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Original Investigation

Effect of Surgery on the Long-Term Functional Outcome of Moyamoya Disease: A Meta-Analysis

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ABSTRACT

AIM: To summarize and calculate the accurate rate of good outcome and the prognosis, using a uniform definition of good outcome, evaluating the long-term effect of surgery.

MATERIAL and METHODS: Through searching the relevant databases, we included eligible studies measuring outcomes with the modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS) and Kim's category. Single group rates were transformed and synthesized to yield the mean weighted probability. Sensitivity analyses were conducted to check the robustness of overall effect. Subgroup analyses were stratified by study type, population, age phase, presentation, surgical procedure and outcome measurement.

RESULTS: The overall estimated rate of good outcome was 0.87 (95%CI, 0.84 0.90), with substantial heterogeneity. In the subgroup analyses, the outcome measured with GOS led to the highest rate of 91%, while Kim's category had the lowest rate of 82%. The combined bypass surgery group resulted in a higher good outcome rate of 0.92 (95%CI, 0.89 0.96) than the indirect bypass group of 0.83% (95%CI, 0.78 0.88).

CONCLUSION: Moyamoya disease after surgical treatment could achieve a good outcome rate of 87%. Kim's category reflected the functional outcome better, resulting in a good outcome rate of 82%. The combined bypass surgery led to better outcomes than indirect bypass.

KEYWORDS: Long-term outcome, Meta-analysis, Moyamoya disease, Surgical treatment

■ INTRODUCTION

Moyamoya disease (MMD) is a cerebrovascular condition, characterized by progressive occlusion of bilateral internal carotid artery terminals and the compensatory formation of abnormal net-like vessels at the base of the brain (32). The incidence of MMD is about 0.35 per 100,000 population worldwide and increases to 3 per 100,000 in Asian population (31). Clinical presentations are mainly divided into two categories: ischemic symptoms (i.e., infarct, seizure and headache) and hemorrhagic symptoms. The pathogenesis of MMD remains unclear and etiological treatment is not yet established. Surgical treatment, including direct bypass, indirect bypass and combined bypass, has become the mainstay for MMD.

Studies have found revascularization surgery to contribute to promote collateral vessel formation and augment cerebral blood flow (17). However, some researchers found no correlation between the change of cerebral blood flow and the functional outcome (3,38), making it questionable whether radiological manifestation should be used as a surrogate of the outcome or not. While most studies paid attention to the angiographic response and recurrent stroke rate, the long-term functional outcome was less focused. The various definitions of good outcome in different studies weakened the comparability between studies (13,29). Besides, the conduction of compared trials was ethically difficult due to the confirmed benefit of surgery, especially in the ischemic MMD population (7,22).

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The prognosis and exact rate of good functional outcome of MMD after operations were controversial. Hence, we conducted a meta-analysis to clarify the probability of good outcome under the uniform outcome measurement tools, in order to shed light on the effect of surgery on MMD outcomes.

■ MATERIAL and METHODS

Search Strategy

We systematically searched databases through Pubmed, Ovid and Web of Science from their starting data up to July 2017. The detailed search strategy was shown in the Table I. The reference lists of extracted articles were also manually searched. Only English language articles were searched without time limitation.

Study Selection

We included studies meeting the following criteria:

[1] Observational studies describing patients with the diagnosis of MMD according to the diagnosis and treatment guideline (31)

[2] Patients that underwent revascularization surgery either by direct bypass, indirect bypass or combined bypass

[3] With an exact definition of good functional outcome

[4] Recording the number of patients with good outcome or the rate

[5] With follow-up time of at least 6 months.

Studies were excluded for the following reasons:

[1] Described quasi-Moyamoya or Moyamoya syndrome

[2] Sample size smaller than 10 patients.

Two researchers (Z.Y. and C.Y.) independently screened and selected eligible studies, and the discrepancy was solved by discussion and consensus.

Uniform Definition of the Good Outcome

In this meta-analysis, three common clinical outcome measurement tools of the modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS) and Moyamoya Disease outcome category proposed by Kim et al.(18), were used as uniform standard measurement. Kim et al. classified the outcomes into four categories: Excellent, the preoperative symptoms had totally disappeared without fixed neurological deficits; good, the symptoms had totally disappeared, but neurological deficits remained; fair, the symptoms persisted, albeit less frequently; poor, where the symptoms remained unchanged or had worsened. Of these, categories of excellent and good were considered as favorable outcomes (18). According to usual practice, we defined good outcome as mRS≤2, GOS>3 and favorable outcomes in Kim's category.

