

Predictors of Hemorrhagic Transformation After Intravenous Recombinant Tissue Plasminogen Activator

Prognostic Value of the Initial Apparent Diffusion Coefficient and Diffusion-Weighted Lesion Volume

Magdy Selim, MD, PhD; John N. Fink, MB, ChB, FRACP; Sandeep Kumar, MD; Louis R. Caplan, MD; Clare Horkan, MD; Yi Chen, MS; Italo Linfante, MD; Gottfried Schlaug, MD, PhD

Background and Purpose—Hemorrhagic transformation (HT) is a potentially dangerous complication of thrombolytic therapy. Recent studies suggest that diffusion-weighted MRI (DWI) can help to predict the risk of intracerebral hemorrhage (ICH) after thrombolysis. We sought to examine which pretreatment DWI parameters and clinical data are predictive of ICH after intravenous thrombolysis.

Methods—We retrospectively reviewed our prospective stroke database for patients with ischemic stroke treated with intravenous recombinant tissue plasminogen activator (rtPA) within 3 hours from symptom onset who had DWI before treatment and MRI with T2* sequence or CT 24 to 48 hours later to assess for ICH over the past 4 years. We measured the volumes and voxel-by-voxel apparent diffusion coefficient (ADC) values of the initial DWI lesions and retrieved demographic data, risk factors, National Institutes of Health Stroke Scale (NIHSS) scores on admission, and blood tests results. We examined several variables using univariate and multivariate regression analyses to determine predictors of ICH.

Results—Twenty-nine patients fulfilled our inclusion criteria; 17 patients (58%) had ICH, and of these 4 (13%) had symptomatic ICH and fatal outcome. On univariate analysis, higher systolic blood pressure, NIHSS score, serum glucose level, volume of initial DWI lesion, and absolute number of voxels with ADC value $\leq 550 \times 10^{-6}$ mm²/s were statistically associated with ICH, and all were subjected to multivariate analysis. However, only the absolute number of voxels, ie, volume of ischemic tissue on DWI, with ADC $\leq 550 \times 10^{-6}$ mm²/s emerged as an independent predictor of ICH.

Conclusions—Our findings suggest that volumetric ADC analysis can be used to assess ICH risk after thrombolysis. This may be particularly helpful if rtPA is to be given outside the 3-hour window. (*Stroke*. 2002;33:2047-2052.)

Key Words: hemorrhage ■ magnetic resonance imaging, diffusion-weighted ■ thrombolysis ■ tissue plasminogen activator

Recombinant tissue plasminogen activator (rtPA) remains the only approved treatment for acute ischemic stroke to date.¹ Intracerebral hemorrhage (ICH) is a potentially fatal complication of rtPA therapy. The rate of ICH after rtPA thrombolysis in the National Institute of Neurological Disorders and Stroke (NINDS) study² was 6.4%. Most of these hemorrhages occurred within 24 hours after patients received intravenous rtPA, and almost half of these patients died. Higher rates of ICH (7% to 9%) were reported in the European Cooperative Acute Stroke Study (ECASS) II³ and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS)⁴ trials, which used a 6-hour window for rtPA administration. The risk of ICH, therefore,

is a major concern that limits more widespread use of rtPA in treating acute stroke patients, particularly in patients presenting beyond 3 hours from stroke onset. Identifying clinical, radiological, biochemical, or hematologic predictors of thrombolysis-associated ICH would facilitate clinical decision making and expansion of rtPA use beyond the current 3-hour time window.

In the past few years, diffusion-weighted MRI (DWI) has been increasingly used in stroke centers to guide therapeutic decisions including thrombolysis, particularly outside the 3-hour window.⁵ Recent studies suggest that the DWI findings may help to identify patients who are at increased risk for ICH after thrombolysis.^{6–10} Assessment of the apparent

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From the Department of Neurology, Division of Cerebrovascular Diseases, Beth Israel Deaconess Medical Center, Boston, Mass, and Christchurch School of Medicine, Christchurch, New Zealand (J.N.F.).

