Management of intracranial cavernous malformations using conservative vs. surgical and/or radiosurgical treatment: A systematic review and meta-analysis

GEORGE FOTAKOPOULOS[1], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[2], PETROS PAPALEXIS[3,4], DEMETRIOS A. SPANDIDOS[5], NIKOLAOS TRAKAS[6], PAGONA SKLAPANI[6] and KOSTAS N. FOUNTAS[1]

[1]Department of Neurosurgery, General University Hospital of Larissa, 41221 Larissa; [2]Department of Pathophysiology; [3]Unit of Endocrinology, First Department of Propedeutic and Internal Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, 11527 Athens; [4]Department of Biomedical Sciences, University of West Attica, 12243 Athens; [5]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion; [6]Department of Biochemistry, Sismanogleio Hospital, 15126 Athens, Greece

Received November 20, 2023; Accepted March 5, 2024

DOI: 10.3892/etm.2024.12503

Abstract. Intracranial cavernous malformations (CMs) are vascular lesions with a high bleeding rate. At present, the debate regarding their treatment is still ongoing. The present systematic review and meta-analysis aimed to evaluate the safety of surgery or radiosurgery (SRS) for the management of CMs and to determine their potential outcomes compared with conservative treatment. The present systematic review and meta-analysis investigated the relative articles involving the management of intracranial CMs, namely their natural history (conservative treatment) vs. surgical/SRS treatment through electronic databases until June, 2023. The collected variables included the first author's name, the study period covered, the year of publication, the total number of patients examined and their age, and the number of males. In total, six articles met the eligibility criteria. The total number of patients was 399 (157 in the surgery/SRS group and 242 in the conservative treatment group). The results revealed that surgical or SRS management is a safe procedure for CMs compared with conservative treatment. Notably, the use of hemosiderin in the pre-MRI, the free of seizures parameter and the neurological deficit parameters were associated with improved outcomes in the surgical or SRS group of patients.

Correspondence to: Dr George Fotakopoulos, Department of Neurosurgery, General University Hospital of Larissa, Mezourlo 1, 41221 Larissa, Greece
E-mail: gfotakop@yahoo.gr

Key words: cerebral cavernous malformation, natural history, surgery, radiosurgery, outcome

Introduction

Intracranial cavernous malformations (CMs) are vascular lesions that have an annual bleeding rate of ~0.2 to 3% per individual per year (1). In the literature, there are three management options for addressing CMs: Operative resection, radiosurgery (SRS) and conventional treatment; however, the debate regarding the treatment options for CMs has a long history and remains controversial (2).

The effects of SRS on cavernoma remain hypothetical (3-5). The outcome of CM management can be stated only as a decreased bleeding rate for a large number of patients, which then necessitates dependable data on the natural course. On an individual level, the treatment result is extremely hypothetical, as it is necessary to have knowledge of the natural history of the condition to ensure that a good benefit is achieved (6,7).

Surgery is an alternative treatment option for CMs, with a complete resection to reach a temporary morbidity rate varying from 29 to 67% and a 1.9% combined post-operative re-bleeding and surgery-related mortality rate (1,8). In addition, 58% of incomplete resection cases re-bleed. Hence, concerning surgical management, the proportion of no active treatment cases, the direct morbidity and mortality rates, and the risk of partial removal of CMs with the prospect of re-hemorrhage have to be recalculated (1).

In addition, a number of CMs are considered untreatable due to their placement in eloquent areas. Thus, surgically approachable cavernomas consist of a detailed assortment, whereas a number of untreatable cases can eventually be managed with SRS. Hence, the effectiveness of surgery and SRS can only be estimated based on an accurate designation of exclusion criteria and the exact risks for complications and re-hemorrhage for both treatment options.

The present systematic review and meta-analysis compared with previous reports (9,10), aimed to evaluate the safety of surgical or SRS treatment for the management of CMs and also evaluate their potential outcomes compared with conservative treatment.

Materials and methods

Literature research strategy. The present meta-analysis investigated the relative articles involving intracranial cavernous malformation (CMs) natural history vs. surgical or radiosurgical (SRS) treatment option through electronic databases, counting the Cochrane Library, PubMed (until June, 2023), Embase (until June, 2023), and MEDLINE (until June, 2023). For the study protocol establishing and design, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied. 'Cerebral Cavernous Malformation', 'Cerebral Cavernus Malformation natural history vs. surgical or radiosurgical treatment', 'Intracranial Cavernus Malformation natural history vs. surgical or radiosurgical treatment option', and 'Cerebral Cavernous Malformation natural history vs. surgical treatment', were used in the MeSH list as keywords.

Selection of studies. In the present study, two authors (VEG and GF) separately pulled out data from the contained articles, following the guidelines for the epidemiology of meta-analysis. The subsequent crucial information was attained: The main authors, year of publication, sample size in the CM natural history vs. surgical or SRS treatment option groups, study type, outcome indicator, etc. The extracted data were contributed to a designed, standardized table according to the Cochrane Handbook. The flow of the study selection process is presented in Fig. 1.

Inclusion and exclusion criteria. If an article fulfilled the subsequent population, intervention, comparison, outcomes and study (PICOS) design criteria, it was eligible for inclusion in the present meta-analysis: i) Population: Limited to patients with intracranial CMs; ii) Intervention: Limited to patients with CMs natural history vs. surgical or/and SRS treatment option; iii) Comparison: Studies comparing the outcomes between the CM natural history (conservative treatment; Cons) vs. the surgical or/and SRS (surg/SRS) treatment option; iv) the comprehensive data of these articles are presented in Table I. To avoid publication bias, the final aim was to collect a homogeneous pool of manuscripts, including articles that compare only two modalities: Patients with intracranial CMs treated with the Cons vs. Surg/SRS treatment option.

All retrospective and prospective studies that assessed these two modalities together were included, whereas editorials, reviews, case reports and articles focusing on the pediatric population, unrelated outcomes, co-morbidities, experimental techniques, or one of the two modalities separately from that article pool were excluded. Additionally, to decrease the risk of bias in the included articles, a quality assessment tool [the Newcastle-Ottawa Scale (NOS)] was used (Table II) (11).

Outcomes' definition. The primary outcome was 'poor outcome', defined as at least two successive ratings of the Oxford Handicap Scale (OHS) (12) and OHS 2-6 (suggestive of 'some restraints to lifestyle, but the patient can look after themselves', or worse). It was used only for OHS ratings after the initial presentation to time progression to this event at the midpoint between the last OHS score of 0-1 and the first of the successive OHS 2-6 ratings for the conservatively managed group (12).

Table I. Design and baseline characteristics of the trials included in the present meta-analysis.

