


REVIEW ARTICLE

Inflammation indices in association with periodontitis and cancer

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Abstract

Inflammation is a complex physiological process that plays a pivotal role in many if not all pathological conditions, including infectious as well as inflammatory diseases, like periodontitis and autoimmune disorders. Inflammatory response to periodontal biofilms and tissue destruction in periodontitis is associated with the release of inflammatory mediators. Chronic inflammation can promote the development of cancer. Persistence of inflammatory mediators plays a crucial role in this process. Quantification and monitoring of the severity of inflammation in relation to cancer is essential. Periodontitis is mainly quantified based on the severity and extent of attachment loss and/or pocket probing depth, in addition with bleeding on probing. In recent years, studies started to investigate inflammation indices in association with periodontal diseases. To date, only few reviews have been published focusing on the relationship between blood cell count, inflammation indices, and periodontitis. This review presents a comprehensive overview of different systemic inflammation indices, their methods of measurement, and the clinical applications in relation to periodontitis and cancer. This review outlines the physiological basis of inflammation and the underlying cellular and molecular mechanisms of the parameters described. Key inflammation indices are commonly utilized in periodontology such as the neutrophil to lymphocyte ratio. Inflammation indices like the platelet to lymphocyte ratio, platelet distribution width, plateletcrit, red blood cell distribution width, lymphocyte to monocyte ratio, delta neutrophil index, and the systemic immune inflammation index are also used in hospital settings and will be discussed. The clinical roles and limitations, relationship to systemic diseases as well as their association to periodontitis and treatment response are described.

KEYWORDS

cancer, delta neutrophil index, inflammation indices, inflammation markers, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, periodontitis, platelet distribution width, platelet to lymphocyte ratio, plateletcrit, red blood cell distribution width, systemic immune inflammation index

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1 | INTRODUCTION

Periodontitis, characterized by progressive destruction of the tooth-supporting structures, is a chronic inflammatory disease with a multifactorial etiology¹ linked to the patient's individual oral microbiome and immune response.² The manifestation of periodontitis depends on a dysbiotic biofilm,³ whereas microbial factors alone are insufficient to induce onset of the disease.⁴⁻⁶ Dysregulation of the immune response in periodontitis plays a major role in pathogenesis.⁷ The susceptibility to periodontitis is influenced by genetic⁸⁻¹⁰ and lifestyle factors, particularly smoking and poor oral hygiene, which facilitate the expression of bacterial pathogenicity.¹¹

Progression of periodontitis results primarily from the host's response to the microbial biofilm, mediated by neutrophils, monocytes, macrophages, and T- and B-lymphocytes.⁴ Neutrophils, being the most abundant leukocytes, are central to inflammatory pathways, bridging innate and adaptive immunity and are often seen as a double-edged sword in immune response.¹² The involvement of T- and B-lymphocytes in the pathogenesis of periodontitis has been extensively studied. The activation of various T cells, monocytes, and macrophages leads to the production of numerous pro-inflammatory cytokines, culminating in the progressive destruction of the tooth-supporting structures.⁴

The dentogingival epithelial surface, encompassing the pocket epithelium in direct contact with the subgingival biofilm, acts as a crucial interface where local inflammation can affect systemic health. The dentogingival junction is a semi-permeable barrier that permits the entry of the numerous bacteria, whether planktonic or in biofilm, into the bloodstream, known as bacteremia. Under conditions where microbial loads are minimal and gingival tissues are healthy, such bacteremia typically constitutes minimal threat to host tissues and shows low systemic impact.^{13,14} This is attributed to the activity of the innate immune system in dentate mammals, which are well able to respond to and prevent the entry of bacteria through the dentogingival junction. Approximately, the size of an adult's palm is the area of inflamed epithelial surface which persists during severe periodontitis.¹⁵ As a result, locally produced pro-inflammatory mediators such as interleukins, tumor necrosis factor alpha, and prostaglandins may enter the circulation, contributing to an elevated inflammatory load at a systemic level and potentially affecting remote organs.^{3,13,16} Conversely, systemic inflammation can also influence periodontal health (Figure 1).¹⁷

Diagnosing periodontitis during its active phase and identifying individuals' risk of developing a severe form are challenges for clinicians and researchers. Advances in diagnostic techniques for periodontal diseases tend to methods for identification and quantification of the periodontal risk in patients through various biomarkers that can be detected in saliva, gingival crevicular fluid, or serum.^{18,19} Studies have shown that patients with periodontitis, influenced by the composition of the oral microbiome,²⁰ exhibit higher systemic levels of various inflammatory markers, and this indicates increased low-grade systemic inflammation.^{18,21-24} Blood inflammation indices such as neutrophil to lymphocyte ratio (NLR),²⁵⁻³⁴ platelet

to lymphocyte ratio (PLR),³⁵⁻⁴⁰ and lymphocyte to monocyte ratio (LMR)⁴¹⁻⁴⁵ have been demonstrated as being helpful in diagnosis and prognosis of several chronic inflammatory diseases, including cardiovascular diseases, diabetes mellitus, chronic lung disease, and various cancers. However, these have hardly been used in the periodontology.

In the pathophysiology of most hematopoietic and solid malignancies, inflammation plays a central role.⁴⁶ Tumorigenesis can be induced by chronic inflammation and as a pathological response to persisting infection, immune disorders, and aging in susceptible individuals. The initiation of tumor formation activates "cancer-elicited inflammation" based on a chemokines and pro-inflammatory cytokine storm. This cascade leads to the recruitment of immune cells, the induction of angiogenesis, and a transition to the promoting phase.⁴⁶ Stimulation of tumor-associated macrophages to secrete IL-1 β and activation of tumor-associated neutrophils contribute to metastatic progression and enhance systemic neutrophilic inflammation. This perspective underscores the potential of systemic inflammation indices as simple, economical, and easily accessible tools to indicate systemic inflammation⁴⁷ especially to study cancer-related inflammation and these could be valuable indicators of prognosis for different cancers.^{48,49} Numerous meta-analyses have investigated the prognostic significance of the discussed inflammation indices in this review in relation to various cancers.

A recently published review by Baima et al.⁵⁰ provides a good overview of the pathogenic mechanisms between periodontitis and different types of cancer. However, the relationship between different systemic inflammation indices and periodontitis, which could serve as potential markers of systemic inflammation, especially as risk for various forms of cancer, remains poorly understood and warrants further investigation. To date, no study has investigated inflammation indices in periodontitis patients with cancer. Therefore, this review discusses the current literature of systemic inflammatory indices in relation to periodontitis and cancer, including blood values for NLR, PLR, platelet distribution width (PDW), plateletcrit (PCT), red blood cell distribution width (RDW), LMR, delta neutrophil index (DNI), and systemic immune inflammation index (SII) and to assess their usefulness in diagnosis, screening, and predicting the risk of developing severe diseases like cancer.

2 | BLOOD INFLAMMATION MARKERS

Currently, periodontitis is diagnosed using local clinical and radiographic criteria, with minimum use of diagnostic tools that evaluate systemic biomarkers.⁵¹ Notably, during the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, it became evident that integration of inflammation markers into the diagnosis and monitoring of periodontitis is needed.⁵² In medical practice, a full blood count or hemogram is commonly used to detect the presence of infection or inflammation. This raises the question of whether periodontitis influences hematological parameters, including the counts of white blood

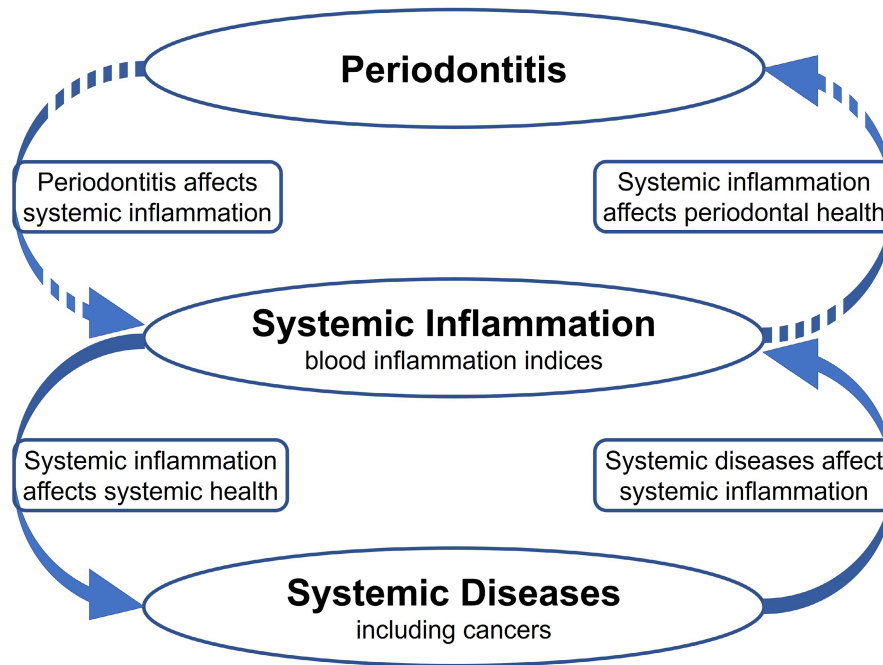


FIGURE 1 Inflammation resulting from periodontitis may extend to a systemic level, thereby influencing the subject's overall inflammatory burden and systemic health.¹⁶ Conversely, systemic diseases can influence systemic inflammation, which in turn may affect periodontal health.¹⁷ Patients suffering from periodontitis may have elevated levels of circulating systemic inflammatory markers, including higher inflammation indices. Figure modified after Cecoro et al.²¹

cells (WBC), red blood cells, and platelets.^{53,54} In particular, the components of the most frequently used inflammation indices like neutrophils, platelets, and lymphocytes play a crucial role in innate and adaptive immunity.⁵⁵

2.1 | Neutrophils

Neutrophils are the most abundant WBC and are crucial in the innate immune system as initial answer in the immune response.⁵⁶ In healthy individuals, in the periodontal tissues, neutrophils are typically located in the superficial layers of the epithelium and at the base of the gingival sulcus.⁵⁷ Microscopically, neutrophils are present in the intercellular spaces of the permeable junctional epithelium and along tooth surfaces, with their distribution being highest at the base of the gingival sulcus, decreasing toward the entrance of the gingival crevice. Neutrophils are essential for protecting periodontal tissues against microbial challenges. Over 50 years ago, Schiött and Löe⁵⁸ described, that in the presence of periodontal disease, the migration rate of neutrophils into the oral cavity increases. Since then, numerous studies demonstrated that their hyperactive state could be responsible for periodontal tissue damage.^{59,60} If neutrophils are overloaded by any biofilm, lysosomal enzymes and reactive oxygen species (ROS) can cross into the extracellular matrix and increase the risk of host tissue damage and as such they act as a double-edged sword.⁶¹ Neutrophils also extend their antimicrobial activity beyond their lifespan through neutrophil extracellular traps (NETs) formation, a process known as NETosis.⁶² During NETosis, neutrophil nuclei

swell, chromatin dissolves, and DNA is unwound and is exported out of the cells with histones and proteins from granules and cytosol. NETs trap and immobilize pathogens in the web of DNA, preventing their spread and preventing direct antimicrobial activity through proteolytic and ROS interactions in the extracellular matrix.⁶²⁻⁶⁴

Aggregatibacter actinomycetemcomitans (*A. actinomycetemcomitans*) as well as different virulence factors from *Porphyromonas gingivalis* (*P. gingivalis*) compromise numerous neutrophil functions. These gram-negative bacteria secure their access to nutritional proteinaceous resources and as such facilitate the perpetuation of inflammation and evade microbial destruction. Neutrophils play a role in the progression of periodontitis due to impaired antimicrobial activity, including a dysregulation of immune tolerance, altered neutrophil apoptosis, and disrupted mechanisms that mediate the resolution of inflammation. Nevertheless, possibly after bacterial encounters, these manipulations of neutrophils can lead to divergent outcomes, manifesting either pro-inflammatory or anti-inflammatory effects.^{65,66}

An increase in peripheral blood neutrophil count in patients with periodontitis was observed in several studies.^{60,67} Studies have analyzed changes in neutrophil counts in peripheral blood to identify and monitor periodontitis, similar to diagnosis and monitoring of systemic diseases. It could be demonstrated, that patients with generalized aggressive periodontitis (GAgP), who are otherwise healthy, exhibited decreased neutrophil counts following periodontal therapy.⁶⁸ Overall, systemic neutrophil counts are an essential component as part of inflammatory indices for any disease and also periodontitis.

2.2 | Platelets

Platelets (also known as thrombocytes) are small, anucleate cells in the blood that are essential for hemostasis, and also play a significant role in wound healing and the inflammatory processes.^{69,70} They are increasingly recognized for their role in both the initiation and progression of periodontitis.

Prospective epidemiological studies consistently demonstrated an association between elevated platelet counts, including their activation levels and inversely correlated mean volume and the subsequent manifestation and progression of fatal coronary heart disease.⁷¹ Additionally, thrombocytosis has been identified as a prognostic marker for conditions such as venous thromboembolism, stroke, cancer, and ultimately increased mortality rates.⁷¹⁻⁷³

Periodontitis has been linked to increased serum levels of IL-6.⁷⁴ This cytokine has the capability to stimulate hepatic thrombopoietin production and subsequently thrombopoiesis, leading to increased platelet counts (thrombocytosis).⁷⁵⁻⁷⁷ Additionally, platelets share a signaling pathway with WBC, that maintains differentiation of the cells, highlighting their significant role in immunity and microbial defense.^{36,78,79} Platelets express various antigen recognition molecules and can directly interact with microbes during bacteremia, resulting in an increase in their number and activity.^{80,81} Platelets can interact with periodontal pathogens like *P. gingivalis*.⁸² This interaction can lead to a formation of platelet-bacteria aggregates, serving as a target for neutrophils for phagocytosis and NETosis to eliminate bacteria facilitated by these bundles.⁸³ Furthermore, platelets are involved in tissue repair processes due to their role in angiogenesis and wound healing. In the periodontium, these capabilities of platelets can be harnessed therapeutically, for example, in the application of platelet-rich plasma applications to promote periodontal regeneration.⁸⁴

Several studies documented a significant elevation in platelet counts among patients with periodontitis.⁸⁵⁻⁸⁹ Studies also observed no difference in platelet levels when comparing patients with severe periodontitis to healthy individuals.^{37,90,91} This suggests that the activation and function of platelets, rather than their absolute counts, may play a critical role in the pathogenesis of periodontitis and in the systemic effects of periodontitis.⁹² One of the largest cohort studies including 5197 South Korean subjects demonstrated elevated platelet counts in periodontitis patients. The association between severe periodontitis and platelet counts has been demonstrated to be stronger than the associations of age and smoking status with platelet counts in the same statistical models.⁸⁹ Studies that evaluated the results of nonsurgical periodontal therapy observed a decrease in both the number of platelets and their hyperreactivity in peripheral circulation.^{68,92-94} Furthermore, the inhibition of platelet activation has been found to contribute to the reduction of periodontal inflammation.⁹⁵

In summary, platelets play a multifactorial role in the inflammatory processes, and therefore, are important parameters in inflammatory indices. In particular, this review not only includes the platelet

count in the PLR but also the PCT and PDW are indices specific to platelet proliferation kinetics and morphology.