Correspondence to Magdy H. Selim, MD, PhD, Beth Israel Deaconess Medical Center and Harvard Medical School, Department of Neurology, 330 Brookline Ave, Boston, MA 02215. E-mail mselim@caregroup.harvard.edu

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diffusion coefficient of water (ADC) within the DWI lesions, in humans and stroke animal models, shows that ADC values are significantly lower in DWI lesion regions that develop ICH than in regions that are salvaged or become infarcted after rtPA.⁷⁻⁹ Using frequency-based ADC analysis, Tong et al⁶ showed that ischemic areas on DWI, obtained within 8 hours from stroke onset, with higher percentage of pixels with $ADC \leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ are at higher risk for developing ICH.

The purpose of this study is 2-fold: (1) to test whether we can replicate the findings of Tong et al⁶ when DWI is obtained within 3 hours from stroke onset and (2) to use pretreatment DWI and clinical data to identify other possible potential predictors of ICH after intravenous rtPA.

Subjects and Methods

Study Design and Patient Selection

We retrospectively reviewed our prospectively collected stroke database from July 1997 until May 2001. We included patients with ischemic stroke, treated with intravenous rtPA within 3 hours from symptom onset according to current guidelines,¹¹ who had DWI before treatment and MRI with T2* sequence or nonenhanced CT scan 24 to 48 hours later to assess for ICH. Patients who were treated after 3 hours, those who received antiplatelet agents or anticoagulants before their second MRI/CT, and those treated with intra-arterial thrombolysis were excluded. The rationale for excluding these patients was based on the possibility that such factors could represent confounding variables to increase the risk of ICH irrespective of initial DWI, clinical, or laboratory parameters.

Data Collection

We retrieved demographic data, risk factors for stroke and hemorrhage, the severity of neurological deficit on admission as assessed by the National Institutes of Health Stroke Scale (NIHSS) score, and blood test results. We examined 27 baseline variables. These included the following: age, sex, symptom-to-needle time, blood pressure at presentation (systolic, diastolic, and mean), history of hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of smoking and aspirin use before thrombolysis, blood glucose, partial thromboplastin time, international normalized ratio, complete blood counts, renal function, and creatine kinase.

We measured the total volumes and ADC, voxel by voxel, of initial DWI lesions; evaluated MRI for the presence of periventricular white matter lesions (leukoaraiosis); and reviewed pretreatment MRI for the vascular distribution of the DWI lesion, MR angiography (MRA) for site of the vascular occlusion, and posttreatment MRA to assess for recanalization. These variables were selected on the basis of the results of previous analyses of the risk factors for ICH after thrombolysis.^{3,6,12}

Clinical Assessment

Clinical status at presentation and during subsequent hospitalization was assessed by NIHSS. Stroke fellows certified for the application of the NIHSS recorded the score. Decision to treat patients with intravenous rtPA was based on NINDS criteria.² Each patient received 0.9 mg/kg of rtPA (maximum 90 mg).

Neurological deterioration after thrombolysis-induced ICH (ie, symptomatic hemorrhagic transformation [HT]) was defined as an increase of ≥ 4 points on the NIHSS score from baseline assessment. Fatal outcome refers to death during hospitalization after the development of ICH. Only in-hospital mortality was addressed in this study. Asymptomatic HT refers to evidence of posttreatment ICH on T2*-weighted MRI or CT without clinical evidence of neurological deterioration (ie, NIHSS is within 3 points of pretreatment score).

MRI Protocol

The MRI protocol in our institution routinely includes DWI, T2*, T1-, and T2-weighted images, non-echo-planar imaging fluid-attenuated inversion recovery (FLAIR) images, and MRA of the intracranial vessels. All MRI studies were performed on a Siemens Vision 1.5-T MR whole-body scanner with echo-planar imaging capability (Siemens Medical Systems). All sequences typically included 20 axial slices of 7-mm thickness with a matrix size of 128×128 and a field of view of 240 mm. Specific sequence details are described in previous publications.¹³

Imaging Interpretation

Areas of ischemia were identified as regions of hyperintensity on pretreatment DWI, in the territory of occluded/stenotic arteries. An artery was considered occluded or severely stenotic if no or poor signal was seen on MRA. Detection of an improved flow signal on post-rtPA MRA indicated recanalization.

