Thrombus Volume as a Predictor of Nonrecanalization After Intravenous Thrombolysis in Acute Stroke

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Background and Purpose—We investigated whether measuring the volume and density of a thrombus could predict nonrecanalization after intravenous thrombolysis.

Methods—This study included a retrospective cohort to develop a computed tomography marker of thrombus for predicting nonrecanalization after intravenous thrombolysis and a prospective multicenter cohort for validation of this marker. The volume and density of thrombus were measured semiautomatically using 3-dimensional software on a baseline thin-section noncontrast computed tomography (1 or 1.25 mm). Recanalization was assessed on computed tomography angiography or magnetic resonance angiography immediately after intravenous thrombolysis or conventional angiography in patients who underwent further intra-arterial treatment. Nonrecanalization was defined as a modified Thrombolysis in Cerebral Infarction grade 0, 1, 2a.

Results—In the retrospective cohort, 162 of 214 patients (76.7%) failed to achieve recanalization. The thrombus volume was significantly larger in patients with nonrecanalization than in those with successful recanalization (149.5±127.6 versus 65.3±58.3 mm^3; $P<0.001$). In the multivariate analysis, thrombus volume was independently associated with nonrecanalization ($P<0.001$). The cutoff for predicting nonrecanalization was calculated as 200 mm^3. In the prospective multicenter validation study, none of the patients with a thrombus volume ≥200 mm^3 among 78 enrolled patients achieved successful recanalization. The positive and negative predictive values were 95.5 and 29.4 in the retrospective cohort 100 and 23.3 in the prospective validation cohort, respectively. The thrombus density was not associated with nonrecanalization.

Conclusions—Thrombus volume was predictive of nonrecanalization after intravenous thrombolysis. Measurement of thrombus volume may help in determining the recanalization strategy and perhaps identify patients suitable for direct endovascular thrombectomy. **(*Stroke*. 2018;49:2108-2115. DOI: 10.1161/STROKEAHA.118.021864.)**

Key Words: cerebral infarction ■ computed tomography angiography ■ stroke ■ thrombus

Intravenous tPA (tissue-type plasminogen activator) is the standard therapy for acute ischemic stroke.[1,2] However, the recanalization rate is poor for large proximal artery occlusions.[3] Although a meta-analysis demonstrated that endovascular thrombectomy (EVT) was associated with higher rates of successful recanalization than intravenous tPA,[4] the first option in patients with acute stroke is still intravenous tPA treatment. This is partly because intravenous tPA is relatively safe and can be administered more rapidly than EVT. Another reason would be the lack of markers that can accurately predict the group of patients that would fail to achieve recanalization after intravenous tPA treatment.

Assessment of thrombus characteristics may be a key imaging biomarker for predicting response to intravenous tPA. For utility in clinical practice, the measurement of thrombus characteristics on imaging should be accurate, reliable, minimally affected by angioarchitectures, easy, and rapid. The thrombus volume and density can be measured accurately and reliably on thin-section noncontrast computed tomography

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(NCCT) using 3-dimensional (3D) software.[5–7] In this study, we investigated whether nonrecanalization could be predicted by measuring the volume and density of thrombus on thin-section NCCT using semiautomatic 3D software. We also determined a cutoff for predicting nonrecanalization using a retrospective cohort and then validated the cutoff in a prospective multicenter study.

Methods

Study Design and Population

The data that support the findings of this study are available from the corresponding author on reasonable request. This study included patients who received intravenous tPA for anterior circulation stroke. Two different populations were included in this study: a retrospective cohort to develop the CT marker of thrombus for predicting nonrecanalization after intravenous tPA and a prospective multicenter cohort to validate the study.

The population for the retrospective study was derived from a prospectively enrolled CT-based thrombus imaging cohort.[8] The patients were consecutively enrolled in 3 university hospitals between November 2006 and October 2009. One hospital continued enrollment of the patients until December 2015.

For the validation, a multicenter prospective study was designed, and 9 hospitals participated in the study. Inclusion criteria included patients who were treated with intravenous tPA within 4.5 hours of symptom onset and had visible thrombi in the distal internal carotid artery or middle cerebral artery. Patients were consecutively enrolled between February 2016 and August 2017.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board of each study hospital. We obtained written informed consent from the patients for the prospective cohort. The need for informed consent was waived for the retrospective cohort.

