Distal Single Subcortical Infarction Had a Better Clinical Outcome Compared With Proximal Single Subcortical Infarction

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Background and Purpose—Single subcortical infarction (SSI) may be classified as proximal SSI (pSSI) or distal SSI (dSSI) according to its location within the middle cerebral artery territory. Few studies have examined the differences in clinical outcome between the 2. Our study investigated such differences in patients with pSSI or dSSI and examined their baseline characteristics and indicators for small-vessel disease.

Methods—We prospectively enrolled 400 patients with SSI (208 pSSI and 192 dSSI) who had no middle cerebral artery disease on MR angiography. Data compared included clinical information, lesion size, prevalence of lacune and leukoaraiosis at baseline, National Institutes of Health Stroke Scale score and modified Rankin Scale score at discharge, and any deterioration during admission or recurrence of ischemic stroke <1 year.

Results—in multivariable logistic regression analysis, dSSI was independently associated with patient’s history of stroke, admission National Institutes of Health Stroke Scale score ≤3, Fazekas score ≥3, presence of lacune, but not hyperlipidemia. Patients with dSSI had shorter length of hospital stay, lower rate of functional dependence at discharge (modified Rankin Scale score ≥2), and lower deterioration or recurrence risk of ischemic stroke in 1 year. Multivariable logistic regression analysis showed that factors associated with higher deterioration or recurrence risk of ischemic stroke at 1 year included female sex, history of coronary heart disease, pSSI, and not on antithrombotics <48 hours of admission.

Conclusions—Compared with pSSI, patients with dSSI likely had small-vessel diseases but better clinical outcome. (Stroke. 2014;45:00-00.)

Key Words: cerebral small vessel diseases ■ stroke, infarct ■ stroke, lacunar

Single subcortical infarction (SSI) in the middle cerebral artery (MCA) territory can be classified as proximal SSI (pSSI) and distal SSI (dSSI).1,2 pSSI has also been named as intracranial atheromatous branch disease, and previous studies1,2 have shown that pSSI may be caused by arteriosclerotic changes of the orifices or proximal portions of penetrating arteries. Luminal plaques obstructing a branch, junctional plaques extending into a branch, and microatheroma in the orifice of the branch are 3 possible mechanisms of pSSI proposed by Miller Fisher and Louis R. Caplan.1 Patients with pSSI clinically have progressive motor deficits and unfavorable functional outcome.2 On the contrary, dSSI may be caused by fibrinoid degeneration or lipohyalinosis of the distal perforating artery.3 Patients with dSSI often have small-vessel diseases manifested as lacune, leukoaraiosis, and microbleeds on imaging studies.1,2,4 Because most published reports had small number of samples and had not examined differences of clinical outcome in patients with pSSI or dSSI, we investigated such differences in patients with ischemic stroke (IS) in China. Data analyzed from patients with pSSI or dSSI included their vascular risk factors, prevalence of lacune and leukoaraiosis, and clinical outcome.

Methods and Materials

Subjects
Chinese Intracranial Atherosclerosis (CICAS) is a prospective, multicenter, hospital-based study. Clinical and imaging data were prospectively collected from consecutive patients with IS or transient ischemic attack (TIA) presenting to 31 participating hospitals in China between June 2009 and February 2011. From the Department of Neurology, Beijing Tian Tan Hospital, Capital Medical University, Beijing, China (C.Z., Yilong Wang, X. Zhao, L.L., C.W., Y.P., X. Zou, W.D., J.J., Y.P., Yongjun Wang); INI Stroke Network, OSF Healthcare System, University of Illinois College of Medicine, Peoria (D.W.); and Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China (K.S.W.).

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ischemic attack in 22 Chinese general hospitals. From October 2007 to June 2009, 2864 patients with noncardioembolic ischemic cerebrovascular diseases were enrolled in CICAS. Among them, 400 patients with SSI in the MCA territory were classified as having small-artery occlusion (SAO) strokes according to the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) classification criteria.\(^5\) They did not have MCA diseases on MR angiography (MRA). The institutional review board of the participating hospitals approved this study. Each participant signed an informed consent.

