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Review article

Risk factors for re-bleeding of aneurysmal subarachnoid hemorrhage: Meta-analysis of observational studies

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ABSTRACT

Objective: The mortality of re-bleeding following aneurysmal subarachnoid hemorrhage is high, and surviving patients often have poor clinical condition and worse outcome than patients with a single bleed. In this study, we performed an updated systematic review and meta-analysis to determine the most common risk factors for re-bleeding in this patient population, with the goal of providing neurologists, neurosurgeons, neuro-interventionalists with a simple and fast method to evaluate the re-bleeding risk for aneurysmal subarachnoid hemorrhage.

Method: We conducted a thorough meta-analysis of the risk factors associated with re-bleeding or re-rupture of intracranial aneurysms in cases published between 2000 and 2013. Pooled mean difference was calculated for the continuous variables (age), and pooled odds ratio (OR) was calculated for categorical factors. If heterogeneity was significant ($p < 0.05$), a random effect model was applied; otherwise, a fixed model was used. Testing for pooled effects and statistical significance for each potential risk factor were analyzed using Review Manager software.

Results: Our literature search identified 174 articles. Of these, only seven retrospective studies met the inclusion criteria. These seven studies consisted of 2470 patients, 283 of which had aneurysmal re-bleeding, resulting in a weighted average rate of re-bleeding of 11.3% with 95% confidence interval [CI]: 10.1–12.6. In this population, sex (OR 1.46; 95% CI: 1.11–1.92), high systolic blood pressure [SBP] (OR 2.52; 95% CI: 1.40–4.53), aneurysm size (OR 3.00; 95% CI: 2.06–4.37), clinical condition (Hunt & Hess) (OR 4.94; 95% CI: 2.29,10.68), and Fisher grade (OR 2.29; 95% CI: 1.45, 3.61) were statistically significant risk factors for re-bleeding.

Conclusion: Sex, high SBP, high Fisher grade, aneurysm size larger than 10 mm, and poor clinical condition were independent risk factors for aneurysmal re-bleeding. The importance of early aneurysm intervention and careful consideration of patient risk factors should be emphasized to eliminate the risk of re-bleeding and poor outcome.

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1. Introduction

10–15% of patients with aneurysmal subarachnoid hemorrhage (SAH) die before reaching medical care [1]. A further 5% die within the first 24 h of SAH, and by the 30th day following SAH, the overall case fatality rate increases to nearly 50% [1,2]. 25–30% of survivors re-bleed within the first four weeks following the initial SAH [5]. After the first six weeks following SAH, the re-bleeding rate drops to about 4% per year, and 50–90% of re-bleeding episodes occur in the first 6 h after the primary bleed [3,4]. Patients who experience re-bleeding have especially high mortality, reportedly as high as 75–80% [5–8]. Risk of re-bleeding is high if the aneurysm is left untreated, and 25% of patients die as a result of medical complications of SAH [9], such as neurogenic pulmonary edema and neurogenic stunned myocardium. For these reasons, early detection and accurate evaluation of the incidence of and predictors for re-bleeding are critical, as risk factors associated with aneurysm re-bleeding are still controversial. Moreover, re-bleeding can occur before patients are admitted or during transfer to the hospital [10,11] or after hospitalization.

In this study, we analyzed potential risk factors for aneurysmal re-bleeding among patient information that is available after admission to the hospital. We reviewed 9 factors that may have significant impact on the likelihood of re-rupture after primary bleeding. These findings will assist neurologists, neurosurgeons, and health care providers in optimizing patient outcome by informing them of the most common risk factors of re-bleeding in subarachnoid hemorrhage patients.

2. Materials and methods

2.1. Literature search and selection of relevant studies

We conducted a careful meta-analysis of data from all publications between 2000 and 2013 pertaining to the risk of re-bleeding or re-rupture of intracranial aneurysms. Relevant literature was identified by a MEDLINE, EMBASE, COCHRANE, Web of Science search using the following keywords in different combinations: cerebral aneurysms, intracranial aneurysms, re-bleeding, re-rupture, recurrent hemorrhage, risk factors. Additionally, we searched the reference lists of articles identified in our initial search for other relevant publications, as well as the references found in articles identified in this secondary search. Quality control of the selected studies was performed using the Newcastle-Ottawa Scale (NOS, Ottawa Hospital Research Institute), which was collaboratively developed by the University of Newcastle and University of Ottawa as a means of evaluating the reliability and validity of non-randomized studies. It uses the means of study group selection, comparability of those groups, and how the outcome or exposure was determined to assign a reliability score to the study in question.

