

# Leukoaraiosis is Associated with Worse Short-Term Functional and Cognitive Recovery after Minor Stroke

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## Abstract

Whether leukoaraiosis burden retards short-term recovery after minor stroke is unclear. We investigated the association between leukoaraiosis and early recovery of neurological function after a first minor ischemic stroke in 217 acute stroke patients (National Institutes of Health Stroke Scale (NIHSS) score  $\leq 5$ ). Leukoaraiosis severity was graded according to the Fazekas scale and categorized into none to mild (0–2;  $n = 143$ ) or severe (3–6;  $n = 74$ ) groups. NIHSS and Minimum Mental State Examination (MMSE) were assessed at baseline and at 30 days. Univariate analysis revealed that the severe leukoaraiosis group was older in age ( $P < 0.001$ ) and had fewer low MMSE patients than non-mild group at baseline (39.1% vs 55.9%,  $P = 0.003$ ). However, the MMSE improved in none to mild group but not in the severe group at 30-day (15.4% vs 36.5%,  $P < 0.001$ ). At 30-day, the severe leukoaraiosis group had higher NIHSS scores than the none-mild group ( $P = 0.04$ ). Multiple linear regression analyses demonstrated that leukoaraiosis severity and admission NIHSS were independently associated with the NIHSS score on day 30 ( $P = 0.034$ , 95% CI 0.004–0.091 and  $P = 0.001$ , 95% CI 0.011–0.04). Binary regression analyses showed that leukoaraiosis severity and admission MMSE were significantly associated with MMSE (dichotomized) at 30-day (OR 2.1,  $P < 0.01$ , 95% CI 1.7–2.6 and OR 5.1,  $P < 0.01$ , 95% CI 2.1–12.8). Leukoaraiosis burden is an independent predictor of worse short-term functional and cognitive recovery after a minor ischemic stroke.

Key words: leukoaraiosis, white matter hyperintensities, ischemic stroke, predictors of outcome

## Introduction

Ischemic stroke remains a leading cause of disability worldwide, particularly among the elderly.<sup>1</sup> Some patients with mild ischemic stroke incur substantial functional disability.<sup>2–4</sup> Leukoaraiosis has attracted attention because it may predict stroke and cognitive degeneration.<sup>5–7</sup> Anecdotal evidence suggests that leukoaraiosis burden may contribute to worse outcome after stroke. However, few studies have rigorously explored the association between pre-stroke leukoaraiosis and recovery after minor stroke.<sup>8–13</sup> Onteddu et al found that leukoaraiosis was associated with worse outcome after minor stroke. There are two weaknesses of their study: first, computed tomography (CT) scan was used to evaluate severity of leukoaraiosis and this modality tends to misclassify the severity of leukoaraiosis compared to magnetic resonance imaging (MRI) scan assessment. Second, cognitive function—which is associated with stroke outcome—was not taken into account.

Although thrombolysis is a well-established effective therapy for ischemic stroke, a patient with sufficiently mild neurological deficit usually is not provided thrombolysis.<sup>13,14</sup> To explore the effect of leukoaraiosis burden on the recovery of minor stroke might help to identify potential minor stroke patients who will gain benefit from thrombolysis treatment and tailor individualized therapeutic strategies.

Our hypothesis is that leukoaraiosis, which is associated with brain senescence, provides an important indicator of poor clinical outcome after stroke.<sup>2,3</sup> More precisely, our primary hypothesis is that there is a continuous and an independent relation between preexisting leukoaraiosis severity and worse short-term recovery after minor stroke as assessed by 30-day National Institutes of Health Stroke Scale (NIHSS—a validated quantitative measure of stroke severity). Because cognitive impairment, which closely relates to functional independence, is not reflected by the NIHSS, we used the Minimum Mental State Examination (MMSE) to evaluate global neurocognitive function after stroke. The 17-item Hamilton

Depression Scale (HAMD) was used to control the effect of depression on cognitive function.<sup>15,16)</sup>

## Materials and Methods

### Study population

The protocol of this prospective study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. Patients with first-ever acute ischemic stroke admitted to the Stroke Unit of our hospital between October 2013 and September 2014 were consecutively screened for study entry. Written informed consents were obtained from patients or their relatives. The inclusion criteria were: (i) age  $\geq 18$  years old; (ii) first acute ischemia stroke occurring within 7 days before admission; (iii) MRI was available; (iv) minor ischemia stroke (defined as NIHSS  $\leq 5$ ). The exclusion criteria included: (i) transient ischemic attack; (ii) patients with a history of any central nervous system disease resulting in a modified Rankin Scale (mRS)  $\geq 1$ ; (iii) severe aphasia; (iv) severe dementia before the stroke.

