Original Contribution

# Natural Course of Moyamoya Disease in Patients With Prior Hemorrhagic Stroke

## Clinical Outcome and Risk Factors

Shuai Kang, MD*; Xingju Liu, MD*; Dong Zhang, MD; Rong Wang, MD; Yan Zhang, MD; Qian Zhang, MD; Wuyang Yang, MD; Ji-zong Zhao, MD

***Background and Purpose***—Evidence on the natural history of hemorrhagic moyamoya disease is still insufficient. We investigated the incidence of recurrent intracranial bleeding, mortality, and risk factors for rebleeding in patients with moyamoya disease.

***Methods***—A total of 128 conservatively managed patients with hemorrhagic presentation and complete follow-up data were included. Recurrent hemorrhages during long-term follow-up were documented. Annual and cumulative incidence rate of bleeding was generated via Kaplan-Meier survival analysis, and risk factors were analyzed using logistic regression analysis.

***Results***—The median follow-up time was 10.1 (1–27) years. During a total of 1300.7 patient-years, 47 (36.7%) patients experienced 59 occurrences of recurrent hemorrhages, rendering an average annual incidence of 4.5%. Among them, 9 patients (19.1%) died from rebleeding and 12 patients sustained severe disability (modified Ranking scale score of ≥3). The cumulative risk of rebleeding was 7.8% at 5 years, 22.6% at 10 years, and 35.9% at 15 years. Only 4 (3.1%) patients experienced ischemic stroke, yielding an average annual incidence of 0.3%. Multivariate analysis showed that smoking (odds ratio, 4.85; $P$=0.04) was an independent risk factor of rebleeding. Rebleeding (hazard ratio, 11.04; $P$=0.02) and hypertension (hazard ratio, 4.16; $P$=0.04) were associated with increased mortality. Age, type of initial bleeding, digital subtraction angiography staging, family history, and coexisting cerebral aneurysms were not associated with increased risk of rebleeding.

***Conclusions***—Rebleeding events were common and the main cause of death in patients with hemorrhagic moyamoya disease. The risk of rebleeding steadily increased during long-term follow-up. Smoking was a risk factor for rebleeding, and hypertension was associated with increased mortality. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.022771.)**

**Key Words:** hemorrhage ■ hypertension ■ moyamoya disease ■ natural history ■ stroke



Moyamoya disease (MMD) is a chronic, progressive, steno-occlusive disorder at the distal carotid and proximal middle and anterior cerebral arteries. Intracranial ischemia and hemorrhage are the 2 main manifestations associated with this disease. The exact underlying mechanism of MMD remains unknown. Although intracranial hemorrhage was less common than ischemic attack, it is the major cause of death in patients with MMD.[1,2] The reported mortality rate of intracranial hemorrhage in patients with MMD may be as low as 6.8% or as high as 28.6%.[3,4] Key among the goals of treating hemorrhagic MMD is to reduce the risk of future intracranial hemorrhages. However, the effectiveness of revascularization for hemorrhagic MMD remains controversial. The recent Japanese Adult Moyamoya trial demonstrated the protective effect of direct bypass against rebleeding, whereas other studies have reported suboptimal outcomes in similar settings.[2,5–7] At present, it is challenging to evaluate the outcome of surgical management of hemorrhagic MMD, largely because of the paucity of data on long-term natural history of hemorrhage.

Recent studies have shown that the proportions of hemorrhagic MMD in mainland China and Taiwan are much higher than that of Japan.[8–10] The mean follow-up period per patient was <5 years in most studies, and evidence is limited

Received July 20, 2018; final revision received January 11, 2019; accepted January 30, 2019.

From the Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, China (S.K., X.L., D.Z., R.W., Y.Z., Q.Z., J.-z.Z.); China National Clinical Research Center for Neurological Diseases, Beijing (S.K., X.L., D.Z., R.W., Y.Z., Q.Z., J.-z.Z.); Center of Stroke, Beijing Institute for Brain Disorder, China (S.K., X.L., D.Z., R.W., Y.Z., Q.Z., J.-z.Z.); and Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD (W.Y.).

*Drs Kang and Liu contributed equally.

**The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.022771.**

Correspondence to Ji-zong Zhao, MD, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, 6 Tiantan Xili, Chongwen District, Beijing 100050, China, Email zhaojz205@163.com or Dong Zhang, MD, Beijing Tiantan Hospital, Capital Medical University, 6 Tiantan Xili, Chongwen District, Beijing 100050, China, Email zhangdong0660@aliyun.com

in incidence hemorrhagic risk based on long-term natural history, such as the rebleeding rate, cumulative incidence, and risk factors. To better chart the natural course of the disease, we observed the clinical course of 128 patients over a long-term follow-up.

## Methods

### Patients and Materials

The data that support the findings of this study are available from the corresponding author on reasonable request.

