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# Evaluation of nCD64 in Patients with Periodontitis

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***Abstract***

*Periodontitis causes tissue destruction and tooth loss if untreated. Neutrophil CD64 (nCD64), a biomarker will help in the early and precise diagnosis of inflammation. Thus, the aim of this study is to evaluate the potential of neutrophil nCD64 as a diagnostic marker by looking at the expression levels of nCD64 in people with periodontitis. This study involved 12 participants comprising of 6 healthy controls and 6 of patients with periodontitis. nCD64 levels were measured on acquired blood samples using flow cytometry. Mean fluorescence intensity (MFI) of nCD64 was compared between the two groups. When compared to healthy controls, patients with periodontitis had noticeably higher nCD64 MFI levels. In a patient, the greatest nCD64 MFI level was 861, whereas in a control, the lowest level was 19. Comorbid conditions like diabetes did not always correspond with elevated nCD64 levels, suggesting that periodontitis severity was the main factor affecting nCD64 expression. The current study suggests nCD64 as a useful biomarker for identifying periodontal inflammation, which helps with the timely and precise diagnosis of periodontitis. Future studies are necessary to corroborate these results using more extensive and heterogeneous groups.*

**Keywords:** Biomarker, Flow cytometry, Inflammatory Marker, Neutrophil, Periodontal Disease.

## Introduction

Periodontitis refers to the chronic inflammation of the tooth supporting tissues including the gingiva, periodontal ligament, surface of the root surface, and adjacent bone. This occurs due to a complex relationship between the body's immune system and the bacteria found in dental plaque. Neutrophil CD64 (nCD64) (Fc-gamma receptor) is an increasingly useful biomarker for the diagnosis and surveillance of inflammatory illnesses such as sepsis and systemic diseases. [1,2,3]. There are several research works on this marker used on other lesions that have explained the function of nCD64 for the diagnosis and treatment of periodontitis. Periodontitis being a global health issue, affects around 10–15% of the population. Between 2009 and 2012, 46% of adults in the United States were reported to have periodontitis, or 64.7 million people, with 8.9% showing severe stages. 3.8% of gingival sites had probing depths of at least 4 mm, and 19.3% of them had attachment loss of at least 3 mm. Periodontitis is more common in males than females, and its incidence increases with age. Diabetics are three times more susceptible to periodontitis than non-diabetics. Dental practitioners should treat all diabetic patients, including young patients as high-risk patients since diabetes raises the risk in both type 1 and type 2 instances [4].

The risk of getting periodontitis is increased by several lifestyle choices. Adiposity predisposes people to several health problems, including periodontitis, so obesity, for example, is associated with an increased risk of periodontal disease [5]. Stress, age, drinking alcohol, depression, and exposure to certain environmental variables like cigarette smoke are additional

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risk factors. The way in which these variables interact with periodontal health highlights the intricacy of periodontitis and the demand for an all-encompassing strategy in both prevention and treatment. When periodontitis is diagnosed clinically, symptoms include calculus formation, bleeding, swollen and inflamed gingiva, pus discharge, poor breath, and erosion of the bone surrounding the teeth. Pathological periodontal pockets, gingival recession with exposed roots, and increased tooth movement are further markers [4]. In addition to harming oral health, periodontitis is linked to systemic diseases such as diabetes, heart disease, respiratory problems, and unfavorable pregnancy outcomes. These connections emphasize the significance of healthy gingiva for general health and the necessity of incorporating periodontal therapy into more comprehensive medical plans [6]. The host's defense against periodontal infections is greatly aided by neutrophils. Neutrophils are activated and may be part of an ongoing inflammatory response when they have nCD64 on them. According to studies conducted by Doganyigit et al. (2022) [7], Liu et al. (2022) [8], and Wang et al. (2015) [9], increased levels of nCD64 have been seen in a variety of inflammatory and infectious conditions, making it a valuable biomarker for tracking the progression of disease and early identification. The disease progression and tissue destruction associated with periodontitis are partly caused by dysregulated neutrophil function. Therefore, measuring nCD64 levels in periodontitis patients may lead to improved diagnostic and therapeutic strategies as well as a better knowledge of the inflammatory processes underlying the illness [10,11]. It has been suggested that interleukins like IL-8 and IL-27 have excellent sensitivity and specificity in diagnosing newborn sepsis, which further supports the diagnostic use of inflammatory biomarkers. This emphasizes how incorporating several biomarkers, such as nCD64, might improve the precision of inflammatory disease diagnosis and monitoring [12].

