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The value of diffusion weighted imaging in predicting the clinical progression of perforator artery cerebral infarction

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ABSTRACT

Objectives: To investigate the value of diffusion weighted imaging (DWI) in predicting the clinical progression of perforator artery cerebral infarction.

Methods: The magnetic resonance imaging (MRI) data of patients with perforator artery cerebral infarction hospitalized in our hospital from October 2015 to February 2022 were analyzed retrospectively. Then we compared the differences of apparent diffusion coefficient (ADC) value, maximal size, location of cerebral infarction, clinical data and treatment plan between the two groups.

Results: A total of 81 patients with perforating artery cerebral infarction were included, with 33 patients in the progressive cerebral infarction (PCI) group and 48 patients in the non-progressive cerebral infarction (NPCI) group. The ADC value in the progressive group was lower than that in the non-progressive group ($P < 0.001$), and ADC value was an independent factor influencing the clinical progression (OR = 0.974, 95 %CI = 0.960–0.989, $P = 0.001$); The average area of cerebral infarction in the progressive group was larger than that in the non-progressive group ($P = 0.004$). There was no difference between the two groups ($P > 0.05$) in terms of clinical data and treatment plan.

Conclusions: The ADC value and maximal size of infarction were correlated with the clinical Progression. ADC value was an independent factor influencing the clinical progression of perforating artery cerebral infarction, which could be used for the prediction of clinical progress and provide guidance for the development of individualized treatment.

1. Introduction

Progressive cerebral infarction (PCI) is a common and severe clinical subtype of acute cerebral infarction, accounting for 25 % to 40 % of all stroke incidence, and can increase the rate of disability and mortality (Zang et al., 2016). Previous studies have shown that progressive cerebral infarction usually causes cerebral tissue ischemia, hypoxia and necrosis, and eventually leads to gradual aggravation of neurological deficits in patients (uriakose and Xiao, 2020). Thus, clinically, progressive cerebral infarction is usually defined as an increase of 2 or more points in the National Institutes of Health Stroke Scale (NIHSS) score during hospitalization (Poh et al., 2020). In recent years, with the continuous development of China's economy and the increase of aging population, the incidence and mortality of cerebral infarction in China have increased (Wu et al., 2019). However, the early recognition and treatment of cerebral infarction progression is not very successful, and the prognosis is relatively poor, with most patients left with paralysis, aphasia or dementia after treatments (Ginex et al., 2020). Therefore, during the onset of cerebral infarction, the early recognition of whether the clinical symptoms will be further aggravated will help choose

Abbreviations: MRI, Magnetic resonance imaging; DWI, Diffusion weighted imaging; PCI, Progressive cerebral infarction; NPCI, Non-progressive cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; ROI, Region of interest; M, Median; IQR, Interquartile range; TG, Triglyceride; TC, Total cholesterol; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; ADC, Apparent diffusion coefficient; AUC, Area under the curve; ROC, Receiver operating characteristic; ICC, Interclass correlation coefficient; CI, Credibility interval.

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treatment options and improve the prognosis of patients.

Obstructive cerebral infarction caused by perforating arteries is a common type of acute ischemic stroke. The locations of cerebral infarction are mainly in the basal ganglia, and pons, as well as adjacent to the body of the lateral ventricle. Over the past few years, clinicians have found that in the early course of cerebral infarction caused by perforator artery occlusion, although the clinical symptoms of patients are mild and non-disabling, such mild clinical symptoms may recur or aggravate and even cause disability in the course of treatment (Ninomiya et al., 2020). Therefore, clinicians are paying more and more attention to the assessment of clinical progression of perforating artery cerebral infarction.

Diffusion weighted imaging (DWI) has important value in identifying early cerebral infarction and has been widely used in the diagnosis of acute cerebral infarction (Yin et al., 2018; Huang et al., 2021; Bateman et al., 2017). DWI is more sensitive to the random translational movement of water molecules in the body, by calculating the apparent diffusion coefficient (ADC). It can reflect the degree of diffusion of water molecules in the tissue, thereby indirectly reflecting the changes in the microstructure of the surrounding tissues. Therefore, this study aims to explore the value of ADC in the prediction of clinical progression in patients with cerebral infarction by comparing the imaging characteristics of infarct area in the progressive cerebral infarction group (PCI) and the non-progressive cerebral infarction group (NPCI).

