


# Predictive value of Alberta stroke program early CT score for perfusion weighted imaging - diffusion weighted imaging mismatch in stroke with middle cerebral artery occlusion

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## Abstract

This study aimed to quantitatively assess the consistency and correlation between perfusion weighted imaging (PWI)/ diffusion weighted imaging (DWI) Alberta Stroke Program Early CT Score (ASPECTS) mismatch and PWI/DWI mismatch.

Sixty-eight acute ischemic stroke with middle cerebral artery occlusion who underwent magnetic resonance imaging before thrombectomy were eligible. DWI volume, PWI volume and PWI-DWI mismatch were measured. DWI-, PWI-, PWI-DWI ASPECTS were evaluated. Statistical analysis was performed to compare the correlation between volume and ASPECTS of DWI-, PWI- and PWI-DWI mismatch. Receiver operating characteristic curve analysis was used to assess the predictive value of the PWI-DWI ASPECTS mismatch for the occurrence of PWI-DWI mismatch in acute ischemic stroke patients with middle cerebral artery occlusion.

Of 68 patients, the DWI volume, PWI volume and PWI-DWI mismatch volume were  $(27.76 \pm 17.53)$  mL,  $(167.09 \pm 59.64)$  mL and  $(139.33 \pm 58.18)$  mL respectively. DWI-ASPECTS was  $6.75 \pm 1.90$  with the interobserver agreement was  $\kappa=0.98$  (95% CI, 0.95–0.99); PWI-ASPECTS was  $3.09 \pm 2.11$  with the interobserver agreement was  $\kappa=0.95$  (95% CI, 0.91–0.99); PWI-DWI ASPECTS mismatch was  $6.75 \pm 1.90$ . Spearman's rank correlation analysis revealed that PWI-DWI mismatch volume was negatively correlated with PWI-DWI ASPECTS mismatch ( $r = -0.802$ ;  $P = .000$ ). Receiver operating characteristic analysis showed that when the PWI-DWI ASPECTS mismatch cut point was  $\geq 2$ , the under curve of PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch was 0.954 (95%CI, 0.911–0.998), with the sensitivity and specificity were 84.00% and 100% respectively.

PWI-DWI ASPECTS mismatch may represent a convenient surrogate for penumbra in clinical trials.

**Abbreviations:** AIS = acute ischemic stroke, ASPECTS = Alberta stroke program early CT score, CBV = cerebral blood volume, DWI = diffusion weighted imaging, EVT = endovascular thrombectomy, MCA = middle cerebral artery, MRI = magnetic resonance imaging, PWI = perfusion weighted imaging, ROC = receiver operating characteristic.

**Keywords:** Alberta Stroke Program Early CT Score, diffusion-weighted imaging, perfusion-weighted imaging, stroke

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## 1. Introduction

Acute ischemic stroke (AIS) is mainly caused by embolic or thromboembolic occlusion of artery that supplies the brain.<sup>[1,2]</sup> It has a high disability and mortality, which is affected by many risk factors.<sup>[3–5]</sup> In the first few hours after AIS, the severity and irreversibility of brain injury increase as time passes. There is often a larger component of brain tissue that is hypoperfused but viable surrounding the irreversible infarction of brain tissue (core infarction), that is penumbra.<sup>[6,7]</sup> The current available AIS treatments are administration of intravenous tissue plasminogen activator during the first 4.5 hour after clinical onset and endovascular thrombectomy (EVT) during the first 6–8 hour after symptom onset.<sup>[8]</sup> The primary goal of these treatments is to promote the rapid revascularization of the brain tissue, impeding the evolution of the reversible ischemic brain tissue (penumbra) into irreversible brain tissue (core infarction).<sup>[9,10]</sup>

