Penumbra volume predicts unfavorable outcome in patients with acute minor stroke or transient ischemic attack

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Abstract

Background: A subgroup of patients with acute minor stroke (AMS) or transient ischemic attack (TIA) become disabled due to disease progression (DP) or recurrent stroke within 3 months. The aim of this article is to identify the risk factors for DP in AMS/TIA patients. In the literature, no studies focused on computed tomography perfusion (CTP) in AMS/TIA patients at the acute stage.

Methods: This retrospective study included patients with AMS or TIA (onset of symptoms ≤4.5 hours, baseline National Institutes of Health Stroke Scale [NIHSS] score of 0-4). DP was defined as a deterioration of NIHSS score of ≥2 points during hospitalization or modified Ranking Scale ≥2 at 3-month follow-up. Clinical data and imaging results were retrieved and measured for statistical analysis.

Results: From 2011 to 2017, total 135 patients were eligible for further analysis: 28 patients (20.7%, DP group) and 107 patients (79.3%, non-DP group). The DP group had significantly higher larger penumbra volumes (p = 0.028). In univariate model of the logistic regression, patients with the following risk factors tended to have unfavorable outcome: female gender, higher HbA1c, chronic kidney disease stage ≥3b, intracranial atherosclerosis, and penumbra volume were associated unfavorable outcome, but larger deadcore volume was not. In further multivariate analysis, only penumbra volume >5 cm^3 (p = 0.049, odds ratio [OR] = 3.21, 95% CI: 1.00-10.27) had the statistical significance. The cut-point value of the penumbra volume for unfavorable outcome in AMS/TIA patients was 4.73 cm^3.

Conclusion: One fifth of the AMS/TIA patients had unfavorable outcome at 90 days. In CTP performed within 4.5 hours after the onset of AMS/TIA, the penumbra volume (>5 cm^3) was a significant risk factor for DP, and the cut-point value was 4.73 cm^3. Further studies could be designed to involve this subgroup of patients for more aggressive treatment.

Keywords: Computed tomography angiography; Ischemic attack, transient; Risk factors

1. INTRODUCTION

In the current management of ischemic stroke, patients with acute minor stroke (AMS) or transient ischemic attack (TIA) are treated with antiplatelet agents and excluded from the intravenous thrombolysis or endovascular treatment.[1,2] However, about 15% of patients with AMS/TIA became disabled (modified Ranking Scale [mRS] score ≥2) at 90 days,[3] and disease progression (DP)/recurrent stroke in such patient group led to poor outcomes.[1,4] Hence, it is important to identify the risk factors for DP/recurrent stroke in AMS/TIA patients at the acute stage. Computed tomographic angiography/perfusion (CTA/CTP) is the imaging modality of choice used in patients with acute ischemic stroke (AIS) in the emergent department (ED). Although CTP has been demonstrated to have some predictive value in stroke patients,[5,6] there were no studies focusing on the role of CTP in AMS/TIA patients at the acute stage (≤4.5 hours). In this study, the authors aimed to identify the risk factors for DP/recurrent stroke in AMS/TIA patients by analyzing clinical data and CTP imaging.

2. METHODS

2.1. Study Population and Data Acquisition

This was a retrospective study. The study population was from the stroke registry of a single medical center from January 2011 to December 2017. Patients with (1) the confirmed diagnosis of

