Ischemic Stroke in Young Adults of Northern China: Characteristics and Risk Factors for Recurrence

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Key Words

Stroke · Young adult · Risk factor · Etiology · Disease severity · Recurrence

Abstract

Background: Young adults accounted for 10–14% of ischemic stroke patients. The risk factors may differ in this population from elder patients. In addition, the factors associated with stroke recurrence in this population have not been well investigated. **Objective:** The study aimed to investigate the characteristics and risk factors associated with recurrence of ischemic stroke in young adults. **Methods:** Clinical data of 1,395 patients of age 18–45 years who were treated between 2008 and 2014 in 3 centers located in northern China was reviewed. The first onset of stroke was taken as the initial events and recurrent stroke as the end point events. The end point events, age, gender, duration after first onset of stroke, history of disease, National Institutes of Health Stroke Scale (NIHSS) score at admission, Trial of Org 10172 in Acute Stroke Treatment classifications of the cause of stroke and adherence to medication were recorded. These factors were analyzed and compared between recurrence and non-recurrence group. Information about recurrent stroke was collected through clinical (readmission to hospital with ischemic stroke) or telephone follow-up survey. Logistic regression

was used to analyze the risk factors of recurrence. **Results:** The most common causes of stroke were large vessel atherosclerosis and small vessel occlusion, followed by cardioembolism. NIHSS score at admission (OR 1.088; 95% CI 1.028–1.152; $p = 0.004$) were associated with recurrence. **Conclusions:** Vascular disease, especially premature atherosclerosis, is the major risk factor for ischemic stroke in the young adult population of northern China. Timely screening of the cause of stroke with severe NIHSS score needs further attention.

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Introduction

Ischemic stroke in young adults is defined as acute ischemic cerebrovascular disease that occurs in patients aged 18–45 years [1]. Approximately 10–14% of ischemic strokes occur in young adults [2]. Although the short-term prognosis of this population is better than in older patients, ischemic stroke can have lasting detrimental effects in the lives of young adults [3]; with cumulative mortality rate ranging 1–7% in 5 years [4]. Furthermore, young adults may suffer long-term dysfunction after having suffered a stroke. Understanding of factors associated with the occurrence and recurrence of stroke in these patients would help clinical prevention and intervention.

Previous studies have been undertaken to examine the risk factors associated with initial and recurrent ischemic stroke in young adults [5]. Burden of vascular risk factors, family history of cardiovascular disease, and increased intima-media thickness of the internal carotid artery have been reported to be risk factors for ischemic stroke in young and middle aged adults (15–60 years) [6]. It has also been reported that certain genetic mutation (prothrombin G20210A) was associated with ischemic stroke in young adults [7]. A review of data from population-based studies in the United States identified increasing prevalence of stroke risk factors among persons aged 15–44 years of age, including hypertension, diabetes mellitus, obesity, lipid disorders, congenital heart disease, and smoking [8].

The available studies with respect to populations and ethnicity are still limited. The potential factors related with the severity of stroke have not been considered. Specifically, there is very limited data available on the causes and risk factors of ischemic stroke in Chinese young adults. Therefore, the current study aims to investigate the characteristics and recurrence risk factors for ischemic stroke in young adults, as well as their relations with disease severity.

Methods

Patients

We retrospectively reviewed data of patients of age 18–45 years who were treated for ischemic stroke between 2008 and 2014 at 3 stroke centers in northern China. Ischemic stroke was defined as a sudden neurological deficit, and the infarct site was assessed by MRI. Symptoms onset include sudden weakness, numbness, or loss of control of face, arm, or leg on one side of the body, sudden dimness, or loss of vision in one or both eyes, loss of speech, or trouble talking and understanding speech, dizziness, unsteadiness, or sudden fall and difficulty in wallowing. Patients with the following were excluded from the study: intracranial venous thrombosis, transient ischemic attack, cerebral hemorrhage, and brain tumors. The study was approved by the Human Research Committee of the First Affiliated Hospital of Jinzhou Medical University, China.

