Original Article

Predictive accuracy of an ADC map for hemorrhagic transformation in acute ischemic stroke patients after successful recanalization with endovascular therapy

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Background: Hemorrhagic transformation (HT) of acute ischemic stroke (AIS) is associated with poor outcome. Previous studies only reported the association of mean ischemic severity or total infarct volume with HT after endovascular therapy (EVT). We aimed to investigate the predictive value of preoperative apparent diffusion coefficient (ADC) map for HT by combinated ischemic severity and corresponding volume in AIS after successful recanalization with EVT.

Methods: We retrospectively analyzed 119 consecutive cases of AIS with large vessel occlusion of anterior circulation within 24 hours after symptom onset and successful recanalization after EVT. All cases had baseline magnetic resonance imaging (MRI), follow-up computed tomography (CT), and magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Volumes of ADC $<0.6\times10^{-3}$, 0.5×10^{-3}, 0.4×10^{-3}, and 0.3×10^{-3} mm^2/s, baseline characteristics and outcomes of patients with and without HT identified by European Collaborative Acute Stroke Study (ECASS) were compared. The optimal ADC and volume threshold for predicting HT were analyzed using receiver operating characteristic (ROC) curve, and multivariate logistic regression analysis were performed with clinical characteristics and volumes of optimal ADC threshold to determine risk factors for HT.

Results: Among 119 patients, 42 patients had HT on follow-up CT, including 24 hemorrhagic infarct (HI) cases and 18 parenchymal hematoma (PH) cases. The optimal volumes were 6.46 mL with ADC $<0.4\times10^{-3}$ mm^2/s for predicting both HT and PH, with a larger area under curve (AUC) of 83.3% for HT than that for PH of 80%. In logistic regression analysis, intravenous tissue plasminogen activator (IV tPA) treatment, atrial fibrillation, and volume of ADC $<0.4\times10^{-3}$ mm^2/s were identified as independent predictors for HT and volume of ADC $<0.4\times10^{-3}$ mm^2/s had the highest odds ratio (OR) value.

Conclusions: The combination of ischemic severity and corresponding volume in ADC map may predict HT after thrombectomy. In addition to the total infarct volume, volume with severe ischemia should be taken into consideration in preoperative patient selection.

Keywords: Acute ischemic stroke (AIS); endovascular therapy (EVT); apparent diffusion coefficient (ADC); hemorrhagic transformation (HT)

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Introduction

Endovascular therapy (EVT) has become the standard treatment for acute ischemic stroke (AIS) caused by large vessel occlusion in the anterior circulation (1-3). However, despite highly successful recanalization rates, more than half of patients do not achieve a favorable outcome [modified Rankin Scale (mRS) score ≤2] at 3 months after thrombectomy (1-4). Early neurological deterioration and unfavorable outcomes are reportedly associated with hemorrhagic transformation (HT), which can be caused by the disruption of the blood-brain barrier due to reperfusion of ischemic brain tissue (5,6). Preoperative evaluation of the risk of HT may guide therapeutic strategies and improve the safety of EVT.

The severity of hypoperfusion and the volume of infarction core are important predictors of HT (6-8). To predict HT, perfusion parameters have previously been used to assess the degree of ischemia (8,9), but the vascular recanalization situation of most analyzed patients was unclear, and only a few studies combined ischemic severity and the corresponding volume for the prediction. The apparent diffusion coefficient (ADC) value is associated with the severity of the perfusion deficit (10) and has been used to quantify ischemia severity in the prediction of HT after recanalization with EVT (9). Given the onion-like distribution of successively decreasing ADC values from the periphery toward the center of the infarct core (10), we hypothesized that a combination of ADC thresholds and corresponding volumes may predict the occurrence of HT. In this study, we aimed to evaluate the predictive role of the volume below each ADC threshold value for HT following EVT. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2255/rc).

Methods

Data selection

We retrospectively analyzed the consecutive patient data from January 2018 to June 2020 collected prospectively from stroke database of Henan Provincial People's Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by ethics committee of Henan Provincial People's Hospital (No. 2017-034-01). Individual consent for this retrospective analysis was waived. Patients were selected according to the following criteria: (I) those diagnosed with AIS with internal carotid artery (ICA), M1, or M2 middle cerebral artery (MCA) segment occlusion; (II) the time from symptom onset to groin puncture was less than 24 hours; (III) National Institutes of Health Stroke Scale (NIHSS) score ≥6; (IV) completion of an acute ischemic stroke workup including diffusion weighted imaging (DWI) at admission and non-contrast computed tomography (NCCT), magnetic resonance angiography (MRA), or computed tomography angiography (CTA) follow-up within a week after EVT; (V) modified thrombolysis in cerebral infarction score (mTICI) ≥ 2b after EVT; (VI) no hemorrhagic foci was observed on the preoperative magnetic resonance imaging (MRI); and (VII) no reocclusion of target vessel was found on follow-up MRA or CTA.