Imaging Protocol and Reperfusion Therapy

All patients were treated with intravenous tPA (Actilyse; Boehringer-Ingelheim, Ingelheim, Germany) at a standard dose of 0.9 mg/kg (10% as a bolus and then 90% as an infusion for 60 minutes) within 3 hours after onset until December 2013 and within 4.5 hours of onset between January 2014 and August 2017.

For the retrospective cohort, patients underwent thin-section (1 or 1.25 mm) NCCT before intravenous thrombolysis. At the end of intravenous tPA infusion, follow-up NCCT and CT angiography (CTA) were performed. Further intra-arterial thrombolysis or EVT was performed if the NIHSS score had not improved by >51% at the end of tPA infusion or proximal arterial occlusion was detected on the follow-up CTA.

For the prospective multicenter study, patients underwent thin-section (1 or 1.25 mm) NCCT and CTA before intravenous thrombolysis. Further EVT was undergone if patients did not show clinical improvement after the intravenous tPA treatment. EVT was also allowed before the end of intravenous tPA infusion. In patients who were not treated with EVT or who were not evaluated with conventional angiography, CTA or magnetic resonance angiography was performed immediately after intravenous tPA infusion.

Assessment of Arterial Recanalization and Clinical Outcomes

The status of recanalization after intravenous tPA treatment was determined according to the modified Thrombolysis in Cerebral Infarction grade on diagnostic angiograms taken during intra-arterial or endovascular treatment or follow-up CTA or magnetic resonance angiography taken immediately after tPA.[9] For the retrospective cohort, recanalization was also assessed based on the arterial occlusive lesion (AOL) grade because most patients were assessed on CTA. Two neurologists (Drs Yoo and Park) independently graded the recanalization status without any information on the patients' clinical status. Two investigators (Drs Hwang and Kim), who were blinded to the recanalization status, independently assessed the degree of collaterals in the prospective validation cohort based on the Tan collateral score.[10] Any discrepancy was resolved by consensus. Nonrecanalization was defined as modified Thrombolysis in Cerebral Infarction grade 0, 1, or 2a, or AOL grade 0 or 1. Functional outcomes at 3 months were assessed using the modified Rankin Scale. We defined modified Rankin Scale 0 or 1 as an excellent outcome.

Measurement of Thrombus Volume and Density on NCCT

The volume and density of thrombus were measured semiautomatically on baseline thin-section NCCT by using 3D software (Xelis; Infinitt, Seoul, Korea).[6,11] Briefly, the thrombus area was identified by pixel segmentation at the threshold between 50 and 100 Hounsfield unit (HU). The pixels between 50 and 100 HU were shown in red, which helped to identify the thrombus. When a hyperdense artery (thrombus area) was identified, a region of interest for thrombus was determined by clicking any portion within the hyperdense area. Then, by clicking the Dilate icon, automatic pixel dilation and region growing were performed to the thrombus margin at a range of 40 and 100 HU. After this process, the volume and density of the thrombus were automatically calculated and shown on a screen. In patients with available CTA source images, by opening the CTA source and NCCT images, the CTA source image was instantly processed to render maximum intensity projection images, and these were displayed on a screen side by side with the NCCT images. By clicking the crosslink button, maximum intensity projection and NCCT images were synchronized and moved simultaneously on scrolling. This allowed easy identification of the occlusion site and thrombus. In most cases, this entire process could be completed in 1 minute in patients with a large proximal artery occlusion (Movie I in the online-only Data Supplement).

When determining the thrombus density, the standardization process was performed. The HU value of the culprit thrombus was standardized to the HU value of the contralateral normal M1 segment of the middle cerebral artery. The corrected HU of the thrombus (HU corrected) was equal to the mean contralateral HU×(HU ipsilateral/HU contralateral).[8] When any artery other than the middle cerebral artery was occluded, the HU of the normal M1 segment was used for the standardization. Two neurologists (Drs Yoo and Baek) performed the measurements independently without knowledge of any clinical information, and the interrater agreement was excellent (k=0.989, $P<0.001$).

Measurement of Thrombus Length on CTA

Two neurologists (Drs Hwang and Kim), who were blinded to the results of recanalization, measured the thrombus length independently on CTA-maximum intensity projection images in the prospective validation cohort. The interrater reliability was good (intraclass correlation coefficient, 0.795; 95% CI, 0.653–0.879; $P<0.001$). The mean values of the length measured by the 2 raters were used for further analyses.

