



Gingival Inflammatory Profile of Intensive Care Unit Patients with COVID-19: A Pilot Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors GHGS, IMP prepared original draft, did clinical and experimental studies, data and statistical analysis; edited and reviewed the manuscript. Authors PADD, ASJ, ÍSC helped in preparation; performed experimental studies in the manuscript. Authors CAN, PON wrote definitions of intellectual content; designed the study; did clinical and experimental studies, data and statistical analysis; prepared, edited and reviewed the original draft of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

There is minimal evidence to provide robust conclusions on how periodontal disease may be associated with COVID-19 infection. The objective of this research was to evaluate the gingival inflammatory profile of patients with COVID-19 in the ICU of the Western Paraná State University Hospital (HUOP) in Cascavel/PR, through a pilot clinical study. Data such as age, sex, exams and health history were performed by searching the information system - Tasy®. Patients were divided into two groups: Patients without COVID-19 (control group) and patients with COVID-19 (case

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group) and were evaluated: Plaque Index (IP), Probing Depth (PS), clinical attachment level (NI) and bleeding on probing (SS) and 3 sites were selected to collect the amount of Gingival Crevicular fluid (GCF). It was observed that in both groups the majority of patients were male, with no differences between them for sex and age. Patients in the COVID-19 group had statistically higher values of IP and FCG and lower values of PS and NI. In addition, patients with COVID-19 had an increase in Hemoglobin and a decrease in Lymphocytes and Platelets compared to the control group. As for Hospital Medication, only the variable Corticosteroids was administered with greater statistical frequency in patients with COVID-19 and each NI unit increases the chance of the patient dying by 10.59 times. It is concluded that there was an increase in the periodontal inflammatory profile of patients with COVID-19, however dexamethasone therapy may have led to an inhibition in the development of periodontitis in these patients.

Keywords: COVID-19; inflammation; periodontitis; corticosteroids.

1. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus and expresses a protein (Protein S) that mediates adhesion and invasion of host cells. The S protein of SARS-CoV-2 specifically binds to angiotensin-converting enzyme 2 (ACE-2) expressed in the lungs and kidneys, and myocardial cells. ACE-2 has also been found intraoral, especially in the salivary glands and tongue. Currently, a new and more virulent variant of SARS-CoV-2, D614G, is spreading worldwide; the S protein of this variant contains a G614 substitution for D614 [1]. There are also suggestions that COVID-19-related deaths may be associated with deprivation and ethnicity, although few studies have been done on periodontal disease's impact on COVID-19 infection so far [2].

Periodontitis is the leading cause of tooth loss in adults and the sixth most prevalent disease globally, affecting between 10 and 50% of adults [2]. It is a complex infectious inflammatory condition with multifactorial contributing factors that destroy tooth support tissues, leading to alveolar bone destruction and tooth loss. Understanding the dynamic interactions between various periodontal pathogens and inflammatory immunosuppression mediated host responses has increased significantly, highlighting the importance of genetic, epigenetic, lifestyle, and environmental factors in the pathogenesis of periodontitis [3].

Existing evidence suggests that people with periodontitis may have an increased risk of developing subsequent systemic diseases, including cardiovascular disease, hypertension, respiratory disease, diabetes, and cancer. It has been suggested that COVID-19 could be linked

to periodontal disease due to shared risk factors, including obesity, age, and hypertension. Furthermore, there is increasing evidence of bacterial coinfection in COVID-19 hospitalizations, while ventilator-associated pneumonia is also a reported complication in hospitalized COVID-19 patients. Oral dysbiosis resulting from increased dental plaque in periodontitis may provide an environment for oral transport of respiratory pathogens and cause complications in COVID-19. To date, there is minimal evidence sufficient to provide robust conclusions about how periodontal disease may be associated with infection and outcomes by COVID-19 [2].

Early detection and treatment of periodontal disease, as well as identification of hyper-responsive individuals through cytokine profiling, may help in the selection of appropriate anti-cytokine drugs. Although promising results are reported after treating patients with COVID-19 with immunomodulators, clinical trials are still needed to understand the efficacy and safety of these drugs according to the stage and severity of the disease [1].

Corticosteroids were first thought of for COVID-19 as a means to prevent the "cytokine storm" and its consequences such as adult respiratory distress syndrome, disseminated intravascular coagulation, hypotension, shock, and death. In this regard, the use of dexamethasone showed a positive patient response within the first seven days of this therapy [4].