We conducted a retrospective study with long-term follow-up assessing the natural history of hemorrhagic MMD. This study was approved by the Beijing Tiantan Hospital Institutional Review Board. The goal is to determine the risk of recurrent hemorrhages. From 1985 to 2012, a total of 274 patients with hemorrhagic MMD were identified in Beijing Tiantan Hospital. Among them, 128 patients who were treated conservatively were included in this study. The diagnosis of MMD was based on digital subtraction angiography (DSA). All patients initially presented with intracranial hemorrhage, which was confirmed by brain computed tomographic (CT) scan. It should be noted that Beijing Tiantan Hospital is one of the major referral centers for MMD in China; therefore, most patients in our study cohort were not in the acute stage of hemorrhage. Conservative treatment is determined on a basis of shared decision-making between physicians and patients and their family members. Provided with the rarity of disease, there was no specific treatment protocol established for these patients. Patients with ischemic symptoms as the initial presentation, pseudo-MMD, and moyamoya syndrome caused by other systemic diseases were excluded.

### Follow-Up Methods

Baseline clinical characteristics and imaging data were reviewed, including age, sex, risk factors (hypertension, family history of MMD, smoking, drinking, and coexisting intracranial aneurysms), disease stage based on DSA review, and types of hemorrhage (intracerebral hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage). All patients were solicited for annual follow-up visits in outpatient clinic. At each visit, brain CT angiography or magnetic resonance angiography was performed to evaluate cerebral vessels. In addition, brain CT scans were performed when patients experienced a recurrent hemorrhage. Overall, all patients had completed annual follow-up visits in outpatient clinic at the first 3 years. For patients who were unavailable for in-person interviews, we attempted to obtain basic clinical information over the phone for the assessment of onset of rebleeding, ischemic events, and survival status. The time interval from the initial episode to rebleed, site and treatment of recurrent hemorrhage were investigated. The following items constitute primary end points: (1) patient's death from recurrent bleeding or other medical cause and (2) patients who received bypass surgery. Clinical functional outcome after hemorrhage was recorded using the modified Rankin scale.

### Data Analysis

All analyses were conducted using IBM SPSS statistical software (version 19.0). The average annual rebleeding rate was calculated by dividing the number of recurrent hemorrhage events from the initial episode by patient-years. Logistic regression was used to generate odds ratios (ORs) and 95% CIs. Cumulative risk of rebleeding and survival curves were estimated by the Kaplan-Meier product-limit method. Log-rank test statistics were used to determine whether Kaplan-Meier transition curves differed among subgroups. A logistic regression model was built to identify predictors of rebleeding. Cox proportional hazards models were used to calculate multivariate hazard ratios for survival. The primary end points were any deaths from MMD, including lethal hemorrhagic stroke, cerebral infarction, and other fatal events. Patients who were alive at the end of the follow-up period, lost to follow-up, and deaths from other disease were considered censoring events. Information on variables was collected before follow-up and included age (continuous variable), sex, types of hemorrhage, coexisting with intracranial aneurysms, cigarette-smoking status or alcohol consumption, a family history of MMD, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or use of antihypertensive medication), DSA stage, and characteristics of brain CT perfusion. A 2-tailed *P* value <0.05 was considered statistically significant.

## Results

### Patient Characteristics

The final cohort consisted of 128 patients. Baseline presentation and characteristics of the patient cohort are presented in Table 1. The mean age of the patients at the time of the first bleeding episode was 34.5±9.7 years (range, 8–61 years), and 95% were adult patients. The female-to-male ratio was 2:1. Intraventricular hemorrhage and intracerebral hemorrhage were the most frequent presentations observed on CT scans, accounting for 43.0% and 28.9%, respectively. The DSA stage of patients mostly were

**Table 1. Patient Demographics and Baseline Characteristics Grouped by Rebleeding**

| Demographics | All Patients (N=128) | No Rebleeding (n=81) | Rebleeding (n=47) | *P* Value |
|---|---|---|---|---|
| Women, % | 86 (67) | 50 (61) | 36 (76) | 0.08 |
| Age, y; mean±SD | 34.5±9.7 | 35.0±9.7 | 33.7±9.9 | 0.47 |
| History of risk factors, % | | | | |
| Family MMD | 9 (7.0) | 5 (6.1) | 4 (8.5) | 0.88 |
| Hypertension | 15 (11.7) | 7 (8.6) | 8 (17.0) | 0.15 |
| Aneurysm | 14 (10.9) | 10 (12.3) | 4 (8.5) | 0.70 |
| Smoking | 16 (12.5) | 6 (7.4) | 10 (21.2) | 0.02 |
| Drinking | 10 (7.8) | 3 (3.7) | 7 (14.8) | 0.03 |
| Types of hemorrhage, % | | | | |
| ICH | 37 (28.9) | 20 (24.7) | 17 (36.1) | 0.16 |
| IVH with ICH | 22 (17.1) | 15 (18.5) | 7 (14.8) | 0.60 |
| IVH | 55 (43.0) | 38 (46.9) | 17 (36.1) | 0.23 |
| SAH | 14 (10.9) | 8 (9.9) | 6 (12.7) | 0.61 |
| DSA stage, % | | | | |
| I | 6 (4.6) | 4 (4.9) | 2 (4.2) | 0.81 |
| II | 15 (11.7) | 10 (12.3) | 5 (10.6) | 0.77 |
| III | 42 (32.8) | 26 (32.0) | 16 (34.0) | 0.82 |
| IV | 40 (31.2) | 23 (28.3) | 17 (36.1) | 0.36 |
| V | 23 (17.9) | 16 (19.7) | 7 (14.8) | 0.49 |
| VI | 2 (1.5) | 2 (2.4) | 0 | … |
| CT perfusion, % | 117 | 77 | 40 | … |
| Normal | 14 (11.9) | 8 (10.3) | 6 (15.0) | 0.46 |
| CBF↓ | 38 (32.4) | 20 (25.9) | 18 (45.0) | 0.03 |
| MTT↑ | 103 (88.0) | 69 (89.6) | 34 (85.0) | 0.46 |

