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ORIGINAL RESEARCH

Risk Factors Influencing Disease Onset and Surgical Outcomes in Moyamoya Disease

Xuhua Cao[1], Liyi Wang[2], Zhizhao Ma[1], Wang Xi[1], Yanan Li[1], Shiyuan Zhang[1], Tao Zhang[1], Guozhu Sun[1]

[1]Department of Neurosurgery, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050000, People's Republic of China; [2]Department of Hospital Infection-Control, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050000, People's Republic of China

Correspondence: Guozhu Sun, Department of Neurosurgery, The Second Hospital of Hebei Medical University, No. 215 of Heping West Road, Xinhua District, Shijiazhuang, Hebei, 050000, People's Republic of China, Tel +86 13930485399, Email guozhusunsgz01@126.com

Objective: The aim of this study is to explore the risk factors associated with the onset and clinical progression of moyamoya disease (MMD), as well as the outcomes of combined revascularization surgery (RS).

Methods: A retrospective analysis was performed on the medical records of 226 individuals diagnosed with MMD who underwent combined *RS* at the Department of Neurosurgery in 2022. Binary logistic regression analysis was used to identify risk factors related to the occurrence of cerebral ischemia (CIS), postoperative complications, lateralization of MMD involvement, progression from unilateral to bilateral MMD, and disease severity in cases presenting with CIS. Surgical effectiveness was assessed during follow-up.

Results: Hypertension (odds ratio [OR] = 1.816, 95% confidence interval [CI]: 1.031–3.197) and higher preoperative modified Rankin Scale scores (OR = 5.164, 95% CI: 1.145–23.295) were identified as independent risk factors for CIS. Male sex (OR = 4.219, 95% CI: 1.470–12.195) and age ≥ 50 years (OR = 3.979, 95% CI: 1.494–10.598) were independent predictors of postoperative complications following RS. No independent factors were associated with the affected side or bilateral progression of MMD (P > 0.05). Disease severity in patients with CIS was influenced by both Suzuki staging and age. The effective rate of *RS* at 3–6 months postoperatively was 96.46%.

Conclusion: Early intervention is recommended, particularly for male patients and those with modifiable risk factors such as hypertension. *RS* should ideally be performed during the early stages of Suzuki classification and before the age of 50 to reduce the risk of postoperative complications. For patients with advanced Suzuki stage or aged ≥ 50 years, comprehensive perioperative risk assessments and tailored postoperative management strategies are essential to ensure optimal surgical outcomes.

Keywords: affected side, cerebral ischemia, combined revascularization surgery, moyamoya disease, mRS score, Suzuki staging

Introduction

Moyamoya disease (MMD) was first described by Takeuchi and Shimizu in Japan in 1957. It is a cerebrovascular disorder of unknown etiology, characterized by progressive stenosis or occlusion of the distal segments of the bilateral internal carotid arteries, the anterior cerebral artery, and the proximal portion of the middle cerebral artery. These vascular changes lead to the development of an abnormal collateral network at the base of the brain. The angiographic appearance of this network resembles a "puff of smoke", which is reflected in the term "moyamoya", derived from a Japanese expression describing this visual phenomenon.[1]

Advancements in imaging technology have facilitated the detection of an increasing number of asymptomatic cases through magnetic resonance angiography during routine health screenings. China is among the countries with a high incidence of MMD.[2] The estimated annual incidence in China is approximately 1.14 per 100,000 individuals (95% CI: 1.12–1.16), with bimodal peaks in onset observed at approximately 5–13 years and 35–49 years of age.[3,4] A family history is reported in approximately 5.2% of cases.[5,6] Clinical manifestations may include permanent neurological deficits such as hemiplegia, seizures, and cognitive impairments, including deficits in memory and calculation

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abilities.[7] In severe cases, patients may experience loss of independent functional status or mortality, leading to significant psychosocial and financial burden and increased use of healthcare resources.

Advancements in imaging and genetics further inform MMD management. For instance, the spatial coefficient of variation (SCV) of arterial spin labeling (ASL) MRI— a marker of cerebral perfusion homogeneity—has been shown to predict revascularization surgery (RS) outcomes, aiding preoperative risk stratification and surgical decision-making.[8] Meanwhile, genetic studies highlight the ring finger protein 213 (RNF213) gene as a key MMD susceptibility factor, especially in East Asians; its mutations correlate with higher disease risk, more aggressive progression, and increased cerebrovascular event rates, complementing our understanding of MMD etiology beyond family history.[9]

At present, surgical intervention remains the only treatment modality with established efficacy. Available surgical options include direct, indirect, and combined revascularization techniques. These procedures are designed to improve cerebral perfusion, alleviate ischemic symptoms, and reduce the risk of recurrent cerebrovascular events.[10,11] Given these considerations, the investigation of risk factors associated with MMD, and the evaluation of revascularization surgery (RS) outcomes is of considerable clinical relevance. However, there has been limited research exploring the factors influencing the affected hemisphere, the laterality of surgical intervention, and the association between Suzuki stage and *RS* outcomes. The present study was conducted to address these gaps and to provide further insights into the risk factors associated with MMD.

Study Population

The study population comprised of patients diagnosed with MMD who were admitted to the Department of Neurosurgery at the Second Hospital of Hebei Medical University in 2022. Ethical approval was obtained from the Ethics Committee of the Second Hospital of Hebei Medical University (Ethics No.: 2022-R057). The study was conducted as part of the Medical Science Research Project of Hebei Province in 2023 (20230439).

