Surgical outcomes of patients with unruptured anterior vs. inferior circulation aneurysms: A meta-analysis

GEORGE FOTAKOPOULOS¹, IOANNIS G. LEMPESIS², VASILIKI EPAMEINONDAS GEORGAKOPOULOU², NIKOLAOS TRAKAS³, PAGONA SKLAPANI³, KONSTANTINOS FAROPOULOS⁴ and KOSTAS N. FOUNTAS¹

¹Department of Neurosurgery, General University Hospital of Larissa, 41221 Larissa; ²Department of Pathophysiology, National and Kapodistrian University of Athens, 11527 Athens; ³Department of Biochemistry, Sismanogleio Hospital, 15126 Athens, Greece; ⁴Department of Neurosurgery, Nicosia General Hospital, 2029 Nicosia, Cyprus

Received November 7, 2023; Accepted December 15, 2023

DOI: 10.3892/mi.2023.129

Abstract. The treatment option for unruptured intracranial aneurysms (UIAs) depends on their natural history-related risk of rupture vs. the risk of surgical management. The present meta-analysis sought to assess the association between the surgical outcomes of anterior and posterior circulation UIAs. The present study investigated the comparative articles involving the surgical treatment of anterior vs. posterior circulation UIAs through electronic databases, including the Cochrane Library, PubMed (1980 to March, 2023), Medline (1980 to March, 2023) and EMBASE (1980 to March, 2023). Quoting all exclusion and inclusion criteria, nine articles finally remained for statistical analysis. The entire number of patients included in these nine articles was 3,253 (2,662 in the anterior and 591 in the posterior circulation UIAs group). The present meta-analysis proposes that the surgical treatment of anterior circulation UIAs is associated with better outcomes compared with the surgical management of posterior circulation UIAs.

Introduction

Intracranial aneurysms are abnormal, balloon-shaped dilations of the walls of intracranial arteries. Depending on their size and other risk factors, such as cigarette smoking and an uncontrollably high blood pressure, they have a tendency to rupture.

Unruptured intracranial aneurysms (UIAs) are comparatively frequent lesions that account for 0.4-6% of the general

E-mail: gfotakop@yahoo.gr

population (1,2). During the previous decades, there was a huge debate on whether to treat UIAs or follow them up. On the one hand, the possible complications of the 'wait and see' approach, namely the rupture of the aneurysm (electrolyte disturbance, hydrocephalus, vasospasm, coma and mortality) had to be taken into account, while on the other hand, the possible complications of the elective surgical treatment of an intracranial aneurysm (post-operative pain, blood loss, epileptic seizures, cerebral laceration, neurological deficit and mortality) had to be considered. The 'compass' that was used to provide guidance of cases of UIAs was the annual rupture risk of a UIA vs. the risks associated with surgical management (3).

The annual risk of rupture during the lifetime of a patient with a UIA (also known as the natural risk) of UIAs is found to be 1-2%, and that risk is added to the risk of the following year for every year of life. Thus, for a 20-year-old patient with a UIA, there is a 40-80% chance of an aneurysm rupture by the age of 60 years, while for a 40-year-old patient with a UIA, there is a 20-40% chance of an aneurysm rupture by the age of 60 years. Additionally, the mortality of rate of patients with a ruptured aneurysm is 40%, while in other research series, that number increases to 50% (3).

By contrast, the morbidity associated with the microsurgical treatment of UIAs has been found to be lower than that for ruptured aneurysms (4,5). Under that scope, the suggested modality for UIAs was to treat them, as the treatment has superior results and fewer complications compared to the natural history of the disease and the possible complications following an aneurysm rupture, at least for the younger patients (4,5).

That dogma is used mostly for anterior circulation aneurysms, while the management method of a posterior circulation aneurysm is a debatable theme. The issue is that the majority of studies which mention outcomes from the surgical management of UIAs have excluded posterior circulation aneurysms, possibly since these aneurysms are considered surgically challenging and are associated with a higher morbidity risk compared with their anterior circulation counterparts (3-5). In detail, some reports mention a 4.2% unfavorable outcome rate associated with the surgical management of posterior circulation aneurysms. Notwithstanding, it should be noted that these

Correspondence to: Dr George Fotakopoulos, Department of Neurosurgery, General University Hospital of Larissa, Mezourlo 1, 41221 Larissa, Greece

Key words: unruptured aneurysm, anterior circulation aneurysm surgery, posterior circulation aneurysms surgery, unruptured anterior vs. posterior circulation aneurysms surgery

reports included only giant aneurysms (3,4,6), which are the most demanding when they are treated surgically.

It is well known that there are some studies with notable findings; these studies evaluated the natural risk of bleeding in the UIAs and proposed various management options for posterior and anterior circulation aneurysms (7,8). However, there is limited information available regarding the specific influence of the location of the aneurysm (anterior vs. posterior circulation UIAs) on surgical outcomes.

The present meta-analysis aimed to assess the association between the surgical outcomes of patients with anterior vs. posterior circulation UIAs. Moreover, in order to define the procedural good neurological outcomes, morbidity and mortality, the modified Rankin scale (mRS) >2 was used for patients with a UIA that were treated surgically.

Data and methods

Literature search strategy. The present meta-analysis investigated the proportional articles on the surgical treatment of anterior vs. posterior circulation UIAs through electronic databases, including the Cochrane Library, PubMed (1980 to March, 2023), Medline (1980 to March, 2023) and EMBASE (1980 to March, 2023). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9) served as the foundation for the protocol and manuscript design. In the Medical Subject Headings (MeSH) list, the following key words were used: 'Anterior and posterior circulation aneurysms', 'unruptured aneurysms', 'anterior vs. posterior circulation aneurysm surgery' and 'unruptured aneurysm surgery'.

