Seizure incidence of angiogram-negative subarachnoid hemorrhage: An updated meta-analysis

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Abstract

Background: To provide updated information on seizure events and patterns in patients with angiogram-negative subarachnoid hemorrhage based on the initial hemorrhage patterns: perimesencephalic subarachnoid hemorrhage (PMH) vs non-PMH.

Methods: A review of online database literature from January 1990 to November 2017 was systematically performed. In case of heterogeneity <50%, a fixed effect model was used. Publication bias was determined using Begg funnel plot and the trim-and-fill method.

Results: A total of 9 studies with 645 patients were included for final analysis after excluding one study without any seizure within either cohort. PMH patients had lower seizure rates (odds ratio, 0.393; 95% CI, 0.158–0.978) compared with non-PMH patients. The funnel plot showed a relatively asymmetric pattern, suggesting possible publication bias. After correction of the forest plot, the adjusted odds ratio was 0.362 (95% CI, 0.148–0.886), indicating significant relationships between PMH and lower incidence of seizure.

Conclusion: PMH is associated with lower seizure risk than non-PMH. However, possible publication bias could be a concern to the interpretation. Additional meta-analyses based on individual patient data from prospective large-scale studies are necessary.

Keywords: Outcome; Seizure; Subarachnoid hemorrhage

1. INTRODUCTION

Subarachnoid hemorrhage (SAH) is a life-threatening neurologic emergency with a high mortality rate of up to 57% within the first 6 months.[1] Among patients initially presenting with SAH, approximately 15% of the patients do not have vascular abnormalities and are referred to as angiogram-negative SAH.[2] Based on hemorrhage patterns, angiogram-negative SAH is classified into 2 groups: perimesencephalic SAH (PMH) and non-PMH.[3] It is universally agreed that PMH patients experience better neurologic outcomes with lower incidence of rebleeding and delayed cerebral ischemia (DCI) than non-PMH patients.[4–6] Boswell et al[4] reported that rebleeding events in the PMH group were significantly reduced than those in the non-PMH group (p = 0.013). A recent meta-analysis[6] revealed that PMH patients suffered significantly decreased DCI (odds ratio [OR], 0.219; 95% CI, 0.144–0.334) and cerebral vasospasm (OR, 0.445; 95% CI, 0.337–0.589) than non-PMH patients. Regarding hydrocephalus, patients with PMH exhibited lower incidence of hydrocephalus (OR, 0.269; 95% CI, 0.208–0.348) and permanent shunt placements (OR, 0.263; 95% CI, 0.169–0.411),[7] but possible publication bias is a limitation to the interpretation.

The incidence of seizure has been reported in up to 27.5% of aneurysmal SAH patients and is thought to be associated with severity of the initial brain injury.[8] Choi et al[8] reported that age <40 years, thick SAH, acute hydrocephalus, and rebleeding are risk factor for ictal or immediate seizures following SAH. However, to date, detailed information on seizure activity after ictus has not been well elucidated in patients with angiogram-negative SAH, although literature review regarding DCI and hydrocephalus has been continuously updated.[7] Here, we conducted a meta-analysis to evaluate differences in seizure events between PMH and non-PMH patients.

2. METHODS

2.1. Literature search and selection criteria

Medline through PubMed, Embase, and the Cochrane Central Register of Controlled trials in the Cochrane Library were

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searched using MeSH or key words between January 1990 and November 2017.[6,7] The search strategy is described in detail in the supplemental data, http://links.lww.com/JCMA/A48. Our inclusion criteria were as follows: (1) studies of patients with spontaneous, angiogram-negative SAH; (2) prospective controlled or retrospective case-controlled studies with Newcastle-Ottawa Scale (NOS) score over 5[9,10]; and (3) newly diagnosed seizure during the follow-up, not presenting symptoms. Exclusion criteria were as follows: (1) SAH development after trauma, infection, or other cases of hemorrhage such as aneurysm or arteriovenous malformations; (2) bleeding or xanthochromia during lumbar puncture without hemorrhage on initial computed tomography (CT); (3) incomplete data, absence of interest outcomes, or overlapping data; (4) review articles or case reports; and (5) study not written in English.[4] We evaluated the differences in seizure events according to hemorrhage patterns, PMH vs non-PMH. PMH in angiogram-negative SAH was defined as follows[6,7]: (1) hemorrhage localized to the basal cistern; (2) SAH with little expansion into the anterior interhemispheric or the Sylvian fissure; (3) absent or minimal intraventricular hemorrhage. Two authors (J.P.J. and S.-E.K.) independently evaluated study eligibility for analyses and extracted the data using a uniform standardized form. Disagreements between the 2 authors were resolved by a third author (E.P.H.). This study was approved by the Institutional Review Boards. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

