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High neutrophil to lymphocyte ratio is associated with white matter hyperintensity in a healthy population

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ABSTRACT

High neutrophil to lymphocyte ratio (NLR) is correlated with the occurrence, morbidity and mortality of cerebrovascular disease as a marker of systemic inflammation. However, its effect on cerebral white matter hyperintensity (WMH) is unclear. We investigated high NLR burden as a surrogate marker of WMH volume in a healthy population. Healthy subjects with voluntary health check-ups between January 2006 and December 2013, including brain MRI and laboratory examination, were collected. WMH volumes were rated quantitatively. A total of 2875 subjects were enrolled, and the mean volume of WMH was 2.63 ± 6.26 mL. In multivariate linear regression analysis, NLR [β = 0.191, 95% confidence interval (CI) = 0.104 to 0.279, $P < 0.001$] remained significant after adjusting for confounders. Age (β = 0.049, 95% CI = 0.045 to 0.054, $P < 0.001$), hypertension (β = 0.191, 95% CI = 0.101 to 0.281, $P < 0.001$), diabetes (β = 0.153, 95% CI = 0.045 to 0.261, $P = 0.006$), and extracranial atherosclerosis (β = 0.348, 95% CI = 0.007 to 0.688, $P = 0.045$) were also significant independently from NLR. Additionally, the high NLR group (NLR ≥ 1.52) was related to male sex, hypertension, diabetes, current smoking, extracranial atherosclerosis, silent brain infarct, and high WMH volumes. In conclusion, high NLR is associated with larger WMH volumes in a healthy population. Assessment of NLR may be helpful in detecting cerebral WMH burdens in high risk groups.

1. Introduction

Cerebral white matter hyperintensity (WMH) is a pathologic marker of tissue rarefaction, commonly found in the elderly, especially those with vascular risk factors or symptomatic cerebrovascular disease (CVD) [1]. It is a well-known prognostic marker of CVD [2–6]. However, its pathophysiologic mechanisms are still unclear. Only diffuse hypoperfusion and chronic endothelial dysfunction have been suggested as causes, however these appear inadequate to fully explain the association [7–9].

Inflammation has a key role in development of CVD [10,11]. Focal inflammation which follows local arterial occlusion and systemic inflammation which is related to atherosclerosis formation have been known to be associated with the burden, morbidity, and even mortality of CVD [12–15]. However, the impact of inflammation on WMH, which shares various risk factors and is thought to be closely related to CVD [16], remains unknown.

Neutrophil to lymphocyte ratio (NLR) is a simple marker of systemic inflammation [17], and is easily obtained from differential blood cell counts. Elevated NLR has been used as a predictor of poor prognoses in vascular disease; including cardiovascular disease, peripheral vascular disease, and CVD [10,18–21]. In this study, we evaluated the relationship between NLR levels and WMH volumes, thereby gaining clues as to mechanisms underlying pathophysiology of WMH.

2. Methods

2.1. Patients and population

We reviewed medical records from a consecutively enrolled registry of participants who visited Seoul National University Hospital Health Promotion Center to obtain a voluntary routine health check-up, between January 2006 and December 2013 (n = 3259). The health check-up was designed for participants who have age over 19 years.

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Any, participants without blood cell counts data, including neutrophil or lymphocyte counts, were excluded (n = 44). We also excluded subjects who suffered from severe systemic inflammatory conditions as follows: history of stroke or severe neurological deficit (n = 64), hemato-oncologic conditions or use of immunosuppressant (n = 71), severe allergic disease (n = 77), severe hepatic or renal disease (n = 100), having major surgery or severe trauma (n = 15), or active infections within prior 2 weeks (n = 11). Ultimately, a total of 2875 subjects were included in the analysis (Fig. 1). The current study was approved by the institutional review board at Seoul National University Hospital (IRB No. 1502-026-647).

2.2. Clinical assessment

Baseline demographic, clinical, cardiovascular risk factors, and laboratory factors were evaluated, including sex, hypertension (using anti-hypertensive drug, or ≥140 mmHg systolic blood pressure, or ≥90 mmHg diastolic blood pressure), diabetes (using glucose lowering agents, or ≥6.5% hemoglobin A1c levels), hyperlipidemia (using lipid lowering agents, or ≥240 mg/dL total cholesterol levels, or ≥160 mg/dL low-density lipoprotein cholesterol levels), ischemic heart disease, and current smoking [22]. Blood pressure was checked after 5 min rest in sitting position. All laboratory examinations, including glucose, cholesterol, blood cell counts, and C-reactive protein levels, were conducted on the same day after 12 h of overnight fasting. Blood cell samples were collected in a calcium ethylene diamine tetra-acetic acid (EDTA) tube, and were separated immediately with centrifugation (2000 rpm for 20 min at 4 °C). Blood cell count analysis including total white blood cell, neutrophil, lymphocyte, and platelet was conducted using an auto-analyzer in our hospital (XE-2100, Sysmex, Kobe, Japan). We calculated platelet to lymphocyte ratio and NLR after dividing by absolute lymphocyte counts in peripheral blood [23,24].

