High neutrophil-to-lymphocyte ratio is associated with increased carotid artery intima-media thickness in type 2 diabetes

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Keywords
Carotid artery intima-media thickness, Neutrophil-to-lymphocyte ratio, Type 2 diabetes

ABSTRACT
Aims/Introduction: Emerging evidence suggests that the neutrophil-to-lymphocyte ratio (NLR) is a novel potential marker of inflammatory responses. The objective was to evaluate the association between NLR and carotid artery intima-media thickness (cIMT) in type 2 diabetes.

Materials and Methods: We carried out a case-control study involving 320 patients with type 2 diabetes, and 250 age-, sex- and body mass index-matched healthy controls who all underwent carotid ultrasonography and took a blood examination. We divided the diabetes patients into two groups according to cIMT: 188 diabetes patients with high cIMT and 132 diabetes patients with low cIMT, and compared baseline characteristics and NLR between the two groups and healthy controls.

Results: The mean NLR was significantly higher in the group of diabetes patients with high cIMT than the group of diabetes patients with low cIMT, who in turn showed a significantly higher NLR compared with control participants. Logistic regression analysis showed that the NLR was an independent risk factor for diabetes patients with high cIMT (odds ratio 140.89, 95% CI 1.71-11615.30, P = 0.028). Based on the receiver operating characteristic curve, use of the NLR as an indicator for diabetes patients with high cIMT diagnosis was projected to be 3.16, and yielded a sensitivity and specificity of 36.2% and 93.2%, respectively, with an area under the curve of 0.606 (95% CI 0.544–0.667).

Conclusions: High NLR might be a potential biomarker for the increased cIMT in type 2 diabetes patients. Future studies are required to validate our findings.

INTRODUCTION
Type 2 diabetes has become a major public health problem in the late 20th and 21st centuries. There are 28 million people in the USA who have type 2 diabetes, and more than 350 million people who have type 2 diabetes worldwide. The chronic complications of type 2 diabetes, such as diabetic retinopathy, nephropathy, and peripheral and autonomic neuropathies, increases with patients’ age, disease course and diabetes mellitus severity. In addition, type 2 diabetes also increases the risk of atherosclerosis/cardiovascular disease two- to fivefold. Carotid artery intima-media thickness (cIMT), which serves as a well-established biomarker of subclinical atherosclerosis, is a risk factor for cardiovascular disease and can be used to predict cardiovascular events; it is significantly greater in patients with type 2 diabetes than that in non-diabetes subjects.

Some studies have pointed out that inflammation plays an important role in diabetes and its chronic complications, and is also associated with cardiovascular events. Inflammatory cells contribute to atherosclerotic lesion initiation and lesion disruption, which could cause acute coronary syndrome and other cardiovascular events. Several inflammatory markers (such as fibrinogen, C-reactive protein [CRP], interluekin-18 and tumor necrosis factor-α), which are associated with markers of asymptomatic atherosclerosis in type 2 diabetes, are difficult to obtain in common clinical practice. Therefore, simpler and more convenient markers are required.

Mounting evidence has shown that the white blood cell (WBC) count and its subtypes are classic indicators of inflammation. The neutrophil-to-lymphocyte ratio (NLR) was...
calculated as a simple ratio of the absolute neutrophil count to
the absolute lymphocyte count. It was defined as a potential
biomarker of inflammation in tumors, cardiovascular condi-
tions, and diabetes and its complications. Previous studies
have shown that a higher level of NLR was related to a
higher severity of coronary artery disease and worse clinical
outcome in patients undergoing percutaneous coronary inter-
vention. Akbas et al. reported that the level of NLR was
significantly higher in diabetic nephropathy patients with albu-
minuria. Ulu et al. also reported a positive correlation
between the NLR and different diabetic retinopathy grades.
The exact mechanisms of the higher level of NLR being associ-
ated with diabetes and its complications are still unclear, and
the most important mechanism might be inflammation. How-
ever, the relationship between diabetic cIMT and NLR has not
been investigated to date. The objective of the present study was
to investigate the role of NLR in cIMT development among type
2 diabetes patients.

METHODS
Participants
Written approval for the study was obtained from the ethics
committee of Huai’an First People’s Hospital, Nanjing Medical
University. The approval number of the institution review was
IRB-PJ2011-009-01. Informed consent was obtained from each
participant.