Statistical Analyses

Continuous variables were presented as mean±SD or median (interquartile range). Categorical variables were presented as number (percentage). Patient characteristics, total dose of tPA, and the thrombus location and volume were compared according to the recanalization status using the Student t test, χ^2 test, Wilcoxon rank-sum test, or Fisher exact test. After univariate analyses, multiple logistic regression analysis was performed to identify the factors associated with nonrecanalization and excellent outcomes. Age, sex, thrombus volume, thrombus density, and variables with P values of <0.1 in the

univariate analyses were used for multivariate analysis. The possibility of recanalization according to the thrombus volume was calculated by a regression curve. We also sought to identify the optimal cutoff value of the thrombus volume for predicting nonrecanalization. For this, we calculated reference intervals by using a mean±2 SD.[12] This cutoff value was verified by calculating the Youden index and 95th percentile (assuming type I error of 5%) on jitter distribution. After determining the cutoff value, we also sought to identify the sensitivity and specificity for predicting nonrecanalization.

The sample size for the prospective study was calculated based on the data of the retrospective cohort. In the retrospective analysis, the area under the curve (AUC) of the receiver operating characteristics according to the thrombus volume was 0.744, and the nonrecanalization to recanalization ratio was 162:52. We set the AUC criteria at 0.5, the significance level at 0.05, and the power at 0.9. Considering these parameters, the estimated sample size was 78 patients.

In addition, we performed comparative analysis between the volume and the length in 78 patients of the prospective validation cohort. We calculated the AUC using the bootstrapping method. A general estimation equation was calculated to determine the diagnostic performance for the optimal cutoff. We also calculated Nagelkerke R-square to evaluate how much of the variation in tPA success was explained by the thrombus volume or the thrombus length. Statistical analyses were performed with SAS (version 9.2, SAS Inc, Cary, NC) or R package (version 3.4.0). Variables with P values <0.05 were considered statistically significant, and all P values were 2 sided.

Results

Demographic Characteristics

A total of 214 patients were included in the retrospective cohort, and 78 patients were enrolled in the prospective validation study (Figure I in the online-only Data Supplement). Demographic characteristics were not different between the retrospective cohort and the prospective validation cohort except that dyslipidemia was more frequent in the prospective validation cohort (Table 1). Hemoglobin levels and number of platelets were higher in the retrospective cohort (Table 1). The mean thrombus volume was 129.0±120.1 mm^3 in the retrospective cohort and 133.1±108.6 in the prospective validation cohort (P=0.780). The mean thrombus density was higher in the retrospective cohort than in the prospective validation cohort (53.5±9.0 versus 51.5±3.6; P=0.007). The median time from tPA bolus to follow-up angiography was similar (52.5 minutes [interquartile range, 38–76 minutes] in the retrospective cohort and 54.5 minutes [interquartile range, 37–86 minutes] in the prospective validation cohort; P=0.467; Table 1).

Factors Associated With Nonrecanalization

In the retrospective cohort, recanalization status was assessed with CTA in 204 patients (95.3%) and with digital subtraction angiography in 10 patients (4.7%). Of the 214 patients, 162 patients (76.7%) failed to achieve recanalization (Table I in the online-only Data Supplement). In the prospective validation cohort, recanalization status was assessed with digital subtraction angiography in 70 patients (89.7%), with magnetic resonance angiography in 7 patients (9.0%), and with CTA in 1 patient (1.3%). Of the 78 patients, recanalization failed in 64 patients (82.1%; Table I in the online-only Data Supplement).

The mean thrombus volume was significantly larger in the group of patients with nonrecanalization than in those with recanalization, both in the retrospective cohort and in the prospective validation cohort (retrospective cohort, 149.5±127.6 versus 65.3±58.3 mm^3; P<0.001 and prospective validation cohort, 147.8±111.4 versus 66.1±62.5 mm^3; P=0.001). As the thrombus volume increased, the probability of successful recanalization decreased both in the retrospective and prospective validation cohorts (Figure 1A and 1B). The AUC value according to the thrombus volume was 0.741 (95% CI, 0.668–0.815) in the retrospective cohort and 0.744 (95% CI, 0.604–0.884) in the prospective validation cohort. On multivariate analysis, the thrombus volume was independently associated with nonrecanalization (Tables 2 and 3). In the analysis with the AOL grade, thrombus volume was also associated with nonrecanalization (Tables II and III in the online-only Data Supplement).

