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Relationship Between Oral Lesions and Severe SARS-CoV-2 Infection in Intensive Care Unit Patients.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/odi.14515

Running title: Relationship between oral lesions and COVID-19.

Abstract.

Objective

Oral lesions received increased attention as likely new signs or secondary manifestations of COVID-19. Therefore, we clinically examined oral cavity of patients with COVID-19 and investigated oral lesions and patient comorbidities as possible risk-factors of COVID-19 disease outcome.

Methods

From January to March 2022, a prospective study was conducted by recruiting all COVID-19 patients admitted to the Intensive Care Unit and Respiratory Intensive Care Unit of Maxi-Emergencies Hospital in Bari, Italy.

Results

From the enrolled 103 COVID-19 patients, 46.6% were females and 53.4% were males. Findings show that risk of presenting with severe COVID-19 disease was higher in patients who developed oral lesions related to COVID-19 than those with no oral lesions (RR = 7.998, $p = .002$). Next, patients with concomitant autoimmune diseases were at higher risk of a negative COVID-19 disease outcome than those without comorbidities (OR= 8.838, $p = .026$).

Conclusions

COVID-19-related lesions of oral mucosa should not be ignored as they can be early and easily-detectable signs of severe COVID-19 disease condition, thus, serving as a prevention measure for any potential unfortunate event. Findings of this study, without implying causation, offer a direction for future investigations that aim to confirm the presence of specific oral lesions in COVID-19 patients as signs of severe disease progression.

Introduction

On the 11th of March 2020, the World Health Organization (WHO) declared the beginning of the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] So far, the outbreak has produced a global healthcare crisis, with over 500 million people infected and over 6 million deaths.[1,2] Moreover, new viral variants are appearing and the pandemic seems to be far from over. Most cases are classified as asymptomatic infections or mild illnesses, but a considerable number of patients developed severe respiratory problems leading to acute severe respiratory distress, and multiple organ failures causing death. Apart from the common COVID-19 manifestations like fever, fatigue, dry cough, sore throat, dyspnoea, headache, pneumonia, and respiratory problems, the SARS-CoV-2 infection may also cause other complications involving kidneys, heart, gastrointestinal tract, central and peripheral nervous system.[3]

Currently, oral lesions are receiving increasing interest as the possible new signs of COVID-19 or secondary manifestations of the disease.[4] The interest in the identification of oral lesions in COVID-19 patients is justified by the prospect of considering them as predictors of disease progression. Empirical reports have demonstrated that taste and smell dysfunctions could be symptoms of the disease in most infected patients. The SARS-CoV-2 infection pathway may be related to ACE-2 (angiotensin-converting enzyme 2) and transmembrane serine protease (TMPRSS2 and TMPRSS4), which are expressed in both the salivary glands and the oral mucosal epithelia.[5,6] Several other studies described the appearance of oral lesions after the onset of COVID-19 symptoms but did not correlate it to the disease progression or outcome.[4,7–9] The most frequently reported oral manifestations are white plaques, multiple painful ulcers, non-specific nodules, geographic and fissured tongue, small blisters, petechiae, pustular enanthema, desquamative gingivitis, angina bullosa, and erythema multiforme-like lesions. The most involved oral sites are the tongue, palate, lips, labial commissure,

gingiva, and buccal mucosa.[4,7–9] Based on this evidence, the current study aimed to clinically examine the incidence of oral lesions in a group of patients affected by COVID-19 and to carry out an analysis to investigate the relationship between the clinically examined oral lesions and the COVID-19 disease outcome.

