Original Article

Utility of Transcranial Magnetic Stimulation and Diffusion Tensor Imaging for Prediction of Upper-Limb Motor Recovery in Acute Ischemic Stroke Patients

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Abstract

Background: The recovery of the upper-limb (UL) motor function after ischemic stroke (IS) remains a major scientific, clinical, and patient concern and it is hard to predict alone from the clinical symptoms. **Objective:** To determine the accuracy of the prediction of the recovery of UL motor function in patients with acute ischemic middle cerebral artery (MCA) stroke using individual clinical, transcranial magnetic stimulation (TMS) or diffusion tensor imaging (DTI) parameters or their combination. **Methods and Material:** The first-ever acute ischemic MCA stroke patients within 7 days of the stroke onset who had an obvious UL motor deficit underwent TMS for the presence of motor-evoked potential (MEP) and DTI to evaluate the integrity of corticospinal tracts. Multivariate logistic regression analysis was done to test for the accuracy of the prediction of the recovery of UL motor function. **Results:** Twenty-nine acute ischemic MCA stroke patients (21 males and 8 females) with a mean age of 51.45 ± 14.26 years were recruited. Model-I included clinical scales (Fugl-Meyer Assessment [FMA] + Motricity Index [MI]) + TMS (MEP) + DTI (fractional anisotropy [FA]) were found to be the most accurate predictive model, with the overall predictive ability (93.3%; 95% confidence interval [CI]: 0.87–0.99) and sensitivity: 94.9% (95% CI: 0.87–1.0) and specificity: 95.8% (95% CI: 0.89–1.0); respectively. **Conclusion:** The accuracy of UL motor recovery can be predicted through the clinical battery and their elements as well as TMS (MEP) and DTI (FA) parameters. Further, well-designed prospective studies are needed to confirm our findings.

Keywords: Acute stroke, diffusion tensor imaging, motor-evoked potential, motor function, transcranial magnetic stimulation, upper-limb recovery

Introduction

The prediction of the upper-limb (UL) motor recovery in post-stroke patients with UL weakness is extremely vital when making an overall treatment plan. UL motor recovery following an ischemic stroke (IS) is highly variable and hard to predict only through the clinical symptoms. The clinical scales including the Fugl-Meyer Assessment (FMA), Action Research Arm Test (ARAT), and Motricity Index (MI); the neuroimaging tools such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and neurophysiological techniques like transcranial magnetic stimulation (TMS) parameters have been reported to be used to measure the extent of the damage to the motor system and predict the subsequent UL recovery of the function after the IS onset, but these techniques are not yet used routinely due to lack of enough evidence.[1-9]

TMS and diffusion tensor tractography (DTT) were performed in the early stage (7–28 days) of a stroke by Kwon *et al.* (2011)[10] in 53 patients with complete motor weakness of the affected hand. TMS showed higher positive predictability and DTT showed higher negative predictability. Kwon *et al.* (2011)[10] concluded that a combined study of TMS and DTT appeared to be more advantageous in the prediction of negative motor outcomes than did every single study. Single TMS appeared to be more advantageous in the prediction of positive motor outcomes. In another published study of forty-three patients with first MCA stroke using TMS and DTT by Kim *et al.* (2016)[11] showed a better motor recovery and ambulatory function than the other groups at the 4-week follow-up in the patients with the presence of both measurable MEPs and a preserved corticospinal tracts (CST). To date, all the published studies had measured the baseline parameters beyond 2 weeks or more of the stroke onset and have not utilized these parameters in a combination. A limited number of studies had measured UL recovery only through the clinical scales including finger extension and shoulder abduction

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in the acute phase (within 1 week) of IS but TMS and DTI have not been performed within the acute phase of stroke onset.[4,7]

Therefore, there is an extreme need for investigating these measures either alone or in combinations for predicting the UL motor recovery during the acute phase of IS onset. The present study was performed to ascertain the accuracy of the prediction of the UL motor recovery in the acute ischemic middle cerebral artery (MCA) stroke using individual clinical, DTI, or TMS parameters or their combinations.

