ORIGINAL RESEARCH

# Hemispheric Asymmetry of White Matter Hyperintensity in Association With Lacunar Infarction

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***Background*—**White matter hyperintensities (WMHs) are commonly asymmetric between hemispheres but for unknown reasons. We investigated asymmetric WMHs associated with lacunar infarcts.

***Methods and Results*—**A total of 267 consecutive patients with small first-ever supratentorial infarcts (≤20 mm) were included. None had a relevant vascular stenosis. WMH asymmetry was measured based on the hemispheric difference of a modified Scheltens scale score (≥3 defined as asymmetric). We analyzed the association of the hemispheric WMH asymmetry with old silent lacunar infarcts or acute lacunar infarcts. We compared lesion frequency maps between groups and generated t-statistics maps. The mean age of patients was 64 years, and 63% were men. Asymmetric WMH was more than 3-fold as frequent ($P<0.001$) in the group with old silent lacunar infarcts (42%, 43/102) than in the group without old silent lacunar infarcts (15%, 24/165). In patients with left hemispheric dominance of WMHs, an acute lacunar infarct was more likely to be located in the left (versus right) hemisphere (74% versus 26%, $P<0.001$). In patients with right hemispheric dominance of WMHs, an acute lacunar infarct was more likely to be located on the right (versus left) hemisphere (81% versus 19%, $P<0.001$). Mapping studies showed that the side of hemispheric dominance of WMHs was associated with acute and silent lacunes on the same side.

***Conclusions*—**These are the first data to show that asymmetric WMHs are associated with both old silent lacunar infarcts and acute lacunar infarcts ipsilateral to the greatest WMH burden. This suggests that the hemisphere with relatively large WMHs is more vulnerable to ischemia. **(*J Am Heart Assoc*. 2018;7:e010653. DOI: 10.1161/JAHA.118.010653.)**

**Key Words:** asymmetry • lacunar infarct • lacunar stroke • leukoaraiosis • magnetic resonance imaging • white matter disease

Cerebral white matter hyperintensities (WMHs), the most common abnormality found on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), triple the risk of stroke[1] and double the risk of poor outcome at 3 months after stroke.[2] Pathological studies have suggested that WMHs represent incomplete ischemia mainly related to cerebral arteriolosclerosis.[3] Serial MRI studies have shown that acute infarcts do not always cavitate over time and thus become indistinguishable from preexisting WMHs by imaging.[4,5] Thus, FLAIR-hyperintense white matter regions could be composed of: (1) noncavitating old lacunar infarcts, superimposed with (2) arteriolosclerosis-related noninfarcted ischemic lesions.

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Accompanying Data S1, Tables S1 through S6, and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010653

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## Clinical Perspective

### What Is New?

- Although the asymmetry of white matter hyperintensities (WMHs) between bilateral hemispheres was not uncommon, its clinical implications have not been elucidated. In this study, we address the significance of WMH asymmetry: (1) the relationship between asymmetric WMHs and old silent lacunar infarcts, and (2) the association of asymmetric WMHs with acute lacunar infarct.
- We revealed that: (1) an asymmetric WMH distribution was more likely to be associated with old silent lacunar infarcts than symmetric WMHs, and (2) an acute lacunar infarct tended to occur in the cerebral hemisphere with relatively more severe WMH.

### What Are the Clinical Implications?

- These data imply that patients with asymmetric WMHs may be vulnerable to infarct, and thus might benefit from antiplatelet therapy to prevent symptomatic lacunar stroke.

A serial MRI study in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy demonstrated that incidental lacunes preferentially localized to the edge of WMHs, leading to the expansion of WMHs.[6] Our clinical experience indicates that acute lacunar infarction tends to repeatedly occur in the same hemisphere (Data S1). Therefore, we hypothesized that hemispheric asymmetry of WMHs might actually be the result of infarcts (asymmetric process) versus noninfarcted ischemic damage (symmetric process). If so, then silent old lacunes would be expected to be associated with asymmetric WMHs, while a lack of silent lacunes should have greater symmetry. We pose this is as our first hypothesis in this article, and also test for a similar association for acute lacunar infarcts as our second hypothesis.

## Methods

Data underlying the findings described in this article are available from the corresponding author upon reasonable request.

## Study Population

From May 2011 to December 2011, 3113 patients with acute (≤7 days) ischemic stroke from 11 academic and regional stroke centers participating in the Korean Nationwide Image-based Stroke Database Project[7] were screened. We consecutively enrolled 331 patients meeting the following criteria: (1) a first-ever ischemic stroke; (2) a classical lacunar syndrome; (3) a single supratentorial infarct with an axial diameter ≤20 mm on diffusion-weighted imaging (DWI)[8]; and (4) without a significant (≥50%) focal stenosis in the M1 segment of the middle cerebral artery (MCA) or P1 segment of the posterior cerebral artery (PCA) relevant to the acute lesion. We excluded 64 patients with poor quality (n=7) or unavailability of FLAIR MRI (*n*=52) and/or atrial fibrillation (n=5), leaving 267 patients for analysis. The institutional review boards of all participating centers approved this study. All patients or their legally authorized representatives provided written informed consent.

## Clinical Data Collection

Under a standardized protocol,[9] we collected demographic information and prior medication history and screened for the presence of vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and smoking (current or quit <5 years) history. The presence of "nonsignificant" stenosis (<50%) of the MCA or PCA and the information on external internal carotid artery stenosis were established using magnetic resonance or computed tomography angiograms, and these data were registered to our multicenter image-based stroke database.[9]

## Registration and Analysis

Brain MRI was performed on 1.5 Tesla (n=242) or 3.0 Tesla (n=25) MRI systems. The MRI protocol included the following sequences: FLAIR (echo time 76–160 ms, repetition time 6000–11 000 ms, voxel size $1\times1\times3$ to 7 $mm^3$, and interslice gap 0–2.25 mm), DWI (b values of 0 and 1000 $s/mm^2$, echo time 50 to 99 ms, repetition time 2400 to 9000 ms, voxel size $1\times1\times3$ to 5 $mm^3$, and interslice gap 0–2 mm), T2-weighted image (echo time 97–130 ms, repetition time 4000–6600 ms, voxel size $1\times1\times3$ to 7 $mm^3$, and interslice gap 0–2.25 mm), and T2*-weighted gradient echo image (echo time 14–26 ms, repetition time 450–980 ms, voxel size $1\times1\times3$ to 7 $mm^3$, and interslice gap 1–2 mm). As previously reported,[2,7,10,11] all scans were transferred to the Korean Brain MRI Data Center and converted into a patient-independent quantitative visual format using the Montreal Neurological Institute brain template. After normalization of images, each patient's high signal intensity lesions on FLAIR images, DWI, and T2-weighted images were segmented and registered semiautomatically by research assistants onto the brain templates under slice-by-slice supervision by a vascular neurologist (W.-S.R.). In the segmentation and registration of FLAIR WMHs, only chronic lesions were registered by excluding high signal DWI lesions due to acute infarction.[2,7] When T2-weighted images (n=154) were not available for the segmentation and registration of old lacunar infarcts (≥3 mm) with the high signal intensity of cerebrospinal fluid, B0 images

of DWI were used instead (n=113).[12] Dilated perivascular spaces were excluded based on their location (along perforating or medullary arteries, often symmetrical bilaterally, usually in the lower third of the basal ganglia or in the centrum semiovale), margins, and form (round/oval).[13] Cerebral microbleeds on gradient echo images (n=234) were defined as hypointense lesions <10 mm in diameter.[14]

Because many patients did not have T2-weighted images, we defined the group "with silent old lacunar infarcts" as patients who had any supratentorial cavitating lacunar infarcts that were found in subcortical white matter, basal ganglia, internal capsule, and thalamus on FLAIR imaging. Cavitating lesions were ≥3 mm that followed cerebrospinal fluid signal, slit or wedge-shaped with an irregular margin, and having a gliotic hyperintense rim on FLAIR imaging.[13] There was a high interobserver agreement for the identification of such lacunar infarcts between 2 observers (S.-H.P. and W.-S.R.) with a κ of 0.79. WMH volumes were calculated as a percentage of total brain volume, as previously described.[7] During the quantification process of WMH, inter-rater variability was minimal, ranging from 0.987 to 0.995.[7] For sensitivity analysis, we also reviewed T2-weighted images and B0 images of DWI to count old silent lacunar infarcts.