Neuroimaging is critical in the diagnosis, triage, and treatment of AIS patients.<sup>[11]</sup> Ischemic penumbra is defined using magnetic resonance imaging (MRI) as the mismatch between the hypoperfused area on perfusion-weighted imaging (PWI) and the abnormal area on diffusion-weighted imaging (DWI).<sup>[12]</sup> The presence of PWI/DWI mismatch has been used as inclusion criteria in clinical trials.<sup>[13]</sup> However, it is difficult to accurate assessment of PWI/DWI mismatch in clinical work. For example, volumetric measurements are time consuming, which may delay

acute stroke therapy; alternative surrogates in case of software for ultrafast automated assessment of PWI/DWI mismatch failure; some hospitals not equipped with ultrafast automated software. The Alberta Stroke Program Early CT score (ASPECTS) is a validated semiquantitative scale useful for assessing the extent of ischemic changes within the middle cerebral artery (MCA) territory.<sup>[14]</sup> The DWI-ASPECTS is widely used due to its straightforwardness and reproducibility.<sup>[15]</sup> ASPECTS scoring was also applied to PWI to rapidly estimate the extent of hypoperfusion and PWI/DWI mismatch, which showed that MR mismatch score was excellent in the between-rater agreement with PWI/DWI mismatch.<sup>[16]</sup>

Therefore, in this study, we hypothesized that PWI-ASPECTS/DWI-ASPECTS mismatch (PWI-DWI ASPECTS mismatch) is associated with PWI/DWI mismatch. We sought to quantitatively assess the consistency and correlation between PWI/DWI ASPECTS mismatch and PWI/DWI mismatch.

## 2. Materials and methods

### 2.1. Subjects and clinical data

Data for this retrospective analysis were extracted from a monocentric register of AIS patients treated by EVT from January 2017 to June 2019. The patients included in the present study met the following criteria:

- (1) first-ever acute stroke with MCA occlusion or acute stroke with MCA occlusion with a history of previous stroke with hemiplegia sequelae that did not affect the neurological score;
- (2) AIS patients  $\leq$  8 hours of symptom onset;
- (3) pretreatment MRI with PWI, DWI;
- (4) AIS patients with MCA occlusion and
- (5) thrombectomy treatment.

The exclusion criteria were as follows:

- (1) cerebral hemorrhage, tumor or trauma detected by the CT scanner;
- (2) any contraindication for MRI;
- (3) refusal to undergo thrombectomy;
- (4) AIS patients with internal carotid artery or anterior cerebral artery occlusion; and
- (5) any MRI or digital subtraction angiography that could not be evaluated due to a motion artifact.

The hospital review board of Nanjing Medical University approved the study protocol.

Age, gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, homocysteine, and the National Institutes of Health Stroke Scale score at the admission hospital were collected. All patients had written informed consent by themselves or their family members prior to their participation in this study.

### 2.2. MRI Protocol

MRI scans were performed using a 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems) with an 8-channel receiver array head coil. The MRI protocol included fluid-attenuated inversion recovery axis sequencing, DWI axial scanning, magnetic resonance angiography and PWI. Some of the scanning parameters were as follows: DWI (spin echo (SE) sequence, TR, 2501 ms; TE, 98 ms; acquisition matrix, 152\*122; 3 directions; FOV, 230 mm\*230 mm; FA, 90°; slices, 18; section thickness, 6 mm; and intersection gap, 1.3 mm. DWI was obtained with b

values of 0 and 1000 s/mm<sup>2</sup>). DSC-PWI (repetition time msec/echo time msec, 2000/30; acquisition matrix, 96\*93; 2 field of view; FOV, 224 mm\*224 mm; FA, 90°; section thickness, 4 mm; and duration=88 s).

