UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"
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Malformações Arteriovenosas Cerebrais Não Rotas: revisão sistemática e metanálise de morbimortalidade nos estudos ARUBA- elegíveis.

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Mestre em Ciências.

Orientadora: Profa. Titular Maria Aparecida Marchesan Rodrigues
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Summary

CHAPTER I

LITERATURE REVIEW

Unruptured Brain Arteriovenous Malformations: Literature Review

Abstract

Arteriovenous malformations (AVMs) are high flow vascular lesions related to anomalous connections between arteries and veins through a complex tangle of dysplastic small vessels called *nidus*. Although rare in the brain, AVMs are an important cause of cerebral hemorrhage in young adults. Hemorrhagic stroke is the most common clinical presentation affecting 50% of patients and are fatal in the first episode of bleeding in 25% of cases. Besides previous hemorrhage, other risk factors for bleeding include deep location of the lesion, deep venous drainage and associated aneurisms. The diagnosis of brain AVMs is based on imaging methods such as computed tomography, magnetic resonance imaging and catheter angiography, which provide important information about the structure and hemodynamics of the lesion. Treatment for AVMs may be performed by microsurgical resection of the lesion, endovascular embolization, stereotactic radiosurgery, all modalities as single method or in combination. For unruptured AVMs there is no consensus on the most appropriate type of management, whether clinical follow-up or therapeutic intervention due to treatment related risks. In conclusion the choice of treatment should consider several indicators such as the topography and size of the lesion, the vascular drainage, patient's age, surgeon experience and the risks related to the intervention.

Key words: Brain arteriovenous malformations, diagnosis, treatment

Resumo

Malformações arteriovenosas (MAVs) são lesões vasculares de alto fluxo relacionadas a conexões anômalas entre artérias e veias, através de um emaranhado de vasos malformados denominados *nidus*. MAVs são lesões raras no cérebro, mas constituem importante causa de sangramento em adultos jovens. Hemorragia cerebral é a manifestação clínica mais frequente, ocorre na metade dos portadores de MAVs e são fatais no primeiro episódio de sangramento em 25% dos casos. Outros fatores de risco para sangramento, além de hemorragia prévia, incluem localização profunda da lesão, drenagem venosa profunda e associação com aneurismas. O diagnóstico de MAV é confirmado por exames de imagem, como tomografia computadorizada, ressonância magnética e por exames angiográficos. O tratamento para MAVs com sangramento prévio pode ser feito por ressecção microcirúrgica da lesão, embolização endovascular, radiocirurgia estereotáxica ou por combinação destes procedimentos. Para MAVs íntegras não há consenso sobre a conduta mais adequada, se deve ser feito acompanhamento clínico ou intervenção terapêutica, tendo em vista os riscos relacionados ao tratamento. Em síntese, a escolha do tipo de tratamento deve considerar vários indicadores, como tamanho e local da lesão, drenagem vascular, a idade e o contexto clínico do paciente, bem como a experiência do serviço e os riscos relacionados ao tratamento.

Palavras Chave: Malformações arteriovenosas cerebrais, diagnóstico, tratamento.

1. Introduction

Arteriovenous Malformations (AVMs) are high-flow vascular lesions composed by anomalous connections between arteries and veins through a tangle of anomalous vessels called nidus that replace normal capillary bed. They can occur in several organs, including the brain (Friedlander 2007; Solomon and Connolly 2017) (Figure 1). The arterialization of drainage veins is another feature of AVMs and can be noticed in macroscopic inspection.

