Leukoaraiosis Predicts Short-term Cognitive But not Motor Recovery in Ischemic Stroke Patients During Rehabilitation

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Background: Leukoaraiosis has been shown to impact functional outcomes after acute ischemic stroke. However, its association with domain specific recovery after ischemic stroke is uncertain. We sought to determine whether pre-existing leukoaraiosis is associated with short-term motor and cognitive recovery after stroke. *Methods:* We retrospectively studied ischemic stroke patients admitted to acute inpatient rehabilitation (AIR) between January 2013 and September 2015. Patient baseline characteristics, infarct volume, prestroke modified Rankin Scale, stroke cause, rehabilitation length of stay, and Functional Independence Measure (FIM) scores were recorded. Leukoaraiosis severity was graded on brain magnetic resonance imaging using the Fazekas scale. Multiple linear regression was used to determine factors independently associated with the total, cognitive, and motor FIM scores at AIR discharge, respectively. *Results:* Of 1600 ischemic stroke patients screened, 109 patients were included in the final analysis. After adjustment, the initial National Institute of Health Stroke Scale (β −0.541, confidence interval [CI] −0.993 to −0.888; $P = 0.020$) and pre-existing leukoaraiosis severity (β −1.448, CI −2.861 to −0.034; $P = 0.045$) independently predicted the total FIM score. Domain specific analysis showed that infarct volume (β −0.012, CI −0.019 to −0.005; $P = 0.002$) and leukoaraiosis severity (β −0.822, CI −1.223 to −0.410; $P = 0.0001$) independently predicted FIM cognitive scores at discharge from AIR. Leukoaraiosis did not predict FIM motor score ($P = 0.17$). *Conclusions:* Leukoaraiosis severity is an independent predictor of total and cognitive, but not motor FIM scores after AIR for acute ischemic stroke. This highlights that leukoaraiosis affects poststroke recovery in a domain specific fashion, information that may aid counseling of patients and families as well as tailor rehabilitative efforts.

Key Words: Leukoaraiosis—ischemic stroke—cognition—rehabilitation—functional independence measure

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Introduction

Recent advances in hyperacute endovascular recanalization strategies, organized systems of stroke care, and improved secondary prevention strategies have significantly reduced stroke mortality.[1,2] In light of these critical advances, an increasing number of stroke survivors in the United States are now in need of dedicated rehabilitative efforts, imparting a high socioeconomic burden.[3]

Accordingly, it is important to understand factors that impact poststroke outcome and response to rehabilitation to improve patient care. Several factors have been identified to impact poststroke disability, including patient age, initial deficit severity, as well as infarct size and location.[4] Nonetheless, recovery after intensive rehabilitation remains difficult to predict given significant interindividual variability and differential response to therapy across functional domains.[5] A better understanding of this issue is important to predict the pattern and extent of recovery for assisting in personalized treatment plans for stroke survivors requiring rehabilitation.[6]

In this respect, leukoaraiosis, which is commonly present in ischemic stroke patients and has been repeatedly shown to relate to disability,[4,7,8] is a promising imaging marker of poststroke recovery and cognitive impairment.[4,9,10] Furthermore, leukoaraiosis impairs neuroplasticity by adversely affecting white matter tract organization and functional network integrity, providing a mechanistic background for observed detriment in functional outcomes.[11-14] Nevertheless, the specific impact of pre-existing leukoaraiosis on rehabilitation outcomes in ischemic stroke survivors remains uncertain.

To address this issue, we sought to determine the association between leukoaraiosis and functional outcomes after acute inpatient rehabilitation (AIR). To this end we assessed the Functional Independence Measure (FIM)—a validated comprehensive functional assessment tool to determine the degree of independence in activities of daily living in poststroke patients in a domain specific (cognitive versus motor) fashion.[15-19] We hypothesized that leukoaraiosis is associated with worse poststroke recovery on both the cognitive and motor domains of the FIM.

Methods

The study was approved by our Institutional Review Board, and Health Insurance Portability and Accountability Act waiver of informed consent was granted. We adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Study Population

This was a retrospective analysis of prospectively collected data and included consecutive patients with ischemic stroke hospitalized for acute stroke in a Comprehensive Stroke Center with subsequent rehabilitation at our AIR unit between January 2013 and September 2015 in a single health care system (Spectrum Health). Patient demographics, laboratory data, comorbidities, preadmission medications, prestroke modified Rankin scale (mRS), and stroke etiology (using the Trial of Org 10 172 in Acute Stroke Treatment classification)[20] after completion of diagnostic evaluation and National Institute of Health Stroke Scale (NIHSS) scores were assessed at the time of presentation to the acute care hospital by members of the stroke team certified in NIHSS in a prospective quality registry maintained by the AIR unit.

