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Itemized NIHSS subsets predict positive MRI strokes in patients with mild deficits

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Abstract

Background—While imaging is useful in confirming the diagnosis of ischemic stroke, negative diffusion weighted imaging (DWI) is reported in up to 25% of patients. Our aim was to identify predictors of MRI-positive stroke from the itemized NIHSS.

Methods—Data were derived from the Stroke Warning Information and Faster Treatment study from February 2006 to February 2010 among patients with mild deficits (NIHSS 0-5) and a final diagnosis of stroke by a vascular neurologist. All MRI sequences were reviewed for the presence or absence of an acute infarct on DWI. Multivariate logistic regression assessed factors predicting DWI-positive strokes; $p<0.05$ was considered significant.

Results—894 patients had a discharge diagnosis of stroke; 709 underwent MRI and 28.0% were DWI negative. All patients with visual field deficits or neglect were DWI positive. On multivariate analysis including total NIHSS (0-2 vs. 3-5) and itemized NIHSS score subsets, predictors of a positive DWI were NIHSS score of 3-5 (OR= 3.3, 95% CI: 1.8-6.1), motor deficits (OR= 1.7, 95% CI: 1.1-2.8), ataxia (OR=1.9, 95% CI: 1.0-3.5), and absence of sensory deficits (OR = 1.7, 95%

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CI: 1.0-2.7). We developed the NIHSSm score that predicts DWI positivity in patients with mild deficits in the absence of neglect or visual field deficits.

Conclusion—NIHSS score subsets predict DWI positivity in mild strokes. The presence of neglect or visual field deficits on the NIHSS subsets is most likely to have an MRI correlate even in patients with low NIHSS.

Keywords

Stroke; MRI; NIHSS; Diffusion weighted imaging; mild deficits; DWI negative stroke

Background

Diffusion weighted imaging (DWI) from magnetic resonance imaging (MRI) is the gold standard imaging modality to diagnose acute ischemic stroke[1]. A negative finding on DWI however can occur in up to 25-30% of ischemic stroke patients.[2, 3] Ultimately the diagnosis of stroke is dependent on the appropriate clinical history and neurological examination findings, particularly when there are DWI negative scans or contraindications to MRI. The diagnosis of stroke remains a challenge however when the DWI is negative, particularly in minor stroke, prompting physicians to consider alternate diagnoses. Predictors of a positive DWI in patients with transient ischemic attack have been investigated[4, 5]; however there is limited data on clinical variables that are associated with a positive DWI in patients with minor stroke. Identifying predictors of DWI positivity, based on the itemized NIHSS score subsets, may provide a standardized way to assist physicians in evaluating suspected stroke patients who have minor deficits, particularly when the DWI sequence is negative. This may be helpful in identifying stroke mimics who require evaluation for non-vascular etiologies. The aim of our study is to identify predictors of MRI-positive stroke from the itemized NIHSS subsets in patients with minor stroke.

Methods

Study Population

We included all patients with minor stroke (NIHSS 0-5)[6, 7] who were enrolled in the prospective Stroke Warning Information and Faster Treatment (SWIFT) study between February 2006 until February 2010 and untreated with thrombolytic therapy. SWIFT enrolled 1635 patients, 18 years or older with stroke or transient ischemic attack, and randomized them to a stroke intensive educational intervention versus enhanced standard of care. The primary outcome was proportion of emergency room arrival within three hours from symptom onset for recurrent neurological events including stroke, TIA or stroke mimics. Patients unable to sign informed consent were excluded from the study. We included all patients admitted to the hospital and discharged with a final diagnosis of ischemic stroke by a vascular neurologist.[8] We focused on the DWI negative final diagnosis of stroke subset given the unique clinical challenge they pose. The admission NIHSS score was obtained by a certified vascular neurology fellow. Our hospital policy is to obtain MRI on all suspected ischemic stroke patients and TIA's within 24 hours from admission; however, an MRI was not performed on patients who had MRI contraindications or

claustrophobia. All patients who did not receive an MRI for these reasons were excluded. The DWI sequence of each patient was reviewed by a stroke neurologist (S.Y.) for DWI positivity, defined as a hyperintensity on the DWI sequence that has a dark correlate on the apparent diffusion coefficient (ADC) sequence.

Outcome

The primary outcome of our study was DWI positive MRI.

