# Early Fiber Number Ratio Is a Surrogate of Corticospinal Tract Integrity and Predicts Motor Recovery After Stroke

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***Background and Purpose***—The contribution of imaging metrics to predict poststroke motor recovery needs to be clarified. We tested the added value of early diffusion tensor imaging (DTI) of the corticospinal tract toward predicting long-term motor recovery.

***Methods***—One hundred seventeen patients were prospectively assessed at 24 to 72 hours and 1 year after ischemic stroke with diffusion tensor imaging and motor scores (Fugl-Meyer). The initial fiber number ratio (iFNr) and final fiber number ratio were computed as the number of streamlines along the affected corticospinal tract normalized to the unaffected side and were compared with each other. The prediction of motor recovery (ΔFugl-Meyer) was first modeled using initial Fugl-Meyer and iFNr. Multivariate ordinal logistic regression models were also used to study the association of iFNr, initial Fugl-Meyer, age, and stroke volume with Fugl-Meyer at 1 year.

***Results***—The iFNr correlated with the final fiber number ratio at 1 year (r=0.70; P<0.0001). The initial Fugl-Meyer strongly predicted motor recovery (≈73% of initial impairment) for all patients except those with initial severe stroke (Fugl-Meyer<50). For these severe patients (n=26), initial Fugl-Meyer was not correlated with motor recovery ($R^2$=0.13; p=ns), whereas iFNr showed strong correlation ($R^2$=0.56; P<0.0001). In multivariate analysis, the iFNr was an independent predictor of motor outcome (β=2.601; 95% confidence interval=0.304–5.110; P=0.031), improving prediction compared with using only initial Fugl-Meyer, age, and stroke volume (P=0.026).

***Conclusions***—Early measurement of FNr at 24 to 72 hours poststroke is a surrogate marker of corticospinal tract integrity and provides independent prediction of motor outcome at 1 year especially for patients with severe initial impairment.   (***Stroke***. 2016;47:1053-1059. DOI: 10.1161/STROKEAHA.115.011576.)

**Key Words:** diffusion tensor imaging ■ magnetic resonance imaging ■ stroke ■ stroke volume ■ Wallerian degeneration

Cerebral ischemic stroke is a major cause of motor impairment[1] with significant impact on the ability of patients to be self-sufficient in activities of daily living. Providing accurate prognosis of long-term motor impairment within the first few days after an insult is highly desirable (1) to correctly inform patients and caregivers; (2) to rapidly anticipate the type, duration, and goals of rehabilitation; and (3) to improve patient selection for clinical trials, such as those focusing on brain repair and reorganization.

Clinically, patient age and initial stroke severity are important predictors of motor disability in the medium to long-term.[2,3] Most patients exhibit a proportional recovery of ≈70% of their initial motor impairment,[4,5] which, therefore, already conveys strong predictive information. Nevertheless, this 70% rule fails in patients with initial severe deficit,[4,5] and the variability in medium to long-term outcome is not adequately explained by initial clinical severity alone for those patients. The interindividual variability in the relation between initial impairment and subsequent recovery hampers accurate individualized prognosis.[6] Although infarct volume could be helpful to improve prognostication,[7] its power as an independent predictor of clinical outcome is still debated.[8]

Stroke's impact on corticospinal tract (CST) integrity might constitute a more relevant determinant of motor impairment and recovery.[9] In line with this concept, Byblow et al[10] recently demonstrated that CST integrity as assessed by the presence of motor-evoked potentials (MEPs) was a better predictor of the ability to recover compared with initial clinical impairment, thus improving the 70% rule. Furthermore, they also demonstrated the added value of fractional anisotropy (FA) measurements in the CST toward improving prediction of motor function recovery in combination with MEPs.[10] Measurement of CST integrity with diffusion tensor imaging (DTI)[11] has been proposed both by assessment of decreases in FA distal to the stroke area and by the quantification of a decrease in the number of CST fibers, as an index of fiber degeneration (Wallerian degeneration).[12,13] In most previous work, including the one by Byblow et al,[10] these measurements were primarily obtained weeks or months after stroke[14,15] precluding their use for early prognostication. At the subacute stage, Feng et al[16] quantified the overlap of the acute stroke with a canonical CST derived from DTI of healthy controls instead of using DTI in patients. Referring to work by Puig et al[17] argue that in acute/subacute stage, DTI measurements along the CST might not accurately reflect CST damage because degeneration takes time to develop and might not be detected by this magnetic resonance imaging (MRI) technique. Nevertheless, a decrease in FA or in the number of CST fibers has already been reported even after only few days after the insult with promising correlations with longer term outcome.[18–21] Therefore, direct DTI measurements of the CST integrity rapidly after a stroke might be clinically feasible and could obviate the need for relatively complicated image analysis, which might experience image coregistration errors, and necessitates a canonical CST model derived from healthy volunteers. Here, we assessed the relationship between acute and chronic (1 year) tractographic analysis of the CST after stroke, under the hypothesis that DTI in the acute phase might provide a straightforward, quantitative, and objective predictor of CST motor fiber integrity, and, ultimately, of the potential for motor recovery over that provided by the 70% rule for resolution of motor impairment. The primary aim of this work is to investigate the added value of early DTI, compared with established and easy-to-collect variables, such as age and bedside tests for initial motor impairment to improve the prediction of long-term motor recovery.

