Impact of Revascularization Timing on Clinical Outcomes of Symptomatic Moyamoya Disease: A Systematic Review and Multivariate Analysis

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Received, July 16, 2024; **Accepted,** October 22, 2024; **Published Online,** January 7, 2025.

Neurosurgery Practice 2025;6(1):e00126. https://doi.org/10.1227/neuprac.0000000000000126

BACKGROUND AND OBJECTIVES: Despite a substantial body of literature describing the efficacy of revascularization compared with conventional management of moyamoya disease (MMD), the impact of the timing of revascularization relative to stroke onset remains inadequately characterized. The aim of this review was to synthesize existing research to guide clinicians in the optimal timing of revascularization in symptomatic MMD.

METHODS: A comprehensive literature review was performed to identify studies reporting on timing of revascularization. Studies were divided into revascularization within 3 months of stroke, between 3 and 6 months of stroke, or >6 months from stroke event.

RESULTS: A total of 3049 cases and 3151 treated cerebral hemispheres were included. There were 91 individuals (2.98%) in the 3 months to intervention cohort, 152 (4.92%) individuals in the 3 to 6 months to the intervention cohort, and 2806 (92.0%) individuals in the >6 months to the intervention cohort. The average follow-up time was 43.8 ± 35.19 months. Clinical improvement was reported in 83.4% of cases overall. The 3-to-6-month poststroke preoperative interval has the highest frequency of clinical improvement (90.2%), followed by the >6-month preoperative interval (83.4%). The preoperative interval of <3 months had the lowest frequency of clinical improvement (76.5%). Comparison of average treatment effect in the treated demonstrated reduced frequency of improved clinical outcome (Mean difference: −22.6, SE: 9.15, *P* = .013) and increased frequency of worse clinical outcome (Mean difference: 20.1, SE: 7.38, *P* = .006) in the <3 months cohort. The >6 months cohort was found to be associated with a reduced frequency of worse clinical outcome (Mean difference −1.81, SE: 0.349, *P* = .001).

CONCLUSION: The findings of this meta-analysis suggest that, in cases where it is clinically feasible to delay revascularization following an acute neurological event in patients with MMD, postponing intervention is warranted.

KEY WORDS: Clinical outcomes, Moyamoya disease, Preoperative interval, Revascularization, Stroke, Complication rate

Moyamoya disease (MMD) is a rare cerebrovascular disorder characterized by the progressive stenosis of the internal carotid arteries resulting in the development of immature collateral vasculature around the circle of Willis.[1] MMD has an increased incidence among women and is more frequently reported in Eastern Asian countries.[2] MMD exhibits a bimodal age distribution with peaks observed around the ages of 5 and 40 years.[3] Cerebral infarctions and transient ischemic attacks are more frequent in the pediatric population while in adults, presentation consists of either intracranial hemorrhage or infarction.[4]

ABBREVIATIONS: ANOVA, analysis of variance; **ATT,** average treatment effect in the treated; **MMD,** moyamoya disease; **NOS,** Newcastle-Ottawa Scale; **PSM,** propensity score matching.

Historically, MMD diagnosis relies on cerebral computed tomography angiography and conventional cerebral angiogram and is classified using the Suzuki staging system.[5] Magnetic resonance angiography, positron emission tomography, single photon emission computed tomography, and magnetic resonance perfusion–weighted imaging may also be used to evaluate cerebral hemodynamics and metabolism, enhancing the assessment of MMD progression.[4,6-8]

The management of MMD varies significantly between ischemic and hemorrhagic types. In ischemic-type MMD, antiplatelet therapy is used to manage thrombotic events, and in hemorrhagic-type MMD, antihypertensive therapy may be used to manage elevated blood pressure.[9,10] For symptomatic MMD, the management is vested in surgical revascularization techniques. Surgical revascularization of MMD is achieved through direct, indirect, or combined revascularization techniques.[11] Direct surgical revascularization consists of direct anastomosis between superficial temporal artery or occipital artery and a cortical vessel in the hypoperfused territory.[12,13] Indirect vascularization uses a variety of tissues as an impetus for cortical neovascularization. This includes encephalomyosynangiosis, encephaloarteriosynangiosis, omental transplantation, and multiple burr hole surgery.[14,15]

Several meta-analyses regarding the efficacy of the surgical revascularization techniques have been published. Li et al[16] found that surgical intervention was associated with increased cerebral perfusion and that direct revascularization was associated with improved prognosis compared with indirect revascularization. Yao et al[17] found that combined revascularization was also associated with a higher frequency of good clinical outcomes when compared with indirect revascularization. These findings were corroborated by an additional meta-analysis conducted by Sun et al[18] who additionally found that direct revascularization had improved long-term outcomes in preventing hemorrhage.

