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ORIGINAL PAPER

The Outcome after Surgical Management of Ruptured *Versus* Unruptured Anterior Circulation Aneurysms

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ABSTRACT

Objectives: *The present article aimed to review the safety and the clinical and radiological outcomes of clipped ruptured and unruptured anterior circulation aneurysms.*

Materials and methods: *The study investigated the relative articles involving the outcome after surgical management of ruptures* versus *unruptured anterior circulation aneurysms through electronic databases from January 1980 to January 2023. The primary outcomes were mortality and modified Rankin scale (mRS) >3.*

Results: *Information on mRS >3 was found in six articles totalizing 2096 patients, of whom 130 subjects had ruptured and unruptured aneurysms. Data about mortality was provided by eight studies totalizing 2454 participants, of whom 140 subjects had ruptured and unruptured aneurysms.*

Conclusions: *The current meta-analysis indicates that surgical clipping is a safe procedure for both ruptured and unruptured aneurysms of anterior circulation.*

Keywords: anterior circulation aneurysms, aneurysms, surgical outcome, rupture andunruptured aneurysms, microsurgical clipping.

INTRODUCTION

Intracranial aneurysms (IAs) (Figure 1) have an incidence of 3–5% in the general population (1, 2). They have been the subject of numerous studies as a part of which the natural history, differences between endovascular and microsurgical management (3, 4), various approaches (pterional, ministerial, lateral supraorbital, etc) (5), complications like stroke (6-11) and treatments of subarachnoid hemorrhage (SAH) have been extensively examined (12, 13). In addition, the advances in the endovascular techniques in the last two decades (14-17) have provided a new therapeutic prospect, mainly for some complex aneurysms (18). However, sufficient microsurgical abilities are still necessary for difficult cases unsuitable for endo-

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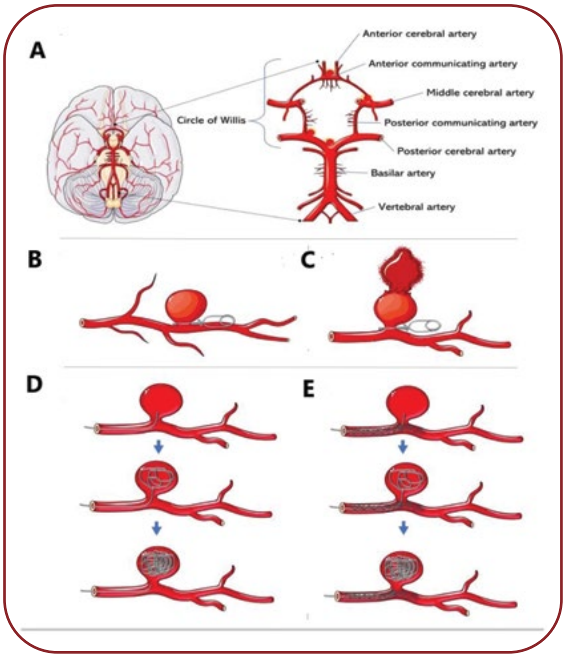

FIGURE 1. A) Major arteries and frequent locations of development of intracranial saccular aneurysms; **B) and C)** aneurysm clipping unruptured *versus* ruptured; **D and E)** other interventional methods, endovascular treatment with coiling, in which tiny platinum coils are placed directly into the aneurysm and stent-assisted coiling parts of this image derived from the free medical site http://smart.servier.com/ (accessed on 18 July 2023) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence

vascular management. Furthermore, authors of some studies reported a high percentage of residual aneurysms (19), and the long-term effectiveness of endovascular treatment has also been debated (11, 20, 21).