Methods

This was a prospective cohort study in which the patients with the first-ever MCA IS within the acute phase (7 days of stroke onset) were recruited after their proper informed consent. The ethical clearance was obtained by the local Institutional Ethical Committee. The inclusion criteria were: (1) the first-ever acute ischemic MCA stroke, (2) hemiplegic motor weakness, and (3) no serious medical complications such as pneumonia. The exclusion criteria were: (1) a previous history of stroke, (2) patients with any implanted metal (e.g. artificial pacemaker), (3) refusal to DTI or TMS.

All the assessors were blinded to the clinical assessment, MEP, and DTI observations during the entire study. The follow-up assessment for the stroke recovery was done by a blinded third investigator at the third month post-stroke. TMS (MEP) were recorded from both the abductor pollicis brevis (APB) and biceps brachii muscle (BB) muscles in a relaxed state, and both hemispheres were examined. The diffusion tensor calculation and tractography were performed by using the DTIStudio Software version 3.03 (*www.mristudio.org*). Three regions of interest were drawn on a two-dimensional FA color map: medulla, middle anterior pons, and posterior limb of the internal capsule (PLIC). The demographic and comorbidities details such as age, sex, hypertension, diabetes mellitus, dyslipidemia, and cardiac disease were captured from the medical records. The recovery outcome was based on the ARAT scale; good recovery was to be considered as ARAT >10 and poor recovery ARAT ≤9. The study methods and protocols are reported in the Supplementary Appendix-1.

Sample size calculation

It was estimated that out of the 200 stroke patients, approximately 80 patients (40%) meeting the eligibility criteria would recover in 3 months. One variable per 10 patients as a prediction in the logistic regression model was considered for the sample size calculation.

Statistical analysis

Descriptive statistics were examined using a mean/median, range depending on the distribution of the data. Bivariate analysis was conducted using the Chi-square test for categorical data and *t*-test for continuous data. Multivariable analysis was done using logistic regression with recovery (Yes = Recovery; ARAT >10; No = Recovery; ARAT ≤9 as dependent variable[12] and (1) sex, (2) hemisphere affected, (3) mean diffusivity (MD), (4) fractional anisotropy (FA), (5) the presence or absence of motor cortex damage MEPs in the affected target muscle, (6) the days between the stroke and first assessment, (7) consciousness after stroke onset (National Institute of Health Stroke Scale [NIHSS], –42 points), (8) Barthel Index [BI], 0–100 points), (9) MI-Arm score and (11) FMA-Arm score as independent variables. The prognostic test properties were expressed as sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV). The P value < 0.05 was considered to be statistically significant. All the statistical analysis was performed using the STATA 13.0 software.

Results

Twenty-nine acute ischemic MCA stroke patients (21 males and 8 females with a mean age of 51.45 ± 14.26 years) were recruited after the screening of 386 stroke patients. Figure 1 represents the study flow diagram for the inclusion, exclusion, investigations, and follow-up details conducted in the study. The clinical assessment and TMS were done in 29 patients but only 24 patients had data on DTI. We had complete data (clinical assessment and TMS) for 24 acute MCA IS patients at baseline and 3 months of follow-up. The mean duration of the stroke onset was 5.24 ± 1.39 days. The time interval between the DTI and TMS assessments in each patient was between 03 and 36 h. All the investigations were performed within 7 days of the stroke onset with a deviation of ± 02 days.

Table 1 shows the patients' demographics and clinical data. Seventeen (58.6%) patients had an infarction in the left while the remaining 12 (41.4%) had an infarction in the right hemisphere. Five patients died within 3 months after the stroke because of a recurrent stroke or other comorbidities. The data were tested for normal distribution and accordingly non-parametric Mann–Whitney U test for continuous variables as well as the Chi-square test were applied for categorical variables and were finally used for the baseline and clinical characteristics analysis. Based on the logistic regression analysis, 6 out of 11 variables were significantly associated

