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Original Article

Application of arterial spin labeling and susceptibility weighted imaging in the diagnosis of ischemic cerebrovascular diseases

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Abstract: Objective: To investigate the application value of arterial spin labeling (ASL) and susceptibility weighted imaging (SWI) in the diagnosis of acute ischemic cerebrovascular disease (CVDs). Methods: A total of 124 patients who received fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), ASL, time of flight magnetic resonance angiography (TOF-MRA) and SWI scan sequentially were included in this study. The area of the abnormal perfusion region was compared with that of the restricted diffusion region. The cerebral blood flow (CBF) value and apparent diffusion coefficient (ADC) value were compared in ischemic penumbra (IP), infarct core and mirror region. The susceptibility vessel sign (SVS) detection rate was compared with the major vessel severe stenosis or occlusion rate as revealed by MRA. A receiver operating characteristic curve (ROC) was used to analyze the value of SVS as revealed by SWI. Results: In total, 124 cases were included in this study, and 77 cases showed acute cerebral infarction. Among the 77 cases, 59 cases showed an IP. There were significant differences in ADC and CBF values between the infarct core and mirror region ($P < 0.01$). There was no significant difference in ADC value between IP and mirror region ($P = 0.176$), but there was significant difference in CBF value between IP and mirror region ($P < 0.01$). There was no significant difference in SVS detection rate compared with the vessel severe stenosis or occlusion rate in MRA ($P = 0.111$). Based on the MRA standards, the area under curve (AUC) of ROC for the SVS as revealed by SWI was 0.86 (95% CI: 0.753-0.962). Conclusions: ASL combined with DWI contributed to IP evaluation of acute cerebral infarction. SWI showed higher diagnostic value for intravascular thrombus in acute cerebral infarction.

Keywords: Ischemic cerebrovascular disease, arterial spin labeling, susceptibility weighted imaging

Introduction

Cerebrovascular accident (CVA), also designated as stroke, is an intracranial angiostenosis, occlusion, or rupture, which triggers acute disorders in cerebral blood circulation [1]. In clinical settings, CVA is featured by transient or permanent cerebral disorder with a high prevalence, mortality, and morbidity leading to threats to the public health. Among these patients, more than a half of the cases are diagnosed with ischemic stroke (IS), including transient ischemic attack (TIA), cerebral thrombosis, and embolism [2, 3]. It is mainly associated with cerebrovascular insufficiency induced by angiostenosis or embolism, together with cerebral disorders caused by decline of cerebrovascular perfusion [1]. Thus, more attention should be paid to the diagnosis of early-stage cerebral infarction and identification of involved vessels.

Nowadays, the diagnosis of stroke relies on computed tomography (CT), digital subtraction angiography (DSA) and magnetic resonance imaging (MRI) [4]. CT shows a high sensitivity to hemorrhagic stroke, but it shows lower sensitivity for IS. For example, as a severe condition with no symptoms, TIA is not clearly screened by CT. Besides, CT cannot display the lesions of cerebral infarction within 24 hr after disease onset. Angiostenosis or occlusion can be presented as dense artery sign on CT imaging [5], which is the main sign reflecting cerebral artery stenosis or occlusion, but the sensitivity is not high. To date, DSA has been considered as the gold standard for the diagnosis of CVDs as it can display the site of stenosis and occlusion of

