



Leukoaraiosis is associated with poor outcomes after successful recanalization for large vessel occlusion stroke

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Abstract

Background Leukoaraiosis (LA) is related to the dysfunction of the microcirculation and results in the impairment of the perfusion state. We investigated the association of LA and poor outcomes after successful recanalization by thrombectomy.

Methods We retrospectively analyzed 97 patients with anterior large-artery occlusion who underwent thrombectomy and had successful recanalization (modified Treatment in Cerebral Ischemia Scale score 2b or 3). All patients underwent magnetic resonance imaging (MRI). LA was evaluated using fluid-attenuated inversion recovery MRI and graded using the Fazekas scale. Poor functional outcome at day 90 and symptomatic intracerebral hemorrhage (sICH) were compared between patients with absent to mild LA and moderate to severe LA. Logistic regression analyses were performed to determine the association of LA severity and outcomes.

Results Moderate and severe LA occurred in 28.9% and 26.8% patients respectively. A higher proportion of poor outcomes were observed in patients with moderate to severe LA compared to patients with absent to mild LA (77.8% vs. 39.5%, $p < 0.001$). Logistic regression analyses showed patients with moderate to severe LA had 3.77 times (95%CI 1.21–11.76, $p = 0.022$) higher risk of having poor outcomes compared to patients with absent to mild LA.

Conclusions LA severity may be associated with poor outcomes after successful recanalization for ischemic stroke with anterior large vessel occlusion.

Keywords Leukoaraiosis · Recanalization · Thrombectomy · Ischemic stroke · Large vessel occlusion stroke

Introduction

Mechanical thrombectomy performed using a stent retriever has been strongly recommended as a first-line treatment strategy for patients with ischemic stroke caused by large vessel occlusion [1, 2]. Compared with intravenous thrombolysis, thrombectomy efficiently removes clots resulting in better recanalization rate to improve stroke prognosis [3]. Nevertheless, up to 54% of patients experience disability or death after thrombectomy, even after prompt and successful revascularization [4]. It is of clinical value to identify patients

who may be insensitive or resistant to thrombectomy before initiation of treatment.

Leukoaraiosis (LA) is usually diagnosed by magnetic resonance imaging (MRI) as hyperintensities around the lateral ventricle or subcortical area. It is recognized as nonspecific imaging signals in cerebral small vessel disease and frequently observed in patients with ischemic stroke [5]. The risk factors include advanced age, arterial hypertension and smoking, while clinical symptoms included cognitive decline, dysarthria, gait impairment, and incontinence [6]. Pathologically, LA is thought to represent chronic white matter lesions that include ependymal loss, cerebral ischemia, demyelination, venous collagenosis, and microcystic infarct. This ultimately results in microcirculatory dysfunctions [7]. Previous studies have demonstrated that severe LA and large LA volume predicted poor outcomes and increasing hemorrhage transformation risk after intravenous or intra-artery thrombolysis [8, 9]. However, this correlation may be due to impaired recanalization rates. Little is known regarding the impact of LA on patient prognosis after thrombectomy. In this study, we

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investigated the potential association of LA severities and poor outcomes after successful recanalization by thrombectomy.

Materials and methods

We performed a retrospective analysis using a prospective hospital-based stroke registry from October 2015 to December 2017. A total of 128 consecutive stroke patients with anterior large vessel occlusion (middle carotid artery or internal carotid artery) who received mechanical thrombectomy were screened, of whom 105 (82.0%) had successful recanalization (modified Treatment in Cerebral Ischemia Scale [mTICI] score 2b or 3). Of these patients, eight did not receive any MRI examinations for contraindication, intolerance or sudden death; based on the selection criteria, 97 patients were selected for the final analyses. The mean age was 70.0 ± 12.4 years old, and 61.9% of the patients were male. Sixty (61.9%) patients received intravenous thrombolysis before endovascular treatment. The median of onset-to-recanalization time was 338 min. Admission stroke severities were measured using the National Institutes of Health Stroke Scale (NIHSS), and functional outcomes were determined using the modified Rankin Scale (mRS) at 3 months. mRS scores of more than 2 (3–6) were defined as poor outcomes. Symptomatic intracerebral hemorrhage (sICH) was defined as any sign of hemorrhage on follow-up head CT within 24 h combined with clinical deterioration of 4 points or more on the NIHSS score [10]. All medical care and endovascular treatment procedures met the guidelines [1]. Informed consents were obtained from all patients before being included in the stroke registry and were approved by the Ethics Committee of Nanjing First Hospital.