Patients enrolled into the study had the onset of symptoms <7 days and were aged between 18 and 80 years. Patients were excluded if they were clinically unstable, required close monitoring, disabled before admission (modified Rankin Scale [mRS] score >2), physically or subjectively unable to comply with MRI. We excluded patients with cardiomyoembolic risk factors (atrial fibrillation, valvular heart disease, postcardiac valve replacement, etc) and patients with ≥50% stenosis of the ipsilateral carotid artery. Patients with IS with undetermined causes or other causes were also excluded. The final analysis included 400 patients, who had MRI and MRA of brain <4 days after stroke onset.

**Clinical Information Assessment**

The clinical information collected included age, sex, hypertension (defined as a history of hypertension or diagnosed at discharge), diabetes mellitus (defined as a history of diabetes mellitus or diagnosed at discharge), hyperlipidemia (defined as low-density lipoprotein cholesterol ≥2.6 mmol/L at the time of admission or a history of hyperlipidemia or received lipid-lowering treatments or diagnosed at discharge), history of IS or intracerebral hemorrhage, history of coronary heart disease (defined as a history of myocardial infarction or angina pectoris), National Institutes of Health Stroke Scale (NIHSS) score at admission and discharge, and mRS at discharge and 1 year after stroke onset. Smoking history, current or previous smokers (continuously smoking ≥1 cigarette a day for 6 months), and history of heavy alcohol use (drinking ≥2 U per day on average for men or ≥1 U per day on average for women) were also collected. Uses of antithrombotics <48 hours of admission, at discharge, and in 1 year after stroke onset were recorded.

**MRI Analysis**

All 400 patients underwent MRI on a 3.0-T MR scanner. Imaging sequences obtained included 3-dimensional time-of-flight MRA (repetition time, 20–25 ms; echo time, 3.3–3.9 ms; flip angle, 15°–20°; slice thickness, 0.65–1.0 mm), axial T2-weighted (repetition time, 4500 ms; echo time, 84 ms), T1-weighted imaging (repetition time, 1200 ms; echo time, 11 ms), fluid-attenuated inversion recovery sequences (repetition time, 7000 ms; echo time, 94 ms), and diffusion-weighted imaging (repetition time, 3000 ms; echo time, 75 ms). All above sequences except MRA had 5 mm slice thickness and 1.5 mm interslice gap. MR images were viewed by using software (RadiAnt DICOM Viewer1.0.4.4439; Medixant Ltd, Poznan, Poland). Intracranial vessels were judged by 3-dimensional time-of-flight MRA, and extracranial carotid artery was examined by duplex color Doppler ultrasound or contrast-enhanced MRA.

Lesion location of SSI in the MCA territory was classified as pSSI (extending to the basal surface of MCA) and dSSI (not extending to the basal surface of MCA) according to the method described by Nah et al.\(^4\) A diagram for the possible mechanisms of dSSI and pSSI is illustrated in Figure 1. Involvement of the lower portion of the basal ganglia was considered as an extension to the basal surface of MCA.\(^4\) The largest lesion was used to determine the volume of infarction: 1/2x×diameter of length×diameter of width×numbers of MRI diffusion-weighted imaging slices of SSI.

Leukoaraiosis was defined as hyperintense signals on fluid-attenuated inversion recovery and T2 images, not usually seen on T1-weighted MRI. We rated leukoaraiosis with the Fazekas method.\(^6\) Periventricular white matter hyperintensities and deep white matter hyperintensities were evaluated separately and totaled together as Fazekas scores. Lacune was defined as lesions of ≥3 mm in size with the same signal characteristics as cerebrospinal fluid on all sequences, and with a hyperintense rim on the fluid-attenuated inversion recovery sequence (when located supratentorially),\(^7\) and differentiated from dilated Virchow–Robin spaces by their wedge shape with surrounding hyperintensity on fluid-attenuated inversion recovery.\(^8\) To be diagnosed as lacune by MRI, the lesion should not be located in

**Figure 1.** Two types of single subcortical infarction without parent artery disease in the middle cerebral artery (MCA) perforator territory. A, Distal single subcortical infarction without disease of MCA. B, Proximal single subcortical infarction without disease of MCA.