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AMS or TIA (onset of symptoms ≤4.5 hours, baseline NIHSS score of 0-4) and (2) CTA and CTP within 60 minutes upon the arrival in the ED were included. Exclusion criteria were as follows: (1) patients treated with intravenous thrombolysis or (2) initial mRS >2. In our institute, the treatment protocol for the AMS patients with disabling symptoms includes intravenous thrombolysis,[7] and this group of patients was also excluded from the study. As a ≥2-point neurologic deterioration in NIHSS score has been demonstrated to be a sensitive indicator of poor outcome and in-hospital mortality,[8] DP in this study was defined as a deterioration of NIHSS score of ≥2 points during hospitalization not owing to other systemic causes (eg, infections), or mRS score ≥2 at 3-month follow-up, which was deemed as unfavorable outcome. Patients with DP were in the DP group; patients without DP were in non-DP (NDP) group. All of the patients received standard clinical care in accordance with the current stroke guidelines. The following data were collected from the participants in the ED and during admission on a standardized data collection form: age, gender, body mass index, systolic and diastolic blood pressure, history of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, casual blood glucose, complete blood count, high-sensitivity C-reactive protein (hsCRP), creatinine (Cr), chronic kidney disease (CKD) staging, HbA1c, serum triglyceride, total cholesterol, low-density and high-density lipoprotein, and TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification.[9] As to the classification of CKD, we adopted a modified National Kidney Foundation,[10] which classifies estimated glomerular filtration rate in the following ranges: ≥60 mL/min/1.73 m^2, 45 to 59 mL/min/1.73 m^2 (stage 3a), 30 to 44 mL/min/1.73 m^2 (stage 3b), 15 to 29 mL/min/1.73 m^2 (stage 4), and <15 mL/min/1.73 m^2 (stage 5). In the literature, patients with CKD stage ≥3b have been considered with increased risks of death and cardiovascular events.[11] Neuro-imaging characteristics on CTA/CTP were also recorded and measured. The local institutional ethics committee had approved this study and waived the need for patient informed consent due to the retrospective nature of this study.

2.2. CTA protocol

In our institute, all stroke patients who have symptom onset time within 4 hours receive routine cerebral CTA/CTP. Written informed consent is signed by the patient/parent/guardian/next of kin before the study. CTA scans were performed on a 64-slice multidetector helical scanner (Philips, Best, The Netherlands) and images were acquired with 60-mL bolus injection of contrast at 4 mL/s. Scan parameters were slice thickness 0.67 mm, no slice gap, field of view 200 mm, matrix 512 × 512, 120 kV, and 250 mAs. Coverage was from the carina to the vertex and the source images were reformatted into 1.5-mm-thick axial, coronal, and sagittal projections. CTA was assessed for the presence of any symptomatic ipsilateral intracranial or extracranial occlusion or stenosis ≥50%.[12] The severity of extracranial stenosis was calculated using the standard North American Symptomatic Carotid Endarterectomy Trial (NASCET) method applied to reformatted axial CTA images.[13] Similar methods were used to evaluate the intracranial vessels.

2.3. CTP protocol and postprocessing

In our institute, all stroke patients who have symptom onset time within 4 hours receive routine cerebral CTA/CTP. Written informed consent is signed by the patient/parent/guardian/next of kin before the study. CTP scans were performed on a 64-slice multidetector helical scanner (Philips). For each series, a 40-mL bolus of nonionic iodinated contrast material was administered into an antecubital vein using a power injector at an injection rate of 4 to 5 mL/s for all patients. The acquisition parameters were 80 kVp and 125 mAs. CT scanning was initiated 6 to 7 seconds after start of the injection of the contrast bolus. Color-coded maps were visually assessed for hypo-perfused area. Ischemic changes were defined as focal areas of decreased cerebral blood flow. The deadcore and the penumbra were defined by a combined approach using two CTP parameters: (1) the absolute cerebral blood volume (CBV), with a threshold at 2.0 mL × 100 g^{-1} lower than the CBV values for normal white matter (about 3 mL × 100 g^{-1}), allowing accurate delineation of the acute infarct core and (2) the mismatch between the CBV, with a threshold at 2.0 mL × 100 g^{-1}, and the relative mean transit time, with a threshold at 145%, was used to define the tissue at risk of infarction in the absence of recanalization (penumbra).[5,14] Based on this technique, the penumbra and infarct core maps were delineated and calculated via the CTP postprocessing software (Extended Brilliance Workstation version 5.0; Philips). Each of the color-coded map area multiplied by 5 mm (thickness between slices) was summed up, which resulted to the volume of penumbra and deadcore. The neuro-radiologists who checked the CTP protocol and postprocessing quality were unaware of the patients' clinical data (ie, NIHSS, mRS).

