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ORIGINAL ARTICLE

Elevated neutrophil-to-lymphocyte ratio but not platelet-to-lymphocyte ratio is associated with generalized aggressive periodontitis in a Chinese population

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Abstract

Background: Host inflammatory mediators are associated with tissue destruction in patients suffering from generalized aggressive periodontitis (GAgP). However, the correlations between neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with GAgP remain unknown.

Methods: Periodontal clinical parameters, including probing depth (PD), bleeding index (BI) and attachment loss (AL) were collected from patients with GAgP and healthy controls. Complete blood cells analyses were obtained; further, NLR and PLR were calculated using neutrophil, platelet, and lymphocyte counts. Smooth curve fitting and segmented regression models were used to analyze the roles and predictive value of NLR with GAgP.

Results: In total, 505 participants from a Chinese population were recruited, including 133 healthy controls and 372 patients with GAgP. Periodontal clinical parameters, NLR, and neutrophil counts were significantly higher in patients with GAgP than the control group. Moreover, NLR was positively correlated with the risk and clinical parameters of GAgP. When NLR < 3, the risk of GAgP increased by 20.6% for each 0.1 increase in NLR, reaching saturation when NLR > 3. An increase in NLR equivalent to 1 was associated with an increase in PD, BI, and AL by 0.41 mm, 0.26, and 0.57 mm, respectively. Notably, PLR did not show obvious correlations with GAgP.

Conclusions: NLR but not PLR may be a potential marker to identify GAgP in healthy individuals, particularly in a Chinese population.

KEYWORDS
neutrophil-to-lymphocyte ratio, periodontal diseases, periodontitis, platelet-to-lymphocyte ratio

1 | INTRODUCTION

Generalized aggressive periodontitis (GAgP) is an inflammatory disease characterized by severe and rapid periodontium destruction in otherwise healthy patients.[1,2] Previous literature has highlighted the value of systemic inflammation as an important element in determining the severity of GAgP.[3,4] Neutrophils and lymphocytes are key players in inflammatory and immune responses in patients with GAgP.[5,6] Platelets are also involved in immune responses in inflamed gingivae through interactions with leukocytes.[5] In recent studies, the

neutrophil-to-lymphocyte ratio (NLR) and platelet-to-leukocyte ratio (PLR), defined as the ratio of absolute neutrophil or platelet and lymphocyte counts, have been proposed as effective biomarkers in the prognosis of several cardiovascular diseases (CVDs),[7,8] diabetes[9,10] and other inflammatory diseases.[11,12] NLR was reported to increase in patients with periodontitis and systemic diseases, for example, in the presence of hyperlipemia, NLR was higher in patients with periodontitis than those without.[13] In patients with diabetes, NLR was associated with periodontitis severity, but not glycemic status, whereas PLR was associated with both periodontitis severity and glycemic status.[14] Thus, NLR and PLR may serve as potential biomarkers of the systemic inflammatory response to chronic periodontitis, bridging the association between periodontal and systemic conditions.[15] However, there has been a lack of scientific evidence to define the roles of NLR and PLR in the assessment of patients with GAgP.

Therefore, this study aimed to analyze the correlations between NLR and PLR with clinical parameters of GAgP, and their utility in identifying patients at high risk of GAgP.

2 | MATERIALS AND METHODS

2.1 | Study population

This study is a case-control study. Patients with GAgP were recruited* from February 2010 to May 2017. The inclusion criteria for the GAgP group were based on the 1999 International Workshop for the Classification of Periodontal Diseases and Conditions[1]: (1) 16 to 35 years old; (2) presented with at least 20 functional teeth in the mouth; (3) probing depth (PD) > 5 mm and attachment loss (AL) > 3 mm in over six teeth, with radiographic evidence of alveolar bone loss, and at least three of the affected teeth were not incisors or first molars. Healthy controls were recruited from the volunteers or staff and students†. Inclusion criteria were: (1) age below 36; (2) teeth with PD ≤3 mm; and (iii) no clinical evidence of AL. Exclusion criteria of participants were: (1) pregnancy; (2) lactation period; (3) intake of antibiotics or anti-inflammatory drugs in the previous three months; (4) systemic diseases; (5) history of periodontal treatment within six months; or (6) history of orthodontic treatment. All smokers were excluded from the study to avoid potential confounding variables.