Although the causal link is not clear, periodontal disease could increase the severity of COVID-19 by causing microbial dysbiosis, bacterial superinfection, host hyperresponsiveness, and overstimulation of the immune system. As such, nonsurgical periodontal therapy and anti-cytokine

inhibitor treatment may have beneficial effects in patients infected with SARS-CoV-2 [1].

2. OBJECTIVE

To evaluate the gingival inflammatory profile of patients with COVID-19 admitted to the ICU of the Western Paraná State University Hospital in Cascavel-PR through a pilot clinical study

3. METHODS

3.1 Type of Study

This is clinical research with quantitative analysis. The clinical outcome was the prevalence and severity of periodontal disease involving patients with COVID-19 treated in the COVID-19 ward of the Intensive Care Unit (ICU) of the Western Paraná State University Hospital (HUOP/UNIOESTE) in Cascavel, Paraná.

3.2 Data Collection

3.2.1 Study design

This cross-sectional case-control study is classified as clinical observational and exploratory with a clinical and laboratory basis. It presents an analysis of the prevalence of periodontal disease in patients admitted to the ICU of the Western Paraná State University Hospital (HUOP/UNIOESTE), in Cascavel/PR, with a positive diagnosis for COVID-19 from the PCR test (Reverse transcription-polymerase chain reaction), a test considered as the gold standard for laboratory diagnosis of COVID-19. The selected patients were evaluated with a complete extraoral and intraoral clinical examination (as much as possible, considering the inpatient condition), focusing on diagnosing periodontal changes. In addition to the clinical examination, analysis of the health history and relevant hematological tests were performed, considering the possible association with the periodontal changes evaluated and allowing correlation of systemic, blood, and periodontal data.

3.2.2 Case and control selection

Between July and December 2020, a total of 55 patients admitted to the ICU of the Western Paraná State University Hospital (HUOP/UNIOESTE), in Cascavel/PR, with a diagnosis of respiratory failure, were evaluated.

These patients were divided into two different groups: group 1 (n=37) and group 2 (n=18).

Group 1 (case) consisted of patients admitted to the COVID-19 ICU ward with the confirmed diagnosis for COVID-19 (PCR test). Group 2 (control) was made up of patients admitted to the general ICU with a respiratory syndrome (fever, cough, sore throat, myalgia, headache or arthralgia, respiratory distress, and dyspnea), but with a negative result for COVID-19.

During data collection, it was verified that, for some selected patients, data collection was not possible for different reasons: the patient had total upper and lower edentulousness, the patient was in the prone position, or the patient was hemodynamically unstable at the time of collection. Thus, a total sample of 33 patients was obtained, as shown in Fig. 1.

As inclusion criteria for the patients, the individuals analyzed in the research were aged between 18 and 80 years old, admitted to the ICU of the Western Paraná State University Hospital (HUOP/UNIOESTE), in Cascavel/PR, with confirmation of infection by SARS-COV-2 and patients admitted to the general ICU with a respiratory syndrome (fever, cough, sore throat, myalgia, headache or arthralgia, respiratory distress, and dyspnea), but with a negative result for COVID-19. All patients should have at least 6 teeth.

As exclusion criteria, total edentulous patients, patients or family members who refused to participate or to sign the Informed Consent Form (ICF); patients who were not authorized by the responsible physician due to: hemodynamic instability or use of medication that altered the patient's coagulation; patients with braces and pregnant patients.

The patients did not undergo any type of periodontal treatment as part of the research.

3.3 Periodontal Clinical Exam

The clinical examination was performed by two previously trained examiners under ergonomic and adequate lighting conditions for intra/inter-examiner repetition regarding the positioning and inclination of the millimeter probe and probing pressure, which should be approximately 25 grams. The training was maintained during data collection and, in order to perform it,

