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White matter hyperintensity adjusted critical infarct thresholds to predict a favorable 90-day outcome

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Abstract

Background and Purpose—There is increasing interest in defining stroke lesion volume thresholds to predict post-stroke outcome. However, there is a paucity of data regarding factors that impact the association between critical infarct thresholds volume and outcome. We sought to determine whether lesion thresholds best predicting outcome depend on the degree of pre-existing white matter hyperintensity (WMH) lesion burden.

Methods—MRI infarct volumes were quantified in 414 consecutive patients with anterior circulation ischemic strokes evaluated between January 2014 and December 2014. The WMH lesion volume was graded according to the Fazekas scale and dichotomized to absent-to-mild vs. moderate-to-severe. Receiver operator characteristics curves were calculated to determine the infarct volume threshold best predicting the 90-day outcome. Multivariable logistic regression was used to determine whether the critical lesion thresholds independently predicted a favorable 90-day outcome after adjusting for pertinent confounders.

Results—The infarct volumes thresholds predicting the 90-day outcome for the entire cohort (standard thresholds) were ≤29.5 mL (mRS 0–1), ≤29.9 mL (mRS 0–2), and ≤34.1 mL (mRS 0–3). For patients with absent-to-mild WMH lesion burden WMH-adjusted critical infarct thresholds were significantly greater than the standard infarct thresholds. In the fully adjusted multivariable

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Disclosures

Dr. Puri is a consultant for Codman Neurovascular, Stryker Neurovascular, CereVasc, and Covidien. He serves as speaker for the Miami Cardiovascular Institute and holds stocks in InNeuroCo.

Author contributions

Jatinder Patti	Data acquisition, interpretation of data, and drafting the article
Johanna Helenius	Data acquisition, interpretation of data, critical revision of the manuscript for important intellectual content
Ajit S. Puri	Interpretation of data, critical revision of the manuscript for important intellectual content
Nils Henninger	Study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting the article

regression models the WMH-adjusted infarct thresholds correctly predicted the outcome to a similar degree as the standard thresholds

Conclusions—In this proof-of-concept study the WMH lesion burden impacted the critical outcome-predicting infarct thresholds. If confirmed, using a WMH-adjusted infarct threshold could allow defining patients that have a favorable outcome despite having relatively large infarct volumes.

Keywords

ischemic stroke; infarct; small vessel disease; outcome; subcortical; threshold; white matter hyperintensity

Introduction

The infarct volume is one of the most powerful predictors for functional outcome after ischemic stroke. However, it is unlikely that a single lesion volume threshold applies to all patients, which may explain why lesion volume threshold predicting a poor outcome differ between studies.[1–3] In particular, it has been shown that younger patients may have better outcomes than expected in relation to their infarct volume.[1,4] Yet, a patient's chronological age is not always available in the acute situation when a patient is aphasic and may not be well reflective of the biological brain age. For this reason, it would be desirable to define an easily accessible imaging marker that allows for adjustment of the infarct volume threshold predictive of a favorable outcome based on the brain's biological age. White matter hyperintensity (WMH) lesions are frequently seen on clinical and research MRI and are considered to be such a marker.[5,6] Moreover, the WMH lesion burden has been shown to adversely affect the infarct extent and final functional outcome after ischemic stroke.[7,8]

We, therefore, sought to determine whether the critical final infarct threshold predicting a favorable functional outcome after ischemic stroke differs between patients dependent on the pre-existing WMH lesion burden. Specifically, we hypothesized that the critical final infarct volume threshold is greater in patients with absent-to-mild WMH lesion burden as compared to patients with moderate-to-severe WMH lesions.

Methods

Study Population

This study was reviewed and approved by our Institutional Review Board. We retrospectively analyzed consecutive patients with acute supratentorial ischemic stroke as shown on brain MRI that were prospectively included in our single academic center stroke registry between January 2013 and December 2014. Of note, a subset of the included patients has previously been reported as part of separate investigations.[9,10]

Patient demographics, laboratory data, comorbidities, pre-admission medications, and stroke etiology (according to the [TOAST]) were collected on all patients. NIHSS scores were assessed at the time of presentation. The mRS was assessed at the time of presentation (pre-admission mRS), and at 90-days by a stroke-trained physician or stroke study nurse certified

mRS.[7,10] When the mRS was unavailable, the same observers reconstructed the score from the case description, according to the mRS criteria. We adhere to the strengthening the Reporting of observational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Neuroimaging protocol

Brain MRI was obtained between 1 to 7 days after stroke and included T1-, T2-, and fluid attenuated inversion recovery (FLAIR)-sequences as well as DWI. MRI was performed on a 1.5 Tesla scanner (GE Signa; GE Medical Systems, Milwaukee, WI). DWI was obtained using echo-planar imaging with a repetition time of 8000 ms, an echo time of 102 ms, a field of view of 22×22 cm, image matrix of 128×128, slice thickness 5 mm with a 1-mm inter-slice gap, and b-values of 0 s/mm^2 and 1000 s/mm^2. FLAIR was obtained with a repetition time of 9002 ms, an echo time of 143 ms, a field of view of 22×22 cm, image matrix of 256×224, and slice thickness 6 mm with a 1-mm inter-slice gap.