### 2.3. Image analysis

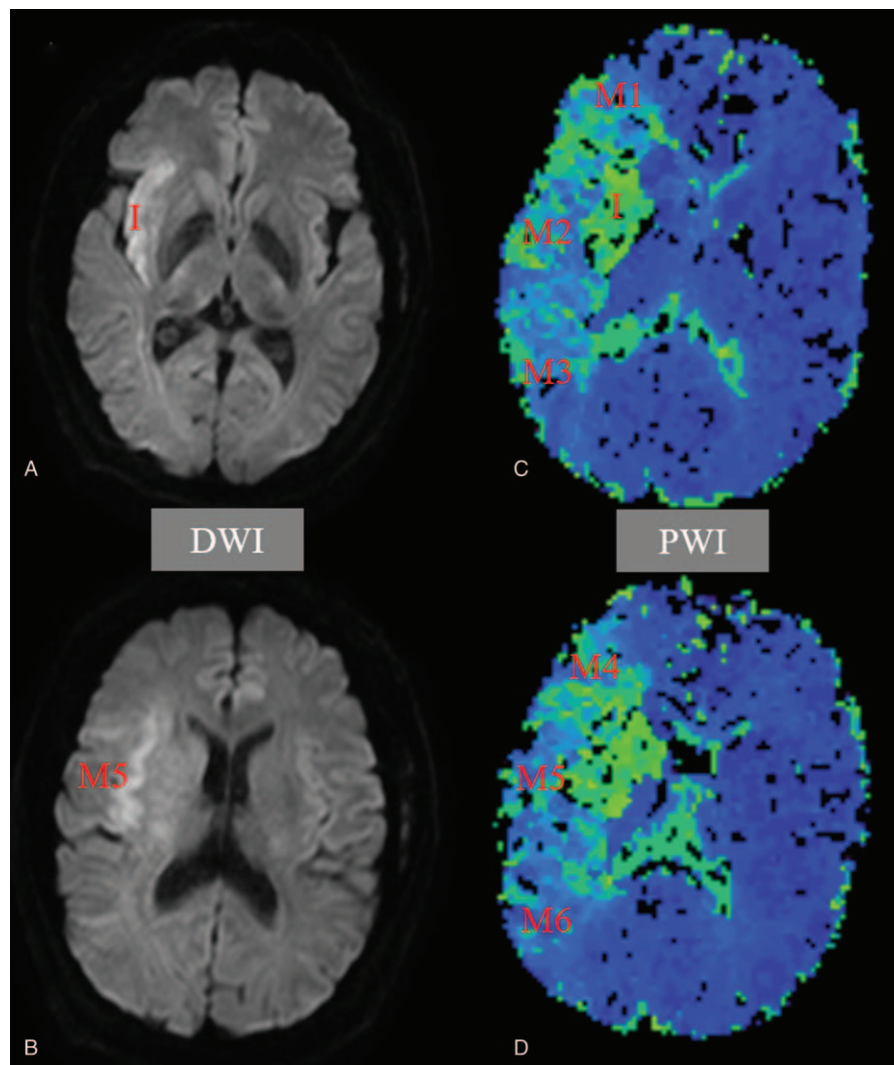
The PWI data were analyzed using a Philips advanced workstation. The arterial input function was selected by manually identifying the M2 segment of the middle cerebral artery ipsilateral to the acute infarction. The cerebral blood flow, cerebral blood volume (CBV), time to peak, and mean transit time maps were generated after circular singular value decomposition of the concentration-time curve. DWI volume and PWI volume were measured by using ITK-SNAP software (<http://www.itksnap.org/pmwiki/pmwiki.php>). As follows: all DWI and CBV images of AIS patients were derived in "DICOM" format, and then converted all DICOM format into "NII" format by using mricron software (<https://www.nitrc.org/projects/mricron>). The high intensity signal area on DWI and abnormal perfusion area on CBV were drawn using ITK-SNAP software, then DWI volume and CBV volume were automatic calculated separately. CBV volume represented PWI volume in this study.<sup>[17]</sup> PWI/DWI mismatch was defined as  $\text{Volume}_{\text{PWI}} / \text{Volume}_{\text{DWI}} \geq 1.8$ , a volume difference  $\geq 15$  mL, and a volume  $\text{DWI} < 70$  mL.<sup>[18]</sup> ASPECTS scores of DWI (DWI-ASPECTS) and CBV (PWI-ASPECTS) images were independently evaluated by 2 experienced neuroradiologists (KX and TZ) blinded to the clinical data, in case of a discrepant assessment results between the 2 readers, images were reviewed, and a consensus was established. The 2 ASPECTS slices at and immediately superior to the basal ganglia were first identified on the structural fluid-attenuated inversion recovery images on which DWI and PWI sequences are based. The territory of the MCA is allotted 10 points (caudate, lentiform, internal capsule, insular ribbon, M1-M6).<sup>[19]</sup> Hyperintensity on DWI or abnormal perfusion on CBV within an ASPECTS region is 1 point. 1 point is subtracted for an area of hyperintensity on DWI or abnormal perfusion on CBV. PWI-DWI ASPECTS mismatch were then calculated by subtracting PWI-ASPECTS score from DWI-ASPECTS score (Fig. 1).