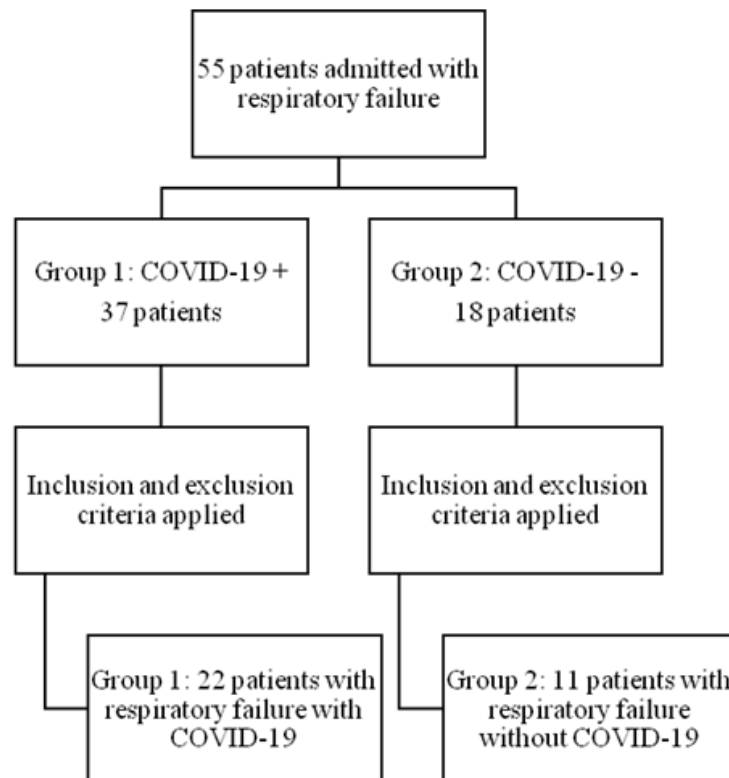


Fig. 1. Selection and distribution of patients according to groups

the examiner should use a periodontal manikin, positioned on the tray of the AX200 precision digital scale (Shimadzu®, Japan), and then simulate a periodontal probing, applying a force until the value of 25 g using a North Carolina model millimeter periodontal probe (Millennium®, São Paulo), modified pen-shaped handle, keeping the active tip perpendicular to the manikin's tooth until it reached 10 repetitions.

Parameters evaluated: In sequential and convenience order, the following were evaluated:

- A. O'Leary's Plaque Index (PI) [5].
- B. Clinical probing depth (PD): distance from the Gingival Margin (GM) to the bottom of the sulcus/pocket with a record of presence or absence and measured in mm.
- C. Bleeding on Probing (BoP): every three teeth, with an interval of approximately 30 seconds for recording the parameter, which corresponds to the probing time with a record of presence or absence.
- D. Clinical Attachment Level (CAL) distance from the cemento-enamel junction (CEJ) to the bottom of the sulcus/pocket, recorded as presence or absence and measured in

mm. Obtained from the sum of gingival recession and clinical probing depth. $CAL = GR$ (gingival regression) + PD used in extensive epidemiological studies such as the National Health and Nutrition Examination Survey (NHANES) and recent clinical studies [6].

Dental groups and sites evaluated:

considering that the study population was patients with possible hematological, oral, and systemic alterations, who need practical and minimally invasive examinations, partial mouth examination was performed, excluding third molars. All teeth were evaluated, and, in each tooth, two sites were evaluated: Mesio-Vestibular (MV), Vestibular (V) and Disto-Vestibular (DV). The palatal and lingual surfaces were not evaluated, considering that some patients were under invasive mechanical ventilation, which would make the evaluation difficult and time-consuming.

Hematological tests for analysis: the patients' complete blood count was analyzed, and the hemoglobin index, platelet count, leukocyte and lymphocyte count, C-reactive protein, and glycemic index were collected.

3.4 Gingival Crevicular Fluid (GCF) Analysis

GCF collections were performed at the same four sites selected in the previous analysis, and on average, three days after the patient's admission to the ICU, using an absorbent paper cone (Tanari, Manaus, Brazil). All cones were previously sterilized. The supragingival plaque was carefully removed according to the standard operating procedure of oral hygiene already established in the ICU. After the sites were isolated with cotton rolls and dried, the paper cones were inserted below the gingival margin for 30 seconds and immediately placed in a 0.2% alcoholic solution of ninhydrin (2,2-dihydroxyindane-1,3-dione) for one minute. The cones were photographed and immediately discarded along with the ninhydrin. Then they were analyzed with software (Image Pro Plus® 4.5.0.29, Media Cybernetics, Silver Spring, MD, USA) to determine the amount of fluid absorbed in mm² [7], with three daily measurements and repetition of this process for three days, with a 2-day interval between conferences.

