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A cohort study of isolated brainstem infarction based on head MR imaging and clinical findings

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Abstract

Objective: The prognosis of patients with isolated brainstem infarction (BSI) differs on an individual patient basis. This study was undertaken to analyze the influences of different imaging and clinical features with the prognosis of patients with BSI.

Methods: The study population was derived from a multicenter study of intracranial atherosclerosis in China. In the present study, 300 patients were selected who had experienced non-cardiogenic brain stem infarction within the prior 7 days. Evaluations included clinical characteristics, location and size of the brainstem infarction, and whether the infarction was located in multiple perforating branches of the brainstem. Poor prognosis was defined as the presence of disability within 1 year from the onset of disease.

Results: In total, 281 patients were followed up at 1 year post-infarction. Of these 281 patients, 84 (29.9%) exhibited disability at 1 year; these patients showed a median National Institutes of Health Stroke Scale score of 6 on admission. Multiple logistic regression analysis showed that patients with BSI located in the territory of multiple perforating arteries, who were discharged without administration of statins, showed a poor 1-year prognosis.

Conclusion: Isolated BSI involving multiple perforating arteries, without statin medication at discharge, indicated poor prognosis for patients with BSI.

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Introduction

An isolated brainstem infarction (BSI), either large or small, can be positioned in the territory of a single perforating artery or within the supply area of multiple groups of perforators.[1–4] It can be caused either by the obstruction of branches due to atherosclerotic plaques, or by the occlusion of small arteries due to blood vessel degeneration. According to the shape and location of the lesion, a larger medial or paramedian infarction that abuts the basal surface of brainstem is typically related to branch blocking due to atherosclerotic plaque, while a distal small lesion that does not reach the surface of the brainstem is often caused by small artery disease.[4–8] Kim et al. found that clinical manifestations and prognosis in patients who suffer from medial medullary infarction differed with respect to etiology and imaging type.[4] However, Ju et al. found that patients with paramedian pontine infarction of the basilar artery branch disease were common, and that there were no significant differences in long-term prognosis among the three lesion types of large artery disease, branch disease, and small artery disease.[9]

Previous studies were single center studies comprising small numbers of samples and only involving the influences of imaging features on patient prognosis, without considering the influences of clinical features and clinical interventions on the outcome.[10–13] Thus, we designed this study to examine the influence of multiple factors on the outcome of single brainstem lesions.

Methods

Study participants

Chinese Intracranial Atherosclerosis (CICAS) is a prospective, multicenter, hospital-based study that encompasses 22 general hospitals. The study protocol was approved by the Institutional Review Board of the Capital Medical University of China. All patients, or their designated relatives, signed informed consent. Patient privacy and data confidentiality were ensured. The study included a total of 2864 cases of first-episode non-cardiac ischemic stroke within 7 days of onset. The patients were aged between 18 and 80 years. Of these, we selected a subset of ischemic stroke patients with first-time single brainstem infarction. We excluded patients who: were in need of intensive care or were dying, had a modified Rankin Scale (mRS) score >2, were unable to undergo MRI examinations under special situations, were at high risk of cardiogenic embolism such as atrial fibrillation, valvular heart disease or heart diseases with valve replacement, and had unknown or other etiologies.

Baseline data collection

Data collected from patients included risk factors of cerebrovascular disease, primary clinical manifestations of the disease, treatment with secondary prevention drugs, location and size of new brain stem infarcts, whether lesions were located in the territories of multiple groups of perforators,

etiological classification according to the Stop Stroke Study Trial Order of Org 10172 in Acute Stroke Treatment (SSS-TOAST), as well as the presence of leukoaraiosis, old and severe lacunar infarction, and similar situations. Patients were followed up to evaluate activities of daily living (ADL) for 1 year from the onset of disease. The mRS was used to evaluate each patient's ADL, and an mRS $\geq$2 was considered disabled.

