

ORIGINAL ARTICLE

Outcome Prediction of Patients with Intracerebral Hemorrhage by Measurement of Lesion Volume in the Corticospinal Tract on Computed Tomography

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Objective: This study investigated the potential utility of computed tomography for outcome prediction in patients with intracerebral hemorrhage. **Methods:** Patients with putaminal and/or thalamic hemorrhage for whom computed tomography images were acquired in our hospital emergency room soon after onset were retrospectively enrolled. Outcome measurements were obtained at discharge from the convalescent rehabilitation ward of our affiliated hospital. Hemiparesis was evaluated using the total score of the motor component of the Stroke Impairment Assessment Set (SIAS-motor; null to full, 0 to 25), the motor component of the Functional Independence Measure (FIM-motor; null to full, 13 to 91), and the total length of hospital stay. After registration of the computed tomography images to the standard brain, the volumes of the hematoma lesions located in the corticospinal tract were calculated. The correlation between the corticospinal tract lesion volumes and the outcome measurements was assessed using Spearman's rank correlation test. **Results:** Thirty patients were entered into the final analytical database. Corticospinal tract lesion volumes ranged from 0.002 to 4.302 ml (median, 1.478). SIAS-motor scores ranged from 0 to 25 (median, 20), FIM-motor scores ranged from 15 to 91 (median, 80.5), and the total length of hospital stay ranged from 31 to 194 days (median, 106.5). All correlation tests were statistically significant ($P < 0.01$). The strongest correlation was for SIAS-motor total ($R = -0.710$), followed by FIM-motor ($R = -0.604$) and LOS ($R = 0.493$). **Conclusions:** These findings suggest that conventional computed tomography images may be useful for outcome prediction in patients with intracerebral hemorrhage.

Key Words: function; imaging; prognosis; recovery; registration

INTRODUCTION

Outcome prediction is critically important when scheduling appropriate rehabilitative treatment for patients after stroke.^{1,2} Some biomarkers, including brain images, may be useful for outcome prediction in these patients.³ Computed tomography (CT) is a conventional neuroimaging technique used for the diagnosis of stroke, particularly in cases of intracerebral hemorrhage.⁴ Although the volume of hemorrhage assessed by CT is a powerful predictor of mortality,^{5,6} a recent systematic review indicated that such CT data are not

useful for the prediction of functional outcome.³

It is well known that assessment of the neural integrity of the corticospinal tract (CST) is essential for prediction of the functional outcome in patients after stroke.^{7,8} Some reports have suggested that modern techniques such as transcranial magnetic stimulation (TMS) and magnetic resonance diffusion tensor imaging (DTI) may be useful for such predictions.^{9,10} There are also some reports describing the utility of TMS combined with motor evoked potentials.^{2,3} However, TMS is not yet widely available in real-world clinical settings because the equipment is costly. Furthermore, DTI allows

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quantitative assessment of CST integrity (e.g., fractional anisotropy)^{11–13} but is not in widespread use because of the complex procedures required for image analysis.¹⁴

Unlike TMS and DTI, CT is used extensively in daily clinical practice. Nevertheless, there is limited information on its potential utility for quantitative assessment of CST integrity.¹⁵ Consequently, we developed a simple method for evaluating CST integrity in patients with intracerebral hemorrhage based on conventional CT data, and in this study, we evaluated its clinical utility for predicting long-term outcome in these patients.

METHODS

Patients

This retrospective study included patients with intracerebral hemorrhage who were admitted to Nishinomiya Kyoritsu Neurosurgical Hospital between April 2019 and March 2021. Patients are typically transferred to our hospital soon after stroke onset and undergo conservative treatment, including antihypertensive medication. When necessary, hematoma is removed surgically. Patients also undergo rehabilitative treatment, including physical therapy, occupational therapy, and speech therapy, for a combined daily total of up to 180 min in accordance with the 2015 revisions to the Japanese Guidelines for the Management of Stroke.¹⁶

To minimize any variability arising from differences in pre-stroke health status and the site of the lesion, the sample population was limited to first-ever stroke patients with thalamic and/or putaminal hemorrhage who had been able to walk unaided and were functionally independent in activities of daily living (ADL) before the stroke. Patients with a history of comorbid neurological disease (e.g., Parkinson's disease or Alzheimer's disease) were excluded. Patients in whom there was a subsequent deterioration in consciousness level and those with other comorbidities were also excluded. To minimize differences in the rehabilitative protocols used, this study included data only from patients who were transferred to our affiliated long-term rehabilitation facility (Nishinomiya Kyoritsu Rehabilitation Hospital).