Data Collection

All patients completed the follow-up for at least 1 year. The median recurrence time of the patients was 231 days (ranged from 21 to 734 days). Medical records of study subjects were reviewed by 2 senior physicians from the Department of Neurology. Demographic data, medical history, and family history (hypertension, diabetes mellitus, and stroke) were extracted. In addition, disease severity was categorized based on National Institutes of Health Stroke Scale (NIHSS) score as mild (0–6), moderate (7–14), or severe (≥ 15). Etiology was categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification as large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, and undetermined etiology. NIHSS score and TOAST classification were extracted from clinical

records when available. In cases (53 of 1,395 cases, 3.8%) not evaluated according to the original records, they were re-assessed by the physician who reviewed records based on the data available.

Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein, fasting plasma glucose, and glycosylated hemoglobin levels were measured by standard laboratory methods. Homocysteine levels were assayed by stable isotope dilution gas chromatography–mass spectrometry. Hypersensitive C-reactive protein (hs-CRP) levels were determined using a latex-enhanced immunonephelometric method on a Hitachi 7600 autoanalyzer. Antinuclear antibody were assessed by indirect fluorescence, the type of antinuclear antibody was identified by immunoblotting. The results of diagnostic blood tests (e.g., total cholesterol and LDL) were classified as normal or abnormal according to the reference ranges of the laboratory of the First Affiliated Hospital of Jinzhou Medical University, China. The cardiac factors in clinical records included atrial fibrillation or atrial flutter assessed with electrocardiogram or dynamic electrocardiogram, and mural thrombus or congenital structural abnormalities observed on echocardiography. Infarct sites were determined using cranial MRI (T1-, T2-, and diffusion-weighted sequences). Radiographic examination findings included stenosis or occlusion of the culprit vessel (specific vessel affected), poor fibromuscular dysplasia observed using vascular ultrasonography (1,137/1,328, 85.6%), transcranial Doppler ultrasonography (1,137/1,328, 85.6%), magnetic resonance angiography (MRA, 306/1,328, 23.0%), CT angiography (CTA, 138/1,328, 10.4%), or digital subtraction angiography (DSA, 613/1,328, 46.2%).

Recurrent stroke was defined as new persisting (≥ 24 h) neurological deficit occurring > 24 h after the index event and not attributable to other causes of neurological deterioration. In this article, the data about recurrence of ischemic stroke were collected through clinical (readmission to hospital with ischemic stroke) or telephonic follow-up survey. The first onset of stroke was taken as the initial event, and recurrent stroke as the end point event. The end point events, age, gender, duration after first onset of stroke, history of disease, NIHSS score at admission, TOAST classifications of the cause of stroke, and adherence to medication were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS software version 17.0. Descriptive statistics were analyzed for total subjects. Categorical data was expressed as frequency (percentage). Comparisons among groups were performed using the χ^2 test. The risk factors associated with disease recurrence were analyzed using multivariate logistic regression analysis, including all factors that showed statistical significant differences between groups. Correlations between ranked variables were analyzed using Spearman rank correlation analysis. A value of $p \leq 0.05$ was considered statistically significant.

Results

Baseline Demographic and Clinical Characteristics

A total of 1,395 patients were included in this study, with a mean age of 38.50 ± 6.318 years (range 18–45 years). The population included 1,104 (79.1%) men aged 38.77 ± 5.980 years and 291 (20.9%) women aged 37.46 ± 7.382

Table 1. Baseline characteristics

	Constituent ratio, % total number (<i>n</i> = 1,395)
Demographic data	
Age, years, mean (SD)	38.50 (6.318)
Gender, male	1,104 (79.1)
History of disease	
Hypertension	620 (44.4)
Diabetes mellitus	192 (13.8)
Abnormal lipid metabolism	234 (16.8)
Valvular disease	19 (1.4)
Cardiomyopathy	7 (0.5)
Atrial fibrillation	14 (1.0)
Other arrhythmia	12 (0.9)
Atrial septal defect/patent foramen ovale	15 (1.1)
Myxoma	2 (0.1)
Heart failure	4 (0.3)
Angina	23 (1.6)
Myocardial infarction	14 (1.0)
Smoking	657 (47.1)
Drinking	581 (41.6)
History of transient ischemic attack	38 (2.7)
Cancer	3 (0.2)
History of migraine	18 (1.3)
Family history	547 (39.2)
NIHSS severity at admission	
Mild (0–6)	1,066 (76.4)
Moderate (7–14)	293 (21.0)
Severe (≥15)	22 (1.6)
Missing	14 (1.0)
Missing: data of NIHSS score in 14 patients was missing. NIHSS, National Institutes of Health Stroke Scale.	