Magnetic resonance imaging (MRI) examination

MRI studies were performed in all cases by using either a 1.5-T or 3.0-T MRI unit. Scanning sequences included axial T1-weighted imaging, axial T2-weighted imaging, fluid-attenuated inversion recovery sequence, and diffusion-weighted imaging, apparent diffusion coefficient maps, and intracranial magnetic resonance angiography (MRA) (three-dimensional time-of-flight MRA). Diffusion imaging was performed by using a slice thickness of 5 mm with no interslice gap and two levels of diffusion sensitization (b values of 0, 1000 s/mm^2). MRA was used to determine the presence of stenosis and evaluate the severity in intracranial arteries; contrast-enhanced MRA or cervical ultrasonography was applied to determine the presence of stenosis and evaluate the severity of stenosis in extracranial arteries. The degree of intracranial stenosis on MRA was calculated by using the method from the WASID study.[14]

On the basis of the location of infarcts in the brain stem axis, brainstem infarction was categorized into the territories of paramedian branch, short circumferential branch, long circumferential branch, paramedian branch + short circumferential branch, short circumferential branch + long circumferential branch, and paramedian branch + short circumferential branch + long circumferential branch.[15] Damage that involves a single perforating artery was classified as "single perforator involvement" group, while damage related to more than two perforators was classified as "multiple perforators involvement" group. As an example, an infarction in the pons was categorized as follows: Infarction A and B in Figure 1 represent an isolated infarction located in the territory of a single perforating artery. Infarction C in Figure 2 represents an isolated infarction located in the territory of two perforating arteries (multiple perforating arteries involvement).[4,16]

The maximum length and width of the infarct were measured at the largest area of the lesion. The maximum height of the infarct was equal to the sum of all scanning slides of the infarct damage; the infarct

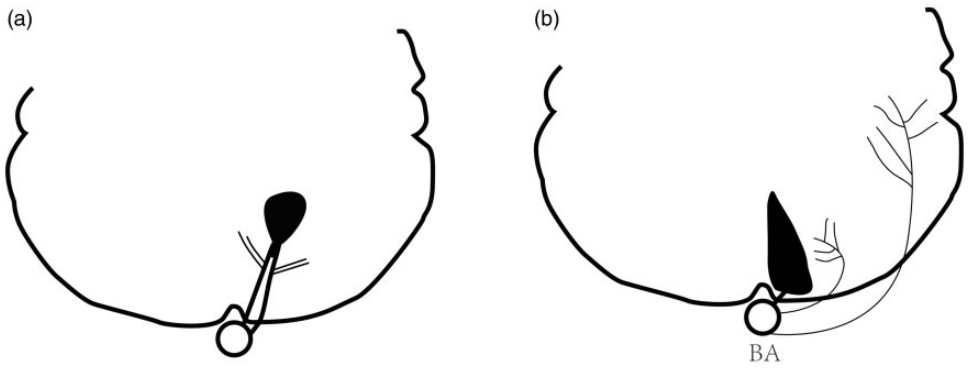

Figure 1. A single brainstem lesion caused by involvement of a single perforating artery

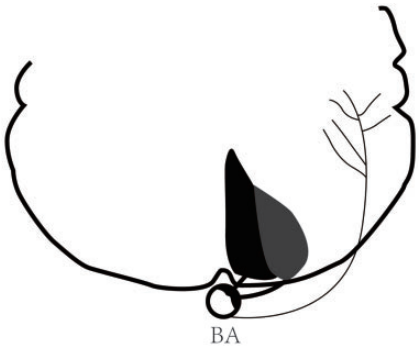

Figure 2. A single brainstem lesion caused by involvement of multiple perforating arteries

volume was calculated as $1/2 \times$ the maximum length diameter $\times$ the width diameter-$\times$ height of the lesion. The maximum length and width, together with the height of the infarction, were measured by using head magnetic resonance diffusion-weighted imaging sequence images.

The etiologic subtypes of ischemic stroke were classified on the basis of the SSS-TOAST classification criteria.[17]

Statistical analysis

Patients were divided into two groups (poor prognosis, mRS $\geq$2; good prognosis, mRS $<$2), based on their neurological statuses. Patient characteristics were compared between these two groups by using the Mann–Whitney U test for continuous variables and chi-squared test for categorical variables. Multiple regression analysis was performed to identify independent variables that could predict prognosis. Logistic regression models tested associations among the predictors (e.g., age, uric acid, diabetes, hypertension, and admission fasting blood glucose) and poor prognosis. Statistical analysis was performed by using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean $\pm$ standard deviation in the text and tables. Values of $P < 0.05$ were considered statistically significant.