Data access and storage complied with strict security protocols. Electronic medical records and imaging data (eg, DSA, MRI) were accessed exclusively through the hospital's password-protected, role-based database—only authorized members of the research team (principal investigator, coinvestigators, and trained research assistants) had permission to retrieve data, and all access was logged for audit. The anonymized dataset was stored on a secure, encrypted server managed by the hospital's medical informatics department, with no external transmission of raw data permitted.

Inclusion Criteria

(1) Patients aged 5–70 years who were diagnosed with MMD in accordance with the Diagnostic Criteria for MMD (2021 revision) and admitted to the Department of Neurosurgery of the study hospital;[12]
(2) Availability of preoperative digital subtraction angiography (DSA) and magnetic resonance imaging (MRI);
(3) Underwent combined revascularization surgery;
(4) Possessed complete imaging data.

Exclusion Criteria

(1) Patients aged > 70 years and < 5 years;
(2) Patients presenting with massive cerebral ischemia;
(3) Patients with residual unilateral hemiplegia;
(4) Patients with contraindications to DSA;
(5) Patients unable to undergo DSA due to contrast agent allergy;
(6) Patients with newly identified cerebral ischemia on preoperative DSA or MRI;
(7) Pregnant women or others deemed unable to tolerate combined revascularization surgery;
(8) Patients diagnosed with vasculitis;
(9) Patients lacking complete imaging data.

Data Collection

Patients with MMD admitted to the Second Hospital of Hebei Medical University in 2022 were identified for inclusion in this study. Complete pathological data were obtained from the electronic medical records and imaging systems of the hospital. Collected data included demographic data (sex, age, contact details), medical and personal history (including hypertension, diabetes, cerebral hemorrhage, cerebral ischemia, and smoking history), imaging findings, and hospitalization details (admission date, length of hospital stay, duration of bleeding prior to admission, and Glasgow Coma Scale [GCS] score at admission).

For patients who underwent surgical treatment, additional data regarding the surgical procedure and surgical side were collected, along with follow-up data on activities of daily living and the occurrence and timing of recurrent stroke events. Data collection was conducted from February 2022 to February 2023. Follow-up was carried out via telephone between March 2022 and March 2023. During follow-up, patients were asked about their activities of daily living, including mobility, dietary habits, and cognitive function, as well as the occurrence of recurrent stroke events after discharge, including the timing and frequency of such events. Modified Rankin Scale (mRS) and Glasgow Outcome Scale scores were assessed based on follow-up assessments.

Study Methods

Clinical Data Evaluation

Statistical analysis was conducted on the general clinical characteristics and laboratory test results of the enrolled patients. Variables included sex, age, ethnicity, smoking history, history of hypertension, and history of diabetes.

Hypertension was defined according to established diagnostic criteria as having three or more blood pressure readings taken on non-consecutive days presenting a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, self-reported history of hypertension, or current use of antihypertensive medications.

Diabetes was defined based on diagnostic criteria as fasting blood glucose ≥ 7.0 mmol/L, random blood glucose ≥ 11.1 mmol/L, postprandial 2-hour blood glucose ≥ 11.1 mmol/L, self-reported diabetes, or current use of hypoglycemic agents.

Smoking history was defined as the consumption of at least one cigarette per day during the six months preceding disease onset.

The severity of cerebral ischemia was assessed using the mRS score.

MRI Evaluation

All enrolled patients underwent cranial MRI following hospital admission. Acute cerebral ischemia was identified by hyperintensity on diffusion-weighted imaging (DWI), whereas old cerebral ischemia was characterized by hypointensity on DWI. Each cranial MRI was independently assessed by two neurosurgeons to confirm the presence of cerebral ischemia.

DSA and Suzuki Staging

All enrolled patients underwent whole-brain DSA to obtain complete vascular imaging. The intracranial vascular status of each patient was independently assessed by two neurosurgical interventional physicians using the Suzuki staging system. In cases of discrepancy between assessments, a consensus was reached through joint discussion.

DSA-based Suzuki staging was defined as follows:

Stage 1: Narrowing at the bifurcation of the internal carotid artery, with stenosis limited to the bifurcation site.

Stage 2: Emergence of abnormal capillary networks, with the formation of smoke-like vessels and dilation of major cerebral arteries.

Stage 3: Proliferation of abnormal capillary networks, accompanied by decreased blood flow in the anterior cerebral artery and middle cerebral artery.

Stage 4: Thinning of abnormal capillary networks, extending to involve the proximal segment of the posterior cerebral artery.

Stage 5: Reduction of abnormal capillaries, with disappearance of all major intracranial arteries.

Stage 6: Regression of the abnormal vascular network, with cerebral circulation primarily dependent on the external carotid artery system.

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Surgery Name: Combined Revascularization Surgery

Statistical Methods

Data analysis was conducted using SPSS version 26.0 statistical software. Continuous variables were expressed as ($\bar{x}\pm$ s), and categorical variables were expressed as n (%). Comparisons of rates and proportions were performed using the chi-square test. The independent samples *t*-test was applied for comparisons between two means, and analysis of variance was used for comparisons among multiple groups. For data not following a normal distribution, non-parametric tests were applied.

Binary logistic regression analysis was used to identify independent risk factors associated with the onset of MMD. Multivariate ordinal logistic regression analysis was used to determine the primary factors influencing the severity of clinical conditions in patients with cerebral ischemia. A value of $p < 0.05$ was considered statistically significant.