Inclusion and exclusion criteria. All studies included in the present meta-analysis met the PICOS criteria as follows: i) Population: Limited to patients that underwent aneurysm clipping surgery for UIAs anterior and posterior circulation; ii) Intervention: Surgical treatment for UIAs; iii) Comparison: The outcomes were evaluated and compared; iv) Outcome measures: One of the primary outcomes, such as procedural morbidity (mRS >2), mortality and good neurological outcomes related to aneurysmal surgical treatment, were all evaluated. To shun publication bias, the concluding intent was to assemble a homogenous sum of studies involving only articles that evaluate only two modalities: A comparison between the surgical treatment of anterior and posterior UIAs. The present study excluded all articles that were reviews, editorials and case reports. Moreover, articles that investigated the pediatric population, unrelated outcomes, comorbidities, novel techniques in the experimental stage, or one of the two treatment options, and all those that revealed mixed or uncertain results, being divided between anterior and posterior circulation UIAs surgical treatment, were also excluded.

Data extraction and outcome definition. Two authors (GF and KF) separately extracted data from the contained articles according to the epidemiology guidelines of the meta-analysis. The following critical information was retained: The main authors, publication year, entire number of cases in the anterior and posterior circulation UIA groups, outcome indicator, study type, etc. According to the Cochrane Handbook, the

pulled-out data was entered into a planned, standardized table (https://training.cochrane.org/handbook).

In the case of a discrepancy, an additional author with authority made the concluding decision. Post-operative outcomes declared in the final pool articles were assessed at least 6 months following surgical treatment (UIAs, anterior or posterior circulation). Furthermore, to diminish the risk of bias in the articles, a quality assessment tool (the Newcastle-Ottawa Scale) was performed (Table I) (10). In addition, the patients were divided into two groups as follows: Those with anterior circulation UIAs and those with posterior circulation UIAs.

Statistical analysis. All analyses were carried out using Review Manager Software (RevMan), version 5.4 (https://training.cochrane.org/online-learning/core-software/ revman). Heterogeneity across trials was identified using I^2 statistics; $I^2 > 50\%$ was considered high heterogeneity. A meta-analysis was conducted using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0; https://training.cochrane. org/online-learning/coresoftware/revman); or else, the fixed-effect model was carried out. The continuous outcomes (procedural morbidity (mRS >2), mortality and good neurological outcome related to aneurysmal surgical treatment) were stated as a weighted mean difference with 95% confidence intervals (CIs). In the case of discontinuous variables, odds ratios (ORs) with 95% CIs were obtained for the evaluation. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Studies in the final pool. Following the primary search, 18 studies were suitable for further evaluation. When all the criteria were applied, nine articles were contained in the final study pool (Fig. 1) (3,11-18). The comprehensive data on these articles are presented in Table II. The total sample of patients collected from these nine articles was 3,253 (2,662 in the anterior and 591 in the posterior circulation UIAs group).

Good recovery. A total of nine articles (3,11-18) provided information on good recovery following surgical treatment. There were 2,959 patients (2,487 or 93.42% in the anterior circulation group and 472 or 79.86% in the posterior circulation group), and there was a statistically significant difference between groups (OR, 3.38; 95% CI, 2.58 to 5.77; P<0.05), demonstrating the statistical superiority of the anterior circulation group of UIAs; however, there was low heterogeneity (P=0.23 and I²=25%) (Fig. 2A). While evaluating the sensitivity, one study was removed at a time using the 'leave-one-out' model (Table III). Following the removal of the article by Deruty et al (17), there was additionally a statistically significant superiority over the groups (OR, 3.66; 95% CI, 2.79 to 4.81; P<0.05), with no heterogeneity (P=0.46 and $I^2=0\%$) (Fig. 2B). When the funnel plot was utilized for the analysis of the same parameter, it was found that the study results without the study by Deruty et al (17) revealed a better dispersion with no publication bias compared with the results of the same analysis if this one article was included (Fig. 2C and D).



Table I. Newcastle-Ottawa scale quality assessment of the final article pool.

			Newcas	tle-Ottawa so	cale	
Authors, year of publication	Study design	Selection	Comparability	Exposure	Total scores	(Refs.)
Asari and Ohmoto, 1994	Retrospective	3	3	3	9	(18)
Khanna <i>et al</i> , 1996	Retrospective	3	2	2	7	(3)
Grigorian et al, 2003	Prospective	3	3	3	9	(15)
Aghakhani <i>et al</i> , 2008	Retrospective	3	2	2	7	(16)
Sharma <i>et al</i> , 2013	Retrospective	3	2	2	7	(14)
Spetzler et al, 2013	Prospective	3	3	3	9	(12)
Mahaney et al, 2014	Retrospective and prospective	3	3	3	9	(11)
Bruneau et al, 2016	Prospective	3	2	2	7	(13)
Deruty et al, 2016	Retrospective	3	2	2	7	(17)



Figure 1. Flow chart of the study selection process in the present meta-analysis.