2. Materials and methods

2.1. Patients

This was a retrospective analysis, which was approved by the ethics committee of The First.

Affiliated Hospital of Zhejiang Chinese Medical University. Due to its retrospective nature, informed consent from patients was waived. The patients with perforating artery cerebral infarction were retrospectively collected from this hospital during October 2015 to February 2022. Inclusion criteria are as follows: (1) a first-single cerebral infarction; (2) the time from the onset of cerebral infarction to MRI examination ≤ 7 days; (2) clinical data and imaging data are intact. Exclusion criteria including:(1) hemorrhagic stroke or transient ischemic attack; (2) associated with other brain lesions (e.g., subdural hematoma, intracranial tumor); (3) received intravenous thrombolysis and endovascular thrombectomy; (4) patients on whom NIHSS assessment could not be undertaken for clinical stroke severity due to mental state or osteoarthropathy that affects limb movement.

2.2. Definition of progressive cerebral infarction

Patients were given NIHSS score daily during admission and hospitalization, and the NIHSS score during hospitalization increased by ≥ 2 points compared with that at admission, which was regarded as the progressive cerebral infarction (PCI) (Poh et al., 2020). However, the patients were excluded if clinical progression occurred after admission, but prior to obtaining MRI.

2.3. MRI acquisition

The patients underwent MR examination with either 1.5 T or 3 T scanners, the MRI protocol included T1WI, T2WI, DWI. The imaging protocol parameters at 1.5 T scanners were as follows: (1) T1WI: repetition time (TR)/echo time (TE) = 550 ms/8.4 ms, slice thickness/slice spacing = 5.0 mm/1.5 mm, FOV = 240 mm*240 mm; (2)T2WI: TR/TE = 4000 ms/99 ms, slice thickness/slice spacing = 5.0 mm/1.5 mm, FOV = 240 mm*240 mm; (3)DWI: TR/TE = 3600 ms/102 ms, slice thickness/slice spacing = 5.0 mm/1.0 mm, FOV = 240 mm*240 mm, b = 1000 mm^2/s, b = 0 mm^2/s; The imaging protocol parameters at 3.0 T scanners were as follows: (1)T1WI: TR/TE = 1800 ms/9.4 ms, slice thickness/slice spacing = 5.0 mm/0.7 mm, FOV = 256 mm*256 mm; (2)T2WI: TR/TE = 6000 ms/95 ms, slice thickness/slice spacing = 5.0 mm/0.6 mm, FOV = 256 mm*256 mm; (3)DWI: TR/TE = 6300 ms/94 ms, slice thickness/slice spacing = 5.0 mm/1.0 mm, FOV = 256 mm*256 mm, b = 1000 mm^2/s, b = 0 mm^2/s. In our study, the ADC maps were generated by inline mono-exponential fitting of the lowest and highest b-value data of DWI maps (b = 0 mm^2/s and b = 1000 mm^2/s) by the scanner software.

2.4. Data collection

(1) Clinical data: gender, age, smoking, drinking, NIHSS score during admission and hospitalization, systolic and diastolic blood pressure at admission, hematology examination at admission (blood glucose, TG, TC, LDL, HDL), mono antiplatelets or dual antiplatelets.
(2) MRI imaging data: The largest layer of cerebral infarction lesions was selected as the area of interest (ROI). The ADC values and size of each ROI were measured manually to avoid CSF effect, and the locations of cerebral infarction area were also recorded (Fig. 1). All measurements were taken by two neuroimaging diagnostic radiologists with >5 years of experience. Then the average value of the measurement results was taken. If the measurement results were significantly different, they were determined by the two physicians through consultation.

2.5. Statistical analysis

Statistical analyses were performed with SPSS Statistics (version 25.0). Normality test was performed on all measurement data, and the data conforming to normal distribution or approximate normal distribution were described by mean ± standard deviation ($\bar{x} \pm s$), the data conforming to skewness distribution were described by median [interquartile ranges (IQRs)]. Comparison of quantitative data: T test was used for normal distribution, and rank sum test was used for skewness distribution, while the Chi-square test and Fisher's exact probability method were used for qualitative data. Multivariate analysis was performed using Logistic regression analysis. Area under the receiver operating characteristic (ROC) curve (AUC) analysis was performed to identify the optimal ADC threshold to distinguish PCI from NPCI, specificity and sensitivity were calculated according to the cut-off value that maximized the Youden index. Interobserver agreement between the two observers on the measurement of ADC values was analyzed by calculating the interclass correlation coefficient (ICC). ICCs were interpreted as follows: 0–0.40, poor agreement; 0.41–0.60, ordinary agreement; 0.61–0.80, moderate agreement; and 0.81–1.00, good agreement. The $P < 0.05$ was considered as statistically significant difference.