Image acquisition

All patients underwent a 3.0T MRI (Skyra, Siemens, Germany) exam using the following sequences: DWI [spin echo, echo time (TE) =64 ms, repetition time (TR) =4,140 ms, field of view (FOV) =230 mm, matrix =160×160, and 6.0-mm section thickness with a 1.2-mm intersection gap], ADC (spin echo, TE =64 ms, TR =4,140 ms, FOV =230 mm, matrix =160×160, and 6.0-mm section thickness with a 1.2-mm intersection gap), fluid attenuated inversion recovery (FLAIR) (turbo spin echo, TE =81 ms, TR =7,500 ms, FOV =230 mm, matrix =320×256, time of inversion (TI) =2,300 ms, and 6.0-mm section thickness with 1.2-mm intersection gap), T2 (turbo spin echo, TE =96 ms, TR =5,000 ms, FOV =230 mm, matrix =384×384, and 6.0-mm section thickness with a 1.2-mm intersection gap), and MRA [time of flight (TOF)-MRA; fast field

echo, TE =3.45 ms, TR =21 ms, FOV =200 mm, matrix =320×288, and 0.7-mm section thickness with a −6.3-mm intersection gap]. The follow-up exam included at least NCCT and CTA (SOMATOM Definition AS, Siemens, Germany) or MRA.

Image analysis

The baseline and follow-up imaging analyses were respectively performed by two interventional neuroradiologists who were blinded to the other clinical and imaging information using Olea Sphere 23.0 (Olea medical S.A.S, La Ciotat, France) software. Inconsistent cases were determined by discussion between the two blind evaluators. The infarction core was defined as the area with a high preoperative DWI signal and ADC $<0.6\times10^{-3}$ mm^2/s. Artifacts and ischemic infarction in non-target vessel territory were eliminated manually. The preoperative volume of the ischemic lesions with ADC values below thresholds ranging from 0.3×10^{-3} to 0.6×10^{-3} mm^2/s at 0.1 intervals was measured. The mTICI grade of the occluded vessel was evaluated on digital subtraction angiography (DSA) before and after recanalization. CT was performed within a week after EVT to diagnose HT caused by blood-brain barrier damage due to severe ischemic based on the European Cooperative Acute Stroke Study (ECASS) scoring system (11). Follow-up CTA or MRA was used to identify target vessel patency after successful recanalization with EVT.

Statistical analysis

Patients were stratified into 'HT' and 'non-HT' groups. All data processing, statistical analysis, and plotting were conducted using R 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria). The intraclass correlation coefficient (ICC) or Cohen Kappa Statistic was used to analyze the inter- and intra-observer agreement for the diagnosis of HT. We used the Student's *t*-test, Mann-Whitney U test, and Chi-square test to compare the clinical variable differences between the two groups. Receiver operator characteristic (ROC) curves were generated for thresholded ADC lesion volumes, and the areas under the curve (AUCs) were determined to compare their individual test characteristics in predicting HT. To determine which factors were associated with HT, multivariate logistic regression analysis were performed with clinical variables with statistically significant differences in univariate analysis, factors significantly associated with HT in previous studies and volume of optimal ADC threshold. All P values were two-tailed, and variables were considered significant at $P<0.05$.

Results

From a total of 424 patients, 119 met the inclusion criteria and were included in this research. No adverse event associated with MRI examination occurred. The inter-observer agreement for diagnosing HT was good ($\kappa=0.862$). Forty-two (35.29%, HT group) patients had HT on follow-up CT, including 10 patients with hemorrhagic infarct (HI) 1, 14 patients with HI2, as well as nine cases with parenchymal hematoma (PH) 1 and PH2, respectively. The mean time between baseline MRI and CT diagnosis of HT was 72 h. The remaining 77 (64.71%, non-HT group) patients did not show HT on the follow-up CT scan. *Figure 1* shows the flow of participants throughout the study.

