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Bypass Treatment versus EDAS for Moyamoya Disease: a systematic review

Tratamiento de Derivación frente a EDAS para la Enfermedad de Moyamoya: una revisión sistemática

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ABSTRACT

Moyamoya disease (MMD) is a cerebrovascular disorder characterized by the formation of fragile collateral vessels, which leads to an increased risk of ischemic and hemorrhagic stroke. The principal treatment for MMD is surgical revascularization. This review compares two surgical modalities: direct bypass surgery and encephalo-duro-arterio-synangiosis (EDAS). A search was performed on PubMed, Embase, LILACS, and Cochrane. Inclusion required clinical studies published in English in a journal with an impact factor >1 since 2000, comparing direct versus EDAS in MMD patients. Efficacy was assessed using mRS, incidence of ischemic events, and rebleeding, while safety included complications. The review included 7 retrospective cohorts (n = 604): 224 (37.1%) direct, 312 (51.6%) EDAS, and 68 not specified. The incidence of ischemic and cerebral hemorrhagic events was generally higher in the indirect group, with similar results in overall functional improvement (mRS). However, patients undergoing direct bypass experienced higher surgical complication rates. Mortality was low across all studies, with slightly more deaths reported in the indirect group in one cohort. The current evidence suggests that direct bypass may offer superior long-term efficacy, although with a higher risk.

Keywords: *Moyamoya disease; Cerebral revascularization; Cerebrovascular disorders; Neurosurgical procedures.*

RESUMEN

La enfermedad de Moyamoya (EMM) es un trastorno cerebrovascular caracterizado por la formación de vasos colaterales frágiles, lo que aumenta el riesgo de accidente cerebrovascular isquémico y hemorrágico. El tratamiento principal para la EMM es la revascularización quirúrgica. Esta revisión compara dos modalidades quirúrgicas: la cirugía de bypass directo y la encefaloduroarteriosinangiosis (EDAS). Se realizó una búsqueda en PubMed, Embase, LILACS y Cochrane. Se incluyeron estudios clínicos publicados en inglés en una revista con un factor de impacto >1 desde 2000, que comparaban la cirugía directa con la EDAS en pacientes con MMD. La eficacia se evaluó mediante la escala mRS, la incidencia de eventos isquémicos y la rehemorragia, mientras que la seguridad incluyó las complicaciones. La revisión incluyó 7 cohortes retrospectivas (n = 604): 224 (37,1%) directas, 312 (51,6%) EDAS y 68 sin especificar. La incidencia de eventos isquémicos y hemorrágicos cerebrales fue generalmente mayor en el grupo indirecto, con resultados similares en la mejora funcional general (mRS). Sin embargo, los pacientes sometidos a bypass directo experimentaron mayores tasas de complicaciones quirúrgicas. La mortalidad fue baja en todos los estudios, con un número ligeramente superior de muertes en el grupo indirecto en una cohorte. La evidencia actual sugiere que el bypass directo puede ofrecer una eficacia superior a largo plazo, aunque con un mayor riesgo.

Palabras clave: *Enfermedad de Moyamoya; Revascularización cerebral; Trastornos cerebrovasculares; Procedimientos neuroquirúrgicos.*

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1 INTRODUCTION

Moyamoya disease (MMD) is a rare and progressive cerebrovascular disorder characterized by stenosis of the internal carotid arteries and the formation of fragile collateral vessels, known as moyamoya vessels. This condition leads to a reduction in cerebral blood flow, which in turn increases the risk of ischemic and hemorrhagic stroke, particularly in children and individuals of East Asian descent[1]. Symptoms of MMD include headache, transient ischemic attack, and seizures. Diagnosis is typically established using image exams, such as magnetic resonance imaging (MRI) or digital subtraction angiography (DSA)[2].

Regarding treatment options, MMD's main treatment is surgical intervention that aims to restore cerebral blood flow and mitigate the risk of ischemic and hemorrhagic stroke. A Conservative approach is warranted in specific cases, employing antiplatelet therapy designed to mitigate the risk of thrombosis[1].

As for surgical approaches, several techniques exist, such as direct bypass surgery, which involves connecting a healthy artery directly to the moyamoya vessels. This procedure demonstrates excellent long-term results and a good functional prognosis[3], and it is readily adaptable to most presentations of the disease[4]. However, bypass surgery carries a risk of hyperperfusion syndrome and complications related to the craniotomy (hematomas, infections, surgical dehiscence, for example)[5], and it may also increase the risk of hemorrhagic stroke in asymptomatic MMD when compared to conservative management[4].

Another treatment modality is encephalo-duro-arterio-synangiosis (EDAS), which is an indirect cerebral revascularization technique. The surgical procedure involves dissecting a superficial temporal artery (STA), which remains attached to the systemic circulation, and laying it onto the surface of the cerebral cortex, in direct contact with the opened dura mater. The central objective is to stimulate the gradual formation of new collateral vessels from the implanted artery over time[6]. The literature reports that this surgery has a high success rate and leads to neurological functional improvement[7], particularly in pediatric patients, in whom EDAS has demonstrated a ten-year survival rate of 96.5%, with a low stroke risk of 0.33% per person-year[8]. Regarding complications, the most common is the rebleed risk, suggesting that EDAS may not be the most effective for hemorrhagic MMD, as shown in a previous meta-analysis about this type of disease[9].

