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Periodontal disease severity in patients with long COVID and non-COVID-19

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ABSTRACT

Background: *Previous research studies have found the persistence of various COVID-19 symptoms even after the patient tested negative on a PCR test; this incident is now known as long COVID. These long COVID symptoms are reported to appear in the oral cavity including long COVID effects on periodontal disease, as both long COVID and periodontal disease release similar proinflammatory cytokines such as Acute phase proteins, CRP, TNF-α, IL-1β, IL-2, IL-6, and IFN-γ.* ***Purpose:*** *This study aims to show periodontal-disease severity-frequency distribution in COVID-19 survivors with long COVID and in non-COVID-19 patients.* ***Methods:*** *Patients' secondary data in the Periodontics Clinic Faculty of Dentistry at Trisakti University Dental Hospital (n=40) consisted of 20 samples from COVID-19 survivors who experienced long COVID and 20 samples from the non-COVID-19 group selected according to the inclusion criteria. Afterward, the data was recapitulated and processed into a research report.* ***Results****: The distribution percentage of generalized gingivitis was highest in non-COVID-19 patients, while generalized periodontitis was highest in COVID-19 survivors with long COVID. Based on periodontitis staging and grading methods, it is not proven that long COVID increases the severity of the periodontitis.* ***Conclusion:*** *This research shows that the distribution of gingivitis in COVID-19 survivors with long COVID has not increased. Meanwhile, the distribution of general periodontitis increased in survivors with long COVID. However, there was no increased severity of periodontitis based on the staging and grading method of periodontitis in the COVID-19 survivors with long COVID.*

Keywords: *Long COVID; periodontal disease; periodontitis; gingivitis; COVID-19 survivors*

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INTRODUCTION

Long COVID is a term used when a patient still has various COVID-19 symptoms for weeks to months after being confirmed negative on a PCR test.[1] The prevalence of long COVID

symptoms is estimated to be experienced by one third of the total number of COVID-19 survivors, with percentages ranging from 30–80%. The report shows some patients have at least one persistent symptom months after the acute phase.[2] The exact cause of long COVID is yet to be identified. However, several factors including organ damages, varying chronic inflammations, alterations of the immune response, drug side effects or interactions, viral persistence, coagulopathies, and complications of comorbidities may cause this condition.[1,3]

Based on the duration of symptoms, long COVID or post-COVID is divided into post-acute COVID and chronic COVID. Post-acute COVID is defined as symptoms persisting for 3–12 weeks after the patient is confirmed negative for COVID, while chronic COVID is defined as symptoms persisting for more than 12 weeks after being confirmed negative for COVID.[1] Persistent symptoms generally appear as fatigue, muscle and joint pain, insomnia, cough, and headache, among others.[4]

Data reported by Rafalowicz et al.[5] found that long COVID symptoms in the oral cavity were found in 68% of patients including 49% of women and 51% of men. The most common locations for symptoms to appear were the palate, tongue, gingiva, and lips.[6] Long COVID in the oral cavity can be oral lesions such as ulceration, erythematous plaques, etc., and some oral symptoms such as ageusia, dysgeusia, burning mouth sensation, salivary gland disorders, and periodontal disease.[5,7,8] These oral lesions and symptoms can heal within 3–21 days either spontaneously, through topical treatment, or depending on the patient's oral hygiene.[6] These symptoms can change or return for reasons that cannot be explained with certainty. Based on literature observation data on the symptoms of long COVID in the oral cavity, it is known that this condition is generally related to a decrease in the immune system, stress, oral health, and the general health condition of the patient; and it is still debatable whether the oral manifestations of COVID-19 are due to the primary infection of this virus.[5,9] However, the composition and activity of organisms in the oral cavity and respiratory system due to long COVID also strongly impact oral conditions; for example, the bacterium *Porphyromonas gingivalis (P. gingivalis)* is one of many oral pathogenic organisms that can cause dysbiosis of the oral microbiome leading to periodontal disease, since SARS-CoV-2 infection also might occur as a coinfection of *P. intermedia* and could worsen periodontal disease.[10,11] *P. gingivalis* enhances the production of bacterial products and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-a by macrophages that may relate to the COVID-19 cytokine storm.[12,13] The findings obtained by the studies included in the reviews suggest that this association may be feasible since the reports indicate that the connection is based on the oral viral load or by

cytokines, which have a fundamental role in the immune-inflammatory response to infections, including periodontal pathogens.[13]

