Online Supplement Methods

Study population

Our prospectively collected database (ClinicalTrials.gov ID: NCT03367286) was reviewed for AIS patients who were admitted in our hospital between May 2009 and September 2017. All subjects had given written informed consent prior to the study, and the protocols had been approved by local human ethics committee. Patients were enrolled who (1) received thrombolysis within 9 hours after stroke onset, (2) underwent CT perfusion (CTP) or MR perfusion (MRP) before thrombolysis, and (3) confirmed AIS in the unilateral middle cerebral artery (MCA) territory. Patients were excluded who (1) had internal carotid occlusion (ICA), (2) had poor image quality, (3) received endovascular treatment, (4) had sICH or malignant edema within 24 hours after thrombolysis [1].

Imaging protocol

CTP was performed on a dual-source 64-slice CT scanner (SOMATOM Definition Flash; Siemens, Forchheim, Germany), including non-enhanced CT (NECT) head scan (120 kV, 320 mA, contiguous 5 mm axial slices), and volume perfusion CT (100 mm in the z-axis, 4 seconds delay after start of contrast medium injection, 74.5 seconds total imaging duration, 80 kV, 120 mA, effective dose = 3.68 mSv, slice thickness 10 mm, collimation 32 × 1.2 mm). A 60-mL bolus of contrast medium (Iopamidol; Braccosine, Shanghai, China) was used at a flow rate of 6 ml/s, followed

by a 20 mL saline chaser at 6 ml/s. 4D CT angiography (CTA) images were reconstructed from CTP in axial, coronal and sagittal planes with 20-mm-thick maximum intensity projection.

MRP was performed on a 3.0-T system (Sigma Excite HD, General Electric, Milwaukee, USA). Foam pads were inserted into the space between the patient's head and the MRI head coil to minimize head motion. The MRP protocol included perfusion weighted imaging (PWI), which was performed with gradient echo-planar imaging (field of view = 240 mm, TR = 1500 ms, TE = 30 ms, acquisition matrix = 128 × 128, Repetitive scanning times = 50, Gadolinium dose = 15 ml, contrast speed = 4–5 ml/s, duration = 1 min 15 s). Other sequences included diffusion weighted imaging (DWI) (TR = 4000 ms; TE = 69.3 ms; b-value = 1000 s/mm^2; slice thickness 5.0 mm; interslice gap = 1.0 mm) and time-of-flight magnetic resonance angiography (TOF-MRA) (TR = 20 ms; TE = 3.2 ms; flip angle = 15°; slice thickness = 1.4 mm, three slabs).

Imaging process methods

Two experienced neurologist (YZ, and AW) checked all the images and corrected the hypoperfusion and infarct core lesions manually, including 2 steps: (1) correction of nonparenchymal areas, including ventricles and leptomeninges which was mislabeled as hypoperfusion or infarct core; (2) correction of cerebral parenchymal areas in the

unaffected hemisphere which was mislabeled as hypoperfusion or infarct core. Then we recalculated the results of hypoperfusion volumes.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc, Chicago, USA). All metric and normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables as median (25th-75th percentile). Categorical variables were presented as frequency (percentage). Comparison between groups were assessed by using Student's *t* test for data that followed normal distribution, Mann-Whitney *U* test for data that did not follow normal distribution, and Fisher's Exact test for categorical data. Binary logistic regression analysis was used to analyze clinical outcome and generate odds ratios. Variables with a p value of < 0.05 in univariate analyses were included in the multivariate analysis besides age and baseline NIHSS which were forced into multivariate analysis. A p value of < 0.05 was considered to be statistically significant.

