• Clinical Research •

How retinal artery occlusion reveals moyamoya disease—a case series and descriptive study

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Abstract

● **AIM:** To systematically characterize the clinical features, correlations, and therapeutic implications of participants with moyamoya disease (MMD)-related retinal artery occlusion (RAO) through a case series and pooled descriptive analysis.

● **METHODS:** A total of 9 participants with MMD-RAO (2020–2025) and 9 cases retrieved from published literature (1981–2025) were retrospectively reviewed to descriptively explore the association between MMD and RAO. Mean difference (MD) was adopted as the effect size for continuous variables, while odds ratio (OR) was used for categorical variables. Heterogeneity was evaluated using the *Q* statistic and I^2 index. Publication bias was assessed *via* funnel plots, and sensitivity analysis was performed using the leave-one-out method.

● **RESULTS:** Eighteen participants were enrolled in the final analysis, with a male predominance (male:female=1.25:1). Limited improvement in best-corrected visual acuity (BCVA) was observed after treatment (logMAR range: 0.22–3.0). Central retinal artery occlusion (CRAO) was the predominant subtype (83.3%), followed by branch retinal artery occlusion (BRAO, 11.1%) and cilioretinal artery occlusion (CLRAO, 5.6%). Participants in our institutional cohort were significantly older than those reported in literature (52.89±9.53 *vs* 25.56±12.58y, *P*<0.001). Our cohort presented slightly worse initial BCVA (2.04±0.9 *vs* 1.90±0.68; MD=0.14, 95%CI: -0.60–0.88, *P*=0.711, I^2=78.3%) and inferior visual recovery (1.99±0.9 *vs* 1.22±1.14; MD=0.77, 95%CI: -0.19–1.73, *P*=0.132, I^2=82.5%), whereas complete visual recovery (logMAR=0.1) was documented in one BRAO case from published reports. The efficacy of intra-arterial thrombolysis (IAT) reached 60% (3/5) in our cohort, and the overall rate of visual improvement was 41.2%. Mild publication bias was detected; however, sensitivity analysis verified the robustness of primary results.

● **CONCLUSION:** Participants with MMD-related RAO exhibit unique clinical characteristics differing from those with isolated RAO or uncomplicated MMD. This study identifies an "older MMD phenotype" complicated by RAO, and highlights the necessity of comprehensive vascular screening in elderly participants presenting with RAO to facilitate timely combined ophthalmological and neurological intervention.

● **KEYWORDS:** intra-arterial thrombolysis; moyamoya disease; retinal artery occlusion; stroke
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INTRODUCTION

Retinal artery occlusion (RAO) is characterized by acute, painless vision deterioration and often devastating prognosis[1]. Two primary types are central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO)[2-3]. The incidence of CRAO is approximately 2.1 per 100 000 people, increasing to 12.38 per 100 000 in individuals over 80 years old. BRAO has an incidence of about 4.99 per 100 000 people. RAO primarily affects women and older adults, significantly correlated to metabolic disorders and cardiovascular diseases such as moyamoya disease (MMD)[4-6].

MMD is a rare, progressive cerebrovascular disorder characterized by stenosis or occlusion of the internal carotid artery (ICA) at the base of the brain, leading to abnormal vascular network formation as the body attempts to compensate for the reduced blood flow[7-8]. Children, young adults, and females are predominantly affected[9]. It is most prevalent in East Asian countries, particularly Japan, Korea, and China, with an estimated incidence of 0.35 to 18.1 per 100 000

individuals[10-13] and much rarer in Western countries[14-15]. The exact etiology of MMD remains unclear, but genetic, environmental, and immunological factors are believed to play a role[16-18].

The pathophysiology underlying MMD, such as chronic cerebral ischemia and compensatory vascular network formation, can impact the ICA bifurcation of the ophthalmic artery[19]. Recent studies have shown that MMD significantly affects ocular blood vessels and thickness of the retina and choriod, which may predispose individuals to RAO[20-21]. Early identification of retinal vascular complications in MMD participants can lead to more comprehensive management and mitigate severe visual outcomes[22]. Several case studies have reported RAO-associated MMD. However, the literature remains sparse and needs more extensive clinical research to elucidate the MMD-RAO associations.

PARTICIPANTS AND METHODS

Ethical Approval This study was carried out following the institutional guidelines and ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Renmin Hospital of Wuhan University (WDRY2022-K278). Written informed consents for publication of clinical details and any identifying images were obtained from all the participants.

Study Design and Participants By reviewing the medical records from the hospital information system of the Ophthalmic Center, Renmin Hospital of Wuhan University, a retrospective study was performed in the RAO-MMD participants between June 1, 2020, and June 1, 2025.

The inclusion criteria were: 1) RAO diagnosis: a) typical clinical features of acute painless monocular vision loss; b) characteristic clinical manifestations of funduscopy and fundus imaging: formation of cherry-red spot in the macular area, marked narrowing of retinal arterioles with delayed arterial filling on angiography on fundus fluorescein angiography (FFA), or inner retinal edema with disruption of the ellipsoid zone on optical coherence tomography (OCT). 2) MMD diagnosis: brain computed tomography angiography (CTA) or digital subtraction angiography (DSA) showing: a) Progressive stenosis or occlusion at the terminal ICA and proximal segments of anterior cerebral artery (ACA)/middle cerebral artery (MCA); b) abnormal vascular networks at the skull base. The exclusion criteria include: 1) Concurrent retinal vascular diseases (*e.g.*, retinal vein occlusion, diabetic retinopathy); 2) Severe refractive media opacities; 3) History of craniocerebral surgery or central nervous system disorders.

Data Collection All RAO participants referred to our hospital underwent a comprehensive ophthalmological assessment, including best corrected visual acuity (BCVA), intraocular pressure (IOP), fundus imaging, and CTA. Local intra-arterial thrombolysis (IAT) surgical process is described in the literature[23]. Conservative therapy included oxygen therapy, vasodilators, ocular circulation-improving medications, and neuroprotective agents.

