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ORIGINAL ARTICLE

# Outcome in Stroke Patients Is Associated with Age and Fractional Anisotropy in the Cerebral Peduncles: A Multivariate Regression Study

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**Objectives:** Diffusion tensor fractional anisotropy (FA) in the corticospinal tracts has been used to assess the long-term outcome in stroke patients. Patient age and the type of stroke may also affect outcomes. In this study, we investigated the associations of age, type of stroke, and FA in the ipsilesional and contralesional cerebral peduncles with stroke outcomes. **Methods:** This study involved 80 patients with stroke (40 hemorrhagic, 40 ischemic) that we had investigated previously. Diffusion tensor FA images were obtained between 14 and 21 days post-stroke. FA values in the ipsilesional and contralesional cerebral peduncles were extracted and their ratio (rFA) was calculated. Outcome was assessed using the Brunnstrom stage, the motor component of the Functional Independence Measure (FIM-motor) at discharge, and the length of stay until discharge from rehabilitation. Using forward stepwise multivariate regression, we assessed the associations of rFA, contralesional FA, age, and type of stroke with outcome measures. **Results:** rFA and contralesional FA were included in the final model for the Brunnstrom stage in the upper limbs. There was a strong association between hemorrhagic stroke and poorer lower extremity function. rFA, contralesional FA, and age were included in the final model for FIM-motor and length of stay. The effect of rFA on all outcome measures was stronger than that of contralesional FA. The effect of age on FIM-motor was as strong as that of rFA. **Conclusions:** Neural damage in the corticospinal tracts (indicated by rFA) had the strongest effect on outcome measures, whereas the level of disability (measured by FIM-motor) was associated with a broader range of factors, including age.

**Key Words:** correlation; hematoma; ischemia; outcome; prognosis

## INTRODUCTION

The prediction of outcome is critically important when planning appropriate rehabilitation for stroke patients.[1–3] Magnetic resonance imaging, transcranial magnetic stimulation, magnetoencephalography, and other modalities have been used for rehabilitation planning.[4] A recent systematic review suggested that magnetic resonance diffusion tensor imaging (DTI) is potentially one of the most useful techniques to predict poststroke motor recovery.[5] Fractional anisotropy (FA) is the most frequently used DTI-derived parameter,[6] and several studies have found an association between decreased FA in the corticospinal tracts and poorer outcome.[7–10]

A variety of factors have been suggested to affect stroke outcome. Some previous studies have identified age as the strongest predictor of stroke outcome,[11,12] whereas others have indicated that the type of stroke (hemorrhagic or ischemic) is also important.[13,14] Furthermore, recent studies have suggested a possible contribution of the neural integrity

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of the corticospinal tracts in the contralesional intact hemisphere.[15,16] However, there is little evidence available on the relative contributions of these potential factors in predicting stroke outcome. Therefore, the aim of this study was to assess, by multivariate regression analysis, the effects of age, type of stroke, and neural integrity of the corticospinal tracts in the ipsilesional and contralesional hemispheres on the long-term outcome of stroke.

## METHODS

### Study Samples

The work presented here is an extension of earlier studies by our research group[17–19] and is based on further analysis of previously reported data.[19] The study population consisted of 80 stroke patients (40 with hemorrhagic lesions, 40 with ischemic lesions).[17,18] Patient demographics (e.g., age, lesion site, severity of hemiparesis) have been reported elsewhere.[17,18] The study protocol was approved by the Hyogo College of Medicine Ethics Committee (No. 2454).

Most patients were transferred to our hospital soon after the onset of symptoms. The diagnosis of stroke was confirmed on computed tomography and/or diffusion-weighted magnetic resonance images. All patients underwent physical, occupational, and speech therapy for up to 180 min daily, in line with the recommendations of the Japanese Guidelines for the Management of Stroke.[20] The study population was limited to patients with first-ever stroke with hemorrhagic or ischemic supratentorial lesions who had been able to walk unaided and had been functionally independent in activities of daily living (ADL) before the stroke. This limitation was imposed to minimize the effects of variability in pre-stroke health status and lesion site. To minimize the effects of variability resulting from differences in the rehabilitation regimen, we used only data for patients who were transferred to our affiliated long-term rehabilitation facility (Nishinomiya Kyoritsu Rehabilitation Hospital) for at least 1 month of inpatient rehabilitation.