2.4. Statistical analysis

The demographic data and CTA/CTP postprocessing results were analyzed between the DP and non-DP groups. Numerical variables were presented as median and interquartile ranges; categorical variables as percentages. Numerical variables were tested by the Mann-Whitney *U* test; categorical variables evaluated by chi-square test. In logistic regression for the analysis of risk factors, the variables that were statistically significant ($p < 0.05$) in univariate model were further analyzed in the multivariable model. Odds ratios (ORs) and 95% CIs were presented. All analyses were performed with IBM SPSS Statistics Version 22 (Armonk, New York, USA).

3. RESULTS

3.1. Demographic data and clinical features

A total of 217 patients with AMS/TIA were enrolled from January 2011 to December 2017. The reasons and patient numbers of exclusion were as follows: having received intravenous alteplase therapy (n = 9), premorbid mRS score ≥2 (n = 25), incomplete imaging study (n = 38), lost to follow up (n = 8), and mortality due to other causes (n = 2). There were 135 patients eligible for further analysis: 28 patients (20.7%) in the DP group and 107 patients (79.3%) in the NDP group, which meant that about 20% of the patients with AMS or TIA in this study were associated with unfavorable outcome at 3 months after symptom onset. Comparisons of demographics, clinical characteristics, and CTA/CTP imaging features between the two groups are shown in Table 1. There were no significant differences in patients' previous medical history, such as stroke history, atrial fibrillation, or heart disease. Patients in the DP group had significantly higher serum levels of creatinine ($p = 0.015$), hsCRP ($p = 0.019$), HbA1c ($p = 0.037$), and percentage of CKD stage ≥3b ($p = 0.032$). As to imaging characteristics, we classified the penumbra volume and the deadcore volume into 3 groups (<5, 5-10, >10 cm^3), and patients in the DP group had larger penumbra volumes ($p = 0.028$). However, deadcore volumes ($p = 0.818$), ipsilateral intracranial atherosclerosis (ICAS) ($p = 0.070$), and ipsilateral extracranial stenosis ($p = 0.100$) showed no differences between groups.

3.2. Risk factors for DP

Table 2 shows the logistic regression in both univariate and multivariate models for the risk factors of DP in patients with AMS/TIA. Female gender ($p = 0.013$), higher HbA1c ($p = 0.029$),

Table 1

Comparisons of demographics, clinical characteristics, and CTP image features between the two groups of disease progression (DP) and non–disease progression (NDP)