Image review and analysis

Images were reviewed independently by two readers (JP, JH) blinded to both clinical data and any follow-up scans. Lesions that were hyper intense on DWI and hypo- or isointense on the apparent diffusion coefficient (ADC) maps were considered acute ischemic lesions. Ischemic lesions on DWI were manually outlined using careful windowing to achieve the maximal visual extent of the acute DWI (b1000 trace-weighted) lesion and with reference to the ADC image to avoid regions of T2 shine-through.

WMH was defined on FLAIR MRI according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)[6] criteria and graded according to the Fazekas scale as previously described in detail.[9,10] The total Fazekas score was calculated by adding the periventricular and subcortical scores.[10] In addition, we dichotomized the degree of WMH according to the median Fazekas score to 0–2 (n=204) vs. 3–6 (n=210) for statistical purposes. We have previously demonstrated a high inter rater reliability of WMH ratings in a set of 50 consecutive patients with an intra class correlation coefficient for the total Fazekas score of 0.969 (95%-CI 0.943–0.983).[10]

Statistics

Unless otherwise stated, continuous variables are reported as mean ± s.d. or as median (interquartile range). Categorical variables are reported as proportions. Between-group comparisons for continuous variables were made with unpaired t-Test and Mann-Whitney U test. Within-group comparisons were made using paired t-Test or Signed Rank test. Categorical variables were compared using the χ2-test or Fisher's Exact test. Correlative analyses were conducted using Spearman's rank test. ANOVA on Ranks with post-hoc Dunn's method was used to compare between-group differences in the NIHSS and infarct volume, respectively.

The main goal of our study was to determine whether the critical infarct threshold predicting a favorable 90-day outcome differs depending on the pre-existing WMH lesion burden. Since the definition of favorable outcome differs between clinical stroke trials, we conducted

separate analyses for a favorable 90-day outcome defined as (i) mRS 0–1, (ii) mRS 0–2, and (iii) mRS 0–3, respectively.

Receiver operating characteristic (ROC) curves were plotted to determine the infarct volume best predicting a favorable 90-day outcome. Optimal thresholds were determined by maximizing Youden index (sensitivity+specificity−1). To test whether the critical lesion thresholds were independently associated with a favorable 90-day functional outcome we constructed multivariable logistic regression models with backward elimination (likelihood ratio). All models were adjusted for age, sex, history of stroke or transient ischemic attack, atrial fibrillation, congestive heart failure, antiplatelet use, Fazekas score, admission NIHSS, pre-admission mRS, and random blood glucose at admission.

To explore the possible biological interaction (joint effects) of the WMH burden and infarct volume with a poor outcome we investigated interaction as departure from additivity by assessing the relative excess risk due to interaction (RERI), proportion attributable due to interaction (AP), and synergy index (S) using the interaction macro available at www.juliuscenter.nl/additive-interaction.xls.[11]

Since the presence of WMH could represent a biological plausible explanation for the age effect on outcome[5,9] we conducted mediation analyses to examine the potential mediating role of preexisting WMH lesion burden on the relationship between age and the 90-day functional outcome. Models were analyzed using PROCESS macro version 2.15 for SPSS (http://processmacro.org/index.html[12]) with bias-corrected, accelerated (BCa) 1000 resample bootstrap technique. Sex, preadmission mRS, and infarct volume were included as covariates.

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. Two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using IBM® SPSS® Statistics, Version 22 (IBM®-Armonk, NY).

Results

Patient cohort

During the study period, 874 patients were admitted to our stroke service and had a brain MRI allowing for reliable assessment of the WMH lesion burden. Of these, 414 eventually met the eligibility criteria (Figure 1). Small subcortical infarcts were excluded given their (by definition) small size below the known critical infarct thresholds.[3,6] Of note, a subset of patients has previously been described as part of separate investigations.[9,10]

Univariable associations of factors with a favorable 90-day outcome

Factors associated with a 90-day mRS of 0–1 included right-hemispheric infarct location (P=0.047), younger age (P=0.043), lower admission blood glucose level (P<0.001), as well as a lower pre-admission mRS (P<0.001), admission NIHSS (P<0.001), smaller final infarct volume (P<0.001), and lower WMH lesion burden (P=0.001; not shown).

