

Oral lesions in patients with COVID-19 hospitalized in an intensive care unit: a case-series study

Amanda Alves Feitosa BATISTA^(a) 

Karen Perez Pereira RAMOS^(b) 

Mayra Alves Soares do AMARAL^(c) 

Luiz Flávio Andrade PRADO^(c) 

Adriano Antunes de Souza

ARAÚJO^(b) 

Paulo Ricardo MARTINS-FILHO^(d) 

Paula Santos NUNES^(b) 

^(a)Universidade Federal de Alagoas – UFAL, Graduate Program in Medical Sciences, Maceió, AL, Brazil.

^(b)Universidade Federal de Sergipe – UFS, Graduate Program in Health Sciences, Aracaju, SE, Brazil.

^(c)Fundação de Beneficência Hospital de Cirurgia, Aracaju, SE, Brazil.

^(d)Universidade Federal de Sergipe – UFS, Investigative Pathology Laboratory, Aracaju, SE, Brazil.

Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

Corresponding Author:
Paulo Ricardo Martins-Filho
E-mail: prmartinsfh@gmail.com

<https://doi.org/10.1590/1807-3107bor-2022.vol36.0108>

Abstract: This study evaluated the presence of oral lesions in patients with COVID-19 hospitalized in an intensive care unit (ICU). Data included demographic, clinical, and laboratory information. Clinical assessment of the oral cavity was performed on the 2nd and 5th days of orotracheal intubation. Thirty-eight patients were evaluated and 16 (42.1%) presented oral lesions during their ICU stay. The median age and length of stay were 75 years and 15 days, respectively. Among the patients with oral lesions, ulcerative oral lesions were reported in 14 (87.5%) patients, of which 11 (78.6%) were found on the lips. This study highlights the importance of oral examination for patients admitted to the ICU with COVID-19.

Keywords: COVID-19; SARS-CoV-2; Mouth Diseases; Oral Ulcer; Glossitis.

Introduction

SARS-CoV-2 is an RNA virus associated with a severe acute respiratory disease known as COVID-19. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to invade host cells in the kidney, lungs, and heart leading to an abnormal induction of cytokines and a dysregulated hyperinflammatory state, which are implicated in multi-organ injury and increased mortality in severe COVID-19 cases.¹

Moreover, there is evidence that the oral cavity may be an entry route for SARS-CoV-2 due to the high expression of ACE2 receptors in the epithelial cells of different oral anatomical sites.^{2,3} Studies have shown that patients who present the most severe forms of COVID-19 can develop hemorrhagic ulcers on the lips and oral mucosa^{4,5}, but the underlying biological mechanisms of the association between SARS-CoV-2 infection and oral lesions are still poorly defined.

It has been suggested that oral lesions in patients with COVID-19 may be caused by direct viral vascular and mucosal damage, or are due to immune dysregulation, endothelial dysfunction, and coagulation changes.^{4,6} In this study, we evaluated the presence of oral lesions in patients with severe or critical SARS-CoV-2 infection admitted to an intensive care unit (ICU).

Submitted: November 17, 2021
Accepted for publication: March 24, 2022
Last revision: May 6, 2022



Methodology

This observational study included patients aged ≥ 18 years with RT-PCR-confirmed COVID-19, diagnosed with severe (oxygen saturation $< 94\%$, respiratory rate ≥ 30 breaths/min, and lung infiltrates $> 50\%$) or critical (respiratory failure, shock, and multiorgan dysfunction or failure) illness, and who were being treated in the ICU of a not-for-profit hospital in Sergipe state, Northeast Brazil.

Data were collected from 30 July to 30 November 2020 and included demographic (age and sex), clinical (pre-existing medical conditions, medications, length of ICU stay, complications, and deaths), and laboratory (hematological, biochemical, infection-related indices, and coagulation function) information. For each patient, a clinical assessment of the oral cavity was performed on the 2nd and 5th days of orotracheal intubation through visual observation and displacement of the oral structures with the aid of a wooden spatula.⁷ Clinical examination was performed in six distinct anatomic areas (lips, buccal mucosa, tongue, floor of mouth, palate, and attached gingiva) and changes in the oral mucosa were classified as (1) erosive or ulcerative; (2) swelling; (3) vesicles or bullae; and (4) petechiae, erythema, ecchymosis, or spontaneous bleeding.⁸ Data were described descriptively.

