



# White Matter Integrity and Early Outcomes After Acute Ischemic Stroke

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## Abstract

Chronic white matter structural injury is a risk factor for poor long-term outcomes after acute ischemic stroke (AIS). However, it is unclear how white matter structural injury predisposes to poor outcomes after AIS. To explore this question, in 42 AIS patients with moderate to severe white matter hyperintensity (WMH) burden, we characterized WMH and normal-appearing white matter (NAWM) diffusivity anisotropy metrics in the hemisphere contralateral to acute ischemia in relation to ischemic tissue and early functional outcomes. All patients underwent brain MRI with dynamic susceptibility contrast perfusion and diffusion tensor imaging within 12 h and at day 3–5 post stroke. Early neurological outcomes were measured as the change in NIH Stroke Scale score from admission to day 3–5 post stroke. Target mismatch profile, percent mismatch lost, infarct growth, and rates of good perfusion were measured to assess ischemic tissue outcomes. NAWM mean diffusivity was significantly lower in the group with early neurological improvement (ENI, 0.79 vs.  $0.82 \times 10^{-3}$ ,  $\text{mm}^2/\text{s}$ ;  $P = 0.02$ ). In multivariable logistic regression, NAWM mean diffusivity was an independent radiographic predictor of ENI ( $\beta = -17.6$ ,  $P = 0.037$ ). Median infarct growth was 118% (IQR 26.8–221.9%) despite good reperfusion being observed in 65.6% of the cohort. NAWM and WMH diffusivity metrics were not associated with target mismatch profile, percent mismatch lost, or infarct growth. Our results suggest that, in AIS patients, white matter structural integrity is associated with poor early neurological outcomes independent of ischemic tissue outcomes.

**Keywords** Ischemic stroke · Leukoaraiosis · Diffusion tensor imaging · Stroke outcomes

## Introduction

White matter hyperintensity (WMH), or leukoaraiosis on T2 MRI, is thought to represent end-stage white matter disease and loss of structural integrity [1]. Importantly, patients with increased white matter structural injury have a greater risk of poor long-term functional outcomes after acute ischemic stroke (AIS) [2, 3]. Specifically, increasing WMH burden is predictive of poor long-term functional outcomes after AIS [2, 4]. At the microvascular level, decreased structural integrity and increased blood-brain barrier permeability (BBB-P) of

normal-appearing white matter (NAWM) are also associated with poor long-term post-stroke outcomes [5, 6]. An unresolved question, however, is how white matter structural injury contributes to poor stroke outcomes.

There is some evidence to suggest that patients with increased WMH burden are at risk of infarct growth in the acute setting [7]. In select patient populations, WMH burden is also associated with early neurologic deterioration after AIS [8, 9]. These data suggest that patients with increasing WMH burden are at risk for infarct growth and poor early neurologic outcomes. An important consideration of these findings, however, is that visible WMH represents radiographic injury to only a small fraction of total brain white matter [10]. As a result, it is not known whether characterization of microstructural integrity of NAWM, representing the large majority of total white matter, will provide additional information on ischemic tissue and early clinical outcomes after AIS. Addressing this question could advance knowledge on the influence of NAWM structural integrity on the early trajectory after stroke, which has been shown to be a significant predictor of long-term outcomes [11], and provide insight into the mechanisms of white matter injury in post-stroke outcomes.

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We hypothesize that decreased white matter structural integrity contributes to worse ischemic tissue and early clinical outcomes post stroke. In a population of AIS patients with moderate to severe WMH, at risk for infarct growth [7] and poor early neurologic outcomes, [8] we set out to characterize the clinical and radiographic variables associated with ischemic tissue and early clinical outcomes. Analysis of white matter structural integrity in the hemisphere contralateral to the acute infarct was performed to minimize any influence from acute cerebral ischemia and to investigate the effects of chronic white matter injury on early clinical outcomes. We used a prespecified definition of early neurological improvement (ENI) as part of a retrospective analysis of an ongoing prospective study of AIS patients with serial MRIs obtained in the acute (< 12 h from stroke onset) and subacute phases (3–5 days post stroke). Utilizing this radiographic approach, in the hemisphere contralateral to the acute infarct, we measured NAWM and WMH diffusivity anisotropy metrics in relation to ischemic tissue outcomes and ENI.