2.1.1. Inclusion criteria

Studies meeting the following criteria were included in our analysis:

1. Studies pertaining to patients with SAH due to aneurysmal re-rupture after previous bleeding, as demonstrated by neuroimaging such as magnetic resonance image (MRI), computed tomography angiography (CTA), digital subtraction angiography (DSA).
2. Studies comparing multiple risk factors in re-bleeding and non-re-bleeding groups such as: sex, age, clinical conditions at admission (assessed by Hunt & Hess scale), hypertension, location of aneurysm, presence of multiple aneurysms, size of aneurysm, Fisher grade, external ventricle drainage (EVD).

2.1.2. Exclusion criteria

Studies meeting the following criteria were excluded from our analysis:

1. Studies with fewer than 20 patients, as smaller studies are more likely to suffer from selection bias.
2. Studies where multiple reports were published for the same study population.
3. Studies reported as a review, case report, or editorial.
4. Studies of SAH due to non-aneurysmal pathology (i.e. trauma, arteriovenous malformation (AVM), etc.).
5. Studies reported in languages other than English.

2.2. Data extraction

Two reviewers independently extracted data on patient and aneurysm characteristics and pre-operative treatment from all studies that met the inclusion criteria. In the event of disagreement between the 2 reviewers regarding whether a study met inclusion criteria, consensus was reached by joint review.

2.3. Index of measurements

We extracted data on age, sex, hypertension, aneurysm location, multiple aneurysms, size, clinical condition (Hunt & Hess), Fisher grade, and external ventricle drainage (EVD) wherever possible. With the exception of age, which was evaluated as a continuous variable, each factor was classified into one of the two categories, as follows: sex (male or female), hypertension (>160 mmHg), aneurysm location (anterior or posterior circulation, see below), multiple aneurysms (yes or no), size (≥10 mm or <10 mm), clinical condition (good, I–II–III on Hunt & Hess scale, or poor, IV–V on Hunt & Hess scale), Fisher grade (≥3 or <3), and EVD (yes or no). The location of the aneurysms was classified as either (1) anterior circulation: anterior communicating artery, internal carotid artery, anterior cerebral artery, middle cerebral artery, posterior communicating artery, or (2) posterior circulation: vertebral artery, basilar artery, posterior cerebral artery.

2.4. Data analysis

1. Data (9 factors) were extracted from the 7 studies that met inclusion criteria and entered into a spreadsheet in Microsoft Excel software.

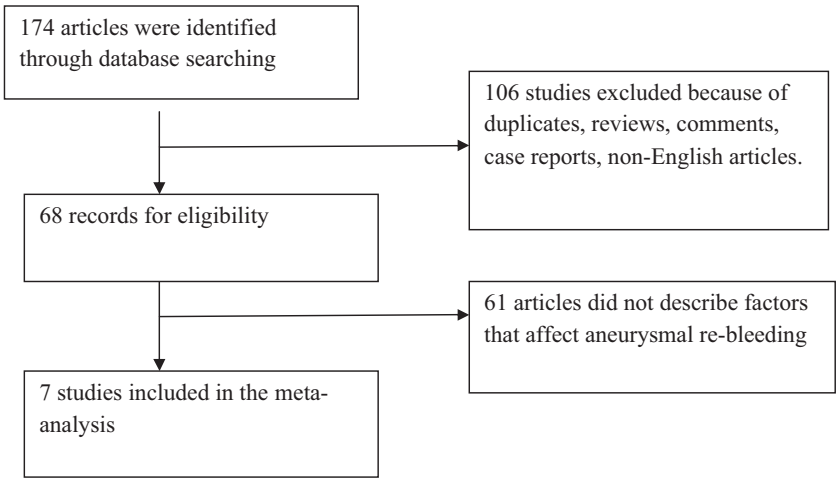

Fig. 1 – Flow chart for identifying articles to be included in the meta-analysis.

2. Review Manager software (RevMan, version 5.1, The Nordic Cochrane Centre) was used to find pooled effects and perform significance testing for each potential risk factor. RevMan is available free of charge for academic use at the Cochrane Informatics and Knowledge Management Department website.
3. Pooled mean difference was calculated for the continuous variables (age), and pooled odds ratio was calculated for categorical factors.
4. For risk factors with significant ($p < 0.05$) heterogeneity, a random effect model was applied. For risk factors without significant heterogeneity, a fixed model was used.