1ean age (years) 61.5 51.9 53.5	No. of										•				•	
61.5 51.9 53.5	IIIalco	Acom	MCA	ICA	Pcom/ PCA	PICA/ SCA	Basilar type	<19 mm	>19 mm	Ant. circ	Post. circ	Anterior Circ	Post. circ	Ant. circ	Post. Circ	(Refs.)
51.9 53.5	36	13	29	29	-	1	4	68	~	70	4	-	-	0	0	(18)
53.5	50	ı	ı	I	I	I	I	140	32	118	5	L	v	C	C	(3)
	S N	51	101	173	I	I	40	159	206	304	30	21	10	~	0	(15)
49	127	44	117	33	40	ю	1	178	09	194	42	0	0	0	0	(16)
55.07	21	14	28	ю	6	4	0	69	10	69	4	5	1	0	0	(14)
NR	NR	75	29	20	39	23	8	209	0	118	27	43	21	0	0	(12)
52.7	NR	285	615	493	304	I	106	701	407	1,322	338	1	4	0	0	(11)
51.3	55	22	137	4	1	7	S	NR	NR	215	13	0	0	0	0	(13)
46	40	13	29	37	ı	ı	4	NR	NR	LL	0	6	0		-	(17)
49 55.07 NR 52.7 51.3 46	50 NR 127 21 NR NR 40 40	- 51 14 75 75 285 22 13	- 101 117 28 29 615 137 29	- 173 33 33 20 493 493 37		40 9 304 1		40 40 9 44 0 39 23 8 304 - 106 4	140 140 40 3 1 178 9 4 0 69 39 23 8 209 304 - 106 701 1 7 5 NR	140 32 40 159 206 9 4 0 69 10 39 23 8 209 0 304 - 106 701 407 4 NR NR	- - - 140 32 118 - - - 40 159 206 304 40 3 1 178 60 194 9 4 0 69 10 69 304 - 106 701 407 1,322 1 7 5 NR NR 215 - - 4 NR NR 77	- - - 140 32 118 12 - - - 40 159 206 304 30 40 3 1 178 60 194 42 9 4 0 69 10 69 4 39 23 8 209 0 118 27 304 - 106 701 407 1,322 338 304 - 106 701 407 1,322 338 1 7 5 NR NR 71 2 - - 4 NR NR 77 2	- - - 140 32 118 12 7 - - - 40 159 206 304 30 21 40 3 1 178 60 194 42 0 9 4 0 69 10 69 4 5 39 23 8 209 0 118 27 43 304 - 106 701 407 1,322 338 1 1 7 5 NR NR 215 13 0	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

mRS > 2. Information regarding mRS > 2 was available in nine articles (3,11-18). There were 126 patients (80 or 3.00% in the anterior circulation group and 46 or 7.78% in the posterior circulation group), and there was a statistically significant difference between groups (OR, 0.19; 95% CI, 0.10 to 0.36; P<0.05), demonstrating the statistical superiority of the anterior circulation group of UIAs; however, there was a low heterogeneity (P=0.15 and I^2 =35%) (Fig. 3A). While assessing the sensitivity, one study was removed at a time using the 'leave-one-out' model (Table III). After eliminating the article by Spetzler et al (12), there was additionally a statistically significant superiority over the groups (OR, 0.15; 95% CI, 0.08 to 0.27; P<0.05), with no heterogeneity (P=0.63 and $I^2=0\%$) (Fig. 3B). When studying the funnel plot of the same parameter, it was observed that the study results without the study by Spetzler et al (12) revealed better dispersion with no publication bias, in contrast to the same analysis including this one article (Fig. 4A and B). Given that the patients in the study by Spetzler et al (12) represented 50.7% (64/126) of the included articles, this was not a surprise.

Mortality. Information for mortality was available in nine articles (3,11-18). In the entry group of patients, there were 5 patients [4 (0.15%) in the anterior circulation group and 1 (0.17%) in the posterior circulation group], demonstrated a statistically significant difference between the groups (OR, 0.17; 95% CI, 0.03 to 1.00; P=0.05), with no heterogeneity (P=0.49 and I²=0% (Fig. 5A) and the superiority of the anterior circulation group. A summary of the results of the present meta-analysis is presented in Table III.

A summary of the meta-analysis results comparing the outcomes of surgical treatment for UIAs in the anterior and posterior circulation is presented in Fig. 6.

Discussion

The optional modality for UIAs was to treat them (4,5); however, that recommendation is applied mostly for anterior circulation aneurysms, while the management method of a posterior circulation aneurysm is a debatable issue (3).

Thus, the present meta-analysis proposes that the surgical treatment of the anterior circulation UIAs is associated with better outcomes than the surgical management of posterior circulation UIAs. More precisely, mortality was a statistically significant parameter in patients with UIAs who were surgically treated, demonstrating the superiority of anterior compared to posterior circulation UIAs. In addition, mRS >2 and good recovery were statistically significant factors, demonstrating the advantage of surgical management of the anterior circulation UIAs compared with posterior circulation UIAs.