2.2. Statistical analysis

Dichotomous variables are presented using Mantel–Haenszel OR with a 95% CI.[11] Heterogeneity was evaluated using the I^2 test. If I^2 was <50%, a fixed effect model was used.[10] Publication bias was determined using Begg funnel plot. Additional trim-and-fill method was performed to estimate the number and outcome of missing studies.[12,13] The comprehensive meta-analysis (CMA) software (CMA v2.2.064; Biostat, Englewood, NJ) was used for all the above, with statistical significance defined as a p value of <0.05.

3. RESULTS

3.1. Identification of relevant studies

A flow diagram of the detailed search process is described in Figure 1. After screening of records and determining eligibility, we initially enrolled 33 articles. After excluding 23 articles (3 review articles, 3 with overlapping data, 9 with lack of extractable data, and 8 with absence of outcomes of interest), we included 10 articles in the final analysis. The detailed characteristics of the studies are described in Table 1.

3.2. Seizure and publication bias

The 10 articles compared seizure events during follow-up for PMH and non-PMH.[4,14–22] One article[18] was excluded from analysis because it did not report any seizure within either cohort and OR could not be calculated. A total of 645 patients

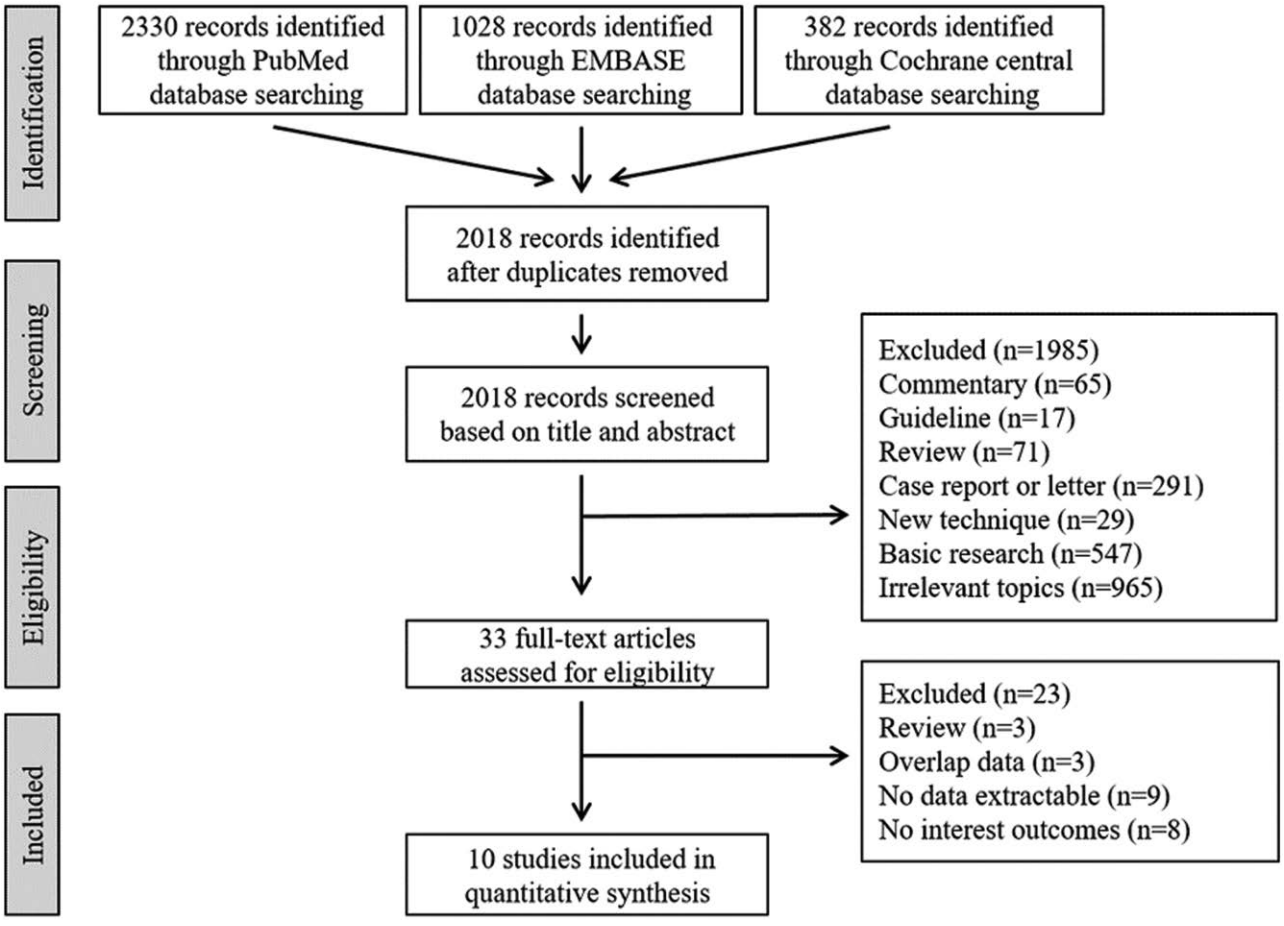

Fig. 1. Flow diagram for identification of relevant studies.

Table 1

Clinical data of studies included in this meta-analysis

No	Study	Design	PMH		Non-PMH		Newcastle-Ottawa Scale
			Total	Seizure	Total	Seizure	