### Acquisition of Diffusion Tensor Images

DTI was performed between 14 and 21 days post-admission using a 3.0-T magnetic resonance scanner (Trio; Siemens AG, Erlangen, Germany) with a 32-channel head coil. The DTI acquisition protocol has been described in detail elsewhere.[21] Following this protocol, a single-shot echo-planar imaging sequence was used to obtain 1 non-diffusion-weighted image (b=0 s/mm$^2$) and 12 images with noncollinear diffusion gradients (b=1000 s/mm$^2$) for a total of 64 axial slices per patient (field of view, 230.4 mm × 230.4 mm; acquisition matrix, 128 × 128; gapless slice thickness, 3 mm; echo time, 83 ms; and repetition time, 7000 ms).

### Outcome Measures

The functional status of the extremities was assessed using the Brunnstrom staging system (BRS),[22] which is widely used by Japanese rehabilitation therapists.[20] The BRS assesses stroke-related motor impairment (hemiparesis) of the upper and lower extremities. The recovery of affected extremities was evaluated using flexion and extension synergy patterns on a 6-point scale (1, very poor; 6, normal). BRS is widely used for functional evaluation of the lower extremity as well as the proximal (shoulder/elbow/forearm) and distal (hand/finger) components of the upper extremity, and its reliability and validity have been confirmed.[23] Scores at discharge from the rehabilitation facility were entered into the analysis database.

We also obtained scores for the motor component of the Functional Independence Measure (FIM-motor).[24] This measure comprises a battery of tests used to evaluate stroke patients during rehabilitation.[20] It consists of the following 13 items, each graded on a 7-point scale (1, total dependence; 7, complete independence): eating, grooming, bathing, dressing the upper body, dressing the lower body, toileting, bladder management, bowel management, transfers to a bed/chair/wheelchair, transfers to a toilet, transfers to a tub/shower, walking/propelling a wheelchair, and using stairs. The total score for these items is frequently employed as an index of independence in ADL (scale range, 13–91). Patients were considered eligible for discharge from the rehabilitation hospital when there was no further increase in the FIM-motor score. The BRS stage and FIM-motor score were assessed at monthly intervals, and the data were collected at discharge from the facility. The length of hospital stay (LOS) was recorded in all cases.

### Image Processing

We processed all images using the FSL brain image analysis package (version 6.0.1, Oxford Centre for Functional MRI of the Brain, Oxford, UK).[25] The methods used have been described elsewhere.[21] In summary, the DTI data were initially corrected for motion and eddy current distortions via alignment of later images to the first image (b=0 s/mm$^2$). Extracerebral regions were then removed from the images. Next, regional FA values for the brain were calculated to generate an FA brain map. This map was subsequently converted to a standard stereotaxic space. Regions of interest (ROIs) were

