Original Article

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in chronic periodontitis before and after nonsurgical therapy

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Abstract:

Background: Various biomarkers have been evaluated for understanding the systemic inflammatory response (SIR) to periodontitis. Hematological markers have been reported to be useful biomarkers in a variety of diseases, including periodontal diseases. The role of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in periodontitis and their possible role in the SIR are not extensively documented. Therefore, this study assessed NLR and PLR in chronic periodontitis (CP) patients before and after periodontal treatment, which to the best of knowledge has not been reported in the literature. **Materials and Methods:** Sixty participants were grouped as systemically and periodontally healthy (H) (n = 30) and with CP (n = 30). Plaque index, gingival index, probing pocket depth, clinical attachment loss, leukocyte counts, platelet (PLT) counts, NLR, and PLR were estimated at baseline and also after treatment in the CP group. NLR was calculated as total neutrophil count/absolute lymphocyte count, and PLR was calculated as total PLT count/absolute lymphocyte count. The data were statistically analyzed. **Results:** Periodontal parameters differed significantly between groups H and CP at baseline and posttreatment. A pair-wise comparison of NLR and PLR between CP patients at baseline and posttreatment was significant. Correlation analyses were not remarkable. Receiver operating characteristics analyses provided significant NLR and PLR predictive cutoff values to differentiate between CP patients at baseline and posttreatment. **Conclusion:** NLR and PLR may serve as potential biomarkers of the SIR to CP to bridge the association between periodontal and systemic conditions.

Key words:

Blood platelets, chronic periodontitis, dental, lymphocytes, neutrophils, scaling

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INTRODUCTION

Chronic periodontitis (CP) is described as an infectious disease resulting in the inflammation of the supporting structures of the teeth with connective tissue attachment loss and alveolar bone loss.[1] Inflammation is the driving phenomenon in CP. The inflammatory cells have an important role in the aggravation or resolution of CP. The role of neutrophils in the innate inflammatory response,[2] lymphocytes in adaptive immunity[3,4] is known. Platelets (PLT) deliver important mediators and sustain a local inflammatory response.[5] Leukocytes and PLT may be elevated in numbers as a response to periodontal pathogens[6] and are likely to decrease after periodontal treatment.[7,8] Changes in peripheral blood parameters have been reported in periodontal diseases and are associated with a systemic inflammatory response (SIR).[9-13] These include white blood cells (WBCs), red blood cells, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red-cell distribution width, PLT, mean platelet volume (MPV), and platelet large cell ratio index (PLCRi).

It is understood that neutrophils and lymphocytes are key players in inflammation and immune responses. PLT have important functions (other than in blood clotting mechanisms) in inflammation because of their involvement in the formation of PLT-leukocyte aggregate (by expressing PLT P-selectin), mediating T-cell immune responses,

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producing a variety of pro-inflammatory cytokines, as well as synchronizing innate and adaptive immunity.[14] For example, to assess PLT function, MPV is obtained with routine blood counts in automated hemograms. MPV and MPV/PLT is considered a reliable biomarker in inflammatory conditions.[15,16] The PLCRi is also a dependable estimator, in conjunction with PLT volume indices of diseases such as hypertension, atherosclerosis, and diabetes.[17]

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are additions to the list of the aforementioned markers. NLR and PLR are calculated from complete blood count with differential. It is an economical, simple to acquire, and convenient to perform laboratory test. NLR is considered to mirror a balance between the innate and adaptive immune mechanisms.[18] Pro-inflammatory cytokines may be increased if NLR is elevated.[19-21] PLR is a useful parameter for the SIR[22] and contributes to clinical symptoms. A combination of NLR and PLR are effective markers reflecting the inflammatory response which are also considered prognostic markers or predictors of systemic diseases and may be associated with increased levels of pro-inflammatory mediators resulting in a heightened inflammatory status.[23-33] Hence, it is hypothesized that NLR-PLR variation has a negative impact in disease. This aspect of NLR and PLR with regard to periodontal diseases has not been addressed extensively in the literature.

To the best of knowledge, NLR and PLR have not been evaluated as a systemic marker of periodontal disease before and after scaling and root planing (SRP). The aim of this study was to estimate NLR and PLR in CP before and after SRP to evaluate their possible role as a marker of periodontal disease.

MATERIALS AND METHODS

Sixty volunteers (healthy individuals and patients visiting our institution and associated hospital) were recruited for this study after an ethical clearance was obtained from the Institution's Ethical Committee. A written informed consent was obtained from all participants, and the study was in accordance with the World Medical Association Declaration of Helsinki.

