

## Clinical Research



# Association between Leukoaraiosis Severity and Functional Outcomes in Patients with Subcortical Infarct

## OPEN ACCESS

**Received:** Jul 6, 2017

**Revised:** Sep 21, 2017

**Accepted:** Sep 26, 2017

### Correspondence to

**Min Ho Chun**

Department of Rehabilitation Medicine,  
University of Ulsan College of Medicine, Asan  
Medical Center, 88 Olympic-ro 43-gil, Songpa-  
gu, Seoul 05505, Korea.

Tel: +82-2-3010-3800

Fax: +82-2-3010-6964

E-mail: mhchun@amc.seoul.kr

**Go Eun Kim, Min Ho Chun, Min Cheol Jang, Kyung Hee Do, Su Jin Choi**

## Highlights

- LA is a risk factor for stroke, and in stroke patients, the severity of LA is related to clinical and functional outcomes.
- In this study, as in previous studies, negative effects of LA on functional outcomes were found in patients with a subcortical infarct.
- The severity of LA, predicts poor functional outcomes, including in ambulatory function, in the subacute phase after stroke onset.

## Clinical Research



# Association between Leukoaraiosis Severity and Functional Outcomes in Patients with Subcortical Infarct

Go Eun Kim ,<sup>1</sup> Min Ho Chun ,<sup>1</sup> Min Cheol Jang ,<sup>2</sup> Kyung Hee Do ,<sup>3</sup> Su Jin Choi <sup>4</sup>

<sup>1</sup>Department of Rehabilitation Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Yeungnam University College of Medicine, Daegu, Korea

<sup>3</sup>Department of Physical Medicine and Rehabilitation, Veterans Health Service Medical Center, Seoul, Korea

<sup>4</sup>Department of Physical Medicine and Rehabilitation, Parkside Rehabilitation Hospital, Busan, Korea

## OPEN ACCESS

**Received:** Jul 6, 2017

**Revised:** Sep 21, 2017

**Accepted:** Sep 26, 2017

### Correspondence to

Min Ho Chun

Department of Rehabilitation Medicine,  
University of Ulsan College of Medicine, Asan  
Medical Center, 88 Olympic-ro 43-gil, Songpa-  
gu, Seoul 05505, Korea.

Tel: +82-2-3010-3800

Fax: +82-2-3010-6964

E-mail: mhchun@amc.seoul.kr

Copyright © 2017. Korea Society for  
Neurorehabilitation

This is an Open Access article distributed  
under the terms of the Creative Commons  
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>)  
which permits unrestricted non-commercial  
use, distribution, and reproduction in any  
medium, provided the original work is properly  
cited.

### ORCID iDs

Go Eun Kim

<https://orcid.org/0000-0003-1481-1317>

Min Ho Chun

<https://orcid.org/0000-0001-8666-7225>

Min Cheol Jang

<https://orcid.org/0000-0002-7629-7213>

Kyung Hee Do

<https://orcid.org/0000-0003-4235-8759>

Su Jin Choi

<https://orcid.org/0000-0002-3443-2237>

### Conflict of Interest

The authors have no potential conflicts of  
interest to disclose.

## ABSTRACT

To investigate the influence of leukoaraiosis (LA) on the functional outcomes of subcortical stroke in the subacute phase after onset. We retrospectively analyzed 41 patients with subacute subcortical infarct at a single center from 2011 to 2015. We explored the relationship between LA severity at admission/transfer (initial evaluation) and functional outcome at the time of discharge (follow-up evaluation), as assessed using the modified Rankin Scale (mRS), Functional Ambulation Category (FAC), and modified Barthel Index (mBI). LA severity was graded as mild, moderate, or severe according to the Fazekas scale. Scores of the mRS, FAC, and mBI were compared in patients grouped based on LA severity: no LA (n = 12), mild LA (n = 19), and moderate-to-severe LA (n = 10). Significant inter-group differences were observed in all 3 scores at both the initial and follow-up evaluations. After adjustment for age, scores at follow-up evaluation were significantly different between the 2 groups. LA is related to functional outcomes of subcortical stroke in the subacute phase after onset. After adjustment for age, severe LA was correlated with poor functional outcomes in the subacute phase.