Studying nCD64 as a biomarker for periodontitis shows potential to improve our knowledge of the disease and create better methods for diagnosing and treating it. Incorporating nCD64 assessment into periodontal evaluation may lead to more tailored and accurate patient care, ultimately enhancing results for individuals with this ongoing condition [13,14]. Therefore, the aim of this study was to examine the levels of expression of neutrophil CD64 (nCD64) in individuals with periodontitis. The primary objective was to assess the participation and possible diagnostic importance of nCD64 in periodontitis by comparing its levels in patients with the disease to those in individuals without it. This comparative analysis aimed to determine if nCD64 could be a dependable biomarker for recognizing and comprehending the inflammatory processes linked to periodontitis, thus aiding in more precise diagnoses and targeted treatment approaches.

## Materials and Method

### Study Design and Participants

12 participants were included in this study who were grouped into two with 6 healthy control subjects in one and 6 patients with a diagnosis of periodontitis the second group. To guarantee a representative sample for precise comparison analysis, the participants were chosen in accordance with predetermined inclusion criteria.

### Blood Sample Collection

500 µl of blood was extracted from each participant and put right away in an EDTA vacutainer to stop the blood from clotting. The samples were treated carefully so that the analysis process would not compromise their integrity.

### Antibody Labeling

The blood samples were tagged with CD64PE and IgG PE antibodies to detect and measure the expression of neutrophil CD64 (nCD64). The following actions were taken throughout the labelling procedure:

1. **Addition of Antibodies**: Each blood sample was mixed with 5ml each of CD64 PE and IgG PE antibodies.
2. **Incubation**: To achieve optimal antibody binding to their respective antigens on the neutrophil surface, the labelled samples were incubated for 20 minutes at room temperature in the dark.

### Lysis and Preparation for Flow Cytometry

Following the antibody incubation, the samples were mixed with lysis buffer to lyse red blood cells and make leukocyte extraction easier. The detailed steps are as follows:

1. **Lysis Buffer Addition**: The lysis buffer was added to each sample, followed by gentle mixing.
2. **Second Incubation**: The samples were incubated again at room temperature for 15 minutes to allow complete lysis of red blood cells.
3. **Centrifugation**: The samples were centrifuged for five minutes at 1500 revolutions per minute (rpm) after incubation. In this stage, the cellular constituents were isolated from the supernatant.
4. **Resuspension**: To prepare the samples for flow cytometry, the pellet produced after centrifugation was resuspended in 500 µl of phosphate-buffered saline (PBS).

### Flow Cytometry Analysis

A flow cytometer (BD FACSLyric, USA) was used to measure to analyze the produced samples. The process included:

1. **Sample Introduction** : The resuspended samples were introduced into the flow cytometer.
2. **Data Acquisition**: The flow cytometer was set to acquire data from 10,000 events (individual cells). This data acquisition step was crucial for obtaining a comprehensive profile of the cellular populations present in each sample.
3. **Immunophenotyping**: The flow cytometer used laser technology and fluid dynamics to analyze the MFI levels of nCD64 on neutrophils, providing detailed immunophenotyping results.