3.5 Data Analysis

Individuals from two groups were evaluated: 33 affected by COVID-19 (COVID-19 Group) and 11 not affected (Control Group). To obtain data with little confounding bias, the initial sample was matched using the propensity score. Individuals who have similar or equal propensity scores have the same probability distributions, so groups can be compared. The matching algorithm identifies matching pairs (one patient

from the COVID-19 group and one from the Control group) within a range of numerical proximity. Once this limit is exceeded, the other patients in the control group are disregarded [8,9]. After this pairing, the n of the groups was distributed as shown in Fig. 2.

Data from quantitative variables (Periodontal Parameters and Blood Tests) were compared between groups using the t test for paired samples or the Wilcoxon test, when the data did not meet the normality assumption assessed by the Shapiro-Wilk test. The results are reported in tables using the mean+standard deviation in the variables with parametric data (normal distribution) and median [interquartile range] for non-parametric data (non-normal distribution).

Data from qualitative variables (Comorbidities/Habits, Hospital Medication (ICU) and Outcome) were compared between groups using the Chi-Square test for Independence. When there was a statistically significant difference (p<0.05) between the groups, the Adjusted Residuals follow-up test was applied to detect the value at which such difference was found. Results are represented with absolute and relative percentage frequencies.

To identify whether any variable has an influence on the outcome (Discharge or death), a mathematical model was adjusted using the Binary Logistic Regression method. The criteria for inclusion of variables in the model were adapted to each realization of a new model. First, variables whose p-values in previous analyzes were lower than 0.05 were selected.

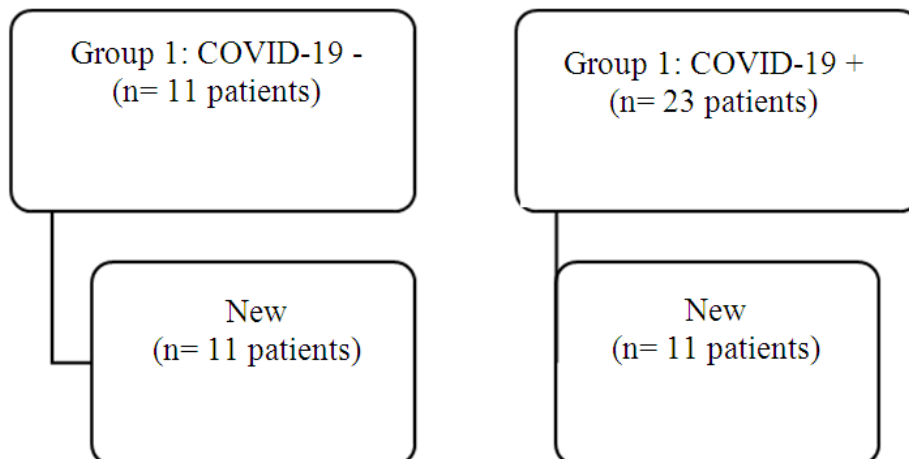


Fig. 2. Sample distribution flowchart after matching by Propensity Score. Above, full sample. Below, n sample after matching

We considered the maximization of the Wald function and the verification of the fit of the models through the Hosmer & Lemeshow statistics. To assess the fidelity of the model created in relation to reality, a ROC (Receiver Operating Characteristic) curve was created, in which the percentage values of sensitivity (probability of the model predicting death) and specificity (probability of the model predicting death) are graphically represented. high) of the fitted model.

The analyzes were performed using the software R (2019) version 3.6.2 using the packages "Mathching" [10], "dplyr" [11] and "ggplot2" [12]. The XLSTat software version 2017 [13] was also used, always considering a significance level of 5%.

4. RESULTS

4.1 Sample Characterization

Group 1 was composed of most male patients (82.61%), with a mean age of 55 years. Group 2 also had a majority of male patients (54.55%), with a mean age of 57 years. When comparing

these groups, it is noted that there is no difference between them for sex or age ($p>0.05$) (Table 1).

4.2 Comparison between Patients with and without COVID-19

Patients in the COVID-19 group had values of PI and Crevicular Gingival Fluid statistically higher than the Control group. On the other hand, the COVID-19 Group presented values of PD and CAL statistically lower than the Control group (Table 2).

The COVID-19 group had statistically higher Hemoglobin values than the Control group. For the variables Lymphocytes and Platelets, the COVID-19 group showed statistically lower values than the Control group (Table 3).