## Methods

All aspects of this study have been approved by our Institutional Review Board. Informed consent was obtained from all individual participants included in the study or their surrogates.

The current study was a retrospective analysis of an ongoing, prospective study, the Statins Augment small Vessel function and improve stroke Outcomes (SALVO, NIH 5R01NS082285) study of the effect of statin pretreatment in patients with AIS and moderate to severe WMH.

## Participants, Inclusion/Exclusion Criteria

Between April 2014 and February 2017, all AIS subjects > 18 years presenting to our Emergency Department within 12 h from symptom onset were screened for eligibility and underwent a brain MRI. AIS was defined as (a) acute onset of focal neurological symptoms consistent with cerebrovascular syndrome, (b) MRI findings consistent with acute cerebral ischemia, and (c) no evidence of other neurological disorders to explain the symptoms. Subjects with moderate to severe WMH, as defined by Fazekas grade  $\geq 2$  in either category, [12] were eligible for enrollment in this study. Participants unable to obtain gadolinium-based contrast because of medical contraindications were excluded. Participants with pre-morbid functional status deemed by the investigator likely to interfere with study participation or follow-up were also excluded. All enrolled subjects had a repeat MRI at day 3–5 post stroke contemporaneous with clinical outcome assessment.

## Clinical Variables

All participants were evaluated by a neurologist on admission and at day 3–5 post stroke, and the NIHSS score, as a measure of stroke severity, was determined. Age and past medical history (including atrial fibrillation, prior myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia, and prior ischemic stroke) were obtained on admission from the patient or their surrogate, or abstracted from the medical record. Tobacco use was defined as patient reported current or any prior cigarette smoking. Admission systolic and diastolic blood pressures were abstracted from the first documented vital signs in the medical record. Treatment with intravenous thrombolysis was also recorded. Large-vessel occlusion of the anterior circulation was defined as occlusion of the internal carotid artery or proximal middle cerebral artery, M1 segment. AIS subtypes were categorized by a trained neurologist (M.R.E, N.S.R.) according to the criteria established by the Trial of Org 10172 in Acute Stroke Treatment [13]. ENI was defined as a reduction in the NIHSS of  $\geq 2$  points from the admission to day 3–5 assessment post stroke or a NIHSS score of 0 on follow-up assessment (ENI+).

## Imaging Analysis

### MRI Data Acquisition

Each participant underwent two separate brain MRIs with perfusion-weighted imaging (PWI): one (acute) within 12 h from stroke onset and the second (follow-up) at day 3–5 post stroke. Except for one participant, all acute MRIs were performed on a 1.5-T General Electric scanner. The follow-up MRI was performed using a 3-T Siemens Skyra scanner in all but five participants that could not undergo a dedicated 3-T MRI due to medical contraindications.

For the acute MRI, axial T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) sequences were acquired, in most subjects, on a 1.5-T General Electric MRI system with TR/TE/TI = 9002/133/2200 ms, 220-mm field-of-view (FOV), 5-mm slice thickness with 1-mm gap, and in-plane resolution of  $0.86 \times 0.86 \text{ mm}^2$ . Diffusion-weighted (DWI)/diffusion tensor imaging (DTI) was obtained on the acute MRI with echo-planar imaging using the following acquisition parameters for most cases: TR/TE = 5000/92 ms, 240-mm FOV, 5-mm slice thickness with 1-mm gap, in-plane resolution of  $0.94 \times 0.94 \text{ mm}^2$  ( $128 \times 128$  acquisition matrix up-sampled to  $256 \times 256$ ), three 0 s/mm<sup>2</sup> (b-zero) and 25 directions (1000 s/mm<sup>2</sup> b-value). Eddy current distortion and motion correction was performed on DTI datasets as described previously [14]. Dynamic susceptibility contrast (DSC) PWI was acquired using gradient echo echo-planar imaging read-out with the following parameters: TR/TE = 1500/40 ms, 220–240 ms FOV, 5 mm slice thickness with 1 mm gap, and