2.3. Radiological assessment

In this study, all participants underwent brain MRI and MRA using 1.5-Tesla MR scanners (Signa, GE Healthcare, Milwaukee, WI, or Magnetom SONATA, Siemens, Munich, Germany). The slice thickness was 5 mm, excluding time of flight MRA imaging, and detailed acquisitions of MRI were as following: T1-weighted images (repetition time (TR) / echo time (TE) = 500 / 11 ms), T2-weighted images (TR/TE = 5000 / 127 ms), T2 fluid-attenuated inversion recovery images (TR/TE = 8800 / 127 ms), T2-gradient echo images (TR/TE = 57 / 20 ms), and three-dimensional time of flight MRA images (TR/TE = 24 / 3.5 ms, slice thickness = 1.2 mm). WMH was rated quantitatively using Medical Imaging Processing, Analysis, and Visualization (MIPAV, version 7.3.0, National Institutes of Health, Bethesda, MD) by an investigator (K.-W.N.) who was blinded to any clinical information [22]. We used a computer-assisted semi-automated technique, measuring from converted DICOM files. We also performed a sensitivity analysis for the relationship between WMH volume and NLR with the Fazekas scale [25]. Periventricular and subcortical WMH were respectively graded, and summed up to compare with the results from total WMH volume by MIPAV. We also evaluated the presence of silent brain infarcts (SBI) and cerebral microbleeds (CMB) as additional small vessel diseases. SBI was defined as an asymptomatic ≥3 mm size well-defined lesion with the same signal characteristics as cerebrospinal fluid on T2 and T1 MRI [26]. CMBs were <10 mm size focal round lesions with low signal on T2-gradient echo images [26]. Intracranial atherosclerosis (ICAS) [27] and extracranial atherosclerosis (ECAS) [28] were also defined as an occlusion or >50% stenosis of intracranial or extracranial vessels on flight MRA images, respectively. The presence of SBI, CMB, ICAS, and ECAS were rated by two neurologists (K.-W.N. and H.-Y.J) without clinical data, and the mean inter-rater reliability coefficient was $P = 0.890$.

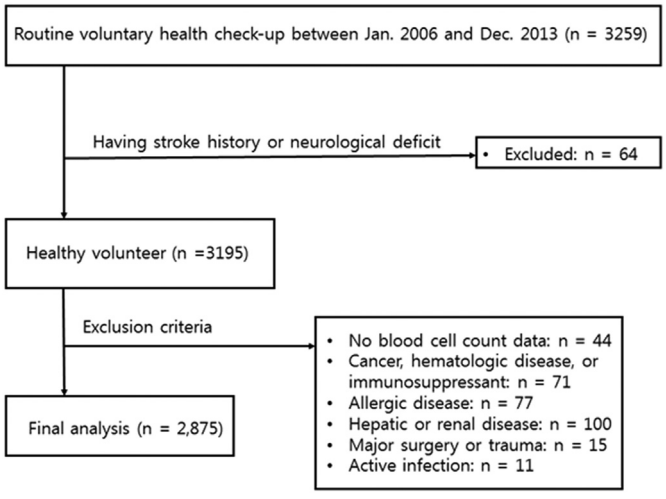

Fig. 1. Inclusion and exclusion criteria of the study.

2.4. Statistical analysis

We presented all continuous variables with normal distributions as the mean ± standard deviation, while the others were presented as the median + interquartile range. Continuous variables with skewed data were transformed into a log scale. However, some variables were transformed into a squared root scale, since they had zero values (e.g., hs-CRP, WMH). Univariate linear regression analyses were conducted for the association between WMH volumes and the demographic, clinical, laboratory and radiological factors. Then, variables with $P < 0.05$ from the results of univariate analysis and sex were introduced as confounders into the multivariate linear regression analysis.

Additionally, to evaluate the characteristics of subjects with high NLR values, we dichotomized the cohort with NRL values. Then, we evaluated the baseline demographic, clinical, and radiological characteristics between upper (NLR ≥ 1.52) and lower half (NLR < 1.52) NLR group. The Student's *t*-test or the Mann-Whitney *U*-test were conducted for continuous variables, and chi-squared test or Fisher's exact test were used for categorical variables. All statistical analyses were performed using SPSS version 21 (IBM SPSS, Chicago, IL, USA) and all variables with $P < 0.05$ were considered significant.

3. Results

A total of 2875 participants were evaluated. The median age of the cohort was 56 years (range 22 to 86 years), and we had 54% male subjects. Other baseline characteristics are presented in Table 1. As small vessel diseases, the mean WMH volumes were 2.63 ± 6.26 mL, and 245 (9%) and 119 (4%) subjects had SBI and CMBs, respectively. In univariate linear regression analysis, WMH volumes were significantly associated with older age ($\beta = 0.053$, $P < 0.001$), hypertension ($\beta = 0.471$, $P < 0.001$), diabetes ($\beta = 0.448$, $P < 0.001$), current smoking ($\beta = -0.232$, $P < 0.001$), ICAS ($\beta = 0.606$, $P < 0.001$), ECAS ($\beta = 876$, $P < 0.001$), and high levels of white blood cell counts ($\beta = 0.046$, $P < 0.001$), platelet counts ($\beta = -0.001$, $P = 0.020$), neutrophil counts ($\beta = 0.075$, $P < 0.001$), and NLR ($\beta = 0.273$, $P < 0.001$) (Table 2).

In multivariate linear regression analysis, NLR [$\beta = 0.191$, 95% CI = 0.104 to 0.279, $P < 0.001$] remained significant after adjusting for confounders (Table 3). Additionally, age ($\beta = 0.049$, 95% CI = 0.045 to 0.054, $P < 0.001$), hypertension ($\beta = 0.191$, 95% CI = 0.101 to 0.281, $P < 0.001$), diabetes ($\beta = 0.153$, 95% CI = 0.045 to 0.261, $P = 0.006$), and ECAS ($\beta = 0.348$, 95% CI = 0.007 to 0.688, $P = 0.045$) were also significant independently from NLR. These positive associations remained significant when ICAS was introduced alternatively to ECAS, considering their close relationship (Supplementary Table 1). Total white blood cell