Therefore, although previous trials could indicate that surgery still has a role in a subset of ruptured or unruptured aneurysms, the goal of the present meta-analysis was to review the safety and clinical and radiological outcomes of clipped ruptured or unruptured anterior circulation aneurysms. ❑

MATERIALS AND METHODS

Literature search strategy

The current study investigated the relative articles involving the outcome after surgical management of ruptures *versus* no ruptures of anterior circulation aneurysms through electronic databases, including the Cochrane Library, Medline, PubMed and EMBASE, from January 1980 to January 2023. PRISMA was used to ascertain the protocol and manuscript design (22). The search strings 'anterior circulation aneurysms', 'aneurysms', 'surgical outcome', 'ruptured and unruptured aneurysms', 'anterior circulation aneurysms' and 'surgical outcome ruptured and unruptured' were used in the MeSH list.

Inclusion and exclusion criteria

The current meta-analysis included only studies that accomplished the following PICOS criteria: (i) population – related to patients with ruptured or unruptured aneurysms; (ii) intervention – surgical clipping for anterior circulation aneurysms; (iii) comparison – outcome assessment; (iv) outcomes resolved – modified Rankin scale (mRS) >3 and mortality were included as primary outcomes. In order to reduce publication bias, the final aim was to collect studies without heterogeneity, involving researches evaluating only two modalities: ruptured and unruptured aneurysm surgery. Letters to the editor, case presentations or reviews that were not written in English, pediatric studies, distinct results, comorbidities, new uncertain methods, or one of the two modalities separately, and any study with indistinct results were all excluded.

Data and outcome classification

GF and VEG independently exported pertinent results from the included studies, in related to the plan for meta-analyses. The subsequent essential data was attained: the name of first writers, the publication's year, the number of patients in groups, study category, prognostic markers, etc. The extracted data were entered into a reliable table created for this reason, according to the *Cochrane Handbook* (https://training.cochrane.org/handbook). In case of disagreement, an additional author completed the finishing conclusion.

Information concerning one of the main outcomes, including mortality and mRS > 3, was registered and documented. The mRS is a severity-of-disease classification system that estimates the level of morbidity during the everyday actions of participants who have suffered a stroke or have other diseases leading to neurological disability. A numerical score from 0 to 6 was assigned based on several factors, with higher scores indicating a more severe situation and a greater risk of death (23). Postoperative outcomes in the reviewed

TABLE 1. Newcastle-Ottawa scale (NOS) quality assessment of final article pool

Trial, year	Study design	Newcastle-Ottawa scale			
		Selection	Comparability	Exposure	Total scores
Miyazawa N *et al*, 2002 (32)	retro	3	3	3	9
Steven DA *et al*, 2007 (30)	retro	3	3	3	9
Wester K, 2009 (33)	prosp	3	3	3	9
Fischer G *et al*, 2011 (31)	retro	3	3	3	9
Yamahata H *et al*, 2014 (29)	retro	3	2	2	7
Figueiredo EG *et al*, 2016 (25)	retro	3	2	2	7
Alkhalili KA *et al*, 2017 (26)	retro	3	2	2	7
Tomatis A *et al*, 2019 (28)	retro	3	2	2	7
Park JS *et al*, 2020 (27)	retro	3	2	2	7