Factors associated with a 90-day mRS of 0–2 included male sex (P=0.040), absent history of stroke/transient ischemic attack (P=0.043), congestive heart failure (P=0.029), atrial fibrillation (P=0.004), non-cardioembolic stroke etiology (P=0.027), no antiplatelets use (P=0.024), younger age (P=0.003), lower admission blood glucose level (P=0.001), as well as a lower pre-admission mRS (P<0.001), admission NIHSS (P<0.001), smaller final infarct volume (P<0.001), and lower WMH lesion burden (P=0.003; Table 1).

Factors associated with a 90-day mRS of 0–3 included an absent history of stroke/transient ischemic attack (P=0.025), congestive heart failure (P=0.011), hypertension (P=0.037), cardioembolic stroke etiology (P=0.037), no antiplatelets use (P=0.007), younger age (P<0.001), lower admission blood glucose level (P<0.001), as well as a lower LDL-C (P=0.010), pre-admission mRS (P<0.001), admission NIHSS (P<0.001), smaller final infarct volume (P<0.001), and lower WMH lesion burden (P<0.001; not shown).

Association of the 90-day outcome with the WMH lesion burden and infarct volume

Figure 2A depicts the positive correlation between WMH lesion burden and 90-day mRS (r=.174, P<0.001) and the increasing proportion of patients with worse 90-day mRS scores among patients with worse pre-existing WMH lesions (P<0.001, χ^2-test).

There was an additive interaction between WMH lesion burden and the critical infarct volume threshold on a poor outcome for mRS 2–6 (RERI=1.50, AP=0.125, S=1.16), mRS 3–6 (RERI=0.13, AP=0.013,S=1.01), and mRS 4–6 (RERI=2.50, AP=0.206, S=1.29), respectively. Results were similar when we entered the infarct volume in 10 mL increments: mRS 2–6 (RERI=0.19, AP=0.091, S=1.22), mRS 3–6 (RERI=0.09, AP=0.052, S=1.13), and mRS 4–6 (RERI=0.11, AP=0.062,S=1.15). A RERI of 0.11 means that with every 1 point increase in Fazekas score, and 10 mL increase in infarct volume, the relative risk of having a poor outcome is 0.11 more than if there were no interaction.

Given the association between infarct volume with WMH lesion burden as well as the 90-day outcome we analyzed the association of the infarct volume as stratified by Fazekas score and the 90-day outcomes. In summary, across favorable outcome categories (mRS 0–1, mRS 0–2, and mRS 0–3, respectively) patients with absent-to-mild WMH lesion burden had greater infarct volumes than patients with a moderate-to-severe WMH lesions (Figure 2B–D) indicating that they tolerate greater infarct volumes and still have a favorable outcome (P<0.05 each). Conversely, patients with moderate-to-severe WMH lesion burden on average had very large infarcts (>68mL) before being at risk for an unfavorable outcome (mRS 2–6, mRS 3–6, and mRS 4–6, respectively; P<0.01 each).

Critical infarct volume thresholds predicting favorable outcomes

First, we conducted ROC analyses in the entire cohort. In this analysis the critical infarct volumes predicting a favorable 90-day outcome were ≤29.5 mL for mRS 0–1, ≤29.9 mL for mRS 0–2, and ≤34.1 mL for mRS 0–3, respectively (Figure 3). Area under the curve (AUC) analysis indicated fair accuracy of these estimates (AUC ranging from 0.71 to 0.74; Figure 3B).

When we stratified our analyses according to the degree of pre-existing WMH lesion burden we found that the critical threshold for predicting an mRS of 0–1 as well as mRS 0–2 outcome was significantly greater in subjects with absent-to-mild WMH (Fazekas score 0–2) vs. the group-average threshold (P<0.05 each, Figure 3A) as well as compared to the thresholds for subjects with moderate-to-severe WMH (P<0.01 each, Figure 3A). Although the critical threshold for predicting an mRS of 3–6 was numerically greater in patients absent-to-mild WMH (49.9 mL) as compared to the threshold derived for the entire cohort (34.1 mL) as well as the moderate-to-severe WMH subgroup (29.9 mL) this difference did not reach significance in unadjusted analyses (P>0.05, Figure 3A). These results suggest that the WMH-adjusted critical infarct volume may be substantially greater for patients with absent-to-mild pre-existing WMH lesion burden than a standard infarct threshold (in our cohort 6% for mRS 0–1, 26% for mRS 0–2, and 32% for mRS 0–3).