Therefore, based on the AHA/American Stroke Association Guidelines, surgical revascularization is recommended (class 2a) for adult patients with symptomatic MMD, as there is sufficient supporting evidence[10].

The primary objective of this review is to determine the efficacy and safety of the treatment modalities for MMD by comparing the efficacy using clinical parameters, such as modified ranking scale (mRS), ischemic or hemorrhage stroke, rebleeding, and mortality; and the analysis of the complications.

2 METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines[11]. It was prospectively registered in PROSPERO (CRD420251230380).

A meta-analysis was not conducted due to substantial heterogeneity in how the included studies defined and measured both efficacy and safety outcomes, as well as the impossibility of combining pediatric and adult population subgroups with very different baseline characteristics.

Eligibility criteria

Studies were included in this systematic review if they met all of the following eligibility criteria[1]: clinical studies published since 2000, in English, and in journals with with impact factor greater than 1[2]; involving patients of any age diagnosed with moyamoya disease[3] treated with direct revascularization (superficial temporal artery to middle cerebral artery STA-MCA) versus indirect revascularization (encephalo-duro-arterio-synangiosis – EDAS)[4]; evaluating clinical outcomes, procedure complications or angiographic outcomes.

Search strategy, study selection, and data extraction

We performed a comprehensive search on PubMed, Embase, LILACS, and Cochrane databases from inception to July 5, 2025, with the following strategy: "(moyamoya OR "moyamoya disease") AND (bypass OR "direct revascularization") AND (EDAS OR "encephaloduroarteriosynangiosis" OR "indirect revascularization")". Two authors (A.B.B.B. and A.M.V.F.) independently screened the studies, with conflicts resolved by the senior author (P.H.P.A.). The references from all included studies were also searched manually for any additional studies.

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Two authors (A.B.B.B. and A.M.V.F.) independently extracted data from the studies, and any conflicts were resolved by consensus.

Outcomes

The primary objective of this systematic review is to compare the effectiveness of direct bypass versus EDAS in patients with MMD, focusing specifically on major clinical outcomes: ischemic events, hemorrhagic events, and postoperative mortality. Secondary objectives include evaluating differences in functional outcomes (e.g., modified Rankin Scale scores), the incidence of surgical complications such as transient neurological events, infections, and seizures.

Quality assessment

The risk of bias was assessed using the ROBINS-I tool[12]. This tool was used to assess bias risk in observational studies, providing a comprehensive framework for evaluating the methodological quality of non-randomized intervention studies. Two independent reviewers (A.B.B.B. and A.M.V.F.) performed the assessments manually, according to the tool's established criteria. Disagreements were resolved by a third author (J.S.M.).

3 RESULTS

Study selection

A total of 763 records were identified from PubMed (n = 411), Embase (n = 270), LILACS (n = 55), and Cochrane (n = 27). After removing 218 duplicates, 545 records remained for title and abstract screening. Among these, 28 articles were selected for full-text evaluation. A total of 15 reports were excluded for the following reasons: two were not published in English; three were abstracts, letters, reviews, or study protocols; seven did not include a direct versus indirect (EDAS) bypass comparison or failed to report these results separately; and three did not evaluate the outcomes of interest. Ultimately, 7 studies were included in the present analysis (Figure 1).

Baseline characteristics of the included studies and patients

The included studies comprised 7 retrospective cohorts, conducted across 3 countries (6 single-center and 1 multicenter studies) between 1983 and 2022. A total of 604 patients diagnosed with MMD were included: 224 (37.1%) undergoing direct bypass, 312 (51.6%) undergoing EDAS, and 68 (11.3%) not specified. A total of 342 (56.6%) were female. Mean ages ranged from 11.2 to 45.2 years. The most common MMD presentation was unilateral (181 cases), reported in 5 studies, followed by bilateral (124 cases), reported in 3 studies. Four studies provided information on the Angiographic Staging System Suzuki Scale: 248 patients with Suzuki ≤3, and 238 patients with Suzuki ≥4. Further details on baseline characteristics of the included studies and patients are provided in Table 1.

Clinical follow-up

The follow-up period varied. Abla et al. reported 36.6±35.6 months for direct bypass and 25.1±31.1 months for indirect bypass[13]. Deng et al. described medians of 40.5 months and 31.5 months, respectively[14]. The Kawaguchi et al. cohort had longer follow-up, of 7.7±3.1 years and 6.8 ±2.1 years[15]. Lai et al. had a follow-up of approximately 4 years[16]. Nielsen et al. did not report the follow-up time[17]. Yuan et al. evaluated patients at 6.45±0.65 months, while Zhao et al. reported follow-up of 71.9±22.2 months (direct bypass) and 60.2±24.3 months (EDAS)[18,19].