The periodontal disease consists of gingivitis and periodontitis.[14] Gingivitis is generally defined as a gingival inflammatory condition caused by an accumulation of biofilm on the teeth characterized by redness and gingival edema without loss of attachment of the supporting gingival tissues.[15] The leading cause of gingivitis is periodontal pathogens such as *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola*.[16] Typical clinical findings of gingivitis are bleeding on probing, erythema, missing stippling, and edema.[15] Gingivitis on intact and reduced periodontium in patients without a history of periodontitis is defined as ≥ 10% of the bleeding area with a probing depth of ≤ 3 mm. Gingivitis can be divided into localized and generalized gingivitis. Gingivitis is said to be localized if the BOP (Bleeding on Probing) score is 10–30% and is said to be generalized if the BOP score is > 30%.[17]

Periodontitis is a multifactorial disease of the dental supporting tissues caused by biofilm (dental plaque) and usually develops from pre-existing gingivitis. However, not all gingivitis develops into periodontitis, and the disease development can be fast or slow; it varies among periodontal sites and individuals.[18] The primary clinical sign of periodontitis is the destruction of alveolar bone due to the extension of inflammation from the gingival margin to the supporting tissue resulting from the transition of gingivitis to periodontitis.[19] The specific bacteria that cause periodontitis are *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis,* and *Tannerella forsythia*.[20,21] Periodontitis is now classified based on the staging and grading method. Periodontitis is diagnosed by looking at the signs of changes on the gingiva and the attachment loss accompanied by periodontal pockets.[22] It is called a periodontal pocket if the cementoenamel junction is ≥ 4 mm from the alveolar bone crest. Clinically, periodontitis can be identified if clinical attachment loss is present in ≥ 2 non-adjacent teeth or loss of attachment in the buccal or oral area ≥ 3 mm in ≥ 2 teeth.[22] The diagnosis can also be made by radiographic investigations to see if there is bone loss representation.[18]

Increasing proinflammatory cytokines (cytokine storm) such as IL-6, IL-1, and TNF may have various systemic effects and specific effects on several organs that may be associated with the manifestations of the post-COVID-19 syndrome.[3,23] Cytokines play a vital role to initiate and regulate the inflammatory process of periodontitis through activation and differentiation of osteoblasts, activation, and proliferation of fibroblasts and production of collagen and neovascularization.[24] Disturbances and deregulation of some organ systems in long COVID are also hypothesized to be the result of hyperinflammation and cytokine storms, including

those that cause oral manifestations such as periodontal disease.[7,25] There is a possible relationship between long COVID and periodontal disease since both release similar proinflammatory cytokines, specifically: Acute phase proteins, C Reactive Protein (CRP), Tumor Necrosis Factor-Alpha (TNF-α), Interleukin (IL)-1β, IL- 2, IL-6, and Interferon Gamma (IFN-γ).[3,26] The similarity of cytokines released in these two diseases could indicate a possible relationship between periodontal disease and long COVID.[11,26] This study is expected to show periodontal disease severity frequency distribution in COVID-19 survivors with long COVID and non-COVID-19 patients.

MATERIALS AND METHODS

This research is a pilot study (n = 40) using a consecutive sampling method on 20 samples of patients' secondary data from the group of COVID-19 survivors who experienced long COVID symptoms and 20 samples from the group of non-COVID-19 (patients who never tested positive on their COVID-19 PCR tests) in the Periodontics Clinic Faculty of Dentistry at Trisakti University Dental Hospital from March–May 2022. These 20 samples of both COVID-19 survivors with long COVID and non-COVID-19 patients were divided into 10 samples of patients who suffer from gingivitis and 10 samples of patients who suffer from periodontitis. After applying for ethical clearance and receiving it with number 620/S1/KEPK/FKG/9/2022 from the Health Research Ethics Committee Faculty of Dentistry at Trisakti University, secondary data from these patients were selected according to the inclusion criteria. The inclusion criteria referred to are data on patient status from survivors who experienced at least one symptom of long COVID and non-COVID-19 patients, both of whom had suffered from gingivitis or periodontitis between March and May 2022 when they came to the clinic.