Literature Research Literature retrieval targeted studies reporting MMD-RAO cases published between 1981 and 2025, using the search string: ("Moyamoya disease" OR "Moyamoya") AND ("Retinal artery occlusion" OR "CRAO" OR "BRAO" OR "CLRAO" OR "Retinal ischemia") across PubMed, Web of Science, and Embase. Two independent reviewers (Li ZY, Li Y) performed study selection (screening titles, abstracts, and full texts) and quality assessment using the JBI Case Report Checklist—studies with a score of ≥6 were considered high-quality and included. Disagreements were resolved by a third reviewer (Chen T).

The inclusion criteria were as follows: 1) MMD and ocular manifestations were simultaneously mentioned in the title or abstract; 2) original studies or case reports. The exclusion criteria included: 1) non-English articles; 2) lack of a definitive idiopathic MMD diagnosis; 3) moyamoya syndrome caused by various underlying factors; 4) not RAO.

Statistical Analysis Given the small sample size and exploratory nature of the study, the quantitative analysis was designed as a pooled descriptive comparison. Statistical analyses were performed using IBM SPSS Statistics (Version 27.0, IBM Corp., Armonk, NY, USA) and Stata (Version 17.0, StataCorp LLC, College Station, TX, USA), with a two-tailed $P<0.05$ considered statistically significant. BCVA was converted to logMAR values as previously reported[24-25]. One case of missing BCVA from the literature was not included in the statistical analysis. Continuous variables were summarized as mean±standard deviation (SD). The mean difference (MD) with 95% confidence interval (95%CI) was used to quantify the magnitude of between-group differences, and statistical significance was determined *via* independent samples *t*-test. Categorical variables were reported as counts and percentages (*n*, %). The odds ratio (OR) with 95%CI was employed to compare group associations. For cells with zero events, a continuity correction (adding 0.5 to each cell) was applied to prevent biased OR estimates. Fisher's exact test was used to assess significance, given the small sample size (n=9 per group) and expected frequencies <5 for most categorical variables.

Heterogeneity between our cohort and literature cases was evaluated using two complementary metrics: the Q-test and the I^2 statistic. Heterogeneity was interpreted as low ($I^2<25\%$), moderate ($25\%\leq I^2\leq 50\%$), or high ($I^2>50\%$). A fixed-effects model was used for low heterogeneity, while a random-effects model was applied for high heterogeneity to account for between-group variance. Initial missing values in the table—

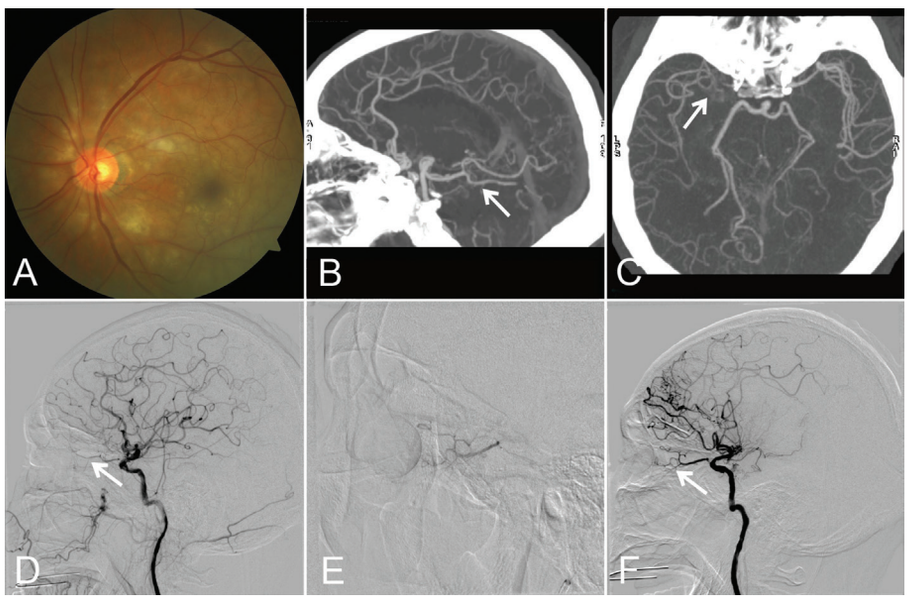

Figure 1 Case 1 imaging findings A: Left fundus image at disease onset; B–C: CTA image showing characteristic MMD vessels; D: Cerebral angiography before thrombolytic injection; E: Cerebral angiography during the thrombolytic injection; F: Cerebral angiography after the thrombolytic injection. CTA: Computed tomograph angiography; MMD: Moyamoya disease.

including effect sizes (OR/MD) and heterogeneity metrics (I^2/*Q*-test *P*) for variables such as dyslipidemia were completed using the aforementioned methods.

Publication bias was assessed *via* funnel plot. Sensitivity analysis for final BCVA was conducted *via* the leave-one-out method to assess the stability of pooled descriptive analysis results. Briefly, one study was sequentially excluded across 10 scenarios (1 "no exclusion" +9 "one-study exclusion"), and the pooled MD with 95%CI was recalculated for each scenario. For single cases in the literature group, the overall standard error of 9 cases was used for estimation.

RESULTS

Basic Information and Clinical Features of Participants

Our retrospective case series included 9 participants with acute RAO concurrent with MMD. Participant demographics, clinical characteristics and visual outcomes are summarized in Table 1. Eight were diagnosed with CRAO, and 1 cilioretinal artery occlusion (CLRAO). Four had bilateral MMD. The mean age were 52.89±9.53y. The majority (88.9%) had multiple cardiovascular and cerebrovascular events or risk factors. Most MMD participants (77.8%) were identified firstly through CTA. Only 2 participants were found to have MMD through DSA during thrombolysis therapy.

The mean time from disease onset to clinical visit was 8.66±10.73d. The logMAR BCVA of these 9 participants at presentation were as follows: 3.0 (*n*=2/9, 22.2%), 2.7 (*n*=1/9, 11.1%), 2.5 (*n*=1/10, 11.1%), <2.5 (5/9, 55.6%), and ≤0.3 (*n*=1/9, 11.1%). Of the 8 CRAO participants, 5 underwent whole-brain angiography and IAT at the central retinal artery (CRA). The remaining 4 participants received conservative treatment. Three participants after IAT exhibited improved BCVA, 1 maintained stable vision, and 1 experienced declined BCVA. In contrast, the conservative group observed no BCVA change from admission to discharge.