Univariate and multivariate analyses showed that the mean thrombus density (corrected HU) was higher in the patients with nonrecanalization than in those with successful recanalization in the retrospective cohort (Table 2) but not in the prospective validation cohort (Table 3).

Cutoff of Thrombus Volume for Predicting Nonrecanalization

We determined the cutoff in the retrospective cohort based on the modified Thrombolysis in Cerebral Infarction grade. The mean and SD of the successful recanalization group was 65.3±58.3 mm^3, and accordingly, the upper range of the calculated reference intervals was 181.9 mm^3. On the jitter distribution, the Youden index was the highest at a thrombus volume of 50.2 mm^3, fluctuated until 191.5 mm^3, and then continuously decreased (Figure IIA in the online-only Data Supplement). The cutoff based on AOL grade was also calculated as 191.5 mm^3. From these results, we estimated 200 mm^3 as the optimal cutoff for predicting nonrecanalization.

We investigated the validity of this cutoff of 200 mm^3 in the prospective multicenter validation cohort. The mean and SD of thrombus volume in the successful recanalization group was 78.1±63.8 mm^3, and accordingly, the upper range of the calculated reference intervals was 205.7 mm^3. On the jitter distribution, the Youden index was the highest at a thrombus volume of 82.4 mm^3, fluctuated until ≈190.1 mm^3, and then continuously decreased (Figure IIB in the online-only Data Supplement). These findings were similar to those in the retrospective cohort. None of the patients with a thrombus volume ≥200 mm^3 achieved successful recanalization. The positive and negative predictive values for predicting nonrecanalization were 95.5 (95% CI, 89.3–101.6) and 29.4 (95% CI, 22.6–36.3) in the retrospective cohort, and those were 100 (100–100) and 23.3 (12.6–34.0) in the prospective validation cohort (Table IV in the online-only Data Supplement).

Comparison Between the Thrombus Volume and Length

Among 78 patients, the length of thrombus could be measured in the 69 patients (88.5%). In the remaining 9 patients, the distal end of thrombus could not be determined because of poor collaterals. The AUC for predicting nonrecanalization was significant in the volume (0.744, 95% CI, 0.604–0.884; P=0.0006) but insignificant in the length (0.677, 95% CI, 0.490–0.865; P=0.064). Although the AUC was higher

Table 1. Baseline Characteristics of the Enrolled Patients

	Retrospectively Enrolled Patient (n=214)	Prospectively Enrolled Patient (n=78)	*P* Value
Demographics			
Age, y	66.6±11.7	67.4±13.2	0.630
Sex, male	125 (58.4)	37 (47.4)	0.124
Risk factors			
Hypertension	141 (65.9)	48 (61.5)	0.582
Diabetes mellitus	50 (23.4)	26 (33.3)	0.117
Dyslipidemia	26 (12.1)	23 (29.5)	0.001
Current smoker	47 (22.0)	11 (14.1)	0.186
Atrial fibrillation	115 (53.7)	37 (47.4)	0.411
Stroke cause			0.077
Cardioembolism	118 (55.1)	41 (52.6)	
Large artery atherosclerosis	44 (20.6)	10 (12.8)	
Negative evaluation	22 (10.3)	17 (21.8)	
≥2 causes	25 (11.7)	7 (9.0)	
Other determined	5 (2.3)	3 (3.9)	
Initial NIHSS score	16 (12–19)	15 (11–19)	0.358
Location of thrombus			0.117
Distal internal carotid artery	32 (15.0)	16 (20.5)	
Middle cerebral artery M1	119 (55.6)	48 (61.5)	
Middle cerebral artery M2	63 (29.4)	14 (17.9)	
tPA dose, mg	55.4±10.1	55.6±10.7	0.879
Thrombus volume, mm^3	129.0±120.1	133.1±108.6	0.780
Thrombus density, HU	53.5±9.0	51.5±3.6	0.007
Hemoglobin, g/dL	13.9±1.6	13.4±1.8	0.034
White blood cells, $\times 10^9$/L	8.1±2.6	7.7±2.6	0.230
Platelets, $\times 10^9$/L	230.4±62.7	208.5±58.9	0.007
Follow-up angiography modality			<0.001
CT angiography	204 (95.3)	1 (1.3)	
MR angiography	0	7 (9.0)	
Conventional angiography	10 (4.7)	70 (89.7)	
Time parameters			
Onset to initial NCCT time, min	63 (44–104)	81.5 (46–131)	0.107
Initial NCCT to tPA time, min	23 (17–30)	20 (14–33)	0.194
tPA to follow-up angiography time, min	52.5 (38–76)	54.5 (37–86)	0.467
Initial NCCT to follow-up angiography time, min	80 (61–103)	79.5 (59–112)	0.947