## Results

The data in the table includes in-depth clinical observations and nCD64 MFI levels for six individuals with periodontitis and six individuals without the condition. Both men and women between the ages of 25 and 50 were included in the group of patients. Each patient showed symptoms of periodontitis, such as gingiva inflammation, pockets around the teeth, and their teeth being loose. Some individuals also encountered the loss of their teeth. Two patients, namely P1 and P6, had diabetes as an additional health issue. The patients showed significant variation in nCD64 MFI levels. The greatest nCD64 MFI level, measuring 861, was seen in P6, a 39-year-old woman with widespread gingival inflammation and periodontal pockets (Figure 3). The 30-year-old male named P2 had the lowest level recorded at 82. Different patients demonstrated nCD64 MFI levels spanning from 102 to 645. On the other hand, the healthy individuals showed significantly lower nCD64 MFI levels, varying between 19 and 71 (Figure 2). The notable variation in nCD64 MFI levels between patients and controls suggests the potential of nCD64 as a biomarker for periodontitis. The existence of diabetes in certain patients did not consistently show a connection with increased nCD64 MFI levels, suggesting that the severity of periodontitis, rather than accompanying health conditions, could have a more significant impact on nCD64 expression. In general, the data indicates a significant correlation between high nCD64 MFI levels and the existence of periodontitis (Table 1, Figure 1).

| Patients | Age/sex | Clinical Observation | Co-morbidities | nCD64 MF1 | Healthy Controls | nCD64 MFI |
|---|---|---|---|---|---|---|
| P1 | 44/M | Gingival inflammation, pockets, tooth mobility, tooth loss | Diabetic | 262 | C1 | 19 |
| P2 | 30/M | Gingival inflammation, pockets, tooth mobility | Nil | 82 | C2 | 30 |
| P3 | 25/M | Gingival inflammation, pockets, tooth mobility | Nil | 149 | C3 | 58 |
| P4 | 50/F | Gingival inflammation, pockets, tooth mobility | Nil | 645 | C4 | 50 |
| P5 | 38/M | Gingival inflammation, pockets, tooth mobility, tooth loss | Nil | 102 | C5 | 71 |
| P6 | 39/F | Generalized gingival inflammation, generalized periodontal pockets, tooth mobility | Diabetic | 861 | C6 | 30 |

