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The relationship between neutrophil to lymphocyte ratio and artery stiffness in subtypes of hypertension

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Recently, neutrophil/lymphocyte ratio (NLR) has been proved to be a useful indicator of inflammation and cardiovascular risk. Brachial-ankle pulse wave velocity is an indicator for early atherosclerotic changes. It is unknown whether NLR differs in subtypes of hypertension, and little research has been performed on the relationship between NLR and arteriosclerosis in subtypes of hypertension. The purpose of this article was to investigate their relationship. A total of 217 consecutive patients with hypertension and 132 persons without hypertension were included. All hypertension patients were divided into three groups according to office blood pressure. Brachial-ankle pulse wave velocity was elevated in patients with isolated systolic hypertension, isolated diastolic hypertension, and systolic and diastolic hypertension compared with normotensive controls. NLR in patients with isolated systolic hypertension and systolic and diastolic hypertension were higher than in normotensive controls. Correlation analysis revealed a positive correlation between NLR and brachial-ankle pulse wave velocity. Multivariate linear regression analysis showed that NLR was an effective indicator for brachial-ankle pulse wave velocity.

1 | INTRODUCTION

The prevalence rate of hypertension in China is 27.2%, with rates of 7.6% for isolated systolic hypertension (ISH), 4.4% for isolated diastolic hypertension (IDH), and 7.4% for systolic-diastolic hypertension (SDH).[1] Different types of hypertension have different mechanisms and therefore distinct clinical prognoses.[2]

Since hypertension is considered an inflammatory condition, inflammatory cytokines, including C-reactive protein (CRP), as well as interleukin (IL) 6, are closely related to blood pressure (BP).[3] Increased white blood cell (WBC) count and neutrophil/lymphocyte ratio (NLR) are known risk factors for cardiovascular disease.[4–6] Furthermore, supraventricular tachycardia,[7] idiopathic dilated cardiomyopathy,[8] and right ventricular dysfunction in patients with acute inferior ST-segment elevation myocardial infarction[9] all influence NLR. Target organ damage, which consists of the heart, brain, and kidney, results from long-term hypertension and simultaneously leads to arteriosclerosis. NLR, which has been shown to be an indicator of inflammation, is widely used in cardiovascular diseases, such as supraventricular tachycardia, coronary artery disease, and after percutaneous coronary intervention.[8,10,11] One meta-analysis showed that the occurrence and reoccurrence of atrial fibrillation were significantly correlated with a high NLR.[12] In addition, an increased NLR results in more vulnerable plaque and higher risk of thrombotic diseases.[13] A follow-up investigation of 248 patients who underwent primary percutaneous coronary intervention with ST-segment elevation myocardial infarction reported that 36 patients experienced major adverse cardiovascular events.[14] The authors concluded that higher NLR and lower hemoglobin independently predicted 1-year major adverse cardiac events.[14]

Pulse wave velocity can predict central and periphery artery stiffness and is regarded as an index of artery stiffness. Brachial-ankle pulse wave velocity (baPWV) is a noninvasive method used to detect the elastic state of arteries.[15] Artery stiffness is an independently predictive factor of mortality from hypertension and incidence of coronary diseases.[16]