Associations of the critical infarct volumes with the 90-day outcome in multivariable analyses

To determine whether the ROC-defined critical infarct volumes are independently associated with the pre-defined favorable 90-day outcomes (mRS 0–1, mRS 0–2, and mRS 0–3, respectively) we built multivariable logistic regression models adjusting for pertinent clinical covariates including the WMH lesion burden. Additionally we forced the Fazekas score × infarct threshold interaction in all models to determine whether the association between the critical infarct volume and 90 day outcome is dependent on the degree of preexisting WMH lesion burden. In all models a greater WMH lesion burden and larger infarct volume were independently associated with an unfavorable 90 day outcome (Supplemental Table II).

There was a significant negative Fazekas score × infarct threshold interaction for the clinically most frequently used dichotomization scheme to mRS 0–2 vs. 3–6 (P=0.001, Supplemental Table II). I.e., in the absence of WMH an infarct volume below the critical threshold has less impact on the outcome. In other words, it is too restrictive. Analysis of the other predefined outcomes also demonstrated a negative interaction coefficient, though, this did not reach statistical significance (P>0.05, Supplemental Table II).

We then repeated all multivariable analyses stratified by the WMH lesion status and individually entered the critical thresholds derived from the entire cohort (standard thresholds) as well as the critical thresholds derived from patients with absent-to-mild and moderate-to-severe WMH lesion status (WMH-adjusted thresholds), respectively. Overall, we found that that the WMH-adjusted infarct volume thresholds correctly predicted the outcome to a similar degree as the standard thresholds (Table 2). Using the adjusted (more lenient) thresholds resulted in one additional patients achieving an mRS of 0–1 and no additional poor outcome despite applying a smaller infarct threshold. Likewise 5 (1.21%) additional patients achieved an mRS of 0–2 with 1 (0.24%) additional patient having a poor (mRS 3–6) outcome and 9 (2.17%) additional patients achieved an mRS of 0–3 with 1 (0.24%) additional patient having a poor (mRS 4–6) outcome.

Pre-existing WMH lesion burden mediates the age effect on the 90-day outcome

Mediation analyses indicated that there was a significant indirect effect with WMH mediating the effect of age on the 90 day functional outcome (mRS), βa*βb=0.009, 95% BCa CI 0.021–0.016 (R^2=0.302, Supplemental Figure I). WMH (mediator) could account for roughly half of the total effect, percent mediation P_M=0.478. Results were similar when we entered the 90 day outcome dichotomized to 0–1 vs. 2–6 (βa*βb=0.017, 95% BCa CI 0.006–0.029) and 0–2 vs. 3–6 (βa*βb=0.013, 95% BCa CI 0.001–0.025). Confidence interval for the 90 day outcome dichotomized to 0–3 vs. 4–6 included zero (βa*βb=0.013, 95% BCa CI 0.000–0.028).

Discussion

The most important finding of our study was that that the burden of preexisting WMH lesions significantly modulates the relationship between infarct volumes and patient outcomes. Specifically, patients with absent-to-mild WMH lesion burden tolerated significantly greater infarct volumes than patients with moderate-to-severe WMH lesion burden to still achieve favorable functional outcome at 90 days.

Importantly, the critical WMH-unadjusted infarct thresholds derived from our cohort are in general agreement with the results from several prior investigations[3,4,13] indicating the generalizability of our data. For example, Parsons and colleagues[3] found that a DWI lesion volume <25 mL was the most important factor predicting an mRS of 0–1 after iv thrombolysis. The fact that our critical thresholds are slightly greater than previously reported[3,13] is likely related to the fact that we used the final infarct volume, which accounts for additional lesion growth. Indeed, Ribo and colleagues reported a lesion cut-off (29 mL) that is strikingly similar to our cut-off (29.9 mL) for predicting an mRS of 0–2 when relying on follow-up (rather than acute) imaging.[4]

More important, several studies demonstrated age-dependence of the critical thresholds with younger patients tolerating larger infarcts than older patients to achieve the same outcome.[1,4] Our results now provide a biological plausible explanation for this phenomenon by showing that the critical threshold is significantly modulated by the degree of the pre-existing WMH lesion burden, which is strongly associated with patient age.[5,6] Indeed, our mediation analysis supports the hypothesis that the age effect in our study was mediated by the preexisting WMH lesion burden—results that add to mounting evidence that WMH may serve as a measure of brain frailty and thus allow for identifying (elderly) patients with greater vulnerability to brain ischemia.[5,14] A major advantage of our approach compared to relying on patient age is that age cannot always be reliably ascertained in the acute setting because of a patient's functional deficits (e.g., presence of aphasia or pre-existing cognitive impairment). Nevertheless, our findings require replication in an external consecutive stroke cohort ideally in the acute setting. If the preexisting WMH burden relates to the hyperacute ischemic core, final infarct volume, and outcome we envision the use of an imaging index that incorporates automated assessments of the WMH- and ischemic core volumes in conjunction with markers of collateral and perfusion status that allows for more accurate and rater-unbiased selection of patients for emergent recanalization therapies. For example, despite the recent landmark advances in improving stroke outcome via endovascular

recanalization approaches[15–17] there remains a significant proportion of patients that is deemed ineligible to therapy particularly in the setting of a large infarct. If our results translate to the hyperacute lesion it could provide the rationale for offering therapy to patients that are otherwise deemed ineligible candidates for therapy. Even if using the WMH adjusted thresholds results in reallocation of a small number of patients, this could still have significant healthcare implications given the large number of acute ischemic stroke patients that are eligible for recanalization therapies each year.[18,19]

