Corticospinal Tract Lesion Load: An Imaging Biomarker for Stroke Motor Outcomes

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Objective: The aim of this work was to investigate whether an imaging measure of corticospinal tract (CST) injury in the acute phase can predict motor outcome at 3 months in comparison to clinical assessment of initial motor impairment.
Methods: A two-site prospective cohort study followed up a group of first-ever ischemic stroke patients using the Upper-Extremity Fugl-Meyer (UE-FM) Scale to measure motor impairment in the acute phase and at 3 months. A weighted CST lesion load (wCST-LL) was calculated by overlaying the patient's lesion map on magnetic resonance imaging with a probabilistic CST constructed from healthy control subjects. Regression models were fit to assess the predictive value of wCST-LL and compared with initial motor impairment.
Results: Seventy-six patients (37 from cohort 1 and 39 from cohort 2) completed the study. wCST-LL as well as assessment of motor impairment (UE-FM) in the acute phase correlated with motor impairment (UE-FM) at 3 months in both cohort 1 ($R^2 = 0.69$ vs. $R^2 = 0.67$; $p = 0.43$) and cohort 2 ($R^2 = 0.69$ vs. $R^2 = 0.62$; $p = 0.25$). In the severely impaired subgroup (defined as UE-FM ≤ 10 at baseline), wCST-LL correlated with outcomes significantly better than clinical assessment ($R^2 = 0.47$ vs. $R^2 = 0.11$; $p = 0.03$). In the nonseverely impaired subgroup, stroke patients recovered approximately 70% of their maximal recovery potential. All stroke patients in both cohorts had poor motor outcomes at 3 months (defined as UE-FM ≤ 25) when wCST-LL was ≥ 7.0 cc (positive predictive value was 100%).
Interpretation: wCST-LL, an imaging biomarker determined in the acute phase, can predict poststroke motor outcomes at 3 months, especially in patients with severe impairment at baseline.

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Motor impairment is the most common complication after stroke, negatively affecting quality of life. Making accurate predictions about motor outcome and recovery potential continues to be challenging for stroke clinicians. Several factors may influence poststroke motor recovery, including age,[1] sex,[2] intensity of therapy,[3] initial motor impairment,[4–6] lesion volume,[7,8] and degree of injury to the corticospinal tract (CST).[9–11]

Previous research has explored various ways to assess the degree of injury to the CST and use it to predict motor recovery. Most simply, clinical assessment of motor impairment in the acute phase has been shown to be prognostic of motor impairment in the chronic phase.[12,13] For example, the ability to perform finger extension tasks 3 or more days poststroke has been shown to predict hand function at 3 months and beyond.[4,6] However, bedside clinical assessments have limitations, particularly in the group of patients with severe initial motor impairment, who often show significant interindividual variability in recovery.[12]

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Neuroimaging and/or neurophysiological measures are able to uncover the pathophysiological basis of an injury and might better reveal a patient's recovery potential, especially for those with severe impairment acutely. The absence or presence of motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) has been used to determine the injury of the CST and can predict motor outcome to some degree. Although MEPs have a high sensitivity,[14,15] their specificity is low (i.e., absence of MEPs does not necessarily mean poor recovery).[16,17] Neuroimaging can also be used to determine to what extent and by what mechanism recovery can be achieved.[18] Fractional anisotropy (FA) values derived from diffusion tensor imaging (DTI) of the posterior limb of the internal capsule (PLIC)[10] have been associated with motor recovery in chronic stroke patients. However, in the acute phase, FA does not seem to be significantly altered,[9] likely owing to the fact that Wallerian degeneration takes time to manifest. In addition, measuring FA is subject to the confounding influence of tissue edema secondary to acute injury. Alternatively, task-related brain activation using functional magnetic resonance imaging (fMRI), which might be related to the integrity of the CST,[19] has been correlated with motor recovery.[13,20] However, fMRI is difficult to implement and standardize in the acute phase, particularly in patients with hemiplegia, global aphasia, or neglect. Approaches to combine clinical assessment of the initial motor impairment with imaging or electrophysiological tools have been statistically susceptible to colinearity issues. Our group has recently developed a new imaging marker—the weighted CST lesion load (wCST-LL)[11]—which was shown to highly correlate with motor impairment in chronic stroke patients. Thus, the aims of this study were to: (1) test whether the wCST-LL, calculated by overlaying lesion maps derived from the stroke patients' diffusion-weighted images (DWIs) in the acute phase, with a canonical CST tract derived from healthy elderly control subjects, predicts motor outcome at 3 months; (2) replicate the results in a second cohort at another site; and (3) test whether wCST-LL leads to better outcome predictions than the clinical assessment of the initial motor impairment.

Subjects and Methods

Study Subjects

This is a two-site prospective cohort study consisting of patients with first-ever acute ischemic stroke with various degrees of unilateral motor impairment at baseline. They were assessed at 2 to 7 days after stroke onset and followed up for 3 months poststroke (90 ± 15 days). It was conducted at two academic stroke centers (Beth Israel Deaconess Medical Center as cohort 1 or derivation cohort and Medical University of South Carolina as cohort 2 or validation cohort) in the United States. Inclusion criteria were as follows: greater than 18 years old of any ethnicity; first-ever acute ischemic stroke with unilateral limb weakness; and Upper Extremity Fugl-Meyer (UE-FM) score < 60 at baseline (to avoid ceiling effects), assessed between 2 and 7 days after stroke onset, and brain magnetic resonance imaging obtained in the acute phase as a part of routine clinical care. Exclusion criteria were as follows: bihemispheric strokes; history of previous stroke documented either on imaging or by medical history; any concomitant neurological disorder causing motor impairment; and documented history of severe dementia or medication uncontrolled depression either before or after stroke. A patient who suffered a recurrent stroke before his or her follow-up visit would be discontinued from the study.