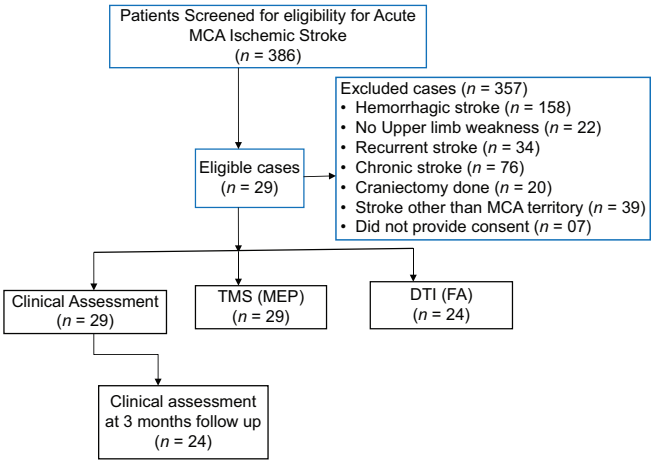

Figure 1: Flow chart for inclusion in the study.

Table 1: Baseline clinical characteristics of acute ischemic MCA stroke

Clinical Characteristics	Acute Ischemic MCA Stroke (*N*=29)
Sex (Male/Female); *n*	21/08
Age (Years); Mean±SD	51.45±14.26
Systolic BP; Mean±SD	139.8±73.2
Diastolic BP; Mean±SD	87.5±34.9
Risk Factors	
Diabetes mellitus; *n* (%)	4 (13.7)
Hypertension; *n* (%)	7 (24.1)
Dyslipidemia; *n* (%)	2 (7)
Smoking; *n* (%)	6 (20.6)
Alcohol intake; *n* (%)	4 (13.7)
Hemisphere of stroke (Left/Right); *n*	17/12
Subcortical/Cortical/Cortical+Subcortical stroke; *n*	18/7/4
Stroke onset (Days); Mean±SD	5.24±1.39
Length of hospital stay (Days); Mean±SD	14.62±8.25
Clinical assessment (Days) from onset of stroke [*n*=29]	5.67±2.67
TMS sssessment (Days) from onset of stroke [*n*=29]	6.59±2.12
DTI assessment (Days) [*n*=24] from onset of stroke	4.32±3.4
NIHSS Score (0-42); median (range) at admission	11.5 (7.3-20)
BI Score (0-100) at admission; Mean±SD	50.20±25.02
MI-Arm (0-100) at admission; Mean±SD	58.5±21.9
FMA-Arm (0-52) at admission; Mean±SD	29.5±17.3
ARAT total score (0-57) at admission; Mean±SD	32.5±11.6
mRS at discharge; Mean±SD	3.58±1.13

Table 2: UL motor recovery between baseline and 3 months based on the ARAT scale

Group	Total	ARAT ≥10	ARAT ≤9
DTI (*n*=24)	Number	Good UL recovery	Poor UL recovery
DTT (+)	18	10	08
DTT (−)	06	04	02
	Value	**95% CI**	
Sensitivity	71.43%	41.90-91.61%	
Specificity	20.00%	2.52-55.61%	
Positive likelihood ratio	0.89	0.57-1.41	
Negative likelihood ratio	1.43	0.32-6.34	
Positive predictive value	55.56%	44.26-66.30%	
Negative predictive value	33.33%	10.12-68.95%	
Accuracy	50.00%	29.12-70.88%	
TMS (*n*=29)			
MEP (+)	17	12	05
MEP (−)	12	03	09
	Value	**95% CI**	
Sensitivity	80%	51.9-96%	
Specificity	64.3%	35.1-87.2%	
Positive likelihood ratio	2.24	1.10-4.82	
Negative likelihood ratio	0.31	0.11-0.92	
Positive predictive value	70.59%	53.2-83.5%	
Negative predictive value	75.00%	50.3-89.8%	
Accuracy	72.41%	52.8-87.2%	

to the chance of the return of the dexterity on the ARAT scale acquired 3 months after the stroke. The highest odds ratio (OR) for the total scores of FMA (Arm), TMS (MEP) present, and DTI (FA) parameters was observed. The specificity and sensitivity of the TMS (MEP) (82.3 and 64.2%) were higher than that of DTI (FA) (71.4 and 20.0%) [Table 2].