The study protocol was approved by the Hyogo College of Medicine Ethics Committee (approval number 3850) and was performed in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Provisional Translation as of March 2015) and its later amendments. Informed consent was obtained by the opt-out method.

CT Acquisition

On arrival at our hospital, patients with suspected stroke based on hemiparesis or other symptoms underwent head CT using a 320-row-detector CT scanner (Aquilion ONE; Canon Medical Systems Corporation, Tochigi, Japan). The CT images were obtained helically using a standard protocol. Imaging parameters were 120 kVp and 300 mAs with an in-plane resolution of 0.43 mm × 0.43 mm (512 × 512 matrix) and a slice thickness of 5 mm. The CT data were stored in DICOM (Digital Imaging and Communications in Medicine) format.

Image Processing

The procedures used to process the brain CT images analyzed in this study followed those described previously.^{17–19} The CT data stored in DICOM format were converted into NIFTI (Neuroimaging Informatics Technology Initiative) format using *dcm2niix* software (<https://github.com/rordenlab/dcm2niix>, accessed July 31, 2021).²⁰ The brain image analysis package FSL²¹ version 6.0.4 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>, accessed April 30, 2021) was used for further analyses. This package includes a mathematical manipulation tool (FSLUTILS), an image viewer tool (FSLEYES), and the FMRIB Linear Image Registration Tool (FLIRT).

As recommended in previous reports,^{17–19} CT images in NIFTI format were further processed by thresholding Hounsfield units (HU) in the range 0–100 using FSLUTILS. By using FLIRT,^{22,23} the processed CT data were then spatially normalized in reference to a previously reported standard CT template.²⁴ The spatial normalization of the standard CT template was inspected visually using FSLEYES (**Fig. 1**).

The voxels located in the hematoma lesions (lesion masks) were defined as follows. For each patient, two of the authors (UY, TK) visually inspected the CT data registered to the standard space and then set rectangular areas representing voxels of interest (VOI) that touched the edges of the hematoma in the right-to-left (x), posterior-to-anterior (y), and bottom-to-top (z) directions (**Fig. 1**). By using FSLUTILS for each patient, the voxels within the VOI with HU that exceeded 50 percentile were abstracted and binarized as the lesion mask (**Fig. 1**). These lesion masks were then back-projected onto the native CT images (i.e., inverse transformation) using FLIRT and inspected visually using FSLEYES (**Fig. 1**).

The left and right CSTs were abstracted from a brain mapping template (JHU-ICBM-tracts-maxprob-thr0-1mm.nii.gz, implemented in the FSL suite) and then projected onto the CT data registered in the standard space (**Fig. 2**). By using