Quality Assessment

All eligible studies underwent quality assessment with the methodological index for non-randomized studies (MINORS) (33). Every included study was scored 0 to 2 in each of eight items for non-comparative studies.

Table I: Detailed Search Strategy

Database	Search Strategy
Ovid	**1**. (surgery or revascularization or bypass or temporal muscle sticking or encephalo-myo-synangiosis or encephalo-duro-arterio-synangiosis or encephalo-duro-arterio-myo-synangiosis or encephalo-myo-arterio-synangiosis or encephalo-duro-arterio-galeo-synangiosis or superficial temporal artery-middle cerebral artery anastomosis).tw. **2**. (outcome or prognosis or mRS or modified rankin scale or GOS or Glasgow outcome scale).tw. **3**. moyamoya.tw. **4**. 1 and 2 and 3
Pubmed	((((((((((((surgery[Text Word]) OR revascularization[Text Word]) OR bypass[Text Word]) OR temporal muscle sticking[Text Word]) OR encephalo-myo-synangiosis[Text Word]) OR encephalo-duro-arterio-synangiosis[Text Word]) OR encephalo-duro-arterio-myo-synangiosis[Text Word]) OR encephalo-myo-arterio-synangiosis[Text Word]) OR encephalo-duro-arterio-galeo-synangiosis[Text Word]) OR superficial temporal artery-middle cerebral artery anastomosis[Text Word])) AND moyamoya[Text Word]) AND ((((((outcome[Text Word]) OR prognosis[Text Word]) OR mRS[Text Word]) OR modified rankin scale[Text Word]) OR GOS[Text Word]) OR glasgow outcome scale[Text Word]))
Web of Science	#4 #3 AND #2 AND #1 #3 TOPIC: (outcome) OR TOPIC: (prognosis) OR TOPIC: (mRS) OR TOPIC: (modified rankin scale) OR TOPIC: (GOS) OR TOPIC: (glasgow outcome scale) #2 TOPIC: (moyamoya) #1 TOPIC: (surgery) OR TOPIC: (revascularization) OR TOPIC: (bypass) OR TOPIC: (temporal muscle sticking) OR TOPIC: (encephalo-myo-synangiosis) OR TOPIC: (encephalo-duro-arterio-synangiosis) OR TOPIC: (encephalo-duro-arterio-myo-synangiosis) OR TOPIC: (encephalo-myo-arterio-synangiosis) OR TOPIC: (encephalo-duro-arterio-galeo-synangiosis) OR TOPIC: (superficial temporal artery-middle cerebral artery anastomosis)

Data Extraction

Data extraction forms were used to collect relevant information including author names, years of publication, study types, study duration, countries, outcome measurement, follow-up time, sample sizes and rates of long-term good outcome. When the population in different studies totally or partially overlapped, we included the study with bigger sample size or more comprehensive data. We also tried to contact the authors of primary articles for intact data.

Statistic Analyses

Single group rates of good outcome were transformed with the variance-stabilizing Freeman-Tukey arcsine method. Transformed rates and standard errors were re-transformed back to probabilities in the random-effects model meta-analysis, yielding mean weighted probability (MWP) and 95% confidence interval (CI). Heterogeneity was measured with Cochran's Q and I^2 tests and the value of I^2 greater than 50% indicated pronounced heterogeneity. Begg's and Egger's tests were applied to calculate publication bias and a $p<0.05$ showed significant bias. Sensitivity analyses were conducted by omitting one study each time and synthesizing the estimates of reminding studies, so as to check the robustness of the overall effect. Subgroup analyses were stratified by study type, population, age phase, presentation, surgical procedure and outcome measurement. In the subgroup analyses of clinical presentations, characteristics of greater than 90% patients represented the trait of the whole population (i.e. if more than 90% patients exhibited ischemic symptom, we considered this whole population as the ischemic population). The contribution of variables to the heterogeneity was evaluated in the univariate regression analyses and a $p<0.05$ indicated significance. The summarized analyses of good outcomes were on the patient basis. All the statistic tests were implemented with Stata 14.0 software (Stata Cooperation USA).