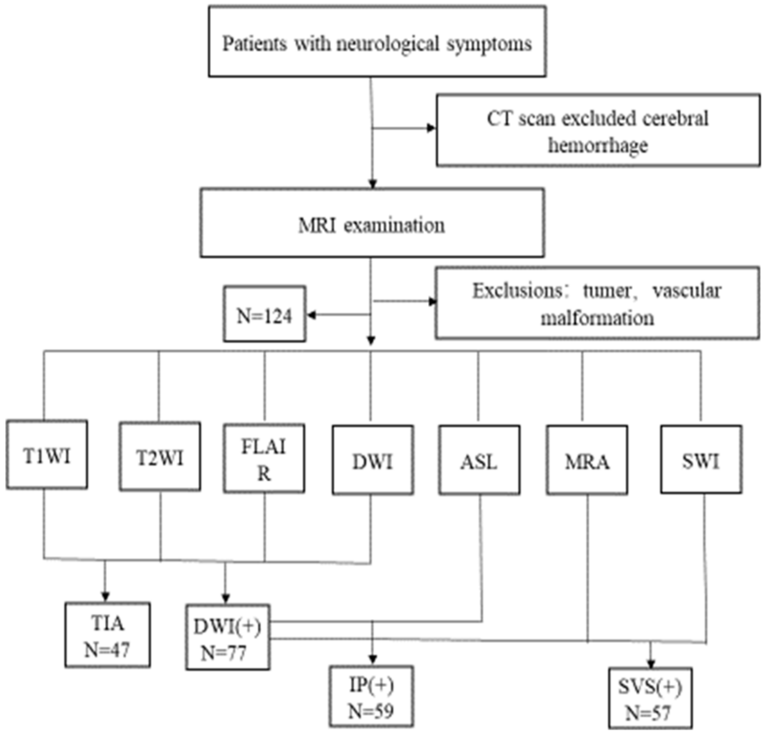

Figure 1. Diagram of the procedure of enrolling participants.

the responsible vessels [6]. Nevertheless, the procedures are complex and expensive involving injection of contrast agent and high dose of X ray irradiation. Similarly, CTA technique also involves irradiation injury and injection of contrast agents. Therefore, these techniques cannot be utilized for the routine examination and follow-up of patients with cerebrovascular disease (CVDs).

For these patients, it is crucial to pay attention to the pre-treatment assessment of ischemic regions and involved vessels [7-9]. In this study, we analyzed the imaging manifestations of arterial spin labeling (ASL) and susceptibility weighted imaging (SWI) to explore their clinical value in acute ischemic CVDs.

Materials and methods

Patients

We selected a set of patients who came to the emergency department of our hospital from September 2016 to February 2018, generally with dizziness, headache, diplopia, amaurosis, walking instability, hemiplegia, language disorders, and other neurological symptoms. First, CT scan was performed to exclude patients with cerebral hemorrhage. Patients with contraindications of MR examination were also excluded. According to our inclusion and exclusion criteria, 124 patients (male: 73; female: 51; age: 40-81 yr; median: 60.5±8.7 yr) were finally included in this study (**Figure 1**). Each patient signed an informed consent. The study protocols were approved by the Ethical Committee of Taiwan City Central Hospital.

The inclusion criteria were as follows: (a) Those with dizziness, instability of gait, powerless, logagnosis, deviation of mouth, as well as consciousness disorders; (b) Those who received MRI within 24 hrs after the disease onset; (c) CT examination without cerebral hemorrhage.

The exclusion criteria were as follows: (a) Those who had prosthesis, stent implantation, or fear of confined spaces; (b) Those with poor image quality due to severe artifacts; (c) CT or MRI indicated cerebral hemorrhage, tumor, vascular malformation; (d) Those with cerebral infarction by vasculitis or allergic conditions.

Methods

MRI scan was performed using MR750 (3.0T, GE Healthcare, CA, USA) facilitated with 8 channel coils. The scanning sequences included FLAIR, DWI, 3D- TOF-MRA, 3D-ASL, and SWI.

The scanning parameters for FLAIR were as follows: TR, 8500 ms; TE, 145 ms; FOV, 240 mm×240 mm; matrix, 256×256; slice thickness, 5 mm. For DWI, the scanning parameters were as follows: TR, 3000 ms; TE, 66 ms; FOV, 240 mm×240 mm; matrix, 256×256; slice thickness, 5 mm; b value, 1000 ms. MRA parameters were as follows: TE, out of phase (phase, 224 ms); TR, 23 ms; FOV, 220 mm×220 mm; matrix, 512×512; slice thickness, 1.4 mm. The ASL parameters were as follows: TR, 4781 ms; TE, 11 ms; post delay time, 1525 ms; FOV, 220 mm×220 mm; matrix, 128×128; slice thickness, 3 mm. The total scanning duration was 6 min 52 sec. The parameters for SWI were