years. The median interval between onset of stroke to admission was 36 h (ranged from 4 to 156 h) for all patients. Hypertension was detected in 44.4% of patients, positive family history in 39.2%, abnormal lipid metabolism in 16.8%, diabetes mellitus in 13.8%, smoking in 47.1%, and alcohol ingestion in 41.6%. The medical history included transient ischemic attack in 2.7% of patients, coronary heart disease (angina or myocardial infarction) in 2.6%, valvular heart disease in 1.4%, headaches in 1.3%, patent foramen ovale in 1.1%, and atrial fibrillation in 1.0%.

NIHSS Score at Admission

The severity of stroke according to the NIHSS score was recorded as mild in 1,066 (76.4%) patients, moderate in 293 (21.0%), severe in 22 (1.6%), and undetermined because of missing data in 14 (1.0%) patients (Table 1).

Table 2. Results of diagnostic tests

Item	Positive rate
Blood	
Total cholesterol >200 mg/dL	115/1,336
Low-density lipoprotein >130 mg/dL	99/1,336
High-density lipoprotein <35 mg/dL	408/1,336
Fasting plasma glucose >7 mmol/L	191/1,332
Glycosylated hemoglobin >7 mmol/L	83/332
Homocysteine >12 mmol/L	451/688
Antinuclear antibody	23/498
ANCA	18/602
LA	10/348
aCL IgG	6/348
aCL IgM	7/348
hs-CRP >1.2 mg/L	4/836
Echocardiography	
Mural thrombosis	9/703
Patent foramen ovale/atrial septal aneurysm	60/703
Valvular heart diseases	9/703
Cardiomyopathy	4/703
Atrial fibrillation	9/940
Cranial MRI	1,088/1,088
Cranial CT	506/621
Vascular tests (CTA, MRA, DSA, vascular ultrasound)	891/1,328
Anterior circulation	587/1,328
Posterior circulation	143/1,328
Both anterior and posterior circulations	161/1,328
Moyamoya disease	49/1,328
Artery dissection	11/1,328
Poor muscle fiber development	3/1,328
DSA (+) = 550; MRA (+) = 229; CTA (+) = 91; vascular ultrasonography, culprit vessel >50% stenosis (+) = 753. CTA, CT angiography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography.	

Diagnostic Tests

The diagnostic test results are shown in Table 2. Diagnostic tests (including blood tests, electrocardiogram or dynamic electrocardiogram, echocardiography, and MRI) were performed in every patient. Vascular ultrasonography and transcranial Doppler ultrasonography were performed in 85.6% patients, and other patients were observed using MRA, CTA, or DSA.

A high proportion of patients (44.6%) had abnormal lipid metabolism. The majority of patients underwent the following tests: antinuclear antibody, anti-neutrophil cytoplasmic antibody (ANCA), lupus anticoagulants (LA), anti-cardiolipin antibody (aCL), b2-glycoprotein I antibody (b2GPI), and hs-CRP concentrations. Antinuclear antibodies and ANCA were detected in 41 patients, IgM aCL was positive in 7 patients, IgG aCL in 6 patients.

Among of these 13 patients (IgM aCL or IgG aCL was positive), LA was positive in 10 cases. There were no b2GPI-positive patients. Abnormal hs-CRP was recorded in 4 patients.

Complete echocardiography data were available for 703 patients, including 60 with a patent foramen ovale (7 combined with an atrial septal aneurysm), 9 with valvular heart disease, 9 with mural thrombus, and 4 with cardiomyopathy. A low proportion of patients had atrial fibrillation on electrocardiography or dynamic electrocardiography (9/940, 1%).