3. Results

3.1. *Literature search and study selection*

Our literature search identified 174 articles. Of those, only seven retrospective studies met the inclusion criteria (Fig. 1). Those seven studies included 2470 patients, 283 of which had aneurysmal re-bleeding (Table 1). To control for the quality of the studies we selected for further analysis, we performed a quality evaluation of each study using the Newcastle-Ottawa Scale (NOS). Each study included in our analysis rated above

Table 1 – Overview of the 7 included studies.

Author	Publication year	Number of patients			Re-bleeding rate	Study period (year)	Study design	Diagnosis of re-bleeding	Journal	Details of patient selection provided
		Total	Re-bleed	No-re-bleed						
Cha et al. [22]	2010	492	38	454	8.4%	12 (1995–2007)	Retrospective	CT	J Korean Neurosurg Soc	No
Beck et al. [28]	2006	237	23	214	10.7%	3 (1999–2002)	Retrospective	CT	Stroke	No
Guo et al. [23]	2013	326	70	256	27.3%	9.3 (2002–2010)	Retrospective	CT or lumbar puncture	World Neurosurg	No
Cong et al. [14]	2012	458	63	395	15.9%	3 (2005–2008)	Retrospective	CT	Turkish Neurosurgery	Yes
Naidech et al. [13]	2005	574	40	534	7.5%	6 (1996–2002)	Retrospective	CT	Arch Neurol	Yes
Ohkuma et al. [4]	2001	273	37	236	15.7%	10 (1989–1998)	Retrospective	CT	Stroke	Yes
Wu et al. [30]	2012	110	12	98	12.2%	3 (2007–2010)	Retrospective	CT	J Comput Assist Tomogr	Yes
Total		2470	283							

Table 2 – Risk factors investigated and quality evaluation for each included study.

Authors	Risk factors investigated	Score, NOS scale
Cha et al.	A B C D E F G H	7
Beck et al.	A B F H I	8
Guo et al.	A B C D F G H	8
Cong et al.	A B C D E G	8
Naidech et al.	G I	8
Ohkuma et al.	A B C D G	7
Wu et al.	A B C D F H	7

A: Age, B: Sex, C: High SBP, D: aneurysm location, E: multiple aneurysms, F: aneurysm size, G: Hunt & Hess grade, H: Fisher grade, I: EVD.

seven on the NOS, indicating that a sufficiently high standard of data was collected (Table 2). In these seven studies, the weighted average rate of re-bleeding was 11.3% with 95% confidence interval [CI]: 10.1–12.6.

3.2. *Meta-analysis*

We performed a meta-analysis of the data presented in the seven selected studies to evaluate the likelihood of nine different factors to correlate with increased risk of aneurysm re-bleeding. Of those nine factors, sex (males are at greater risk than females) (OR 1.46; 95% confidence interval [CI]: 1.11, 1.92), high systolic blood pressure [SBP] (OR 2.52; 95% CI: 1.40, 4.53), aneurysm size (greater than 10 mm) (OR 3.00; 95% CI: 2.06–4.37), poor clinical condition (as defined by Hunt & Hess) (OR 4.94; 95% CI: 2.29–10.68), and high Fisher grade (OR 2.29; 95% CI: 1.45–3.61) were associated with significantly increased odds of re-bleeding. In contrast, age (OR 1.72;95% CI:−1.61–5.04), aneurysm location (OR 1.59; 95% CI: 0.72–3.48), presence of multiple aneurysms (OR 1.11; 95% CI: 0.58–2.09), and EVD (OR 2.96; 95% CI: 0.86–10.22) were not significant risk factors for re-bleeding in aneurysmal SAH patients according to our analysis (Table 3 and Figs. 2–10).

4. Discussion

The cases studied in this report had a re-bleeding incidence of 7.5–27.3%, with a weighted average rate of re-bleeding of 11.3% with 95% confidence interval [CI]: (10.1, 12.6)%.

4.1. *Age and sex*

Previous reports indicate that patients of advanced age have poor outcome after SAH [12], and several studies have reported that older people have a higher tendency to re-bleed than control cases [12]. However, studies by Naidech et al. and Cong et al. suggested that age was not associated with re-bleeding [13,14]. Our meta-analysis of patient data published since 2000 did not find significant differences between the ages of patients who did and did not experience re-bleeding following SAH (Fig. 2).