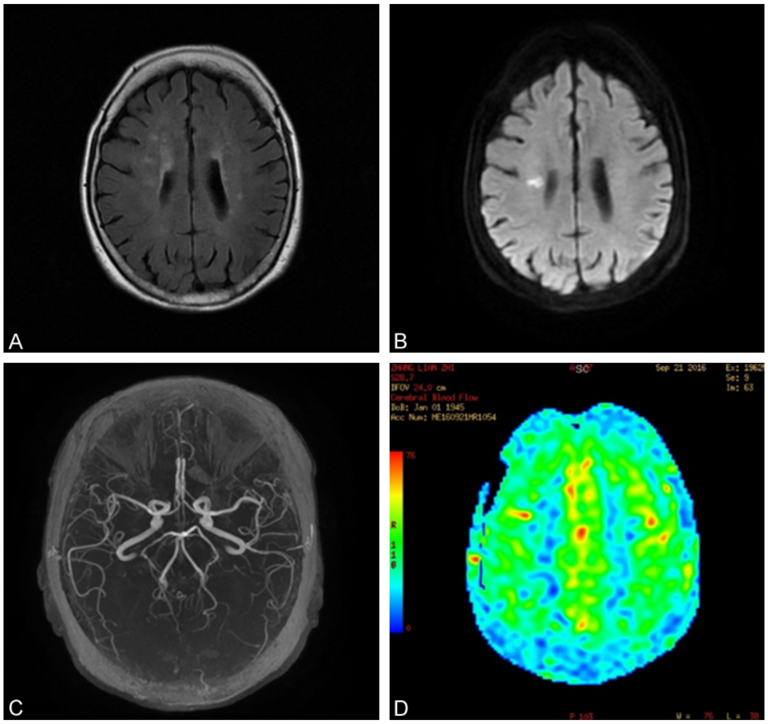

Figure 2. Imaging findings of brain for a 70-yr-old female patient. A. FLAIR showed multiple ischemic lesions in brain. B. DWI indicated acute lacunar infarction lesions in the right corona radiata. C. MRA indicated that the distribution of the large vessels in brain was almost normal. D. ASL perfusion artificial image showed there was no region with obvious decline in blood perfusion.

as follows: TE, 20 ms; TR, 30 ms; FOV, 256 mm×256 mm; matrix, 512×512; slice thickness, 2 mm.

Image analysis

Post-image processing was performed on the Functool (GE Healthcare, CA, USA) workstation. High signal region on diffusion weighted imaging (DWI) was defined as acute infarction. Small infarction was defined as an infarction area with a diameter of < 3 cm, while large infarction was defined that with a diameter of about >3 cm [10]. High signal region on DWI and aberrant perfusion region on ASL were depicted manually, as well as for comparison. In part of the patients, the area with low perfusion on ASL was larger than that of an area with DWI high signal, and unmatched region was defined as IP. The cerebral blood flow (CBF) value and apparent diffusion coefficient (ADC) value in the infarct core, IP and mirror region were determined.

MRA imaging was carried out based on 3D-TOF method. The evaluation for MRA was performed according to the previous description [11]. The grades 0 and 1 were defined as severe stenosis or occlusion.

Magnitude images and phase images were obtained after SWI scan. Minimal intensity projection (MinIP) reconstruction was conducted using 3DMIP software, in order to obtain the SWI MiniIP images. Susceptibility vessel sign (SVS) was defined as previously described [9, 12, 13].

All the images were evaluated by two experienced physicians specialized in MR. In case of any disputes, a comprehensive discussion was held until consensus was reached.

Statistical analysis

ADC and CBF values were expressed in the form of mean ± standard deviation. Levene test showed that the data were in accordance with normal distribution. Student's t-test was used for the comparison of CBF and ADC values in the ischemic penumbra (IP), infarct core, and mirror region. Chi square test was conducted for the comparison of the detection rate of SVS compared with the stenosis or occlusion rates of the major vessels as revealed by MRA. Based on the MRA findings, the AUC was calculated according to the ROC. Data analysis was conducted using SPSS 20.0 software. $P < 0.05$ was considered significant.

Results

Imaging findings of DWI and ASL

In total, 124 cases were included in this study, among which 47 showed no obvious changes in DWI. There was decline in local blood perfusion. On this basis, these patients were diagnosed with TIA. Seventy-seven cases were diagnosed with acute cerebral infarction manifested by high DWI signals. Among the 77 cases with acute cerebral infarction, 6 showed punctiform or mottling high DWI signals (**Figure 2**), no areas with obvious decline of perfusion were noticed. Seventy-one cases presented with