Results

During the study period, 38 patients with severe or critical COVID-19 were evaluated and 16 (42.1%) presented oral lesions during their ICU stay. The median age was 75 years (interquartile range [IQR], 58.5–81.3) and most patients were female (62.5%). Hypertension and diabetes were the most common pre-existing medical conditions and all patients received antibiotic therapy and corticosteroids (Table 1).

Of the 16 patients with oral lesions, the median length of ICU stay was 15 days (IQR, 7.5–24.3) and at least 50% of patients presented anemia, leukocytosis, and lymphopenia. All these patients had increased levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, and D-dimer. Acute respiratory distress syndrome (ARDS) and sepsis were described

in 87.5% and 75% of cases, respectively, and eight (50%) patients died from COVID-19 (Table 2). Ulcerative lesions were reported in 14 (87.5%) patients, being found on the lips in 11 patients (78.6%). Three ulcers were covered with hemorrhagic crusts. One (6.25%) case of ecchymosis on the lip and one (6.25%) of erosion in the palate were also found during the clinical examination. Glossitis with patchy depapillation was found in six (37.5%) patients. Candidiasis or blisters were not reported (Table 3; Figure).

Discussion

The dysregulated immune response found in COVID-19 has been associated with poor clinical outcomes in severe and critically ill patients with the disease. Moreover, observational studies have shown that patients with COVID-19 may present oral mucosal changes, but the frequency of these manifestations seems to vary according to the severity of the infection and the clinical setting.^{5,9} In this study, 42.1% of patients with COVID-19 admitted to the ICU had early oral lesions, mainly lip ulcers and glossitis.

Ulcerative lesions have been reported as the most common oral findings in patients with COVID-19. Although there is a potential causal association

Table 1. Clinical characteristics and treatment of patients with COVID-19 included in this case series.

Variable	Values	
	Absolute	Relative (%)
Age > 60 years	12	75.0
Sex		
Male	6	37.5
Female	10	62.5
Pre-existing clinical conditions		
Hypertension	7	43.8
Diabetes	6	37.5
Cerebrovascular disease	5	31.3
Renal disease	5	31.3
Cardiac disease	3	18.8
Obesity	5	31.3
Medications		
Antibiotic therapy	16	100.0
Corticosteroids	16	100.0
Anticoagulant	13	81.3

IQR: interquartile range.

Table 2. Length of ICU stay, laboratory findings, and complications of patients with COVID-19 included in this case series.

Variables	Values
Length of ICU stay (median, IQR)	15.0 (7.5 – 24.3)
Hematological	
RBC	3.3 (2.8 – 3.7)
Anemia	75.0%
WBC	14,950.0 (9,377.5 – 17,707.5)
Leukocytosis	62.5%
Lymphocytes	987.4 (647.1 – 1,414.2)
Lymphopenia	56.3%
Platelet count	240,500 (193,250.0 – 292,250.0)
Thrombocytopenia	18.8%
Biochemical	
ALT	44.0 (33.0 – 78.0)
AST	52.0 (26.5 – 82.0)
Blood urea nitrogen	121.5 (78.0 – 163.8)
Creatinine	2.3 (1.1 – 3.6)
LDH	874.5 (651.0 – 1250.0)
Infection-related indices	
CRP	74.8 (29.3 – 159.3)
Serum ferritin	2,111.0 (725.0 – 2,164.3)
Coagulation function	
PT	13.6 (13.1 – 14.7)
D-dimer	2,251.3 (1,804.0 – 3,961.7)
ICU complications	
Acute kidney injury	62.5%
ARDS	87.5%
DIC	6.3%
Sepsis	75.0%
Deaths	50.0%

ICU: intensive care unit; IQR: interquartile range; RBC: red blood cells; WBC: white blood cells;

ALT: alanine transaminase; AST: aspartate transaminase; LDH: lactate dehydrogenase; CRP:

C-reactive protein; PT: prothrombin time; ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation.