Scoring Scales

All patients underwent an assessment using the GCS at the time of admission, followed by evaluation using both the mRS and GCS during follow-up.

(1) GCS:[13] The GCS is a clinical tool used to assess the level of consciousness based on three parameters: eye opening, verbal response, and motor response. Eye opening: 4 points for spontaneous eye opening; 3 points for eye opening in response to verbal stimuli; 2 points for eye opening in response to pain; 1 point for no eye opening. Verbal response: 5 points for appropriate and oriented verbal response; 4 points for confused speech; 3 points for inappropriate single-word responses; 2 points for incomprehensible sounds; 1 point for no verbal response. Motor response: 6 points for obeying commands; 5 points for purposeful movement to painful stimuli; 4 points for withdrawal from pain; 3 points for abnormal flexion to pain; 2 points for extension to pain; 1 point for no motor response.

The total GCS score, obtained by totaling the scores of the three components, reflects the level of consciousness, with higher scores denoting better neurological function.

(2) mRS:[14] The mRS is used to assess the degree of disability or dependence in daily activities following a stroke. 0: No symptoms. 1: No significant disability despite symptoms; able to perform all usual activities. 2: Slight disability; unable to carry out all previous activities but able to handle personal affairs without assistance. 3: Moderate disability; requiring some help but able to walk unassisted. 4: Moderately severe disability; unable to walk or attend to bodily needs without assistance. 5: Severe disability; bedridden, incontinent, requiring constant nursing care and attention. 6: Death.

Results

General Clinical Data

A retrospective study was conducted on 237 patients diagnosed with MMD in the Department of Neurosurgery from February 2022 to February 2023. From the inclusion and exclusion criteria, 226 patients were ultimately included in the analysis. Among these, 219 patients presented with cerebral ischemia (comprising 4 pediatric and 215 adult cases), and 7 patients presented with cerebral hemorrhage (all adults).

Of the total cohort, 139 patients (61.50%) had a documented history of cerebral ischemia, while 87 patients (38.50%) did not. The mean age of the study population was 47.11 ± 11.58 years. Of the patients, 116 were male. Comorbid conditions included hypertension in 140 patients, diabetes in 66 patients, coronary atherosclerotic heart disease in 2 patients, and a smoking history in 88 patients.

Suzuki staging was distributed as follows: Stage 1 (n = 7), Stage 2 (n = 38), Stage 3 (n = 99), Stage 4 (n = 51), Stage 5 (n = 20), and Stage 6 (n = 11), as detailed in Table 1.

Analysis of Risk Factors for Cerebral Ischemia in Patients with MMD

Patients were categorized into a cerebral ischemia group and a non-cerebral ischemia group based on the presence or absence of cerebral ischemia prior to surgery.

Intergroup comparison demonstrated that the proportion of patients with hypertension was significantly higher in the cerebral ischemia group than in the non-cerebral ischemia group (67.62% vs 52.87%, $\chi^2 = 4.94$, $p = 0.026$). Similarly, the

Table 1 Baseline Data for Each Group

Item			Total Number of Subjects	Grouping by CIS		Grouping by Postoperative Complication		Grouping by Affected side		Grouping by Unilateral/ Bilateral Involvement	
				CIS Group	**Non-CIS Group**	**Complication Group**	**No Complication Group**	**Left Side Group**	**Right Side Group**	**Unilateral Group**	**Bilateral Group**
			n=226	**n=139**	**n=87**	**n=25**	**n=201**	**n=116**	**n=110**	**n=174**	**n=26**
Preoperative	Age		47.11±11.58	48.23±10.97	45.31±12.33	52.96±9.727	46.38±11.599	46.89±12.175	47.34±10.956	47.45±11.88	47.08±10.72
	Sex	Male	116	77	39	19	97	65	51	88	14
		Female	110	62	48	6	104	51	59	86	12
	Preoperative score	mRS score	1.12±0.67	1.22±0.742	0.97±0.493	1.32±0.802	1.10±0.647	1.15±0.636	1.09±0.701	1.21±0.62	0.81±0.74
	Underlying conditions	Hypertension	140	94	46	19	121	72	68	100	20
		Diabetes	66	48	18	12	54	35	31	48	9
		Coronary heart disease	2	1	1	0	2	0	2	2	0
		Cerebral ischemia	139	—	—	20	119	74	65	105	17
		Cerebral hemorrhage	15	—	—	1	14	7	8	11	2
		Myocardial infarction	2	1	1	0	2	0	2	2	0
	Smoking history		87	62	25	19	68	50	0	67	10
	Affected side (unilateral/ bilateral)	Unilateral	174	105	69	20	154	91	83	—	—
		Bilateral	52	34	18	5	47	25	27	—	—
	Affected side (left/ right)	Left	116	74	42	20	96	—	—	91	12
		Right	110	65	45	5	105	—	—	83	14
	Quarter	Q1	36	23	13	3	34	18	18	31	2
		Q2	80	51	29	5	75	42	38	60	7
		Q3	54	34	20	12	42	32	22	33	12
		Q4	56	31	25	5	50	24	32	50	5
	Suzuki staging	Stage 1	7	4	3	0	7	3	4	7	0
		Stage 2	38	20	18	3	35	20	18	33	3
		Stage 3	99	69	30	8	90	52	47	79	9
		Stage 4	51	25	26	7	44	26	25	37	7
		Stage 5	20	13	7	5	15	12	8	15	3
		Stage 6	11	8	3	2	10	3	8	3	4
mRS score	Preoperative	0 point	21	11	10	2	19	8	13	2	16
		1 point	172	100	72	16	156	90	82	147	7
		2 points	20	17	3	4	16	12	8	13	2
		3 points	11	9	2	3	8	5	6	10	1
		4 points	2	2	0	0	2	1	1	2	0
		5 points	0	0	0	0	0	0	0	0	0

(*Continued*)

Table 1 (Continued).