A total of 320 patients with type 2 diabetes, and 250 age-,
sex- and body mass index (BMI)-matched healthy controls were
recruited from January 2012 to December 2013. Type 2 diabetes
patients were recruited from the Department of Gerontology and
Endocrinology, Huai’an First People’s Hospital, Huai’an, Jiangsu,
China – they were all hospitalized patients. Healthy participants
were recruited from the Checkup Center, Huai’an First People’s
Hospital, and were not receiving any medications. All patients
with type 2 diabetes met the 2015 American Diabetes Associa-
tion diabetes standards and classification. Patients were
excluded if they were aged younger than 18 years or had type 1
diabetes mellitus, any acute inflammation, active infection, can-
cer, chronic liver diseases, renal disorders, hypertension, coronary
heart disease, cerebrovascular disease, lower extremity arterial
disease, or any acute diabetic complications.

Design
Data at the time of admission for demographics (age, sex, body
mass index [BMI] and waist circumference), smoking status,
duration of type 2 diabetes, family history of diabetes, oral
antidiabetic drugs and insulin used, aspirin or statins used, and
systolic (SBP) blood pressure and diastolic blood pressure
(DBP) were obtained from medical records. Systemic BP was
measured as described previously. BMI was calculated as
weight in kilograms divided by height in meters squared.

Fasting blood samples were taken for measurement of a rou-
tine blood test, fasting plasma glucose (FBG), creatinine (Cr),
glycosylated hemoglobin A1c (HbA1c), high-sensitivity CRP
(hs-CRP) and lipid profile (total cholesterol [TC], triglyceride
[TG], high-density lipoprotein cholesterol [HDL-C] and low-
density lipoprotein cholesterol [LDL-C]). The routine blood test
was measured using an automated complete blood cell counter
(model XT 2000i; Sysmex, Kobe, Japan), which simultaneously
provided values for total white blood cell count, red blood
count, hemoglobin, platelet count, absolute neutrophil count
and absolute lymphocyte count. NLR was calculated as a simple
ratio of the absolute neutrophil count to the absolute lympho-
ocyte count. HbA1c levels were measured by the high-perform-
ance liquid chromatography method. The hs-CRP was
measured using a latex-enhanced immunoturbidimetric method
with lower limits of detection at 0.02 mg/L. Serum lipids, FBG
and creatinine were measured by enzymatic methods on a
Hitachi 7600 automatic clinical chemistry analyzer (Boehringer
Mannheim, Mannheim, Germany) using reagent kits supplied
by the manufacturer.

The cIMT of both carotid arteries was measured by using
high-resolution ultrasound Doppler system (SSl6000; Kai-Li
Ultrasound, Shenzhen, China). Two assessors measured the
degree of cIMT based on the ultrasound images respectively
(Excel S1). When there was a discrepancy in the measurement
of the degree of cIMT, or the cIMT difference was greater
than 0.2 mm between the two assessors, a third assessor was asked
to carry out the measurements, and the averaged results of the
findings were used. All the participants were measured in a
supine position. We measured the minimum and maximum
cIMT in each carotid artery, and selected the thickest as the
maximum cIMT value of the carotid artery. Type 2 diabetes
patients were divided into two groups according to the maxi-
mum cIMT values: the low cIMT group (maximum cIMT
≤ 1 mm; DM-Low cIMT group) and the high cIMT group
(maximum cIMT > 1 mm; DM-High cIMT group).

Statistical analysis
The Kolmogorov–Smirnov normality test was used to evaluate
the distribution of all quantitative data. Normally distributed
data were expressed as mean ± standard deviation, and ana-
lyzed by SPSS software version 20.0 (SPSS, Inc., Chicago, IL,
USA). Non-parametric statistics was used if data were not nor-
mally distributed. The independent samples t-test was used for
normally distributed data to compare continuous variables; the
chi square-test was used to compare categorical variables.

Logistic regression was used to analyze the cIMT risk factors.
Receiver operating characteristic (ROC) curve analysis was used
to compare the prognostic powers of the NLR for cIMT. The
predictive validities were quantified as areas under the ROC
curves. The positive predictive value and negative predictive
value were calculated, and $P < 0.05$ was considered statistically
significant.

RESULTS
We divided the diabetes patients into two groups according to
the maximum cIMT values: DM-high cIMT group and DM-low
cIMT group. The baseline characteristics of the diabetes patients and healthy controls are shown in Table S1 and Table 1.