There were no differences between the HT and non-HT groups in terms of age, sex, the proportion of patients with hypertension, and the use of antiplatelet and anticoagulant drugs before EVT. Furthermore, the onset-to-recanalization times were similar between the two groups. In the HT group, more patients had diabetes mellitus, atrial fibrillation, and tandem occlusion, in addition to larger numbers of passes and intravenous tissue plasminogen activator (IV tPA) treatment. The NIHSS scores at admission were similar between patients with and without HT. However, the NIHSS score at discharge was significantly higher and the rate of patients with a mRS of 0–2 at 3 months was lower in the HT group. The details are shown in *Table 1*.

The median volume of the HT group was larger than that of the non-HT group ($P<0.001$) for ADC thresholds $<0.6\times10^{-3}$, 0.5×10^{-3}, 0.4×10^{-3}, and 0.3×10^{-3} mm^2/s. The volume of ADC $<0.4\times10^{-3}$ mm^2/s showed a better ability to differentiate the occurrence of HT (including HI and PH) from non-occurrence and the occurrence of the PH subtype from non-occurrence, but with different accuracies [AUC value of 83.3% (95% confidence interval (CI): 75.3%, 91.3%) for HT and a lower AUC value of 80% (95% CI: 68.5%, 91.5%) for PH]. Under this ADC threshold, the cutoff volumes for predicting HT and PH were both

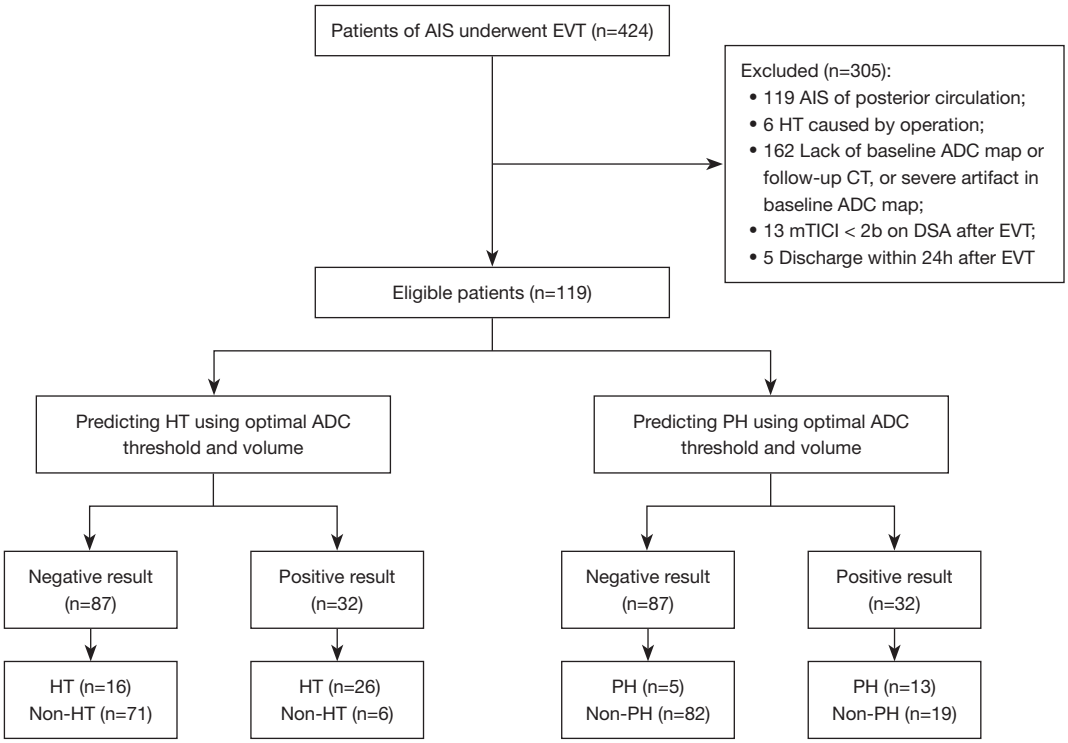

Figure 1 Flow of patients throughout the study. AIS, acute ischemic stroke; EVT, endovascular therapy; HT, hemorrhagic transformation; ADC, apparent diffusion coefficient; mTICI, modified Thrombolysis in Cerebral Infarction scale; DSA, Digital Subtraction Angiography; PH, parenchymal hematoma.