$1.72 \times 1.72 \text{ mm}^2$  in-plane resolution and 80 time points. The time-to-maximum ( $T_{\text{max}}$ , s) maps were calculated as described previously [6, 15, 16].

Follow-up FLAIR sequences were acquired with TR/TE/TI = 9000/119/2500 ms, 220-mm FOV, 5-mm slice thickness with 1-mm gap, and in-plane resolution of  $0.86 \times 0.86 \text{ mm}^2$ . The follow-up DSC PWI imaging protocol consisted of 80 acquisitions at a TR/TE = 1500/35 ms, 220 ms FOV, 5 mm slice thickness with 1 mm gap and  $1.72 \times 1.72 \text{ mm}^2$  for most cases.

### Volumetric Analysis

WMH and chronic strokes were outlined on the acute FLAIR sequence using a validated, semiautomated method utilizing MRIcro software ([www.mricro.com](http://www.mricro.com)) as described previously [5, 17]. Briefly, supratentorial WMH maps were derived in the ipsi- and contralesional hemispheres using automated signal intensity thresholding with subsequent manual editing to finalize the WMH maps. The acute DWI sequence was used for comparison to exclude any confounding due to acute cerebral ischemia. Total WMH volume (WMHv) was normalized to intracranial area [18]. Volumes of the acute infarct on DWI (DWIv), acute  $T_{\text{max}}$  with a threshold  $> 6$  s on DSC perfusion, and final infarct volume (FIV), defined as infarct volume on the follow-up FLAIR sequence, were determined. The PWI-DWI mismatch ratio was defined as acute  $T_{\text{max}}$ /DWIv. Percent infarct growth was calculated as  $(\text{FIV} - \text{DWIv})/\text{FIV} \times 100$ . Good reperfusion was defined based on the criteria of a greater than 50% reduction in  $T_{\text{max}}$  lesion volume between the baseline and day 3–5 follow-up MRI [19]. Percent mismatch lost was calculated as  $(\text{FIV} - \text{DWIv})/(\text{acute } T_{\text{max}} - \text{DWIv}) \times 100$  [7]. Target mismatch profile was defined as PWI-DWI mismatch ratio  $> 1.8$  and mismatch volume  $\geq 15 \text{ cm}^3$  [19].

### DTI Analysis

The DWI and FLAIR data were coregistered to one another in a semiautomated manner [20] to the ICBM-152 T1 Atlas [21]. Probabilistic NAWM masks were determined as described previously [6]. In brief, NAWM in the hemisphere contralateral to the acute infarct was segmented using the ICBM probabilistic atlas [22] with 95% WM probability and subtracting the WMH and chronic stroke masks. NAWM masks were further restricted by dilating the WMH masks three times (mincmorph, [23]) prior to subtraction and setting an ADC value threshold of less than  $1500 \times 10^{-6} \text{ mm}^2/\text{s}$ . Mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and fractional anisotropy (FA) were subsequently measured in WMH and NAWM contralateral to the acute infarct. One participant was excluded from analysis because the 95% probability NAWM volume was less than  $0.1 \text{ cm}^3$ .

### Statistical Analysis

For statistical comparison of the ENI+ versus ENI– groups, Wilcoxon rank sum and Fisher's exact test were used, as appropriate (RStudio version 1.0.153). Effect size was determined for statistically significant ( $P < 0.05$ ) and selected additional variables. Univariable logistic regression was performed to assess the association of ENI with clinical and radiographic variables. Stepwise, backward elimination logistic regression analysis was performed using minimization of Akaike information criterion to determine predictors of ENI. To avoid the influence of collinearity between the diffusivity anisotropy metrics on the regression analysis [24], three models were run including (1) AD and RD, (2) MD, and (3) FA. Statistical significance was set at  $P < 0.05$ .