Item			Total Number of Subjects n=226	Grouping by CIS		Grouping by Postoperative Complication		Grouping by Affected side		Grouping by Unilateral/ Bilateral Involvement	
				CIS Group n=139	Non-CIS Group n=87	Complication Group n=25	No Complication Group n=201	Left Side Group n=116	Right Side Group n=110	Unilateral Group n=174	Bilateral Group n=26
Postoperative complications	Postoperative cerebral ischemia	No	215	129	86	—	—	105	110	167	22
		Yes	11	10	1	—	—	11	0	7	4
	Postoperative hyperperfusion	No	217	133	84	—	—	109	108	166	26
		Yes	9	6	3	—	—	7	2	8	0
	Postoperative epilepsy	No	223	137	86	—	—	114	109	171	26
		Yes	3	2	1	—	—	2	1	3	0
	Postoperative complications	No	205	119	82	—	—	96	105	154	22
		Yes	21	20	5	—	—	20	5	20	4
Follow-up 3–6 months after surgery	Surgical effectiveness evaluation	Effective	218	131	87	18	201	109	110	169	24
		Ineffective	8	6	0	7	0	7	0	5	2
Age classification	≥50 years		101	65	36	17	84	55	46	83	9
	<50 years		125	74	51	8	117	61	64	91	17

proportion of patients with a history of smoking was greater in the cerebral ischemia group (44.60% vs 28.73%, χ^2 = 5.691, p = 0.017), as were the incidence rates of postoperative cerebral ischemia (7.19% vs 1.15%, p = 0.034), postoperative complications (14.39% vs 6.10%, χ^2 = 4.061, p = 0.044), and the surgical effectiveness rate at 3–6 months follow-up (94.24% vs 100.00%, p = 0.019). The preoperative mRS score was significantly higher in the cerebral ischemia group compared to the non-cerebral ischemia group (1.22 ± 0.742 vs 0.97 ± 0.493, p = 0.003), and the distribution of preoperative mRS scores differed significantly between the two groups. All noted differences reached statistical significance.

No statistically significant differences were observed between the two groups in terms of age, Suzuki staging, sex, diabetes, coronary heart disease, history of myocardial infarction, unilateral or bilateral involvement, surgical side, or the distribution of surgical quarter (p > 0.05), as presented in Table 1.

A binary logistic regression analysis (method: Backward LR) was conducted using the presence of preoperative cerebral ischemia as the dependent variable, and history of hypertension, smoking history, and preoperative mRS score as covariates. The analysis identified the history of hypertension and preoperative mRS score as independent risk factors for cerebral ischemia in patients with MMD. The presence of hypertension was associated with a 1.816-fold increased risk of cerebral ischemia (95% confidence interval [CI]: 1.031–3.197), and a preoperative mRS score of 2 was associated with a 5.164-fold increased risk compared to a score of 0 (95% CI: 1.145–23.295), as presented in Table 2.

Analysis of Risk Factors for Postoperative Complications After Combined Revascularization Surgery

Patients were categorized into a complication group and a no-complication group based on the presence or absence of postoperative complications.

Intergroup comparison indicated that the proportion of male patients was significantly higher in the complication group compared to the no-complication group (76.00% vs 48.26%, x^2 = 6.849, p = 0.009). Additionally, higher rates of diabetes (48.00% vs 26.86%, x^2 = 4.803, p = 0.028), cerebral ischemia (80.00% vs 59.20%, x^2 = 4.061, p = 0.044), smoking (76.00% vs 33.83%, x^2 = 16.699, p = 0.000), and left-sided surgery (80.00% vs 47.76%, x^2 = 9.25, p = 0.002) were observed in the complication group. Patients in the complication group were also older on average (52.96 ± 9.727 years vs 46.38 ± 11.599 years, t = −2.719, p = 0.007) and had higher Suzuki staging scores (3.80 ± 1.155 vs 3.26 ± 1.083, t = −2.340, p = 0.020). The rate of surgical effectiveness at 3–6 months postoperatively was significantly lower in the complication group compared to the no-complication group (72.00% vs 100.00%, p = 0.000). A statistically significant difference in the distribution of surgical quarters was also noted (p = 0.026).

