Original research

Long-term outcomes of moyamoya disease versus atherosclerosis-associated moyamoya vasculopathy using high-resolution MR vessel wall imaging

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ABSTRACT

Objectives We aimed to compare the long-term outcomes and surgical benefits between moyamoya disease (MMD) and atherosclerosis-associated moyamoya vasculopathy (AS-MMV) using high-resolution MRI (HRMRI).

Methods MMV patients were retrospectively included and divided into the MMD and AS-MMV groups according to vessel wall features on HRMRI. Kaplan-Meier survival and Cox regression were performed to compare the incidence of cerebrovascular events and prognosis of encephaloduroarteriosynangiosis (EDAS) treatment between MMD and AS-MMV.

Results Of the 1173 patients (mean age: 42.4±11.0 years; male: 51.0%) included in the study, 881 were classified into the MMD group and 292 into the AS-MMV group. During the average follow-up of 46.0±24.7 months, the incidence of cerebrovascular events in the MMD group was higher compared with that in the AS-MMV group before (13.7% vs 7.2%; HR 1.86; 95% CI 1.34 to 3.76; p=0.008) or AS-MMV group after propensity score matching (6.1% vs 7.3%; HR 2.24; 95% CI 1.34 to 3.76; p=0.002). Additionally, patients treated with EDAS had a lower incidence of events than those not treated with EDAS, regardless of whether they were in the MMD (HR 0.49; 95% CI 0.51 to 0.98; p=0.048) or AS-MMV group (HR 0.42; 95% CI 0.42 to 0.97; p=0.043) compared with AS-MMV patients.

Conclusions Patients with MMD had a higher risk of ischaemic stroke than those with AS-MMV, and patients with both MMD and AS-MMV could benefit from EDAS. Our findings suggest that HRMRI could be used to identify those who are at a higher risk of future cerebrovascular events.

INTRODUCTION

Moyamoya vasculopathy (MMV), which is divided into moyamoya disease (MMD) and other underlying diseases that can cause secondary moyamoya phenomena, is characterised by the progressive stenosis of the intracranial internal carotid artery (ICA), proximal middle cerebral artery (MCA) and anterior cerebral artery (ACA), with the development of a collateral network at the base of the brain.1 2 Atherosclerosis-associated MMV (AS-MMV), a special type of intracranial atherosclerotic disease (ICAD) that is mostly characterised by prominent moyamoya collaterals and bilateral carotid terminus stenoo-occlusive disease, is easily confused with primary MMD.3 In recent years, although several studies have reported that AS-MMV could be distinguished from MMD using high-resolution MR (HRMR) imaging (HRMRI),4-5 differentiating between them has not been deemed very important, and the identical treatment strategy is usually used for them in clinical work. Thus, the necessity of differentially diagnosing MMD and AS-MMV needs to be confirmed.

HRMRI vessel wall imaging, which has been increasingly used in recent years, makes it possible to directly observe the vessel wall pathology and differentiate MMD from AS-MMV.6 Kim et al7 8
revealed that the wall thickening and signal intensity characteristics and changes in the outer diameter of the involved arteries could help to distinguish AS-MMV from MMD on HRMRI. As mentioned above, AS-MMV shares similar luminal patterns and collateralization with MMD, as well as similar clinical presentations. However, it remains unclear whether AS-MMV and MMD share a similar prognosis and surgical benefit. A better understanding of the differences in prognosis between MMD and AS-MMV will help to better clarify the importance of a differential diagnosis between them, enabling personalised treatment strategies.

Hence, we conducted a real-world study from a single centre with the largest volume of MMD cases in China and aimed to investigate the differences in long-term outcomes and surgical benefits between MMD and AS-MMV based on HRMRI.