When they came to the clinic, all patients filled out Google forms and underwent a swab test and anamnesis processes to determine whether they classified as long COVID. After that, patients took intraoral examinations such as OHIS and other periodontal parameters. Periodontitis patients also underwent supporting examinations such as panoramic X-rays. Patients are categorized as having gingivitis if gingival inflammation is characterized by probing depth ≤ 3 mm and BOP score ≥ 10%. On the other hand, patients are classified as having periodontitis if the inflammation of the periodontal tissue is characterized by Clinical Attachment Loss (CAL) present in ≥ 2 non-adjacent teeth or loss of attachment in the buccal or oral area ≥ 3 mm in ≥ 2 teeth. Periodontitis is also diagnosed by staging and grading methods. Afterward, the data was recapitulated and processed to be presented as a graphical frequency distribution to make a research report.

RESULTS

Based on 20 long COVID survivors' samples, it was found that nine out of 20 patients had long COVID categorized as chronic COVID because symptoms persisted for more than 12 weeks after being confirmed negative for the SARS-CoV-2 virus PCR test. It shows that the percentage of survivors with chronic COVID is 45%, and post-acute COVID is 55% of the total sample (Figure 1). Research results show that eight long COVID patients with post-acute COVID had gingivitis, and three patients had periodontitis. Whereas in long COVID patients with the chronic COVID type, it was found that two had gingivitis and seven had periodontitis (Figure 2). Fatigue is the symptom with the highest percentage—35% of the total amount—followed by a cough experienced by 30%, headache experienced by 20%, and the rest experience other symptoms such as sore throat, concentration disturbance, flu, nausea, and shortness of breath (Figure 3).

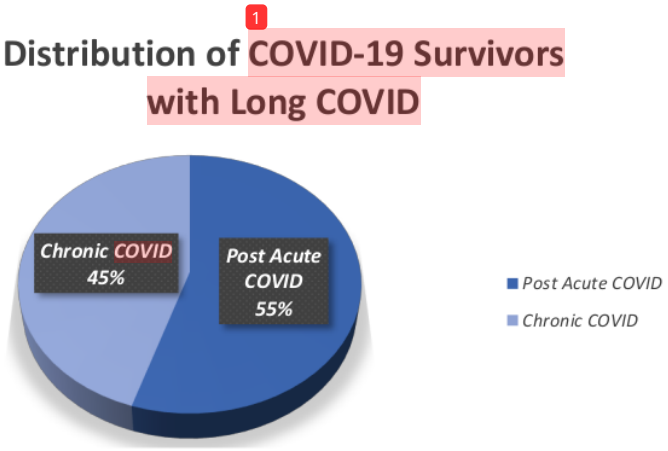

Figure 1. Distribution diagram of COVID-19 survivors with long COVID symptoms based on symptom duration.

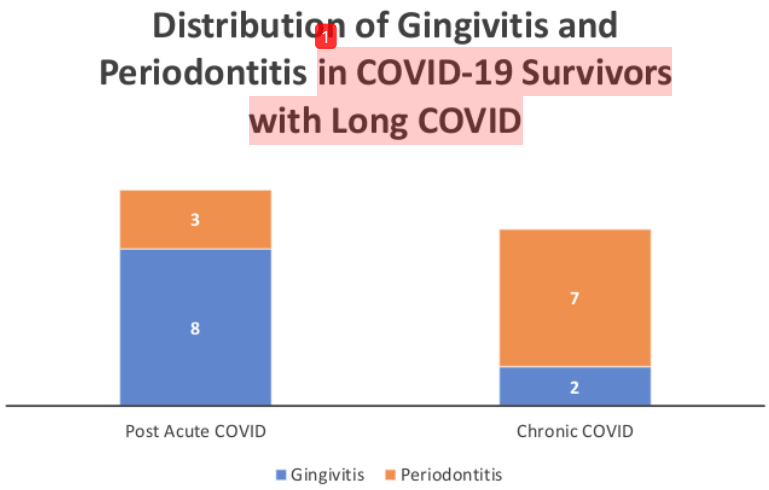

Figure 2. Distribution of gingivitis and periodontitis in COVID-19 survivors with post-acute COVID and chronic COVID.