MRI scans were performed using a 3.0 T unit (Ingenia; Philips Medical Systems, Netherlands). The MRI protocol included the fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and 3D-TOF MR angiography (MRA). FLAIR MRI parameters were obtained axially using an inverse recovery (IR) sequence: repetition time (TR), 7000 ms; echo time (TE), 120 ms; acquisition matrix, 356×151 ; field of view (FOV), $230 \text{ mm} \times 230 \text{ mm}$; flip angle (FA), 90° ; slices, 18; section thickness, 6 mm; and intersection gap, 1.3 mm. Eleven (11.3%) and 38 (39.2%) of the patients underwent MRI test before and after thrombectomy respectively, while 48 (49.5%) of the patients were imaged at both time points.

The presence for LA was defined as hyperintense supratentorial white matter lesions on FLAIR images in the non-ischemic hemisphere. The severity of LA was rated based on the Fazekas scale with scores ranging from 0 to 3, both for the periventricular (0 = absence, 1 = caps or pencil-thin lining, 2 = smooth halo, 3 = irregular periventricular hyperintensity extending into the deep white matter) and subcortical areas

(0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas). The total Fazekas scale score was calculated by adding the periventricular and subcortical scores. The total score ranged from 0 to 6, and was graded as absent (0), mild (1–2), moderate (3–4), and severe (5–6) [11]. Examples of different grades of LA severity are shown in Fig. 1. Two trained investigators (Yukai Liu and Pengyu Gong) blinded to patient data independently assessed LA severity. Consensus was reached through discussions for patients with divergent scores.

Statistical analyses

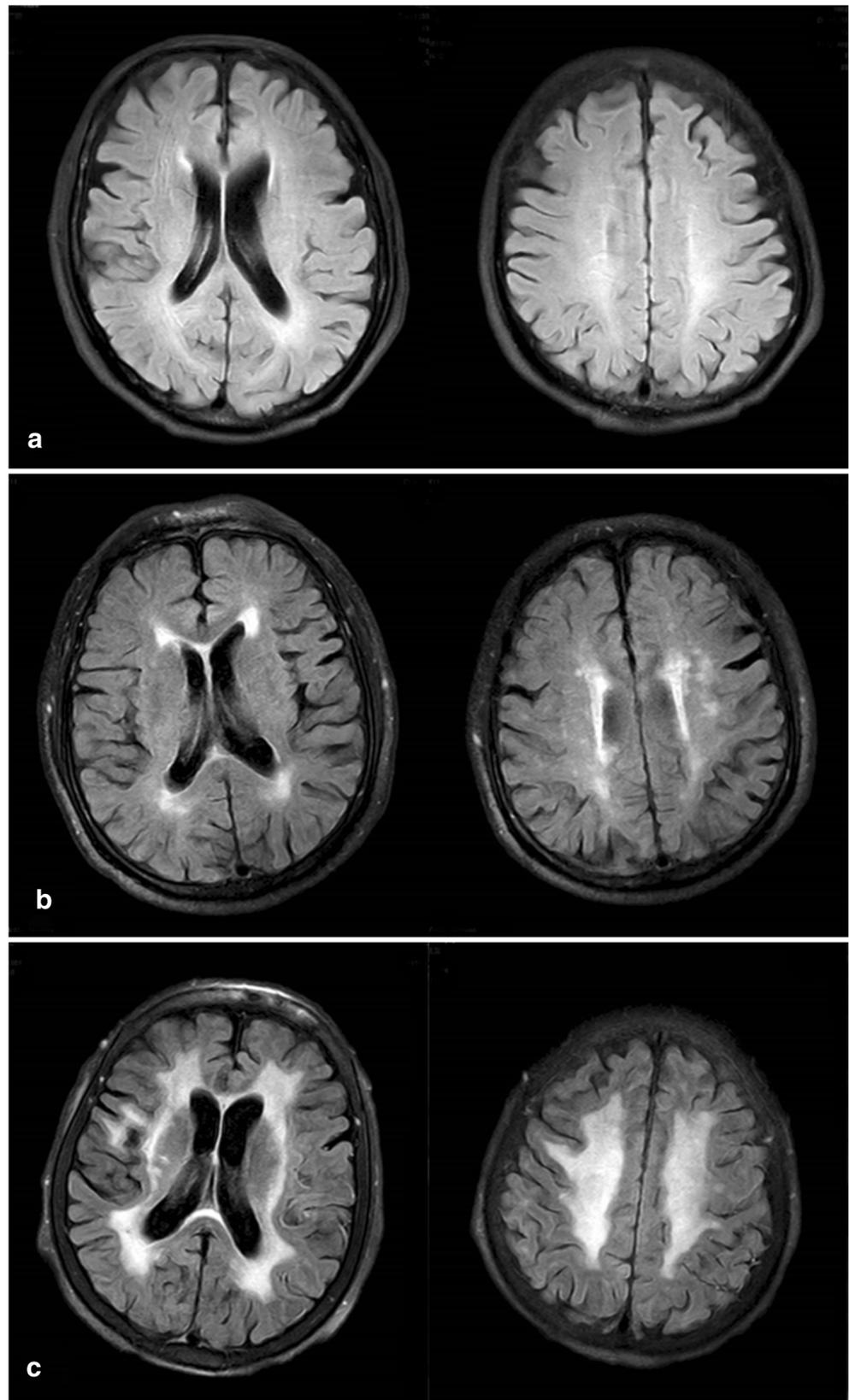
We analyzed potential association of LA and stroke prognosis after thrombectomy. Patients were dichotomized by LA severity (absent to mild LA vs. moderate to severe LA). Baseline characteristics, treatment information, and outcomes were compared between the two groups. Data were presented as mean \pm standard deviation or median (interquartile range) for continuous variables and numbers (percentage) for categorical variables. Metric and ordinal variables were analyzed by one-way ANOVA and Kruskal-Wallis test respectively, while frequencies were compared using Fisher's exact method. Univariate and multivariate logistic regression analyses were performed to ascertain the independent relation of LA severity to poor outcome at day 90, any cerebral hemorrhage and sICH within 24 h. The absent to mild LA group was analyzed as reference. Variables with $p < 0.1$ in univariate analysis were adjusted in multivariate models. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc. Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Of the 97 patients, absent, mild, moderate, and severe LA was present in 2 (2.1%), 41 (42.3%), 28 (28.9%), and 26 (26.8%) patients respectively. Table 1 shows the baseline characteristics and outcomes. Patients with moderate to severe LA were older (74.9 ± 8.3 vs. 63.9 ± 14.0 , $p < 0.001$), had higher proportion of atrial fibrillation (59.3% vs. 32.6%, $p = 0.014$) and higher serum creatinine (87.6 ± 35.6 vs. 72.9 ± 21.7 , $p = 0.017$) compared to patients with absent to mild LA.