ICHs were identified as areas of susceptibility effect (signal loss; darkening) on post-rtPA T2* images that were not present on corresponding pretreatment images. Hemorrhages on CT were defined as high signal, heterogeneous, or homogeneous in regions not associated with calcification seen on initial T2* images. A neuroradiologist interpreted all images, and results of the official neuroradiology report were used to determine the presence versus absence of ICH. Similarly, the neuroradiologist determined the presence versus absence of periventricular white matter lesions on initial MR scans.

Imaging Processing

All images were processed offline with the use of custom-made software implemented in the Advanced Visualization Systems software package (Advanced Visualization Systems) running on a Hewlett Packard workstation. Volumetric assessment of the DWI lesion was performed by drawing a region of interest (ROI) around the hyperintense diffusion lesion, as previously described.¹³ The drawn ROIs were delimited just within the boundary of the visible DWI lesion to avoid partial-volume effects at the boundary of the lesions and inadvertent inclusion of cerebrospinal fluid spaces or normal brain within the region. These ROIs were then transferred to the ADC maps. Two independent observers (M.S. and J.N.F.) drew the ROI on a subset of 8 patients. Because the interobserver agreement was extremely high ($r > 0.91$), only 1 observer (M.S.) drew the remainder of ROI twice, and the average of his measurements was used for the data analysis. The intraobserver agreement was $r = 0.95$.

ADC values were calculated on a voxel-by-voxel basis within the ROI. The image analysis software automatically determined the distribution of ADC values within each DWI lesion. Voxel-by-voxel ADC values within each DWI lesion were grouped into 7 distinct classes ($\leq 450 \times 10^{-6}$ to $\geq 950 \times 10^{-6} \text{ mm}^2/\text{s}$, with an interval of $100 \text{ mm}^2/\text{s}$). The absolute number and percentage of voxels within each class were determined. We also calculated a mean lesional ADC value for each patient.

Statistical Analysis

Patients were classified into 2 major groups: those with ICH and those without ICH. Statistical significance for intergroup differences was assessed by Student's *t* test for continuous variables, Wilcoxon rank sum test for nonparametric data, and Fisher exact test for categorical comparisons. A probability value of < 0.05 was regarded as significant; a corrected probability value for multiple tests on the same sample was calculated for each data set (corrected $P = 0.05/\text{number of variables in each data set}$). Variables with $P \leq 0.1$ on univariate testing were tested in a multivariate linear regression model. In the final model, a level of $P \leq 0.05$ was accepted as statistically significant.

Results

Patient Characteristics

A total of 813 patients were seen by our stroke service between July 1997 and May 2001. Of these, 41 patients were

TABLE 1. Patient Characteristics (Demographic and Clinical Features)

	HT Group (n=17)	Non-HT Group (n=12)	P
Demographics			
Age, mean±SD, y	71±14	73±19	
Sex, men/women	8/9	6/6	
Clinical features			
Symptom-to-needle time, mean±SD, min	164±18	157±22	
NIHSS score, median (range)	20* (5–32)	16.5 (7–22)	0.04
Blood pressure, mean±SD, mm Hg			
Systolic	144±26	158±20	0.07
Diastolic	76±17	74±16	
Mean	87±37	94±33	
Risk factors			
History of hypertension	53%	58%	
History of diabetes	6%	17%	
History of high cholesterol	23%	50%	
History of smoking	29%*	8%	0.03
Aspirin use	41%	50%	

Absent P value indicates $P>0.1$.