Predictors

Clinical predictors investigated were the total NIHSS score and the itemized NIHSS score subsets. The itemized NIHSS subsets were segregated so that any score on each item was considered 1 and no score was considered 0. For simplicity, levels of consciousness (LOC) scores were combined as one score item. NIHSS at baseline was stratified into two groups, those with NIHSS 0-2 and those with NIHSS 3-5 to investigate NIHSS subsets as predictors of DWI positive findings in these groups.

Statistical Analysis

Participants were divided into two groups (DWI positive or negative).Univariate analysis was performed to determine predictors of positive DWI using the itemized NIHSS subsets (LOC, visual, facial, motor, ataxia, sensory, dysarthria, language, and neglect) and the total NIHSS score. Multivariable logistic regression models were used to determine the association (odds ratio (OR) and 95% confidence intervals (CI) between the itemized NIHSS subsets and DWI positivity.Univariable logistic regression was used to assess the association between NIHSS subsets and DWI positive lesions in patients with a baseline NIHSS of 0-2 to establish which variables should be considered in the development of a DWI positive prediction score. All variables that met a criterion of $p \leq 0.2$ were evaluated for the final prediction model using logistic regression models. Model performance was assessed using the c-statistic, corrected for optimism. To correct for optimism, reduce bias and internally validate the model we calculated the estimated decrease in the c-statistic that would be expected in an independent dataset using the 0.632 bootstrap method.[9] This option was chosen over the traditional split-sample modeling because the bootstrap resampling technique has been shown to reduce bias and produce a stable and efficient estimate of predictive accuracy when compared to other methods. For this study we created 100 datasets through bootstrap sampling with replacement. The models were fit in each dataset and the average difference in the c-statistic between the bootstrap dataset (the derivation dataset) and the original dataset (the validation dataset). This value represents the expected optimism in the c-statistic calculated in this study. The points assigned to the variables in the score were assigned based on the beta coefficients from the logistic regression models. A cut point of the DWI positive prediction model was established based on sensitivity and specificity of the dichotomized score in predicting which patients had a positive finding on the DWI MRI. As this was an exploratory analysis, no adjustments were made for multiple comparisons. An alpha of 0.05 was used as the level of significance.

Results

Our sample included 894 subjects with a discharge diagnosis of stroke and admission NIHSS 0-5; 709 (79.3%) underwent MRI with 199 (28.0%) who were DWI negative. The mean age was 63.5 ± 15.1 and 49% were males. The percentage (number) of patients with each NIHSS score is as follows: [NIHSS 0: 29% (205), NIHSS 1: 20% (145), NIHSS 2: 19% (133), NIHSS 3: 13% (92), NIHSS 4: 11% (78), NIHSS 5: 8% (56)]. The median NIHSS was higher in patients with DWI positive vs. DWI negative MRI (2 vs. 1, p<0.001).

Itemized NIHSS score subsets were similar between patients with and without MRI (Supplemental table I). Subjects with a baseline NIHSS of 3-5 were at higher odds of having a positive DWI lesion (OR 4.1, 95%CI 2.6-6.4) as were subjects with cortical involvement (OR 2.8, 95%CI 1.7-4.8). Subjects presenting with ataxia (OR 2.3, 95%CI 1.3-4.0), dysarthria (OR 2.3, 95%CI 1.3-4.0), facial (OR 1.5, 95%CI 1.1-2.2), and motor deficits (OR 2.9, 95%CI 1.9-4.2) had a higher odds of DWI positive lesions. All patients in our cohort with neglect and visual deficits (n = 71) were DWI positive (Table 1). On multivariable analysis that included the total NIHSS (0-2 vs. 3-5) and the itemized NIHSS score subsets, predictors of a positive DWI were NIHSS score of 3-5 (OR= 3.3, 95% CI: 1.8-6.1), motor deficits (OR= 1.7, 95% CI: 1.1-2.8), ataxia (OR=1.9, 95% CI: 1.0-3.5), and absent sensory deficits (OR = 1.7, 95% CI: 1.0-2.7).