	Total (n = 135)	DP group (n = 28)	NDP group (n = 107)	*p*
Male gender, %	98 (72.6)	15 (53.6)	83 (77.6)	0.022
Age, y	69.0 (58.0-77.0)	73.0 (64.0-79.8)	67.0 (56.8-76.0)	0.081
BMI, kg/m^2	25.3 (23.1-27.4)	26.2 (23.1-28.1)	25.3 (23.1-27.2)	0.257
Systolic blood pressure, mmHg	159 (139-178)	166 (140-190)	157 (139-176)	0.220
Diastolic blood pressure, mmHg	94 (77-105)	96 (77-107)	93 (77-104)	0.747
Smoking, %	70 (52.6)	16 (59.3)	54 (50.9)	0.578
Hypertension, %	106 (79.7)	22 (81.5)	84 (79.2%)	1.000
Dyslipidemia, %	94 (70.7)	16 (59.3)	78 (73.6)	0.221
DM, %	54 (40.6)	12 (44.4)	42 (39.6)	0.813
Previous stroke, %	36 (27.1)	7 (25.9)	29 (27.4)	1.000
Heart disease, %	53 (39.3)	10 (35.7)	43 (40.2)	0.830
Atrial fibrillation, %	30 (22.2)	6 (21.4)	24 (22.4)	1.000
Heart failure, %	9 (6.7)	1 (3.6)	8 (7.5)	0.685
Coronary heart disease, %	21 (15.6)	3 (10.7)	18 (16.8)	0.565
WBC, 10^3/μL	7.6 (6.3-8.8)	8.2 (7.4-9.0)	7.4 (6.2-8.8)	0.051
Casual blood glucose, mg/dL	117.0 (101.0-153.0)	123.5 (106.3-171.3)	115.0 (100.0-152.0)	0.263
Serum creatinine, mg/dL	1.0 (0.8-1.2)	1.2 (0.8-1.6)	0.9 (0.8-1.1)	0.015
hs-CRP, mg/L	0.1 (0.1-0.5)	0.3 (0.1-0.7)	0.1 (0.1-0.4)	0.019
HbA1c, %	5.7 (5.5-6.3)	6.1 (5.6-7.3)	5.7 (5.5-6.3)	0.037
Total cholesterol, mg/dL	170.0 (152.0-192.0)	169.5 (154.8-192.8)	171.0 (147.0-192.0)	0.766
Triglyceride, mg/dL	117.0 (91.0-160.8)	121.0 (95.5-156.3)	117.0 (87.5-162.5)	0.711
HDL, mg/dL	43.0 (35.0-51.5)	41.0 (32.5-51.0)	43.0 (37.5-52.0)	0.537
LDL, mg/dL	109.0 (88.5-127.0)	110.5 (90.0-128.5)	107.0 (88.0-127.0)	0.740
CKD stage 3b, %				0.032
<3b	84 (62.2)	10 (35.7)	74 (69.2)	
≥3b	51 (37.8)	18 (64.3)	33 (30.8)	
TOAST classification, %				0.129
LAA	40 (29.6)	10 (35.7)	30 (28.0)	
SVO	40 (29.6)	9 (32.1)	31 (29.0)	
Other determined	1 (0.7)	1 (3.6)	0 (0.0)	
Undetermined	10 (7.4)	0 (0.0)	10 (9.3)	
Cardioembolic	44 (32.6)	8 (28.6)	36 (33.6)	
Extracranial stenosis (ipsilateral), %	16 (11.9)	6 (21.4)	10 (9.3)	0.100
ICAS (ipsilateral), %	25 (18.5)	9 (32.1)	16 (15.0)	0.070
Deadcore volume, cm^3				0.818
<5	124 (91.9)	25 (89.3)	99 (92.5)	
5-10	8 (5.9)	2 (7.1)	6 (5.6)	
>10	3 (2.2)	1 (3.6)	2 (1.9)	
Penumbra volume, cm^3				0.028
<5	78 (57.8)	10 (35.7)	68 (63.6)	
5-10	24 (17.8)	8 (28.6)	16 (15.0)	
>10	33 (24.4)	10 (35.7)	23 (21.5)	

BMI = body mass index; CKD = chronic kidney disease; CTP = computed tomography perfusion; DM = diabetes mellitus; GFR = glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein; ICAS = intracranial atherosclerosis; LAA = large-artery atherosclerosis; LDL = low-density lipoprotein; SVO = small-vessel occlusion; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; WBC = white blood cell.

CKD stage ≥3b (p = 0.027), ICAS (p = 0.042), and penumbra volume (p = 0.010) were associated unfavorable outcome, but larger deadcore volume was not (p = 0.579). In further multivariate analysis, only penumbra volume >5 cm3 (p = 0.049, OR = 3.21, 95% CI: 1.00-10.27) had the statistical significance. Other risk factors that were associated with unfavorable outcome in the univariate model did not show significance in multivariate model: female gender (p = 0.117, OR = 0.41, 95% CI: 0.14-1.25), higher HbA1c (p = 0.062, OR = 1.48, 95% CI: 0.98-2.25), CKD stage ≥3b (p = 0.113, OR = 3.89, 95% CI = 0.72-20.93), and ICAS (p= 0.210, OR = 2.18, 95% CI = 0.64-7.36).

3.3. Predictive value of penumbra volume

The receiver operating characteristic (ROC) curve was used to determine the cut-point value of the penumbra volume for unfavorable outcome in AMS/TIA patients (Fig. 1) The result for the cut-point value was 4.73 cm^3 (sensitivity 0.643 and specificity 0.636).

