Original Article

Relationship between Neutrophil-to-Lymphocyte Ratio and Pulse Wave Velocity in Young Patients with Systemic Lupus Erythematosus

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Abstract

Background: The incidence of atherosclerosis-related myocardial infarction can be as much as 50-fold greater in young patients with systemic lupus erythematosus (SLE) than in age-matched controls. There are several explanations for this phenomenon, all of which result in a chronic state of low-grade inflammation. Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a useful biomarker of inflammation. Pulse wave velocity (PWV) is a reliable indicator of vascular damage and atherosclerosis. There is a paucity of data concerning the relationship between NLR and atherosclerosis as measured by PWV in patients with SLE. This study aimed to verify whether there is a positive correlation between NLR and PWV and to explore factors that influence PWV in young SLE patients.
Methods: A total of 90 female patients with SLE were enrolled in this cross-sectional investigation. Traditional and nontraditional cardiovascular risk factors were assessed on the same day that brachial-ankle PWV (baPWV) was examined. The patients were divided into three groups according to their mean baPWV values: patients whose mean baPWV value was lower than the first tertile were placed in Group 1; patients whose mean baPWV value was between the first tertile and the second tertile were placed in Group 2; and patients whose mean baPWV value was higher than the second tertile were placed in Group 3. SPSS 20.0 was used to perform all statistical analyses in this study. Both univariate linear regression and multivariate regression models were utilized to analyze the association between NLR and arterial stiffness.
Results: Systolic blood pressure, diastolic blood pressure (DBP), and triglycerides were all significantly different among Groups 1, 2, and 3 (111.90 ± 12.85 mmHg vs. 114.60 ± 12.88 mmHg vs. 129.43 ± 16.21 mmHg, $P < 0.001$; 68.77 ± 8.63 mmHg vs. 71.87 ± 9.77 mmHg vs. 82.57 ± 14.89 mmHg, $P < 0.001$; and 1.44 [0.91–2.47] mmol/L vs. 0.98 [0.78–1.26] mmol/L vs. 2.20 [0.94–3.66] mmol/L, $P = 0.030$; respectively), as were creatinine (57.50 [52.00–69.00] μmol/L vs. 55.50 [49.00–64.00] μmol/L vs. 64.00 [56.00–86.00] μmol/L, $P = 0.045$) and blood urea nitrogen (4.27 [3.79–6.22] mmol/L vs. 4.16 [3.47–4.84] mmol/L vs. 5.88 [4.04–8.19] mmol/L, $P = 0.011$). NLRs were significantly different among Groups 1, 2, and 3 (2.16 [1.56–3.42] vs. 3.12 [1.91–4.19] vs. 5.29 [2.63–7.25], $P = 0.001$). NLR, together with DBP and the SLE disease activity index, independently predicts PWV.
Conclusions: This study demonstrated that there was a positive correlation between NLR and PWV. Moreover, we found that disease activity and DBP were also positively correlated with PWV.

Key words: Arterial Stiffness; Neutrophil-to-Lymphocyte Ratio; Pulse Wave Velocity; Systemic Lupus Erythematosus

Introduction

Atherosclerosis is known to be a dynamic accumulation of oxidized cholesterol over time that is primarily driven by the immune system.[1] Both the innate and adaptive immune systems take part in this process. Similarly, systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a wide range of clinical manifestations and complications.[2] In particular, patients with SLE are prone to premature atherosclerosis. Potential explanations for the accelerated atherosclerosis observed in conjunction with SLE include a high prevalence of conventional risk factors,[3] long-term corticosteroid use,[4] and the presence