## Grading of WMHs and Definition of Asymmetry

In our pilot study, we found that differences in WMH volumes between the hemispheres increase as total WMH volumes increase (Figure S1, $P<0.001$). Therefore, using the quantitative definition of a hemispheric WMH asymmetry may lead to underestimation of relatively subtle but clinically significant asymmetry in patients with mild to moderate WMHs. Thus, we decided to visually grade the severity of cerebral WMHs using a modified Scheltens method.[15] The Scheltens method is used for grading the burden of periventricular and deep WMHs separately, evaluating the presence and extent of WMH in different anatomic regions (Data S1). Infratentorial WMH was not considered in this study.[16–18] The scoring was performed using raw FLAIR images by an experienced neurologist (H.-S.A.) who was blinded to the study hypothesis and patients' characteristics. Initially, the scoring was performed on the right and left hemispheres (0–60 for each side) separately, and then a composite score for both hemispheres was also calculated. To determine interobserver agreement, a second rater (W.-S.R.) graded WMHs in 40 randomly selected patients. The intraclass correlation coefficient was 0.81. Because there has not been a consensus on the hemispheric asymmetry of WMH, we arbitrarily defined it by selecting various cutoff points (2, 3, 4, or 5) for the differences of modified Scheltens scale (mSS) scores between the right and left hemispheres in individual patients, thereby dichotomizing the patients into symmetric versus asymmetric WMH groups.

## Mapping Hemispheric WMH Asymmetry Versus Old Silent Lacunar Infarcts/Acute Lacunar Infarcts

We generated color-coded lesion-frequency maps for acute infarcts (on DWI), old silent lacunar infarcts (on T2-weighted images in 154 patients and B0 images of DWI in 113 patients) and WMHs (FLAIR images) after stratification by the hemispheric WMH dominance (right versus left, or symmetric), as previously published,[7,10] by plotting the frequency of incidence of lesions at each voxel coordinate of 5 Montreal Neurological Institute template slices (centered on 15.3 mm, 21.5 mm, 27.5 mm, 33.5 mm, and 39.5 mm on the z axis). These slices were chosen on the basis of clinical experience to represent the levels of striatocapsular (z=15.5±3 mm and 21.5±3 mm), corona radiata (z=27.5±3 mm and 33.5±3 mm), and centrum semiovale (z=39.5±3 mm) regions.

Based on 2-dimensional random field theory,[7] statistical parametric mapping analyses were performed using custom-built software to generate age-adjusted t-statistics maps comparing the regional differences in the frequency of having acute or old lacunar infarct (at each voxel) between the groups of right versus left hemispheric dominance of WMHs.

## Statistical Analysis

The correlations between the total WMH volume in the entire brain and the absolute difference of the hemispheric WMH volumes and between mSS scores and log-transformed WMH volumes were examined using linear regression analysis. Patients' baseline characteristics after stratification into symmetric/asymmetric WMH (absolute difference of mSS score ≥3) or with/without old silent lacunar infarcts were compared using Student *t* test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables as appropriate. The relationship between hemispheric asymmetry of WMH and the presence or absence of old silent lacunar infarcts was examined using chi-square test. The association between acute infarct locations (corona radiata, basal ganglia, internal capsule, and thalamus) and the severity of WMHs (tertiles) was evaluated using the Cochran-Mantel-Haenszel test. For the analysis, WMHs were stratified into tertiles based on quantitative WMH volume. In addition, the relationship between the lesion side (ie, either the left or right hemispheric location of an acute lacunar infarct) and the hemispheric asymmetry of WMH, with or without stratification for the presence of nonsignificant stenosis of the relevant large artery, were tested by chi-

square test or Fisher exact test as appropriate. The relationship of WMH asymmetry with the presence of any cerebral microbleeds and deep cerebral microbleeds were tested by Fisher exact test. *P* values <0.05 were considered statistically significant. All statistical analyses were conducted with STATA version 14.0 (StatCorp).

## Results

The mean age (SD) of patients was 63.6 (13.3) years, and 63% were men. As expected, mSS scores correlated well with WMH volumes (*P*<0.001, Figure S2). WMH volumes tended to be higher in patients with asymmetric WMH, which was defined by the hemispheric difference of mSS scores (*P*<0.001 by ANOVA, Figure S3). However, the absolute value of the hemispheric difference of mSS scores was not significantly associated with WMH volume (Figure S4, linear regression analysis coefficient=0.07; *P*=0.18). When the WMH asymmetry was defined based on the hemispheric difference of mSS score <3 versus ≥3, 35 patients (13.1%) had left hemispheric dominance and 32 (12.0%) had right hemispheric dominance.

**Table 1.** Baseline Characteristics of the Study Population Stratified by the Hemispheric Difference of mSS Score: ≥3 Versus <3

| | | Absolute Difference of mSS Score | | |
|---|---|---|---|---|
| | All (N=267) | <3 (n=200) | ≥3 (n=67) | *P* Value |
| Age, mean±SD, y | 63.6±13.3 | 62.6±13.4 | 66.6±12.4 | 0.03 |
| Men | 168 (62.9) | 127 (63.5) | 41 (61.2) | 0.74 |
| Hypertension | 169 (63.3) | 119 (59.5) | 50 (74.6) | 0.03 |
| Diabetes mellitus | 77 (28.8) | 57 (28.5) | 20 (29.9) | 0.83 |
| Hyperlipidemia | 110 (41.2) | 88 (44.0) | 22 (32.8) | 0.11 |
| Smoking | 126 (47.2) | 96 (48.0) | 30 (44.8) | 0.65 |
| Coronary artery disease | 14 (5.2) | 10 (5.0) | 4 (6.0) | 0.76* |
| Prior use of antiplatelets | 67 (25.1) | 48 (24.0) | 19 (28.4) | 0.48 |
| Prior use of statins | 27 (10.1) | 22 (11.0) | 5 (7.5) | 0.41 |
| Location of acute infarct | | | | |
| Corona radiata | 101 (37.8) | 73 (36.5) | 28 (41.8) | 0.10 |
| Basal ganglia | 62 (23.2) | 46 (23.0) | 16 (23.9) | |
| Thalamus | 55 (20.6) | 48 (24.0) | 7 (10.5) | |
| Internal capsule | 49 (18.4) | 33 (16.5) | 16 (23.9) | |
| Old silent lacunar infarct† | | | | |
| 0 | 165 (61.8) | 141 (70.5) | 24 (35.8) | <0.001 |
| 1 or 2 | 58 (21.7) | 34 (17.0) | 24 (35.8) | |
| ≥3 | 44 (16.5) | 25 (12.5) | 19 (28.4) | |
| Cerebral microbleeds (n=234)‡ | | | | |
| 0 | 173 (73.9) | 134 (77.5) | 39 (63.9) | 0.11 |
| 1 or 2 | 31 (13.3) | 19 (11.0) | 12 (19.7) | |
| ≥3 | 30 (12.8) | 20 (11.6) | 10 (16.4) | |
| NIHSS, median (IQR) | 3 (1–4) | 3 (1–4) | 4 (2–5) | 0.03§ |
| Modified Scheltens scale score, median (IQR) | 21 (10–33) | 17 (9–27) | 25 (18–38) | <0.001§ |
| WMH volume,‖ median (IQR) | 0.7 (0.3–1.4) | 0.6 (0.3–1.3) | 1.0 (0.6–2.0) | 0.003§ |

Data are presented as number (percentage) unless otherwise indicated. IQR indicates interquartile range; mSS, modified Scheltens scale; NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensity.

*Fisher exact test.

†Old silent lacunar infarcts with cavitation on fluid-attenuated inversion recovery images.

‡Data were available in 234 patients.

§Wilcoxon rank sum test.

‖Percent of total brain volume.

## Old Silent Lacunar Infarcts Were More Frequently Observed in Patients With Asymmetric WMH Than in Patients With Symmetric WMH

Clinical characteristics of patients with symmetric versus asymmetric WMH are presented in Table 1. The patients with asymmetric WMHs were likely to be older and have hypertension compared with the patients with symmetric WMHs. In addition, admission National Institutes of Health Stroke Scale score and total (right and left) mSS scores were higher in the asymmetric WMH group than in the symmetric WMH group. Old silent lacunar infarcts were more frequently observed in the asymmetric WMH group (64.2%) than in the symmetric group (29.5%, $P<0.001$). Compared with the symmetric WMH group, the asymmetric WMH group was likely to have more old silent lacunar infarcts (median 0 versus 1, $P<0.001$ by rank sum test). In addition, more patients (28.3%) in the asymmetric WMH group had ≥3 old silent lacunar infarcts compared with the symmetric WMH group (12.5%, $P<0.001$).