**Figure 2.** Presumed mechanism of single subcortical infarction (SSI). A, Distal SSI resulted by fibrinoid degeneration or lipohyalinosis of the distal perforating artery. B, Proximal SSI resulted by microatheroma in the orifice of the branch. C, Proximal SSI resulted by luminal plaque extending into a branch.
cortical territories and have the morphological and topographical distribution consistent with border-zone infarctions. Microbleeds were defined as homogeneous, punctate, focal, rounded, or oval lesions of low signal on T2*-weighted gradient-recalled echo and <10 mm in diameter. Symmetrical hypointense signals in the globus pallidus likely represented calcification or iron deposition and were disregarded. Hypointense lesions in the subarachnoid space (likely represent pial blood vessels) were excluded. Two radiologists blinded to the clinical details read all MRI scans. Consensus was reached by them if they had disagreement on interpretations.

**Follow-Up and Clinical Outcome Evaluations**

Patients or their authorized proxies were contacted at 3, 6, and 12 months after stroke onset by telephone for follow-up. The primary outcome was progressive deterioration or recurrence of IS in 1 year. Progressive deterioration of IS was defined as worsening by ≥4 points of the initial NIHSS score from the index stroke. Recurrence of IS was defined as a new focal neurological deficit of vascular origin lasting >24 hours and without hemorrhage on computed tomography or MRI of the brain.

At 3, 6, and 12 months after discharge, patients or their relatives were contacted over the telephone by trained research personnel at Beijing Tian Tan hospital and were asked whether patients had new symptoms or hospitalized again with another stroke. All recurrence or progressive deterioration of IS was verified at the index hospitals based on the NIHSS score and the presence of new neurological deficits documented in the medical records in combination with computed tomography or MRI images. An experienced stroke neurologist reviewed the patients’ medical document to ensure a reliable diagnosis of recurrence or progressive deterioration of IS. In case of an unclear event that was not hospitalized, the case would be adjudicated by a stroke neurologist and the principle investigator. Any death was verified by examining the hospital medical records or local citizen registry.

Stroke severity at admission and discharge were assessed by using NIHSS. Activities of daily living was assessed by mRS before stroke onset, at discharge, and 1 year after stroke onset. Function dependence was defined as mRS ≥2.

**Statistical Analyses**

Continuous variables with non-normal distribution were summarized as median (interquartile range). Categorical variables were presented as absolute numbers and percentages. The Mann–Whitney U test was used for comparison of continuous variables with non-normal distribution such as age, Fazekas scores, number of lacune, diameter of SSI, NIHSS, and mRS scores. χ² test was used for comparison of categorical variables such as sex, smoking status, and vascular risk factors. All statistical analyses were performed using SPSS software (version 21.0; IBM, Armonk, NY).