## Methods

### Study Population

Patients admitted for an ischemic stroke between June 2012 and February 2014 were consecutively enrolled in a prospective cohort study. The study design included initial (between 24 and 72 hours) and chronic (1 year) clinical and MRI poststroke evaluations. The institutional ethics committee approved the study, and written informed consent was obtained for all patients from them or their relatives before inclusion. Primary inclusion criteria were men or women, older than 18 years old, with a suspected clinical diagnosis of minor-to-severe supratentorial cerebral infarct (National Institutes of Health Stroke Scale between 1 and 25) 24 to 72 hours after the insult confirmed on trace diffusion magnetic resonance. The exclusion criteria were a prestroke functional deficit determined as a modified Rankin ≥1 or a previous stroke along the CST documented on

imaging, an infratentorial ischemic stroke or hemorrhagic stroke, and patients presenting psychiatric disorders, pregnant women, coma, and contraindications to MRI.

### Clinical Assessment

The main outcome was motor impairment at 1 year evaluated by the Fugl-Meyer score. Motor recovery was estimated by subtracting the initial (24–72 hours) Fugl-Meyer from the chronic (1 year) scores (ΔFugl-Meyer=Fugl-Meyer recovery). The Fugl-Meyer score provides a detailed evaluation of motor impairment with inter- and intrarater reliability close to 1.[22] The motor function domains of the Fugl-Meyer score measure movement, coordination, and reflex action about upper extremity (shoulder, elbow, forearm, wrist, and hand) and lower extremity (hip, knee, and ankle) and range from 0 (hemiplegia) to a maximum of 100 points (normal motor performance). The patients were followed-up to 1 year to allow recovery to plateau.[23] All clinical evaluations were performed by a neurologist assisted by a trained physical therapist, without knowledge of MRI findings.

### Magnetic Resonance Imaging

#### Image Acquisition

MRI scans were acquired at the time of clinical evaluations (24–72 hours and 1 year after stroke) by using a 3T Discovery MR 750w scanner (GE Medical System, Milwaukee, WI) with a 32-channel phased-array head coil. The imaging protocol included a DTI sequence using dual echo-planar imaging (40 axial slices; repetition time: 15 000 ms; echo time set to minimum; slice thickness: 3.5 mm; matrix: 160×160; field of view: 24 cm²; $b$ values: 0 and 1000 s/mm² applied in 16 noncolinear directions; scan time: 4 minutes and 30 seconds).

#### Rationale for Early DTI Analysis

Wallerian degeneration distal from the primary lesion (typically within the brain stem) is not expected to be detectable during the first 72 hours after the insult.[17] Nevertheless, FA decreases within the stroke itself from this early time point correspondingly with ischemic damage.[24] We reasoned that when tracking the CST from primary motor cortex to the brain stem, a significant reduction of FA within a stroke along the CST could interrupt the reconstructed streamlines, even in the absence of Wallerian degeneration. Therefore, although the real number of fibers may not yet be significantly decreased in <3 days MRI as there is not yet anatomic anterograde degeneration, we hypothesized that a measurement of so-called virtual fibers from DTI at an early time point could be a surrogate of the real fiber count at follow-up and, in turn, could be helpful for early prognostication of motor recovery.

#### Image Processing and Analysis

DTI inherently showed low signal-to-noise ratio because scan time had to be short to be tolerated by most patients, especially in the acute/subacute phase of disease. We consequently used a new DTI denoising filter[25] to recover higher signal-to-noise ratio and thus improve image quality and accuracy of diffusion parameters. Distortions induced by eddy currents and head motion were corrected by performing rigid registration of diffusion weighted images to b0 images.[26] The direction table was updated with the estimated motion matrices.

Stroke volumes were first calculated by segmenting each slice of the trace DTI from the initial MRI scan using a semiautomatic tool available in 3D slicer (http://www.slicer.org).

