Online January 14, 2021
Journal of Neuroendovascular Therapy 2021; 15: 574–582
DOI: 10.5797/jnet.oa.2020-0100

Original Article

Clinical Evaluations of the Ischemic Core in Acute Ischemic Stroke Using Modified Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Scores by Ischemic Reversibility Using the Signal Intensity

Daisuke Izawa,[1] Hiroyuki Matsumoto,[1] Hirokazu Nishiyama,[1] Naotsugu Toki,[1] and Naoyuki Nakao[2]

Objective: Early recanalization of acute stroke caused by large vessel occlusion (LVO) may improve high signal intensity (HSI) on diffusion-weighted imaging (DWI). In this study, we investigated whether subtraction of reversible ischemic lesions (RIL) from the HSI lesions on DWI improves the diagnostic accuracy for the ischemic core.

Methods: A total of 35 patients from April 2013 and December 2019 were included in this study. These patients presented acute ischemic stroke due to anterior circulation LVO and underwent thrombectomy. All patients underwent DWI within 48 hours after thrombectomy. HSI ratios were calculated, and compared between ischemic lesions and contralateral normal tissue. Ischemic lesions with improvement in the HSI ratio from initial to postoperative DWI were defined as RIL. Based on a receiver operating characteristic (ROC) curve analysis that compared the HSI ratio of all ischemic lesions, the cutoff value of HSI ratio of RILs was calculated.

Results: In all, 127 ischemic lesions were identified in 35 patients. HSI ratios of RILs were significantly lower than those of irreversible ischemic lesions (IILs) ($p < 0.0001$). Based on a ROC curve analysis that compared the HSI ratio of all 127 lesions, the cutoff value of the HSI ratio of RILs was 1.4. After applying this cutoff value to the 127 ischemic lesions of the 35 patients, 20 patients (57%) were identified as having RILs with a HSI ratio of <1.4. In this 20 patients, the postoperative National Institutes of Health Stroke Scale (NIHSS) score at 24 hours was significantly lower ($p = 0.007$) and improvement in the NIHSS score was significantly higher ($p = 0.018$) than in the other patients.

Conclusion: A HSI ratio of <1.4 on preoperative DWI may reflect ischemic reversibility. In this study, the HSI ratio correlated with clinical findings associated with cerebral ischemia, and our method may be useful in assessing ischemic cores.

Keywords ▶ modified diffusion-weighted imaging-the Alberta Stroke Program Early Computed Tomography Score, signal intensity ratio, reversivility, ischemic core

[1]*Department of Neurological Surgery, Kishiwada Tokushukai Hospital, Kishiwada, Osaka, Japan*
[2]*Department of Neurological Surgery, Wakayama Medical University, Wakayama, Wakayama, Japan*

Received: May 25, 2020; Accepted: November 30, 2020
Corresponding author: Daisuke Izawa. Department of Neurosurgery, Kishiwada Tokushukai Hospital, 4-27-1, Kamoricho, Kishiwada, Osaka 596-8522, Japan
Email: daisuke.izawa@tokushukai.jp

Introduction

The Alberta Stroke Program Early Computed Tomography Score including the deep white matter (ASPECTS+W) using magnetic resonance imaging (MRI)-diffusion-weighted imaging (DWI) is feasible for the semi-quantitative assessment of the ischemic core volume, and useful for evaluating the indication of recanalization therapy for acute ischemic stroke.[1)]

Furthermore, high signal intensity (HSI) areas on DWI b-1000 may recover after recanalization in acute ischemic stroke patients caused by large vessel occlusion (LVO).[2–4)] In this study, regarding this area as a reversible ischemic lesion (RIL), we retrospectively investigated whether subtraction of RIL from the HSI lesions on DWI improves the diagnostic accuracy for the ischemic core.

Materials and Methods

Indication criteria for mechanical thrombectomy were as follows: (1) those with an ASPECTS+W of ≥6, and mechanical thrombectomy was performed within 6 hours after the time last known well, (2) those with an interval of ≥6 hours from the time last known well, ASPECTS+W of ≥7, and National Institutes of Health Stroke Scale (NIHSS) score of ≥8 in whom treatment was able to be started within 24 hours after the time last known well. A total of 114 patients from April 2013 and December 2019 were performed mechanical thrombectomy according to these indication criteria. The anterior circulation system was affected in 100 patients and the posterior circulation system was affected in 14. In this study, we included these patients who fulfilled the following four criteria: (1) the anterior circulation system was affected, (2) preoperative DWI demonstrated ischemic lesions, (3) mechanical thrombectomy led to complete recanalization on postoperative cerebral angiography, and (4) postoperative DWI was performed within 48 hours after mechanical thrombectomy. Patients were excluded if they had sustained poor quality images on preoperative or postoperative DWI made it difficult to evaluate ischemic lesions caused by some artifacts. We analyzed 35 patients according to the above inclusion and exclusion criteria (**Fig. 1**). Ischemic lesions were evaluated based on the ASPECTS+W (**Fig. 2**) by three neurosurgeons with ≥10-year clinical career. HSI lesions on DWI b-1000 for which the results of assessment were consistent by ≥2 neurosurgeons were evaluated as ischemic lesions.