The following variables were assessed: age; sex; ethnicity; handedness; stroke subtype based on TOAST criteria[21]; reperfusion therapy (yes or no); days of therapy (the total number of physical and/or occupational therapy days that the patient received between the day of hospital admission and the 3-month follow-up visit) as a surrogate measure of the dosage of rehabilitation therapy; and level of education (high school or less, some college, or college degree or above).

In addition to the stroke patients, 12 healthy subjects were recruited from our imaging database as an age-matched control group (9 male; mean age: 56.5 ± 14.8 years) to reconstruct a canonical CST. This study was approved by the institutional review boards at both sites.

Outcome Measures

The UE-FM Scale[22] and the National Institutes of Health Stroke Scale (NIHSS) were collected at baseline (between 2 and 7 days after onset of stroke symptoms) and again at 3 months (90 ± 15 days) poststroke. The UE-FM assessment,[22] a validated impairment scale with excellent inter- and intrarater reliability,[23] was the primary outcome variable (maximum score is 66). The NIHSS[24] is a 42-point scale that quantifies global neurological deficits in 11 categories. The NIHSS arm motor score is the score from the item of arm function (ranges from 0 to 4).

Image Processing and Lesion Mapping

The methods for lesion mapping and calculation of the lesion load of the CST are detailed in a previous publication.[11] In the this study, the wCST-LL was determined in the acute stroke phase using the lesion maps drawn on

spatially normalized DWIs obtained as part of the standard-of-care stroke workup. The DWI provides the strongest contrast between the ischemic lesion and normal tissue. Lesion maps were manually drawn on the normalized DWI in MRIcro[25] by a rater who was blind to the behavioral assessment, and overlaid with the canonical CST to determine the wCST-LL for each patient. The wCST-LL was calculated by weighting each slice for overlap with the CST by the ratio of the maximum cross-sectional area of the CST over the cross-sectional area of that specific slice. This weighting option corrects for the narrowing of the CST descending into the PLIC from the motor cortex.

In contrast to the previous study,[11] the canonical tract was determined by a probabilistic fiber tracing approach using FSL 3.1.2 (http://www.fmrib.ox.ac.uk). Preprocessing steps include correction for eddy current effects, skull stripping, as well as estimation and fitting of diffusion parameters. Single-slice regions of interest (ROIs) were drawn on the FA images in the pons, PLIC, and white matter underlying the posterior part of the precentral gyrus. Exclusion ROIs were drawn on the superior and middle cerebellar peduncle to exclude fibers to the cerebellum, as well as the middle sagittal region covering the brain stem and corpus callosum to exclude transhemispheric fibers. Probtrackx (http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_probtrackx.html) was run to track fibers from the pons ROI as the seeding region. Tracts were normalized to the SPM5 T2 template from SPM5 (Wellcome, Department of Neurology, London, UK) implemented in MATLAB (The Mathworks, Inc., Natick, MA), which was achieved by normalizing the DWI image to the SPM5 T2 template, and then applying the normalization parameter to each CST tract. A 50th FA percentile threshold was applied to each CST fiber, and then the 12 tracts were each binarized and summed to create the canonical CST.

The DWI of the patients were normalized to a skull-stripped T1-weighted SPM5 brain template with isotropic $2 \times 2 \times 2$ mm voxels. Skull stripping was achieved using BET implemented in the FSL 4.1.4 software package. The skull-stripped T1 template was found to be the most appropriate template because the T1-weighted images and the diffusion trace images have dark signals representing the cerebrospinal fluid compartment. For 14 patients, the large hyperintense lesion on the DWI images distorted the normalization process and an alternate two-step normalization process was applied. The two-step normalization process consisted of normalizing the apparent diffusion coefficient images of the DWI sequences to the SPM T2-weighted template first, and then applying those normalization parameters to the T2-weighted diffusion trace images. A visual inspection of normalization was done by using well-known anatomical landmarks (e.g., anterior and posterior commissure, corpus callosum extents, frontal horns of the lateral ventricles, location of the central sulcus, and outer contour of the brain) to determine whether or not the normalization was adequate. To find more objective measures and to standardize the process of normalization in lesioned brains, we came up with a way of quantitatively describing the precision of the normalization process. First, we realized that even in brains that showed distortions and warping after normalization, typically the outer contour was still well normalized. It was more the inner structures, close to the midline and above the anterior commissure (AC), that ended up showing distortions. Therefore, we created a bounding box ($x = 37$–41; $y = 43$–59; $z = 24$–39) that spanned around the AC and posterior commissure (PC), included five sagittal slices centered around the midline (interhemispheric fissure) and 15 slices dorsal from a horizontal line connecting the AC and PC. All voxels and their values were extracted from the SPM template brain and each patient's brain after the one-step normalization process (DWI trace to SPM5 T1 template). In the next step, we regressed each voxel value of this bounding box from the SPM template with each patient's voxel value from the bounding box. The brains that were visually determined to have a satisfactory normalization had a median r value of 0.49 (standard deviation [SD]: 0.09), whereas brains that were visually determined to be unsatisfactory had a median r value of 0.28 (SD, 0.15). These two groups differed significantly from each other ($p < 0.001$). Subjecting the "badly" normalized brains to the two-step process described above improved their r value to 0.49 (SD, 0.15). There were significant differences between the badly normalized brains and the two-step normalized brains ($p < 0.001$), whereas the previously badly normalized brains did not significantly differ from the one-step normalized brains anymore after the badly normalized brains had undergone the two-step process. This two-step process worked well for these patients with large lesions.