4. DISCUSSION

In this study, there were about 20% of the patients with AMS or TIA associated with unfavorable outcome at 3 months after symptom onset, which is compatible with that of the percentage in other studies.[1,3,4] In the literature, possible risk factors for minor stroke or TIA patients to have DP include previous TIA episodes, size of the lesion, female gender, diabetes mellitus, or stenosis of intracranial/extracranial arteries.[3,15–18] There have been no CTP parameters shown to be independently related to unfavorable outcome in AMS/TIA patients.[19] Our

Table 2

Logistic regression in univariate and multivariate models of the risk factors for disease progression in AMS/TIA patients at the acute stage (onset of symptoms ≤4.5 hours)

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Gender						
Female	1	1		1	1	
Male	0.33	(0.14-0.80)	0.013	0.41	(0.14-1.25)	0.117
Age	1.03	(1.00-1.07)	0.066	...	...	...
Systolic blood pressure, mmHg	1.01	(1.00-1.02)	0.090	...	...	...
Diastolic blood pressure, mmHg	1.01	(0.98-1.03)	0.595	...	...	...
Atrial fibrillation	0.94	(0.34-2.59)	0.910	...	...	...
WBC, $10^3/\mu L$	1.20	(0.97-1.47)	0.092	...	...	...
Serum creatinine, mg/dL	1.28	(0.83-1.96)	0.268	...	...	...
hs-CRP, mg/L	1.53	(0.93-2.50)	0.092	...	...	...
HbA1c, %	1.51	(1.04-2.18)	0.029	1.48	(0.98-2.25)	0.062
LDL, mg/dL	1.00	(0.99-1.02)	0.627	...	...	...
CKD stage 3b						
<3b	1	1		1	1	
≥3b	4.43	(1.19-6.59)	0.027	3.89	(0.72-20.93)	0.113
Smoking	1.40	(0.59-3.30)	0.441	...	...	...
TOAST classification						
LAA	1	1		...	...	...
SVO	0.94	(0.31-2.82)	0.906	...	...	...
Other determined	...	...	...	...	...	...
Undetermined	0.35	(0.07-1.79)	0.206	...	...	...
Cardioembolic	1.31	(0.44-3.89)	0.633	...	...	...
Hypertension	1.15	(0.39-3.39)	0.797	...	...	...
Dyslipidemia	0.52	(0.22-1.26)	0.148	...	...	...
DM	1.22	(0.52-2.86)	0.649	...	...	...
Previous stroke	0.93	(0.36-2.43)	0.881	...	...	...
Extracranial stenosis (ipsilateral)	2.65	(0.87-8.05)	0.087	...	...	...
ICAS (ipsilateral)	2.69	(1.04-7.00)	0.042*	2.18	(0.64-7.36)	0.210
Deadcore volume, cm^3						
≤5	1	1		...	...	...
>5	1.48	(0.37-6.01)	0.579	...	...	...
Penumbra volume, cm^3						
≤5	1	1		...	...	...
>5	3.14	(1.32-7.47)	0.010	3.21	(1.00-10.27)	0.049

AMS/TIA = acute minor stroke/transient ischemic attack; CKD = chronic kidney disease; DM = diabetes mellitus; hs-CRP = high-sensitivity C-reactive protein; ICAS = intracranial atherosclerosis; LDL = low-density lipoprotein; LAA = large-artery atherosclerosis; SVO = small-vessel occlusion; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; WBC = white blood cell.

study, aiming at AMS/TIA patients at the acute stage, demonstrated that clinical factors, including female gender, advanced CKD, higher HbA1c, ICAS, and higher penumbra volume (>5 cm^3) were risk factors for DP in the univariate analysis of logistic regression, and penumbra volume (>5 cm3) remained statistically significant in the multivariate analysis. The cut-point value of the penumbra volume for unfavorable outcome in AMS/TIA patients was 4.73 cm^3 (sensitivity 0.643 and specificity 0.636). However, the deadcore volume on CTP did not show statistical significance in the univariate and multivariate analysis.