(1) Evaluation of the HSI ratio and establishment of optimum cutoff values

Initially, the three points of HIS values were measured on each SHI lesions of the ASPECTS+W, and defined the mean HSI values at the 3 points as representative values at each ischemic site (Vi: value of ischemic lesion). Subsequently, three sites, the contralateral thalamus which may not be influenced by anterior circulation ischemia, contralateral caudate nucleus and contralateral cerebral cortex which were visualized favorably in all 35 patients determined by the ASPECTS+W, were regarded as control sites, and three random points of signal intensity values were also measured at each control sites, respectively. In each control sites, the mean signal intensities at the three random points were defined as representative values for the control sites (Vc: value of control sites). The HSI ratio was calculated by dividing the mean HSI of each ischemic lesion by that of a control site [Vi/Vc] (**Fig. 3**). Ischemic lesions with improvement of the postoperative HSI ratio in comparison with the preoperative HSI ratio were defined as RILs, and those without such improvement of the HSI were defined as irreversible ischemic lesions (IILs). We calculated the cutoff value of the preoperative HSI ratio

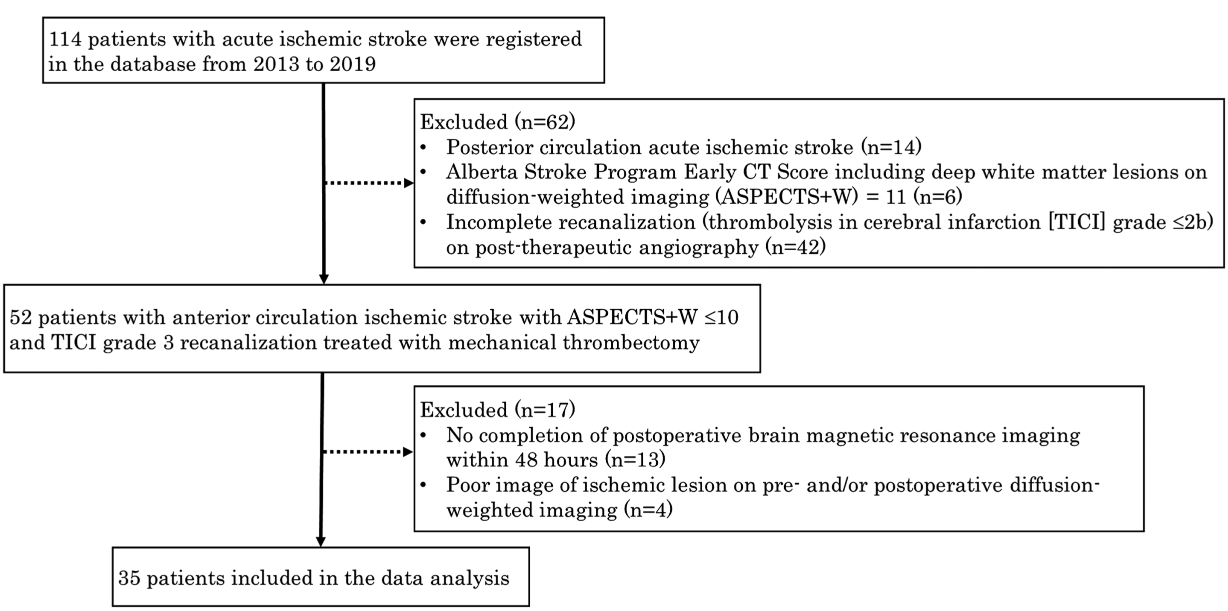
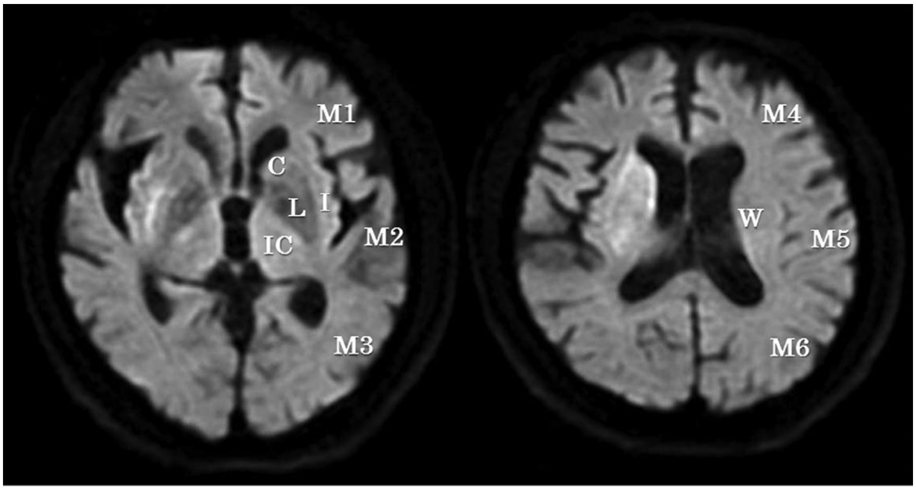