Results

Baseline features

A total of 300 newly diagnosed single brainstem infarct patients were enrolled in the study, with a median age of 63. Of these, 112 patients (37.1%) were female. Two hundred fifty (83.1%) patients had hypertension and 143 (47.4%) had diabetes. Four (1.3%) patients had medulla infarction, 284 (94%) had damage in the pons, eight (2.6%) in the midbrain, and six (2.0%) in both pons and midbrain. With respect to etiology, 150 cases (49.7%) were small artery occlusion type (Figure 3) and 152 (50.3%) were atherosclerotic type (Figure 4). A total of 156 cases exhibited single perforator involvement, and 146 cases (48.3%) exhibited multiple groups of perforators.

Related risk factors of one-year disability

Of 300 patients enrolled, 105 had severe neurological deficits at discharge. Nineteen patients were lost to follow-up; thus, 281 patients were followed up at 1 year post-infarction, of whom 84 (29.9%) exhibited a disability at the 1 year examination. The average age of these 84 patients with disabilities was 68 years, which contrasted with the average age of 62 years among 197 patients without disabilities; thus, patients with disabilities were older (P=0.004).

Of these 281 patients, 84 were physically handicapped, with a median National Institutes of Health Stroke Scale score of 6 on admission, which contrasted with the score of 4 for non-disabled patients (P<0.0001). The infarct size of the handicapped patients was larger, with an average volume of 0.56 mL vs. 0.34 mL among non-disabled patients (P=0.014). Regarding