## Results

### Clinical and Radiographic Variables Associated with Early Neurological Outcomes

Forty-two participants were enrolled in our study. The acute and follow-up MRIs were obtained at a mean time  $\pm$  standard deviation of  $6.15 \pm 2.78 \text{ h}$  and  $65.03 \pm 26.5 \text{ h}$  from last known well time, respectively. 52.3% of participants met criteria for ENI and eight (19.1%) had a worsening of NIHSS by 2 or more points from admission to day 3–5. We observed no difference in age, sex, pre-stroke disability, history of ischemic stroke, stroke secondary to large-vessel occlusion, or administration of intravenous tPA between the groups with and without ENI (Table 1). The ENI+ group, however, had decreased rates of diabetes, hyperlipidemia, hypertension, and strokes attributed to a small-vessel occlusive etiology (Table 1). Admission NIHSS scores were higher in the ENI+ group than the ENI– group; however, the ENI– group had higher follow-up NIHSS scores (Table 1).

No difference in total WMHv was observed between groups; however, the ENI+ group had a lower burden of periventricular WMH compared with the ENI– group (Table 2). There was no difference in the amount of deep WMH between groups. The PWI-DWI mismatch ratio, percent infarct growth, percent mismatch lost, and FIV were also not different between groups (Table 2). A large, but nonsignificant, difference in the rate of good reperfusion was observed between groups (ENI+, 77.8%; ENI–, 46.7%;  $P = 0.08$ ).

NAWM RD and MD values were lower in the ENI+ group, as compared with the ENI– group (Table 3). Furthermore, effect size calculations suggested a medium practical significance for RD ( $r = 0.29$ ) and MD ( $r = 0.31$ ). No difference in WMH diffusivity anisotropy metrics was observed between ENI groups (Table 3).

In univariate regression analysis for predictors of ENI, hypertension, hyperlipidemia, diabetes, and increased admission

**Table 1** Comparison of clinical characteristics in 42 AIS patients with moderate to severe WMH burden

Early neurologic improvement				
Variables	Entire cohort ( <i>n</i> = 42)	Yes ( <i>n</i> = 22)	No ( <i>n</i> = 20)	<i>P</i> value
Age, y, mean (SD)	70.2 (9.2)	70.0 (10.3)	70.4 (8.5)	0.91
Male, <i>n</i> (%)	24 (57.1)	14 (63.6)	10 (50.0)	0.58
No pre-stroke disability <sup>†</sup> , <i>n</i> (%)	34 (81.0)	20 (90.9)	14 (70.0)	0.12
Past medical history, <i>n</i> (%)				
Atrial fibrillation	16 (38.1)	11 (50.0)	5 (25.0)	0.12
Myocardial infarction	7 (16.7)	3 (14.3)	4 (21.1)	0.68
Diabetes mellitus	9 (21.4)	1 (4.5)	8 (40.0)	0.008
Hyperlipidemia	23 (54.8)	8 (36.4)	15 (75.0)	0.016
Hypertension	29 (69.0)	12 (54.5)	17 (85.0)	0.048
Prior stroke	7 (16.7)	3 (13.6)	4 (20.0)	0.69
Any tobacco use	26 (61.9)	13 (59.1)	13 (68.4)	0.75
Admission and clinical data				
Systolic blood pressure, mmHg, mean (SD)	166.8 (29.1)	163.9 (34.3)	168.8 (22.8)	0.59
Diastolic blood pressure, mmHg, mean (SD)	83.8 (15.6)	83.2 (15.0)	84.7 (16.9)	0.77
Admission NIHSS, median (IQR)	8.0 (3.5–11.5)	10.5 (7.3–13.8)	3.5 (2.0–7.25)	0.0006
Day 3–5 NIHSS, median (IQR)	3.0 (2.0–7.5)	2.0 (1.3–4.0)	6.0 (2.0–10.0)	0.059
Intravenous alteplase, <i>n</i> (%)	19 (45.2)	12 (54.5)	7 (35.0)	0.23
Large-vessel occlusion <sup>0</sup>	6 (14.3)	3 (13.6)	3 (15.0)	1
Stroke subtype, TOAST criteria, <i>n</i> (%)				
Small-vessel occlusive	5 (11.9)	0 (0.0)	5 (25.0)	0.043
Definite cardioembolic	19 (45.2)	11 (50.0)	8 (40.0)	0.73