Fig. 1 Flowchart of study enrollment.



C: caudate	M1: anterior MCA cortex
L: lentiform	M2: MCA cortex lateral to insular ribbon
I: insular ribbon	M3: posterior MCA cortex
IC: internal capsule	M4-6: immediately superior to M1, M2 and M3,
W: deep white matter	rostral to basal ganglia

Fig. 2 ASPECTS+W on DWI with 11 regions distributed over the MCA territory at the ganglionic and supra-ganglionic levels. In this case, DWI showed ischemic lesions at the insular ribbon, internal capsule, and deep white matter (ASPECTS+W=8/11). ASPECTS+W: Alberta Stroke Program Early Computed Tomography Score including deep white matter lesions; DWI: diffusion-weighted imaging; MCA: middle cerebral artery

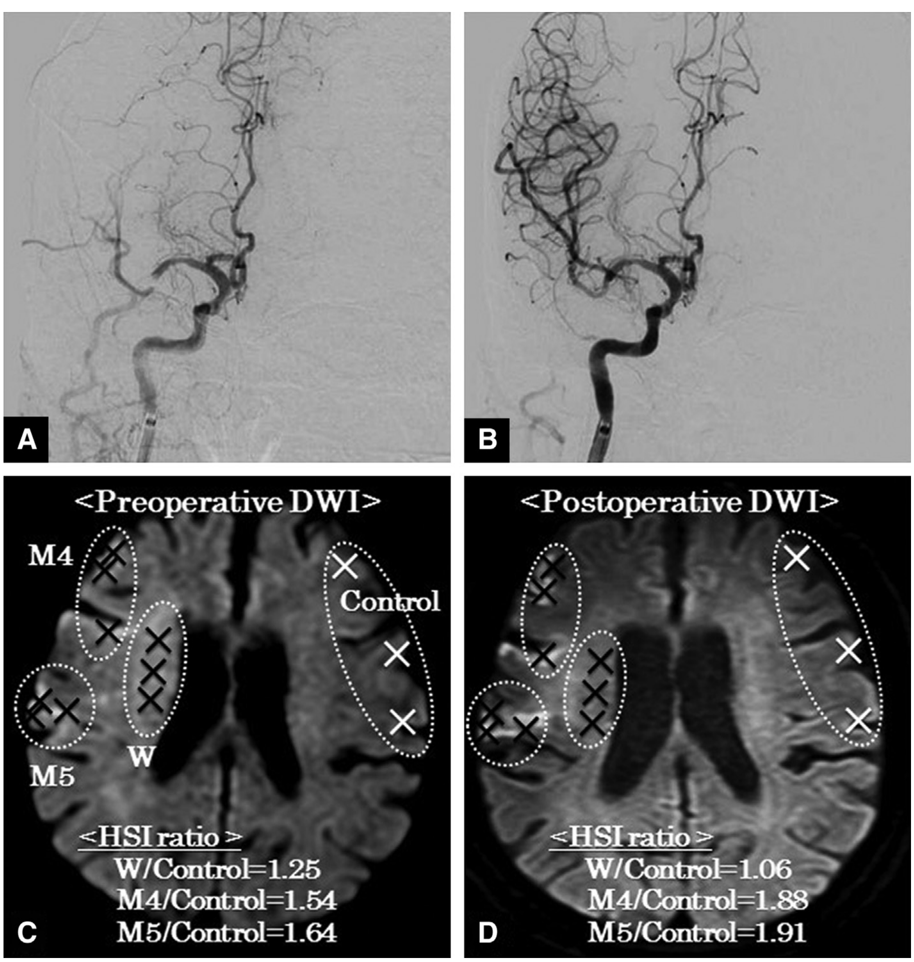


Fig. 3 Preoperative right CAG, AP view, showing MCA occlusion (**A**). Right CAG, AP view, showing complete recanalization (**B**). Preoperative DWI showing acute cerebral ischemia of the right M4, M5, and W based on the ASPECTS+W (**C**). HSI was measured at the three points on each ischemic lesion (black points) and the contralateral normal cerebral cortex as a control site (white points). The HSI ratio was calculated by dividing the mean HSI of each ischemic lesion by that of a control site. In this method, the preoperative HSI ratio was calculated on the right W (HSI ratio=1.25), M4 (HSI ratio=1.54), and M5 (HSI ratio=1.64). Postoperative DWI (**D**) at 24 hours demonstrated improved HSI on the right W (HSI ratio: 1.25–1.06), and unimproved HSI on the M4 (HSI ratio: 1.54–1.88) and M5 (HSI ratio: 1.64–1.91). AP: anteroposterior; ASPECTS+W: Alberta Stroke Program Early Computed Tomography Score including deep white matter lesions; CAG: carotid angiography; DWI: diffusion-weighted imaging; HSI: high-signal intensity; MCA: middle cerebral artery

using receiver operating characteristic (ROC) curve analysis to predict RILs on DWI within 48 hours after complete recanalization. The cutoff point (J) on the ROC curve was calculated as J = maximum (sensitivity + specificity −1).

DWI was performed using 1.5-T (MAGNETOM Symphony; Siemens, Munich, Germany) and 3.0-T (Achieva X-series; Phillips, Eindhoven, Netherlands) MRI systems. DWI b-1000 were prepared using the standardization method proposed by the Acute Stroke Imaging Standardization Group-Japan (ASIST-Japan).[5] The signal intensity value was measured at the 0.5mm thick crossing point of a cross mark using ShadeQuest/ViewR Ver. 1.26 (Yokogawa Medical Solutions Corporation, Tokyo, Japan).

(2) Evaluation using the modified DWI-ASPECTS