* $P\leq 0.05$; corrected $P=0.004$ (0.05/12).

treated with intravenous rtPA within 3 hours from symptom onset; 10 patients were treated with intravenous or intra-arterial thrombolytics between 3 and 6 hours after stroke onset. Twenty-nine patients fulfilled all inclusion criteria for this study (14 men and 15 women). The mean±SD age for all participants was 73±16 years (range, 37 to 94 years). The overall median NIHSS score before administration of rtPA was 18 (range, 5 to 32). The mean±SD symptom-to-needle time was 160±20 minutes (range, 111 to 180 minutes). Twenty-six patients had a follow-up MRI; 3 patients had CT. There were 16 patients with middle cerebral artery (MCA) occlusions, 12 patients with internal carotid artery/MCA occlusions, and 1 patient with basilar artery occlusion, as seen on MRA before thrombolysis. The mean DWI lesion volume before thrombolysis was 62.47±38.14 cm³ (range, 6.55 to 154.72 cm³). The mean±SD ADC for all ischemic lesions was 713±173×10⁻⁶ mm²/s (range, 630×10⁻⁶ to 975×10⁻⁶ mm²/s).

Patient Outcomes

Clinical Features and Risk Factor Profile

Seventeen of the 29 patients (58%; 9 women and 8 men) developed areas of ICH, ranging from small petechiae to parenchymal hematoma,¹⁴ on repeated MRI/CT. Of these, 4 patients (13.8%; all men) had symptomatic ICH and ultimately fatal outcome; all had parenchymal hematomas with space-occupying effect. Twelve patients (6 men and 6 women) did not develop ICH after thrombolysis.

Demographic data, risk factor profile, and baseline clinical findings for these patients are shown in Table 1. A higher percentage of patients who developed ICH had a history of smoking (29% versus 8%; $P=0.03$, Fisher test). Similarly,

TABLE 2. Initial Laboratory Data

	HT Group (n=17)	Non-HT Group (n=12)	P
Complete blood count			
White blood cell count, μL	10±4.1*	7.8±2.3	0.038
Hemoglobin, g/dL	13±2.2	12.7±2.3	
Hematocrit	39.2±5.9	38.81±6.1	
Platelet, $\times 10^3/\mu\text{L}$	267±83*	204±71	0.024
Coagulation parameters			
Partial thromboplastin time, s	23.98±2.35	24.82±3.52	
International normalized ratio	1.04±0.12	1.16±0.15	
Chemistries			
Glucose, mg/dL	148.82±51*	125±22	0.051
Blood urea nitrogen, mg/dL	24.35±10.44	22.9±8.4	
Creatinine, mg/dL	1.14±0.59	1.21±0.95	
Creatine kinase, U/L	74.33±24.1	100±44.88	

Values are mean±SD.

* $P\leq 0.05$; corrected $P=0.005$ (0.05/10).

there was a trend toward a higher NIHSS score on admission in patients who developed ICH compared with those who did not (median, 20 versus 16.5; $P=0.04$, Wilcoxon test). However, neither of these variables reached the threshold for statistical significance when we adjusted for multiple tests performed on the same data set. There were no differences in age, symptom-to-needle time, pretreatment blood pressure measurements, and history of hypertension, diabetes, or hyperlipidemia between patients who developed ICH and those who did not.

Laboratory Results

Results of admission routine laboratory studies before administration of rtPA are summarized in Table 2. There was a trend for higher white blood cell and platelet counts and serum glucose in ICH than in non-ICH patients.

Imaging Findings

Results of DWI and ADC analysis for both ICH and non-ICH groups are shown in Table 3. Initial DWI lesions were larger in patients who developed ICH than in those who did not (75.58±44.21 versus 46.74±22.38 cm³; $P=0.03$, t test). However, there was a substantial overlap among individuals within the 2 groups. There was no difference in the mean ADC value between ICH and non-ICH patients (735.4±107.8 versus 742.09±109) or in the cumulative percentage of voxels with ADC below any given cutoff value (Figure 1), including $\leq 550\times 10^{-6}$ mm²/s. There was a trend,

TABLE 3. MRI Findings

	HT Group (n=17)	Non-HT Group (n=12)	P
DWI lesion volume, cm ³	75.58±44.21*	46.74±22.38	0.032
Voxels with ADC $< 550\times 10^{-6}$ mm ² /s			
Percentage	27.7±15.1%	22.2±15.5%	
Absolute number	2617±1843†	1319±549	0.0172

* $P\leq 0.05$.