Values are presented as n (%), mean±SD, or median (interquartile range). Stroke cause was determined based on the Trial of ORG 10172 in acute stroke treatment classification system. CT indicates computed tomography; HU, Hounsfield unit; MR, magnetic resonance; NCCT, noncontrast CT; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

in the volume measurement than length measurement, it was not significant (*P*=0.450). Nagelkerke R-square for the volume (17.03%) was higher than that for the length (10.4%). When we determined the diagnostic performance for the optimal cutoff, the sensitivity was significantly higher in the volume (79.7, 95% CI, 69.831–89.545) than in the length (65.625, 95% CI, 53.989–77.262; *P*=0.0428). The accuracy tended to be higher in the volume (76.923, 95% CI, 67.573–86.273) than in the length (66.667, 95% CI, 56.205–77.128; *P*=0.097).

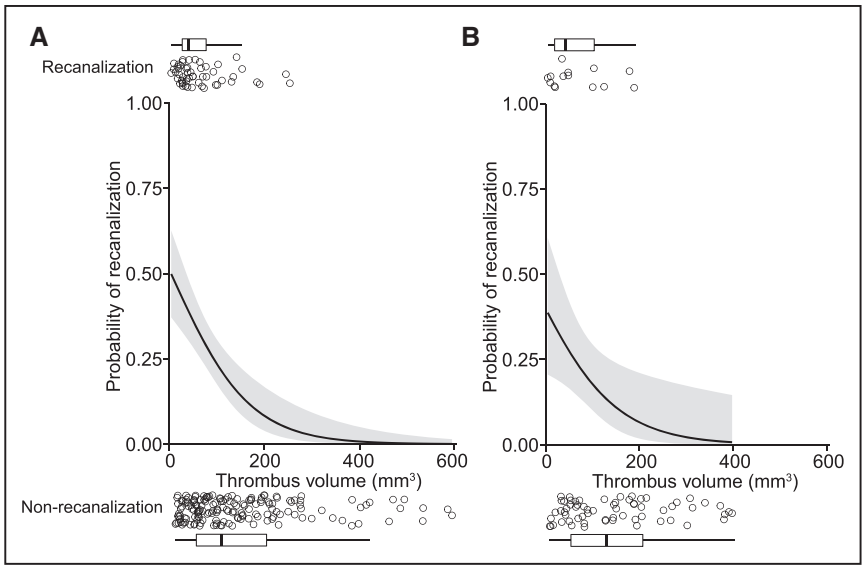

Figure 1. Logistic regression curve of the estimated probability for successful recanalization by intravenous thrombolysis depending on the thrombus volume (**A**, retrospective cohort; **B**, prospective validation cohort).

Association of Thrombus Volume With Functional Outcomes

We investigated the factors associated with excellent functional outcomes at 3 months in the retrospective cohort. Data of modified Rankin Scale at 3 months was available in 209 patients (97.7%). Of them, 94 patients (45.0%) had excellent outcomes (modified Rankin Scale <2). Excellent outcomes were less frequent in patients with a thrombus volume ≥200 mm^3 than in those with a thrombus volume <200 mm^3 (8.5% versus 28.7%; P<0.001; Figure 2). On multivariate analysis, excellent functional outcomes were associated with a smaller thrombus volume, initial stroke severity, and successful recanalization (Table V in the online-only Data Supplement).

Discussion

This study showed that the thrombus volume was associated with recanalization at the end of intravenous tPA treatment. With the increasing thrombus volume, the probability of

Table 2. Factors Associated With the Nonrecanalization of the Occluded Cerebral Artery in the Retrospective Cohort