Online Supplement Tables

Table 1

Baseline characteristics of all include patients

Variable	LSA+Cortex- (n=29)	LSA-Cortex+ (n=139)	LSA+Cortex+ (n=88)	LSA-Cortex- (n=50)	*p* value
Age, years, mean ± SD	59.9 ± 13.9	71.0 ± 11.8	67.1 ± 14.3	65.2 ± 11.8	<0.001
Female, n (%)	8 (27.6)	56 (40.3)	38 (43.2)	18 (36.0)	0.485
Baseline NIHSS, median (IQR)	5 (3-11)	6 (4-11)	12 (7-16)	5 (2-9)	<0.001
Baseline hypoperfusion volume, mL, mean ± SD	6.6 ± 7.0	52.8 ± 45.8	92.6 ± 68.3	0 ± 0	<0.001
Baseline infarct core volume, mL, mean ± SD	3.6 ± 4.6	21.4 ± 27.9	35.6 ± 38.0	0 ± 0	<0.001
ONT, min, median (IQR)	200.0 (137.5-243.0)	200.0 (129.0-280.0)	232.5 (185.0-319.25)	195.5 (143.5-232.5)	0.002
Stroke risk factors					
Hypertension, n (%)	17 (58.6)	94 (67.6)	55 (62.5)	30 (60.0)	0.647
Diabetes mellitus, n (%)	6 (20.7)	24 (17.3)	21 (23.9)	8 (16.0)	0.592
Previous stroke or recent TIA, n (%)	3 (10.3)	20 (14.4)	13 (14.8)	5 (10.0)	0.855

Atrial fibrillation, n (%)	3 (10.3)	74 (53.2)	41 (46.6)	2 (4.0)	<0.001
Smoking, n (%)	14 (48.3)	44 (31.7)	27 (30.7)	24 (48.0)	0.067
MCA stenosis					<0.001
Normal, n (%)	14 (48.3)	79 (56.8)	9 (10.2)	30 (64.0)	
Mild to moderate, n (%)	9 (31.0)	17 (12.2)	7 (8.0)	16 (32.0)	
Severe, n (%)	2 (6.9)	11 (7.9)	19 (21.6)	2 (4.0)	
Occlusion, n (%)	4 (13.8)	32 (23.0)	53 (60.2)	0 (0)	
Unexplained END, n (%)	8 (27.6)	9 (6.5)	8 (9.1)	0 (0)	0.001
Severe unexplained END, n (%)	6 (20.7)	3 (2.2)	5 (5.7)	0 (0)	0.001

NIHSS: National Institutes of Health Stroke Scale; ONT: onset to treatment time; TIA: transient ischemic attack; LSA: lenticulostriate artery; MCA: middle cerebral artery; LSA+Cortex-: presence of hypoperfusion in LSA territory, and absence of hypoperfusion in MCA terminal branch territory; LSA-Cortex+: absence of hypoperfusion in LSA territory, and presence of hypoperfusion in MCA terminal branch territory; LSA+Cortex+: presence of hypoperfusion both in LSA and MCA terminal branch territories; LSA-Cortex-: absence of hypoperfusion both in LSA and MCA terminal branch territories; END: early neurological deterioration.

Table 2

Comparison between unexplained early neurological deterioration (END) patients and non-END patients

Variable	Unexplained END (n=25)	Non-END (n=281)	*p* value
Age, years, mean ± SD	63.4 ± 10.7	68.3 ± 13.3	0.079
Female, n (%)	10 (40.0)	110 (39.1)	1.000
Baseline NIHSS, median (IQR)	6 (4-9)	7 (4-13)	0.238
Baseline hypoperfusion volume, mL, mean ± SD	56.4 ± 67.7	50.8 ± 57.5	0.645
Baseline infarct core volume, mL, mean ± SD	17.5 ± 30.4	20.5 ± 30.4	0.634
ONT, min, median (IQR)	245.5 (206.5-279.5)	206 (134.5-266.5)	0.033
Stroke risk factors			
Hypertension, n (%)	17 (68.0)	179 (63.7)	0.828
Diabetes mellitus, n (%)	6 (24.0)	53 (18.9)	0.596