6.46 mL; the sensitivity and specificity were 61.9% (95% CI: 45.65%, 76.01%) and 92.21% (95% CI: 83.21%, 96.79%) with positive and negative predictive values of 81.25% (95% CI: 62.96%, 92.14%) and 81.61% (95% CI: 71.55%, 88.81%), respectively, for predicting HT, and 72.22% (95% CI: 46.41%, 89.29%) sensitivity and 81.19% (95% CI: 71.93%, 88.02%) specificity with positive and negative predictive values of 40.63% (95% CI: 24.22%, 59.21%) and 94.25% (95% CI: 86.50%, 97.87%) for predicting PH, respectively. However, the volumes of ADC $<0.6\times10^{-3}$ mm^2/s, ADC $<0.5\times10^{-3}$ mm^2/s, and ADC $<0.3\times10^{-3}$ mm^2/s showed comparatively inferior differentiation abilities for HT (AUC 71.5–80.1%) and PH (AUC 69.2–75.2%) prediction (*Figure 2A,2B*). *Figures 3,4* show the ADC threshold and volume distribution in the respective preoperative infarct areas of patients with HI2 and PH2 on follow-up CT after EVT. Tables S1,S2 in the supplemental material display the contingency tables on the relationship between the actual HT and predicted results of the ADC map.

The multivariate logistic regression analysis with selected clinical variables and volume below optimal ADC threshold of 0.4×10^{-3} mm^2/s shows larger volume of ADC $<0.4\times10^{-3}$mm^2/s [odds ratio (OR), 34.164; 95% CI: 6.825–171.022; P<0.001], atrial fibrillation (OR, 5.807; 95% CI: 1.234–27.339 P=0.026), intravenous thrombolysis (OR, 7.898; 95% CI: 2.032–30.697; P=0.003) were all independent predictors of HT (*Table 2*). And the OR value for the dichotomous volume according to 6.46 mL of ADC below 0.4×10^{-3} mm^2/s is higher than that of other potential risk factors.

Discussion

In the present study, we obtained a volume of ADC $<0.4\times10^{-3}$ mm^2/s reaching 6.46 mL as the optimal threshold for predicting both HT and PH but with different accuracies in AIS patients following successful recanalization with EVT. The multivariate logistic regression analysis shows volume below optimal threshold is independent predictors of HT.

Table 1 Univariate analysis between HT and non-HT group

Patient characteristics	HT group (n=42)	Non-HT group (n=77)	P values
Sex, men	26 (61.90)	55 (71.43)	0.287
Age, y	63.67 (SD, 12.199)	61.82 (SD, 13.082)	0.452
Smoking	15 (35.71)	35 (45.45)	0.304
Hypertension	24 (57.14)	44 (57.14)	1.00
Diabetes mellitus	20 (47.62)	22 (28.57)	0.038
Atrial fibrillation	20 (47.62)	17 (22.08)	0.04
Previous stroke or of TIA	10 (23.81)	22 (28.57)	0.576
Preoperative use of antiplatelets	4 (9.52)	9 (11.69)	0.718
Preoperative use of anticoagulants	3 (7.14)	1 (1.30)	0.247
Admission NIHSS score	13 (11.0–15.0)	13 (11.0–15.5)	0.924
Volume of ischemic lesion with ADC <0.6 ($\times10^{-3}$ mm^2/s)	37.9645 (15.7635–90.1765)	13.431 (5.5945–26.1915)	<0.001
Volume of ischemic lesion with ADC <0.5 ($\times10^{-3}$ mm^2/s)	20.007 (8.320–70.626)	5.673 (1.731–12.096)	<0.001
Volume of ischemic lesion with ADC <0.4 ($\times10^{-3}$ mm^2/s)	8.498 (2.288–25.236)	0.805 (0–3.096)	<0.001
Volume of ischemic lesion with ADC <0.3 ($\times10^{-3}$ mm^2/s)	0.554 (0–4.480)	0 (0–0)	<0.001
Occlusion site			<0.001
ICA	18 (42.86)	25 (32.47)	
MCA	10 (23.81)	45 (58.44)	
Tandem occlusion	14 (33.33)	7 (9.09)	
IV tPA treatment	19 (45.24)	15 (19.48)	0.003
Number of passes	2 (1.0–3.0)	1 (1.0–2.0)	<0.001
Complete reperfusion (mTICI 3)	29 (69.05)	50 (64.94)	0.650
Onset-to-baseline ADC time, min	335.5 (260.75–494.0)	332 (138.0–621.5)	0.666
Baseline ADC to final reperfusion time, min	166 (139.25–209.5)	168 (128–200.5)	0.519
Onset to final reperfusion time, min	518 (428.75–678.75)	509 (325.50–786.5)	0.619
NIHSS score at discharge	9 (6.0–18.5)	6 (2.0–9.0)	<0.001
mRS 0–2 at 3 months	14 (33.33)	51 (66.23)	0.001

HT, hemorrhagic transformation; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; ADC, apparent diffusion coefficient; ICA, internal carotid artery; MCA, middle cerebral artery; IV tPA, intravenous tissue plasminogen activator; mTICI, modified Thrombolysis in Cerebral Infarction scale; mRS, modified Rankin Scale.