*IQR*, interquartile range; *SD*, standard deviation; *TOAST*, Trial of ORG 10172 in Acute Stroke Treatment

<sup>†</sup> Pre-stroke modified Rankin Scale score of 0

<sup>0</sup> Defined as occlusion of the intracranial internal carotid artery or proximal middle cerebral artery (M1 segment)

NIHSS score were all predictors of ENI (Table 4). Increasing periventricular, but not deep, WMH burden was also negatively associated with ENI in univariable analysis. In addition, analysis of NAWM and WMH diffusivity anisotropy metrics showed that increasing NAWM RD ( $\beta = -17.64$ ,  $P = 0.037$ ) and MD ( $\beta = -16.17$ ,  $P = 0.037$ ) decreased the likelihood of ENI (Table 4). In multivariable, backward elimination stepwise logistic regression, diabetes and admission NIHSS score were associated with decreased and increased likelihood of ENI, respectively.

In backward elimination, stepwise logistic regression analyses for radiographic markers of ENI, NAWM MD ( $\beta = -17.64$ ,  $P = 0.037$ ) was an independent predictor of ENI (Table 5).

### Clinical Variables Associated with Ischemic Tissue Outcomes

Fifteen patients (34.0%) had a target mismatch profile present. Admission systolic blood pressure ( $\beta = -0.035$ ,  $P = 0.023$ )

was negatively associated with presence of target mismatch profile on univariable logistic regression. On multivariable logistic regression analysis adjusting for WMHv, admission systolic blood pressure was an independent predictor for presence of a target mismatch profile ( $\beta = -0.16$ ,  $P = 0.04$ ).

The median percent infarct growth in our cohort was 118% (IQR 26.8–221.9) excluding patients with strokes attributed to small-vessel occlusive disease. WMHv, age, sex, and WMH and NAWM diffusivity anisotropy metrics were not predictive of percent infarct growth (data not shown). In our population, 65.6% achieved good reperfusion on follow-up imaging. There was no association between WMHv or NAWM diffusivity anisotropy metrics and reperfusion status.

### Discussion

In this study, we report that in individuals with moderate to severe WMH, preserved NAWM microstructural integrity is associated with ENI. We also demonstrate that clinical

**Table 2** Comparison of radiographic characteristics in 42 AIS patients with moderate to severe WMH burden

Early neurologic improvement				
Variable	Entire cohort (n = 42)	Yes (n = 22)	No (n = 20)	P value
WMH volume, cm <sup>3</sup> , median (IQR)	5.3 (2.3–9.3)	3.8 (2.0–8.8)	5.3 (2.9–9.6)	0.39
Periventricular WMH, Fazekas score, median (IQR)	2 (2–3)	2 (2–2)	2 (2–3)	0.04
Deep WMH, Fazekas score, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.63
DWI volume, cm <sup>3</sup> , median (IQR)	4.1 (0.8–18.1)	4.4 (0.9–15.3)	2.9 (0.6–20.7)	0.72
Final infarct volume, cm <sup>3</sup> , median (IQR)	8.3 (1.3–45.1)	8.4 (1.4–44.9)	7.7 (1.2–39.7)	0.81
Acute T <sub>max</sub> volume, cm <sup>3</sup> , median (IQR)	8.0 (0–51.9)	17.3 (0.8–60.3)	3.3 (0.0–43.5)	0.23
PWI-DWI mismatch ratio, median (IQR)	1.2 (0–4.4)	1.5 (0.5–5.6)	0.4 (0–2.8)	0.20
Infarct growth (%), median (IQR)	111.4 (20.7–221.9)	104.7 (19.0–230.7)	121.5 (57.7–209.9)	0.81
Good reperfusion, n (%)	21 (50.0)	14 (77.8)	7 (46.7)	0.08
Percent mismatch lost (%), median (IQR)	11.4 (–62.6–77.0)	15.7 (–19.0–47.3)	4.6 (–111.5–109.6)	0.65