CBF indicates cerebral flood flow; CT, computed tomography; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MMD, moyamoya disease; MTT, mean transit time; and SAH, subarachnoid hemorrhage.

stage III and stage IV according to Suzuki classification. One-hundred seventeen patients underwent CT perfusion. Please note, the measure of CT perfusion was completed within 3 days after admission, and all patients were not in the acute stage of cerebral hemorrhage. Of them, 38 (32.4%) patients had reduction of regional cerebral blood flow (rCBF), and 103 (88%) patients had prolonged mean transit time.

### Incidence of Recurrent Stroke

The median follow-up time was 10.1 (1–27) years. For a follow-up total of 1300.7 patient-years, 51 (39.8%) patients experienced recurrent stroke. Of them, 59 rebleeding events occurred in 47 patients (36.7%), yielding an annual incidence of rebleeding of 4.5%. Nineteen percent (9 of 47) of patients died because of rebleeding, whereas 35% (12 of 47) patients had severe disability (modified Rankin scale score of ≥3). None of the patients died from other diseases during follow-up period. The mean age of the 47 patients at the first rebleeding was 40±10 years (range, 13–61 years). Nine patients experienced multiple rebleeding events, which includes 7 patients having 2 events, 1 patient having 3 events, and 1 having 4 events. The interval from the first hemorrhage to the episode of rebleeding ranged from 0.1 to 20 years (mean, 6.6 years). Of them, 8 patients (17.0%) experienced rebleeding at the first year after the initial bleeding, 14 patients (29.7%) experienced rebleeding at 2 to 5 years, 14 patients (29.7%) experienced rebleeding at 6 to 10 years, and 11 patients (23.4%) experienced rebleeding >10 years after the first hemorrhage. The time interval distributions of 59 episodes of rebleeding are shown in Figure 1. The cumulative risk of rebleeding was 7.8% at 5 years, 22.6% at 10 years, and 35.9% at 15 years. Kaplan-Meier curves for rebleeding-free survival and given baseline characteristics are shown in Figures 2 and 3. Only 4 (3.1%) patients experienced ischemic stroke, yielding an average annual incidence of 0.3%.

### Risk Factors Associated With Rebleeding and Mortality

Univariable and mutivariable ORs for the risk factors of rebleeding are shown in Table 2. Univariate analysis showed