	Sample size		Mean age (years)		No. of males		Location								Size				Hemos. in the pre-MRI		Free of seizures		Neurol. deficit		Re-bleeding		OHS 2-6		Mortality		
							Lobar		Deep		Brain stem		Cereb.		<2 cm		2-6 cm														
Authors, year of publication	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	*S/S*	*C*	(Refs.)
Mathiesen *et al*, 2003	34	34	N	N	33	33	0	N	23	N	6	N	5	N	N	N	N	N	33	34	20	9	6	11	21	14	26	11	4	0	(15)
Tarnaris *et al*, 2008	6	9	34.2	37.9	3	4	0	N	1	N	4	N	1	N	N	N	N	N	4	7	0	1	6	8	0	4	3	13	0	2	(16)
Fernández *et al*, 2012	26	17	44.8	50.2	16	10	24	13	0	0	0	0	0	0	11	8	15	8	20	10	14	16	2	0	N	N	N	N	N	N	(1)
Moultrie *et al*, 2014	25	109	34	43	10	45	19	71	1	8	1	16	4	14	N	N	N	N	8	10	N	N	8	17	5	1	9	40	17	30	(17)
Dammann *et al*, 2017	41	38	39	36	21	10	19	24	14	17	0	0	0	0	N	N	N	N	41	38	30	9	9	9	3	0	4	18	N	N	(18)
Kang *et al*, 2018	25	35	44	56	13	17	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	5	2	N	N	(19)

C, conservative management; S/S, surgical or radiosurgical management; Cereb., cerebellum; Hemos., hemosiderin; pre-MRI, pre-operative magnetic resonance imaging; Neurol. deficit, neurological deficit; N, not reported; OHS, Oxford Handicap Scale.

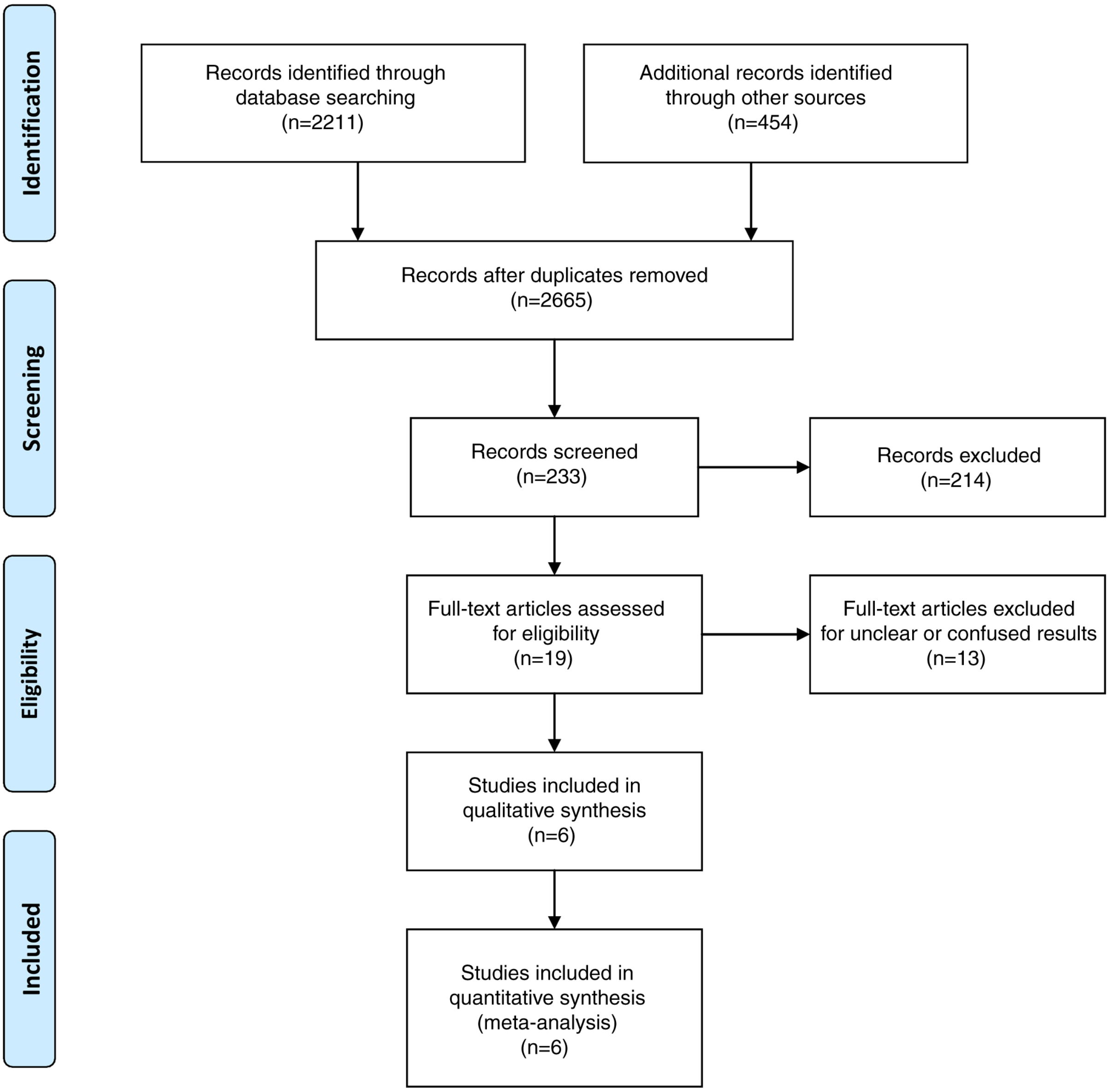

Figure 1. Flowchart of the study selection process.

Secondary outcomes were the frequency of seizures in the surgical or + SRS and cons patients, neurological deficit, re-bleeding and mortality. Information regarding age, sex, localization (lobar, deep, brainstem, cerebellum), size (<2, 2-6 mm) and use of hemosiderin in the pre-surgical MRI is presented in Table I. Re-bleeding was defined as hemorrhage clearly demonstrated on imaging at the time of admission.

Evaluation of the risk of bias. The Cochrane Collaboration tool was used to assess the risk of bias and was used by two authors (GF and VEG) for each study (13). The assessment contained allocation concealment, random sequence generation, the blinding of outcome evaluation, the blinding of participants and assessors, unfinished outcome data, discriminating reports and other biases. The evaluated results were classified into three levels: Low risk, high risk and unclear risk. In the case of a discrepancy, another author with authority gave the final solution.

Statistical analysis and assessment of heterogeneity. All analyses were carried out using Review Manager Software (RevMan), version 5.4. Heterogeneity across trials was identified using I^2 statistics; considering I^2 >50% as 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) (14). Otherwise, the fixed-effect model was performed. The continuous outcomes were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables, odds ratios (OR) with 95% CIs were applied for the assessment. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

In total, six articles (1,15-19) met the eligibility criteria. The total number of patients was 399 (157 in the Surg/SRS group and 242 in the Cons treatment group). The study sample was

Table II. Newcastle-Ottawa Scale (NOS) quality assessment of the final article pool.