To illustrate the clinical heterogeneity and key characteristics of MMD associated RAO, we present four representative cases. These cases were selected to highlight variations in disease severity, vascular comorbidities, imaging findings, and response to therapy.

Case 1: Typical CRAO combined with ipsilateral MMD, and thrombolysis improved vision A 64-year-old male with hypertension and cerebral arteriosclerosis presented with 8-day history of painless left eye vision loss (initial logMAR BCVA: 1.33). Fundus examination revealed posterior pole retinal pallor, cherry-red spot in the macula, and exudates along retinal arteries, consistent with CRAO (Figure 1A). CTA demonstrated bilateral ICA stenosis, left ACA and MCA occlusion, and right MCA stenosis (Figure 1B–1C). Cerebral angiography confirmed left MMD with characteristic moyamoya vessels and poor visualization of the left CRA (Figure 1D). He underwent IAT (Figure 1E). At discharge, the final BCVA was logMAR 1.1.

Case 2: A special subtype of unilateral MMD combined with cilioretinal artery sparing and stable visual prognosis A 58-year-old female presented with a 15-hour history of acute right eye blurred vision, without prior cardiovascular history. Initial BCVA was logMAR 0.22. Fundus examination revealed posterior pole retinal pallor and edema, with a distinct lingual blood supply area in the macula, indicative of preserved cilioretinal artery perfusion (Figure 2A–2C).

Table 1 Clinical and demographic details of the MMD participants presenting with ocular symptoms included in the study

No.	Sex & age	Eye	Onset duration	Presenting BCVA (logMAR)	Fundus findings	IOP (mm Hg)	Diagnosis	Comorbidities	Intracranial vascular findings	Discovery examination of MMD	Treatment	Final BCVA (logMAR)
1	M, 64	LE	8d	CF 1 m (1.33)	Posterior pole retinal pallor and edema, darkened macula, exudates along retinal artery	16/17	CRAO; left MMD	Multiple lacunar cerebral infarctions, encephalatrophy, hypertension	Bilateral ICA stenosis, left ACA/MCA occlusion, right MCA stenosis	Cerebral angiography	IAT	20/250 (1.1)
2	F, 58	RE	15h	20/33 (0.22)	Posterior pole retinal pallor and edema, tongue-like blood supply in the macula	14/13	CRAO; left MMD	Multiple lacunar cerebral infarctions	Left ICA thinning, right PCA aneurysm	CTA	IAT	20/33 (0.22)
3	M, 57	RE	15d	CF 20 cm (2.03)	Posterior pole retinal pallor and edema, cherry-red spot	12/15	CRAO; bilateral MMD	Left carotid atherosclerotic plaques, hypertension, hyperlipemia	Bilateral MCA M1 segment occlusion	CTA	IAT	CF 30 cm (1.85)
4	M, 56	RE	1d	CF 40 cm (1.73)	Retinal artery narrowing, posterior pole retinal edema, scattered cotton wool spots	35/25	CRAO; right MMD	CHD, T2DM, cerebral infarctions	Right MCA M1 segment occlusion	CTA	IAT	CF 20 cm (2.03)
5	M, 34	LE	7h	HM 0 cm (2.5)	Posterior pole retinal pallor and edema, cherry-red spot	18/21	CRAO; left MMD	None	Bilateral ICA stenosis	Cerebral angiography	IAT	CF 15 cm (2.15)
6	M, 40	LE	1d	CF 30 cm (1.85)	Posterior pole retinal pallor and edema, cherry-red spot	19/16	CRAO; bilateral MMD	Hypercholesterolemia	Left ICA C1 segment occlusion	CTA	Conservative	CF 30 cm (1.85)
7	M, 57	RE	2d	NLP (3.0)	Grayish-white retina, cherry-red spot	11/12	CRAO; bilateral MMD	Multiple lacunar cerebral infarctions, encephalatrophy, hypertension	Right ICA occlusion	CTA	Conservative	NLP (3.0)
8	M, 54	RE	20d	LP (2.7)	Macular edema, cherry-red spot with punctate hemorrhages at superior and inferior vascular arcades	Tn/14	CLRAO; right MMD	Multiple lacunar cerebral infarctions, multiple carotid atherosclerosis	Right MCA M1 segment occlusion	CTA	Conservative	LP (2.7)
9	F, 56	RE	30d	NLP (3.0)	Posterior pole retinal pallor and edema, cherry-red spot	16/14	CRAO; bilateral MMD	Hyperlipemia	Bilateral ICA occlusion, bilateral ACA thinning	CTA	Conservative	NLP (3.0)

BCVA: Best corrected visual acuity; M: Male; F: Female; LE: Left eye; RE: Right eye; CF: Counting fingers; HM: Hand move; LP: Light perception; NLP: No light perception; CRAO: Central retinal artery occlusion; CLRAO: Cilioretinal artery occlusion; CHD: Coronary heart disease; T2DM: Type 2 diabetes mellitus; ICA: Internal carotid artery; PCA: Posterior communicating artery; MCA: Middle cerebral artery; ACA: Anterior cerebral artery; IAT: Intra-arterial thrombolysis; CTA: Computed tomography angiography; IOP: Intraocular pressure; MMD: Moyamoya disease.

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CTA demonstrated left MMD with thinning of the left ICA and MCA, alongside a right posterior communicating artery aneurysm and atherosclerotic plaque at the right ICA origin (Figure 2D). Cerebral angiography confirmed characteristic moyamoya collaterals in the left hemisphere and occlusion of the right CRA, while the right cavernous sinus aneurysm was incidentally detected (Figure 2E). She underwent IAT (Figure 2F–2G). At discharge, her final BCVA stabilized at logMAR 0.22.