Surgical characteristics of the procedures

All studies used standardized revascularization techniques: STA-MCA as the direct method and EDAS as the indirect method. Only Deng and Zhao reported operative time, with consistently longer durations for direct bypass (medians of 210 minutes with a range of 90–340 minutes in Deng et al.[14]; and a mean of 203.0 ± 50.9 min in Zhao et al.[19]) compared to indirect bypass (160 minutes with a range of 60–314 minutes; and 138.2 ± 40.6 min, respectively)[15,19].

Complementary procedures

Abla et al. was the only study that reported the need for complementary procedures[13]. In the adult direct group, complementary burr hole procedures were performed in three patients. One patient underwent burr holes with dural inversion bilaterally following direct bypass, another patient underwent burr holes with dural inversion unilaterally after direct bypass, and a third patient underwent an indirect bypass followed by burr holes after the initial direct bypass.

In the adult indirect group, burr hole procedures were performed in four patients. Three patients underwent burr holes with dural inversion bilaterally after indirect bypass, and one patient underwent burr holes as the first procedure following an indirect bypass performed at another center.

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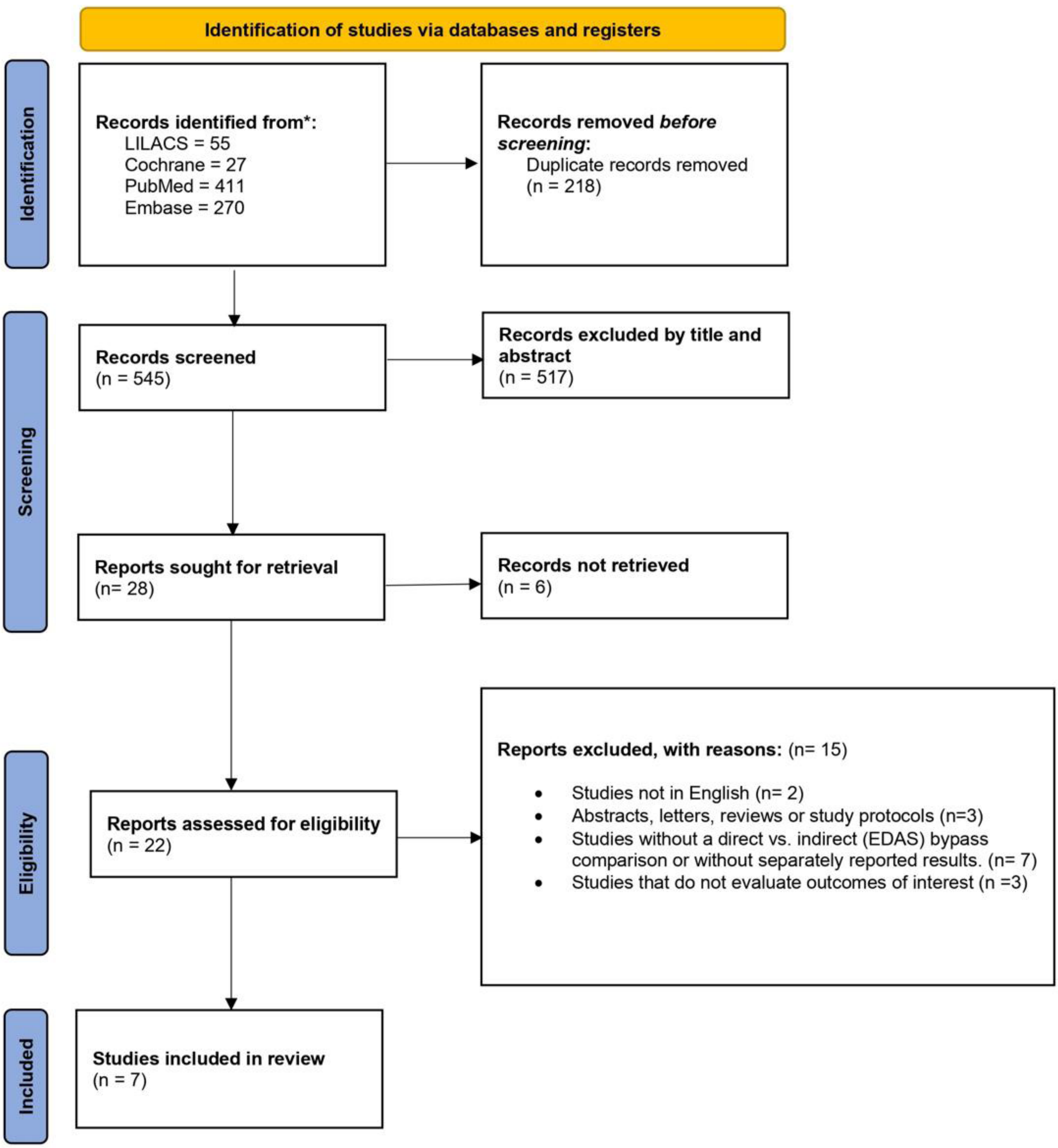

Figure 1. PRISMA flow diagram.