### Table 1. Baseline Characteristics of pSSI and dSSI Patients

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total (n=400)</th>
<th>pSSI (n=208)</th>
<th>dSSI (n=192)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* y</td>
<td>61 (52, 71)</td>
<td>60 (51, 68)</td>
<td>63 (54, 73)</td>
<td>0.013</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>160 (40.0)</td>
<td>70 (33.7)</td>
<td>90 (46.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Male sex</td>
<td>289 (72.3)</td>
<td>143 (68.8)</td>
<td>146 (76.0)</td>
<td>0.104</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or previous smoker</td>
<td>208 (52.0)</td>
<td>110 (52.9)</td>
<td>98 (51.0)</td>
<td>0.712</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>24 (6.00)</td>
<td>13 (6.30)</td>
<td>11 (5.70)</td>
<td>0.827</td>
</tr>
<tr>
<td>Hypertension</td>
<td>320 (80.3)</td>
<td>167 (80.3)</td>
<td>153 (79.7)</td>
<td>0.881</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>110 (27.5)</td>
<td>60 (28.8)</td>
<td>50 (26.0)</td>
<td>0.530</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>308 (77.0)</td>
<td>172 (82.7)</td>
<td>136 (70.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>25 (6.30)</td>
<td>11 (5.30)</td>
<td>14 (7.30)</td>
<td>0.408</td>
</tr>
<tr>
<td>History of IS</td>
<td>78 (19.5)</td>
<td>29 (13.9)</td>
<td>49 (25.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>History of ICH</td>
<td>15 (3.80)</td>
<td>0 (0)</td>
<td>15 (7.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>89 (22.3)</td>
<td>29 (13.9)</td>
<td>60 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severity of stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission NIHSS score ≤3</td>
<td>203 (50.8)</td>
<td>77 (37.0)</td>
<td>126 (65.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission NIHSS*</td>
<td>3 (2, 6)</td>
<td>4 (3, 8)</td>
<td>2 (2, 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Imaging features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of leukoaraiosis</td>
<td>389 (97.3)</td>
<td>199 (95.7)</td>
<td>190 (99.0)</td>
<td>0.045</td>
</tr>
<tr>
<td>Fazekas scores*</td>
<td>3 (2, 4)</td>
<td>2 (2, 4)</td>
<td>4 (3, 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fazekas score ≥3</td>
<td>247 (61.8)</td>
<td>101 (48.6)</td>
<td>146 (76.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of lacune</td>
<td>205 (51.3)</td>
<td>84 (40.4)</td>
<td>121 (63.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of lacune*</td>
<td>1 (0, 2)</td>
<td>0 (0, 1)</td>
<td>1 (0, 3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of microbleeds</td>
<td>38 (29.7)</td>
<td>13 (19.1)</td>
<td>25 (41.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum long diameter of SSI,*</td>
<td>14 (11, 19)</td>
<td>17 (14, 23)</td>
<td>12 (9, 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum transverse diameter of SSI,*</td>
<td>8 (6, 11)</td>
<td>10 (7, 13)</td>
<td>7 (5, 9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum height of SSI,*</td>
<td>18 (13, 24)</td>
<td>21 (19, 28)</td>
<td>13 (7, 14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume of SSI,* mL</td>
<td>0.93 (0.38, 2.09)</td>
<td>1.79 (1.02, 3.90)</td>
<td>0.44 (0.23, 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slight irregularity in the MCA</td>
<td>26 (6.5)</td>
<td>16 (7.7)</td>
<td>10 (5.2)</td>
<td>0.215</td>
</tr>
</tbody>
</table>

dSSI indicates distal single subcortical infarction; ICH, intracerebral hemorrhage; IS, ischemic stroke; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and pSSI, proximal single subcortical infarction.

*Continuous variables with non-normal distribution are expressed as median (interquartile range); other values are expressed as n (%).
used for comparison of categorical variables. The baseline relative factors and their crude distribution were presented according to the location of SSI and progressive deterioration or recurrence of IS in 1 year, respectively. Multivariable logistic regression analysis was used to identify relative factors associated with location of SSI and progressive deterioration or recurrence of IS in 1 year. All parameters that were significant by univariate analysis at $P<0.05$ level were included in the multivariable logistic regression analysis. All probability values were 2-tailed; $P<0.05$ was considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

### Results

#### General Patient Characteristics

The studied population consisted of 400 patients (289 men, 111 women) with a mean age of 61.1±11.2 years (range, 19–80 years). There was no difference in days from stroke onset to MRI scans between patients with pSSI or dSSI ($P=0.17$). As for vascular risk factors, 320 patients (80%) had hypertension, 110 (28%) had diabetes mellitus, 308 (77%) had hyperlipidemia, and 208 (52%) were smokers. In addition,
78 patients (20%) had a history of IS, 15 (4%) had a history of intracerebral hemorrhage, and 25 (6%) had a history of coronary heart disease. Leukoaraiosis was observed in 389 patients (97%) and lacune in 205 (51%). Among 128 patients who underwent gradient-recalled echo sequences, 38 patients (30%) had microbleeds.

**Characteristics of SSI According to the Lesion Location in Relationship to MCA**

Of the 400 patients without MCA pathology, 208 had pSSI and 192 had dSSI. Table 1 summarizes the descriptive statistics of the 2 groups. Comparing to patients with pSSI, patients with dSSI were often older, had a history of stroke, more severe leukoaraiosis, higher prevalence of lacune and microbleeds, and smaller infarct lesion. In addition, patients with dSSI received less intravenous tissue plasminogen activator, had a lower prevalence of hyperlipidemia, a shorter length of hospital stay, lower NIHSS score at admission and discharge, a lower proportion of dependence in activities of daily living at discharge (mRS ≥2), and lower deterioration or recurrence of IS in 1 year. However, there was no significant difference in function dependence and mortality at 1 year in both dSSI and pSSI patients (Table 2).