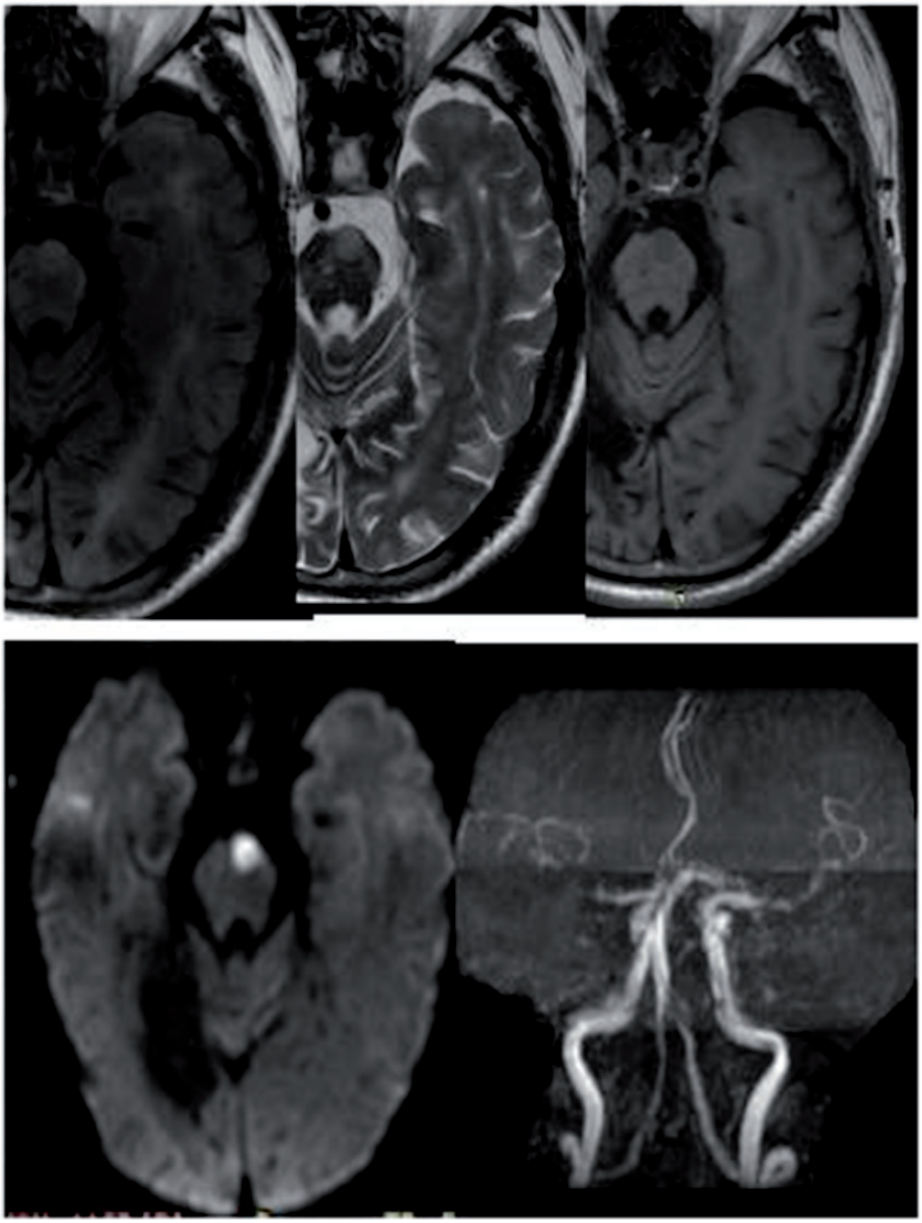

Figure 3. T1, T2, fluid-attenuated inversion recovery, diffusion-weighted imaging, and magnetic resonance angiography sequences of the small artery occlusion type of brainstem infarction

lesions involving multiple perforators, there were 49 (58.3%) in the disabled group and 86 (43.7%) in the non-disabled group (P=0.024). There were 50 patients (59.5%) with disabilities in the LAA classification vs. 91 (46.2%) without disabilities (P=0.041). Our study also found that disturbance of consciousness as the first symptom was a risk factor for disability after 1 year of illness (P=0.047) (Tables 1 and 2).