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of antiphospholipid antibodies,[5] all of which result in a chronic state of low-grade inflammation.[6] Recently, the neutrophil-to-lymphocyte ratio (NLR) was proposed as a useful biomarker of inflammation; the NLR is calculated by dividing the neutrophil count by the lymphocyte count. Pulse wave velocity (PWV) is a reliable indicator of vascular damage and atherosclerosis,[7,8] and it reflects arterial stiffness by measuring the speed of pulse wave transmission. According to Sugawara *et al*.,[9] brachial-ankle PWV (baPWV) value in healthy controls aged 19–34 years is around 950 cm/s. Previous studies have shown that NLR positively correlates with PWV in the general population.[10] However, there is a paucity of data concerning the relationship between NLR and PWV in patients with SLE. The incidence of atherosclerosis-related myocardial infarction can be as much as 50-fold greater in young patients with SLE than in age-matched controls.[11] Thus, we aimed to verify whether there is a positive correlation between NLR and PWV and to explore factors that influence PWV in young SLE patients.

Methods

Ethical approval

This cross-sectional study received approval from the ethics committee of Peking Union Medical College Hospital. All the patients provided written informed consent.

Study population

This study included 90 patients who were enrolled in the Chinese SLE Treatment and Research group (CSTAR) registry between September 2013 and July 2014. All the patients satisfied at least four of the American College of Rheumatology criteria for SLE. The exclusion criteria included the following: serious SLE activity, defined as serious damage to certain major organs, including the central nervous system, the circulatory system, the kidneys, the heart, the liver, and/or the lungs and the presence of any other autoimmune, infectious, or known cardiovascular diseases. All the participants were female and young patients who were below 35 years old. The patients were divided into three groups according to their mean baPWV values: Patients whose mean baPWV value was lower than the first tertile were placed in Group 1; patients whose mean baPWV value was between the first tertile and the second tertile were placed in Group 2; and patients whose mean baPWV value was higher than the second tertile were placed in Group 3.

Clinical examination

All participants underwent a standardized clinical examination and interview; a detailed questionnaire was used to obtain patient information, including medical history, current smoking status, and medication use. Anthropometric parameters were measured according to standardized procedures. Blood pressure was measured in millimeters of mercury (mmHg, 1 mmHg = 0.133 kPa) using an aneroid sphygmomanometer and was recorded as the mean of 2 consecutive measurements after at least 5 min of sitting. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). SLE activity was assessed using the SLE Disease Activity Index (SLEDAI). Other SLE-related parameters were also assessed, such as disease duration and courses of prednisone or other immunosuppressants.

Biochemical examination

Fasting venous blood was drawn between 8 and 10 a.m. after the patients had fasted for 14 h overnight. Within 30 min of acquisition, the plasma samples were centrifuged at 2500 $\times g$ for 20 min and were stored at −80°C for further analysis. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), creatinine (Cr), uric acid, high-sensitivity C-reactive protein, and complement 3 (C3) were evaluated using enzymatic analysis or the transmission turbidity method (Beckman Coulter AU5800; Beckman Coulter Inc., Brea, CA, USA). Estimated creatinine clearance rate (Ccr, ml·min^{-1}·1.73 m^{-2}) was measured using the Cockcroft-Gault formula. Ionic exchange high-performance liquid chromatography was used to determine glycosylated hemoglobin (HbA1c) levels (Variant II automatic analyzer, Bio-Rad Laboratories, Hercules, California, USA). Anti-ANA and anti-dsDNA antibodies were measured by line immunoassay (Euroline ANA profile assay, Euroimmun AG, Luebeck, Germany). Complete blood count was performed in an automated hematology analyzer (Sysmex XE-2100, Kobe, Japan), including a white blood cell (WBC) differential.

Measurement of pulse wave velocity

All patients fasted overnight and were asked to refrain from both caffeine intake and smoking within 4 h prior to the study visit. The baPWV was measured using an automatic device (model MB3000, M and B Electronic Instruments, Beijing, China). The baPWV was automatically calculated by dividing the distance between the two arterial recording sites by the transit time according to the formula (L/PTT), where L represents the difference between the length from the heart to the ankle and the length from the heart to the brachium, and PTT represents the pulse transit time between the brachial and tibial arterial waveforms. The mean right and left baPWV values were obtained for analysis. In addition, we excluded subjects with a low ankle-brachial index (ABI, <0.9) because indices in that range could lead to inaccurate baPWV values.