Clinical efficacy

The clinical efficacy of revascularization procedures was assessed mainly through the occurrence of ischemic events and intracranial hemorrhage, the main outcomes that reflect the therapeutic objective of bypass in the context of MMD.

Ischemic events

The incidence of ischemic events varied between studies, but in general, there was a higher occurrence in the group of indirect revascularization (38 events in direct and 51 in indirect). Table 2 summarizes all reported ischemic events.

Table 1. Baseline characteristics of the included studies and patients.

Author (year)	Study design	Country	Technique	Number of patients	Age during enrollment in years Mean ± SD	Male/ female	Suzuki stage ≤3	Suzuki stage ≥4
Abla et al. (2013)[13]	Retrospective cohort	USA	D	29	43.6 ± 11.5	9/20	NR	NR
Abla et al. (2013)[13]	Retrospective cohort	USA	I	39	40.3 ± 12.8	9/30	NR	NR
Deng et al. (2017)[14]	Retrospective cohort	China	D	70	NR*	32/38	28	42
Deng et al. (2017)[14]	Retrospective cohort	China	I	I: 70	NR*	I: 26/44	28	42
Kawaguchi et al. (2000)[15]	Retrospective cohort	Japan	D	D: 6	39.8± 9.3	1/5	NR	NR
Kawaguchi et al. (2000)[15]	Retrospective cohort	Japan	I	5	34.6± 11.1	2/3	NR	NR
Lai et al. (2021)[16]	Retrospective cohort	USA	D	44	43 ± 11	32/12	NR	NR
Lai et al. (2021)[16]	Retrospective cohort	USA	I	51	Age at presentation 39 ± 11 Age at time of surgery 41 ± 11	42/9	NR	NR
Nielsen et al. (2021)[17]	Retrospective cohort	USA	D	NR	NR	NR	65	68
Nielsen et al. (2021)[17]	Retrospective cohort	USA	I	NR	NR	NR	44	16
Yuan et al. (2023)[18]	Retrospective cohort	China	D	41	44.7 ± 9.7	22/19	25	16
Yuan et al. (2023)[18]	Retrospective cohort	China	I	43	45.2 ± 8.6	20/23	28	16
Zhao et al. (2019)[19]	Retrospective cohort	China	D	34	11.21 ± 4.10	18/16	15	19
Zhao et al. (2019)[19]	Retrospective cohort	China	I	104	11.26 ± 3.61	16/18	15	19

Abbreviations: D: Direct; I: Indirect; NR: Not reported. *Indicates median age in theirs 40s.

Stroke-Free interval

Available data is insufficient for a robust conclusion. In Zhao et al., the mean stroke-free interval was 70.2 ± 22.2 months for the direct bypass group and 47.9 ± 31.2 months for the indirect bypass group, with a statistically significant difference ($p = 0.025$)[19]. In Abla et al., the last patient in the direct group experienced a stroke 148 months after the initial surgery, while the last patient in the indirect group remained stroke-free at 153 months of follow-up ($p = 0.74$)[13]. No other studies analyzedthis outcome.

Cerebral hemorrhagic events

Cerebral hemorrhagic events were more frequent in the indirect bypass group. Deng et al. recorded one case in each group, without reporting the precise timing of occurrence[14]. Kawaguchi et al. documented two hemorrhages in the indirect group (at 0.3 and 6.9 years), versus none in the direct group[15]. Similarly, Lai et al. described two late postoperative hemorrhages in the indirect group occurring more than 14 days after surgery, versus none in the direct group[16]. Other studies did not report hemorrhagic events in both groups[13,17-19].

Modified Rankin Scale for Neurologic Disability (mRS score)

Good neurological status was defined as mRS ≤2, and poor neurological status as mRS ≥3. In most studies, there is no significant difference in overall functional improvement (mRS) between direct and indirect bypass.

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Table 2. Reported ischemic events following direct and indirect bypass techniques in the included studies.

Study / Year	Technique	Event type	Number of patients	Timing
Abla et al. (2013)[13]	D	Ipsilateral ischemic event	5	NR
Abla et al. (2013)[13]	I	Ipsilateral ischemic event	4	NR
Deng et al. (2017)[14]	D	TIA	1	1–19 months (median 8)
Deng et al. (2017)[14]	D	Cerebral infarction	2	1–19 months (median 8)
Deng et al. (2017)[14]	I	TIA	5	10–57 months (median 17)
Deng et al. (2017)[14]	I	Cerebral infarction	3	10–57 months (median 17)
Deng et al. (2017)[14]	I	TIA + cerebral infarction	1	10–57 months (median 17)
Kawaguchi et al. (2000)[15]	D	Ischemic stroke	0	—
Kawaguchi et al. (2000)[15]	I	Ischemic stroke	1	0.7 years
Lai et al. (2021)[16]	D	Late infarction	3	>14 days
Lai et al. (2021)[16]	I	Late infarction	4	>14 days
Lai et al. (2021)[16]	D	Late hypoperfusion (TIA)	2	>14 days
Lai et al. (2021)[16]	I	Late hypoperfusion (TIA)	16	>14 days
Nielsen et al. (2021)[17]	D	Perioperative TIA	23	≤7 days
Nielsen et al. (2021)[17]	I	Perioperative TIA	9	≤7 days
Yuan et al. (2023)[18]	T	Ischemic events	0	-
Zhao et al. (2019)[19]	D	TIA	1	NR
Zhao et al. (2019)[19]	D	Cerebral infarction	1	NR
Zhao et al. (2019)[19]	I	TIA	7	NR
Zhao et al. (2019)[19]	I	Cerebral infarction	1	NR

Abbreviations: D: Direct; I: Indirect; T: Combined groups (individual data not reported); TIA: Transient ischemic attack; NR: Not reported.

