The Relationship between Neutrophil-to-Lymphocyte Ratio and Aortic Arch Calcification in Ischemic Stroke Patients

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Background: Inflammation plays a central role in atherogenesis and artery calcification. Although neutrophil-to-lymphocyte ratio (NLR) has been introduced as an inflammatory marker for atherosclerosis, the relationship between NLR and aortic arch calcification (AAC) has not been studied. This study aimed to determine the association between NLR and AAC. *Methods:* A total of 749 participants were enrolled. Demographic and clinical data were collected. Degree of AAC in each enrolled patient was determined with Agatston method based on a neck computed tomography angiography. NLR was divided into 4 groups according to quartile values. Generalized linear model (ordinal probit) was performed to assess the association between NLR quartiles and severity of AAC. *Results:* There were 151 (20.2%), 153 (20.4%), and 445 (59.4%) patients classified as without AAC, with mild AAC, and with severe AAC, respectively. Patients with severe AAC had the highest NLR values (2.37[1.79-3.42] versus 2.29[1.55-2.96] versus 2.17[1.64-2.91], $P = .025$) compared to patients without AAC and with mild AAC. In age- and sex-adjusted models, patients with the highest NLR (quartile 4) were correlated with severer AAC ($\beta = .348 \pm .128$, $P = .006$) compared to those with the lowest levels (quartile 1). The correlation between NLR quartile 4 and severer AAC still existed ($\beta = .335 \pm .129$, $P = .009$) in multivariable-adjusted model. *Conclusions:* This study suggested that NLR may reflect the severity of AAC. NLR may be considered as a valuable predictor of the degree of artery calcification. **Key Words:** Aortic arch calcification—neutrophil-to-lymphocyte ratio—ischemic stroke—atherosclerosis.

Introduction

Inflammation plays a central role in the development of atherosclerosis and artery calcification.[1,2] Some inflammatory biomarkers, such as C-reactive protein, interleukin-6, and fibrinogen, have been associated with coronary heart disease,[3] carotid atherosclerosis,[4] ischemic stroke,[5] and subclinical cardiovascular diseases.[6] In recent years, neutrophil-to-lymphocyte ratio (NLR) has been suggested as a marker for inflammation in patients with coronary heart disease or ischemic stroke.[7,8]

Atherosclerotic plaques in aortic arch are an important etiology for cardiovascular events.[9,10] Aortic arch calcification (AAC) has been suggested as an appropriate index for atherosclerosis burden in aortic arch.[11] Studies focused on inflammatory markers and artery calcification are increasing.[12-14] However, the potential relationship

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between NLR and AAC has not been investigated to date. This study aimed to evaluate the association between NLR and AAC in patients with ischemic stroke.

Methods

Study Population

Consecutive patients with ischemic stroke were screened from Nanjing Stroke Registry Program[15] between December 2009 and September 2013 retrospectively. Patients were included if they met the following criteria: (1) diagnosed with ischemic stroke within 7 days of onset; (2) aged 18 years or older; and (3) completed a neck computed tomography angiography (CTA). Ischemic stroke was diagnosed if there were new focal neurological deficits explained by relevant lesions detected on diffusion-weighted imaging or computed tomography (CT). Patients were excluded if they met the following criteria: (1) had evidence of active infection, such as fever, cough, or diarrhea; (2) had a history of autoimmune diseases or malignant neoplasm; (3) had a history of severe liver or kidney diseases, parathyroid gland diseases, or calcium-phosphorus metabolism disorder; and (4) had a history of stenting in aortic arch. Figure 1 showed the flow diagram of selecting patients. Written informed consent was obtained from all patients. This study was approved by the Ethical Review Board of Jinling Hospital. Baseline data were collected from medical records including age; sex; and history of hypertension, diabetes mellitus (DM), dyslipidemia, NIHSS (National Institutes of Health Stroke Scale) scores, cigarette smoking, and alcohol drinking.

Biochemical Measurements

Fasting blood was drawn in the next morning after admission for assaying the laboratory parameters. Total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and glucose levels were measured. Total leukocyte, neutrophil, and lymphocyte counts were determined using a COULTER LH780 Hematology Analyzer (Beckman Coulter, Inc, Orange County, CA). NLR was calculated as the ratio of neutrophil counts to lymphocyte counts, both obtained from the same blood sample.

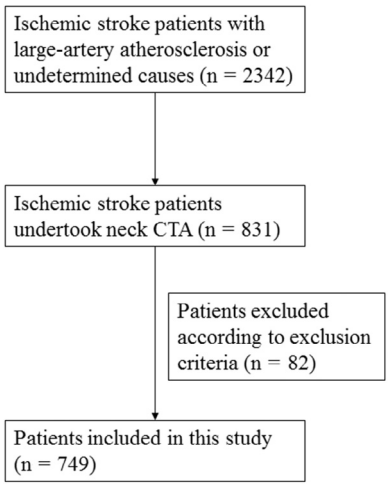

Figure 1. *Brief flow diagram of patient enrollment in this study. Abbreviation: CTA, computed tomography angiography.*

Quantification of AAC

Each enrolled patient underwent a neck CTA within 7 days after stroke onset. CTA was performed with a dual-source 64-slice CT system (Siemens, Forchheim, Germany). Imaging was acquired by scanning from 4 cm below aortic arch to the superior border of orbit in craniocaudal direction. The aortic arch was recognized as a section from the initial segment to the first centimeter of the common carotid arteries, the vertebral arteries, and the subclavian arteries beyond the origin of the vertebral arteries. Details of scanning parameters have been reported elsewhere.[16] Calcification scores in aortic arch were measured with Syngo Calcium Scoring system (Siemens). A focus of greater than or equal to 4 contiguous pixels accompanied by a CT density greater than or equal to 130 Hounsfield units (HU) was defined as calcification according to the method of Agatston score.[17] For each calcified lesion, the Agatston score was calculated as the product of the area (mm^2) and a factor assigned according to the maximum attenuation value of the lesion (HU = 130-199,[1] 200-299,[2] 300-399,[3] >399[4]). The total score of aortic arch was calculated by adding up the scores of all lesions. Measurement of AAC was evaluated by 2 radiologists. Disagreements were solved with discussion.

Statistical Analysis

Normality of quantitative variables was assessed by Shapiro–Wilk test. As all quantitative variables in this study did not meet the normality assumption, they were described as median (interquartile range). According to the Agatston scores, patients were classified as without AAC (Agatston score = 0), with mild AAC (0 < Agatston score ≤ 100), and with severe AAC (Agatston score > 100). Baseline characteristics were compared among patients without AAC, with mild AAC, and with severe AAC using Kruskal–Wallis test.

NLR was divided into 4 groups according to quartile values with reference to previous studies.[12,18] Generalized linear model (ordinal probit) was performed to explore the relationship between NLR quartiles and severity of AAC. Severity of AAC (without, mild, and severe) was used as dependent variable. Age and sex were adjusted in Model 1. Age, sex, TG, hypertension, DM, and smoking were adjusted in Model 2. The independent variables were chosen because they were known to be predictors of artery