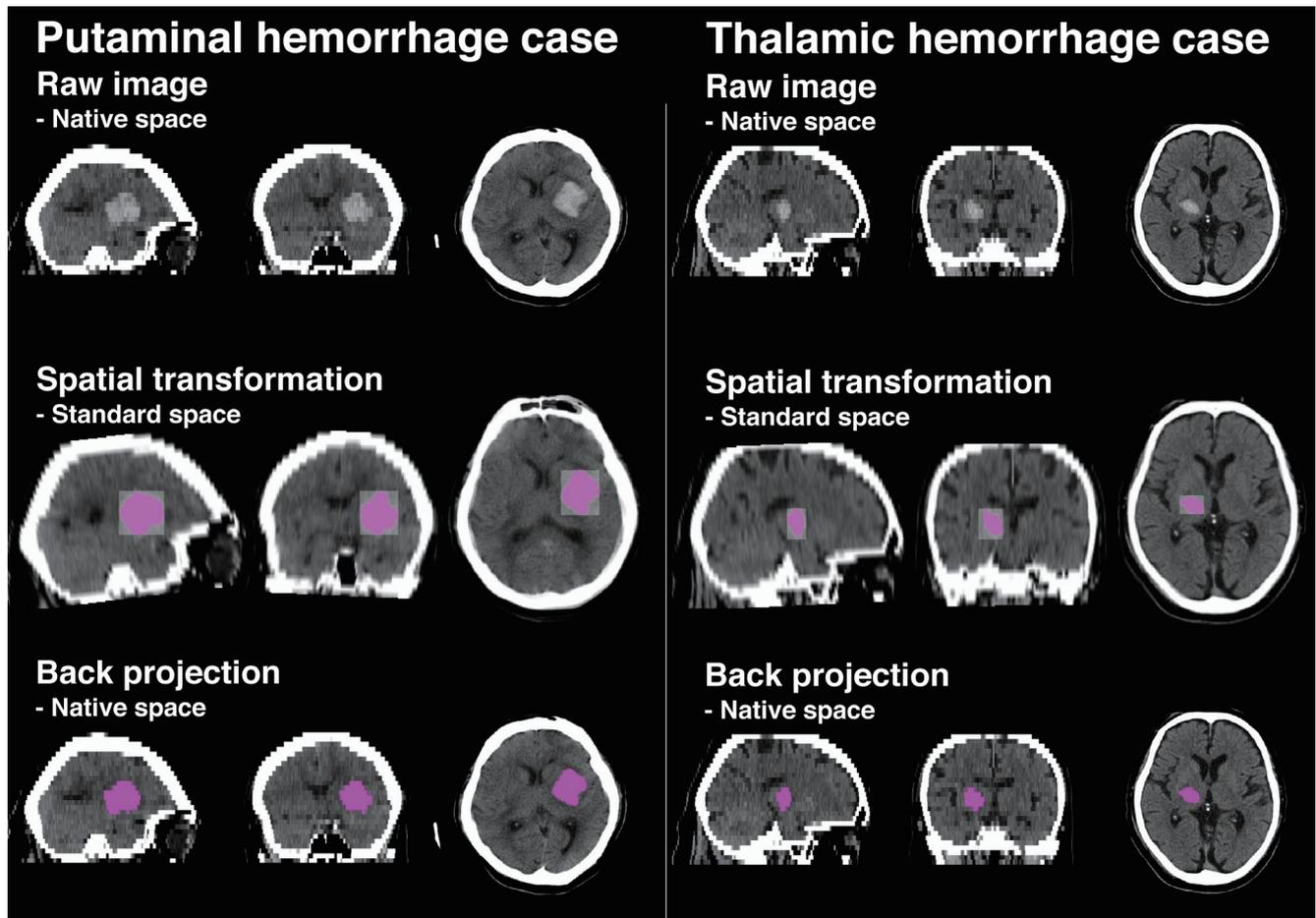


Fig. 1. Examples of computed tomography brain images including raw brain images (upper panels), images after spatial transformation into the standard brain (middle panels), and back projection of the transformed brain images into the original forms (lower panels). The left panel shows a case of putaminal hemorrhage (patient 16 in **Table 1**), and the right panel shows a case of thalamic hemorrhage (patient 19 in **Table 1**). The gray rectangular areas (middle panels) indicate the voxels of interest used to generate lesion masks (shown in purple).

FSLUTILS, the voxels showing overlap of the CST and the lesion (CST-lesion) were abstracted.^{25–27} The volume (ml) of these CST-lesion voxels was calculated for each patient.

Outcome Measurements

Impairment of motor function in the upper and lower extremities on the hemiparetic side post-intracerebral hemorrhage was evaluated using the motor component of the Stroke Impairment Assessment Set (SIAS-motor).²⁸ This assessment includes five components, namely, arm, finger, hip, knee, and ankle functions (null to full, 0 to 5). In this study, to index gross motor function on the paralyzed side, the total sum of SIAS-motor scores was calculated for each patient. The scores for the motor component of the Functional Independence Measure (FIM)²⁹ were also obtained

for each patient. This scoring system is commonly used to assess the functional status of patients with regard to ADL (total dependence to full independence, 13 to 91). SIAS-motor and FIM-motor scores were assessed every 2 weeks, and data were collected from our long-term rehabilitation facility at discharge. The total length (days) of hospital stay (LOS), which involved provision of acute medical care, was also recorded.