Then, a diffusion tensor model was fitted at each voxel using Trackvis (http://www.trackvis.org) to generate FA maps and to investigate CST integrity. The CST was identified using deterministic tractography between 2 distal seed-regions of interest (ROI): one in the primary motor cortex (M1) and its underlying white matter, the central sulcus serving as the posterior border, and the other in the anterior cerebral peduncles. This approach was applied as implemented in Trackvis and ensures that supratentorial strokes will fall between the 2-seed ROIs. ROIs were placed by a specialized neuroradiologist symmetrically based on color-coded FA maps and trace DTI images using previously published and easy to determine

landmarks[9,14] (Figure I in the online-only Data Supplement for illustration of ROI positions). Fibers that were not homogeneously blue coded (ie, superior-inferior fiber direction) and whose direction were not corresponding to the CST based on anatomic knowledge and a DTI-derived atlas[27] were excluded by slight adjustment of the seed ROIs. Fiber tract propagation was terminated for FA <0.2 and angle <35° based on agreed-upon thresholds.[9] The total number of fibers connecting the 2 ROIs ipsilateral to the stroke were normalized by the total number of fibers from the contralateral side to correct for age-related variations or preexisting diffuse microstructural alterations. Whether this strategy perfectly corrects the impact of leukoaraiosis in the ability to accurately quantify the CST integrity transcends scope of work and will be addressed in future analyses. We will refer to initial fiber number ratio (iFNr) for the 24 to 72 hours MRI and to final fiber number ratio (fFNr) for the 1 year follow-up MRI.

## Statistical Analysis

To identify whether an early measure of fiber number could be a surrogate for real Wallerian degeneration at the chronic stage, we first assessed the correlation between iFNr and fFNr by using Spearman's rank order correlation.

Then, we tested the value of iFNr to predict motor recovery compared with the other predictors. We reasoned that the first tests to predict motor recovery should be bedside tests. So we first tested the amount of variance ($R^2$) explained by an initial Fugl-Meyer score with respect to motor recovery at 1 year with linear regression analysis. From this step, we identified a meaningful subpopulation (severely affected patients with initial Fugl-Meyer<50) whose motor recovery at 1 year was not predicted by initial Fugl-Meyer. A subsequent regression was, therefore, conducted in this subpopulation to test whether iFNr can explain more variance than initial Fugl-Meyer with respect to motor recovery at 1 year by comparing $R^2$. For these patients who are severely affected at baseline (initial Fugl-Meyer<50), we also performed receiving operating characteristic analysis to test whether an iFNr cutoff might identify additional patients with a potential to recover by 70% or more despite their initial clinical severity.

The added value of iFNr compared with the other predictors was finally tested with multivariate ordinal logistic regression in the whole population. The dependent variable to predict was motor impairment at 1 year categorized as severe (Fugl-Meyer<50), marked (50≤Fugl-Meyer≤84), and moderate-to-slight (Fugl-Meyer>84) according to previously published thresholds.[28] The independent variables introduced in the model were initial Fugl-Meyer, age, and stroke volume (model 1). The model was repeated with all the previous parameters plus the iFNr (model 2), and the overall discrimination of the 2 models was compared using an analysis of deviance table. To test whether prediction of the Fugl-Meyer impairment score would translate to prediction of motor disability, we finally conducted a binary logistic regression analysis including all previous parameters with the aim to predict the modified Rankin scale dichotomized at a threshold of 2 as outcome.

All statistical analyses were performed with the R software package (Version 3.0.1) and the GraphPad Prism version 6.0 software with a type I error set at α=0.05.

## Results

### Patient Characteristics

Out of the first 230 patients screened between June 2012 and February 2014, we analyzed 117 patients with a complete set of data at 1-year follow-up at the time of analysis (Figure 1). Main characteristics of patients are summarized in Table 1.

### Relationship Between iFNr and fFNr

The denoising procedure[25] provided improved image quality with 3 minutes of processing per sequence (Figure I in the
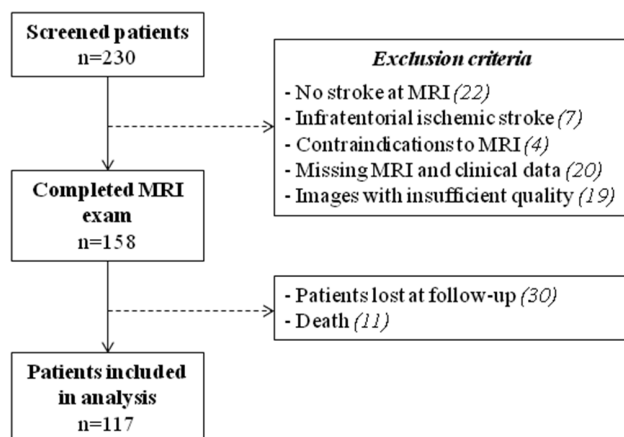


**Figure 1.** Flow chart. MRI indicates magnetic resonance imaging.

online-only Data Supplement) and allowed to quantify the fiber number with the same standardized procedure for each patient. The iFNr measured at 24 to 72 hours was strongly correlated to the fFNr measured at 1 year (r=0.70; P<0.0001). Therefore, these results suggest that iFNr could be an early surrogate marker of the integrity of the CST 1 year later.

