

# Postoperative incidence of seizure and ischemic events in patients with epileptic type moyamoya disease: a meta-analysis of single rate

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## Research

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# Abstract

## Background

Surgery is a conventional mature treatment for moyamoya disease (MMD). However, whether surgery is also an effective therapy for epileptic type MMD has seldom been investigated systematically. The study aims to summarize the pooled postoperative incidence of seizure and ischemic events in patients with epileptic type moyamoya disease.

## Method

The study was a systematic review and critical appraisal with a meta-analysis of cohort studies, both prospective and retrospective. Studies were identified by a computerized search of Pubmed, EMBASE, Web of Science, Wanfang, and CNKI databases. In a literature search, a total of 8 cohort studies were identified. The  $I^2$  statistic was used to quantify heterogeneity. A fixed-effect model was used to synthesize the results. The linear regression test of funnel plot asymmetry was used to estimate the potential publication bias.

## Results

The pooled estimated postoperative incidence of seizure in patients with epileptic type moyamoya disease was 21.52%. The pooled estimated postoperative incidence of ischemic events in patients with epileptic type moyamoya disease was 7.42%. Low substantial heterogeneity and potential publication bias were present.

## Conclusion

Evidence from this study suggests that the postoperative incidence of seizure and ischemic events is relatively low. Surgery is an effective and secure therapy for patients with epileptic type moyamoya disease.

## 1. Background

Moyamoya disease (MMD) is a type of progressive occlusive cerebrovascular disease, with the significant characteristic of steno or blocked blood vessels at the end of the internal carotid artery (ICA), proximal middle cerebral artery (MCA) and anterior cerebral artery (ACA) [1]. The name "moyamoya" means "puff of smoke" in Japanese and describes the appearance of the formation of smoke-like abnormal blood vessels in the base of the skull in cerebral angiography. It frequently occurs in the East Asian population, may cause ischemic or hemorrhage stroke, epilepsy, headache, or transient ischemic attack (TIA) [2]. The epileptic seizure is the second common symptom of MMD in pediatric patients [3], and the third most common manifestation of MMD in all patients [4]. The treatment methods and clinical outcomes for this type of MMD are seldom reported.

Some of the epileptic type patients suffer seizures as the first symptom, and others may be secondary to ischemic stroke [5]. The clinical manifestation and progression of this type may be nonspecific [6]. Some scholars believe that epileptic seizures in epileptic type patients is not a specific symptom but mostly caused by cerebral ischemia [7]. The cause of epilepsy in MMD could be various, including ischemic or hemorrhagic stroke [6], hyperperfusion [8], and so on. About 20–30% of MMD patients present with seizures [9], but only 3–4% epileptic type MMD without vascular event [10,11].

Revascularization operation is effective for MMD presenting with the cerebral ischemic event has been proved by multiple studies [11-14]. Surgery could reduce the frequency of TIAs and cerebral infarction, and improve the long-term prognosis of brain functions. The cerebral hemodynamics and metabolism are also improved following surgery treatment, which could be evaluated by SPECT or PET [13]. Both direct and indirect revascularizations or the combination of these two types could obtain satisfactory results. Since epileptic type, MMD has rarely been discussed in detail before, whether surgery could improve these patients still lack research systematically. In this study, we will summarize the pooled postoperative incidence of seizure and ischemic events in patients with epileptic type MMD, in order to estimate the effect of the surgery treatment on these patients.

## 2. Methods

### 2.1 Literature search

We computerized searched the Pubmed, Web of Science, Embase, Wanfang, and CNKI databases. A combination of keywords and similar strategies was used to identify previously published studies. The medical subject heading (MeSH) key words were: moyamoya disease, epilepsy or seizure, surgery or operation. Two independent researchers (Liu J, Xu X) conducted separate literature searches. The last update for research was done in August 2019. No limitation on language was considered. After the removal of duplicate articles, a total of 523 articles were found (Fig. 1).