**Keywords:** Leukoaraiosis; Stroke; Cerebral Infarction

## INTRODUCTION

Stroke is a leading cause of major disability. Most stroke patients remain moderately or severely disabled throughout life [1]. One risk factor for stroke is leukoaraiosis (LA), an age-related small-vessel disease. LA is a neuroimaging term referring to magnetic resonance imaging (MRI) white matter hyperintensities (WMHs) or periventricular white matter disease [2]. Cerebral LA is frequently observed in patients suffering from acute stroke and is associated with increasing age, hypertension, and heart disease. Although the pathophysiological mechanisms underlying LA are poorly understood, it is currently presumed to be the result of ischemic or hypoperfusion-induced microvascular changes.

Several studies have shown that LA presence or degree is related to post-stroke function and cognition in patients suffering from ischemic stroke. Podgorska et al. [3] has reported lower survival rates and Mini-Mental State Examination (MMSE) scores in patients with LA than in those without LA at 1 year after stroke onset. In a large cohort study performed in

2009 [4], LA was associated with poor functional recovery, worse quality of life, and higher psychological distress in post-stroke periods. In a recent study [5], the relationship between LA severity and rehabilitation outcomes was explored using the Functional Independence Measure, and the resulting scores had a significant relationship with LA degree. In this study, we examined overall functional outcomes, including gait function, in patients suffering from subacute subcortical stroke.

## MATERIALS AND METHODS

### Subjects

We retrospectively analyzed 152 patients with subcortical infarct (corona radiata with or without basal ganglia infarct) at a single center from September 2011 to May 2015. Patients who had undergone a brain MRI with diffusion-weighted imaging performed within the first 24 hours of symptom onset that confirmed a clinically relevant infarct were eligible. The inclusion criteria were as follows: patients aged > 20 years who were admitted/transferred to the Department of Rehabilitation Medicine during the subacute phase of stroke. Patients with the following characteristics were excluded: those with a previous history of stroke or previous disability (modified Rankin Scale [mRS]  $\geq 2$ ) [1] and those who experienced dementia or cognitive impairment before the current ischemic stroke. In total, 41 patients were enrolled.

### Measures

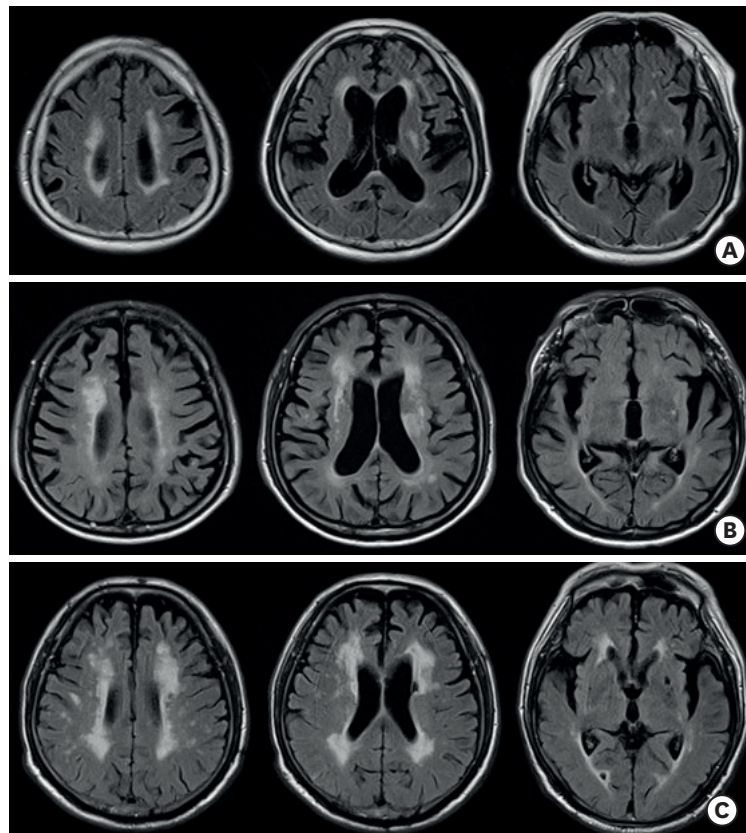
Data on patient baseline characteristics, including age, sex, LA presence and severity, and admission duration, were collected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and additional information suggesting stroke status, such as the location of the lesion (whether it involved corona radiata with or without basal ganglia) and the side of brain where lesion was located, was recorded. Previous medical history of hypertension and/or diabetes mellitus was also documented.