Despite a substantial body of literature describing the efficacy of revascularization techniques, the impact of revascularization timing relative to stroke onset remains inadequately characterized. The aim of this review was to synthesize existing research to guide clinicians in making informed decisions about the optimal timing of revascularization in symptomatic MMD.

METHODS

Search Strategy and Selection Criteria

The literature review and data extraction were completed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and this study was not registered in the PROSPERO registry. A comprehensive literature search was performed in the PubMed, Embase, and Cochrane databases through June 2024 to identify studies reporting on timing of revascularization after stroke in MMD. The search terms used were "moyamoya disease," "surgical treatment," "superficial temporal artery-middle cerebral artery anastomosis," "indirect bypass surgery," "combined surgery," "SMA (superficial temporal artery to middle cerebral artery bypass) with encephalomyosynangiosis," "encephaloduroarteriosynangiosis," "encephaloduroarteriomyosynangiosis," "secondary stroke," "angiographic outcomes," and "perioperative complications." The literature review was limited to articles published in English, and the reference lists of the articles found through these search terms were searched to identify any additional studies.

Inclusion criteria included as follows: (1) patient population must have formal diagnosis of MMD, through computed tomography angiography or MRI; (2) patient must present with symptoms suggestive of stroke (either hemorrhagic or ischemic); and (3) the study must include data regarding the timing of revascularization relative to stroke onset. Single case repots, conference abstracts, review articles, and editorials were excluded. Additional exclusion criteria included secondary causes of moyamoya syndrome, incomplete clinical trials, use of animal models, medical management, endovascular interventions, and studies including highly variable time to intervention (with range of time to intervention spanning more than 2 cohorts). The results of this literature review are described in Figure 1.

The initial literature search yielded 757 studies. One author independently screened the titles and abstracts of studies according to the search protocol. After the initial screening, 213 studies were included. The full text of these remaining articles was examined to determine adherence to the inclusion criteria.

Data Extraction

Data were independently extracted from each study and stored on a standardized data collection form. The following information was extracted from each study: type of study, year of publication, cohort size and demographics, risk factors (including hypertension, diabetes, hyperlipidemia, history of smoking, and family history of MMD), stroke presentation, Suzuki grading, involvement of the posterior cerebral artery, revascularization technique, laterality of revascularization, clinical outcome, extent of postoperative neovascularization, complications, morbidity and mortality, and follow-up period. Good clinical outcome was defined in the studies included in the literature review as improvement of modified Rankin Scale (mRS) scores, mRS scores of <2 or disappearance of clinical symptoms, and no new development of neurological dysfunction. Worse clinical outcome was defined as mRS of >2 at follow-up.

Statistical Analysis

Descriptive statistics were used to summarize demographic, clinical, and radiographic characteristics of the patient population. Continuous variables were expressed as means with SDs or medians with interquartile ranges. Categorical variables were summarized as frequencies and percentages. The population was stratified according to timing of revascularization (<3 months, between 3 and 6 months, and >6 months). This selection of time intervals was based on 2 randomized controlled trials conducted by Xu et al.[19,20] Both trials compared outcomes of revascularization at different time intervals (either greater or <6 months or greater or <3 months). Between-group comparisons for demographic, clinical, and radiographic data were assessed by conducting analysis of variance (ANOVA). If any population variable was significant, Tukey multiple comparisons of means at the 95% family-wise confidence level was conducted to identify specific differences in between-group means.

The primary outcomes of interest were follow-up time, improved clinical outcome, worse clinical outcome, percentage of morbidity and mortality, and rate of all complications. Continuous variables were expressed as means with SD, and categorical variables were summarized as frequencies and percentages. Between-group comparisons for outcome data were assessed by ANOVA. Outcome data which were statistically significant among the 3 time to revascularization groups were then analyzed through univariate regression to assess the association between outcomes variables and time to revascularization. Owing to accentuated heterogeneity in revascularization technique at the <3 months and >6 months cohorts, propensity score matching (PSM) was used to estimate the average treatment effect in the treated (ATT) for clinical