The findings from the multivariate logistic regression for UL motor outcome at 3 months post-stroke suggest that the MI (Arm) score, FMA (Arm) score, the duration between the stroke onset and first assessment, TMS (MEP) presence, DTI (FA) parameters are strong predictors for UL recovery after acute stroke [Table 3]. For developing models, we included 24 acute ischemic MCA stroke patients in our final analysis as the data for all the three components (clinical, TMS, DTI) during the first week of the stroke onset and the survived patients during 3 months of follow-up was available for 24 patients. Five predictive models were made including the following variables. Model-I includes clinical scales [FMA-Arm score + MI-Arm score] + TMS (MEP) + DTI (FA); Model-II: Clinical scales [FMA-Arm score + MI-Arm score] + TMS (MEP); Model-III: Clinical scales [FMA-Arm score + MI-Arm score]+ DTI (FA); Model-IV: TMS (MEP) + DTI (FA); and Model-V: Clinical scales [FMA-Arm score + MI-Arm score]. Among the five models, Model-I including clinical scales (FMA + MI) + TMS (MEP) + DTI (FA) was found to be the most accurate predictive model, with an overall predictive ability of 93.3% (95% confidence interval [95% CI] 0.87–0.99) and sensitivity 94.9% (95% CI 0.87–1.0) and specificity 95.8% (95% CI 0.89–1.0), respectively [Table 4].

Discussion

In the present study, we examined the prognostic value of clinical scales, TMS, and DTI for UL motor outcome at the acute phase within 7 days of the IS onset. Our results specify that the patients who showed MEP response in TMS and had a preserved CST integrity in DTT had a better chance of UL motor recovery than those patients without these characteristics. The FA values of the DTI parameter indicate CST integrity of white matter lesions and the decreased FA

values indicate interrupted integrity of the neural tract and correlate with the motor deficits. On comparing these two predictive tools, TMS reveals a higher PPV than DTI and DTI has a higher NPV than TMS. In contrast, the presence or absence of MEPs, as well as the disruption of the CST tract detected at an early stage of the stroke onset, can predict the motor outcome by their unique characteristics.

The previously published studies had confirmed the correlation of the neuromotor outcome with the conventional neuroimaging variables such as the extent of infarction, infarct size, and volume.[14-17] The individual utility of DTI or TMS has been reported by numerous studies;[13-27] however, only two studies to date have been performed to investigate the combined utility of TMS and DTI for the prediction of motor outcome during the acute phase of intracerebral hemorrhage and corona radiata infarct.[10,20] More recent studies have investigated the correlation between a decrease in the FA value measured through DTI and the motor function in the patients with subacute or chronic stages of IS.[28-30] Two recent meta-analyses conducted by Kumar P *et al*.[31,32] reported that DTI-based FA is a strong predictor of UL motor recovery after subacute ischemic as well as hemorrhagic stroke.

Presently, we investigated the clinical, TMS, and DTI measured for the accuracy of prediction in the acute phase (within 7 days of the stroke onset). Although we screened 386 stroke patients, only 29 acute ischemic MCA stroke patients were recruited due to our stringent inclusion criteria of evaluation. The reason behind the exclusion of the screened cases include (a) most of the patients were unstable as they had both upper and lower limb weaknesses, (b) hemicraniectomy done in some of the MCA stroke patients, (c) the patients mostly reached All India Institute of Medical Sciences (AIIMS), New Delhi as a referral center and that time they were at a subacute and chronic phase of the stroke, (d) denied providing consent, (e) stroke other than MCA territory, and (f) hemorrhagic stroke. The enrolment of a small number of subjects, lack of bounded time of investigations, and resources deficit in terms of funding were found to be the major limitations of the study.

Up to 80% of the stroke survivors have UL impairment early after the stroke, and a few demonstrate complete functional recovery at 6 months post-stroke.[33-36] The UL rehabilitation trials designed to improve the recovery rates have been largely unsuccessful. As a result, the burden of the UL impairment after a stroke remains high.[37] Therefore, understanding how to improve the potential for the recovery of the UL function remains a major scientific, clinical, and patient priority. There is a growing interest in using biomarkers to predict motor recovery and outcomes after a stroke. The Predict REcovery Potential (PREP2) algorithm proposed by Connell *et al*. (2021), Smith *et al*. 2019, and Stinear *et al*. (2017)[38-40] combines the clinical assessment with biomarkers in an algorithm, to predict the UL functional outcomes for individual patients. Active and theoretically underpinned implementation strategies are needed to ensure that the biomarkers are successfully used in clinical practice for predicting motor outcomes after a stroke, and should be considered in parallel with biomarker development. The past work has suggested that the brain biomarkers may help advance our understanding of the recovery phenotypes.[41] Routine clinical scans (often CT, a few MRIs) describe the lesion location as defined by a neurologist: cortical, subcortical, mixed). Unfortunately, this approach to analyze routine scans is not helpful to identify the meaningful UL recovery in stroke