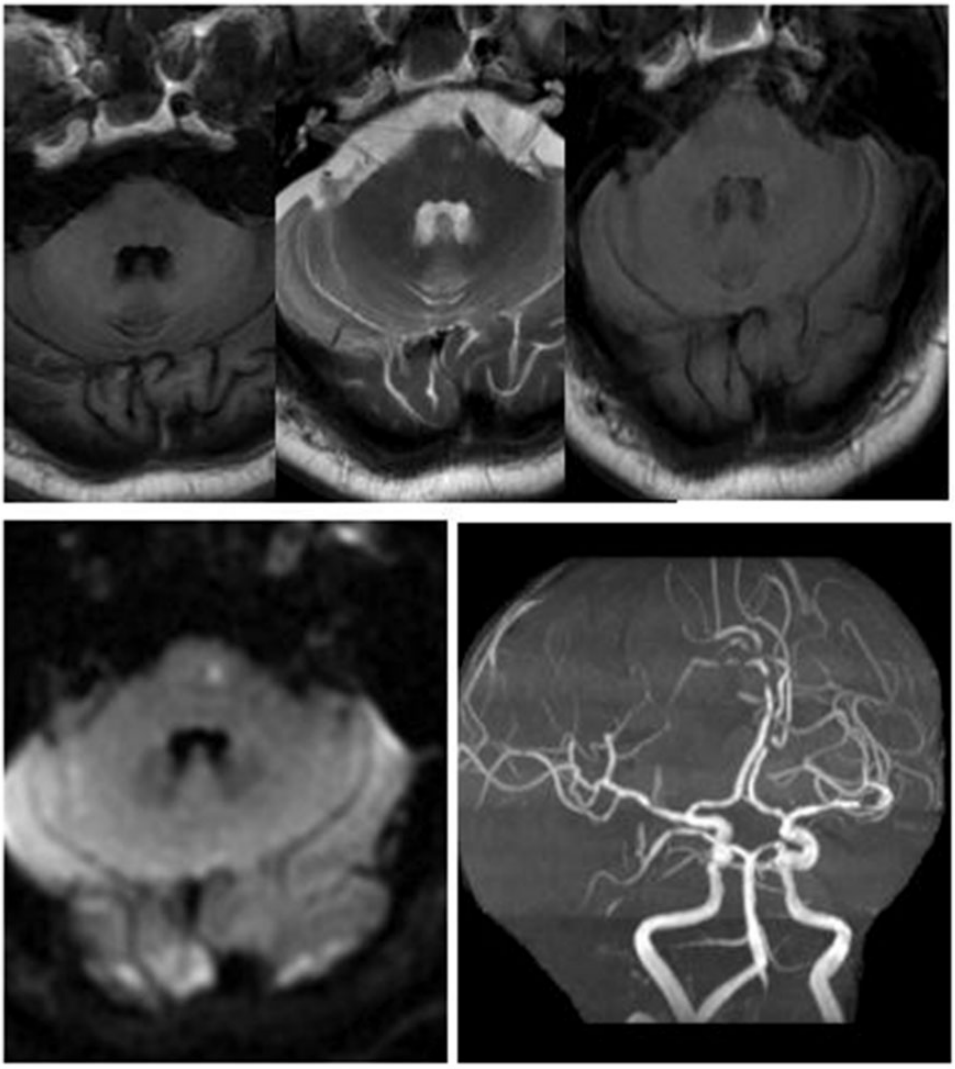

Figure 4. T1, T2, fluid-attenuated inversion recovery, diffusion-weighted imaging, and magnetic resonance angiography sequences of the atherosclerotic type of brainstem infarction

Correlation between related risk factors and poor prognosis

Multivariate logistic regression analysis demonstrated that patients with BSI located in the territories of multiple perforating arteries, who were discharged without statin treatment, were likely to exhibit poor prognosis at 1 year post-infarction (Table 3).

Discussion

The brainstem is an important brain function center that aids in the maintenance of physiological activities and state of consciousness. It plays an essential role in controlling balance, coordinated movement, hearing, speech, eye movement, and swallowing; patients who have sustained

Table 1. Clinical factors associated with disability at 1 year after acute single brainstem infarct.

Variables	Total (n=281)	Non-disability (mRS<2) (n=197)	Disability (mRS≥2) (n=84)	P value
Age, median (IQR), y	63 (56,72)	62 (54,71)	68 (58,74)	0.004
Age ≥65 y	129 (45.9)	80 (40.6)	49 (58.3)	0.006
Female	102 (36.3)	74 (37.6)	28 (33.3)	0.500
Smoking	120 (42.7)	81 (41.1)	39 (46.4)	0.410
Hypertension	230 (81.9)	159 (80.7)	71 (84.5)	0.448
Diabetes mellitus	135 (48.0)	91 (46.2)	44 (52.4)	0.342
Hyperlipidemia	226 (80.4)	158 (80.2)	68 (81.0)	0.885
Coronary heart disease	27 (9.6)	18 (9.1)	9 (10.7)	0.681
Thrombolytic treatment	5 (1.8)	4 (2.0)	1 (1.2)	0.626
Early antithrombotics after admission	269 (95.7)	190 (96.4)	79 (94.0)	0.363
Antithrombotics at discharge	265 (95.3)	188 (96.4)	77 (92.8)	0.188
Antithrombotic at 1 year after onset	217 (77.2)	157 (79.7)	60 (71.4)	0.130
Statins in hospital	217 (77.2)	157 (79.7)	60 (71.4)	0.130
Statins at discharge	198 (70.5)	144 (73.1)	54 (64.3)	0.138
Statins at 1 year after onset	107 (38.1)	81 (41.1)	26 (31.0)	0.108
Rehabilitation evaluation or treatment in hospital	206 (73.8)	139 (71.3)	67 (79.8)	0.139
Admission NIHSS	5 (3,7)	4 (2,6)	6 (4,9)	<0.0001
Recurrence of ischemic stroke or TIA within 1 year after onset	11 (3.9)	6 (3.0)	5 (6.0)	0.250

Data are n (%) unless otherwise indicated. CI, confidence interval; IQR, interquartile range; LAA, large artery atherosclerosis; LCA, long circumferential artery; PA, paramedian artery; SCA, short circumferential artery; MRI, magnetic resonance imaging; mRS, the modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale

*It is in contrary to small artery occlusion subtype of ischemic stroke according to SSS-TOAST (Stop Stroke Study Trial of ORG 10172 in Acute Stroke Treatment) classification criteria. The difference between groups was confirmed with statistical significance ($P < 0.05$).