### Prediction of Motor Recovery by Using Initial Clinical Severity

From the initial severity, we calculated the potential for motor recovery as the maximum Fugl-Meyer score (=100) minus the initial Fugl-Meyer.[4] In the whole population, the initial severity (and in turn the potential of recovery) was only moderately correlated with Fugl-Meyer recovery ($R^2$=0.35; P<0.001; n=117; Figure 2A). The residuals (difference between the observed recovery and the predicted recovery by using the linear regression model) showed substantial dispersion (heteroscedasticity) especially for the more severely affected patients with initial Fugl-Meyer<50 (and in turn a potential of recovery>50, Figure 2B). To formalize the finding of more variable recovery in severe patients, we repeated the regression by excluding these patients (n=26). The overall fit of this new model was strong ($R^2$=0.65, P<0.0001, n=91, Figure 2C), and the residuals were highly concentrated around 0 (Figure 2D). The estimated regression model without the severe patients (Figure 2C) showed that the remaining mild-to-moderate patients recovered ≈73% of their maximum potential. Therefore, the initial Fugl-Meyer provided a strong estimation of the motor recovery except for the subpopulation with high initial impairment, defined as initial Fugl-Meyer<50, who demonstrated high variance in motor recovery.

### Added Prognostic Value of iFNr Compared With Initial Fugl-Meyer

We investigated the value of the iFNr to predict motor recovery when initial Fugl-Meyer was less informative (initial Fugl-Meyer<50). There was no recurrent stroke on the 1 year magnetic resonance scan that might have contributed to the poor motor recovery of some of these patients. Interestingly, although initial Fugl-Meyer was not correlated with motor recovery for these severe patients ($R^2$=0.13; P=ns; Figure 3,

**Table 1.    Characteristics of the Population (n=117)**

| Sociodemographic factors | |
|---|---|
| Age, y | 67 (58–78) |
| Sex, % male | 67.5 |
| Hypertension, % | 53.8 |
| Diabetes mellitus, % | 12.8 |
| Clinical factors | |
| Initial NIHSS score | 4 (2–8) |
| Initial NIHSS motor subitems (5a, 5b, 6a, 6b) | 0 (0–3) |
| Initial Fugl-Meyer score | 88 (55–97.5) |
| Fugl-Meyer score at 1 y | 97 (88.5–99) |
| mRS score at 1 y | 1 (0–3) |
| Imaging factors | |
| Stroke side, % left-hemispheric stroke | 47.9 |
| Stroke volume, cm³ | 13.7 (2.4–38.3) |
| iFNr | 0.76 (0.37–1.03) |
| Absolute fiber numbers (ipsilesional/contralesional) | 102/134 |
| fFNr at 1 y | 0.92 (0.44–1.13) |
| Absolute fiber numbers (ipsilesional/contralesional) | 134/146 |

Values are median (Q1–Q3). iFNr and fFNr indicates initial and final fiber number ratios; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

red), the iFNr correlated strongly with motor recovery ($R^2$=0.56; $P$<0.0001; Figure 3, black). Some patients showed low initial Fugl-Meyer and low iFNr and did not recover (Figures 3 and 4A). On the other hand, patients with low initial Fugl-Meyer, but preservation of some fibers based on the iFNr, showed substantial recovery (Figures 3 and 4B). Such

clinical-to-DTI discrepancies are illustrated by the blue arrows in Figure 3. Using receiving operating characteristic analysis, we showed that severe patients with initial Fugl-Meyer <50 can recover by 70% or more of their initial motor impairment if iFNr>0.26 (sensitivity=100%; specificity=83.5%; negative predictive value=100%; positive predictive value=72.7%; area under the curve=0.93±0.05; $P$=0.006). Figure II in the online-only Data Supplement shows the recovery of these severe patients as a function of initial impairment and iFNr.

### Added Value of iFNr Compared With Other Predictors
In multivariate ordinal analysis conducted on the whole population, initial Fugl-Meyer was the strongest predictor of motor outcome (model 1), higher initial Fugl-Meyer being associated with better recovery (β=0.083; 95% confidence interval=0.059–0.115; $P$≤0.001; Table 2). When iFNr was added in the analysis (model 2), the predictive strength toward motor outcome (β=2.601; 95% confidence interval=0.304–5.110; $P$=0.031; Table 2) was significantly increased compared with model 1 ($P$=0.026). These results on the overall population probably reflect the contribution of the more severe patients highlighted before. Such prediction of impairment also translated in improving the prediction of disability according to the modified Rankin Scale (Table I in the online-only Data Supplement).