Table 3: Multivariate logistic regression for upper-limb motor outcome at 3 months post-stroke

Predictors	Odds Ratio (OR)	95% CI	*P*
Demographics (*n* = 29)			
Sex (M/F)	0.59	0.34-1.02	0.060
Hemisphere affected (L/R)	0.87	0.38-2.01	0.75
Days between stroke onset and first assessment	0.94	0.89-0.98	0.009
Clinical Scales [*n* = 29]			
NIHSS	1.96	1.16-3.31	0.012
MI-Arm score	24.80	7.96-77.30	<0.001
BI at admission	1.39	1.18-1.64	<0.001
FMA-Arm score	22.71	7.63-67.63	<0.001
TMS [*n* = 29]			
MEP present	28.33	9.18-87.46	<0.001
DTI [*n* = 24]			
FA	7.00	2.70-18.72	<0.001
MD	0.71	0.42-1.19	0.191

Table 4: Predictive properties of the models for predicting upper-limb motor outcome at 3 months post-stroke (*n*=24)

Recovery=No; ARAT (Arm) ≤ 9, Yes; ARAT (Arm) ≥ 10					
	Model-I (95% CI)	Model-II (95% CI)	Model-III (95% CI)	Model-IV (95% CI)	Model-V (95% CI)
Sensitivity %	94.9 (0.87-1.0)	89.3 (0.81- 0.94)	63.1 (0.43-0.69)	64.7 (0.37-0.76)	74.9 (0.56-0.81)
Specificity %	95.8 (0.89 -1.0)	86.4 (0.76-0.95)	54.3 (0.41-0.58)	59.3 (0.39-0.85)	73.4 (0.67-0.85)
PPV%	92.7 (0.76-0.96)	85.2 (0.63-0.83)	55.2 (0.44-0.67)	65.2 (0.43-0.72)	69.1 (0.52-0.78)
NPV %	93.3 (0.87-0.99)	82.7 (0.54-0.88)	54.1 (0.59-0.72)	62.7 (0.54-0.89)	74.3 (0.77-0.91)
Overall %	94.4 (0.76-0.95)	83.7 (0.65-0.90)	51.5 (0.45-0.67)	53.7 (0.65-0.70)	68.7 (0.64-0.83)

Model-I: Clinical scales [FMA-Arm score+MI-Arm score] + TMS (MEP) + DTI (FA); Model-II: Clinical scales [FMA-Arm score+MI-Arm score] + TMS (MEP); Model-III: Clinical scales [FMA-Arm score+MI-Arm score] + DTI (FA) Model-IV: TMS (MEP) + DTI (FA); Model-V: Clinical scales [FMA-Arm score+MI-Arm score]

patients. Therefore, there is a need for longitudinal studies that include measures that are potentially more sensitive to change than clinical measures and the lesion location which may include biomarkers such as the impact of the stroke on the primary motor pathways (corticospinal tract) using TMS to index MEP status (present or absent),[41] as well as more nuanced interpretations of the lesion location (e.g. internal capsule impacted yes/no)[42] that account for the primary motor pathway impact. There is an ongoing study focused on people with severe paresis that is focused on identifying the brain biomarkers of recovery.[43] Together, the advancements in the biomarkers may improve the prediction of recovery, patient selection, and individualized intervention.

Further research regarding the re-perfusion, MRI signal changes, imaging of Wallerian degeneration in the descending cortico-spinal tracts, may be other imaging methods which may be implemented in further research. To recruit a large number of subjects, a long duration of studies with extensive follow-up is required in order to reach a definite conclusive finding. Future prospective cohort studies are recommended to put a spotlight on the perceptive mechanisms that can define the decisive time frame of motor recovery after a stroke.