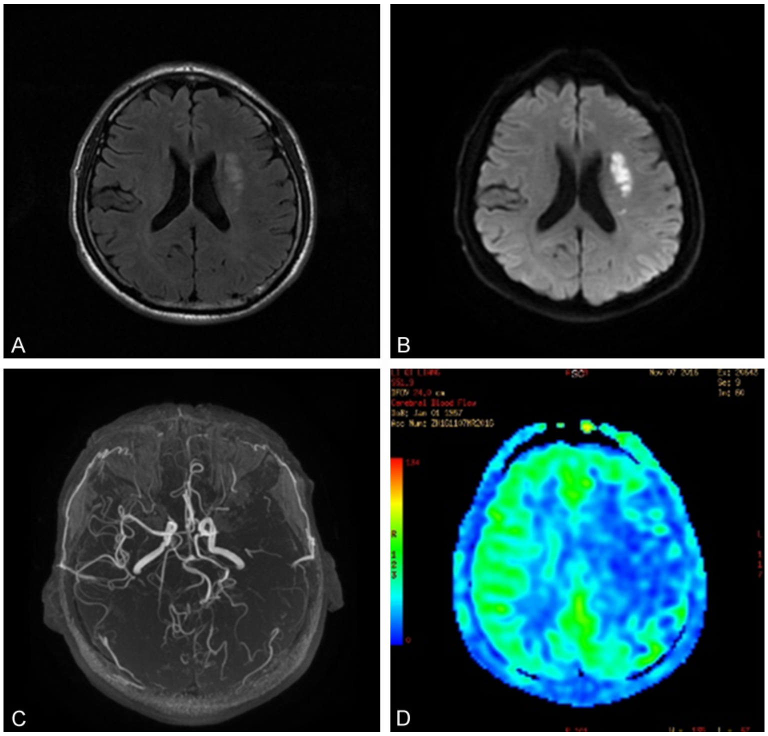

Figure 3. Imaging findings of brain for a 59-yr-old male patient. A, B. FLAIR and DWI showed high signals in a lamellar profile in the left corona radiata. C. MRA showed there was no obvious imaging in the left middle cerebral artery and the other branches. D. ASL indicated the presence of a massive, decreased blood perfusion area in the left middle cerebral artery. The areas with decreased perfusion were larger compared with those with high DWI signals.

Table 1. Comparison of CBF and ADC values between the infarct core, ischemic penumbra, and mirror region

	CBF (ml·100 g^{-1}·min^{-1})	ADC (×10^{-6} mm^2/s)
Infarct core	18.111±3.46	444.24±99.27
Mirror region	50.318±9.25	897.88±234.52
t	-27.199	-15.298
P	0.000	0.000
Ischemic penumbra	26.658±4.73	834.69±119.84
Mirror region	49.356±11.46	812.15±102.20
t	-21.289	1.371
P	0.000	0.176

massive cerebral infarction, among which 59 showed an IP region (**Figure 3**).

Comparison of CBF and ADC values between IP, infarct core and mirror region

There were significant differences in ADC and CBF values between the infarct core and mirror region (P = 0.000, 0.000, **Table 1**). There was no significant difference in ADC value between IP and mirror region (P = 0.176, **Table 1**), but there was a significant difference in CBF value between IP and mirror region (P = 0.000, **Table 1**).

Comparison of SVS detection rate of SWI and severe stenosis or occlusion rate based on MRA

A total of 63 cases showed severe stenosis or occlusion after MRA, and SWI showed SVS in 57 cases (**Figure 4**). Among these patients, 49 cases showed consistent stenosis of occlusion displayed by MRA and SVS. Fourteen cases showed severe stenosis or occlusion after MRA, but SVS was not detected in SWI. MRA showed approximately normal vessels, but SVS was detected in 8 patients, including 5 cases of M3, 2 cases of M4 and 1 case of P3. Chi square test showed that there was no significant difference between SVS detection rate and MRA stenosis or occlusion rate (χ^2 = 2.537, P = 0.111, **Table 2**). Based on the MRA standards, the AUC of ROC for the SWI was 0.86 (95% CI: 0.753-0.962, **Figure 5**). In addition, 31 cases showed cerebral microbleeds (CMBs), 9 of which 9 were acute cerebral infarction.