Author, year of publication	Study design	Newcastle-Ottawa Scale				(Refs.)
		Selection	Comparability	Exposure	Total scores	
Mathiesen *et al*, 2003	Prosp	3	3	3	9	(15)
Tarnaris *et al*, 2008	Prosp	3	3	3	9	(16)
Fernández *et al*, 2012	Retro	3	2	2	7	(1)
Moultrie *et al*, 2014	Prosp	3	3	3	9	(17)
Dammann *et al*, 2017	Retro	3	3	2	8	(18)
Kang *et al*, 2018	Retro	3	2	2	7	(19)

Retro, retrospective; prosp, prospective.

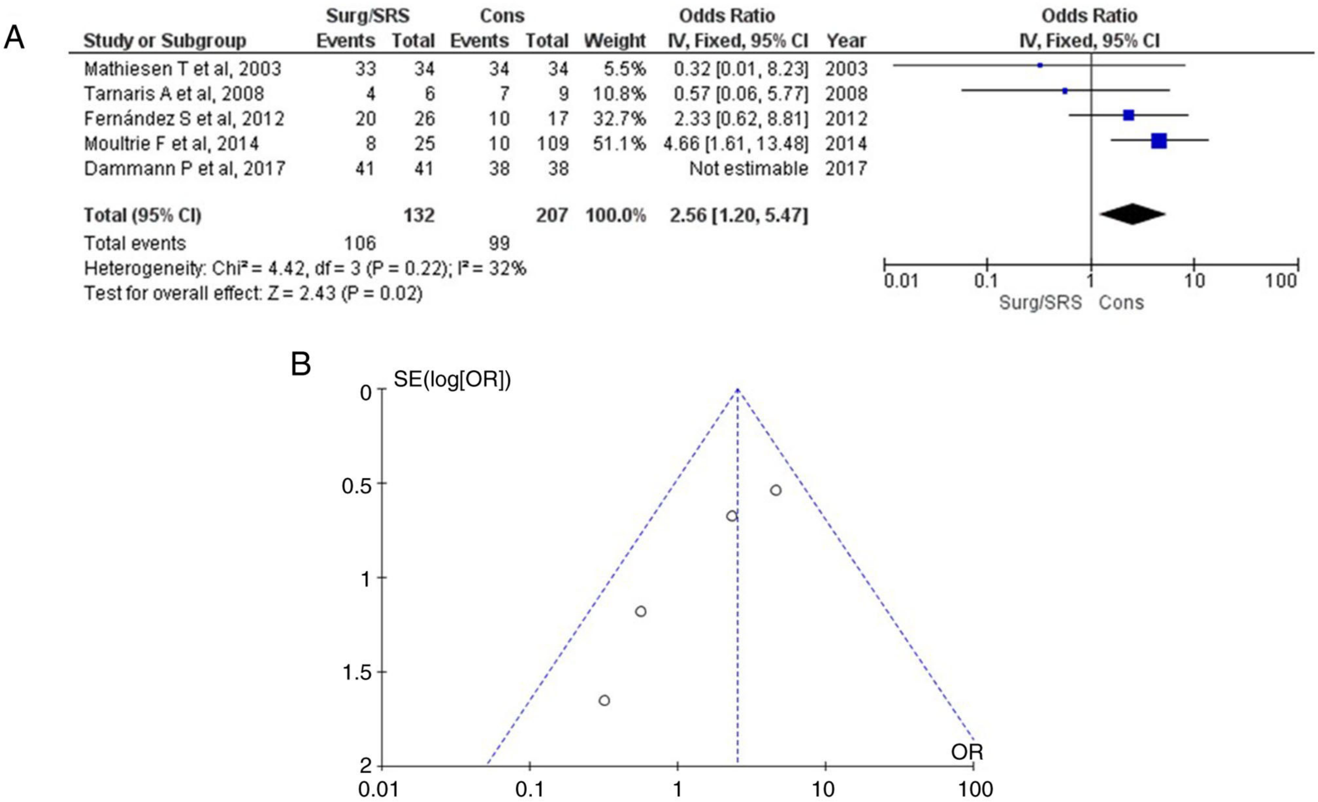

Figure 2. (A) Forest plot for the use of hemosiderin in the pre-MRI. The results demonstrated a statistically significant difference between the surgical or/+ SRS and Cons groups (OR, 2.56; 95% CI, 1.20 to 5.47; P<0.05. (B) Funnel plot, testing the sensitivity for the use of hemosiderin in the pre-MRI; there was very low heterogeneity (P=0.22; I^2=32%). MRI, magnetic resonance imaging; SRS, radiotherapy; Cons, conservative management group; OR, odds ratio; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

based on six studies (Table I). Of these six studies, two studies were retrospective and four studies were prospective.

Epidemiological and clinical features. The mean age of the patients among the included studies ranged from 34.9 to 56 years. The male-to-female ratio was 1.5 for the Surg/SRS group and 0.9 for the Cons treatment group (95/62 and 119/123) (Table I).

Location

Lobar. Information regarding lobar brain location was available in three articles (1,17,18). No significant difference was found between the Surg/SRS and Cons groups (OR, 1.03; 95% CI, 0.55 to 1.93; P=0.07), with heterogeneity (P=0.92 and I^2=62%) (Table III and Fig. S1).

Deep. Information regarding deep brain location was available in three articles (1,17,18). No significant difference was found between the Surg/SRS and Cons groups (OR, 0.62; 95% CI, 0.27 to 1.43; P=0.87), without heterogeneity (P=0.26 and I^2=0%) (Table III and Fig. S2).

Brainstem. As regards brainstem location, information was available in three articles (1,17,18). No significant difference was found between groups (OR, 0.24; 95% CI, 0.03 to 1.92; P=0.18) (Table III and Fig. S3).

Table III. Parameters for the results of the present meta-analysis.