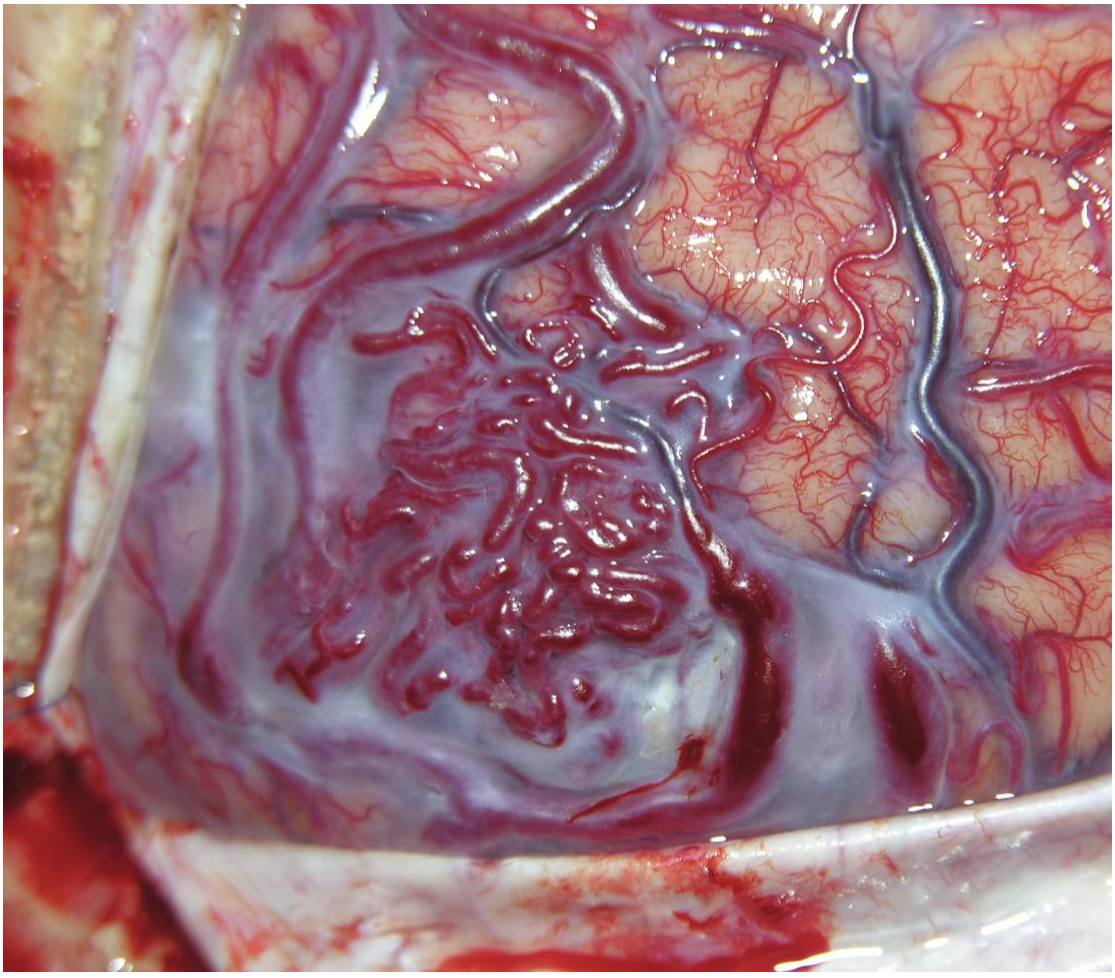

Figure 1: Cerebral arteriovenous malformation: macroscopic appearance. (Professor Marco Antonio Zanini, HCFMB – Unesp)

2. Epidemiology

Brain AVMs are rare lesions, with an estimated annual incidence of 1 per 100,000 (Stapf et al 2001; Osbun et al 2017). The lack of accurate information on the incidence and prevalence of brain AVMs is related to the relative rarity of these lesions and the limited availability of large-scale epidemiological studies. Studies focused on the epidemiology of brain AVMs indicate that the prevalence of undetected cases can be as high as 10 per 100,000 individuals (Berman et al, 2000). Brain AVMs usually occur randomly in the population, with no sex predilection, but they may eventually be associated with hereditary genetic syndromes, such as Rendu-Osler-Weber disease and other specific genetic alterations (van Beijnun et al 2007). Regarding ethnicity, some studies have observed that Hispanics have a higher risk of bleeding, about two to three times greater than other individuals with AVMs. (Kim et al 2007; Yang et al 2015).

Brain AVMs can occur at any age, but usually manifest between the 2nd and 4th decades. A recent meta-analysis showed that the mean age of clinical manifestation is 33.7 years (Gross and Du 2013).

Lesions are predominantly located in the cerebral hemispheres, in cortical or deep regions such as the insula, basal ganglia, thalamus, corpus callosum, but can occur in other locations such as the brainstem, cerebellum and spinal cord (Zafar et al 2020). The location of the lesion correlates with the risk of surgical and postoperative neurological complications (Spetzler and Martin, 1986).