Material and methods

Study design, patient selection, and variables

The current prospective study was carried out following the principles of the Declaration of Helsinki and approved by the local Ethical Committee (Prot. 156/CE/2020 of 30/11/2020). From January to March 2022, all COVID-19 patients admitted to the Intensive Care Unit (ICU) or Respiratory Intensive Care Unit (RICU) of Maxi-Emergencies Hospital, University Hospital Policlinic of Bari (Italy), were included. The specific selection criterion was patients aged ≥18 years diagnosed with COVID-19 based on a positive SARS-CoV-2 nasopharyngeal swab on real-time polymerase chain reaction (RT-PCR) in addition to the presence of clinical and/or radiological signs of COVID-19. In the follow-up, all patients were examined by two experienced oral pathologists wearing proper personal protective equipment. The patients' clinical oral health examination included assessment of the lips, cheeks, salivary glands, hard palate, oropharynx, tongue, mucous membranes, and frenula.[10] The type of ventilation and vital parameters were evaluated, followed by the extraoral and intraoral physical examination (IOE) based on the WHO guidelines.[11]

The oral lesions were classified into 4 groups, following the criteria previously published by the authors in 2021:[12]

0. No oral lesions/conditions;
1. Pre-existing oral conditions: lesions diagnosed before COVID-19 onset;

2. Lesions that are unlikely to be COVID-related but have never been diagnosed before (i.e., leukoplakia, papilloma-like lesions, traumatic lesions);
3. COVID-19-related lesions: lesions that occurred simultaneously or within one week after the onset of systemic symptoms of COVID-19, and before the beginning of therapies;
4. Treatment-related lesions: lesions that appeared after the beginning of COVID-19-specific therapies;
5. Lesions related mainly to poor oral hygiene.

Patients' comorbidities were classified into different macro groups to express every single disease into dichotomic variables matching oral lesions:

- Cardiac pathologies: ischemic cardiomyopathy, dilated cardiomyopathy, atrial fibrillation, congestive heart failure, and valvulopathy;
- Respiratory pathologies: Chronic Obstructive Pulmonary Disease (COPD), chronic bronchitis, pulmonary fibrosis, pulmonary emphysema, pleural effusion, asthma, and obstructive sleep apnea syndrome (OSAS);
- Autoimmune pathologies: rheumatoid arthritis, Sjogren syndrome, myasthenia gravis, autoimmune platelet disease, Systemic lupus erythematosus (SLE), and pemphigoid;
- Obesity: body mass index (BMI) >30;
- Renal pathologies: chronic kidney disease, kidney transplantation, and monokidney;
- Circulatory pathologies: deep vein thrombosis, aortic aneurism, aortic failure, and arteriosclerosis obliterans;
- Viral pathologies: HBV, HCV, HIV, or HSV infection;
- Psychiatric or neurological disorders: Parkinson's Disease, Alzheimer's Disease, cerebral stroke, epilepsy, schizophrenia, depression, and cognitive deficit;
- Oncological pathologies;

- Diabetes;
- Essential hypertension.

Statistical Analysis

The dependent variable considered for the statistical analysis was the *negative outcome* of the COVID-19; defined as hospitalization in the Intensive Care Unit (ICU) and/or death in the Respiratory Intensive Care Unit (RICU). Predictor variables were the presence of oral lesions and pre-existing medical conditions. The correlation between the presence of oral lesions, patients' multiple comorbidities, and the negative outcome was assessed as a first step, followed by multivariable regression including every comorbidity; based on the significant values of the earlier regression. The relative risk estimated and 95% confidence interval were reported to demonstrate the strength of the associations[13,14]. The strength of the model (i.e., how the model fits the data) was indicated by an R-squared value, as described by McFadden et al. [$R^2_{McF} = 1\text{-}1n(L_M)/1n(L_O)$]. The precision of the estimation was demonstrated by the Standard Error (SE) and the 95% Confidence Interval (CI).

Results

From the enrolled 103 COVID-19 patients, 48 were females (46.6%) and 55 were males (53.4%). The mean age of the participants was 69.94 ± 10.99 years. All COVID-19 patients were assumed to be infected by the Omicron-1 variant of the SARS-CoV-2 virus because the Italian "Istituto Superiore di Sanità" (ISS) confirmed it during the study period (January-March 2022). The intra-oral examinations found oral lesions in 70 patients (68%). Descriptive data showed that most of the lesions were treatment-related (n = 49, 47.7%), followed by COVID-19-related oral lesions (n = 13, 12.7%). Four lesions (3.8%) were classified as pre-existing conditions, whereas the remaining four (3.8%) were related to poor oral hygiene.