In the 35 patients, the ASPECTS+W was calculated based on preoperative DWI without deducting the points for sites below the cutoff value of HSI ratio. We defined it as the "modified DWI-ASPECTS." The patients were divided into two groups: Modified group in which an increase in the modified DWI-ASPECTS was more marked than that in the ASPECTS+W, and Unchanged group in which there was no such increase. In both the groups, the following data were collected: age, ASPECTS+W, initial NIHSS score, DWI to recanalization time (DTR), and hemorrhagic complications as background factors, in addition to the NIHSS score after 24 hours, improvement rate in the NIHSS score (ΔNIHSS), and rate of patients with a modified Rankin Scale (mRS) score of ≤2 as treatment results.

For statistical analysis, Statflex version 6 (Artech Co., Ltd., Osaka, Japan) was used. Continuous variables were described as the mean±standard deviation or median (25–75 percentiles), and compared with Student's t-test or Mann–Whitney U test, as appropriate. Category variables were described as the frequency and percentage, and compared using χ^2 or Fisher exact test as appropriate. A p value <0.05 was considered significant.

Results

(3) Calculation of the HSI ratio and establishment of cutoff values

The background of patients is shown in **Table 1**. A total of 127 ischemic lesions were evaluated based on the ASPECTS+W. At the 127 points, the HSI ratio was calculated and the rate of RILs was evaluated. The rate of RILs to each control site is shown in **Table 2**. As control sites of the contralateral thalamus and contralateral caudate nucleus, RILs were observed at 27 sites. The contralateral cerebral cortex was selected as a control site, they were observed at 29 sites. There were no significant differences in the rate of RILs among the three control sites.

As shown in **Fig. 4**, the HSI ratio of RILs was compared with that of IILs. The contralateral thalamus was selected as a control site, the median HSI ratios on preoperative

Table 1 Clinical characteristics of 35 patients

Age (years), mean (±standard deviation)	70.7±12.4
Male sex	20 (57.1)
Baseline NIHSS, median (IQR)	19 (11–23)
ASPECTS+W, median (IQR)	7 (7–9)
Location of occlusion	
ICA	8 (22.8)
MCA-M1segment	17 (48.6)
MCA-M2 segment	10 (28.6)
Ischemic stroke subtypes	
Cardioembolism	24 (68.6)
ESUS	6 (17.1)
Large artery atherosclerosis	5 (14.3)
Unclear-onset stroke	6 (17.1)
DWI to puncture time (minutes), median (IQR)	77 (61–93.5)
Puncture to recanalization time (minutes), median (IQR)	30 (24–38)
DWI to recanalization time (minutes), median (IQR)	110 (87.5–139)
Modified Rankin Scale≦2 at discharge	22 (62.9)

Values are the number (%) except where indicated otherwise. ASPECST+W: Alberta Stroke Program Early Computed Tomography Score including the deep white matter; DWI: diffusion-weighted imaging; ESUS: embolic stroke of undetermined source; ICA: internal carotid artery; IQR: interquartile range; MCA: middle cerebral artery; NIHSS: National Institutes of Health Stroke Scale