**Table 1.** CD64 Expression of Patients and Healthy Controls

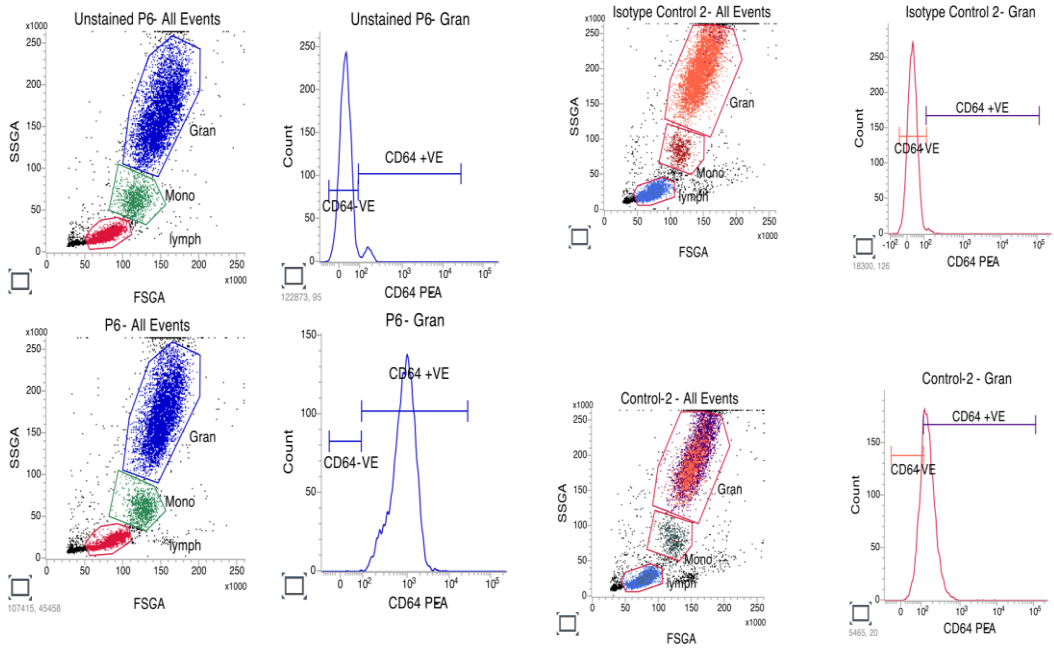


**Figure 1.** Representative Dot Plot and Histogram Showing CD64 Expression of a Patient (Left) and Healthy Control (Right)

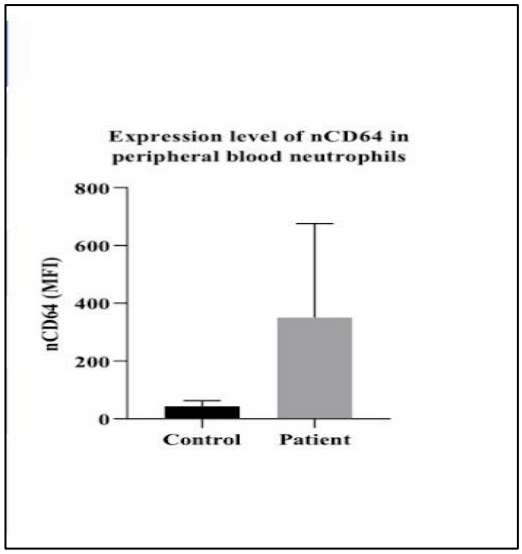


**Figure 2.** Graph Showing the Expression Level of nCD64 in Peripheral Blood Neutrophils of Control and Patient.

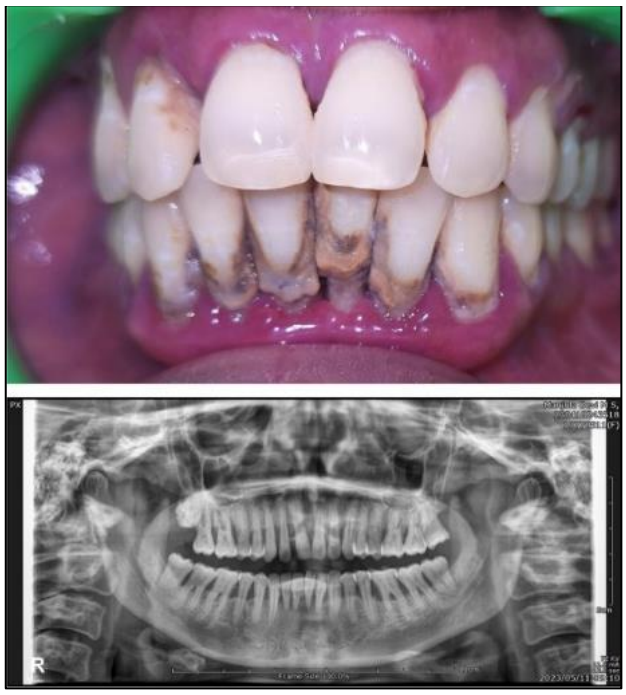

**Figure 3.** Representative Image if a Patient in the Study Group. (a) Top panel showing patient generalized gingival inflammation, generalized periodontal pockets and tooth mobility); (b) bottom panel showing the orthopantomogram of the same patient depicting generalized horizontal bone loss extending till 1/3rd to 2/3rd of the root and extending till apical third of the root in relation to lower anteriors

## Discussion

The current study compares periodontitis patients to healthy controls to examine the increase of neutrophil CD64 (nCD64) which means fluorescence intensity (MFI). The findings show that nCD64 expression is much higher in patients with periodontitis, suggesting that this biomarker may be used to diagnose periodontal disease. The outcomes are consistent with past research. Mony et al. (2019) [1], for example, found that patients had considerable up-regulation of nCD64 and down-regulation of mHLA-DR following surgery, demonstrating the function of nCD64 in identifying immune response dysregulation. Ng et al.