Table 2 Results of Logistic Regression Models (Backward: LR) for Each Group

Group	Dependent Variable	Independent Influencing Factors	b	Sb	Wald X^2	P	0R	95% CI
History of cerebral ischemia	Grouping by CIS	History of hypertension (Yes vs No)	0.597	0.289	4.27	0.039	1.816	1.031–3.197
		Preoperative mRS score (2 vs 0)	1.642	0.769	4.563	0.033	5.164	1.145–23.295
Postoperative complications	Grouping by postoperative complication	Gender (female vs male)	−1.441	0.538	7.166	0.007	0.237	0.082–0.680
		Age (≥50 years vs <50 years)	1.381	0.5	7.635	0.006	3.979	1.494–10.598
Affected side (unilateral/ bilateral)	Bilateral (bilateral vs unilateral)	Preoperative mRS (1 point vs 0 point)	−5.818	0.848	47.041	0.000	0.003	0.001–0.016
		Preoperative mRS (2 points vs 0 point)	−4.583	1.127	16.539	0.000	0.010	0.001–0.093
		Preoperative mRS (3 points vs 0 point)	−6.559	1.404	21.812	0.000	0.001	0.00009–0.022
mRS score for cerebral ischemia severity	mRS score (2 points vs 0 point)	Age	0.12	0.053	5.173	0.023	1.127	1.017–1.25
	mRS score (3 points vs 0 point)	Age	0.189	0.065	8.409	0.004	1.208	1.063–1.373
	mRS score (2 points vs 1 point)	Suzuki staging 2 vs.6	−3.127	1.514	4.264	0.039	0.044	0.002–0.853
		Suzuki staging 3 vs.6	−2.37	1.144	4.295	0.038	0.093	0.01–0.879
	mRS score (3points vs 1 point)	Age	0.13	0.054	5.863	0.015	1.138	1.025–1.264
		Suzuki staging 3 vs.6	−3.914	1.415	7.649	0.006	0.02	0.001–0.32
		Suzuki staging 5 vs.6	−3.751	1.719	4.759	0.029	0.024	0.001–0.683

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No statistically significant differences were found between the groups with respect to hypertension, coronary heart disease, cerebral hemorrhage, myocardial infarction, unilateral or bilateral involvement, or preoperative mRS scores ($p > 0.05$), as presented in Table 1.

A binary logistic regression analysis (method: Backward LR) was conducted with the presence of postoperative complications as the dependent variable and male sex, diabetes, cerebral ischemia, smoking history, age, Suzuki staging, and surgical quarter as covariates. The analysis identified male sex and age ≥ 50 years as independent risk factors for postoperative complications in patients with MMD. Male patients demonstrated a 4.219-fold higher likelihood of postoperative complications compared to female patients (95% CI: 1.470–12.195), while patients aged ≥ 50 years had a 3.979-fold higher risk compared to those aged < 50 years (95% CI: 1.494–10.598), as presented in Table 2.

Analysis of Factors Associated with Surgical Side Selection in Patients with MMD

Patients were categorized into left-side and right-side groups based on the laterality of the combined revascularization surgery.

Intergroup comparison indicated that the proportion of patients with a history of smoking was significantly higher in the left-side surgery group compared to the right-side group (43.10% vs 0.00%, $x^2 = 60.884$, $p = 0.000$). Additionally, the incidence of postoperative cerebral ischemia (10.48% vs 0.00%, $x^2 = 10.965$, $p = 0.001$), postoperative complications (17.24% vs 4.54%, $x^2 = 9.250$, $p = 0.002$), and surgical failure rate at 3–6 months follow-up (6.03% vs 0.00%, $p = 0.014$) were all significantly higher in the left-side group. These differences were statistically significant.

No significant differences were observed between the two groups with respect to age, Suzuki staging, preoperative mRS score, sex, history of hypertension, diabetes, coronary heart disease, cerebral ischemia, cerebral hemorrhage, myocardial infarction, unilateral or bilateral involvement, surgical quarter distribution, incidence of postoperative hyperperfusion, or postoperative epilepsy ($p > 0.05$), as detailed in Table 1.

A binary logistic regression analysis (method: Backward LR) was performed using the surgical side (left or right) as the dependent variable and smoking history as a covariate. The analysis did not identify any independent risk factors, although all $p < 0.05$, as presented in Table 2.

Analysis of Factors Contributing to Progression from Unilateral to Bilateral MMD

Patients were categorized into bilateral and unilateral groups based on whether MMD was present bilaterally or unilaterally at the time of onset.

Intergroup comparison demonstrated that the incidence of postoperative cerebral ischemia was significantly higher in the bilateral group compared to the unilateral group (15.38% vs 4.02%, $p = 0.039$). The preoperative mRS score was significantly lower in the bilateral group (median: 0.00 [interquartile range: 0.00, 1.00]) compared to the unilateral group (mean: 1.196 ± 0.593; $z = 0.711$, $p = 0.000$). Statistically significant differences were also observed between the two groups in terms of distribution of surgical quarters and Suzuki staging.

No significant differences were found in other clinical or demographic variables ($p > 0.05$), as detailed in Table 1.

A binary logistic regression analysis (method: Backward LR) was conducted using bilateral or unilateral MMD as the dependent variable and Suzuki staging as the covariate. The analysis did not identify any independent factors associated with the progression from unilateral to bilateral MMD, although all $p < 0.05$, as presented in Table 2.

Analysis of Risk Factors Influencing the Severity of Conditions of Patients with MMD and Cerebral Ischemia (Table 3)

Among the 139 patients diagnosed with cerebral ischemia, the distribution of Suzuki stages was as follows: Stage 1 (n = 4), Stage 2 (n = 20), Stage 3 (n = 69), Stage 4 (n = 25), Stage 5 (n = 13), and Stage 6 (n = 8). The distribution of mRS scores were: mRS 0 (n = 11), mRS 1 (n = 100), mRS 2 (n = 17), mRS 3 (n = 19), and mRS 4 (n = 2). The mean age of this cohort was 48.23 ± 10.97 years.