### *Imaging study*

The Fazekas scale, which is used to grade the WMH lesions and has been shown to have good reliability, was used to categorize LA lesions [6]. Periventricular WMH (PVWMH) and deep WMH (DWMH) were not considered separately [7]. LA lesions were categorized into 3 groups based on LA severity using the modified Fazekas criteria for periventricular hyperintensity and DWMH on T2-weighted or fluid-attenuated inversion recovery images [8]. Mild LA (single lesions of < 10-mm diameter; areas of grouped lesions of < 20-mm diameter); moderate LA (single hyperintense lesions of 10–20-mm diameter; areas of grouped lesions of  $\geq 20$  mm in any diameter; no more than “connecting bridges” between individual lesions); and severe LA (single lesions or confluent areas of hyperintensity of  $\geq 20$  mm in any diameter) (Fig. 1) [8]. LA severity of the final cohort of enrolled patients was as follows: no LA, 28.6% (n = 12); mild LA, 45.2% (n = 19); moderate LA, 19.0% (n = 8); and severe LA, 4.8% (n = 2). Subjects were then grouped according to LA presence/severity: no or mild LA and moderate-to-severe LA.

### *Functional outcomes*

Functional outcomes were assessed at the time of admission or transfer to the Department of Rehabilitation Medicine (initial evaluation) and at discharge (follow-up evaluation). The mean time interval between the initial and follow-up evaluations was 23.1 days. Functional



**Fig. 1.** LA severity according to the modified scale of Fazekas et al. [7]. (A) Mild, (B) moderate, and (C) severe LA. LA, leukoaraiosis.

outcomes were measured using the mRS, Functional Ambulation Category (FAC), and modified Barthel Index (mBI).

The mRS is a measure of the degree of dependence or disability in performing daily activities [9] and ranges from 0 to 6, with lower scores indicating less disability. The FAC was used to describe dependence on gait assistance [10]. It categorizes patients based on basic motor skills necessary for functional ambulation and is scored on a scale ranging from 0 to 5, with higher scores representing less assistance needed for ambulation. The mBI is used to measure the performance of activities of daily living (ADL) [11] and ranges from 0 to 100, with higher scores indicating higher independence in ADL.

### Intervention

All subjects underwent intensive rehabilitation beginning the day after their transfer or admission to the Department of Rehabilitation Medicine. Rehabilitation programs comprised physical therapy and occupational therapy, twice a day each; a trained physiotherapist or occupational therapist introduced and guided individualized exercises for 120 minutes a day, and aerobic exercise was performed for 30 minutes a day. These rehabilitation programs were conducted until the day of patient discharge.

### Statistical analyses

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). All data are reported as means  $\pm$  standard deviations. A *p* value of  $< 0.05$  was

considered to indicate a statistical significant difference. Differences in baseline characteristics between groups of patients with LA and those without LA were determined using Mann-Whitney U test. Analysis of variance was used to analyze differences in functional outcomes according to LA severity. Because LA severity is affected by age, analyses were adjusted for age of the subjects using analysis of covariance.

## RESULTS

### General characteristics of study subjects

The general characteristics of subjects are presented in Table 1. The cohort contained predominantly male subjects (73.8%); 17 subjects had only corona radiata infarction, whereas 24 had corona radiata and/or basal ganglia infarction. The mean score of the modified NIHSS at stroke onset was 5.7, and that of the Korean version of the MMSE was 25.4. The mean duration of hospitalization in the Department of Rehabilitation Medicine was 21.3 days. No baseline characteristic, except age, was significantly different between subjects with and those without LA; age was significantly higher in the subjects with LA than in those without LA (Table 1).

### Functional outcomes

mRS, FAC, and mBI scores were compared based on LA severity (Table 2). Because only 2 patients had severe LA, we combined the moderate and severe groups into one moderate-to-severe LA group, and no or mild groups into another group for analysis.