### 2.4. Statistical analysis

All statistical analyses were conducted using commercially available software (SPSS for Windows, version 19.0; SPSS). Continuous data were shown as the mean  $\pm$  SD and categorical variables are presented as absolute and relative frequencies. Interobserver agreement on PWI-ASPECTS, DWI-ASPECTS and PWI-DWI ASPECTS mismatch scores was evaluated using Cohen kappa statistic. Spearman rank correlation analysis was used to evaluate the correlations between PWI-ASPECTS, DWI-ASPECTS, PWI-DWI ASPECTS mismatch scores and volumetric measurements. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of PWI-DWI ASPECTS mismatch for the presence of PWI-DWI mismatch in patients with acute stroke after thrombectomy.

## 3. Results

Among 175 AIS patients in the study, 68 (41 males and 27 females; mean age [years old  $\pm$  SD] 68.83  $\pm$  12.47; range, 56–80 years old) fulfilled the inclusion criteria. 107 patients were



**Figure 1.** Case of PWI-DWI ASPECTS mismatch. The DWI-ASPECTS score was 8, due to DWI hyperintense I and M5 (A, B). The PWI-ASPECTS score was 3, due to hypoperfused I, M1, M2, M3, M4, M5, M6. The PWI-DWI ASPECTS mismatch was 5 score (C, D). I: insular ribbon, M1: anterior middle cerebral artery (MCA) cortex, M2: MCA cortex lateral to the insular ribbon, M3: posterior MCA cortex, M4, M5, M6: anterior, lateral, and posterior MCA territory immediately superior to M1, M2 and M3.

excluded (9 patients, without pretreatment MRI; 13 patients, severely artifacts on DWI or PWI sequences; 10 patients, refusal to undergo thrombectomy; 33 patients, with internal carotid artery or anterior cerebral artery occlusion; 25 patients, a volume difference  $< 15$  mL; 17 patients, a volume  $_{\text{DWI}} \geq 70$  mL). Of 68 patients, 29 (42.65%) received EVT therapy, and 39 (57.35%) received both IVT and EVT therapy. The DWI volume, PWI volume and PWI-DWI mismatch volume were  $(27.76 \pm 17.53)$  mL,  $(167.09 \pm 59.64)$  mL and  $(139.33 \pm 58.18)$  mL respectively. DWI-ASPECTS was  $6.75 \pm 1.90$  with the interobserver agreement was  $\kappa=0.98$  (95% CI, 0.95–0.99); PWI-ASPECTS was  $3.09 \pm 2.11$  with the interobserver agreement was  $\kappa=0.95$  (95% CI, 0.91–0.99); PWI-DWI ASPECTS mismatch was  $6.75 \pm 1.90$  (Table 1).

Spearman rank correlation analysis revealed that DWI volume was negatively correlated with DWI-ASPECTS ( $r=-0.978$ ;  $P=.000$ ), PWI volume was negatively correlated with PWI-ASPECTS ( $r=-0.842$ ;  $P=.000$ ), and PWI-DWI mismatch volume was negatively correlated with PWI-DWI ASPECTS mismatch ( $r=-0.802$ ;  $P=.000$ ) (Table 2, Fig. 2).