RESULTS

Literature Search

After removing duplicates, a total of 1928 articles were screened, of which 64 records entered the full-text reading assessment for eligibility. Then 44 citations were excluded for certain reasons: review articles, without pertinent data, non-standard or self-defined outcome measurement, and overlapped population in different studies (5,6,21,22,27,34). Finally, 20 observational studies were included in the data synthesis. The literature search process was outlined in Figure 1.

Main Characteristics of Included Studies

Totally we included 2666 MMD patients with a female predominance, most of which were from East Asian countries.

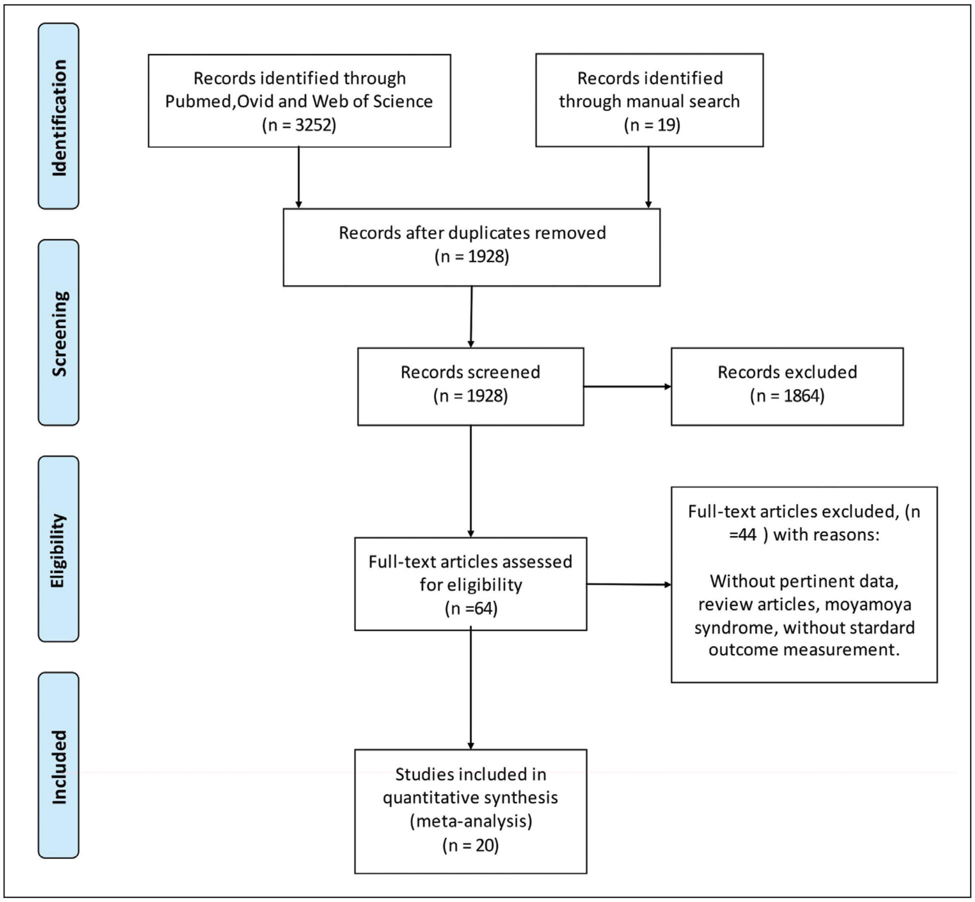

Figure 1: Flow diagram for literature search.

Of all, 16 included studies were published after the date of 2012, when the diagnosis and treatment guideline was reported (31). The main surgery procedures are superficial temporal artery-middle cerebral artery bypass, encephaloduroarteriosynangiosis and modified operation procedures based on the encephaloduroarteriosynangiosis. The mean follow-up time varied ranging from 6 to 171 months. Most included studies were of high or moderate quality, with a mean score of 12 in MINORS. The detailed characteristics were depicted in the Table II.