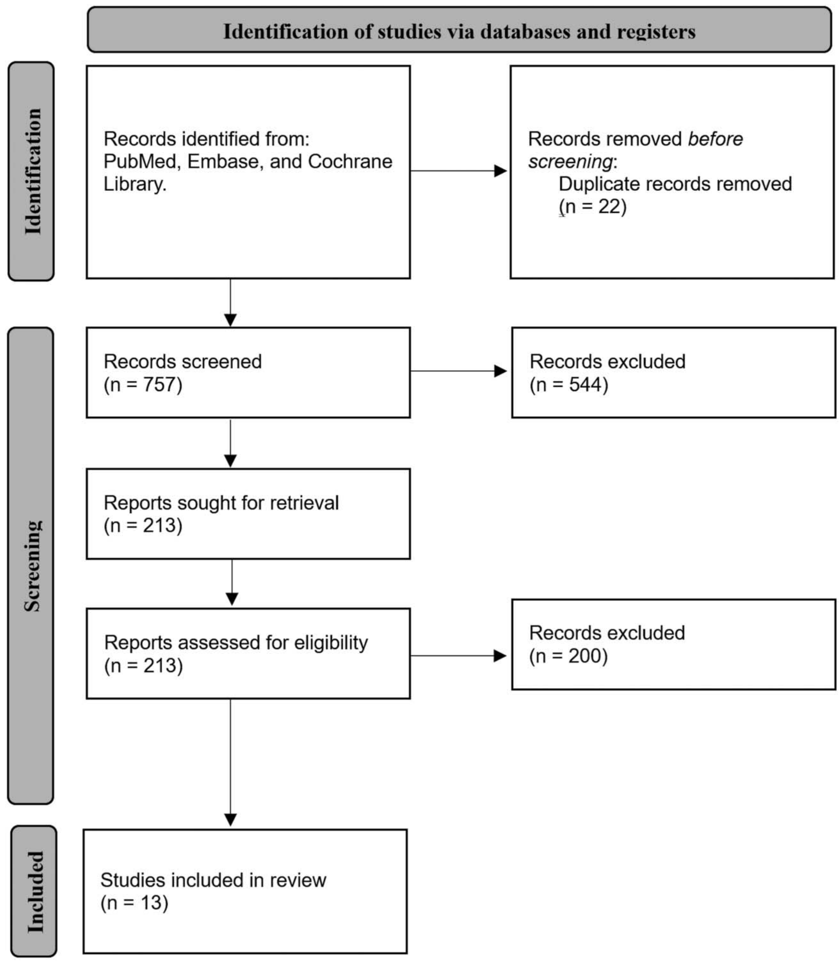

FIGURE 1. *Flow chart representing methodology of literature search.*

outcome, worsened clinical outcome, and complication rate. Propensity score was estimated using logistic regression with direct, indirect and combined revascularization as covariates, and matching was completed using optimal full matching, the results of which are depicted on Figures 2 and 3. ATT was estimated and then using linear regression to fit the outcome according to time to intervention and covariates. Then G-computation was used to estimate the ATT. Power of tests used to determine the power of ATT estimates of G-computation.

Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing). Statistical significance was set at $P < .05$, and all tests were 2-tailed. PSM score calculated using "MatchIt" and ATT estimated using "marginaleffects" package in R.

Bias Assessment

The methodological quality and risk of bias in the included studies was assessed with the Newcastle-Ottawa Scale (NOS) which consists of 3 domains: selection (rated 0-4), comparability (rated 0-2), and outcome (rated 0-3). These 3 domains are combined to give a total score (rated 0-9). The results of this assessment are depicted in Table 1. The NOS assessment revealed that most studies (11 of 13) had low risk of bias in the selection and outcome categories, however, significant variation in the comparability category. Three studies were rated 2, 8 studies were rated 1, and 4 studies received a rating of 0. Of the studies receiving poor comparability rating, Kang et al[6] and Deckers et al[7] conducted imaging studies and did not include substantial population description, Kawaguchi et al[25] conducted a comparison between surgical and conventional management of MMD, but focused on outcomes rather than population description, and lastly, Hu et al[8] assessed brain functional networks and included noncomparable population demographics.

RESULTS

The literature review yielded 13 studies published from 2000 to 2023.[6-8,19-30] Eight of these studies were retrospective chart reviews, 3 were clinical trials, and 2 were prospective cohort studies. Six of the studies were completed in China, 3 in United States, 1 in South Korea, 2 in Japan, and 1 in the