3. Pathogenesis

Brain AVMs have been considered congenital lesions, related to disorganized development of vessels during embryogenesis, with atypical differentiation of capillaries resulting in anomalous communications between arteries and veins (McCormic et al 1966). However, experimental

models and reports of de novo AVMs, as well as lesion development after some type of vascular aggression suggest the possibility of an alternative origin for these lesions (Milton et al 2012; Ito et al 2018; Kilbourn et al 2014).

A recent study on the biological nature of AVMs considered that genetic factors participate in the development of lesions. However, additional factors are needed to explain development of the lesions (Tasiou et al 2020).

4. Histopathology

The histopathological examination demonstrates that lesions comprehend anastomosing vascular channels, designated as nidus, with thick or thin walls, interposed between arteries and veins, without a capillary network or underlying brain parenchyma (Figure 2).

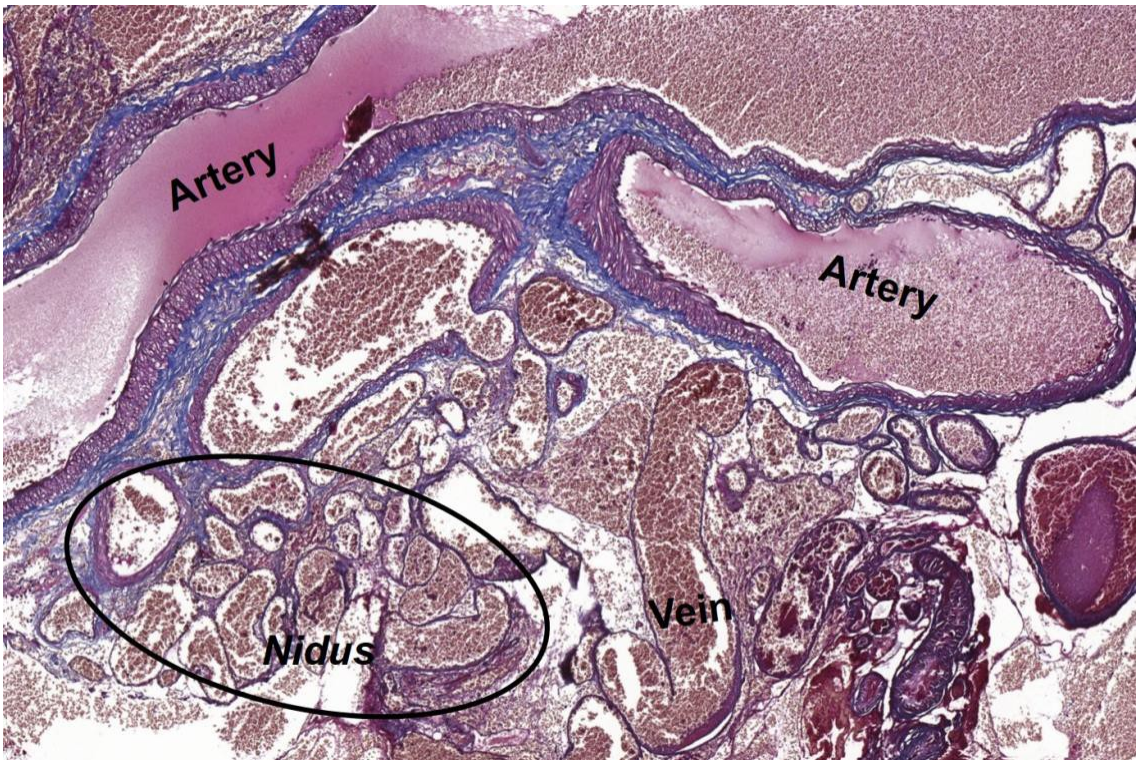

Figura 2: Cerebral arteriovenous malformation. Histological aspect (Masson 200X)

5. Classification

Cerebral AVMs are heterogeneous lesions that vary in size, location, and hemodynamic characteristics, such as supplying or draining vessels. The Spetzler and Martin score, proposed in 1986, is the most widespread classification. It considers the characteristics of lesions to estimate the surgical risk of morbidity and mortality. In this classification, the lesions are graded into 5 categories according to size, venous drainage pattern and eloquence of the underlying brain parenchyma (Table 1). For example, a small, superficial lesion located in a non-eloquent cortical area is classified as grade I, while a large, deep-draining lesion located in a critical neurological area is classified as grade V. Grade IV and V lesions often considered inoperable, or amenable to limited, palliative intervention. These criteria were initially applied retrospectively to a series of surgically resected AVMs and correlated with the frequency of postoperative neurologic complications (Spetzler and Martin 1986).