ROC analysis showed that when the PWI-DWI ASPECTS mismatch cut point was  $\geq 2$ , the under curve of PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch was 0.954 (95% CI, 0.911–0.998), with the sensitivity and specificity were 84.00% and 100% respectively. When the PWI-DWI ASPECTS mismatch cut point was  $\geq 3$ , the under curve of PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch was 0.856 (95% CI, 0.770–0.942), with the sensitivity and specificity were 88.60% and 69.70% respectively (Fig. 3).

#### 4. Discussion

The results of the present study suggested that PWI-ASPECTS could be used as a method to evaluate hypoperfusion volume. The interobserver agreement of ASPECTS-based assessment was high. When the PWI-DWI ASPECTS mismatch  $\geq 2$ , the PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch had a high sensitivity and specificity.

**Table 1**  
**Clinical and imaging characteristics of the study population.**

Variable	Mean ± SD or Number (%) (n=68)
Sex, male	41 (60.29%)
Age, yr	68.83 ± 12.47
Median time to onset, h	3.38 ± 0.98
Median time to MRI scan, h	3.70 ± 1.88
Median time to thrombectomy, h	4.83 ± 1.97
NIHSS at admission	12.37 ± 4.84
Smoking, n	6 (8.82%)
Alcohol drinking, n	6 (8.82%)
Diabetes mellitus, n	20 (29.41%)
Hypertension, n	62 (91.18%)
Atrial fibrillation, n	38 (55.88%)
Hyperlipidemia, n	6 (8.82%)
Homocysteine, n	4 (5.88%)
Site of artery occlusion	
Proximal M1	45 (66.18%)
Distal M1	14 (20.59%)
M2	9 (13.24%)
Reperfusion treatment	
EVT	29 (42.65%)
IVT+EVT	39 (57.35%)
DWI volume, mL	27.76 ± 17.53
PWI volume, mL	167.09 ± 59.64
PWI-DWI mismatch volume, mL	139.33 ± 58.18
DWI-ASPECTS scores	6.75 ± 1.90
PWI-ASPECTS scores	3.09 ± 2.11
PWI-DWI ASPECTS mismatch scores	3.66 ± 1.65

Categorical variables are expressed as numbers (%) and continuous variables as mean ± SD. ASPECTS=Alberta Stroke Program Early CT score, DWI=diffusion-weighted imaging, EVT=endovascular thrombectomy, IVT=intravenous thrombolysis, M1=first segment of the middle cerebral artery, M2=second segment of the middle cerebral artery, NIHSS=National Institutes of Health Stroke Scale, PWI=perfusion-weighted imaging.

DWI is more sensitive than CT for early detection of ischemic signs and can be scored using DWI-ASPECTS.<sup>[20]</sup> DWI-ASPECTS, a semiquantitative estimation method, has been used to substitute for volume in most of the recent EVT trials.<sup>[21-23]</sup> DWI-ASPECTS is a good and reliable clinical tool for descriptive purpose or as a selection tool for the inclusion or exclusion of patients in clinical trials.<sup>[20]</sup> In our study, the κ statistic analysis showed high interobserver agreement between DWI volume and DWI-ASPECTS. Other agreement statistics analyzing the DWI-ASPECTS as a continuous variable could have probably shown a

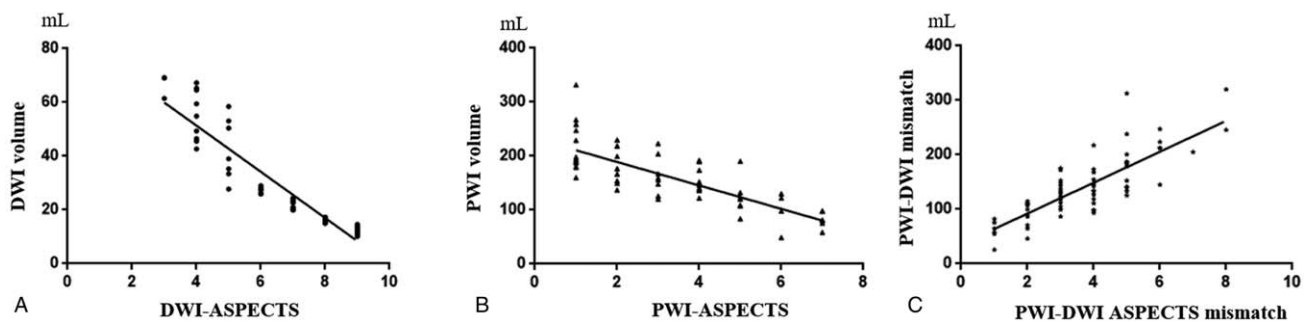
**Table 2**  
**The correlation coefficient between volume and ASPECTS in patients within middle cerebral artery.**