## Asymmetric WMH Was More Frequently Observed in Patients With Old Silent Lacunar Infarcts

As shown in Table 2, 102 patients (38.2%) had old silent lacunar infarct and were more likely to be old and have hypertension, diabetes mellitus, or coronary artery disease compared with those without old silent lacunar infarcts (n=165; all $P<0.05$). Asymmetric WMH was about 3-fold more frequent ($P<0.001$) in the group with old silent lacunar infarct (42.2%, 43/102) than in the group without old silent lacunar infarct (14.6%, 24/165). This association was consistent regardless of an operational definition of the asymmetry (ie, dichotomizations at mSS scores 3, 4, and 5; Table S1). Furthermore, exclusion of patients with mild WMHs (mSS score <10, n=64) did not alter the association between asymmetric WMH and the presence of old silent lacunar infarct (Table S2).

When we defined the group with old silent lacunar infarct using T2-weighted or B0 images, 150 patients (56.2%) were assigned to the T2 or B0-old silent lacunar infarct group, indicating a higher sensitivity of T2-weighted MRI or B0 DWI to detect silent brain infarcts compared with FLAIR MRI (38.2%, $P<0.001$). Differences of the baseline characteristics between the presence and absence of old silent lacunar infarcts based on the T2-weighted or B0 images were similar to those based on the FLAIR images (Table S3).

Lesion frequency maps and age-adjusted t-statistics maps showed that old silent lacunar infarcts on T2-weighted or B0 images tended to be found more often in the hemisphere with more severe WMH on FLAIR images (Figure 1A, purple arrows versus green arrows). The spatial association between WMH and old infarcts appeared to be prominent in the corona radiata than in the centrum semiovale or striatocapsular area. In the symmetric WMH group, old silent lacunar infarcts were distributed symmetrically across both hemispheres (Figure 1B).

## Acute Lacunar Infarction Tended to Occur in the Hemisphere With More Severe WMH

One-hundred fifty patients (56.2%) had an acute lacunar infarct in the left hemisphere, whereas 117 patients (43.8%)

**Table 2.** Baseline Characteristics and Hemispheric Dominance of WMH Stratified by the Presence of Old Silent Lacunar Infarcts

| | Without Old Silent Lacunar Infarcts (n=165) | With Old Silent Lacunar Infarcts (n=102) | *P* Value |
|---|---|---|---|
| Age, mean±SD, y | 62.0±13.9 | 66.3±11.8 | 0.009 |
| Men | 104 (63.0) | 64 (62.8) | 0.96 |
| Hypertension | 93 (56.4) | 76 (74.5) | 0.003 |
| Diabetes mellitus | 40 (24.2) | 37 (36.3) | 0.04 |
| Hyperlipidemia | 64 (38.8) | 46 (45.1) | 0.31 |
| Smoking | 77 (46.7) | 49 (48.0) | 0.83 |
| Coronary artery disease | 3 (1.8) | 11 (10.8) | 0.003* |
| Prior use of antiplatelets | 26 (15.8) | 41 (40.2) | <0.001 |
| Prior use of statins | 12 (7.3) | 15 (14.7) | 0.05 |
| Location of acute infarct | | | |
| Corona radiata | 53 (32.1) | 48 (47.1) | 0.02 |
| Basal ganglia | 45 (27.3) | 17 (16.7) | |
| Thalamus | 40 (24.2) | 15 (14.7) | |
| Internal capsule | 27 (16.4) | 22 (21.6) | |
| Cerebral microbleeds (n=234)† | | | |
| 0 | 127 (88.8) | 46 (50.6) | <0.001 |
| 1 or 2 | 9 (6.3) | 22 (24.2) | |
| ≥3 | 7 (4.9) | 23 (25.3) | |
| NIHSS, median (IQR) | 3 (1–4) | 3 (2–4) | 0.14‡ |
| WMH volume§, median (IQR) | 0.5 (0.2–0.9) | 1.3 (0.6–2.1) | <0.001‡ |
| Scheltens scale, median (IQR) | 14 (7–24) | 29 (21–43) | <0.001‡ |
| Absolute difference of Scheltens scale | | | |
| 0 | 50 (30.3) | 9 (8.8) | <0.001 |
| 1 to 2 | 91 (55.2) | 50 (49.0) | |
| ≥3 | 24 (14.6) | 43 (42.2) | |

Data are presented as number (percentage) unless otherwise indicated. IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensity.
*Fisher exact test.
†Data were available in 234 patients.
‡Wilcoxon rank sum test.
§Percent of total brain volume.

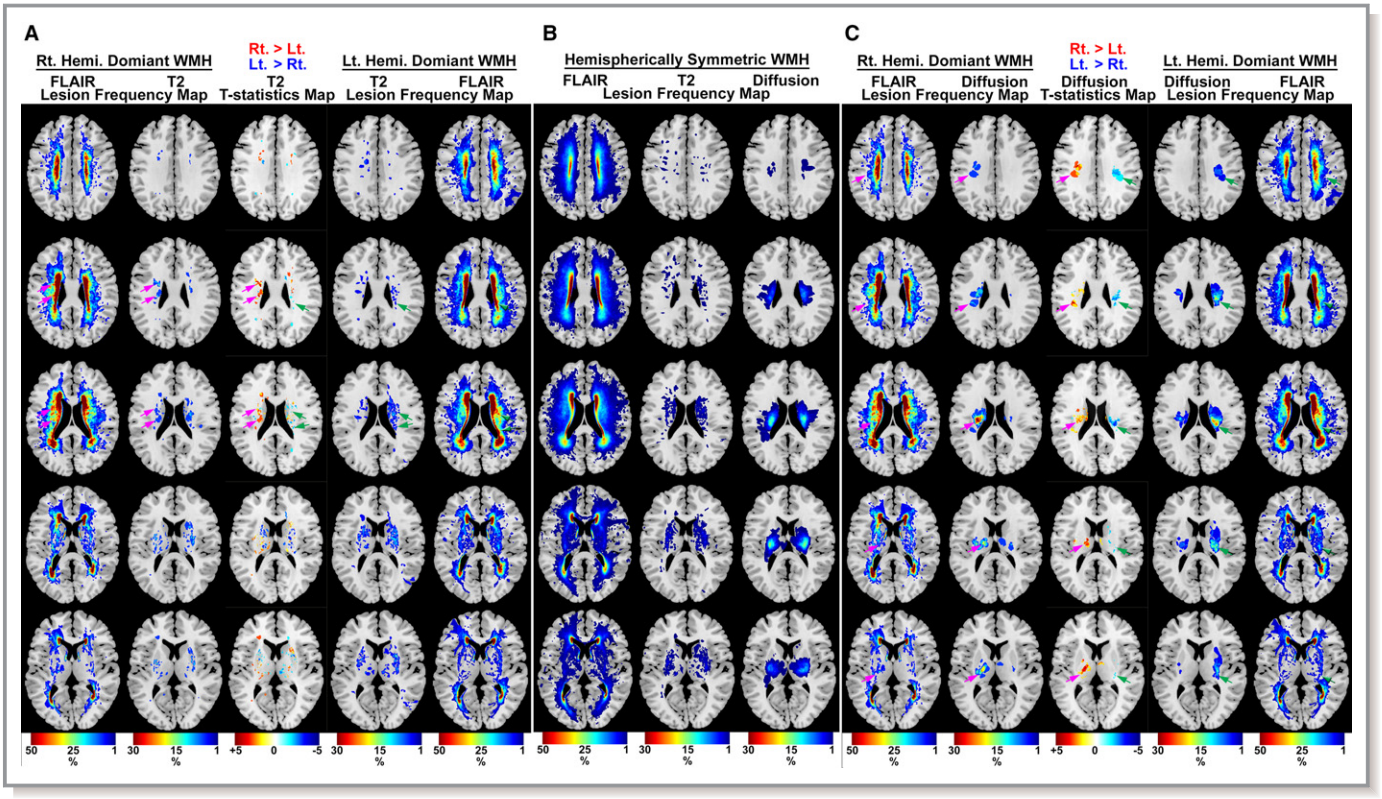


**Figure 1.** Spatial association between the hemispheric asymmetry of white matter hyperintensity (WMH) vs hemispheric predilection sites of old silent lacunar infarcts or acute lacunar infarcts. **A**, Color-coded maps show that old silent lacunar infarcts on T2-weighted images or B0 images of diffusion-weighted imaging (DWI) tend to be more in the hemisphere with larger WMH on fluid-attenuated inversion recovery (FLAIR) images (arrows). Right dominance n=32, and left dominance n=35. **B**, Hemispherically symmetric WMH on FLAIR images is associated with hemispherically symmetric distribution of old silent lacunar infarcts on T2-weighted or B0 images and acute lacunar infarcts on DWI (n=200). **C**, Color-coded maps show that acute lacunar infarcts on DWI are more likely to be found in the hemisphere with larger WMH on FLAIR images (arrows). Right dominance n=32, and left dominance n=35. The red-colored 'Rt.>Lt.' indicates that a voxel is colored in red if its frequency of infarct on T2-weighted images (**A**) or DWI (**C**) is significantly higher in the right hemispheric dominant WMH group than in the left hemispheric dominant WMH group, and vice versa for the blue-colored 'Lt.>Rt.'.

had a lesion in the right hemisphere. Baseline characteristics were not different between the left- versus right-sided lacunar infarcts (Table S4).