Statistical analysis

All the data analyses were performed using SPSS 20.0 (International Business Machines Corporation, Armonk, New York, USA). Normally distributed numeral variables are expressed as the mean ± standard deviation (SD), while numeral variables with skewed distributions are expressed as median (Q1–Q3). Categorical variables are expressed as percentages. Variable analysis, the Kruskal-Wallis test and the Chi-square test were utilized to compare the characteristics of the three groups. Multiple linear regression analysis was used to identify significant determinants of baPWV. The level of statistical significance was set to 0.05.

Results

Demographical and clinical characteristics of 90 female SLE patients (aged 26.0 ± 5.2 years, ranging from 14 to 34 years) are presented in Table 1. The patients were divided into three groups according to their mean baPWV values: patients in Group 1 with median mean baPWV of 973.25 cm/s; patients in Group 2 with median mean baPWV of 1104.75 cm/s; and patients in Group 3 with median mean baPWV of 1291.25 cm/s.

Systolic blood pressure, diastolic blood pressure (DBP), and TG were all significantly different among the three groups, as were CR and BUN. All the groups exhibited homogeneous BMI, fasting blood glucose, and HbA1c values, and TC, HDL-C, and LDL-C were comparable among the groups. One patient was diagnosed with type 2 diabetes and two patients in Group 2 were going through menopause. One patient in Group 3 had a history of smoking. The median SLEDAI was significantly higher in Group 3 (10.50) than those in Group 1 (4.00) and Group 2 (4.00). The WBC and neutrophil counts were significantly different among the three groups, while the lymphocyte count was comparable; therefore, the resulting NLRs were different among three groups. The percentages of positive anti-ANA and anti-dsDNA immunoassay results were not significantly different among three groups, and steroid courses and cumulative

Table 1: Characteristics of analyzed participants according to mean pulse wave velocity