Statistical Analysis

The primary outcome variable was the UE-FM Scale at 3 months. Secondary outcome variables included the NIHSS arm motor score and the NIHSS total score at 3 months. A univariate regression analysis was conducted to assess the amount of variance (R^2) explained by wCST-LL or initial UE-FM with regard to UE-FM scores at 3 months. Regression model diagnostics included model fit, influence diagnosis, and

TABLE 1. Patients' Demographic and Clinical Characteristics

	Cohort 1 (N = 37)	Cohort 2 (N = 39)	Combined (N = 76)
Demographic			
Age, yrs	60.7 (16.4)	56.9 (11.2)	58.8 (14.0)
Male, %	64.9	56.4	60.5
Ethnicity, %			
Caucasian	81.1	64.1	72.4
African American	8.1	35.9	22.4
Others	10.8	0	5.3
Education (college or higher), %	47.2	13.6	30.1
Lesion side (right), %	62.1	69.2	65.4
Right handed, %	91.9	97.4	96.1
tPA or reperfusion therapy, %	37.8	26.8	31.6
Stroke subtype, %			
Small vessel disease	18.9	28.2	23.7
Cardioembolism	32.4	18.0	25.0
Large vessel atherosclerotic disease	18.9	33.3	26.3
Other or unknown etiology	29.7	20.5	25.0
Disposition			
Length of stay, days	5.8 (3.3)	6.6 (6.0)	6.2 (4.9)
Days between onset of stroke symptom and the first assessment	2.9 (1.5)	2.0 (1.2)	2.4 (1.5)
Days between stroke admission and follow-up	92.6 (14.4)	94.3 (10.5)	93.5 (13.4)
Days of rehabilitation therapy	39.8 (18.8)	29.8 (17.5)	34.5 (18.7)
Acute rehabilitation facility, %	91.9	71.8	81.6
Behavioral assessment			
NIHSS at baseline	9.2 (6.4)	8.7 (5.2)	9.0 (5.8)
NIHSS at 3 months	4.4 (5.1)	3.9 (3.5)	4.2 (4.3)
UE-FM at baseline	24.8 (19.7)	25.1 (19.6)	25.0 (19.5)
UE-FM at 3 months	42.5 (23.8)	42.3 (23.3)	42.4 (23.4)
mRS	2.3 (1.5)	2.5 (1.3)	2.4 (1.4)
Imaging information			
wCST-LL (cc)	4.16 (3.06)	3.74 (3.21)	3.94 (3.12)
Lesion volume (cc)	43.33 (59.78)	42.90 (49.95)	43.11 (54.58)
Outcome prediction (R^2)			
Clinical assessment (initial motor impairment)	0.67	0.62	0.64
Imaging assessment (wCST-LL)	0.69	0.69	0.69

UE-FM = Upper-Extremity Fugl-Meyer Scale; NIHSS = National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; wCST-LL = weighted corticospinal tract lesion load; All values are means and standard deviation (in brackets).