Strength of our study relate to the investigation of a well-characterized and large patient population. We included consecutive patients with imaging confirmed, ischemic stroke that were evaluated by clinicians certified in NIHSS and mRS. Furthermore, we excluded patients with small subcortical infarcts and utilized MRI to determine the WMH lesion burden and infarct volumes in a masked fashion with respect to clinical variables. Finally, we separately analyzed several frequently outcome categories and all analyses were rigorously adjusted for clinically relevant confounders that have been associated with the post-stroke outcome and infarct volume.

Limitations relate to the retrospective study design for which reason a causal relationship remains to be established. Further, because we restricted our analyses to patients with supratentorial strokes it remains to be shown whether the noted associations also apply to infratentorial ischemic strokes. Lastly, we assessed the infarct volume in the subacute phase. Therefore, our thresholds should not be used for acute decision making and further research is require to determine the exact association between WMH lesions, hyperacute ischemic lesion, and functional outcome. Accordingly, our results should be considered hypothesis generating only. Yet, for the purpose of our study using subacute imaging had the advantage that the infarct volume was maximal and thus results were not confounded by differences in lesion growth related to collateral and reperfusion status as well as spontaneous or therapeutic recanalization.

Conclusion

We show that the burden of pre-existing WMH lesions is strongly associated with the 90-day functional outcome and we provide proof-of-concept that the WMH lesion burden significantly impacts the critical infarct volume threshold predicting a favorable outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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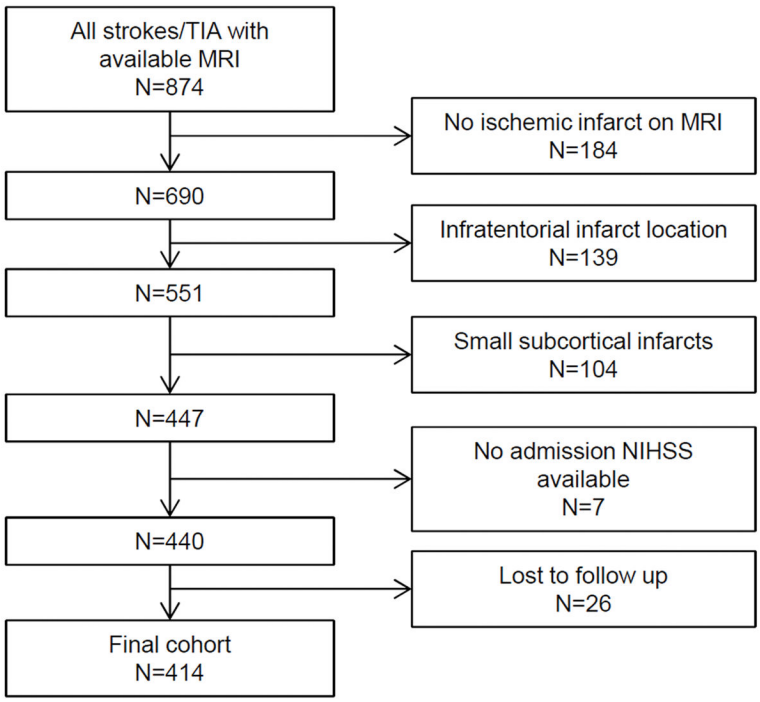