Previous stroke or recent TIA, n (%)	4 (16.0)	37 (13.2)	0.758
Atrial fibrillation, n (%)	5 (20.0)	115 (40.9)	0.053
Smoking, n (%)	10 (40.0)	99 (35.2)	0.666
Hypoperfusion area			0.001
LSA+Cortex-, n (%)	8 (32.0)	21 (7.5)	
LSA-Cortex+, n (%)	9 (36.0)	130 (46.3)	
LSA+Cortex+, n (%)	8 (32.0)	80 (28.5)	
LSA-Cortex-, n (%)	0 (0)	50 (17.8)	
MCA stenosis			0.015
Normal, n (%)	10 (40.0)	124 (44.1)	
Mild to moderate, n (%)	3 (12.0)	46 (16.4)	
Severe, n (%)	8 (32.0)	26 (9.3)	
Occlusion, n (%)	4 (16.0)	85 (30.2)	

NIHSS: National Institutes of Health Stroke Scale; ONT: onset to treatment time; TIA: transient ischemic attack; LSA: lenticulostriate artery; MCA: middle cerebral artery; LSA+Cortex-: presence of hypoperfusion in LSA territory, and absence of hypoperfusion in MCA terminal branch territory; LSA-Cortex+: absence of hypoperfusion in LSA territory, and presence of hypoperfusion in MCA terminal

branch territory; LSA+Cortex+: presence of hypoperfusion both in LSA and MCA terminal branch territories; LSA-Cortex-: absence of hypoperfusion both in LSA and MCA terminal branch territories.

Table 3

Multivariable analysis for unexplained early neurological deterioration (END) and severe END

Variable	odds ratio	95% confidence interval	*p* value
Model 1 (in all included patients for END)			
Age, y	0.987	0.955-1.020	0.423
Baseline NIHSS	0.951	0.876-1.033	0.231
ONT, min	1.005	1.001-1.009	0.009
LSA+Cortex-	5.974	2.091-17.066	0.001
Model 2 (in patients with LSA-Cortex+ or LSA+Cortex+ for END)			
Age, y	0.980	0.932-1.031	0.442
Baseline NIHSS	1.033	0.915-1.166	0.599
ONT, min	1.005	1.000-1.010	0.071

Severe stenosis	3.994	1.164-13.698	0.028
Model 3 (in all included patients for severe END)			
Age, y	0.983	0.940-1.027	0.439
Baseline NIHSS	0.924	0.818-1.042	0.198
ONT, min	1.007	1.002-1.013	0.007
LSA+Cortex-	9.275	2.481-34.678	0.001
Model 4 (in patients with LSA-Cortex+ or LSA+Cortex+ for severe END)			
Age, y	1.011	0.912-1.120	0.837
Baseline NIHSS	0.931	0.747-1.162	0.529
ONT, min	1.008	1.000-1.015	0.041
Severe stenosis	14.473	1.353-154.837	0.027

NIHSS: National Institutes of Stroke Scale; ONT: onset to treatment time; LSA: lenticulostriate artery; MCA: middle cerebral artery; LSA-Cortex+: absence of hypoperfusion in LSA territory, and presence of hypoperfusion in MCA terminal branch territory; LSA+Cortex+: presence of hypoperfusion both in LSA and MCA terminal branch territories.

Reference:

[1]. Kim JM, Moon J, Ahn SW, Shin HW, Jung KH, Park KY. The Etiologies of Early Neurological Deterioration after Thrombolysis and Risk Factors of Ischemia Progression. *Journal of Stroke & Cerebrovascular Diseases*. 2015 **25:** 383-388.

[2]. PJ M, B Y, MW P*, et al.* A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA).%A Campbell BC. *Int J Stroke*. 2014 **9:** 126-132.

[3]. BC C, M S, M M*, et al.* Apparent diffusion coefficient threshold for delineation of ischemic core.%A Purushotham A. *Int J Stroke*. 2015 **10:** 348-353.