3. Results

3.1. Patients' characteristics

A total of 81 patients with perforating artery cerebral infarction were investigated in the study, including 33 patients with progressive cerebral infarction and 48 patients with non-progressive cerebral infarction.

The basic characteristics of the two groups are shown and compared in Table 1. The number of female patients, who range from 42 to 93 years old, was 32 (39.51 %), with an average age of 66.01 ± 11.72 years old. The ICC of ADC values were 0.855 (95 % confidence interval [CI]: 0.783–0.904) between the two observers. The average ADC value was [358 (335.50 ~ 389.50)] × $10^{-6}mm^2/s$ in the progressive group and [418 (402 ~ 454.50)] × $10^{-6}mm^2/s$ in the non-progressive group. A univariate analysis showed that the following variables were significantly associated with the progressive cerebral infarction: NIHSS on admission (P = 0.006), size of infarction (P = 0.004), ADC of infarction (P < 0.001) (Table 1, Fig. 2).

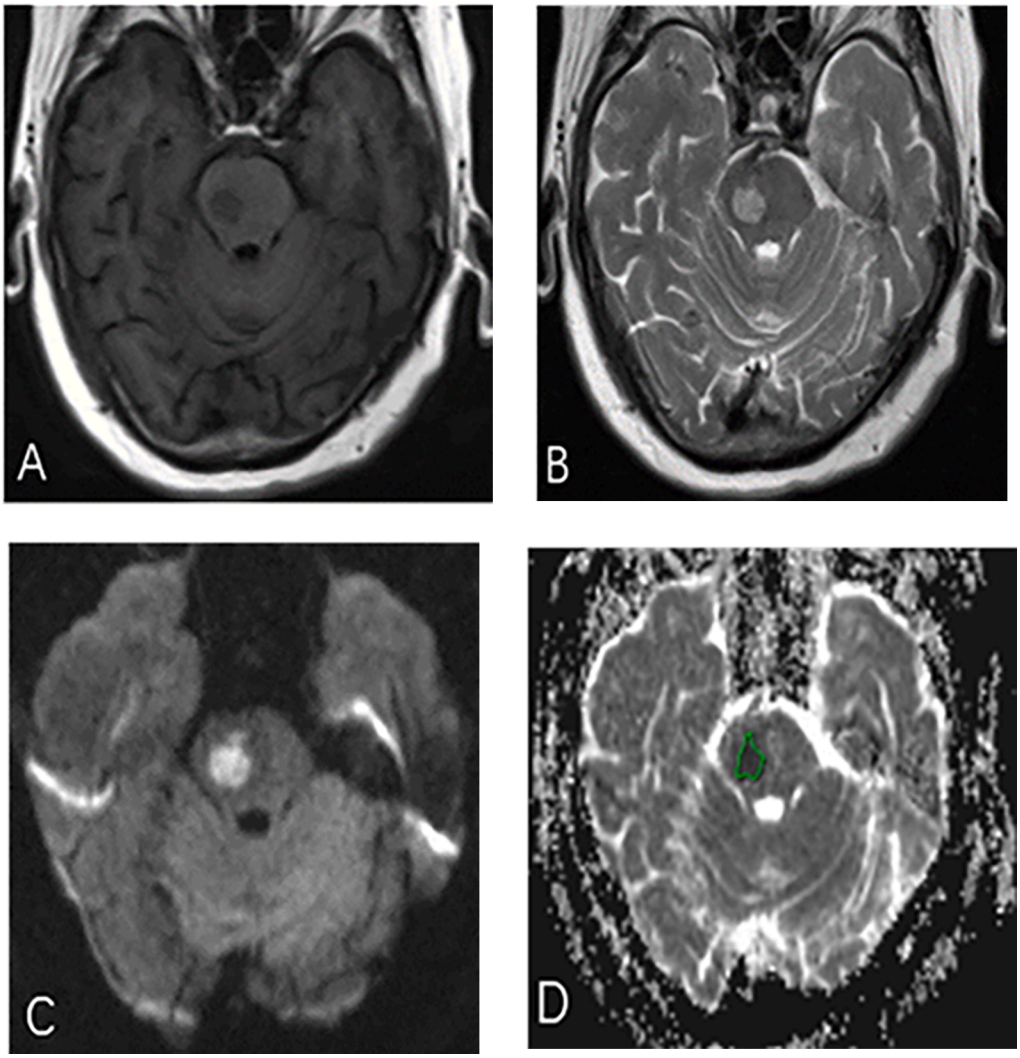

Fig. 1. An 83-year-old female patient presented with cerebral infarction on the right pons and a history of aggravation of cerebral infarction during hospitalization (i.e. The left limbs were able to resist some gravity on admission, but when the cerebral infarction progressed, the left limbs were unable to move). The lesion of cerebral infarction showed low signal on T1WI (A); T2WI showed slightly higher signal (B); DWI was high signal (C); ADC was low signal (D), and the green delineated area on ADC map was the maximal size of infarction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The treatment methods of patients during hospitalization were mainly anticoagulant drugs, such as aspirin and clopidogrel, etc. Statistical results showed that there was no statistical difference in treatment methods between the two groups ($P > 0.05$) (Table 1).

3.2. Lesion size and location of cerebral infarction in progressive and non-progressive groups

There was significant difference of the maximal size of cerebral infarction between the two groups ($P = 0.004$). The average size of cerebral infarction was [60.92(36.00 ~ 93.00)] mm^2 in the progressive group and [43.05(23.06 ~ 56.84)]mm^2 in the non-progressive group (Table 1).