Statistical Analysis

The relationships between CST-lesion volumes and the outcome measurements (SIAS-motor, FIM-motor, and LOS) were assessed using Spearman's rank correlation test. All statistical analyses were performed using the JMP software package (SAS Institute, Cary, NC, USA). A P value of less

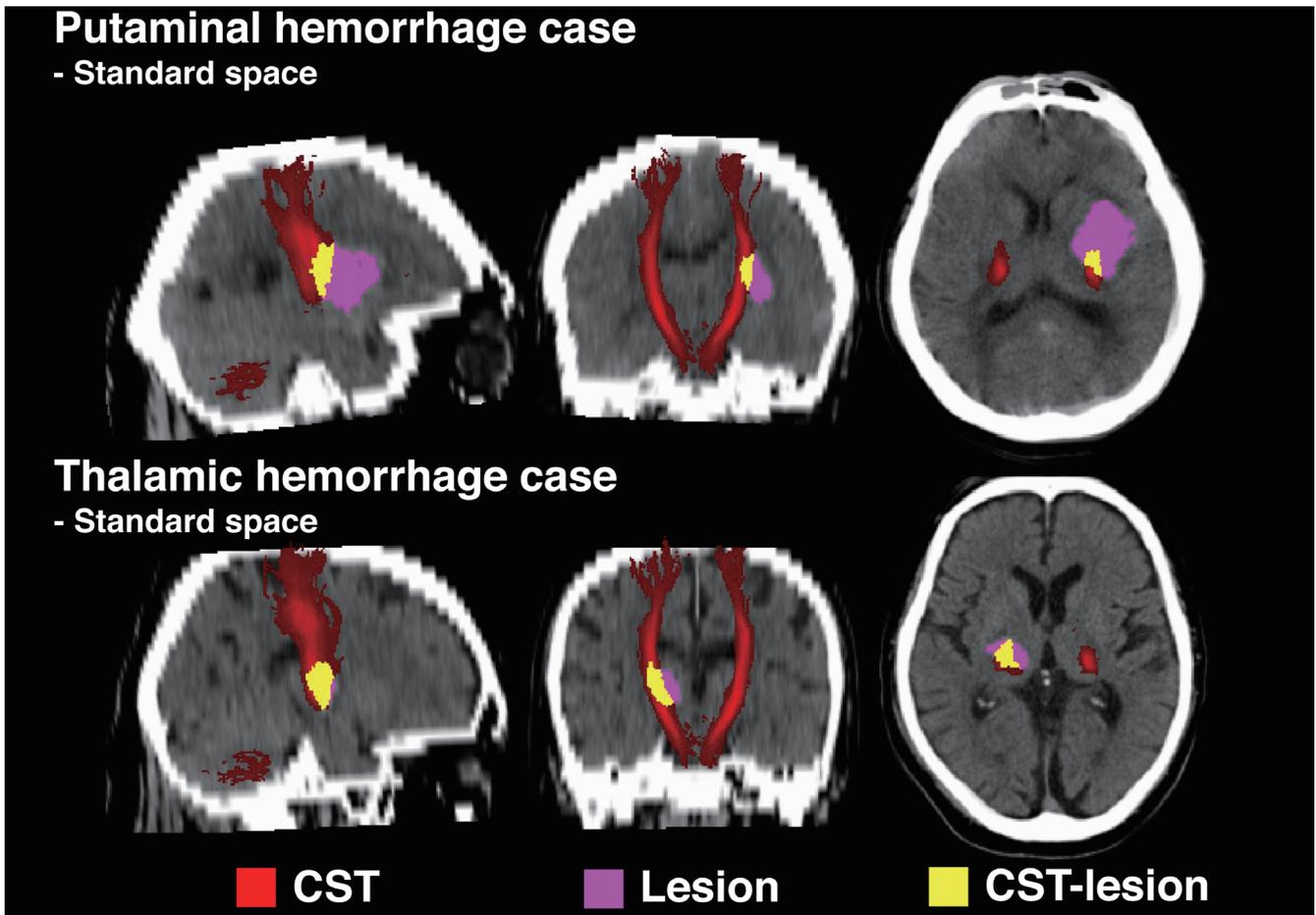


Fig. 2. Corticospinal tract (CST, red), lesion mask (purple), and the overlap of these two areas (CST-lesion, yellow) in two representative cases. The upper row shows a case of putaminal hemorrhage (patient 16 in **Table 1**), and the lower row shows a case of thalamic hemorrhage (patient 19 in **Table 1**).

than 0.01 was considered statistically significant.