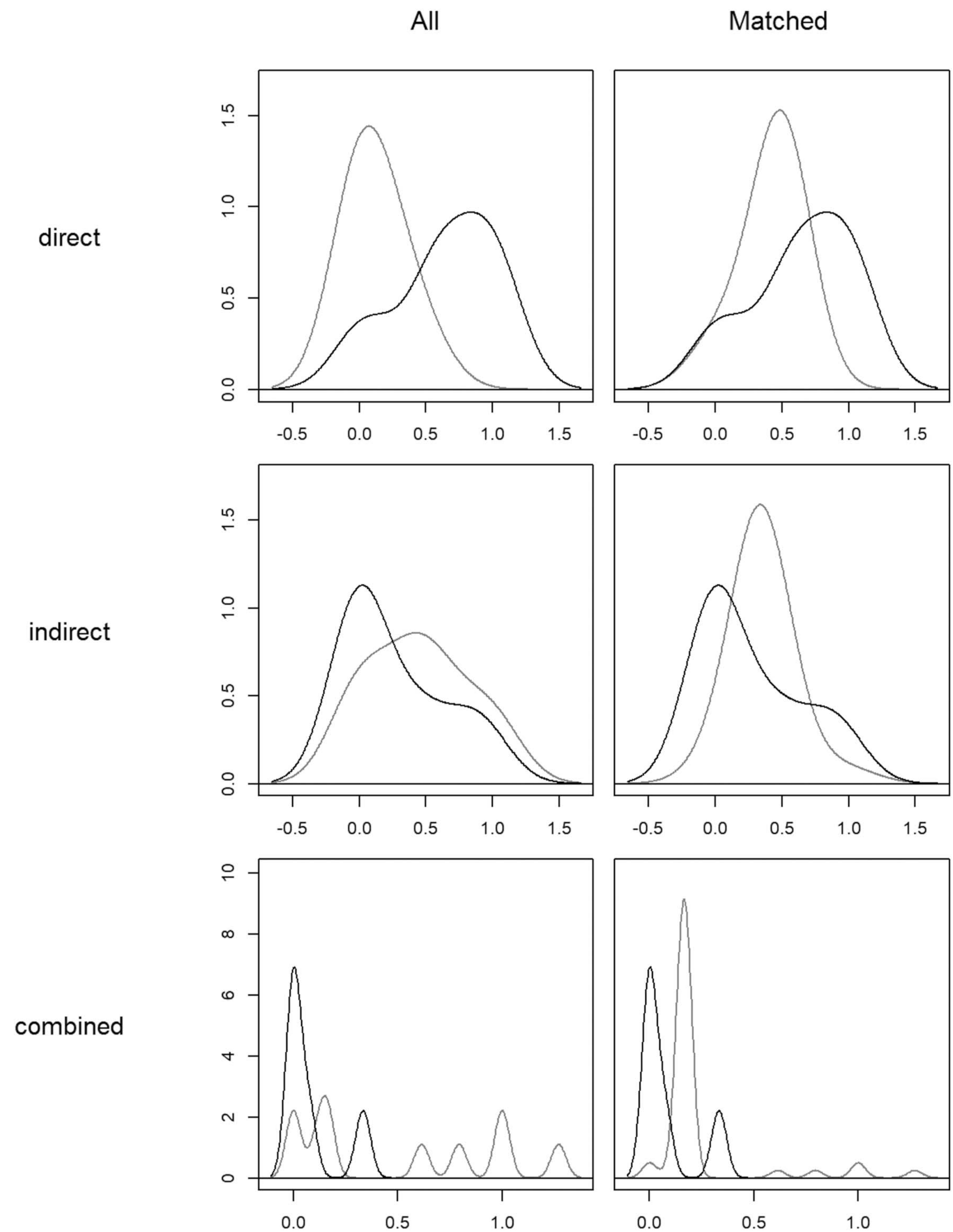

FIGURE 2. *Density plots for 3 covariates demonstrating covariate balance before and after propensity score matching. Black line represents treated cohort (<3 months), and light grey represents control cohort (>3 months).*