### 2.2 Criteria for Inclusion and Exclusion.

Articles were included in the meta-analysis if they met the following criteria: 1) prospective and retrospective cohort studies on patients with epileptic type MMD, 2) at least 5 epileptic type MMD patients were included in the study, 3) chose direct and indirect revascularizations or the combination surgery treatment for these patients, 4) the prognosis of these patients after surgery was described in detail, including the postoperative incidence of seizure and ischemic events. We excluded all of the reviews, case reports, articles without full text, or not be translated into English or Chinese. We also excluded the studies without detail about epileptic type MMD, surgical treatment, or outcome analysis after surgery. No randomized controlled trials were found. Finally, eight cohorts [2,15-21] were considered eligible for the postoperative incidence of seizure and ischemic event in patients with epileptic type MMD (Fig. 1) (Table 1).

## 2.3 Statistical analysis

Meta-analyses of a single rate were carried out by using RStudio version 3.6.1 (2019-07-05). The  $I^2$  statistic was used to quantify heterogeneity ( $I^2 < 25\%$ , low heterogeneity). The fixed-effects models were used to calculate an overall pooled proportion and 95% CI when the results presented as low heterogeneity. Linear regression test of funnel plot asymmetry was used to estimate the potential publication bias ( $P > 0.05$ , no publication bias).

## 3 Results

The summarized pooled postoperative incidence rate of seizure in patients with epileptic type MMD in the eight studies using the fixed effects models was 21.52% (95% CI 12.87%-31.32%) with low heterogeneity ( $\text{Tau}^2 = 0.0016$ ,  $I^2 = 7.1\%$  (95%CI 0%-69.9%),  $P = 0.3752$ ) (Fig. 2a). Low publication bias was estimated by the linear regression test of funnel plot asymmetry ( $P = 0.8178$ ) (Fig. 3a).

The summarized pooled postoperative incidence rate of ischemic event in patients with epileptic type MMD in the 5 studies using the fixed effects models was 7.42% (95% CI 0.33%-19.34%) with low heterogeneity ( $\text{Tau}^2 = 0$ ,  $I^2 = 0\%$  (95%CI 0%-73.8%),  $P = 0.5290$ ) (Fig. 2b). Low publication bias was estimated by the linear regression test of funnel plot asymmetry ( $P = 0.4758$ ) (Fig. 3b).

## 4. Discussion

The management of MMD includes medical treatment and surgical treatment. Platelet aggregation inhibitors<sup>[22]</sup> or calcium channel blockers<sup>[22,23]</sup> may generate excellent but transient effects could be only applied to mild cases<sup>[18]</sup> or acute phase of stroke<sup>[11]</sup>. Surgical treatment is considered to be the most effective method to treat MMD, especially for MMD, manifesting as a cerebral ischemic symptom<sup>[11]</sup>. However, few studies focus on the surgical treatment of epileptic type MMD, and there is a lack of randomized controlled studies and meta-analysis. Thus, we reviewed the current literature and summarized the efficacy of surgical treatment for epileptic type MMD.

We calculated an overall pooled postoperative incidence of seizure in patients with epileptic type MMD, which was 21.52%. That means the rate of seizure freedom after surgery in this population is about 78%. As we know, surgery in children with refractory epilepsy resulted in higher rates of seizure freedom and better outcome than medical therapy alone<sup>[24]</sup>. The most effective surgery is for temporal lobe epilepsy. The seizure-free rate ten years after surgery for temporal lobe epilepsy is about 50%<sup>[25]</sup>, which is still lower than the rate for epileptic type MMD. Furthermore, most of the patients with epileptic type MMD suffered seizures after surgery could be controlled by anti-epileptic drugs<sup>[15,17,18]</sup>, but only very few patients deteriorated or without improvement after surgery<sup>[2,19]</sup>.

Surgical complications of MMD include hyperperfusion syndrome, intracranial hemorrhage, infarction, local hypoperfusion, poor scalp healing and infection, and epilepsy<sup>[26]</sup>. The incidence of seizures after

revascularization in MMD patients was 10.9–18.9% [6,8]. Thus, the seizure recurrence in some of the patients with epileptic type MMD is not because of epilepsy itself, but because of the surgery. Some of the postoperative seizure is associated with increased cerebral cortex excitability caused by increased blood flow [26]. Since the improvement of cerebral hemodynamics, MMD patients with this type of postoperative seizures have been confirmed to have a good prognosis following synangiosis [8].