### Discussion
The iFNr measured by DTI between 24 and 72 hours after the insult provides an early surrogate of chronic CST fiber degeneration measured by the fFNr at 1 year follow-up. This biomarker provides significant independent added value toward predicting long-term motor impairment as measured with Fugl-Meyer compared with detailed clinical testing at
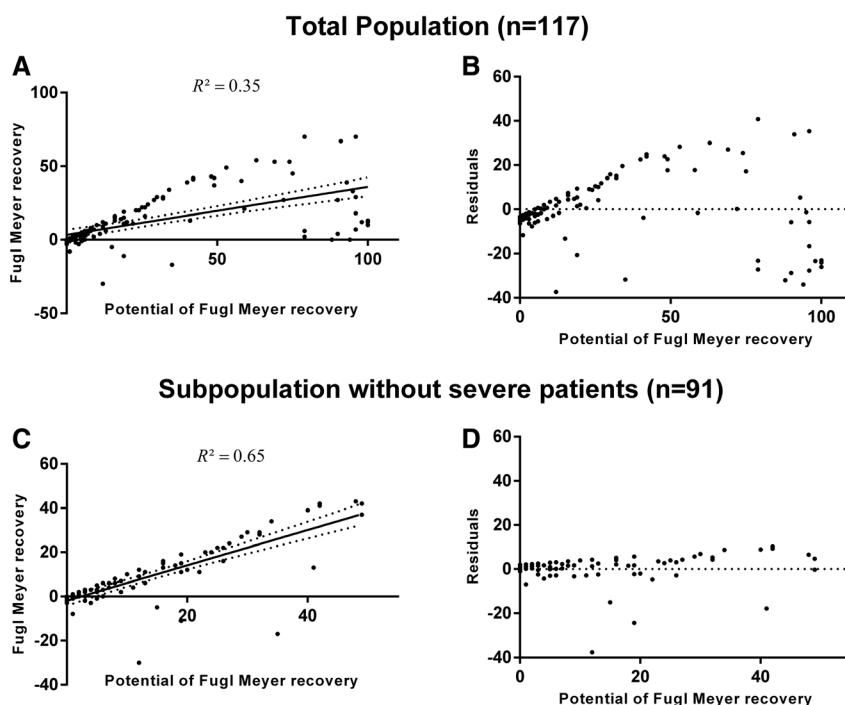
## Total Population (n=117)



## Subpopulation without severe patients (n=91)



**Figure 2.** Relationship between motor recovery and initial clinical severity. Fugl-Meyer recovery at 1 year versus potential of Fugl-Meyer recovery (=100–initial Fugl-Meyer) and representation of the residuals (difference between observed recovery and recovery predicted by the model). **A** and **B** are plotted with all the patients. **C** and **D** are plotted after exclusion of severe patients whose initial Fugl-Meyer was <50. Regression lines and 95% confidence intervals are showed in **A** and **C**.

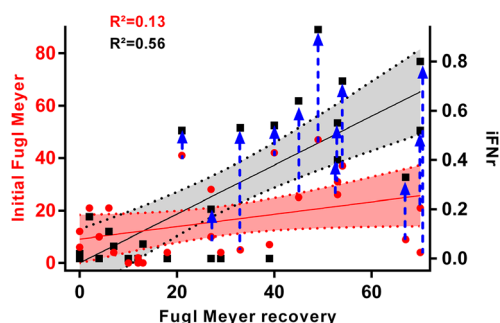## Subpopulation of severe patients (n=26)



**Figure 3.** Relationship between motor recovery, iFNr, and initial severity. Fugl-Meyer recovery at 1 year versus initial Fugl-Meyer (red) and iFNr (black) in the subset of severe patients. Regression lines and 95% confidence intervals are showed. The patients with severe initial clinical scores but preserved iFNr are illustrated with the blue arrows and showed substantial motor recovery at 1 year. iFNr indicates initial fiber number ratios.

baseline, age, and stroke volume. This is especially relevant for the subpopulation of more severely affected patients who demonstrated highly variable motor recovery.