RESULTS

A total of 34 patients were recruited during the study period. After visual inspection of the appropriateness of spatial normalization in each patient (**Fig. 1**), 4 patients with midline shift were excluded, leaving data for 30 patients available for analysis (**Table 1**). Patient age ranged from 45 to 89 years (median, 70) and the CST-lesion (overlapping) volumes ranged from 0.002 to 4.302 ml (median, 1.478). SIAS-motor total scores ranged from 0 to 25 (median, 20), FIM-motor scores ranged from 15 to 91 (median, 80.5), and LOS ranged from 31 to 194 days (median, 106.5).

Figure 1 shows the CT images processed by spatial normalization, indicating that image processing was successful. For each patient, the VOI were easily set in several minutes

because the HU in the hematoma was higher than that in the surrounding tissues. The lesion mask was appropriately derived from the rectangular VOI in each patient, and the area of the lesion mask was carefully inspected by back projection from the standard space images into the original form (**Fig. 1**). **Figure 2** shows representative cases of putaminal hemorrhage and thalamic hemorrhage. As shown in these cases, the voxels of the CST-lesion (shown in yellow in **Fig. 2**) were appropriately abstracted.

Figure 3 shows the results of the correlation analyses. The relationships between the CST-lesion volume and the outcome measurements were all statistically significant. The correlation was strongest for SIAS-motor total ($R=-0.710$), followed by FIM-motor ($R=-0.604$) and LOS ($R=0.493$).

Table 1. Patients' profiles

Case no.	Age (years)	Sex M/F	Lesion site		VOI range			CST-lesion (ml)	SIAS-motor Raw score	FIM-motor Total	LOS (days)	
					x (mm)	y (mm)	z (mm)					
1	71	M	L	Thal	92–111	92–119	75–88	0.002	5–5–5–5–4	24	87	113
2	57	M	L	Put	107–129	106–148	56–86	0.049	5–5–5–5–5	25	90	73
3	89	F	R	Put	54–63	102–120	68–99	0.096	5–5–5–5–5	25	77	67
4	83	F	R	Thal	59–72	95–106	67–91	0.317	5–5–5–5–5	25	86	87
5	60	M	L	Put	104–132	105–137	62–99	0.579	4–4–4–4–4	20	87	105
6	49	F	L	Put	109–129	104–130	57–94	0.764	4–4–5–5–5	23	90	76
7	66	M	R	Thal	50–77	87–110	77–107	0.973	5–5–5–4–4	23	88	44
8	48	F	R	Put	33–69	85–137	49–90	1.001	4–3–4–4–4	19	81	49
9	77	F	R	Thal	61–79	95–113	72–95	1.093	4–4–4–4–4	20	80	105
10	73	F	R	Thal	61–88	88–117	68–96	1.201	5–5–5–5–5	25	57	33
11	70	M	R	Put	44–72	99–133	67–102	1.258	2–1–2–3–1	9	77	155
12	64	M	L	Thal	96–123	93–111	62–89	1.264	4–4–4–4–4	20	86	97
13	67	M	R	Put	60–87	91–111	69–95	1.343	4–4–5–4–4	21	87	76
14	60	M	R	Put/Thal	65–83	96–127	72–98	1.390	5–5–5–5–5	25	91	108
15	58	F	R	Put	43–73	94–149	61–102	1.450	5–4–5–5–5	24	90	68
16	46	M	L	Put	103–137	103–143	67–106	1.505	1–1–3–3–2	10	79	182
17	75	M	L	Thal	104–117	104–116	72–99	1.914	5–5–5–5–5	25	90	31
18	73	F	R	Put/Thal	48–76	92–133	57–97	2.087	2–2–3–3–4	14	58	135
19	70	M	R	Thal	59–80	104–120	63–90	2.195	3–3–3–3–3	15	77	105
20	45	M	L	Put	96–136	90–138	58–103	2.368	5–5–5–5–5	25	90	194
21	70	F	R	Thal	62–88	88–115	62–90	2.457	4–4–4–4–4	20	69	76
22	46	M	R	Put	40–69	91–140	56–102	2.460	1–1–1–3–2	8	74	116
23	52	M	L	Put	104–144	91–131	54–101	2.881	1–1–2–3–1	8	86	192
24	79	F	R	Thal	50–78	86–113	72–108	2.981	2–2–2–2–2	10	25	128
25	74	F	L	Thal	92–126	95–119	65–105	3.336	1–1–1–1–0	4	37	118
26	81	F	R	Put/Thal	50–81	97–124	61–98	3.673	1–0–1–1–1	3	30	156
27	80	M	R	Thal	56–85	91–114	65–108	3.697	2–1–4–4–1	12	76	145
28	87	F	L	Thal	98–122	97–122	60–95	3.777	0–0–0–0–0	0	15	175
29	51	F	L	Put	104–140	94–141	51–106	3.908	3–1–4–3–3	14	83	115
30	74	M	R	Thal	58–80	93–119	70–105	4.302	3–3–3–3–3	15	56	113