Endothelial cell damage, basement membrane degradation, and vascular remodeling caused by an inflammatory response to cerebral infarction and ischemia/reperfusion injury after recanalization lead to the disruption of the blood-brain barrier coupled with other mechanisms, which is an important pathological basis for HT after EVT (12,13). We observed that the volume and ischemia severity of the preoperative infarction core were both associated with the occurrence of HT after recanalization. According to present guidelines, only infarction volume is taken into consideration to avoid HT when selecting eligible patients for mechanical thrombectomy (14). Our study added the

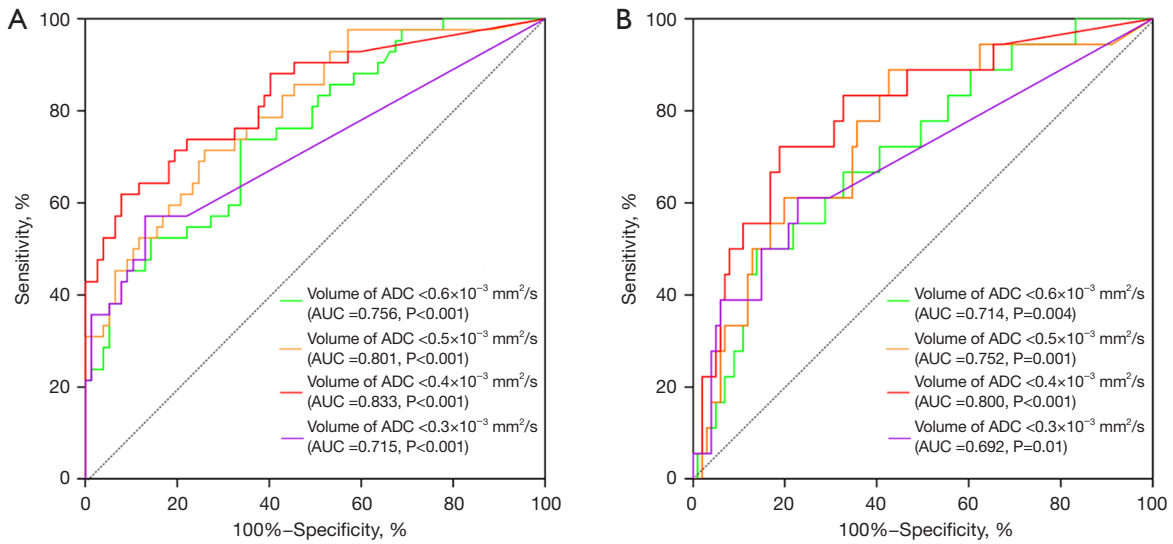

Figure 2 ROC curves of volumes below the different ADC thresholds for predicting HT (A) and the PH subtype (B). AUC, area under curve; ADC, apparent diffusion coefficient; ROC, receiver operator characteristic; HT, hemorrhagic transformation; PH, parenchymal hematoma.

ADC value to quantify the ischemia severity.

For ischemia severity, several researchers have shown that the perfusion parameters of cerebral blood volume (CBV) <0.5 mL/100 g, relative CBV (rCBV) <1.09, relative cerebral blood flow (rCBF) <4.5%, time-to-peak (TTP) >0.27 s, and ADC <300×10^{-6} mm^2/s in the infarct area and the mean relative mean transit time (rMTT) value within the area of rMTT >1.3 can be used to predict HT (8,9,15-18). Previous reports have also applied a combination of ischemia severity and the corresponding volume to predict HT, such as the volume of time-to-maximum (Tmax) >14 s or the volume of very low CBV 2.5 (<2.5th percentile threshold) area greater than 2 mL (8,9). However, most of these studies were published before the popularization of EVT, and the majority of enrolled patients were either untreated or treated with intravenous thrombolysis alone. In our research, only patients who underwent EVT and achieved successful recanalization were enrolled, which avoided infarct expending due to no reperfusion and better reflected the influence of preoperative ischemia on the blood-brain barrier and HT.