There were no differences between the diabetes group and control group in age, sex, BMI, waist circumference, smoking status, serum TG, creatinine, WBC, monocyte, and platelet levels (Table S1). The levels of SBP, DBP, FBG, HbA1c, TC and LDL-C were significantly higher, and the level of HDL-C was significantly lower in the diabetes group than in the control group (Table S1). There were still significant differences between the two groups in the percentage of family history of diabetes, duration of diabetes, insulin and oral antidiabetic drug used, and aspirin or statins used (Table S1). The levels of cIMT, hs-CRP, neutrophils and NLR were significantly higher, and the level of lymphocytes was significantly lower in the diabetes group than in the control group (Table S1).

Furthermore, there were also no significant differences between diabetes patients with high cIMT and low cIMT in age, sex, BMI, waist circumference, smoking status, the levels of SBP, DBP, FBG, HbA1c, TG, TC, LDL-C, HDL-C and creatinine, the percentage of family history of diabetes, duration of diabetes, insulin and oral antidiabetic drug used, and aspirin or statins used (Table 1). Diabetes patients with high cIMT had significantly higher levels of NLR, hs-CRP, neutrophils and cIMT, and significantly lower levels of lymphocytes compared with diabetes patients with low cIMT (Table 1). There were also no significant differences between diabetes patients with high cIMT and low cIMT in the levels of WBC, monocyte, and platelet (Table 1).

Duration of diabetes, levels of TG, WBC, lymphocytes, neutrophils, NLR and hs-CRP were regarded as dependent variables, and the status of cIMT (high or low) were regarded as

### Table 1 | Description and comparison of clinical and hematological parameters among the three groups

| Description and comparison of clinical and hematological parameters among the three groups | DM-High cIMT group (n = 188) | DM-Low cIMT group (n = 132) | Control group (n = 250) |
|---|---|---|---|
| Age (years) | 64.51 ± 6.93 | 65.58 ± 6.81 | 64.33 ± 6.80 |
| Sex (male) | 108 (57.44%) | 76 (57.58%) | 142 (56.80%) |
| BMI (kg/m²) | 23.97 ± 1.68 | 23.92 ± 1.10 | 24.02 ± 1.14 |
| WC (cm) | 91.66 ± 6.31 | 91.07 ± 5.85 | 91.66 ± 6.34 |
| Duration of DM (years) | 3.67 ± 1.56*** | 3.95 ± 1.70*** | 0.00 ± 0.00 |
| Smoking (%) | 46 (24.47%) | 32 (24.24%) | 54 (21.70%) |
| Diabetes family history (%) | 50 (26.60)*** | 34 (25.76)*** | 14 (5.60)*** |
| Insulin used (%) | 112 (59.57)*** | 78 (59.09)*** | 0 (0.00)*** |
| Oral antidiabetic drugs used (%) | 76 (40.43)*** | 54 (40.91)*** | 0 (0.00)*** |
| Aspirin used (%) | 132 (70.21)*** | 90 (68.18)*** | 0 (0.00)*** |
| Statins used (%) | 156 (82.98)*** | 104 (78.79)*** | 0 (0.00)*** |
| cIMT (mm) | 1.14 ± 0.33*** | 0.86 ± 0.07*** | 0.71 ± 0.13 |
| SBP (mmHg) | 132.63 ± 17.40*** | 134.10 ± 11.96*** | 124.16 ± 9.41 |
| DBP (mmHg) | 83.76 ± 7.25*** | 82.85 ± 7.61*** | 78.97 ± 5.96 |
| FBG (mmol/L) | 5.44 ± 0.46*** | 5.47 ± 0.68*** | 4.89 ± 0.60 |
| HbA1c | 6.91 ± 0.46*** | 6.85 ± 0.46*** | 4.92 ± 0.45 |
| TG (mmol/L) | 1.39 ± 0.58 | 1.50 ± 0.59 | 1.42 ± 0.59 |
| TC (mmol/L) | 4.96 ± 0.64*** | 5.03 ± 0.62*** | 4.61 ± 0.51 |
| LDL-C (mmol/L) | 2.89 ± 0.38† | 2.93 ± 0.38† | 2.80 ± 0.40 |
| HDL-C (mmol/L) | 1.23 ± 0.25†† | 1.19 ± 0.25†† | 1.31 ± 0.25 |
| Scr (µmol/L) | 7.44 ± 11.74 | 7.33 ± 11.66 | 7.03 ± 9.88 |
| Hs-CRP (mg/L) | 5.80 ± 0.85*** | 4.29 ± 0.87*** | 2.35 ± 0.96 |
| WBC (×10⁹/L) | 6.27 ± 1.03 | 6.12 ± 0.77 | 6.11 ± 1.05 |
| Lymphocytes (×10⁹/L) | 1.40 ± 0.17*** | 1.45 ± 0.19*** | 1.70 ± 0.28 |
| Neutrophils (×10⁹/L) | 3.86 ± 1.02*** | 3.66 ± 0.68*** | 3.42 ± 1.05 |
| Monocyte (×10⁹/L) | 0.40 ± 0.05 | 0.41 ± 0.07 | 0.40 ± 0.05 |
| Platelet (×10⁹/L) | 208.30 ± 28.68 | 211.84 ± 47.82 | 209.40 ± 46.37 |
| NLR | 2.79 ± 0.80*** | 2.53 ± 0.42*** | 2.08 ± 0.76 |