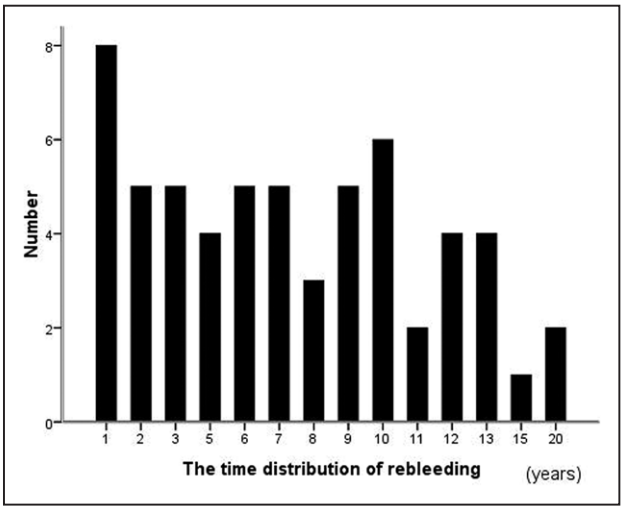


**Figure 1.** The distribution of the time interval from initial hemorrhage to rebleeding (years).

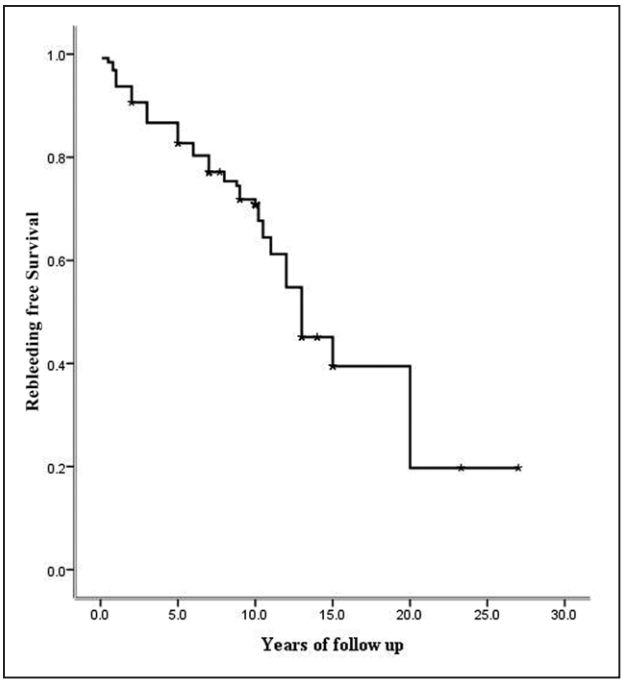


**Figure 2.** Kaplan-Meier curve for cumulative rates of rebleeding for all patients.

that decreased rCBF (OR, 2.33; 95% CI, 1.04–5.21; *P*=0.03), smoking (OR, 3.37; 95% CI, 1.14–10.00; *P*=0.02), and drinking (OR, 4.55; 95% CI, 1.11–18.54; *P*=0.03) were associated with rebleeding. However, multivariate analysis showed only smoking (OR, 4.85; 95% CI, 1.02–23.00; *P*=0.04) was associated with a significantly increased risk of rebleeding, and drinking (OR, 6.02; 95% CI, 0.95–37.80; *P*=0.05) showed a trend toward significance. Age, types of the initial bleeding, DSA stage, hypertension, family history of MMD, and coexisting intracranial aneurysms were not associated with any increased risk of rebleeding in analysis (*P*>0.05). Table 3 provided the associations of risk factors with mortality. Subjects with rebleeding had an 11.04-fold risk of death in comparison with those without rebleeding (hazard ratio, 11.04; 95% CI, 1.30–93.67; *P*=0.02). Multivariate analysis showed sex was associated with mortality (*P*<0.01), although there was no significant difference in univariate analysis (*P*=0.32). It should be noted that there was no significant difference between men and women if removed the impact of rebleeding in the Cox regression analysis (*P*=0.08). The Kaplan-Meier curve for survival for the entire cohort is shown in Figure I in the online-only Data Supplement. The mortality in patients with hypertension was 26.6% (4/15), which was much higher than the mortality (4.4%, 4/113) in patients without hypertension. Cox model and Kaplan-Meier analysis showed that hypertension was an independent risk factor for death (hazard ratio, 4.1; 95% CI, 1.07–16.87; *P*=0.04; Table 3; Figure I in the online-only Data Supplement).

## Discussion

The current goal of treatment for hemorrhagic MMD is to decrease mortality and preserve neurological function by preventing recurrent intracranial hemorrhages. Therefore,