Inclusion criteria

age between 18 and 55 years; CP defined as the presence of at least 20 natural teeth with generalized (i.e., >30% of the sites examined) probing pocket depths (PPD) of ≥4 mm and clinical attachment level (CAL) of ≥2 mm (stent as reference); positive for bleeding on probing; radiographic evidence of bone loss.

Exclusion criteria

Patients with systemic diseases; known allergies; tobacco users; pregnant, lactating women, women in menopause; patients with immunosuppressed conditions such as systemic lupus erythematosus and rheumatoid arthritis; periodontal therapy in the last 6 months; antibiotic and/or anti-inflammatory drug regimen before the study; and teeth with calculus or cervical caries or without a clinical tooth crown (CAL not measured).

A medical and dental history was recorded, and the participants were subjected to a periodontal examination. On the basis of their plaque index (PII),[34] gingival index (GI),[35] PPD, CAL, and radiographic (long cone, paralleling technique) evidence of bone loss, the participants were grouped as thirty healthy individuals (H) and thirty CP patients. PPD and CAL assessments were conducted with a UNC-15 periodontal probe (Hu-Friedy® Manufacturing Inc., Chicago, IL, USA). Measurements were made at six different sites of each tooth present: mesiobuccal, midbuccal, distobuccal, midlingual, distolingual, and lingual. The CP patients were grouped as CP-BL (CP at baseline) and CP-PT (CP posttreatment). The mean value of the measurements was taken into consideration for each patient.

Blood was drawn and collected from the antecubital fossa of the arm using a 21 gauge syringe by a hematology laboratory staff into a vacutainer incrementally in small volumes. The WBCs and PLT were estimated using pocH-100i automated hematology analyzer (Sysmex Corporation, Kobe, Japan), and the differential count was calculated.

Calculation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

NLR was calculated as total neutrophil count/absolute lymphocyte count, and PLR was calculated as total PLT count/absolute lymphocyte count, i.e., NLR was calculated as the ratio of neutrophils to lymphocytes and PLR was calculated as the ratio of PLT to lymphocytes.

All the participants were provided oral hygiene instructions at baseline. The CP patients received SRP with the use of an ultrasonic scaler (Electromedical Systems EMS, Nyon, Switzerland), manual instruments (Hu-Friedy® Manufacturing Inc., Chicago, IL, USA) under local anesthesia when required, over two appointments 1 week apart. The individuals were provided oral hygiene instructions during each appointment. Analgesics were prescribed. None of the patients were prescribed antibiotics or anti-inflammatory drugs. All the parameters were recorded for this group after 1 month.

Statistical analysis

No participants were lost to follow-up. The data were expressed as mean and standard deviation (SD) and statistically analyzed. The normality of the distribution was assessed using the Kolmogorov–Smirnov/Shapiro–Wilk test. Based on this, the independent and dependent *t*-tests were applied for comparing the groups at baseline and after 1 month. The correlation of NLR and PLR with the other variables was estimated by the Karl Pearson's test. Receiver operating characteristics (ROC) was applied to estimate the cutoff point values for NLR and PLR. *P* value was set at ≤0.05. The IBM-SPSS (IBM-SPSS, Armonk, NY, USA) software was employed for the analyses.

RESULTS

The age in years of Group H ($n = 30$) was 39.6 ± 0.96 (mean ± SD) and the CP group ($n = 30$) was 45.08 ± 3.62 with each group comprising 15 female and 15 male participants. Table 1 depicts the mean ± SD of all the variables of the healthy group.

The clinical parameters and hematological variables of CP-BL when compared with CP-PT are depicted in Tables 2 and 3.

NLR showed statistically significant correlations with PLT (negatively in health, positively in CP-BL, CP-PT), with lymphocytes (negatively in health) and neutrophils (positively in health, CP-BL, CP-PT); whereas PLR showed statistically significant correlations with PLT (positively in health, CP-BL, CP-PT) and with lymphocytes (negatively in health). Although NLR in CP-BL correlated positively with PlI, PPD, and CAL (except GI), in CP-PT correlated negatively with GI, PPD, and CAL (except PlI); PLR in CP-BL correlated positively with PlI, GI, and PPD (except CAL), in CP-PT correlated negatively with PlI, PPD, and CAL (except GI), these were not statistically significant [Supplementary Tables 4-7].

The significant cutoff point by ROC for CP-BL versus CP-PT [Supplementary Figure 1] for NLR was 1.546 (sensitivity = 0.756, specificity = 0.756, area under curve = 77.5%) and PLR was 80.205 (sensitivity = 0.867, specificity = 0.622, area under curve = 80.6%).