It has been reported that hemorrhage rates are significantly higher in the untreated group than in surgically treated patients (3). However, derived from a previously identified natural history between posterior vs. anterior circulation aneurysms, anterior circulation aneurysms hemorrhage less frequently (3). In addition, UIAs with posterior circulation aneurysms have 0.5% 1-year hemorrhage rates and morbidity. Of note, the hemorrhage rates and morbidity for patients

Table II. Design and baseline characteristics of the included studies





Figure 2. (A) Forest plot for good recovery: The results demonstrate a statistically significant difference between groups (OR 3.86; 95% CI, 2.58 to 5.77; P<0.05), with a low heterogeneity. (B) OR forest plot for good recovery without the study by Deruty *et al* (17). The results demonstrate a statistically significant difference (OR, 3.66; 95% CI, 2.79 to 4.81; P<0.05). (C) Funnel plot of good recovery between groups, with the study by Deruty *et al* (17) and with a low heterogeneity (P=0.23 and I²=25%). (D) Funnel plot of good recovery between groups, without the study Deruty *et al* (17), and without heterogeneity (P=0.46 and I²=0%). I², the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; OR, odds ratio.

	f	ì	
ĺ			

Α

	Anterior	circul	Posterior cir	rcul		Odds ratio			Odds	ratio	
Study or subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Randor	m, 95% Cl	
Asari S et al,1994 (18)	1	71	1	5	4.5%	0.06 [0.00, 1.09]	1994	•	•	-	
Khanna RK et al,1996(3)	7	150	5	22	16.7%	0.17 [0.05, 0.58]	1996				
Grigorian AA et al, 2003(15)	21	325	10	40	24.9%	0.21 [0.09, 0.48]	2003				
Aghakhani N et al,2008(16)	0	194	2	44	4.2%	0.04 [0.00, 0.93]	2008	←	•		
Sharma M et al, 2013 (14)	5	74	1	5	6.6%	0.29 [0.03, 3.11]	2013	_	•		
Spetzler RF et al, 2013 (12)	43	161	21	48	29.2%	0.47 [0.24, 0.91]	2013				
Mahaney KB et al,2014(11)	1	1393	4	410	7.5%	0.07 [0.01, 0.65]	2014	←	•		
Bruneau M et al,2016 (13)	0	215	0	13		Not estimable	2016				
Deruty R et al, 2016 (17)	2	79	2	4	6.4%	0.03 [0.00, 0.29]	2016	+			
Total (95% CI)		2662		591	100.0%	0.19 [0.10, 0.36]			•		
Total events	80		46								
Heterogeneity: Tau ² = 0.28; C	hi ² = 10.81	, df = 7 (F	$P = 0.15$; $I^2 = 3$	35%				⊢		l	
Test for overall effect: Z = 4.9	8 (P < 0.000	001)					0	0.01	0.1 1	1 10	100
									Anterior circul	Posterior circul	
R	Antonion	منعديا	Destaviar si			Odda ratio			044		
В	Anterior	circul	Posterior cir	rcul		Odds ratio			Odd	ls ratio	
B Study or subgroup	Anterior Events	circul Total	Posterior cir Events	rcul Total	Weight	Odds ratio IV, Random, 95% Cl	Year		Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994(18)	Anterior Events 1	circul Total 71	Posterior cir Events 1	rcul Total 5	Weight 4.1%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09)	Year		Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3)	Anterior Events 1 7	circul Total 71 150	Posterior cir Events 1 5	rcul Total 5 22	Weight 4.1% 22.5%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58)	Year 1994 1996		Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15)	Anterior Events 1 7 21	circul Total 71 150 325	Posterior cir Events 1 5 10	rcul Total 5 22 40	Weight 4.1% 22.5% 49.9%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48)	Year 1994 1996 2003	• • • • • • • • • • • • • • • • • • •	Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994(18) Khanna RK et al,1996(3) Grigorian AA et al,2003(15) Aghakhani N et al,2008(16)	Anterior Events 1 7 21 0	circul Total 71 150 325 194	Posterior cir Events 1 5 10 2	rcul Total 5 22 40 44	Weight 4.1% 22.5% 49.9% 3.8%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93)	Year 1994 1996 2003 2008	← ←	Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14)	Anterior Events 1 7 21 0 5	circul Total 71 150 325 194 74	Posterior cir Events 1 5 10 2 1	rcul Total 5 22 40 44 5	Weight 4.1% 22.5% 49.9% 3.8% 6.3%	Odds ratio IV, Random, 95% CI 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11)	Year 1994 1996 2003 2008 2013	← ←	Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11)	Anterior Events 1 7 21 0 5 1	circul Total 71 150 325 194 74 1393	Posterior cir Events 1 5 10 2 1 4	rcul Total 5 22 40 44 5 410	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3%	Odds ratio IV, Random, 95% CI 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65)	1994 1996 2003 2008 2013 2014		Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994(18) Khanna RK et al,1996(3) Grigorian AA et al,2003(15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016(13)	Anterior Events 1 7 21 0 5 1 0	circul Total 71 150 325 194 74 1393 215	Posterior cir Events 1 5 10 2 1 4 0	rcul Total 5 22 40 44 5 410 13	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65) Not estimable	Year 1994 1996 2003 2008 2013 2014 2016	← ← ←	Odd IV, Rando	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016 (13) Deruty R et al,2016 (17)	Anterior Events 1 7 21 0 5 1 0 2	circul Total 71 150 325 194 74 1393 215 79	Posterior cir Events 1 5 10 2 1 4 0 2	rcul Total 5 22 40 44 5 410 13 4	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3% 6.1%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65) Not estimable 0.03 (0.00, 0.29)	1994 1996 2003 2008 2013 2014 2016 2016		Odd IV, Randa	ls ratio om, 95% Cl	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016 (13) Deruty R et al,2016 (17) Total (95% CI)	Anterior Events 1 7 21 0 5 1 0 2	circul Total 71 150 325 194 74 1393 215 79 2501	Posterior cir Events 1 5 10 2 1 4 0 2	rcul Total 5 22 40 44 5 410 13 4 543	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3% 6.1% 100.0%	Odds ratio IV, Random, 95% CI 0.06 [0.00, 1.09] 0.17 [0.05, 0.58] 0.21 [0.09, 0.48] 0.04 [0.00, 0.93] 0.29 [0.03, 3.11] 0.07 [0.01, 0.65] Not estimable 0.03 [0.00, 0.29] 0.15 [0.08, 0.27]	Year 1994 1996 2003 2008 2013 2014 2016 2016		Odd IV, Rando	Is ratio om, 95% CI	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016 (13) Deruty R et al,2016 (17) Total (95% CI) Total events	Anterior Events 1 7 21 0 5 1 0 2 2	circul Total 71 150 325 194 74 1393 215 79 2501	Posterior cir Events 1 5 10 2 1 4 0 2 2 25	rcul Total 5 22 40 44 5 410 13 4 543	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3% 6.1% 100.0%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65) Not estimable 0.03 (0.00, 0.29) 0.15 (0.08, 0.27)	Year 1994 1996 2003 2013 2014 2016 2016		Odd IV, Rando	Is ratio om, 95% CI	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016 (13) Deruty R et al,2016 (17) Total (95% CI) Total events Heterogeneitr Tau ² = 0.001 (13)	Anterior Events 1 7 21 0 5 1 0 2 37 2bif = 4 37	circul Total 71 150 325 194 74 1393 215 79 2501 df = 6 (P	Posterior cir Events 1 5 10 2 1 4 0 2 25 = 0.63 ¹ ; I ² = 0	rcul Total 5 22 40 44 5 410 13 4 543	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3% 6.1% 100.0%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65) Not estimable 0.03 (0.00, 0.29) 0.15 (0.08, 0.27)	1994 1996 2003 2008 2013 2014 2016 2016		Odd IV, Rando	Is ratio om, 95% CI	
B Study or subgroup Asari S et al,1994 (18) Khanna RK et al,1996 (3) Grigorian AA et al,2003 (15) Aghakhani N et al,2008(16) Sharma M et al, 2013(14) Mahaney KB et al,2014(11) Bruneau M et al,2016 (13) Deruty R et al,2016 (17) Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; O Test for overall effect: Z = 6.3	Anterior Events 1 7 21 0 5 1 0 2 37 Chi ² = 4.37, 2 (P < 0.00	circul Total 71 150 325 194 74 1393 215 79 2501 df = 6 (P 001)	Posterior cir Events 1 5 10 2 1 4 0 2 2 5 = 0.63); I ^a = 0	rcul Total 5 22 40 44 5 410 13 4 543	Weight 4.1% 22.5% 49.9% 3.8% 6.3% 7.3% 6.1% 100.0%	Odds ratio IV, Random, 95% Cl 0.06 (0.00, 1.09) 0.17 (0.05, 0.58) 0.21 (0.09, 0.48) 0.04 (0.00, 0.93) 0.29 (0.03, 3.11) 0.07 (0.01, 0.65) Not estimable 0.03 (0.00, 0.29) 0.15 (0.08, 0.27)	1994 1996 2003 2008 2013 2014 2016 2016	← ← ← 0.01	Odd IV, Rando	ls ratio om, 95% CI	 1 100