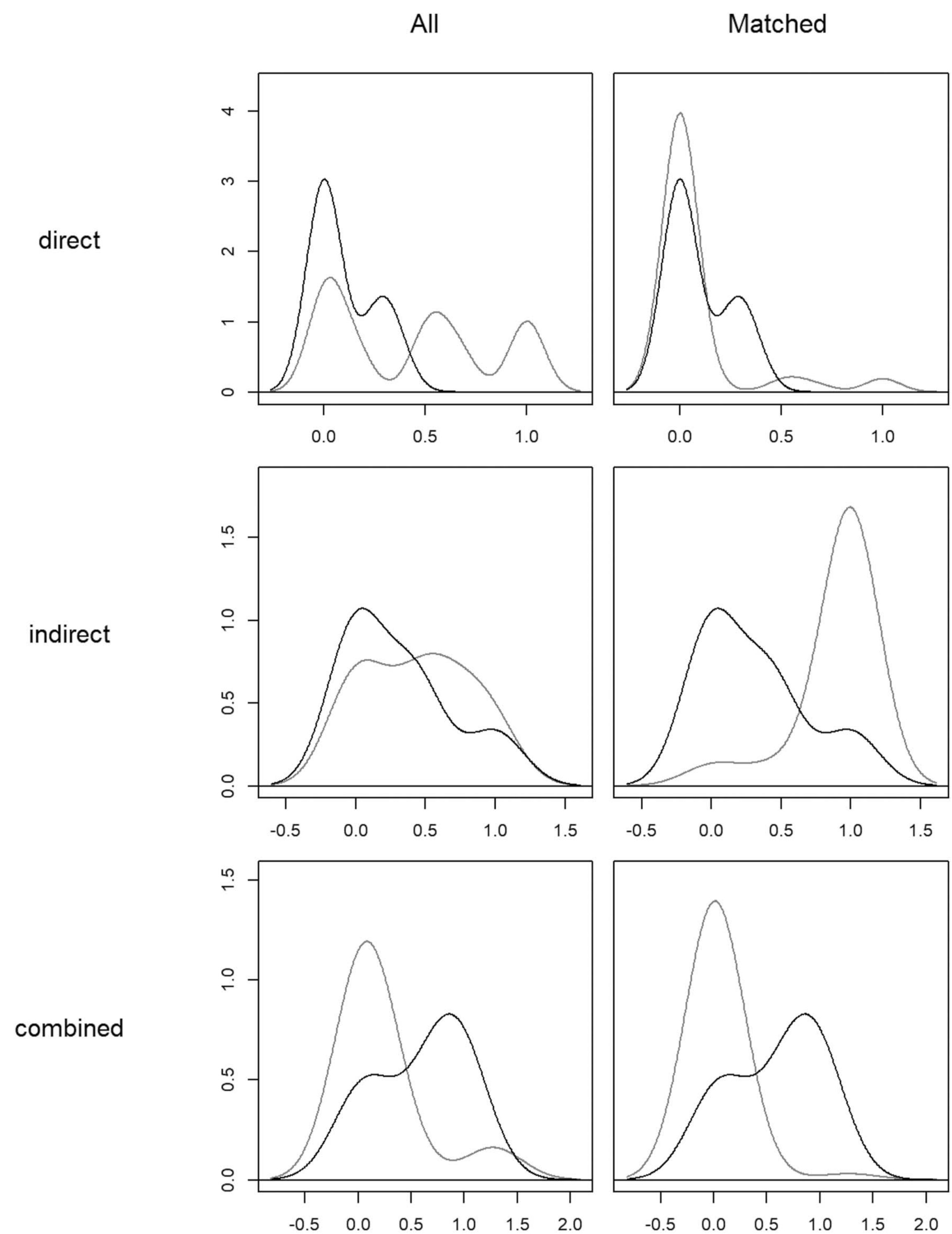

FIGURE 3. *Density plots for 3 covariates demonstrating covariate balance before and after propensity score matching. Black line represents treated cohort (>6 months), and light grey represents control cohort (<6 months).*

TABLE 1. Risk of Bias Assessment Using the Newcastle-Ottawa Scale

Study	Selection (0-4)	Comparability (0-2)	Outcome (0-3)	Total Newcastle-Ottawa Scale score (0-9)
Tao et al[21]	3	1	3	7
Kang et al[6]	3	0	2	5
Wang et al[22]	3	1	2	6
Deckers et al[7]	4	0	1	5
Zhao et al[23]	3	2	3	8
Reed et al[24]	4	1	3	8
Kawaguchi et al[25]	3	0	2	5
Ahn et al[26]	2	1	1	4
Kuroda et al[27]	4	1	2	7
Sun et al[28]	3	1	2	6
Hu et al[8]	3	0	2	5
Xu et al[19]	4	1	3	8
Xu et al[20]	3	1	2	6

Netherlands. These studies included a total of 3049 cases and 3151 treated cerebral hemispheres. Four studies included data with pediatric patients, and 12 studies included data with adult patients. In 5 studies, the timing of revascularization was <3 months.[7,20,21,24,25] In 5 studies, the timing of revascularization was between 3 months and 6 months,[19,20,24,26,28] and in 6 studies, the timing of revascularization was >6 months.[6,8,19,22,23,27] There were 91 (2.98%) individuals in the cohort operated on in <3 months from ictus, 152 (4.92%) individuals in the cohort operated on between 3 and 6 months from ictus, and 2806 (92.0%) individuals in the cohort operated on >6 months from stroke onset.

Demographics

The average age of the entire cohort was 33.9 ± 9.69 years, and the male-to-female ratio was 0.565. The total number of male patients was 1431, and the total number of female patients was 1648. Differences between the cohort age (*P* = .406) and gender (*P* = .508) were not significant between the 3 preoperative interval groups. Comorbidities included hypertension (27.5%), type II diabetes mellitus (7.78%), hyperlipidemia (15.0%), and history of smoking (17.1%). Family history of MMD was present in 4.65% of the cohort, and there was no significant difference between preoperative interval groups (*P* = .372) (Table 2).

Clinical Presentation

The most common clinical presentation was hemorrhagic stroke (54.9%), followed by transient ischemic attack (53.3%), ischemic stroke (41.5%), and, lastly, seizures (14.5%). Headaches and other nonlocalized symptoms were reported in 36.3%. The frequency of Suzuki grade at presentation was 6.60% grade I, 15.2% grade II, 29.0% grade III, 42.7% grade IV, 16.3% grade V, and 4.59% grade VI. There were no significant intergroup differences for Suzuki grade (Table 2). Posterior cerebral artery involvement was observed in 21.0% of cases, and an intergroup variability was not significant (*P* = .395) (Table 2).