Investigating NIHSS subsets Stratified by Baseline NIHSS

The percentage (number) of patients with DWI negative imaging based on the total NIHSS score from 0 to 5 are: [NIHSS 0: 46% (94), NIHSS 1: 32% (47), NIHSS 2: 23% (31), NIHSS 3: 12% (11), NIHSS 4: 10% (8), NIHSS 5: 14% (8)] (Figure 1). Based on these percentages, there appears to be a relatively high proportion of DWI negative strokes among patients with NIHSS 0-2, and this reaches a plateau in patients with NIHSS 3-5.Therefore, we sought to explore NIHSS subset predictors of DWI positivity in patients with NIHSS 0-2 who constitute the more challenging group due to their lower likelihood of DWI positive MRI. On univariate analysis, ataxia (OR 4.7, 95%CI 1.8-12.1, p=0.002), and motor deficits (OR 2.1, 95%CI 1.2-3.7, p=0.008) were associated with a DWI positive finding on MRI in patients with NIHSS 0-2. Furthermore, patients with a sensory deficit were less likely to have a positive DWI finding (OR 0.5, 95%CI 0.3-0.9, p=0.0123). There were no statistically significant differences between NIHSS score subset and DWI positive findings in patients with an NIHSS of 3-5 (Table 2). In the fully adjusted multivariable model, patients with NIHSS 0-2 and presence of ataxia (OR 4.9, 95%CI 1.9-12.8) or motor deficits (OR 2.2, 95%CI 1.2-3.9) remained at increased odds of having a DWI positive lesion, while those with sensory deficits remained less likely to be associated with DWI positive lesion (OR 0.5, 95%CI 0.3-0.9). Sensitivity analysis was performed excluding patients with NIHSS score of 0 and the results remained unchanged.

Prediction Score for DWI Positive Lesion in Patients with a NIHSS of 0-2

In our cohort, all patients with NIHSS 0-2 and visual field deficits and neglect had DWI positive lesion(s), thus it is important to predict the likelihood of DWI positivity in the absence of such deficits. After identifying significant NIHSS subsets associated with DWI

positive lesions in patients with NIHSS 0-2 without visual field deficits or neglect, a model was designed to assess which NIHSS subsets were associated with DWI positive lesions. The scoring model ranged from 0 to 6, with 3 points assigned if ataxia was present on exam, 2 points if dysarthria was present, 2 points if motor deficits were present, and 1 point if the patient did NOT have any sensory deficits (Table 3). The points assigned to the variables in the NIHSS minor “NIHSS-m” score were assigned based on the beta coefficients from the multivariable logistic regression models. The maximum NIHSS-m score one could get while still having a maximum NIHSS of 2 would be 6, in a patient with ataxia AND dysarthria or motor deficits AND no sensory deficits. The AUC for predicting MRI positive lesion 0.623, and after adjusting for optimism with the Harrell's c-statistic, it remains 0.623. For every one point increase in the NIHSS-m score, an individual's odds of having a DWI positive lesion almost doubles according to this model (OR=1.6, 95%CI 1.4-1.9, p<0.0001). Figure 2 illustrates the distribution of patient's NIHSS-m scores stratified by DWI positive lesions. A score of 3 or higher places a patient at a 3.4 fold higher odds of presence of a lesion on MRI (OR 3.4, 95%CI 2.1-5.5, p<0.0001).

Discussion

In our study, motor deficits, ataxia, and higher NIHSS score all increased the odds of finding DWI positive lesions. All patients with visual symptoms and neglect had MRI correlates suggesting that patients with mild stroke who score points on either visual or neglect are likely to have an MRI correlate, and further suggesting that in patients with these deficits with negative DWI an alternate diagnosis should be considered.

Clinical Implications

The relatively large number of DWI negative strokes in our cohort highlights the challenges of using neuroimaging to make the diagnosis of stroke in patients with mild deficits. The relatively high rate of DWI negative stroke observed our study is likely because our study was limited to patients with mild deficits only. In addition, our study provides data to physicians on when to expect a positive DWI MRI in patients with NIHSS score 0-5. Our findings should also encourage physicians to suspect an alternate diagnosis in patients with neglect and visual field deficits who have a negative DWI sequence.

Interestingly,when the NIHSS was stratified into 0-2 and 3-5, there were no predictors of DWI positivity in the 3-5 group whereas the predictors of DWI positivity remained unchanged in the 0-2 group, a group that often constitutes a diagnostic challenge. This suggests that the itemized NIHSS subset is most beneficial in predicting DWI positivity in patients with NIHSS 0-2 and because of the relatively high percentage of DWI negativity in this group, evaluation by a vascular neurologist may be necessary to make the diagnosis of stroke versus stroke mimic. The absence of sensory deficits was associated with DWI positivity, which may be due to the fact that although all patients carried a clinical diagnosis of stroke, it is possible that a certain number of patients with isolated sensory deficits had an alternate diagnosis.