			Groups		Overall effect		Heterogeneity		
Parameter	'Leave out one' model; Authors/(Refs.), year of publication	Included trials, n=6	Surg/SRS	Cons	Effect estimate	95% CI	P-value	I^2 (%)	P-value
Location									
Lobar	-	3	62	108	1.03	(0.55-1.93)	0.93	62	0.07
Deep	-	3	15	25	0.62	(0.27-1.43)	0.26	0	0.87
Brainstem	-	3	1	18	0.24	(0.03-1.92)	0.18	-	0.18
Cerebellum	-	3	4	14	1.29	(0.39-4.32)	0.68	-	0.68
Use of hemosiderin in the pre-MRI	-	5	106	99	2.56	(1.20-5.47)	0.22	32	<0.05
Free of seizures	-	4	64	35	3.49	(1.79-6.83)	<0.05	82	<0.05
	Mathiesen *et al* (15), 2003	3	44	26	3.17	(1.31-7.71)	<0.05	88	<0.05
	Tarnaris *et al* (16), 2008	3	64	34	3.81	(1.92-7.55)	<0.05	87	<0.05
	Fernández *et al* (1), 2012	3	50	19	5.27	(2.60-10.68)	0.18	41	<0.05
	Dammann *et al* (18), 2017	3	34	26	1.72	(0.71-4.20)	0.23	82	<0.05
Neurological deficit	-	5	31	45	0.57	(0.32-1.00)	0.34	11	0.05
Re-bleeding	-	4	29	19	2.84	(1.25-6.46)	<0.05	67	<0.05
	Mathiesen *et al* (15), 2003	3	8	5	4.79	(1.02-22.40)	0.05	76	<0.05
	Tarnaris *et al* (16), 2008	3	29	15	3.65	(1.56-8.57)	<0.05	53	0.12
	Moultrie *et al* (17), 2014	3	24	18	1.97	(0.81-4.78)	0.13	55	0.11
	Dammann *et al* (18), 2017	3	26	19	2.64	(1.12-6.20)	<0.05	77	<0.05
	Mathiesen *et al* (15), 2003 and Tarnaris *et al* (16), 2008	2	8	1	16.83	(2.86-99.12)	0.48	0	<0.05
	Mathiesen *et al* (15), 2003 and Moultrie *et al* (17), 2014	2	3	4	0.89	(0.10-7.80)	0.92	74	0.05
	Mathiesen *et al* (15), 2003 and Dammann *et al* (18), 2017	2	5	5	4.17	(0.69-25,25)	0.12	88	<0.05
	Tarnaris *et al* (16), 2008 and Moultrie *et al* (17), 2014	2	24	14	2.56	(1.02-6.47)	0.49	0	0.05
	Tarnaris *et al* (16), 2008 and Dammann *et al* (18), 2017	2	26	15	3.45	(1.42-8.39)	<0.05	75	<0.05
	Moultrie *et al* (17), 2014 and Dammann *et al* (18), 2017	2	21	18	1.74	(0.69-4.41)	0.24	73	0.06
OHS 2-6	-	5	51	79	1.44	(0.83-2.49)	<0.05	86	0.19
	Mathiesen *et al* (15), 2003	4	25	68	0.83	(0.44-1.57)	<0.05	84	0.57
	Tarnaris *et al* (16), 2008	4	48	71	1.61	(0.92-2.82)	<0.05	88	0.10
	Moultrie *et al* (17), 2014	4	38	39	1.22	(0.60-2.46)	<0.05	90	0.58
	Dammann *et al* (18), 2017	4	47	61	2.72	(1.47-5.03)	<0.05	67	<0.05
	Kang *et al* (19), 2018	4	46	77	1.28	(0.72-2.28)	<0.05	89	0.40
Mortality	-	3	21	32	4.68	(1.97-11.09)	0.15	47	<0.05

Cons, conservative management; Surg/SRS, surgical or radiosurgical management; pre-MRI, pre-surgical magnetic resonance imaging; OHS, Oxford Handicap Scale; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

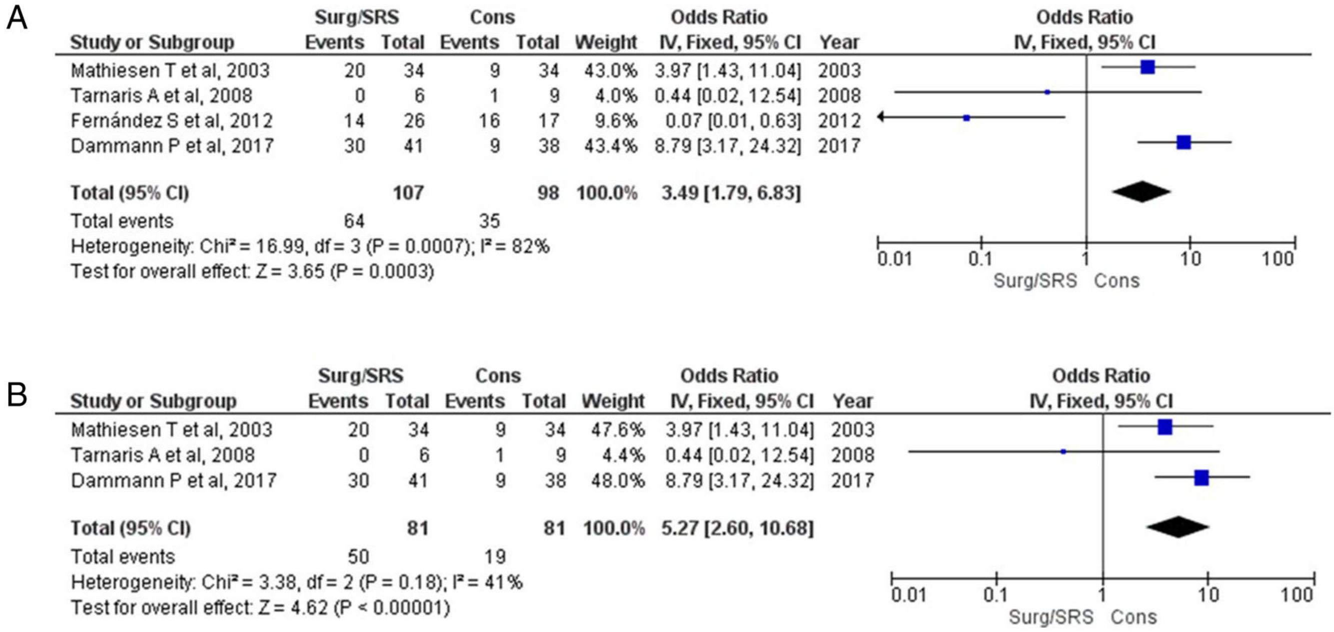

Figure 3. (A) Forest plot for the free of seizures parameter. The results demonstrated a statistically significant difference between the surgical or/+ SRS and Cons groups (OR, 3.49; 95% CI, 1.79 to 6.83; and P<0.05). (B) Forest plot for the free of seizures parameter without the study by Fernández *et al* (1). The results again demonstrated a statistically significant difference (OR, 5.27; 95% CI, 2.60 to 10.68; P<0.05). SRS, radiotherapy; Cons, conservative management group; OR, odds ratio; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

Cerebellum. As regards cerebellum location, information was available in three articles (1,17,18). No significant difference was found between groups (OR, 1.29; 95% CI, 0.39 to 4.32; P=0.68) (Table III and Fig. S4).