In patients with the left hemispheric dominance of WMH (left mSS-right mSS ≥3), an acute lacunar infarct was more likely to be located in the left (versus right) hemisphere (74% versus 26%, Table 3). In patients with the right hemispheric dominance of WMH (right mSS-left mSS ≥3), an acute lacunar infarct was more likely to be located on the right (versus left) hemisphere (81% versus 19%; $P<0.001$ by chi-square test). This association was consistent regardless of the definitions of the WMH asymmetry (Table 3). In addition, an acute lacunar infarct was more likely to develop in the hemisphere with more old silent lacunar infarcts ($P=0.004$ by Fisher exact test, Figure 2).

Acute lacunar infarction occurred in the corona radiata (n=101 patients, 37.8%), thalamus (n=55, 20.6%), basal ganglia (n=62, 23.2%), and internal capsule (n=49, 18.4%). The frequency of having a lacunar infarct in the corona radiata increased as tertiles of WMH increased (19.1%, 41.6%, and 52.8%, respectively; $P$ for trend <0.001). In addition, patients with old silent lacunar infarcts tended to have an acute lacunar infarct in the corona radiata (Table 2).

Lesion frequency maps showed that an acute lacunar infarct on DWI was likely to be found in the hemisphere with more severe WMH (Figure 1C, see also representative cases in Figure 3). Age-adjusted t-statistics maps corroborated the spatial association between WMHs and acute lacunar infarcts. In the symmetric WMH group, acute lacunar infarcts were distributed symmetrically in both hemispheres (Figure 1B).

## Unlike Old or Acute Lacunar Infarcts, Cerebral Microbleeds Did Not Show Hemispheric Predilection Sites in Association With Hemispheric WMH Asymmetry

The number of cerebral microbleeds ranged from 0 to 91 (median 0, interquartile range 0–1). Compared with the

**Table 3.** Association Between the Hemispheric WMH Asymmetry and the Hemispheric Side of Acute Lacunar Infarct, Depending on Multiple Cutoff Points Defining the WMH Asymmetry

| Cutoff Points | Dominance | Side of Acute Lacunar Infarct | | |
|---|---|---|---|---|
| | | Right | Left | Total |
| Difference ≥2 | Right dominance | 40 (63) | 24 (38) | 64 |
| | Symmetric | 64 (43) | 86 (57) | 150 |
| | Left dominance | 13 (25) | 40 (75) | 53 |
| | *P* value | <0.001* | | |
| Difference ≥3 | Right dominance | 26 (81) | 6 (19) | 32 |
| | Symmetric | 82 (41) | 118 (59) | 200 |
| | Left dominance | 9 (26) | 26 (74) | 35 |
| | *P* value | <0.001* | | |
| Difference ≥4 | Right dominance | 16 (89) | 2 (11) | 18 |
| | Symmetric | 96 (42) | 134 (58) | 230 |
| | Left dominance | 5 (26) | 14 (74) | 19 |
| | *P* value | <0.001† | | |
| Difference ≥5 | Right dominance | 8 (100) | 0 | 8 |
| | Symmetric | 108 (43) | 146 (57) | 254 |
| | Left dominance | 1 (20) | 4 (80) | 5 |
| | *P* value | 0.001† | | |

Data are presented as number (percentage). Differences of white matter hyperintensity (WMH) severity defined as the difference of modified Scheltens scale scores between the right and left cerebral hemispheres.
*Chi-square test.
†Fisher exact test.


**Figure 2.** A hemispheric dominance of old silent lacunar brain infarcts (SBIs), defined using fluid-attenuated inversion recovery magnetic resonance imaging, is associated with the hemispheric side of an acute lacunar infarct. An acute lacunar infarct is more likely to develop in the hemisphere with more SBIs (Fisher exact test, *P*=0.006).

symmetric WMH group, the asymmetric WMH group was likely to have numerically more cerebral microbleeds (*P*<0.001 by rank sum test). When we categorized the number of cerebral microbleeds (Table 1), the asymmetric WMH group tended to have ≥3 cerebral microbleeds compared with the symmetric WMH group (11.6% versus 16.4%), albeit not statistically significant (*P*=0.11). Among 61 patients who had cerebral microbleeds, 10 had only cortical-subcortical microbleeds, 32 only deep microbleeds, and 19 had both. In addition, cerebral microbleeds were more frequently found in the group with old silent lacunar infarcts than in the group without old silent lacunar infarcts (50% versus 11%, *P*<0.001, Table 2). However, the hemispheric side of cerebral microbleeds was not associated with the hemispheric dominance of WMH (*P*=0.56 when the asymmetry of WMH was defined as the absolute difference of mSS scores ≥3, Table 4). When we excluded cortical-subcortical microbleeds from the analysis, the association was materially unchanged (*P*=0.12 when the asymmetry of WMH was defined as the absolute difference of mSS score ≥3, Table S5).

## Acute Lacunar Infarction Occurred Predominantly in the Hemisphere With Nonsignificant Large Artery Stenosis

Thirty-eight patients (14.2%) had nonsignificant stenosis (<50%) in the MCA (Table 5). All but 1 patient with nonsignificant left MCA stenosis had an acute lacunar infarct in the left hemisphere (94.4%, 17/18), while most of the patients with nonsignificant right MCA stenosis had a lesion in the right hemisphere (85.0%, 17/20; *P*<0.001 by Fisher exact test). Likewise, the hemispheric side of nonsignificant PCA stenosis was significantly associated with that of acute lacunar infarction (*P*=0.02 by the Fisher exact test).

Among the 18 patients with left MCA stenosis, asymmetric WMH was observed in 5 patients, and 4 of them had a left hemispheric dominance (left-right mSS scores ≥3). Among the 20 patients with right MCA stenosis, asymmetric WMH was observed in 11 patients, and 8 of them had a right hemispheric dominance (right-left mSS scores ≥3; *P*=0.038 by the Fisher exact test).

Among 265 (99.3%) patients with carotid angiograms available, 14 (5.3%) patients had extracranial carotid stenosis: 11 mild (<50%) stenosis and 3 severe (≥50%) stenosis or

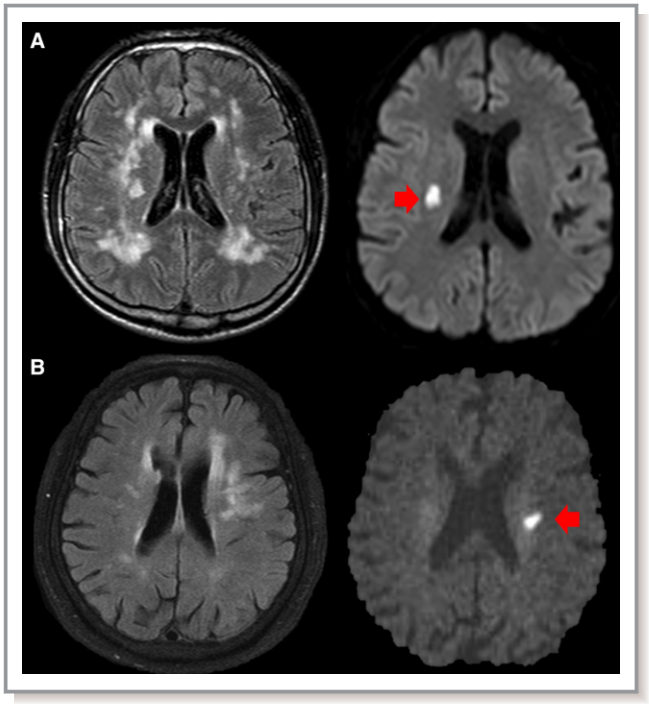


**Figure 3.** Representative cases of asymmetric white matter hyperintensity (WMH) versus acute lacunar infarct. Two cases (**A** and **B**) show the association between the hemispheric dominance of WMH on fluid-attenuated inversion recovery magnetic resonance imaging (left column) and hemispheric predilection site of an acute lacunar infarct on diffusion-weighted imaging (arrows in the right column).

occlusion. WMH asymmetry was not associated with extracranial carotid artery disease ($P$=0.73, Table S6).