In the progressive group, the location of the 16 cases of the cerebral infarction were adjacent to the body of the lateral ventricle, 15 cases in the pons and 2 cases in the thalamus, while in the non - progressive group, 22 cases of the cerebral infarction were adjacent to the body of the lateral ventricle, 15 cases in the pons, and 11 cases in the thalamus, however, there was no significant difference of the distribution of infarction between the two groups (Table 2). In addition to that, at the level of pons, the location of the cerebral infarction was subdivided into ventral medial area, ventral lateral area and dorsal pons area according to the blood supply area of pons artery; At the *para*-body level of the lateral ventricle, the location of the infarction was divided into 3 equal parts which were the anterior, middle and posterior, there was also no statistical difference in the location of cerebral infarction between the two groups after subdivision of the pons and the *para*-body level of lateral ventricles.

3.3. Multivariate Logistic regression analysis with the progressive group

Variables with $P < 0.05$ in Table 1 were taken as independent variables, while the progressive group was taken as dependent variables for multivariate Logistic regression analysis. The results showed that the maximal size of infarction, NIHSS score on admission had no significant correlation with the clinical progression ($P > 0.05$), only the ADC value of infarction was correlated with the clinical progression ($P = 0.001$) (Table 3). According to ROC analysis, the area under the curve value of ADC was 0.838, the sensitivity was 75.76 %, and the specificity was 91.67 % (Fig. 3).

4. Discussion

In this study, we compared the imaging characteristics of the cerebral infarction in the progressive cerebral infarction group and the non-progressive cerebral infarction group. We found that there were significant differences between the two groups in the maximal size of infarction and ADC value of infarction. Besides, the ADC value of the cerebral infarction was an independent factor for the clinical progression of cerebral infarction and could be used to predict the clinical

Table 1
Population characteristics of patients with progressive group and non-progressive group.