retro = retrospective; prosp = prospective

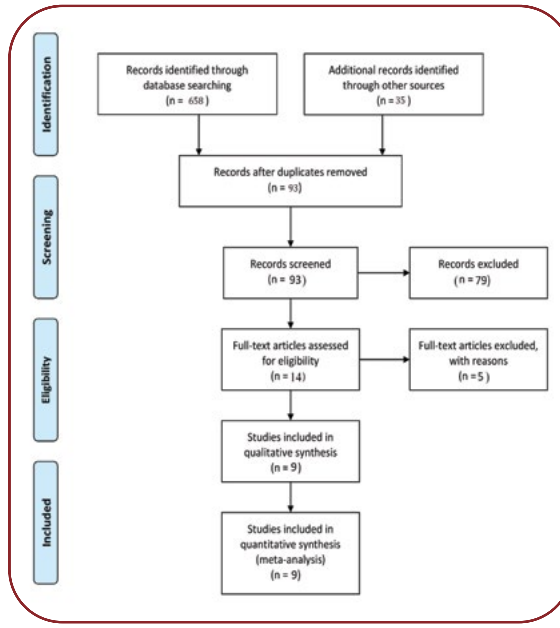

FIGURE 2. Flowchart of the study selection process

TABLE 2. Design and baseline characteristics of included trials

Trial, year	Sample size		Mean age (year)		Number of males		Aneurysm size (mm) < 5 mm		5-10 mm		> 10 mm	
	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt
Miyazawa N *et al*, 2002 (32)	20	5	NR	NR	10	1	NR	NR	NR	NR	NR	NR
Steven DA *et al*, 2007 (30)	36	23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wester K, 2009 (33)	223	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fischer G *et al*, 2011 (31)	651	411	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yamahata H *et al*, 2014 (29)	57	46	60.2	60	38	9	NR	NR	NR	NR	NR	NR
Figueiredo EG *et al*, 2016 (25)	37	49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alkhalili KA *et al*, 2017 (26)	20	36	NR	NR	6	13	8	7	11	27	1	3
Tomatis A *et al*, 2019 (28)	104	117	55.7	55.7	42	38	30	50	66	73	18	13
Park JS *et al*, 2020 (27)	209	437	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Trial, year	Aneurysm location: Pcom		ChA		OphA		ICA		Acom		MCA	
	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt	Rupt	Unrupt
Miyazawa N *et al*, 2002 (32)	2	0	1	0	1	1	13	2	1	0	2	2
Steven DA *et al*, 2007 (30)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wester K, 2009 (33)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fischer G *et al*, 2011 (31)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yamahata H *et al*, 2014 (29)	0	0	0	0	0	0	30	12	35	5	29	29
Figueiredo EG *et al*, 2016 (25)	11	20	3	5	2	0	0	3	10	8	11	29
Alkhalili KA *et al*, 2017 (26)	6	0	0	0	0	0	1	5	0	0	13	32
Tomatis A *et al*, 2019 (28)	16	9	43	30	0	0	13	32	0	0	34	56
Park JS *et al*, 2020 (27)	24	38	0	0	0	0	0	0	53	101	72	184

ICA = internal carotid artery; MCA = middle cerebral artery; Rupt = ruptured; Unrupt = unruptured; Pcom = posterior cerebelar artery; ChA = choroid artery; OphA = ophtalmic artery; NR = not reported studies were evaluated no less than three months following surgical management.

In addition, to reduce publications bias, the Newcastle-Ottawa scale (24) for quality assessment was developed (Table 1). Also, patients were separated into two groups as follows: those who underwent microsurgical clipping with ruptured aneurysms and those with unruptured aneurysms.

Statistical analysis

All extracted information were calculated with Review Manager Software (RevMan), version 5.4. Heterogeneity between included articles was assessed by I^2 statistics, with I^2 >50% signifying high heterogeneity. The current study was carried out using a random-effects model, in agreement with the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0); otherwise, the fixed-effects model was assumed. For evaluation, discontinuous outcomes (mortality and mRS > 3) and odds ratios (ORs) with 95% confidence intervals (CIs) were applied. A p-value < 0.05 indicated a statistically significant difference. ❑

RESULTS

Articles in the terminal collecting process

After preliminary investigation, 14 studies were suitable for further analysis. After taking up all exclusion and inclusion parameters, nine articles accomplished the conditions for the concluding study collection (25-33) (Figure 2). The inclusive information on these articles is summarized in Table 2. A total number of 2,510 patients (1,357 in the ruptured group and 1,153 in the unruptured one) with a mean age of 58.9 years were included in these nine studies, in which information on aneurysm location was available for only 405 subjects, of whom 157 (38.7%) were males (26, 28, 29, 32) (Table 2). Information on aneurysm size was available in two studies (26, 28), in which 95 of 277 (34.2%), 177 of 277 (63.8%) and 35 of 277 (12.6%) patients had aneurysms <5 mm, 5−10 mm and >10 mm in size, respectively. Information on aneurysm location was available in six articles (25-29, 32) as follows: 118 of 1,137 (10.3%) cases were located in posterior cerebellar artery (Pcom); 82 of 1,137 (7.2%) cases in the choroid artery (ChA); three of 1,137 (0.2%) cases in the ophthalmic artery (OphA); 111 of 1,137 (9.7%) cases in the internal carotid artery (ICA); 173 of 1,137 (15.2%) cases in the anterior communicant artery (Acom) and 493 of 1,137 (43.3%) cases in the middle cerebral artery (Table 2).