All included patients ( $n = 217$ ) underwent brain MRI scan within 48 hours after admission. Patient demographics, vascular risk factors, laboratory parameters, comorbidities, stroke etiology (using the Trial of Org10172 in Acute Stroke Treatment [TOAST] classification) were collected on all patients. NIHSS and MMSE scores were assessed at the time of admission and at 30 days by a stroke-trained physician.<sup>17,18)</sup> Cognitive impairment was defined using the education-based cut-off of MMSE in Chinese (illiterate  $< 17$ , primary education  $< 20$  and middle school or higher education  $< 24$ ). We dichotomized MMSE score to low or normal (according to education-based cut-offs). The 17-item HAMD was used to assess distress status.

We adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

### Imaging protocol, review, and analysis

Neuroimaging was analyzed independently by experienced readers (Z.BL, C.JH) blinded to both clinical data and follow-up. MRI scan included  $T_1$ -,  $T_2$ -, Diffusion Weighted Imaging (DWI), Fluid-attenuated inversion recovery (Flair) series (Siemens, Avanto, Erlangen, Germany, 1.5T scanner,  $T_1W$  TR 450 ms, TE 15 ms,  $T_2W$  TR 3000 ms, TE 80 ms, DWI TR 8000 ms, TE 102 ms, image matrix of  $128 \times 128$ , a field of view of  $22 \times 22$  cm, Flair TR 9002 ms, TE 143 ms, a field of view of  $22 \times 22$  cm, image matrix of  $256 \times 224$ , slice thickness 7 mm; no gap).

Leukoaraiosis was defined according to the Standards for Reporting Vascular changes on neuroimaging (STRIVE) criteria.<sup>6)</sup> All imaging interpretations were carried out within 48 h of admission. Lesions consisting of hyperintensities on DWI that were hypo- or isointense on the apparent diffusion coefficient maps were considered to be acute ischemic infarcts. Ischemic infarcts on DWI were manually outlined using careful windowing to achieve the maximal visual extent of the acute DWI infarct and with reference to the apparent diffusion coefficient image to avoid regions of  $T_2$  shine-through and to allow for reliable distinction from leukoaraiosis. Infarcts were categorized according to their location as cortico-subcortical, deep hemisphere and posterior. Using the Flair data, leukoaraiosis was classified into deep white matter hyperintensities (d-WMHs) and periventricular white matter hyperintensities (p-WMHs).<sup>19)</sup> The severity of WMHs was rated using the visual rating scale proposed by Fazekas with scores ranging from 0 to 3.<sup>20)</sup> For d-WMHs, scores correspond to the following characteristics: 0, no lesion; 1, punctuate foci; 2, beginning confluent foci; 3, confluent changes. For p-WMHs, scores correspond to the following characteristics: 0, no changes; 1, caps or a pencil-thin lining; 2, smooth halo; 3, irregular changes extending into the d-WMHs. The total Fazekas score was calculated by adding the periventricular and subcortical scores together. Leukoaraiosis severity was conceptually categorized as none to mild (0–2;  $n = 143$ ), or severe (3–6;  $n = 74$ ). When evaluating the WMHs, recent or old infarcts were excluded. If WMH score was asymmetrically higher on one side, WMH rating was based on the less involved or uninvolved side with the principle of symmetry assumed. The intraclass correlation coefficient for the total and graded Fazekas score were 0.949 (95% confidence interval, 0.932–0.963) and 0.941 (95% confidence interval, 0.912–0.968), respectively.

### Statistics

Unless otherwise stated, continuous variables are reported as mean  $\pm$  standard deviation (SD) or as median (interquartile range [IQR]). Categorical variables are reported as proportions. The normality of data was examined using Kolmogorov-Smirnov test. Between-group comparisons for continuous variables were made with unpaired *t*-Test and Mann-Whitney U test. Categorical variables were compared using the  $\chi^2$ -test.