2.3 | Lymphocytes

Lymphocytes are crucial components of the adaptive immune system and play a significant role in all aspects of immune responses, not only infections but also in cancer. B and T cells, recognize and respond to specific antigens of both, all kinds of pathogens and to cellular antigens. T cells, once activated, show plasticity and can "rotate" into various subsets (like Th1, Th2, Th17, Tfh, and regulatory T cells [Treg]), all playing a distinct role in exerting and modulating the immune response. B cells differentiate into memory B cells or plasma cells that produce antibodies. The suppression of T-cell activation in severe periodontitis can result from interactions with various periodontal pathogens.^{96,97} Th1 cells mainly express the transcription factors STAT-4 and T-bet, they predominantly produce the cytokines IL-12 and interferon gamma (IFN- γ). Their differentiation is induced by IL-12. Conversely, Th2 cells are marked by the expression of transcription factors GATA-3 and STAT-6, and the production of the cytokines IL-4, IL-5, IL-6, IL-10, and IL-13.⁹⁸ Th1 and Th2 cells respond to different stimuli and are associated with various outcomes in infectious and inflammatory diseases. In some studies, T-cell subset cytokine profiles indicate that the number of Th1 cells correlates with stable lesions, while Th2 cells are associated with progressive lesions,⁹⁹⁻¹⁰¹ suggesting a link between Th2 cells and more severe lesions. However, other studies have shown a predominance of Th1 cells in gingival tissues from periodontitis patients, associated with inflammation and disease severity.^{102,103} Remarkably, one study reported that both Th1 and Th2 responses are similarly upregulated in periodontal lesions.¹⁰⁴

Th17 cells expressing the transcription factor ROR γ t produce predominantly the cytokines IL-17 and IL-21. They require IL-6, IL-21, IL-23, and TGF- β for their development and maintenance. Th17 cells play a crucial role in the defense against extracellular pathogens and fungi, as well as in promoting inflammation.¹⁰⁵ Recent studies linked Th17 cells to various inflammatory and autoimmune diseases.¹⁰⁶⁻¹⁰⁸ Interestingly, increased Th17 cell infiltration in periodontal lesions was demonstrated. This supports the presumed association with periodontitis.^{109,110} Furthermore, studies investigated the relationship between *A. actinomycetemcomitans* infection and systemic immune responses associated with Th17 cells.¹¹¹ It has been demonstrated that oral infection with *A. actinomycetemcomitans*, through bacteremia, can contribute up to 20% of the HACEK bacteria group, which is a significant risk factor for infective endocarditis.¹¹² In addition, the differentiation of CD4+ subtypes (in particular Th1 and Th17)¹¹³ can be stimulated through the interaction of lipopolysaccharide (LPS) and toll-like receptors (TLRs), which activates the NF- κ B pathway.^{114,115} Zhang et al.¹¹⁶ demonstrated that LPS from *P. gingivalis* could promote Th17 cell differentiation directly by up-regulating TLR-2 expression on the T-cell membrane.

Tregs are a suppressive lymphocyte subset that maintain down-regulation of activation, proliferation, and function be specific. Tregs are characterized by the secretion of the cytokines TGF- β and IL-10 and express the transcription factor Foxp3. Also, Tregs express higher levels of certain cell surface molecules like GITR, CD25, and CTLA-4, compared to naive Th cells. They play a critical role in maintaining immune homeostasis by modulating the intensity and direction of both adaptive and innate immunity, including inflammation.^{117,118} Several studies demonstrated high levels of Tregs in periodontitis lesions.¹¹⁹⁻¹²¹ Another study reported a reduction in Foxp3⁺CD25⁺ cells in such lesions.¹²²

A special subset of lymphocytes are $\gamma\delta$ T cells, which are mainly located in the epithelial barrier of the gingiva. Within these again, subgroups exist: $\gamma\delta$ T cells exhibit different immunological functions, including immunoregulatory capacities, cytolytic activity, and fast secretion of inflammatory cytokines.¹²³ Investigations in humans and mice have demonstrated that $\gamma\delta$ T cells can exert both antitumor and pro-tumor activities.^{124,125} The dualistic nature of these roles may be attributed to the tendency of murine $\gamma\delta$ T cells to produce IL-17, a cytokine implicated in promoting cancer development.¹²⁶ In contrast, human $\gamma\delta$ T cells demonstrate potent cytotoxic capabilities and IFN- γ production, suggesting a potential antitumor role.¹²⁷ A recent review which summarizes the importance of the $\gamma\delta$ T cells in the oral epithelium during carcinogenesis is further explained in a paper published by Hovav and Wilensky.¹²⁸ The differentiation of Th cells in periodontitis is at least partially attributable to pathogens and their virulence factors. The results of numerous studies suggest a protective function of lymphocytes, while more recent studies underscore the complexity of lymphocyte immunity in periodontitis, partly due to the presence of T-cell subsets that suppress the function of pro-inflammatory T-cell populations.¹²⁹ In conclusion, lymphocytes and their subgroups give us an important insight into the pathogenesis of periodontitis. In future, inflammation indices should also include lymphocyte subgroups.

3 | INFLAMMATION INDICES—SELECTION AND CHARACTERISTICS OF THE INCLUDED STUDIES

To date, there are no comprehensive reviews existing, which focus on the relationship between inflammatory indices, periodontitis, and cancer. The following indices are based on hematological parameters derived from a standard full blood count. Among the indices which have been described in the available literature those were selected where an association with periodontitis has been reported.

A structured electronic search was conducted in May 2023 of the following databases: PubMed/MEDLINE and Web of Science. MeSH and Emtree terms were used. The most actual electronic search was performed on all databases on October 30, 2023.

The search strategy included the terms “inflammation indices,” “inflammation markers,” “neutrophil to lymphocyte ratio,” “platelet to lymphocyte ratio,” “platelet distribution width,” “plateletcrit,”

“red blood cell distribution width,” “lymphocyte to monocyte ratio,” “delta neutrophil index,” “systemic immune inflammation index,” “cancer,” “periodontitis,” and “periodontal” as free text words, along with MeSH or Emtree terms (if available), synonyms, singular as well as plural forms and abbreviations (NLR, PLR, PDW, PCT, RDW, RDW-CV, RCDW, RDW-SD, LMR, DNI, and SII). Furthermore, filters for “Humans” and “English” were used. We excluded editorials, conference abstracts, case reports, mechanistic articles, and animal studies. Consequently, 11 case-control studies, 4 cross-sectional studies, and 1 meta-analysis were included. These studies will be discussed below. An overview with the important characteristics and results is presented in Table 1.

The included studies not only tried to find a possible association between the systemic blood indices and periodontitis, but also partly analyzed an association to systemic diseases like cancer. These in turn are often being associated with periodontal diseases. Therefore, these associations between the diseases are also briefly explained. When evaluating cancer in the periodontitis patients, it should be noted that at least 50% of all patients suffer comorbidity. Periodontitis patients are often “sick” patients.^{50,150}

In clinical practice, the NLR is the most widely used index and is associated to periodontitis and cancer.

4 | NEUTROPHIL TO LYMPHOCYTE RATIO

4.1 | The basis of NLR

The NLR is a marker derived from a standard full blood cell count test. It is calculated by dividing the neutrophil count by the lymphocyte count (both per microliter of blood, Figure 2). NLR is an effective predictor than using either measurement neutrophil or lymphocyte counts alone since it includes both parameters instead of one.^{91,151} The mean NLR in healthy Caucasian populations (Non-Hispanic White without periodontal investigation) is 2.24.¹⁵² This value is comparatively higher than those observed in other ethnical groups with periodontal examination, for example, 1.65 in healthy South Koreans,¹⁵³ 1.76 in healthy Non-Hispanics of African lineage,¹⁵² 1.84 in healthy Han Chinese,⁹¹ and 1.86 in healthy Asian Indians.⁹⁰ Given the demonstrated racial differences in immune responses,¹⁵⁴ it is plausible that the average NLR in healthy individuals exhibits racial predisposition.¹⁵² This ratio is increasingly recognized for its prognostic and diagnostic value in various clinical contexts, particularly in assessing systemic inflammation, infection, and predicting outcomes of various diseases and shows an association to inflammatory markers such as CRP.¹⁵⁵ A high NLR can indicate a relative increase in neutrophils and/or a decrease in lymphocytes. This change often suggests an active inflammatory process, as neutrophils are typically elevated in acute and chronic infections. Lymphocyte counts increase during a viral infection and decreases in infections after trauma or when human immunodeficiency virus spreads. In clinical practice, NLR is used as a marker for systemic inflammation. NLR is advantageous due

TABLE 1 Systemic inflammation indices in association with periodontitis.

Parameters	Autor, year, country, and reference	Analysis	Study design	Number of participants, gender, and age	Number of diagnosed participants	Examiner calibration	Smoking status
Neutrophil to lymphocyte ratio (NLR)	Acharya et al., 2019, India ⁹⁰	Automated hematology analyzer (pocH-100i; Sysmex)	Case-control and prospective cohort	n = 60 (30 males, 30 females, mean age: P 45.08 years and H 39.6 years)	30 CP ¹³⁰ versus 30 H	No	Not reported
	Bhattacharya et al., 2022, India ¹³¹	Not reported	Cross-sectional	n = 80 (40 males, 40 females, mean age P 41.8 years and H 36.93 years)	40 P ¹³² versus 40 H	Yes	Only nonsmokers
	Çetin Özdemir et al., 2022, Turkey ¹³³	Automated hematology analyzer (company not reported)	Case-control	n = 77 (28 males, 46 females, mean age 36 years)	22 stage III grade A P ⁵² versus 26 gingivitis versus 26 H ¹³⁴	Yes	Only nonsmokers
	Doğan et al., 2015, Turkey ¹³⁵	Not reported	Case-control	n = 180 (69 males, 111 females, mean age not reported)	P versus non-P (number and classification not reported); categorized as H (n = 28), type 2 diabetes (n = 75), hyperlipidemia (n = 99), obese (n = 119), and (pre- and post-) menopause (n = 37)	Yes, but weighted kappa coefficients for intra-examiner reliability of one periodontist not reported	Smokers and nonsmokers, significance not reported
	Lu et al., 2021, China ⁹¹	Automated hematology analyzer (Sysmex XS - 1000)	Case-control	n = 505 (205 males, 300 females, mean age 27 years)	372 generalized AgP ¹³⁶ versus 133 H	Yes	Only nonsmokers
	Mishra et al., 2022, India ¹³⁷	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	n = 630 (324 males, 306 females, mean age 34 years)	315 generalized stage III grade C P ⁵² versus 315 H ¹³⁴	Yes	Only nonsmokers

Significant difference in age between groups	Significant difference in gender between groups	Main results	Conclusion
Not reported	Not reported	NLR of pretreatment with CP: 1.90 (SD=±0.5), NLR of posttreatment: 1.48 (SD=±0.4), $p < 0.0001$, NLR of H: 1.86 (SD=±0.81); NLR in pre- and post-treated patients was not associated to local periodontal parameters; cutoff point by ROC for pre- versus post-treated patients = 1.546 (sensitivity=0.756, specificity=0.756, AUC=77.5%)	Significant difference between pre- and posttreatment CP patients
+	-	NLR of P: 2.48 (SD=±1.17), NLR of H: 2.02 (SD=±0.5), significant difference ($p=0.013$)	NLR is associated with P
+	+	NLR of H: 1.85 (SD=±0.67), NLR of gingivitis: 1.96 (SD=±0.78), NLR of P: 2.22 (SD=±0.85), no association between NLR and gingivitis and P ($p=0.156$); correlation for CAL, mGI, plaque index, and NLR but not for BOP (Spearman's correlation test)	NLR is not associated with gingivitis or P
Not reported between periodontal groups	Not reported between periodontal groups	NLR in H: 2.82 (SD=±2.27), NLR in type 2 diabetes: 2.48 (SD=±1.56), and NLR in hyperlipidemia: 2.41 (SD=±1.43), NLR in obese: 2.43 (SD=±1.49), NLR in menopause: 2.57 (SD=±1.36); Hyperlipidemic group ($n=99$): NLR was significant higher in P (NLR: 2.56, SD=±1.50) than in non-P (NLR: 2.05, SD=±1.31), $p < 0.05$	NLR is not associated with type 2 diabetes, hyperlipidemia, obese, or menopause, but associated in hyperlipidemic patients with P
-	-	NLR of AgP: 2.34 (SD=±1.11), NLR of H: 1.84 (SD=±0.85), significant difference between H and AgP ($p < 0.001$); AgP showed significantly higher proportions in NLR 2-3 and NLR ≥3 subgroups; AgP group: 1 unit increment of NLR was associated with an increase in PPD by 0.41 mm (CI=0.25-0.56), BOP by 0.26 (CI=0.15-0.37), and CAL by 0.57 mm (CI=0.34-0.80); Diagnostic ability of NLR by ROC plot: no significant differences, AUC=0.73, (CI=0.68-0.79), cutoff point=1.92, sensitivity=65.6%, specificity=68.7%; Saturation threshold effect of NLR (spline smoothing fitting): 1. linear analysis: 0.1 unit increment of NLR, risk of AgP increases by 10.5%, 2. nonlinear analysis: turning point value of NLR=3, → NLR <3: risk of AgP increased by 20.6% in patients for each 0.1 unit increment of NLR (adjusted OR=3.06, CI=1.91-4.98) → NLR >3: OR did not increase with increment of NLR (adjusted OR=0.94, CI=0.56-1.57) → p -value for likelihood ratio test of the models=0.014, demonstrating a nonlinear relationship between NLR and risk of AgP	NLR is highly associated with generalized AgP
-	-	NLR of P: 2.74 (IQR=2.4-3.28), NLR of H: 2.13 (IQR=1.81-2.47), significant difference between H and P patients ($p < 0.0001$), ROC cutoff value >2.44, MLRA: high significant association of P with NLR (OR=9.65, CI 6.59-14.13, $p < 0.0001$) after adjusting for BMI, WBC count, and oral hygiene habits; predictive validity in discriminating P patients from H individuals as depicted by AUC=0.788 (CI 0.754-0.819, $p < 0.0001$); NLR: sensitivity=73.97% (CI 68.75-78.72%), specificity=80.0% (CI 75.15-84.27%), and diagnostic accuracy=76.98% (CI 73.49-80.21%)	NLR is highly associated with P

(Continues)

TABLE 1 (Continued)