(2004) [2] provided additional evidence for the diagnostic usefulness of nCD64 by highlighting its high sensitivity and negative predictive value in the diagnosis of newborn sepsis. This is illustrated in the current study, which shows a correlation between higher nCD64 levels and periodontitis. Moreover, Davis et al. (2006) [3] demonstrated that nCD64 expression demonstrated superiority over conventional indicators such as CRP in the detection of sepsis, highlighting its potential in a range of inflammatory diseases. These consistent results support the utility of nCD64 as a diagnostic tool for a variety of illnesses, including periodontitis.

Pathogenic microorganisms in dental plaque and the host's immune system are the main causes of periodontitis. Neutrophils express the Fc-gamma receptor CD64, which binds to immunoglobulin G (IgG) to facilitate phagocytosis and antigen presentation. Increased neutrophil activation and an intensified inflammatory response are linked to elevated nCD64 levels [3,8]. The nCD64 MFI levels in this study were substantially greater in periodontitis patients (ranged from 82 to 861) than in healthy controls (19 to 71). This notable distinction highlights nCD64's diagnostic potential in periodontal disease. 6 patients with periodontitis, ages 25 to 50, who showed clinical symptoms like gingival inflammation, periodontal pockets, tooth mobility, and tooth loss were included in the study. The co-morbidity of diabetes affected two of the patients, however it did not seem to have a substantial impact on the nCD64 MFI levels. The mean nCD64 MFI for the patients was 350.16, whereas the healthy controls had an average of 43.0. A p-value of 0.04 indicated statistical significance.

The significance of nCD64 as a marker for inflammatory diseases has been demonstrated by earlier research. In the context of the larger inflammatory response, the function of nCD64 in periodontitis can be understood. Cytokines and chemokines, two examples of inflammatory mediators, are essential to the pathophysiology of periodontal disease. The importance of inflammatory mediators in the pathogenesis of sepsis was highlighted in a study by Doganyigit et al. (2022) [7], which also emphasized how uncontrolled levels of these mediators raise the risk of death from organ failure and septic shock. By identifying novel targets for therapeutic intervention targeted at regulating the inflammatory response, it is possible to improve clinical outcomes for patients with sepsis by focusing on interventions that target cytokines, chemokines, neurotransmitters, and gene regulators. Based on the dysregulation of immune responses, these results are consistent with recent research showing the usefulness of biomarkers such as nCD64 in the diagnosis and treatment of inflammatory diseases, such as sepsis and periodontitis. Pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β) are elevated in periodontitis and have a role in tissue destruction and bone resorption. The increased level of nCD64 in periodontitis patients is indicative of increased neutrophil activation and a heightened inflammatory state.

The present study's results are consistent with those of Liu et al. (2022) [8], who examined the nCD64 index as a prognostic predictor for inflammation in both infectious and non-infectious disorders. They discovered that poorer clinical outcomes were linked to greater nCD64 levels, indicating that nCD64 might be used as a prognostic indicator. Elevated nCD64 levels in the context of periodontitis may signal a severe disease and an increased risk of tissue damage. According to a study by Magán-Fernández et al. (2020) [5], increased neutrophil extracellular trap (NET) production in periodontitis might worsen inflammation and cause damage to gingival tissue. The overexpression of nCD64, which heightens the immune response and consequent tissue damage, is connected to the overproduction of NETs, which are made up of DNA and antimicrobial proteins. These results are consistent with the current investigation, which shows increased levels of nCD64 in individuals with periodontitis.