Abla et al. observed high functional scores in both groups at final follow-up[13]: the direct bypass group showed significant improvement, from an mRS of 1.48 ± 0.738 to 1.09 ± 0.90, while the indirect group showed a slight worsening, from 1.80 ± 1.10 to 1.94 ± 1.51.

Deng et al. reported improvement with both techniques, with 64 patients in the direct group and 66 in the indirect group achieving mRS ≤2 postoperatively, although preoperative mRS data were only partially available (D: 61; I: 64)[14].

Lai and Kawaguchi cohorts did not report postoperative mRS data[15,16].

Nielsen et al. reported reported minimal improvement in both groups, with 82 patients in the direct group and 36 in the indirect group achieving mRS ≤2 postoperatively; preoperative data were partially available (mRS ≤2 – D: 80; I: 34; mRS ≥3 – D: 8; I: 3). Poor neurological status was reported in 8 patients in the direct group and 6 in the indirect group[17].

Yuan and Zhao cohorts did not report preoperative mRS data, making a comparison analysis impossible[18,19].

Angiographic efficacy

Regarding angiographic results, Nielsen et al. was the only study to report revascularization extent and graft patency[17]. Postoperative patency was observed in 88 cases undergoing direct bypass and in 44 cases in the indirect group, although with a considerable amount of missing data in both groups (direct: 44 cases; indirect: 17 cases). Regarding the extent of revascularization in the middle cerebral artery territory, the direct group had greater coverage: 32 cases (versus 8 in indirect) involved 1/3–2/3 of the territory, and 28 cases (versus 11 in indirect) exceeded 2/3. These findings suggest that direct bypass promotes broader immediate perfusion, although a robust conclusion is impossible due to the absence of angiographic evaluation in the other included studies.

Safety

Post-procedure complications

The qualitative data synthesis in Table 3 suggests that patients undergoing direct (53 events) bypass experienced higher surgical complications compared to those undergoing EDAS (36 events).

Mortality

Mortality was generally low across the studies. In Abla et al., no deaths occurred in the direct bypass group, while two deaths were reported in the indirect group, with unspecified causes[13]. Deng et al., Kawaguchi et al., Lai et al., Yuan et al., and Zhao et al. reported no deaths in any of the groups[14-16,18,19].

Table 3. Surgical complications following direct and Indirect bypass.

Author (Year)	Technique	Complication Type	Timing of Event	Management	Number of events
Abla et al. (2013)[13]	D	Bypass occlusion	9 months and 65 months	Managed conservatively	2
Abla et al. (2013)[13]	D	Bypass failure	33 months	Redo high-flow bypass	1
Abla et al. (2013)[13]	D	Bypass failure/revision	Immediate	Revision bypass after surgery	1
Abla et al. (2013)[13]	D	Infection	NR	Reoperation required	1
Abla et al. (2013)[13]	D	Surgical site / subdural hematoma	NR	Reoperation required	1
Abla et al. (2013)[13]	I	Infection	NR	Reoperation required	1
Abla et al. (2013)[13]	I	Surgical site / subdural hematoma	NR	Reoperation required	2
Deng et al. (2017)[14]	D	Hyperperfusion syndrome	NR	NR	2
Deng et al. (2017)[14]	D	Seizure	NR	NR	3
Deng et al. (2017)[14]	D	Infection	NR	NR	2
Deng et al. (2017)[14]	D	Intracranial hemorrhage	NR	NR	1
Deng et al. (2017)[14]	I	Seizure	NR	NR	3
Deng et al. (2017)[14]	I	Subdural effusion	NR	NR	2
Deng et al. (2017)[14]	I	Intracranial hemorrhage	NR	NR	1
Kawaguchi et al. (2000)[15]	D	NR	-	-	-
Kawaguchi et al. (2000)[15]	I	NR	-	-	-
Lai et al. (2021)[16]	D	Wound breakdown	<14 days	NR	1
Lai et al. (2021)[16]	D	Early postoperative thrombosis of bypass	<14 days	1 required reoperation	2
Lai et al. (2021)[16]	I	Early infarction	<14 days	NR	6
Nielsen et al. (2021)[17]	D	Perioperative seizure	First 7 days	NR	12
Nielsen et al. (2021)[17]	D	Perioperative transient neurological event	First 7 days	NR	26
Nielsen et al. (2021)[17]	I	Perioperative seizure	First 7 days	NR	4
Nielsen et al. (2021)[17]	I	Perioperative transient neurological event	First 7 days	NR	15
Yuan et al. (2023)[18]	D	NR	-	-	-
Yuan et al. (2023)[18]	I	NR	-	-	-
Zhao et al. (2019)[19]	D	New transient neurological deficit	NR	NR	3
Zhao et al. (2019)[19]	I	New transient neurological deficit	NR	NR	2
Zhao et al. (2019)[19]	D	Seizure	NR	NR	2
Zhao et al. (2019)[19]	I	Seizure	NR	NR	0

Abbreviations: D: Direct; I: Indirect; NR: Not reported.