Patients are listed in order of increasing volumes of CST-lesion. Four patients (15, 16, 20, 22) underwent surgical removal of hematoma. VOI ranges are shown in the standard brain space defined by the Montreal Neurological Institute.

SIAS-motor raw scores are sequenced as arm–finger–hip–knee–ankle.

VOI, voxels of interest; CST, corticospinal tract; SIAS-motor, the motor component of the Stroke Impairment Assessment Set; FIM-motor, the motor component of Functional Independence Measure; LOS, length of hospital stay; M, male; F, female; L, left; R, right; Put, putamen; Thal, thalamus.

DISCUSSION

This study investigated the potential value of conventional CT data for outcome prediction in patients with intracerebral hemorrhage. Using the simple method that we have developed, brain images were successfully registered to the standard CT template using linear spatial transformation, lesion

volume in the CST was calculated for each patient, and the CST-lesion volume was then assessed in relation to outcome measurements for hemiparesis, ADL, and LOS. All correlations were statistically significant, and the coefficients obtained indicated that the correlations were moderate (around 0.5–0.7). Consequently, our findings imply that conventional CT images may be useful for the prediction of outcomes in

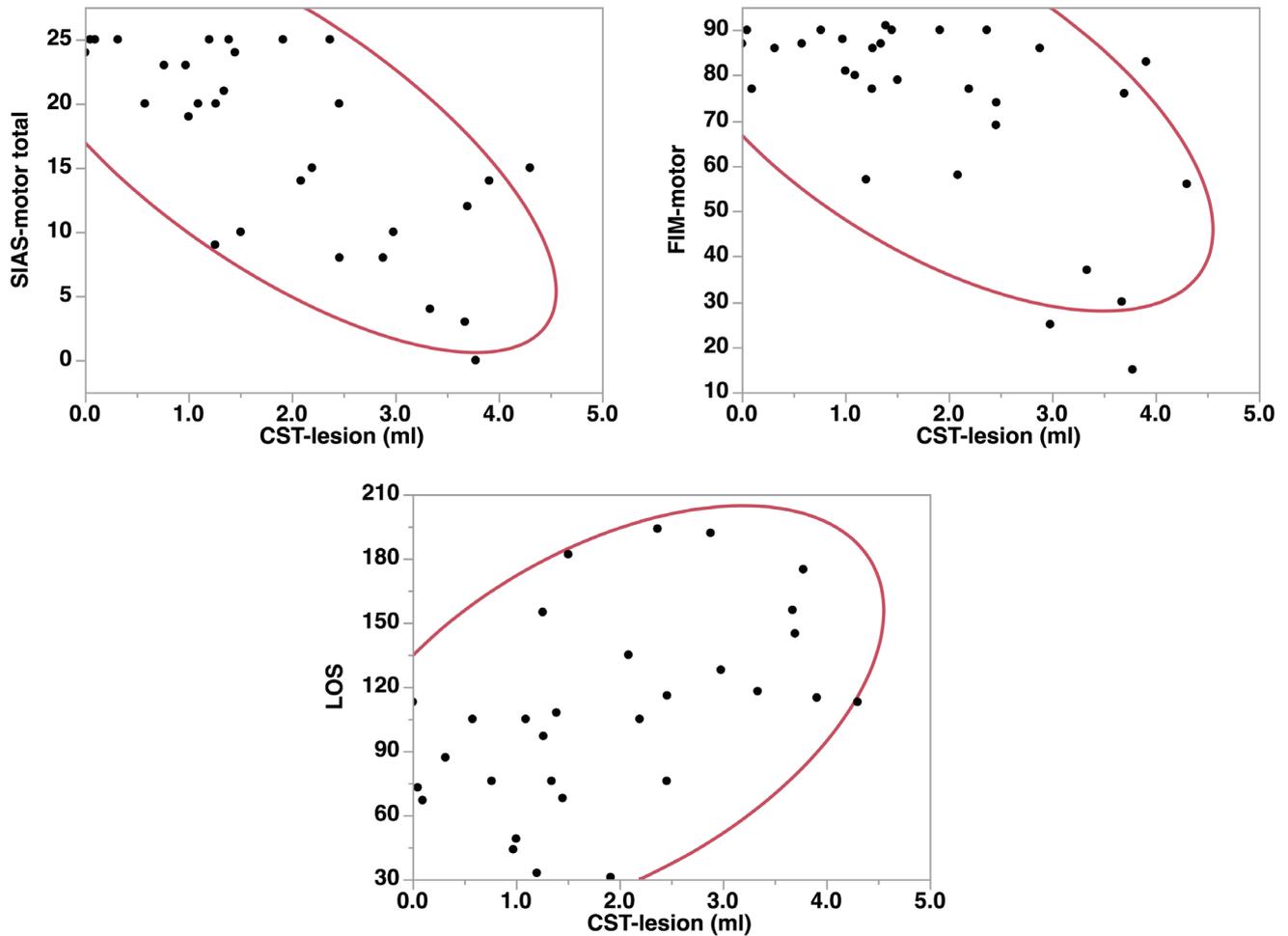


Fig. 3. Scatterplots of CST–lesion volume and outcome measurements. Red lines indicate the density ellipse (0.90). CST, corticospinal tract; FIM-motor, motor component of the Functional Independence Measure; LOS, length of hospital stay; SIAS-motor, motor component of the Stroke Impairment Assessment Set.

patients with intracerebral hemorrhage.