	Univariate Analysis			Multivariate Analysis	
	Not Recanalized (n=162)	Recanalized (n=52)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age, y	66.4±11.9	67.1±11.5	0.696	0.981 (0.946–1.015)	0.284
Sex, male	92 (56.8)	33 (63.5)	0.396	0.630 (0.262–1.460)	0.288
Hypertension	109 (67.3)	32 (61.5)	0.447		
Diabetes mellitus	35 (21.6)	15 (28.8)	0.283		
Dyslipidemia	21 (13.0)	5 (9.6)	0.520		
Current smoker	34 (21.0)	13 (25.0)	0.543		
Atrial fibrillation	88 (54.3)	27 (51.9)	0.763		
Hemoglobin, g/dL	13.8±1.6	14.0±1.6	0.583		
White blood cell count, ×10^9/L	8.2±2.5	8.0±2.9	0.619		
Platelet count, ×10^9/L	234.0±64.9	219.2±54.7	0.138		
tPA dose, mg	55.1±9.9	56.2±10.9	0.485		
Initial NIHSS score, range			<0.001	1.625 (1.135–2.378)	0.010
First quartile (2–11)	27 (57.4)	20 (42.6)			
Second quartile (12–15)	39 (67.2)	19 (32.8)			
Third quartile (16–18)	46 (92.0)	4 (8.0)			
Fourth quartile (19–30)	50 (84.7)	9 (15.3)			
Thrombus volume, mm^3	149.5±127.6	65.3±58.3	<0.001	1.008 (1.003–1.014)	0.006
Thrombus density, HU	54.3±9.3	50.1±7.0	0.002	1.057 (1.002–1.119)	0.047

Values are presented as n (%), mean±SD, or median (interquartile range). HU indicates Hounsfield unit; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

Table 3. Factors Associated With the Nonrecanalization of the Occluded Cerebral Artery in the Prospective Cohort

	Univariate Analysis			Multivariate Analysis	
	Not Recanalized (n=64)	Recanalized (n=14)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age, y	68.5±11.8	62.2±17.7	0.221	1.016 (0.960–1.075)	0.578
Sex, male	27 (42.2)	10 (71.4)	0.047	0.210 (0.023–1.107)	0.076
Hypertension	38 (59.4)	10 (71.4)	0.401		
Diabetes mellitus	20 (31.2)	6 (42.9)	0.404		
Dyslipidemia	21 (32.8)	2 (14.3)	0.211		
Current smoker	7 (10.9)	4 (28.6)	0.102		
Atrial fibrillation	31 (48.4)	6 (42.9)	0.705		
Hemoglobin, g/dL	13.4±1.8	13.3±2.0	0.924		
White blood cell counts, $\times10^9$/L	7.7±2.5	8.0±2.8	0.668		
Platelet counts, $\times10^9$/L	212.3±59.4	191.1±55.2	0.225		
tPA dose, mg	54.3±9.8	61.4±13.3	0.026	0.959 (0.883–1.034)	0.283
Initial NIHSS score, range			0.188		
First quartile (1–11)	15 (71.4)	6 (28.6)			
Second quartile (12–15)	18 (90.0)	2 (10.0)			
Third quartile (16–19)	15 (75.0)	5 (25.0)			
Fourth quartile (19–25)	16 (94.1)	1 (7.1)			
Collateral score	2 (1–2)	2 (2–3)	0.011	0.287 (0.064–0.900)	0.059
Thrombus volume, mm^3	147.8±111.4	66.1±62.5	0.001	1.011 (1.002–1.025)	0.044
Thrombus density, HU	52.2±6.9	52.1±6.0	0.964	0.957 (0.836–1.081)	0.492

Values are presented as n (%), mean±SD, or median (interquartile range). HU indicates Hounsfield unit; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

recanalization was significantly decreased. We found that patients with thrombi ≥200 mm^3 rarely achieved recanalization after intravenous tPA infusion. We demonstrated that this cutoff of 200 mm^3 for predicting nonrecanalization was valid in a prospective multicenter study. This cutoff was also associated with functional outcomes at 3 months, which were independent of the initial stroke severity and recanalization.

Several studies have showed an association between thrombus size and recanalization after intravenous tPA. They have determined thrombus length and shown the association between thrombus length and recanalization/nonrecanalization in patients treated with intravenous tPA.[13–16] However, the reported cutoffs of thrombus length for predicting nonrecanalization after intravenous tPA vary among studies, and they lack validation studies. Determination of thrombus length is affected by angioarchitectures, branching arteries, and spatial orientation of the arteries.[7] On CTA or magnetic resonance angiography, determination of the thrombus length is based on the absence of contrast opacification, which means that the distal end of the thrombus depends on backflow from the collaterals. Therefore, in cases with poor collaterals, the thrombus length is often overestimated or unmeasurable.[7] In fact, we could not measure the length on CTA in 11.5% because of poor collaterals. These limitations could be overcome by direct measurement of the thrombus volume using 3D imaging software.