Functional Outcome Assessment

The total FIM score was measured in all patients both on admission and at discharge from our AIR unit by an occupational, physical, and speech therapist trained in administering this scale in a prospective quality registry maintained by the AIR unit. The FIM is a 126-point instrument comprised of 18 individual subscales measuring a variety of physical and cognitive functions. Each subscale is scored from 1 to 7 (1 = total assist, 7 = complete independence), resulting in a total FIM score that ranges from 18 to 126 with lower numbers indicating worse performance.[21]

Inclusion Criteria

We included adult (age ≥18 years) patients admitted to our AIR Unit who had ischemic stroke as their final diagnosis at discharge from our comprehensive stroke center (CSC) and who had magnetic resonance imaging (MRI) of the brain available for review to reliably diagnose ischemic stroke as well as to determine the degree of pre-existing leukoaraiosis.

Neuroimaging Review and Analysis

MRIs were retrospectively reviewed independently by two readers (M.K and H.H.) blinded to both clinical data and any follow-up scans. Lesions that were hyperintense on diffusion weighted imaging with a corresponding hypointensity on apparent diffusion coefficient maps were considered acute ischemic lesions and manually outlined as previously described.[22] Leukoaraiosis was defined on FLAIR MRI according to the STandards for ReportIng Vascular changes on nEuroimaging[23] and then graded according to the Fazekas scale as previously described.[24,25] The total Fazekas score was calculated by adding the periventricular and subcortical scores as previously described.[26-28] Using this approach we previously demonstrated high inter-rater reliability with an intraclass correlation coefficient of >0.95 for both the total and graded Fazekas score.[26]

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and outcome measures and were stratified

by severity of leukoaraiosis. Normally distributed continuous variables are shown as mean ± standard deviation. Non-normally distributed continuous variables are shown as median (25th percentile, 75th percentile). Categorical variables are shown as count (% frequency). Age; admission NIHSS; infarct volume, prestroke mRS, atrial fibrillation, and severity of leukoaraiosis were used as independent variables. We constructed separate multivariable linear regression models to determine whether the severity of preexisting leukoaraiosis was independently associated with the AIR unit discharge (a) total FIM, (2) motor FIM, and (3) cognitive FIM, respectively. All models were adjusted for age, NIHSS on initial presentation, infarct volume, prestroke mRS, and atrial fibrillation. To avoid model overfitting, variables were sequentially removed from the models at a significance level of 0.1. Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models. Two-sided significance tests were used throughout and unless stated otherwise a two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were generated using SAS (SAS Enterprise Guide software, Version 7.1, SAS Institute Inc, Cary, NC).

Results

Of 1600 subjects with acute ischemic stroke that were admitted to our CSC 109 adult patients fulfilled the study criteria and were included in the analyses (Fig 1). Demographics of the study participants stratified by absent-to-mild leukoaraiosis (Fazekas 0-2) and moderate-to-severe leukoaraiosis (Fazekas 3-6) are summarized in Table 1. Upon admission to the CSC, both groups had a similar NIHSS ($P = 0.24$) and infarct volume ($P = 0.43$). Moderate-to-severe leukoaraiosis patients had higher incidence of atrial fibrillation ($P < 0.05$) and cardioembolic etiology ($P < 0.05$) of stroke. Likewise, the total ($P = 0.59$), motor ($P = 0.83$), and cognitive ($P = .45$) FIM scores at admission to AIR and length of AIR stay ($P = 0.66$) were similar between groups. The mean age of patients with moderate-to-severe leukoaraiosis was significantly higher than that of subjects with none-to-mild leukoaraiosis (70.3 ± 11.2 years versus 57.4 ± 11.3 years, $P < 0.001$) (Table 1). In unadjusted analyses, the total and motor FIM scores at discharge did not differ between patients with absent-to-mild versus moderate-to-severe leukoaraiosis ($P > 0.2$, each). Conversely, the cognitive FIM scores at discharge