DWI, diffusion-weighted imaging; IQR, interquartile range; PWI, perfusion-weighted Imaging; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; WMH, white matter hyperintensity

variables suspected as inciting factors for intrinsic small-vessel disease, namely diabetes, hypertension, and hyperlipidemia, [1] diminish the odds of ENI. Lastly, we show that in patients with moderate to severe WMH, target mismatch profile and infarct growth are common in the early stage of AIS. As the early trajectory of the NIHSS has been shown to predict long-term outcomes, [11] our observations that infarct growth and the lack of ENI are common in patients with severe WMH burden emphasize the vulnerabilities of this population for poor outcomes and advance our understanding of how white matter structural integrity contributes to poor long-term post-stroke outcomes.

In comparison with the ENI+ group, we observed that NAWM diffusivity, specifically RD and MD, was significantly increased in the ENI– group. Decreased NAWM structural integrity, reflected by higher NAWM RD and MD values, was also associated with decreased odds of ENI. These observations were further supported in the multivariable logistic

regression analysis for radiographic predictors of ENI which demonstrated that NAWM MD was an independent predictor of ENI in models including DWIv, PWI-DWI mismatch ratio, and periventricular WMH burden. The multivariable model suggests that decreased NAWM structural integrity, reflected as increased MD, is an independent radiographic predictor of ENI. This observation suggests a role of white matter microstructural integrity in early clinical recovery after AIS. Furthermore, by restricting our DTI analysis to the contralesional hemisphere, we minimized any contribution of acute cerebral ischemia and were able to investigate the effects of chronic white matter injury on ENI.

The observation that diffusivity anisotropy values in WMH did not correlate with ENI is likely due to WMH, as a reflection of end-stage white matter disease, imparting a relative ceiling/floor effect on the respective diffusivity anisotropy analyses within these regions [25]. Accordingly, we observed no significant difference in the WMH diffusivity anisotropy

**Table 3** Comparison of NAWM and WMH diffusivity anisotropy metrics in patients with and without ENI

Early neurologic improvement				
	Entire cohort (n = 42)	Yes (n = 22)	No (n = 20)	P value
NAWM, median (IQR)				
FA	0.37 (0.35–0.41)	0.38 (0.35–0.42)	0.36 (0.35–0.38)	0.36
MD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	0.82 (0.77–0.83)	0.79 (0.77–0.82)	0.82 (0.77–0.84)	0.02
RD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	0.64 (0.61–0.67)	0.62 (0.61–0.64)	0.66 (0.62–0.69)	0.03
AD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	1.15 (1.1–1.2)	1.15 (1.1–1.2)	1.15 (1.1–1.2)	0.54
WMH, median (IQR)				
FA	0.27 (0.24–0.29)	0.27 (0.25–0.29)	0.28 (0.23–0.30)	0.95
MD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	1.22 (1.14–1.31)	1.21 (1.14–1.26)	1.25 (1.18–1.33)	0.40
RD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	1.04 (0.98–1.12)	1.02 (0.98–1.08)	1.06 (1.0–1.15)	0.56
AD (× 10 <sup>−3</sup> ), mm <sup>2</sup> /s	1.58 (1.46–1.66)	1.56 (1.45–1.63)	1.59 (1.51–1.67)	0.34