Revascularization Methodology

The left cerebral hemisphere was revascularized in 51.7% of operations, and the right cerebral hemisphere was revascularized in 49.2% of operations. The most common operative technique was indirect revascularization which was used in 36.8% of cases per study on average. Use of direct revascularization was reported in 29.9% of cases per study on average, and combined revascularization was reported in 30.3% of cases per study on average. There was no significant difference in intergroup variability in indirect and combined revascularization (Table 2); however, there was significant intergroup variability in direct revascularization between cohorts (*P* = .015).

Outcomes of Revascularization

The average follow-up time was 43.8 ± 35.19 months. Clinical improvement was reported in 83.4% of cases overall. The 3-to-6–month poststroke preoperative interval has the highest frequency of clinical improvement (90.2%); however, the intergroup variability for improved clinical outcomes was not significantly different (*P* = .131) (Table 3). The average total frequency of stable outcomes (no difference between preoperative and postoperative

TABLE 2. Demographic, Clinical, and Radiographic Presentation of Patients With Symptomatic Moyamoya Disease Partitioned According to Preoperative Interval

		Timing of revascularization			
Variable	**Total**	**<3 mo**	**3-6 mo**	**>6 mo**	***P* value**
Cohort	3049	91 (2.98)	152 (4.92)	2806 (92.0)	—
Hemispheres treated	3151	110 (3.50)	183 (5.81)	2858 (90.7)	—
Demographics					
Male:female ratio	0.565	0.506	0.458	0.675	.508
Age	33.9 ± 9.69	34.5 ± 7.82	28.4 ± 15.6	37.0 ± 5.50	.406
Risk factors					
Hypertension (%)	27.5	22.2	32.7	25.7	.480
Type II Diabetes Mellitus (%)	7.78	18.5	8.81	5.48	.284
Hyperlipidemia (%)	15.0	22.2	14.5	14.1	.762
Smoking history (%)	17.1	3.70	23.2	16.2	.537
Family history of Moyamoya (%)	4.65	3.70	7.29	2.48	.372
Clinical presentation					
Transient ischemic attacks (%)	53.3	59.5	—	47.1	.812
Ischemic (%)	41.5	66.1	50	19.5	.240
Hemorrhagic (%)	54.9	50	50	61.4	.952
Headache (%)	36.3	32.4	51.3	25.1	.587
Seizures (%)	14.5	18.5	20.8	6.16	.262
Pathologic presentation					
Suzuki Grade I (%)	6.60	3.70	5.83	8.82	.889
Suzuki Grade II (%)	15.2	0.00	21.3	16.3	.638
Suzuki Grade III (%)	29.0	25.1	32.7	29.0	.866
Suzuki Grade IV (%)	42.7	45.2	52.6	36.4	.621
Suzuki Grade V (%)	16.3	9.46	6.25	22.2	.287
Suzuki Grade VI (%)	4.59	5.40	0.00	5.58	.737
Left (%)	51.7	48.1	51.5	53.7	.867
Right (%)	49.2	51.9	48.5	48.5	.949
Posterior cerebral artery involvement (%)	21.0	14.8	14.1	27.5	.395
Management					
Direct revascularization (%)	29.9	65.0	16.4	9.72	**.015**
Indirect revascularization (%)	36.8	26.9	58.2	30.7	.441
Combined revascularization (%)	30.3	8.15	25.4	52.2	.091

Frequencies calculated as an average of reported frequencies from individual studies. *P* values calculated from analysis of variance F-statistic. Bold entries represent results achieving statistical significance ($P < .05$).

TABLE 3. Clinical and Radiographic Outcomes of Direct, Indirect, and Combined Revascularization for Symptomatic Moyamoya Disease Partitioned According to Poststroke Preoperative Interval

		Timing of revascularization			
Variable	**Total**	**<3 mo**	**3-6 mo**	**>6 mo**	***P* value**
Follow-up (mo)	43.8 ± 35.19	41.6 ± 37.10	45.7 ± 25.37	44.7 ± 43.0	.987
Clinical outcome					
Improve (%)	83.4	76.5	90.2	83.4	.131
Worse (%)	11.5	17.6	4.7	13.4	.157
Mortality (%)	1.60	3.45	0.0	0.95	.389
Post-operative perfusion					
Matsushima score III (%)	41.7	—	—	41.7	—
Matsushima score II (%)	60.1	92.8	76.5	35.6	**.029**[a]
Matsushima score I (%)	17.7	7.2	23.5	20.0	.740
Complications					
All complications (%)	18.6	26.7	18.1	12.1	.148
Ischemic stroke (%)	10.6	19.1	9.3	5.33	.133
Seizure (%)	9.5	3.2	16.3	1.75	.684
Hemorrhage (%)	11.1	18.2	10.9	4.41	.352
Hyperperfusion (%)	3.37	3.70	1.56	4.10	.844
Infection (%)	3.59	5.06	3.13	2.35	.624
Transient ischemic attacks (%)	8.06	7.41	6.25	10.5	—
Hematoma (%)	2.62	3.70	1.56	—	—