Parameters	Autor, year, country, and reference	Analysis	Study design	Number of participants, gender, and age	Number of diagnosed participants	Examiner calibration	Smoking status
	Mishra et al., 2022, India ¹³⁸	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	<i>n</i> = 148 (80 male, 68 females, mean age 31 years)	108 generalized stage III grade C P ⁵² versus 40 H	Yes	Only nonsmokers
	Temelli et al., 2018, Turkey ¹³⁹	Selective coronary angiography with contrast agent by means of Judkins technique in multiple projections; clinical chemistry analyzer (AU5800; Beckmann Coulter)	Case-control	<i>n</i> = 77 (47 males, 30 females, mean age Group 1 = 59.5 years, Group 2 = 57.5 years, Group 3 = 50 years, Group 4 = 49 years)	41 P ¹³⁶ versus 36 non-P (gingivitis ¹⁴⁰); divided into group 1 = CAD with P (<i>n</i> = 20), group 2 = CAD without P (<i>n</i> = 20), group 3 = non-CAD with P (<i>n</i> = 21), and group 4 = non-CAD without P (<i>n</i> = 16)	Yes, of periodontists and cardiologists	Discussed smoking and found no significant differences
	Torrunguang et al., 2018, Thailand ¹⁴¹	Automated hematology analyzer (Cell-Dyn Ruby System; Abbott Diagnostics)	Cross-sectional	<i>n</i> = 2036 (gender and age not reported)	1555 normoglycemic, 331 IFG and 150 diabetes patients ¹⁴² ; divided into: 365 no/mild P, 1058 moderate P, and 613 severe P ¹⁴³	Yes	Nonsmokers, former smokers, and current smokers with significant differences
Delta neutrophil index (DNI)	Çetin Özdemir et al., 2022, Turkey ¹³³	Automated hematology analyzer (company not reported)	Case-control	<i>n</i> = 77 (28 males, 46 females, and mean age 36 years)	26 gingivitis versus 22 stage III grade A P ⁵² versus 26 H ¹³⁴	Yes	Only nonsmokers
Lymphocyte to monocyte ratio (LMR)	Mishra et al., 2022, India ¹³⁸	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	<i>n</i> = 148 (80 male, 68 females, and mean age 31 years)	108 generalized stage III grade C P ⁵² versus 40 H	Yes	Only nonsmokers

Significant difference in age between groups	Significant difference in gender between groups	Main results	Conclusion
-	-	<p>NLR of P: 2.84(SD=±1.18), NLR of H: 2.10(SD=±1.08), significant difference between H and P patients ($p < 0.0001$); NLR is significant positive associated with mean CAL, mean PPD, mean BOP, mean PI, and mean mGI; ROC analysis yielded cutoff values of >2.15 in predicting risk of P, predictive validity as indicated by AUC=0.743 (CI 0.627–0.779, $p < 0.0001$); based on these cutoff values: OR of $p = 11.43$ (CI 4.80–27.19, $p < 0.0001$) with every 0.1 unit increment in NLR; Logistic regression analysis (age, male gender, and BMI as explanatory variables and NLR values as dependent variables): age was a significant predictor of difference ($p = 0.02$), but not male gender ($p = 0.49$) and BMI ($p = 0.72$); NLR: sensitivity=76.85% (CI 67.75%–84.42%), specificity=77.50% (CI 61.54%–89.16%) and diagnostic accuracy=77.02% (CI 69.40%–83.53%)</p>	NLR is highly associated with P
+	-	<p>NLR of group 1: 2, NLR of group 2: 2, NLR of group 3: 2, NLR of group 4: 1,5; no significant differences between groups</p>	NLR is not associated to patients with/without CAD and/or P
+	+	<p>NLR of normoglycemic: 1.4 (IQR=1.1–1.8), NLR of IFG: 1.4 (IQR=1.1–1.8), and NLR of diabetes: 1.4 (IQR=1.1–1.8), $p = 0.212$; NLR of no/mild P: 1.4 (IQR=1.1–1.8), NLR of moderate P: 1.4 (IQR=1.1–1.8), and NLR of severe P: 1.5 (IQR=1.2–1.9), $p = 0.057$; Comparison between no/mild/moderate P versus severe P was more likely to have higher NLR ($p = 0.019$); after controlling for P severity, NLR was not associated with diabetes ($p > 0.05$)</p>	NLR is not associated to patients with/without diabetes and with/without P
+	+	<p>DNI of H: 0.23 (SD=±0.07), DNI of gingivitis: 0.33 (SD=±0.11), DNI of P: 0.46 (SD=±0.22), DNI was significant associated between groups ($p < 0.001$); no correlations for CAL, BOP, mGI, plaque index, and DNI (Spearman's correlation test), ROC analysis: 0.25 cutoff value for DNI in diagnosis of periodontal disease (sensitivity=91% and specificity=65%)</p>	DNI is associated with gingivitis and P
-	-	<p>LMR of P: 7.26%(SD=±4.94%), LMR of H: 9.31%(SD=±4.88%), significant difference between H and P patients ($p = 0.004$); LMR is significant negative associated with mean PPD, mean CAL, and not associated with mean BOP, mean mGI, and mean plaque index; ROC analysis yielded cutoff values of $\leq 7.16\%$ in predicting risk of P, predictive validity as indicated by AUC=0.654 (CI 0.529–0.691, $p = 0.003$); Based on these cutoff values, OR of $p = 4.93$ (CI 2.26–10.76, $p = 0.0001$) with each 0.1 decrease in LMR; Logistic regression analysis (age, male gender, and BMI as explanatory variables and LMR values as dependent variables): age is a significant predictor of differences ($p = 0.004$), not male gender ($p = 0.36$) and BMI ($p = 0.58$); LMR: sensitivity=70.37% (CI 60.81% - 78.77%), specificity=67.50% (CI 50.87% - 81.42%), and diagnostic accuracy=69.59% (CI 61.50%–76.88%)</p>	LMR is associated with P

(Continues)

TABLE 1 (Continued)

Parameters	Autor, year, country, and reference	Analysis	Study design	Number of participants, gender, and age	Number of diagnosed participants	Examiner calibration	Smoking status
Platelet to lymphocyte ratio (PLR)	Acharya et al., 2019, India ⁹⁰	Automated hematology analyzer (Sysmex pochH-100i;)	Case-control and prospective cohort	n = 60 (30 males, 30 females), mean age P 45.08 years and H 39.6 years	30 CP ¹³⁰ versus 30 H	No	Not reported
	Lu et al., 2021, China ⁷¹	Automated hematology analyzer (Sysmex XS -1000)	Case-control	n = 505 (205 males, 300 females, mean age 27 years)	372 generalized AgP ¹³⁶ versus 133 H	Yes	Only nonsmokers
	Mishra et al., 2022, India ¹³⁷	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	n = 630 (324 males, 306 females, mean age 34 years)	315 generalized stage III grade C P ⁵² versus 315 H ¹³⁴	Yes	Only nonsmokers
	Mishra et al., 2022, India ¹³⁸	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	n = 148 (80 male, 68 females, mean age 31 years)	108 generalized stage III grade C P ⁵² versus 40 H	Yes	Only nonsmokers
	Torrunguang et al., 2018, Thailand ¹⁴¹	Automated hematology analyzer (Cell-Dyn Ruby System; Abbott Diagnostics)	Cross-sectional	n = 2036 (gender and age not reported)	1555 normoglycemic, 331 IFG, and 150 diabetes patients ¹⁴² ; divided into: 365 no/mild P, 1058 moderate P, and 613 severe P ¹⁴³	Yes	Nonsmokers, former smokers, and current smokers with significant differences
Platelet distribution width (PDW)	Mutthineni et al., 2021, India ¹⁴⁴	Automated cell counter (UBM F-19)	Cross-sectional	n = 75 (gender not reported, age between 35 years and 50 years)	Severe CP ¹⁴³ versus moderate CP versus H	Yes	Only nonsmokers
	Temelli et al., 2018, Turkey ¹³⁹	Selective coronary angiography with contrast agent by means of Judkins technique in multiple projections; clinical chemistry analyzer (AU5800; Beckmann Coulter)	Case-control	n = 77 (47 males, 30 females, and mean age Group 1 = 59.5 years, Group 2 = 57.5 years, Group 3 = 50.0 years, Group 4 = 49.0 years)	41 P ¹³⁶ versus 36 non-P (gingivitis, as described in the discussion ¹⁴⁰); divided into group 1 = CAD with P (n = 20), group 2 = CAD without P (n = 20), group 3 = non-CAD with P (n = 21), and group 4 = non-CAD without P (n = 16)	Yes, of periodontists and cardiologists	Discussed smoking and found no significant differences

Significant difference in age between groups	Significant difference in gender between groups	Main results	Conclusion
Not reported	Not reported	PLR of pretreatment with CP: 121.08 (SD = ±43.58), PLR of post-treatment: 80.0 (SD = ±26.50), $p < 0.0001$, PLR of H: 111.6 (SD = 37.36); PLR in pre- and post-treated patients was not associated to local periodontal parameters; cutoff point by ROC for pre- versus post-treated patients = 80.205 (sensitivity = 0.867, specificity = 0.622, and AUC = 80.6%)	Significant difference of PLR between pre- and post-treated CP patients
-	-	PLR of AgP: 132.23 (SD = ±45.48), PLR of H: 125.82 (SD = ±42.41), no significant difference between H and AgP ($p = 0.157$), AgP group: PLR was not associated to PPD, CAL, and BOP	PLR is not associated with generalized AgP
-	-	PLR of P: 135.58 (IQR = 112.73–164.08), PLR of H: 124.16 (IQR = 102.14–154.09), significant difference between H and P ($p = 0.02$); ROC cutoff value >126.08, MLRA: high significant association of P with PLR OR = 2.16 (CI 1.56–3.01, $p < 0.0001$) after adjusting for BMI, WBC count, and oral hygiene habits; predictive validity in discriminating P patients from H individuals as depicted by AUC = 0.788 (CI 0.754–0.819, $p < 0.0001$); PLR: sensitivity = 64.12% (CI 58.55–69.42%), specificity = 53.33% (CI 47.65–58.95%), and diagnostic accuracy = 58.73% (CI 54.77–64.03%)	PLR is associated with P
-	-	PLR of P: 143.98 (SD = ±59.0), PLR of H: 134.16 (SD = ±38.53), no significant difference between H and P patients ($p = 0.574$); PLR was significant positive associated with mean PPD, mean plaque index, and not associated with mean CAL, mean BOP, and mean mGI	PLR is not associated with P
+	+	PLR of normoglycemic: 120.7 (IQR = 97.3–149.3), PLR of IFG: 109.6 (IQR = 91.2–135.2), PLR of diabetes: 103.0 (IQR = 81.7–127.6), significant differences between groups ($p < 0.001$); PLR of no/mild P: 125.2 (IQR = 101.1–156.7), PLR of moderate P: 118.8 (IQR = 96.5–145.9), PLR of severe P: 109.8 (IQR = 87.0–136.4), comparison between no/mild/moderate P versus severe P was more likely to have lower PLR ($p = 0.015$); after controlling for P severity, PLR was negatively associated with diabetes ($p = 0.007$)	PLR is highly associated to patients with/without diabetes and with/without P
Not reported	Not reported	PDW of H: 10.51 (SD = ±2.71), PDW of moderate CP: 10.61 (SD = ±1.58), PDW of severe CP: 10.87 (SD = ±1.40), $p = 0.805$ (ANOVA with post hoc Games-Howell test), mean PDW levels showed no significant changes from normal to diseased individuals; one-sample t-test showed significant differences between groups ($p < 0.001$)	Association unclear
+	-	PDW of group 1: 17 (min. = 15.7, max. = 18.3), PDW of group 2: 16.35 (min. = 15.7, max. = 17.4), PDW of group 3: 16.6 (min. = 15.9, max. = 17.3), and PDW of group 4 = 16.45 (min. = 15.9, max. = 16.9), significant differences among the groups with CAD and P versus non-CAD and non-P, with CAD and with P versus with CAD and non-P and with CAD and with P versus non-CAD with P ($p < 0.01$); significant association between PDW and CAL ($p = 0.033$)	PDW is associated to CAD patients with/without P

(Continues)

TABLE 1 (Continued)

Parameters	Autor, year, country, and reference	Analysis	Study design	Number of participants, gender, and age	Number of diagnosed participants	Examiner calibration	Smoking status
Plateletcrit (PCT)	Mutthineni et al., 2021, India ¹⁴⁴	Automated cell counter (UBM F-19)	Cross-sectional	n = 75 (gender not reported, age between 35 years and 50 years)	Severe CP ¹⁴³ versus Moderate CP versus H (n not reported)	Yes	Only nonsmokers
	Ustaoglu et al., 2020, Turkey ¹⁴⁵	Automated hematology analyzer (Cell-Dyn 3700 System; Abbott Diagnostics)	Case-control	n = 114 (55 males, 59 females, mean age P group 37.4 years and H group 35.6 years)	57 stage III P ⁵² versus 57 H	Yes	Only nonsmokers
Systemic immune inflammation index (SII)	Cao et al., 2023, USA ¹⁴⁹	Automated hematology analyzer (company not reported)	Cross-sectional	n = 10 301 (data from National Health and Nutrition Examination Survey, 48.86% male, 51.14% female, mean age 50.88 years)	62.29% moderate/severe P ¹⁴³ versus 37.71% no/mild P	Not reported	Nonsmokers, former smokers, and smokers; significant differences
	Mishra et al., 2022, India ¹³⁷	Automated hematology analyzer (Sysmex XN - 1000)	Case-control	n = 630 (324 males, 306 females, mean age 34 years)	315 generalized stage III grade C P ⁵² versus 315 H ¹³⁴	Yes	Only nonsmokers
Red blood cell distribution width (RDW)	Anand et al., 2014, India ¹⁴⁶	Automated hematology analyzer (BC-3000 Plus; Shenzhen Mindray Bio-Medical Electronics)	Case-control	n = 122 (65 males, 57 females, mean age P group 32.8 years and H group 30.4 years)	64 generalized AgP ¹³⁶ versus 58 H	Yes	Nonsmokers, former smokers, and current smokers with significant differences (logistic regression model)
	Bhattacharya et al., 2022, India ¹³¹	Not reported	Cross-sectional	n = 80 (40 males, 40 females, mean age P 41.8 years and H 36.93 years)	40 P ¹³² versus 40 H	Yes	Only nonsmokers
	López et al., 2012, Chile ¹⁴⁷	Automated hematology analyzer (Cell-Dyn 3500 System; Abbott Diagnostics)	Case-control	n = 160 (72 males, 88 females, mean age P 16.7 years and H 16.4 years)	87 P versus 73 H	Yes	Nonsmokers and smokers; no significant difference