Characteristics	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	Statistical values	P
Age (years), mean ± SD	24.1 ± 5.4	27.4 ± 4.8	26.4 ± 5.1	3.353*	0.040§
BMI (kg/m^2), median (Q1–Q3)	20.65 (19.50–24.70)	20.55 (18.70–22.50)	22.15 (18.70–24.20)	1.962†	0.375
SBP (mmHg), mean ± SD	111.90 ± 12.85	114.60 ± 12.88	129.43 ± 16.21	13.506*	<0.001§
DBP (mmHg), mean ± SD	68.77 ± 8.63	71.87 ± 9.77	82.57 ± 14.89	12.046*	<0.001§
FBG (mmol/L), mean ± SD	4.71 ± 0.53	4.50 ± 0.53	4.48 ± 0.54	1.318*	0.274
HbA1c (%), median (Q1–Q3)	5.35 (5.20–5.70)	5.65 (5.20–5.90)	5.30 (5.20–5.50)	4.177†	0.124
Cr (μmol/L), median (Q1–Q3)	57.50 (52.00–69.00)	55.50 (49.00–64.00)	64.00 (56.00–86.00)	6.219†	0.045§
BUN (mmol/L), median (Q1–Q3)	4.27 (3.79–6.22)	4.16 (3.47–4.84)	5.88 (4.04–8.19)	8.988†	0.011§
UA (μmol/L), mean ± SD	333.32 ± 74.18	292.22 ± 84.82	366.89 ± 158.96	5.446*	0.066
Ccr (ml·min^{-1}·1.73 m^{-2}), mean ± SD	112.71 ± 23.51	109.99 ± 24.46	98.35 ± 38.38	2.199*	0.333
TC (mmol/L), median (Q1–Q3)	3.93 (3.56–4.58)	3.68 (3.46–4.53)	4.89 (3.61–6.16)	5.024†	0.081
TG (mmol/L), median (Q1–Q3)	1.44 (0.91–2.47)	0.98 (0.78–1.26)	2.20 (0.94–3.66)	7.002†	0.030§
HDL-C (mmol/L), median (Q1–Q3)	1.12 (0.98–1.49)	1.14 (0.88–1.34)	1.28 (0.92–1.43)	0.284†	0.867
LDL-C (mmol/L), median (Q1–Q3)	2.26 (1.80–2.55)	2.20 (2.00–2.92)	2.54 (2.09–4.12)	2.987†	0.225
WBC (10^9/L), median (Q1–Q3)	4.78 (3.78–5.87)	4.95 (3.68–6.76)	7.49 (5.08–10.61)	19.196†	<0.001
NC (10^9/L), median (Q1–Q3)	3.01 (2.15–4.08)	3.48 (2.35–4.32)	5.88 (3.60–7.90)	17.189†	<0.001
LC (10^9/L), median (Q1–Q3)	1.33 (0.99–1.83)	1.06 (0.67–1.61)	1.15 (0.99–1.55)	2.083†	0.353
NLR, median (Q1–Q3)	2.16 (1.56–3.42)	3.12 (1.91–4.19)	5.29 (2.63–7.25)	13.403†	0.001§
Prednisone course (months), median (Q1–Q3)	86.50 (28.00–324.00)	132.50 (27.00–324.00)	93.50 (26.00–201.00)	0.153†	0.927
Cumulative prednisone dose (g), median (Q1–Q3)	5.48 (0.82–11.07)	4.02 (1.40–6.80)	5.90 (3.75–11.16)	2.367†	0.306
ESR (mm/h), median (Q1–Q3)	16.50 (8.00–23.00)	10.50 (6.00–20.00)	18.00 (10.00–34.00)	3.214†	0.200
IgG (g/L), mean ± SD	13.91 ± 5.55	16.57 ± 7.56	12.44 ± 5.44	2.784*	0.068
C3 (g/L), mean ± SD	0.76 ± 0.23	0.78 ± 0.22	0.69 ± 0.36	0.915*	0.405
CRP (mg/L), median (Q1–Q3)	0.55 (0.23–1.82)	0.52 (0.23–1.21)	1.19 (0.27–3.96)	1.735†	0.420
SLEDAI, median (Q1–Q3)	4.00 (2.00–8.00)	4.00 (2.00–6.00)	10.50 (4.00–13.00)	10.510†	0.005§
MMF, n (%)	14 (46.67)	3 (10.00)	13 (43.33)	11.100‡	0.004§
CTX, n (%)	11 (36.67)	12 (40.00)	19 (63.33)	5.089‡	0.079
HCQ, n (%)	25 (83.33)	24 (80.00)	26 (86.67)	0.480‡	0.787
ASA, n (%)	4 (13.33)	8 (26.66)	7 (23.33)	1.735‡	0.520
Positive anti-dsDNA, n (%)	12 (40.00)	12 (40.00)	16 (53.33)	1.440‡	0.487
Positive anti-ANA, n (%)	14 (46.67)	15 (50.00)	21 (70.00)	3.870‡	0.144

1 mmHg = 0.133 kPa. The patients were divided into three groups according to their mean baPWV values: patients whose mean baPWV value was lower than the first tertile were placed in Group 1, patients whose mean baPWV value was between the first tertile and the second tertile were placed in Group 2, and patients whose mean baPWV value was higher than the second tertile were placed in Group 3. *F value for normally distributed numeral variables; †χ^2 value for numeral variables with skewed distributions (Kruskal-Wallis test); ‡χ^2 value for categorical variables; §Corresponding P values of variables entering the multivariate analysis. SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HbA1c: Glycosylated hemoglobin; Cr: Creatinine; BUN: Blood urea nitrogen; UA: Uric acid; Ccr: Creatinine clearance rate; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; WBC: White blood cell count; NC: Neutrophil count; LC: Lymphocyte count; NLR: Neutrophil-to-lymphocyte ratio; ESR: Erythrocyte sedimentation rate; IgG: Immunoglobulin G; C3: Complement 3; CRP: C-reactive protein; SLEDAI: SLE Disease Activity Index; MMF: Mycophenolate mofetil; CTX: Cyclophosphamide usage; HCQ: Hydroxychloroquine; ASA: Aspirin; PWV: Pulse wave velocity; baPWV: Brachial-ankle PWV; ANA: Antinuclear antibody.