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In Nielsen's cohort, one patient died after direct bypass[17]: a 46-year-old female with prior strokes and impaired reserve developed multiple progressive ischemic lesions in both hemispheres, leading to extensive bilateral infarction and death on postoperative day 2.

Four deaths occurred in the indirect bypass group of Nielsen's cohort[17]. These included: A 46-year-old male, 4 days after a left-hemisphere EDAS, had a preoperative mRS of 4 due to a prior right-hemisphere stroke, and despite an uncomplicated right-hemisphere direct bypass one week earlier, he developed severe bilateral MCA infarctions postoperatively. A 40-year-old female with a complex medical history—including childhood leukemia, cardiomyopathy post–heart transplant, and kidney failure on dialysis—underwent indirect bypass without postoperative stroke. Another 66-year-old female with bilateral MMD with prior left-hemisphere strokes, severe M1 occlusion, and very low intraoperative flow (0.9 ml/min) died 8 days after EDAS following a malignant MCA infarction despite decompressive hemicraniectomy. There was one death at 13 months of follow-up, due to an unknown cause.

Quality assessment

The risk of bias in the included studies was investigated using the ROBINS-I tool.

In general, most studies had a moderate to serious risk of bias owing to confounding factors, participant selection, missing data, and selective reporting of results. Three studies demonstrated serious risk in Domain 1 (confounding factors): the surgical modality in Lai et al. study[16] was based solely on the neurosurgeon's discretion; Nielsen[17] presented markedly imbalanced baseline characteristics; and Yuan et al.[18] preferentially assigned patients with poorer arterial conditions to EDAS, suggesting confounding by indication.

In Domain 3 (selection of participants), Lai et al. et al.[16] was at moderate risk due to a lack of explanation for exclusions due to insufficient follow-up. Yuan et al.[18] and Zhao et al.[19] were at serious risk due to considerable loss to follow-up (26% and 15%, respectively), with an inadequate explanation of the underlying mechanisms of these losses.

In Domain 4 (missing Data), Zhao et al.[19] and Yuan et al.[18] were rated as having a moderate risk due to incomplete follow-ups and the absence of any bias mitigation strategies.

In Domain 5 (outcome measurement), Kawaguchi et al.[15] was rated as having a moderate risk because some evaluations used subjective, unblinded scales, whereas Zhao et al.[19] was rated as having a serious risk because his follow-up was conducted by telephone, which is prone to misclassification.

Regarding Domain 6 (selection of reported results), Lai et al.[16], Nielsen et al.[17], and Yuan et al.[18] were rated as posing a serious risk because their findings highlighted superiority over selected interventions, even though their results were largely non-significant. Zhao[19]: Moderate risk of overgeneralisation, prioritizing a statistically significant outcome (stroke-free time) over the non-significant functional outcome comparison (mRS).

Overall, four studies[16-19] were identified as posing a serious risk of bias, while other three posed a moderate risk[13-15] (Table 4).

Table 4. Risk of bias using the ROBINS-I tool.

Study	D1	D2	D3	D4	D5	D6	Overall
Abla et al. (2013)[13]	Low	Low	Low	Moderate	Low	Low	Moderate
Deng et al. (2017)[14]	Low	Low	Moderate	Low	Low	Low	Moderate
Kawaguchi et al. (2000)[15]	Low	Low	Moderate	Moderate	Low	Low	Moderate
Lai et al. (2021)[16]	Serious	Low	Moderate	Low	Low	Serious	Serious
Nielsen et al. (2021)[17]	Serious	Low	Moderate	Moderate	Low	Serious	Serious
Yuan et al. (2023)[18]	Serious	Low	Moderate	Moderate	Moderate	Serious	Serious
Zhao et al. (2019)[19]	Low	Low	Moderate	Moderate	Serious	Low	Serious

4 DISCUSSION

This review included 7 studies encompassing 604 patients with MMD: 224 (37.1%) underwent direct bypass, 312 (51.6%) received EDAS, and 68 (11.3%) were not specified. The comparative analysis identified nuanced clinical efficacy and safety differences in both revascularization modalities and demonstrated individual differences across outcome domains and patient populations. In this regard, direct bypass outperformed in some efficacy parameter evaluations, including long-term cerebrovascular events, and EDAS was positively associated with overall effectiveness.