Case 3: Bilateral MMD combined with multiple vascular risk factors attaining stable BCVA after thrombolysis A 57-year-old male with hypertension and hyperlipidemia presented with 15-day history of right eye vision loss (logMAR BCVA: 2.03). Fundus examination showed classic cherry-red spot and retinal edema (Figure 3A). OCT shows hyperreflective signals in the inner retina, suggesting edema (Figure 3B). CTA and angiography revealed bilateral MCA M1 segment occlusion with extensive collateral vessels, diagnostic of bilateral MMD (Figure 3C–3F). IAT was performed (Figure 3G–3H), but BCVA only slightly improved to logMAR 1.85. Notable vascular comorbidities (carotid atherosclerotic plaques) and diffuse retinal arteriolar narrowing on fundus imaging underscored the chronic ischemic burden in MMD-RAO. This case illustrates the association between MMD, atherosclerotic risk factors, and suboptimal visual recovery due to chronic retinal hypoperfusion.

Case 4: MMD combined with multiple metabolic and cardiovascular risk factors presents typical retinal microvascular lesions A 56-year-old male with coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), and prior cerebral infarction presented with a 1-day history of sudden right eye vision loss (initial logMAR BCVA: 1.73). Notable findings included elevated IOP and characteristic fundus changes: narrowed retinal arteries with white line-like lesions (arterial wall sclerosis), diffuse cotton wool spots, and macular edema—hallmarks of severe retinal ischemia and microvascular dysfunction (Figure 4A–4E).

CTA revealed right-sided MMD with occlusion of the right MCA M1 segment and bilateral carotid artery sclerosis (Figure 4F–4H). Cerebral angiography confirmed abnormal moyamoya vessels at the right skull base (Figure 4I). IAT was performed (Figure 4J–4K), resulting in a slightly lower BCVA of logMAR 2.03—reflecting limited reperfusion in the context of chronic, multi-vessel disease.

Literature Review: Basic Information and Clinical Features of Reported Participants Of 203 initially retrieved citations, 9 studies met the inclusion criteria after screening (Figure 5). Three male cases and 6 female cases were reviewed and summarized in Table 2[22,26-33]. Seven of 9 studies (77.8%) were classified as high-quality (JBI score ≥7), and 2 (22.2%) as moderate-quality (JBI score=6). Common limitations included missing long-term follow-up data and unclear documentation of treatment dosages, though no low-quality studies (score <6) were included in the analysis.

Publication Bias and Sensitivity Analysis Funnel plot analysis of final logMAR BCVA showed mild asymmetry. Most effect size points of the literature group were distributed on the left side of the pooled MD, suggesting certain publication bias with more positive vision outcomes reported. Sensitivity analysis using the one-leave-out method revealed all 95%CI across scenarios crossed the no-effect line (MD=0), with no extreme deviations in pooled MD and no influential studies identified (Figure 6). This indicates that no single study unduly influenced the overall result, and the conclusion regarding the difference in visual outcomes between the two groups remained reliable.

Baseline Characteristics of Combined Cohort Totally 18 participants were included in the final analysis, comprising 9 new cases from the current study and 9 cases from literature. There was a slight male preponderance (male/female: 1.25:1) and a shift toward a younger demographic in MMD-RAO participants compared to isolated RAO. The mean age of all participants was 39.22±17.75y, with a range of 6 to 64y. CRAO was the most common RAO subtype, affecting 15 of 18 participants (83.3%), followed by BRAO (2 participants, 11.1%) and CLRAO (1 participant, 5.6%). Initial BCVA ranged from logMAR 3.0 (no light perception, NLP) to 0.22. Regarding MMD features, bilateral MMD was present in 7 participants (38.9%) and unilateral MMD in 11 participants (61.1%), with ICA stenosis the most common intracranial finding (14/18 participants, 77.8%). Regarding treatment, IAT was performed in 5 participants (27.8%), MMD bypass surgery in 1 participant (5.6%), and conservative treatment in 10 participants (55.6%). Final BCVA outcomes showed limited overall improvement: 7 participants (41.2%) had improved vision, 7 (41.2%) had stable vision, and 3 (17.6%) had deteriorated vision.

Pooled descriptive analysis revealed significant differences in baseline characteristics between the current cohort and literature cases (Table 3). The current cohort was significantly older (52.89±9.53 *vs* 25.56±12.58y; MD=27.33, 95%CI: 19.21–35.45, $P<0.001$, $I^2=85.2\%$) and had a higher proportion of males (77.8% *vs* 33.3%; OR=6.82, 95%CI: 1.21–38.57, $P=0.153$, $I^2=42.5\%$). Cardiovascular risk factors were more prevalent in the current cohort (88.9% *vs* 55.6% in literature), with slightly worse initial vision (2.04±0.9 *vs* 1.90±0.68 in literature; MD=0.14, 95%CI: -0.60–0.88, $P=0.711$, $I^2=78.3\%$) and poorer visual recovery (1.99±0.9 *vs* 1.22±1.14; MD=0.77, 95%CI: -0.19–1.73, $P=0.132$, $I^2=82.5\%$). IAT was performed