All values are expressed as mean ± standard deviation for continuous variables and as the number of patients (percentage) for categorical variables. Continuous variables were analyzed by independent-sample t-tests, two-sided type I error of 0.05. Categorical variables were analyzed by chi-square tests. *P < 0.05; **P < 0.01; diabetes patients with high carotid intima-media thickness (DM-High cIMT) group vs diabetes patients with low carotid intima-media thickness (DM-Low cIMT) group. P < 0.05; **P < 0.01; ***P < 0.001, DM-High cIMT group vs the control group. †P < 0.05; ‡P < 0.01; DM-Low cIMT group vs the control group. BMI, body mass index; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; SBP, systolic blood pressure; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride; WBC, white blood cell; WC, waist circumference.
independent variables when we carried out logistic regression analysis. As shown in Table 2, it was shown that independent risk factors for high cIMT were NLR ($\beta = 4.95$, odds ratio [OR] 140.89, 95% confidence interval [CI] 1.71–11615.30, $P = 0.028$) and hs-CRP ($\beta = 1.97$, OR 7.20, 95% CI 4.66–11.11, $P < 0.001$).

Figure 1 shows that based on the ROC, as an independent risk factor for cIMT, the cut-off value of NLR was 3.16, and the sensitivity and specificity of the NLR for cIMT diagnosis were 36.2% and 93.2%, respectively, with an area under the curve at 0.606 (95% CI 0.544–0.667). The positive predictive value and negative predictive value for NLR for cIMT diagnosis was 88.31% and 50.62%, respectively.

**DISCUSSION**

Type 2 diabetes is a major public health problem worldwide, and vascular complications still represent the main cause of morbidity and mortality in type 2 diabetes patients. The main pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls and ischemia throughout the body. Mounting evidence has shown that inflammation plays an important role in the pathogenesis of atherosclerosis and its complications27. There is a series of inflammatory cytokines that are upregulated in patients with diabetes and its complications11. However, some of these biomarkers are difficult to obtain in common clinical practice. NLR is defined as a novel potential biomarker to determine inflammation in diabetes and its complications18,19. Calculation of NLR is a very simple method compared with other inflammatory cytokines tested28. However, no data to date are available regarding the relationship between NLR and cIMT in type 2 diabetes.

In the present study, we found that the levels of SBP, DBP, FBG, HbA1c, TC and LDL-C, and the percentage of family history of diabetes were significantly higher, and the level of HDL-C was significantly lower in diabetes patients than in control participants, which might be the reason that diabetes patients have coexistence of multiple cardiovascular disease risk factors. There were no significant differences in the levels of SBP, DBP, FBG, HbA1c, TC, LDL-C and HDL-C, and the percentage of family history of diabetes between diabetes patients with high cIMT and low cIMT. There were also no differences in duration of diabetes, insulin and oral antidiabetic drug used, aspirin or statins used between diabetes patients with high cIMT and low cIMT. These results might be associated with active and effective treatment between the two groups of diabetes patients.

In the present study, we found that diabetes patients with high cIMT had higher levels of NLR compared with diabetes patients with low cIMT, who in turn showed significantly higher levels of NLR compared with healthy participants. Logistic regression analysis showed that the NLR was an independent risk factor for diabetes patients with high cIMT (OR 140.89, 95% CI 1.71–11615.30, $P = 0.028$). Based on the ROC, use of the NLR as an indicator for diabetes patients with cIMT diagnosis was projected to be 3.16, and yielded a sensitivity and specificity of 36.2% and 93.2%, respectively, with an area under the curve of 0.606 (95% CI 0.544–0.667). It might prove that an increased NLR in peripheral blood could be an independent risk factor for predicting the development of subclinical atherosclerosis in diabetes patients with relatively high sensitivity and specificity.