Figure 1. Flowchart for patient inclusion

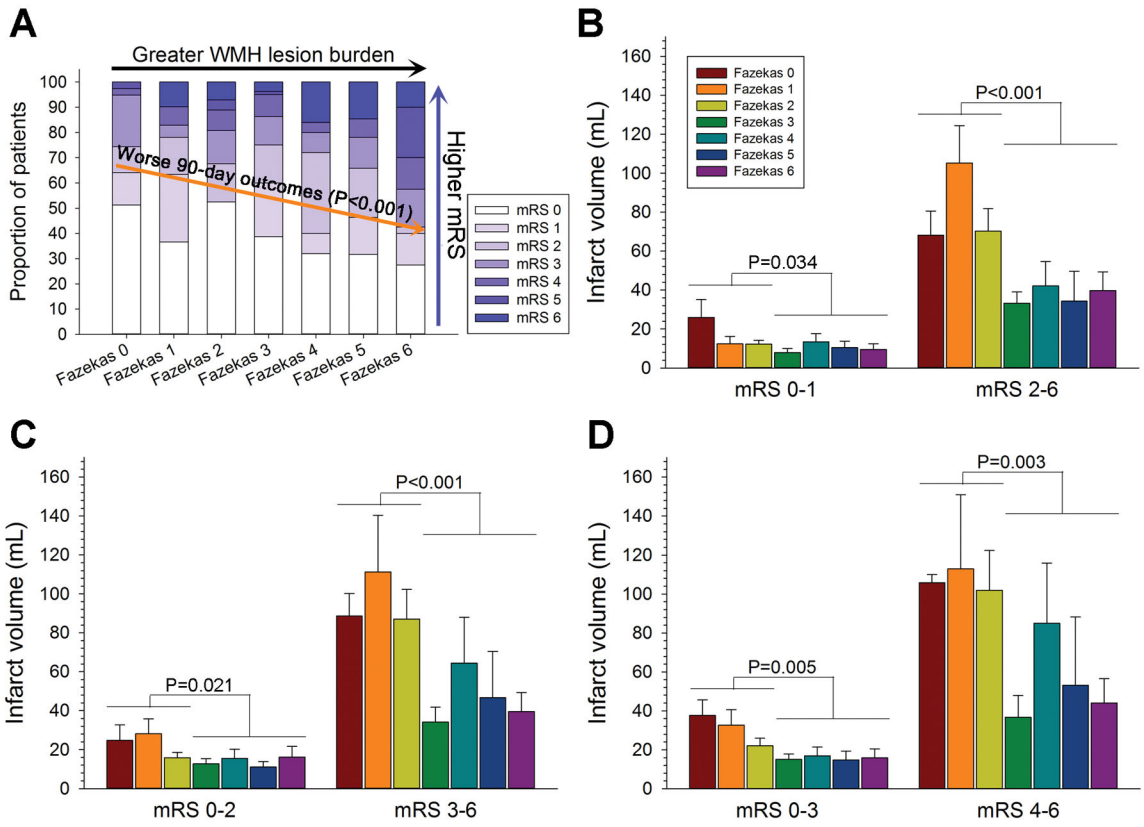
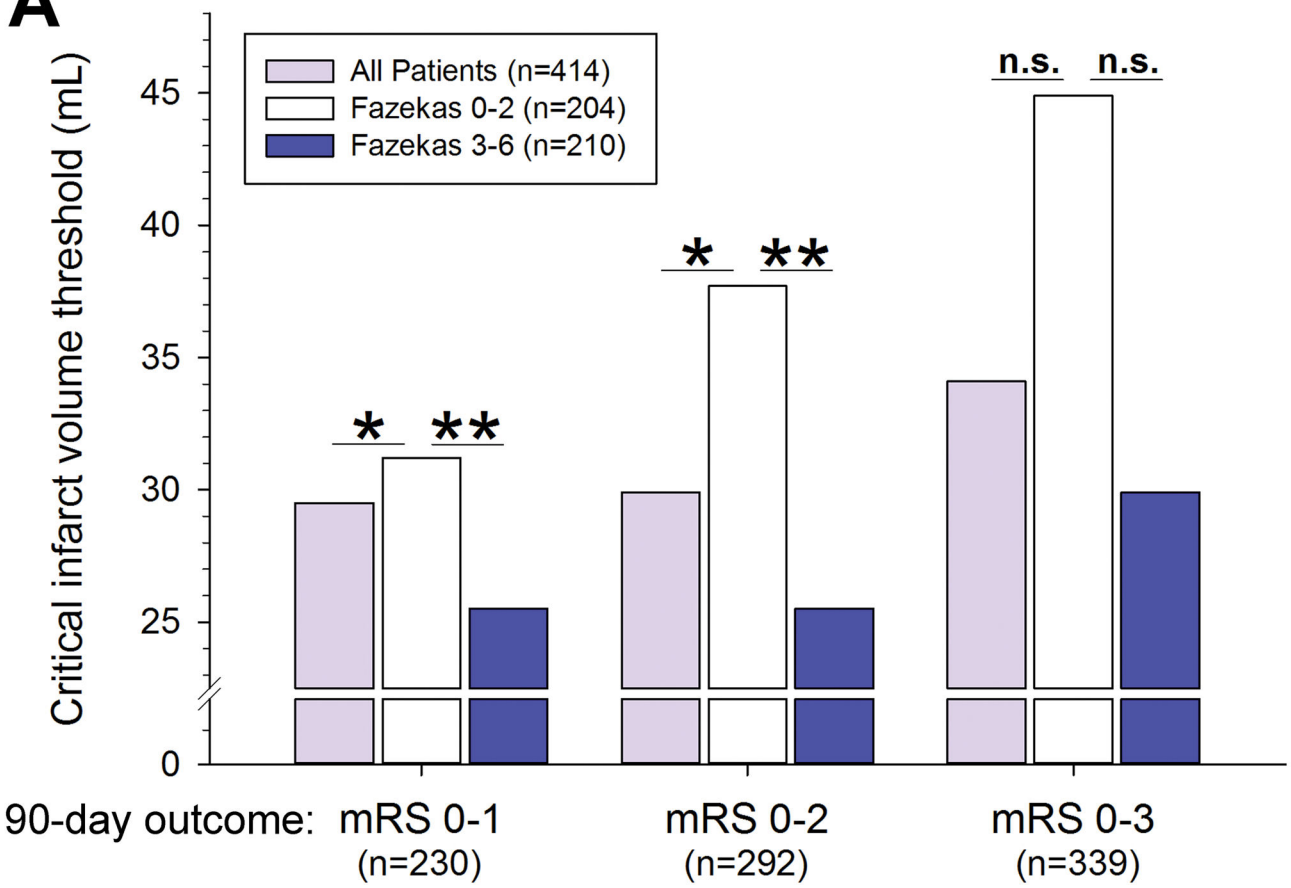