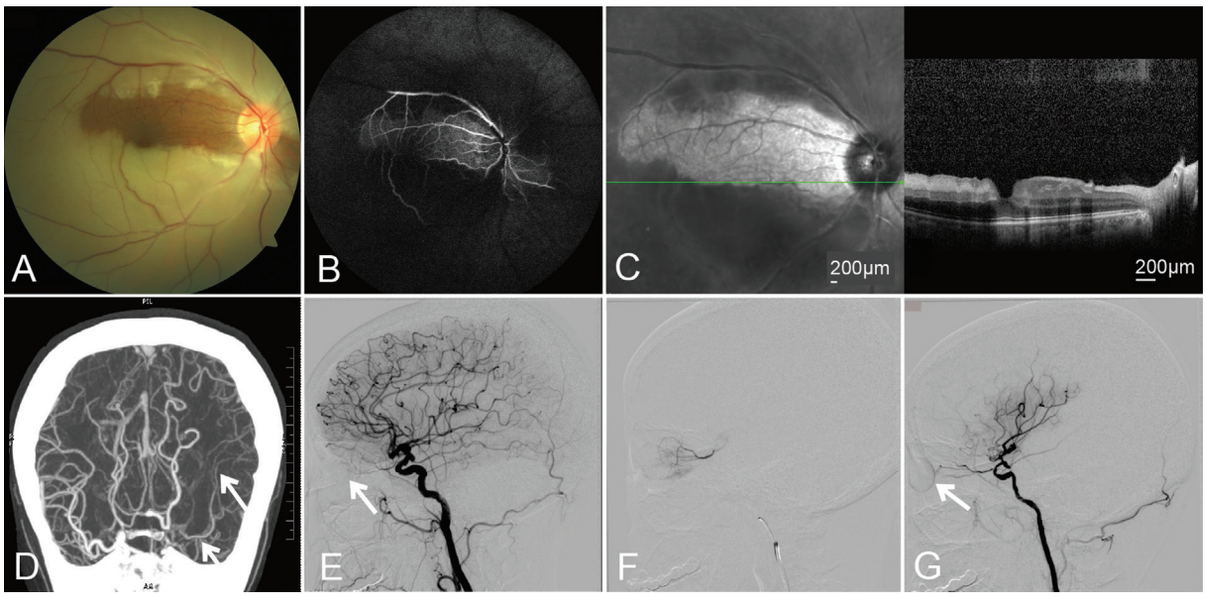

Figure 2 Case 2 imaging findings A: Fundus photography of the right eye at presentation; B: FFA image captured at 20s; C: OCT image of the right eye at presentation; D: CTA image showing left MMD; E: Cerebral angiography before thrombolytic injection; F: Cerebral angiography during the thrombolytic injection; G: Cerebral angiography after the thrombolytic injection. FFA: Fundus fluorescein angiography; OCT: Optical coherence tomography; CTA: Computed tomography angiography; MMD: Moyamoya disease.

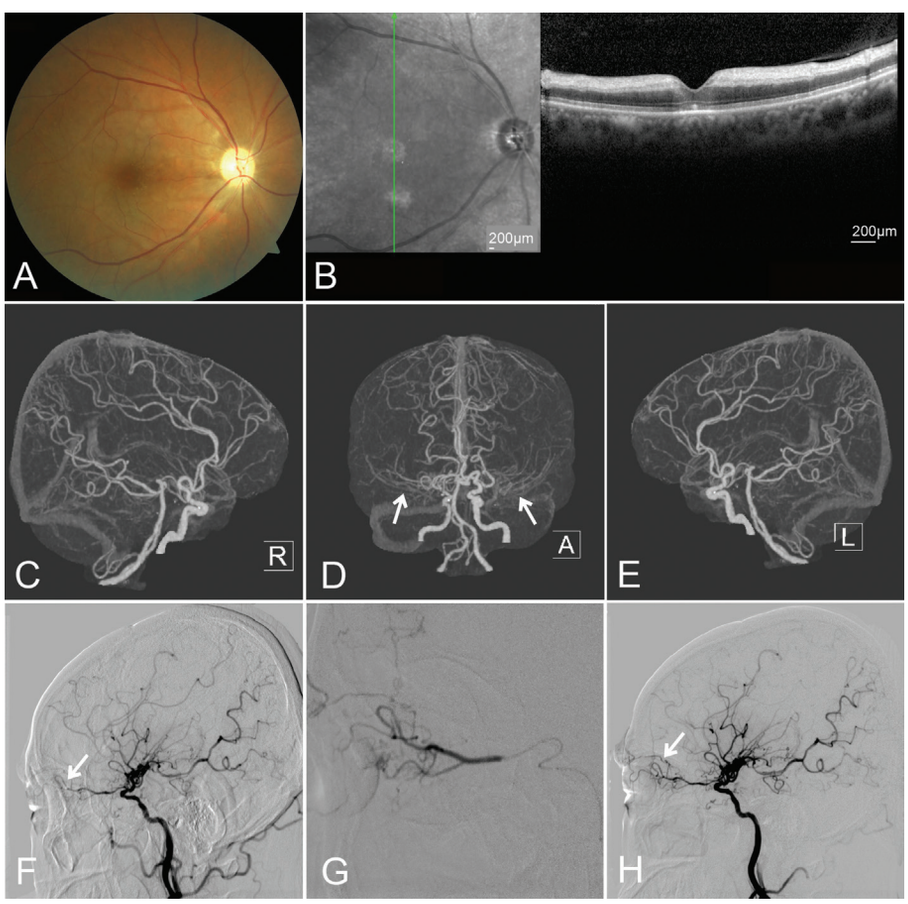

Figure 3 Case 3 imaging findings A–B: Fundus photography and OCT image of the right eye at presentation; C–E: CTA image showing bilateral MMD; F: Cerebral angiography before thrombolytic injection; G: Cerebral angiography during the thrombolytic injection; H: Cerebral angiography after the thrombolytic injection. OCT: Optical coherence tomography; CTA: Computed tomography angiography; MMD: Moyamoya disease.

in 5 of 9 participants (55.6%) in the current cohort, with an efficacy rate of 60%. Three participants had improved vision, 1 had stable vision, and 1 had deteriorated vision. No literature cases reported IAT use (OR=18.00, 95%CI: 0.98–329.71,