Hemosiderin in the pre-MRI. As regards the use of hemosiderin in the pre-MRI, information was available in six articles (1,15-18), and this demonstrated a statistically significant result (OR, 2.56; 95% CI, 1.20 to 5.47; P<0.05), with very low heterogeneity (P=0.22; I^2=32%) (Table III and Fig. 2). The use of hemosiderin in the pre-MRI was found in 106 of 132 (80.3%) patients in the Surg/SRS group and in 99 of 207 (47.8%) patients in the Cons group. When examining the funnel plot of the same parameter, no publication bias was found.

Free of seizures parameter. Information regarding the free of seizures parameter was available in four articles (1,15,16,18) and demonstrated a statistically significant result between the patients in the Surg/SRS and Cons groups (OR, 3.49; 95% CI, 1.79 to 6.83; and P<0.05), but with heterogeneity (P<0.05 and I^2=82%) (Fig. 3A). For testing the sensitivity, the 'leave out one' model was used, and one study was removed at a time (Table III). Low heterogeneity (P=0.18 and I^2=41%) was achieved only after removing the article by Fernández *et al* (1); again, a statistically significant difference was found (OR, 5.27; 95% CI, 2.60 to 10.68; P<0.05) (Fig. 3B). When examining the funnel plot of the same parameter, it was found that the study results without the study by Fernández *et al* (1) displayed better dispersion with a low publication bias (Fig. 4).

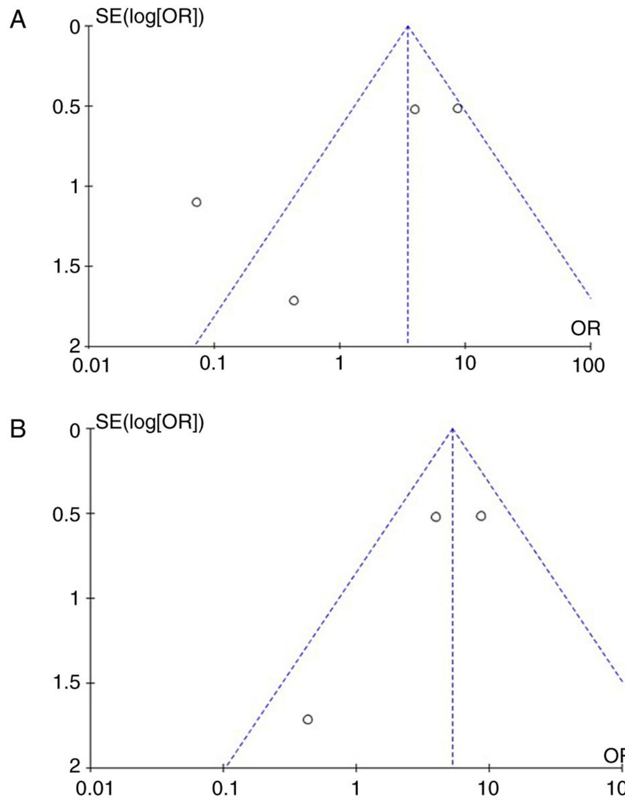

Figure 4. (A and B) Funnel plots of the free of seizures parameter between the groups, with (left) or without (right) the study by Fernández *et al* (1), and with (left) heterogeneity (P<0.05 and I^2=82%) or with low (right) heterogeneity (P=0.18 and I^2=41%). I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; OR, odds ratio.

Neurological deficit parameter. As regards neurological deficit, information was available in four articles (1,15-18), and this demonstrated a statistically significant result (OR, 0.57; 95% CI, 0.32 to 1.00; P=0.05) with no heterogeneity (P=0.34; I^2=11%) (Table III and Fig. 5). A neurological deficit