## Discussion

In the present study on the quantification and mapping of ischemia-related MRI lesions of 267 patients with acute lacunar infarction, we found that: (1) an asymmetric WMH distribution was more likely to be associated with old silent lacunar infarcts than symmetric WMH, and (2) an acute lacunar infarct as well as old silent infarcts tended to be located in the cerebral hemisphere with relatively more severe WMH. In the subset of patients with nonsignificant MCA or PCA stenosis, the acute lacunar infarct tended to be on the same side as that of the nonsignificant large artery stenosis. Taken together, these findings suggest that the larger hemispheric WMH in patients with asymmetric WMH could be infarct-containing WMH or infarct-vulnerable WMH. It would be interesting to study whether antiplatelet therapy in the absence of stroke history could be beneficial in patients with asymmetric (versus symmetric) WMH.

Chronic WMH has been regarded as reflecting incomplete ischemia rather than complete infarction.[19] Recently, Potter et al[4] argued against the traditional "lacune-cavitating lesion" hypothesis because serial imaging showed that not all lacunar infarcts cavitate to become "lacunes" resulting from cystic change and appear as low signal intensity on FLAIR MRI. Some lacunar infarcts eventually look like WMH, and others may even disappear.[4]

Duering et al[6] demonstrated that the edge of WMH is a predilection site for lacunar infarction, indicating a close link between lacunes and WMHs. They examined the spatial relationships between incidental lacunes and WMHs in 276 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. The majority (91.3%) of lacunes developed at the edge of WMH, whereas few lacunes were found to develop fully within or outside WMH.[6] In addition, a post hoc analysis of the North American Symptomatic Carotid Endarterectomy Trial demonstrated that the development and progression of WMHs are associated with higher occurrence of lacunar stroke.[20] Moreover, WMH could expand as a result of asymptomatic lacunar infarcts,

**Table 4.** Association Between the Presence of Cerebral Microbleeds and the WMH Asymmetry According to Different Cutoff Points Defining the WMH Asymmetry, Based on the Difference of mSS scores Between the Right and Left Cerebral Hemispheres

| Cutoff Points | Dominance | Presence of Cerebral Microbleeds (n=234) | | | |
|---|---|---|---|---|---|
| | | Right Hemisphere Only | Left Hemisphere Only | Both Hemispheres | No Microbleed |
| Difference of ≥2 | Right | 4 (7) | 2 (4) | 13 (24) | 35 (65) |
| | Symmetric | 4 (7) | 2 (4) | 13 (24) | 99 (77) |
| | Left | 3 (6) | 3 (6) | 6 (12) | 39 (76) |
| | *P* value | 0.44 | | | |
| Difference of ≥3 | Right | 2 (7) | 2 (7) | 7 (25) | 17 (61) |
| | Symmetric | 12 (7) | 8 (5) | 21 (12) | 132 (76) |
| | Left | 2 (6) | 2 (6) | 5 (15) | 24 (73) |
| | *P* value | 0.56 | | | |

Fisher exact test was used. Data are presented as number (percentage). mSS indicates modified Scheltens scale; WMH, white matter hyperintensity.

**Table 5.** Association Between the Hemispheric Side of Nonsignificant (<50%) Stenosis of the MCA or PCA and that of Acute Lacunar Infarction

| | Side of Acute Lacunar Infarct | | |
|---|---|---|---|
| | Left | Right | *P* Value |
| MCA | | | |
| None | 130 (56.8) | 99 (43.2) | <0.001 |
| Right | 3 (15.0)* | 17 (85.0)* | |
| Left | 17 (94.4) | 1 (5.6) | |
| PCA stenosis | | | |
| None | 144 (55.4) | 116 (44.6) | 0.02 |
| Right | 0 | 1 (100)† | |
| Left | 6 (100)‡ | 0 | |

Fisher exact test. Data are presented as number (percentage). MCA indicates middle cerebral artery; PCA, posterior cerebral artery.
*In each group, 1 patient had a thalamic infarct.
†The patient had a corona radiata infarct.
‡All patients had a thalamic infarct.

which are known to be at least 5 times more common than symptomatic ones.[21] Our study shows that unlike WMH without old silent infarcts, WMH with old silent infarcts is more likely to be hemispherically asymmetric in its shape. Asymmetric growth of WMH likely occurs because lacunar infarction tends to recur in the same hemisphere where previous infarction occurred (Data S1), as previously suggested.[22]

Lacunar infarcts have been linked with small-vessel disease, which is caused by lipohyalinosis or fibrinoid necrosis of small arteries or arterioles supplying the deep subcortical brain structures.[23] However, accumulating evidence indicates that atherosclerosis in the parent artery potentially contributes to the development of lacunar infarction.[24] Our study, which excluded patients with moderate to severe (≥50%) large artery stenosis, support this notion: There was a significant correlation between the hemispheric lesion sides of acute lacunar infarction and relevant large artery stenosis of <50%. In these patients, asymmetric WMH could have formed by tiny atheromas in a normal-looking but atherosclerotic parent artery, causing thromboembolism or hemodynamic compromise in perforating arteries, thereby generating silent or symptomatic infarcts in the ipsilesional hemisphere.[25] In a previous study of 97 patients with high-grade (≥70%) unilateral stenosis of the extracranial internal carotid artery, the hemispheric volume ipsilateral to the stenotic internal carotid artery was significantly smaller and WMH was more extensive.[26] We found no significant association between extracranial carotid steno-occlusion and WMH asymmetry. This discrepancy most likely results from differences between the study populations, including the rarity of extracranial carotid artery disease in our patients with lacunar stroke.

We found no association between the hemispheric side of cerebral microbleeds and the hemispheric dominance of WMH. When only deep cerebral microbleeds were considered, we found no association either. Thus, the hemispheric asymmetry of WMH appears to be infarct-related rather than hemorrhage-related, suggesting a possibility of net clinical benefit of antiplatelet therapy in patients with asymmetric WMH by preventing cerebral infarction without increasing the risk of cerebral hemorrhage as much.

## Study Limitations

Our study has several limitations. First, the definition of "symmetric versus asymmetric" WMH was arbitrary. However, using different cutoff points for the WMH scores in the patient grouping did not change the results. Second, we did not obtain and study follow-up magnetic resonance images. We, therefore, could not confirm whether acute lacunar infarcts actually turn into WMH and thus contribute to WMH asymmetry. Third, we reasoned and showed that infarct-related WMH was hemispherically asymmetric by investigating the spatial association between cavitating infarcts and WMH burden. It is plausible but not clear yet whether noncavitating infarcts could also contribute to hemispheric WMH asymmetry. Fourth, as the severity of WMH increases, acute lacunar infarction more likely occurred in the corona radiata than in other sites including the basal ganglia, internal capsule, and thalamus. Further studies are required to investigate whether the corona radiata is more vulnerable to WMH-related ischemic damage. Last, although noncorrected (but age-adjusted) t-statistics maps also showed the spatial association of the hemispheric side of old infarcts and acute lacunes with the hemispheric dominance of WMH, multiple comparison correction will have to be used in future investigations with larger sample sizes.

## Conclusions

This is the first study to demonstrate that hemispherically asymmetric (versus symmetric) WMHs are more frequently associated with old silent lacunar infarcts and acute lacunar infarcts in the hemisphere with relatively large WMH. Further studies are required to investigate whether antiplatelet drugs are beneficial for the prevention of ischemic stroke in patients with asymmetric WMH who do not have a history of stroke.

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## Disclosures

None.