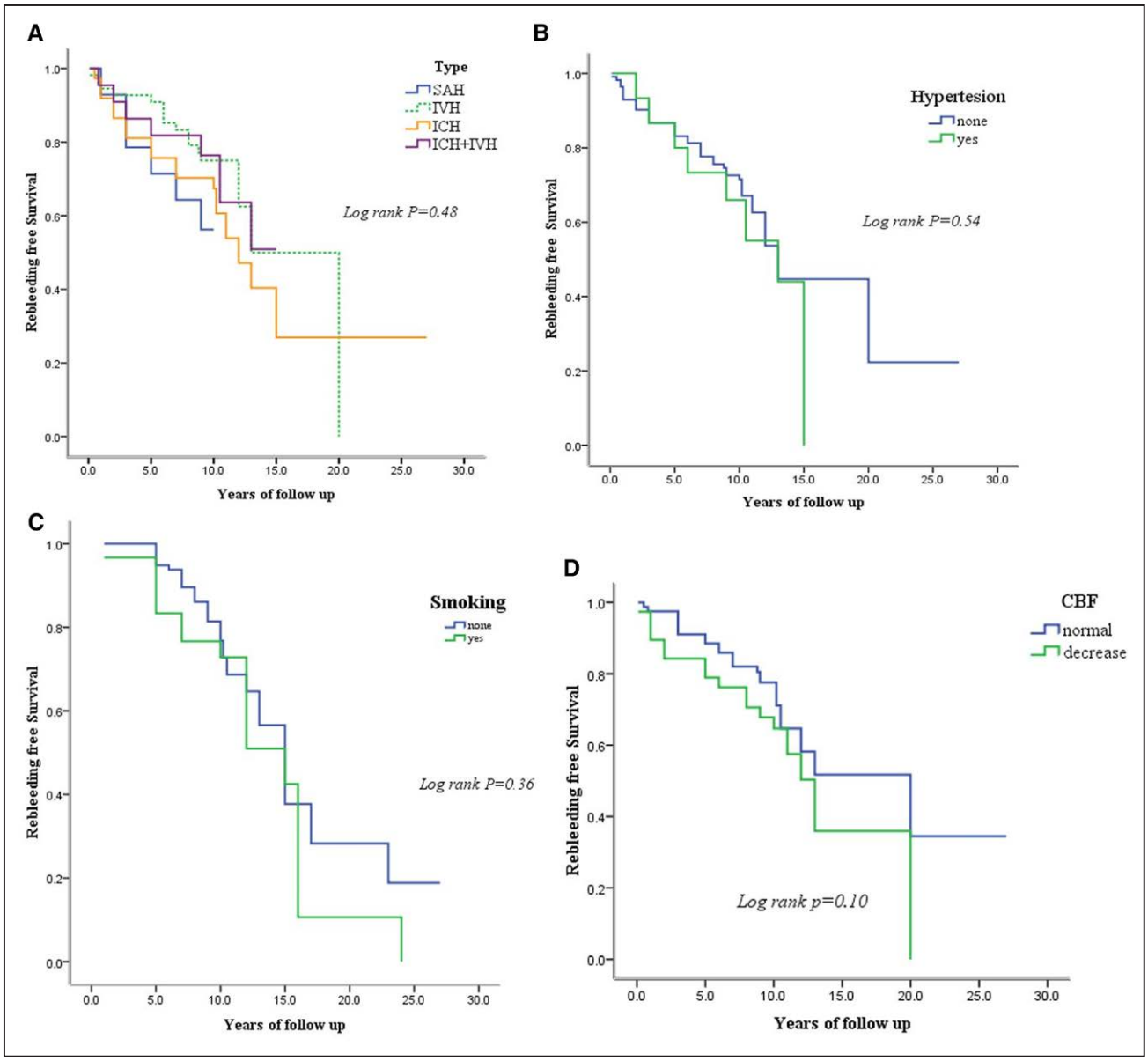


**Figure 3.** Kaplan-Meier curves showing cumulative rates of rebleeding in relation to background factors: (**A**) types of the first hemorrhage, (**B**) hypertension, (**C**) smoking, and (**D**) decreasing of cerebral blood flow at the beginning of follow-up. ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.

understanding the natural history of hemorrhagic MMD in respect to the risk of rebleeding is crucial. However, given the rarity of this disease, existing knowledge on the natural history of hemorrhagic MMD is limited. In current study, we followed 128 patients with hemorrhagic MMD who were treated conservatively through a relatively long follow-up period. As shown in results, rebleeding occurs in ≈40% of our study cohort. Our findings suggest that the natural history of hemorrhagic MMD remains dynamic, and long-term follow-up is needed to fully appreciate the risk of rebleeding.

Rebleeding is the main cause of mortality in hemorrhagic MMD. There is considerable concern for high risk of recurrent hemorrhages in these patients given the exposure of prior hemorrhages. In this study, 47 patients (36.7%) underwent rebleeding events during follow-up, and 9 died as a result. The frequency of rebleeding is within the range (16%–66%) of previous studies.[3–6] Our data also suggest that rebleeding is the most important factor associated with poor prognosis in patients with hemorrhagic MMD.

Previous studies have demonstrated a widely variable range of rebleeding risk. One reason for this variation might be related to the random effects associated with rare events in studies that only have a short-term follow-up, as it often requires long-term follow-up to facilitate observation of such events. Interestingly, Kobayashi et al[3] reported that there was no difference in rebleeding rate during the first 5 years and the last 5 years for MMD patients with hemorrhagic presentation. On the contrary, Morioka et al[4] published the results of 12 years of follow-up in a cohort of 36 patients with hemorrhagic MMD and found there was a higher risk of rebleeding in the first 6 years after initial hemorrhage in patients aged >35 years. In this study, 8 rebleeding events occurred within the

**Table 2. Logistic Regression Analysis for Risk Factors of Rebleeding**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Covariate | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Sex | 2.02 (0.77–2.99) | 0.08 | 2.33 (0.86–6.29) | 0.09 |
| Age, y | 1.05 (0.71–1.54) | 0.79 | 0.45 (0.14–1.46) | 0.18 |
| Type of bleeding | 0.90 (0.64–1.26) | 0.55 | 1.98 (0.55–1.53) | 0.75 |
| DSA stage | 1.13 (0.86–1.47) | 0.35 | 0.95 (0.61–1.48) | 0.85 |
| Hypertension | 0.46 (0.15–1.36) | 0.16 | 2.33 (0.53–10.09) | 0.25 |
| Family history | 0.82 (0.29–2.33) | 0.72 | 1.84 (0.35–9.47) | 0.46 |
| Smoking | 3.37 (1.14–10.00) | 0.02 | 4.85 (1.02–23.00) | 0.04 |
| Drinking | 4.55 (1.11–18.54) | 0.03 | 6.02 (0.95–37.80) | 0.05 |
| Aneurysm | 0.66 (0.19–2.13) | 0.50 | 0.40 (0.08–1.84) | 0.24 |
| rCBF | 2.33 (1.04–5.21) | 0.03 | 0.44 (0.08–2.51) | 0.36 |
| MTT | 0.65 (0.21–2.04) | 0.46 | 3.18 (0.57–17.66) | 0.18 |

DSA indicates digital subtraction angiography; MTT, mean transit time; OR, odds ratio; and rCBF, regional cerebral blood flow.

first year, and 6 rebleeding events occurred at the tenth year after the first hemorrhage (Figure 1). The number of patients with recurrent hemorrhages did not decrease along with extended follow-up time. Therefore, based on this observation, we recommend at least 10 years of follow-up to fully appreciate the risk of recurrent hemorrhage in MMD patients with hemorrhagic presentations. Accordingly, it may be extrapolated that hemorrhagic MMD patients who were treated surgically will also need similar length of follow-up to ascertain treatment effect on hemorrhagic risk.