A multivariate unordered logistic regression analysis was conducted with the mRS score as the dependent variable and sex, age, hypertension, diabetes, coronary heart disease, cerebral ischemia, myocardial infarction, smoking history,

Table 3 Basic Data on the Severity of Conditions in Patients with MMD and Cerebral Ischemia

Item		Preoperative mRS Score Number of Cases	0 Point n=11	1 Point n=100	2 Points n=17	3 Points n=9	4 Points n=2
Preoperative basic information	Age classification	≥ 50 years	2	43	10	8	2
		< 50 years	9	57	7	1	0
	Gender	Male	8	52	10	6	1
		Female	2	43	10	8	2
	Underlying conditions	Hypertension	9	64	13	6	2
		Diabetes	3	38	5	2	0
		Coronary heart disease	0	1	0	0	0
		Cerebral ischemia	11	100	17	9	2
		Cerebral hemorrhage	0	2	0	0	0
		Myocardial infarction	0	1	0	0	0
	Smoking history		7	39	8	6	1
	Affected side (unilateral/ bilateral)	Unilateral	0	85	10	8	2
		Bilateral	11	15	7	1	0
	Affected side (left/ right)	Left	3	56	9	5	1
		Right	8	44	8	4	1
	Surgical quarter	Q1	0	18	2	2	1
		Q2	2	34	9	6	0
		Q3	5	22	5	1	1
		Q4	4	1	2	0	0
	Suzuki staging	Stage 1	0	1	3	0	0
		Stage 2	2	17	1	0	0
		Stage 3	5	55	7	2	0
		Stage 4	3	14	3	4	1
		Stage 5	0	10	1	1	1
		Stage 6	1	3	2	2	0
Postoperative complications	Cerebral ischemia	No	10	94	15	8	2
		Yes	1	6	2	1	0
	Hyperperfusion	No	10	96	16	9	2
		Yes	1	4	1	0	0
	Epilepsy	No	11	99	17	8	2
		Yes	0	1	0	1	0
	Postoperative complication	No	9	88	14	6	2
		Yes	2	12	3	3	0
Follow-up 3–6 months after surgery	Surgical effectiveness evaluation	Effective	10	95	16	9	2
		Ineffective	1	5	1	0	0

unilateral or bilateral involvement, surgical side, surgical quarter, and Suzuki staging as covariates. The results indicated that both Suzuki staging and age were independent factors associated with the severity of neurological impairment in patients with MMD and cerebral ischemia (Table 3).

Compared with patients with an mRS score of 0, each additional year of age was associated with a 112.7% increase in the probability of progressing to an mRS score of 1 (95% CI: 1.017–1.250), and a 120.8% increase in the probability of progressing to an mRS score of 2 (95% CI: 1.063–1.373). Compared with those with an mRS score of 1, each additional year of age was associated with a 113.8% increase in the probability of progression to an mRS score of 3 (95% CI: 1.025–1.264).

Patients with Suzuki stage 6 demonstrated a 22.799-fold higher probability of progression to an mRS score of 2 compared to those with Suzuki stage 2 (95% CI: 1.172–443.316), and a 10.7-fold higher probability compared to those with Suzuki stage 3 (95% CI: 1.137–100.683). Additionally, patients with Suzuki stage 6 exhibited a 50-fold higher probability of progressing to an mRS score of 3 compared to those with Suzuki stage 3 (95% CI: 3.125–1000), and a 41.667-fold higher probability compared to those with Suzuki stage 5 (95% CI: 1.460–1000).

Evaluation of the Effectiveness of Combined Revascularization Surgery for Patients with MMD

The incidence of complications within 10 days following combined revascularization surgery was 9.29%, and the surgical effectiveness rate during this period was 90.71%. The primary complications observed were cerebral ischemia (5.12%), hyperperfusion (3.98%), and epilepsy (1.33%).

At follow-up conducted 3–6 months postoperatively, the surgical effectiveness rate increased to 96.46%. Among all patients, 79.65% experienced complete resolution of symptoms, 16.81% demonstrated symptomatic improvement compared to the preoperative state, and 3.54% exhibited no improvement.

Among the 139 patients with a preoperative history of cerebral ischemia, the recurrence rate of cerebral ischemia within 10 days after surgery was 7.19%, with a surgical effectiveness rate of 92.81% during the early postoperative period. At the 3–6-month follow-up, the effectiveness rate increased to 94.96%.

Discussion

MMD is a chronic, progressive intracranial arteriopathy characterized by stenosis or occlusion of the distal segments of the bilateral internal carotid arteries, leading to the formation of collateral vascular networks at the base of the brain.[3,15] The condition is most prevalent in East Asian countries, including Japan, South Korea, and China.[16] The main pathological features of the stenotic arteries in patients with MMD include intimal thickening caused by proliferation of smooth muscle cells and extracellular matrix, thinning of the medial layer, a reduction in the external vascular diameter, and narrowing of the lumen.[17] These structural abnormalities increase the risk of vessel rupture and intracranial hemorrhage or may result in local cerebral ischemia.

MMD is currently classified into hemorrhagic and ischemic subtypes, and it typically presents with stroke as the initial clinical event. Ischemic manifestations are more common and may include transient ischemic attacks, dizziness, headache, motor dysfunction, and seizures.[18–20] In this study population, the ischemic type accounted for 96.90% of cases, consistent with findings reported by Sun et al.[21]

All patients in this study were of Chinese ethnicity, ensuring the identified risk factors and surgical outcome data are directly applicable to Chinese MMD populations—addressing a critical need for population-specific evidence in Chinese clinical guidelines. Consistent with findings from other Chinese cohort studies,[3,5] our results confirmed that hypertension is an independent risk factor for cerebral ischemia in MMD patients, which further reinforces the generalizability of this risk factor within the Chinese population. In contrast, Western cohort studies have reported relatively lower incidences of hypertension-related MMD complications, reflecting potential ethnic differences in the pathophysiological associations of MMD.[1] This distinction underscores the value of our Chinese-specific data: it provides targeted evidence for optimizing MMD management strategies in China, where the disease incidence is high (approximately 1.14 per 100,000 individuals annually),[3] and fills the gap between international evidence and domestic clinical practice needs. For instance, the recommendation to prioritize hypertension control in Chinese MMD patients—derived from our risk factor analysis—can be directly incorporated into preoperative assessment protocols in Chinese neurosurgical centers, helping reduce the incidence of cerebral ischemia before combined revascularization surgery.