†Statistically significant; corrected $P=0.0166$ (0.05/3).

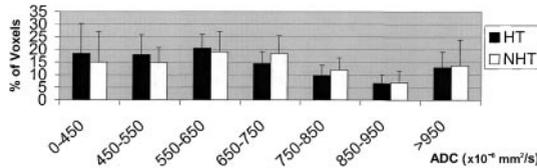


Figure 1. Frequency distribution of ADC values within DWI lesions. NHT indicates non-HT group.

however, for a higher number of voxels with $ADC \leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ in ICH patients (mean, 2617 ± 1843 ; range, 127 to 6091) than non-ICH patients (mean, 1319 ± 549 ; range, 49 to 1932; $P=0.018$, t test).

Pretreatment MRA revealed M1 MCA segment occlusion in 35% of patients with ICH versus 16.6% of non-ICH patients. Approximately 62% (18/29) of all participants recanalized after rtPA; 38% of patients who recanalized developed ICH. Sixty-four percent of patients who developed ICH showed successful recanalization of occluded arteries after treatment with rtPA versus 42% of non-ICH patients. The presence of periventricular white matter disease did not seem to contribute to ICH (41% of patients with ICH versus 50% of those without ICH had MRI evidence of periventricular white matter disease).

Results of Multivariate Analysis

Variables tested in multivariate analysis included systolic blood pressure, NIHSS score before administration of rtPA, white blood cell and platelet counts, serum glucose level, history of smoking, pretreatment DWI ischemic lesion volume, and absolute number of voxels with ADC values $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$. Only the absolute number of voxels with ADC values $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ emerged as an independent predictor of ICH in multiple logistic regression analysis models (odds ratio, 1.176; $P=0.042$).

Symptomatic Versus Asymptomatic HT

Table 4 summarizes the major demographic data, clinical features, laboratory data, and MRI parameters for patients who developed ICH (symptomatic versus asymptomatic). Patients whose ICH led to clinical deterioration or death had higher admission NIHSS score ($P=0.02$, Wilcoxon), greater DWI lesion volume ($P=0.043$, t test), and larger number of voxels with ADC values $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ ($P=0.023$, t test) than those with asymptomatic ICH. The absolute number of voxels with ADC $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ ranged from 2037 to 6091 for symptomatic ICH patients versus 127 to 2781 for asymptomatic ICH (Figure 2). There were no significant differences in age or symptom-to-needle time between these patients. Pretreatment systolic blood pressure, serum glucose level, and percentage of voxels with ADC $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ were higher in patients with symptomatic ICH. The mean ADC of DWI lesions in patients with symptomatic ICH was lower than that of patients with asymptomatic hemorrhages. However, none of these differences approached the threshold for statistical significance. Similarly, a higher percentage of these patients used aspirin before their stroke compared with those whose ICH was asymptomatic (60% versus 36%).

TABLE 4. Patient Characteristics, Laboratory Data, and MRI Findings in HT Patients

	Asymptomatic HT Group (n=13)	Symptomatic HT Group (n=4)
Patient characteristics		
Age, y	70±16	72±11
Symptom-to-needle time, min	162±17	169±21
NIHSS score, median	17	23*
Systolic blood pressure, mm Hg	138±20	158±36
History of hypertension	73%	17%
History of smoking	36%	18%
Aspirin use	36%	60%
Laboratory data		
White blood cell count, μL	10±4	8.8±3
Hemoglobin, g/dL	12.5±1.9	13.9±2.6
Hematocrit	37.8±4.4	41.7±7.7
Platelet, $\times 10^3/\mu\text{L}$	297±75	201±62
Glucose, mg/dL	137.6±51.8	169.3±46.7*
MRI findings		
DWI volume, cm^3	67.86±35.53	118.86±31.31*
Mean ADC, $\times 10^{-6} \text{ mm}^2/\text{s}$	740.8±114.1	719.1±106.3
Voxels with ADC $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$		
Percentage	28.5±14.7	31.3±17.9
Absolute number	2185±1312	4598±1712*
Periventricular white matter disease	36.4%	50%

Values are mean±SD unless indicated otherwise. * $P<0.05$.