Our results support the rapidly increasing evidence base supporting the rationale for age- and vascular anatomy-based surgical decision-making in Moyamoya disease. Direct revascularization is associated with better outcomes in adult populations with sufficient donor and recipient vessels. A meta-analysis by Nguyen et al. in a cohort of 143 trials including 3,827 direct bypass procedures showed significant reductions of early stroke (OR 0.62, 95% CI 0.48–0.79; P < 0.0001), late stroke (OR 0.44, 95% CI 0.32–0.59; P < 0.0001), and late intracerebral hemorrhage (OR 0.56, 95% CI 0.42–0.74; P < 0.0001) compared to indirect procedures and therefore more favorable use in individuals with significant hemodynamic compromise or recurrent ischemic signs[20].

In contrast, indirect revascularization using EDAS is significantly efficient in children. Shahbandi et al. found dramatic reductions in ischemic stroke risk compared to conservative management (OR 0.33, 95% CI 0.11–0.97; P = 0.04), in 1,091 pediatric patients[21]. Most saliently, direct/combined versus indirect approaches showed no significant difference in follow-up stroke rates (OR 0.79, 95% CI 0.31–1.97; P = 0.61) or functional outcomes in 875 children, which reinforced the potential of pediatric patients to develop effective collateral circulation following EDAS[21].

Combined revascularization strategies combine immediate hemodynamic benefit with the potential for angiogenic long-term outcome. Nguyen et al. showed that using combined bypass (3,801 procedures) reduced early stroke (OR 0.53, 95% CI 0.41–0.69; P < 0.0001), late stroke (OR 0.28, 95% CI 0.20–0.41; P < 0.0001), and late hemorrhage (OR 0.41, 95% CI 0.30–0.56; P < 0.0001) compared to performing indirect techniques[20]. Nevertheless, combined strategies presented greater early hemorrhage risk (OR 3.1, 95% CI 1.7–5.6; P < 0.0001), while El Naamani et al. noted a tendency to increase perioperative stroke in direct bypass (6.1% vs. 2.0%; OR 3.129, P = 0.052), which supports an assessment of the benefits vs. the complications immediately after surgery[22].

In case of hemorrhagic presentations, simultaneous approaches may provide added benefit. Sun et al. indicated improved collateral formation, hemodynamics, and clinical prognosis with combined versus indirect procedures for hemorrhagic Moyamoya cohorts[23]; Nguyen et al. show a significantly reduced late hemorrhage with the combined bypass in patients (OR ~0.30, P < 0.00001)[20]. These results imply that hybrid treatments with an emphasis on direct flow augmentation coupled with a prolonged evolution of the collateral are most likely for targeted patients.

This is consistent with several reviews in the last few years that have reported mixed results for stroke prevention in adult MMD patients. Deng et al. showed greater stroke-free survival among adults with direct bypass, which may allow for a longer survival against a longer time than indirect strategies[14]. Similarly, Lai et al. reported decreased likelihood of a total number of combined ischemic and hemorrhagic events with bypass, but not isolated ischemic outcomes or function with direct bypass was observed less[16].

However, these results are inconsistent with those from larger multicenter studies. El Naamani et al. examined 515 hemispheres at 13 North American centers and found no meaningful difference in symptomatic stroke rate in direct revascularization compared to indirect techniques[24]. Those differences in results may be explained by variations in indirect bypass techniques applied across multicenters with heterogeneous surgical expertise, patient characteristics, and protocols.

In our review, limited data were found for hemorrhagic events (stroke and rebleeding), which is a key gap in the original studies, given that these are measures of bypass efficacy.

However, a number of articles document good functional outcomes in response to both direct bypass and EDAS among adult populations. These results indicate that although direct bypass may decrease some cerebrovascular events, such an advantage does not necessarily lead to superior functional independence or quality of life in adult MMD patients. This paradox can be attributed to a few different factors, notably that 1) in both groups, the majority of strokes can be slight but not necessarily functional; 2) both

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techniques can also offer enough revascularization to avoid disabling strokes in majority of patients; 3) baseline disease severity and person-specific differences can be more important to long-term functional status than the choice of revascularization.

Park et al. observed improvement of symptoms in 83.7% of patients with encephaloarteriosynangiosis (EIAB, a direct technique) versus those with a modified EDAS (77%), although their mRS comparisons were not reported[25]. The study was excluded from the quantitative analysis because it did not detect the primary outcomes (recurrence, complications, mortality, or functional prognosis), instead reporting entirely subjective symptoms and angiographic measures. The similar outcomes of symptom modification among procedures further reinforce the idea that good functional results can be achieved in appropriately selected patients with various surgical procedures.

There are mixed signals from the literature on perioperative safety. Lai et al.[16] found early surgical complication rates of 3.5% for direct bypass and 8.6% for indirect bypass (P=0.24), implying no statistically significant difference in early complications in their single-center cohort. The large multicenter study by El Naamani et al.[24] also found a trend for increased perioperative stroke with direct revascularization than with indirect revascularization (6.1% DR vs 2.0% IR, OR 3.129, 95% CI 0.991–9.875, P = 0.052), but this difference narrowly missed conventional statistical significance.