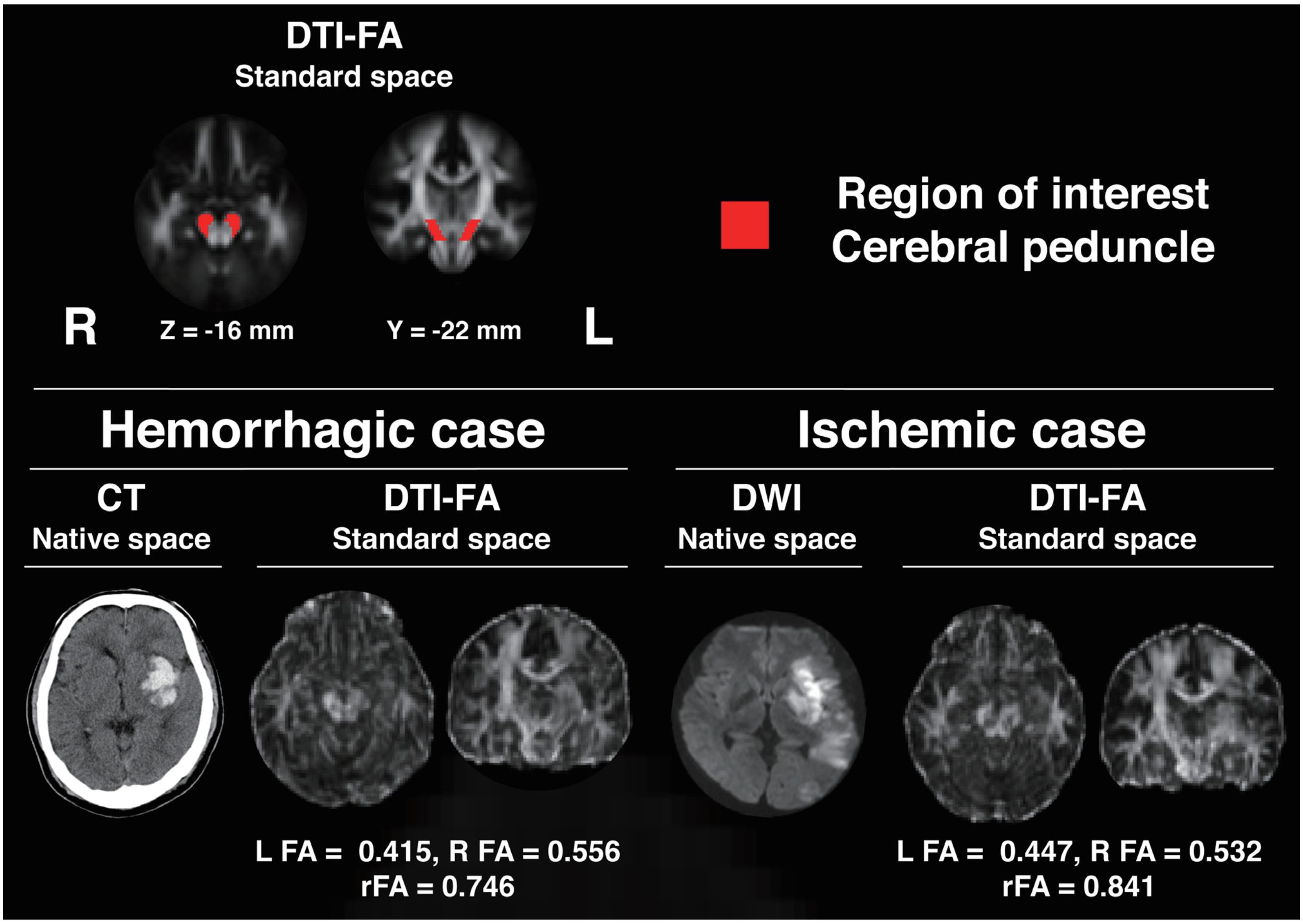


**Fig. 1.** Regions of interest in cerebral peduncles and examples of DTI-FA images from a patient with hemorrhagic stroke and a patient with ischemic stroke transformed into the standard space. CT, computed tomography; DWI, diffusion-weighted imaging.

set within the corticospinal tracts in the right and left cerebral peduncles (**Fig. 1**). These regions were selected because of the potential for magnetic resonance susceptibility effects of supratentorial stroke lesions to interfere with the validity of DTI data.[26)] The ROIs for the cerebral peduncles were set with reference to the International Consortium for Brain Mapping DTI-81[27)] (**Fig. 1**). FA values were calculated for the left and right ROIs with subsequent estimation of mean values for single voxels. The ratio of FA values between the ipsilesional and contralesional hemispheres (rFA) was calculated as the index of neural degeneration in the corticospinal tracts for each patient (**Fig. 1**).[5,28)]

## Statistical Analysis

Data were analyzed by multivariate regression, and separate analyses were performed for the BRS subsets, FIM-motor, and LOS. rFA, contralesional FA, age, and type of stroke were set as explanatory variables in all analyses. A dummy variable for the type of stroke took the value of 1 for hemorrhagic stroke and 0 for ischemic stroke. The parameters included in the final regression models were identified by forward stepwise selection ($P < 0.1$). Spearman's correlation test was performed for all possible pairings of the four explanatory variables to identify any multicollinearity. All statistical analyses were performed using the JMP software package (SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was considered statistically significant.

# RESULTS

Patient demographics and clinical characteristics are shown in **Table 1**. The study population included 80 patients (40 with hemorrhagic stroke, 40 with ischemic stroke; 47 men, 33 women). The lesion was in the right hemisphere in

**Table 1.** Patient demographics and clinical characteristics

| | |
|---|---|
| Type of stroke (hemorrhagic/ischemic) | 40/40 |
| Sex (male/female) | 47/33 |
| Hemisphere affected (right/left) | 37/43 |
| Age, years | 64.4 ± 12.4 |
| rFA | 0.880 ± 0.103 |
| Contralesional FA | 0.574 ± 0.031 |
| FIM-motor | 76.5 ± 8.2 |
| LOS, days | 140.9 ± 54.2 |
| BRS S/E/F | 4.1 ± 1.6 |
| BRS H/F | 3.9 ± 1.7 |
| BRS L/E | 4.6 ± 1.2 |

Data are shown as the mean and standard deviation or as the number, as appropriate.
S/E/F, shoulder, elbow, and forearm; H/F, hand and finger; L/E, lower extremity.