Laredo *et al.* reported that patients in the HT group after EVT had a larger region of very low CBV and more patients in this group had exceedingly low CBV regions (19). Another study showed that rADC <0.65 in the infarct core is the optimal point to predict HT after EVT (20). There are currently no reports on the predictive value of combining different ischemia severity and the corresponding volume only using EVT patients. In our research, the occurrence of HT was predicted by analyzing the brain tissue volume measured below the specific ADC thresholds. The results indicated a higher predictive value for HT than other imaging methods utilized in previous research (8,15). In addition, the ADC sequence in preoperative MRI was used to quantify the ischemia severity, which is non-invasive and more routine relative to perfusion imaging.

Previous studies have reported that the admission NIHSS score, delayed recanalization, baseline glucose, hypertension, cardiogenic stroke, and intravenous thrombolysis are independent risk factors for HT after recanalization (13,15,21). In our study, intravenous thrombolysis, atrial fibrillation, and larger volumes of ADC <0.4×10^{-3} mm^2/s were found to be independent predictors of HT. The bigger OR of volume below ADC <0.4×10^{-3} mm^2/s indicates the feasibility of optimal ADC parameter and volume threshold in our ROC result for predicting HT.

Our study has some limitations that should be noted. Firstly, this was a retrospective and single-center study.