**MATERIALS AND METHODS**

**Study sample**

The data supporting the findings of this study are available from the corresponding author on reasonable request. Consecutive patients suspected of having MMV between June 2015 and October 2021 were retrospectively analysed. All patients underwent digital subtraction angiography and met the current diagnostic criteria recommended by the 2012 Research Committee on Moyamoya Disease of the Ministry of Health and Welfare of Japan. All patients underwent conventional and high-resolution MRI examinations (figure 1). Patients with cerebral ischaemic symptoms or intracranial haemorrhage were all included in the study. The exclusion criteria were as follows: (1) an age <18 years; (2) secondary moyamoya phenomenon caused by other definite disease entities, except for atherosclerosis and (3) poor imaging quality. Clinical variables, including the age, sex, history of smoking, baseline symptoms, and history of hypertension, diabetes, and hyperlipidaemia, were ascertained at the time of baseline MR. Hypertension was diagnosed if the systolic blood pressure was >140 mm Hg or the diastolic blood pressure was >90 mm Hg. Hyperlipidaemia was considered present when the levels of low-density lipoprotein exceeded 1.58 mmol/L, total cholesterol exceeded 2.26 mmol/L or triglycerides exceeded 1.69 mmol/L. Diabetes mellitus was considered present when the fasting blood sugar level exceeded 126 mg/dL, 2-hour oral glucose tolerance test result exceeded 200 mg/dL or haemoglobin A1c level was at least 6.5%. Patients with a history of smoking identified if they had smoked or were current smokers. Transient ischaemic attack (TIA) was defined as rapidly developing signs of a neurological deficit or loss of vision lasting less than 24 hours with no apparent cause other than that of vascular origin. Ischaemic stroke was defined as rapidly developing clinical signs of a neurological deficit lasting at least 24 hours with no apparent cause other than that of vascular origin and without evidence of an intracranial haemorrhage on CT/MRI.

**MRI protocols**

All recruited patients underwent MRI at a 3.0 T MR scanner (MAGNETOM SKYRA, Siemens Healthcare) with an eight-channel head coil. The detailed information of conventional MRI was as follows: (1) three-dimensional time of flight (3D TOF): repetition time (TR)/echo time (TE) was 20 ms/3.5 ms; field of view (FOV) was 200×200×60 mm³; matrix size was 360×360 and slice thickness was 0.5 mm; (2) T1-weighted imaging (T1WI): TR/TE was 2000 ms/8.6 ms; FOV was 230×230 mm²; matrix size was 256×224; and slice thickness was 5 mm; (3) T2-weighted imaging: TR/TE was 3940 ms/95 ms; FOV was 230×230 mm²; matrix size was 384×336 and slice thickness was 5 mm; (4) fluid attenuated inversion recovery: TR/TE was 9000 ms/98 ms; FOV was 230×230 mm²; matrix size was 512×416; and slice thickness was 5 mm.

The intracranial high-resolution vessel wall imaging was acquired and the detailed parameters were as follows: pre- and post-contrast 3D T1WI: TR/TE was 566 ms/22 ms; FOV was 204×204×45 mm³; spatial resolution was 0.4×0.4×0.8 mm³; and number of excitations was 2. 3D T2WI: TR/TE was 3000 ms/50 ms; FOV was 130×130×45 mm³; spatial resolution was 0.4×0.4×0.8 mm³. The fat suppression technique was used during the imaging. The postcontrast T1WI sequence was performed 5 min later by intravenous administration of Gadodiamide (Gd-DTPA, 0.1 mmol/kg).

**Analysis of MRI**

All vessel wall MRI were reviewed by two experienced radiologists (ML and HZ) who were blinded to the clinical information on a Siemens MR workstation (Siemens Syngo AV1.1). The presence of stenotic lesions that involved the terminal portion of the ICA, proximal portion of the MCA, ACA and posterior cerebral artery were determined on HRMR.

Patients were considered to have MMD when at least two of the following three HRMRI characteristics were found at the involved segments of the terminal portion of the ICA or the proximal portion of the MCA/ACA: (1) no eccentric wall thickening; (2) a decrease in the outer diameter and (3) signal homogeneity. Patients were considered to have AS-MMV when at least two of the following three HRMRI characteristics were found at the involved segments of the terminal portion of the ICA or the proximal portion of the MCA/ACA: (1) eccentric wall thickening; (2) an increase or no change in the outer diameter and (3) signal heterogeneity (figure 2). When the grouping results between the two readers were inconsistent, grouping was decided by consensus. Given that the significance of vessel wall enhancements has not been fully understood and postcontrast HRMR vessel wall imaging has not been widely accepted by clinicians, only those with wall thickening were considered to be included in the AS-MMV group.