The pathogenesis of MMD presented with epilepsy is not very clear. Most scholars believed that it could be associated with ischemia [21]. The epileptic type of MMD has an analogical progression as the ischemic stroke type of MMD [16]. In a cohort study, 4 out of 7 patients with epileptic type MMD showed decreased cerebral perfusion [2]. Since decreased cerebral perfusion could give rise to disturbance of cerebrovascular reactivity and could result in regional cerebral hypoxia, seizure recurrence should be prevented by the cerebral perfusion improvement via revascularization surgery [2].

We also calculated the overall pooled postoperative incidence of ischemic events in patients with epileptic type MMD, which was 7.42%. A review from 1,448 pediatric MMD patients showed that the rate of perioperative ischemic events was 4.4–6.1% [27], which was lower than the rate in epileptic type MMD from our calculation. However, that may be because of the limitation of the number of studies included in our study. Choi et al. [2] reported that surgery could prevent epileptic seizures and obtained more approving clinical outcomes when applied to patients with epileptic type MMD compared to ischemic type MMD, but there were no differences in postoperative neuroimaging and hemodynamic changes between the two groups.

Since the postoperative incidence of seizure and the ischemic event showed low heterogeneity and publication bias in our study, we did not analyze the risk factors for epilepsy and ischemic event after cerebral revascularization in patients with epileptic type MMD. Different operation methods (indirect, direct, or combined), age of patients, course of epilepsy, and severity of clinical presentations may affect the prognosis of operation. Only one study [21] explored the risk factor of seizure recurrence in epileptic type MMD. They identified the duration of epilepsy as an independent risk factor for recurrent seizure after surgery in pediatric patients with epileptic type MMD, but the surgical modalities would not affect the outcome of the surgery. Nevertheless, no other studies discussed the correlation between the course of epilepsy and seizure recurrence. These suggest us to do more studies, including more patients with epileptic type MMD under different conditions.

Evidence from this study suggests that the postoperative incidence of seizure and ischemic events is relatively low. Surgery is an effective and secure therapy for patients with epileptic type MMD.

There were several limitations in our study: the numbers of patients and studies were all tiny, and all of these studies were retrospective and nonrandomized. That may be because the incidence of epileptic type MMD is relatively low, and few scholars focus on this type of MMD. Follow-up periods were not consistent among individuals, ranging from 0.2 to 25 years, which implies that the observational time of

some patients may not be sufficient. In a word, future studies should focus on the epileptic type MMD in large-scale randomized controlled clinical studies.

## 5. Conclusions

Evidence from this study suggests that the postoperative incidence of seizure and ischemic events is relatively low. Surgery is an effective and secure therapy for patients with epileptic type moyamoya disease.

## 6. List Of Abbreviations

MMD moyamoya disease

ICA internal carotid artery

MCA middle cerebral artery

ACA anterior cerebral artery

TIA transient ischemic attack

## Declarations

### **Ethics approval and consent to participate**

Not applicable

### **Consent for publication**

Not applicable

### **Availability of data and material**

All data generated or analyzed during this study are included in these published articles.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

Not applicable

### **Authors' contributions**

JL computerized searched the Pubmed, Web of Science and Embase databases, identified 8 cohort studies finally, conducted the statistical analysis, and was the major contributor in writing this manuscript. QX computerized searched the Wanfang and CNKI databases, assisted JL to aggregate data for analysis. HN was responsible for proofreading the collected studies and rechecking the data. RW was responsible for ensuring that the final statistical analysis of the data was accurate and reliable. XY mainly designed the structure of this manuscript, reviewed and modified it at last. XL reviewed and modified this manuscript, and was the major corresponding author of this manuscript. All authors read and approved the final manuscript.