Our analysis indicated that males had a significantly higher risk of re-bleeding than females, in contrast to previous data suggesting that female patients have particularly high risk [15] (Fig. 3). In part, this may be due to a greater prevalence of smoking in male patients, as smoking can lead to damage of the cerebral vessels and increase the risk of SAH recurrence.

4.2. *Hunt & Hess grade*

Generally, a patient's clinical and neurological condition at admission is evaluated by the Hunt & Hess grading system [16]. Several studies reported that poor condition at admission, as indicated by a high Hunt & Hess grade, was associated with aneurysmal re-bleeding [4,5,13,17–19]. Our analysis supports these studies, which showed that SAH patients who initially presented with high Hunt & Hess grades (IV–V), indicative of poor clinical condition, have greater likelihood of re-bleeding than those with low Hunt & Hess grades (I–III) (Fig. 4). Though one study in our analysis, by Inagawa et al., did not find a relationship between poor patient condition and re-bleeding [20], this may be a result of the frequent necessity to intubate and sedate patients with higher Hunt & Hess scores, making clinical diagnosis difficult.

Table 3 – Meta-analysis.

Risk factor	Number of studies	Heterogeneity Chi-squared		Models of meta-analysis	Pooled OR/ odd ratio	95% CI	Z	p
		p	I^2 (%)					
Age (mean)	6	0.009	67	Random	1.72	−1.61 to 5.04	1.01	0.31
Sex	6	0.61	0	Fixed	1.46	1.11–1.92	2.71	0.007
Male vs. female								
Hypertension	4	0.01	72	Random	2.52	1.40–4.53	3.08	0.002
Location anterior circulation vs. posterior circulation	5	0.83	0	Random	1.59	0.72–3.48	1.15	0.25
Multiple aneurysms	2	0.12	58	Fixed	1.11	0.58–2.09	0.31	0.76
Size ≥10 mm vs. <10 mm	4	0.11	50	Fixed	3.00	2.06–4.37	5.74	0.00001
Hunt & Hess grade IV–V vs. I–II–III	5	0.0001	83	Random	4.94	2.29–10.68	4.07	<0.0001
Fisher grade ≥3 vs. <3	4	0.34	11	Fixed	2.29	1.45–3.61	3.55	0.0004
External ventricular drainage (EVD)	2	0.03	78	Random	2.96	0.86–10.22	1.72	0.09

There are 6 studies describing age and re-bleeding. Pooled effects: OR (95% CI): 1.72 (-1.61,5.04).

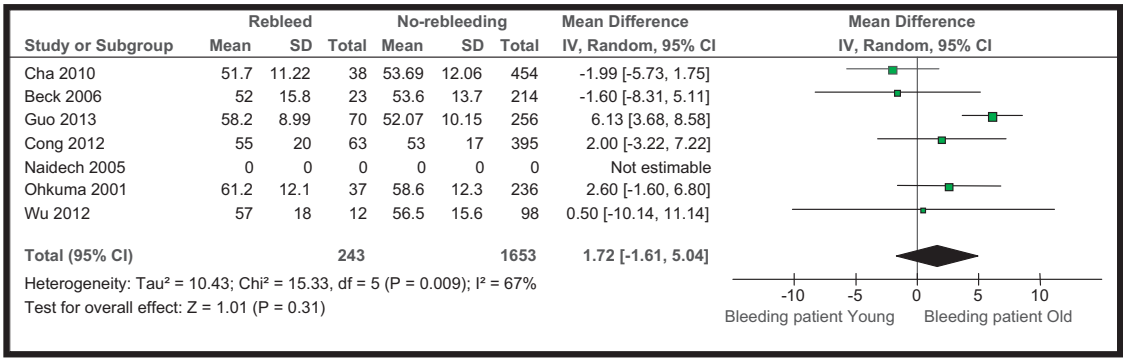

Fig. 2 – Meta-analysis of re-bleeding and age.

There are 6 studies describing sex and re-bleeding. Pooled effects: OR (95% CI): 1.46 (1.11,1.92).