**Figure 1** Flow chart. AS-MMV, atherosclerosis-associated moyamoya vasculopathy; MMD, moyamoya disease; PSM, propensity score matching.
The outer diameter of the involved arteries was evaluated on T2WI generated using HRMRI at the site where the outer diameter was smallest. The outer diameter of the involved arteries was evaluated on T2WI generated using HRMRI at the site where the outer diameter was smallest. The signal heterogeneity was considered on T1WI when the signal intensity of the stenotic wall contained a mixture of high-signal or low-signal intensity lesions. Otherwise, signal homogeneity was considered. The presence or absence of the wall enhancement of stenotic lesions was determined and compared with the corresponding precontrast images.

Assessment of clinical outcomes

During the follow-up, long-term outcomes were obtained via clinical visits, telephone calls or letter-based interviews. Cerebrovascular events, including ischaemic stroke and intracranial haemorrhage, were recorded to evaluate the patient outcomes. All patients were clinically followed up for at least 6 months from baseline unless a cerebrovascular event occurred during that period.

Encephaloduroarteriosynangiosis (EDAS) treatment was performed in most patients within 2 weeks of the MR scan. EDAS treatment is an indirect surgical revascularisation procedure performed by placing an external carotid artery branch beneath the dura in ischaemic territories. The superficial temporal artery was chosen during most procedures, while the occipital artery was used occasionally, depending on the territory at risk. EDAS was performed for symptomatic affected hemispheres, for both ischaemic and haemorrhagic MMD. The final decision on whether to proceed with the surgery was made by the neurosurgeon and the patient or the patient’s family. Because of objective factors such as economy and culture, if the patient decided not to accept surgical procedures, surgery was not performed.

Reproducibility

Inter-reader and intrareader agreement in the grouping of MMD and AS-MMV, identification of eccentric/concentric wall thickening, signal heterogeneity/homogeneity and presence of wall enhancement was analysed based on HRMRI. One hundred patients selected randomly from the study population were reviewed by one reader (ML) twice with time interval of 2 months to minimise the memory bias. All the HRMRI were independently reviewed by another reader (HZ) for testing the inter-reader agreement. When the results between the two readers were inconsistent, the results would be decided by consensus.

Statistical analyses

Continuous variables are expressed as mean±SD, while categorical variables are presented as frequencies. Propensity score matching (PSM) was used to reduce the influence of confounding factors and selection bias, and enrolled patients were matched using 1:1 nearest neighbour matching with a calliper distance (0.2 times the SD of propensity score) between the MMD and AS-MMV groups. Baseline comparisons between the two groups were conducted using the Student’s t-test, Mann-Whitney U test or χ² test. Cox regression analysis and Kaplan-Meier survival analysis were used to estimate the cumulative event-free rates based on the grouping of MMD and AS-MMV and the grouping of surgery or not. The intrareader and inter-reader agreement in the grouping of MMD and AS-MMV, identification of eccentric/concentric wall thickening, signal heterogeneity/homogeneity and presence of wall enhancement were evaluated by Cohen’s Kappa test. Statistical significance was defined at p<0.05, and all analyses were conducted using the software of SPSS (V22.0; IBM).

RESULTS

Baseline characteristics

A total of 1229 patients were included in the study. Of these patients, 56 were excluded from the study for the following reasons: (1) secondary moyamoya phenomenon caused by other definite disease entities except for atherosclerosis (n=22), autoimmune disease (n=9), brain tumour (n=6), neurofibromatosis (n=5) and vascular lesions after head irradiation (n=2); (2) poor MRI quality (n=5) and (3) lost to follow-up (n=29). The baseline clinical characteristics are shown in table 1. Among the remaining 1173 patients (age range: 18–77 years old, mean: 42.4±11.0 years; male patients: 51.0%) who were finally included for statistical analysis, 854 presented with TIA/infarction, 163 presented with intracranial haemorrhage and 156 had other symptoms (headache, epilepsy, etc) at baseline. The average time interval between patient enrolment and MRI was 3.4±1.0 days. A total of 82.2% (964/1173) of the patients underwent revascularisation surgery (EDAS) with a mean time to surgery of 25.3±47.9 months (the average time from initial symptoms to surgery) and 78.1% (916/1173) were identified as having a Suzuki stage of ≥IV.