Conclusion

The accuracy of UL motor recovery can be predicted through a clinical battery and their elements as well as TMS (MEP) and DTI (FA) parameters. Further, well-designed prospective studies are needed to confirm our findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chen S-Y, Winstein CJ. A systematic review of voluntary arm recovery in hemiparetic stroke: Critical predictors for meaningful outcomes using the international classification of functioning, disability, and health. J Neurol Phys Ther 2009;33:2-13.
2. Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: A longitudinal prospective study. Restor Neurol Neurosci 2007;25:453-60.
3. Beebe JA, Lang CE. Active range of motion predicts upper extremity function 3 months after stroke. Stroke 2009;40:1772-9.
4. Smania N, Paolucci S, Tinazzi M, Borghero A, Manganotti P, Fiaschi A, *et al*. Active finger extension: A simple movement predicting recovery of arm function in patients with acute stroke. Stroke 2007;38:1088-90.
5. Wandel A, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Prediction of walking function in stroke patients with initial lower extremity paralysis: The Copenhagen stroke study. Arch Phys Med Rehabil 2000;81:736-8.
6. Patel AT, Duncan PW, Lai SM, Studenski S. The relation between impairments and functional outcomes post-stroke. Arch Phys Med Rehabil 2000;81:1357-63.
7. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, EPOS Investigators. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: Early prediction of functional outcome after stroke: The EPOS cohort study. Stroke 2010;41:745-50.
8. DeVetten G, Coutts SB, Hill MD, Goyal M, Eesa M, O'Brien B, *et al*. Acute corticospinal tract Wallerian degeneration is associated with stroke outcome. Stroke 2010;41:751-6.
9. Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW. Early imaging correlates of subsequent motor recovery after stroke. Ann Neurol 2009;65:596-602.
10. Kwon YH, Son SM, Lee J, Bai DS, Jang SH. Combined study of transcranial magnetic stimulation and diffusion tensor tractography for prediction of motor outcome in patients with corona radiata infarct. J Rehabil Med 2011;43:430-4.
11. Kim BR, Moon WJ, Kim H, Jung E, Lee J. Transcranial magnetic stimulation and diffusion tensor tractography for evaluating ambulation after stroke. J Stroke 2016;18:220-6.
12. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Early Prediction of Functional Outcome After Stroke Investigators. Accuracy of physical therapists' early predictions of upper-limb function in hospital stroke units: The EPOS study. Phys Ther 2013;93:460-9.
13. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain 2007;130:170-80.
14. Cho SH, Kim DG, Kim DS, Kim YH, Lee CH, Jang SH. Motor outcome according to the integrity of the corticospinal tract determined by diffusion tensor tractography in the early stage of corona radiata infarct. Neurosci Lett 2007;426:123-7.
15. Cho SH, Kim SH, Choi BY, Cho SH, Kang JH, Lee CH, *et al*. Motor outcome according to diffusion tensor tractography findings in the early stage of intracerebral hemorrhage. Neurosci Lett 2007;421:142-6.
16. Escudero JV, Sancho J, Bautista D, Escudero M, López-Trigo J. Prognostic value of motor-evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. Stroke 1998;29:1854-9.
17. Gillard JH, Papadakis NG, Martin K, Price CJ, Warburton EA, Antoun NM, *et al*. MR diffusion tensor imaging of white matter tract disruption in stroke at 3 T. Br J Radiol 2001;74:642-7.
18. Heald A, Bates D, Cartlidge NE, French JM, Miller S. Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. Brain 1993;116:1371-85.
19. Hendricks HT, Hageman G, van Limbeek J. Prediction of recovery from upper extremity paralysis after stroke by measuring evoked potentials. Scand J Rehabil Med 1977;29:155-9.
20. Jang SH, Ahn SH, Sakong J, Byun WM, Choi BY, Chang CH, *et al*. Comparison of TMS and DTT for predicting motor outcome in intracerebral hemorrhage. J Neurol Sci 2010;290:107-11.
21. Jang SH, Bai D, Son SM, Lee J, Kim DS, Sakong J, *et al*. Motor outcome prediction using diffusion tensor tractography in pontine infarct. Ann Neurol 2008;64:460-5.
22. Jang SH, Cho SH, Kim YH, Han BS, Byun WM, Son SM, *et al*. Diffusion anisotrophy in the early stages of stroke can predict motor outcome. Restor Neurol Neurosci 2005;23:11-7.
23. Konishi J, Yamada K, Kizu O, Ito H, Sugimura K, Yoshikawa K, *et al*. MR tractography for the evaluation of functional recovery from lenticulostriate infarcts. Neurology 2005;64:108-13.
24. Kusano Y, Seguchi T, Horiuchi T, Kakizawa Y, Kobayashi T, Tanaka Y, *et al*. Prediction of functional outcome in acute cerebral hemorrhage using diffusion tensor imaging at 3T: A prospective study. AJNR Am J Neuroradiol 2009;30:1561-5.
25. Nelles M, Gieseke J, Flacke S, Lachenmayer L, Schild HH, Urbach H.