Considering the clinical manifestations (Table 1), COVID-19-related lesions were single or multiple ulcers (Figures 1 and 3) in 76.9% of the cases, petechiae (Figure 2) in 15.4%, and blisters in 7.7%. Candida infection represents 83.7% of treatment-related manifestations. The geographic tongue represents 50% of pre-existing conditions, which were probably reactivated by SARS-CoV-2 infection.

A negative outcome (hospitalization in ICU or death in RICU) was seen in 37.9% of the study participants. The distribution of participants concerning the assessed dependent and independent variables is presented in Table 2. Descriptive findings related to systemic diseases showed that essential hypertension was prevalent in 39.8% of the study participants, followed by cardiac conditions (29.1%). The regression analysis revealed that the risk of having a negative outcome was 8 times higher (RR = 7.998, $p = 0.002$) in patients with COVID-19-related oral lesions (Table 3).

With regards to all oral lesions, a statistically significant relationship was observed (even if with a lower impact), and the risk of having a severe course of the diseases was 3 times higher than in patients who did not show any oral manifestations (RR = 3.128, $p = 0.029$). The multiple regression analysis further confirmed the results (Table 4). The autoimmune comorbidities were considered a strong risk factor to develop a severe clinical course (RR = 8.838, $p = 0.026$). The hypothesis was substantiated by the results displayed in Table 5: oral lesions ($p = 0.049$), COVID-19-related oral lesions ($p = 0.004$), and autoimmune comorbidities ($p = 0.023$) were statistically associated with a severe course of the COVID-19 disease outcome.

Discussion

Oral tissue inflammation and destruction during the SARS-CoV-2 replication, probably related to its action on the ACE-2 has been described suggesting a possible correlation between oral lesions and COVID-19.[7] Despite this, low certainty of evidence has been reported until now, probably because of the lack of studies and homogeneous data. In a review, Brandini et al. (2021) suggested that oral lesions genesis could be related to the presence of ACE-2 on the oral mucosa and its bonding with SARS-CoV-2 leading to direct epithelial damage.[15,16] Moreover, opportunistic infections by Candida and Herpes Viruses, probably related to an immune dysregulation induced by SARS-CoV-2 infection, have been reported and represent indirect oral damage secondary to virus infection.[16,17] Further it was suggested that the oral cavity may be considered a target inhabitation site for SARS-CoV-2.[18] In contrast with these studies, different works considered the direct association between oral lesions and COVID-19 to be unlikely. Amorim dos Santos et al. (2021) suggested that different clinical presentation of a single viral infection is very uncommon, and considered oral lesions as a result of coinfections and adverse reactions to drug therapies.[19]

In previous work, Favia et al. (2021) classified the different oral manifestations depending on the etiopathogenetic criteria and distinguished them into pre-existing conditions, lesions related to COVID-19 (if appeared together with general symptoms or within one week after the onset of general symptoms, and before the beginning of therapies), treatment-related lesions, and lesions due to poor oral hygiene.[12] To avoid potential bias and present more valid findings, in the current study, oral lesions were classified according to the system previously published by the authors.[12] Additionally, the study analyzed a group of COVID-19 patients treated in a single university hospital for three months. The recruitment interval was defined to minimize the incidence of the different viral variants, and all the patients were likely affected by the Omicron-1 as reported by ISS.[20] Finally, the same treatment and observation protocol was applied in all cases.