A high proportion of patients had abnormal angiography findings (891/1,328, 67%). The abnormal findings were detected on DSA in 550 patients, on MRA in 229, on CTA in 91, and on vascular ultrasonography in 753. Vascular anomalies were detected in the internal carotid artery system in 587 (44.2%) patients, in the vertebrobasilar system in 143 (10.8%), and in both the internal carotid artery and vertebrobasilar systems in 161 (12.1%). Forty-nine patients had Moyamoya disease (29 men and 20 women), and 11 had dissection of the culprit artery (9 men and 2 women) including 2 with Marfan syndrome, who also had vertebral artery dissection. Poor muscle fiber development was detected in 3 men.

Causes of Stroke

Etiology of stroke was assessed according to TOAST classifications. Large artery atherosclerosis and small vessel occlusion accounted for nearly 50% of all cases. Large artery atherosclerosis was detected in 596 (42.7%) patients (including 244 extracranial and 352 intra acranial), small vessel occlusion in 225 (16.1%), cardioembolism in 90 (6.5%) (53 with patent foramen ovale, 7 with patent foramen ovale as well as atrial septal aneurysm, 6 with valvular disease, 7 with atrial fibrillation, 5 with valvular disease as well as atrial fibrillation, 4 with cardiomyopathy, 1 with angina, 1 with myocardial infarction, 2 with other arrhythmia, 2 with left atrial appendage thrombosis, 1 with acute infective endocarditis, and 1 with Keshan disease), other determined etiology in 84 (6.0%) (49 with Moyamoya disease, 11 with dissection of the culprit artery, 3 with poor muscle fiber development, 3 with pregnancy-related stroke, 4 with multiple arteritis, and 1 with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), 2 or more causes in 153 (11.0%), negative evaluation in 204 (14.6%) (29 with undetermined cause and 175 with incomplete data), and incomplete evaluation in 41 (2.9%; Table 3).

Table 3. TOAST classifications of the cause of stroke

TOAST classification	n	Constituent ratio, %
Large artery atherosclerosis	596	42.7
Cardioembolic stroke	90	6.5
Patent foramen ovale	53	
Patent foramen ovale + atrial septal aneurysm	7	
Valvular disease	6	
Atrial fibrillation	7	
Valvular disease + atrial fibrillation	5	
Cardiomyopathy	4	
Angina	1	
Myocardial infarction	1	
Other arrhythmia	2	
Left atrial appendage thrombosis	2	
Acute infective endocarditis	1	
Keshan disease	1	
Small vessel disease	225	16.1
Other clear causes	84	6.0
Moyamoya disease	49	
Antiphospholipid syndrome	13	
Artery dissection	11	
Poor muscle fiber development	3	
Pregnancy-related stroke	3	
Polyarteritis	4	
CADASIL	1	
Multiple potential causes	153	11.0
Unclear cause + incomplete work up	204	14.6
Missing	41	2.9

TOAST, Trial of Org 10172 in Acute Stroke Treatment; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Characters and Risk Factors for Recurrence of Ischemic Stroke

Among studied patients, a total of 94 (6.7%) patients inclusive of 72 men (6.5% in total male subjects) and 22 women (7.6% in female subjects), experienced recurrence of ischemic stroke. The average age was 37.98 ± 5.30 years, the average duration after first onset of stroke was 338.7 days; 81 patients adhered to medication, such as managing arterial hypertension, disorders of lipid metabolism, and diabetes mellitus, and administering antiplatelets, but adherence to anticoagulants was poor (Table 4).

Associations between the baseline characteristics and recurrent ischemic stroke were first analyzed using univariate logistic regression analyses. Factors showing significant association with recurrent ischemic stroke on univariate analysis ($p < 0.1$) were then included in the multivariate logistic regression analysis. Univariate regression analyses found that recurrence was associated with abnormal lipid metabolism (OR 0.321; 95% CI