brainstem infarction exhibit both ataxia and dysphagia, as well as paralysis, diplopia, and dysarthria.[18] Stenosis and/or occlusion in the vertebrobasilar artery and its branches are common causes of brainstem infarction. Owing to rapid developments in neuroimaging technology, it has become possible to accurately determine the location of brainstem infarction and its associated etiology. With the application of head MRI, the rate of detection can be measured, as well as detailed information regarding the infarct lesion, such as size, volume, perforating artery involvement, and whether the lesion is located in the supply territory of single or multiple groups of perforating arteries.[4,15,16] Our analysis was based on a multicenter cohort study, in order to avoid the bias inherent in a small sample from a single center. Our results suggest that a single brainstem lesion constitutes a syndrome of multiple etiologies, and that these etiologies and prognoses can differ widely. Our findings indicate that a single lesion involving multiple atherosclerotic arteries is the worst prognosis; such patients showed a high degree of disability at the 1-year

Table 2. MR imaging features associated with disability at 1 year after acute single brainstem infarct.

Variables	Total (n=281)	Non-disability (mRS<2) (n=197)	Disability (mRS≥2) (n=84)	P value
Location of brainstem infarction				0.011
medulla	4 (1.3)	4 (2.6)	0 (0.0)	
pons	284 (94.0)	144 (92.3)	140 (95.9)	
midbrain	8 (2.6)	7 (4.5)	1 (0.7)	
pons + midbrain	6 (2.0)	1 (0.6)	5 (3.4)	
Perforating artery involved				0.214
PA	130 (46.3)	98 (49.7)	32 (38.1)	
SCA	13 (4.6)	11 (5.6)	2 (2.4)	
LCA	3 (1.1)	2 (1.0)	1 (1.2)	
PA+SCA	115 (40.9)	75 (38.1)	40 (47.6)	
SCA+LCA	6 (2.1)	4 (2.0)	2 (2.4)	
PA+SCA+LCA	14 (5.0)	7 (3.6)	7 (8.3)	
LAA subtype*	141 (50.2)	91 (46.2)	50 (59.5)	0.041
Multiple perforating artery involved	145 (48.3)	63 (60.0)	82 (42.1)	0.003
Infarct volume, median (IQR), mL	0.38 (0.20,0.91)	0.34 (0.17,0.87)	0.56 (0.26,1.01)	0.014

Data are n (%) unless otherwise indicate. CI, confidence interval; IQR, interquartile range; LAA, large artery atherosclerosis; LCA, long circumferential artery; PA, paramedian artery; SCA, short circumferential artery; MRI, magnetic resonance imaging; mRS, the modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
*It is in contrary to small artery occlusion subtype of ischemic stroke according to SSS-TOAST (Stop Stroke Study Trial of ORG 10172 in Acute Stroke Treatment) classification criteria.

Table 3. Multivariate logistic regression analysis of factors associated with disability at 1 year after acute single brainstem infarct.

Variables	OR* (95% CI)	P value
Age ≥65 y	1.79 (0.93-3.44)	0.083
Female	0.53 (0.27-1.02)	0.058
Hypertension	1.25 (0.55-2.88)	0.593
Diabetes mellitus	1.49 (0.81-2.73)	0.204
Hyperlipidemia	1.08 (0.49-2.38)	0.855
Coronary heart disease	0.83 (0.29-2.39)	0.733
Admission NIHSS ≤3	1.29 (0.58-2.86)	0.534
Multiple perforating arteries involved	1.99 (1.06-3.74)	0.032
LAA subtype*	1.67 (0.90-3.11)	0.106
Antithrombotics at discharge	3.40 (0.74-15.7)	0.117
Statins at discharge	0.40 (0.19-0.86)	0.019

CI, confidence interval; LAA, large artery atherosclerosis; LCA, long circumferential artery; OR, odds ratio; mRS, the modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
*Contrary to small artery occlusion subtype of ischemic stroke according to SSS-TOAST (Stop Stroke Study Trial of ORG 10172 in Acute Stroke Treatment) classification criteria.