DWI positivity is thought to be less likely seen in posterior versus anterior circulation stroke.[10] However,this hypothesis could not be tested in our cohort since we could not

accurately determine the location (posterior vs. anterior circulation) of the infarct in patients with DWI negative stroke. For example, a patient with a DWI negative stroke causing hemi-sensory or hemi-motor symptoms could localize to either anterior circulation or posterior circulation. In general, the NIHSS score is of limited use in differentiating anterior versus posterior circulation location of symptoms. For example, the presence of a score on the ataxia item of the NIHSS score may be suggestive of posterior circulation infarction; but this could also be seen in anterior circulation infarcts especially subcortical infarcts of the internal capsule or corona radiata which may be DWI negative as well.[11] However, based on the Oxfordshire classification system[12], the presence of certain high cortical elements such as neglect, that are also captured by the NIHSS score, may be more suggestive of anterior vs. posterior circulation infarcts and have been associated with DWI positivity in our cohort.

Minor Stroke Scale Score

Based on our results, we developed a minor stroke scale score that helps predict DWI positivity in patients with NIHSS 0-2, in which the itemized NIHSS score subsets were shown to predict DWI positivity. Although this score had a fair predictive ability (AUC 0.623) (Figure 2), the NIHSS-m is particularly helpful when the NIHSS 0-2, the minor stroke scale score is 5 or 6, and the MRI is negative (Figure 3), prompting physicians to look for an alternate diagnosis.

Limitations and Strengths

Our study has several limitations including its retrospective nature, the lack of MRI data on about one-third of our patients, the lack of follow up MRI in patients with negative DWI, and excluding patients in whom consent could not be obtained. In addition, it is possible that a number of patients with a diagnosis of DWI negative stroke may not have a vascular etiology to their symptoms. Furthermore, there has been report to suggest that the timing of MRI is possibly a predictor of DWI positivity[13]; however this has a greater impact on the presence or absence of a DWI lesion when the MRI is performed in the hyperacute setting i.e. few hours after stroke onset.[4, 14] Since, a hyper-acute MRI is not part of our acute stroke protocol; it is less likely though possible that the time from symptoms to MRI variable will affect the results of our study. However, its strength lies in the fact that all patients were evaluated by a vascular neurologist who made the clinical diagnosis of stroke as well as one of the very few studies looking at the itemized NIHSS score to predict DWI positivity in minor stroke patients. Using the itemized NIHSS score provides a standardized way to predict infarct presence in patients with mild deficits may help clinicians with management decisions in this patient population. Larger prospective studies are needed to validate the results of our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- There is a relatively high percentage of negative imaging in minor stroke patients.
- Motor deficits, ataxia, and absence of sensory deficits predicted positive imaging.
- All patients with neglect or visual deficits had positive imaging.
- Predictors of positive imaging varied based on the NIHSS score.