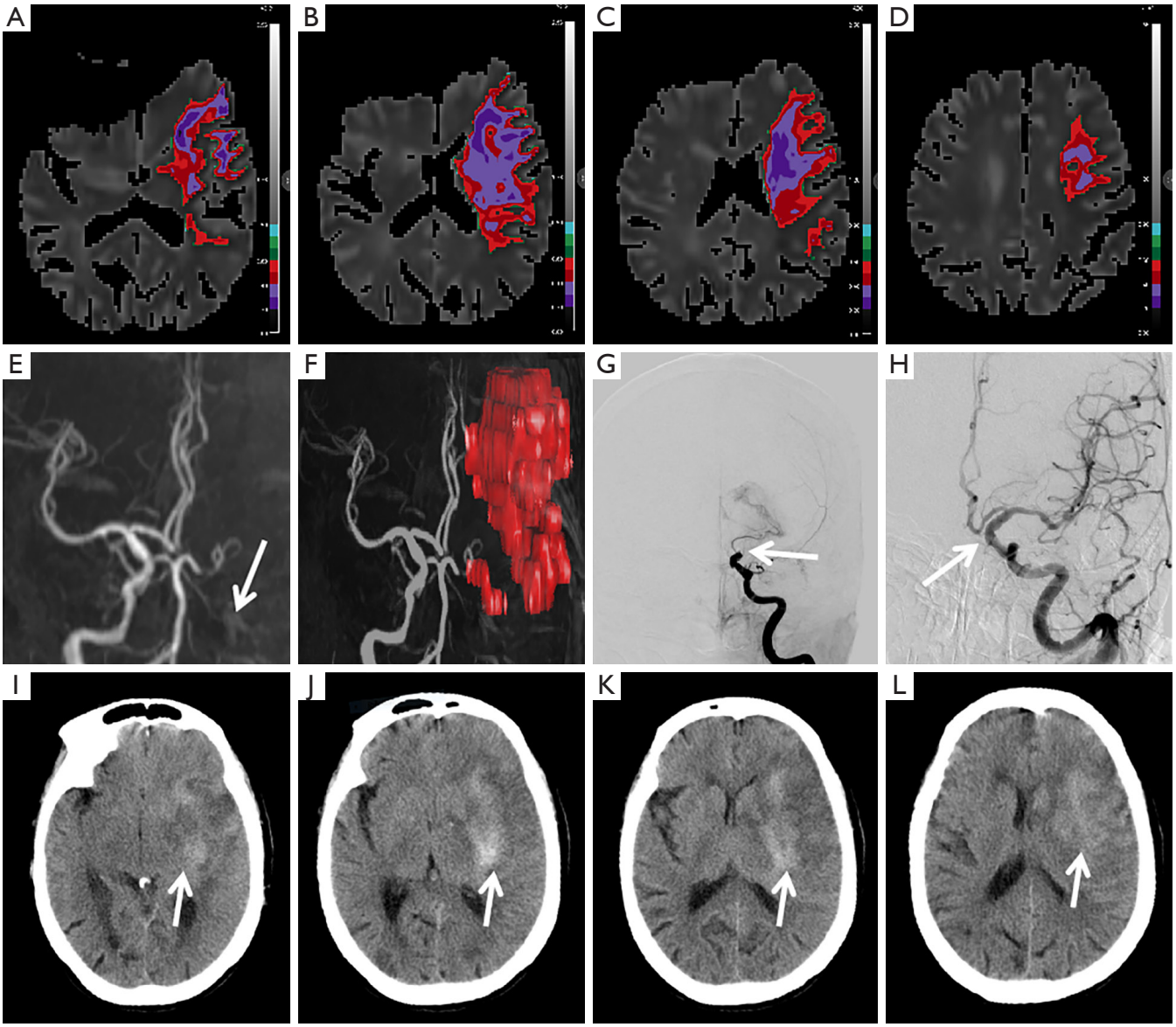

Figure 3 Imaging of a patient with HI2. (A-D) Preoperative ADC map showing the ADC value distribution in the infarct core. The severity of the ischemic area is represented by different colors with the related ADC value range (unit: 10^{-3} mm^2/s): bright red, 0.5–0.6; dark red, 0.4–0.5; light purple, 0.3–0.4; and dark purple, <0.3. The volume (unit: ml) of the areas with ADC <0.4 is 20.33. (E) MRA image before EVT showing left internal carotid artery (LICA) occlusion (white arrow). (F) Image fusion using MRA and DW images. DSA image before (G) and after (H) EVT showing LICA occlusion (mTICI 0) (G, white arrow) and complete recanalization (mTICI 3) (H, white arrow). (I-L) Follow-up CT showing petechial hyperdensity throughout the wedge-shaped hypodensity in the territory of the left middle cerebral artery (white arrows), which indicates HI2. HI, hemorrhagic infarct; ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography; EVT, endovascular therapy; DW, diffusion weighted; DSA, digital subtraction angiography; LICA, left internal carotid artery; mTICI, modified Thrombolysis in Cerebral Infarction scale; CT, computed tomography.