The median dimension of dSSI was 12×7×13 mm, which were smaller than that (17×10×21 mm) of pSSI (P<0.0001). Patients with dSSI had more severe leukoaraiosis (76%), also more lacune (63%) and microbleeds (42%). The median NIHSS score in patients with dSSI at admission and discharge were 2 and 1, respectively, which were significantly lower than those (4 and 2) with pSSI. One hundred forty (73%) patients with dSSI achieved independent activities of daily living (mRS <2), whereas only 109 (52%) patients with pSSI were independent at discharge (P<0.0001). More pSSI patients (10 of 208) received combined treatment of aspirin and low-molecular-weight heparin <48 hours of admission compared with patients with dSSI (2 of 192; P=0.027); however, there were no differences in other types of antithrombotic treatments <48 hours of admission between dSSI and pSSI patients. Meanwhile, there were no differences in the types of antithrombotic treatment at discharge and 1 year after stroke onset between pSSI and dSSI patients (Table 2).

In multivariable logistic regression analysis (Table 3), absence of hyperlipidemia (odds ratio [OR], 1.78; P=0.03), history of stroke (OR, 1.88; P=0.03), admission NIHSS score ≤3 (OR, 4.23; P<0.001), Fazekas score ≥3 (OR, 2.86; P<0.001), and presence of lacune (OR, 2.05; P=0.003) were significantly related with the development of dSSI.

**Risk Factors Associated With Progressive Deterioration or Recurrence of Ischemic Stroke for Patients With SSI in 1 Year**

Nine patients (2.3%) had progressive deterioration or recurrence of IS, and 2 patients (0.5%) died. One patient (0.5%) in the dSSI group developed progressive deterioration of IS during admission, whereas 8 patients (3.8%); 4 with deterioration of the index stroke during admission, 1 with recurrence of pSSI because of SAO during admission, and 3 with recurrence of dSSI because of SAO after discharge (in the pSSI group had progressive deterioration or recurrence of IS (P=0.04).

Univariate analysis found that patients with history of coronary heart disease, pSSI, and not on antithrombotics treatment <48 hours after admission had a higher stroke deterioration or recurrence risk in 1 year (Table I in the online-only Data Supplement).

After adjustment for age, vascular risk factors, and volume of SSI in multivariable logistic regression, the 1-year risk of deterioration or recurrence of IS was high if the patient was woman (OR, 7.25; P=0.03), had history of coronary heart disease (OR, 10.4; P=0.01), had pSSI (OR, 13.8; P=0.05), and did not receive antithrombosis treatment <48 hours of admission (OR, 11.2; P=0.04; Table 4).

**Discussion**

We classified patients with SSI into either pSSI or dSSI group and found that patients with dSSI had significantly more severe leukoaraiosis and lacune compared with patients with pSSI. Of the 400 patients enrolled, 128 patients underwent gradient-recalled echo sequence evaluation for microbleeds. We also found that patients with dSSI had a higher proportion of microbleeds (42%) than those with pSSI (19%). Because leukoaraiosis, lacune, and microbleeds are all indicators of small-vessel diseases, our results support that dSSI is more closely related to small-vessel diseases compared with pSSI. These results are consistent with previous studies. For example, Cho et al found that patients with dSSI had more severe white matter changes, and Nah et al found that these patients had a higher prevalence of microbleeds and leukoaraiosis compared with patients with pSSI.

High-resolution MRI of MCA stenosis can now offer excellent visualization of plaque. Yoon et al and Chung et al found that patients with pSSI had a higher prevalence of branch atheromatous plaque in MCA than those with dSSI.
prior studies.4,17 The lesion size and volume were significantly
cal deficit compared with dSSI, which was consistent with
with larger volume of infarction and more severe neurologi-
recurrence of IS in 1 year compared with pSSI patients.
at discharge, and a lower risk of progressive deterioration
proportion of progressive motor deficits compared with those
vascular risk factors (Table
formed multivariable logistic regression analysis and found
so we cannot exclude the presence of mild atherosclerotic plaque that did not cause significant luminal
Lastly, our patients were followed up by telephone interview, which could miss identifying minor strokes
without apparent symptoms and underestimate the recurrence
rate of IS to some extent.

Conclusions
Our study demonstrated that patients with dSSI had likely
small-vessel diseases but with smaller lesions, milder clinical
signs, and better clinical outcome compared with patients with pSSI. The pathogenesis of SSI without MCA disease on
MRA may be heterogeneous depending on the lesion location in relation to MCA.