		r	p
DWI volume	DWI-ASPECTS	-0.978	.000
PWI volume	PWI-ASPECTS	-0.842	.000
PWI-DWI mismatch	PWI-DWI ASPECTS mismatch	-0.802	.000

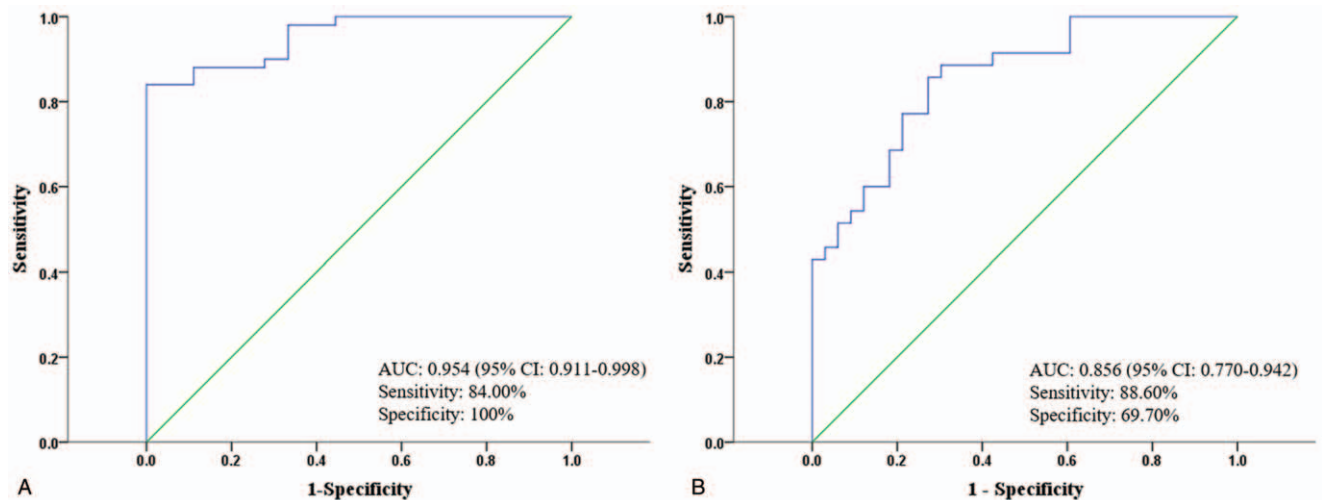
ASPECTS=Alberta Stroke Program Early CT score, DWI=diffusion-weighted imaging, PWI=perfusion-weighted imaging.

high agreement.<sup>[24]</sup> The ASPECTS score method is based on ten territories, and 1 point is subtracted for an area of abnormal lesion, which is simple, convenient, and has high accuracy. Therefore, it is feasible and consistent for different doctors to evaluate the ASPECTS score. Many previous studies showed that there was excellent correlation between this semiquantitative and DWI volume.<sup>[23,25]</sup> Consistent with previous studies, we also found that DWI volume was negatively correlated with DWI-ASPECTS. While the correlation between PWI volume and PWI-ASPECTS, PWI-DWI mismatch volume and PWI-DWI ASPECTS mismatch have received little attention so far.