Table II: Main Characteristics of Included Studies

Author	Duration	Country	Sample size (n)	Female ratio (%)	Main Surgical Procedures	Mean follow-up time (months)	MINORS
Bao et al., 2015 (1)	2002-2010	China	288	49	EDAS	52	11
Cheung et al., 2017 (4)	2000-2014	China	24	68	extracranial-intracranial bypass and synangiosis	27	13
Czabanka et al., 2016 (8)	NA	Germany	37	64	combined STA-MCA bypass and EMS	6	11
Darwish et al., 2005 (9)	1982-2004	Australia	10	50	EDAS, STA-MCA bypass	72	12
Deng et al., 2017 (10)	2009-2015	China	529	53	EDAS, STA-MCA bypass, combination	40	12
Gonzalez et al., 2015 (11)	1989-2014	America	46	78	EDAS	22	13
Hishikawa et al., 2014 (12)	1989-2011	Japan	32	72	STA-MCA bypass with EDMS or EMS	40	13
Jiang et al., 2014 (14)	2007-2011	China	106	58	combined STA-MCA bypass and EDMS	30	12
Karasawa et al., 1992 (15)	1974-1991	Japan	104	61	STA-MCA bypass with EMS	115	13
Kazumata et al., 2017 (17)	1980-2015	Japan	10	50	combined STA-MCA bypass and EDMAS	116	11
Kim et al., 2007 (19)	NA	Korea	24	50	EDAS, EDAMS, STA-MCA and EDMAS	18	13
Kim et al., 2010 (20)	1988-2006	Korea	410	57	ribbon EDAS	61	13
Kim et al., 2016 (23)	2000-2014	Korea	301	62	STA-MCA bypass with or without IB	45	12
Liu et al., 2015 (24)	1984-2010	China	271	51	STA-MCA bypas, EDAS, multiple burr holes	39	12
Mukawa et al., 2012 (26)	1979-2012	Japan	172	NA	EDAS	171	12
Rahmanian et al., 2017 (28)	2009-2016	Iran	13	62	STA-MCA bypass, EMS	6	13
Rashad et al., 2016 (29)	2004-2015	Japan	23	70	SAT-MCA bypass combined with EDMS	77	13
Ren et al., 2016 (30)	2004-2013	China	180	35	EDAS	45	12
Williamson et al., 2017 (37)	2002-2015	America	29	67	STA-MCA bypass, IB	18	12
Zhao et al., 2015 (39)	2009-2013	China	57	61	multiple burr hole	6	13

***EDAS:** encephaloduroarteriosynangiosis; **EDMAS:** encephaloduroarteriomyosynangiosis; **EDMS:** encephaloduromyosynangiosis; **EMS:** encephalomyosynangiosis; **IB:** indirect bypass; **MINORS:** methodological index for non-randomized studies; **NA:** not available; **STA-MCA:** superficial temporal artery-middle cerebral artery.*

Meta-analyses

The overall MWP was 0.87 (95% CI, 0.84 0.90) for all included studies and the heterogeneity was obvious between studies (I^2=82.2%, p<0.0001, Figure 2). In the sensitivity analyses by excluding any single study each time, overall MWP did not change significantly (Figure 3). Publication bias was not substantial in Egger's test (p=0.09), though the funnel plot was slightly asymmetric (Figure 4).

Stratified by outcome measurement, the MWP was 0.82 (95% CI, 0.80 0.85) when the outcome measured by Kim's category, and MWP increased to 0.91 (95% CI, 0.82 0.99) when measured by GOS. The heterogeneity was 0 and 71.7% in Kim's category and GOS subgroups respectively (Figure 2). The most commonly used outcome measurement tool was mRS (12 studies), resulting in the MWP of 0.89 (95%CI, 0.85 0.93). In addition, non-significant differences of MWP existed between prospective and retrospective studies, Asian and non-Asian populations, children and adults, ischemic and hemorrhagic presentations. 273 patients in six studies underwent combined bypass surgery and 1377 patients in eight studies experienced indirect bypass, but no studies documenting solo direct bypass were included. The higher MWP was shown in the combined bypass surgery group