mRS >3

Information on mRS > 3 was provided by six articles (25-28, 31, 32) totalizing 2,096 patients, of whom 120 subjects in the ruptured group and 10 in the unruptured one. The collective results showed a statistically significant difference among the two groups (OR = 10.16; 95% CI [2.69, 38.41]; $p < 0.05$) but a high heterogeneity was found ($p = 0.02$ and $I^2 = 64\%$) (Figure 3). Applying the 'leave out one' model for the assessment of sensitivity, one article was removed at a time. After eliminating the article published by Figueiredo EG *et al* in 2016 (25) (Table 3), the results demonstrated an additionally statistically significant difference between the two groups (OR = 6.55; 95% CI [3.33, 12.88]; $p < 0.05$) (Figure 4) and no heterogeneity ($p = 0.45$ and $I^2 = 0\%$). When assessing the funnel plot of the same variable, it was noted that the study findings without those reported by Figueiredo EG *et al* (25) showed better dispersion and no publication bias compared to the same analysis including the above-mentioned study (Figure 5A&B).

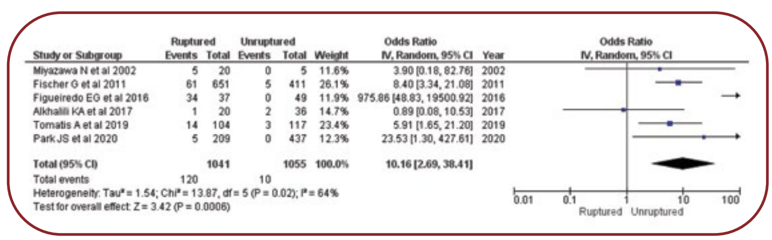

FIGURE 3. Forest plot for mRS >3, with results revealing a statistically significant difference among ruptured and unruptured groups [OR 10.16; 95% CI 2.69 to 38.41; $P < 0.05$] but with a high heterogeneity ($P = 0.02$ and $I^2 = 64\%$)

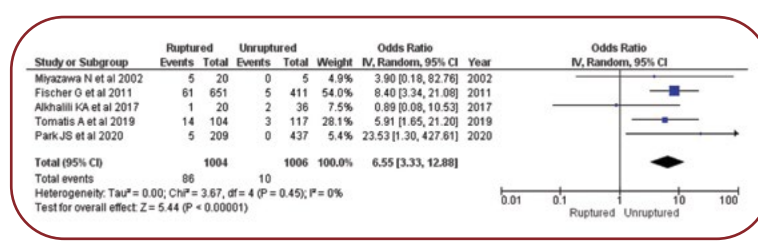

FIGURE 4. Forest plot for mRS >3 without the study by Figueiredo EG *et al*, 2016 (25), showing an additionally statistically significant difference among groups (OR 6.55; 95% CI 3.33 to 12.88; $P < 0.05$).