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# SUPPLEMENTAL MATERIAL

# Data S1.

## Supplemental Methods

*Population with recurrent lacunar infarct*

To examine whether recurrent supratentorial lacunar infarcts preferentially develop in the same hemisphere as an index stroke, we studied the data of Comprehensive Registry Collaboration for Stroke in Korea (CRCS-K). From 2008 to 2015, 64 patients had a recurrent lacunar infarct confirmed by diffusion weighted magnetic resonance imaging. We excluded the patients who had index lacunar infarction in the brainstem (n = 15) and recurrent lacunar infarction in the brainstem (n = 5), leaving 44 patients with recurrent supratentorial lacunar infarction for the final analysis. We used the chi-square test to analyze the association between the hemispheric lesion sides (i.e. right vs. left) of the index and recurrent lacunar infarcts.

*Modified Scheltens method*

Periventricular WMHs are rated as follows: caps, occipital 0/1/2 and frontal 0/1/2; bands, lateral ventricles 0/1/2 (0 = absent, 1 = ≤ 5 mm, 2 = ≥ 6 mm and ≤ 10 mm). Deep WMH rating addresses deep white matter (frontal, parietal, occipital, and temporal regions; maximum 24 points) and basal ganglia areas (caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule; maximum 30 points) with a 0-to-6-point scale: 0 = absent, 1 = < 3 mm in ≤ 5, 2 = < 3 mm in ≥ 6, 3 = 4 to 10 mm in ≤ 5, 4 = 4 to 10 mm in ≥ 6, 5 = < 11 mm in >1, and 6 = confluent.

## Supplemental Results

Fourteen patients (31.8%) had an index lacunar stroke in the basal ganglia / internal capsule, 26 (59.1%) corona radiata, and 4 (9.1%) thalamus. Among the 18 patients who had an index lacunar infarct in the left hemisphere, 12 (66.7%) subsequently had recurrent lacunar infarction in the same hemisphere, and 6 (33.3%) developed a lesion in the contralateral hemisphere. In addition, among 26 patients who had an index

lacunar infarction in the right hemisphere, 19 (73.1%) subsequently had recurrent lacunar infarction in the same hemisphere, and 7 (26.9%) had a lesion in the contralateral hemisphere. Chi-square test showed that a recurrent lacunar infarction preferentially develops in the hemisphere that had the index lacunar infarction (Pearson chi = 6.85, $P = 0.009$).

**Table S1. Distribution of the absolute differences of modified Scheltens Scale scores between the hemispheres, stratified by the presence of silent old silent lacunar infarcts.**

| Absolute difference of modified Scheltens Scale score | With old silent lacunar infarct (n = 102) | Without old silent lacunar infarct (n = 165) |
|---|---|---|
| 0 | 9 (8.8%) | 50 (30.3%) |
| 1 | 33 (32.4%) | 58 (35.2%) |
| 2 | 17 (16.7%) | 33 (20.0%) |
| 3 | 19 (18.6%) | 11 (6.7%) |
| 4 | 16 (15.7%) | 8 (4.9%) |
| 5 | 5 (4.9%) | 5 (3.0%) |
| 6 | 1 (1.0%) | 0 |
| 7 | 0 | 0 |
| 8 | 1 (1.0%) | 0 |
| 9 | 0 | 0 |
| 10 | 0 | 0 |
| 11 | 0 | 0 |
| 12 | 1 (1.0%) | 0 |

$P < 0.001$ by Fisher's exact test.

**Table S2. Association between the hemispheric difference of Scheltens scale scores and the presence of silent old lacunar infarcts, after exclusion of the patients with mild WMH (modified Scheltens Scale score < 10, n = 64).**

| | Without old silent lacunar infarct (n = 67) | With old silent lacunar infarct (n = 139) | P value |
|---|---|---|---|
| Absolute difference of Scheltens scale | | | 0.027 |
| 0 | 18 (26.9%) | 21 (15.1%) | |
| 1 - 2 | 36 (53.7%) | 69 (49.6%) | |
| ≥ 3 | 13 (19.4%) | 49 (35.3%) | |

Chi-square test was used.

**Table S3. Baseline characteristics and a hemispheric dominance of white matter hyperintensity (WMH), stratified by the presence of silent old lacunar infarcts identified by using T2-weighted magnetic resonance images (n = 154) or B0 images (n= 113) instead of fluid attenuation inversion recovery images.**

| | Without old silent lacunar infarct (n = 117) | With old silent lacunar infarct (n = 150) | P value |
|---|---|---|---|
| Age, years | 60.8 ± 13.9 | 65.8 ± 12.3 | 0.002 |
| Sex, men | 74 (63.3%) | 94 (62.7%) | 0.92 |
| Hypertension | 64 (54.7%) | 105 (70.0%) | 0.01 |
| Diabetes | 27 (23.1%) | 50 (33.3%) | 0.07 |
| Hyperlipidemia | 53 (45.3%) | 57 (38.0%) | 0.23 |
| Smoking, current or quit < 5years | 53 (45.3%) | 73 (48.7%) | 0.58 |
| Coronary artery disease | 2 (1.7%) | 12 (8.0%) | 0.026* |
| Prior use of anti-platelet | 13 (11.1%) | 54 (36.0%) | < 0.001 |
| Prior use of statin | 11 (9.4%) | 16 (10.7%) | 0.73 |
| Location of infarct | | | 0.001 |
| Corona radiata | 33 (28.2%) | 68 (45.3%) | |
| Basal ganglia | 34 (29.1%) | 28 (18.7%) | |
| Thalamus | 33 (28.2%) | 22 (14.7%) | |
| Internal capsule | 17 (14.5%) | 32 (21.3%) | |
| Cerebral microbleeds (n = 234)‡ | | | < 0.001 |
| 0 | 93 (90.3%) | 80 (61.1%) | |
| 1–2 | 5 (4.9%) | 26 (19.9%) | |
| ≥ 3 | 5 (4.9%) | 25 (19.1%) | |
| NIHSS, median (IQR) | 2 (1–4) | 3 (2–4) | 0.04† |
| Scheltens scale, median (IQR) | 11 (5–22) | 24 (18–40) | < 0.001† |
| Absolute difference of Scheltens scale | | | <0.001 |
| 0 | 34 (29.1%) | 25 (16.7%) | |

| | | |
|---|---|---|
| 1 - 2 | 67 (57.3%) | 74 (49.3%) |
| ≥ 3 | 16 (13.7%) | 51 (34.0%) |

Data presented as mean ± standard deviation, number (percentage), or median (interquartile range)

IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale.

*Fisher's exact test was used.

†Rank-sum test was used.

‡Data were available in 234 patients.

**Table S4. Baseline characteristics of the study population by the hemispheric side of acute lacunar infarction (n = 267).**

| | All (N = 267) | Left (n = 150) | Right (n = 117) | P value |
|---|---|---|---|---|
| Age, years | 63.6 ± 13.3 | 62.3 ± 13.2 | 65.4 ± 13.2 | 0.06 |
| Sex, men | 168 (62.9%) | 91 (60.7%) | 77 (65.8%) | 0.39 |
| Hypertension | 169 (63.3%) | 92 (61.3%) | 77 (65.8%) | 0.45 |
| Diabetes | 77 (28.8%) | 43 (28.7%) | 34 (29.1%) | 0.94 |
| Hyperlipidemia | 110 (41.2%) | 63 (42.0%) | 47 (40.2%) | 0.76 |
| Smoking, current or quit < 5years | 126 (47.2%) | 69 (46.0%) | 57 (48.7%) | 0.66 |
| Coronary artery disease | 14 (5.2%) | 6 (4.0%) | 8 (6.8%) | 0.30 |
| Prior use of anti-platelet | 67 (25.1%) | 37 (24.7%) | 30 (25.6%) | 0.86 |
| Prior use of statin | 27 (10.1%) | 17 (11.3%) | 10 (8.6%) | 0.45 |
| Location of infarct | | | | 0.52 |
| Corona radiata | 101 (37.8%) | 52 (34.7%) | 49 (41.9%) | |
| Basal ganglia | 62 (23.2%) | 36 (24.0%) | 26 (22.2%) | |
| Thalamus | 55 (20.6%) | 35 (23.3%) | 20 (17.1%) | |
| Internal capsule | 49 (18.4%) | 27 (18.0%) | 22 (18.0%) | |
| Cerebral microbleeds (n = 234)† | | | | 0.93 |
| 0 | 173 (73.9%) | 98 (72.2%) | 75 (75.5%) | |
| 1–2 | 31 (13.3%) | 18 (13.6%) | 13 (12.8%) | |
| ≥ 3 | 30 (12.8%) | 16 (12.1%) | 14 (13.7%) | |
| NIHSS, median (IQR) | 3 (1–4) | 3 (2–4) | 3 (2–4) | 0.97* |
| Scheltens scale, median (IQR) | 21 (10–33) | 20 (10–28) | 22 (10–35) | 0.64* |

Data presented as mean ± standard deviation, number (percentage), or median (interquartile range)

IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale.