The study protocol was approved by the Ethics Committee of Peking University Health Science Center (IRB00001052-08010). All participants provided informed written consent, and data collection was performed following the principles outlined in the Declaration of Helsinki.

2.2 | Clinical examination

A comprehensive clinical examination was performed by two calibrated examiners (XW and DS). Full mouth PD and AL calculated by combined PD and gingival recession measurements were obtained at six points per tooth using a UNC-15 probe‡, excluding the third molars. Bleeding index (BI) was recorded 30 seconds after probing,[16] and the most severe sites in the buccal (labial) side and lingual (palatal) side were recorded. Ten patients with moderate-to-severe chronic periodontitis were recruited and used for calibration. The intraclass correlation coefficients (ICC) were calculated, ranging from 0.92 to 0.96 for PD and from 0.93 to 0.96 for AL.

Height and weight were measured for all participants, and body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2).

2.3 | Whole blood cell analysis and calculation of NLR and PLR

Venous blood was collected from fasted participants between 8:00 and 10:00 am. Complete blood cells analyses of blood samples in EDTA-containing tubes were performed by a calibrated Sysmex XS-1000 automated hematology analyzer§. NLR was calculated as total neutrophil count/lymphocyte count, and PLR was calculated as total platelet count/lymphocyte count.

2.4 | Data entry and statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were reported as N (%). For continuous variables group comparison, the *t* test was performed for normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. Chi-square tests were used for categorical data comparison between groups. Effect estimates including the odds ratio (OR) and corresponding 95% confidence intervals (CI) were presented. The ability of NLR in discriminating patients with GAgP from those without was assessed. To investigate if NLR might predict GAgP, a receiver operating characteristic (ROC) analysis, with its area under the

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‡ Hu-Friedy, Chicago, IL.
§ Sysmex, Kobe, Japan.

TABLE 1 The general status of patients with GAgP and healthy controls

Variables	Control group ($n = 133$) Mean ± SD/n (%)	GAgP group ($n = 372$) Mean ± SD/n (%)	P-value
Age (years)	26.77 ± 5.05	27.50 ± 5.24	0.299
Male	53 (39.85%)	152 (40.86%)	0.839
BMI (kg/m^2)	21.35 ± 2.93	22.24 ± 5.49	0.046
Mean PD (mm)	1.97 ± 0.88	4.62 ± 1.35	<0.001
Mean BI	1.31 ± 0.68	3.36 ± 0.80	<0.001
Mean AL (mm)	0.00±0.00	4.18 ± 1.84	<0.001
PLT (× 10^9/L)	229.78 ± 45.63	219.87 ± 53.57	0.686
NEUT (× 10^9/L)	3.48 ± 1.08	4.07 ± 1.48	<0.001
LYM (× 10^9/L)	1.96 ± 0.53	1.85 ± 0.50	0.068
PLR	125.82 ± 42.41	132.23 ± 45.48	0.157
NLR	1.84 ± 0.85	2.34 ± 1.11	<0.001
NLR.CS			
NLR < 2	85 (63.91%)	156 (41.94%)	<0.001
NLR ≥2, < 3	38 (28.57%)	143 (38.44%)	<0.001
NLR ≥3	10 (7.52%)	73 (19.62%)	<0.001

AL, attachment loss; BI, bleeding index; BMI, body mass index; LYM, lymphocyte count; NEUT, neutrophil count; NLR, neutrophil to lymphocyte ratio; PD, probing depth; PLR, platelet to lymphocyte ratio; PLT, platelet count.
Continuous variables of age and BMI were analyzed by Kruskal Wallis Rank Sum Test because of abnormal distribution.