Table 2 Comparison of the reversible signal intensity lesion at the ASPECTS+W on each control sites

Location of DWI-ASPECTS	Contralateral thalamus (n=27/127)	Contralateral caudate head (n =27/127)	Contralateral cerebral cortex (n =29/127)	p value
Caudate	4/15 (26.7)	4/15 (26.7)	4/15 (26.7)	p =1.00
Lentiform	2/14 (14.3)	2/14 (14.3)	2/14 (14.3)	p =1.00
Internal capusule	2/5 (40)	2/5 (40)	2/5 (40)	p =1.00
Insular ribbon	2/20 (10)	2/20 (10)	3/20 (10)	p =0.38
M1	0/4 (0)	0/4 (0)	0/4 (0)	p =1.00
M2	3/15 (20)	3/15 (20)	4/15 (26.7)	p =0.38
M3	1/9 (11.1)	1/9 (11.1)	2/9 (22.2)	p =0.75
M4	1/4 (25)	1/4 (25)	1/4 (25)	p =1.00
M5	2/12 (16.7)	2/12 (16.7)	1/12 (8.3)	p =0.79
M6	1/8 (12.5)	1/8 (12.5)	1/8 (12.5)	p =1.00
Deep white matter	8/21 (38.1)	9/21 (42.9)	9/21 (42.9)	p =0.94

Values are the number of reversible lesions / total ischemic lesions (%). M1: anterior middle cerebral artery (MCA) cortex, M2: MCA cortex lateral to the insular ribbon, M3: posterior MCA cortex, M4-6: immediately superior to M1, M2, and M3 rostral to basal ganglia. ASPECST+W: Alberta Stroke Program Early Computed Tomography Score including the deep white matter; DWI: diffusion-weighted imaging

DWI of RILs and IILs were 1.18 (IQR: 1.12–1.20) and 1.58 (IQR: 1.50–1.82), respectively (p <0.0001). The contralateral caudate nucleus was selected as a control site, the values were 1.27 (IQR: 1.05–1.34) and 1.55 (IQR: 1.43–1.67), respectively (p <0.0001). The contralateral cerebral cortex was selected as a control site, the values were 1.29 (IQR: 1.06–1.35) and 1.54 (IQR: 1.42–1.66), respectively (p <0.0001). These HSI ratios were analyzed using ROC curves. The cutoff values of HSI ratios for the contralateral thalamus, contralateral caudate nucleus, and contralateral normal cerebral cortex were 1.37 (95% confidence interval [CI]: 1.33–1.39), 1.44 (95% CI: 1.42–1.46), and 1.40 (95% CI: 1.38–1.42), respectively (**Fig. 4**). As there were no significant differences in the rate of RILs or distribution of DWI-ASPECTS among the control sites, then the mean cutoff value of these control sites (HSI ratio = 1.40) was defined as the cutoff value of RILs.

(4) Clinical assessment based on the modified DWI-ASPECTS

In the 35 patients, ischemic lesions were reassessed using the modified DWI-ASPECTS in which ischemic lesions with an HSI ratio of <1.4 were excluded from the lesions with ASPECTS+W. The Modified group consisted of 20 patients (57.1%) and the Unchanged group consisted of 15 (42.9%). Furthermore, the median modified DWI-ASPECTS in the Modified group was 9 (IQR: 8–10).

As shown in **Table 3**, the background and treatment outcome were compared between the two groups. At the background, there were no significant differences in both groups. On the other hand, at the treatment outcome, there was no significant difference in the rate of patients with an mRS score of ≤2, but the NIHSS score after 24 hours was significantly lower (p = 0.007) and the ΔNIHSS was significantly higher (p = 0.018) in the Modified group.

Discussion

In this study, we evaluated ischemic lesions using the modified DWI-ASPECTS, in which RILs with an HSI ratio of <1.4 were excluded, and in these patients, complete recanalization was achieved with a median DTR of 110 minutes. As a result, neurological symptoms using the NIHSS score was significantly more improved in the Modified group; hence, we suggested that assessment of the modified DWI-ASPECTS more strictly reflects ischemic cores than of the ASPECTS+W.