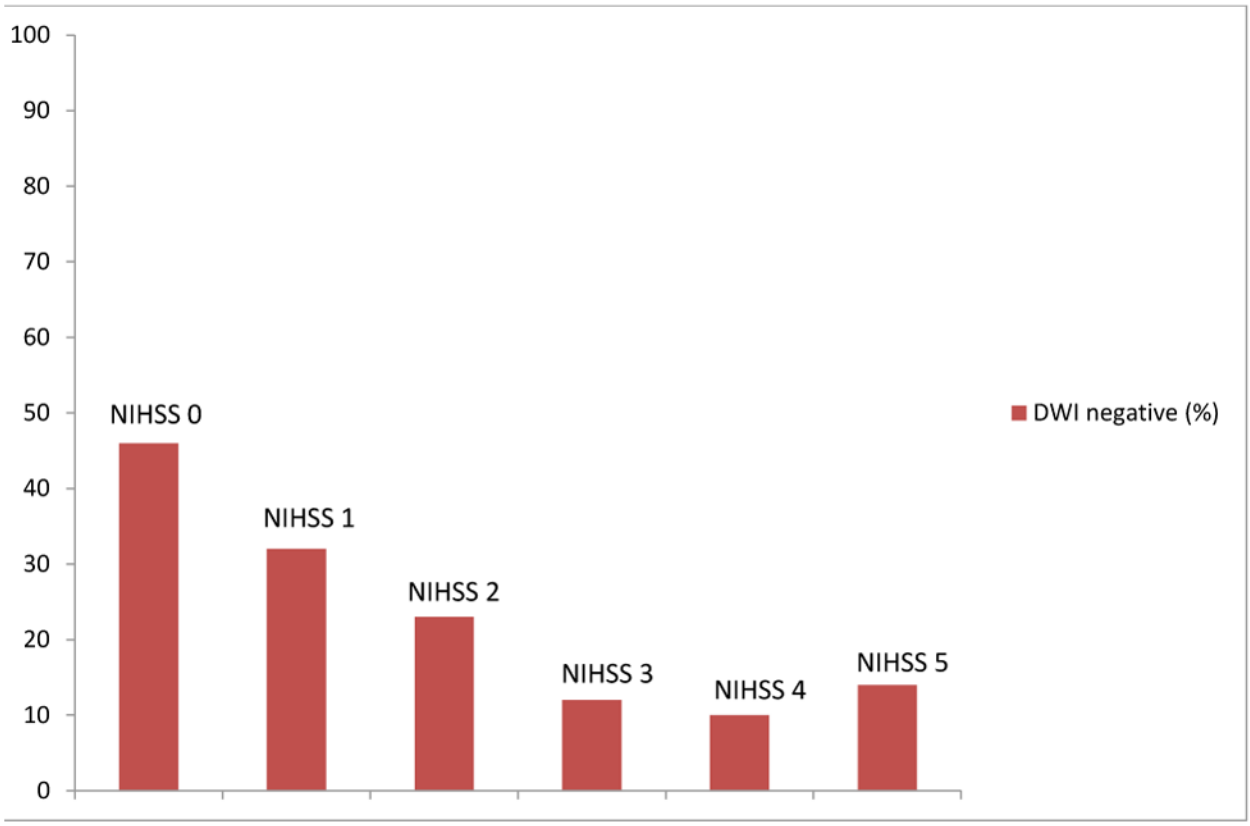

Figure 1. Plot showing the percentage of patients with DWI negative stroke (y-axis) in each NIHSS category (x-axis)