Discussion

ASL is a technique focusing on the monitoring of blood perfusion in brain based on the protons in arterial blood [14]. Upon labeling of the protons upstream of the imaging plane, the labeled arterial blood may enter into the tissues to generate the labeling images. The contrast images were unlabeled images with the same parameters of the same level, and the ASL perfusion images were obtained after sub-

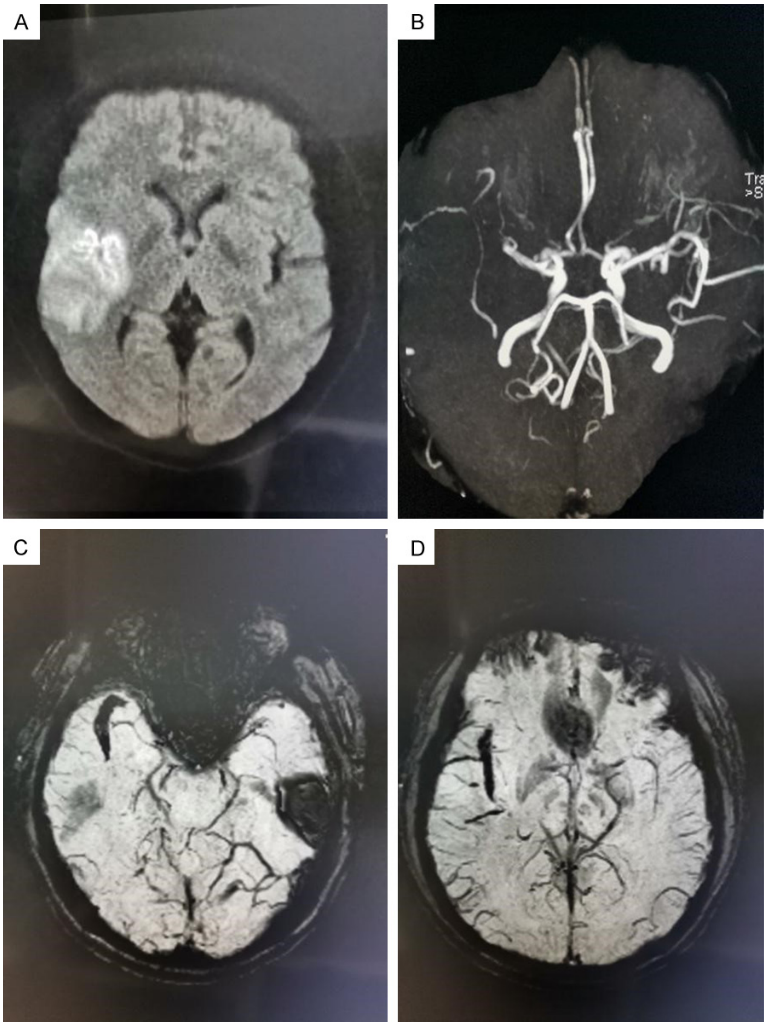

Figure 4. Imaging findings of brain for a 38-yr-old male patient. A. DWI showed high signals in the right cerebral hemisphere. B. MRA revealed occlusion in the M2 and M3 segments of the right middle cerebral artery. The distal branches were not observed. C, D. SWI MinIP image showed SVS in the M2, M3, and M4 segments of the right middle cerebral artery.

Table 2. Comparison of SVS detection rate of SWI and severe stenosis or occlusion rate as revealed by MRA

	MRA+	MRA-	Total	χ^2	*P*
SVS+	49	8	57		
SVS-	14	6	20		
Total	63	14	77	2.537	0.111

traction between the labeled images and the contrast images. ASL was superior as it involved no necessity of contrast media, was a non-invasive procedure, and had high repeatability [14, 15]. TIA refers to transient neurologic impairment induced by cerebral or retinal ischemia with the symptoms lasting for less than 1 hr. Stenosis caused by vasospasm is an important cause for TIA. In cases of ischemia and anoxemia, there is a high possibility of hypoperfusion in the distal part of arterial blood. For these cases, there were no positive findings on the conventional MRI images, however, the sites and scale with decline in the cerebral perfusion could be displayed by ASL [16]. The symptoms of cerebral ischemia occurred frequently in patients with TIA, and prolonged duration was likely to further develop into cerebral infarction [17]. In this study, 47 patients with TIA were detected. Timely clinical intervention to restore cerebral blood perfusion can reduce the risk of stroke.