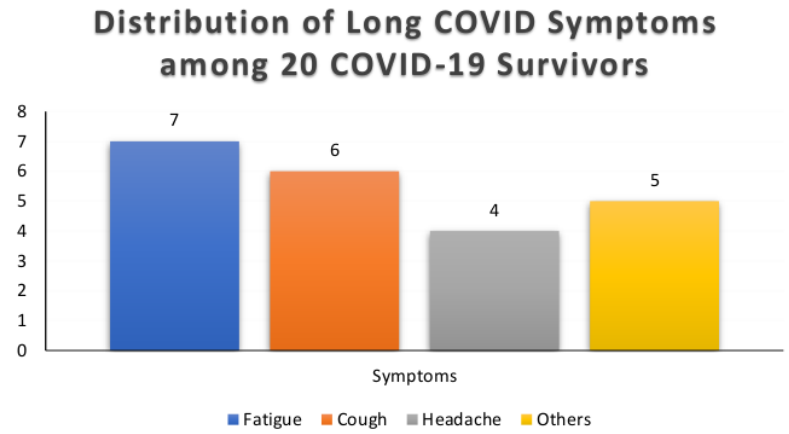

Figure 3. Distribution chart of long COVID symptoms among COVID-19 survivors.

Figure 4 shows that all of the 10 non-COVID-19 patients had gingivitis with a generalized distribution and BOP percentages ranging from 30–68%. Whereas in 10 survivors with long COVID, it was found that 50% had a localized distribution and 50% had a generalized distribution with a BOP percentage ranging from 23–90%. These results may lead to the perception that these two diseases are coincidental because based on research results, it is known that non-COVID-19 patients have a higher percentage of generalized gingivitis than patients with long COVID.

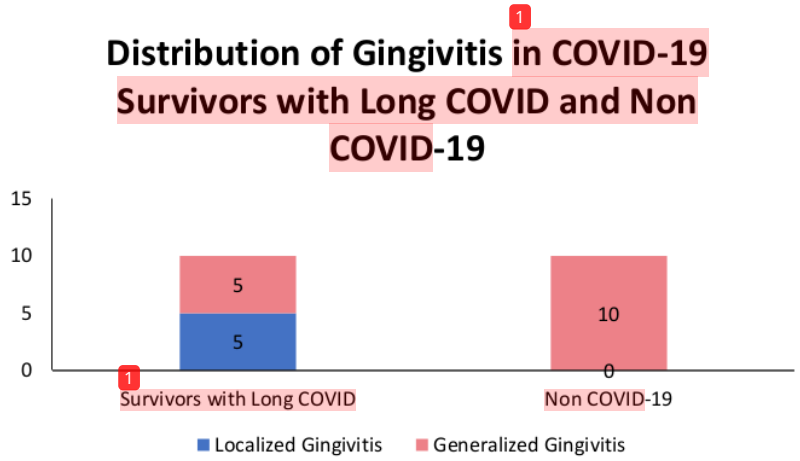

Figure 4. Gingivitis distribution chart in COVID-19 survivors with long COVID and non-COVID-19.

The results for non-COVID-19 showed that the highest percentage was periodontitis stage II with a total amount of 60%. Stages I and III had the same percentage with a total amount of 20% (Figure 5). The grading method also shows that periodontitis grade B has the highest percentage total of 70% (Figure 6). The distribution of periodontitis in non-COVID-19 shows that 60% of patients have a generalized distribution (Figure 7).

From the results of 10 survivors with long COVID, it was found that 30% of patients had localized distribution and 70% had periodontitis with a generalized distribution (Figure 7). The percentage of stage II periodontitis is the highest percentage, with a total 50% of the patients (Figure 5). Meanwhile, based on the grading method, the highest percentage is grade B, which is 60% (Figure 6).