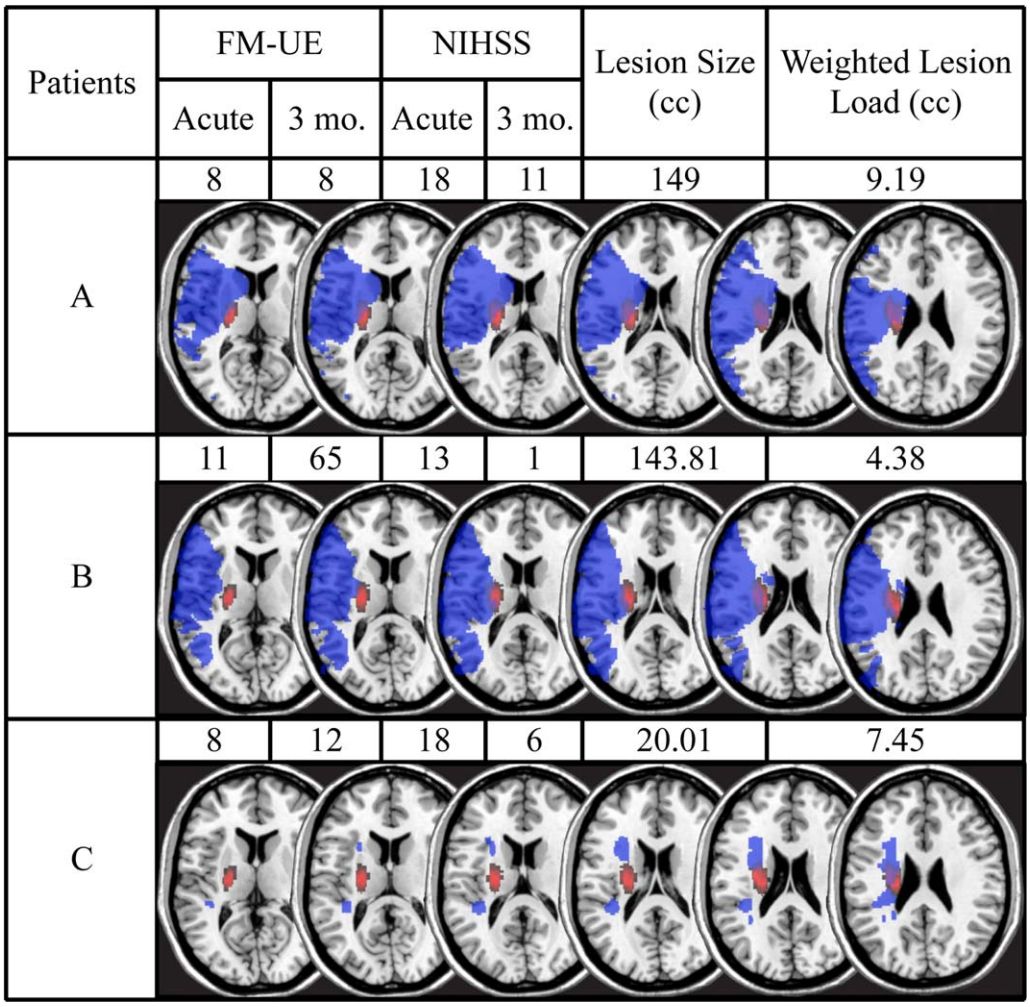

FIGURE 1: Examples of 3 patients with their UE-FM and NIHSS scores (at baseline and 3 months poststroke) and their lesion maps (blue) overlaid onto the probabilistic CST map (red) as well as their lesion volume and weighted corticospinal tract (CST) lesion load (wCST-LL). The overlap between lesion and CST is displayed in purple. The axial slices depicted correspond to Z = 0, 4, 8, 10, 20, and 28 in Talairach space. A comparison of Patients A and B shows that two similarly sized lesions can have markedly different wCST-LL and, accordingly, results in very different levels of motor impairment both at baseline and 3 months poststroke. A comparison of Patients A and C shows that 2 patients have similar wCST-LL and motor recovery, but drastically different lesion volumes. UE-FM = Upper-Extremity Fugl-Meyer Scale; NIHSS = National Institutes of Health Stroke Scale.

multicolinearity diagnostic. Fisher's r-to-z test was used to test the statistical difference of R^2. Cohort 1 was treated as a derivation cohort; the coefficient and intercept from the regression analysis based on cohort 1 were applied to cohort 2 to calculate predicted R^2 in cohort 2. A subsequent regression analysis was conducted in the combined severely impaired subgroup (defined as UE-FM score ≤ 10 at baseline). Regression analysis was also applied to the NIHSS arm score as an alternative outcome variable and the NIHSS total score as a global outcome variable. Last, a multivariate regression was fit with variables acute UE-FM, wCST-LL, and additional variables with significant correlation with outcome variables. A backward elimination procedure for variable selection ($p = 0.05$) was used to obtain a more parsimonious model.

UE-FM score ≤ 25 at 3 months was arbitrarily defined as poor motor outcomes in our analysis (all patients with UE-FM score ≤ 25 at 3 months in the combined cohort had a modified Rankin Scale [mRS] > 3, which is considered as a poor outcome). A receiver operating characteristic curve was generated by logistic regression by modeling the poor motor outcomes in cohort 1. Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated with regard to different cut-off values of wCST-LL. These cut-off values of wCST-LL were applied to cohort 2 (validation cohort) to calculate the specificity, sensitivity, PPV, NPV, and accuracy. The main interests are specificity and PPV.

A proportional recovery score[12] was calculated by relating the actual change score in the UE-FM between