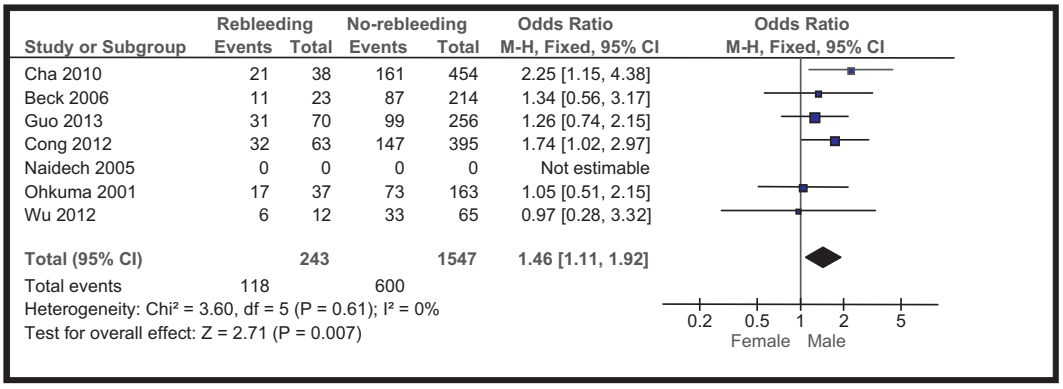

Fig. 3 – Meta-analysis of re-bleeding and sex.

There are 5 studies describing Hunt & Hess and re-bleeding. Pooled effects: OR (95% CI):4.94(2.29,10.68).

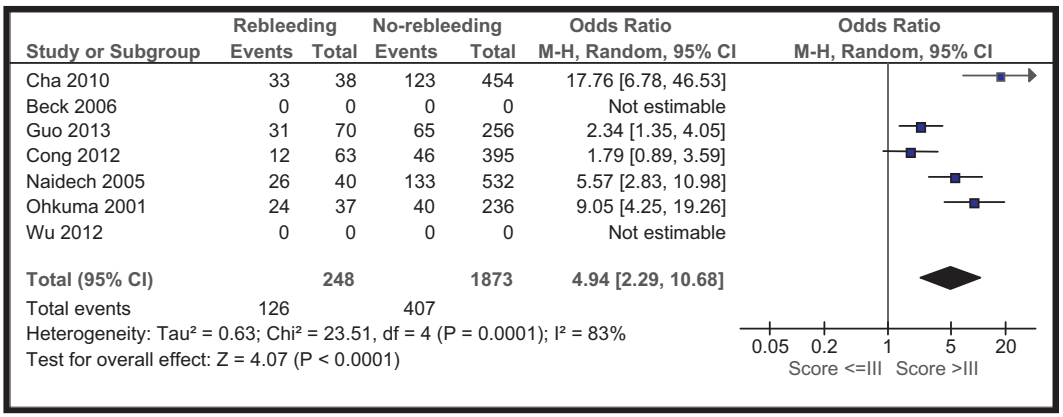

Fig. 4 – Meta-analysis of re-bleeding and hypertension.

There are 4 studies describing hypertension and re-bleeding. Pooled effects: OR (95% CI): 2.52 (1.40,4.53).

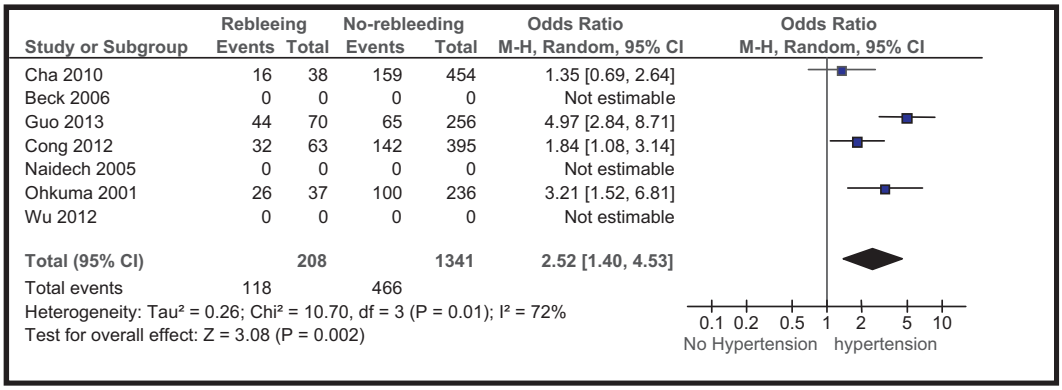

Fig. 5 – Meta-analysis of re-bleeding and aneurysm location.