doses were also homogeneous. A total of 85 patients were using immunosuppressants, and over 80% of the patients were using hydroxychloroquine. Only 10.00% of the patients in Group 2 were treated with mycophenolate mofetil, which was significantly less than those in Group 1 (46.67%) and Group 3 (43.33%).

To determine the relationship between NLR and PWV, a univariate linear regression analysis was performed. As shown in Figure 1, mean PWV positively correlated with NLR (β = 0.241, P = 0.022, R^2 = 0.058). Furthermore, multiple linear regression analysis was applied to the entire study population; variables incorporated in the model are listed in Table 1 as marked on their P values, and the results of the analysis are shown in Table 2. The full list of independent predictors for PWV consisted of DBP, SLEDAI, and NLR.

Discussion

In this study, we demonstrated that there was a positive correlation between the NLR and PWV in young SLE patients. A high NLR is an indicator of systemic inflammation, and many studies have shown that the NLR is positively associated with different malignancies, such as ulcerative colitis, diabetic retinopathy, and cardiovascular disease.[12-15] It is a common knowledge that the classification of circulating WBCs exhibits certain changes during systemic inflammation, which is typically characterized by lymphopenia and neutrophilia. In SLE, lymphopenia is the most frequent WBC abnormality and is reported in up to 93% of SLE cases.[16] When the disease is active, the occurrence of lymphopenia and neutrophilia can be even higher. Moreover, lupus neutrophils typically cannot be cleared by the C1q/calreticulin/CD91-mediated apoptotic pathway,[17] which can lead to the accumulation of neutrophils.

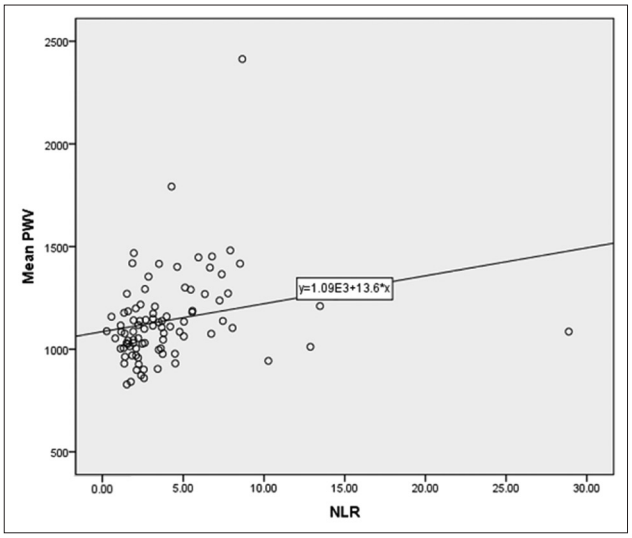

Figure 1: Correlation of mean PWV and NLR in young systemic lupus erythematosus patients (n = 90; P = 0.022, R^2 = 0.058). PWV: Pulse wave velocity; NLR: Neutrophil-to-lymphocyte ratio.