The exact mechanism for hemorrhage in MMD has not been fully elucidated. Previous studies have revealed that the rupture of microaneurysm and moyamoya vessels were related to the hemorrhagic presentation in patients with MMD[11–13]; however, whether microaneurysm is one of the risk factors of rebleeding remains uncertain. Iwama et al[14] analyzed 15 patients who experienced rebleeding events during follow-up, and 4 of these cases were found to have associated cerebral aneurysms. In contrast, a recent study found no relationship between rebleeding and visible aneurysms on angiography.[3] In this series, 14 patients were identified with ruptured aneurysms on angiography at first bleeding, and 4 of them experienced rebleeding. Univariable analysis revealed that the presence of aneurysms on angiography was not a significant predictor of subsequent rebleeding. Furthermore, most patients with hemorrhagic MMD present with intraventricular hemorrhage instead of subarachnoid hemorrhage, which does not represent the typical presentation of a ruptured aneurysm. Additionally, our study also revealed inconsistency between the first bleeding site and rebleeding site, which indicated that the rebleeding is unlikely to result from a single lesion. These results suggested that despite a risk factor for hemorrhagic

**Table 3. Cox Regression Analysis for Time to Death as Outcome**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Covariate | Hazard Ratio (95% CI) | *P* Value | Hazard Ratio (95% CI) | *P* Value |
| Sex | 0.51 (0.13–1.93) | 0.32 | 0.08 (0.004–0.48) | <0.01 |
| Age, y | 1.10 (0.20–6.00) | 0.29 | 1.13 (0.85–1.50) | 0.39 |
| Type of bleeding | 1.72 (0.75–3.93) | 0.19 | 2.48 (0.97–6.29) | 0.05 |
| DSA stage | 0.62 (0.33–1.17) | 0.14 | 0.62 (0.22–1.75) | 0.37 |
| Hypertension | 5.29 (1.27–21.82) | 0.02 | 4.16 (1.07–16.87) | 0.04 |
| Family history | 1.99 (0.41–9.91) | 0.39 | 1.80 (0.22–14.48) | 0.57 |
| Smoking | 0.48 (0.05–3.98) | 0.49 | 0.83 (0.07–9.98) | 0.88 |
| Drinking | 0.93 (0.11–7.69) | 0.95 | 1.51 (0.26–8.80) | 0.64 |
| Aneurysm | 0.98 (0.12–8.06) | 0.98 | 0.93 (0.09–9.08) | 0.95 |
| rCBF | 0.52 (0.10–2.68) | 0.44 | 0.51 (0.08–3.03) | 0.46 |
| MTT | 1.49 (0.17–12.47) | 0.71 | 1.40 (0.15–12.70) | 0.76 |
| Rebleeding | 10.76 (1.29–89.33) | 0.02 | 11.04 (1.30–93.67) | 0.02 |

DSA indicates digital subtraction angiography; MTT, mean transit time; and rCBF, regional cerebral blood flow.

presentation, the occurrence of rebleeding might not be attributed to the presence of microaneurysms. However, it should be noted that some microaneurysms may not be detected by DSA; therefore, for patients with subarachnoid hemorrhage, especially for those whose rebleeding site suggested a typical subarachnoid hemorrhage, a meticulous search for the potential aneurysms is still warranted.

The determination of the rebleeding risk is essential to provide information for appropriate management for hemorrhagic MMD. At present, multiple factors were found to be involved in the increased risk of rebleeding in hemorrhagic MMD. Kikuta et al[15] reported the presence of asymptomatic microbleeds on magnetic resonance imaging to be an independent predictor of rebleeding. Takahashi et al[16] found that patients with posterior-type hemorrhage were at higher risk of rebleeding. Recently, Kim et al[6] found that the presence of intraventricular hemorrhage was a significant risk factor for recurrent hemorrhage. In this study, we found that smoking was an important risk factor for rebleeding. Cigarette smoking has already been acknowledged as a risk factor for ischemic and hemorrhagic stroke.[17,18] Recent study also found that smoking was a risk factor for rupture of aneurysm.[19] In addition, smoking may enhance aneurysm formation, while the rupture of aneurysm was one of the main causes of bleeding among patients with MMD.[20]

Furthermore, our CT perfusion study found that most patients have abnormal cerebral perfusion, which was mainly marked by prolonged mean transit time. Interestingly, only 32.4% of patients experience decreased rCBF, yet nearly half of them had recurrent intracranial hemorrhage, and univariate analysis confirmed the significance of association between decreased rCBF and increased risk of rebleeding (OR, 2.33; $P$=0.03). However, multivariate analysis showed no significant. Usually, the decreased rCBF can promote collateral circulation compensation, while ruptured collateral vessels were important causes of bleeding.[6,14] Our findings coincide with those of Funaki et al[21] who claimed that choroidal anastomosis was associated with recurrent posterior hemorrhage.