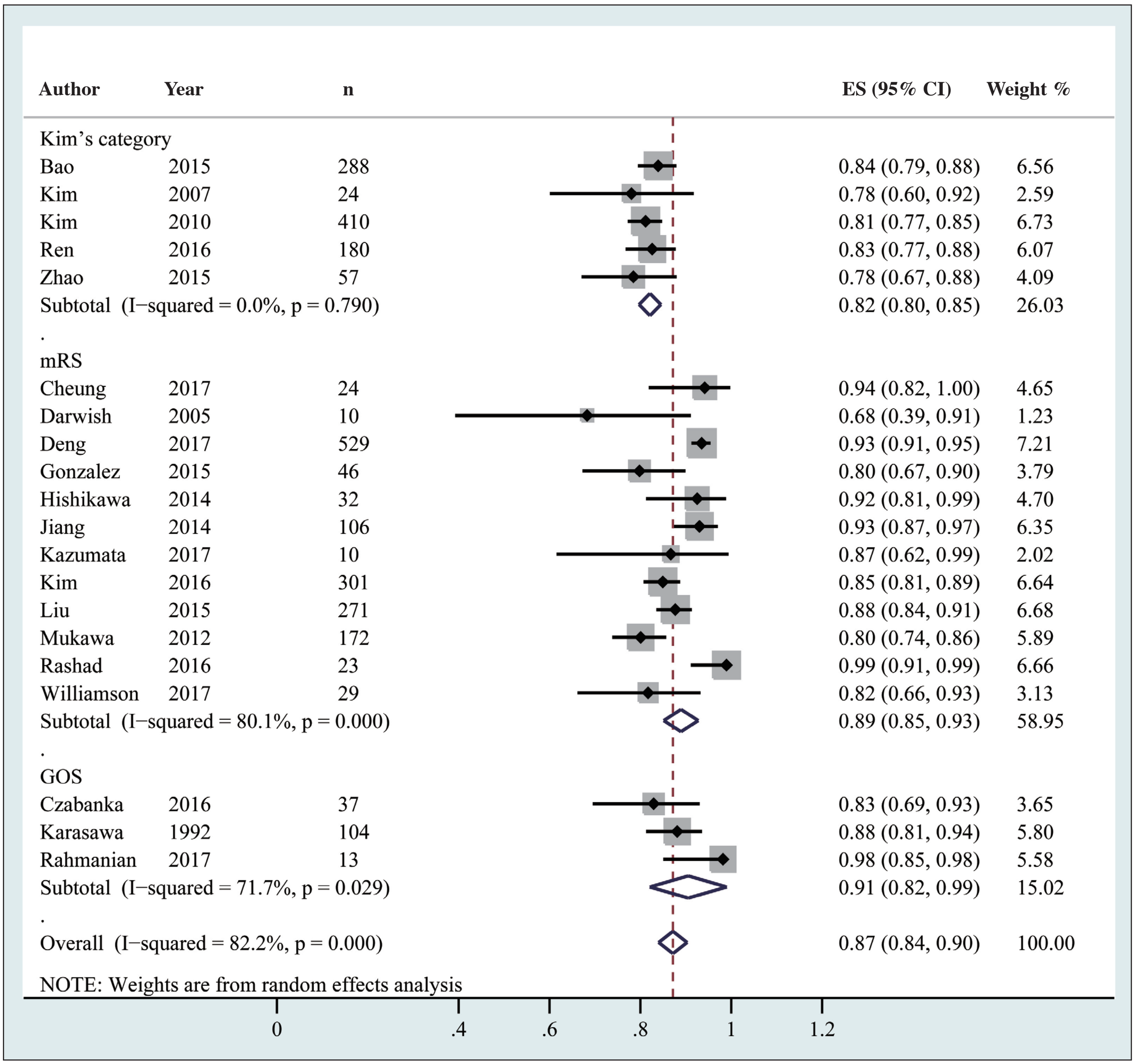

Figure 2: Forest plot of studies stratified by outcome measurement, with single group rates, synthesized mean weighted probability and 95% confidence intervals.

(0.92[95%CI, 0.89 0.96]) than in the indirect bypass group (0.83[95%CI, 0.78 0.88]), without intersections between these two CIs (Table III). Substantial heterogeneity existed within indirect bypass studies (I^2=83%, p<0.0001), but not in combined bypass studies (I^2=0, p=0.61). In the regression analyses, variables of study type, population and outcome measurement exhibited no significant relationship with the overall MWP, contributing little to the heterogeneity.

DISCUSSION

The overall estimated rate of good outcome was 87% under the uniform outcome measurement. In the subgroups, measurement by GOS showed the highest good outcome rate, while measurement by Kim's category indicated the lowest rate. This was in line with previous study which evaluated the same population with two outcome measurement tools achieving different results (30). In spite of heterogeneity, the combined bypass surgery brought about a significant higher good outcome rate than the indirect bypass did.