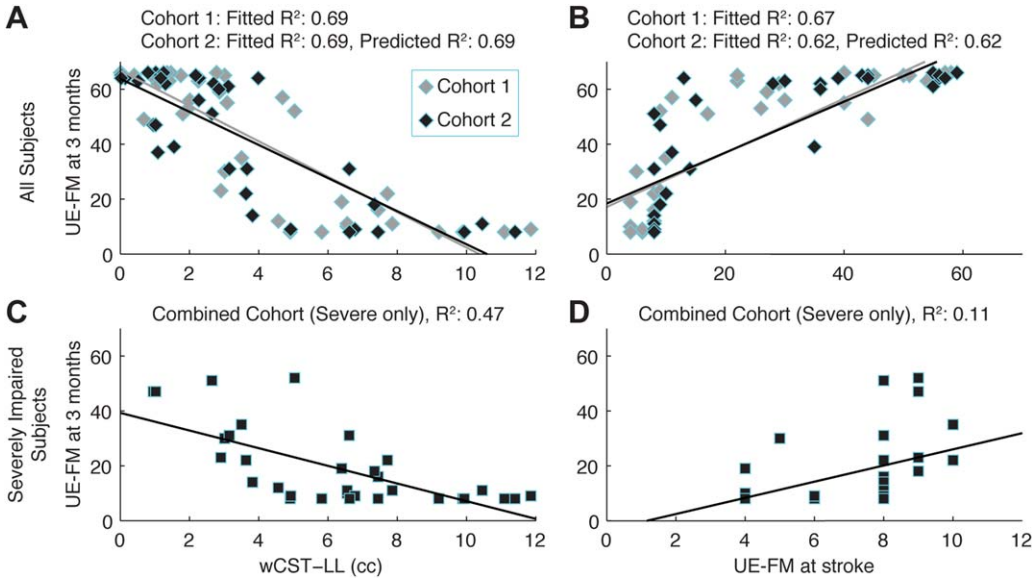

FIGURE 2: Scatter plot and correlation for wCST vs. initial motor impairment (UE-FM). (A) For cohort 1, fitted R^2 for weighted corticospinal tract lesion load (wCST-LL) is 0.69; for cohort 2, the fitted R^2 for wCST-LL is 0.69 and predicted R^2 is 0.69. (B) For cohort 1, fitted R^2 for initial motor impairment is 0.67; for cohort 2, the fitted R^2 for initial motor impairment is 0.62 and predicted R^2 is 0.62. (C) R^2 for wCST-LL is 0.47 for the severely impaired subgroup. (D) R^2 for initial motor impairment is 0.11 for the severely impaired subgroup. UE-FM = Upper-Extremity Fugl-Meyer Scale. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

baseline and 3 months to the maximal recovery potential, which was defined as the difference between the maximal UE-FM score (66) minus the baseline UE-FM score.

All statistical analyses were performed using SAS software (V9.2; SAS Institute Inc., Cary, NC).

Results

Patients' Characteristics

Seventy-six Patients (37 in cohort 1 and 39 in cohort 2) completed both baseline and 3-month follow-up assessment. The two groups were largely comparable, but did have differences in some demographics, as shown in Table 1. Cohort 2 had more African Americans (35.9% vs. 8.1%), was slightly younger (56.9 vs. 60.7 years old), had fewer subjects who attended college or higher education (13.6% vs. 47.2%), and had fewer subjects who were discharged to an inpatient rehabilitation facility (71.8% vs. 91.9%).

Overall, patients were assessed at 2.4 ± 1.5 days after onset of stroke symptoms and average length of hospital stay was 6.4 ± 4.9 days. A total of 81.6% of patients were discharged to an acute rehabilitation facility and the average days of therapy that a patient received were 34.5 ± 18.7 days. The follow-up visit occurred at 93.5 ± 13.4 days after stroke admission. Mean UE-FM score was 25.0 ± 19.5 points at baseline and 42.4 ± 23.4 points at 3 months. Mean NIHSS score at baseline was 9.0 ± 5.8 points at baseline and 4.2 ± 4.3 points at 3 months. Average mRS was 2.4 ± 1.4 at 3 months. Overall lesion volume was 43.11 ± 54.58 cc and the wCST-LL was 3.94 ± 3.12 cc. Figure 1 shows an example of 3 patients with different lesion patterns with their UE-FM and NIHSS scores (at baseline and 3 months), lesion volumes, and wCST-LL value with regard to recovery.

Regression Analysis

Five outliers were excluded from the analysis. They were first identified by regression model diagnostics. By reviewing clinical characteristics of these outliers, various reasons were revealed, including very large lesion, unusually excessive amount of rehabilitation therapy, possibility of a recurrent stroke, and so on. The fitted R^2 (0.69) and predicted R^2 (0.69) in cohort 2 were the same for wCST-LL with respect to UE-FM at 3 months. Similarly, the fitted R^2 (0.67) and predicted R^2 (0.67) in cohort 2 were the same for initial motor impairment with respect to UE-FM at 3 months. R^2 for wCST-LL and for initial motor impairment were statistically equivalent ($R^2 = 0.69$ vs. $R^2 = 0.67$; $p = 0.43$) with respect to motor outcomes at 3 months for cohort 1 as well as for cohort 2. ($R^2 = 0.69$ vs. $R^2 = 0.62$; $p = 0.25$). By pooling data from both cohorts, wCST-LL correlated with motor outcomes at 3 months significantly better than the initial motor impairment ($R^2 = 0.47$ vs. $R^2 = 0.11$; $p = 0.03$; Fig. 2) in the subgroup of patients with severe motor impairment at baseline (UE-FM ≤ 10). This is further illustrated (Fig. 3) in a group of stroke patients