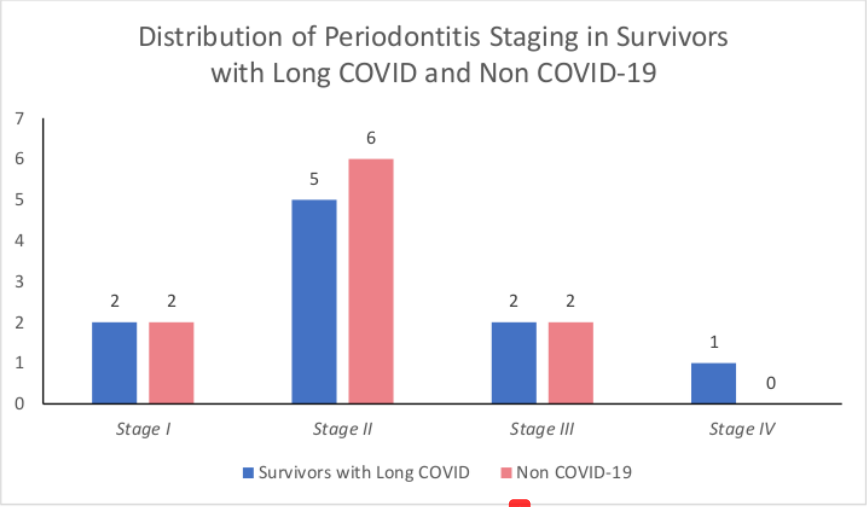

Figure 5. Periodontitis staging distribution chart in survivors with long COVID and non-COVID-19.

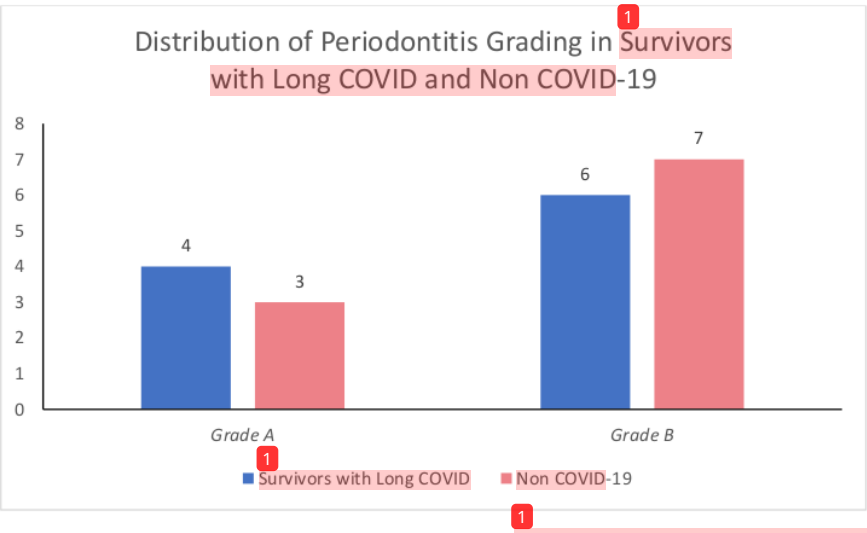

Figure 6. Periodontitis grading distribution chart in survivors with long COVID and non-COVID-19.

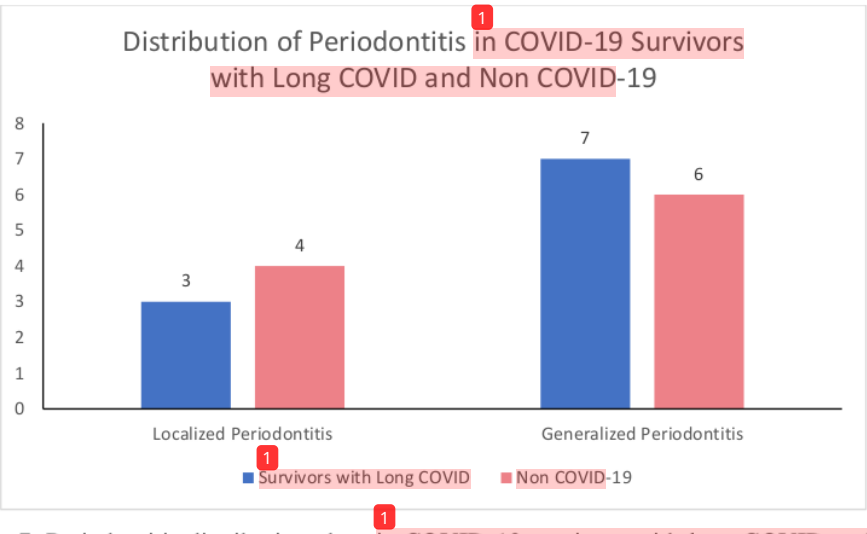

Figure 7. Periodontitis distribution chart in COVID-19 survivors with long COVID and non-COVID-19.