The Spearman rank test was used to identify factors correlated with the 30-day NIHSS. Age, severity of leukoaraiosis, baseline NIHSS as well as other important factors were included in the

multivariable linear regression analysis to test our primary hypothesis that there is a continuous and an independent relation between leukoaraiosis severity and 30-day NIHSS. To achieve a more suitable distribution for multivariable linear regression, we transformed non-normally distributed data (NIHSS score) on the basis of rank case. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess all models for final model fit. Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models.

To explore whether leukoaraiosis was independently associated with MMSE (dichotomized) at 30-day, we constructed binary logistic regression. Demographic data, WMH and other important related factors are included in the regression analyses.

Two-sided  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS Statistics 10.0.0.

## Results

### Recruitment

During the study period, 552 patients were admitted to our stroke service. Of these, 217 patients with minor ischemic stroke were included for analysis. We excluded patients whose infarct was not ischemic ( $n = 86$ ), those with no available MRI ( $n = 12$ ), those with admission NIHSS  $>5$  ( $n = 149$ ), mRS before stroke  $\geq 1$  ( $n = 23$ ), and those who were lost to followup ( $n = 65$ ).

### Clinical characteristics

No patient had a recurrent stroke during the follow-up period. Baseline characteristics of the included 217 patients as classified by leukoaraiosis severity are summarized in Table 1. The detail Fazekas scores were: 0 ( $n = 36$ ), 1–2 ( $n = 107$ ), 3–4 ( $n = 72$ ), 5–6 ( $n = 2$ ). The education levels in the none-to-mild leukoaraiosis group and moderate leukoaraiosis group were: illiterate (30% vs 31%;  $P = 0.9$ ), primary school (26.7% vs 29%;  $P = 0.8$ ), middle school or higher (43.3% vs 40%;  $P = 0.7$ ). The patients with a low MMSE score at admission were 109 (50%). The patients with a low MMSE score in none-to-mild leukoaraiosis group and severe leukoaraiosis group were 80 (55.9%) and 29 (39.1%) cases respectively (Fig. 1). Baseline HAMD of the none-to-mild leukoaraiosis group and severe leukoaraiosis group were not significantly different (Table 1).

At 30 days, more patients with severe leukoaraiosis had a residual deficit (NIHSS  $>0$ ) than patients with none-to-mild leukoaraiosis, but the difference was

not significant ( $n = 30$ , 68.9% vs.  $n = 82$ , 57.3%;  $P = 0.09$ ). Patients with both none-to-mild and severe leukoaraiosis showed improvement of their respective absolute and relative NIHSS by 30 days as compared to admission ( $P < 0.01$  each; Fig. 2). However, patients with none-to-mild leukoaraiosis had significantly less absolute and relative deficits at 30 days as compared to patients with severe leukoaraiosis ( $P = 0.03$ ; Fig. 2).

At 30-day, HAMD in none-to-mild and severe leukoaraiosis group was 4.5 (1–7) and 4 (2–6) respectively, (not significantly different;  $P = 0.7$ ).

The MMSE in the none-to-mild leukoaraiosis group was 26 (25–29) and that of severe leukoaraiosis group was 23 (18–27) at the 30-day assessment ( $P < 0.001$ ). There were 22 subjects with low MMSE in the none-to-mild leukoaraiosis group (15.4%) and 27 cases in the severe leukoaraiosis group (36.5%) (Fig. 1). 93 (65%) of cases showed improvement of MMSE by 30 days in the none-to-mild leukoaraiosis group. In the severe leukoaraiosis group, 50 (67%) improved their MMSE ( $P = 0.7$ ). The MMSE deteriorated in 25 cases (17.5%) in the none-to-mild leukoaraiosis group, and in 14 (19%) cases in the severe group ( $P = 0.8$ ).

### Association of leukoaraiosis with degree of neurological deficit recovery

Neither infarct volume nor distribution of infarct location was of significant difference in two groups (Table 1). Multivariable linear regression analyses demonstrated an independent association of leukoaraiosis severity with the 30-day NIHSS (coefficient 0.047,  $P = 0.034$ , 95% CI 0.004–0.091). Age was not related to 30-day NIHSS (Table 2). Another independent predictor of the 30-day NIHSS was admission NIHSS (coefficient  $b = 0.026$ ,  $P = 0.001$ , 95% CI 0.011–0.04) (Table 2). Additional adjustment for the MMSE and HAMD did not meaningfully change the results.