[a]Post hoc Tukey Honestly Significant Difference analysis revealed difference between Matsushima score II was significantly different between those revascularized <3 mo and those revascularized >6 mo from stroke event. Bold entries represent results achieving statistical significance (*P* <.05).

neurological states) was 18.5% with the highest frequency of stable outcomes in the 3-to-6 months cohort (20.5%, *P* = .883). The average frequency of worse clinical outcome was 11.5%, with the highest subgroup frequency in the <3 months cohort (17.6%, *P* = .389). The average combined frequency of mortality was 1.60% with the highest subgroup frequency in the <3 months cohort (3.45%, *P* = .389). The average frequency per study of postoperative Matsushima scores were 41.7% grade III, 60.1% grade II, and 17.7% grade I.

Owing to the imbalance in revascularization-type distributions across the time-to-intervention cohorts, PSM was performed to compare clinical outcomes for interventions occurring at <3 months. Table 4 summarizes the matched data, with the treated group representing studies in which intervention occurred within 3 months and control representing those occurring at >3 months. Table 5 summarizes the matched data before and after 6 months of intervention.

Comparison of ATT using G-computation demonstrated a significantly reduced frequency of improved clinical outcome in the <3 months cohort (Mean difference: −22.6, SE: 9.15, *P* = .013) and significantly increased frequency of worse clinical outcome in the <3 months cohort (Mean difference: 20.1, SE: 7.38, *P* = .006). The >6 months cohort was found to be associated with a reduced frequency of worse clinical outcome (Mean difference −1.81, SE: 0.349, *P* = .001) (Table 6).

DISCUSSION

This review synthesizes the available research on the timing of revascularization in symptomatic MMD. A total of 3049 cases of MMD were included and partitioned into those who received revascularization within 3 months of stroke, between 3 and 6 months of stroke, or >6 months from stroke event. Although there was a large difference in cohort population size and revascularization methodology, there were no differences in intergroup variability between subgroup population demographics and clinical and radiographic presentation. Owing to imbalance in

TABLE 4. Summary of Balance for All Data and Propensity Score Matching Matched Data at 3 Months

Covariate	Means treated (matched), %	Means control (matched), %	SMD (matched)
Direct	65.0	41.6	0.591
Indirect	26.9	35.8	−0.224
Combined	8.15	24.3	−1.120

SMD, standardized mean difference.
Control group represents >3 mo cohort, and treated group represents <3 mo cohort. All data represent unadjusted covariate data, and matched data represent propensity matched data.

revascularization-type distributions across time-to-intervention cohorts, there was significant possibility that revascularization type was confounding data on time-to-revascularization as each procedure. Consequentially, PSM was used to construct comparisons in each time-to-intervention cohort. Before matching, substantial imbalances were noted between the <3 months and >6 months cohorts regarding revascularization type. Standardized mean difference for all revascularization types in both time-to-intervention cohorts was significantly reduced (Tables 4 and 5). However, it is important to note that PSM was not able to achieve standardized mean difference of <0.1. Thus, the model was not able to completely eliminate all sources of confounding, and the results should be interpreted with caution.

The cohort revascularized in <3 months was associated with an increased frequency of worse clinical outcome, mortality, and all-cause complication rate when analyzed with ANOVA. These results were supported by G-computation of PSM modeled data, which demonstrated the <3 month to intervention cohort, were associated with higher frequency of worse clinical outcome (P = .006) and reduced frequency of good clinical outcomes (P = .013). In addition, while not significant on ANOVA, the >6 month to intervention cohort was associated with reduced frequency of worse clinical outcome (P = .001). Although this result was statistically significant, the association estimate was small (Table 6).

There was a trend toward higher frequency of all-cause complications in the 3 months to intervention cohort; however, this result was not statistically significant through ANOVA or G-computation. In addition, individual complications were not found to be significant between time-to-intervention cohorts.

Although Matsushima score II was associated with significantly higher rates in the <3 months to intervention cohort (P = .029), these results are likely secondary to the confounding effects of the large proportion of individuals receiving direct revascularization in the <3 months to intervention cohort, and due to paucity of data on Matsushima scores, it was not feasible to analyze the significance of this confounding factor.

Reed et al conducted a retrospective analysis of patients revascularized early (average 1.4 weeks) or delayed (average 12.7 weeks). Reed et al[24] found no difference between outcomes or complication rates between the 2 groups; however, in this study, there was no investigation of influence of procedure type on outcomes. In addition, Reed et al[24] found that early direct bypass had increased revascularization when compared with delayed indirect surgery. This outcome was reflected in this review, the early revascularization cohorts (<3 months and between 3 and 6 months) had higher frequencies of Matsushima Score III and II compared with delayed intervention. However, in this review, this difference was only significant for Matsushima score II.