**Table 1.** General sample characteristics of study subjects grouped based on LA severity

Characteristics	Total	LA (-)	LA (+)	p value
No. of patients	41	12	29	-
Age	63.0 ± 12.4	54.5 ± 8.7	66.5 ± 12.0	< 0.002*
Gender (male)	31 (73.8)	11 (91.7)	20 (69.0)	0.731
Hypertension	16 (38.1)	3 (25.0)	13 (44.8)	0.501
Diabetes mellitus	14 (33.3)	2 (16.7)	12 (41.4)	0.329
Lesion	CR 17 (40.5) CR and/or BG 24 (57.1)	CR 5 (41.7) CR and/or BG 7 (58.3)	CR 12 (41.4) CR and/or BG 17 (58.6)	0.601
Side of lesion (right:left)	17:24 (41.5:58.5)	3:9 (35.0:75.0)	14:15 (48.3:51.7)	0.482
mNIHSS	5.7 ± 3.2	5.6 ± 2.9	5.7 ± 3.4	0.255
K-MMSE	25.4 ± 4.8	26.4 ± 2.0	24.9 ± 5.5	0.286
Time interval between onset and initial evaluation (day)	12.1 ± 16.6	8.7 ± 3.6	13.6 ± 19.5	0.133
Time interval between initial and follow-up evaluation (day)	23.1 ± 6.8	20.8 ± 7.5	24.0 ± 6.3	0.272

Values are mean ± standard deviation or number of patients (percentages).

LA, leukoaraiosis; CR, corona radiata; BG, basal ganglia; mNIHSS, modified National Institutes of Health Stroke Scale; K-MMSE, Korean version of the Mini-Mental State Examination.

\*p < 0.05 according to Mann-Whitney U test.

**Table 2.** Functional outcome (mRS and FAC) of study patients at transfer and discharge to the Department of Rehabilitation Medicine, who were grouped by LA severity

Functional outcome*	No LA (n = 12)	Mild LA (n = 19)	Moderate-to-severe LA (n = 10)	p value	p value†
mRS 1	3.2 ± 0.9	3.6 ± 0.9	4.2 ± 0.4	0.002*	0.331
mRS 2	2.0 ± 0.8	2.7 ± 0.9	3.7 ± 0.5	0.010*	0.003*
Δ mRS	1.1 ± 0.8	0.9 ± 0.5	0.5 ± 0.5	0.463	-
FAC 1	2.6 ± 1.2	1.8 ± 1.0	1.3 ± 0.5	0.027*	0.131
FAC 2	3.8 ± 0.8	3.2 ± 1.3	2.0 ± 1.1	< 0.001*	0.011*
Δ FAC	1.3 ± 0.9	1.4 ± 0.8	0.7 ± 0.8	0.076	-

Values are mean ± standard deviation.

mRS, modified Rankin Scale; FAC, Functional Ambulation Category; LA, leukoaraiosis.

\*p < 0.05 according to analysis of variance. †p value adjusted for age. \*Time point: 1, score at transfer (initial evaluation); 2, score at discharge (follow-up evaluation); Δ, difference in measurements between time points 1 and 2.

**Table 3.** Functional outcome (mBI) of study patients at transfer and discharge to Department of Rehabilitation Medicine, who were grouped by LA severity

Functional outcome <sup>‡</sup>	No LA (n = 8)	Mild LA (n = 17)	Moderate-to-severe LA (n = 8)	p value	p value <sup>†</sup>
mBI 1	57.6 ± 20.4	44.5 ± 17.3	26.0 ± 22.9	0.015*	0.052
mBI 2	82.5 ± 15.7	67.1 ± 23.5	47.9 ± 20.4	0.002*	0.043*
Δ mBI	32.4 ± 20.1	24.1 ± 14.7	26.1 ± 10.7	0.130	-

Values are mean ± standard deviation.

mBI, modified Barthel Index; LA, leukoaraiosis.

\*p < 0.05 according to analysis of variance. †p value adjusted for age. ‡Time point: 1, score at transfer (initial evaluation); 2, score at discharge (follow-up evaluation); Δ, difference in measurements between time points 1 and 2.

**Table 4.** Correlation between LA and functional outcome in study patients at transfer and discharge to Department of Rehabilitation Medicine

Functional outcome <sup>‡</sup>	Correlation coefficient	p value <sup>*</sup>
mRS 1	0.434	0.005
mRS 2	0.613	0.000
FAC 1	-0.457	0.003
FAC 2	-0.506	0.001
mBI 1	-0.500	0.001
mBI 2	-0.537	0.001

LA, leukoaraiosis; mRS, modified Rankin Scale; FAC, Functional Ambulation Category; mBI, modified Barthel Index.