There is an additional question of whether hypertension is a risk factor for rebleeding in patients with hemorrhagic MMD. Despite confirmation of hypertension as a major cause of spontaneous intracerebral hemorrhage,[22,23] recent studies failed to establish association between hypertension and increased risk of bleeding or rebleeding in MMD.[4,5] In current study, only 11.7% of the patients had hypertension, and we have shown that hypertension was not an independent risk factor for rebleeding ($P$=0.25); however, the mortality of patients with hypertension was higher than that of patients without hypertension ($P$=0.04). Hemorrhagic MMD usually had chronic cerebral hypoperfusion,[24–26] whereas systemic blood pressure is critical to maintain adequate cerebral blood flow. Therefore, despite the need for preventing an ischemic stroke, we advise that blood pressure control should be more liberalized in these patients to decrease mortality when rebleeding events occurred.

There are study limitations that need to be addressed for accurate interpretation of our data. In this study, only patients treated conservatively were included, and this introduced selection bias as patients with more severe MMD disease might have been treated surgically and were excluded; therefore, the conclusion drawn may not be generalizable to all patients with MMD. Although brain CT or magnetic resonance imaging scans have been performed at the point of new symptom manifestations during follow-up, DSA was not routinely performed, and the data are, therefore, not available in some of the patients; thus a limited radiographic evidence of disease progression must be noted. In addition, similar to all retrospective studies, this is a single-center study over a time span of ≈30 years, and not all patients were followed up on a regular basis. This may render the results prone to potential attrition biases.

In summary, the natural history of rebleeding with hemorrhagic MMD is high and may progress dynamically during a long-term follow-up, with rebleeding events still being common even >10 years after the first bleeding. Our data support smoking as an important preventable rebleeding risk factor. Rebleeding was strongly associated with increased mortality, and hypertension was also associated with mortality. Cigarette smoking and blood pressure control are modifiable risk factors and should be advocated in patients. Sex, types of first bleeding, DSA stage, and associated aneurysm were not significantly associated with increased risk of rebleeding.

## Acknowledgments

Drs Kang and Liu designed the study, drafted the manuscript, performed data collection and data analysis, and contributed to the discussion. Dr D. Zhang designed the study, contributed to the discussion, and edited the manuscript. Drs Wang and Y. Zhang contributed to the discussion and edited the manuscript. Drs Q. Zhang and Yang contributed to the discussion. Dr Zhao designed the study, edited the manuscript, and contributed to the discussion.

## Sources of Funding

This study was supported by the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (grants 2006BAI01A13 and 2015BAI12B04), Beijing Municipal Organization Department Talents Project (grant 2015000021469G219), Beijing Municipal ST Commission (grant D161100003816005), and National Natural Science Foundation of China (grant 81701137).

## Disclosures

None.

## References

1. Kuriyama S, Kusaka Y, Fujimura M, Wakai K, Tamakoshi A, Hashimoto S, et al. Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. *Stroke*. 2008;39:42–47. doi: 10.1161/STROKEAHA.107.490714
2. Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, et al; JAM Trial Investigators. Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. *Stroke*. 2014;45:1415–1421. doi: 10.1161/STROKEAHA.113.004386
3. Kobayashi E, Saeki N, Oishi H, Hirai S, Yamaura A. Long-term natural history of hemorrhagic moyamoya disease in 42 patients. *J Neurosurg*. 2000;93:976–980. doi: 10.3171/jns.2000.93.6.0976
4. Morioka M, Hamada J, Todaka T, Yano S, Kai Y, Ushio Y. High-risk age for rebleeding in patients with hemorrhagic moyamoya disease: long-term follow-up study. *Neurosurgery*. 2003;52:1049–1054; discussion 1054.