Table 3. Oral lesions in patients with COVID-19 admitted to the ICU.

Patient	Age	Sex	Type of lesion	Site
1	54	M	Ulcer	Tongue
2	62	M	Hemorrhagic ulcer, glossitis	Lip, tongue
3	82	F	Ulcer, glossitis	Alveolar ridge, tongue
4	75	F	Hemorrhagic ulcer	Lip
5	81	F	Ulcer, glossitis	Lip, tongue
6	81	F	Ulcer	Lip
7	60	F	Ecchymosis	Lip
8	85	F	Ulcer, glossitis	Lip, tongue
9	48	M	Ulcer	Lip
10	44	M	Ulcer	Lip
11	75	M	Ulcer	Lip
12	60	M	Ulcer, glossitis	Lip, tongue
13	80	F	Ulcer	Lip
14	93	F	Erosion, glossitis	Palate, tongue
15	83	F	Hemorrhagic ulcer	Palate
16	44	F	Ulcer	Lip

ICU: intensive care unit; M: male; F: female.

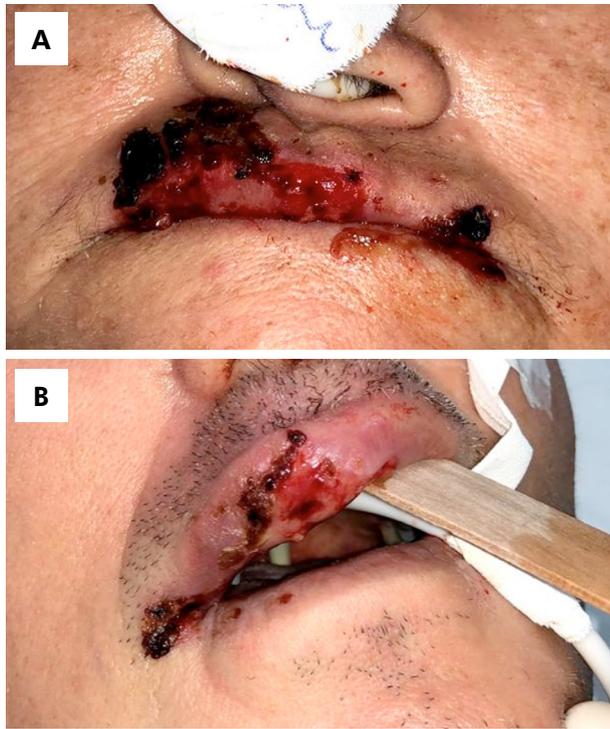


Figure. (A and B). Labial hemorrhagic ulcers in patients submitted to tracheostomy on day 5-7 post-intubation.

between SARS-CoV-2 and oral lesions, this still needs to be clarified, and other factors such as opportunistic pathogens, peripheral thrombosis, trauma secondary to intubation, and medications have been suggested as factors associated with mucosal manifestations.^{5,10,11} In addition, work overload and the highly stressful environment of the ICU can lead to unintentional neglect of oral health, increasing the risk of lesions and complications. There is evidence of an increased

risk of oral mucosa pressure ulcers among intensive care patients with hematological and biochemical abnormalities using an orotracheal tube.¹²

Our sample included patients with severe forms of COVID-19 and important alterations in hematological, biochemical, and inflammatory markers, as well as in coagulation parameters. It is plausible that oral ulcers and other mucosal lesions are associated with immune system disorders and the use of orotracheal tubes in patients with SARS-CoV-2 infection treated in the ICU. The persistent systemic immunological imbalance in COVID-19 requires close monitoring of infected patients.⁶ Moreover, daily oral hygiene care, the correction and repositioning of the endotracheal tube, maintenance of hydration of the oral and labial mucosa, the use of foam dressings in areas of high pressure, and topical corticosteroids can be useful in the prevention or treatment of these lesions. Since most studies published to date are case reports, further research should compare laboratory findings in patients with and without oral lesions and determine the presence of the virus in affected tissues.