Significant difference in age between groups	Significant difference in gender between groups	Main results	Conclusion
Not reported	Not reported	PCT of H: 0.19 (SD=±0.04), PCT of moderate CP: 0.30 (SD=±0.06), PCT of severe CP: 0.42 (SD=±0.09), and mean PCT levels showed significant changes from normal to diseased individuals (ANOVA with post hoc Games-Howell test, $p < 0.001$); One-sample t-test showed for H and severe P significant differences ($p < 0.001$) and for moderate P, no significant differences ($p = 0.132$)	PCT is highly associated with P
-	-	PCT of P: 0.223 (SD=±0.04), PCT of H: 0.196 (SD=±0.04), $p < 0.001$; significant associations between PCT and mean PPD, mean CAL, and BOP (all $p < 0.001$)	PCT is highly associated with P
Not reported	Not reported	Association between SII and p followed a j-shape curve (p for nonlinearity < 0.001); Risk of moderate/severe P decreased by 17% per unit SII when $\log_2(\text{SII}) \leq 8.66$ ($or = 0.83$; CI=0.69-0.999) and increased by 19% per unit when $\log_2(\text{SII}) > 8.66$ ($or = 1.19$; ci 1.02-1.38); Significant differences between SII levels: average age, gender, ethnicity, marital status, smoking habit, obesity rates, diabetes prevalence, hypertension rates, mean cal, mean ppd, number of sites ppd ≥ 4 mm, number of sites cal ≥ 3 or 5 mm, and the prevalence of P	SII is highly associated with P
-	-	SII of P: 723.87 (IQR=605.16-968.37), SII of H: 537.74 (IQR=468.38-588.41) ($\times 10^9/L$), significant difference between H and P patients ($p < 0.0001$); ROC cutoff value > 591.48 , MLRA: high significant association of P with SII (OR=11.86, CI 7.99-17.59, $p < 0.0001$) after adjusting for BMI, WBC count, and oral hygiene habits; predictive validity in discriminating P patients from H individuals as depicted by AUC=0.766 (CI 0.731-0.799, $p < 0.0001$); SII: sensitivity=81.27% (CI 76.51-85.42%), specificity=76.50% (CI 71.43-81.08%), and diagnostic accuracy=78.89% (CI 75.49-82.01%)	SII is highly associated with P
-	-	RDW of AgP: 15.27% (SD=±1.44%), RDW of H: 15.16% (SD=±1.07%), no significant differences between groups ($p = 0.617$)	RDW is not associated with generalized AgP
+	-	RDW of P: 50.31% (SD=±8.93%), RDW of H: 40.52% (SD=±5.48%), significant differences between groups ($p < 0.001$)	RDW is highly associated with P
-	+	RDW of P: 14.40% (SD=±0.87%), RDW of H: 14.38% (SD=±0.83%), no significant difference between groups ($p = 0.887$)	RDW is not associated with P

(Continues)

TABLE 1 (Continued)

Parameters	Autor, year, country, and reference	Analysis	Study design	Number of participants, gender, and age	Number of diagnosed participants	Examiner calibration	Smoking status
	Sridharan et al., 2021, India ¹⁴⁸	Automated hematology analyzer (Sysmex KX - 21N)	Case-control	n = 80 (26 males, 54 females, and mean age Group 1 = 41.6 years, Group 2 = 50.8 years, Group 3 = 42.6 years, and Group 4 = 48.4 years)	Group 1: non hypertensive without P (n = 20), group 2: nonhypertensive with P (n = 20), group 3: hypertensive without P (n = 20), and group 4: hypertensive with P (n = 20)	Yes	Nonsmokers, former smokers, and smokers; no significant differences
	Temelli et al., 2018, Turkey ¹³⁹	Selective coronary angiography with contrast agent by means of Judkins technique in multiple projections; clinical chemistry analyzer (AU5800; Beckmann Coulter)	Case-control	n = 77 (47 males, 30 females, and mean age Group 1 = 59.5 years, Group 2 = 57.5 years, Group 3 = 50 years, and Group 4 = 49 years)	41 P ¹³⁶ versus 36 non-P (gingivitis ¹⁴⁰); divided into group 1 = CAD with P (n = 20), group 2 = CAD without P (n = 20), group 3 = non-CAD with P (n = 21), and group 4 = non-CAD without P (n = 16)	Yes, of periodontists and cardiologists	Discussed smoking and found no significant differences
	Ustaoglu et al., 2020, Turkey ¹⁴⁵	Automated hematology analyzer (Cell-Dyn 3700 System; Abbott Diagnostics)	Case-control	n = 114 (55 males, 59 females, and mean age P group 37.4 years and H group 35.6 years)	57 stage III P ⁵² versus 57 H	Yes	Only nonsmokers

Abbreviations: %, percentage; -, no significant differences between groups; +, significant differences between groups; AgP, aggressive periodontitis; AUC, area under the curve; BMI, body mass index; BOP, bleeding on probing; CAD, coronary artery disease; CAL, clinical attachment level; CI, 95% confidence interval; SD, mean standard deviation; CP, chronic periodontitis; DNI, delta neutrophil index; H, systemically and periodontal healthy controls; IFG, impaired fasting glucose; IQR, interquartile range; LMR, lymphocyte to onocyte ratio; mGI, modified gingival index; MLRA, multiple logistic regression analysis; n, number; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; P, periodontitis; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio; PPD, probing pocket depth; RDW, red blood cell distribution width; ROC, receiver operating characteristics; SII, systemic immune inflammation index; WBC, white blood cell.

to its simplicity, cost-effectiveness, and accessibility, as it can be calculated from routine blood tests. However, its interpretation should be integrated with other clinical findings and laboratory tests for a comprehensive evaluation of a disease.

An elevated NLR in cardiovascular diseases, particularly heart failure and myocardial infarction, is associated with a poor prognosis, with NLR values often exceeding 3.²⁵⁻²⁷ For instance, a recent systematic review by Angkananard et al.²⁸ on NLR and cardiovascular disease risk, identifying cutoff values ranging from 1.80 to 2.60 for coronary artery disease (CAD), 2.19 to 5.70 for acute coronary syndrome, and 3.0 to 3.17 for cerebrovascular stroke. Furthermore, a higher NLR has been linked to poor glycemic control and an increased risk of type 2 diabetes mellitus, with varying cutoff values from 2.44 to 4.34.²⁹⁻³¹ In diabetic patients, who often

have comorbid systemic conditions, NLR values can exceed 4.³² An NLR >3 has been associated with increased 2-year follow-up mortality in medical in-patients with multiple chronic conditions.¹⁵⁶ Additionally, NLR has been recognized as a significant prognostic marker for people with obstructive sleep apnea with mean NLR values ranging from 1.61 to 4.18,¹⁵⁷ deteriorating renal function¹⁵⁸ and lung disorders.³⁴

4.2 | The use of NLR in cancer

NLR has emerged as a widely studied and recognized biomarker in the field of cancer. To date, over 300 reviews have been published exactly on this topic. The underlying mechanism involves the role of

Significant difference in age between groups	Significant difference in gender between groups	Main results	Conclusion
+	-	P groups (hypertensive and nonhypertensive) showed significant association with RDW ($p < 0.001$); mean PI, GI, PPD, CAL (dependent variables), and RDW were significant associated with P (hypertensive and nonhypertensive, $p < 0.001$)	RDW is highly associated with P
+	-	RDW of group 1: 14% (min. = 12.3%, max. = 17.2%), RDW of group 2: 14.1% (min. = 12.8%, max. = 16.3%), RDW of group 3: 13.6% (min. = 12.3%, max. = 20.3%), And RDW of group 4: 13% (min. = 12.3%, max. = 16.6%), no association between groups; moderate association between PPD and RDW ($p = 0.049$) in non-CAD groups with/without P	RDW is not associated to patients with/without CAD and/or P
-	-	RDW of P: 14.80% (SD = $\pm 1.88\%$), RDW of H: 15.20% (SD = $\pm 1.51\%$), no significant difference between H and P ($p = 0.212$); no associations between PCT and mean PPD, mean CAL, and BOP	RDW is not associated with P

neutrophils in promoting tumor-associated inflammation, angiogenesis, and immune suppression, while decreased lymphocyte counts contribute to compromised antitumor immune responses. As described in a systematic review and meta-analysis by Cupp et al.,¹⁵⁹ numerous studies across diverse malignancies have reported a consistent association between elevated NLR and advanced disease stages, tumor aggressiveness, and reduced overall survival. In an additional meta-analysis, Templeton et al.⁴⁸ illustrated that a NLR > 4 is independently associated with a reduced overall survival in solid tumors. Moreover, NLR serves as a predictive factor for cancer-specific survival, progression-free survival, and disease-free survival, showing highly significant hazard ratios of more than 1.61 (95% CI = 1.36–1.91), 1.63 (95% CI = 1.39–1.91), and 2.27 (95% CI = 1.85–2.79), respectively. However, while NLR holds promise as

a prognostic marker, its universal applicability necessitates careful consideration of cancer type-specific variations and a precise cutoff value for every type of cancer has not been decided so far.

4.3 | Findings from the use of NLR in periodontology

In patients with periodontitis and concurrent systemic diseases, NLR values may reflect both periodontitis and systemic conditions. This requires consideration of potential confounding systemic diseases influencing NLR. These observations suggest that NLR could be a linking factor between periodontitis and other systemic inflammatory diseases.

$$\text{Neutrophil to lymphocyte ratio (NLR)} = \frac{\text{Neutrophil count}}{\text{Lymphocyte count}}$$

FIGURE 2 Calculation of the neutrophil to lymphocyte ratio (NLR).

NLR is the most studied “cancer” biomarker in periodontitis. Many systemic blood indices others than NLR have been studied. Six of nine studies did find an association between NLR and periodontitis. However, the largest study with 2036 participants included diabetic patients,¹⁴¹ which is a confounding factor. While previous research has documented that high levels of NLR are associated with type 2 diabetes,^{31,160,161} the specific association between these altered NLR levels and periodontitis has only been reported in one study by Torrungruang et al.¹⁴¹ This cross-sectional study investigated the relationship between different glycemic status, NLR, and periodontitis in a Thai population. The study benefited from its robust sample size, encompassing 2036 subjects, which facilitated exhaustive control for potential confounding factors. Based on the 2014 diagnostic criteria by the American Diabetes Association,¹⁴² the study participants were divided into three groups: normoglycemia ($n=1555$), impaired fasting glucose ($n=331$), and diabetes ($n=150$, without differentiation whether type 1 or type 2). Analysis of the parts of NLR showed that counts of both neutrophils and lymphocytes were significantly elevated with worsening glycemic status and with increasing severity of periodontitis. Similar outcomes were observed when utilizing mean pocket probing depth (PPD) or clinical attachment level (CAL) as indicators of periodontitis severity. Mean PPD and CAL values were higher among the diabetic cohort, subsequently lower by the impaired fasting glucose and normoglycemic groups. As a result, the absence of a link between NLR and diabetes within this study might be explained by simultaneous elevations in both neutrophil and lymphocyte counts with worsening of the glycemic status. Nonetheless, in the group with severe periodontitis, these increases appeared more distinct for neutrophils. One weakness of this study is its high heterogeneity of the study population with significant differences in age, gender, and smoking habits.

The second study which included patients with type 2 diabetes mellitus and other systemic diseases confirmed the results of Torrungruang et al.¹⁴¹ Thus, these systemic risk factors were investigated in a study by Doğan et al.¹³⁵ across a cohort of 180 patients with and without periodontitis. The study had some limitations, such as no specified periodontal classification, a lack of diet analysis, participants had poor oral hygiene habits, and included smokers and nonsmokers. As a result of this study, periodontitis patients with type 2 diabetes ($n=75$), hyperlipidemia ($n=99$), obese ($n=119$), and menopause ($n=37$) compared to healthy controls ($n=28$) showed no significant difference in NLR. Only the hyperlipidemia group ($n=99$) showed a significant higher NLR (2.56 ± 1.50) in the periodontitis group compared to the nonperiodontitis group (NLR: 2.05 ± 1.31) and a significant positive association between clinical periodontal parameters and NLR was reported. The association between periodontitis

and hyperlipidemic patients had already been reported in other studies.^{162,163} The data cumulatively indicate that hyperlipidemia may increase the inflammatory processes associated with periodontitis. Specifically, hypercholesterolemia contributes to monocytic activity, which in turn could increase neutrophil count.¹⁶⁴

Another study that included patients with CAD confirmed the results of Torrungruang et al.¹⁴¹ and Doğan et al.¹³⁵ Temelli et al.¹³⁹ evaluated in a cross-sectional design the relationship between NLR in patients with and without CAD, respectively, and also with and without periodontitis. A total of 77 patients who underwent coronary angiography due to suspected CAD and periodontal assessment, were enrolled. The NLR was not significantly different among the study groups with and without CAD and periodontitis, similar to the neutrophil and leukocyte counts.

The absence of significant differences of the hematological parameters and NLR may be attributable either to the acute severity of periodontitis within the study participants or the limited sample size encompassed by the investigation.

Çetin Özdemir et al.¹³³ investigated the potential association of NLR in relation to three different groups in a Turkish systemically healthy nonsmoking population: periodontally healthy ($n=26$), gingivitis ($n=26$), and generalized stage III periodontitis ($n=26$).^{52,134} The results demonstrated no significant differences in NLR, neutrophil counts, and lymphocyte counts between the groups.

Five out of six studies who excluded patients with systemic diseases demonstrated a significant association between NLR and periodontitis. Mishra et al.¹³⁷ conducted one of the largest studies including 630 individuals in a multicenter design. They included 315 generalized stage III grade C periodontitis patients and 315 periodontally and systemic healthy individuals. Participants in this study were age and gender matched. Additionally, smokers were excluded.¹⁶⁵ The study identified a notably elevated body mass index (BMI) in subjects with periodontitis. Although the BMI values of numerous participants fell within the standard range, there was a moderate statistically higher BMI in the periodontitis group in comparison to the healthy group. Several studies observed an association between BMI and reduced total WBC count and increased counts of neutrophils and lymphocytes in GAgP patients.^{166,167} Furthermore, the results of selected studies indicated that an increased BMI is linked to an increase in NLR.^{91,168} While absolute neutrophil counts (5.14 vs 4.6) were significantly higher in the periodontitis group, absolute lymphocyte counts (1.93 vs 2.2) were significantly lower. This resulted in a significantly different NLR of 2.74 in patients with periodontitis compared to 2.13 in healthy individuals. Receiver operating characteristics (ROC) yielded cutoff value of >2.44 in discriminating patients with periodontitis. Based on this cutoff value, multiple logistic regression analysis indicated significant association of periodontitis with NLR (OR=9.65, 95% CI=6.59–14.13) after adjusting for oral hygiene habits, BMI, and WBC count. The sensitivity of NLR was 74%, the specificity was 80%, and diagnostic accuracy was 77%.