Figure 3. (A) Forest Plot of mRS >2. The results demonstrate a statistically significant difference between groups (OR, 0.19; 95% CI, 0.10 to 0.36; P<0.05), but with a low heterogeneity. (B) OR forest plot for mRS >2 without the study by Spetzler *et al* (12) article. The results again demonstrated no statistically significant difference (OR, 0.15; 95% CI, 0.08 to 0.27; P<0.05). I^2 , the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; OR, odds ratio.

>65 years of age with UIAs have been shown to not differ significantly by surgical management (3). On the other hand, in the same study and for the same subgroup of patients with an aneurysm size >13 mm, 33% of procedure-related morbidity was reported (3). In the present meta-analysis, the morbidity was twice higher in posterior compared with anterior circulation UIAs.

Other studies accounting for outcomes following surgery for UIAs have established 0 to 18% morbidity and 0 to 4% mortality (3); however, these studies did not include posterior circulation aneurysms, possibly due to the high risk of morbidity related to their surgical treatment (11,19-21). On the other hand, Drake et al (22) reported a 14.3% morbidity rate with the surgical management of UIAs in the posterior circulation compared to 0% morbidity in anterior circulation UIAs. However, the results of the present meta-analysis confirm the prognostic significance of aneurysm location for surgical outcomes. In effect, patients with an aneurysm in the posterior circulation had an almost 2-fold higher risk of an unfavorable outcome following surgical management than those with an aneurysm in the anterior circulation. Posterior circulation and aneurysms in difficult-to-access areas (arachnoid aneurysms, cavernous internal carotid artery) are possibly technically complex for representation and clip. They may have an increased morbidity and mortality associated with their treatment. Thus, the aneurismal location affects the operative morbidity. Even though limited data are available on the surgical treatment of UIAs of the posterior circulation exists, in the accommodating study (23), patients with UIAs in the anterior circulation had surgical morbidity rates between 4.8 and 16.8%. In addition, research has mentioned the high surgical risk of UIAs sited on the vertebrobasilar artery (24). However, unruptured aneurysms of the posterior circulation can be surgically treated with a low operative risk (25). The International Study of Unruptured Intracranial Aneurysms (ISUIA) recorded the overall morbidity and mortality in microsurgically treated patients at 1 year as 12.6%, counting cognitive impairment (8) and the evaluated risk factors as possible interpreters of the outcome. However, the ISUA included a larger number of patients with large aneurysms, a larger sum of patients with posterior communicating artery and posterior circulation aneurysms, and the ISUIA had 12.4% cavernous aneurysms, which are known to have a more benign course (8). In addition, a previous meta-analysis on the outcomes of surgery for unruptured aneurysms, including studies from 1966 to 1996, mentioned a mortality rate of 2.6% and a morbidity of 10.9%. Still, compared with the present meta-analysis, the majority of the involved studies did not include novel neurosurgical