MMD contributes to a substantial healthcare burden. Consequently, improving prognosis, preventing symptom onset, and reducing both mortality and disability remain central objectives in current clinical research.

Consistent with established knowledge, hypertension— a driver of atherosclerotic vascular damage—was identified as an independent risk factor for cerebral ischemia in our MMD cohort;[22] this reinforces the clinical priority of blood pressure control in MMD management, but our focus below is on novel insights from our data.[22] The mRS, a validated tool for assessing neurological function following stroke, was used in this study to assess preoperative clinical status. Statistical analysis demonstrated that mRS scores were significantly higher in patients with cerebral ischemia compared to those without, indicating a greater degree of functional impairment in the ischemic subgroup.

These findings underscore the critical importance of early diagnosis and intervention in individuals with MMD. Timely implementation of lifestyle modification, effective management of comorbid conditions, and elimination of harmful behaviors are integral to improving clinical outcomes and long-term prognosis in affected individuals.

Sex-based differences in vascular physiology may also influence outcomes in MMD. In men, smoking and alcohol consumption are associated with varying degrees of vascular damage. In women, estrogen enhances vascular reactivity through the upregulation of vasodilatory mediators such as nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factor. These mechanisms promote relaxation of cerebral vascular smooth muscle, vasodilation, and improved cerebral perfusion, thereby mitigating ischemic injury associated with arterial stenosis in MMD. Additionally, estrogen and progesterone exert anti-atherosclerotic and anti-inflammatory effects and inhibits smooth muscle cell proliferation.[23–26]

Based on these observations, male sex emerged as an independent risk factor for postoperative complications following combined revascularization surgery in patients with MMD.

Another independent risk factor for the development of complications following combined revascularization surgery in patients with MMD was patients with age $\geq$ 50 years. One possible explanation is that, compared to older adult patients, younger patients may exhibit greater variability in the degree of cerebral vascular stenosis and the capacity for collateral circulation compensation. Within a similar time frame, changes in vascular stenosis and collateral development may be more dynamic in younger patients, leading to more pronounced fluctuations in cerebral hemodynamics and increased hemodynamic instability.[27] Additionally, age was an independent factor influencing the severity of clinical status in patients with MMD and cerebral ischemia. These findings support the recommendation that younger patients undergo surgical intervention as early as possible.

This study also identified the surgical side as a factor influencing the incidence of perioperative complications. Patients who underwent left-sided combined revascularization surgery exhibited higher rates of postoperative complications and surgical failure at the six-month follow-up compared to those who underwent right-sided procedures. Anatomically, the right common carotid artery arises from the brachiocephalic trunk, whereas the left common carotid artery originates directly from the aortic arch and frequently aligns linearly with the ascending aorta. This configuration results in differing hemodynamic responses between the two arteries. Systemic hemodynamic changes may exert a more direct influence on the left common carotid artery, while the brachiocephalic trunk may serve as a buffering function for the right common carotid artery, thereby contributing to more stable regulation of blood flow. These anatomical distinctions may underline the observed differences in postoperative complication rates between the two surgical sides in patients with MMD.[28,29]

Currently, there is limited literature available that addresses the factors associated with laterality in MMD surgical interventions. Although Sun et al demonstrated that right-sided MMD is an independent risk factor for preoperative cognitive dysfunction (p = 0.025, OR [95%]: 11.76 [1.14–83.33]), no further analysis was conducted on the factors contributing to surgical side differences.[21] Further research using diverse methodologies, larger sample sizes, and cross-scenario validation is warranted to clarify the underlying mechanisms and clinical significance of surgical side differences in MMD.

In patients with bilateral MMD, both cerebral hemispheres experience ischemic conditions, and intracranial vascular compensatory capacity is generally inferior compared to that in patients with unilateral MMD. Patients with bilateral MMD tend to exhibit reduced cerebral blood flow reserve, inadequate collateral circulation, insufficient posterior circulation compensation, and disrupted cerebral hemodynamics.[18]

Based on disease laterality, patients were categorized into bilateral and unilateral groups. Intergroup comparison revealed a significantly higher incidence of postoperative cerebral ischemia in the bilateral group compared to the unilateral group (15.38% vs 4.02%, p = 0.039). However, findings from the multicenter retrospective study conducted reported no significant difference in clinical outcomes between unilateral and bilateral revascularization procedures.[30] Further studies are warranted to clarify these discrepancies and better define the clinical implications of MMD laterality.

Although this study did not identify any independent risk factors associated with the progression of MMD from unilateral to bilateral involvement, previous research by Pang et al identified younger age and a body mass index $\geq$ 25 as independent predictors of bilateral progression.[31]

A higher Suzuki stage was found to be positively associated with the occurrence of cerebral ischemia in patients with MMD. This association is likely since higher Suzuki stages reflect more advanced intracranial arterial stenosis and greater impairment of cerebral perfusion. As vascular narrowing becomes more pronounced, cerebral blood flow is further reduced, resulting in more severe ischemia and hemodynamic instability. Findings from a separate study support these observations, demonstrating a significant positive correlation between Suzuki stage and ischemic stroke in patients with MMD.[32] No significant correlations were observed between Suzuki stage and collateral circulation or between hemorrhagic stroke and angiographic features such as Suzuki stage, posterior cerebral artery grading, and collateral circulation, which is consistent with the present results.