\*p < 0.05 according to Spearman's correlation analysis. ‡Time point: 1, score at transfer (initial evaluation); 2, score at discharge (follow-up evaluation).

mRS scores showed significant inter-group differences at both the initial and follow-up evaluations (Table 2). mRS scores tended to be higher in patients with more severe LA. Similarly, FAC scores demonstrated significant inter-group differences at both the initial and follow-up evaluations; severe LA was associated with lower FAC scores. However, changes in both mRS and FAC scores between the initial and follow-up evaluations were not statistically different between the groups. After adjustment for age, the initial inter-group difference in mRS and FAC scores disappeared. Meanwhile, after adjustment for age, the inter-group difference in follow-up mRS and FAC scores remained significant.

In total, 33 subjects underwent both initial and follow-up evaluations, 8 of whom (24.2%) had no LA, 17 (51.5%) had mild LA, and 8 (24.2%) had moderate-to-severe LA. We compared mBI scores, which were measured twice, among the 3 groups (no, mild, and moderate-to-severe LA) (Table 3). The mean time interval between the initial and follow-up evaluation of mBI was 17.7 days. Significant inter-group differences were observed in both the initial and follow-up mBI scores among these 33 subjects; however, these inter-group differences in mBI scores not statistically significant. After adjustment for age, follow-up mBI scores significantly differed among the groups and were significantly lower in the moderate-to-severe LA group than in the no LA and mild LA groups.

Finally, we investigated the correlation between LA severity and mRS, FAC, and mBI scores (Table 4). All scores at the initial and follow-up evaluations were significantly correlated with LA severity: LA severity was positively correlated with mRS scores and negatively correlated with FAC and mBI scores.

## DISCUSSION

In this study, LA severity was associated with subacute phase functional outcomes of stroke. Significant differences were observed between the no or mild LA group and moderate-to-severe LA group at both initial and follow-up evaluations, and only severe LA was related to worse functional outcomes.



Because LA is known to be strongly associated with age [12], the significant mean age difference would have contributed to the difference in functional outcomes observed between the initial and follow-up evaluations. After adjusting the data for age, differences in initial mRS, FAC, and mBI scores between the 2 groups disappeared with significant lower scores in the moderate-to-severe group compared to no or mild LA groups at follow-up. As no significant inter-group differences in disability observed at the initial evaluation (in terms of the NIHSS scores), these results demonstrated that LA severity can predict functional outcomes in the subacute phase of stroke.

The findings of this study are consistent with those of previous research. Several studies on stroke patients have been conducted to identify post-stroke functional outcomes according to LA severity. There is substantial evidence showing that LA is associated with cognitive impairment in stroke patients [13], and previous studies have found correlations between LA and gait disturbance in community residents [14].

Previous studies have provided several explanations for the mechanism by which LA affects post-stroke functional outcomes. First, LA is a chronic ischemic injury caused by compromised tissue perfusion [15]; thus, due to reduced blood flow in blood vessels, brain tissue may be more impaired after stroke. Decreased cellular function of self-repair might cause unfavorable tissue outcomes after acute ischemia [16]. In addition, LA is known to be associated with blood–brain barrier dysfunction, which can cause chronic toxic edema and exacerbate tissue damage by acute ischemia [17]. According to Ay [18], patients with severe LA are more vulnerable to infarct growth after ischemic stroke. In addition, the functional deterioration observed after acute stroke can be explained by the association of LA with nerve fiber loss and reduced neuronal connectivity [16].

These effects could explain the poorer outcomes of study patients with more severe LA during the subacute phase in our study. Notably, inter-group differences in functional outcomes at the follow-up evaluation remained significant even after adjustment for age. Considering that there was no significant difference in baseline characteristics (except for age), stroke severity, or function, it is believed that the effect of histological level caused by LA is expressed as a functional outcome.

This study had several limitations. It analyzed the cases of a relatively small number of patients, and its 2 groups (no or mild LA group and moderate-to-severe LA group) had an unequal sample size distribution; only 2 patients were present in the severe LA group. The post-stroke period observed in this study was the subacute phase, with a relatively short follow-up period that might not have been sufficiently long for significant functional changes to occur. In particular, compared with changes in other outcomes, those in mBI scores might not have been sufficiently reflected in the results because of the relatively short-term follow-up period for this indicator. In addition, some enrolled patients were excluded from the mBI analysis due to a lack of follow-up evaluation, although no significant difference was observed between the excluded patients and included subjects. Considering these limitations, a longitudinal study with a larger number of patients should be conducted to examine the detailed relationship between LA severity and functional outcomes in patients with stroke.