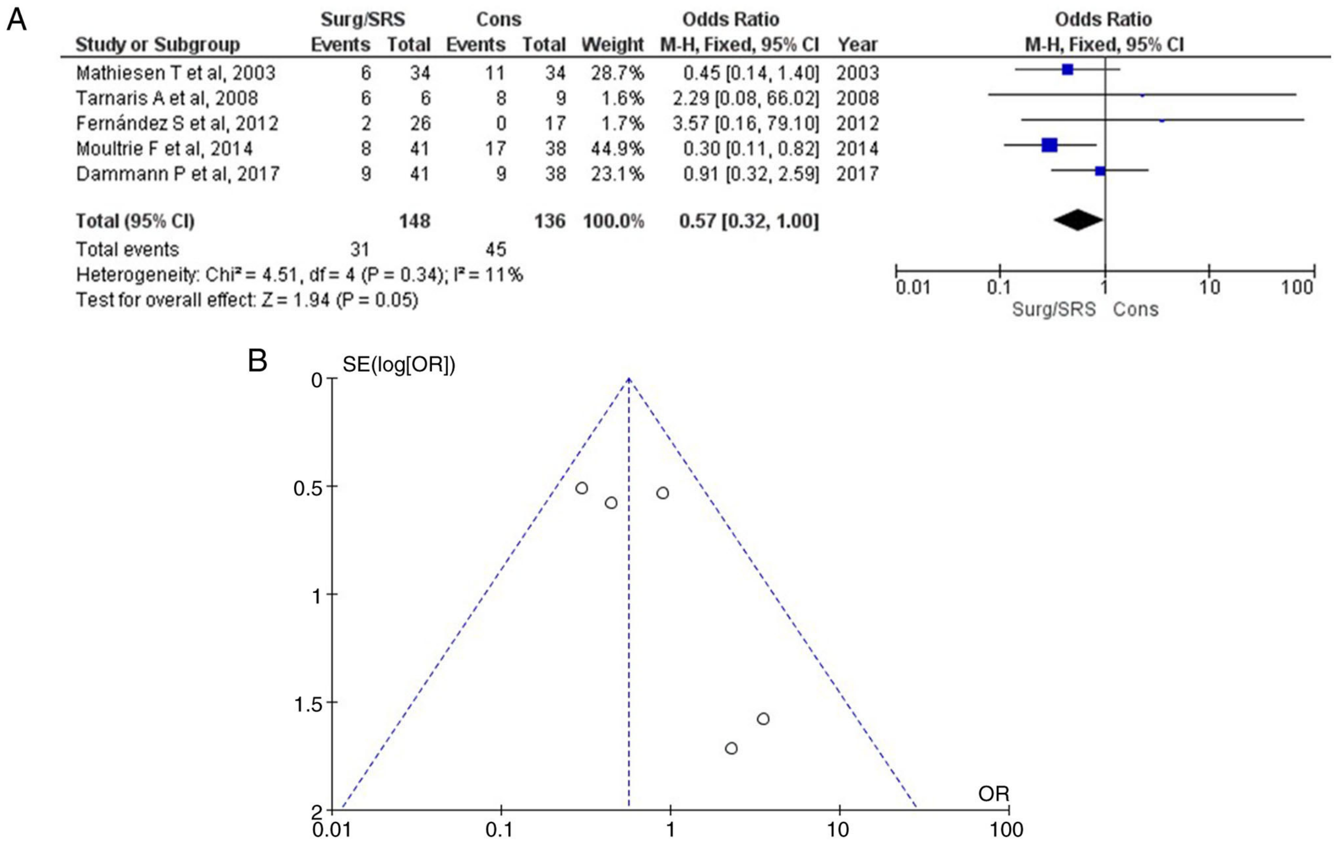

Figure 5. (A) Forest plot for the neurological deficit parameter. The results demonstrated a statistically significant difference between the surgical or/+ SRS and Cons groups (OR, 0.57; 95% CI, 0.32 to 1.00; P=0.05). (B) Funnel plot, testing the sensitivity of the neurological deficit parameter; there was no heterogeneity (P=0.34; I^2=11%). SRS, radiotherapy; Cons, conservative management group; OR, odds ratio; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

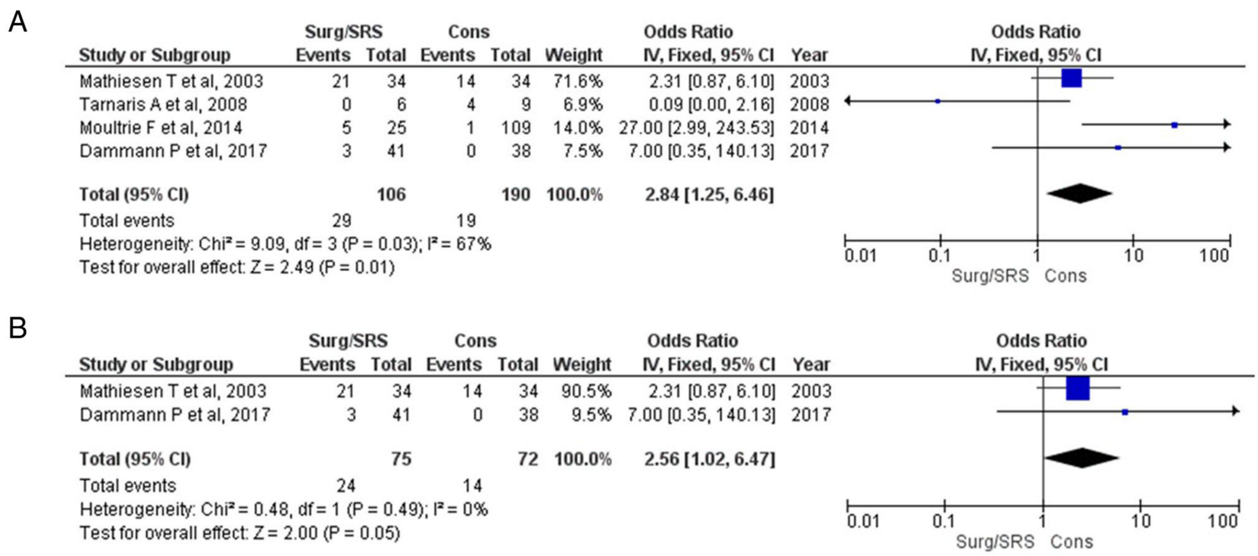

Figure 6. (A) Forest plot for the re-bleeding parameter. The results demonstrated a statistically significant difference between the surgical or/+ SRS and Cons groups (OR, 2.84; 95% CI, 1.25 to 6.46; and P<0.05). (B) Forest plot for the re-bleeding parameter without the studies by Tarnaris *et al* (16) and Moultrie *et al* (17). The results again demonstrated a statistically significant difference (OR, 5.56; 95% CI, 1.02 to 6.67; P=0.05). SRS, radiotherapy; Cons, conservative management group; OR, odds ratio; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

was found in 31 of 148 (20.9%) patients in the Surg/SRS group and in 45 of 136 (33.0%) patients in the Cons group. When examining the funnel plot of the same parameter, no publication bias was found. Thus, the Surg/SRS (experimental) group exhibited superiority over the Cons (control) group.

Re-bleeding. Information regarding the re-bleeding parameter was available in four articles (15-18) and demonstrated a statistically significant result between the patients with Surg/SRS and the Cons groups (OR, 2.84; 95% CI, 1.25 to 6.46; and P<0.05), but with heterogeneity (P<0.05 and I^2=67%) (Fig. 6A). For testing the sensitivity, the 'leave out one' model was used, and one study was removed at a time (Table III). No heterogeneity (P=0.49 and I^2=0%) was achieved only after removing the articles by Tarnaris *et al* (16) and Moultrie *et al* (17); again, a statistically significant difference was found (OR, 5.56; 95% CI, 1.02 to 6.67; P=0.05) (Fig. 6B). When examining the funnel plot of the same parameter, it was found that the study results without the studies by Tarnaris *et al* (16) and Moultrie *et al* (17) displayed better dispersion with a low publication bias (Fig. 7).

OHS 2-6. As regards OHS 2-6, information was available in five articles (15-19). No significant difference was found between groups (OR, 1.44; 95% CI, 0.83 to 2.49; P=0.19) (Table III and Fig. S5). In addition, after applying the 'leave out one' model, no statistically significant result was obtained (Table III).

Mortality. Information regarding mortality was available in three articles (15-19) and demonstrated a statistically significant result between the patients with Surg/SRS and the Cons groups (OR, 4.68; 95% CI, 1.97 to 11.09; and P<0.05) (Table III and Fig. 8A). Mortality was found in 21 of 65 (32.3%) patients in the Surg/SRS group and in 32 of 152 (21.1%) in the Cons group of patients. When examining the funnel plot of the same parameter, it was found that the study results had low heterogeneity (P=0.15 and I^2=47%) and a low publication bias (Fig. 8B). Thus, the Cons (control) group exhibited superiority over the Surg/SRS (experimental) group.