There were studies using magnetic resonance image (MRI) to evaluate the relationships between the DWI/PWI mismatch in AMS/TIA patients within a 24-hour frame.[20–22] However, CTA/CTP is quick to perform and all-day available in most medical facilities for AIS patients. The accuracy and predictive values of CTA/CTP in DP among patients with AIS have been validated.[19,23–25] Some studies showed that more hypoperfused tissues in CTA/CTP were associated with unfavorable functional outcome in patients with AIS,[5,6] which gave us the idea to find out whether the same phenomenon could be found in AMS/TIA patients at the acute stage (≤4.5 hours). In our study, we utilized the penumbra volume as a quantitative CTP parameter to predict DP in AMS/TIA patients. The automated CTP post-processing measurement could offer a timely result to stratify the risks of AMS/TIA patients in the ED.

In our opinion, in addition to existing clinical scoring system (eg ABCD2 score or NIHSS in CHANCE substudy) to stratify AMS/TIA patients for different treatment regimen,[1] the quantitative penumbra volume of CTP imaging can help further differentiate whether DP is likely to happen among this subgroup of patients, who are usually regarded as having favorable outcome and excluded from acute reperfusion therapy. By identifying these AMS/TIA patients who tend to have DP, more precise regimens, such as dual antiplatelets, intravenous thrombolysis, or endovascular treatment could be considered.

This is a single center registry study, retrospective in design. The patient number limited the statistical power for further subgroup analysis. In the literature, CTP had higher sensitivity when the size of infarction was larger or a patient's NIHSS scores were higher.[26,27] In our study, the AMS/TIA patients harbored smaller sizes of penumbra volumes and lower NIHSS scores, which might affect the result in multivariate analysis. A larger randomized study should be considered. In addition, because the amount of contrasts used in CTA/CTP study might impose a burden on the renal function among patients with

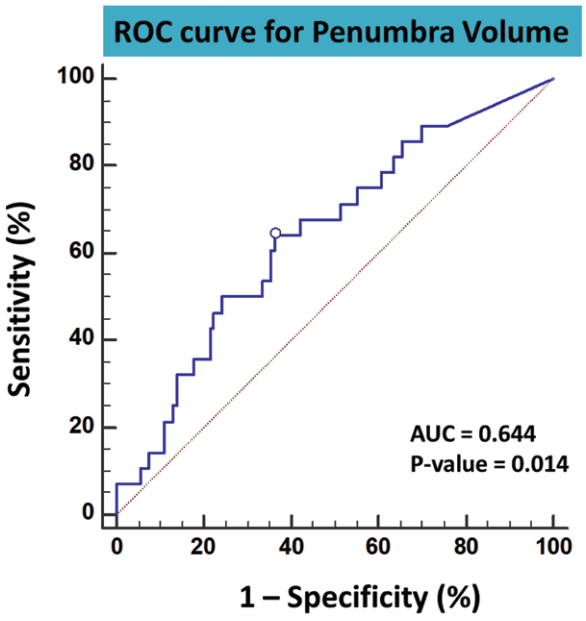

Fig. 1 ROC curve of the penumbra volume for unfavorable outcome in AMS/TIA patients at the acute stage. The cut-off point of the reference volume was 4.73 cm^3 (sensitivity 0.643 and specificity 0.636). AMS/TIA = acute minor stroke/transient ischemic attack; ROC curve = receiver operating characteristic curve.

CKD, we do not routinely perform CTA/CTP for follow-up. In conclusion, about one fifth of the AMS/TIA patients had unfavorable functional outcome at 90 days in this series. In CTP performed within 4.5 hours after the onset of AMS/TIA, the penumbra volume (>5 cm^3) was a significant risk factor for DP, and the cut-point value was 4.73 cm^3 (sensitivity 0.643 and specificity 0.636). Using quantitative penumbra volume of the CTP imaging, we could identify AMS/TIA patients with high risks of DP, in addition to clinical scores. Further studies could be designed to answer whether more aggressive treatment (eg dual antiplatelets, intravenous thrombolysis, or even endovascular intervention) would be suitable for this specific patient group.

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