1	Ildan et al[14]	Retrospective	29	1	30	1	5
2	Maslehaty et al[15]	Retrospective	47	0	132	1	5
3	Lin et al[16]	Retrospective	27	0	39	1	5
4	Boswell et al[4]	Retrospective	14	1	16	1	5
5	Zhong et al[17]	Retrospective	49	0	34	1	7
6	Patel et al[18]	Retrospective	45	0	43	0	7
7	Canneti et al[19]	Retrospective	17	0	24	2	7
8	Sprenker et al[20]	Retrospective	25	0	26	1	5
9	Konczalla et al[21]	Prospective[a]	37	1	37	4	7
10	Coelho et al[22]	Retrospective	29	1	33	4	7

PMH=perimesencephalic subarachnoid hemorrhage.

[a]Prospective: prospective case series.

from 9 studies were included. Among them, 4/274 (1.5%) PMH and 16/371 (4.3%) non-PMH patients experienced seizure events during the follow-up interval, suggesting that PMH patients may have a lower risk of seizure (OR, 0.393; $p = 0.045$) (Fig. 2). The funnel plot showed a relatively asymmetric pattern, suggesting possible publication bias (Fig. 3A). We trimmed one study to resolve publication bias (Fig. 3B). The adjusted OR was 0.362 (95% CI, 0.148–0.886), suggesting a significant association between PMH and lower risk of seizure (Table 2).

4. DISCUSSION

To the best of our knowledge, this is the largest comparative analysis of seizure risk in patients with angiogram-negative SAH according to hemorrhage patterns (PMH vs non-PMH), a topic that has not been delved into in-depth in prior studies but may have significant implications for patient outcomes. Our study found that PMH patients seem to have significantly decreased seizure risk, but possible publication bias may limit these findings.