## Acknowledgements

Not applicable

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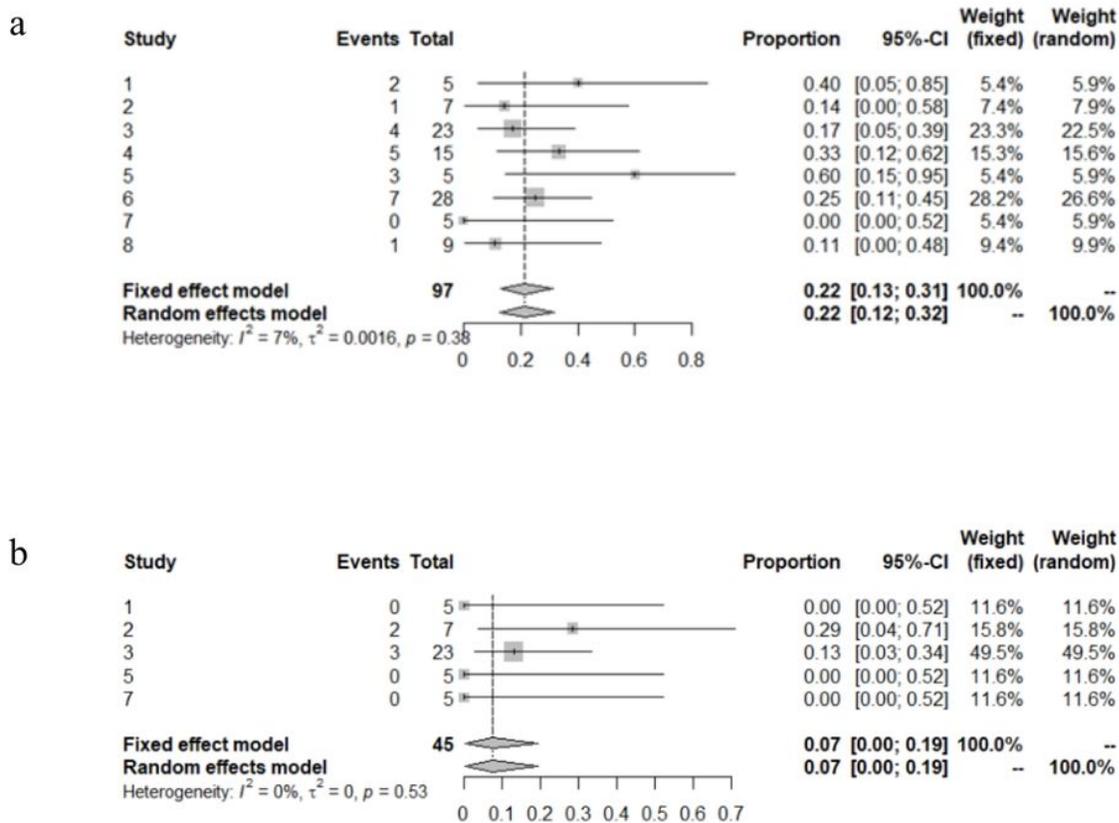
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## Tables

Table-1 The postoperative incidence of seizure and ischemic events in patients with epileptic type MMD.