A decrease in FNr is supposed to reflect Wallerian degeneration of the CST, but an accurate physiopathological interpretation early after stroke is difficult. Indeed, Wallerian degeneration takes time to manifest and one might argue that fiber degeneration is not yet present at 24 to 72 hours after stroke onset. T2 hyperintensity along the affected tract is indeed only seen weeks to months after stroke,[29] and reduced FA along the CST distal to the stroke area has been shown to be significant at day 30 but not yet at day 3.[17] There are 2 alternatives to explain our measurement of reduced DTI fiber measurements at such an early time point. The first is that reduced iFNr reflects the beginning signs of actual histological fiber degradation that could be more or less acute depending on stroke severity.[30] In line with this interpretation,

**Table 2. Ordinal Logistic Regression Analysis: Predictors of Good Motor Outcome (n=117)**

| Predictors | β (95% CI) | Z | P Value |
|---|---|---|---|
| Model 1 | | | |
| Initial Fugl-Meyer score | 0.083 (0.059–0.115) | 5.947 | <0.001* |
| Age | −0.024 (−0.075–0.023) | −0.982 | 0.326 |
| Stroke volume | −0.004 (−0.017–0.007) | −0.687 | 0.492 |
| Model 2 | | | |
| Initial Fugl-Meyer score | 0.074 (0.048–0.107) | 5.035 | <0.001* |
| Age | −0.010 (−0.061–0.038) | −0.406 | 0.685 |
| Stroke volume | −0.002 (−0.015–0.011) | −0.246 | 0.806 |
| iFNr | 2.601 (0.304–5.110) | 2.157 | 0.031* |

Model 2 showed statistically better performances than model 1 (*P*=0.026). β indicates regression coefficient; CI, confidence interval; and iFNr, initial fiber number ratio.

*Significant *P* value <0.05.

histological signs of Wallerian degeneration were already detectable in the brain stem 2 days after experimental stroke in rats.[31] In humans, a significant reduction of apparent diffusion coefficient in cerebral peduncles downstream of strokes with severe prognosis was reported on MRI performed 12 hours after insult,[18] and early signs of Wallerian degeneration were also observed with DTI.[12,19] Alternatively, although destruction of fiber structure is not yet evident histologically, the reduction of FA within a stroke located along the CST might influence the computation of tracking and force streamlines to interrupt. FA values within ischemic strokes progressively diminish, especially after 24 hours (mean delay in our population=58 hours) although they might be elevated hyperacutely (<6 hours).[24,32] The severity of cytotoxic edema, and the associated reduction in FA, might represent ischemic damage and determine whether fibers are tracked or not through a stroke along the CST (Figure 4), and ultimately whether fibers will degenerate or not, as well as a patient's potential for motor function recovery. Further work is needed to shed more light on the specific histological correlates of iFNr, which, nevertheless, seems to be clearly related to the degree of chronic CST damage.

Recently Feng et al[16] used a metric called weighted-CST lesion load to provide an early quantification of CST integrity similar to our iFNr. The weighted-CST lesion load consists in quantifying stroke voxels that overlap a canonical CST derived from healthy controls.[16,33] Although this approach is interesting, it requires projecting the patient's diffusion weighted images into the space of the canonical CST, thereby facing the challenge of spatial normalization of lesioned brains. In contrast, the iFNr could be calculated in clinical routine with minimal postprocessing from a DTI that can be acquired within an acceptable scan time; denoising procedure[25] being available to rapidly recover signal-to-noise ratio if needed. Furthermore, overlap between stroke and the canonical CST with weighted-CST lesion load might not invariably be consistent with fiber degeneration depending on the severity of ischemia-related histological changes, which can range from edema without irreversible destruction to full necrosis. iFNr might provide more specific information relative to fiber degeneration. Comparative work is required to address this question. The iFNr has nevertheless its own limitations. Contralateral alterations can confound the ratio in some patients with preexisting damage, but we chose it to reduce interindividual and interscan variability. Vasogenic edema that peaks within the first week[34] can also alter CST tracking in large strokes inducing mass effect and reduced anisotropy on a CST that is nonetheless intact, and that will remain intact at follow-up. As edema is reabsorbed, the number of fibers identified tractographically will be found to increase, as the tissue recovers part of its anisotropic architecture. These confounding factors might contribute to the imperfect relation between true fFNr at 1 year and iFNr during the subacute phase (fFNr being higher than iFNr). However, we consider this ratio as a realistic parameter of Wallerian degeneration as assessed by its capability to predict motor recovery. Functional quantification of CST integrity by measurement of MEPs has also shown to improve predictive models of motor function recovery based
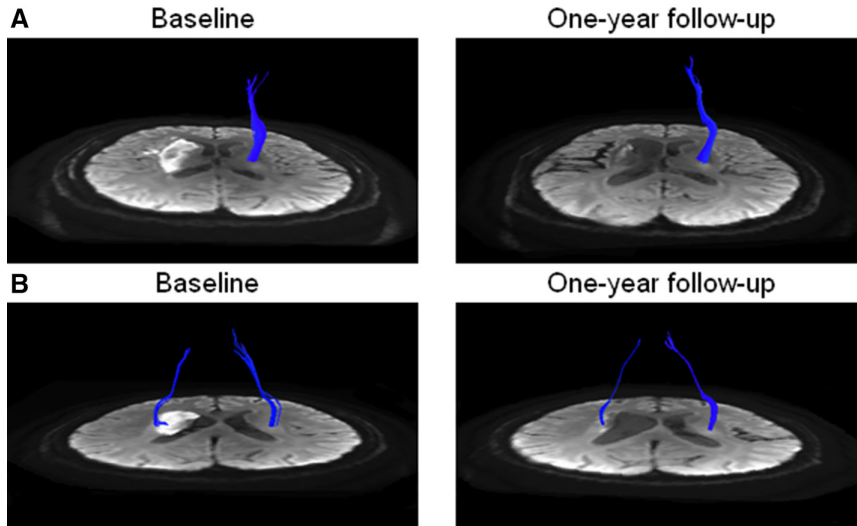
**Figure 4.** Illustrative examples of iFNr and fFNr. CST tractography overlaid on denoised diffusion-weighted images in 2 patients with initial severe impairment but different recovery, which was predicted by the iFNr. **A**, 69-year-old man with a 25 cm³ right-hemispheric stroke. Initial Fugl-Meyer score=12. The iFNr was 0.04 (number of fibers right/left=5/119), and the fFNr was 0 (0/125). No clinical recovery was measured: Fugl-Meyer at 1 year=12. **B**, 84-year-old man with a 21 cm³ right-hemispheric stroke. Initial Fugl-Meyer=26. The iFNr was 0.4 (number of fibers right/left=81/204) and fFNr was 0.52 (108/207) at 1 year. The patient recovered 53 points: Fugl-Meyer at 1 year=79. CST indicates corticospinal tract; fFNr, finial fiber number ratio; and iFNr, initial fiber number ratio.