Characteristics	PCI(n = 33)	NPCI(n = 48)	P
Female (n,%)	17 (51.52 %)	15 (31.25 %)	0.067
Age(years, $\bar{x} \pm s$)	64.45 ± 10.26	67.08 ± 12.62	0.324
NIHSS on admission (M, IQR)	3.00 (2.00 ~ 4.00)	2.00(1.00 ~ 3.00)	0.006
Systolic pressure (mmHg, $\bar{x} \pm s$)	163.15 ± 28.51	158.48 ± 22.47	0.413
Diastolic pressure (mmHg, $\bar{x} \pm s$)	87.33 ± 12.81	86.35 ± 13.38	0.743
Blood glucose (mmol/L,M, IQR)	6.22 (5.02 ~ 7.53)	6.15(4.64 ~ 7.78)	0.836
TG(mmol/L, M,IQR)	1.44(1.16 ~ 1.74)	1.42(1.00 ~ 2.00)	0.939
TC(mmol/L, M,IQR)	4.49(3.60 ~ 5.19)	4.30(3.68 ~ 4.85)	0.690
LDL(mmol/L, M,IQR)	2.33(1.59 ~ 2.96)	2.38(1.93 ~ 2.86)	0.523
HDL(mmol/L,M,IQR)	1.12(0.91 ~ 1.39)	1.12(0.94 ~ 1.30)	0.784
Smoking (n,%)	8(24.24 %)	9 (18.75 %)	0.551
drinking (n,%)	5 (15.15 %)	11(22.92 %)	0.388
Mono antiplatelets(n,%)	19 (57.58 %)	27 (56.25 %)	0.785
Dual antiplatelets(n,%)	14 (42.42 %)	21 (43.75 %)	0.785
Size of infarction (mm^2, M,IQR)	60.92 (36.00 ~ 93.00)	43.05 (23.06 ~ 56.84)	0.004
ADC of infarction ($x10^{-6}mm^2/s$, M,IQR)	358 (335.50 ~ 389.50)	418 (402 ~ 454.50)	<0.001

Abbreviations: PCI: Progressive cerebral infarction, NPCI: Non-progressive cerebral infarction, NIHSS:National Institutes of Health Stroke Scale, M: Median, IQR: Interquartile range, TG: Triglyceride, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ADC: Apparent diffusion coefficient.

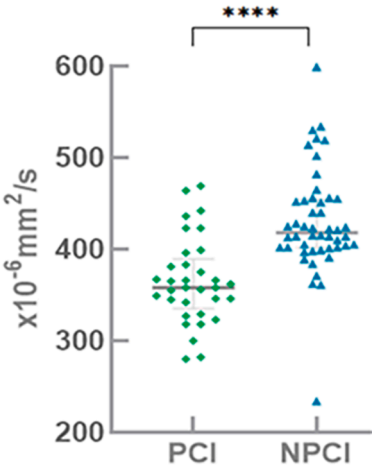

Fig. 2. Comparison of ADC values of infarction between the two groups.

Table 2
Comparison of the overall location distribution of infarction between the two groups.

	The *para*-body level of lateral ventricles	The pons	The thalamus	P
PCI(n = 33)	16	15	2	0.102
NPCI(n = 48)	22	15	11	

Abbreviations: PCI: Progressive cerebral infarction, NPCI: Non-progressive cerebral infarction,

progression of cerebral infarction.

The main cause of ischemic cerebral infarction is thrombosis or embolism, which leads to the reduction of effective circulation blood flow in the brain area, and then to the reduction of oxygen supply in

Table 3
Multivariate Logistic regression analysis with the progressive group of the perforator artery cerebral infarction.

Independent variables	OR	95 %CI	P
The maximal size of infarction	1.005	0.990–1.020	0.540
NIHSS score on admission	1.248	0.898–1.734	0.188
ADC value of infarction	0.974	0.960–0.989	0.001

Abbreviations: NIHSS: National Institutes of Health Stroke Scale, ADC: Apparent diffusion coefficient, OR: Odds ratio, CI: Confidence interval.

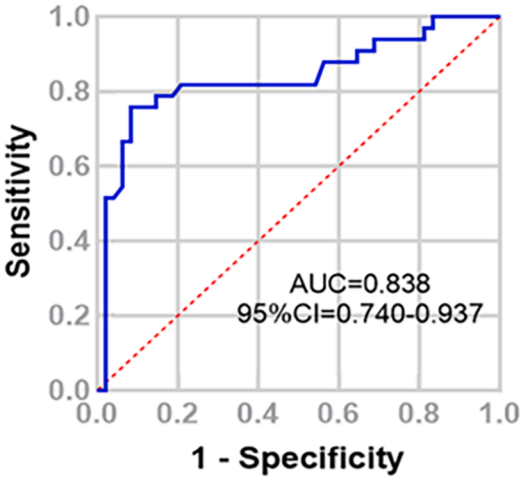

Fig. 3. ROC curve of ADC for predicting PCI.