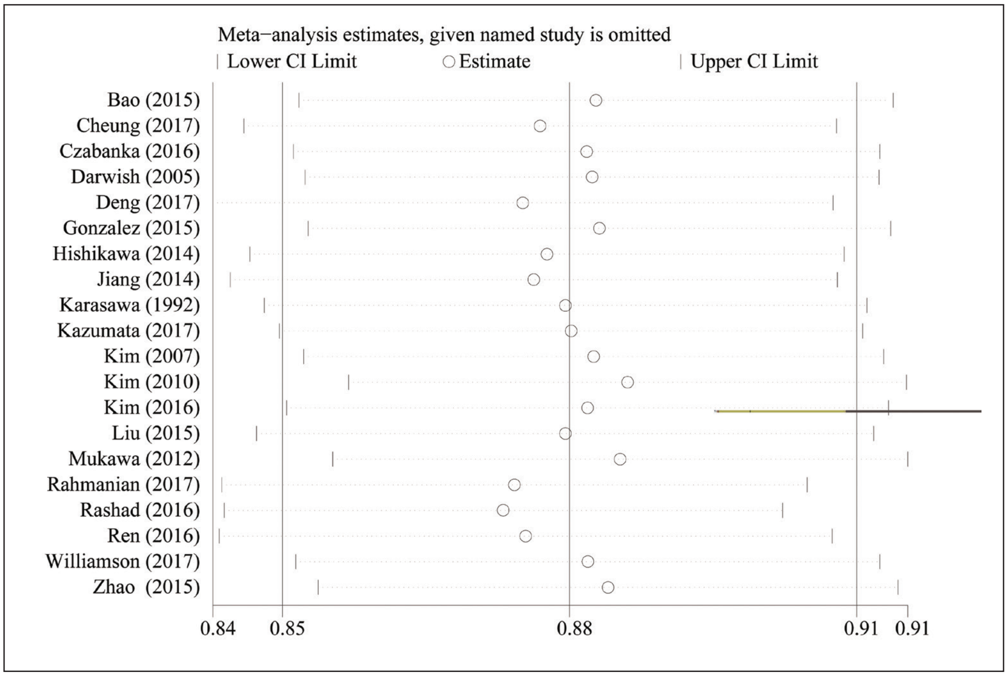

Figure 3: Sensitivity analyses by excluding single one study each time.

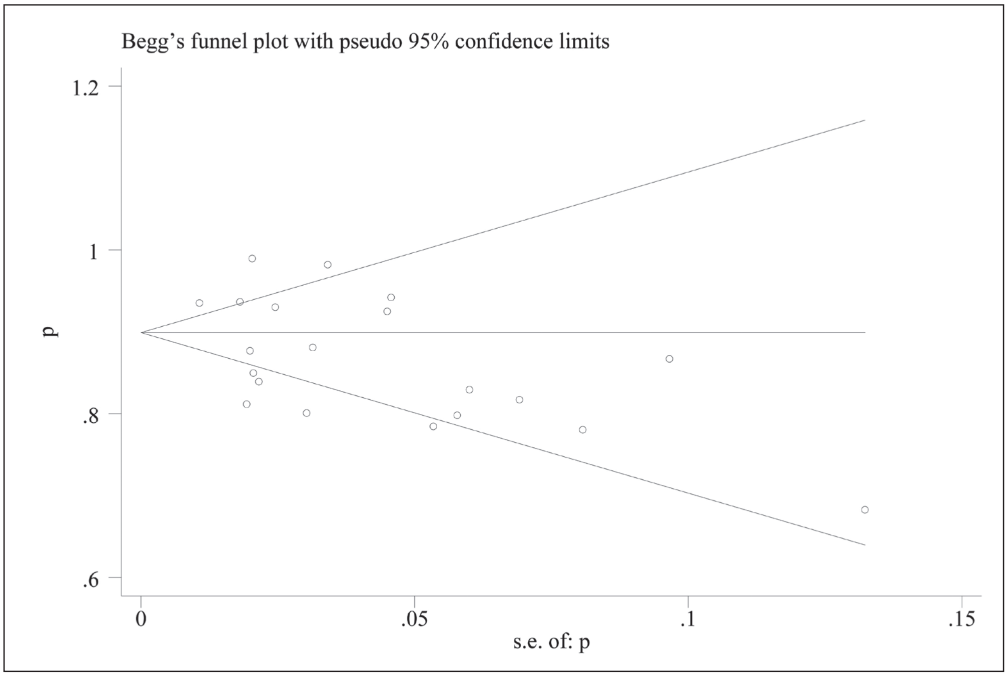

Figure 4: Begg's funnel plot for publication bias.