TABLE 3. Summary of meta-analysis results

Parameters	'Leave out one' model	Trial, n = 9	Groups Ruptured	Groups Unruptured	Overall Effect Effect estimate	Overall Effect CI 95%	Overall Effect P-value	Heterogeneity I^2 (%)	Heterogeneity P-value
Mortality	-	8	136	4	11.9	3.46-41.20	< 0.05	**53**	0.04
	Miyazawa N *et al*, 2002 (32)	7	133	4	14.5	3.78-55.83	< 0.05	57	0.03
	Steven DA *et al*, 2007 (30)	7	124	4	11.1	2.83-44.19	< 0.05	58	0.03
	Wester K, 2009 (33)	**7**	**121**	**2**	**21.4**	**8.16-56.23**	**< 0.05**	**0**	**0.74**
	Fischer G *et al*, 2011 (31)	7	74	3	9.4	2.51-35.31	< 0.05	49	0.07
	Yamahata H *et al*, 2014 (29)	7	125	3	12.5	2.90-54.33	< 0.05	59	0.02
	Figueiredo EG *et al*, 2016 (25)	7	124	4	10.1	2.69-38.29	< 0.05	55	0.04
	Tomatis A *et al*, 2019 (28)	7	120	4	10.2	2.70-39.08	< 0.05	55	0.04
	Park JS *et al*, 2020 (27)	7	131	4	11.2	2.83-44.33	< 0.05	58	0.03
mRS> 3	-	6	120	10	10.6	2.69-38.41	<0.05	**64**	0.02
	Miyazawa N *et al*, 2002 (32)	5	115	10	11.8	2.64-53.19	<0.05	71	<0.05
	Fischer G *et al*, 2011 (31)	5	59	5	11.9	1.60-88.63	0.02	71	<0.05
	Figueiredo EG *et al*, 2016 (25)	**5**	**86**	**10**	**6.5**	**3.33-12.88**	**<0.05**	**0**	**0.45**
	Alkhalili KA *et al*, 2017 (26)	5	119	8	14.9	3.82-58.87	<0.05	62	0.03
	Tomatis A *et al*, 2019 (28)	**5**	106	7	12.8	1.95-83.95	<0.05	70	<0.05
	Park JS *et al*, 2020 (27)	5	115	10	9.6	2.05-41.07	<0.05	70	0.01

mRS = modified Rankin scale; I^2 shows the percentage of total variation across studies that is due to heterogeneity rather than chance; CI = confidence interval.

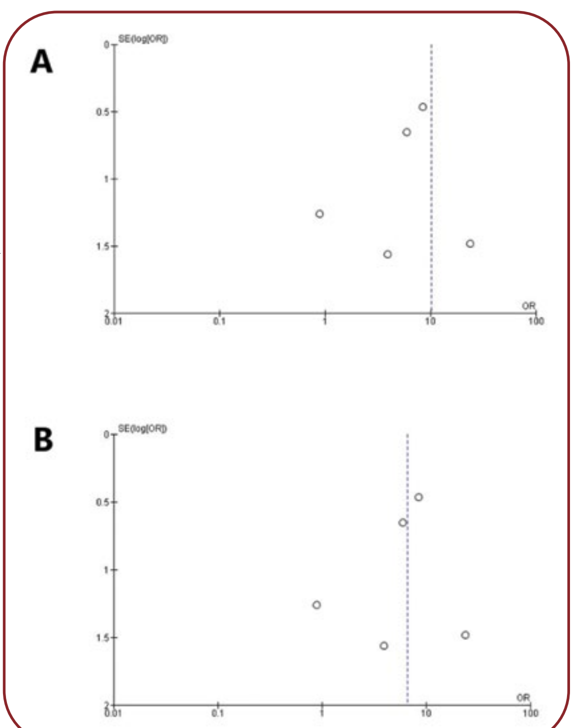

FIGURE 5. A&B) Funnel plots for mRS >3 in the two groups, with (left) or without (right) the study by Figueiredo EG *et al*, 2016 (25), and with a high (left) heterogeneity ($P = 0.02$ and $I^2 = 64\%$) or no (right) heterogeneity ($P = 0.45$ and $I^2 = 0\%$). mRS: modified Rankin scale; I^2: percentage of total variation across studies that is due to heterogeneity rather than chance; CI: confidence interval.