Conclusion

This study showed that a large proportion of patients with severe COVID-19 develop oral lesions within the first few days of orotracheal intubation and highlights the importance of oral examination and early diagnosis for the proper management of these patients.

References

1. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* 2020 May;27(5):1451-4. <https://doi.org/10.1038/s41418-020-0530-3>
2. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci.* 2020 Feb;12(1):8. <https://doi.org/10.1038/s41368-020-0074-x>
3. Zhong M, Lin B, Pathak JL, Gao H, Young AJ, Wang X, et al. ACE2 and furin expressions in oral epithelial cells possibly facilitate COVID-19 infection via respiratory and fecal-oral routes *Front Med (Lausanne).* 2020 Dec;7:580796. <https://doi.org/10.3389/fmed.2020.580796>
4. Brandão TB, Gueiros LA, Melo TS, Prado-Ribeiro AC, Nesrallah AC, Prado GV, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2021 Feb;131(2):e45-51. <https://doi.org/10.1016/j.oooo.2020.07.014>
5. Hocková B, Riad A, Valky J, Šulajová Z, Stebel A, Slávik R, et al. Oral complications of ICU patients with COVID-19: case-series and review of two hundred ten cases. *J Clin Med.* 2021 Feb;10(4):581. <https://doi.org/10.3390/jcm10040581>
6. Bezerra TM, Feitosa SG, Carneiro DTO, Costa FWG, Pires FR, Pereira KMA. Oral lesions in COVID-19 infection: Is long-term follow-up important in the affected patients? *Oral Dis.* 2020 Nov. <https://doi.org/10.1111/odi.13705> Epub ahead of print.

7. Cruz MK, Morais TM, Trevisani DM. Clinical assessment of the oral cavity of patients hospitalized in an intensive care unit of an emergency hospital. *Rev Bras Ter Intensiva*. 2014 Oct-Dec;26(4):379-83. <https://doi.org/10.5935/0103-507X.20140058>
8. Iranmanesh B, Khalili M, Amiri R, Zartab H, Aflatoonian M. Oral manifestations of COVID-19 disease: A review article. *Dermatol Ther*. 2021 Jan;34(1):e14578. <https://doi.org/10.1111/dth.14578>
9. Nuño González A, Magaletsyy K, Martín Carrillo P, Lozano Masdemont B, Mayor Ibarguren A, Feito Rodríguez M, et al. Are oral mucosal changes a sign of COVID-19? A cross-sectional study at a field hospital *Actas Dermosifiliogr (Engl Ed)*. 2021 Feb;112(7):640-4. <https://doi.org/10.1016/j.adengl.2021.05.010>
10. Santos JA, Normando AG, Silva RC, Acevedo AC, Canto GL, Sugaya N, et al. Oral manifestations in patients with COVID-19: A living systematic review. *J Dent Res*. 2021 Feb;100(2):141-54. <https://doi.org/10.1177/0022034520957289>
11. Favia G, Tempesta A, Barile G, Brienza N, Capodiferro S, Vestito MC, et al. Covid-19 symptomatic patients with oral lesions: clinical and histopathological study on 123 cases of the University Hospital Policlinic of Bari with a purpose of a new classification. *J Clin Med*. 2021 Feb;10(4):757. <https://doi.org/10.3390/jcm10040757>
12. Kim CH, Kim MS, Kang MJ, Kim HH, Park NJ, Jung HK. Oral mucosa pressure ulcers in intensive care unit patients: a preliminary observational study of incidence and risk factors. *J Tissue Viability*. 2019 Feb;28(1):27-34. <https://doi.org/10.1016/j.jtv.2018.11.002>