Of 1173 patients, 881 were classified into the MMD group and 292 into the AS-MMV group. Compared with patients in the MMD group, those in the AS-MMV group were older (44.5±11.3 vs 41.7±10.8 years; p<0.001) and had higher incidences of hypertension (48.3% vs 39.2%; p=0.007), hyperlipidaemia (38.7% vs 21.2%; p<0.001)
Long-term outcomes between MMD and AS-MMV

Before PSM, over a mean follow-up of 46.0±24.7 months (range: 0.2–85.9 months), a total of 142 patients (12.1%) had cerebrovascular events. Among these patients, 115 (9.8%) had an ischaemic stroke and 27 (2.3%) had a haemorrhagic stroke (table 3). The incidence of ischaemic stroke during the first 2 years (13.7% vs 7.2%; HR 1.86; 95% CI 1.17 to 2.96; p=0.008) in the MMD group were significantly higher than those in the AS-MMV group (figure 3A). The incidence of ischaemic stroke during the first 2 years (8.5% vs 3.4%; HR 3.30; 95% CI 1.87 to 5.82; p<0.001) and long-term follow-up (11.1% vs 5.8%; HR 1.85; 95% CI 1.11 to 3.11; p=0.018) in the MMD group were significantly higher than those in the AS-MMV group (figure 3C). No difference in the incidence of intracranial haemorrhage was found between the MMD and AS-MMV groups during either the first 2 years (1.8% vs 1.4%; HR 2.26; 95% CI 0.74 to 6.84; p=0.606) or the long-term follow-up (2.6% vs 1.4%; HR 1.85; 95% CI 0.64 to 5.35; p=0.256) (figure 3E).

After PSM, over a mean follow-up of 44.1±25.0 months (range: 0.2–85.9 months), a total of 67 patients (11.7%) had cerebrovascular events. Of these, 55 (9.6%) had an ischaemic stroke and 12 (2.1%) had a haemorrhage. The mean and diabetes (18.5% vs 10.3%; p<0.001). After PSM, all clinical-matching variables were balanced, and 286 cases in each group were included in the analyses. The patient data before and after matching are shown in table 1. A comparison of the MR characteristics of the vessel wall between the MMD and AS-MMV groups is shown in table 2.
interval from the recruitment to the occurrence of events was 17.8±17.9 months (range: 0.2–69.8 months). The incidence of cerebrovascular events during both the first 2 years (11.9% vs 4.9%; HR 2.79, 95% CI 1.45 to 5.22; p=0.003) and the long-term follow-up (16.1% vs 7.3%; HR 2.24, 95% CI 1.34 to 3.76; p=0.002) in the MMD group were significantly higher than those in the AS-MMV group (figure 3B). The incidence of stroke during both the first 2 years (9.4% vs 3.8%; HR 2.85; 95% CI 1.58 to 6.79; p=0.001) and long-term follow-up (12.9% vs 6.3%; HR 2.09; 95% CI 1.19 to 3.68; p=0.010) in the MMD group were significantly higher compared with those in the AS-MMV group (figure 3D). No difference in the incidence of haemorrhage was found between the MMD and AS-MMV groups during either the first 2 years (2.4% vs 1.0%; HR 2.85; 95% CI 0.72 to 11.21; p=0.333) or long-term follow-up (3.1% vs 1.0%; HR 3.07; 95% CI 1.19 to 3.68; p=0.142) (figure 3F).

The results of the subgroup analysis regarding the overall cerebrovascular events between the MMD and AS-MMV groups did not show significant heterogeneity in the analyses of the 12 subgroups after matching, with one exception (hypertension, interaction p=0.015) (figure 4). The trend of higher event rates in the MMD group than in the AS-MMV group was attenuated in patients with hypertension (HR 1.22; 95% CI 0.57 to 2.61; p=0.015).