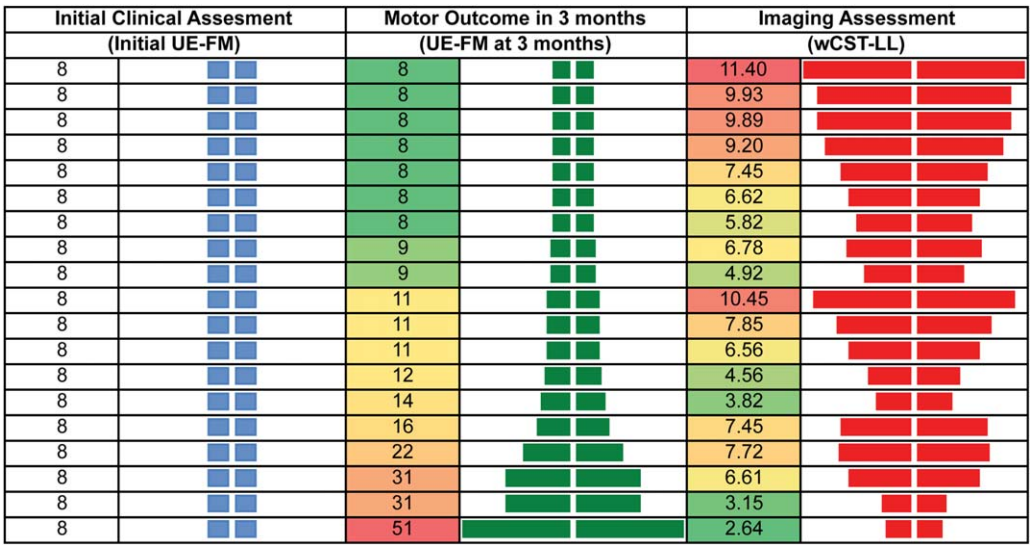

FIGURE 3: Relationship between initial motor impairment, weighted corticospinal tract (CST) lesion load (wCST-LL), and motor outcomes at 3 months. Despite the fact that all patients presented with the same initial motor impairment by clinical assessment, those patients with smaller weighted CST lesion load recovered better at 3 months. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

who presented with the exact same motor impairment at baseline (i.e., UE-FM score = 8), but recovered to different levels at 3 months (UE-FM score ranges from 8 to 51). Although all these patients had the same low UE-FM score initially, the wCST-LL was able to differentiate the degree of injury to the CST and correlated with motor outcomes at 3 months ($R^2 = 0.47$) significantly better than the initial UE-FM, which had a very low R^2 of 0.11. Specifically, a higher wCST-LL value indicated a more injured CST and a greater likelihood that a patient would have a poor motor outcome at 3 months.

When the NIHSS arm motor score, as an alternative motor outcome variable, was modeled, wCST-LL had an equivalent correlation with the 3-month NIHSS arm motor score ($R^2 = 0.58$ vs. $R^2 = 0.55$; $p = 0.39$), as compared to the initial NIHSS arm motor score. But when a measurement of global outcome—total NIHSS score—was modeled, the initial NIHSS score was found to correlate with NIHSS score at 3 months significantly better than the wCST-LL ($R^2 = 0.71$ vs. $R^2 = 0.45$; $p = 0.01$; Table 2). This provides strong evidence that wCST-LL, an imaging measure of CST injury, is specialized at predicting motor outcome only.

wCST-LL Threshold Analysis

In cohort 1, a wCST-LL cutoff of 5.5 cc had sensitivity of 77%, specificity of 100%, and PPV of 100% (i.e., when the wCST was ≥5.5 cc in the acute phase, the chance of a patient to have poor motor outcome, defined as UE-FM ≤ 25 at 3 months, is 100%). If wCST-LL cutoff was increased, for example, ≥7.0 cc, sensitivity decreased to 46% but specificity remained at 100% and

TABLE 2. Comparison of Predictive Value of wCST-LL vs. Initial Impairment With Regard to Different Outcome Variables

Outcome Variable	Predictive Value (R^2)		*p*
UE-FM Scores at 3 Months	Initial UE-FM score $R^2 = 0.69$	wCST-LL $R^2 = 0.64$	0.30
NIHSS Arm Motor Scores at 3 months	Initial NIHSS Motor Score $R^2 = 0.55$	wCST-LL $R^2 = 0.58$	0.39
NIHSS Total Scores at 3 months	Initial NIHSS score $R^2 = 0.71$	wCST-LL $R^2 = 0.45$	0.01

UE-FM = Upper-Extremity Fugl-Meyer Scale; NIHSS = National Institutes of Health Stroke Scale; wCST-LL = weighted corticospinal tract lesion load.

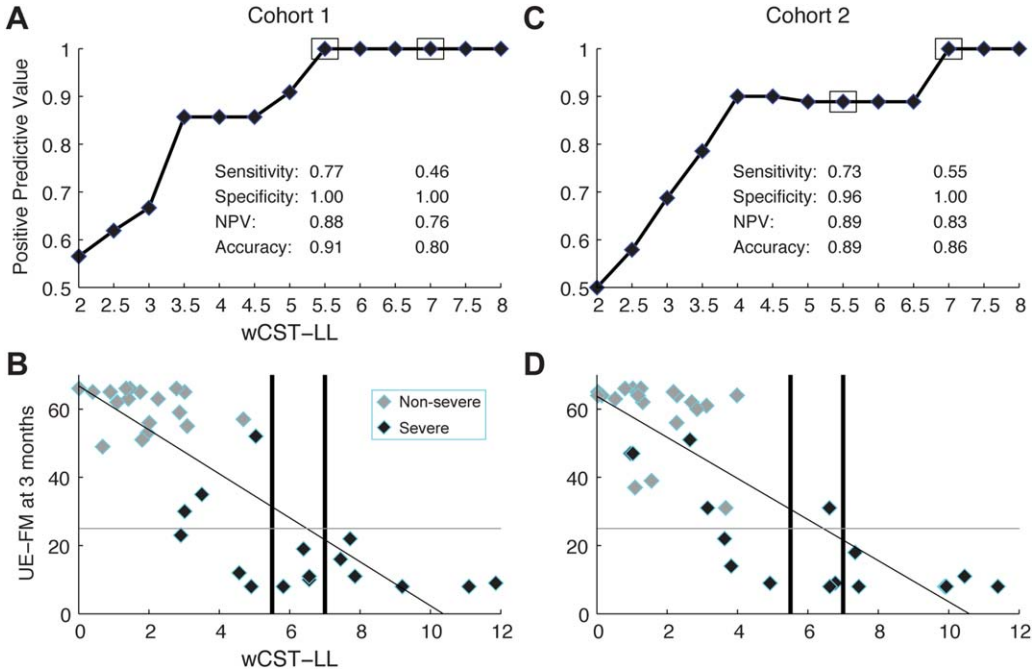

FIGURE 4: Positive predictive value of poor motor outcomes (defined as UE-FM ≤ 25 at 3 months) at different cut-off value of weighted corticospinal tract lesion load (wCST-LL) in both cohort 1 and 2. When wCST-LL in the acute phase exceeds 7.0 cc, all stroke patients in our cohort have poor motor outcomes at 3 months in both cohorts (i.e., UE-FM ≤ 25). NPV = negative predictive value; UE-FM = Upper-Extremity Fugl-Meyer Scale. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