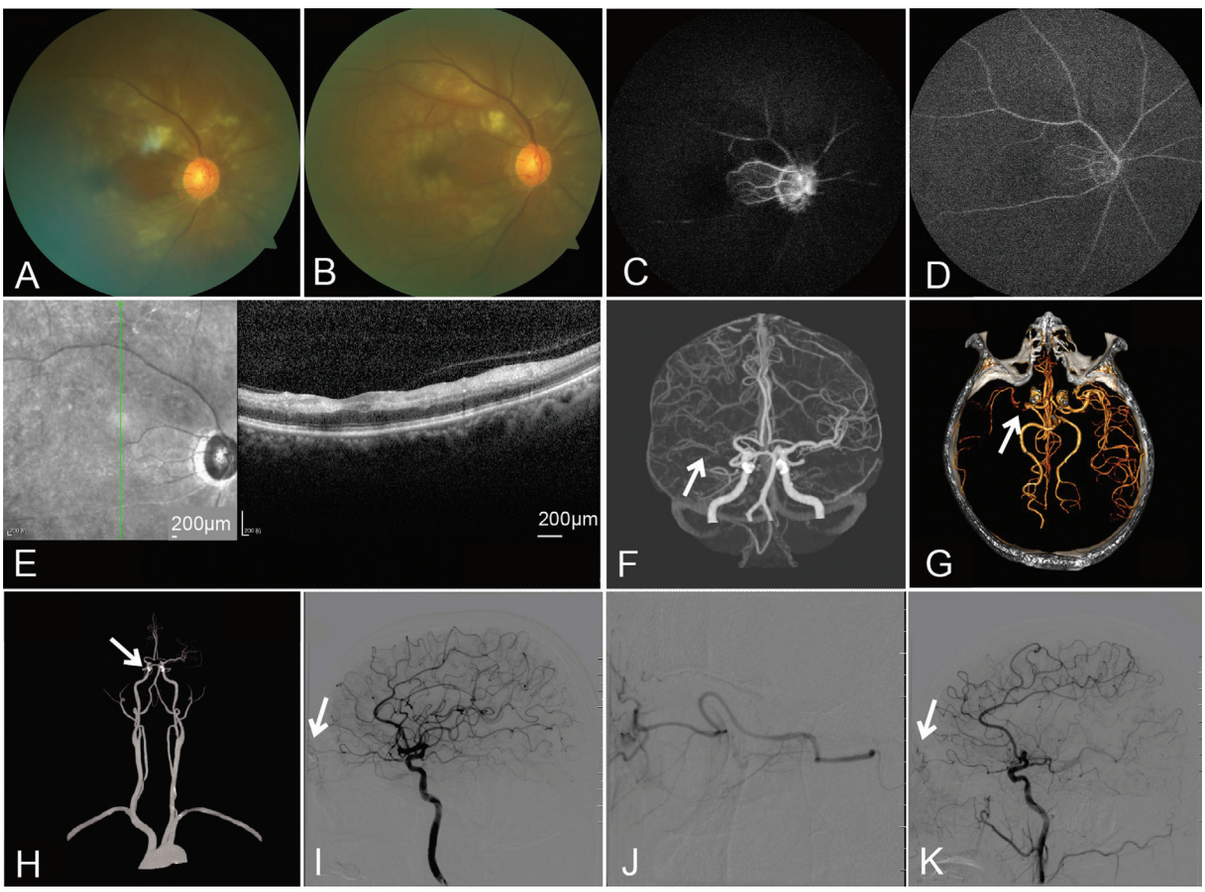

Figure 4 Case 4 imaging findings A and C: Fundus photography and FFA image captured at 1min 27s (before surgery); B and D: Fundus photography and FFA image captured at 44s (1wk post surgery); E: OCT image of the right eye at presentation; F–H: CTA image showing right MMD and bilateral carotid artery sclerosis; I: Cerebral angiography before thrombolytic injection; J: Cerebral angiography during the thrombolytic injection; K: Cerebral angiography after the thrombolytic injection. FFA: Fundus fluorescein angiography; OCT: Optical coherence tomography; CTA: Computed tomography angiography; MMD: Moyamoya disease.

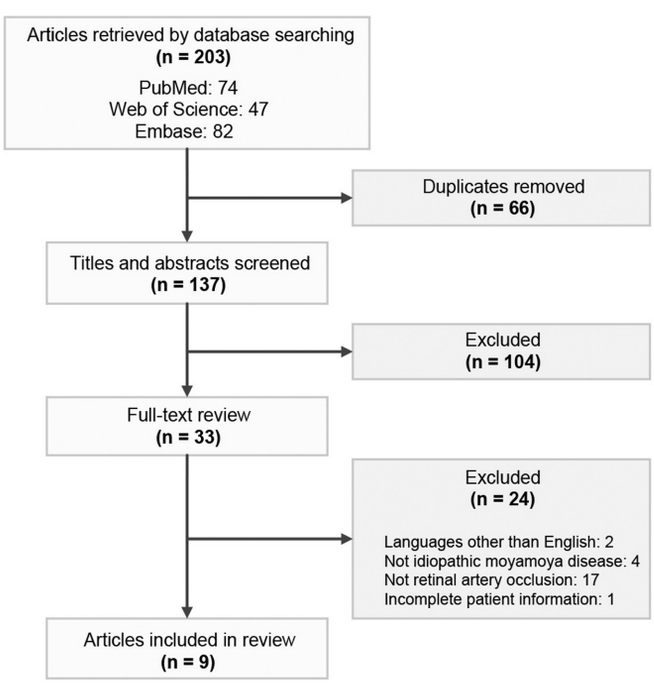

Figure 5 Flow chart of the process of literature retrieval.

P=0.052, I^2=52.7%). Conservative therapy was administered to 4 participants (44.4%) in the current cohort and 7 participants (77.8%) in the literature, though no vision improvement was observed in the current cohort.

DISCUSSION

Research Innovation and Significance This study integrates a single-center retrospective case series (9 MMD-RAO cases) with a pooled descriptive analysis (9 literature cases) to systematically characterize the clinical features, pathophysiological links, and therapeutic implications of MMD-RAO, addressing the limitations of previous small-scale, single-case studies.

A hallmark observation of this study was the severe visual impairment in MMD-RAO cohort, with initial BCVA ranging from logMAR 0.22 to 3.0 (NLP)—consistent with isolated CRAO, where 74% of participants present with BCVA of counting fingers (CF) or worse[1,34]. However, pooled descriptive analysis revealed marked heterogeneity in visual outcomes between our cohort and literature (I^2>78% for both initial and final logMAR BCVA), underscoring the critical role of RAO subtype in shaping prognosis. In our cohort, CRAO was the dominant subtype (88.9%, 8/9 cases), and only 33.3% (3/9)

Table 2 Reported cases of moyamoya disease associated with retinal artery occlusion