This suggests that nCD64 and NETs contribute significantly to the etiology of the disease by fostering an inflammatory milieu. The results of this study are also pertinent when considering systemic diseases linked to periodontitis. According to Naiff et al. (2021) [4], diabetes patients have a higher risk of developing periodontitis. They also noted that diabetes is linked to a weakened immune system and a higher vulnerability to infections. Even though there were only two diabetic individuals in the current study, their nCD64 levels were among the highest ever, which may indicate that diabetes exacerbates periodontal inflammation. Nevertheless, the limited sample size makes it difficult to make firm judgments regarding how diabetes affects nCD64 levels in people with periodontitis.

Rastogi et al. (2012) [6] assessed how non-surgical periodontal treatment affected serum inflammatory markers in individuals with chronic periodontitis and CAD. The results indicated notable decreases in bleeding on probing (BOP) and probing depth (PD) after treatment, as well as significant reductions in high-sensitivity C-reactive protein (hsCRP) and white blood cell (WBC) levels, suggesting a decrease in overall inflammation. Nevertheless, there was no statistically significant decrease in the levels of tumor necrosis factor-α (TNF-α). These findings indicate that enhancing periodontal health may decrease systemic inflammatory markers and potentially mitigate the likelihood of CAD. The present study is consistent with recent discoveries of increased nCD64 levels in individuals with periodontitis, suggesting overall inflammation that may heighten the chance of cardiovascular issues. It is essential to track inflammatory markers, like nCD64, in individuals with periodontitis to identify those more prone to systemic conditions, highlighting the link between gum health and heart health.

Studies which demonstrated nCD64's capacity to identify inflammatory conditions [16-20] and studies like Allen et al. (2002) [14] and Bakke et al. (2001) [15], differentiate between acute inflammatory autoimmune illnesses and systemic infections, have proven the diagnostic utility of nCD64 in differentiating inflammatory conditions from infections. This is especially important for periodontitis because the disease frequently exhibits systemic signs that can be mistaken for infections. The results of this study, which show that patients with periodontitis have higher levels of nCD64 than in other studies, support the idea that nCD64 may be a good indicator of the inflammatory state associated with the disease. This can direct focused treatment plans and help with differential diagnosis. The study by Wang et al. (2015) [9] supports the diagnostic value of nCD64, finding it to be a reliable marker for sepsis with pooled sensitivity of 76% and specificity of 85%. This meta-analysis underscores nCD64's effectiveness in detecting systemic infections, which aligns with the current study's observation of elevated nCD64 levels in periodontitis patients. These elevated levels indicate a significant inflammatory response, suggesting that nCD64 could be a valuable biomarker for assessing periodontal inflammation. The findings highlight nCD64's potential utility in differentiating severe periodontitis from other inflammatory conditions.

The presence of healthy subjects in this study provides a standard reference for nCD64 levels, highlighting the significant contrast between individuals with periodontitis and those who are healthy. This difference is crucial in confirming nCD64 as a diagnostic indicator. The substantial rise in nCD64 mean fluorescence intensity (MFI) seen in patients with periodontitis validates its potential as a biomarker for periodontal inflammation [21-25]. There are different docking studies involved in these kind of pathologies [26-29]. The study strengthens the comprehension of the inflammatory reaction in periodontitis and its impact on the entire body. Additional research with bigger and more varied groups is necessary to validate the role

of nCD64 as a diagnostic and prognostic indicator and to evaluate its effectiveness in directing treatment plans.

## Conclusion

The present study suggests that patients with periodontitis have notably higher levels of neutrophil CD64 (nCD64) compared to healthy individuals, indicating its value as a diagnostic indicator for periodontal inflammation. nCD64 offers the benefit of quantifying inflammation, facilitating early and precise detection for improved periodontitis management. Nevertheless, it can also rise in different inflammatory disorders, leading to potential diagnostic confusion. The importance of nCD64 lies in its specificity and ability to distinguish periodontitis from other inflammatory diseases, informing treatment choices. Future studies need to confirm the diagnostic precision of nCD64 with bigger and more varied groups, evaluate its predictive significance, and investigate its combination with other diagnostic methods for a holistic approach to managing periodontal disease.

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