TABLE 1 Clinical and Biochemical Characteristics of Study Patients

Parameters	NC	SDH	IDH	ISH	*P* Value
No.	132	92	45	80	
Men, %	73 (55.30)	56 (60.86)	20 (44.44)	48 (60.00)	**.294**
Age, y	37.5 (28.00–46.00)	47.54±12.29	43.51±10.44	56.00 (36.5–72.00)	**.00**
BMI, kg/m^2	22.00 (20.00–22.75)	27.74±3.74	27.06±3.59	25.60 (23.87–28.75)	**.00**
SBP, mm Hg	113.00 (105.00–123.00)	149.00 (144.00–155.00)	135.00 (131.50–136.50)	144.00 (142.00–147.75)	**.00**
DBP, mm Hg	69.00 (63.00–76.00)	95.50 (92.00–99.75)	92.00 (90.00–94.00)	83.00 (78.00–86.00)	**.00**
WBC count, mmol/L	6.00 (5.42–6.87)	6.45 (5.60–7.50)	7.00 (6.00–8.00)	6.25 (5.23–7.30)	**.004**
Lymphocytes, mmol/L	2.10 (1.90–2.50)	2.15 (1.80–2.50)	2.20 (1.90–2.80)	1.90 (1.50–2.4)	**.006**
Neutrophils, mmol/L	3.65 (3.00–4.00)	3.85 (3.20–4.77)	3.90 (3.25–4.90)	3.95 (3.00–4.70)	**.007**
Glucose	5.00 (4.90–5.40)	5.60 (5.02–6.20)	5.50 (5.00–5.90)	5.45 (4.90–6.10)	**.000**
ApoA1	1.31 (1.17–1.48)	1.37 (1.27–1.51)	1.34 (1.20–1.45)	1.31 (1.20–1.45)	**.216**
ApoB	0.87 (0.72–1.00)	1.03 (0.87–1.21)	0.99 (0.77–1.09)	0.98 (0.80–1.14)	**.099**
Triglycerides, mmol/L	1.20 (0.96–1.86)	1.89 (1.37–2.89)	1.80 (1.15–3.39)	1.70 (1.03–2.30)	**.000**
Cholesterol, mmol/L	4.6 (4.00–5.57)	5.00 (4.52–5.75)	4.80 (4.25–5.30)	5.00 (4.40–5.48)	**.026**
HDL-C, mmol/L	1.06 (1.00–1.27)	1.05 (0.97–1.24)	1.00 (0.92–1.20)	1.02 (0.96–1.22)	.509
LDL-C, mmol/L	2.53 (2.05–3.19)	3.11 (2.75–3.54)	2.74 (2.35–3.34)	3.00 (2.62–3.58)	**.000**
Urea	4.98 (4.17-5.79)	4.89 (4.20-5.98)	5.00 (4.18-5.46)	5.09 (4.45–6.00)	.299
Creatinine	69.54±12.85	75.65±13.56	72.59±13.12	74.25 (67.37–91.15)	**.000**
Uric acid	322.00 (275.18–380.27)	414.66±95.11	383.50 (343.20–427.05)	383.75±91.86	**.000**
NLR	1.69 (1.28–2.00)	1.94 (1.43–2.18)	1.64 (1.32–1.93)	2.22 (1.50–2.78)	**.004**
baPWV, cm/s	1299.28±173.74	1557.53±276.92	1471.26±198.42	1563.25 (1382.50–1883.12)	**.000**
CHD, %	–	22 (23.91)	8 (17.78)	16 (20.00)	.674
T2DM, %	–	13 (14.13)	6 (13.33)	10 (12.50)	.952
ACEI, %	–	52 (56.52)	16 (35.36)	38 (47.50)	.067
CCB, %	–	41 (44.57)	12 (26.67)	29 (36.25)	.120
β-Blocker, %	–	34 (36.96)	10 (22.22)	35 (43.75)	.055

ACEI, angiotensin-converting enzyme inhibitor; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CCB, calcium channel blocker; CHD, chronic heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LDL-C, low-density lipoprotein cholesterol; NH, normotension; NLR, neutrophil/lymphocyte ratio; SBP, systolic blood pressure; SDH, systolic-diastolic hypertension; T2DM, type 2 diabetes mellitus; WBC, white blood cell. Bold values indicate significance.

To date, there are no reports on the relationship between NLR and baPWV in patients with hypertension with artery stiffness. Therefore, the research aims at evaluating the changes and relationship between NLR and baPWV in hypertension with artery stiffness.

2 | METHODS

2.1 | Sample selection

This study used a cross-sectional design and consisted of 217 consecutive patients with hypertension and 132 participants without hypertension. All participants were enrolled from the medical center of the Southern District of Guang'anmen Hospital of China Academy of Chinese Medical Sciences in July 2015 and July 2016. Patients were divided into the following three groups according to BP measurements: ISH (n=80), IDH (n=45), and SDH (n=92). The protocol was approved by the ethics committee of Guang'anmen Hospital, and informed consent was obtained from each patient.

The following data were collected: height, weight, BP, WBC count, lymphocytes, neutrophils, fasting glucose, Apolipoprotein A1, Apolipoprotein B, triglycerides, cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, urea, creatinine, uric acid. Medications and medical history were obtained by patient interview. Body mass index was obtained, and NLR was calculated by neutrophils divided by lymphocytes.

Patients with the following characteristics were excluded: secondary hypertension, malignancy, severe arrhythmia, frequent ventricular premature, second-degree type II atrioventricular block, third-degree atrioventricular block, serious liver and kidney dysfunction, clinical evidence of infection, and pregnancy.

TABLE 2 Correlation Coefficient (*r*) for NLR in Relation to baPWV

	baPWV, cm/s	
	r	*P* Value
For normotensive controls		
NLR	.043	.625
For SDH patients		
NLR	.315	**.042**
For IDH patients		
NLR	.505	**.008**
For ISH patients		
NLR	.380	**.005**

Abbreviations: baPWV, brachial-ankle pulse wave velocity; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; NLR, neutrophil/lymphocyte ratio; SDH, systolic-diastolic hypertension. Bold values indicate significance.