Mortality

Data on mortality was provided by eight studies (25, 27-33) totalizing 2,454 patients, of whom 140 cases of mortality were recorded (136 in the ruptured group and four in the unruptured group), showing a statistically significant difference between the two groups (OR = 15.04; 95% CI [6.88, 32.87]; $p < 0.05$), but a high heterogeneity was seen ($p = 0.02$ and $I^2 = 57\%$) (Figure 6). Using the 'leave out one' model for the evaluation of sensitivity, one article was removed at a time. After removing the study conducted by Wester K in 2009 (33) (Table 3), the results demonstrated an additionally statistically significant difference between the two groups (OR = 26.49; 95% CI [10.09, 69.56]; $p < 0.05$) (Figure 7) and no heterogeneity ($p = 0.72$ and $I^2 = 0\%$). After evaluating the funnel plot of the same parameter, it was found that the results of the explored articles, apart from the study by Wester K (33), demonstrated better dispersion and no risk of bias (Figure 8 A&B).

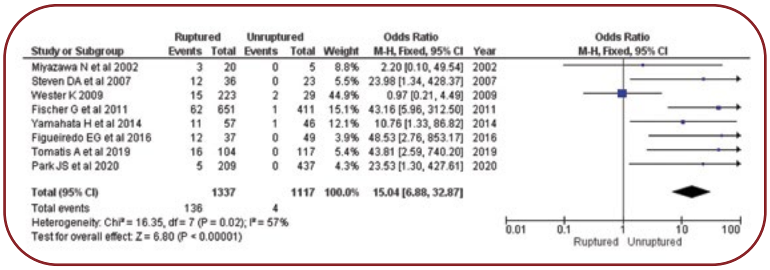

FIGURE 6. Forest plot for mortality showing a statistically significant difference between the ruptured and unruptured groups (OR 15.04; 95% CI 6.88 to 32.87; P <0.05), but with high heterogeneity (P = 0.02 and I^2 = 57%).

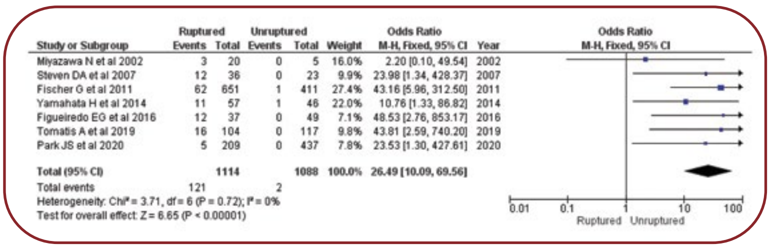

FIGURE 7. Forest plot for mortality without the study by Wester K, 2009 (33), showing an additionally statistically significant difference between the two groups (OR 26.49; 95% CI 10.09 to 69.56; P <0.05)

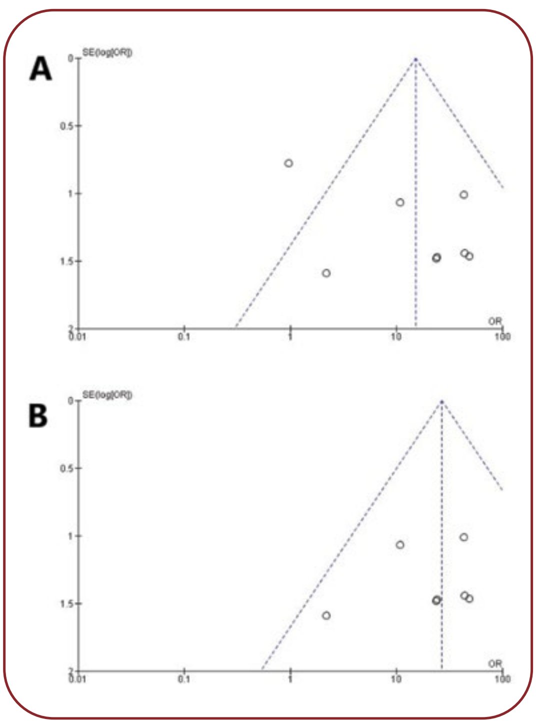

FIGURE 8. A&B) Funnel plots for mortality in the two groups, with (left) or without (right) the study by Wester K, 2009 (33), and with a high (left) heterogeneity (P = 0.02 and I^2 = 57%) or no (right) heterogeneity (P = 0.72 and I^2 = 0%)
I^2: percentage of total variation across studies that is due to heterogeneity rather than chance;
CI: confidence interval

A summary of our results is displayed in Table 3.