Table 4. Recurrence event characters

	Recurrence group (n = 94), %	Non-recurrence group (n = 1,301)	p value
Demographic data			
Age, years, mean (SD)	37.98±5.30	38.53±4.98	0.477
Gender, male	72 (6.5)	1,032 (93.5)	0.411
Duration after first onset of stroke, days	338.7		
History of disease			
Hypertension			0.962
Yes	42 (6.8)	578 (93.2)	
No	52 (6.7)	723 (93.3)	
Diabetes			0.342
Yes	16 (8.3)	176 (91.7)	
No	78 (6.5)	1,125 (93.5)	
Hyperlipidemia			0.404
Yes	6 (2.6)	228 (97.4)	
No	88 (7.6)	1,073 (92.4)	
Valvular heart disease			1.000*
Yes	1 (5.3)	18 (94.7)	
No	93 (6.8)	1,283 (93.2)	
Cardiomyopathy			0.482 [#]
Yes	1 (14.3)	6 (85.7)	
No	93 (6.7)	1,295 (93.3)	
Atrial fibrillation			0.280 [#]
Yes	3 (21.4)	11 (78.6)	
No	91 (6.6)	1,290 (93.4)	
Other arrhythmia			0.239 [#]
Yes	2 (16.7)	10 (83.3)	
No	92 (6.7)	1,291 (93.3)	
Atrial septal defect/PFO			0.612*
Yes	2 (13.3)	13 (86.7)	
No	92 (6.7)	1,288 (93.3)	
Myxoma			0.597 [#]
Yes	0 (0.0)	2 (100.0)	
No	94 (6.7)	1,299 (93.3)	
Hear failure			0.455 [#]
Yes	0 (0.0)	4 (100.0)	
No	94 (6.8)	1,297 (93.2)	
Angina			0.425*
Yes	3 (13.0)	20 (87.0)	
No	91 (6.6)	1,281 (93.4)	
Myocardial infarction			0.952 [#]
Yes	1 (7.1)	13 (92.9)	
No	93 (6.7)	1,288 (93.3)	
Smoking			0.490
Yes	35 (5.3)	622 (94.7)	
No	59 (8.0)	679 (92.0)	
Drinking			0.265
Yes	34 (5.9)	547 (94.1)	
No	60 (7.4)	754 (92.6)	
Prior TIA			0.778 [#]
Yes	3 (7.9)	35 (92.1)	
No	91 (6.7)	1,266 (93.3)	
Cancer			0.172 [#]
Yes	1 (33.3)	2 (66.7)	
No	93 (6.7)	1,299 (93.3)	
History of headache			0.500*
Yes	0 (0.0)	18 (100.0)	
No	94 (6.8)	1,283 (93.2)	

Table 4. (continued)

	Recurrence group (<i>n</i> = 94), %	Non-recurrence group (<i>n</i> = 1,301)	<i>p</i> value
Family history			0.453
Yes	38 (6.9)	509 (93.1)	
No	56 (6.6)	792 (93.4)	
NIHSS severity at admission			0.004
Mild (0–6)	63 (5.9)	1,003 (94.1)	
Moderate (7–14)	29 (9.9)	264 (90.1)	
Severe (≥15)	2 (9.1)	20 (90.9)	
Missing	0 (0.0)	14 (100)	
TOAST classifications of the cause of stroke			0.943
Large artery atherosclerosis	49 (8.2)	547 (91.8)	0.440
Cardioembolic stroke	5 (5.6)	85 (94.4)	0.203
Small vessel disease	4 (1.8)	221 (98.2)	0.740
Other clear causes	2 (2.4)	82 (97.6)	0.845
Multiple potential causes	18 (11.8)	135 (88.2)	0.999
Unclear cause	2 (6.9)	27 (93.1)	0.426
Incomplete work up	10 (5.7)	165 (94.3)	0.823
Missing	3 (7.3)	38 (92.7)	
Adherence to medication			0.833
Yes	81 (7.2)	1,046 (92.8)	
No	13 (4.9)	255 (95.1)	

Values are mean ± SD or *n* (%).

* Continuity correction; # likelihood ratio.

PFO, patent foramen ovale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

0.139–0.743; *p* = 0.008), atrial fibrillation (OR 3.866; 95% CI 1.060–14.104; *p* = 0.041), smoking (OR 1.544; 95% CI 1.002–2.379; *p* = 0.049), TOAST type of patients with unclear cause (OR 2.375; 95% CI 1.147–4.918; *p* = 0.020), and NIHSS score at admission (OR 1.092; 95% CI 1.032–1.155; *p* = 0.002). Fisher's exact test found that recurrence had no association with adherence to medication (*p* = 0.833). Multivariate analysis found that NIHSS score at admission was significantly associated with recurrence (OR 1.088; 95% CI 1.028–1.152; *p* = 0.004).