PPV remained at 100% as well. A high specificity and PPV are important in making a prediction of poor motor outcomes in the acute phase in order not to misclassify patients as having a poor outcome and to potentially miss out on any rehabilitation opportunity. A wCST-LL of 7.0 cc threshold was validated in cohort 2 with a specificity of 100% and PPV of 100%.

Multivariate Analysis

In a multivariate regression analysis with initial motor impairment (UE-FM), wCST-LL, age, race, sex, days of therapy, reperfusion therapy, and lesion volume, only two variables (wCST-LL and initial UE-FM) remained in the model by the backward elimination procedure. These two variables together explained 81% of the variance in outcome at 3 months; however, there was some colinearity between the initial UE-FM and the wCST-LL and both variables correlated significantly with each other ($r = 0.65$ and $p < 0.0001$). This suggests that clinical assessment (initial UE-FM) and imaging assessment (wCST-LL) both reflect the degree of injury to the CST.

Proportional Recovery

Prabhakaran et al[12] first discovered that stroke patients with mild-to-moderate initial impairments show an almost fixed proportional upper extremity motor recovery when tested again around 3 months. This phenomenon was confirmed later by the other study.[26] We examined whether this proportional recovery rule was also true for our sample of stroke patients. Similar to these studies,[12,26] proportional recovery was not obvious when all patients were included. After excluding a subgroup of severely impaired patients (UE-FM ≤ 10 at baseline), the remaining patients indeed showed a recovery pattern of approximately 70% of their maximal recovery potential at 3 months (Fig 5).

Discussion

Our study demonstrates that either the wCST-LL by imaging assessment or the initial motor impairment by

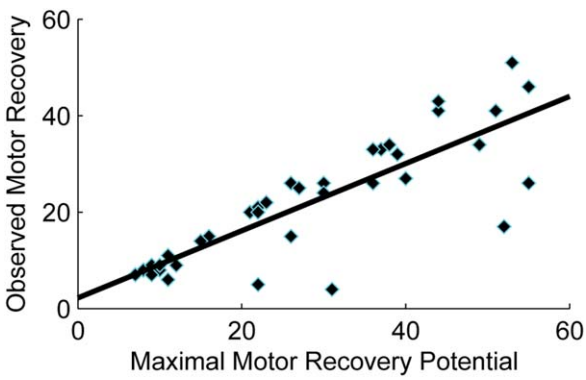

FIGURE 5: Proportional recovery in a subgroup of patients with less severe motor impairment in the acute phase (UE-FM > 10). Patients recovered approximately 70% of their maximal recovery potential. UE-FM = Upper-Extremity Fugl-Meyer Scale. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

clinical assessment (UE-FM) is well correlated with motor impairment measured at 3 months after stroke. Although the overall R^2 value regarding motor outcome using wCST-LL and UE-FM is equivalent, the initial motor impairment assessment had limited predictive value in the subgroup of patients with severe motor impairment (UE-FM score ≤ 10 at baseline) whereas the wCST-LL was a significantly better predictor in this subgroup. Furthermore, a wCST-LL of ≥ 7.0 cc implies severe injury to the CST tract to such a degree that poor motor outcome at 3 months (i.e., UE-FM ≤ 25) cannot be avoided. Similar to other studies, we found evidence for a proportional recovery rule[12,26] in the nonseverely impaired group, that is, most patients with an initial UE-FM of > 10 can recover approximately 70% of their maximal recovery potential at 3 months.

Consistent with previous studies,[11,27] the overall lesion volume was not found to be correlated with motor impairment at 3 months, suggesting that information about which relevant anatomic structures (i.e., the CST) are affected by a stroke lesion is necessary to increase correlations with outcomes or the predictive power of an imaging variable, as illustrated in Figures 1 and 3, and 4.

The wCST-LL also correlates with another motor outcome measure—the NIHSS arm motor score, but less well with a global outcome (NIHSS total score). This specificity of the wCST-LL variable suggests that it is a unique imaging marker for poststroke motor outcome prediction. Our results include an effective replication in two separate cohorts collected in two academic centers. Though similar, the two cohorts do have some differences in race, age, educational level, and disposition. Nevertheless, the wCST-LL imaging variable still effectively correlated with motor outcomes with an equivalent R^2 per regression model, suggesting that the wCST-LL is a robust motor outcome predictor. Stroke motor recovery depends on the degree of injury to the CST. In this study, we were able to demonstrate that once the lesion cumulated to a certain total volume in the acute phase (i.e., ≥ 7.0 cc), patients were highly likely to have poor motor outcomes at 3 months. This might have important clinical as well as economic implications. It can help set an appropriate expectation for the clinician, patient, and caregiver at the very early stage after a stroke. Additionally, it might give the clinician the opportunity to triage a patient with predicted poor outcome to different rehabilitation modalities with more appropriate focus. A similar approach to early patient rehabilitation planning has been investigated.[28]