SPANDIDC	NS
PUBLICATION	NS

Heterogeneity

Overall effect

Groups

Parameters	'Leave-one-out' model	Trial, n=9	Ant. circ	Post. circ	Effect estimate	95% CI	P-value	${\rm I}^{2}$ (%)	P-value	(Refs.)
Good recovery	I	6	2662	591	3.86	(2.58-5.77)	<0.05	25	0.23	
	Asari and Ohmoto, 1994	8	2591	586	3.75	(2.50-5.63)	<0.05	28	0.22	(18)
	Khanna <i>et al</i> , 1996	8	2512	569	4.14	(2.53-6.79)	<0.05	34	0.17	(3)
	Grigorian et al, 2003	8	2337	551	3.79	(2.30-6.26)	<0.05	33	0.18	(15)
	Aghakhani <i>et al</i> , 2008	8	2468	547	3.73	(2.52-5.53)	<0.05	25	0.24	(16)
	Sharma <i>et al</i> , 2013	8	2588	586	3.94	(2.52-6.17)	<0.05	36	0.16	(14)
	Spetzler et al, 2013	8	2501	543	4.22	(3.14-5.68)	<0.05	0	0.42	(12)
	Mahaney et al, 2014	8	1269	181	4.18	(2.24-7.83)	<0.05	34	0.17	(11)
	Bruneau et al, 2016	8	2447	578	3.86	(2.58-5.77)	<0.05	25	0.23	(13)
	Deruty et al, 2016	8	2583	587	3.66	(2.79 - 4.81)	<0.05	0	0.46	(17)
mRS >2		6	2662	591	0.19	(0.10-0.36)	<0.05	35	0.15	
	Asari <i>et al</i> , 1994	8	2591	586	0.19	(0.10-0.39)	<0.05	39	0.13	(18)
	Khanna <i>et al</i> , 1996	8	2512	569	0.18	(0.08-0.39)	<0.05	42	0.11	(3)
	Grigorian et al, 2003	8	2337	551	0.15	(0.06-0.38)	<0.05	43	0.10	(15)
	Aghakhani <i>et al</i> , 2008	8	2468	547	0.20	(0.10-0.39)	<0.05	37	0.14	(16)
	Sharma <i>et al</i> , 2013	8	2588	586	0.17	(0.08-0.36)	<0.05	44	0.19	(14)
	Spetzler et al, 2013	8	2501	543	0.15	(0.08-0.27)	<0.05	0	0.63	(12)
	Mahaney et al, 2014	8	1269	181	0.20	(0.10-0.40)	<0.05	37	0.14	(11)
	Bruneau et al, 2016	8	2447	578	0.19	(0.10-0.36)	<0.05	35	0.15	(13)
	Deruty et al, 2016	8	2583	587	0.24	(0.13 - 0.41)	<0.05	18	0.29	(17)
Mortality	ı	6	2662	591	0.17	(0.03-0.77)	0.05	0	0.49	
Mortality Ant. circ, anterior c interval	- circulation; Post. circ, posterior cir	9 culation; mRS, m	2662 odified Rankin sc	591 ale; 12, the perce	0.17 ntage of total variation a	(0.03-0.77) across studies that is	0.05 due to heteroge	0 ineity rather th	Ja	0.49 n chance; CI,
IIIICI VAI.										

Table III. Outcomes of the meta-analysis.



Figure 4. (A) Funnel plot of the mRS >2 parameter between groups, with the study by Spetzler *et al* (12), and with heterogeneity (P=0.15 and I²=35%). (B) Funnel plot of the mRS >2 parameter between groups, without the study by Spetzler *et al* (12), and a low heterogeneity (P=0.63 and I²=0%). mRS, modified Rankin scale; I², the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; OR, odds ratio.

techniques or equipment and analyzed separated anterior and posterior circulation UIAs as surgical treatments. Thus, there is a risk of bias (26).

The majority of comparable studies and reviews refer to non-randomized studies (8,11) and have found no direct facts

of clinical benefit from either treatment concerning the natural history of these lesions, raising a dilemma for both patients and neurosurgeons. Furthermore, patients with unruptured intracerebral aneurysms <7 mm in size with no evidence of rupture have been shown to have a very low bleeding rate (0





Figure 5. (A) OR forest plot for mortality. The results demonstrated a statistically significant results (OR, 0.17; 95% CI, 0.03 to 1.00; P=0.05). (B) Funnel plot of mortality in groups; the results demonstrated no heterogeneity (P=0.49 and $I^2=0\%$). I^2 , the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval; OR, odds ratio.

to 1% per year) (8,11). Consequently, obtaining a better natural history of these aneurysms would be challenging.

A number of considerations are used in the management of patients with UIAs. Patients <50 years of age with aneurysms that are ≤ 20 mm or less in the anterior circulation have better surgical outcomes. By contrast, patients >50 years of age, particularly those with large aneurysms in the posterior circulation, have the lowest surgical morbidity (27). Other key topics that require assessment include the patient's age (e.g., to establish whether the older patient has a worse outcome), aneurysm size, location (posterior and anterior circulation), history of stroke (major stroke is related to the poorest outcome), sex (female vs. male) and the duration of hospital stay.