Cerebral hemorrhage and sICH occurred in 25 (25.8%) and 10 (10.3%) of the patients respectively. Compared to patients with absent to mild LA, patients with moderate to severe LA appeared to have a higher risk of any type of hemorrhage (31.5% vs. 18.6%, $p = 0.169$) or sICH (14.8% vs. 4.7%, $p = 0.177$), although no significant differences was seen. At 3 months, the median mRS score was 3 for all patients, with 39.2% having a mRS score of 0–2. 17.5% of the patients died

Fig. 1 Grades of leukoaraiosis (LA) severity based on the Fazekas scale. **a** Mild LA, with penci-thin lining in the periventricular (Fazekas score 1). **b** Moderate LA, with smooth halo in the periventricular and beginning confluence of foci in the subcortical area (Fazekas score 4). **c** Severe LA, with irregular periventricular hyperintensity in the periventricular extending into the deep white matter and large confluent areas (Fazekas score 6)



during this period. Patients with moderate to severe LA had higher mRS scores (4 vs. 2, $p = 0.001$) and worst outcomes

(60.8% vs. 39.5%, $p < 0.001$) compared to patients with absent to mild LA.

Table 1 Baseline characteristics and functional outcomes of patients with absent to mild leukoaraiosis and moderate to severe leukoaraiosis