No.	Author	Year	Sex & age	Eye	Presenting BCVA (logMAR)	IOP	Diagnosis	Concomitant diagnosis	Intracranial vessels	Treatment	Final BCVA (logMAR)
1	Wang *et al*[26]	2024	F, 32	RE	20/160 (0.9)	N/A	CRAO	Left MMD (RNF213 gene mutation); SLE; cerebral ischemia stroke	Left MCA stenosis (M1 segment); right PCA fenestration	Aspirin, butylphthalide, urinary kallidinogenase, and sodium methylprednisolone	20/160 (0.9)
2	Shakeel *et al*[27]	2023	F, 34	RE	N/A	N/A	BRAO	Bilateral MMD; Alagille syndrome status post liver transplant; hypertension	Bilateral ICA stenosis	N/A	N/A
3	Li *et al*[28]	2023	F, 23	RE	HM 50 cm (2.3)	15.88	BRAO; bilateral retinal vein tortuosity	Bilateral MMD	Bilateral ICA stenosis	Puerarin, ox serum albumin, atropine sulfate, dexamethasone sodium phosphate injection	20/25 (0.1)
4	Rajanala *et al*[29]	2020	F, 48	RE	HM (2.3)	N/A	CRAO	Right MMD; hypertension	Right ICA stenosis	extracranial-intracranial bypass surgery	CF 2 feet (1.54)
5	Karsten *et al*[30]	2020	F, 6	LE	HM (2.3)	N/A	CRAO	Right MMD; rectal atresia and a cloacal anomaly; cerebral ischemia stroke; history of pial synangiosis	Right ICA stenosis	Clopidogrel, aspirin	NLP (3.0)
6	Lad *et al*[22]	2013	M, 17	LE	HM (2.3)	14/13	CRAO	Left MMD; NF-1	Left ICA stenosis and proximal MCA occlusion	Intermittent ocular massage, intraocular pressure-lowering medications, and aspirin	20/25 (0.1)
7	Kumar and Ganesh[31]	2013	M, 26	RE	LP (2.7)	N/A	CRAO	Right MMD	Right ICA occlusion	Aspirin and clopidogrel	LP (2.7)
8	Ushimura *et al*[32]	1993	F, 31	RE	20/290 (1.16)	8/14	CRAO	Bilateral MMD; 4th month of pregnancy; cardiac valvular disease	Bilateral ICA stenosis	Mecobalamin (Methycobal®) and Kal-likrein@ (Kallidinogenase)	20/30 (0.18)
9	Chace and Hedges[33]	1984	M, 13	RE	CF 4 feet (1.24)	N/A	CRAO	Right MMD; “Pseudothalidomide” or “SC-syndrome”	Left ICA stenosis and MCA occlusion; right ICA occlusion (M1 segment)	N/A	CF 4 feet (1.24)

BCVA: Best corrected visual acuity; F: Female; M: Male; LE: Left eye; RE: Right eye; HM: Hand move; LP: Light perception; CF: Counting fingers; CRAO: Central retinal artery occlusion; BRAO: Branch retinal artery occlusion; MMD: Moyamoya disease; SLE: Systemic lupus erythematosus; NF-1: Neurofibromatosis type 1; RF: Rheumatic fever; MCA: Middle cerebral artery; PCA: Posterior communicating artery; ICA: Internal carotid artery; NLP: No light perception.

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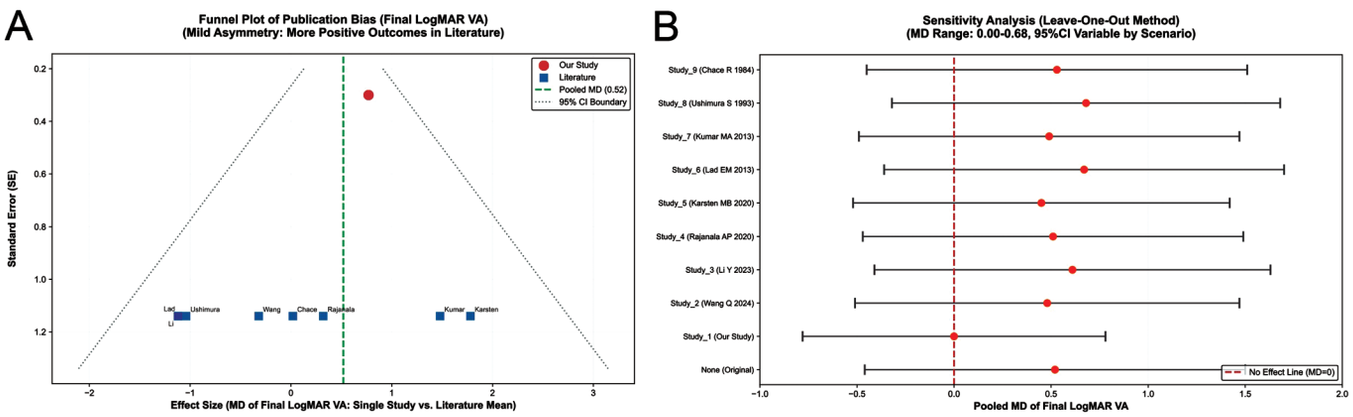

Figure 6 Funnel plot and sensitivity analysis A: Funnel plot of publication bias; B: Sensitivity analysis for final logMAR visual acuity. MD: Mean deviation; VA: Visud acuity.

Table 3 The comparison results between our cohort (*n*=9) and literature cases (*n*=9) *n* (%)