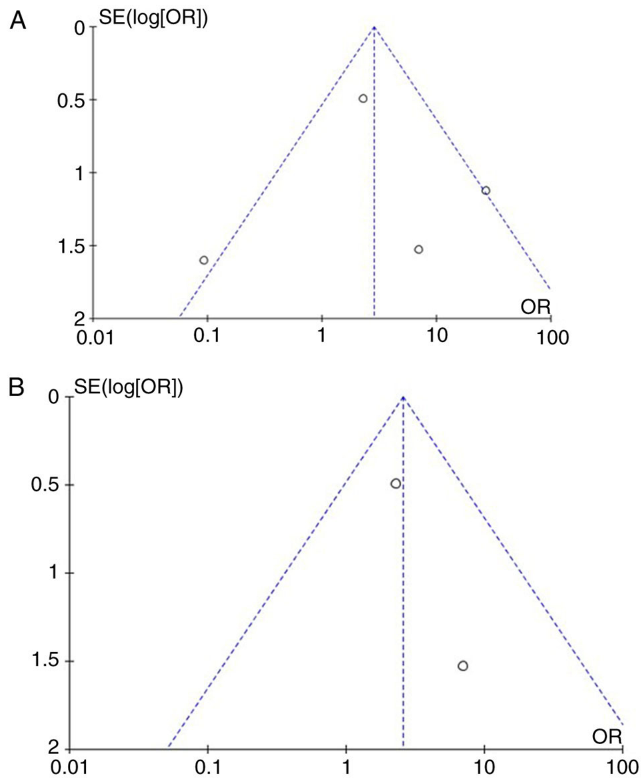

Figure 7. (A and B) Funnel plots of the re-bleeding parameter between the groups, with (left) or without (right) Tarnaris *et al* (16) and Moultrie *et al* (17), and with (left) (P<0.05 and I^2=67%) or without (right) heterogeneity (P=0.49 and I^2=0%). I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; OR, odds ratio.

Discussion

The present study suggests that surgical or SRS management may be a safe procedure as regards the outcomes of patients with CMs compared with conservative treatment. More precisely, neurological deficit was a statistically significant parameter in these patients, exhibiting the superiority of surgery and/or SRS over conservative management. Of note, the of hemosiderin in the pre-MRI, the free of seizures parameter, and the re-bleeding and neurological deficit parameters yielded statistically significant results, predicting a better outcome in the surgical or SRS group of patients. On the other hand, the mortality rate was lower in the Cons group of patients compared with the surgical or SRS treatment groups.

The treatment of CMs has been an ongoing topic of debate due to the issues concerning their management. The major difficulty with obtaining a clear perspective of their natural history is determining when these injuries should be operated on. In addition, published surgical series may ignore cases that never hemorrhage and are only found on the follow-up for other reasons. SRS is applied for the obliteration of the CMs, preventing any risk of re-bleeding, and is an alternative to surgical treatment (20,21). However, it appears that CMs following SRS re-hemorrhage repeatedly and thus no benefit has been observed (22,23). The present meta-analysis demonstrated that the re-bleeding rate was a statistically significant parameter in patients with CM who underwent surgical or/and SRS management.

Based on the literature data, it appears evident that the microsurgical management of CMs is the best option for patients with epilepsy (1). Nevertheless, there are no randomized studies evaluating pharmaceutical and surgical treatment in patients with CMs and epilepsy. In the present meta-analysis, the free of seizures parameter yielded a statistically significant result, predicting a better outcome in the surgical or SRS group of patients.

Researchers have asserted that patients with CMs have an amplified risk of re-hemorrhage following an initial bleed (21). Since a brain MRI is needed to diagnose CMs without other pathological examinations, apart from the use of hemosiderin in the MRI, intracranial hemorrhage in the pre-MRI brain imaging may increase the risk of re-hemorrhage (24). These risks may help to determine whether to treat CMs with neurosurgical excision and/or SRS or to opt for conservative management. In the present meta-analysis, the use of hemosiderin in the pre-MRI was a statistically significant parameter, predicting a better outcome in the surgical or SRS group of patients than in patients in the Cons group.

As regards outcomes due to surgical or/and SRS-related morbidity or CM-related mortality, a poorer outcome in surgically managed patients, such as that detailed in a previous

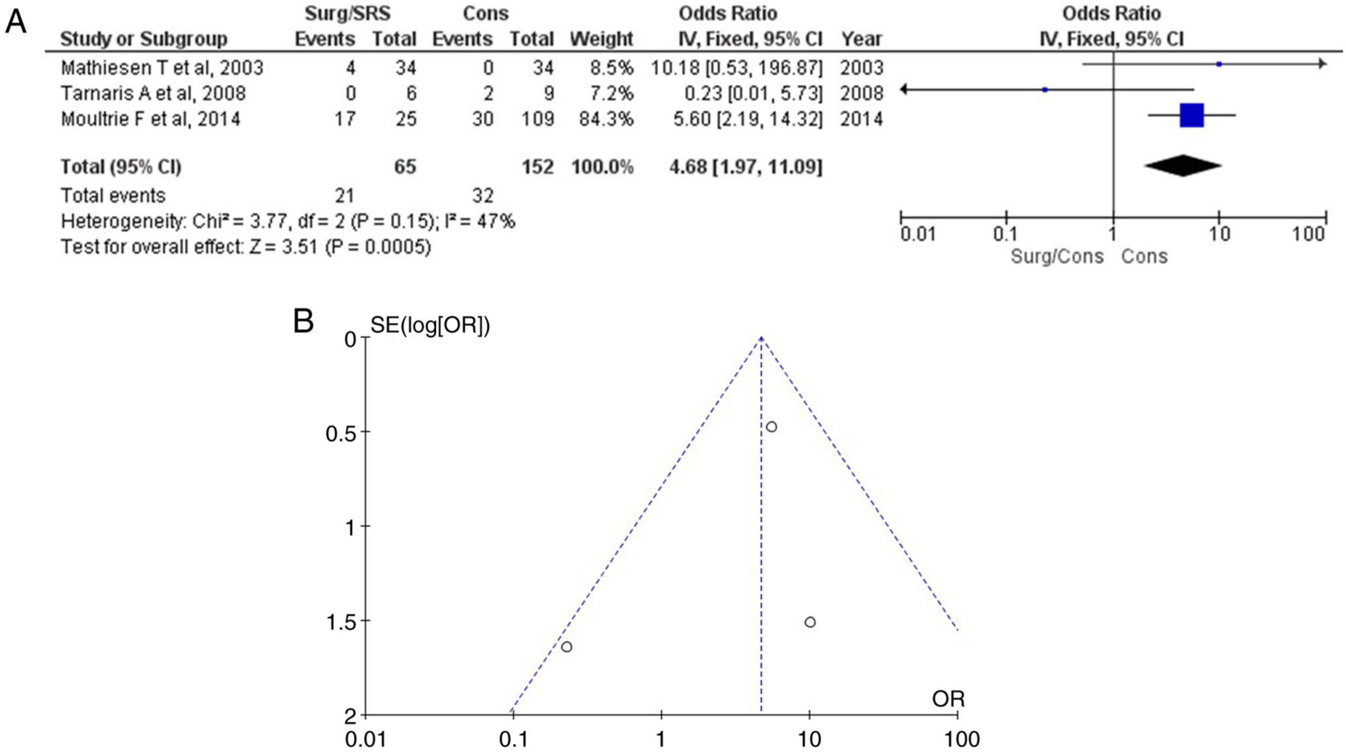

Figure 8. (A) Forest plot for the mortality parameter. The results demonstrated a statistically significant difference between the surgical or/+ SRS and Cons groups (OR, 4.68; 95% CI, 1.97 to 11.09; and P<0.05). (B) Funnel plot, testing the sensitivity of the mortality parameter; there was a low heterogeneity (P=0.15 and I^2=47%). SRS, radiotherapy; Cons, conservative management group; OR, odds ratio; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

study (17), was also found in the present meta-analysis. This may be explained by the complications associated with CM excisions. In the present meta-analysis, mortality was a statistically significant parameter, predicting a better outcome in the Cons group of patients.