**Table 2.** Results of multivariate regression analyses of BRS data

| | BRS S/E/F | | | | BRS H/F | | | | BRS L/E | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | *t* | P | Estimate | SE | *t* | P | Estimate | SE | *t* | P |
| Age | - | - | - | - | - | - | - | - | - | - | - | - |
| rFA | 10.40 | 1.23 | 8.48 | <0.001 | 11.17 | 1.24 | 8.95 | <0.001 | 6.98 | 0.96 | 7.27 | <0.001 |
| Contralesional FA | 8.06 | 3.94 | 2.05 | 0.044 | 9.43 | 4.01 | 2.35 | 0.021 | 6.00 | 2.91 | 2.06 | <0.001 |
| Type of stroke | - | - | - | - | - | - | - | - | −0.47 | 0.20 | −2.39 | 0.019 |
| Intercept | −9.69 | 2.43 | −3.99 | <0.001 | −11.32 | 2.47 | −4.58 | <0.001 | −4.75 | 1.84 | −2.58 | 0.012 |
| Adjusted $R^2$ | 0.496 | | | | 0.526 | | | | 0.517 | | | |

Dummy values were assigned for the type of stroke: 1, hemorrhagic; 0, ischemic.
SE, standard error.

37 cases and in the left in 43. Patient demographics showed an almost normal distribution and were appropriate for regression analysis.

**Table 2** shows the results of multivariate regression analyses for the BRS subsets. The rFA and contralesional FA values for the shoulder/elbow/forearm and hand/finger components were taken into the final models. The *t*-values indicated that more of the variability in BRS outcome data was accounted for by rFA than by the contralesional FA. When the type of stroke was added to rFA and contralesional FA in the final model, the BRS scores suggested a strong association between hemorrhagic stroke and poorer lower extremity function. Age was not included in the final model. The upper row in **Fig. 2** shows the relationship between the observed and predicted values derived from the parameter estimates shown in **Table 2**.

**Table 3** shows the results obtained by multivariate regression for FIM-motor and LOS. Unlike for BRS, age was included in the final models for both FIM-motor and LOS. The *t*-values obtained for FIM-motor indicated that age contributed as much as rFA to stroke outcome. The bottom row in **Fig. 2** shows scatter plots of the observed and predicted values derived from the parameter estimates shown in **Table 3**.

**Table 4** shows the correlations between the explanatory variables. Hemorrhage (dummy value, 1) was associated with a lower rFA (P=0.002), indicating that neural damage was more severe in patients with hemorrhagic stroke. Although not a statistically significant finding, patients with hemorrhagic stroke were younger than those with ischemic stroke (P=0.065). This result was consistent with the negative correlation between age and rFA (P=0.046).

## DISCUSSION

Multivariate regression analyses of patients with supratentorial hemorrhagic or ischemic stroke in this study revealed that FA in the cerebral peduncles of the ipsilesional and contralesional hemispheres was associated with long-term outcome. Furthermore, age influenced the FIM-motor and