TABLE 3 Stepwise Multivariate Linear Regression Analysis With baPWV

Variables	β	SE	*r*	*P* Value
Normotensive controls				
SBP	6.538	0.996	.439	**.000**
Age	4.783	0.981	.332	**.000**
Uric acid	0.434	0.140	.218	**.002**
Cholesterol	−91.006	18.942	−.516	**.000**
ApoB	275.644	82.307	.345	**.001**
ApoA1	105.863	47.329	.161	**.027**
Hypertension patients				
Age	3.836	1.386	.179	**.006**
SBP	9.187	1.951	.290	**.000**
BMI	−16.390	5.061	−.193	**.001**
NLR	67.778	25.928	.161	**.001**
Glucose	29.151	10.271	.170	**.005**
DBP	−4.622	2.260	−.126	**.042**

Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; NLR, neutrophil/lymphocyte ratio; SBP, systolic blood pressure; SE, standard error. Bold values indicate significance.

2.2 | Laboratory evaluation

Venous blood samples were drawn from the antecubital vein following a 12-hour fasting period. The lipid profile was measured by automated biochemical counter (Beckman Coulter AU5822, Brea, CA, USA). Hematological indices were measured by an automated blood cell counter (Beckman Coulter LH780).

2.3 | Brachial-ankle pulse wave velocity

baPWV was measured by arteriosclerosis instrument (Vision BP-203RPE III; Omron Corporation, Kyoto, Japan). Measurements were performed in a quiet room with the patient in the supine position after more than 5 minutes of rest. The patients' palms rested on both sides of the body, limbs were bound with the BP cuff, electrocardiographic sensors were placed on the interior forearms, and a phonocardiographic sensor was placed on the fourth intercostal space of the left margin of the chest. The measurement was repeated twice, and the second value was taken as the final result. The mean baPWV in both the left and right sides was used for evaluation.

2.4 | BP measurements

Office BP was measured by adjusting the mercury sphygmomanometer with the right arm on the same level of the heart in a quiet condition. The measurement was repeated three times in 30-second intervals and the mean of the systolic pressure and diastolic pressure was the final figure, respectively. According to BP, normotension was defined as systolic BP <140 mm Hg and diastolic BP <90 mm Hg, ISH was defined as systolic BP >140 mm Hg and diastolic BP <90 mm Hg, IDH was defined as systolic BP <140 mm Hg and diastolic BP >90 mm Hg, and SDH was defined as systolic BP >140 mm Hg and diastolic BP >90 mm Hg.

2.5 | Statistical analysis

Data analysis was performed using SPSS software version 20.0 (IBM, Armonk, NY, USA). The normality was examined using Kolmogorov-Smirnov test. Continuous variables were expressed as mean±standard deviation and median (interquartile), and quantitative data were summarized by percentages. Chi-square test was applied for quantitative data. Normally distributed variables were analyzed using variance analysis, but non-normally distributed variables were analyzed using Kruskal-Wallis H test. Student *t* test and Mann-Whitney *U* test were adopted for the comparisons between the two groups for normally and abnormally distributed data, respectively. Correlation analysis was performed based on the results of Spearman's correlation test. Multiple linear regression analysis was performed to determine the independent predictors of baPWV. Statistical significance was set at $P<.05$.

3 | RESULTS

3.1 | Characteristic of the study sample

A total of 349 patients (56.45% men, 44.69±14.83 years) were enrolled in the study. The clinical and biochemical characteristics of the patients are outlined in Table 1. There was no significant difference among groups in terms of Apolipoprotein A1, Apolipoprotein B, high-density lipoprotein cholesterol, and urea. All other parameters were shown to be significantly different in the groups ($P<.05$). Office systolic BP and diastolic BP were significantly different among the groups ($P<.01$). The patients with hypertension had higher age and levels of body mass index, neutrophils, glucose, triglycerides, uric acid, and baPWV compared with the NC group. The levels of cholesterol,

low-density lipoprotein cholesterol, creatinine, and NLR in the SDH and ISH groups were significantly different than that in the NC group. WBC counts in the SDH and IDH groups were significantly elevated compared with those in the NC group, whereas the WBC count in the IDH group was significantly higher than in the ISH group. However, no differences were seen in medication history or complications ($P>.05$). baPWV in the ISH group was significantly higher than in the IDH group ($P<.05$).

The correlations between NLR and baPWV are summarized in Table 2. No statistically significant correlation was observed in NCs, whereas there was a statistically significant correlation between NLR and baPWV in all hypertension patients (SDH: $r=.315$, $P=.042$; IDH: $r=.505$, $P=.008$; ISH: $r=.380$, $P=.005$).