	Total (<i>n</i> = 97)	Absent or mild LA (<i>n</i> = 43)	Moderate or severe LA (<i>n</i> = 54)	<i>p</i>
Age (years)	70.0 ± 12.4	63.9 ± 14.0	74.9 ± 8.3	< 0.001
Sex, male (%)	60 (61.9%)	25 (58.1%)	35 (64.8%)	0.534
Medical history				
Hypertension (%)	65 (67.0%)	26 (60.5%)	39 (72.2%)	0.278
Diabetes (%)	18 (18.6%)	4 (9.3%)	14 (25.9%)	0.064
Atrial Fibrillation (%)	46 (47.4%)	14 (32.6%)	32 (59.3%)	0.014
Alcohol consumption (%)	29 (29.9%)	12 (27.9%)	17 (31.5%)	0.824
Current smoking (%)	27 (27.8%)	10 (23.3%)	17 (31.5%)	0.495
Heart rate (per min)	73.3 ± 17.2	73.9 ± 20.3	72.8 ± 14.5	0.754
Systolic blood pressure (mmHg)	137.2 ± 20.7	134.3 ± 23.8	139.4 ± 17.9	0.226
Laboratory test				
Platelet, $\times 10^9/L$	188.4 ± 77.5	198.3 ± 60.6	180.8 ± 88.3	0.281
INR	1.03 ± 0.13	1.02 ± 0.15	1.04 ± 0.12	0.360
Serum creatinine (umol/L)	81.3 ± 31.2	72.9 ± 21.7	87.6 ± 35.6	0.017
Fasting glucose (mmol/L)	6.71 ± 2.12	6.31 ± 1.72	6.99 ± 2.34	0.141
Low-density lipoprotein (mmol/L)	2.64 ± 0.83	2.59 ± 0.92	2.67 ± 0.76	0.627
Admission NIHSS score	13 (9–17)	13 (9–16)	13 (9–18)	0.290
Intravenous thrombolysis (%)	60 (61.9%)	28 (65.1%)	32 (59.3%)	0.675
Onset-to-recanalization time (min)	338 (285–390)	334 (276–390)	342 (294–383)	0.506
mTICI 3	55 (56.7%)	26 (60.5%)	29 (53.7%)	0.542
Functional outcomes				
mRS at 3 months	3 (1–5)	2 (1–4)	4 (3–5)	0.001
mRS 3–6 at 3 months (%)	59 (60.8%)	17 (39.5%)	42 (77.8%)	< 0.001
Cerebral hemorrhage				
Any hemorrhage at 24 h (%)	25 (25.8%)	8 (18.6%)	17 (31.5%)	0.169
sICH at 24 h (%)	10 (10.3%)	2 (4.7%)	8 (14.8%)	0.177
Death at 3 months (%)	17 (17.5%)	5 (11.6%)	12 (22.2%)	0.192

Abbreviations: LA, Leukoaraiosis; INR, International normalized ratio; NIHSS, National Institute of Health Stroke Scale; mTICI, modified Thrombolysis in Cerebral Infarction scale; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage

Univariate and multivariate logistic regression analyses of LA severity are shown in Table 2. After adjusting for age, admission NIHSS scores, onset-to-recanalization time, serum creatinine, and fasting glucose, patients with moderate to severe LA were 3.77 times (95% CI 1.21–11.76, $p = 0.022$) more likely to have worst outcomes compared to patients with absent to mild LA, while the risk increased to 5.16 times (95% CI 1.02–25.99, $p = 0.047$) for patients with severe LA.

Discussion

Our study found that LA severity was associated with poor functional outcomes after recanalization by thrombectomy for patients with ischemic stroke caused by anterior large vessel occlusion. After compensating for age, stroke severity and other variables, risk of disability or death (mRS 3–6) for patients with moderate to severe LA was more than three times higher compared to patients with absent to mild LA.

The influence of LA on stroke outcomes post thrombolysis has been well established. In 2017, a meta-analysis on 15 prospective and retrospective studies assessed the outcomes between patients with moderate to severe LA and patients with absent to mild LA after intravenous or intra-arterial thrombolysis [9]. The relative risk (RR) of poor outcomes in the included studies ranged from 1.23 to 2.07 and the pooled RR was 1.31 (95% CI 1.22–1.42). However, only a few studies have reported this association after mechanical thrombectomy. There are discrepancies in the recanalization rates between thrombectomy and thrombolysis. A previous study by Shi et al. investigated patients who received thrombectomy with first-generation devices [12]. The moderate to severe LA group had a higher in-hospital mortality compared to absent to mild LA group (48.0% vs. 11.5%), but had similar mRS 3–6 at discharge (76.0% vs. 74.4%). In our study, LA severity not only was associated with increased mortality but also had impaired functional outcomes at 3 months. This discrepancy may be partly attributed to the

Table 2 Logistic regression analysis of leukoaraiosis severities with outcomes

	Crude OR (95% CI)	P	Adjusted OR* (95% CI)	<i>p</i>
Poor outcome (mRS \geq 2)*				
Moderate or severe LA vs. absent or mild LA	5.35 (2.21–12.99)	<0.001	3.77 (1.21–11.76)	0.022
Severe LA vs. others	7.45 (2.05–27.08)	0.002	5.16 (1.02–25.99)	0.047
Any hemorrhage [†]				
Moderate or severe LA vs. absent or mild LA	2.01 (0.77–5.25)	0.154	1.19 (0.41–3.49)	0.749
Severe LA vs. others	1.82 (0.68–4.86)	0.232	1.21 (0.42–3.55)	0.724
sICH [‡]				
Moderate or severe LA vs. absent or mild LA	3.57 (0.72–17.76)	0.121	1.83 (0.293–11.43)	0.517
Severe LA vs. others	1.97 (0.51–7.63)	0.327	1.45 (0.31–6.72)	0.633