DISCUSSION

The study was conducted on 40 samples consisting of 20 patients with long COVID-19 and 20 non-COVID-19 patients with ages ranging from 21–66 years. Based on the research results, the percentage of post-acute COVID sufferers is higher than those with chronic COVID. This is in accordance with the results of a study by Sudre et al.,[27] who collected data on 4,182 patients for six months and found that only 108 (2.6%) patients had symptoms of long COVID ≥ 12 weeks. The study stated that the etiology of post-acute COVID high percentage is multifactorial, including factors such as drug consumption, age, gender, comorbidities, and the length of time the patient was hospitalized during the COVID-19 infection period.[27,28]

Post-acute COVID was found more in patients who were not being hospitalized when they were infected with COVID-19. In contrast, chronic COVID was found more in patients hospitalized when they were infected, in females, in older patients, and in patients who experienced more than five symptoms when infected.[27,28] This group of patients may have lower immunity, making them more susceptible to chronic COVID.[28,29] Then, chronic inflammation frequently leads to low-degree systemic inflammation and increased levels of cytokines such as TNF and interleukins.[30]

Gingivitis patients' data were taken according to the inclusion criteria for 10 long COVID patients and 10 non-COVID-19 patients. A previous study by Rafalowicz et al.[5] with 1,256 patients who were monitored for four weeks to six months stated that one of the symptoms of long COVID found in the periodontal tissues was spontaneous gingival bleeding. Manzalawi et al.[31] reported two cases of persistent gingival bleeding in COVID-19 survivors who are still recovering and were allowed to go home from the hospital 21–30 days after confirmed positive on PCR test. Research by Wang et al.[32] also found that patients who have been infected with COVID-19 are more susceptible to gingival bleeding due to an increased number of angiotensin-converting receptors enzyme II (ACE2) in the mucosa of the oral cavity, which can be a gateway for infectious agents.

In this study, it was found that the distribution of generalized gingivitis was greater in non-COVID-19 patients, whereas patients with long COVID had the same distribution of localized and generalized gingivitis. This is contrary to previous studies by Rafalowicz et al and Wang et al, which found that patients with long COVID were more prone to increased gingival bleeding. The results of this study raise the conjecture that there is no long COVID effect on the distribution of gingivitis. However, these results may be due to the small number of samples used, so the results shown might not be representative.

According to research by Marouf et al.,[30] periodontitis can be exacerbated by COVID-19 infection. The study found that most survivors suffer from stage II–IV periodontitis, which may get worse as long as the symptoms of COVID-19 are still present because it is related to the presence of a cytokine storm in the patient's body. Cytokines such as IL-6, CRP, TNF, and IL-1β have an essential role in the inflammatory response and tissue damage.[30,33] Additionally, 80% of patients who had experienced complications from COVID-19 were found to have periodontitis. This percentage is considered high compared to patients without COVID-19 complications with a total amount of 43%.[30] This is due to the relationship between periodontitis and systemic inflammatory biomarkers such as CRP, IL-1, and IL-6. Inflammatory cytokines, including interleukins (ILs) and tumor necrosis factors (TNFs), have been verified for their usefulness in diagnosing and monitoring diseases. Many studies have attempted to identify the key salivary biomarkers for diagnosing periodontal diseases, since cytokines demonstrated a high specificity and sensitivity to predict collagen and alveolar bone loss, showing clinically fair effectiveness for diagnosing periodontitis.[34] The severity of periodontitis can also be affected by age, gender, smoking habits, and other comorbidities.[35] Periodontitis is also caused by dysbiosis of oral microorganisms due to increased inflammation caused by long COVID.[10,32]

This study found the same percentage of stage I and stage III periodontitis in long COVID patients and non-COVID-19 patients. Stage II periodontitis is also reported to be more common in non-COVID-19 patients, although it is known that there are long COVID individuals suffering from stage IV periodontitis. In addition, no visible results in this study showed that long COVID affects grading periodontitis. Rather, results indicate that more non-COVID-19 patients have the highest percentage of grade B periodontitis. This may be due to the small number of samples.

The study's results also showed that the generalized distribution of periodontitis was more common in long COVID patients than in non-COVID-19 patients. This finding is in accordance with the study of Marouf et al.,[30] who reported that patients with long COVID symptoms are more susceptible to periodontal disease due to an increase in proinflammatory cytokines.

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