5. Yoshida Y, Yoshimoto T, Shirane R, Sakurai Y. Clinical course, surgical management, and long-term outcome of moyamoya patients with rebleeding after an episode of intracerebral hemorrhage: an extensive follow-up study. *Stroke*. 1999;30:2272–2276.
6. Kim KM, Kim JE, Cho WS, Kang HS, Son YJ, Han MH, et al. Natural history and risk factor of recurrent hemorrhage in hemorrhagic adult moyamoya disease. *Neurosurgery*. 2017;81:289–296. doi: 10.1093/neuros/nyw179
7. Fujii K, Ikezaki K, Irikura K, Miyasaka Y, Fukui M. The efficacy of bypass surgery for the patients with hemorrhagic moyamoya disease. *Clin Neurol Neurosurg*. 1997;99(suppl 2):S194–S195.
8. Kim T, Oh CW, Bang JS, Kim JE, Cho WS. Moyamoya disease: treatment and outcomes. *J Stroke*. 2016;18:21–30. doi: 10.5853/jos.2015.01739
9. Kleinloog R, Regli L, Rinkel GJ, Klijn CJ. Regional differences in incidence and patient characteristics of moyamoya disease: a systematic review. *J Neurol Neurosurg Psychiatry*. 2012;83:531–536. doi: 10.1136/jnnp-2011-301387
10. Bao XY, Yang BX, Duan L, Yang WZ, Sun WJ, Zhang ZS, et al. Clinical features, surgical treatment and long-term outcome in adult patients with moyamoya disease in China. *Cerebrovasc Dis*. 2012;34:305–313. doi: 10.1159/000343225
11. Kim JS. Moyamoya disease: epidemiology, clinical features, and diagnosis. *J Stroke*. 2016;18: 2–11. doi: 10.5853/jos.2015.01627
12. Suzuki J, Takaku A, Asahi M. Evaluation of a group of disorders showing an abnormal vascular network at the base of the brain with a high incidence among the Japanese 2 follow-up studies by cerebral angiography. *No To Shinkei*. 1996:18:897–908.
13. Liu X, Zhang D, Shuo W, Zhao Y, Wang R, Zhao J. Long term outcome after conservative and surgical treatment of haemorrhagic moyamoya disease. *J Neurol Neurosurg Psychiatry*. 2013;84:258–265. doi: 10.1136/jnnp-2012-302236
14. Iwama T, Morimoto M, Hashimoto N, Goto Y, Todaka T, Sawada M. Mechanism of intracranial rebleeding in moyamoya disease. *Clin Neurol Neurosurg*. 1997;99(suppl 2):187–190.
15. Kikuta K, Takagi Y, Nozaki K, Sawamoto N, Fukuyama H, Hashimoto N. The presence of multiple microbleeds as a predictor of subsequent cerebral hemorrhage in patients with moyamoya disease. *Neurosurgery*. 2008;62:104–111, discussion 111. doi: 10.1227/01.NEU.0000311067.41239.E6
16. Takahashi JC, Funaki T, Houkin K, Inoue T, Ogasawara K, Nakagawara J, et al; JAM Trial Investigators. Significance of the hemorrhagic site for recurrent bleeding: prespecified analysis in the Japan Adult Moyamoya Trial. *Stroke*. 2016;47:37–43. doi: 10.1161/STROKEAHA.115.010819
17. Yamagishi K, Iso H, Kitamura A, Sankai T, Tanigawa T, Naito Y, et al. Smoking raises the risk of total and ischemic strokes in hypertensive men. *Hypertens Res*. 2003;26:209–217.
18. Nordahl H, Osler M, Frederiksen BL, Andersen I, Prescott E, Overvad K, et al. Combined effects of socioeconomic position, smoking, and hypertension on risk of ischemic and hemorrhagic stroke. *Stroke*. 2014;45:2582–2587. doi: 10.1161/STROKEAHA.114.005252
19. Backes D, Rinkel GJ, Laban KG, Algra A, Vergouwen MD. Patient- and aneurysm-specific risk factors for intracranial aneurysm growth: a systematic review and meta-analysis. *Stroke*. 2016;47:951–957. doi: 10.1161/STROKEAHA.115.012162
20. Jabbarli R, Dinger TF, Darkwah Oppong M, Pierscianek D, Dammann P, Wrede KH, et al. Risk factors for and clinical consequences of multiple intracranial aneurysms: a systematic review and meta-analysis. *Stroke*. 2018;49:848–855. doi: 10.1161/STROKEAHA.117.020342
21. Funaki T, Takahashi JC, Houkin K, Kuroda S, Takeuchi S, Fujimura M, et al. Angiographic features of hemorrhagic moyamoya disease with high recurrence risk: a supplementary analysis of the Japan Adult Moyamoya Trial. *J Neurosurg*. 2018;128:777–784. doi: 10.3171/2016.11.JNS161650
22. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. doi: 10.1056/NEJMoa1603460
23. Lattanzi S, Silvestrini M. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology*. 2015;85:557–558. doi: 10.1212/01.wnl.0000470918.40985.d0
24. Jo KI, Kim MS, Yeon JY, Kim JS, Hong SC. Recurrent bleeding in hemorrhagic moyamoya disease: prognostic implications of the perfusion status. *J Korean Neurosurg Soc*. 2016;59:117–121. doi: 10.3340/jkns.2016.59.2.117
25. Nariai T, Matsushima Y, Imae S, Tanaka Y, Ishii K, Senda M, et al. Severe haemodynamic stress in selected subtypes of patients with moyamoya disease: a positron emission tomography study. *J Neurol Neurosurg Psychiatry*. 2005;76:663–669. doi: 10.1136/jnnp.2003.025049
26. Derdeyn CP, Zipfel GJ, Zazulia AR, Davis PH, Prabhakaran S, Ivan CS, et al. Baseline hemodynamic impairment and future stroke risk in adult idiopathic moyamoya phenomenon: results of a prospective natural history study. *Stroke*. 2017;48:894–899. doi: 10.1161/STROKEAHA.116.014538