Table 1: Example of the Spetzler-Martin model for scoring and classifying AVMs. The minimum score is 1 point for lesions smaller than 3 cm without deep drainage or involvement of an eloquent area. The highest score is for lesions larger than 6 cm with eloquent area involvement and deep drainage (Spetzler and Martin 1986).

Size	Score
<3cm	1
3-6cm	2
>6cm	3

Venous drainage	
Superficial	0
Deep	1

Cerebral eloquence	
No	0
Yes	1

In 2011, an attempt to simplify the classification by Spetzler and Martin was published (Spetzler and Ponce, 2011). In this classification, groups I and II were grouped into class A, group III was classified as B and groups IV and V were classified as C. The reasoning for this change was the better correlation of surgical results and the improvement in statistical power for subsequent studies.

Table 2: Spetzler-Ponce classification (2011). The original Spetzler-Martin classification was simplified and more clearly associated with the proposed treatment suggested by the authors.

Class	Spetzler-Martin	Treatment
A	I-II	Resection
B	III	Multimodal treatment
C	IV-V	Conservative management

Lawton-Young's (2010) supplementary classification represents an additional milestone for the classification of MAVs. Characteristics not previously examined in the classification such as patient age, previous bleeding episode and the compact appearance of AVMs were included in a classification model (Table 3).

Table 3: Lawton-Young's (2010) supplementary classification

		Score
Age	<20 years	1
	20-40 years	2
	>40 years	3
Bleeding	Yes	0
	No	1
Compact structure	Yes	0
	No	1

6. Clinical Presentation

Although rare, AVMs are an important cause of cerebral hemorrhage in young adults (Stapf et al 2006, da Costa et al 2009; Gross and Du 2013). Studies on the natural history of AVMs began in the 1960s and demonstrated that cerebral hemorrhage and seizures are the most common clinical manifestations (McCormick et al, 1966; Solomon and Conolly, 2017).

Cerebral hemorrhage is the most frequent clinical manifestation, occurring in approximately 50% of individuals with AVMs (Stapf et al 2006, da Costa et al 2009; Gross and Du 2013). In a prospective study of the natural history of unruptured AVMs, Brown et al. 1988 identified a morbidity rate of 35% and a mortality rate of 29%. Bleeding episodes are more frequent in intraparenchymal, followed by ventricular, and subarachnoid locations (Stapf et al 2006, da Costa et al 2009; Gross and Du 2013).

Seizures are the second most common clinical manifestation in individuals with AVMs. A meta-analysis study demonstrated that seizures occur in 27% of individuals with AVMs (Gross and Du 2013). Other clinical manifestations of individuals with AVMs include chronic headache and progressive neurological deficits (Crawford et al 1986; Stapf et al 2006).

Incidental lesions have been identified more frequently due to the use of high resolution neuroimaging methods. Recent studies have reported that the frequency of asymptomatic lesions is around 10% of cases (Stapf et al 2006, da Costa et al 2009; Gross and Du 2013).

7. Natural History

Bleeding episodes are fatal in 10 to 30% of cases (Brown et al 1988; Ondra et al 1990; Osbun et al 2017). Studies on the natural history of AVMs have assessed the risk of bleeding at different follow-up periods (Friedlander et al, 2007; McCormick et al, 1966; Solomon and Conolly, 2017). Hernesniemi et al 2008 retrospectively analyzed 238 individuals with unruptured AVMs, followed for 13.5 years. They observed that the risk of bleeding was 2.4% per year. These results were confirmed by later studies that showed that annual bleeding rates for non-ruptured AVMs were 2.2% in the ARUBA study (Mohr et al 2014) and 3% in the Gross and Du meta-analysis, 2013.