AD, axial diffusivity; FA, fractional anisotropy; IQR, interquartile range; MD, mean diffusivity; NAWM, normal-appearing white matter; RD, radial diffusivity; WMH, white matter hyperintensity

**Table 4** Association with early neurologic improvement in 42 patients with acute ischemic stroke

Variables	Univariable		Multivariable	
	Estimate	<i>P</i> value	Estimate	<i>P</i> value
Age	−0.004	0.91		
Sex	−0.56	0.37		
No pre-stroke disability <sup>†</sup>	1.46	0.10		
Atrial fibrillation	1.10	0.10		
Diabetes mellitus	−2.64	0.019	−6.35	0.007
Hypertension	−1.55	0.041		
Hyperlipidemia	−1.66	0.015		
Prior stroke	−0.46	0.58		
Any tobacco use	−0.41	0.54		
Admission systolic blood pressure	−0.006	0.58		
Admission diastolic blood pressure	−0.006	0.76		
Admission NIHSS	0.26	0.003	0.49	0.002
Intravenous alteplase	0.80	0.21		
WMHv	−0.02	0.51		
Periventricular WMH, Fazekas score	−1.48	0.047		
Deep WMH, Fazekas score	−0.18	0.63		
Small-vessel occlusive stroke	−17.95	0.99		
Definite cardioembolic stroke	0.41	0.52		
Final infarct volume	−0.002	0.80		
Mismatch ratio	0.004	0.71		
Acute $T_{\max}$ volume	$7.5 \times 10^{-6}$	0.27		
Percent infarct growth	−0.0002	0.46		
Percent mismatch lost	−0.0001	0.65		
NAWM				
FA	6.7	0.36		
AD	−4.39	0.25		
RD	−17.64	0.037		
MD	−16.17	0.037		
WMH				
FA	−1.65	0.82		
AD	−1.89	0.42		
RD	−1.05	0.74		
MD	−1.30	0.66		

*AD*, axial diffusivity; *FA*, fractional anisotropy; *IQR*, interquartile range; *MD*, mean diffusivity; *NAWM*, normal-appearing white matter; *RD*, radial diffusivity; *WMH*, white matter hyperintensity

<sup>†</sup> Pre-stroke modified Rankin scale score of 0

values between ENI groups. Based on this reasoning, the DTI analysis of contralesional NAWM represents a broader spectrum of chronic white matter pathology, which we have previously shown influences long-term stroke outcomes [5].

We also show that patients with moderate to severe WMH burden are at high risk for poor early clinical outcomes. In part, this is likely due to the association between increased WMH burden and infarct growth [7]. In our population, the median percent infarct growth was 118%. We also observed that 34% of our population had a target mismatch profile present despite only 14.3% with a confirmed large-vessel

occlusion. An explanation for this discrepancy could be that patients with severe WMH have hemodynamic impairment of the distal arteries/terminal arterioles and that this produces a tendency for poor ischemic tissue outcomes. This hypothesis is supported by prior work showing region-specific differences in cerebral blood flow in patients with WMH [26] and reduced cerebrovascular reactivity contributing to WMH progression [27].

Collectively, our findings confirm that individuals with advanced WMH burden are at high risk of poor ischemic tissue and early functional outcomes and that decreased NAWM

**Table 5** Backward logistic regression for acute radiographic predictors of ENI

Model	Variable	Estimate	P value
Model 1	MD	− 17.64	0.037
Model 2	RD	− 15.17	0.067
	Periventricular WMH	− 1.14	0.14
Model 3	n.s.		