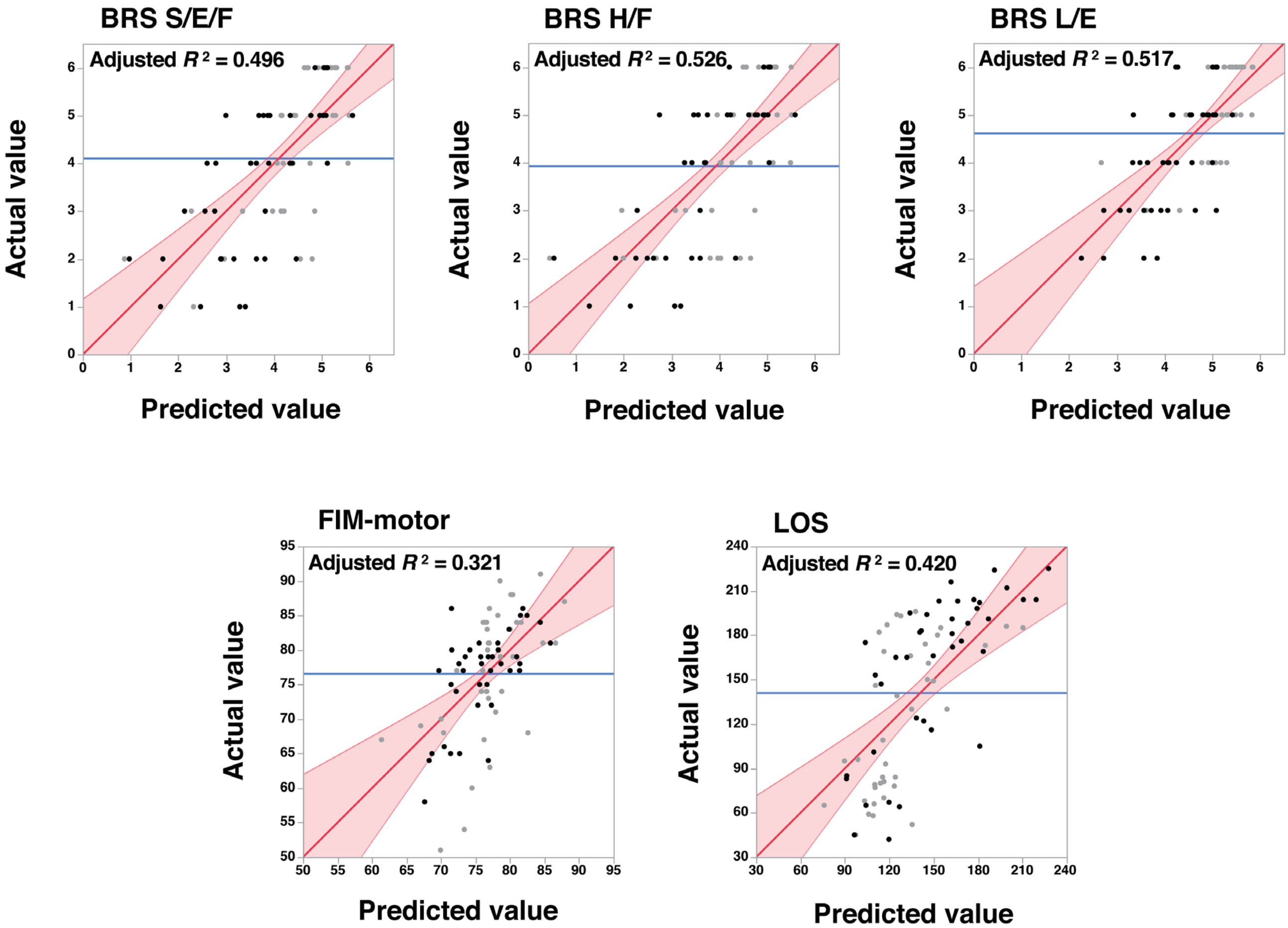


**Fig. 2.** Scatter plots showing the actual measured values (vertical axes) and the predicted values derived from the parameter estimates of multivariate regression analyses (see **Tables 2 and 3**). Black dots represent data from patients with hemorrhagic stroke and gray dots represent data from those with ischemic stroke. Red lines with a slope of 1 indicate a perfect fit, i.e., where the predicted and actual values are identical. Reddish areas indicate the 95% confidence intervals. Blue lines indicate the mean of the actual values obtained.
S/E/F, shoulder, elbow, and forearm; H/F, hand and finger; L/E, lower extremity.

LOS outcome data. However, the type of stroke had a minimal effect on outcome, except for the function of the lower extremities. These findings highlight the contributions of age and neural integrity in the corticospinal tracts to stroke outcome.

Previous studies have identified age as one of the most powerful predictors of stroke outcome.[29,30] This study quantitively evaluated the impact of age in combination with neural integrity on outcome measures of BRS, FIM-motor, and LOS. For FIM-motor, multivariate regression analysis revealed that the impact of age was as robust as that of neural damage indexed by rFA. However, age had a minimal effect on outcome in terms of function in the extremities as assessed by the BRS. This discrepancy may reflect differences in the nature of the measures used, in that the BRS evaluates impairment, whereas FIM-motor assesses disability. Nevertheless, this finding suggests a direct relationship between impairment and neural damage, whereas disability reflects broader factors, including age.