Table 1: Mean±standard deviation of the variables in the healthy group

Variables	*H*
PlI	0.841±0.27
GI	0.584±0.35
PPD	0
CAL	0
Neutrophils	4402.15±1449.87
Lymphocytes	2570.51±877.18
Platelets	281.93±99.04
NLR	1.86±0.81
PLR	111.6±37.36

PlI – Plaque Index; GI – Gingival Index; PPD – Probing pocket depths; CAL – Clinical attachment level; NLR – Neutrophil-to-lymphocyte ratio; PLR – Platelet-to-Lymphocyte Ratio; *H* – Health

DISCUSSION

It is known that changes in peripheral blood parameters are useful in disease prognosis of many diseases. NLR and PLR are believed to be reliable markers of the inflammatory response. This investigation was an attempt to study the association of NLR and PLR in CP. The NLR and PLR can provide a reflection of the initial innate immune mechanisms (involving cells such as the neutrophils and macrophages providing a nonspecific response) which trigger the adaptive immune mechanisms (T-cell/B-cell mediated and stimulated in part by PLT) resulting in periodontal destruction. If NLR and PLR is higher, the inflammatory response will be more severe.[36] A study[37] involving periodontitis compared MPV/PLT, PLCRi, NLR, and PLR in dogs (which were healthy, with periodontal disease and with oropharyngeal tumors) and concluded no significant associations between these parameters and periodontitis. It will be difficult to draw comparisons with our study as there is hardly any available literature addressing NLR and PLR together as potential systemic biomarkers of CP in humans before and after SRP. Only one study by Torrungruang *et al*.[38] examined NLR and PLR in CP and diabetes in humans and reported an increased NLR with more severe periodontitis, but PLR decreased with more severe periodontitis and with worsening glycemic status. However, both these parameters have been assessed as systemic inflammatory indices in other diseases such as Mediterranean fever, prosthetic valve thrombosis, and especially, carcinomas.[39-42]

The average NLR in healthy Caucasians controls has been shown to be 2.15 which is higher when compared with other races (for example, 1.76 in Non-Hispanic of African lineage),[18] and to our sample of healthy controls which was Asian Indian,

Table 2: Comparison of baseline and posttreatment clinical parameters in chronic periodontitis groups at baseline and posttreatment by dependent *t*-test

Variables	Time points	Mean±SD	Mean difference	SD difference	Percentage of change	Paired *t*	*P*
PlI	BL	1.86±0.29	0.88	0.37	47.56	15.9303	0.0001*
	PT	0.97±0.22					
GI	BL	1.81±0.30	0.57	0.32	31.61	11.9044	0.0001*
	PT	1.24±0.28					
PPD	BL	6.83±0.92	0.99	0.63	14.54	10.5212	0.0001*
	PT	5.83±0.86					
CAL	BL	7.76±1.16	1.25	0.89	16.08	9.4432	0.0001*
	PT	6.51±0.91					

*$P \leq 0.05$. PlI – Plaque Index; GI – Gingival Index; PPD – Probing pocket depth; CAL – Clinical attachment loss; BL – Baseline; PT – Posttreatment; SD – Standard deviation

Table 3: Comparison of baseline and posttreatment platelets', lymphocytes', and neutrophils' counts in chronic periodontitis group by dependent *t*-test

Variables	Time points	Mean±SD	Mean difference	SD difference	Percentage of change	Paired *t*	*P*
Platelets	BL	320.33±108.11	82.13	58.75	25.64	9.3777	0.0001*
	PT	238.20±69.34					
Lymphocytes	BL	3008.51±679.26	265.42	583.94	8.82	3.0491	0.0039*
	PT	2743.09±721.48					
Neutrophils	BL	5111.71±1529.96	750.58	577.18	14.68	8.7235	0.0001*
	PT	4361.13±1326.30					
NLR	BL	1.90±0.50	0.42	0.49	22.08	5.7190	0.0001*
	PT	1.48±0.40					
PLR	BL	121.08±43.58	41.08	39.11	33.93	7.0476	0.0001*
	PT	80.00±26.50					

*$P \leq 0.05$. NLR – Neutrophil-to-lymphocyte ratio; PLR – Platelet-to-lymphocyte ratio; BL – Baseline; PT – Posttreatment; SD – Standard deviation

which means that NLR values may have a racial predilection. The average PLR in healthy controls has been reported to be approximately 103, lower compared with patients with cancerous lesions.[43] Our study had lower PLR in health when compared with periodontitis, which means that PLR increases in a local inflammatory disease. It was interesting to note that NLR and PLR were lower in the CP-PT group as compared with the healthy group in the present evaluation, which may imply that there is a marked decrease due to therapeutic intervention. The ROC cutoff point values for NLR (1.546) and PLR (80.204) indicate that these measurements may be useful as a prognostic marker of CP.