Discussion

The main finding of this study is that voxel-by-voxel volumetric analysis of pretreatment ADC can help to identify patients at increased risk for ICH. We found that the absolute volume of ischemic tissue on DWI with ADC values below a cutoff of $550 \times 10^{-6} \text{ mm}^2/\text{s}$ was significantly associated with ICH risk after treatment with intravenous rtPA.

Few experimental and clinical studies have investigated the use of modern DWI findings in acute stroke patients to predict impending ICH.⁶⁻¹⁰ In a study of 18 patients treated with either combined intravenous/intra-arterial or only intra-arterial rtPA within 6 hours from stroke onset,⁹ pretreatment

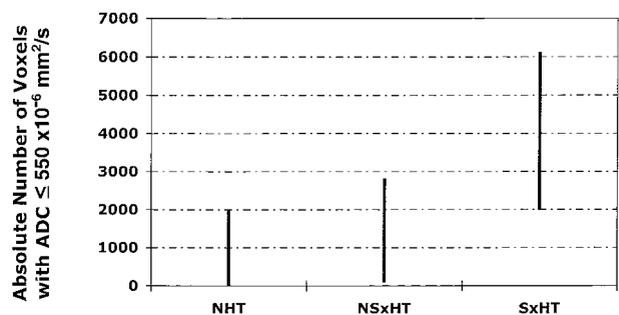


Figure 2. Differences in absolute number of voxels with ADC $\leq 550 \times 10^{-6} \text{ mm}^2/\text{s}$ (range) between patients with symptomatic HT (SxHT), patients with asymptomatic HT (NSxHT), and patients without HT (NHT).

MRI ADC values were significantly lower in ischemic subregions that developed ICH than in regions that did not. A more recent study of 16 patients treated with rtPA (14 intravenous, 2 intra-arterial) within 3 hours from stroke onset⁸ showed similar results, suggesting that measurement of ADC values within the DWI ischemic lesions may be a useful tool to predict the risk of ICH. Using voxel-by-voxel frequency-based ADC analysis, Tong et al⁶ reported that at least 40% of voxels in DWI lesions of patients with HT possessed an ADC value of $\leq 550 \times 10^{-6}$ mm²/s, suggesting that this cutoff ADC value could be used to discriminate between HT- and non-HT-destined lesions. However, these studies had some limitations. The initial DWI scans were performed 3 to 8 hours after stroke onset,^{6,8,9} only after administration of rtPA,^{6,8} and all patients included in 1 study⁹ were treated with intra-arterial rtPA. Therefore, it is uncertain whether these results would hold if DWI were obtained within 3 hours from stroke onset and before intravenous administration of rtPA.

We sought to avoid the drawbacks of earlier studies and to replicate the findings of Tong et al⁶ in patients with ischemic stroke treated with intravenous rtPA within 3 hours from symptom onset, according to NINDS criteria, who had DWI before administration of rtPA.

In contrast to earlier findings by Tong et al,⁶ we were unable to identify any significant differences in cumulative percentages of voxels with ADC below any cutoff value, including 550×10^{-6} mm²/s, between ICH and non-ICH patients. Instead, we found that the absolute number, not percentage, of voxels with ADC values $\leq 550 \times 10^{-6}$ mm²/s is significantly higher in patients who developed ICH. These findings are nonetheless concordant with those of Tong et al⁶ in that a cutoff ADC value of 550×10^{-6} mm²/s could be used to discriminate between HT- and non-HT-destined DWI lesions. The discrepancy in results between these 2 studies is likely attributed to differences in study design and a relatively small number of patients.