Although previous studies have shown the association between recanalization and the average density of the thrombus.[17–19] No such association was found in the prospective multicenter cohort of this study. This finding suggests that thrombus density may not be a reliable marker for predicting nonrecanalization after intravenous tPA treatment. In previous studies, the region of interest for measurement was defined by manually outlining the thrombus margin or drawing small circles within the thrombi. In this study, pixels of the entire thrombus could be included for measurement without the risk of a selection bias because the region of interest was defined automatically based on HU. However, determination of perviousness based on simultaneous measurements of density on NCCT and CTA may be helpful for the prediction

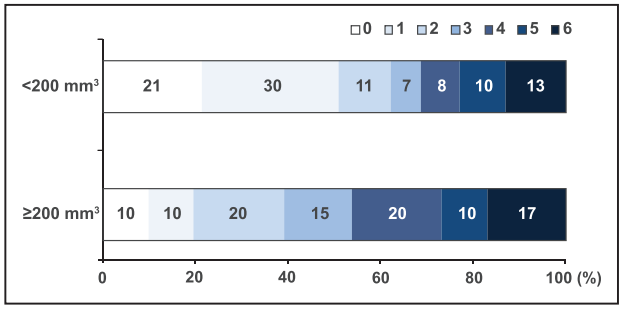

Figure 2. Functional outcomes (modified Rankin Scale) at 3 months according to the thrombus volume.

of recanalization after tPA treatment. The perviousness of thrombus can be determined by calculating the increase in HU on CTA compared with NCCT. Complete recanalization was more frequent in the presence of pervious thrombus, which may suggest that thrombus was more pervious to tPA.[20]

In addition to its accuracy, the major limitation of predicting nonrecanalization based on thrombus imaging has been its usability in clinical practice in terms of rapidity, ease of use, and reliability. In this study, the volume and density of the thrombus could be measured rapidly. Easy identification of the thrombus was made possible by providing a side by side view of CTA-maximum intensity projection images synchronized with thin-section NCCT with colored pixels of the potential thrombus areas. Interrater agreement was also excellent. These features may enhance its usability in clinical practice.

Currently, one of the most important questions in patients with large proximal artery occlusions is whether intravenous tPA before EVT is beneficial. Previous meta-analysis and post hoc analysis of clinical trials showed no apparent benefit of intravenous tPA to patients who received intravenous tPA followed by EVT.[21–23] However, other meta-analysis showed better outcomes and higher recanalization in patients who underwent EVT with intravenous thrombolysis than those with direct EVT.[24] Although we need evidence from ongoing or future randomized trials on this issue, direct EVT may benefit at least some patients. Thrombus imaging–based identification of patients who may fail to achieve recanalization after intravenous tPA may aid in the selection of those who could benefit from direct EVT.

This study has limitations. Because the retrospective cohort lacked baseline CTA data, the presence of arterial thrombi on initial thin-section NCCT was regarded as an occlusion when assessing recanalization status. As such, small thrombi with low density might not be detected. This might have resulted in higher mean HU in the retrospective cohort than the prospective cohort. In addition, recanalization status in many patients was graded on CTA, not on conventional angiography. Therefore, we determined the recanalization status based on AOL, as well as modified Thrombolysis in Cerebral Infarction grades in the retrospective cohort. Nevertheless, the 200 mm^3 cutoff for the thrombus volume was demonstrated as being valid in the prospective study, in which baseline CTA was available in all patients, and conventional angiography was utilized to determine recanalization in most patients. Despite theoretical superiority of volume to length, comparison analysis in this study showed marginal superiority of the volume for predicting nonrecanalization. This may be in part ascribed to the small sample size. Finally, in this study, stroke experts measured the volume and density of the thrombi. Therefore, to be more widely used in clinical practice, the feasibility test may be necessary to see whether the measurement can be done by nonexperts in the emergency department without a significant time delay.

Conclusions

The thrombus volume and density can be measured rapidly and easily using 3D imaging software. We showed and validated that recanalization was rarely achieved after intravenous tPA infusion in patients with a thrombus ≥200 mm^3. This may help in determining the strategy of the recanalization treatment and perhaps identifying patients suitable for direct EVT.

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Disclosures

None.

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