The correlations seen in this study are very similar to those established in our previous studies using DTI,^{11–13} in which we found that neural damage in the CST, indexed by the decrease in fractional anisotropy, correlated with long-term outcomes in regard to hemiparesis, ADL, and LOS. In particular, the correlation coefficient was strongest for hemiparesis, followed by ADL and LOS. DTI detects Wallerian degeneration caused by stroke; therefore, acquisition of DTI data for this type of research is often scheduled for approximately 2 weeks after stroke onset when reliable signal changes have occurred.³⁰ In contrast, CT shows high-density areas at the time of stroke onset in patients with intracerebral hemorrhage, so there is no need to wait for significant signal changes. In general terms, it is reasonable to predict the outcome of stroke by CT on the day of onset and then confirm

it by DTI several weeks later. However, further studies are needed to clarify the clinical utility of the combination of CT and DTI for outcome prediction of stroke.

In the current study, we generated lesion masks by a simple combination of manual and computer-automated procedures. The ACB/2 method is traditionally used to estimate the volume of intracerebral hemorrhage^{5,6} and was used in the present study to define the lesion mask. In each patient, rectangular VOI areas were set to include the hematoma in the x, y, and z directions, after which the area of voxels that exceeded 50 percentile HU was taken to be the lesion mask (**Fig. 1**). Several fully computer-automated techniques have been developed for delineation of hematoma lesions on CT images^{31–34}; in contrast, our methodology is rather primitive. However, visual inspection confirmed that definition of lesion masks in this way was adequate. Furthermore, it takes

around 5 min only to complete the analysis for each patient. Accordingly, we consider that the image analysis procedure used in this study is readily applicable in real-world clinical settings.