In patients with aneurysmal SAH, the risk of seizure has been studied multiple times. The risk of seizures after surgical treatment of ruptured aneurysms has been reported from 1% to 27.5%.[8] For ruptured aneurysms, surgical techniques of clipping (10.7%) and coiling (11.1%) did not affect the seizure development (OR, 0.596; $p = 0.445$).[23] Lin et al[24] reported more specific seizure rates according to its presenting time: onset of seizure within 12 hours of initial hemorrhage (n = 17; 7.8%), perioperative (n = 5; 2.3%), postoperative (n = 4; 1.8%), and late-onset (n = 15; 6.9%). Comparatively fewer studies[4,14] have investigated the seizure risk during follow-up in patients with angiogram-negative SAH, with a reported mean seizure risk of 1.9% (range, 0%–6.5%). In our meta-analysis, PMH patients seem to have lower seizure rates than non-PMH patients (1.5% in PMH vs 4.3% in non-PMH; $p = 0.045$). The funnel plot was slightly asymmetric to the left, suggesting possible publication bias or unpublished studies.[6] To reduce potential publication bias, we imputed one study and then recomputed the pooled effect using the trim-and-fill method. The adjusted OR was 0.362 (95% CI, 0.148–0.886), suggesting a meaningful association between lower risk of seizure and PMH.

The negative impact of seizures on SAH outcome has been well studied in patients with aneurysmal SAH. Huttunen et al[25] reported that comorbid seizure in 1-year survivors is an independent risk factor for mortality (hazard ratio, 1.8; 95% CI, 1.1–3.0). Accordingly, early identification and treatment of comorbid seizure are essential to reduce morbidity and mortality. Prophylactic antiepileptic drugs (AEDs) are routinely administered for spontaneous SAH. Nevertheless, its clinical efficacy is still controversial. A propensity score-matched analysis by Panczykowski et al[26] did not demonstrate significant seizure risk reduction using prophylactic AED ($p = 0.49$). For patients with angiogram-negative SAH, AEDs have been prescribed in clinical circumstances, although the impact of seizure on neurologic outcomes in angiogram-negative SAH remains undetermined. In most studies, seizure onset in patients with angiogram-negative

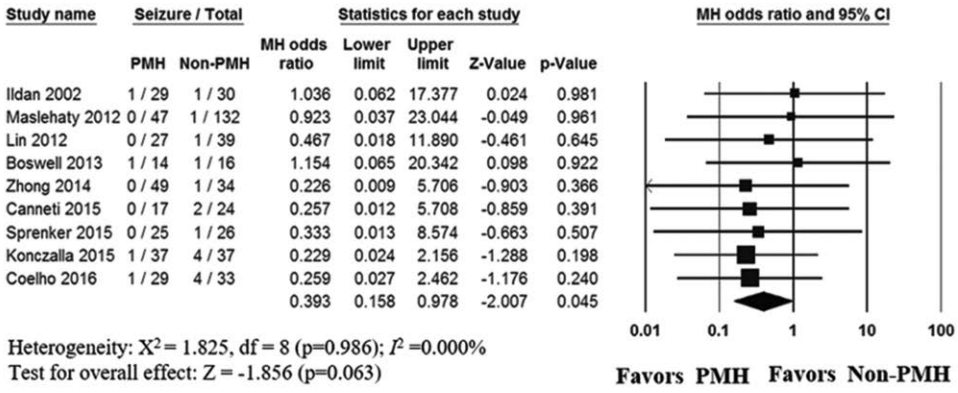

Fig. 2. Seizure risk according to hemorrhage pattern during follow-up period=PMH vs non-PMH. MH=Mantel–Haenszel; PMH=perimesencephalic subarachnoid hemorrhage; SAH=subarachnoid hemorrhage.