The risk of bleeding increases significantly, about 5-fold, after the first bleeding episode (Stapf et al 2006; Kim et al 2014). The annual bleeding rate of AVMs with previous bleeding was 4.5% in the meta-analysis study by Gross and Du 2013.

8. Bleeding Risk Factors

In addition to previous bleeding, other risk factors for bleeding from AVMs include: deep location of the lesion, AVM with deep venous drainage, and association with aneurysms (Gross and Du 2013).

About 30% of AVMs are located deep in the brain parenchyma, which is an independent risk factor for bleeding (Hernesniemi et al 2008). Bleeding rates for deep AVMs range from 3.4% to 5.4% (Hernesniemi et al 2008; da Costa et al 2009).

Studies on the natural history of AVMs have shown association with aneurysms occurs in 20% of cases (da Costa et al 2009; Gross and Du 2013). Aneurysms can be located in the nidus, in the arteries supplying the AVMs or in other peripheral arteries not related to the lesion. Several studies have indicated that the association with aneurysms constitutes a risk factor for bleeding from AVMs (da Costa et al 2009; Gross and Du 2013).

Pregnancy has been implicated as a risk factor for bleeding from AVMs (Crawford et al 86; Skidmore et al 2001). Gross and Du (2012) reported that the annual rate of bleeding in pregnant women was 10.8% compared to 1.1% in non-pregnant women.

Other factors such as age, sex and lesion size were extensively investigated in early studies as risk factors for bleeding AVMs. However, more recent studies suggest that these criteria are not risk factors for bleeding from AVMs (Gross and Du 2013; Can et al 2017).

9. Diagnosis

The diagnostic investigation of AVMs is performed with imaging exams, such as computed tomography, magnetic resonance imaging, and by angiographic tests that demonstrate the anatomical and hemodynamic characteristics of the lesions (Osbun et al 2017).

The gold standard for diagnosis is digital subtraction cerebral angiography. These exams provide information on the size, location and drainage pattern of the lesions, which are essential criteria for estimating the surgical risk through the Spetzler and Martin classification.

The angioarchitectural characteristics of the lesions have been correlated with clinical manifestations and bleeding risk in several studies (Kubaleck et al 2003; Shankar et al 2013; Batista et al 2022).

A recent retrospective study from Brazil analyzed the angioarchitectural characteristics of 183 individuals with AVMs found hemorrhage in 30.6% (56/183) and a significant correlation with grade 3 Spetzler-Martin lesions, low-flow lesions and with the female gender (Batista et al 2022).

10. Treatment

Treatment for ruptured AVMs is indicated whenever feasible. This is due to the high risk for rebleeding after the first bleeding episode (Bendok et al 2014; Lawton et al 2015). Treatment aims to eradicate the lesion and can be done by different procedures, such as surgical resection of the lesion, endovascular embolization, stereotaxic radiosurgery for small lesions (less than 3 cm) or a combination of these procedures (Bendok et al 2014; Lawton et al 2014; Lawton et al. al 2015).

The choice of type of treatment should consider several indicators such as lesion size and location, vascular drainage, age and natural history of the individual with the lesion, as well as the risks related to the treatment.

A meta-analysis study on therapeutic procedures for ruptured AVMs reported that complete lesion resolution rates were 96% for surgical resection, 38% for stereotactic radiosurgery, and 13% for embolization (Van Beijnum et al 2011).

There is no consensus on the most appropriate management for unruptured AVMs (Davis and Donnan 2007; Lawton et al 2015, Morgan et al 2017). The risks related to the treatment, such as death or permanent neurological deficits, must be considered and compared to the risk of spontaneous hemorrhage in the evolution of the natural history of the individual with an intact cerebral AVM.

The ARUBA (A Randomized Trial of Unrupted Brain AVMs) study was a randomized, prospective, multicenter trial, with participation from Brazil, that compared therapeutic interventions for unruptured AVMs with clinical follow-up of lesions (Mohr et al 2014). A total of 223 individuals with unruptured AVMs, submitted to different procedures, such as surgical resection of the lesion, endovascular embolization, radiosurgery or clinical follow-up, were analyzed. The primary outcome of death or stroke after 33.3 months of follow-up occurred in 10% (11/109) patients in the group receiving conservative medical treatment and in 30.7% (35/114) patients who underwent interventional procedures. With these results, the study was interrupted, and clinical follow-up was recommended for patients with unruptured AVMs.