Spearman's rank correlation analysis revealed that PWI volume was negatively correlated with PWI-ASPECTS, and PWI-DWI mismatch volume was negatively correlated with PWI-DWI ASPECTS mismatch. All AIS patients in our study had MCA occlusion, the core infarction in AIS patients with MCA occlusion was mainly involved the deep territory early and the penumbra was the more superficial.<sup>[26]</sup> Therefore the hypoperfusion area most often involved superficial cortical ASPECTS regions. This may be the reason for the correlation between PWI-DWI ASPECTS mismatch and PWI-DWI mismatch. PWI-DWI mismatch is the most widely used clinical method for estimating the volume of viable penumbra tissue.<sup>[27,28]</sup> Non-invasive quantification of AIS and differentiation of core infarction and penumbra tissue is critical to treatment planning.<sup>[29-32]</sup> However current MRI techniques requires dedicated software and are time consuming.<sup>[33,34]</sup> Evaluation of hypoperfusion volume and PWI-DWI mismatch by using ASPECTS had more advantages. An estimate of mismatch tissue could be obtained with no additional time by simply scoring ASPECTS. In our study, ROC analysis showed that when the PWI-DWI ASPECTS mismatch cut point was ≥ 2, PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch had a higher sensitivity and specificity. While when the PWI-DWI



**Figure 2.** Scatterplot representing correlations between DWI volume and DWI-ASPECTS (A), PWI volume and PWI-ASPECTS (B), PWI-DWI mismatch and PWI-DWI ASPECTS mismatch (C). DWI volume, PWI volume and PWI-DWI ASPECTS mismatch were all negatively correlated with DWI-, PWI-, PWI-DWI ASPECTS mismatch.



**Figure 3.** Receiver operating characteristic curve for PWI-DWI ASPECTS mismatch for predicting the PWI-DWI mismatch. When the optimal cut point was  $\geq 2$ , the sensitivity and specificity were 84.00% and 100% (A); when the optimal cut point was  $\geq 3$ , the sensitivity and specificity were 88.60% and 69.70% (B).

ASPECTS mismatch cut point was  $\geq 3$ , would also has higher sensitivity but lower specificity. From our study, PWI-DWI ASPECTS mismatch cut point  $\geq 2$  was more accurately in predicting the PWI-DWI mismatch. Although a score of 2 seems a relatively small number of affected ASPECTS regions, they often located in cortical areas in our data set, which corresponded to sizeable volumes of mismatch. Moreover, although PWI-DWI ASPECTS mismatch is a semiquantitative evaluation method, it could provide geographic information that are not available with simple volumetric assessment. A mismatch in 2 contiguous cortical ASPECTS regions could be due to a dominant M2 branch occlusion, which may be treatable by thrombectomy. In addition, the ROC analysis of the other cut points was also evaluated. However, the AUC, sensitivity and specificity of the other cut points in predicting the PWI-DWI mismatch were not statistically significant.

This study has some limitations. First, All AIS patients in our study had MCA occlusion, whereas ICA occlusion was excluded. The ASPECTS is mainly useful for assessing the extent of ischemic changes within the MCA territory. Further study is still needed to prove the value of PWI-DWI ASPECTS mismatch in predicting the PWI-DWI mismatch of patients with ICA occlusion. Second, due to lack of post-processing software for Tmax maps, PWI volume and PWI-ASPECTS were evaluated on the CBV maps instead of the Tmax  $> 6$  sec maps with higher accuracy in our study. Third, we focused on the diagnostic value of PWI-DWI ASPECTS to identify the PWI-DWI mismatch, but not assess its prognostic value in terms of infarct growth or clinical outcome. Finally, this was a single-center trial. Thus, the results of this study cannot be generalized to whole population of stroke patients. Multicenter trials with larger cohorts and different study populations are warranted.

## 5. Conclusion

PWI-ASPECTS could be used as a method to evaluate hypoperfusion volume. When the PWI-DWI ASPECTS mismatch  $\geq 2$ , the PWI-DWI ASPECTS mismatch for predicting PWI-DWI mismatch had a high sensitivity and specificity.

## Author contributions

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