Findings showed that the presence of oral lesions is a negative prognostic factor for the development of a severe COVID-19 disease outcome (hospitalization in ICU or death in RICU). In addition, the authors distinguished different subgroups of oral lesions, which comprehended pre-existing oral lesions, COVID-19-related lesions, treatment-related lesions, and lesions due to poor oral hygiene. Anyway, the treatment-related oral lesions could have occurred before and/or after the admission to ICU/RICU. Therefore, the authors investigated the correlation between the COVID-19-related oral lesions and the severe form of the disease, to avoid confounding factors. The analysis found that COVID-19-related oral lesions were strong risk factors for the severe form of the disease. The correlation is stronger when considering the patients with COVID-19-related oral lesions who also have underlying comorbidities. Autoimmune diseases are related to a higher risk of acute respiratory distress syndrome (ARDS) or other life-threatening complications in COVID-19 patients. At the same time, the virus, through alterations of the immune status, could cause the relapse of pre-existing autoimmune pathologies.[21–23] The observed results are consistent with those of Rusu et al. who suggested in a systematic review that oral lesions could represent "*a sign of potentially life-threatening conditions*" considering them as negative prognostic factors.[24] Contrariwise, authors suggested that oral lesions can hardly be considered a direct manifestation of the SARS-CoV-2 infection or a marker of COVID-19 progression.[4,25,26] Further, Hocková et al. stated that oral lesions among patients hospitalized in ICU could be caused by trauma due to prolonged mechanical pressure during pronation, or by immunosuppressive treatment.[27–29] To avoid the aforementioned bias, before considering COVID-19-related oral lesions, we excluded all the possible causal elements such as previous autoimmune diseases, herpetic infections (with HSV negative serology test), and trauma during intubation procedures.

Though the current study provides a new understanding of the relationship between oral and general health, the findings should be interpreted considering several limitations. Based on the current study design, a causal relationship between oral lesions and death due to COVID-19 cannot be determined, and further histological studies (using experimental study designs) must be conducted. Nonetheless, preliminary data reported in other studies demonstrated the presence of occlusive thrombosis of small and medium vessels within the ulcerative lesions observed in COVID-19 patients.[12,30–32] At the same time it's to date confirmed that diffuse thrombotic complications are common in severe course patients, despite the wide use of anticoagulants that could be administered even as prophylactic therapy.[33,34] Moreover, the presence of microthrombi was described in many studies as a result of hypercoagulability syndrome and considered a negative prognostic factor considering its higher prevalence in ICU admitted patients.[35–37] Because of the small sample size, the findings cannot be generalized. This study did not consider important variables such as socio-economic status, health behaviour, smoking habits, etc. which if considered, could provide more substantial findings. On the other hand, the current investigation has several strengths. The current study was performed on a homogenous group of patients likely affected by the same viral variant (Omicron-1), they were all admitted to a single hospital and treated and observed following standardized procedures. Each step of the disease condition was recorded on a general database as the temporality and the sequence of events had been considered. The current study presents a direction for future investigations to confirm the development of oral lesions in COVID-19 as initial signs of a severe disease outcome. Thus, the detection of COVID-19-related lesions of the oral mucosa can constitute a first and easily detectable sign of an impaired COVID-19 disease condition and potentially help in preventing any unfortunate event.

Conclusion

In conclusion, this study is the first that analysed the correlation between oral manifestations and the severity of COVID-19 disease outcome. The preliminary data allowed us to hypothesize the role of oral lesions related to SARS-CoV-2 as a prognostic factor for a possible negative outcome. Though further studies supported by histologic findings on a larger number of patients are needed, the current results may lead to considering the examination of the oral cavity as a non-invasive tool for an early prediction of the evolution of the disease, thus allowing a more targeted treatment.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ACKNOWLEDGEMENT

The authors would like to thank Doctor Antonio D'Aleno, Medical Director of COVID-19 Hospital, University Hospital Policlinic of Bari, for his precious support to the research.

FIGURE LEGEND

Figure 1. Presence of ulcerative lesion >1cm on the right buccal mucosa of a patient hospitalized in ICU

Figure 2. Multiple palatal erosive/ulcerative lesions and petechiae of different size in a patient hospitalized in RICU

Figure 3. Large. deep and bleeding ulcer (>1cm) on the anterior upper jaw of an edentulous patient hospitalized in ICU

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Table 1. Clinical presentation of COVID-19-related oral lesions.

COVID-19-Related Lesions		**13 (12.7% of oral lesions)**
Ulcers	Single	3 (23.1% of group 2 lesions)
	Multiple	7 (53.8% of group 2 lesions)
Petechiae	Multiple	2 (15.4% of group 2 lesions)
Blisters	Multiple	1 (7.7% of group 2 lesions)

Table 2: Sample distribution according to the dependent and independent variables (N= 103).