Mishra et al.¹³⁸ also investigated the association between severe periodontitis in patients in India between 20 and 40 years. Healthy

controls were assessed in a separate retrospective and single center study where the participants were age, gender, and BMI matched. Furthermore, a multicenter study was performed by the same group.¹³⁷ The major findings revealed significantly higher neutrophil counts and NLR (2.84 vs 2.10) values in periodontitis patients. Also, the risk of severe grade C periodontitis increased with the height of NLR values. The NLR was significantly positive related with all recorded periodontal parameters like CAL, PPD, and bleeding on probing (BOP). The ROC analysis yielded a cutoff value of >2.15. This cutoff value determined an OR of 11.4 for severe grade C periodontitis. Every 0.1 increase in NLR stands for a major elevation of the risk to have periodontitis. This leads to a very high sensitivity of 77%, a specificity of 78%, and a total diagnostic accuracy of 77% in predicting severe grade C periodontitis in young adults in an Indian population. These cutoff values identified by Mishra et al.¹³⁸ diverged from those established in a study on young Chinese adults. Additionally, the predictive accuracy of the leukocyte ratios was observed to be superior in opposite to Lu et al.⁹¹ This variation in cutoffs underscores the necessity for further investigations across diverse racial populations.

As discussed previously in this review, this underscores the significance of systemic inflammation as a critical factor in determining the severity of GAgP.^{169,170} Neutrophils and lymphocytes serve as pivotal components in both inflammatory and immunological reactions observed in patients diagnosed with GAgP.^{171,172} Studies highlighted a significant increase in the number of neutrophils and a significantly lower numbers of lymphocytes in the periphery blood of GAgP patients. This suggests that clinical periodontal parameters might be directly associated to the numbers of these cell types.¹⁷² The only study including GAgP patients based on the old periodontitis classification¹³⁶ was published by Lu et al.⁹¹ The group by Mishra et al.^{137,138} included comparable grade C periodontitis⁵² patients. Notably, the BMI of the 372 Chinese GAgP patients was significant higher (21.4 vs 22.2 kg/m²) than in the 133 healthy controls. No significant differences were noted in the distribution of age and gender between the two groups. Moreover, a statistically significant difference was observed in neutrophil numbers, while lymphocyte counts displayed no evident discrepancies. NLR was significantly higher in GAgP patients than in the control group (mean NLR = 2.34 vs mean NLR = 1.84). Subsequently, the values of NLR were differentiated in different subgroups. The distribution in the NLR subgroups differed between the GAgP and healthy groups. Significantly, more patients of the GAgP group were found in the NLR 2–3 and NLR ≥3 subgroups. Additionally, the NLR values were positively associated with PPD and CAL in patients with GAgP. Furthermore, an incremental rise of one unit in the NLR corresponded to respective increases of 0.41 mm in PPD and 0.57 mm in CAL. Additionally, the cutoff point was defined by 1.92. Lymphocyte counts exhibited a negative association with CAL, while neutrophil counts were significantly linked to different periodontal parameters such as CAL and PPD. Lu et al. (2021) concluded that NLR could serve as a prospective biomarker for inflammation and disease severity in Chinese GAgP patients.

One study analyzing NLR before and after an anti-infective therapy was published by Acharya et al.⁹⁰ 30 Indian chronic periodontitis

patients were provided oral hygiene instructions at baseline. SRP was divided into two appointments 1-week apart with additionally oral hygiene instructions. After 1 month, the PPD and the CAL showed a reduction of 1 mm to 5.83 mm and 1.25 mm to 6.51 mm which still indicates severe periodontitis. The limited reduction of the plaque index (1.86 vs 0.97) and gingival index (1.81 vs 1.24) did not indicate a successful periodontal treatment. Nevertheless, NLR showed a significant reduction from 1.90 to 1.48. This determined a cutoff point of 1.54 between pre- and post-treated patients. The NLR was positively associated to PPD and CAL before periodontal treatment and negatively after treatment, which means that the therapeutic intervention had a remarkable influence on NLR. It has to be considered that the selection of the controls was disputable and the smoking status of the patients was not addressed. The 30 periodontal and systemic healthy controls included in this study showed a mean NLR of 1.86, which was close to the pretreatment values in the periodontitis group. Furthermore, a comparison between healthy controls and patients before treatment was not reported.

A recent meta-analysis included some of the above referred studies.^{90,91,133,135,138,139,141} It was found that the mean NLR was statistically significant higher by 0.41, in the periodontitis group compared to the control group.¹⁷³ These findings indicate that the increased NLR is related to periodontitis and may be an important systemic blood index. Depending on racial predisposition, it can be hypothesized, in cases with NLR >2, that periodontitis has systemic effects.

5 | DELTA NEUTROPHIL INDEX

5.1 | The basis of DNI

The DNI is a hematological parameter used primarily to assess the severity and prognosis of infections, particularly in the context of systemic inflammatory response syndrome (exaggerated defense response of the immune system to a noxious stressor resulting in dysregulation of the immune response) and sepsis. It quantifies the distribution of immature to mature neutrophils in the blood. DNI can be measured by deducting the proportion of mature polymorphonuclear leukocytes from the aggregate of myeloperoxidase-reactive cells.¹⁷⁴ As a result of the emergence of immature granulocytes, changes occur in alterations in peripheral total WBC counts during the granular leukocyte differentiation process.^{174,175} This is indicative of an ongoing inflammatory process or infection. The DNI is calculated using automated blood analyzers that measure the difference in the absorbance of light by mature and immature neutrophils. These analyzers employ two different wavelengths to differentiate between these cell types based on their nuclear segmentation and cytoplasmic granularity. Figure 3 illustrates how DNI is calculated. The DNI provides a more precise measure of the proportion of immature to mature neutrophils than a simple immature granulocyte count, thereby offering a more accurate reflection of the body's response to (severe) infection or inflammation.

$$\text{Delta neutrophil index (DNI)} = \frac{\text{Neutrophil count} - (\text{Band of neutrophil count} + \text{Metamyelocyte count})}{\text{Total white blood cell count}} \times 100$$

FIGURE 3 Calculation of the delta neutrophil index (DNI).

The DNI is characterized by a half-life of approximately 3 h, substantially shorter than the 24–30 h half-life of procalcitonin, also used as a marker for bacterial infectious diseases.¹⁷⁶ This shorter half-life allows for a more rapid reflection of a patient's status of infection, proving advantageous in monitoring and evaluating the effectiveness of therapeutic interventions. Generally, a higher DNI value correlates with increased systemic inflammation. The calculation and reporting of DNI are straightforward and does not incur additional costs.^{133,177} Previous studies highlight the benefits of DNI as a diagnostic and prognostic marker in various infectious or inflammatory diseases such as septic shock, bacteremia,¹⁷⁸ sudden cardiac arrest,¹⁷⁹ and covid-19.¹⁸⁰

5.2 | The use of DNI in cancer

The DNI has been investigated as a potential biomarker in the context of cancer, reflecting alterations in neutrophil subpopulations and their response to inflammatory stimuli. In various malignancies, elevated DNI levels have been observed, suggesting a potential association with the inflammatory processes associated with tumor development and progression. The heightened inflammatory state in cancer often leads to an increased release of immature neutrophils, contributing to elevated DNI. Studies have reported that an elevated DNI is associated with adverse prognostic outcomes in cancer patients. Ko et al.¹⁸¹ investigated the DNI in early diagnosed suspected acute promyelocytic leukemia patients and found DNIs between 52% and 56% at different time periods during treatment. In nonacute promyelocytic leukemia, DNIs varied between 10% and 12%. Increased predictability for acute promyelocytic leukemia was associated with a DNI >24.2% in early diagnosed patients. Study groups from a university clinic in Turkey published studies on thyroid malignancy,¹⁸² axillary metastasis of breast cancer,¹⁸³ and renal cell carcinoma patients.¹⁸⁴ In all studies, pretreatment DNI was significantly higher in the malignant group compared to benign or nonmalignant group with high sensitivity and specificity in detecting cancer. After treatment, the differences were negligible. No systemic reviews or meta-analyses have been published yet. Therefore, it is too early to assess whether the DNI is a useful marker for the detection of carcinoma.

5.3 | Findings from the use of DNI in periodontology

So far, only one study by Çetin Özdemir et al.¹³³ has investigated the association between periodontitis and DNI. As described above, the study also investigated the relationship between periodontitis

and DNI in three different groups in a Turkish population: periodontally healthy, gingivitis, and generalized stage III periodontitis patients.^{52,134} The DNI was significantly higher in the periodontitis and gingivitis group compared to the health group. Furthermore, the DNI demonstrated a positive association to all periodontal parameters. The ROC analysis revealed that DNI exhibited a sensitivity of 91% and specificity of 65% with an optimal cutoff at 0.25 in diagnosing periodontal disease, suggesting its potential as a biomarker for periodontitis. But DNI has shown promise as a diagnostic tool for infection; its role in chronic inflammatory diseases like periodontitis remains underexplored. The shorter half-life of DNI predicts more effectively systemic inflammatory load and may serve as a better monitor marker for therapeutic efficacy. Therefore, DNI could be a potential novel biomarker for periodontal diseases. However, further studies are needed to verify the results.

6 | LYMPHOCYTE TO MONOCYTE RATIO

6.1 | The basis of LMR

LMR operates as an inflammatory complex analogous to the role of NLR.⁵⁵ This marker presents a distinctive systemic inflammatory indication, integrating two distinct metrics of inflammation (Figure 4). A limited number of studies have determined reference values of LMR in healthy adults, for example, in South Korea (5.31)¹⁵³ and in China (5.3).¹⁸⁵ However, the values are influenced by ethnicity, age, and gender.^{138,153,185,186} Recent studies indicated a significant reduction in LMR levels among rheumatoid arthritis patients from 6.1 (healthy) to 4.04 (patients).¹⁸⁶ Moreover, an investigation assessing the relationship between LMR and the severity of CAD determined that severe atherosclerosis is associated with an LMR value of <5.06.⁵⁵

6.2 | The use of LMR in cancer

LMR has also emerged as a prognostic marker in cancer research, reflecting the complex interplay between the immune system and tumorigenesis. Elevated LMR has been associated with better prognosis in various malignancies, suggesting a potential role as a favorable prognostic indicator. The LMR's predictive value is attributed to the dynamic interaction between lymphocytes, key effectors of anti-tumor immunity and monocytes, which can exhibit pro-tumorigenic or antitumorigenic activities. High LMR is generally indicative of a robust immune response, suppressing tumor progression and enhancing the overall anticancer defense mechanisms.^{187,188} Two

$$\text{Lymphocyte to monocyte ratio (LMR)} = \frac{\text{Lymphocyte count}}{\text{Monocyte count}}$$

FIGURE 4 Calculation of the lymphocyte to monocyte ratio (LMR).

meta-analyses showed an association between high pretreatment LMR levels and improved overall survival and disease-free survival for pancreatic cancer (HR=0.68, 95% CI=0.58–0.80; HR=0.55, 95% CI=0.31–0.96)¹⁸⁷ and colorectal cancer (HR=0.57, 95% CI=0.52–0.62; HR=0.77, 95% CI=0.70–0.84).¹⁸⁸ Conversely, a reduced LMR value may signify compromised immune system, allowing tumor manifestation and progression. Numerous meta-analyses across different types of cancer reported an inverse association between LMR and worse overall survival, for example, glioma (HR=1.35, 95% CI=1.13–1.61),¹⁸⁹ lung cancer (HR=1.61, 95% CI=1.45–1.79),¹⁹⁰ esophageal squamous cell carcinoma (HR=0.67, 95% CI=0.58–0.78),¹⁹¹ gastric cancer (HR=0.66, 95% CI=0.54–0.82),¹⁹² and rectal cancer (HR=1.57, 95% CI=1.29–1.90).¹⁹³ Finally, a low LMR, but not a high LMR, was often inversely correlated with complete pathologic remission rate (complete absence of cancer cells in tissue after treatment).^{189–193} A review by Gu et al.¹⁹⁴ provides a useful overview. However, the cited meta-analyses were more recently published. Pretreatment LMR cutoff values between 2.8 and 4.6 indicate high heterogeneity between studies, patients, and types of cancer.^{187,189,192,195} Therefore, there is no generalized cutoff value.

6.3 | Findings from the use of LMR in periodontology

The correlation between LMR and periodontitis remains largely unexplored, but such a relationship could provide valuable insights into systemic inflammation and contribute to the diagnosis and prognostic evaluation of periodontitis. Only one study by the group of Mishra et al.¹³⁸ investigated LMR in periodontitis patients and healthy controls. There were no significant differences in age and gender distribution between the groups. The major outcome of the study revealed a significant lower LMR values (7.26 vs 9.31) in patients diagnosed with generalized stage III grade C periodontitis. Furthermore, LMR is significantly negative related with PPD and CAL. ROC analysis yielded cutoff values of ≤ 7.16 in predicting the risk of periodontitis. Based on these cutoff values, the OR of having stage III grade C periodontitis was 4.9327 with each 0.1 decrease in LMR. The predictive validity of LMR, as indicated by the area under the curve, was moderately valid by 0.654. Logistic regression analysis demonstrated that age but not gender and BMI is a significant predictor of differences in LMR. Finally, this study highlights that the diagnostic accuracy of LMR was 70% with a sensitivity of 70% and a specificity of 68%. A limited number of studies have explored the reference values for LMR as described above, with findings indicating cutoff values lower than those reported in the study by

Mishra et al.¹³⁸ These cutoff values in young Indian periodontitis patients¹³⁸ were different from the study accomplished on Chinese young adults and the predictive validity of the leukocyte ratios was also higher than in a Chinese population.⁹¹

The variation in cutoff values indicates the need for expanded research across different ethnical groups. Consequently, the reduced LMR observed in periodontitis patients, as reported by Mishra et al.,¹³⁸ may potentially serve as a prospective biomarker in elucidating the connection between periodontitis and other systemic diseases. Nonetheless, it is essential to consider that systemic diseases might also impact LMR which should be considered in predicting periodontitis.