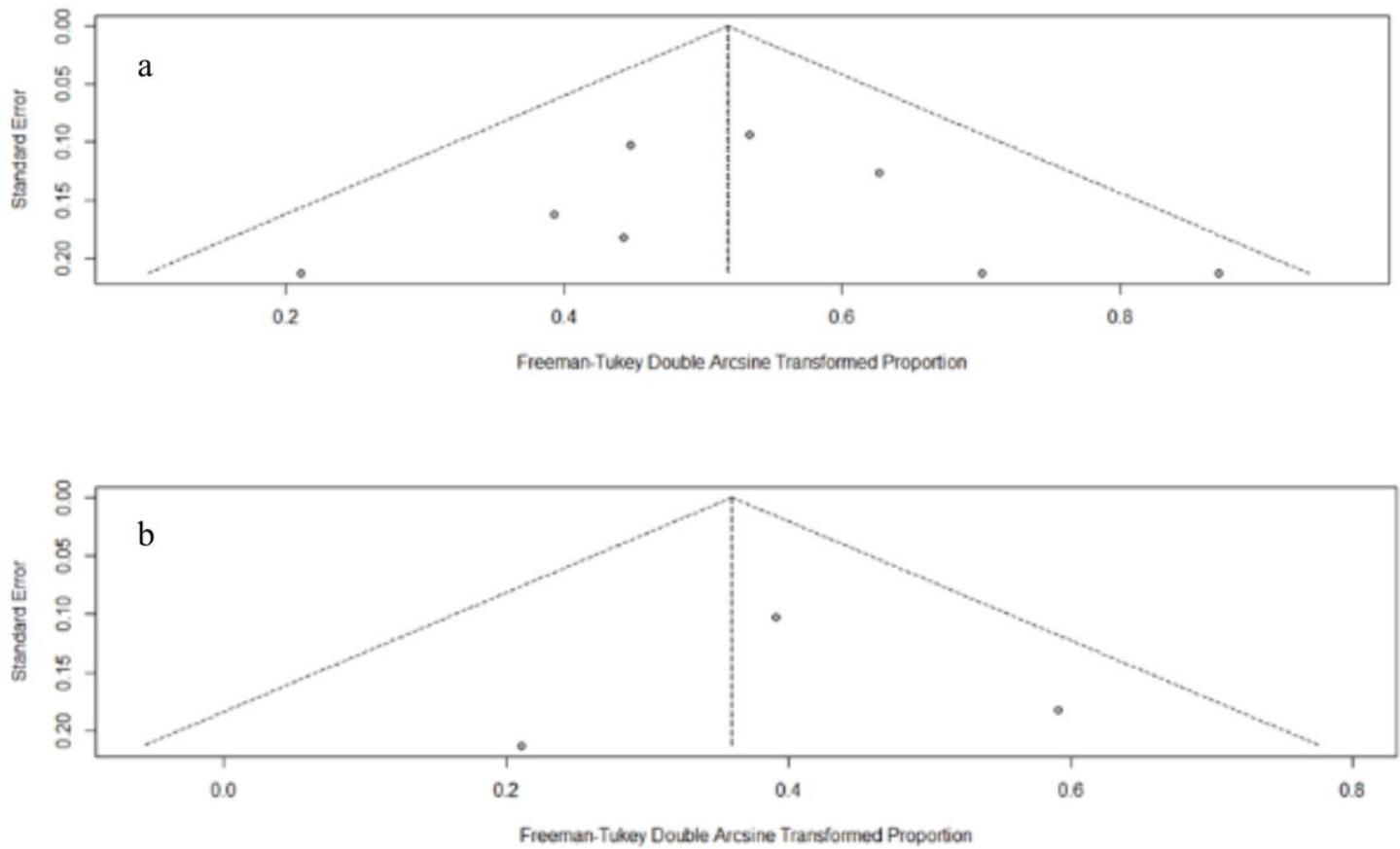
n	Publish year	authors	Epileptic type	MMD cases	Age (years)	Follow up period(years)	Surgery type	Postoperative seizure cases	Postoperative ischemic event cases
1	2006	Sainte-Rose C, et al.		5	3.5-16	2.1-5.6	Indirect	2	0
2	2015	Choi JI, et al.		7	2-15	2-12	Indirect	1	2
3	1993	Nakase H, et al.		23	0.4-12	0.5-17.3	combined	4	3
4	2011	Ulrich PT, et al.		15	1-18	2-25	Indirect, direct, or combined	5	Unknown
5	2001	Caldarelli M, et al.		5	0.6-9	1.2-19	Indirect	3	0
6	2018	Ma Y, et al.		28	2-18	0.5-7.5	Indirect, direct, or combined	7	Unknown
7	2018	Li M, et al.		5	2-16	2.4±0.6	Indirect or direct	0	0
8	2019	Yang H, et al.		9	3.5-16	0.2-1.2	combined	1	Unknown