Model 1: ENI ~ DWIv + mismatch ratio + periventricular WMH + MD

Model 2: ENI ~ DWIv + mismatch ratio + periventricular WMH + AD + RD

Model 3: ENI ~ DWIv + Mismatch ratio + periventricular WMH + FA  
 AD, axial diffusivity; DWIv, diffusion-weighted imaging lesion volume; ENI, early neurological improvement; MD, mean diffusivity; n.s., not significant; RD, radial diffusivity; WMH, white matter hyperintensity

microstructural integrity is associated with poor early post-stroke recovery. This is of clinical importance because the early trajectory of neurological improvement, as defined by the 2-day longitudinal NIHSS, has been shown to be a predictor of 90-day outcomes [11]. These observations highlight the influence of white matter structural integrity on stroke outcomes and agree with prior reports demonstrating a negative relationship between WMH burden and both early [8, 9] and long-term functional outcomes after AIS [2, 4, 28].

The design and patient population of this study offer several strengths including (1) a study of thoroughly ascertained, AIS patients including standardized measures of functional outcomes; (2) sequential MRIs obtained in the acute and sub-acute setting with PWI and DTI; (3) a standardized approach to MRI processing and analysis; and (4) utilizing acute clinical imaging sequences to identify early markers of ENI.

There are several limitations of this study that are important to consider in the overall interpretation and generalizability of our findings. First, while our sample size was large enough to detect significant differences in diffusivity anisotropy metrics relative to ENI with medium effect size ( $r = 0.3$ ), the small study size could contribute to the lack of statistical power to detect smaller influences from other clinical or radiographic variables. Secondly, this was a study of patients with severe WMH and relatively small strokes (median DWIv 4.1 cm<sup>3</sup>), which could limit the overall generalizability. How our results translate to patients with different clinical demographics such as ethnicity or prevalence of vascular risk factors, large infarcts, or different stroke subtypes is unclear. We maintain, however, that this focused study of AIS patients at risk for poor outcomes demonstrates the added utility of characterizing NAWM structural integrity to inform on the clinical trajectory. The difference in initial stroke severity between groups, with the ENI− group having a lower admission NIHSS, could also suggest a floor effect to the lack of improvement in this group. This seems unlikely given that this group actually deteriorated from admission to day 3–5 as evidenced by the median NIHSS (ENI−

NIHSS, admission 3.5 versus day 3–5, 6.0). Specifically, 60% (12 patients) of patients in the ENI− group had a worse NIHSS score on follow-up and an additional 20% (4 patients) had no change in NIHSS score. This observation suggests that the ENI− group, despite the low admission NIHSS, was in fact at risk for poor early neurologic outcomes. In addition, we have selected an NIHSS score cut-off for detection of ENI at a conservative, previously referenced margin ( $\geq 2$ ) [8, 9] to capture small variation in the neurological status. Therefore, our results suggest that the clinical and radiographic characteristics of the ENI− cohort are indicative of a vulnerable stroke population. An additional limitation of our approach was the utilization of the acute MRI scans for characterization of NAWM diffusivity anisotropy metrics. As these were clinical scans, nonisotropic voxels were used for diffusivity anisotropy analysis and thus could have introduced some bias due to partial volume averaging [29]. We would maintain, however, that utilizing clinical scans to identify predictors of ENI functions is a clinically pragmatic approach for translation to patient care.

In summary, we report the association of NAWM diffusivity anisotropy metrics with ENI after acute cerebral ischemia. Our findings strengthen the line of evidence for a relationship between white matter structural integrity and post-stroke outcomes with new evidence for a role in the early trajectory of recovery after AIS. Furthermore, these findings suggest that characterizing white matter structural integrity in the acute stages of ischemic stroke is feasible and can potentially identify susceptible populations at risk for early clinical improvement or deterioration. Overall, these findings merit a prospective, large-scale investigation of the impact of NAWM diffusivity anisotropy metrics on early neurologic outcomes after AIS.

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Ona Wu: study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content.

Anne-Katrin Giese: analysis and interpretation of data, critical revision of the manuscript for intellectual content.

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## Compliance with Ethical Standards

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**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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