7 | PLATELET TO LYMPHOCYTE RATIO

7.1 | The basis of PLR

The PLR is a hematological parameter derived from a standard full blood count. It is calculated by dividing the platelet count by the lymphocyte count (both are measured in cell number/ μL , Figure 5). This ratio is emerging as a significant marker in various clinical settings, especially in the context of inflammation, in relation to cancer and cardiovascular diseases.^{35–38} Furthermore, PLR exhibits greater predictive capability because of its high sensitivity and specificity compared to the sole use of either platelet or lymphocyte counts.⁴⁰ The importance of PLR is based on its ability to reflect the balance between thrombotic risk and immune response. An elevated PLR can indicate a prothrombotic state and/or a suppressed immune response, which is relevant in various pathological conditions. In cardiovascular conditions, PLR is being studied as a potential marker for the severity and prognosis of diseases like CAD.⁴⁰

7.2 | The use of PLR in cancer

PLR has emerged as a potential prognostic marker in cancer, reflecting the intricate interplay between pro-tumorigenic and antitumorigenic components of the immune system. The underlying mechanisms involve the role of platelets in promoting tumor-associated inflammation, angiogenesis, and metastasis, while lymphocytes play a critical role in antitumor immune responses. To date, a large number of reviews and meta-analyses have been published on the relationship between PLR and different types of cancer. Elevated PLR values are commonly observed across various types of cancer and have been associated with adverse clinical outcomes, including advanced disease stages and reduced overall survival (HR=1.45, 95% CI=1.31–1.61), as described in a systematic review and meta-analysis by Li et al.¹⁹⁶ Therefore, PLR has been widely accepted as an useful prognostic factor for, that is, lung cancer,¹⁹⁷ colorectal cancer,¹⁹⁸ esophageal cancer,¹⁹⁹ and oral cancer.²⁰⁰ However, the utility of PLR as a universal prognostic marker requires more validation across different types of

$$\text{Platelet to lymphocyte ratio (PLR)} = \frac{\text{Platelet count}}{\text{Lymphocyte count}}$$

FIGURE 5 Calculation of the platelet to lymphocyte ratio (PLR).

cancer and stages. High PLR levels of >150 are discussed as such a value, but have not been established yet.¹⁹⁶ In contrast, to the proposed cutoff value for PLR in cancer, there is no cutoff value defined in other diseases and studies indicate that average PLR values vary across different racial backgrounds and different age groups.^{90,91,153,173,196,201,202}

7.3 | Findings from the use of PLR in periodontology

PLR in relationship to periodontal diseases has not been sufficiently addressed in the literature.¹⁷³ Both lymphocyte and platelet levels may be increased as a response to periodontal pathogens.⁸⁶ It can be presumed that after periodontal treatment, the levels respond to it with a decrease.^{68,74} PLR is valued for its simplicity, cost-effectiveness, and accessibility, as it can easily be calculated from routine blood tests. However, its interpretation must be contextualized within the broader clinical picture, as it can be influenced by various factors like infection, systemic inflammation, and hematological disorders.⁴⁰ The combination of PLR and NLR has been identified as effective in reflecting the inflammatory response and is considered as prognostic marker and predictor of systemic diseases. These indices correlate with elevated levels of pro-inflammatory mediators, attesting to a proinflammatory status.²⁰³⁻²⁰⁵

Some of the studies published so far have failed to show an association between PLR and periodontitis. The largest GAgP study based on a Chinese population by Lu et al.⁹¹ which has already been discussed in the paragraph on NLR, did not find differences between patients and controls (periodontitis: mean PLR=132 vs healthy: mean PLR=126). The authors suggested that in patients diagnosed with GAgP, the functional activation of platelets may be of greater clinical significance than the numerical count.

These results were confirmed by Mishra et al.¹³⁸ The authors analyzed the PLR which was in contrast to the NLR not associated with severe periodontitis (periodontitis: mean PLR=144 vs healthy: mean PLR=134, $p=0.574$). Furthermore, PLR was not associated with most of the recorded periodontal parameters.

The same study group published a further study with a larger study population with controversial results. While absolute platelet counts (periodontitis: 278 vs healthy: 266) were not significantly higher in the periodontitis group, absolute lymphocyte counts (periodontitis: 1.93 vs healthy: 2.2) were significantly lower. This resulted in a significantly different PLR of 136 in patients with generalized stage III grade C periodontitis compared to 124 in healthy individuals. ROC yielded cutoff values of $\text{PLR} > 126$ in discriminating patients with periodontitis from healthy individuals. Based on the

cutoff values, multiple logistic regression analysis reported a lower but significant association of periodontitis with PLR (OR=2.16, 95% CI=1.56–3.01) after adjusting for oral hygiene habits, BMI, and total WBC count. Nevertheless, the area under the curve for PLR was only 0.576 and therefore distinctly lower than NLR or SII. Furthermore, the accuracy of both NLR and SII were found to be superior to PLR since PLR exhibits higher sensitivity (64%), specificity (53%), and diagnostic accuracy (59%). As a result, PLR did not improve predictive quality and accuracy of generalized stage III grade C periodontitis diagnosis.¹³⁷

Stronger evidence supporting the hypothesis that periodontitis is associated with PLR was published by Acharya et al.⁹⁰ This study analyzed PLR before and after anti-infective periodontal therapy. The included study population and the limitations of the study were discussed above in the NLR part. After 1 month, the 30 treated chronic periodontitis patients showed a significant reduction of PLR from 121 to 80. Before treatment, PLR correlated positively with PPD (not CAL; PPD: $r=0.1762$, $t=1.1740$, $p=0.2469$). However, after successful treatment, PPD and CAL correlated negatively (PPD: $r=-0.0612$, $t=-0.4023$, $p=0.6894$; CAL: $r=-0.1578$, $t=-1.0481$, $p=0.3005$). Furthermore, the included healthy controls had a PLR of 112. That means PLR increases in a periodontal inflammation and a therapeutic intervention had a remarkable influence on PLR.

Another interesting study was published by Torrungruang et al.¹⁴¹ including diabetics and periodontitis patients. This cross-sectional study investigated the relationship between different glycemic status, PLR, and periodontitis in a Thai population. It benefited from its robust sample size of 2036 participants. The study design, the inclusion criteria, and the results between the association of periodontitis and type 2 diabetes are shown above in this review. Between no/mild, moderate, and severe periodontitis patients' smaller differences were observed but not statistically significant. In comparison to subjects with nonsevere periodontitis (encompassing both no/mild and moderate cases), patients with severe periodontitis demonstrated a significantly lower PLR ($p=0.015$). Furthermore, PLR decreased with significantly worsening glycemic status. When controlling for the severity of periodontitis, PLR was significant negatively associated with diabetes ($p=0.007$). A possible association of periodontitis with diabetes through the PLR was found to be significant. Analyzing the single components of the PLR revealed a reverse relationship of these components in diabetes or periodontitis. The rather high increase of the lymphocyte counts seems to be of greater importance than the minor decrease in the platelet number. These results were in contrast to the findings by Mishra et al.^{137,138} Potential reasons for this discrepancy could include variations in the study design, the high heterogeneity of the study population (age, gender, and smoking habits), and in blood cell counts in both studies. While the authors mentioned the smoking status, they did not discuss the effects on PLR. The study's cross-sectional design precludes the elucidation of temporal and longitudinal associations among periodontitis, glycemic status, and in between PLR. The authors concluded, that PLR

is an important risk indicator and highly reverse dose-dependent in patients with/without diabetes and periodontitis.¹⁴¹

PLR values presented in these studies are in line with those documented in Korean,¹⁵³ Chinese,⁹¹ and Nigerian patients.²⁰¹ However, they are notably higher compared to studies from India.^{90,202} This discrepancy may be attributed to regional variations or the inclusion of a younger age group. A recent meta-analysis that included four^{90,91,137,141} out of five studies¹³⁸ found a mean PLR increase of 1.83 in periodontitis patients compared to control groups, but the result was not statistically significant. One of the studies that included diabetic patients had to be excluded since it had a disproportionate influence on the statistical significance.¹⁴¹ After its exclusion, the results showed a much lower heterogeneity. Notably, 25% of the participants in this study exhibited impaired glucose tolerance or type 2 diabetes mellitus, contrasting with other studies investigating PLR that did not include patients with systemic diseases. This exclusion, as suggested by Almäşan et al.,¹⁷³ was necessary because it resulted in a more homogeneous health profile which enhances the validity of the meta-analysis. However, the authors concluded that PLR is not a good single systemic inflammation biomarker for severe periodontitis. More studies are needed to verify the existing results.

8 | PLATELET DISTRIBUTION WIDTH

8.1 | The basis of PDW

Larger platelets, characterized by an increased granular content, indicate the potential for a rapid aggregation with collagen. Further, it indicates elevated thromboxane A2 levels and increased expression of glycoprotein Ib and IIb/IIIa receptors compared with smaller platelets.^{206,207} These findings show that mean platelet volume (MPV) and PDW may be influenced by many inflammatory and cardiovascular risk factors.^{144,208} Figure 6 illustrates how DNI is calculated. A study by Zhan et al.¹⁶⁹ examined gingival biopsies using immunohistochemistry and electron microscopy. They observed a reduction in platelet size in patients with GAgP. Weak negative associations between platelet size and periodontal parameters were detected ($p \leq 0.025$). Platelet aggregates and adhesion to the endothelium and leukocytes were shown in venules and connective tissues of gingival biopsies. Platelet large cell ratio increased after periodontal therapy ($p \leq 0.038$). The authors concluded from these results that the reduced platelet size was due to the consumption of large platelets at sites of periodontal inflammation. Additionally, in a study addressing platelet volume indices among patients with CAD and acute myocardial infarction, Khandekar et al.²⁰⁹ concluded from the results that MPV and PDW levels are elevated in patients with myocardial infarction and angina pectoris.

FIGURE 6 Calculation of the platelet distribution width (PDW).

$$\text{Platelet distribution width (PDW)} = \frac{\text{Standard deviation of platelet volume}}{\text{Mean platelet volume}} \times 100$$

8.2 | The use of PDW in cancer

PDW has been investigated as a potential biomarker in cancer research, reflecting alterations in platelet size and heterogeneity. The specific mechanisms underlying PDW variations in cancer remain complex, involving interactions between platelets and the tumor microenvironment. Studies suggest a nuanced relationship, with both increased and decreased PDW values that were reported in various types of cancer.^{210,211} Elevated PDW levels have been associated with certain types of cancer, that is, breast cancer,²¹² laryngeal cancer,²¹³ and colorectal cancer.²¹⁴ A meta-analysis by Xia et al.²¹¹ demonstrated strong evidence for high pretreatment PDW levels in association with poor advanced prognosis. High levels of PDW were related to poor overall survival (HR=1.54, 95% CI=1.18–2.00), especially for pharyngolaryngeal (HR=3.06, 95% CI=1.68–5.57) and breast cancer (HR=1.21, 95% CI=1.07–1.36). While PDW shows promise as a diagnostic and prognostic marker, its utility is not universally consistent across all cancer types. Therefore, a precise PDW cutoff value for every cancer or a general cutoff value has not been found yet.

8.3 | Findings from the use of PDW in periodontology

Two studies evaluated PDW in periodontitis patients. Temelli et al.¹³⁹ included 77 periodontitis patients with and without CAD in a cross-sectional design. In one out of four groups, a significant difference in PDW could be detected. The level of PDW was significantly higher in the group with both CAD and periodontitis compared with the CAD group without periodontitis. It has to be considered that the small sample size ($n=20$ in each group) could be a confounder. This association between periodontitis and elevated PDW is further corroborated by statistically significant correlations between PDW and periodontal inflamed surface area (PISA, correlation coefficient=0.24, $p=0.036$), respectively, CAL (correlation coefficient=0.243, $p=0.033$). Evidence of prothrombotic activation in relation to PDW and periodontitis was also shown in this study. These important findings should be given attention since the authors reported for the first time the connection between CAD and periodontitis through markers such as PISA, MPV, and PDW. The implication that PDW may serve as a valuable prognostic biomarker in patients with cardiovascular disease should be integrated into future research identifying the linkages between these two diseases.

The second study was published by Mutthineni et al.¹⁴⁴ The authors included an Indian population which is notably limited by a small sample size, encompassing 25 healthy individuals, 25 patients with moderate, and 25 with severe periodontitis. The mean PDW

levels showed slight but not significant differences compared to healthy (10.51), moderate (10.61), and severe (10.87) periodontitis. Both studies conclude that PDW can be used as simple, practical, and cost-effective systemic biomarker for periodontitis. However, there is currently too little evidence for a possible association.

9 | PLATELETCRIT

9.1 | The basis of PCT

PCT serves as an analytical index that offers insights into the aggregated mass of platelets. There are two ways in which PCT can be calculated, both options are shown in Figure 7.²¹⁵ MPV constitutes a component of PCT but can also be used alone as a biomarker in various inflammatory diseases.²¹⁶ Studies present divergent findings concerning the correlation between MPV and systemic inflammation, documenting either a positive or negative association.^{216,217} Moreover, Ekici et al.²¹⁸ reported a robust association between MPV values and the angiographic severity of CAD. PCT levels fluctuate within the scope of 0.22%–0.24%, making the evaluation of this metric a valuable tool for enhancing the precision of inflammation and the diagnosis of an elevated inflammatory event.²¹⁵ Additionally, PCT has been validated as a dependable marker for diagnostic and therapeutic management of several diseases.^{219,220} Growing evidence confirms that platelet indices, including PCT, disclose significant associations with vascular risk factors.²²¹ A retrospective study conducted by Aslan et al.²²² that incorporated 230 patients with more than 50% stenosis of the carotid artery, observed statistically elevated PCT levels in these patients. Furthermore, the authors suggested that PCT could predict long-term adverse outcomes and has the potential to be an independent predictive marker for long-term mortality. Şahin et al.²²³ concluded that PCT serves as an indicator of the numbers of platelets/μl. This deduction was based on their observation that PCT levels were elevated in patients suffering from pulmonary tuberculosis compared to those afflicted with pneumonia. A further investigation indicated a robust association between elevated PCT levels and both saphenous vein disease and slow coronary flow.²²⁴

9.2 | The use of PCT in cancer

A paucity of studies has reported on findings regarding PCT across different types of cancer, which may indicate a complex relationship

Plateletcrit (PCT)=	$\frac{\text{Platelet count} \times \text{Mean platelet volume}}{10,000}$
	$\frac{\text{Platelet count}}{\text{Total blood volume}} \times 100$

FIGURE 7 Calculation of the plateletcrit (PCT).

between PCT and tumorigenesis. Studies with elevated PCT levels have been associated with certain malignancies, suggesting potential connections to tumor-related inflammation, angiogenesis, and platelet activation, that is, in lung cancer,^{225,226} colorectal cancer,^{227,228} and breast cancer.²²⁹ Hur et al.²²⁶ described a PCT of >0.2755% as factors for overall survival and disease-free survival that predicts a poor prognosis for lung cancer, showing hazard ratios of more than 4.18 (95% CI=1.54–11.34) and 4.07 (95% CI=1.52–10.94), respectively. Zhu et al.²²⁷ demonstrated that PCT levels of colorectal cancer patients were associated with tumor size and TNM stages. In addition, another study showed a PCT level of 0.26% in colorectal cancer patients in contrast to 0.22% in healthy controls.²²⁸ Therefore, elevated PCT levels in individuals who were systemically healthy could indicate an increased susceptibility to systemic diseases. However, conflicting reports also highlight decreased PCT in some cancer studies,^{230,231} indicating potential alterations in platelet production and turnover. The underlying mechanisms maintaining PCT variations in cancer remain intricate and involve interactions between platelets and the tumor microenvironment. While PCT holds promise as a diagnostic and prognostic marker but its utility is not demonstrated yet to be universally usable for all types of cancer.