Demographic and clinical characteristics	Our cohort (mean±SD/frequency)	Literature cases (mean±SD/frequency)	Effect size (95%CI)	Heterogeneity	*P*
Continuous variables			MD (95%CI)	I^2 (%)/*Q*-test *P*	(*t*-test)
Age (y)	52.89±9.53 (34-64)	25.56±12.58 (6-48)	27.33 (19.21–35.45)	85.2/<0.001	<0.001
Initial BCVA, logMAR (all participants)	2.04±0.9 (0.22 to 3.0)	1.9±0.68 (0.9 to 2.7)	0.14 (-0.6-0.88)	78.3/<0.001	0.711
Final BCVA, logMAR (all participants)	1.99±0.9 (3.0 to 0.22)	1.22±1.14 (3.0 to 0.1)	0.77 (-0.19-1.73)	82.5/<0.001	0.132
BCVA changes (all participants)	-0.05±0.19 (0.3 to -0.35)	-0.68±1.07 (0.7 to -2.2)	0.63 (-0.08–1.34)	99.2/<0.001	0.102
Categorical variables			OR (95%CI)	I^2 (%)/*Q*-test *P*	(Fisher's exact)
Sex (male)	7 (77.8%)	3 (33.3%)	6.82 (1.21–38.57)	42.5/0.113	0.153
MMD type (bilateral)	4 (44.4%)	3 (33.3%)	1.58 (0.34–7.35)	0/0.987	1.000
Vascular risk factors					
ICA stenosis	6 (66.7%)	8 (88.9%)	0.33 (0.05–2.09)	28.3/0.225	0.576
MCA stenosis	4 (44.4%)	1 (11.1%)	6.36 (0.71–57.02)	45.1/0.108	0.294
Cerebral infarctions or ischemic stroke	5 (55.6%)	2 (22.2%)	4.38 (0.76–25.17)	31.2/0.196	0.335
Hypertention	3 (33.3%)	2 (22.2%)	1.83 (0.32–10.47)	0/0.896	1.000
Dyslipemia	4 (44.4%)	0	15.55 (0.70–343.70)	0/0.912	0.082
Carotid atherosclerosis	2 (22.2%)	0	6.33 (0.26–153.70)	0/0.875	0.471
Heart disease	0	1 (11.1%)	0.30 (0.01–8.34)	0/0.953	1.000
T2DM	1 (11.1%)	0	3.35 (0.12–93.80)	0/0.926	1.000
Treatment					
IAT	5 (55.6%)	0	18.00 (0.98–329.71)	52.7/0.076	0.029*
Conservative treatment	4 (44.4%)	7 (77.8%)	0.28 (0.06–1.31)	40.5/0.127	0.334
RAO subtype (CRAO)	8 (88.9%)	7 (77.8%)	2.50 (0.35–17.86)	0/0.964	1.000
BCVA changes					
Improvement	3 (33.3%)	4 (44.4%)	0.64 (0.13–3.12)	35.7/0.168	1.000
Stabilization	3 (33.3%)	3 (33.3%)	1.00 (0.14–7.39)	0 / 0.971	1.000
Deterioration	3 (33.3%)	1 (11.1%)	4.00 (0.33–48.70)	0/0.938	0.576

MD: Mean difference; OR: Odds ratio; MMD: Moyamoya disease; ICA: Internal carotid artery; MCA: Middle cerebral artery; T2DM: Type 2 diabetes mellitus; IAT: Intra-arterial thrombolysis; CRAO: Central retinal artery occlusion; RAO: Retinal artery occlusion; BCVA: Best corrected visual acuity; SD: Standard deviation; CI: Confidence interval.

of participants achieved visual improvement. In contrast, literature cases exhibited broader outcome variability, including complete visual recovery (logMAR=0.1) in participants with BRAO. These findings highlight the need for stratified analysis by RAO subtype in future studies on MMD-RAO.

Notably, MMD-RAO profiles differed significantly from isolated RAO. With a mean age of 52.89y, our cohort was older than the classic MMD participants (30–40y[35]) but younger than isolated RAO (60–70y[2]), likely due to the additional effects of MMD and vascular risk factors. Sex distribution showed a male predominance (male:female ratio, 1.25:1), contrasting with classic MMD (1:1.8 or 1:1.2[35]) but aligning with RAO epidemiology (1.5:1[36] or 1.7:1[37]), suggesting vascular risk factors like ischemic stroke and hypertension

may override sex-related predispositions in MMD-RAO. This "older MMD phenotype" may reflect age-related exacerbation of vascular stenosis, bridging MMD pathophysiology with typical RAO risk factors. In isolated RAO, focal vessel obstruction due to emboli is typical, and diffuse arteriolar narrowing is less common[2]. Cotton-wool spots—signs of retinal nerve fiber layer ischemia, were observed in Case 4 and Case 7, aligning with literature linking MMD-related RAO to broader microvascular dysfunction due to ICA occlusion[30,38]. Besides, bilateral MMD with unilateral RAO was observed in nearly half of our cases (44.4%), reflecting the "steal phenomenon" where collateral vessels prioritize cerebral perfusion, exacerbating retinal hypoperfusion[19]. This also illustrates how systemic vasculopathy predisposes to retinal ischemia beyond local emboli—a contrast to isolated RAO, where carotid plaque emboli are the primary cause[3].

Therapeutically, our data highlights that MMD-RAO shares acute treatment responses with isolated RAO. The 5/9 (55.6%) participants in our cohort underwent IAT, and 60% (3/5) achieving visual improvement. This efficacy rate is comparable to isolated CRAO treated with thrombolysis (60%–70% improvement[39-41]), suggesting that IAT can be a viable option for MMD-RAO participants. While IAT addresses acute retinal ischemia, it does not resolve the underlying MMD-related cerebrovascular disease—a critical oversight in long-term care. The 2/5 (40%) of our IAT-treated participants had no visual improvement, likely due to chronic retinal hypoperfusion from unresolved ICA stenosis. In contrast, a literature case[29] reported visual stabilization in a participant after extracranial-intracranial (EC-IC) bypass surgery, highlighting the role of revascularization in improving chronic ocular and cerebral hypoperfusion. These findings underscore a "two-step" management paradigm for MMD-RAO: 1) acute intervention (*e.g.*, IAT) to treat RAO and salvage vision; 2) comprehensive cerebrovascular evaluation (*e.g.*, DSA) to assess MMD severity, followed by chronic management (*e.g.*, EC-IC bypass, antiplatelet therapy) to prevent recurrent ischemia. Clinicians should avoid focusing solely on retinal outcomes, as untreated MMD carries a high risk of cerebral infarction—a more morbid complication.

Current Research Limitations This study has several limitations that should be considered when interpreting its findings. First, the single-center, retrospective design introduces potential selection bias and limits generalizability. Second, the pooled descriptive comparisons are exploratory and hypothesis-generating, highlighting the need for larger prospective studies to validate the observed associations. Nevertheless, this study aids clinicians in screening for MMD in RAO participants, particularly those with systemic vascular diseases.

Conclusion and Future Perspectives This case series and pooled descriptive analysis identifies RAO as a potential diagnostic clue for MMD, particularly in older participants with cardiovascular comorbidities. The identification of an "older MMD phenotype" challenges traditional notions of MMD as a disease of children and young adults, highlighting the need for comprehensive vascular assessment in RAO participants. Future multi-center, prospective studies across disease subtypes, ethnicities, and comorbidity profiles are needed to validate RAO as an early warning sign of MMD.

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