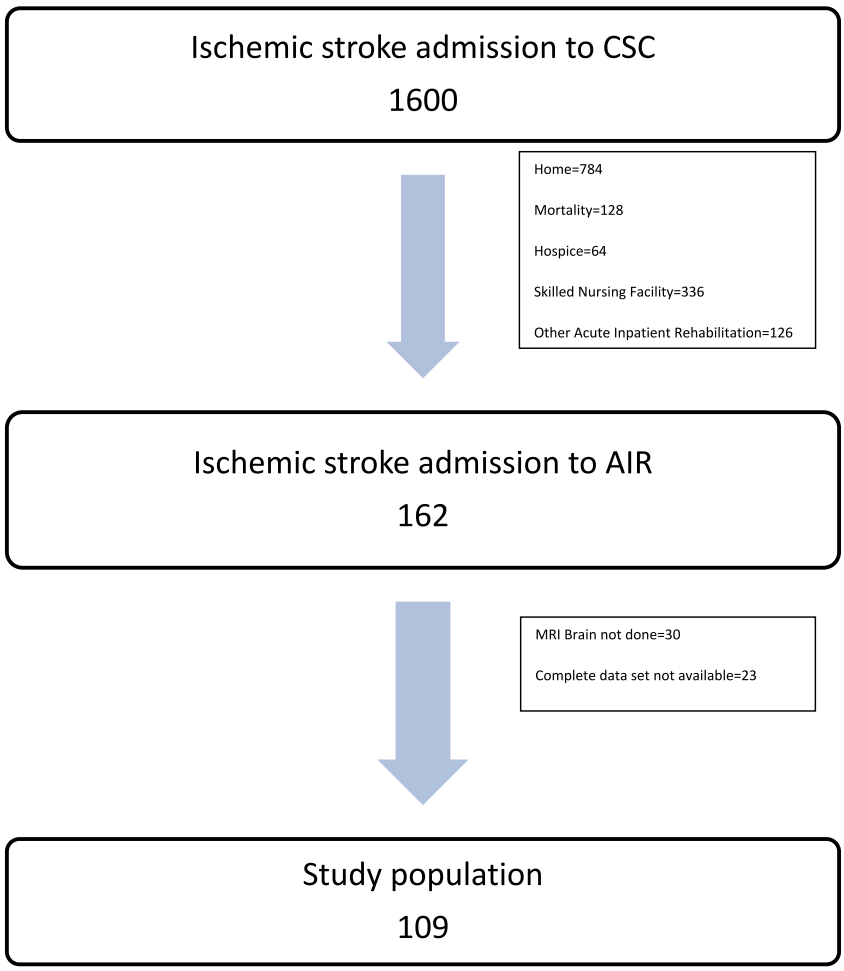

Figure 1. *Flowchart of study population selection. Abbreviations: CSC, comprehensive stroke center; AIR, acute inpatient rehabilitation.*

Table 1. *Baseline characteristics of the studied patient population*

Characteristics	All patients (n = 109)	None to mild leukoaraiosis (Fazekas 0-2) (n = 30)	Moderate to severe leukoaraiosis (Fazekas 3-6) (n = 65)	*P* value
Age, years	66.6 ± 12.4	57.4 ± 11.3	70.3 ± 11.2	<.001
Baseline NIHSS at CSC	7 [5,12]	8 [5,12]	6 [4,10]	.24
AIR unit Length of Stay, days	12 [8,17]	12 [8,17]	13 [9,17]	.66
Female sex	44 (40.4%)	6 (20.0%)	33 (50.8%)	<.01
Cerebrovascular risk factors				
Hypertension	84 (80.0%)	22 (75.9%)	54 (84.4%)	.33
Diabetes	43 (39.5%)	12 (40.0%)	27 (41.5%)	.89
Atrial fibrillation	22 (20.2%)	1 (3.3%)	16 (24.6%)	<.05
Prestroke modified Rankin scale (mRS)				
0	52 (47.7%)	23 (76.7%)	23 (35.4%)	<.001
1	32 (29.4%)	2 (6.7%)	25 (38.5%)	
2	19 (17.4%)	4 (13.3%)	13 (20.0%)	
3	6 (5.5%)	1 (3.3%)	4 (6.1%)	
TOAST classification				
Cardioembolic	33 (30.3%)	3 (10.0%)	22 (33.8%)	<.05
Undetermined	29 (26.6%)	7 (23.3%)	17 (26.2%)	
Large artery atherosclerosis	6 (5.5%)	4 (13.3%)	2 (3.1%)	
Small vessel disease	37 (33.9%)	15 (50.0%)	22 (33.8%)	
Other determined	4 (3.7%)	1 (3.3%)	2 (3.1%)	
Acute Intervention				
rtPA administration only	20 (18.4%)	6 (20.0%)	8 (12.3%)	.43
Mechanical thrombectomy only	4 (3.7%)	1 (3.3%)	2 (3.1%)	
Both rtPA and mechanical thrombectomy	8 (7.3%)	3 (10.0%)	3 (4.6%)	
Conservative management	77 (70.6%)	20 (66.7%)	52 (80.0%)	
Infarct volume, mL	25 [10,63]	22.5 [10,70.5]	20 [6.2,39.6]	.43
FIM Score				
Total FIM admission	91.0 ± 18.7	93.9 ± 15.3	92.0 ± 16.4	.59
FIM motor admission	66.6 ± 15.7	68.1 ± 12.1	67.5 ± 14.7	.83
FIM cognitive admission	25 [21,29]	26.5 [21,31]	25 [22,28]	.45
Total FIM discharge	125 [113,132]	124.5 [117,134]	125 [114,131]	.40
FIM motor discharge	93 [83,100]	93 [83,100]	93 [84,99]	.77
FIM cognitive discharge	32 [29,34]	33.5 [30,35]	31 [29,34]	<.05
Discharge disposition (n = 107)				
Home	94 (87.9)	26 (86.7)	57 (89.1)	.74
Institution	13 (12.1)	4 (13.3)	7 (10.9)	