**Table 3** Comparison of cerebrovascular events between patients with MMD and AS-MMV

<table>
<thead>
<tr>
<th></th>
<th>Before PSM</th>
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<th>After PSM</th>
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<tr>
<td></td>
<td>(n=1173)</td>
<td>MMD (n=881)</td>
<td>AS-MMV (n=292)</td>
<td>All cases (n=572) MMD (n=286)</td>
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<td>Cerebrovascular events during overall follow-up</td>
<td></td>
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<td></td>
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<tr>
<td>All events</td>
<td>142 (12.1%)</td>
<td>121 (13.7%)</td>
<td>21 (7.2%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>115 (9.8%)</td>
<td>98 (11.1%)</td>
<td>17 (5.8%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>27 (2.3%)</td>
<td>23 (2.6%)</td>
<td>4 (1.4%)</td>
<td>0.256</td>
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<tr>
<td>Cerebrovascular events in the first 2 years</td>
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</tr>
<tr>
<td>All events</td>
<td>105 (9.0%)</td>
<td>91 (10.3%)</td>
<td>14 (4.8%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ischaemic stroke</td>
<td>85 (7.2%)</td>
<td>75 (8.5%)</td>
<td>10 (3.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>20 (1.7%)</td>
<td>16 (1.8%)</td>
<td>4 (1.4%)</td>
<td>0.606</td>
</tr>
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AS-MMV, atherosclerosis-associated moyamoya vasculopathy; MMD, moyamoya disease; PSM, propensity score matching.

**Figure 3** Kaplan-Meier curves of survival free of cerebrovascular events between patients with MMD and AS-MMV. (A) Overall events before matching; (B) overall events after matching; (C) ischaemic stroke before matching; (D) ischaemic stroke after matching; (E) haemorrhage before matching; (F) haemorrhage after matching.

**Figure 4** Subgroup analyses for comparing MMD versus AS-MMV in predicting cerebrovascular events after matching. AS-MMV, atherosclerosis-associated moyamoya vasculopathy; MMD, moyamoya disease; PCA, posterior cerebral artery; TIA, transient ischaemic attack.
Cerebrovascular disease

Surgical benefit between MMD and AS-MMV
As shown in figure 5, among all included patients, those treated with EDAS had a significantly lower incidence of cerebrovascular events than those not treated with EDAS, regardless of whether it was before PSM (11.0% vs 16.7%; HR 0.61; 95% CI 0.41 to 0.90; p=0.013) than those not treated with EDAS after adjusting for age, gender, hypertension, diabetes, smoking and time to surgery in the multivariate Cox regression analysis. After further adjustment for PCA involvement, bilateral involvement and Suzuki stage, the lower incidence of cerebrovascular events in patients treated with EDAS remained statistically significant (11.0% vs 16.7%; HR 0.62; 95% CI 0.42 to 0.93; p=0.021) compared with those not treated with EDAS.

Reproducibility
As regard with the intrareader agreement, we found the Kappa values for grouping of MMD and AS-MMV, identification of eccentric/concentric wall thickening, signal heterogeneity/homogeneity and wall enhancement were 0.93, 0.92, 0.84 and 0.89, respectively. As for the inter-reader agreement, we found the Kappa values for grouping of MMD and AS-MMV, identification of eccentric/concentric wall thickening, signal heterogeneity/homogeneity and wall enhancement were 0.89, 0.83, 0.75 and 0.79, respectively.

DISCUSSION
This study is the first real-world study with a large sample size using PSM to directly compare long-term outcomes between MMD and AS-MMV based on HRMRI, aiming to provide new insight into the prognosis of different subtypes of MMV. We found that AS-MMV patients were more likely to be older and male and had a higher incidence of hypertension, diabetes and hyperlipidaemia. Patients with MMD had a higher incidence of ischaemic stroke than those with AS-MMV. In terms of surgical benefit, we found that patients treated with EDAS had a lower event rate than those not treated with EDAS, regardless of whether they were in the MMD or AS-MMV group. Our findings suggest that HRMRI could be used to identify those who have a higher risk of future cerebrovascular events.