curve (AUC), sensitivity and specificity were performed. AUC ranged from 0.5 to 1, with 0.5 indicating no discrimination whereas 1 represents perfect discrimination. The cutoff point was determined by the Youden index, which was calculated using the equation of sensitivity plus specificity −1 at each curve point, with the maximum value was recommended as the cutoff point. Smooth curve fitting was performed to analyze the relationships between NLR and the risk of GAgP, according to the methods described by Motulsky.[17] Segmented regression models and likelihood ratio tests were used to compare the difference between Model I and Model II, and the Bootstrap resampling method was used to analyze the threshold effect between NLR and the risk of GAgP. All data were double entered and analyzed with the SPSS software[**], R and Empower Stats software[††].

3 | RESULTS

3.1 | Study population

A total of 505 individuals from the Han race were enrolled in this study, comprising 372 patients with GAgP and 133 healthy controls (mean age was 27.50 ± 5.24 years and 26.77 ± 5.05 years, respectively). There were no significant differences in age and gender distribution between the two groups. BMI of GAgP patients was statistically higher than healthy controls, 22.24 ± 5.49 versus 21.35 ± 2.93, respectively, $P = 0.046$. Mean PD, BI, and AL in GAgP group were 4.62 ± 1.35 mm, 3.36 ± 0.80, and 4.18 ± 1.84 mm, respectively. All clinical periodontal variables in patients with GAgP were significantly higher than healthy controls ($P < 0.001$). Neutrophil count and NLR were significantly higher in the GAgP group than in the control group ([4.07 ± 1.48] × 10^9/L versus [3.48 ± 1.08] × 10^9/L, 2.34 ± 1.11 versus 1.84 ± 0.85, respectively, $P < 0.001$). There were no obvious differences in the lymphocyte count, platelet count, or PLR between the two groups. Because there is no widely accepted cutoff point for NLR, the value of NLR was subdivided into three groups. Notably, the GAgP group showed significantly higher proportions of participants in the NLR 2-3 and NLR ≥3 subgroups, $P < 0.001$ (Table 1).

3.2 | Clinical relevance of NLR and PLR in GAgP

The value of NLR was positively correlated with differences in PD, BI, and AL in patients with GAgP. An increase in one unit of NLR was associated with an increase in PD by 0.41 mm (95% CI: 0.25 to 0.56), BI by 0.26 (95% CI: 0.15 to 0.37), and AL by 0.57 mm (95% CI: 0.34 to 0.80) in patients with GAgP. Conversely, the lymphocyte counts were negatively associated with AL, whereas PLR and neutrophil

[**] IBM-SPSS, Armonk, NY.
[††] X&Y solutions, Inc. Boston, MA.

TABLE 2 The linear regression analyses for the relationship of hematological indexes with clinical parameters in patients with GAgP

	Mean PD	Mean BI	Mean AL
Variables	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
NLR	0.41 (0.25 to 0.56)*	0.26 (0.15 to 0.37)*	0.57 (0.34 to 0.80)*
PLR	0.00 (−0.00 to 0.01)	0.00 (−0.00 to 0.00)	0.00 (−0.00 to 0.01)
NEUT ($\times 10^9$/L)	0.03 (0.00 to 0.07)	0.02 (0.00 to 0.05)	0.04 (−0.01 to 0.09)
LYM ($\times 10^9$/L)	−0.21 (−0.63 to 0.21)	−0.05 (−0.23 to 0.13)	−0.56 (−1.10 to −0.02)*

AL, attachment loss; BI, bleeding index; LYM, lymphocyte count; NEUT, neutrophil count; NLR, neutrophil to lymphocyte ratio; PD, probing depth; PLR, platelet to leukocyte ratio.
*$P < 0.05$.