As a potential imaging biomarker of poststroke motor outcome, the wCST-LL has several advantages over other methods. The most obvious advantage is that it only requires a clinical MRI scan, which most stroke patients will have as a part of the standard of care in the majority of hospitals in the United States, making the components to determine wCST-LL widely available and easy to implement. Other methods, such as fMRI and TMS, are difficult to do in the acute stroke phase, are not available in most medical centers, and may not yield useful information in stroke patients with severe impairment. DTI in the acute phase may provide information about the integrity of CST; however, studies have shown that a tract distal to the lesion might still appear as structurally intact up to several days after an infarct because Wallerian degeneration takes time to develop and manifest as an imaging abnormality.[9]

This study also observed a similar recovery pattern, as outlined by other studies,[12,26] that most stroke patients, except those with severe motor impairment, recover in a proportional manner that is roughly 70% of their maximal potential recovery potential (Fig 5). This proportional recovery pattern was not observed in the subgroup of patients with severe impairment, who had a much greater interindividual variability in terms of recovery potential posing a challenge for motor outcome predictions. For example, of many patients with the same severe initial motor impairment (i.e., UE-FM score = 8), some reached a UE-FM score in the 50s at 3 months (Fig 3). Whereas the motor assessment (a behavioral measure) shows limited correlation in these severely impaired patients in the acute phase (as first pointed out and emphasized by Prabhakaran et al in 2008,[12] suggesting that a nonbehavioral measure was needed for better correlation of motor outcomes in this group), it is the wCST-LL (an imaging measure) that better reflects the differential injury to the CST and better correlates with motor outcome at 3 months in this subgroup. Given that wCST-LL is superior to the clinical assessments in predicting outcome in this subgroup, it could also serve as a stratification variable in experimental stroke recovery studies, particularly for cases in which clinical assessment is not a good predictor of outcome or of response to interventions.

Days of therapy (DoT), a surrogate measure for rehabilitation dosage, was shown[3] to correlate with stroke outcome. It was significantly related to UE-FM at 3 months in the univariate analysis. However, it did not survive as a covariate in the multivariate regression analysis. Our study revealed that the more severely impaired at baseline, the more DoT a patient likely received. But there was no linear relationship between DoT and the degree of motor improvement. The DoT variable is a complex variable, given that it does not always indicate the amount or intensity of therapy that is dedicated

toward the affected limbs, especially in severely impaired patients; rehabilitation therapy may also focus on training compensatory activities by working on the nonaffected limb. Additionally, the DoT variable is vulnerable to external factors, such as insurance status and other personal factors. A note of caution is that our measure of DoT may not capture the exact amount of therapy that the patients should have or actually received because it was based on self-report. Future studies should obtain more detailed information on activities done during rehabilitation sessions.

Reperfusion therapy did not survive as a covariate in the multivariate regression analysis. There are several explanations for this. Patients were assessed between 2 and 7 days (average, 2.4) after the onset of stroke symptoms, and our assessments might have captured a new baseline after the immediate effects of a reperfusion therapy.

There is still some variance that remains to be explained. One source of variability could be factors that were not measured in this study and have not been proven to play a strong role, such as genetic predisposition.[29,30] Another source of variability could be the effect of poststroke depression and use of antidepressant, which have been shown to have an effect on stroke motor recovery.[31]However, in our study, use of antidepressants after a stroke was not a significant predictor in the univariate analysis. Finally, the integrity of alternative motor fibers, such as the corticorubral or corticotegmental tracts,[32,33] with crossed and uncrossed connections to alpha-motor neurons in the spinal cord could have an influence on motor recovery and their influence on recovery should be considered in future studies.

Our study and approach do have some limitations. First, spatially normalized brain images of acute stroke patients may contain distortions owing to large ventricles in elderly patients and/or very large lesions with edema. Though we have developed solutions to improve spatial normalization even in brains with large lesions, CST location could potentially be more inaccurate in brains with large lesions than with smaller lesions. Second, we only included first-ever acute ischemic stroke patients in this cohort and excluded patients with their second or third stroke; this could affect somewhat the generalization of the study results. Third, although the wCST-LL cutoff of 7.0 cc was validated by two independent cohorts, the sample sizes are still relatively small (especially the subgroup with severe impairment at baseline); this wCST-LL threshold needs to be further defined and validated in a new large cohort before it can be used as a biomarker in experimental trials or clinical practice.

In summary, the wCST-LL, an imaging biomarker obtained in the acute stroke phase, is well correlated with poststroke motor outcomes at 3 months in two independent cohorts, especially in a subgroup of patients with severe impairment at baseline. Further validation of this imaging biomarker in another cohort with large sample size is required, and automation of the quantification process is actively pursued to establish wCST-LL as a tool for clinical stroke outcome predictions and as a stratification variable for future stroke recovery trials.

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Authorship

W.F., D.L., S.K., and G.S. contributed to concept and design of this study; W.F., J.W., P.Y.C., C.D., D.L., V.A.L., and G.S. participated in the data acquisition and analysis; and W.F., J.W., P.Y.C., C.D., D.L., V.A.L., S.K., and G.S. drafted the manuscript or figures.

Potential Conflicts of Interest

Nothing to report.

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