Dependent variable	Number
Severe COVID-19 condition (including death)	
Yes	39 (37.9%)
No	64 (62.1%)
Independent variables	
Classification of oral lesions	
No lesions	33 (32%)
Pre-existing lesions	4 (3.8%)
COVID-19-related lesions	13 (12.7)
Treatment-related lesions	49 (47.7%)
Lesions due to poor oral hygiene	4 (3.8%)
General Health Conditions	
Cardiac pathologies	
Yes	30 (29.1%)
No	73 (70.9%)
Pulmonary pathologies	
Yes	24 (23.3%)
No	79 (76.7%)
Oncological pathologies	
Yes	26 (25.2%)
No	77 (74.8%)
Autoimmune pathologies	
Yes	7 (6.8%)
No	96 (93.2%)
Diabetes	
Yes	21 (20.3)
No	82 (79.7%)
Essential Hypertension	
Yes	41 (39.8%)
No	62 (60.2%)
Renal pathologies	
Yes	10 (9.7%)
No	93 (90.3%)
Circulatory pathologies	
Yes	16 (15.5%)
No	87 (84.5%)
Viral pathologies	

Yes	8 (7.8%)
No	95 (92.2%)
Psychiatric or Neurological disorders	
Yes	20 (19.4%)
No	83 (80.6%)
Obesity	
Yes	16 (15.5%)
No	87 (84.5%)
Vaccination	
None	50 (48.5%)
First dose	2 (1.9%)
Two doses	30 (29.1%)
Three doses	21 (20.3%)
Reinfection	
Yes	4 (3.8%)
No	99 (96.2%)

Table 3: Bivariate analyses to investigate the factors that are associated with severe COVID-19 condition or death (N =103).