on clinical measures,[10] but DTI still adds predictive value when MEPs are absent.

Recent strategies to assess motor recovery recommend sequential identification of subsets of patients by combining predictors in a stepwise manner rather than considering them in isolation.[10,16,35,36] In line with these strategies[10,16,35,36] and in accordance with previous studies,[4,5] we found that most stroke patients exhibit a proportional motor recovery of ≈70% of their initial impairment. This means that starting with bedside measures can already provide a strong indication of motor recovery. DTI could be reserved to resolve uncertainty for the subset of patients with more severe initial clinical impairment. Within these severe patients, there were 2 distinct clusters: (1) patients with concordant low iFNr and low clinical score who did not recover and (2) patients with preserved iFNr despite low clinical score who recovered substantially. Residual integrity of ≈30% of the motor fibers (iFNr≈0.26) was associated with motor recovery of 70% or more of the initial impairment despite the initial severity with a positive predictive value of 72.7%. There were still intermediate patients, whose recoveries were difficult to predict accurately (slight recovery despite low fiber ratio and low clinical scores). This might be because of the contribution of alternate motor fiber pathways, such as corticorubrospinal and corticoreticulospinal tracts,[14] or to brain reorganization[37] and compensation.[38] Alternate strategies to capture the residual ability to recover over that provided by the proportional recovery rule include task-related brain activation using functional MRI[39,40]; MEPs from transcranial magnetic stimulation[10]; or a combination of methods such as clinical evaluation, transcranial magnetic stimulation, and DTI.[10,35,36] These strategies might be helpful to further refine prognostic modeling in combination with the iFNr especially in patients with severe initial deficit.

Our study is not without limitations. Although the initial sample size was relatively substantial, only 117 patients had a complete set of data and an even smaller number presented with severe stroke. Further confirmation by including a more significant proportion of severe patients will be needed. We used clinically available DTI acquisition and deterministic tractography. More advanced image acquisition and analysis models might be helpful, eg, to track fibers at the crossing of the CST with the superior longitudinal fasciculus.[41] The reproducibility of the measures was not formally assessed, but the ROI positioning is straightforward with minimal training. Finally, the iFNr might experience a ceiling effect in the sense that it does not correlate linearly with the final outcome in patients with a benign disease course, which can anyway be predicted based on a good initial score.

These limitations notwithstanding, we identified a strategy applicable in clinical routine, before patient discharge from the hospital, which seems to significantly improve prediction of upper/lower limb motor impairment after stroke for patients with initially severe paresis. This strategy has the potential to significantly improve stroke patient management by aiding in determining goals, type, and duration of rehabilitation. Furthermore, applying the proposed iFNr to stratify patients at inclusion in neuroprotective or neuroregenerative treatment trials might help increase statistical power and accelerate discovery and validation of efficacy of novel approaches to stroke treatment.