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Disclosures
None.

References

Table 4. Multivariable Logistic Regression for Relative Factors Associated With Progressive Deterioration or Recurrence of Ischemic Stroke in 1 Year for SSI Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>P Value</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
<td>0.911</td>
<td>0.910 (0.175–4.72)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.028</td>
<td>7.25 (1.23–42.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.663</td>
<td>1.69 (0.161–17.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.292</td>
<td>0.291 (0.029–2.89)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.633</td>
<td>1.77 (0.169–18.6)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0.013</td>
<td>10.4 (1.63–66.0)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>0.139</td>
<td>4.25 (0.625–28.9)</td>
</tr>
<tr>
<td>Admission NIHSS score ≤3</td>
<td>0.838</td>
<td>1.20 (0.203–7.15)</td>
</tr>
<tr>
<td>pSSI†</td>
<td>0.045</td>
<td>13.8 (1.06–180)</td>
</tr>
<tr>
<td>Volume of SSI, per mL</td>
<td>0.751</td>
<td>0.949 (0.688–1.31)</td>
</tr>
<tr>
<td>Early antithrombotics</td>
<td>0.037</td>
<td>0.089 (0.009–0.860)</td>
</tr>
<tr>
<td>Discharge antithrombotics</td>
<td>0.344</td>
<td>0.266 (0.017–4.13)</td>
</tr>
<tr>
<td>Antithrombotics in 1 y</td>
<td>0.730</td>
<td>1.39 (0.216–8.90)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and pSSI, proximal single subcortical infarction (SSI). †It is contrary to distal SSI.

on high-resolution MRI. Meanwhile, we found that patients with pSSI had a higher prevalence of hyperlipidemia. Because hyperlipidemia is an important risk factor for the development of atherosclerosis and significantly associated with severity of intracranial stenosis,18 pSSI is possibly more closely related to atherosclerosis compared with dSSI.

Yamamoto et al12 found that patients with dSSI had a lower proportion of progressive motor deficits compared with those with pSSI. We also found that patients with dSSI had a lower NIHSS score on admission and at discharge, a lower mRS at discharge, and a lower risk of progressive deterioration or recurrence of IS in 1 year compared with pSSI patients. Meanwhile, we found that pSSI was significantly associated with larger volume of infarction and more severe neurologically deficient compared with dSSI, which was consistent with prior studies.3,17 The lesion size and volume were significantly bigger in pSSI than in dSSI patients (Table 1). So we performed multivariable logistic regression analysis and found that patients with pSSI had a 13.8-fold increase of the risk of recurrence or progressive deterioration of IS compared with patients with dSSI after adjustment of lesion volume and vascular risk factors (Table 4). So we think that it was the location and not the size of the lesion that determined the recurrence or progressive deterioration in patients with SSI.

In our study, 4 patients with SSI underwent recurrence of SAO subtype IS (1 pSSI patient with pSSI because of SAO during admission, 3 pSSI patients with dSSI because of SAO during 1 year follow-up). The result was similar to that of Yoon et al26 who found that SAO subtype stroke patients more often developed recurrence of SAO subtype stroke during follow-up. Because of a small number of patients with recurrent IS in our study, we did not find that patients with pSSI developed more recurrence of large artery disease subtype stroke compared with patients with dSSI.

Our study has limitations. First, all patients in our study had SAO subtype stroke, and SAO subtype stroke was found to have a lower recurrence rate.21 Second, ours was a hospital-based study, and selection bias was inevitable. Third, our patients were younger, which might bring lower rate of stroke recurrence. Fourth, MCA was not examined by high-resolution MRI in our study, so we cannot exclude the presence of mild atherosclerotic plaque that did not cause significant luminal stenosis. Lastly, our patients were followed up by telephone interview, which could miss identifying minor strokes without apparent symptoms and underestimate the recurrence rate of IS to some extent.