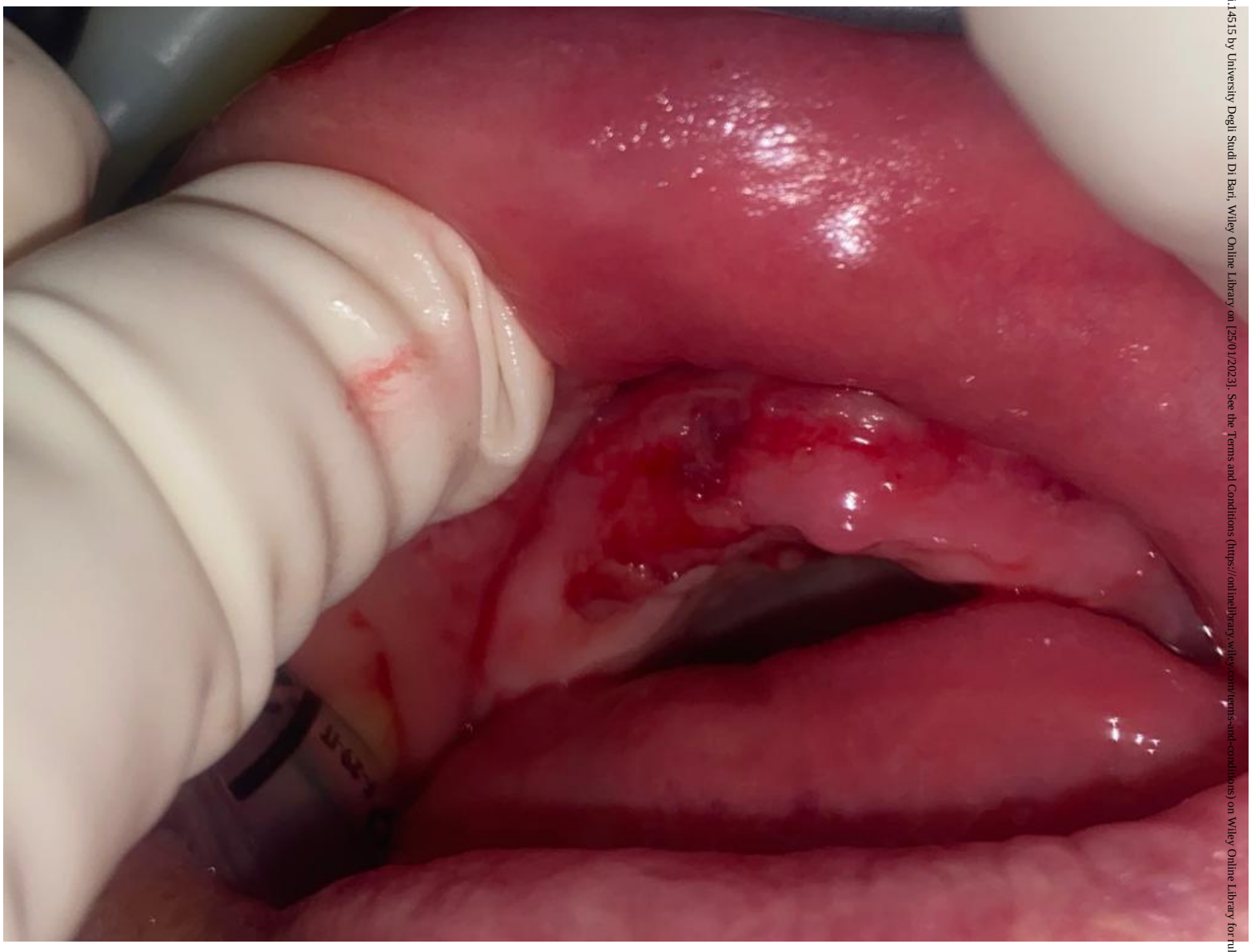
INDEPENDENT VARIABLES	POSITIVE OUTCOME n (%)	NEGATIVE OUTCOME n (%)	RR	95% $CI_{(OR)}$	P-value
Patients number	64 (62.10 %)	39 (37.90 %)			
Oral lesions	38 (59.37 %)	32 (82.05%)	3.128	1.200 - 8.152	.029
COVID-19-related Oral Lesions	3 (4.69 %)	10 (25.64 %)	7.988	2.065 - 30.898	.002
Cardiac pathologies	15 (23.44 %)	15 (38.46 %)	2.042	0.858 - 4.856	.160
Pulmonary pathologies	17 (26.56 %)	7 (17.95 %)	0.605	0.225 - 1.625	.446
Oncologic pathologies	17 (26.56 %)	9 (23.08 %)	0.829	0.328 - 2.010	.872
Autoimmune pathologies	2 (3.12 %)	5 (12.82 %)	4.559	0.839 - 24.765	.135
Diabetes	11 (17.19%)	10 (25.64 %)	1.661	0.631 - 4.377	.435
Essential Hypertension	23 (35.94%)	18 (46.15 %)	1.528	0.679 - 3.437	.412
Renal pathologies	5 (7.81%)	5 (12.82 %)	1.735	0.468 - 6.428	.624
Circulatory pathologies	9 (14.06 %)	7 (17.95 %)	1.337	0.454 - 3.935	.804
Viral pathologies	3 (4.69 %)	5 (12.82 %)	2.990	0.673 - 13.289	.264
Psychiatric or Neurological disorders	14 (21.89 %)	6 (15.38 %)	0.649	0.227 - 1.860	.582
Obesity	9 (14.06 %)	7 (17.95 %)	1.337	0.454 - 3.935	.804

Table 4: Bivariate analysis with negative outcome as dependent variable (N =103).