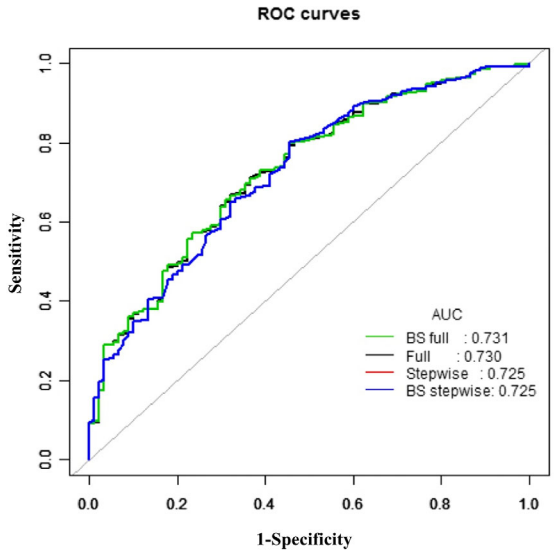

FIGURE 1 Receiver operating characteristic (ROC) analysis of NLR for GAgP. There were four curves for the NLR prediction of GAgP risk. The green curve, BS full model, AUC (area under the curve) = 0.731; the black curve, full model, AUC = 0.730; the red curve, stepwise model, AUC = 0.725; and the blue curve, BS stepwise model, AUC = 0.725. There were no significant among these models

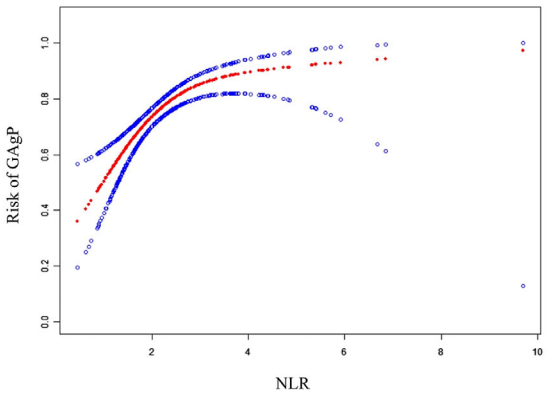

FIGURE 2 A smooth curve fitting for the relationship between NLR and the risk of GAgP. Smooth curve fitting was conducted to explore the association between NLR and the risk of GAgP. It showed a nonlinear relationship between them. The red line presents the OR value of association of NLR and GAgP, the blue lines present the 95% confidence interval

counts did not show associations with differences in clinical parameters of GAgP (Table 2).

3.3 | Association between NLR and the risk of GAgP

A ROC plot was used to evaluate the diagnostic ability of NLR in GAgP (Figure 1). There were four models used, including the BS full model, full model, stepwise model, and BS stepwise model. There were no significant differences among them. The stepwise model could be used in the analysis, which showed that AUC was 0.73, 95% CI (0.68 to 0.79). With a sensitivity of 65.6%, and specificity of 68.7%, a cutoff point of 1.92 was determined by the Youden index (Figure 1).

A saturation threshold effect of NLR with the risk of GAgP was observed by spline smoothing fitting (Figure 2). There were two methods to analyze the relationship between NLR and GAgP. Model I was a linear analysis, which showed that when NLR increases by 0.1, the risk of GAgP increased by 10.5%. Model II was a nonlinear analysis, revealing a turning point value of NLR 3 was found by segmentation regression modeling comparing NLR and the risk of GAgP. When NLR < 3, the risk of GAgP increased by 20.6% in patients for each 0.1 increase in NLR (adjusted OR = 3.06, 95% CI: 1.91 to 4.98). When the value of NLR was > 3, the OR did not increase with increasing NLR values, and reached a saturation (adjusted OR = 0.94, 95% CI: 0.56 to 1.57). The *P* value for the likelihood ratio test of the models was 0.014, demonstrating a nonlinear relationship between NLR and risk of GAgP (Table 3).