There are some mechanisms that could explain the significant relationship between NLR and arterial stiffness, as discussed below. SLE is a chronic autoimmune disease, and SLE patients are in a constant state of inflammation. Stimulated WBCs have an increased tendency to adhere to vascular endothelium, and they easily penetrate the intima, causing both capillary leukostasis and increased vascular resistance.[18-20] Additionally, stimulated WBCs release a variety of hydrolytic enzymes, cytokines, and growth factors, which can induce further vascular damage.[21,22] Particularly in SLE, patients possess a distinct granulocyte population named low-density granulocytes (LDGs);[23] these cells exhibit an enhanced capacity to synthesize pro-inflammatory cytokines, including type I interferons, and LDGs are significantly toxic to endothelial cells.[24,25] Additionally, the NLR could reflect the autonomic balance and subsequent chronic inflammation of the vascular bed. The distribution of WBC subtypes has been reported to be regulated by the autonomic nervous system because granulocytes have adrenergic receptors, whereas lymphocytes have cholinergic receptors.[26,27] Therefore, a higher NLR may indicate a higher ratio of sympathetic/parasympathetic activity. An increased sympathetic tone is positively correlated with higher rates of oxygen consumption and increased production of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha.[28,29] These cytokines play key roles in regulating vessel wall tone by affecting the release of nitric oxide and endothelin-1 in the subendothelial space.

In this study, SLEDAI was determined to be a significantly independent determinant for PWV. It has been reported that PWV observed in children and adolescents with SLE was higher than that in the controls.[30] Similarly, in a study of older patients with SLE, PWV was also increased, and the factors associated with increased PWV included disease severity in premenopausal women and age in postmenopausal

Table 2: Multivariate analysis of risk factors for arterial stiffness in systemic lupus erythematosus (adjusted R^2 = 0.424)

Factors	*B*	SE	Beta	*t*	*P*	95% *CI*	
						Lower bound	Upper bound
DBP	8.362	3.158	0.482	2.648	0.010	2.057	14.667
SLEDAI	9.558	4.072	0.242	2.347	0.022	1.428	17.687
NLR	16.738	7.220	0.220	2.318	0.024	2.323	31.152

B: Unstandardized coefficient; SE: Standard error; Beta: Standardized coefficient; *CI*: Confidence interval; DBP: Diastolic blood pressure; SLEDAI: Systemic lupus erythematosus Disease Activity Index; NLR: Neutrophil-to-lymphocyte ratio.

women.[31] Prolonged periods of immune complex-mediated manifestations associated with hypocomplementemia, such as vasculitis and glomerulonephritis, render SLE patients more prone to developing arterial stiffness.

Together with NLR and SLEDAI, there was also a positive relationship between DBP and PWV. Age and blood pressure are well-known risk factors related to PWV. A systematic review of the literature reported that age and blood pressure are significantly and independently associated with PWV in over 90% of studies. Moreover, aside from age and blood pressure, there were poor relationships between PWV and other established cardiovascular risk factors.[32] The mechanism of age-related arterial stiffness has been shown to include elastin degradation and collagen accumulation in the arterial wall.[33] However, in our study, age was not incorporated in the regression model, as the age range in our study was relatively narrow; it is also possible that the arterial wall alterations were not sufficient to be indicated by PWV measurements. Besides, DBP cannot substantially explain the difference of baPWV value among groups, for subtle DBP discrepancy might not cause such obvious difference.

There are several potential limitations of our study. First, because of the cross-sectional design of our study, our data do not directly indicate a cause-effect relationship. The association between NLR and baPWV in SLE requires further investigation via prospective studies. Second, although most of the known risk factors for atherosclerosis progression in association with NLR and baPWV in SLE were considered, we cannot definitively exclude potential confounding factors that could have possibly affected our regression models. Third, the sample size of our study was relatively small, which may contribute to the relative low R^2.

In conclusion, we demonstrated a positive correlation between NLR and PWV. Moreover, we found that disease activity and DBP also positively correlated with PWV. These results suggest that disease-induced inflammation might be a cause of increased arterial stiffness. Further research could focus on the diagnostic value of the NLR and explore whether the NLR could serve as a marker to assess subclinical atherosclerosis in young SLE patients.

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Conflicts of interest

There are no conflicts of interest.

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