*Rank-sum test was used.

†Data were available in 234 patients.

**Table S5. Association between deep cerebral microbleeds and white matter hyperintensity (WMH) asymmetry.**

| Cutoff points: Hemispheric difference of mSS scores | Hemispheric Dominance of WMH | Presence of deep cerebral microbleeds (n=234) | | | |
|---|---|---|---|---|---|
| | | Right hemisphere only | Left hemisphere only | Both hemispheres | No microbleed |
| Difference of 2 or more | Right | 3 (6%) | 0 (0%) | 5 (10%) | 43 (84%) |
| | Symmetric | 8 (6%) | 9 (7%) | 9 (7%) | 103 (79%) |
| | Left | 3 (6%) | 0 (0%) | 5 (10%) | 43 (84%) |
| | P value | | 0.12 | | |
| Difference of 3 or more | Right | 2 (6%) | 0 (0%) | 6 (21%) | 17 (61%) |
| | Symmetric | 9 (5%) | 11 (6%) | 14 (8%) | 139 (80%) |
| | Left | 2 (6%) | 0 (6%) | 4 (12%) | 27 (82%) |
| | P value | | 0.12 | | |

Only deep cerebral microbleeds were considered for the analysis (P values from Fisher's exact test). mSS denotes modified Scheltens scale.

**Table S6. Association between extracranial carotid steno-occlusion and WMH asymmetry.**

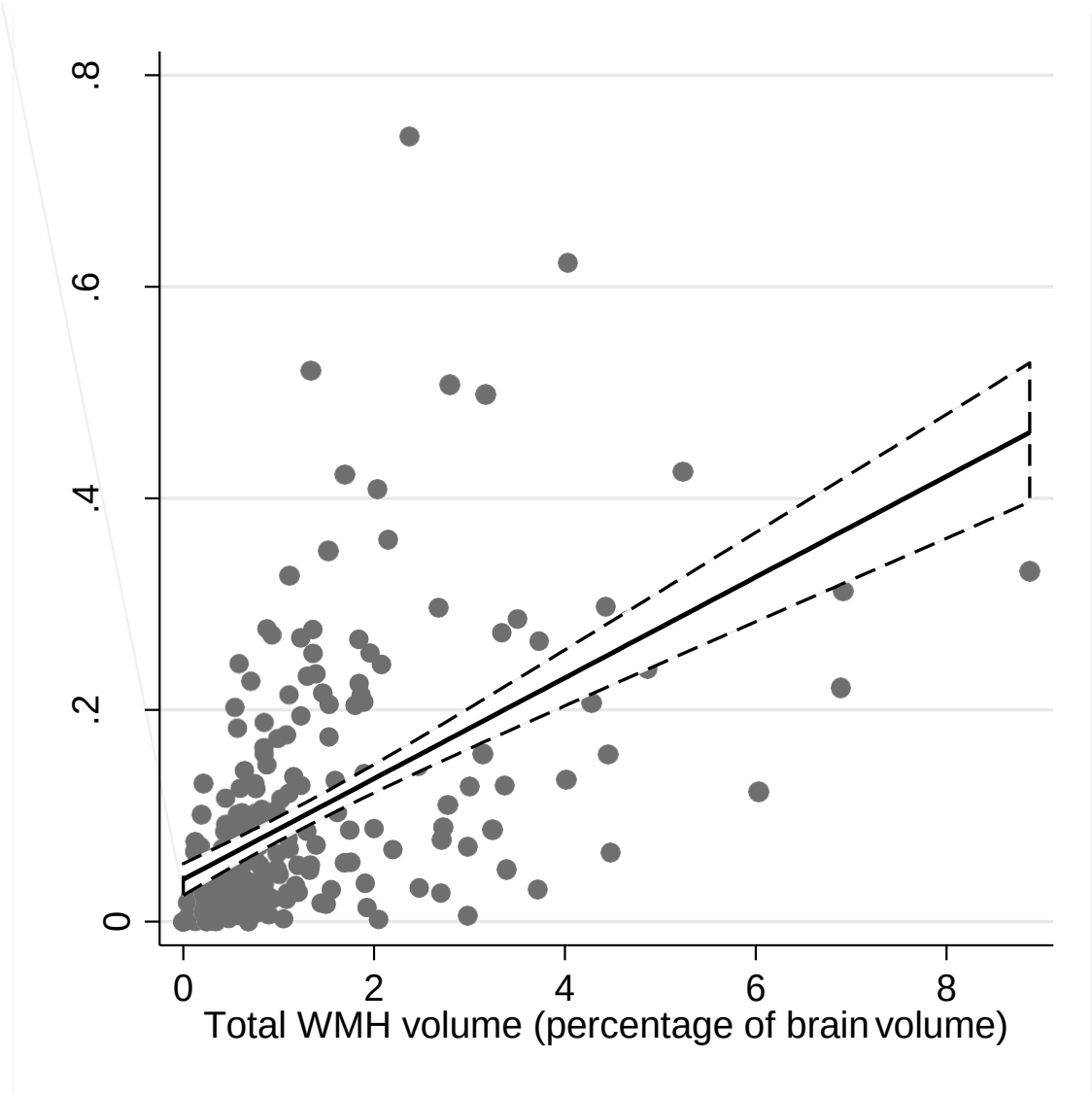
| Extracranial carotid steno-occlusion* | Symmetric | Asymmetric | | Total |
|---|---|---|---|---|
| | | Right dominance | Left dominance | |
| No | 188 | 32 | 31 | 251 |
| Right | 6 | 0 | 2 | 8 |
| Left | 4 | 0 | 2 | 6 |

Pearson chi-square = 0.12, P=0.73

Carotid angiograms were not available in two patients.

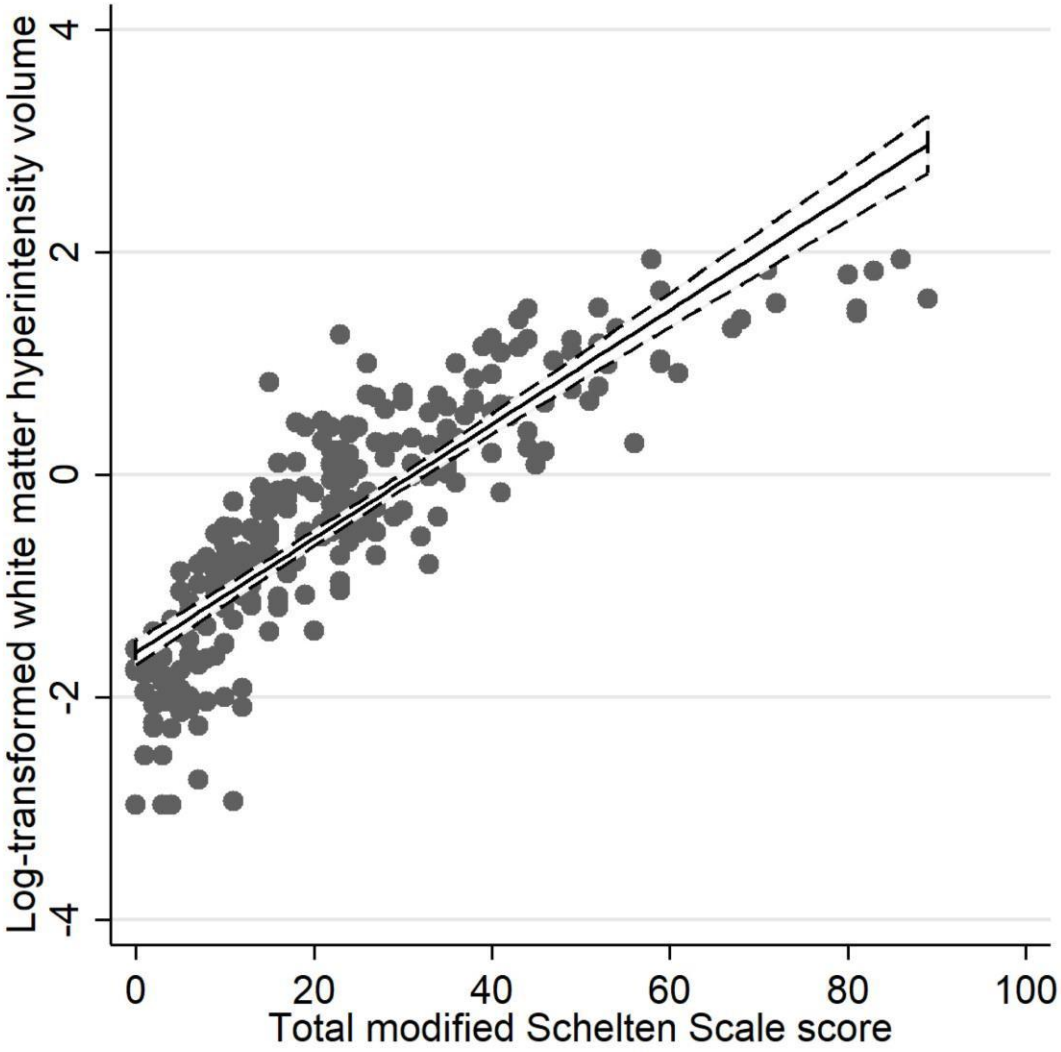
*11 were mild (<50%) stenosis and 3 severe (≥ 50%) stenosis or occlusion