The literature suggests that DTI-FA, an index of the integrity of neural fibers, can be used to predict the stroke outcome.[4,9,31] Many previous studies have used the severity of neural damage in the ipsilesional hemisphere relative to that in the intact contralesional hemisphere, which is indexed by rFA.[4,9,31] As in those studies, we found a strong correlation between rFA as an index of neural damage and stroke outcome (**Tables 2 and 3**). Correlation analyses of the explanatory variables indicated that hemorrhagic stroke was

**Table 3.** Results of multivariate regression analyses for FIM-motor and LOS

| | FIM-motor | | | | LOS | | | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | *t* | P | Estimate | SE | *t* | P |
| Age | −0.26 | 0.06 | −4.09 | <0.001 | 0.84 | 0.39 | 2.19 | 0.032 |
| rFA | 34.72 | 7.62 | 4.56 | <0.001 | −332.88 | 46.60 | −7.14 | <0.001 |
| Contralesional FA | 57.99 | 23.91 | 2.42 | 0.018 | −317.44 | 146.29 | −2.17 | 0.033 |
| Type of Stroke | - | - | - | - | - | - | - | - |
| Intercept | 29.22 | 15.14 | 1.93 | 0.057 | 562.01 | 92.59 | 6.07 | <0.001 |
| Adjusted $R^2$ | 0.321 | | | | 0.420 | | | |

Dummy values were assigned for the type of stroke; 1, hemorrhagic; 0, ischemic.

**Table 4.** Correlations between explanatory variables

| | Age | rFA | Contralesional FA |
|---|---|---|---|
| rFA | 0.224 (P=0.046) | - | - |
| Contralesional FA | −0.067 (P=0.555) | 0.085 (P=0.452) | - |
| Type of stroke | −0.208 (P=0.065) | −0.340 (P=0.002) | −0.055 (P=0.628) |

Dummy values are assigned for the type of stroke: 1, hemorrhagic; 0, ischemic.

associated with a lower rFA (**Table 4**). However, multivariate regression analyses did not take the type of stroke into the final models, except for the lower extremity data. This observation suggests that hemorrhagic stroke is associated with more severe neural damage and symptoms.[19] However, the neural damage indexed by rFA accounted for most of the variability in clinical severity. These findings confirm the usefulness of rFA in the cerebral peduncles for predicting outcome in stroke patients with hemorrhagic or ischemic lesions.[4,9,19,31]

It has been suggested that a small number of corticospinal fibers project ipsilaterally and that they may contribute to motor recovery in patients with hemiparesis after stroke.[32] As in previous studies,[16,33] FA in the contralesional hemisphere was used in the final models for all multivariate regression analyses in the present study. This observation implies that better neural integrity within the ipsilateral corticospinal tracts is associated with a more favorable outcome.[34] However, our results for parameter estimates (*t*-values) suggest that the contribution of FA in the contralesional hemisphere was relatively small (**Tables 2 and 3**). Accordingly, in terms of clinical significance, the role of ipsilateral (contralesional) corticospinal projections in motor recovery remains unclear.[35]

Clinical severity in the initial phase of stroke is another important determinant of long-term outcome.[3,36,37] We previously reported that the National Institutes of Health Stroke Scale score[38] during the acute phase can predict the extent of FIM-motor recovery.[39] The speed of recovery is also important for predicting stroke outcome.[3,30] However, in this study, we could not systematically obtain data for initial clinical severity or for the speed of recovery because of the retrospective nature of the research. Nevertheless, the predictive accuracy of the models derived from multivariate regression analyses (adjusted $R^2$) ranged from 0.321 to 0.526. Greater accuracy could be expected if the initial clinical severity and speed of recovery were included as explanatory variables. Further studies are needed to clarify this issue.

This study has several limitations. First, the outcome measures used were somewhat crude in that we sampled only BRS, FIM-motor, and LOS. However, patients with stroke have a variety of symptoms, including dysphagia, hemiparesis, and higher brain dysfunction (e.g., aphasia and hemispatial neglect), so our outcome measures might not have adequately accounted for other important symptoms. Second, we did not include a confirmatory analysis of the models derived from the multiple regression analyses. As a result of our stringent inclusion criteria, data for only 80 patients were used in the analysis. Therefore, the focus of the study was on model development. Future studies with larger numbers of patients are needed to assess the applicability of the models derived in the present study. However, given that the aim of this study was to assess the contributions of age, type of stroke, and FA in the ipsilesional and contralesional cerebral peduncles, we believe that our analysis was appropriate. Third, only patients who were functionally independent before stroke were enrolled in the study; such patients are likely to have a relatively good recovery. Moreover, we did not include patients with subarachnoid hemorrhage or those with brainstem or cerebellum lesions because their symptoms (altered consciousness, ataxia) are different from those in patients with supratentorial intramedullary lesions. Therefore, caution is needed when generalizing the present findings to the entire stroke population. Nevertheless, despite these limitations, the present study confirms that neural integrity within the corticospinal tracts and patient age are critical factors for predicting long-term stroke outcome.

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## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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