Distal Single Subcortical Infarction Had a Better Clinical Outcome Compared With Proximal Single Subcortical Infarction
Changqing Zhang, Yilong Wang, Xingquan Zhao, David Wang, Liping Liu, Chunxue Wang, Yuehua Pu, Xinying Zou, Wanliang Du, Jing Jing, Yuesong Pan, Ka Sing Wong and Yongjun Wang

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### SUPPLEMENTAL MATERIAL

**Table I. Relative Factors Associated with Deterioration or Recurrence of Ischemic Stroke in one year for SSI patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=400)</th>
<th>No deterioration or recurrence (n=391)</th>
<th>Deterioration or recurrence (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*, y</td>
<td>61 [52.71]</td>
<td>61 [52.71]</td>
<td>64 [50.72]</td>
<td>0.837</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>160(40.0)</td>
<td>156(39.9)</td>
<td>4(44.4)</td>
<td>0.783</td>
</tr>
<tr>
<td>Female</td>
<td>111(27.8)</td>
<td>106(27.1)</td>
<td>5(55.6)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Vascular Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or previous smoker</td>
<td>208(52.0)</td>
<td>204(52.2)</td>
<td>4(44.4)</td>
<td>0.646</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>24(6.00)</td>
<td>24(6.10)</td>
<td>0(0)</td>
<td>0.443</td>
</tr>
<tr>
<td>Hypertension</td>
<td>320(80.0)</td>
<td>312(79.8)</td>
<td>8(88.9)</td>
<td>0.500</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>110(27.5)</td>
<td>109(27.9)</td>
<td>1(11.1)</td>
<td>0.265</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>308(77.0)</td>
<td>300(76.7)</td>
<td>8(88.9)</td>
<td>0.391</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>25(6.30)</td>
<td>22(5.60)</td>
<td>3(33.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of IS</td>
<td>78(19.5)</td>
<td>75(19.2)</td>
<td>3(33.3)</td>
<td>0.289</td>
</tr>
<tr>
<td>History of ICH</td>
<td>15(3.80)</td>
<td>15(3.80)</td>
<td>0(0)</td>
<td>0.549</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>89(22.3)</td>
<td>86(22.0)</td>
<td>3(33.3)</td>
<td>0.419</td>
</tr>
<tr>
<td><strong>Severity of stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission NIHSS score ≤3</td>
<td>203(50.8)</td>
<td>200(51.2)</td>
<td>3(33.3)</td>
<td>0.290</td>
</tr>
<tr>
<td>Prestroke mRS*</td>
<td>0 [0,0]</td>
<td>0 [0,0]</td>
<td>0 [0,0]</td>
<td>0.947</td>
</tr>
<tr>
<td><strong>Imaging Features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pSSI†</td>
<td>208(52.0)</td>
<td>200(51.2)</td>
<td>8(88.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>Presence of Leukoaraiosis</td>
<td>389(97.3)</td>
<td>380(97.2)</td>
<td>9(100)</td>
<td>0.610</td>
</tr>
<tr>
<td>Fazekas scores*</td>
<td>3 [2,4]</td>
<td>3 [2,4]</td>
<td>3 [2,5]</td>
<td>0.810</td>
</tr>
<tr>
<td>Fazekas scores ≥3</td>
<td>247(61.8)</td>
<td>242(61.9)</td>
<td>5(55.6)</td>
<td>0.699</td>
</tr>
<tr>
<td>Presence of old lacunar infarctions</td>
<td>205(51.3)</td>
<td>202(51.7)</td>
<td>3 (33.3)</td>
<td>0.277</td>
</tr>
<tr>
<td>Number of old lacunar infarctions*</td>
<td>1 [0,2]</td>
<td>1 [0,2]</td>
<td>0 [0,3]</td>
<td>0.435</td>
</tr>
<tr>
<td>Presence of microbleed</td>
<td>38(29.7)</td>
<td>37(29.4)</td>
<td>1(50.0)</td>
<td>0.526</td>
</tr>
<tr>
<td>Maximum transverse diameter of SSI†</td>
<td>8 [6,11]</td>
<td>8 [6,11]</td>
<td>10 [7,14]</td>
<td>0.161</td>
</tr>
<tr>
<td>Maximum height of SSI†</td>
<td>18 [13,24]</td>
<td>17 [12,24]</td>
<td>20 [18,27]</td>
<td>0.067</td>