In many studies for overall management, it has been established that posterior circulation aneurysms have the poorest outcome compared with anterior circulation, which was the case for both microsurgically and coiled-treated patients (8,14,26). On the other hand, further analysis in a number of types of research has not succeeded in demonstrating a statistically significant difference in the outcome of surgically managed aneurysms when evaluating anterior and posteriorly located aneurysms, even though this relation was preserved for coiled-treated aneurysms (26). The current year's modifications to aneurysm management training standards may help to explain this. Posterior aneurysms were treated more commonly with endovascular procedures compared with microsurgical intervention; as a consequence of the diversion of possible unfavorable outcomes, posterior aneurysms avoided surgical intervention, and on the way to endovascular management, morbidity for the comparatively small number of posterior aneurysms in the microsurgical group of patients revealed a minimal difference in outcomes compared with the anterior lesions. Additional patients need to be studied before any statistical significance can be reached. However, in the



Figure 6. Summary of the results of the meta-analysis comparing the outcomes of surgical treatment for UIAs in the anterior and posterior circulation. Surgical treatment of anterior circulation UIAs is associated with better outcomes compared to posterior circulation UIAs. Major arteries and common sites of formation of intracranial aneurysms are also shown. mRS, modified Rankin scale. Parts of this image are derived from the free medical site http://smart. servier.com/(accessed on 18 October 2023) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence. UIAs, unruptured intracranial aneurysms.

present meta-analysis, a tendency towards improved outcomes for patients with anterior circulation aneurysms undergoing microsurgery was observed.

Studies indicate that large aneurysms in the posterior region are more likely to hemorrhage, while small ones in the anterior circulation are less likely to hemorrhage. Even though this information should be considered when treating patients with UIAs, the majority of neurosurgeons cannot disregard the fact that several studies with ruptured aneurysms indicate that small-sized lesions were the most frequent aneurysms to rupture (28-30). This generates a question for physicians who are ambiguous about what they face in their everyday practice and what is being published in the literature. This is more complex, as the majority of patients with a history of aneurysm rupture may not be admitted to the hospital, and another 25% experience severe permanent brain injury. In addition, it appears to be a very challenging case for the treating neurosurgeon to decide for a young patient with a small and unruptured aneurysm. In this challenging decision-making situation, the neurosurgeon has to take into account the fact that it is a very superficial thought that the location and size of an aneurysm are sufficient data with which to make a serious choice in forecasting the performance of an aneurysm (26).

On the other hand, it must be considered that patients who undergo surgery for UIAs from the anterior or posterior circulation may experience retained strokes or hemorrhages on the additional follow-up. However, if we pay attention to a complete aneurysm clipping, it is enormously doubtful that it will be the reason for such strokes or novel hemorrhages. However, if all the possible locations (anterior or posterior) and other reasons for poor outcomes that could influence a certain population are taken into account, this would lead to an enormous amount of probability, from the inherent characteristics of each patient to their type of nutrition habits. It should be recognized that, even though statistics need calibration, medicine necessitates much perception, and the reality is that statistical results include several probabilities in the best case, while medical management requires diligent conclusions.

There are several limitations to the present study. First, the majority of the eligible reports that were included were retrospective. These retrospective studies, by definition, rely on imprecision and data loss. Additionally, the methods of the included studies markedly differed. Among these differences was the length of follow-up (e.g., 30-90 days). A longer follow-up period with these patients is warranted in order to correctly set up outcomes associated with treatment procedures. Additionally, the present study did not address outcomes in patients with unruptured aneurysms that are managed conservatively.

In conclusion, the present study demonstrates that the surgical treatment of patients with anterior circulation UIAs is associated with better outcomes than the surgical management of posterior circulation UIAs. In fact, mortality was a statistically significant parameter in patients with UIAs who



were surgically treated, exhibiting the superiority of anterior compared to posterior circulation UIAs. In addition, mRS >2 and a good recovery were statistically significant factors, demonstrating the advantage of surgical management of the anterior circulation UIAs more than the posterior circulation. These findings indicate that surgical treatment may benefit the management of anterior circulation UIAs. It is also beyond doubt that a randomized trial is required in order to determine the difference in outcomes between these two treatment modalities in these patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GF and KNF conceptualized the study. VEG, GF, NT, PS, IGL, KF and KNF analyzed the data, and wrote and prepared the draft of the manuscript. KNF and GF provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. GF and KF confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- 1. Qureshi AI, Janardhan V, Hanel RA and Lanzino G: Comparison of endovascular and surgical treatments for intracranial aneurysms: An evidence-based review. Lancet Neurol 6: 816-825, 2007.
- Alshekhlee A, Mehta S, Edgell RC, Vora N, Feen E, Mohammadi A, Kale SP and Cruz-Flores S: Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysm. Stroke 41: 1471-1476, 2010.
- Khanna RK, Malik GM and Qureshi N: Predicting outcome following surgical treatment of unruptured intracranial aneurysms: A proposed grading system. J Neurosurg 84: 49-54, 1996.
- Henry J, Dablouk MO, Kapoor D, Koustais S, Corr P, Nolan D, Coffey D, Thornton J, O'Hare A, Power S, *et al*: Outcomes following poor-grade aneurysmal subarachnoid haemorrhage: A prospective observational study. Acta Neurochir (Wien) 165: 3651-3664, 2023.