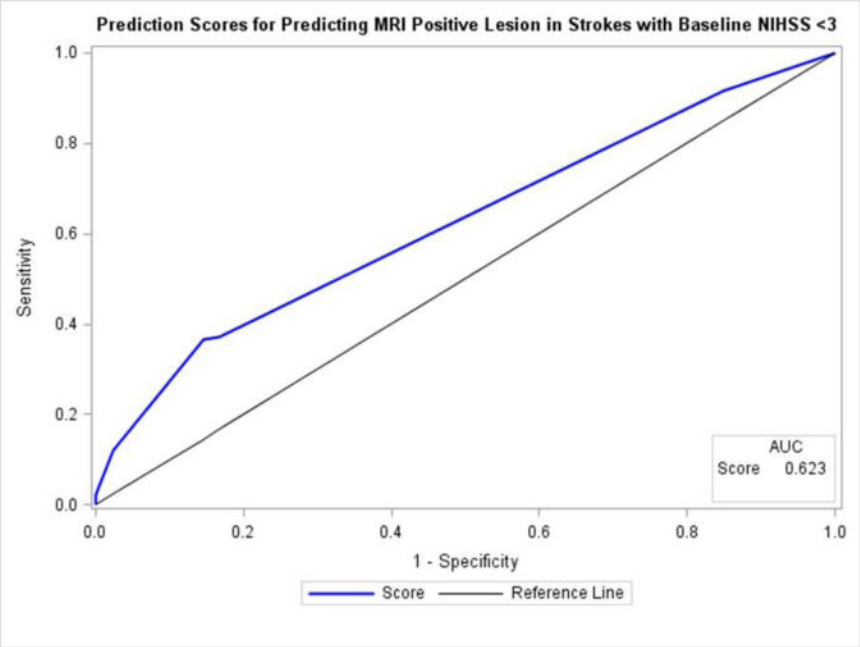

Figure 2. ROC curve of the newly developed prediction score

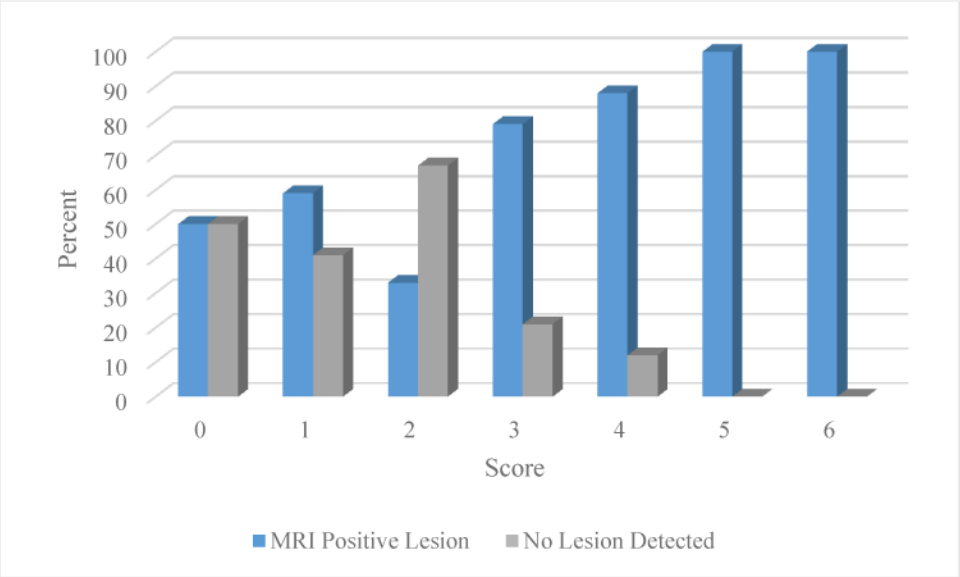

Figure 3. Distribution of Scores stratified by presence of an MRI lesion in Patients with a Baseline NIHSS of 0-2

Table 1

DWI Positive Status vs. Deficit Type

Deficit Type	Patients With DWI Positive Status (n = 510)
Visual (n=40)	n=40 (100%)
Best Gaze (n = 21)	n = 18 (86%)
Neglect (n=31)	n=31 (100%)
NIHSS 3-5 (n=226)	n=199 (88%)
Motor (n=243)	n=205 (84%)
Ataxia (n=94)	n=79 (84%)
Dysarthria (n=101)	n=85 (84%)
Language (n=62)	n=49 (79%)
Level of Consciousness (n=9)	n=7 (78%)
Facial (n=244)	n=189 (77%)
Sensory (n=139)	n=97 (69%)

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Table 2

Odds Ratios for NIHSS Subset stratified by Baseline NIHSS Score

	Baseline NIHSS 0 -2(N=483)			Base line NIHSS 3-5(N=226)		
	OR	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Crude Models						
Best Gaze	1.67	0.33-8.38	0.7177	1.66	0.21-13.37	1.000
Ataxia	4.65	1.79-12.05	**0.0016**	0.44	0.19-1.04	0.0601
Dysarthria	2.21	0.88-5.54	0.0907	0.77	0.33-1.78	0.5390
Facial	0.97	0.61-1.55	0.8993	0.53	0.20-1.37	0.1870
LOC	n/a*	n/a	n/a	0.39	0.07-2.03	0.2625
Language	1.62	0.67-3.91	0.2838	0.59	0.22-1.61	0.3068
Motor	2.13	1.22-3.74	**0.0083**	0.89	0.36-2.23	0.8098
Sensory	0.50	0.29-0.86	**0.0123**	0.72	0.32-1.64	0.4371
Neglect	n/a*	n/a	n/a	n/a*	n/a	n/a
Visual	n/a*	n/a	n/a	n/a*	n/a	n/a
Adjusted Models**						
Ataxia	4.91	1.88-12.8	**0.0011**	n/a	n/a	n/a
Motor	2.20	1.24-3.88	**0.0067**	n/a	n/a	n/a
Sensory	0.54	0.31-0.93	**0.0269**	n/a	n/a	n/a

*all of those with LOC, neglect and visual had MRI positive lesions in the NIHSS 0-2 group had a DWI positive lesion

**Full model includes ataxia, motor, and sensory

Table 3

Breakdown of the Prediction Score for Detecting MRI lesion in Patients with a baseline NIHSS of 0-2

Ataxia on Exam	**Dysarthria on Exam**
3 points if present	2 points if present
0 points if not present	0 points if not present
Motor deficits on Exam	**Sensory deficits on Exam**
2 points if present	1 point if **NO** sensory deficits on exam
0 points if not present	0 points if there is a sensory deficit on exam
Prediction Score for detecting an MRI Lesion in Minor Strokes (score range 0-6)	