follow-up. Multiple groups of perforating arteries are frequently affected by atherosclerotic plaques within their parent arteries, such as the vertebral or basilar arteries, thus blocking multiple perforating branches. Such single lesions comprise large infarct volume, regardless of whether the nucleus and fibrous bundle are involved in the lateral view, and are not restricted to the medulla oblongata, pons, or midbrain; generally, two or three levels are involved.[14,19]

Our study found that the pons was the most common area of involvement for brainstem infarction (94%), consistent with the results of other studies.[20] The paramedian perforating arteries, arising either directly from the dorsal surface of the basilar artery, or from short circumferential arteries running around and into the pons,[21] may help to easily derive the hyaline degeneration information from kinetic changes of blood flow related to hypertension, diabetes, or other risk factors. These small perforators are easily occluded. Fisher reported that pontine lacunar or small deep pontine infarctions were frequently associated with abnormal thickening of the penetrating arteries, along with segmental arterial disorganization, lipohyalinosis, and fibrinoid degeneration of the media; this was a unique pattern that differed from atherosclerosis.[22] However, the vascular pathology in these branches may be related to branch atheromatous disease, where the orifices of penetrating branches are blocked by an atheroma in the parent artery or a microatheroma at the origin of the branch itself.[23–25] Regardless of the pathological type of pontine lesion, the long-term prognosis of such patients was relatively benign.[9] Kunz[26] followed 26 patients with paramedian pontine infarctions for 4 to 9 years. Of these, 17 patients lived independently, five died, and four had recurrent stroke. The majority of patients had a benign prognosis. In our study, patients who had a single paramedian pontine lesion or single perforator involvement demonstrated small-volume lesions and reduced neurological dysfunction at the time of admission and discharge. Although the diagnostic rate of the small artery occlusion type of ischemic stroke was not considerable in this group of patients, they often exhibited severe leukoaraiosis and several old lacunar lesions on imaging, suggesting imaging features of small artery disorders.

Previous studies have reported that, in the posterior cerebral circulation system, the location of the infarct, as well as its etiology, pathogenesis, and clinical manifestations are highly related to patient prognosis. In the New England Medical Center Posterior Circulation Stroke Study,[27] brain lesions were categorized as proximal, middle, and distal intracranial posterior circulation territories (according to the method of Caplan); that study concluded that, in embolic stroke, the involvement of basilar artery infarctions, or infarctions located at multiple vascular perfusion territories in the posterior circulation, was associated with severe disability and death. The risk of poor outcome was highest (approximately 50%) in cases involving both the middle and distal territories (which supply the major blood flow to the tegmentum of the pons and midbrain). Thus, distal territory involvement is a probable marker for embolism. Kim et al.[28] observed a higher incidence rate of progressive neurological dysfunction in patients with cerebral infarction in the distal perfusion region of posterior circulation. However, patients enrolled in the above study exhibited multiple brainstem infarcts, rather than single brainstem infarcts. Kunz et al.[26] followed up 26 patients with single pontine infarction and revealed that reduced systolic blood pressure was a risk factor for the onset of progressive neurological deficits. Our study analyzed risk factors associated with neurological deficits at discharge and disability of single brainstem infarction patients within 1 year. We found that vertigo as one of the

initial symptoms, a brainstem larger than 0.5 mL, atherosclerotic type of brainstem infarction, and a lack of statin drug usage at discharge were independent factors for disability at 1 year post-infarction. Therefore, it is necessary to provide rapid assessment and implement preventive secondary treatment for high-risk patients.

However, there were some limitations to this study. First, the study selected only inpatients, and excluded patients who had an unstable condition, required continuous monitoring, were disabled before hospitalization, or were unable to undergo head MRI, thus causing possible selection bias. Second, the study did not include high-resolution MRI owing to the presence of plaques in the parent artery, which might have led to the misclassification of the atherosclerotic type of cerebral infarction as a small artery infarction type.[7,28]

In summary, this study demonstrated that clinical and imaging findings of BSI contribute to the prediction of prognosis. Isolated BSI involving multiple perforating arteries and a lack of statin medication at discharge were associated with poor patient prognosis. The classification of isolated BSI based on clinical and imaging findings, such as etiology, location, and size, will help predict prognosis among such patients.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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