Several studies reported that lower HSI areas included the penumbra even when HSI was detected on DWI in acute ischemic stroke, suggesting that the lower HSI values on DWI at b-1000 may be correlated the ischemic reversibility.[2–4,6,7]

Sato et al.[7] reported the evaluation of ischemic lesions using HSI ratio, in which the frontal horn of the lateral ventricle, contralateral thalamus, and anatomical symmetric site were selected as control sites on DWI at b-1000 within 3 hours after onset. They concluded that HSI ratio of <1.4 on DWI at b-1000 before recanalization was reversibly correlated. In their report, reversibility was qualitatively evaluated based on the final extent of infarction on cerebral computed tomography (CT) or MRI one month after onset. In contrast, we quantitatively evaluated based on

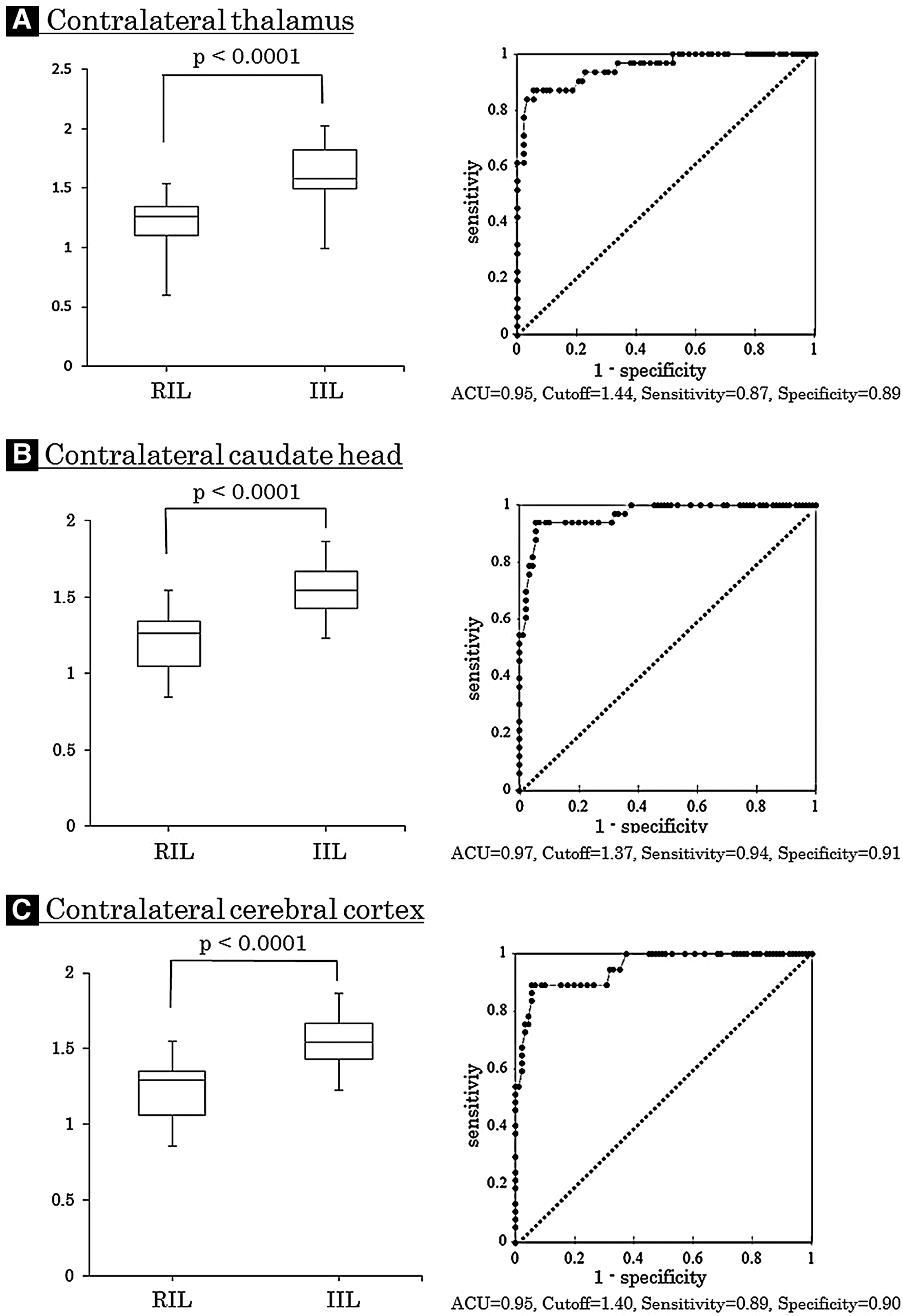


Fig. 4 Comparison of the HSI ratios of the ischemic lesions to each control site on preoperative DWI; (**A**) contralateral thalamus, (**B**) contralateral caudate head, and (**C**) contralateral normal cerebral cortex. Left: Box-plot showing the HSI ratio of RIL and IIL. Right: ROC curve analysis of the reversibility by each HSI ratio yielding the area under the curve, cutoff value, sensitivity, and specificity. DWI: diffusion-weighted imaging; IIL: irreversible ischemic lesion; RIL: reversible ischemic lesions; ROC: receiver operating characteristic

Table 3 Comparison of background and treatment effect between modified goup and unchanged group