Figure 2. Association between the 90-day mRS with the white matter hyperintensity (WMH) lesion burden and infarct volume

(A) With increasing WMH lesion burden patients were more likely to have a higher 90-day modified Rankin Scale (mRS) score (P<0.001, χ^2-test). Patients with absent-to-mild WMH lesion burden had greater infarct volumes than patients with a moderate-to-severe WMH lesions when stratified by the 90-day outcome to (B) mRS 0–1 vs. 2–6, (C) mRS 0–2 vs. 3–6, and (D) mRS 0–3 vs. 4–6. Given the modest number of patients in each Fazekas category, comparisons were made using the WMH lesion burden dichotomized to Fazekas 0–2 vs. Fazekas 3–6) using Mann-Whitney U test. Data are mean ± S.E.M.

A



B

	All Patients (n=414)				Fazekas 0-2 (n=204)				Fazekas 3-6 (n=210)			
	Threshold	Sensitivity	Specificity	AUC	Threshold	Sensitivity	Specificity	AUC	Threshold	Sensitivity	Specificity	AUC
mRS 0-1	29.5 mL	0.51	0.89	0.74	31.2 mL	0.67	0.88	0.82	25.5 mL	0.42	0.90	0.70
mRS 0-2	29.9 mL	0.57	0.84	0.74	37.7 mL	0.78	0.85	0.84	25.5 mL	0.46	0.84	0.69
mRS 0-3	34.1 mL	0.58	0.81	0.71	44.9 mL	0.76	0.80	0.79	29.9 mL	0.50	0.85	0.69

Figure 3. Critical lesion thresholds

The critical threshold for predicting a modified Rankin Scale (mRS) of 0–1 as well as mRS 0–2 outcome was significantly greater for patients with absent-to-mild WMH (Fazekas score 0–2) as compared to the threshold derived from the entire cohort and from patients with moderate-to-severe WMH, respectively. Though a similar trend was noted for predicting an mRS of 0–3, this did not reach statistical significance. *P<0.05. **P<0.01.

Table 1

Baseline characteristics (unadjusted) of the studied patient population as dichotomized to an mRS 0–2 vs. mRS 3–6 at 90-days