## Sources of Funding

## Disclosures

None.

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## Early Fiber Number Ratio Is a Surrogate of Corticospinal Tract Integrity and Predicts Motor Recovery After Stroke

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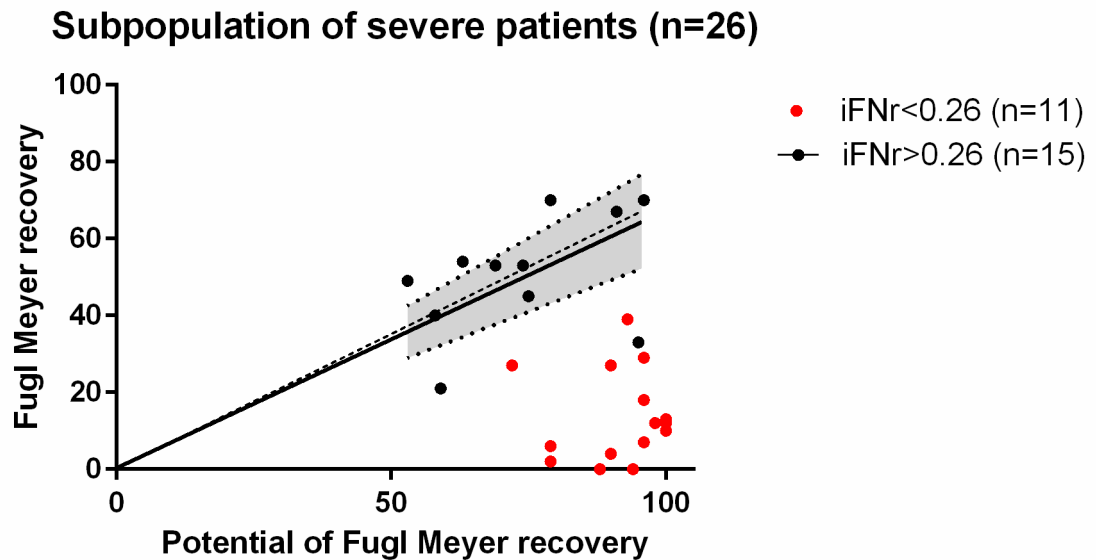
# SUPPLEMENTAL MATERIAL

## Supplemental Figure I: Preprocessing and ROIs position



**A** shows the improvement of signal-to-noise ratio (SNR) and the higher number of fibers tracked when raw FA data (left) are denoised (right). **B** shows the regions of interest at the level of the cerebral peduncles and at the level of the primary motor cortex.

**Supplemental Figure II: Relationship between motor recovery and initial clinical severity as a function of iFNr for the subgroup of patients severely impaired at baseline.**



Fugl-Meyer recovery at 1 year versus potential of Fugl-Meyer recovery (=100 minus initial Fugl-Meyer) for the 26 severe patients with initial Fugl-Meyer<50. The patients with iFNr<0.26 are shown in red and those with iFNr>0.26 are shown in black. The dashed line indicates the 70% rule prediction. The linear regression and the 95% confidence interval (CI) are shown for the patients with iFNr>0.26 for the special case of the model where y-intercept=0. The β of this model was 0.67 (95%CI, 0.5468 to 0.8024; p<0.0001) indicating that the severe patients can also recover about 70% of their initial impairment (β=0.67) if residual fibers are depicted (iFNr>0.26). There were 3 patients who recovered less than expected by falling below the 70% rule line (and only 2 who fell outside the 95%CI of the β value) contributing to the imperfect specificity and positive predictive value.

**Supplemental Table I. Binary Logistic Regression Analysis: Predictors of good functional outcome (mRS ≤2) (n=117)**

|  | Predictors | β | 95% CI | p-value |
|---|---|---|---|---|
| **Model 1** | Initial Fugl-Meyer score | -0.0771 | [-0.1124; -0.0512] | **< 0.001** |
|  | Age | 0.0837 | [0.0264; 0.1544] | **0.01** |
|  | Stroke volume | 0.0046 | [-0.0126; 0.0209] | 0.59 |
| **Model 2** | Initial Fugl-Meyer score | -0.0611 | [-0.0962; -0.0343] | **<0.001** |
|  | Age | 0.0716 | [0.0127; 0.1446] | **0.03** |
|  | Stroke volume | 0.0004 | [-0.0188; 0.0202] | 0.97 |
|  | iFNr | -3.0957 | [-5.8627; -0.7208] | **0.02** |

β =regression coefficient. CI, confidence interval; iFNr, initial fiber number ratio.
Model 2 showed statistically better performances than model 1 (p=0.01).