**Figure S1. Correlation between the total white matter hyperintensity (WMH) volume and the inter-hemispheric difference of WMH volumes.**



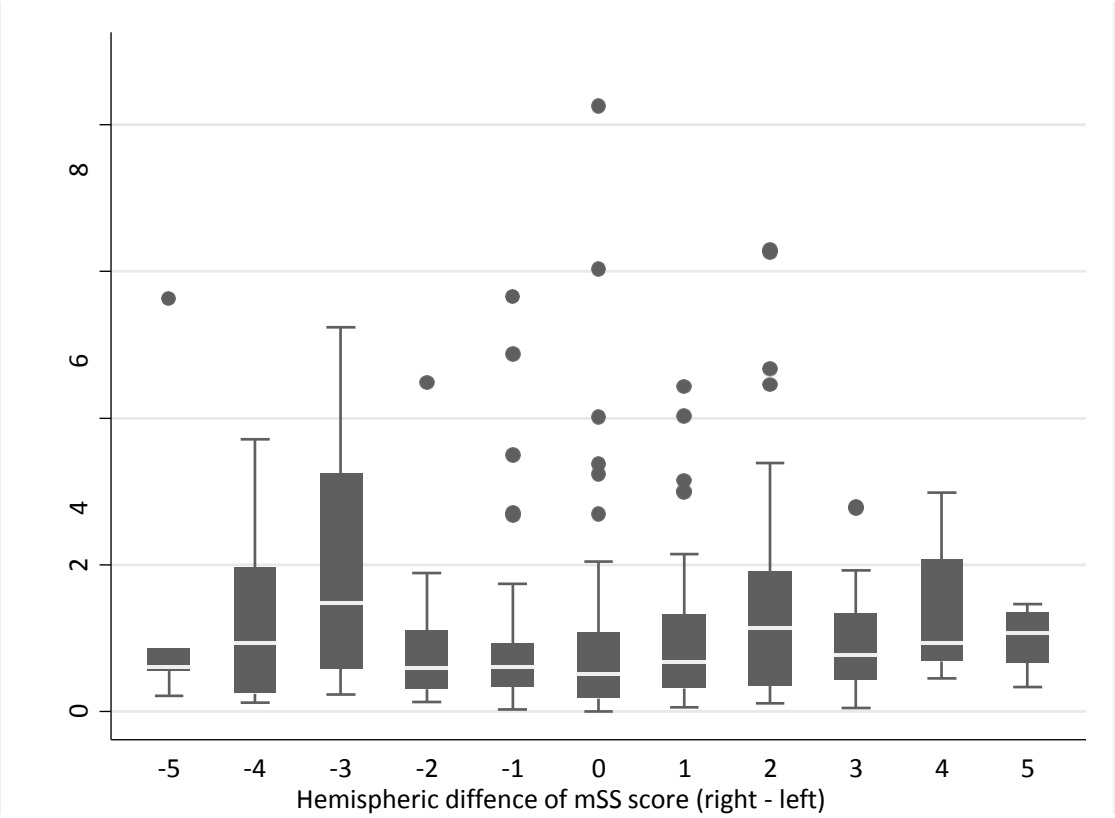

Each dot represents a single patient. Linear regression analysis showed a significant relation between the total WMH volume and the absolute difference of WMH volumes between the cerebral hemispheres ($P < 0.001$). Solid line and dot lines indicate a regression line and its 95% confidence interval, respectively.

**Figure S2. Correlation between modified Scheltens Scale scores and log-transformed white matter hyperintensity (WMH) volumes**



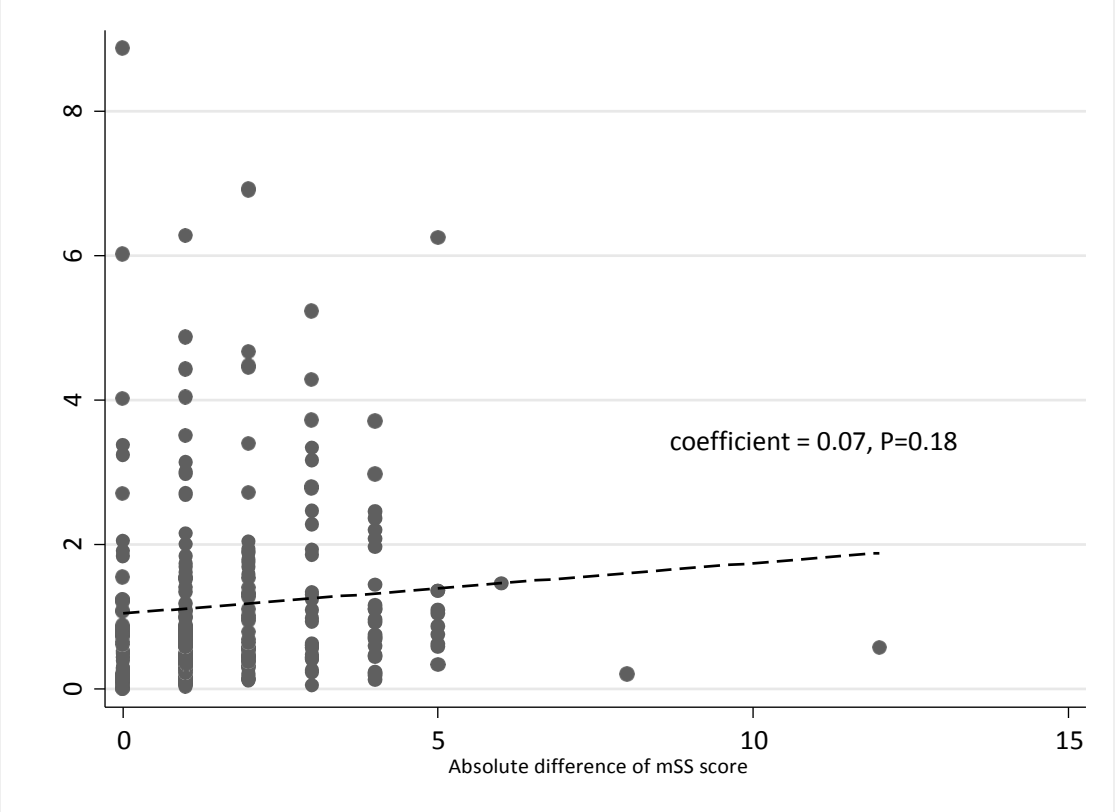

Each dot represents a single patient. Modified Scheltens Scale scores significantly correlate with log-transformed WMH volumes ($P < 0.001$ by linear regression). Solid line and dot lines indicate a regression line and its 95% confidence interval, respectively.

**Figure S3. Volumetric white matter hyperintensity volume stratified by hemispheric difference of modified Scheltens Scale score.**




The difference of WMH volume was significant by ANOVA (*P*<0.001).

**Figure S4. Linear regression analysis between absolute hemispheric difference of modified Scheltens Scale score and Volumetric white matter hyperintensity volume**




There is no association between absolute hemispheric difference of modified Scheltens Scale (mSS) score and volumetric white matter hyperintensity volume