	Modified group (n = 20)	Unchanged group (n = 15)	p-value
Backgound			
Age (years), mean (±standard deviation)	72.1 ± 12.3	68.9 ± 12.8	0.526
Baseline NIHSS, median (IQR)	17.5 (10–22.3)	22 (16–23.5)	0.243
ASPECTS+W, median (IQR)	7.5 (7–8.3)	7 (6-9)	0.463
Picture(DWI) to recanalization time (minutes), median (IQR)	116.5 (97–141)	95 (82–121)	0.325
Ischemic and hemorrhagic complications (PH type 2)	1 (5)	1 (7)	0.843
Modified DWI-ASPECTS, median (IQR)	9 (8–10)	–	–
Treatment effect			
24-hour postoperative NHISS, median (IQR)	3 (2–8)	12 (5–19)	0.007*
ΔNIHSS, median (IQR)	10.5 (7–14.8)	5 (3.5–11)	0.018*
Modified Rankin Scale≦2 at discharge	13 (65)	9 (60)	0.762

*Significant. Values are the number (%) except where indicated otherwise. ΔNIHSS: change between initial and postoperative NIHSS score at 24 hours, PH type 2: parenchymal hematoma occupying 30% or more of the infarcted tissue with obvious mass effect. ASPECST+W: Alberta Stroke Program Early Computed Tomography Score including the deep white matter; DWI: diffusion-weighted imaging; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale

the preoperative and postoperative HSI ratios on DWI b-1000 in patients with acute ischemic stroke in whom complete recanalization was achieved. No study has examined the association between DWI reversibility and clinical symptoms in patients with acute ischemic stroke through quantitative assessment.

Previous studies reported that areas contralateral to a lesion were the most markedly correlated.[7,8] In this study, the contralateral thalamus, contralateral caudate nucleus, and contralateral cerebral cortex were established as control sites, and there were no significant differences in reversibility among these control sites. Therefore, even if any area of the gray matter or basal ganglia is established as a control site, there may be no distinction. However, in some patients, the thalamus or caudate nucleus may also be influenced by old ischemic lesions or degenerative diseases; therefore, contralateral cerebral cortex, where widely plotting is possible was suitable for the control sites.

In some reports, HSI values were analyzed by outlining the regions of interest with a round or manually enclosed frame, and the mean SHI values in the frame is calculated.[7,9,10] However, in the case of a complexly shaped HSI lesions, it is sometimes difficult to accurately extract only the ischemic lesions; this may lead to a measurement error. For this reason, plotting with points may facilitate the simple and accurate assessment of lesions. In this method, the accuracy of evaluation increases with the number of plots. On the other hand, we adopted a three-plotting assessment method to promptly evaluate lesions in the limited time of the acute ischemic stroke. As a result, there was an association between RILs and improvements of the NIHSS score; therefore, this method may be acceptable for assessment of the acute ischemic lesions.

Previously, mechanical thrombectomy was performed according to time-based indication criteria for many acute ischemic stroke with major artery occlusion.[11–14] On the other hand, recent studies reported that the results of thrombectomy for patients with a small ischemic core were favorable even in those in whom the time of onset was unclear. In these studies, the indication of treatment was determined through tissue viability base assessment in consideration of the penumbra region based on DWI-perfusion or clinical-DWI mismatch (CDM).[15–18] However, automated brain-imaging software, such as a RAPID (iSchema View Inc., Menlo Park, CA, USA), is required to evaluate these mismatches or measure the ischemic core volume, which is not always possible at all institutions. At our institution, such analytical software has not been introduced, and the indication of treatment is determined based on CDM using ASPECTS+W in patients with unknown time of onset. In this study, acute ischemic stroke patients with unknown time of onset also included, and the indication of thrombectomy for these patients was determined at the CDM; therefore, the initial to DWI time was not analyzed.

Dávalos et al. adopted an NIHSS score of ≥8 as an index of the severity of clinical symptoms and defined an ischemic core volume of <25 mL on DWI in the presence of this score as CDM.[19] Furthermore, Terasawa et al. reported an assessment of the CDM to substitute the ischemic core volume for the DWI-ASPECTS in cases with insufficient measurement of the ischemic core volume. They defined CDM as NIHSS scores ≥8 and DWI ASPECTS ≥7.[20] At our institution, patients with an ASPECTS+W of ≥7 and NIHSS score of ≥8 were also regarded as exhibiting CDMs in accordance with their method. However, it was controversial whether a lower HSI area should be regarded as an ischemic focus among the evaluators. The modified DWI-ASPECTS that we proposed involves quantitative evaluation based on the HSI ratio on DWI at b-1000; therefore, it may reduce ASPECTS+W-related variations among evaluators, and facilitating the indication of different treatments for lesions with an ASPECTS+W of ≤6. Thus, ischemic core assessment using the modified DWI-ASPECTS may improve the accuracy of CDM at institutions without analytical software.