9.3 | Findings from the use of PCT in periodontology

Two studies investigated the PCT in periodontitis patients. Ustaoglu et al.¹⁴⁵ evaluated the PCT in 57 stage III periodontitis patients and 57 healthy controls. Unfortunately, grading, extent, and distribution were not described in this study. Smokers were excluded as smoking was considered a confounder and no significant differences in age and gender between the study groups were detected. MPV was significantly higher in the periodontitis group, platelet counts were higher in the periodontitis group but the difference was not statistically significant. As a result, PCT was found to be significantly elevated in the periodontitis group (periodontitis: mean PCT=0.223%, healthy controls: mean PCT=0.196%). Additionally, PCT was positively associated to periodontal clinical parameters such as PPD, CAL, and BOP. These data offer a more precise understanding of platelet mass and activity in periodontal disease. However, the limitation of this study is a small sample size and a cross-sectional study design.

The second study which investigated the association between PCT and periodontitis was published by Mutthineni et al.,¹⁴⁴ which was conducted on an Indian population. It is constrained due to its relatively small sample size. Included were 25 healthy, 25 moderate, and 25 severe periodontitis patients. The study did not account for variables such as platelet disorders and the race or gender of the patients, which are factors with additional influence. The mean PCT levels were 0.19% in healthy individuals, 0.3% in those with moderate, and 0.42% in cases with severe periodontitis. As indicated by ANOVA with post hoc Games-Howell testing, significant differences in PCT levels were observed from healthy to diseased individuals. This was confirmed by one-sample t-test showing for healthy and severe periodontitis

significant differences. The chronic inflammatory response in periodontitis leads to a tendency for platelet aggregation and to activation, resulting in alterations in platelet size, shape, and number. These changes in platelet indices substantiate their reliability as biomarkers for evaluating both periodontal and various inflammatory diseases.

10 | SYSTEMIC IMMUNE INFLAMMATION INDEX

10.1 | The basis of SII

SII is a novel, good, and stable marker, reflecting both immune response and systemic inflammation at low costs, making it a useful indicator for clinical applications.^{232–234} This index was developed by Hu et al.²³² and integrates the analysis of neutrophils, platelets, and lymphocyte counts. Figure 8 illustrates the calculation of the DNI. SII has no universally acknowledged cutoff value, with limited research exploring reference values in healthy adults. Luo et al.²³⁵ identified a reference value of $334.0 \times 10^9/L$ (range: $142–804 \times 10^9/L$) in a large multicenter study of a Chinese population. Correspondingly, Fei et al.²³⁶ determined a reference interval for SII in an indigenous Chinese population to be $190.5–760.9 \times 10^9/L$. Additionally, a longitudinal population-based study by Fest et al.²³⁷ in the Netherlands reported an average SII value of $459 \times 10^9/L$. Furthermore, in a recent study investigating the association between SII and psoriasis, it was suggested that a cutoff value of $578.8 \times 10^9/L$ could indicate psoriasis activation.²³⁸ Additionally, a large-scale US study with a 20-year-follow-up including 42875 adults showed that SII levels of $>655 \times 10^9/L$ had higher all-cause mortality and cardiovascular mortality than those participants with SII levels $<335 \times 10^9/L$.²³⁹

10.2 | The use of SII in cancer

To date, a large number of reviews and meta-analyses have been published on the relationship between SII and different types of cancer. Elevated pretreatment SII levels have been observed in various kinds of cancer, reflecting a systemic inflammatory response and an imbalance in the immune milieu. Increased SII values have been associated with poor prognosis in several malignancies, indicating a potential association with tumor aggressiveness and systemic inflammatory conditions. The underlying mechanism involves the role of platelets and neutrophils in promoting tumor-associated inflammation, angiogenesis, and immune evasion, while decreased lymphocyte counts contribute to compromised antitumor immune responses. Therefore, SII has been widely accepted as a useful prognostic factor which has been presented in meta-analysis for head and neck cancer (HR for poorer overall survival = 2.09, 95% CI = 1.62–2.70; cutoff

value $\geq 520 \times 10^9/L$),²⁴⁰ breast cancers (HR for poorer overall survival = 2.12, 95% CI = 1.61–2.79; cutoff value $>600 \times 10^9/L$),²⁴¹ lung cancer (HR for poorer overall survival = 1.52, 95% CI = 1.15–2.00; cutoff value $\geq 700 \times 10^9/L$),²⁴² pancreatic cancer (HR for poorer overall survival = 1.55, 95% CI = 1.34–1.78; cutoff value $\geq 900 \times 10^9/L$),²⁴³ and gastric cancer (HR for poorer overall survival = 1.40, 95% CI = 1.08–1.81; cutoff value $\geq 600 \times 10^9/L$).²⁴⁴ A recent study by Nøst et al.²⁴⁵ used a prospective UK biobank cohort of 442 115 participants to investigate a possible association between SII, NLR, PLR, and LMR aiming to assess the risks of 17 cancer types by estimation of the specific hazard ratios. The authors observed a positive risk association for seven out of 17 cancers with SII, NLR, PLR, and a negative association with LMR. SII exhibited the strongest associations with lung and colorectal cancer risk. In conclusion, the elevated risk observed in the year preceding diagnosis may signify a systemic immune reaction to an existing but asymptomatic cancer. SII could serve as a biomarker for the risk of cancer incidence, offering the potential for early disease detection in the final year preceding clinical diagnosis. However, the utility of SII as a universal prognostic marker requires further validation across different types of cancer and stages because cutoff values varied widely in studies and meta-analyses.

10.3 | Findings from the use of SII in periodontology

In patients with rheumatoid arthritis, Liu et al.²⁴⁶ observed a nonlinear association to SII. Based on this finding, two recent studies investigated the hypothesis that a similar nonlinear relationship between SII and periodontitis may exist,^{137,149} because lower neutrophil recruitment in periodontal tissue is associated with significant bone loss as demonstrated by Hajishengallis.²⁴⁷

Periodontitis can be regarded as a model of low-grade systemic inflammation that exhibits similar pathophysiology as in rheumatoid arthritis. SII also is used for various systemic diseases such as diabetes mellitus,²⁴⁸ CAD,^{44,249} hypertension,²⁵⁰ rheumatoid arthritis,^{246,251} psoriasis,²⁵² and psoriatic arthritis.²⁵³ Thus, SII may serve as a potential indicator of systemic inflammatory response in patients in both periodontitis as well as the systemic diseases listed above.

A cross-sectional study by Cao et al.¹⁴⁹ included a large population of 10301 US adults based on three cycles of survey data obtained from the National Health and Nutrition Examination Survey (NHANES) 2009–2014. The NHANES is a comprehensive multistage, stratified, clustered probability sampling research initiative to assess the health and nutritional landscape of the US civilian population.²⁵⁴ The individuals underwent a full-mouth periodontal examination and the SII was categorized into five levels: $\log_2(\text{SII})$: ≤ 8.21 , $>8.21–8.81$, $>8.81–9.42$, $>9.42–9.75$, and >9.75 . Statistical comparisons among these levels revealed significant variations in numerous parameters

FIGURE 8 Calculation of the systemic immune inflammation index (SII).

$$\text{Systemic immune inflammation index (SII)} = \frac{\text{Neutrophil count} \times \text{Platelet count}}{\text{Lymphocyte count}}$$

encompassing average age, gender, ethnicity, marital status, smoking habit, obesity rates, diabetes prevalence, hypertension rates, mean CAL, mean PPD, number of sites PPD ≥ 4 mm, number of sites CAL ≥ 3 or 5 mm, and the prevalence of periodontitis. The association between SII and periodontitis demonstrates a J-shaped curve (p for nonlinearity < 0.001), with an inflection point value of $\log_2(\text{SII})$ at 8.66 (Figure 9). When $\log_2(\text{SII})$ is ≤ 8.66 , each unit increment in $\log_2(\text{SII})$ reduces the risk of moderate to severe periodontitis by 17% (OR=0.83, 95% CI=0.69–0.999). However, post this threshold ($\log_2(\text{SII}) > 8.66$), the risk amplifies by 19% for each unit increase (OR=1.19, 95% CI=1.02–1.38). Interestingly, these individuals with moderate to severe periodontitis with an SII beyond the inflection point had lower SII values compared to no/mild periodontitis patients at $\log_2(\text{SII}) \leq 8.66$. Yet, for those with $\log_2(\text{SII}) > 8.66$, the SII values increased, indicating heightened host immune activity. An explanation for this could be that the immune responses strongly vary between the different occurrences of periodontitis ranging from moderate to severe.²⁵⁵

A preceding investigation established a similar but inverse U-shaped curve between SII and the prognosis of gastric cancer.²⁵⁶ Therefore, integrating anti-inflammatory therapies alongside conventional periodontal therapy^{257,258} might be particularly advantageous for patients with $\log_2(\text{SII})$ values of > 8.66 . On the other hand, stimulating the immune mechanism during periodontal therapy could prove to be beneficial for those with $\log_2(\text{SII})$ values of ≤ 8.66 . Additionally, non-Hispanic Whites showed a J-shaped SII and periodontitis association, while both Mexican Americans and non-Hispanic Blacks showcased a linear association. This divergence might arise from inherent ethnical differences in inflammatory response and genetic predispositions.²⁵⁹

SII was significantly higher in periodontitis patients ($724 \times 10^9/\text{L}$) compared to the periodontally healthy group ($538 \times 10^9/\text{L}$). ROC yielded cutoff values of > 591 and a sensitivity of 81%, a specificity of 77%, and a diagnostic accuracy of 79%. Thus, SII was highly associated with severe periodontitis in young adults after adjustments (OR=11.86, 95% CI=7.99–17.59). The SII exhibited reasonable predictive accuracy for the identification of severe periodontitis in young adults and may offer insights for disease diagnosis and therapeutic interventions. Through pairwise comparison, it was observed that the SII was not statistically distinct from the NLR but both were superior when compared to PLR.

The observed discrepancies of SII values between the studies including periodontitis and other inflammatory diseases may also be attributable to the type of automated blood analyzer and the differences in ethnicity, a factor that requires consideration in future research. As a result, SII could be used as an adjunctive diagnostic tool in conjunction with standard clinical assessments for the identification and monitoring of patients with severe periodontitis. However, more studies are needed to verify the present results.

11 | RED BLOOD CELL DISTRIBUTION WIDTH

11.1 | The basis of RDW

In this review, RDW was selected because it is a robust, independent diagnostic, and prognostic indicator for various diseases. RDW quantifies the variation in the size of erythrocytes. It is usually

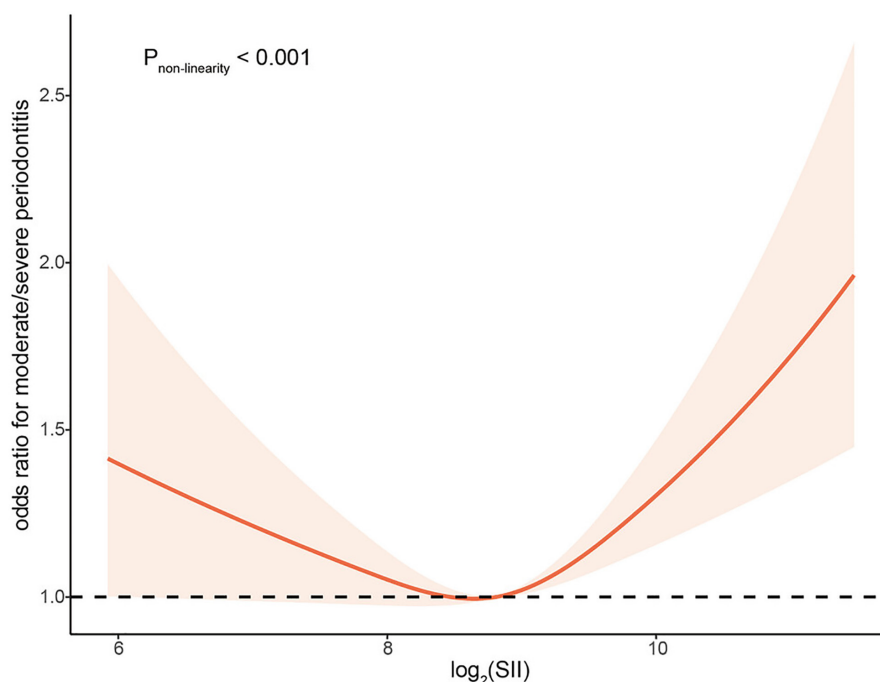


FIGURE 9 The relationship between systemic immune inflammation index (SII) and moderate/severe periodontitis follows a J-shaped curve. Figure was published by Cao et al.¹⁴⁹ and reprinted here with editorial permission.

FIGURE 10 Calculation of the red blood cell distribution width (RDW).

$$\text{Red blood cell distribution width (RDW)} = \frac{\text{Standard deviation red blood cell volume}}{\text{Mean red blood cell volume}} \times 100$$

expressed as a percentage, is calculated as part of a standard full blood test, and is relatively inexpensive. It is a coefficient of variation of red blood cell volume and its calculation is shown in Figure 10.²⁶⁰ MCV is the average volume of individual red blood cells. The standard deviation in this context measures how much the sizes of the erythrocytes vary around this mean volume. A higher RDW value indicates a greater variation in size among the erythrocytes in the sample, which is termed anisocytosis. This can be indicative of various medical conditions such as early detection of iron deficiency and differentiating iron-deficiency states, in which the RDW level is increased. Nevertheless, RDW may be normal in anemia of chronic disease.^{261,262} However, several investigators have observed that while RDW may be elevated in patients with iron-deficiency anemia compared to those with anemia of chronic disease, it demonstrates limited efficacy in distinguishing between these two conditions.^{263,264}

Normal RDW values typically range between 11% and 15%.^{260,265} RDW is often used in conjunction with other hematological measurements, like the previously discussed parameters, to provide a more comprehensive understanding of hematological disorders and the overall health of the erythrocyte's population. Studies demonstrated that RDW is a predictor of adverse outcomes in patients with heart failure, CAD, stroke, hypertension, and as a novel marker for erythropoiesis.²⁶⁶⁻²⁶⁹ Therefore, RDW is an accepted prognostic index for cardiovascular diseases.^{269,270}

11.2 | The use of RDW in cancer

RDW has been investigated as a potential biomarker for different kinds of cancer, indicating potential diagnostic and prognostic significance. The link between increased RDW and cancer may be attributed to the inflammatory and oxidative stress responses commonly associated with malignancies, influencing erythropoiesis and red blood cell morphology. Additionally, cancer-related anemia, characterized by altered red blood cell dynamics, can contribute to elevated RDW values. Several systematic reviews and meta-analyses reported an independent association between elevated RDW and poorer outcomes in cancer patients, emphasizing its potential as a prognostic indicator. Meta-analyses showed an association between high pretreatment RDW levels and worse overall survival in breast cancer (HR=2.12, 95% CI=1.47-3.08),²⁷¹ glioma (HR=1.40, 95% CI=1.13-1.74),²⁷² lung cancer (HR=1.55, 95% CI=1.26-1.92),²⁷³ esophageal cancer (RDW cutoff value >13%, HR=1.45, 95% CI=1.13-1.76),²⁷⁴ gastric cancer (RDW cutoff value >14%, HR=1.79, 95% CI=1.21-2.66),²⁷⁵ colorectal cancer (HR=1.99, 95% CI=1.59-2.49),²⁷⁶ and urological cancer (HR=1.52, 95% CI=1.27-1.82).²⁷⁷ The review by Wang et al.²⁷⁸ provides a good overview. The authors summarize that high pretreatment RDW levels with cutoff values >14% or >15% are associated with poor survival outcomes

in various malignancies. The use of RDW as a stand-alone marker for cancer diagnosis or prognosis requires further validation because most of different types of cancer lead to controversial results.