No variables were statistically different between groups for Comorbidities/Habits (Table 4). The variables Chronic Diseases, Heart Diseases and Ischemic Diseases and Lung Diseases showed $p=1$, since the absolute frequency of individuals is very similar or equal between groups.

Table 1. Absolute and percentage frequencies (in parentheses) of sex and mean \pm standard deviation of patients' ages in groups 1 and 2

Variable		Group 1 (case)	Group 2 (control)	p-value
Sex	Female	4 (17,39%)	5 (45,45%)	0.08 ¹
	Male	19 (82,61%)	6 (54,55%)	
Age		55 \pm 17	57 \pm 13	0.73 ²

¹p-value of the Chi-square test for independence; ²p-value of the t-test

Table 2. Comparison of periodontal parameters variables between patients with and without COVID-19. The values indicate mean \pm standard deviation

Periodontal Parameters	COVID-19	Control	p-valor
PI	48,64 \pm 28,2	41,81 \pm 34,56	<0,0001 ¹
BoP (%)	3,7 [0,0-6,65]	16,7 [4,6-22,35]	0,05802 ²
PD (mm)	1,53 \pm 0,42	1,95 \pm 0,49	<0,0001 ¹
CAL (mm)	2,13 \pm 0,61	2,55 \pm 0,8	<0,0001 ¹
CGF (mm ²)	88,73 \pm 53,47	11,15 \pm 8,05	0,0004 ¹

¹Paired t test. ²Wilcoxon. Values in bold indicate statistical significance. $p<0,05$

Table 3. Comparison of blood test variables between patients with and without COVID-19. The values indicate mean \pm standard deviation

Blood Tests	COVID-19	Control	p-valor
Hemoglobin (g/dL)	11,9 \pm 2,23	9,89 \pm 2,9	<0,0001 ¹
Leukocytes (mm ³)	9711 [8190-15150]	14310 [12065-15600]	0,3652 ²
Lymphocytes (mm ³)	1176,09 \pm 570,81	1491,36 \pm 611,09	<0,0001 ¹
Platelets (mm ³)	187336,59 \pm 118370,01	244800 \pm 111677,68	<0,0001 ¹
CRP (mg/dL)	8,6 [6,5-16,55]	6,4 [6-17,4]	0,7002 ²
Glucose (mg/dL)	109 [94,5-143]	124 [117-148]	0,3652 ²

¹Paired t test. ²Wilcoxon. Values in bold indicate statistical significance. $p<0,05$

Table 4. Comparison of comorbidities/habits variables between patients with and without COVID-19. The values indicate absolute (relative) frequency

Comorbidities/Habits	COVID-19	Control	p-value
Not applicable	4 (36,36%)	2 (18,18%)	0,6321
Chronic Diseases	7 (63,63%)	7 (63,63%)	1
Heart diseases and ischemic diseases	2 (18,18%)	3 (27,27%)	1
Smoking	1 (9,09%)	5 (45,45%)	0,151
Lung Diseases	2 (18,18%)	1 (9,09%)	1
Alcoholism	0	2 (18,18%)	0,4583

Values in bold indicate statistical significance

As for Hospital Medication, only the Corticosteroids variable was statistically different between the groups, as this medication was administered more frequently in patients with COVID-19 (Table 5).

4.3 Influence of Significant Variables on Patient Outcomes

According to the Hosmer-Lemeshow statistics (p=0.2492; GL=8, Chi-square: 10.2304) the model presents a good fit. According to the

model, each NI unit increases the chance of the patient dying by 10.59 times (Table 6).

The calculation of the model's sensitivity and specificity is represented in Fig. 3, whose area under the curve indicates that the model has 80.95% of capacity to predict the factors associated with the outcome. Specificity indicates that the model is 93.33% efficient in identifying individuals who will be discharged, and sensitivity indicates that the model is 71.43% efficient in identifying individuals who will die.