There are some limitations in this retrospective single-center study. Initially, apparent diffusion coefficient (ADC) images should also be evaluated for ischemic core assessment. However, among the DWI obtained in this study, it was difficult to match HSI sites on DWI at b-1000 to those on ADC images due to artifacts in some patients; ischemia assessment with ADC images was not conducted. Furthermore, DTR may be associated with reversibility. Therefore, the cutoff value of the HSI ratio might be <1.4, if the DTR is shorter than that obtained in this study. In addition, it remains to be clarified whether similar results are obtained even when different DWI conditions or signal intensity-measuring software are used. Therefore, the clinical data or cutoff value of the HSI ratio at each institution should be confirmed prior to assessment using the modified DWI-ASPECTS.

Conclusion

HSI ratio of <1.4 on preoperative DWI may reflect ischemic reversibility. The modified DWI-ASPECTS using the HSI ratio could be a new evaluation method of the ASPECTS+W correlated with clinical symptoms after recanalization, and may be useful for evaluating the indication of mechanical thrombectomy.

Disclosure Statement

The authors declare no conflicts of interest.

References

1) Kawano H, Hirano T, Nakajima M, et al: Modified ASPECTS for DWI including deep white matter lesions predicts subsequent intracranial hemorrhage. *J Neurol* 2012; 259: 2045–2052.
2) Labeyrie MA, Turc G, Hess A, et al: Diffusion lesion reversal after thrombolysis: a MR correlate of early neurological improvement. *Stroke* 2012; 43: 2986–2991.
3) Sakamoto Y, Kimura K, Shibazaki K, et al: Early ischaemic diffusion lesion reduction in patients treated with intravenous tissue plasminogen activator: infrequent, but significantly associated with recanalization. *Int J Stroke* 2013; 8: 321–326.
4) Soize S, Tisserand M, Charron S, et al: How sustained is 24-hour diffusion-weighted imaging lesion reversal? Serial magnetic resonance imaging in a patient cohort thrombolyzed within 4.5 hours of stroke onset. *Stroke* 2015; 46: 704–710.
5) Hirai T, Sasaki M, Maeda M, et al: Diffusion-weighted imaging in ischemic stroke: effect of display method on observers' diagnostic performance. *Acad Radiol* 2009; 16: 305–312.
6) Kidwell CS, Saver JL, Mattiello J, et al: Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol* 2000; 47: 462–469.
7) Sato A, Shimizu Y, Koyama J, et al. A study for reversible signal intensity in diffusion weighted image at acute stage of cerebral infarction. *Surg Cerebr Stroke* 2011; 39: 426–431.
8) Heiss WD, Sobesky J, Smekal Uv, et al: Probability of cortical infarction predicted by flumazenil binding and diffusion-weighted imaging signal intensity: a comparative positron emission tomography/magnetic resonance imaging study in early ischemic stroke. *Stroke* 2004; 35: 1892–1898.
9) Cheng Q, Xu X, Zu Q, et al: High b value DWI in evaluation of the hyperacute cerebral ischemia at 3T: a comparative study in an embolic canine stroke model. *Exp Ther Med* 2016; 12: 951–956.
10) Madai VI, Galinovic I, Grittner U, et al: DWI intensity values predict FLAIR lesions in acute ischemic stroke. *PLoS One* 2014; 9: e92295.
11) Hacke W, Donnan G, Fieschi C, et al: Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; 363: 768–774.
12) Hacke W, Kaste M, Bluhmki E, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317–1329.
13) Berkhemer OA, Fransen PS, Beumer D, et al: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372: 11–20.

14) Jovin TG, Chamorro A, Cobo E, et al: Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372: 2296–2306.
15) Campbell BC, Mitchell PJ, Kleinig TJ, et al: Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; 372: 1009–1018.
16) Goyal M, Demchuk AM, Menon BK, et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372: 1019–1030.
17) Albers GW, Marks MP, Kemp S, et al: Thrombectomy for stroke at 6 to 16 Hours with selection by perfusion imaging. *N Engl J Med* 2018; 378: 708–718.
18) Nogueira RG, Jadhav AP, Haussen DC, et al: Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; 378: 11–21.
19) Dávalos A, Blanco M, Pedraza S, et al: The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction. *Neurology* 2004; 62: 2187–2192.
20) Terasawa Y, Kimura K, Iguchi Y, et al: Could clinical diffusion-mismatch determined using DWI ASPECTS predict neurological improvement after thrombolysis before 3 h after acute stroke? *J Neurol Neurosurg Psychiatry* 2010; 81: 864–868.