The regression analyses found no variables contributing significantly to the heterogeneity, which might be explained by the within studies variance as patients' different reactions to surgery and variation of operations. After all, the heterogeneity was not uncommon in the meta-analysis of single group rate due to the one-arm trait (2).

MMD was complicated by the recurrent postoperative stroke, and thus the long-term functional outcome became the important prognosis index. Surgical treatment aimed to augment blood flow to the affected cerebral hemispheres, increase perfusion and improve clinical outcomes (1,4). The collateral circulation took approximate six months to develop well after the operations (25), for which we adopted six months as the shortest follow-up time in the including criteria. The previous review summarized and calculated the mean estimated proportion of the postoperative stroke in MMD was 5.4% (16). Further studies pointed out bypass surgery effectively decreased the occurrence of stroke (24). To what extent the operations were able to improve the long-term functional outcome was under debate. Researchers noted the evaluation of surgical effects on the outcomes of MMD patients was difficult, for surgery was a palliative form in a progressive disease with poor natural history (35).

Sun et al. figured out the rates of favorable outcome were 80%, 78% and 81% in direct, indirect and combined bypass groups respectively (36), but the overall estimates were of obvious heterogeneity due to the various definitions of favorable outcomes. Here, we calculated the mean rate of good outcome with uniform measurement tools and definitions, resulting in a higher rate of 87%. In the review, we excluded studies using self-defined good outcome measurement, which might underestimate the good functional outcome rate. Moreover, we found a higher good outcome rate existed in studies using GOS than those using Kim's category. GOS was used to reflect the ability for daily activity, giving little attention to the recurrent symptoms in MMD. Kim's category was exclusively to measure the outcome of MMD, taking both the recurrent symptoms and the residual functional inability into consideration. The estimated rate of good outcome measured by Kim's category was closer to the previous reported rate. We deemed Kim's category could better reflect MMD patient's prognosis. Besides, combined bypass surgery led to a higher good outcome rate than indirect bypass surgery, in accordance with previous study (10). It was well acknowledged that direct and combined bypass could generate better collateral vessel formation. The main reason impeding the application of

Table III: Subgroup Analyses by Study Type, Population, Age Phase, Presentation, Surgical Procedure and Outcome Measurement

	Number of studies	Number of patients	I^2 (%)	p for heterogeneity	MWP (95% CI)	Weight (%)
Study type						
Retrospective	18	2031	78	**<0.0001**	0.86 (0.83, 0.90)	86
Prospective	2	635	0	0.85	0.93 (0.91, 0.95)	14
Population						
Asian	16	2544	84	**<0.0001**	0.88 (0.85, 0.91)	88
Non-Asian	4	122	0	0.79	0.81 (0.74, 0.87)	12
Age phase						
Children	7	1031	89	**<0.0001**	0.85 (0.78, 0.92)	51
Adults	7	731	56	**0.04**	0.86 (0.82, 0.90)	49
Presentation						
Ischemic	15	1782	83	**<0.0001**	0.87 (0.83, 0.91)	84
Hemorrhagic	2	248	0	0.61	0.92 (0.89, 0.95)	16
Surgical procedure						
Indirect bypass	8	1377	83	**<0.0001**	0.83 (0.78, 0.88)	61
Combined bypass	6	273	0	0.61	0.92 (0.89, 0.96)	39
Outcome measurement						
Kim's category	5	959	0	0.79	0.82 (0.80, 0.85)	26
mRS	12	1553	80	**<0.0001**	0.89 (0.85, 0.93)	59
GOS	3	154	71	**0.03**	0.91 (0.82, 0.99)	15

CI: *Confidence interval;* ***GOS:*** *Glasgow Outcome Scale;* ***mRS:*** *Modified Rankin Scale;* ***MWP:*** *Mean Weighted Probability* combined bypass was the lack of eligible arteries, especially in children. Moreover, postoperative hyperperfusion syndrome should also be noticed.

There were several limitations in this meta-analysis. Firstly, patients' conditions on admission were different among the included studies. Besides, substantial heterogeneity could not be fully explained and further studies were warranted.

CONCLUSION

The overall estimated rate of good outcome was 87% in MMD after operations. Kim's category reflected the functional outcome accurately, resulting in a good outcome rate of 82%. Combined bypass surgery brought about a higher good outcome rate than the indirect bypass did.

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