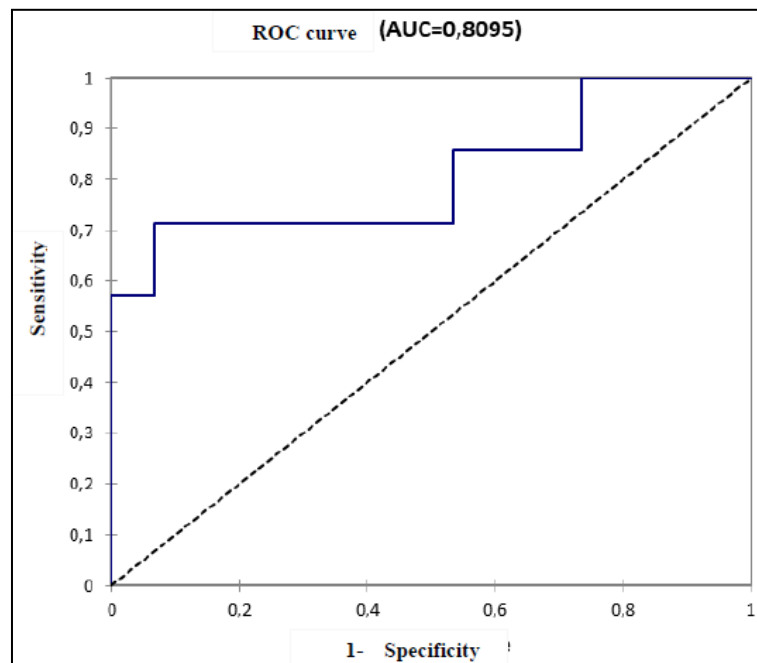


Fig. 3. ROC curve for the binary logistic regression model with predictive factors for death

Table 5. Comparison of hospital medication and outcome variables between patients with and without COVID-19. The values indicate absolute (relative) frequency

Hospital medication (ICU) and outcome	COVID-19	Control	p-value
Antibiotics	10 (90,9%)	9 (81,81%)	1
AAS	0	2 (18,18%)	0,4583
Corticosteroids	8 (72,72%)	1 (9,09%)	0,0093
Antivirals	5 (45,45%)	1 (9,09%)	0,151
Deaths	3 (27,27%)	4 (36,36%)	1

Values in bold indicate statistical significance. p<0,05

Table 6. Influence of significant variables on patient outcomes

Variables	Value	Pr > Qui ²	OR [IC95%] *
Intercept	-6,40	0,02	
NI	2,36	0,03	10,59 [1,32-84,76]

*OR = Odds Ratio or Odds Ratio. *CI95% = Lower limit and Upper limit of the interval with 95% confidence

5. DISCUSSION

A growing body of evidence reveals that the male sex is a risk factor for more severe illness, including death. Globally, approximately 60% of COVID-19 deaths are reported in men, and a cohort study of 17 million adults in England reported a strong association between male sex and risk of death from COVID-19 (hazard ratio of 1.59, 95% confidence interval) [14]. In the present study, most patients in group 1 (case) were also male, with a prevalence of 82,61% (Table 1).

Asia and Europe identified older age, male gender, and chronic diseases such as diabetes, hypertension, obesity, coronary artery disease, and heart failure as risk factors associated with worse outcomes [15]. In this study, the mean age of patients in the COVID-19 group was 55 years, and the most frequent comorbidity was chronic diseases (rheumatoid arthritis, diabetes mellitus, chronic kidney disease, primary biliary cirrhosis, hypothyroidism, SAH and obesity) with no statistical difference between the two groups. In fact, there were no significant differences between the frequencies of comorbidities or habits between the groups (Table 4), showing that the only determining factor between the groups was COVID-19.

Infectious and inflammatory links between respiratory disease and periodontitis may also represent potential factors associated with exacerbation of respiratory distress in COVID-19. Although the causal link is unclear, periodontal disease could increase the severity of COVID-19 by causing microbial dysbiosis, bacterial superinfection, host hyperresponsiveness, and overstimulation of the immune system. Along with other systemic conditions, periodontitis may increase the inflammatory response and cytokine storm. Likely, environmental, microbial, and inflammatory factors together contribute to disease progression [1].

To date, consistent information on oral health history (including periodontal status) in critically ill COVID-19 patients has not been reported [16]. Periodontal pockets can be a conducive medium for SARS-Cov-2 replication and, as the viral load in the exudate increases, there is a greater

chance of the virus reaching the bloodstream through saliva [17]. In this study, a significant increase in FCG and IP was observed in patients with COVID-19, on the other hand, PS and NI values were higher in the control group (Table 2), demonstrating the rapid increase in the inflammatory response in patients with COVID-19. The increase in the amount of FCG is considered a manifestation of inflammation [18].