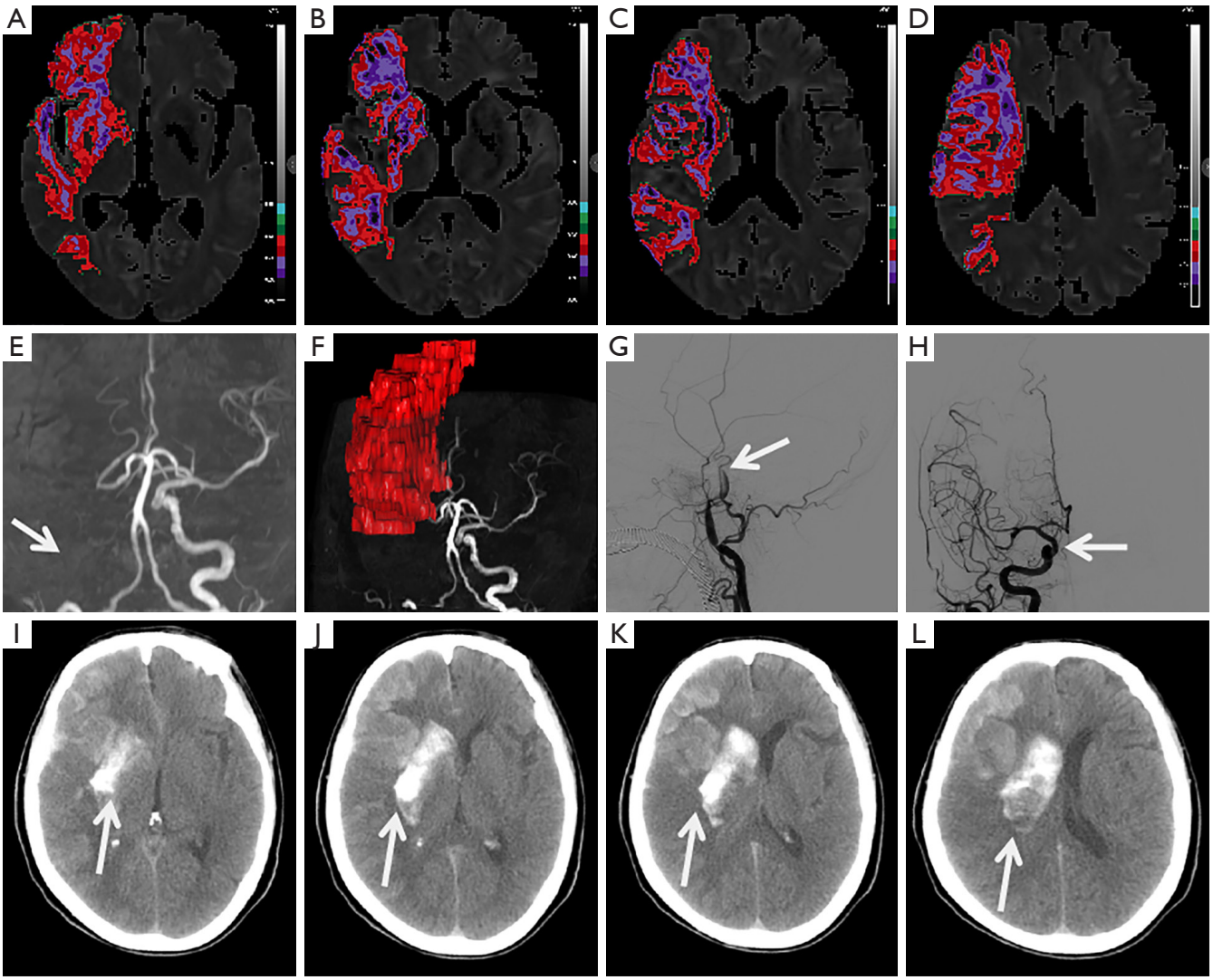

Figure 4 Imaging of a patient with PH2. (A-D) Preoperative ADC map showing the ADC value distribution in the infarct core. The severity of the ischemic area is represented by different colors with related ADC value range (unit: 10^{-3} mm^2/s): bright red, 0.5–0.6; dark red, 0.4–0.5; light purple, 0.3–0.4; and dark purple, <0.3. The volume (unit: mL) of the area with ADC <0.4 is 44.25. (E) MRA image before EVT showing right internal carotid artery (RICA) occlusion (white arrow). (F) Image fusion using MRA and DW images. DSA image before (G) and after (H) EVT showing RICA occlusion (mTICI 0) (G, white arrow) and complete recanalization (mTICI 3) (H, white arrow). (I-L) Follow-up CT shows a patchy and wedge-shaped hyperdense area in the RMCA territory and right ventricle along with a substantial mass effect (white arrows), which indicates PH2. PH, parenchymal hematoma; ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography; EVT, endovascular therapy; DW, diffusion weighted; DSA, digital subtraction angiography; RICA, right internal carotid artery; mTICI, modified Thrombolysis in Cerebral Infarction scale; CT, computed tomography.

Secondly, the sample size was small, especially for the PH subtype, so only a logistic regression analysis for HT was created. Thirdly, the choice of post-processing software may have influenced the optimal ADC value.

Conclusions

The risk of HT after thrombectomy can be predicted using a combination of ischemia severity and the

Table 2 Multivariate logistic regression analysis of factors for HT after EVT

Patient characteristics	B	SE	OR (95% CI) values	P values
Hypertension	0.211	0.603	1.235 (0.379–4.031)	0.726
Diabetes mellitus	0.046	0.659	1.047 (0.288–3.808)	0.944
Atrial fibrillation	1.759	0.790	5.807 (1.234–27.339)	0.026
Volume of ischemic lesion with ADC <0.4 ($\times10^{-3}$mm^2/s) >6.456 mL	3.531	0.822	34.164 (6.825–171.022)	<0.001
Number of passes	0.345	0.252	1.412 (0.862–2.312)	0.170
IV tPA treatment	2.067	0.693	7.898 (2.032–30.697)	0.003
Onset to final reperfusion time	–0.002	0.001	0.998 (0.996–1.001)	0.185
Occlusion site				0.94
Tandem occlusion			Reference	
ICA	–1.247	0.857	0.287 (0.054–1.540)	0.145
MCA	–1.936	0.892	0.144 (0.025–0.829)	0.030

HT, hemorrhagic transformation; EVT, endovascular therapy; SE, standard error; OR, odds ratio; ADC, apparent diffusion coefficient; IV tPA, intravenous tissue plasminogen activator; ICA, internal carotid artery; MCA, middle cerebral artery.

corresponding volume in an ADC map. A volume of ADC <0.4×10^{-3} mm^2/s provides a higher predictive value than the total volume of the infarct core in ROC analysis. In addition to the total infarct volume, preoperative assessment of the volume in severely ischemic area may provide more information for HT risk prediction. These findings may provide a reference for clinicians to identify patients at risk of HT before EVT, which will contribute to more precise and individualized treatment.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2255/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2255/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2255/coif). All authors report that this work was supported by the Key Research and Development Program of Henan Province (Scientific and Technological Project of Henan Province) (No. 202102310037), the Provincial and Ministerial Joint Project of Henan Provincial Medical Science and Technology (No. SBGJ2018063), and the Research and Popularization Project of Appropriate Intervention Techniques for High-risk Population of Stroke in China (No. GN-2018R0007). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by ethics committee

of Henan Provincial People's Hospital (No. 2017-034-01). Individual consent for this retrospective analysis was waived.

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