Diffusion tensor pyramidal tractography in patients with anterior choroidal artery infarcts. AJNR Am J Neuroradiol 2008;29:488-93.
26. Yang Q, Tress BM, Barber PA, Desmond PM, Darby DG, Gerraty RP, *et al*. Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke. Stroke 1999;30:2382-90.
27. Yoshioka H, Horikoshi T, Aoki S, Hori M, Ishigame K, Uchida M, *et al*. Diffusion tensor tractography predicts motor functional outcome in patients with spontaneous intracerebral hemorrhage. Neurosurgery 2008;62:97-103; discussion 103.
28. Thomalla G, Glauche V, Koch MA, Beaulieu C, Weiller C, Röther J. Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. Neuroimage 2004;22:1767-74.
29. Kuhn MJ, Mikulis DJ, Ayoub DM, Kosofsky BE, Davis KR, Taveras JM. Wallerian degeneration after cerebral infarction: Evaluation with sequential MR imaging. Radiology 1989;172:179-82.
30. Delsing BJ, Catsman-Berrevoets CE, Appel IM. Early prognostic indicators of outcome in ischemic childhood stroke. Pediatr Neurol 2001;24:283-9.
31. Kumar P, Kathuria P, Nair P, Prasad K. Prediction of upper limb motor recovery after subacute ischemic stroke using diffusion tensor imaging: A systematic review and meta-analysis. J Stroke 2016;18:50-9.
32. Kumar P, Yadav AK, Misra S, Kumar A, Chakravarty K, Prasad K. Prediction of upper extremity motor recovery after subacute intracerebral hemorrhage through diffusion tensor imaging: A systematic review and meta-analysis. Neuroradiology 2016;58:1043-50.
33. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: The Copenhagen Stroke Study. Arch Phys Med Rehabil 1994;75:394-8.
34. Persson HC, Parziali M, Danielsson A, Sunnerhagen KS. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit. A part of the SALGOT study. BMC Neurol 2012;12:162.
35. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, *et al*. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke 2001;32:1279-84.
36. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke 1992;23:1084-9.
37. Pollock A, St George B, Fenton M, Firkins L. Top 10 research priorities relating to life after stroke--consensus from stroke survivors, caregivers, and health professionals. Int J Stroke Off J Int Stroke Soc 2014;9:313-20.
38. Connell LA, Chesworth B, Ackerley S, Smith MC, Stinear CM. Implementing the PREP2 algorithm to predict upper limb recovery potential after stroke in clinical practice: A qualitative study. Phys Ther 2021;101:pzab040.
39. Smith MC, Ackerley SJ, Barber PA, Byblow WD, Stinear CM. PREP2 algorithm predictions are correct at 2 years post-stroke for most patients. Neurorehabil Neural Repair 2019;33:635-42.
40. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol 2017;4:811-20.
41. Boyd LA, Hayward KS, Ward NS, Stinear CM, Rosso C, Fisher RJ, *et al*. Biomarkers of stroke recovery: Consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. Neurorehabil Neural Repair 2017;31:864-76.
42. Shelton FN, Reding MJ. Effect of lesion location on upper limb motor recovery after stroke. Stroke 2001;32:107-12.
43. Hayward KS, Lohse KR, Bernhardt J, Lang CE, Boyd LA. Characterizing arm recovery in people with severe stroke (CARPSS): Protocol for a 12-month observational study of clinical, neuroimaging and neurophysiological biomarkers. BMJ Open 2018;8:e026435.