To determine independent predictors of baPWV, multiple regression analysis was performed using a stepwise procedure (Table 3). The analysis showed that systolic BP, age, uric acid, cholesterol, Apolipoprotein A1, and Apolipoprotein B were significant determinants of elevated baPWV in the NC group. However, SDH, IDH, ISH, age, systolic BP, body mass index, NLR, glucose, and diastolic BP were independent predictors of baPWV in the hypertension group (NLR: $\beta=67.778$, $P=.001$).

4 | DISCUSSION

In our study, we found that baPWV, neutrophils, and triglycerides were elevated in all three groups (SDH, ISH, and IDH), and the NLR was higher in SDH and ISH patients compared with the NC group. Moreover, there was a positive correlation between NLR and baPWV in hypertension patients. Multiple regression analysis showed that NLR was an independent determinant factor for elevated baPWV in hypertension patients.

Recent research has revealed that body mass index is closely related to WBC count, neutrophils, platelet hematocrit, and platelet count.[17] There are viewpoints that hypertension is related to lymphocytes; however, there is no correlation with body mass index, smoking, and triglycerides.[18] In subtypes of hypertension, there are obvious differences in terms of baPWV.[19] We suppose that different arterial elasticity exists in each subtype of hypertension. IDH is inclined to develop to SDH or ISH.[20,21]

Inflammation, which can predict damage to target organs related to hypertension,[22] plays an important role in the development of hypertension,[23] including IL-1, IL-1b, and tumor necrosis factor α.[24–26] One study revealed that IL-1β and IL-10 are elevated in patients with resistant hypertension compared with those with normotension and controlled hypertension.[27] Reduced CRP can describe lower damage of target organs.[28] On the other hand, increased neutrophils and decreased lymphocytes are associated with the development of hypertension.[29–31] NLR is an economical, effective, and repetitive indicator of inflammation.[32]

Atherosclerosis is a disease driven by chronic inflammation, which plays a critical role in its development.[33] baPWV is an early and sensitive marker for atherosclerosis.[34] It has been shown that CRP, soluble intercellular adhesion molecule-1, and IL-6 can reflect the inflammation condition in atherosclerosis.[35,36] As noted, CRP is increased in patients with SDH, IDH, and ISH, which demonstrates that inflammation is a main cause for the development of atherosclerosis.[37] It is known that increased CRP is associated with lower bone density, resulting in inflammation and artery stiffness in menopausal women.[38] Although CRP was not measured in this study to reflect inflammation, we used NLR as an indicator, which could also indicate inflammation.[39] Belen and colleagues demonstrated that NLR and neutrophil count increased in patients with resistant hypertension compared with patients with controlled hypertension and normotension.[40] In this research, we found that lymphocytes in patients with ISH were higher than in those with normotension, which was complementary to the findings by Belen and associates. However, the WBC counts in IDH, ISH, and SDH patients all increased compared with those with normotension. Increased WBC counts and NLR have been proved to be involved in the risk of cardiovascular diseases.[41–43] Lower levels of inflammation and higher levels of endothelial dysfunction exist in IDH but increased inflammation is present in ISH.[37]

In multiple regression analysis, NLR is the predominant factor for increasing of baPWV, which is a quota for artery stiffness. Recent clinical research has found that antihypertension drugs can effectively reduce NLR in patients with hypertension.[44]

It is not clear whether the activation of leukocytes is related to hypertension.[45] A number of studies reveal that vascular dysfunction, which is caused by inflammation, may be the pathomechanism of artery stiffness.[36] Neutrophils adhere to vascular endothelium, which leads to microvascular dysfunction and inflammation, vascular endothelial dysfunction, and increased expression of proinflammatory cytokines, enhancing vascular inflammation and smooth muscle proliferation and causing artery stiffness.[36]

4.1 | Study limitations and strengths

There were many limitations in our study. First, although we used NLR as an inflammation marker, no specific inflammation markers such as hs-CRP or IL were measured to evaluate and compare the accuracy and effectiveness among them. Second, although the correlation between NLR and artery stiffness was demonstrated, we did not have any direct evidence to explain the cause-effect relationship. Third, the number of patients with IDH was limited. More research should be performed in patients with IDH.

5 | CONCLUSIONS

Compared with NCs, baPWV is elevated in patients with ISH, IDH, and SDH. NLR in patients with ISH and SDH is higher than in NCs. There is a positive correlation between NLR and baPWV. NLR is an effective indicator for baPWV. Subtypes of hypertension differ in different degrees of arteriosclerosis, and an elevated NLR can be an effective predictor for arteriosclerosis in hypertension. Inflammation could be a possible pathogenesis for arteriosclerosis. Hence, it is important and

useful to monitor NLR in hypertension, which could help evaluate inflammation and detect artery stiffness earlier.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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