NLR and PLR are considered better markers of inflammation as they have been found to be more effective predictors than just absolute leukocyte and PLT counts.[43,44] Reports suggest that SIR is associated with neutrophilia and relative lymphocytopenia in systemic diseases.[45,46] We did not note lymphocytopenia in our sample of systemically healthy CP patients. This may mean that CP and the additional presence of a systemic disease might better reflect SIR, as indicated by a study which analyzed only NLR and other mediators in CP and systemic diseases/conditions such as diabetes, hyperlipidemia, obesity, and menopause.[47]

CONCLUSION

Within the limitations of this investigation, we suggest that NLR (the elevation of which may disrupt the balance between pro- and anti-inflammatory mediators in disease) and PLR (which is a marker of systemic inflammation) be included as potential parameters in studies exploring the oral-systemic axis to provide clarity to the impact CP may have on systemic health. NLR and PLR may be useful in stratifying CP patients and probably develop a grading or scoring system such as the Glasgow prognostic score (used in carcinomas) in conjunction with other inflammatory mediators to predict incidence and treatment outcomes.

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Conflicts of interest
There are no conflicts of interest.

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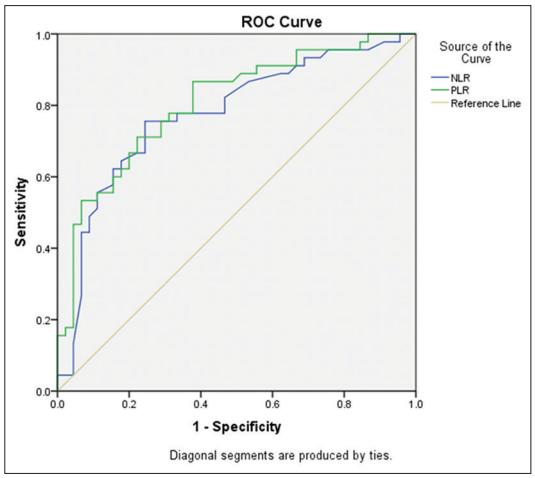

Supplementary Figure 1: Receiver operating characteristics for NLR and PLR for CP-BL versus CP-PT

Area Under the Curve (AUC)

Test result variable (s)	Area (%)
NLR	77.55
PLR	80.6

NLR: Sensitivity=0.756, Specificity=0.756, Cutoff point=1.5460,
PLR: Sensitivity=0.867, Specificity=0.622, Cutoff point=80.2050.
NLR: Neutrophil-to-lymphocyte ratio PLR: Platelet-to-lymphocyte ratio,
BL – Baseline; PT – Posttreatment; CP – Chronic periodontitis

Supplementary Table 4: Correlation of neutrophil-to-lymphocyte ratio as a total, in health and in chronic periodontitis at baseline with other parameters by Karl Pearson's correlation coefficient method

Variables	Total NLR			NLR in *H*			NLR in CP-BL		
	r	*t*	*P*	*r*	*t*	*P*	*r*	*t*	*P*
Platelets	−0.0581	−0.5459	0.5865	−0.3176	−2.1964	0.0335*	0.3164	2.1870	0.0342*
Lymphocytes	−0.3321	−3.3031	0.0014*	−0.5641	−4.4802	0.0001*	0.0959	0.6315	0.5311
Neutrophils	0.4326	4.5017	0.0001*	0.3709	2.6187	0.0121*	0.5900	4.7923	0.0001*
PII	0.0531	0.4990	0.6190	−0.0177	−0.1162	0.9080	0.2079	1.3940	0.1705
GI	−0.0007	−0.0062	0.9951	−0.0353	−0.2316	0.8179	−0.0718	−0.4720	0.6393
PPD	0.0403	0.3788	0.7058	-	-	-	0.1762	1.1740	0.2469
CAL	0.0434	0.4072	0.6849	-	-	-	0.1888	1.2605	0.2143

*P<0.05. PII – Plaque Index; GI – Gingival Index; PPD – Probing pocket depth; CAL – Clinical attachment loss; NLR – Neutrophil-to-lymphocyte ratio; BL – Baseline; PT – Posttreatment; *H* – Health; CP – Chronic periodontitis