DWI reflects the diffusion of water molecules in the tissue, and is represented by ADC values. DWI is considered to be the most sensitive sequence for diagnosing acute cerebral infarction. ASL indicates the cerebral blood perfusion showed decrease, and the areas are larger in size compared to those displayed by DWI with high signals. An unmatched region of low perfusion on ASL with a high DWI signal was defined as ischemic penumbra (IP) [7]. The aberrant DWI region included the irreversible and reversible injuries [18, 19]. The regions with low perfusion by ASL also included the partial regions with decline in the benign perfusion. However, up to now, it is still a challenge to distinguish the reversible injuries and the benign blood flow regions with declined perfusion in the regions with limitations in the diffusion. Therefore, IP recognition that is based on mismatch perfusion-diffusion pattern is still the better choice for clinical evaluation.

SWI is an imaging technique that relies on the magnetic sensitivity difference and blood oxygen levels in different tissues [12, 13]. It is a three-dimensional acquisition, fully flow-com-

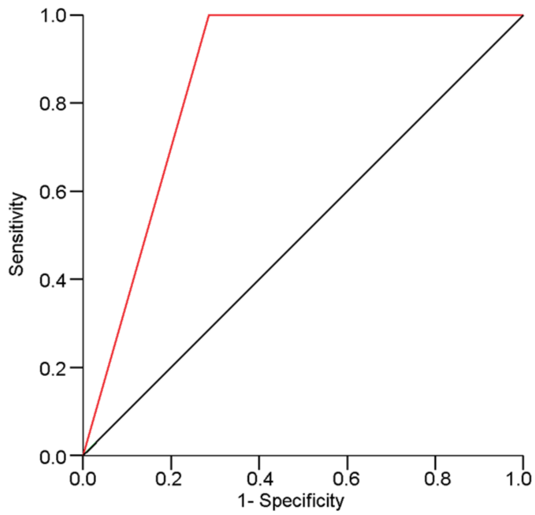

Figure 5. Based on the MRA standards, the AUC of ROC for the SVS as revealed by SWI was 0.86 (95% CI: 0.753-0.962).

pensated, high resolution, and thin-layer scan gradient echo sequence. With the unique data collection method and image processing technique, SWI shows a high sensitivity to hematological metabolites including deoxyhemoglobin, hemosiderin, methemoglobin, and venous blood. In cases of thrombosis or embolism in the infarcted arteries, there would be a decrease of blood flow in the arteries and increase in the content of deoxyhemoglobin. In addition, the ratio of deoxyhemoglobin and oxyhemoglobin is altered, which then induces interruption of the uniformity in the magnetic fields. The acute or super-acute cerebral infarction features red blood cell-predominant thrombosis. SWI canh specifically recognize the paramagnetic red thrombus containing deoxyhemoglobin. In the SWI MinIP image, this is manifested as cord-like low hypointensity shadows distributing along the vessels (i.e. SVS) [9, 12, 20-22]. In this study, there were 57 cases with positive SVS, and 49 showed matched position of stenosis/occlusion by MRA with the SVS. In this study, the AUC of ROC for the SVS as revealed by SWI was 0.86 (95% CI: 0.753-0.962), which indicated that SWI showed a higher diagnostic value for the thrombosis in the acute cerebral infarction.

In our study, 14 cases showed vascular stenosis by MRA, but these patients were negative for SVS. Several explanations are possible. First, some thrombosis (e.g. white thrombus) contains only a few substances that can alter the magnetic sensitive effects, or there might be vascular stenosis by sclerosis plaques that could not be detected by SWI. Also, the imaging of MRA is highly reliant on the blood flow, which may be caused by a phase loss after turbulent flow. This then would lead to loss of blood flow signals, which may lead to false images of vascular stenosis or exaggeration of blood stenosis.

In this study, CMBs were detected in 9 patients with acute cerebral infarction. CMB is a type of cerebral parenchymal injury featuring hemosiderin deposition induced by microvascular lesions in brain. According to the previous description, multiple CMBs in the patients with cerebral infarction reflect a hemorrhagic tendency [23]. CMBs could increase the risk of hemorrhage during the thrombolysis and the application of anticoagulants [24]. However, in a recent study [25], CMBs demonstrated a risk for hemorrhage, but the benefits from revascularization could not be excluded.

There are some limitations to this study. There might be factors affecting the SVS detection rates, as there was a time range of 24 hr for MR examination. We obtained only the baseline imaging findings for the patients, and did not collect the images upon revascularization and brain perfusion after treatment.

Conclusion

ASL combined with DWI contributed to ischemic penumbra (IP) evaluation of acute cerebral infarction. SWI showed a higher diagnostic value for intravascular thrombus in acute cerebral infarction.

Disclosure of conflict of interest

None.

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