DISCUSSION

The current meta-analysis proposes that microsurgical treatment of ruptured aneurysms in the anterior circulation is associated with increased mortality compared to unruptured aneurysms. In addition, mRS >3 was another statistically significant factor, demonstrating the advantage of managing unruptured microsurgical aneurysms relative to the ruptured ones. The results of the current meta-analysis suggest that microsurgical treatment may benefit patients with unruptured aneurysms in the anterior circulation. The decision to manage a ruptured intracranial aneurysm is simple but it has a high heterogeneity, as the selection must be based on each case's specific characteristics (1).

On the other hand, the decision to treat an unruptured aneurysm is associated with evaluating its natural history, prior SAH incidence and aneurysms >7 mm in size (18, 34). The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported cumulatively greater morbidity rates (13.7% *vs.* 9.3% at 30 days) compared with endovascular treatment (15). However, extant meta-analyses indicate that endovascular coiling and surgical clipping of unruptured aneurysms have comparable morbidity and mortality risk ratios (1). In this respect, our meta-analysis, which included a comprehensive review of microsurgical series (35-40), has yielded comparable results to those obtained in these large microsurgical series. Most of the patients with unruptured aneurysms located in the anterior circulation treated with surgical clipping had good outcomes (mRS ≤ 2) compared with those with ruptured aneurysms. In cases with ruptured anterior circulation aneurysms, the underlying pathology of SAH might indicate the main factor contributing to unfavorable outcomes compared with unruptured cases. Thus, microsurgical clipping is a safe procedure for the treatment of both ruptured and unruptured anterior circulation aneurysm.

The perceived therapeutic utility of any current surgical procedure is based on the same principles: effectiveness and patient safety. Regarding intracranial aneurysm surgery, improving microsurgical techniques has become a widespread practice in neurovascular centers. But given the development of endovascular procedures and the heterogeneity between ruptured and unruptured aneurysms, the indications for a treatment procedure, mainly in patients with unruptured aneurysms, remain unclear (36, 40). Regarding the microsurgical treatment option, our meta-analysis indicates that clipping has more favorable outcomes (mRS >3 and mortality) in unruptured compared with ruptured aneurysms in the anterior circulation.

In clinical practice, the treatment options for ruptured anterior circulation aneurysms lie between surgical and endovascular procedures (28). But for unruptured cases, in which the aim of treatment is mainly prophylactic, the technique with the lowest complication rates and the procedure that offers the most favorable aneurysm occlusion with the effects preserved for a longer period should be chosen (28). Our meta-analysis proposes that microsurgical treatment of ruptured aneurysms in the anterior circulation is associated with increased mortality compared with unruptured aneurysms.

The main limitation of the present meta-analysis was the heterogeneity across the surgical approaches discussed in the reviewed articles. In addition, the nature of complications between ruptured and unruptured aneurysms could reduce the accuracy of the meta-analysis results. Therefore, we tried to distinguish the complications of SAH among the included articles. ❑

CONCLUSION

The results of the current meta-analysis suggest that microsurgical treatment may benefit patients with unruptured aneurysms in the anterior circulation. Considering that, in cases with ruptured aneurysm of anterior circulation, the underlying pathology of SAH may be the main contributor to unfavorable outcomes compared with unruptured cases, microsurgical clipping is a safe procedure for both ruptured and unruptured aneurysms of anterior circulation. Although surgical clipping is gradually being replaced by endovascular treatment in the management of aneurysms, our results could help not only in reconsidering the role of surgery in the treatment of ruptured and unruptured intracranial aneurysms but also in rethinking the indications for treatment, mainly in patients with unruptured aneurysms in the anterior circulation. ❑

Conflicts of interest: none declared.
Financial support: none declared.
Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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