The ARUBA study has been considered a benchmark in the management of unruptured AVMs in the modern era, despite having received significant criticism (Magro et al 2017). Among them are the underrepresentation of the microsurgical treatment modality, the absence of stratification of results between the modalities and the participation of centers with low number of treated AVMs cases (Magro et al 2017, Lawton et al 2015).

Thus, the present study aims to join data from ARUBA-eligible studies, perform a systematic review and meta-analysis of the available literature data in order to identify the main trends associated with morbidity and mortality in patients with non-ruptured AVMs.

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CHAPTER II

ARTICLE

Unruptured brain arteriovenous malformations: a systematic review and meta-analysis of mortality and morbidity in ARUBA-eligible studies.

Unruptured brain arteriovenous malformations: a systematic review and meta-analysis of mortality and morbidity in ARUBA-eligible studies.

Abstract:

Introduction: Unruptured brain arteriovenous malformations (bAVMs) are challenging lesions to treat and several uncertainties are still under discussion. The ARUBA (A Randomized Trial of Unrupted Brain AVMs) has inspired the development of studies to further investigate better management strategies for unruptured bAVMs. We present a systematic review and meta-analysis on ARUBA-eligible studies. We correlated patient data with outcomes and performed a discussion of the most important aspects of these studies.

Methods: A systematic review on ARUBA eligible studies was performed using PRISMA guidelines. Variables analyzed included bAVM Spetzler-Martin (SM) grade, treatment modalities and outcomes of mortality and neurologic deficits. We compared studies presenting SM 1-2 ≥ 50% with SM 1-2 <50% studies, studies presenting Microsurgery (MS) ≥ 50% with MS<50% studies. We performed a correlation between mortality incidence, SM distribution and treatment modalities.

Results: Fifteen studies with 2338 patients were included in the analysis. The frequency of bAVMs SM grade1-2 in the studies varied from 44 to 76%, SM grade 3 from 19 to 48% and SM 4-5 from 5 to 23% of cases. We identified that SM 1-2 ≥ 50% studies had smaller mortality than SM1-2<50% studies (p=0.001). No significant difference was identified between studies with MS ≥ 50% and MS<50%. There was an inverse correlation between mortality and the proportion of lesions SM grade 1-2 (p=0.012, r=-0.628). A positive correlation was identified between bAVMs

SM grade 3 and mortality (p=0.006, r=0.673), and no significant relationship was identified between bAVMs SM4-5 and mortality (p=0,41). No significant association was identified between treatment modalities and mortality.

Conclusion:

A relationship between bAVM grade and mortality was found in ARUBA eligible studies. The higher proportion of lesions SM1-2 in the studies was associated with low mortality rates and the higher proportion of bAVMs SM grade 3 was associated with high mortality rates. Mortality was not associated with treatment modalities.

1. Introduction

Brain arteriovenous malformations (bAVMs) are rare vascular lesions with an incidence of about 1 case per 100000 person-year (Berman, Sciacca et al. 2000, Batista, Pereira et al. 2022). They are characterized by the interposition of a vascular tangle called nidus between several arterial sources and one or more drainage veins (Mohr, Parides et al. 2014, Bokhari and Bokhari 2022).

Rupture of a bAVMs can be a deadly event, with brain hemorrhage, loss of consciousness, need for surgical drainage and intensive care (Bokhari and Bokhari 2022). Medical management for bAVMs has been subject of discussion for decades. Few studies have supported conservative management (Al-Shahi Salman, White et al. 2014), while others have demonstrated good results with different interventional strategies (Kato, Dong et al. 2019, Lawton and Lang 2019, Bokhari and Bokhari 2022).

Studies on the natural history of bAVMs have shown a rupture risk of 1.3% for previously unruptured and 4.8% for previously ruptured lesions a year (Kim, Al-Shahi Salman et al. 2014, Morgan, Davidson et al. 2017). For most young patients, the risk of yearly events represents an argument for more aggressive therapies (Schramm, Schaller et al. 2017, Lawton and Lang 2019). Up until the ARUBA study (A Randomized Trial of Unrupted Brain AVMs), no strong case could be made for either rationale.