11.3 | Findings from the use of RDW in periodontology

RDW is one of the most frequently examined systemic indices in periodontitis patients. Bhattacharya et al.¹³¹ and Sridharan et al.¹⁴⁸ demonstrated a significant higher RDW level in periodontitis patients compared to the healthy controls. Furthermore, Sridharan et al.¹⁴⁸ evaluated RDW in 40 hypertensive and 40 nonhypertensive patients with and without periodontitis which were also described above. This study demonstrated that both hypertension and periodontitis independently influence RDW. Furthermore, the study showed that age was significantly related to RDW, but not gender. The combination of periodontitis and systemic hypertension leads to a substantial increase in RDW. Regarding mean CAL, PPD, plaque index, gingival index (as dependent variables), and RDW, statistically significant association for all were demonstrated. These findings also suggest a potential cumulative impact of periodontitis on RDW in hypertensive patients with periodontitis. As a result, it is imperative to underscore rigorous treatment of periodontitis in patients with hypertension, as this could be pivotal in averting detrimental cardiovascular consequences.^{279,280} This was confirmed by Bhattacharya et al.¹³¹ in an Indian population, where RDW was found to be significantly higher in periodontitis patients.

The remaining four studies did not find an association. Anand et al.¹⁴⁶ investigated the relationship between 64 GAgP patients and 58 healthy controls by analysis of the erythrocyte count, hemoglobin levels, and the RDW. As a confounder, there was a significant difference between the two groups concerning smoking habits. However, after adjusting for variables like age, gender, smoking, and BMI through logistic regression analysis, a significant association was identified between GAgP and decreased erythrocyte counts but not for RDW.

Previous findings suggested an improvement of erythrocyte count and hemoglobin post periodontal treatment in anemic patients. This leads to the hypothesis that untreated periodontitis might play a role in reducing total erythrocyte counts.²⁸¹ Studies have shown that patients with GAgP often exhibit a systemic inflammatory response by elevated serum levels of proinflammatory cytokines.^{282,283} This systemic immune response in GAgP could probably explain the observed decrease in erythrocyte counts and hemoglobin levels. Conversely, while the mean RDW value for patients with GAgP was marginally higher than that of the control group (15.27% compared to 15.16%), this difference lacked statistical significance. It is important to note that the demographic features of the sampled

group, encompassing socioeconomic status, tobacco and alcohol consumption patterns, dietary and oral care habits, might diverge from general population.

A study by Ustaoglu et al.¹⁴⁵ evaluated RDW in 57 stage III periodontitis patients and 57 healthy controls. The study design is described above in this review. There were no statistically significant differences between periodontitis patients and healthy controls with a RDW value of 14.6 and 15.2, respectively. Consequently, no association was found between RDW and periodontal clinical parameters. These findings confirm the results of a previous study by Anand et al.¹⁴⁶

One study evaluated RDW in periodontitis and nonperiodontitis patients with and without CAD. Temelli et al.¹³⁹ included 77 patients in a cross-sectional design. The fact that nonperiodontitis patients are gingivitis patients with a reduced periodontium should be considered when interpreting the results. Significant elevated levels of RDW were observed in the group with periodontitis (without CAD) relative to the group without both periodontitis and CAD, but the sample size was small ($n=21$ vs $n=16$). Additionally, a significant positive association was observed between PPD and RDW in the two groups with and without periodontitis and without CAD. This observed associations may suggest that the presence of periodontitis and its inflammatory response could lead to modifications in the size of peripheral blood cells, thereby conferring a heightened susceptibility to cardiovascular diseases, as discussed above in this review addressing platelets. Therefore, a study by López et al.¹⁴⁷ is of importance. 16 years old periodontitis patients with CAL ≥ 3 mm (mean 4.1% of sites per person) and 16 years old healthy controls were included ($n=87$ vs $n=73$) based on a Chilean population. The RDW was not significantly deviated between periodontitis patients (14.40%) and healthy controls (14.38%). Even a sub-analysis of the periodontal parameters could not find any correlation. This implies that the inflammatory load of periodontitis in young patients fails to significantly impact RDW. As a conclusion, the age of patients should be more considered in studies. This conclusion is supported by a recent meta-analysis including four^{139,145,146,148} out of six studies presented in the actual review. Mean RDW higher by 0.1 in the periodontitis group compared to the control group was found, but lacking statistical significance.¹⁷³

In this review, the majority of studies did not yield statistically significant evidence to confirm an association between RDW and periodontitis, as the findings were heterogeneous and characterized by conflicting results regarding the direction of this association.

12 | LIMITATIONS OF STUDIES RELATED TO SYSTEMIC INFLAMMATION INDICES IN PERIODONTITIS

There are several limitations of the reviewed studies such as study design, region, sample size, classification of disease and health, age, gender, plaque score, smoking status, systemic disease as well as time between blood collection and analysis.

The designs of nearly all studies showed weaknesses that led to a low level of evidence in the results for these indices in periodontitis. The observational design of the studies just permits to identify associations.

Only one study, conducted by Acharya et al.,⁹⁰ evaluated the impact of periodontal treatment on NLR as well as PLR and observed a significant reduction in their posttreatment values. Nearly all studies were performed in Asia, only one study was carried out in the USA and another one was from Chile. No study has yet been conducted in Europe. This suggests that the outcomes could potentially exhibit variations attributable to racial differences, as well as regional disparities within the same ethnical group. Another limitation was the small sample size, more than half of the discussed studies included less than 150 participants.

The classification of periodontitis differed between studies;^{52,130,132,136} in addition, authors used different criteria to identify the disease as opposed to official classifications. Furthermore, studies worked with different severity stages of periodontitis. The selection of periodontitis and healthy participants was inconsistent as well as the criteria for periodontal health. Also, exclusion criteria of systemic diseases differed between studies. Participants were often recruited from a single outpatient department, for example, department of periodontology, internal medicine, or cardiology.

A limited number of studies did not elaborate on the potential effects of specific sociodemographic factors such as education, occupation, and socioeconomic status on blood cell ratios and periodontal conditions. Adult individuals more likely exhibit multimorbidity. In 50% of periodontitis patients, comorbidity occurs.^{284,285} In these concurrent inflammatory conditions and additional influential factors are more likely present in adult compared to adolescents. Consequently, comparisons between young patients with periodontitis and healthy controls are likely less impacted by confounding factors. It is reasonable to anticipate that differences in blood parameters and inflammation indices between individuals with and without periodontitis would be more obvious among younger subjects. Only one study by López et al.,¹⁴⁷ compared general hematological values in adolescents based on their periodontal status.

A study on a South Korean population¹⁵³ and one in a Chinese Han population²⁸⁶ demonstrated a positive association between NLR and factors such as age and gender in systemically healthy adults. In contrast, a study in an Indian population observed no significant differences in blood leukocyte ratios relative to age.²⁰² Therefore, the potential influence of age must be taken into account when considering blood cell ratios as predictors for the manifestation and progression of severe periodontitis. Just a limited number of studies matched the groups for age and gender.

This review should also acknowledge that individuals with periodontitis often have poor dental care, leading to an increased plaque accumulation, which in turn may amplify the extent of bacteremia which have been reported to occur transiently, that is, after oral examination and most likely several times a day.^{13,14} The recruitment

of leukocytes, especially polymorphonuclear neutrophils, intensifies the further recruitment of neutrophils in a positive feedback loop during episodes of bacteremia in periodontitis or when lipopolysaccharides infiltrate the systemic circulation.¹³ Consequently, poor oral hygiene practices may likely influence different inflammation indices. Only a few studies considered this aspect and assessed the plaque score as well.^{133,137}

A recent systematic review and meta-analysis investigated the impact of smoking on periodontitis, revealing that smoking exacerbates periodontitis.²⁸⁷ Utilizing an innovative artificial intelligence-based network analysis, the authors identified systemic multimorbidity clusters in individuals with periodontitis and examined factors that may affect the severity of these clusters. They reported that arthritis, hypertension, and obesity had the most significant influence on multimorbidity clusters in subjects with periodontitis. Furthermore, diabetes was found to be more prevalent among those who had increased CAL. A subsequent study indicated that in adults with severe periodontitis, the smoking status affected the clustering patterns of diabetes and cancer.²⁸⁴ This is confirmed by a recent study that classifies demographic data, lifestyle factors, systemic diseases, and periodontitis into different clusters and demonstrated an overlap of the clusters. Therefore, it can be assumed that there is an overlap in pathophysiology which leads to the suggestion, that periodontitis can be regarded as a part of multimorbidity, manifesting as a systemic disease that concurrently affects certain patients.²⁸⁵ In conclusion, periodontitis, systemic diseases, and the other factors listed above may affect inflammation indices.^{284,285}

Furthermore, the duration between blood sample collection and analysis is deemed critical, as the composition of blood cells may undergo alterations or cells may be destroyed upon the time lapse between these procedures.^{153,288,289} Only few studies reported exact times between sampling and analysis of maximum of 30 min. This time frame is recommended by several previous studies.²⁹⁰ Finally, a blood cell analyzer from the Company Sysmex Corporation (Kobe, Japan) was often used for blood cell analysis. However, different analyzers and measurement techniques influences the outcomes of the results of the blood cell parameters.

In adult study populations, high variations in blood parameters are to be expected. In some studies, even as elevated described, values did not exceed normal reference values even considering that the range of normal values is based of more than 10000 people which possibly exhibit morbidities.¹³ However, a challenge in analyzing hematological values in adults with periodontitis is their potential to be influenced by a range of factors beyond periodontal disease. Adolescents with periodontitis tend to represent a more homogeneous group, less impacted by other latent infectious or inflammatory factors. Therefore, investigations including adults exhibit a higher complexity. If the hemogram of adolescents with periodontitis deviates from the norm reference, it could more convincingly be attributed to periodontal status rather than being a coincidental finding. Nevertheless, we need to address the (older) adult population with inflammatory risks.

13 | CONCLUSIONS AND OUTLOOK

Periodontitis is mainly quantified based on the severity and extent of attachment loss and/or PPD, in addition with BOP. This includes signs of the manifestations of past disease like attachment and bone loss, offering minimum insight into current activity of the disease. To assess present and future disease activity, local and systemic inflammation indices are predestined as tools for precise detection and quantification and for monitoring the risk of future development of periodontitis. Furthermore, inflammation indices are possible parameters to evaluate the impact of periodontitis on systemic health and may provide a tool to quantify the influence of periodontitis on systemic diseases and vice versa.

This is the first review that summarizes current scientific evidence and provides an insight on the possible link between periodontal disease and systemic inflammation indices that are used in cancer diagnosis, monitoring, and management. The great advantage of the discussed systemic indices is that they are based on frequently used blood analysis in daily clinical practice that are used worldwide. They are easy to obtain, fast, cheap, and reliable and thus accessible even for patients residing in low- and middle-income countries. A draw of a tube of blood is standard and routine globally.

Evidence exists for an association between the systemic indices NLR, PLR, PCT, LMR, DNI, and SII and periodontitis, but for RDW and PDW, there was only weak evidence. However, there were weaknesses in methodological quality of the presented and discussed studies. One single blood index in predicting severe periodontitis hardly seems sufficient. On the other hand, the evidences described in this review suggest that periodontitis should be defined as inflammatory systemic disease since it clearly affects the blood inflammation indices NLR, PLR, PCT, LMR, DNI, and SII similarly to other systemic diseases.

The following recommendations should be considered for future studies²⁹¹:

First, studies need to be performed including larger populations and in different continents like Europe or Africa in order to evaluate their global validity. The 2017 classification of periodontitis for these studies should be used more consistently.^{1,52} Furthermore, confounders such as age (as young as possible for low inflammaging), gender, smoking status, and racial matched cohorts should be taken account for. It would be useful if studies including more periodontal inflammation indices such as PISA, dentogingival epithelial surface area, periodontal epithelial surface area, and also more current systemic indices such as Extended Inflammation Parameter.²⁹²⁻²⁹⁴

In addition, the evaluation of the combination of different indices may reflect the balance between host immune and inflammatory conditions more precisely since more components of the immune response would be integrated.

Second, standardization and validation of sampling methods, storage conditions, and analytical techniques, along with examiner calibration are crucial to provide more reliability and clinical applicability of the methods.

Third, the establishment of a causal relationship between inflammation indices and periodontitis is not feasible using only a

cross-sectional study design. Consequently, longitudinal multicenter studies are required. These studies should monitor the long-term status of chronic inflammation at different time points pre- and posttreatment. In addition, these studies may determine whether these findings actually illustrate the relationship between periodontitis and both local and systemic inflammation indices, based on the previously mentioned inclusion criteria.

Fourth, a comprehensive investigation of the underlying biological mechanisms of the link between periodontitis and elevated inflammation indices is essential. In patients with concurrent periodontitis and comorbidities, inflammation indices may reflect the combined effects of periodontitis and systemic diseases. Therefore, it is crucial to consider potential confounders such as systemic conditions and diseases that may influence these values. However, these observations could indicate that inflammation indices might serve as link between periodontal and systemic inflammatory diseases. In particular, to date, no study has been conducted in periodontitis patients with cancer in which the inflammation indices and their changes during therapy were examined.

Interventional studies are required to substantiate possible associations. This will help to elucidate a possible causal bidirectional relation between periodontitis and local as well as systemic inflammation indices. The understanding of the biological mechanisms and principles that determine this complex interplay could support substantial advancements in personalized diagnostics, prognostics, and therapeutic management. Inflammation indices may serve as prognostic markers for predicting future destructive events and assessing the efficacy of treatments at a systemic level. Additionally, standardized use of inflammatory markers may facilitate uniform periodontal diagnosis with severity staging and grading. The development and application of biological tools for diagnostics and the assessment of treatment outcomes represents a key step to the growing medicalization of periodontology.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during this study.

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