Characteristics	All patients (n=414)	mRS 0–2 (n=292)	mRS 3–6 (n=122)	P-value
Age, years	70 (50–69)	69 (59–78)	72 (61–85)	0.003
Female sex	207 (50%)	136 (47%)	71 (58%)	0.040
Admission NIHSS	5 (2–13)	4 (2–8)	15 (8–18)	<0.001
Infarct volume, mL	8 (2–38)	5 (2–18)	39 (6–95)	<0.001
Patients with critical infarct volume ≤29.9 mL	298 (72%)	245 (84%)	53 (43%)	<0.001
WMH lesion burden, Fazekas score	3 (2–4)	2 (2–4)	3 (2–5)	0.003
Admission glucose, mg/dL	116 (100–139)	111 (98–131)	132 (107–167)	<0.001
Admission creatinine, mg/dL	0.94 (0.76–1.18)	0.95 (0.78–1.16)	0.90 (0.71–1.19)	0.484
LDL-C, mg/dL (n=369)	90 (68–115)	91 (69–116)	85 (65–110)	0.208
Pre-admission medications				
Statin	187 (45%)	131 (45%)	56 (46%)	0.914
Antihypertensive	282 (68%)	196 (67%)	86 (71%)	0.563
Antiglycemic	87 (21%)	61 (21%)	26 (21%)	1.000
Antiplatelets	212 (51%)	139 (48%)	73 (60%)	0.024
Oral anticoagulant	31 (8%)	18 (6%)	13 (11%)	0.150
Pre-existing risk factors				
Hypertension	315 (76%)	216 (74%)	99 (81%)	0.130
Hyperlipidemia	217 (52%)	155 (53%)	61 (51%)	0.746
Diabetes	117 (28%)	82 (28%)	35 (29%)	0.933
Prior stroke or transient ischemic attack	100 (24%)	62 (21%)	38 (31%)	0.043
Atrial fibrillation	87 (21%)	50 (17%)	37 (30%)	0.004
Coronary artery disease	86 (21%)	57 (20%)	29 (24%)	0.353
Peripheral artery disease	26 (6%)	18 (6%)	8 (7%)	0.828
Congestive heart failure	34 (8%)	18 (6%)	16 (13%)	0.029
Final TOAST stroke mechanism				
Supra-aortic large artery atherosclerosis	98 (24%)	73 (25%)	25 (21%)	0.375
Cardioembolic	127 (31%)	80 (27%)	47 (39%)	0.027
Other determined cause	20 (5%)	12 (4%)	8 (7%)	0.317
Undetermined cause	169 (41%)	127 (44%)	42 (34%)	0.100
Lesion side				
Right	164 (40%)	123 (42%)	41 (34%)	0.123
Left	222 (54%)	152 (52%)	70 (57%)	0.333
Bilateral	28 (7%)	17 (6%)	11 (9%)	0.283
Therapy				
Thrombolysis with intravenous rtPA	80 (19%)	53 (18%)	27 (22%)	0.343
Endovascular stroke therapy	31 (8%)	24 (8%)	7 (6%)	0.538

Characteristics	All patients (n=414)	mRS 0–2 (n=292)	mRS 3–6 (n=122)	P-value
Pre-admission mRS	0 (0–1)	0 (0–0)	0 (0–2)	<0.001

LDL-C indicates low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WMH, white matter hyperintensity. Data are n (%) or median (25^{th}–75^{th} quartile).

Table 2

Comparison of infarct thresholds predicting the 90-day outcome as stratified by WMH-lesion burden after adjustment for pertinent confounders

Independent variable	adjusted OR (95% CI)	correctly predicted	P-value
Absent-to-mild WMH lesion burden (n=204)			
	90-day mRS 0–1 (n=128)		
Infarct volume	1.019 (1.006 to 1.032)	82.8%	0.004
Infarct threshold (<29.5 mL) *	5.369 (2.263 to 12.735)	82.4%	<0.001
Infarct threshold (<31.2 mL) **	7.312 (2.902 to 18.420)	83.8%	<0.001
	90-day mRS 0–2 (n=153)		
Infarct volume	1.016 (1.005 to 1.027)	88.7%	0.003
Infarct threshold (<29.9 mL) *	10.099 (3.500 to 29.144)	88.7%	<0.001
Infarct threshold (<37.7 mL) **	11.057 (3.719 to 32.877)	89.2%	<0.001
	90-day mRS 0–3 (n=176)		
Infarct volume	1.015 (1.004 to 1.025)	93.1%	0.005
Infarct threshold (<34.1 mL) *	7.696 (1.792 to 33.043)	91.2%	0.006
Infarct threshold (<44.9 mL) **	7.634 (1.880 to 30.999)	91.7%	0.004
Moderate-to-severe WMH lesion burden (n=210)			
	90-day mRS 0–1 (n=102)		
Infarct volume	1.024 (1.007 to 1.042)	69.4%	0.006
Infarct threshold (<29.5 mL) *	4.350 (1.773 to 10.673)	69.9%	0.001
Infarct threshold (<25.5 mL) **	3.988 (1.725 to 9.222)	69.9%	0.001
	90-day mRS 0–2 (n=139)		
Infarct volume	1.011 (0.999 to 1.023)	79.4%	0.070
Infarct threshold (<29.9 mL) *	NR	--	--
Infarct threshold (<25.5 mL) **	2.336 (1.024 to 5.328)	79.9%	0.044
	90-day mRS 0–3 (n=163)		
Infarct volume	1.014 (1.003 to 1.025)	82.8%	0.016
Infarct threshold (<34.1 mL) *	3.357 (1.342 to 8.392)	81.3%	0.010
Infarct threshold (<29.9 mL) **	3.384 (1.379 to 8.304)	82.8%	0.008

All analyses were adjusted for age, sex, history of stroke or transient ischemic attack, atrial fibrillation, congestive heart failure, antiplatelet use, admission NIHSS, pre-admission mRS, and random blood glucose at admission. NR indicates not retained in the final model.

* Threshold defined for the entire cohort.

** WMH-adjusted threshold (see text for details).