The present meta-analysis has certain limitations, which should be mentioned. Half of the included studies were retrospective, and a limited number of cases were presented, particularly in the surgically treated group. In addition, there is an argument suggesting that surgical outcome depends on the time of the intervention, and some researchers have advocated for surgery at 4 weeks after ictus (15,23). Thus, the present meta-analysis did not include the time-dependent intervention parameter.

In conclusion, the present meta-analysis proposes that surgical or SRS management is a safe procedure as regards the out outcomes of patients with CMs compared with conservative treatment. More precisely, neurological deficit was statistically significant parameter in these patients, exhibiting the superiority of the surgical or/and SRS option over conservative management. Of note, the use of hemosiderin in the pre-MRI, and the free of seizures, re-bleeding and neurological deficit parameters yielded statistically significant results, predicting a better outcome in the surgical or SRS group of patients. On the other hand, the mortality rate was lower in the Cons group of patients compared with surgical or SRS treatment. Future studies are required to examine more precisely the outcomes in the natural history cases (conservative treatment), as the debate regarding the management of CMs remains controversial.

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

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

References

1. Fernández S, Miró J, Falip M, Coello A, Plans G, Castañer S and Acebes JJ: Surgical versus conservative treatment in patients with cerebral cavernomas and non refractory epilepsy. Seizure 21: 785-788, 2012.
2. Steiner L, Karlsson B, Yen CP, Torner JC, Lindquist C and Schlesinger D: Radiosurgery in cavernous malformations: Anatomy of a controversy. J Neurosurg 113: 16-22, 2010.
3. Fotakopoulos G, Andrade-Barazarte H, Kivelev J, Tjahjadi M, Goehre F and Hernesniemi J: Brainstem cavernous malformations management: Microsurgery vs radiosurgery, a meta-analysis. Front Surg 8: 630134, 2022.
4. Fotakopoulos G, Kivelev J, Andrade-Barazarte H, Tjahjadi M, Goehre F and Hernesniemi J: Outcome in patients with spinal cavernomas presenting with symptoms due to mass effect and/or hemorrhage: Conservative versus surgical management: Meta-analysis of direct comparison of approach-related complications. World Neurosurg 152: 6-18, 2021.
5. Fotakopoulos G, Brotis AG and Fountas KN: Dilemmas in managing coexisting arteriovenous and cavernous malformations: Case report. Brain Circ 8: 45-49, 2022.
6. Robinson JR, Awad IA and Little JR: Natural history of the cavernous angioma. J Neurosurg 75: 709-714, 1991.
7. Sandalcioglu IE, Wiedemayer H, Secer S, Asgari S and Stolke D: Surgical removal of brain stem cavernous malformations: Surgical indications, technical considerations, and results. J Neurol Neurosurg Psychiatry 72: 351-355, 2002.
8. Gross BA, Batjer HH, Awad IA and Bendok BR: Brainstem cavernous malformations. Neurosurgery 64: E805-E818, 2009.
9. Lippitz B: Treatment of cavernoma: An evidence-based dilemma? Acta Neurochir Suppl 116: 99-101, 2013.
10. Rinkel LA, Al-Shahi Salman R, Rinkel GJ and Greving JP: Radiosurgical, neurosurgical, or no intervention for cerebral cavernous malformations: A decision analysis. Int J Stroke 14: 939-945, 2019.
11. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos mM and Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Bamford JM, Sandercock PA, Warlow CP and Slattery J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 20: 828, 1989.
13. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, *et al*: The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928, 2011.
14. Higgins JPT and Green S (eds): Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Updated March 2011
15. Mathiesen T, Edner G and Kihlström L: Deep and brainstem cavernomas: A consecutive 8-year series. J Neurosurg 99: 31-37, 2003.
16. Tarnaris A, Fernandes RP and Kitchen ND: Does conservative management for brain stem cavernomas have better long-term outcome? Br J Neurosurg 22: 748-757, 2008.
17. Moultrie F, Horne MA, Josephson CB, Hall JM, Counsell CE, Bhattacharya JJ, Papanastassiou V, Sellar RJ, Warlow CP, Murray GD and Al-Shahi Salman R; Scottish Audit of Intracranial Vascular Malformations (SAIVMs) steering committee and collaborators: Outcome after surgical or conservative management of cerebral cavernous malformations. Neurology 83: 582-589, 2014.
18. Dammann P, Wrede K, Jabbarli R, Neuschulte S, Menzler K, Zhu Y, Özkan N, Müller O, Forsting M, Rosenow F and Sure U: Outcome after conservative management or surgical treatment for new-onset epilepsy in cerebral cavernous malformation. J Neurosurg 126: 1303-1311, 2017.
19. Kang K, Ju Y, Wang D, Li H, Sun L, Ma K, Zhao X and Lu J: Cerebral venous malformations in a chinese population: Clinical manifestations, radiological characteristics, and long-term prognosis. World Neurosurg 120: e472-e479, 2018.
20. Liscák R, Vladyka V, Simonová G, Vymazal J and Novotny J Jr: Gamma knife surgery of brain cavernous hemangiomas. J Neurosurg 102 (Suppl): S207-S213, 2005.
21. Kondziolka D, Lunsford LD, Flickinger JC and Kestle JR: Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations. J Neurosurg 83: 825-831, 1995.
22. Karlsson B, Kihlström L, Lindquist C, Ericson K and Steiner L: Radiosurgery for cavernous malformations. J Neurosurg 88: 293-297, 1998.
23. Steinberg GK, Chang SD, Gewirtz RJ and Lopez JR: Microsurgical resection of brainstem, thalamic, and basal ganglia angiographically occult vascular malformations. Neurosurgery 46: 260-271, 2000.
24. Al-Shahi Salman R, Berg MJ, Morrison L and Awad IA; Angioma Alliance Scientific Advisory Board: Hemorrhage from cavernous malformations of the brain: Definition and reporting standards. Angioma alliance scientific advisory board. Stroke 39: 3222-3230, 2008.