Abbreviations: AIR, acute inpatient rehabilitation; CSC, comprehensive stroke center; FIM, functional independence measure; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; rtPA, recombinant tissue-type plasminogen activator.

Data are shown as n (%), mean ± SD, or median [25th percentile, 75th percentile], as appropriate.

were lower in patients with moderate-to-severe leukoaraiosis ($P < 0.05$). Discharge disposition to home was similar in both groups ($P = 0.74$).

On multivariable linear regression, the initial NIHSS (β −0.541, confidence interval [CI] −0.993 to −0.888; $P = 0.020$) and leukoaraiosis (β −1.448, CI −2.861 to −0.034; $P = 0.045$) were independent predictors of total FIM score at discharge (Table 2). In the FIM domain-specific analyses, we found that the FIM motor score at discharge was not predicted by age, initial NIHSS, infarct volume, or severity of leukoaraiosis (though the admission NIHSS was approaching significance [$P = 0.065$]). In contrast, both a greater infarct volume (β −0.012, CI −0.019 to −0.005; $P = 0.017$) and worse leukoaraiosis severity (β −0.822, CI −1.223 to −0.410; $P = 0.0001$) independently predicted lower FIM cognitive scores at discharge (Table 3). Accordingly, if all other factors were held constant, each 1 point increase of the initial NIHSS and Fazekas score were associated with a 0.01 and 0.82 decrease of the FIM cognitive score, respectively.

Discussion

In our study, the initial deficit severity as assessed by the NIHSS at presentation to our CSC as well as the degree of pre-existing leukoaraiosis severity related to

Table 2. *Multiple linear regression analysis with backward elimination for factors associated with the rehabilitation outcome (Total FIM score at discharge)*

Independent variable	β (95% CL)	*P* value
Age	———	.1810
NIHSS	−0.541 (−0.993,−0.089)	.0196
Infarct volume	———	.1613
Leukoaraiosis	−1.448(−2.861,−0.034)	.0448
Prestroke mRS	———	.9382
Atrial fibrillation	———	.2115

National Institute of Health Stroke Scale (NIHSS); Age, Infarct Volume, pre-stroke modified Rankin Scale (mRS) and atrial fibrillation were insignificant and excluded from the model.

AIR outcomes after ischemic stroke as measured by the FIM score. Interestingly, domain specific analyses indicated that leukoaraiosis predicted only cognitive but not motor outcomes assessed by the FIM. Previous studies showed that pre-existing leukoaraiosis severity related to both motor and cognitive outcomes after ischemic stroke.[29,30] It is possible that our population characteristics and AIR admission criteria impacted the predictive ability of leukoaraiosis for motor outcomes since admission FIM motor scores are high in our study. Leukoaraiosis has been found to predict global functional outcomes in multiple studies[4,7,8] but there is paucity of data on domain specific outcomes.[29,31] Our results provide novel insight into this issue by suggesting a domain specific impact of leukoaraiosis on stroke recovery with pre-existing leukoaraiosis severity relating to impaired recovery early after stroke predominantly through cognitive impairment.