However, the exact mechanisms of high NLR being related with increased cIMT in diabetes patients are as yet unknown.

**Table 2** | Logistic regression analysis showing independent predictors of carotid intima-media thickness

| Variables                  | $\beta$ | OR  | 95% CI        | $P$-value |
|----------------------------|---------|-----|---------------|-----------|
| Duration of DM (years)     | –0.15   | 0.86| 0.71–1.04     | 0.117     |
| TG (mmol/L)                | –0.70   | 0.93| 0.55–1.59     | 0.798     |
| WBC ($\times 10^9$/L)      | 0.92    | 2.51| 0.02–360.99   | 0.717     |
| Lymphocytes ($\times 10^9$/L)| 6.78 | 876.07| 0.11–6896734.68 | 0.139 |
| Neutrophils ($\times 10^9$/L)| –4.07 | 0.02| 0.00–7.92     | 0.194     |
| NLR                        | 4.95    | 140.89| 1.71–11615.30 | 0.028     |
| hs-CRP (mg/L)              | 1.97    | 7.30| 4.66–11.11    | 0.000     |

CI, confidence interval; cIMT, carotid intima-media thickness; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; TG, triglyceride; WBC, white blood cell.

![ROC curve](http://onlinelibrary.wiley.com/journal/jdi)
Most likely, it can be explained in view of various functions of NLR. As we all know, high NLR could represent not only the increased level of neutrophils, but also the decreased level of lymphocytes. Hyperglycemia, or advanced glycated end-products, leads to persistent activation of neutrophils, as evidenced by the increased activity of neutrophil alkaline phosphatase. Then the neutrophils of diabetes patients show increased necrosis and enhanced production of reactive oxygen species, and significantly lower neutrophil chemotactic responses. Previous studies have also shown that activation of leukocytes and their adhesion to the endothelium could cause endothelial injury. These leukocytes secrete cytokines and growth factors that can promote the migration and proliferation of smooth muscle cells, which can induce further vascular damage and cause most complications of atherosclerosis.

Nevertheless, the presence of lymphopenia might also be an important factor. In the present study, we found that diabetes patients with high cIMT had significantly lower level of lymphocytes compared with diabetes patients with low cIMT, who in turn showed significantly lower levels of lymphocytes compared with control participants. Previous studies have shown that inflammation plays an important role in both diabetes and obesity. Tanaka et al. showed that T lymphocytes and their subsets are characteristically reduced in obese persons. Worsening obesity might increase lymphopenia development, which, in turn, increases NLR. Therefore, we deduced that development of lymphopenia is related with inflammation, which might promote atherosclerosis.

Another possible mechanism is that NLR can reflect an autonomic balance of the vascular bed. Previous studies have shown that the distribution of leukocytes is regulated by the autonomic nervous system in humans and animals. The number and function of granulocytes are stimulated by sympathetic nerves, whereas those of lymphocytes are stimulated by parasympathetic nerves. Therefore, a higher level of NLR might indicate a higher ratio of sympathetic-to-parasympathetic activity. An increased sympathetic tone is positively related with higher rates of oxygen consumption and increased production of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α. These cytokines might play a key role in regulating the vascular tone by affecting the release of nitric oxide and endothelin-1; they also contribute to the development of proliferative vascular lesions by stimulating smooth muscle and interstitial cell proliferation, which could accelerate atherosclerosis development.

However, there were also some limitations to the present study. The main limitation was the limited number of study samples. Future studies are required to clarify these relationships of large sample analysis. Second, the patients in the present study were of Chinese origin. Larger studies are required to determine whether the observations in this study are present in individuals of various races and ethnicities. Finally, the present study was an observational study, further studies regarding clinical outcome should be carried out.

In conclusion, the data presented show for the first time that high NLR might be an independent risk factor for increased cIMT in type 2 diabetes. Early screening of patients might help distinguish a high-risk group and guide prophylactic initiatives.

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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Description and comparison of clinical and hematological parameters between the diabetes group and control group.
Excel S1 | The data of intra- and inter-individual differences between the two assessors.