</tr>
<tr>
<td>Volume of SSI (ml)</td>
<td>0.93 [0.38,2.09]</td>
<td>0.92 [0.36,2.04]</td>
<td>1.68 [0.97,4.30]</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>Performance measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV t-PA thrombolysis</td>
<td>14(3.50)</td>
<td>14 (3.60)</td>
<td>0 (0)</td>
<td>0.563</td>
</tr>
<tr>
<td>Early antithrombotics</td>
<td>386(96.5)</td>
<td>379(96.9)</td>
<td>7(77.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>250(62.5)</td>
<td>244(62.4)</td>
<td>6(66.7)</td>
<td>0.794</td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>70(17.5)</td>
<td>70(17.9)</td>
<td>0(0)</td>
<td>0.162</td>
</tr>
<tr>
<td>Cilostazol only</td>
<td>6(1.5)</td>
<td>6(1.5)</td>
<td>0(0)</td>
<td>0.708</td>
</tr>
<tr>
<td>LMH only</td>
<td>9(2.3)</td>
<td>9(2.3)</td>
<td>0(0)</td>
<td>0.645</td>
</tr>
<tr>
<td>Warfarin only</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>0.879</td>
</tr>
<tr>
<td>Combination</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------</td>
<td>-----</td>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>Aspirin+ Clopidogrel</td>
<td>30(7.5)</td>
<td>30(7.7)</td>
<td>0(0)</td>
<td>0.388</td>
</tr>
<tr>
<td>Aspirin+ Cilostazol</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>0.879</td>
</tr>
<tr>
<td>Aspirin+ Clopidogrel+LMH</td>
<td>5(1.3)</td>
<td>5(1.3)</td>
<td>0(0)</td>
<td>0.733</td>
</tr>
<tr>
<td>Aspirin+ LMH</td>
<td>12(3.0)</td>
<td>11(2.8)</td>
<td>1(11.1)</td>
<td>0.149</td>
</tr>
<tr>
<td>Clopidogrel+ LMH</td>
<td>2(0.5)</td>
<td>2(0.5)</td>
<td>0(0)</td>
<td>0.830</td>
</tr>
<tr>
<td>Discharge antithrombotics</td>
<td>377(94.3)</td>
<td>369(94.4)</td>
<td>8(88.9)</td>
<td>0.485</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>261(65.3)</td>
<td>253(64.7)</td>
<td>8(88.9)</td>
<td>0.132</td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>104(26.0)</td>
<td>104(26.6)</td>
<td>0(0)</td>
<td>0.072</td>
</tr>
<tr>
<td>Ticlopidine only</td>
<td>5(1.3)</td>
<td>5(1.3)</td>
<td>0(0)</td>
<td>0.733</td>
</tr>
<tr>
<td>Aspirin+ Clopidogrel</td>
<td>5(1.3)</td>
<td>5(1.3)</td>
<td>0(0)</td>
<td>0.733</td>
</tr>
<tr>
<td>Aspirin+ Clopidogrel+ Cilostazol</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>0.879</td>
</tr>
<tr>
<td>Aspirin+ warfarin</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>0.879</td>
</tr>
<tr>
<td>Antithrombosis in 1 year†</td>
<td>263(66.1)</td>
<td>256(65.8)</td>
<td>7(77.8)</td>
<td>0.453</td>
</tr>
<tr>
<td>Aspirin only</td>
<td>223(56.0)</td>
<td>216(55.5)</td>
<td>7(77.8)</td>
<td>0.184</td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>33(8.3)</td>
<td>33(8.5)</td>
<td>0(0)</td>
<td>0.362</td>
</tr>
<tr>
<td>Ticlopidine only</td>
<td>1(0.3)</td>
<td>1(0.3)</td>
<td>0(0)</td>
<td>0.879</td>
</tr>
<tr>
<td>Aspirin+ Clopidogrel</td>
<td>6(1.5)</td>
<td>6(1.5)</td>
<td>0(0)</td>
<td>0.707</td>
</tr>
</tbody>
</table>

SSI, single subcortical infarction; IS, ischemic stroke; ICH, Intracerebral Hemorrhage; NIHSS, National Institutes of Health stroke scale; mRS, modified Rankin Scale; pSSI, proximal single subcortical infarction; IV, intravenous; t-PA, tissue plasminogen activator; LWM, low molecular heparin; *Continuous variables with non-normal distribution are expressed as median (IQR), other values are expressed as n (%); †It is contrary to distal single subcortical infarction. †two patients died after discharge, so only 398 patients were included in the analysis.