4 | DISCUSSION

The risk of GAgP increases with elevated NLR in a Chinese population, and reaches saturation when NLR has a value of 3. Importantly, elevated NLR was associated with increased clinical parameters in GAgP patients, which suggests that NLR may be a potential marker for predicting inflammation and severity of GAgP. However, there were

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TABLE 3 Threshold effect analysis of the relationship between NLR and the risk of GAgP

Models	Risk of GAgP Adjusted OR (95% CI)	*P*-value
Model I		
One line slope	2.05 (1.44 to 2.90)	0.0001
Model II		
Turning point (K)	3	
<3 slope 1	3.06 (1.91 to 4.89)	<0.0001
>3 slope 2	0.94 (0.56 to 1.57)	0.8101
Predicted at 3	2.21 (1.60 to 2.81)	
Logarithm likelihood ratio test		0.014*

Data were presented as OR (95% CI) *P*-value; Model I, linear analysis; Model II, non-linear analysis; adjusted for age, gender and BMI.

*$P < 0.05$ indicates that model II is significantly different from Model I.

no obvious differences in PLR between GAgP patients and healthy controls.

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions,[18] the forms of disease previously recognized as "chronic" or " aggressive" are now grouped as "Periodontitis," which is further characterized based on a multidimensional staging and grading system.[19] This group of patients with GAgP all belonged to Stage III or IV, and Grade C, according to the new classification.

Our results demonstrated there was a statistically significant difference in BMI between the GAgP group and healthy controls, although the BMI of all participants ranged from 18 to 28, and the difference between groups was small. Worse periodontal conditions have been reported in patients with higher BMI, and poorer response of non-surgical periodontal therapy was found in obesity patients.[20] Elevated blood neutrophils are associated with higher BMI,[21,22] and BMI positively correlated with lymphocyte percentages.[23] From our previous study, a U–shaped relationship exists between BMI and risk of GAgP and white blood cells (WBC) count. Moreover, WBC counts in patients with GAgP was lowest when the BMI value was 22 kg/m^2 after adjusting for age and gender.[24] However, limited studies report on the effect of BMI on NLR. From a study in Turkey, increased BMI led to increased WBC, lymphocyte, and neutrophil counts, but there was no significant correlation of NLR with BMI.[22] Some investigators have reported that NLR is higher in obese individuals than in control subjects with normal weight.[25] When considering the value of the NLR ratio, the possible influence of BMI should be considered.

Host immune responses determine the severity of tissue destruction during GAgP. Many studies reported elevated leukocytes counts in patients with periodontitis,[3,6,26,27] indicating that GAgP may have effects on markers of systemic inflammation, and the pathogenesis of periodontitis might lead to the increased output of neutrophils. NLR is considered a marker of systematic inflammation, because it is related to many biochemical and cellular activities, and shows correlations with inflammatory markers such as CPR.[28] NLR reflects two complementary immune pathways,[29] as neutrophils are responsible for non-specific inflammation with phagocytic and apoptotic actions, whereas lymphocytes perform adaptive immune responses.[30] In specific conditions that show an imbalance in the inflammatory cells and have a role for activated neutrophils, NLR is a strong biomarker.[31] Although NLR considers both neutrophil and lymphocyte counts, it is a more effective and stable predictor than either measurement alone,[32] which was also demonstrated in this study.