## Figures



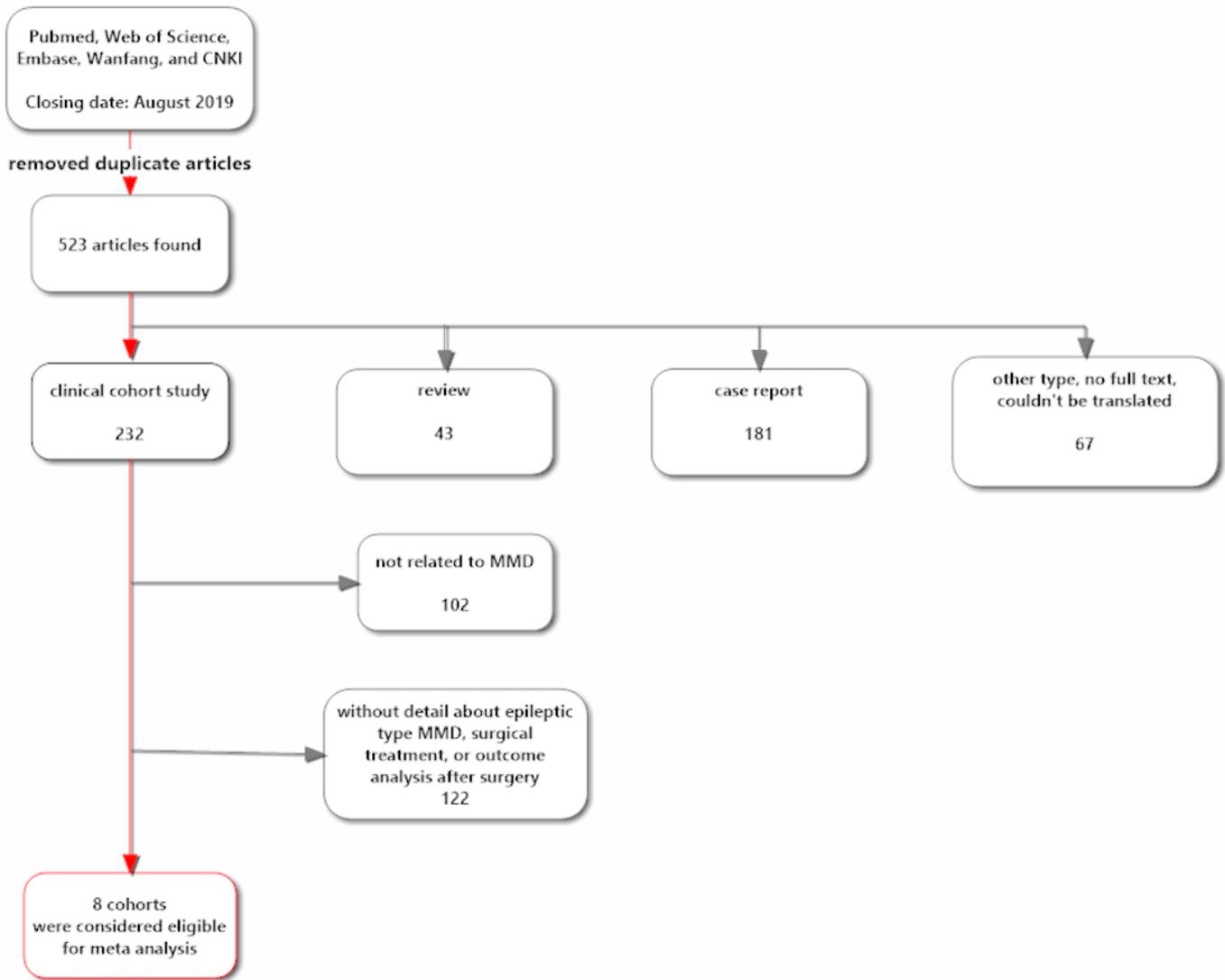
**Figure 1**

forest plot of postoperative incidence a) forest plot of postoperative incidence of seizure in patients with epileptic type MMD. b) forest plot of postoperative incidence of ischemic events in patients with epileptic type MMD.



**Figure 2**

funnel plot of postoperative incidence a) funnel plot of postoperative incidence of seizure in patients with epileptic type MMD. b) funnel plot of postoperative incidence of ischemic events in patients with epileptic type MMD.



**Figure 3**

Flow chart of the literature searches for the systematic review.