*OR is adjusted for age, admission NIHSS scores, onset-to-recanalization time, serum creatinine, and fasting glucose

[†] OR is adjusted for age, sex, and current smoking

[‡] OR is adjusted for age, INR, and serum creatinine

Abbreviations: LA, leukoaraiosis; NIHSS, National Institute of Health Stroke Scale; INR, International normalized ratio

recanalization rate. In the previous study, only 74.3% patients acquired recanalization status, while all participants in our study had an mTICI score of 2b or 3. Fewer patients with absent to mild LA in our study experienced disability or death compared to the previous study (39.5% vs. 74.4%), while the proportions in the moderate to severe LA group were comparable. A recent published retrospective study had comparable findings with ours, in which LA severity was evaluated by CT scan and graded according to the van Swieten scale [13]. The results showed that fewer patients in the severe LA group attained a good functional outcome compared to the absent to moderate group (18.4% vs. 50.2%). In addition, LA was a predictor of futile recanalization (OR 3.59).

Despite successful and prompt recanalization after thrombectomy, a number of patients were still morbid or died. LA seemed to act as an independent risk factor. The exact pathologic mechanisms are yet to be deciphered [7]. Previous studies have demonstrated that the severity of LA was usually associated with advanced age, hypertension history, and other characteristics, which were also risk factors for severe symptoms and poor outcomes after stroke [14, 15]. In addition, accumulating evidence has shown that LA severity was associated with individual variability of cerebral autoregulation which maintains cerebral blood flow [16, 17]. A recent study showed that white matter dysfunction was related to capillary pericyte degeneration in a mouse model [18]. Pericytes are involved in controlling capillary diameter and play a key role in regulating tissue perfusion in healthy and ischemic stroke patients [19]. Considering these evidences, LA may be associated with the impairment of cerebral autoregulation and blood reflow after recanalization. Our study showed a large discrepancy in outcomes between the classifications of LA severity. Future studies are needed to further investigate this relationship and its mechanisms.

Previous studies have shown that LA severity was strongly associated with hemorrhage transformation after thrombolysis and thrombectomy using first-generation devices [9, 11, 20]. In addition to affecting cerebral autoregulation and microcirculation, LA was also found to be associated with higher fragility in small vessels, endothelial dysfunction, and abnormal permeability of the blood-brain barrier. This may increase susceptibility to artery rupture and hemorrhage in cerebral ischemia following recanalization [9, 14]. In our study, a higher sICH rate was also observed in the moderate to severe LA group, but the difference did not reach statistical significance. This may be attributed to the small sample size, while considering the total sICH rate was small (10.4%). Larger cohorts may possibly help acquire statistical differences.

Our study had several advantages. All patients in the study received the standard procedure of thrombectomy using stent retrievers, and were all based on published guidelines. Furthermore, we considered several variables when analyzing the association of LA and mRS scores. However, several limitations should also be mentioned. First, as a retrospective analysis on a single center registry, the selection bias was present. Although we enrolled patients who met the inclusion criteria, eight patients were excluded due to the absence of MRI tests. In addition, several patients refused thrombectomy because of financial or other reasons. Hence, associations were not performed in these patients. Second, we evaluated the severity of LA using a visual scale instead of measuring the volume. Third, we did not analyze the interaction effect of stroke classifications due to the limited sample size. Ischemic stroke is recognized for its different etiologies, which may lead to different prognosis and treatment strategies. The impact of LA severity may also differ for atherosclerotic strokes and cardiac embolisms. Fourth, although we found LA affected patient prognosis after successful recanalization, no conclusion could be made to whether an LA interaction effect on

thrombectomy was present. Further studies are needed to compare thrombectomy in patients with different LA severity.

In summary, LA severity may be associated with poor outcomes after successful recanalization by endovascular thrombectomy for ischemic stroke. Patients with moderate to severe LA were supposed to be more resistant to reperfusion treatment. Our results should be interpreted with caution due to its retrospective nature and small sample size. However, these results may imply its potential predictive value for outcomes after thrombectomy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and adhered to the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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