Given that racial differences in inflammatory responses have been proposed,[33] the average NLR in healthy individuals may have a racial predilection.[34] For example, in India, the mean NLR value was 1.86; whereas in South Korea, the mean NLR across all ages was 1.65, and values for individuals between 20 and 40 years old were 1.74 to 1.77.[35] In healthy Caucasian individuals, the average NLR is 2.15, and in non-Hispanic individuals of African lineage, it is 1.76.[34] In this study, all the participants were from the Han race in a Chinese population, systemically healthy, and non-smokers. The average NLR in healthy young controls in this population was 1.84, which is similar to that reported in Asian studies. A cutoff point of >1.92 was predicted to identify patients with an increased risk of GAgP. However, the sensitivity and specificity were not high; thus, more controlled studies may be required to optimize the cutoff point, improve sensitivity and specificity. Furthermore, because NLR may have racial differences, the NLR value, as a predictor for risk of and clinical parameter severity of GAgP, may be different in countries with more heterogeneous races, which may also need further investigation.

NLR can be affected by and may have a high value in predicting the prognosis of many systemic diseases. Elevated NLR in CVDs, especially in myocardial infarction and heart failure, is indicative of poor prognosis; in these studies, NLR was usually determined to be >3.[7,8,36] Increased NLR is also observed in patients with diabetes.[9] In addition, as patients with diabetics are often co-morbid with other systemic conditions, the NLR ratio can be >4.[10] NLR > 3 is associated with increased 2 years follow-up mortality in medical inpatients with multiple chronic conditions.[12] In patients with obstructive sleep apnea, for example, mean NLR values were reported from 1.61 to 4.18 by different studies.[37] Therefore, in patients with periodontitis combined with these conditions, NLR values can be reflective of periodontitis and systemic diseases. Thus, it is important to be mindful of potential confounding

systemic conditions and diseases that influence the NLR value. These findings could also suggest that NLR may be a link between periodontal diseases with systemic inflammatory diseases.

Currently, periodontal clinical examination remains the best way to monitor periodontal diseases. Periodontitis related biomarkers in blood or gingival crevicular fluids, may help to monitor periodontal conditions. The NLR ratio is easier to obtain than other peripheral blood biomarkers, which may demand more complicated laboratory tests. Furthermore, NLR is relatively inexpensive and can be afforded by most patients.

The role of platelets in inflammation has been investigated in various diseases.[38,39] Platelet size, including mean platelet volume and platelet large cell ratio, decreases in patients with GAgP, and increases after periodontal treatment[4]; however, no obvious changes of platelet counts were reported.[39] There was no significant difference in lymphocyte counts in the present study, some previous studies reported lower lymphocyte counts or percentage,[6,40] whereas one study reported higher lymphocyte counts in patients with GAgP.[41] The platelet counts and PLR did not show significant differences between patients with GAgP and healthy controls, nor did they correlate with periodontal clinical parameters. One possible reason may be that platelet activation and function may play a more important role rather than the absolute number of platelets in patients with GAgP.

Our study has several limitations. First, participants were recruited from a single outpatient department, thus selection biases should be mentioned. This study is based on the limited ethic background of study participants and more studies may help to optimize NLR cutoff point in different racial backgrounds and to determine its strengths and shortcomings. In addition, NLR increases in other conditions such as CVDs, metabolic syndrome, and smokers, and many factors can induce changes in the numbers of neutrophils and/or lymphocytes, which may complicate the use of NLR in patients with GAgP. One important strength of the present study is that this is the first report analyzing the predictive value of NLR and PLR in patients with GAgP. Besides, this is a relatively large population size for a case-control study.

5 | CONCLUSIONS

In summary, our study revealed that elevated NLR is associated with inflammation and disease severity in Chinese patients with GAgP. NLR was positively correlated with increased risk of GAgP and reaches saturation when NLR > 3. These findings indicate that NLR may be a biomarker for GAgP risk assessment in a Chinese population. Conversely, PLR values did not show similar effects. Further controlled prospective studies are needed to elucidate the potential use of NLR in identifying patients with GAgP.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have substantially contributed to conception and design of the study. Ruifang Lu, Wenjing Li, Xiane Wang, and Dong Shi have been involved in data collection; Ruifang Lu and Wenjing Li have been involved in data interpretation, drafting the manuscript. Huanxin Meng has revised the manuscript critically. All authors have approved the version to be published.

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