brain tissue, due to hypoxic changes in brain tissue, the tricarboxylic acid cycle in brain cells slows down, which results in dysfunction of the Na + -K + pump, and ultimately leads to sodium retention, water retention and decreased diffusion rate of water molecules (Kuriakose and Xiao, 2020). In the first few minutes to hours of cerebral infarction, cytotoxic edema dominates, which shows low values on the ADC map, and the area where the ADC value drops sharply is considered to be the most severe cerebral ischemic tissue, that's where the risk of cell death is greatest (Momosaka et al., 2020). In this study, our results showed that the ADC value of infarction in progressive group was significantly lower than that in non-progressive group, which suggested that the degree of cell edema in the infarction area of progressive group was significantly higher than that in non-progressive group. On the one hand, such more severe cell edema may lead to more obvious compression of nerve tissue around the lesion than non-progressive cerebral infarction, aggravating clinical symptoms (Kim et al., 2016). On the other hand, due to the lack of effective collateral circulation in the perforating artery, more severe cell edema may lead to the aggravation of peripheral nerve tissue ischemia, resulting in further aggravation of clinical symptoms. In addition to our study, Oge DD (Oge et al., 2022) et al' study also found that the $rADC_{mean}$ was significantly lower among patients with progression which suggested the mean rADC values of cerebral infarction was closely related with early neurological deterioration in patients with isolated pontine infarcts. Therefore, combined with the above analysis, we can conclude that the ADC value in cerebral infarction region has high sensitivity in predicting the clinical progression of cerebral infarction patients.

The larger the infarct area of perforating artery is, the more likely it will cause the progression of clinical symptoms. This study found that the maximal size of infarction was higher in the clinically progressive group than in the non-progressive group, which was consistent with the results of Li et al. (Li et al., 2020). The reason may be that, the cerebral infarction area is in essence caused by the overtly insufficient blood supply of the brain tissue and the ischemic hypoxic metabolism disorder

of the brain cells, which result in different degrees of brain tissue edema and neuronal cell dysfunction; when the infarct area is large, the number of brain tissue and neuron cells affected increases, which enhances sensitivity of the brain tissue area to ischemia and hypoxia, and easily exacerbates neurological defects.

In addition, we also analyzed the correlation between different location of cerebral infarction and clinical progression of cerebral infarction in this study. The results showed that progressive cerebral infarction of perforating artery was mainly distributed in the areas of the *para*-body of lateral ventricle and pons, which was consistent with previous studies (Li et al., 2020; Nakase et al., 2014). The reason is that the supplying artery of the *para*-body of lateral ventricle is the superficial branch artery of the middle cerebral artery, such as the lenticulostriate artery and the anterior choroid artery. The arteries supplying the pons are paramedian artery, short circumflex artery and long circumflex artery. However, these perforating arteries are terminal arterioles with less collateral circulation and are vulnerable to hemodynamic changes. At the same time, a large number of nerve fibers are distributed in the *para*-body of lateral ventricle and pons area, thus even a small increase in cerebral infarction area will cause progressive aggravation of neurological defects (Yamamoto et al., 2017; Xue et al., 2021).

In our study, there was no significant difference in blood pressure, blood glucose and total cholesterol levels between the two groups. On the contrary, Nakase (Nakase et al., 2013) et al found that male, the presence of diabetes and dyslipidemia were risk of progressive disease, there are two possible reasons for the difference from our results: Firstly, their results were based on patients with atherosclerotic cerebral infarction and our patients included only perforator artery infarction without subdivision; Secondly, our sample size is relatively small, which also led to differences in the results. In addition to that, Jiang (Jiang et al., 2019) et al pointed out that the clinical progression of subcortical small infarction was correlated with the history of hypertension, and whether there was a significant correlation needed to be further studied with a large sample. Meanwhile, in our study, aspirin and clopidogrel were the main drugs that patients received during admission, we found no statistical difference between the two groups in combination or single administration of the two drugs, however, Vynckier (Vynckier et al., 2021) et al suggested that dual antiplatelet therapy was associated with reduced risk of clinical progression, the difference between the two results may be attributed to our small sample size.

The limitations of this study are as follows: (1) the sample size of clinical progression of perforator artery cerebral infarction is relatively small, which needs to be further studied by expanding the sample size; (2) This study is a retrospective analysis, which may have a selection bias. Moreover, this study focuses on the perforator artery cerebral infarction with limited research scope, which calls for further studies from multiple perspectives and in a larger scope in future.

5. Conclusion

In conclusion, the ADC value of the cerebral infarction is proved to be an independent factor for the clinical progression of cerebral infarction, which is instrumental in predicting the clinical progress of perforator artery cerebral infarction and providing a reference for appropriate personalized treatment plan in clinic.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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