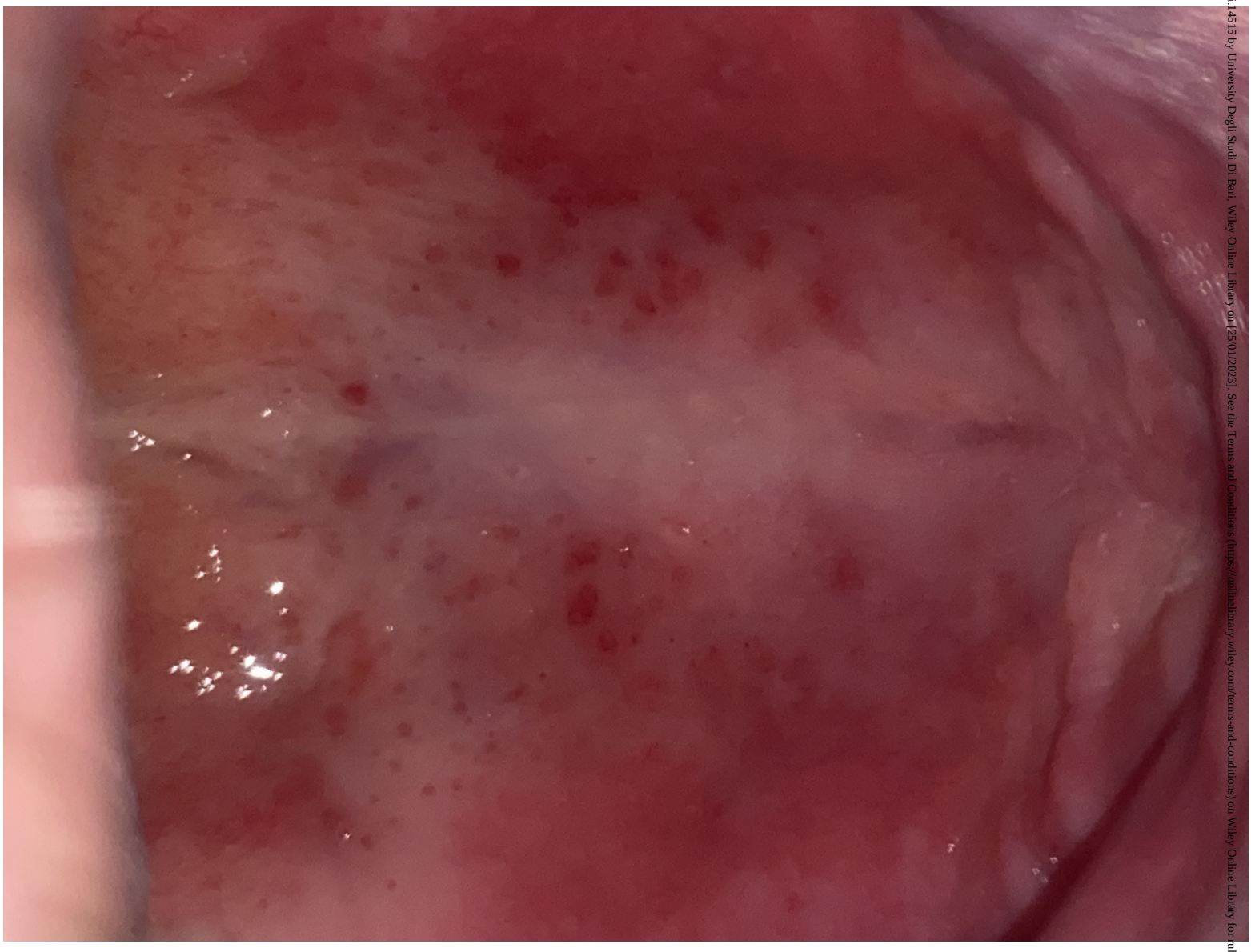
VARIABLE	COEFFICIENT	$SE_{(coefficient)}$	RR	P-value
Oral Lesions	1.178	0.567	3.247	.038
Covid-19-Related Oral Lesions	1.891	0.732	6.626	.010
Autoimmune Pathologies	2.179	0.980	8.838	.026

Table 5: Multiple regression analysis to investigate the factors that are associated with severe COVID-19 condition or death (N =103).

VARIABLE	Coefficient	$SE_{(coefficient)}$	R^2	T	P-value
Oral Lesions	0.198	0.010	0.226	1.987	.049
COVID-19-Related Oral Lesions	0.396	0.134	0.284	2.951	.004
Autoimmune Pathologies	0.410	0.178	0.196	2.310	.023



ODI_14515_Image 1.jpeg



ODI_14515_Image 2.jpeg

ODI_14515_Image_3.jpeg