4.3. *High systolic blood pressure*

Prior to this study, published data have not reached a consensus on the role that high systolic blood pressure plays in risk of aneurysmal re-bleeding following SAH. Naidech et al. found that hypertension is not associated with re-bleeding after SAH [13], and a second, large study reported a re-bleeding rate of 6.9% after admission to the hospital, but did not find a relationship between blood pressure and likelihood of re-bleeding [21]. In contrast, many other studies found that high blood pressure following initial SAH can lead to an increased risk of re-bleeding [4,17,22,23]. In particular, Ohkuma et al. found that re-bleeding is more common in patients with high systolic blood pressure (above 160 mmHg) [4]. Our pooled analysis of multiple studies demonstrated that high systolic blood pressure (above 160 mmHg) is a major risk factor for aneurysmal re-bleeding in SAH patients (Fig. 5).

4.4. *Fisher grade*

The appearance of SAH by CT scan is classified by Fisher grade of 1–4, with 4 being the worst. Patients with intracerebral or intraventricular hematoma usually present with poor clinical condition (high Hunt & Hess grade) and high blood pressure. Previous studies suggest that this may lead to early re-rupture of the aneurysm. For example, Reynold et al. reported higher incidence of intracerebral hematoma in patients with signs of repeated aneurysm rupture [24], which may, in turn, substantially contribute to the poor clinical condition of patients with repeated SAH. However, in contrast to our analysis, which indicates that Fisher grade is a significant risk factor for re-bleeding (Fig. 6), studies by Inagawa et al. and Guo et al. did not find any correlation between Fisher grade and re-bleeding [20,23].

4.5. *External ventricular drainage (EVD)*

Acute hydrocephalus is a common complication after aneurysmal SAH. Treatment of acute hydrocephalus involves emergent cerebral spinal fluid (CSF) drainage, which often results in improvement of the patient's clinical condition. There are many conflicting studies that suggest CSF drainage can lead to aneurysmal re-bleeding [13,25,26]. The most accepted theory is that CSF drainage in patients with an

There are 4 studies describing Fisher Grade and re-bleeding. Pooled effects: OR (95% CI):2.29(1.45,3.61).

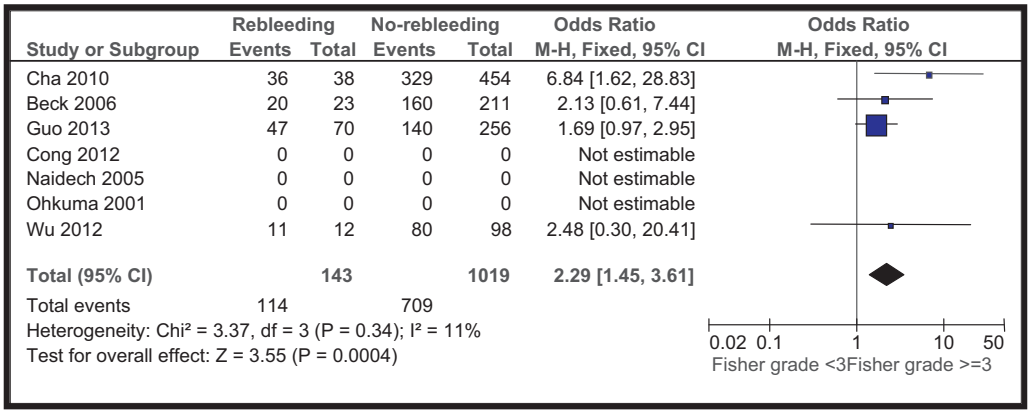

Fig. 6 – Meta-analysis of re-bleeding and multiple aneurysms.

There are 2 studies describing EVD and re-bleeding. Pooled effects: OR (95% CI): 2.96 (0.86-10.22).

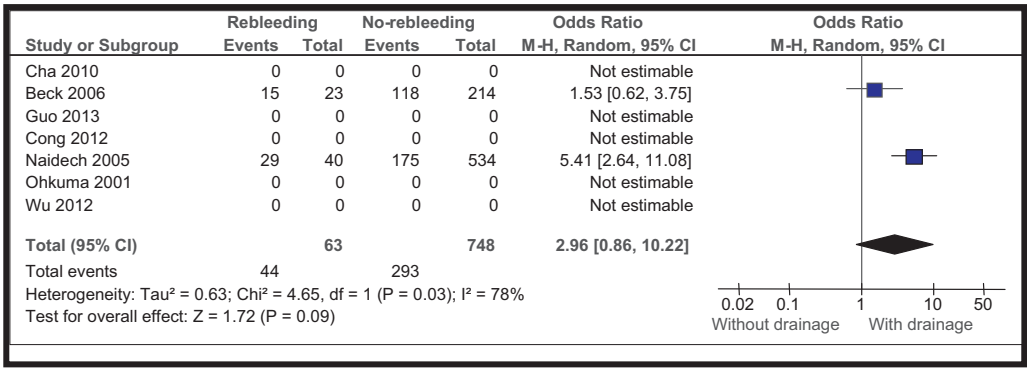

Fig. 7 – Meta-analysis of re-bleeding and aneurysm size.