The methodology established here involves a variation of voxel-based lesion–symptom mapping,³⁵⁾ which requires spatial normalization of individual brain images to the standard brain.³⁶⁾ Two approaches have been developed for spatial normalization of an individual brain, namely, linear registration and nonlinear registration. Linear registration is the classical method, which translates, rotates, zooms, and shears individual brain images to match the standard brain,^{22,23)} and lesion areas are registered to the standard brain in proportion to the whole brain. In contrast, nonlinear registration is a newly developed method that first subsamples the brain structures and then reconstructs the subsampled pieces into the standard brain. Although it is more precise, it often shrinks the lesion areas.^{14,24)} In the present study, we used the CST–lesion volume as an explanatory variable. Consequently, classical linear registration was more suitable for the purposes of the study. The results for the relationships between CST–lesion volumes and symptoms were in line with those established in previous DTI studies using nonlinear registration,^{11–13)} suggesting that the methodology used in the current study was adequate.

We used a standard CT template that is widely employed in CT neuroimaging studies.^{19,24)} Although it is approximately registered to the standard Montreal Neurological Institute brain template,³⁷⁾ there is a slight mismatch in the periventricular areas.²⁴⁾ Therefore, in the preliminary stages of our analyses, we applied some adjustments to the standard CT template by using nonlinear registration methodology.¹⁵⁾ After these adjustments, the right and left CST templates shifted slightly toward the midline. However, the results obtained for the relationship between the CST–lesion volume and the outcome measures were almost the same. For better clinical utility in stroke rehabilitation, we focused on simple image processing procedures using linear registration.

Because the CST narrows as it descends from the primary motor cortex to the cerebral peduncles, the impact of the same sized CST–lesion volumes may be different depending on their locations within the CST. In an attempt to resolve this concern, some previous studies have employed modifications to the counts of CST–lesion voxels according to their location within the CST.^{25–27)} These modifications were typically accomplished by dividing the count of the CST–lesion voxels on each slice by the ratio of the maximum cross-sectional area of the CST to the total cross-sectional

area on that particular slice.^{25–27)} For the preliminary stage of our analyses, we followed this modification methodology. However, the correlations between the modified CST–lesion volumes and long-term outcomes obtained at the preliminary stage were very similar to the final results that were derived without using this modification (**Fig. 3**). In this study we limited the study cohort to patients with putaminal and/or thalamic hemorrhages (**Table 1**). Accordingly, the locations of the lesions were relatively focused in the longitudinal direction (z-axis) within the CST. For clarity of the analytical methodology, in this study, we employed simple estimations of the CST–lesion volumes.

Four patients with severe midline shift were excluded from the final data analysis. The decision to exclude them was based on visual inspection of the images registered to the standard brain. In part because of the linear transformation methodology used, we found that the brain images with midline shift were not appropriately registered to the standard brain. During acute care, the primary clinical concern in such patients is mortality, and the indication for decompression craniotomy is more likely to be the focus than predictors of functional independence in the future. Therefore, we believe that the exclusion of cases with midline shift was reasonable.

This study has several limitations. First, to reduce variability, we sampled only patients with hemorrhage in the thalamus and/or putamen. However, in real-world clinical settings, there are many patients with hemorrhage in the subcortical structures and sub-tentorial regions such as the pons. Further studies that include such patients are needed to clarify the effectiveness of the simple methodology used in this study. Second, the data analyzed were obtained from patients with no history of the neurological disorders commonly encountered in the elderly population (e.g., Parkinson's disease and Alzheimer's disease). Therefore, caution is needed in generalizing the findings of this study to the wider population. Third, the study population was limited to first-ever stroke patients who were functionally independent before the onset of stroke. Consequently, the extent to which our findings are applicable to geriatric patients who needed assistance for ADL before stroke is unclear. Fourth, this study employed only data from conventional CT for the explanatory variable. According to a recent systematic review,³⁾ studies using both imaging data and clinical severity often show better accuracy than those using only imaging data. However, the focus of the current study was to assess the accuracy of conventional CT imaging for outcome prediction. Further studies are needed to determine the relative contributions among various explanatory parameters for

outcome prediction. Fifth, the patient sample size (n=30) was relatively small for a retrospective observational study. However, a recent systematic review³⁾ indicated that, among the 71 existing studies included in the review, the median sample size was 28 (interquartile range 15–50). Accordingly, our sample size was comparable to those of existing studies in this line of research.

Despite these limitations, the results of this study show a correlation between the CST–lesion volume and long-term outcomes in patients with intracerebral hemorrhage, suggesting that conventional CT imaging might be useful for outcome prediction in these patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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