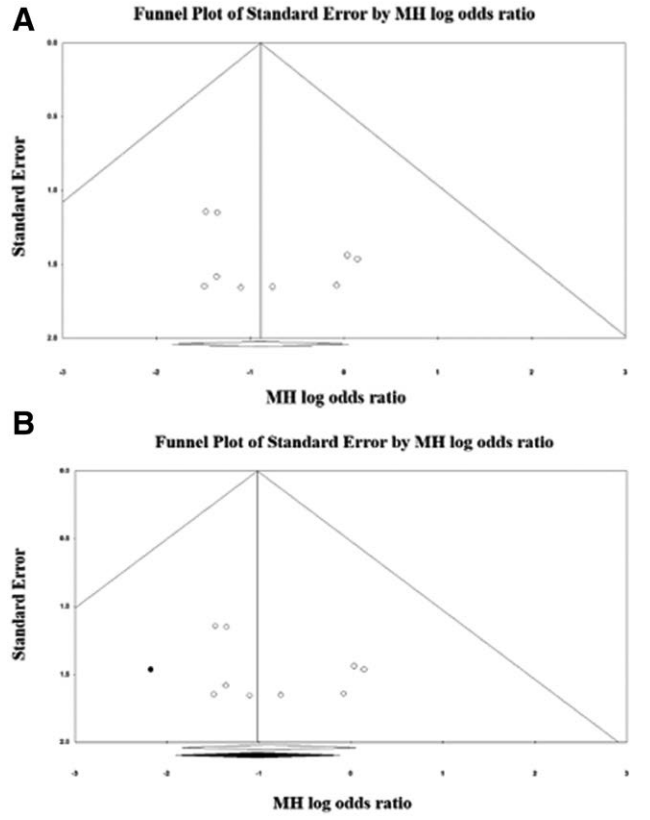

Fig. 3. Funnel plots of unadjusted (A) and adjusted (B) effect estimates after correction of publication bias using "trim-and-fill" method. MH = Mantel–Haenszel.

Table 2

Publication bias analysis using the trim-and-fill method for seizure development in the meta-analysis

Outcome		Fixed effects				*Q* value
Included studies		Studies trimmed	Point estimate	Lower limit	Upper limit	
Seizure	Observed values	…	0.410	0.160	1.051	1.817
Nine studies	Adjusted values	1	0.362	0.148	0.886	2.510

SAH was diagnosed by clinical features. O'Connor et al[27] investigated the frequency and clinical impact of electrographic seizures in patients with spontaneous SAH. In the study, 17.6% of patients had electrographic seizures, which was higher than the baseline rate of 9.6%. Interestingly, more than a third of the seizures were first detected after at least 2 days of continuous electroencephalography (EEG) monitoring. Therefore, future studies should compare outcomes taking into account seizure onset time and AED use, while also using individual patient data according to hemorrhage patterns in angiogram-negative SAH.

Meta-analyses of rare events have methodologic challenges since each study can be underpowered in identifying treatment effect.[11] Most meta-analyses reach their primary outcome using the inverse-variance methods, estimating treatment effects along with an SE and normal approximation. However, such approximation is not well suited for evaluating rare events, in particular, those with zero incidence.[11] In such cases, statistical methods such as Peto method or Mantel–Haenszel can be used. Previous studies[28,29] showed that Peto estimation is appropriate for rare events (>1%) when the 2 groups are balanced in their enrollment size. In our meta-analysis, the 2 groups (PMH and non-PMH) are unequal in size, making Peto estimation invalid. In addition, rare events were observed in >1% of cases. Accordingly, we used the Mantel–Haenszel methods to reduce potential inherent technical bias in calculating OR across studies. Importantly, outcomes of meta-analyses can change according to the size of included studies and we consider this in our interpretation of meta-analysis results.

There are some limitations in this investigation. First, most studies included in this meta-analysis were retrospective studies. Second, potential publication bias was observed in the outcome assessment. Third, the time of seizure onset was not considered in the analysis. Seizures can happen at various time points between post-ictus to perioperative or postoperative period lasting over 1 week. Fourth, detailed information on follow-up period was not provided in most studies. Fifth, most studies enrolled in this meta-analysis did not provide information about AED use in patient management. Thus, differences in AED use according to hemorrhage pattern could affect seizure development which can increase the study heterogeneity across studies. Therefore, a large-scale meta-analysis based on prospective trial registrations dealing with clear information on AED use, seizure onset period during follow-up, and diagnosis method (EEG vs clinical features assessment) is further required.

In conclusion, our meta-analysis showed that seizure events occur less frequently in PMH compared with non-PMH. Additional meta-analysis based on individual patient data from prospective studies is necessary to better elucidate the relationship between hemorrhage pattern in angiogram-negative SAH and seizure risk.

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