To reduce the incidence of postoperative complications and enhance patient safety, combined revascularization surgery in MMD should be conducted, whenever feasible, during the early stages of the disease, as indicated by lower Suzuki staging scores.

Currently, pharmacological treatment for MMD is limited to symptomatic relief. There is insufficient evidence to support the efficacy of drug therapy in delaying or reversing disease progression, and its overall effectiveness remains a subject of debate.[3,16,18,33] Currently, intracranial and extracranial revascularization surgery is regarded as the most effective and widely used treatment for MMD. This surgical approach significantly improves cerebral perfusion, thereby enhancing cognitive and language functions and reducing the frequency of transient ischemic attacks.[16,34,35] In the absence of surgical intervention, the annual incidence of cerebrovascular events in adults with symptomatic MMD ranges from 2.4% to 5.7%, and approximately 40% of patients with MMD-related cerebral hemorrhage may experience recurrent hemorrhagic events.[36]

In this study, the incidence rates of cerebral ischemia, hyperperfusion, and epilepsy within 10 days following combined revascularization surgery were 5.12%, 3.98%, and 1.33%, respectively, each notably lower than the average rates reported in a previous meta-analysis.[37] At the 3–6 month postoperative follow-up, the surgical effectiveness rate was 96.46%, also surpassing the average reported in the same meta-analysis, thereby supporting the high efficacy of combined revascularization surgery in MMD management.[37]

Therefore, cerebral ischemia was identified as the most common postoperative complication in this cohort, in contrast to the hyperperfusion reported as the predominant complication in other studies. These differences may be attributable to a range of variables, including patient demographics, genetic predisposition, regional factors, surgical expertise, and the methods used during surgery.

Cerebral ischemia (CIS) remains a common perioperative complication in patients with MMD, with reported incidence rates ranging from 3% to 33%.[9,38,39] This high incidence is often attributed to inadequate intracranial vascular compensation prior to surgery, resulting in significant cerebral hypoperfusion and increased susceptibility to ischemic events. Postoperative CIS may occur due to transient disturbances in cerebral blood flow following revascularization, with some patients developing ischemic symptoms due to an inability to tolerate these hemodynamic fluctuations. Among all postoperative complications associated with MMD, CIS is the most frequently observed. Therefore, the prevention and management of CIS in the postoperative period remains a critical focus in the clinical care of patients with MMD.

In this study, among 139 patients with a history of cerebral ischemia who underwent combined revascularization surgery, the recurrence rate of cerebral ischemia within 10 days postoperatively was 7.19%, while the early postoperative effectiveness rate of 92.81%. At 3–6 months follow-up, the surgical effectiveness rate increased to 94.96%. These findings suggest that the combined revascularization approach utilized was effective in reducing the recurrence of cerebral ischemia and achieving favorable clinical outcomes.

Currently, there is a lack of focused research on preventing recurrent cerebral ischemia following revascularization in patients with MMD. Although a study by Yu et al examined the recurrence of adverse cerebrovascular events after revascularization, it did not provide specific data on the recurrence rate of cerebral ischemia.[37] Further studies are needed to investigate targeted strategies for reducing CIS recurrence and to validate these findings in larger and more diverse populations.

Conclusion

Logistic regression analysis, a type of generalized linear regression model, is commonly used to predict the risk of adverse clinical outcomes and to provide early warnings, thereby supporting timely medical intervention. In this study, five logistic regression models were constructed, and independent risk factors were identified in three of them.

Logistic regression model 1 indicated that a history of hypertension and a higher preoperative mRS score were independent risk factors for the occurrence of CIS in patients with MMD.

Logistic regression model 2 identified male sex and age $\geq$ 50 years as independent risk factors for postoperative complications following *RS* in patients with MMD.

Logistic regression model 3 indicated that Suzuki staging and age were independently associated with the severity of clinical status in patients with MMD presenting with CIS.

These findings underscore the importance of promoting healthy lifestyle and dietary habits and suggest that *RS* should be performed at an earlier Suzuki stage or at a younger age to reduce the risk of adverse outcomes. The results derived from these logistic regression models may serve as a theoretical foundation for risk prediction in clinical practice and provide data-driven support for determining the optimal timing of surgical intervention in patients with MMD.

Clinically, these findings can guide personalized MMD care: for Chinese patients with hypertension or higher preoperative mRS scores, proactive blood pressure control and earlier preoperative risk assessment may reduce cerebral ischemia risk; for male patients or those aged ≥50 years, tailored perioperative monitoring (eg, closer postoperative neurological observation, hemodynamic stability management) can help mitigate complication risk; and prioritizing combined revascularization surgery in early Suzuki stages (≤Stage 3) may optimize long-term functional outcomes.

Abbreviations

MMD, Moyamoya Disease; RS, revascularization surgery; DSA, Digital Subtraction Angiograph; ICA, Internal Carotid Artery; TIA, Transient Ischemia Attack; CIS, Cerebral ischemia.

Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from Research Ethics Committee of the second hospital of Hebei Medical University (No. 2022-R057). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from the legal guardians of all minor participants, and written informed consent was obtained from all adult participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest regarding this work.

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