Supplementary Appendix-1

Study Methods and Protocols

Clinical Assessments

Clinical assessment at the time of the stroke onset was performed by a certified neurologist using the National Institute of Health Stroke Scale (NIHSS), Motricity Index (MI), Action Research Arm Test (ARAT), and Fugl-Meyer Assessment (FMA) to assess the motor function. The Barthel Index (BI) and Modified Rankin Scale (mRS) were done to assess the functional status. The follow-up assessment for stroke recovery was done by a blinded investigator at the third month post-stroke. The primary clinical outcome was the upper-limb function measured with the ARAT score at 3 months post-stroke. The ARAT scores were used to determine whether the patients achieved the predicted level of the upper-limb function.

Diffusion Tensor Imaging

DTI was performed using a 1.5 T MR unit (MR 450 w; GE Medical Systems, USA) by a phased-array head coil with a single-shot spin echo-planar imaging (EPI) sequence. The routine imaging sequences included three-dimensional fluid-attenuated inversion recovery imaging (FLAIR) and diffusion-weighted imaging (DWI) (*b*-values of 1,000 s/mm^2) with additionally calculated apparent diffusion coefficient (ADC) maps. The technical parameters used in the DTI were as follows: data acquisition matrix, 120 × 120; field of view, 240 mm × 240 mm; echo time 85 ms; repetition time 8,590 ms; 70 slices; slice thickness 2.25 mm; EPI factor 67; and *b*-value 1,000 s/mm^2. The acquired diffusion-sensitized and reference image sets were transferred to an Intel Pentium Windows-based operating system (Microsoft) for further data analysis. The tensor calculation and tractography were performed by using the DTIStudio Software version 3.03 (*www.mristudio.org*). Three regions of interest were drawn on a two-dimensional FA color map: medulla, middle anterior pons, and posterior limb of the internal capsule (PLIC).

Diffusion tensor tractography (DTT) was performed on the basis of fiber assignment by continuous tracking (FACT). A brute force fiber tracking will be initially performed for the whole brain. The fiber propagation was stopped at fractional anisotropy (FA) threshold of < 0.2 or an angle threshold of > 50°. The DTIStudio software allows the isolation of tracts passing through a single region of interest (by using the inclusive "OR" operator) or multiple regions of interest (by using the exclusive "AND" operator). The CST was isolated by drawing an "OR" region of interest around the CST in the brain stem and an "AND" region of interest around the corona radiata in the direction-coded color axial sections. The unrelated fibers, such as the fibers going to the contralateral side, cerebellum, or thalamus were removed by using a "NOT" region of interest. FA and mean diffusivity (MD) of the CST were calculated from the tracts. The patients were classified into two groups according to the integrity of the CST in the affected hemisphere: the DTT (+) group—the patients whose CST was preserved around the infarct, and the DTT (−) group—the patients whose CST was interrupted by the infarct.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) was performed using a Magstim Rapid (Magstim Co., Whitland, Dyfed, UK) magnetic stimulator with a figure of eight coils. Motor-evoked potentials (MEPs) were recorded from both abductor pollicis brevis (APB) and biceps brachii muscles (BB) in a relaxed state, and both hemispheres were examined. Data from the unaffected side were used as a control. The stimulation intensity was set at 100% of the maximum stimulator output (MSO). A synergy machine (Viasys Healthcare) was employed to amplify the signal. We used a single-pulse TMS technique. Each site was stimulated five times at 10 s minimum intervals, from which the shortest latency and the largest peak-to-peak amplitudes were adopted. The procedure was performed for both the upper limbs in all the subjects. MEP was considered absent if no response higher than 50 μV could be obtained after 5 stimuli at 100% intensity. The patients were classified into subgroups. The MEP (+) group was defined as the patients with MEPs on the affected side, and the MEP (−) group was defined as the patients without MEPs on the affected side.