The increased risk of perioperative stroke associated with direct bypass in multicenter data is likely associated with the technical complexity of microsurgical anastomosis, potentially leading to significant intraoperative hemodynamic instability and increased risk of acute thrombosis at the anastomotic site. On the contrary, EDAS is technically simpler, requires shorter operative time, and sidesteps the risks of temporary vessel occlusion and suture anastomosis. But perioperative risks need to be weighed against potential long-term benefits, with some studies showing direct bypass to reduce late cerebrovascular events despite higher upfront procedural risk[10].

Specific complication types cited in the literature are neurological limitations, perioperative infarcts, wound complications, and hyperperfusion syndrome. The frequency of these complications varies according to surgical technique and patient population, although the relative burden of these complications is still an issue, and comparative information studies are relatively inadequate.

The decision-analytic model by Macyszyn et al. gives a valuable perspective for interpreting our results[26]. The latter was an analysis of pooled literature inputs and long-term QA outcomes comparing and concluded that indirect or combined procedures may provide better quality-adjusted life years at multiyear horizons (P < 0.001), and there was an inter-individual tradeoff in long-term stroke prevention vs. perioperative risk at times of life with the former, when both adult and child had increased risk combined (P < 0.001)[26]. The model found that the right revascularization strategy depends critically on individual patient risk profiles, the length of time between benefits evaluation, and the relative weighting of immediate procedural risks as compared to the prevention of long-lasting events. However, this article was not included in the systematic review due to its secondary nature (decision analysis/meta-analysis) and because of the lack of original patient cohort data.

There are some important limitations in this systematic review to be acknowledged. First, all the studies included in the review were retrospective cohorts, which is subject to inherent biases in patient selection, treatment assignment, and outcome determination. The lack of randomized controlled trials on direct bypass and EDAS highlights the problem of conducting such trials in a rare disease with established surgical options and strong surgeon/institutional preferences.

Second, the small number of studies (n=7) restricts the statistical power and generalizability of our results. MMD is relatively rare, especially in Western populations, and many institutions do not sufficiently conduct case volumes to obtain meaningful comparative evidence. This small evidence base is also limited by heterogeneity in surgical techniques (differences in direct bypass conduits and anastomotic sites, changes in EDAS procedures), patient populations (differences in age, presentation, disease severity, and genetic background), and outcome definitions.

Third, clinical and radiographic data were missing from those included studies, preventing exhaustive subgroup analyses or the determination of appropriate patient-selection standards.

Fourth, restricted access to Nielsen's supplementary material. Since this file could not be consulted, we could not perform an analysis of the pediatric subgroup, since most of the pertinent data were found exclusively within the supplementary material (e.g., Nielsen's cohort).

In the future, it will be necessary to systematically collect and report several important variables in this comparative study to elucidate the information in this study. These include preoperative ischemic symptoms and the number and types of events (e.g., transient ischemic attacks, minor strokes, major strokes). They should report on preoperative hemorrhagic symptomology, including counts of patients with hemorrhage, as well as preoperative hemiparesis, with the number of patients affected and the extent of the deficit. Reporting the preoperative modified Rankin Scale, either in mean ± standard deviation or median with interquartile range, is critical to enable baseline-adjusted comparisons of outcomes.

Measures of preoperative vessel stenosis (e.g., Suzuki stage, quantitative grading of M1 and internal carotid artery occlusion) shall also be documented to allow classification by disease severity. Preoperative hemodynamic reserve ought also to be evaluated and classified (including whether impaired or preserved) using acetazolamide-challenged perfusion imaging modalities (e.g., SPECT or PET) to identify patients most likely to benefit from direct revascularization. Surgical duration should be evaluated in terms of technical complexity and resource demand, and patients who require revision of the procedure or need adjunct interventions should be documented as appropriate for adequate revascularization.

Normalization of the measurement of these variables in future studies would result in improved risk stratification, better categorization of patient subgroups who are most likely to be benefited from revascularization therapies, and a set of evidence-based clinical decision-making algorithms. Additionally, prospective registries using standardized data collection, core laboratory adjudication of imaging outcomes, and long-term prognosis would greatly augment evidence for surgical management of MMD.

5 CONCLUSION

Based on this systematic review and comparison with the existing literature, it is possible to conclude that direct bypass may offer superior long-term stroke-free survival for selected patients with MMD, particularly in single-center cohorts with highly experienced microsurgical teams. However, multicenter data indicate that overall stroke prevention appears comparable between direct and indirect techniques. Therefore, the choice of procedure should be individualized, taking into account vascular anatomy, baseline hemodynamic status, the surgeon's expertise, and patient preferences regarding perioperative risks versus potential long-term benefits.

Across age groups, functional outcomes tend to be excellent with both direct and indirect revascularization, suggesting that multiple surgical approaches are capable of effectively preventing disabling strokes when applied appropriately.

The safety profiles of the techniques, however, differ. Indirect procedures such as EDAS are technically simpler and may carry a lower perioperative stroke risk, whereas direct bypass is associated with greater technical complexity and higher rates of wound complications. Nonetheless, in selected patients, direct revascularization may offer improved long-term cerebrovascular protection.

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