unsecured, recently ruptured aneurysm may increase transmural pressure across the aneurysm wall, and this may lead to increased likelihood of re-bleeding [27]. In spite of this, the study performed by Beck et al. did not find a strong correlation between external ventricular drainage and re-bleeding [28]. Our analysis, which included the aforementioned Beck study and one conducted by Naidech et al. [13] in which EVD was a significant risk factor for re-bleeding, did not indicate that, when taken together, those two studies demonstrated a significant relationship between EVD and increased risk of re-bleeding in aneurysmal SAH patients (Fig. 7).

4.6. *Aneurysm location*

Previous studies demonstrated that the location of an aneurysm can have an effect on likelihood of re-bleeding [3,28], especially in the anterior communicating artery (AComA) and posterior communicating artery (PComA) [29]. A study by Cong W et al. indicated that patients with a posterior circulation aneurysm have higher bleeding risk than those with an aneurysm in the non-posterior circulation [14]. The present study reveals that, on aggregate, aneurysm location was not a significant risk factor for re-bleeding (Fig. 8), in agreement with the conclusions drawn by studies performed by Guo et al. and Wu et al. [23,30].

4.7. *Aneurysm size*

Most studies emphasize the importance of aneurysm size in determining risk for initial rupture [31,32]. Guo et al. also found that the probability of re-bleeding in patients with aneurysms larger than 10 mm was 1.624-fold greater than those with aneurysms of 10 mm or less [23], but other studies have not confirmed this association [17,22]. Our analysis demonstrated, however, that large aneurysm size does confer significant risk of aneurysmal re-bleeding (Fig. 9).

4.8. *Multiple aneurysms*

Patients with several aneurysms often have more fragile vessel walls that may be prone to aneurysm formation in general or re-bleeding after the initial aneurysm rupture. In spite of this, some studies have shown that there was no significant difference in likelihood of re-bleeding in patients

There are 5 studies describing aneurysm location and re-bleeding. Pooled effects: OR (95% CI): 1.59 (0.72,3.48).

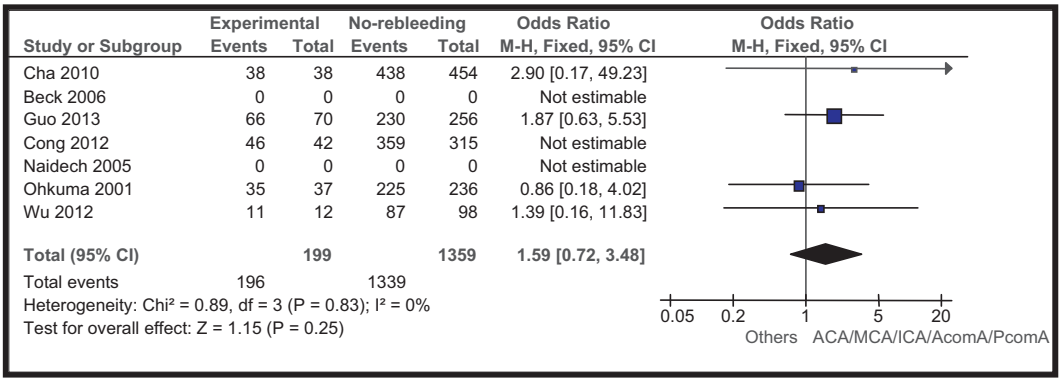

Fig. 8 – Meta-analysis of re-bleeding and Hunt & Hess grade.

There are 4 studies describing aneurysm size and re-bleeding. Pooled effects: OR (95% CI): 2.91 (1.62,5.22).