Binary regression analyses showed that leukoaraiosis severity is an independent predictor of MMSE at 30-day, and also of low admission MMSE (Table 3). HAMD was not related to 30-day MMSE ( $P = 0.9$ ).

## Discussion

From the results of our study, it can be concluded that leukoaraiosis burden-irrespective of chronological age, infarct volume or location-is associated with worse functional and cognitive recovery after a first minor ischemia stroke.

It has been observed that the degree of preexisting leukoaraiosis modulates the association between infarct volume and neurological deficit severity as

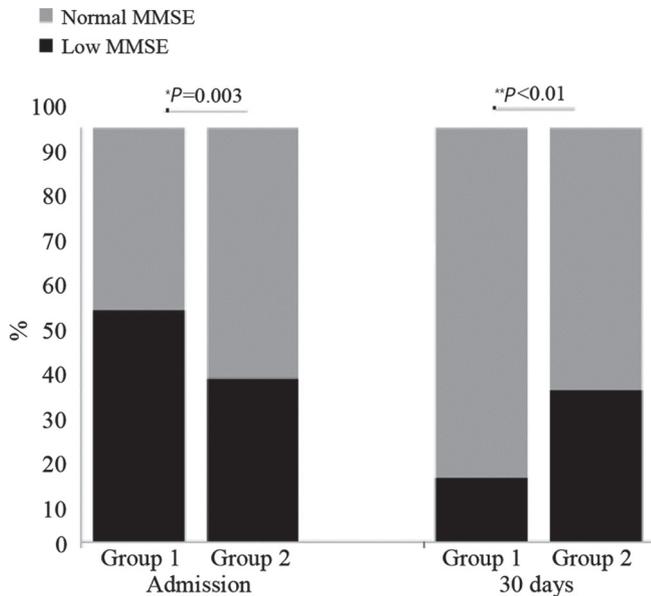
**Table 1** Baseline characteristics of the studied patient population as classified by leukoaraiosis severity

Characteristics	None to mild leukoaraiosis (n = 143)	Severe leukoaraiosis (n = 74)	P/z value
Age (years)	59.8 ± 4.2	67.5 ± 15.5	<0.01
Female sex	50 (34.9)	20 (27)	0.2
Preadmission medications			
Antiplatelet therapies	141 (98.6%)	69 (93.2%)	0.08
Oral coagulants	0	4 (5.4%)	–
Statins	143 (100%)	74 (100%)	–
Antiglycemics	34 (23.8%)	19 (25.7%)	0.7
Antihypertensives	64 (44.7%)	31 (41.9%)	0.7
Admission NIHSS	2 (1–3)	2 (1–3)	0.2
Admission MMSE	24 (19–27)	22 (17–24)	0.025
Admission HAMD	3 (1–6)	4 (1–7)	0.3
Fasting blood glycemia (mmol/l)	5.5 ± 2.8	6.2 ± 0.6	0.6
Glycolated hemoglobin A1c (%)	6.6 ± 1.1	6.2 ± 2.8	0.01
LDL-C (mmol/l)	2.8 ± 0.2	2.5 ± 0.8	0.1
Triglycerides (mmol/l)	1.7 ± 0.2	1.8 ± 0.1	0.4
HDL-C (mmol/l)	1.1 ± 0.9	1.1 ± 0.2	0.9
SBP (mmHg)	155 ± 20	157 ± 21	0.4
DBP (mmHg)	89 ± 9	80 ± 12	0.4
Preexisting risk factors			
Hypertension	99 (69.2%)	57 (77%)	0.2
Diabetes	75 (52.6%)	36 (48.1%)	0.3
Dyslipidemia	34 (23.8%)	19 (25.7%)	0.8
Coronary artery disease	10 (7%)	3 (4.1%)	0.4
Current smoking	63 (44.1%)	27 (36.5%)	0.3
TOAST classification			
Atherosclerosis	123 (86%)	64 (86%)	0.9
Small vessel disease	6 (4.2%)	6 (8.1%)	0.6
Cardioembolic disease	7 (4.9%)	2 (2.7%)	0.7
Undetermined etiology	4 (2.8%)	2 (2.7%)	–
Other determined etiology	3 (2.1%)	0	–
Infarct volume (ml)	1.2 (0.5–4)	1.5 (1–4)	0.2
Infarct location			
Cortical and subcortical	44 (30.8%)	20 (27%)	0.6
Deep brain	55 (38.5%)	30 (40.5%)	0.8
Posterior	44 (30.8%)	24 (32.4%)	0.8
Intravenous thrombolysis	5 (3.5%)	2 (2.7%)	–