LA, an age-related small-vessel disease, is related to functional outcomes of stroke in the subacute phase after onset. After adjustment for age, severe LA was correlated with poorer functional outcomes in patients in the subacute phase after stroke onset.

## REFERENCES

1. Arsava EM, Rahman R, Rosand J, Lu J, Smith EE, Rost NS, et al. Severity of leukoaraiosis correlates with clinical outcome after ischemic stroke. *Neurology* 2009;72:1403-1410.  
[PUBMED](#) | [CROSSREF](#)
2. The LADIS Study Group Poggesi A, Pantoni L, Inzitari D, Fazekas F, Ferro J, et al. 2001–2011: a decade of the LADIS (leukoaraiosis and disability) study: what have we learned about white matter changes and small-vessel disease? *Cerebrovasc Dis* 2011;32:577-588.
3. Podgorska A, Hier DB, Pytlewski A, Czlonkowska A. Leukoaraiosis and stroke outcome. *J Stroke Cerebrovasc Dis* 2002;11:336-340.  
[PUBMED](#) | [CROSSREF](#)
4. Koton S, Schwammenthal Y, Merzeliak O, Philips T, Tsabari R, Orion D, et al. Cerebral leukoaraiosis in patients with stroke or TIA: clinical correlates and 1-year outcome. *Eur J Neurol* 2009;16:218-225.  
[PUBMED](#) | [CROSSREF](#)
5. Senda J, Ito K, Kotake T, Kanamori M, Kishimoto H, Kadono I, et al. Association of leukoaraiosis with convalescent rehabilitation outcome in patients with ischemic stroke. *Stroke* 2016;47:160-166.  
[PUBMED](#) | [CROSSREF](#)
6. Kapeller P, Barber R, Vermeulen RJ, Adèr H, Scheltens P, Freidl W, et al. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. *Stroke* 2003;34:441-445.  
[PUBMED](#) | [CROSSREF](#)
7. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 1993;43:1683-1689.  
[PUBMED](#) | [CROSSREF](#)
8. Inzitari D, Simoni M, Pracucci G, Poggesi A, Basile AM, Chabriat H, et al. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: the LADIS study. *Arch Intern Med* 2007;167:81-88.  
[PUBMED](#) | [CROSSREF](#)
9. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-607.  
[PUBMED](#) | [CROSSREF](#)
10. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Phys Ther* 1986;66:1530-1539.  
[PUBMED](#) | [CROSSREF](#)
11. Mahoney FI, Barthel DW. Functional evaluation: the barthel index. *Md State Med J* 1965;14:61-65.  
[PUBMED](#)
12. Basile AM, Pantoni L, Pracucci G, Asplund K, Chabriat H, Erkinjuntti T, et al. Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. The LADIS (Leukoaraiosis and Disability in the Elderly) Study. *Cerebrovasc Dis* 2006;21:315-322.  
[PUBMED](#) | [CROSSREF](#)
13. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010;341:c3666.  
[PUBMED](#) | [CROSSREF](#)
14. Srikanth V, Beare R, Blizzard L, Phan T, Stapleton J, Chen J, et al. Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. *Stroke* 2009;40:175-180.  
[PUBMED](#) | [CROSSREF](#)
15. Xiong YY, Mok V. Age-related white matter changes. *J Aging Res* 2011;2011:617927.  
[PUBMED](#) | [CROSSREF](#)
16. Feng C, Tan Y, Wu YF, Xu Y, Hua T, Huang J, et al. Leukoaraiosis correlates with the neurologic deterioration after small subcortical infarction. *J Stroke Cerebrovasc Dis* 2014;23:1513-1518.  
[PUBMED](#) | [CROSSREF](#)
17. Taheri S, Gasparovic C, Huisa BN, Adair JC, Edmonds E, Prestopnik J, et al. Blood-brain barrier permeability abnormalities in vascular cognitive impairment. *Stroke* 2011;42:2158-2163.  
[PUBMED](#) | [CROSSREF](#)
18. Ay H, Arsava EM, Rosand J, Furie KL, Singhal AB, Schaefer PW, et al. Severity of leukoaraiosis and susceptibility to infarct growth in acute stroke. *Stroke* 2008;39:1409-1413.  
[PUBMED](#) | [CROSSREF](#)