A number of studies indicate that factors such as advancing age, elevated blood pressure, high serum glucose level, increasing severity of pretreatment deficits as assessed by NIHSS, and embolic occlusion of M1 MCA segment are associated with higher risk for ICH after treatment with rtPA.¹⁴⁻¹⁷ These factors were absent from our final list of ICH predictors. Our results could be related to the relatively small sample size and limited statistical power. The lack of significant association between age and ICH risk is consistent with results from several other studies.^{6,9,18} The potential relationship between smoking and ICH risk, observed in our preliminary analysis, has not been previously reported. Smoking is a well-established risk factor for stroke and vascular disease. This potential relationship should be explored further in future studies. Our findings that more patients with M1 MCA segment occlusion and successful recanalization after thrombolysis had ICH are consistent with previous studies.^{16,17} Reperfusion is likely to cause bleeding owing to perfusion of ischemic and injured tissue and breakdown of blood-brain barrier.¹⁹

In this study the volume of initial DWI lesions was larger in ICH versus non-ICH and in symptomatic ICH than in asymptomatic ICH patients. However, the DWI lesion vol-

ume did not significantly contribute to the final model for predicting ICH. Indeed, patients with both small and large DWI lesions developed ICH. Our results show that it is the volume of ischemic tissue within the DWI abnormality with $\text{ADC} \leq 550 \times 10^{-6}$ mm²/s that predicts the risk of ICH best. Experimental models have confirmed that the ischemic tissues that possess the lowest ADC values are associated with the most severe ischemic histopathological changes^{20,21} and early blood-brain barrier damage^{19,22} and are therefore at higher risk for bleeding.

The reported rate of early ICH after thrombolysis varies from 5% to 50%.^{2-4,14,17,18} The ICH and mortality rates in our study are slightly higher than those of some previous studies. We believe that this is largely attributed to differences in the diagnostic criteria for HT, imaging technique, and patient population. For example, patients in the present study had more severe strokes, as evidenced by their NIHSS score and DWI lesion volume. We performed follow-up T2* (susceptibility-weighted) MRI on 26 of our 29 patients. There is growing evidence that MRI, particularly T2*, is more sensitive than CT to acute ICH.^{23,24} Routine use of T2* may have allowed detection of subtle petechial hemorrhages along the margins of the infarct that would have been missed on conventional MRI/CT scans.

It is noteworthy that performing a follow-up MRI or CT 24 to 48 hours after thrombolysis to assess for HT and recanalization, regardless of the patient's clinical status, is a routine part of our protocol. This excludes possible selection bias in the interpretation of our findings.

Symptomatic ICH, which can be fatal, is of paramount clinical significance. Our results show a trend for a higher NIHSS score, DWI lesion volume, and number of voxels $\leq 550 \times 10^{-6}$ mm²/s among patients whose ICH was symptomatic, in comparison to patients with asymptomatic ICH. Careful review of ADC data, voxel by voxel and patient by patient, shows that all patients who suffered symptomatic ICH and eventually died had ≥ 2000 voxels with $\text{ADC} \leq 550 \times 10^{-6}$ mm²/s. This contrasts with patients who did not develop ICH, who all had < 2000 voxels with $\text{ADC} \leq 550 \times 10^{-6}$ mm²/s. This points to a value of 2000 voxels with $\text{ADC} \leq 550 \times 10^{-6}$ mm²/s as a potential cutoff threshold. However, this study only includes 4 patients with symptomatic ICH. Such a small number makes definite conclusions problematic.

In conclusion, our study shows that the absolute volume of ischemic tissue on DWI with ADC values below a cutoff of 550×10^{-6} mm²/s is significantly associated with HT and that volumetric ADC analysis can be used to assess HT risk before thrombolysis. It should be emphasized that the significance of these findings extends beyond improving the safety of thrombolysis within the current 3-hour window. Identifying reliable predictors of thrombolysis-induced HT would greatly facilitate current efforts to extend the use of rtPA beyond a clock-determined therapeutic window. The present study has limitations caused by its retrospective nature and relatively small sample size. Our findings should be validated in an independent cohort, and the feasibility of volumetric ADC analysis during the hyperacute setting should be examined

prospectively before criteria based on these findings are used for clinical decision making.

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