However, when the medication administered in the ICU was evaluated, the only medication with a statistical difference between the groups was corticosteroids (specifically dexamethasone), being administered to 72.72% of the patients in the COVID-19 group (Table 5). Corticosteroids, including dexamethasone, have anti-inflammatory properties, including reducing systemic inflammation. Current studies [19,20] suggest that the periodontal pocket epithelium may be a focal point of infection for SARS-CoV-2, and therefore periodontal therapy could help to minimize the systemic spread of the virus. None of the groups studied underwent periodontal treatment, however, dexamethasone therapy for patients with COVID-19 may have inhibited the advancement of periodontitis in these patients. A study evaluating the effect of dexamethasone hydrogel on periodontal pockets of rats with experimental periodontitis, after 4 weeks of treatment, observed that alveolar bone loss in the hydrogel group was significantly lower compared to the periodontitis group [21]. This indicates that the hydrogel can partially repair bone in periodontitis. H/E and Masson's trichrome staining evaluated inflammatory cell infiltration and repair of damaged periodontal tissue in periodontitis and TRAP staining analysis revealed fewer osteoclasts in the periodontium of the hydrogel group than in those of the untreated periodontitis group, which may justify the PS and NI results of this study presented in Table 5.

In this sense, the anti-inflammatory properties of corticosteroids, which include reducing systemic inflammation, reducing exudative fluid in lung tissue and preventing alveolar damage, thus improving hypoxia and minimizing the risk of respiratory failure, made corticosteroids thought of in the COVID-19 as a means of avoiding the "cytokine storm". As this usually happens within

the first 5 and 7 days, ideally, steroid therapy should be attempted during this period, particularly at the onset of dyspnea or even earlier to prevent the progression of the “cytokine storm”. In most patients, the collection of periodontal parameters was performed in this period, due to the hemodynamic instability of the patient in the first days.

In addition, dexamethasone has increased glucocorticoid activity and has been one of the main corticosteroids used in the treatment of COVID-19. The most robust data among corticosteroids came with dexamethasone in the RECOVERY trial, which showed the most significant mortality benefit with low-dose dexamethasone, which showed a 35% reduction in mortality among the sickest patients on invasive mechanical ventilation and a reduction in 20% mortality among patients on oxygen therapy (with or without non-invasive ventilation) [4], justifying the result of the influence of NI on patient outcome.

Lymphopenia, a quantitative reduction in blood lymphocytes, is recurrent in common infections and is the most frequent laboratory finding in COVID-19, as is platelet count [22], which was demonstrated in this study (Table 3). On the other hand, one would expect to see anemia or lower hemoglobin in patients with COVID-19, however, the results of this study showed a significantly higher mean in patients with COVID-19 compared to patients without COVID-19 being in according to Asghar et al. These patterns in the increase in hemoglobin may reflect increased production of red blood cells in the bone marrow to counteract severe hypoxemia or hemoconcentration in the sepsis setting [22].

The relationships between COVID-19 and periodontal disease may be mediated by altered cytokine responses following viral replication. Further clinical trials evaluating periodontal conditions in patients with COVID-19 are needed to determine the exact mechanisms. Considering that poor oral hygiene can exacerbate SARS-CoV-2 infection, it is essential to maintain good oral hygiene and periodontal health to preserve overall health [1].

6. CONCLUSION

Within the limits of this study and based on the clinical significance of the results found, it is concluded that there was an increase in the periodontal inflammatory profile of patients with

COVID-19. Considering that the sample studied was small, it is suggested that dexamethasone therapy in the group of patients with COVID-19 may have led to inhibition in the development of periodontitis in these patients.

DISCLAIMER

This paper is an extended version of a Thesis document of the same author.

The Thesis document is available in this link: https://tede.unioeste.br/bitstream/tede/5552/5/Gu-stavo_Silva2021.pdf

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ETHICAL APPROVAL AND CONSENT

According to Resolution 466/12 of the National Health Council, regarding research involving human beings, this study was approved by the Human Research Ethics Committee of the Western Paraná State University - UNIOESTE, Report no.: 4.103.880. The objective and nature of the study were explained, by telephone contact, to all companions/guardians of the patients, and they were included as study participants after agreeing and signing the Informed Consent Form (ICF).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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