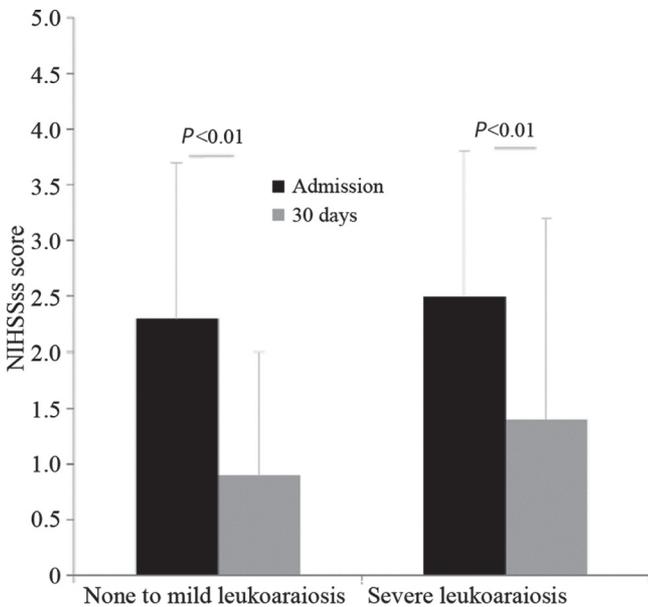
DBP: diastolic blood pressure, HAMD: 17-Hamilton Depression Scale, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, MMSE: Minimum Mental State Examination, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, TOAST, Trial of Org 10172 in Acute Stroke Treatment.

assessed by the NIHSS. To wit, increasing leukoaraiosis severity is associated with greater NIHSS deficits for similar sized infarcts.<sup>21)</sup> One of the mechanisms underlying the association of leukoaraiosis and worse

stroke recovery may be that the preexisting white matter impairment weakens the brain plasticity and compensatory mechanisms after stroke.<sup>22)</sup> Although structural damage from stroke may be local, remote



**Fig. 1** Proportion of patients with low and normal MMSE score at admission and 30-day (%). Group 1, none to mild leukoaraiosis; Group 2, severe leukoaraiosis.  $\chi^2$ -test was used to estimate the potential difference. \*: admission MMSE comparison of two groups. \*\*: 30 days MMSE comparison of two groups.



**Fig. 2** Mean value of NIHSS scores at admission and 30-day in two groups.

dysfunction can occur in regions connected to the area of the lesion.<sup>23)</sup> We found that the short-term functional recovery did not associate with location of infarct. This may be easier explained by the connectivity interruption than structure impaired on neuroimaging. Another mechanism by which preexisting leukoaraiosis might retard stroke

**Table 2** Multiple linear regression analyses of factors associated with the NIHSS scores at day 30

Independent variables	Coefficient (95% CI)	P
Age (>50-years old)	0.017 (-0.033–0.068)	0.3
Leukoaraiosis severity	0.047 (0.004–0.091)	0.034
Admission NIHSS	0.026 (0.011–0.04)	0.001

**Table 3** Binary regression analysis of factors associated with low MMSE score at day 30

Independent variables	OR	P	95% CI
Age	3.6	0.24	0.8–6.5
Sex	0.6	0.7	0.9–1.3
Infarct volume	0.9	0.3	0.8–1.1
Leukoaraiosis severity	2.1	<0.01	1.7–2.6
Low admission MMSE	5.1	<0.01	2.1–12.8

recovery could be through increased final extent of infarct volume.<sup>24,25)</sup> Because the patients in our study underwent only one MRI scan at admission and a second MRI scan at 30-day was unavailable, we cannot rule out that during the period of follow up the infarct volume progressed, contributing to worse recovery of function. In our study, we also found that admission NIHSS score is significantly associated with 30-day recovery. This association of baseline NIHSS and follow up NIHSS is in line with previously reported data.<sup>3)</sup>

