyte-lymphocyte ratio. In this study, (100%) of the patients had elevated results for d-dimer and CRP. It is believed that such observed changes may be related to the pathogenesis of the virus, with changes in coagulation processes and inflammatory reactivity increasing complications of the clinical picture of COVID-19 (Baeder et al., 2021).

Other authors have also observed changes in C-reactive protein, TGO, creatinine and d-dimer analyzes (Wang et al. 2020.; Guan et al., 2020). It was also observed that patients admitted to the ICU had more hemodynamic disorders than those who did not need intensive care, that is, patients who developed the most severe form of the disease had more laboratory alterations.

With regard to the presence of alterations and oral lesions in COVID 19 patients, the literature shows some case studies and research that seek to investigate whether the lesions present in the mouth represent a manifestation of infection by SARS-CoV-2 or if they are conditions secondary to the disease (Al-Khatib, 2020; Diaz Rodriguez; Romera,; Villarroel., 2020, Baeder et al., 2021).

It seems evident that coronavirus damage to target organs may be related to the distribution of angiotensin-converting enzyme (ACE2) receptors. Therefore, cells that express the ACE2 receptor can become hosts for the virus and provoke an inflammatory response in oral organs and tissues. In the oral mucosa, ACE2 receptors are present and, therefore, it is possible that the virus plays a role in the occurrence of changes in the mouth (Baeder et al., 2021; Riad; et al., 2020).

According to Amorim dos Santos et al (2020), the oral conditions presented by patients with COVID-19 are highly suggestive of secondary lesions resulting from the deterioration of general health or due to instituted treatments. In this sense, it should be considered that the drugs used in the treatment of these patients can cause changes in the oral mucosa and favor the development of lesions.

In the study by Brandão et al. (2021), in which oral lesions were evaluated in patients with COVID-19, it was found that although the samples of oral lesions were not investigated for the presence of the COVID-19 virus, the evolution of oral lesions and the healing process occurred in parallel with the resolution of the infection. This fact raised the hypothesis that the development of oral manifestations in these patients may be directly associated with SARS-CoV-2 infection. In the sample studied here, it was observed that more than half of the patients admitted to the hospital had at least one type of alteration in the mouth. However, as the study was retrospective, it is not possible to state whether such changes developed after infection with SARS-CoV-2, since the patients were not examined before the diagnosis of the disease.

Ulcerated lesions were the most frequently observed alterations in this research. It is known that this type of elementary lesion represents one of the most prevalent in the oral mucosa and that several diseases, with different etiologies, can manifest as one or more ulcers in the mouth. This is a point that should also be analyzed, considering that the distribution of ACE2 receptors can determine the infection route of SARS-CoV-2. Thus, the interaction between SARS-CoV-2 and ACE2 can interrupt the function of oral keratinocytes and the epithelial lining of the salivary gland ducts, resulting in painful oral ulcers, being a possible diagnostic hypothesis according to Baeder et al., 2021; Riad; et al., 2020.

The lesions observed in the patients included in this research may represent a secondary manifestation of SARS-CoV-2 infection, thus, we corroborate the study by Hocková et al (2021), which relates changes to the state of immunosuppression, trauma and related movements clinical management of the patient, such as prolonged prone positioning and orotracheal intubation.

In the follow-up of the patients, it was observed that the lesions initially presented regressed over the seven and fourteen day analysis. This fact is directly related to oral health care, improvement of the patient's systemic condition and

normal course of the disease. Although a reduction in the total number of lesions was observed over time, it was found that some cases did not show remission.

The study also observed a statistically significant association between the presence of oral alterations in diabetic patients and those who used digestive tract medication only in periods of 7 and 14 days. Several studies relate diabetic patients to a predisposition to oral pathologies; metabolic alterations related to diabetes cause a delay in wound healing, which can determine an increase in ulcers in patients after 7 and 14 days (Stanko & Izakovicova, 2014; Rohani, 2019; Gonzalez-Moles & Ramos-Garcia, 2021).

At seven and fourteen days it was also found that the patients who were discharged had significantly fewer oral lesions than those who needed to be transferred to the ICU and progressed to death. In the outcome after 7 days and 14 days, patients with oral alterations showed statistical significance regarding the reason for discharge (death) and transfer to the ICU. Thus, patients with alterations in the oral mucosa, presented a more severe evolution of COVID-19, including death, signaling that the presence of oral alterations may be related to an unfavorable prognosis of infection by SARS-CoV-2, which reinforces the studies by several authors (Petrescu and Lucaciu, 2020; Riad; Klugar; Krsek, 2020; Sinadinos and Shelswell, 2020).

Another finding of this research was that of the 120 patients who were admitted to the hospital without changes in their mouth, two developed changes after hospitalization. These patients evolved more severely and died.

#### 4. Conclusion

The lesions observed in the patients included in this research may represent a secondary manifestation of SARS-CoV-2 infection. It can also be correlated that patients who were discharged had significantly fewer oral lesions than those who required transfer to the ICU and/or evolved to death.

Patients with comorbidity may be more susceptible to oral lesions when associated with SARS-CoV-2 infection. However, more clinical studies need to be carried out with larger samples and with anatomopathological evidence to contribute to clarifying the direct relationship between SARS-CoV-2 and the development of oral lesions.

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