Discussion

Results from the current study in northern Chinese population showed that men appeared to be more common in young adult ischemic stroke patients. The most common causes of young stroke were large vessel atherosclerosis and small vessel occlusion, followed by cardioembolism. The severity of stroke at admission in young adults was usually mild. The NIHSS score at admission were associated with recurrence of young stroke.

In a previous study, the most common risk factors identified in young adults with ischemic stroke were abnormal lipid metabolism (52.7%), smoking (47.3%), hypertension (39.3%), and a patent foramen ovale (32.8%) [2]. The causes of stroke in this study were estimated as large artery atherosclerosis in 11.3%, small vessel occlusion in 8%, cardioembolism in 24%, other determined etiology in 27.3%, and undetermined etiology in 29.3%. Other available studies reported that cardioembolism accounted 9.25–25% etiology of young adults ischemic stroke [9, 10]. In contrast, the present study found that cardioembolism associated with a patent foramen ovale was only observed in a small proportion of patients, with large artery atherosclerosis in a relatively high proportion of patients. The proportions of ischemic stroke due to other causes were comparable with previously reported studies. Therefore, the main causes of stroke in young adults in northern Chinese population seem to be vascular disease, especially large vessel atherosclerosis. We surmise that this finding is due to the large proportion of subjects who had undergone vascular investigations (1,328/1,395), and because atherosclerosis has a higher

prevalence in northern China than in other regions of China.

Cardioembolism is associated with prosthetic heart valves, mitral stenosis, infectious and non-infectious endocarditis, dilated cardiomyopathy, intraluminal thrombosis, and cardiac tumors such as myxoma [11]. Other conditions such as a patent foramen ovale, atrial septal aneurysm, abnormal wall motion, and mitral valve prolapse may also be associated with cardioembolism. It has been suggested that patients with stroke caused by cardioembolism should undergo dynamic electrocardiography to exclude paroxysmal atrial fibrillation, but the detection rate is low (5%) [12]. Prolongation of the monitoring time may increase the detection rate (6%) [13]. In this retrospective study, echocardiography was performed in 703/1,395 patients, and electrocardiography and dynamic electrocardiography were performed in 940/1,395 patients. The low proportion of patients diagnosed with cardioembolism was probably associated with the lack of these investigations in all patients. It should be noted that although a patent foramen ovale increases the risk of stroke, it does not cause embolism, and the source of embolism should be identified [14]. Some patients with stroke may therefore have been incorrectly diagnosed with cardioembolism [15], resulting in differences in the reported rates of cardioembolism among studies.

Many studies have investigated the factors associated with stroke recurrence. A recent study reported that age and diabetes mellitus were long-term risk factors for stroke recurrence [16]. Another study reported that a family history of stroke, migraine with aura, anti-phospholipid antibody syndrome, antihypertensive medications, and irregular ingestion of antiplatelet medication increased the risk of recurrence in young adults with

stroke [17]. Other studies found that patients with stroke caused by cardioembolism had a high risk of recurrence [5, 18]. In this study, cardioembolic stroke had no association with recurrence. Our data showed that the major embolic cause was presented as patent foramen ovale, which may have led to inconsistent results with other studies in different regions. We also found that NIHSS score at admission was associated with recurrence of young ischemic stroke. The US NIHSS score is frequently used to describe the severity of stroke and can be used to predict outcome [19]. A high NIHSS score is associated with a high risk of complications [19]. Chumbler et al. [20] reported that the NIHSS score at presentation was associated with the risk of pneumonia in patients with stroke.

This retrospective study is limited by incomplete data in the medical records. This makes it difficult to compare our data with previous studies. Furthermore, the findings of this single-center study may not be generalizable, and further multicenter studies should be performed.

In summary, vascular disease especially premature atherosclerosis is the major risk factor for ischemic stroke in the young adult population of northern China. Timely screening of the cause of stroke with severe NIHSS score needs further attention.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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