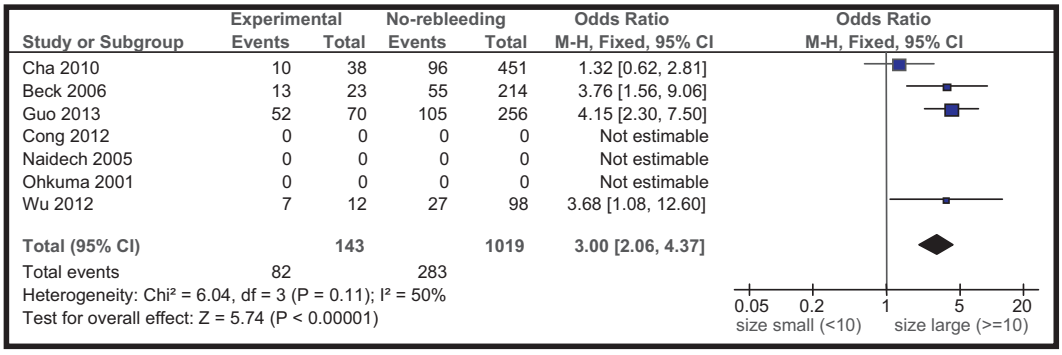

Fig. 9 – Meta-analysis of re-bleeding and Fisher grade.

There are 2 studies describing multi aneurysm and re-bleeding. Pooled effects: OR (95% CI):1.11(0.58,2.09).

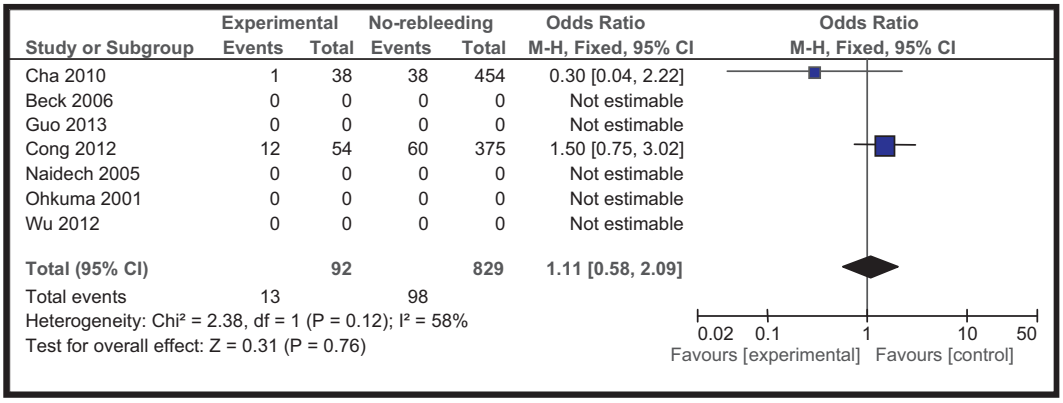

Fig. 10 – Meta-analysis of re-bleeding and external ventricular drainage.

with multiple aneurysms [14]. Beck et al. did report an increased risk of re-bleeding in patients with multiple aneurysms patients [28]; however, our analysis indicated that there is no significant correlation between presence of multiple aneurysms and re-bleeding (Fig. 10).

5. Conclusion

According to our meta-analysis of several published studies of occurrence of re-bleeding in aneurysmal SAH patients, sex, hypertension, patient condition, aneurysm size, and Fisher grade are major risk factors in determining the likelihood a patient will experience re-bleeding. In those same studies, no correlation was found between age, EVD, aneurysm location, and presence of multiple aneurysms and aneurysm re-bleeding. Based on these results, we advocate early surgery for primary ruptured aneurysm in patients with good clinical condition to minimize the risk of re-bleeding. Furthermore, maintenance of systemic blood pressure in a moderately hypertensive range (140–160 mmHg) may help to prevent early re-rupture of the aneurysm. Notably, the studies evaluated here assessed re-bleeding rates prior to treatment of the SAH, and as such, the amount of time between the initial onset of bleeding and treatment of the SAH can have an effect on the likelihood of re-bleeding. Future studies that take this factor into account will be critical to the follow-up of this study.

6. Limitations of this study

All the studies examined here are retrospective, making data quality difficult to monitor. Only a few studies described clear inclusion and exclusion criteria, and each study was conducted with different study objectives. Diagnostic criteria frequently vary from hospital to hospital, which could yield some inconsistency in results. The risk factors studied differ from study to study depending on the study focus. Lastly, a larger sample size would improve the reliability of the analysis. Due to limited availability of data for some risk factors, we were only able to include information from two

independent studies, which decreases the strength of the conclusions drawn from those particular analyses. With a larger number of studies, data collection would be more balanced and result in decreased potential for selection bias. Additionally, a larger sample size would allow for performance of a meta-regression analysis to find the adjusted effect of each risk factor.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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