Xu et al[19,20] conducted 2 clinical trials investigating the role of revascularization timing in outcomes of hemorrhagic-type and ischemic-type MMD. In the hemorrhagic-type MMD trial, the difference between MMD revascularized between <6 months and >6 months and found that early revascularization was associated with higher rates of postoperative seizures and operative site complications, reflecting the trend in complication rate described in this review. In the ischemic-type MMD trial, Xu et al[19] compared revascularization between a preoperative interval of <3 months or >3 months and found that revascularization within 3 months of the last stroke was also associated with increased risk of perioperative conditions.

TABLE 5. Summary of Balance for All Data and Propensity Score Matching Matched Data at 6 Months

Covariate	Means treated (matched), %	Means control (matched), %	SMD (matched)
Direct	9.72	8.14	0.104
Indirect	30.8	89.4	−1.474
Combined	58.7	4.2	1.246

SMD, standardized mean difference.
Control group represents >6 mo cohort, and treated group represents <6 mo cohort. All data represent unadjusted covariate data, and matched data represent propensity matched data.

Limitations

A fundamental source of bias is a large difference in cohort size. Approximately 90% of the all cases of MMD fitting the inclusion criteria had revascularization completed at >6 months from stroke event. Thus, there is a substantial risk of selection bias associated with the results of this study. The extensive ANOVA between the population demographics, clinical and radiological presentation, utilization of PSM, and power analysis was conducted to mitigate this risk. Furthermore, this large difference was propagated by a single study published by Wang et al[22] which included a cohort of 2545 cases of MMD revascularized at >6 months from stroke, leading to the additional risk of weighting bias. Another influential source of bias was the low comparability score according to NOS grading criteria.[31] This limited the assessment of confounding

TABLE 6. Estimated Causal Effects of Revascularization Timing on Clinical Outcomes Using G-Computation

Timing	Estimate[a]	Standard error	*P* value	Power
Good clinical outcome				
<3 mo	−22.6	9.15	**.013**	0.99
>6 mo	8.56	6.94	.217	0.49
Worse clinical outcome				
<3 mo	20.1	7.38	**.006**	0.99
>6 mo	−1.81	0.2349	**<.001**	1
Complications				
<3 mo	−13.1	9.98	.190	0.79
>6 mo	−7.33	4.92	.136	0.64

[a]Estimate defined as difference between the mean of treatment group (either <3 mo or >6 mo) and the control group (>3 mo or <6 mo), respectively.
Bold entries represent results achieving statistical significance (*P* <.05).

factors on clinical outcomes. In this review, only the effect of revascularization type was investigated as potential confounding variables. Additional parameters, such as ethnicity, gender, age, hypertension, diabetes, hyperlipidemia, smoking status, and Suzuki grade, were not able to be addressed due to the low comparability between studies. Thus, this study is associated with a significant risk of confounding bias. Last, as not all studies included time-to-intervention data that corresponded to the time delineations of the cohorts of this review, there is potential reduction in effect size.

These sources of bias implicate new research opportunities including reduction of confounding bias by more substantial reporting of MMD presentation among studies reporting time to revascularization to assess for which factors contribute to the association between complication rate and time to revascularization. In addition, addressing selection bias by including more studies of revascularization timing within the range of <3 months and between 3 and 6 months could assist in the characterization of this underrepresented category.

The findings of this meta-analysis suggest that, in cases where it is clinically feasible to delay revascularization after an acute neurological event in patients with MMD, postponing the intervention may be advisable. Earlier revascularization was associated with lower rates of positive clinical outcomes (mRS grade <2) and higher rates of worse outcomes (mRS >2). However, this recommendation must be considered within the context of the patient's condition. The decision to delay revascularization should be based on the severity of the acute event and the stability of the patient as this meta-analysis did not include subcohort analyses in situations where urgent intervention was required. Although our results suggest that delaying revascularization may improve clinical outcomes, the data do not provide clear guidance regarding the optimal revascularization method. For patients who are stable enough to tolerate delayed intervention, this approach may offer better clinical results, but treatment should be individualized based on the patient's specific clinical context.

CONCLUSION

This review highlights the impact of timing in revascularization procedures for patients with MMD. Earlier revascularization was associated with lower rates of positive clinical outcomes (mRS grade <2) and higher rates of worse outcomes (mRS >2). In addition, while not significant, the complication rate was found to be inversely associated with time to revascularization. Variability in study methodology and the high risk of selection bias highlight the necessity for more controlled studies to further refine these conclusions.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

Author Contributions: Brandon Edelbach was involved in data collection, data analysis, and manuscript preparation. Miguel Angel Lopez-Gonzalez was responsible for project conceptualization, manuscript preparation, and data analysis.