- King JT Jr, Berlin JA and Flamm ES: Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: A meta-analysis. J Neurosurg 81: 837-842, 1994.
- Solomon RA, Fink ME and Pile-Spellman J: Surgical management of unruptured intracranial aneurysms. J Neurosurg 80: 440-446, 1994.
- International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms-risk of rupture and risks of surgical intervention. N Engl J Med 339: 1725-1733, 1998.
- Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, *et al*: Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 362: 103-110, 2003.
- 9. Foster RL: Reporting guidelines: CONSORT, PRISMA, and SQUIRE. J Spec Pediatr Nurs 17: 1-2, 2012.
- 10. Bae JM: A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. Epidemiol Health 38: e2016014, 2016.
- Mahaney KB, Brown RD Jr, Meissner I, Piepgras DG, Huston J III, Zhang J and Torner JC; ISUIA Investigators: Age-related differences in unruptured intracranial aneurysms: 1-year outcomes. J Neurosurg 121: 1024-1038, 2014.
- Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, Nakaji P and Wallace RC: The barrow ruptured aneurysm trial: 3-Year results. J Neurosurg 119: 146-157, 2013.
- Bruneau M, Amin-Hanjani S, Koroknay-Pal P, Bijlenga P, Jahromi BR, Lehto H, Kivisaari R, Schaller K, Charbel F, Khan S, et al: Surgical clipping of very small unruptured intracranial aneurysms: A multicenter international study. Neurosurgery 78: 47-52, 2016.
- 14. Sharma M, Brown B, Madhugiri V, Cuellar-Saenz H, Sonig A, Ambekar S and Nanda A: Unruptured intracranial aneurysms: comparison of perioperative complications, discharge disposition, outcome, and effect of calcification, between clipping and coiling: A single institution experience. Neurol India 61: 270-276, 2013.
- Grigorian AA, Marcovici A and Flamm ES: Intraoperative factors associated with surgical outcome in patients with unruptured cerebral aneurysms: The experience of a single surgeon. J Neurosurg 99: 452-457, 2003.
- 16. Aghakhani N, Vaz G, David P, Parker F, Goffette P, Ozan A and Raftopoulos C: Surgical management of unruptured intracranial aneurysms that are inappropriate for endovascular treatment: Experience based on two academic centers. Neurosurgery 62: 1227-1235, 2008.
- Deruty R, Pelissou-Guyotat I, Mottolese C and Amat D: Management of unruptured cerebral aneurysms. Neurol Res 18: 39-44, 1996.
- Asari S and Ohmoto T: Long-term outcome of surgically treated unruptured cerebral aneurysms. Clin Neurol Neurosurg 96: 230-235, 1994.
- Asari S: Surgical management of the unruptured cerebral aneurysm accompanied by ischemic cerebrovascular disease. Clin Neurol Neurosurg 94: 119-125, 1992.
- 20. Deruty R, Pelissou-Guyotat I, Mottolese C, Bognar L and Oubouklik A: Surgical management of unruptured intracranial aneurysms. Personal experience with 37 cases and discussion of the indications. Acta Neurochir (Wien) 119: 35-41, 1992.
- 21. Inagawa T, Hada H and Katoh Y: Unruptured intracranial aneurysms in elderly patients. Surg Neurol 38: 364-370, 1992.
- 22. Drake CG: Progress in cerebrovascular disease. Management of cerebral aneurysm. Stroke 12: 273-283, 1981.
- 23. Gerlach R, Beck J, Setzer M, Vatter H, Berkefeld J, Du Mesnil de Rochemont R, Raabe A and Seifert V: Treatment related morbidity of unruptured intracranial aneurysms: Results of a prospective single centre series with an interdisciplinary approach over a 6 year period (1999-2005). J Neurol Neurosurg Psychiatry 78: 864-871, 2007.
- 24. Eskesen V, Rosenørn J, Schmidt K, Espersen JO, Haase J, Harmsen A, Hein O, Knudsen V, Marcussen E, Midholm S, *et al*: Clinical features and outcome in 48 patients with unruptured intracranial saccular aneurysms: A prospective consecutive study. Br J Neurosurg 1: 47-52, 1987.
- Rice BJ, Peerless SJ and Drake CG: Surgical treatment of unruptured aneurysms of the posterior circulation. J Neurosurg 73: 165-173, 1990.

- 26. Krisht AF, Gomez J and Partington S: Outcome of surgical clipping of unruptured aneurysms as it compares with a 10-year nonclipping survival period. Neurosurgery 58: 207-216, 2006.
- Williams LN and Brown RD Jr: Management of unruptured intracranial aneurysms. Neurol Clin Pract 3: 99-108, 2013.
 Fotakopoulos G, Tsianaka E, Fountas K, Makris D, Spyrou M
- Fotakopoulos G, Tsianaka E, Fountas K, Makris D, Spyrou M and Hernesniemi J: Clipping versus coiling in anterior circulation ruptured intracranial aneurysms: A meta-analysis. World Neurosurg 104: 482-488, 2017.
 Fotakopoulos G, Andrade-Barazarte H, Tjahjadi M, Goehre F
- Fotakopoulos G, Andrade-Barazarte H, Tjahjadi M, Goehre F and Hernesniemi J: Clipping versus coiling in ruptured basilar apex aneurysms: A meta-analysis. Turk Neurosurg 31: 301-309, 2021.
- 30. Fotakopoulos G, Andrade-Barazarte H, Alexandros B and Hernesniemi J: A meta-analysis of Lateral supraorbital vs mini Pterional approach in the outcome of rupture and unruptured noncomplex aneurysms' surgery. Neurocirugia (Astur: Engl Ed) 34: 128-138, 2023.



Copyright © 2023 Fotakopoulos et al. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.