Previously, the prognosis of MMD and moyamoya syndrome (MMS) was compared by Feghali et al, who found that the stroke-free survival was similar between MMD and MMS. However, the authors excluded atherosclerotic disease from MMS in their study, and differences in the prognosis between MMD and AS-MMV remain unknown. Interestingly, our results showed that patients with MMD had fewer cerebrovascular risk factors but more cerebrovascular events than those with AS-MMV, especially during the first 2 years. After balancing all clinical variables and luminal patterns between MMD and AS-MMV, the trend remained. The distinct pathophysiology between MMD and AS-MMV may account for their different prognoses. The progressive process of arterial stenosis in MMD is genetically determined and difficult to aetiologically change. In contrast, AS-MMV has a late-onset nature and longer disease course, and its pathological process can be delayed or restrained by the management of atherogenic risk factors.

Our results emphasise the importance of differentially diagnosing MMD and AS-MMV using HRMRI in clinical practice. Mossa-Basha et al reported that the likelihood of a correct diagnosis in MMV patients significantly increased from 31.6% to 86.8% when HRMRI was combined with luminal imaging, and this increase was significant for both MMD and AS-MMV. Our results suggest that eccentric wall thickening, no decrease in the outer diameter, and signal
heterogeneity are HRMRI features for the diagnosis of AS-MMV that may serve as predictors of better prognoses in MMV patients. Furthermore, patients with HRMRI features of MMD at stenotic segments should be monitored more frequently and urgently require further treatment because they are more likely to have a future cerebrovascular event. Thus, HRMR should be used in daily clinical practice, as it can help identify patients with MMD who are at risk of rapid disease progression and future cerebrovascular events.

Furthermore, our results showed that patients with MMD treated with EDAS had a lower incidence of cerebrovascular events than those who were not treated with EDAS (p = 0.048 after PSM). Our results are consistent with previous studies that demonstrated that revascularisation surgery is a beneficial treatment option for MMD. In contrast, EDAS treatment of ICAD is thought to be unnecessary. Komotar et al. found that indirect revascularisation surgery did not promote adequate pial collateral development in patients with atherosclerotic disease. Powers et al. reported that bypass surgery plus medical therapy, compared with medical therapy alone, did not reduce the risk of recurrent stroke in atherosclerotic disease. In contrast to previous studies, our results showed that AS-MMV could also benefit from EDAS treatment and that the cerebrovascular event rate decreased from 12.5% to 5.9% after treatment with EDAS in patients with AS-MMV. The reason for the inconsistent results may be that this study only included patients who were diagnosed with AS-MMV rather than with ICAD. AS-MMV is a special type of ICAD and is mostly characterised by prominent moyamoya collaterals and bilaterality of the carotid terminus steno-occlusive disease. The heterogeneity of disease characteristics between AS-MMV and ICAD may contribute to the discrepancy in the results.

Our study had several strengths, including having the largest MMV cohort evaluated using HRMRI, which was used to differentiate AS-MMV from MMD. Furthermore, PSM was employed to balance all cerebrovascular risk factors and luminal patterns between the MMD and AS-MMV groups, which helped reveal the intrinsic differences in prognoses between MMD and AS-MMV.

Several limitations of this study should be considered when interpreting our results. First, selection bias may have played a role in EDAS treatment selection because of the retrospective nature of the study. Second, in this study, it was challenging to make a definite diagnosis for patients with MMD and atherosclerosis. Third, there was no histological confirmation of the diagnosis of AS-MMV or MMD.

In conclusion, patients with MMD had a higher risk of ischaemic stroke than those with AS-MMV had, and patients with MMD and AS-MMV could both benefit from EDAS treatment. Our findings suggest that HRMRI could be used to identify those who are at higher risk of future cerebrovascular events.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Fifth Medical Center of Chinese PLA General Hospital (reference number:20150622). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Cerebrovascular disease
Cerebrovascular disease