An interesting finding of our study is that admission cognitive impairment was more prevalent in the none-to-mild leukoaraiosis group than in the severe leukoaraiosis group, while at 30-day it is reversed. One speculative explanation of the higher prevalence of cognitive impairment at admission in the none-to-mild leukoaraiosis group is that these patients may have higher prevalence of preexisting cognitive impairment resulting from other factors that also increased their risk of having a stroke. Although we excluded patients with severe preexisting cognitive impairment, it is still possible patients with mild pre-stroke cognitive impairment were recruited and caused the baseline imbalances. However, the fact that at 30-day MMSE improved rapidly in this group speaks against this speculation. Another possible reason is that psychological distress may interact with cognitive evaluation and mood distress may lead to worse MMSE score in the higher cognitive function patients.<sup>26,27)</sup> To adjust for such bias, we gave a simultaneous depression test to improve the reliability of our conclusions. Our results showed a similar degree of distress in the two groups both at baseline and at 30-day, which ruled out

the possible interference caused by distress. It is also possible that leukoaraiosis or the advanced age associated with the more severe leukoaraiosis prevents the lower functioning older patients from recognizing an ongoing mild stroke. As a result, only the most functional patients with leukoaraiosis would be aware of the stroke and present for evaluation. This would be a form of selection bias that could explain the unexpected finding. In a word, it should be cautious to interpret this finding because we did not evaluate the baseline cognitive function of patients pre-stroke. Clearly, future studies are needed to clarify the association between leukoaraiosis and cognitive function during the acute phase of stroke.

Fifty percent patients in our study had cognitive impairment at admission. This is similar to findings of other studies in minor stroke patients.<sup>27,28)</sup> It is well known that leukoaraiosis associates with cognitive deterioration in old healthy people.<sup>29,30)</sup> It also observed that cognitive function tends to change over time after minor stroke. Béjot et al examined the presence of dementia during the first month after stroke and reported the prevalence of dementia changes over time.<sup>31)</sup> Some patients gained great improvement while some presented worse cognitive function. Tham et al also found different changes of cognitive function after stroke, and that follow-up MMSE was associated with baseline MMSE, which is in consistent with our findings.<sup>29)</sup> Though the mechanism underlying the change is not clear, the neurologic deterioration that underlies leukoaraiosis appears to contribute also to deterioration of cognitive function after stroke.<sup>32)</sup> Our data demonstrate that leukoaraiosis outweighed neuropsychological factors in regard to cognitive function recovery. Leukoaraiosis severity is one of the mechanisms which predict improvement or deterioration of cognitive function after stroke.

An additional observation of our study is that leukoaraiosis severity is not related to the depression degree after minor stroke. The main predictor of post-stroke depression is the disability and severity of stroke.<sup>33,34)</sup> According to our recruitment criteria, even though the remaining neurological deficits in the severe leukoaraiosis group are higher than that of none-to-mild group, those deficits were generally too mild to cause depression.

One of the strengths of our study is the prospective design and data collection methodology and blinded assessment of imaging variables. Importantly, we dichotomized the MMSE score taking into consideration the education levels of the patients, which are closely related to cognitive function assessed by MMSE. Compared to absolute MMSE score, the

education based cut-off can adjust for the preexisting bias resulting from education level.

There are limitations of the present study. First, the sample is relatively small and we did not stratify more subgroups according to Fazekas score for statistical purposes. Second, the evaluation scale of Fazekas is semi-quantitative and may underestimate leukoaraiosis. But the strengths of this scale include its high inter-rater reproducibility and that it is easily obtained in clinical settings without complex post processing. Our method of neuroimaging evaluation is easily adoptable by other clinical centers or for research comparisons in future. Finally, although we assessed the relation between leukoaraiosis and functional and cognitive recovery as a whole, future study is needed to clarify the association between domain-specific assessment and white matter integrity.

## Conclusion

Leukoaraiosis burden is an independent predictor of worse short-term functional and cognitive recovery after minor ischemic stroke. This is important because leukoaraiosis provides an easily assessed neuroimaging marker for predicting the outcome of minor stroke patients. Selection of patients for thrombolytic therapy in mild ischemic stroke may be improved by considering their leukoaraiosis burden.

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## Conflicts of Interest Disclosure

All of the authors declare that they have no conflicts of interest regarding this paper.

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