Supplementary Table 5: Correlation of platelet-to-lymphocyte ratio as a total, in health and in chronic periodontitis - baseline with other parameters by Karl Pearson's correlation coefficient method

Variables	Total PLR			PLR in *H*			PLR in CP-BL		
	r	*t*	*P*	*r*	*t*	*P*	*r*	*t*	*P*
Platelets	0.5690	6.4910	0.0001*	0.3469	2.4252	0.0196*	0.7294	6.9914	0.0001*
Lymphocytes	−0.0736	−0.6919	0.4908	−0.3606	−2.5353	0.0150*	0.1619	1.0762	0.2879
Neutrophils	0.1347	1.2753	0.2055	−0.0822	−0.5406	0.5916	0.2684	1.8268	0.0747
PII	0.1929	1.8439	0.0686	0.1468	0.9734	0.3358	0.2225	1.4968	0.1417
GI	0.0828	0.7792	0.4380	−0.1143	−0.7546	0.4546	0.0238	0.1562	0.8766
PPD	0.1298	1.2284	0.2226	-	-	-	0.1048	0.6913	0.4931
CAL	0.1101	1.0389	0.3017	-	-	-	−0.0304	−0.1992	0.8431

*P<0.05. PII – Plaque Index; GI – Gingival Index; PPD – Probing pocket depth; CAL – Clinical attachment loss; PLR – Platelet-to-lymphocyte ratio; BL – Baseline; PT – Posttreatment; *H* – Health; CP – Chronic periodontitis

Supplementary Table 6: Correlation of neutrophil-to-lymphocyte ratio as a total, in health and in chronic periodontitis - posttreatment with other parameters by Karl Pearson's correlation coefficient method

Variables	Total NLR			NLR in *H*			NLR in CP-PT		
	r	*t*	*P*	*r*	*t*	*P*	*r*	*t*	*P*
Platelets	−0.0587	−0.5516	0.5826	−0.3176	−2.1964	0.0335*	0.3740	2.6444	0.0114*
Lymphocytes	−0.3380	−3.3690	0.0011*	−0.5641	−4.4802	0.0001*	0.2549	1.7288	0.0910
Neutrophils	0.4129	4.2531	0.0001*	0.3709	2.6187	0.0121*	0.6159	5.1265	0.0001*
PII	−0.0737	−0.6932	0.4900	−0.0177	−0.1162	0.9080	0.0505	0.3318	0.7417
GI	−0.2417	−2.3371	0.0217*	−0.0353	−0.2316	0.8179	−0.0976	−0.6431	0.5236
PPD	−0.2854	−2.7932	0.0064*	-	-	-	−0.0276	−0.1812	0.8571
CAL	−0.2847	−2.7861	0.0065*	-	-	-	−0.0140	−0.0916	0.9275

*$P<0.05$. PII – Plaque Index; GI – Gingival Index; PPD – Probing pocket depth; CAL – Clinical attachment loss; NLR – Neutrophil-to-lymphocyte ratio; BL – Baseline; PT – Posttreatment; *H* – Health; CP – Chronic periodontitis

Supplementary Table 7: Correlation of platelet-to-lymphocyte ratio as a total, in health and in chronic periodontitis - posttreatment with other parameters by Karl Pearson's correlation coefficient method

Variables	Total PLR			PLR in *H*			PLR in CP-PT		
	r	*t*	*P*	*r*	*t*	*P*	*r*	*t*	*P*
Platelets	0.5075	5.5251	0.0001*	0.3469	2.4252	0.0196*	0.6785	6.0572	0.0001*
Lymphocytes	−0.2144	−2.0591	0.0424*	−0.3606	−2.5353	0.0150*	0.1096	0.7232	0.4735
Neutrophils	0.0277	0.2603	0.7953	−0.0822	−0.5406	0.5916	0.1870	1.2480	0.2188
PII	−0.0605	−0.5684	0.5712	0.1468	0.9734	0.3358	−0.0921	−0.6066	0.5473
GI	−0.3379	−3.3678	0.0011*	−0.1143	−0.7546	0.4546	0.1126	0.7432	0.4614
PPD	−0.4398	−4.5939	0.0001*	-	-	-	−0.0612	−0.4023	0.6894
CAL	−0.4500	−4.7265	0.0001*	-	-	-	−0.1578	−1.0481	0.3005

*$P<0.05$. PII – Plaque Index; GI – Gingival Index; PPD – Probing pocket depth; CAL – Clinical attachment loss; PLR – Platelet-to-lymphocyte ratio; BL – Baseline; PT – Posttreatment; *H* – Health; CP – Chronic periodontitis