Infarct volume has been reported as a major predictor of poststroke outcome in earlier studies.[32-34] However, in our fully adjusted models infarct volume was not a predictor of overall functional outcome. This is in agreement with previous studies suggesting an interaction of age with infarct volume, whereby younger patients can achieve similar functional outcomes despite having larger infarcts as compared to older patients.[35-37] Nevertheless, in the domain specific analyses infarct volume was independently associated with cognitive outcomes after rehabilitation. This observation adds to the notion that reducing the overall stroke burden such as through systemic thrombolysis or mechanical thrombectomy may reduce the risk for poststroke cognitive impairment.[38,39] In addition to infarct volume, location is another important predictor of outcome as suggested by earlier studies. Infarct in cortical location tends to predict poor outcomes.[40,41]

Table 3. *Multiple linear regression analysis with backward elimination of rehabilitation outcome as FIM cognitive score at discharge*

Independent variable	β (95% CL)	*P* value
Age	———	.0966
NIHSS	———	.2668
Infarct volume	−0.012(−0.019,−0.005)	.0017
Leukoaraiosis	−0.822(−1.233,−0.410)	.0001
Prestroke mRS	———	.6269
Atrial fibrillation	———	.0514

National Institute of Health Stroke Scale (NIHSS); Age, NIHSS, pre-stroke modified Rankin Scale and atrial fibrillation were insignificant and excluded from the model.

The pathophysiological basis of impaired recovery due to leukoaraiosis is poorly understood. A plausible explanation suggests that leukoaraiosis results in loss of microstructural integrity in white matter tracts, which impedes structural reorganization after stroke as well as reduced functional compensation through remote brain areas.[42-47]

Our study found that despite similar baseline characteristics on admission to our CSC, patients with moderate-to-severe leukoaraiosis had worse cognitive outcome. It is unclear if this difference in cognitive outcome is a result of reduced spontaneous biological recovery, ineffective cognitive rehabilitation strategies or poor cognitive reserves. Earlier work has suggested an interaction of these factors with an opportunity to influence outcome.[48,49] Prior studies indicated the feasibility and efficacy of focused rehabilitation to aid poststroke cognitive recovery.[50,51] However, individualized and structured plans geared toward cognitive recovery are lacking.[52] Cognitive recovery is an important aspect of poststroke outcome and cognitive deficits have a major impact on long-term outcomes after stroke such as return to home and work.[53,54] Earlier studies have shown that multiple factors which include functional status, marital status, cognitive deficits, type of insurance, geographical location, caregiver support, and rehabilitation facility accreditation status impact outcomes.[55-58] Therefore, we did not find a correlation between leukoaraiosis severity and disposition to home due to multiple confounding factors. It is important to note that disposition to home does not necessarily indicate good outcome. Hence, if confirmed in future studies, rehabilitation programs should focus on cognitive rehabilitation specifically for patients with severe leukoaraiosis to determine whether these patients benefit from focused cognitive therapy. Lastly, our data may aid counseling patients and their families who are frequently concerned about the impact of stroke on cognitive status regarding expected outcomes and planning for care at home.

Strengths of our study include comprehensive data collection, blinded assessment of neuroimaging and outcome variables including standardized recovery assessment using the FIM scale and leukoaraiosis grading using a well-established and validated scoring system. By selecting patients who were treated at our CSC and subsequently underwent rehabilitation at our AIR, we are able to provide a longitudinal assessment of poststroke recovery. Limitations relate to the retrospective study design as

well as the modest sample size, exclusion of patients who did not undergo MRI brain as part of initial evaluation, lack of long-term outcomes, length of stay in CSC, Fazekas subscore analysis, infarct location analysis, and detailed neuropsychological assessment for cognitive recovery. However, FIM scores have been shown to predict long-term outcomes and are a reliable measure of cognitive impairment.[18,59]

In conclusion, our data suggests that the degree of pre-existing leukoaraiosis is associated with rehabilitation outcomes in a domain-specific fashion, and specifically relates to cognitive impairment. Our study demonstrates the importance of pre-existing small vessel disease in the context of poststroke recovery. Further studies are needed to validate our findings and help determine whether specialized cognitive rehabilitation programs improve recovery in stroke patients with moderate-to-severe leukoaraiosis.

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