The ARUBA study was the first randomized prospective analysis to compare treatment options for unruptured bAVMs (Mohr, Parides et al. 2014). Even though it was met with criticism, the study is recognized as the first attempt at providing robust evidence on treatment options (Magro, Gentric et al. 2017). It involved 104 centers from 9 countries and was a randomized, open-label, prospective clinical trial between groups of medical clinical treatment or medical plus interventional treatment like surgery, embolization, radiosurgery, alone or in combined. (Mohr,

Parides et al. 2014). As deficiencies one should mention the absence of randomization between treatment modalities, participation of centers with little experience in the management of bAVMs and the short follow-up of 33 months (Magro, Gentric et al. 2017, Link, Winston et al. 2018).

In this study we present a systematic review and metanalysis on ARUBA-eligible studies. We correlated patient data with outcomes and performed a discussion of the most important aspects of the studies

2. Materials and Methods

2.1 Research Question

We applied the PICO strategy to develop a research question. P: patients with unruptured bAVMs. I: studies with Spetzler-Martin (SM) 1-2 ≥ 50% of patients. C: Compared to studies with SM1-2<50% of patients. O: Better outcomes for mortality and stroke-deficit.

A similar research question was also applied for microsurgery proportions. P: patients with unruptured bAVMs. I: intervention in studies with microsurgery cases (MS) ≥ 50% of patients. C: Compared to studies with MS<50% of patients. O: Better outcomes for mortality and stroke-deficit.

2.2 Literature review

This study was a systematic literature review on ARUBA eligible studies, performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page, McKenzie et al. 2021). MEDLINE, Embase, Google Scholar and Web of Science databases were investigated for studies presenting series of ARUBA eligible patients. The complete ARUBA-eligibility protocol is shown in Table 1. The following search terms were applied on July

1st, 2022: (brain arteriovenous malformations) AND (unruptured) AND ((treatment) OR (radiosurgery) OR (Surgery) OR (Endovascular) OR (Microsurgery) OR (ARUBA eligible)).

2.3 Eligibility criteria and selection of studies

A total of 307 unique publications were found using the search term. We included observational and interventionist series in English. Titles and abstracts of studies were evaluated by two authors (L.C.P.P. and M.W.J.) to eliminate those not relevant to the objectives of the study. In cases with duplicates, only studies with the most contemporary cohorts were considered.

Studies with at least ten patients with bAVMs, which presented Spetzler-Martin (SM) classification, and results such as mortality, type of intervention, clinical performance, with clinical follow-up of patients for a minimum period of 6 months and no ARUBA exclusion criteria (Mohr, Parides et al. 2014) were considered eligible for analysis. Sixteen full text articles were included in the analysis (Figure 1).

2.4 Outcomes

The primary outcome considered was mortality. The secondary outcomes were stroke and neurologic deficit incidence, modified Rankin Scale (mRS). All studies were examined and the variables were extracted aiming to obtain the total number of patients in every category for each study. Variables searched included number of patients who died during the study, number of patients in each treatment modality, prospective or retrospective design, multicentered or single centered design, SM classification, incidence of stroke or neurological deficit and mRS. A separate aggregate of data from studies with control groups was also performed.

2.5 Statistical analysis

Proportion meta-analysis was performed as described in previous methodological studies (Barker, Migliavaca et al. 2021). The statistical analysis was performed applying the inverse variance method with a Freeman-Tukey double arcsine transformation to obtain pooled incidence estimates and 95% confidence intervals. The Software R Studio (2021.09.2 Build 382) and the meta package (version 5.2-0) were used for the analysis. Patients from the studies were categorized in four groups to perform subgroup analysis: interventional; interventional with more than 50% of lesions SM1-2; microsurgery performed in more than 50% of cases and clinical care only. We performed subgroup analysis between interventional and clinical care, SM1-2 $\geq$ 50% and SM 1-2<50%, microsurgery $\geq$ 50% and MS <50%. The mortality and neurological deficit of the groups were compared graphically using forest plots.

The percentual value of the studied variables was used in a Pearson's R analysis to identify significant associations between the extracted variables and the outcomes. Values of $p<0,05$ were considered significant. A scattered plot was designed and a best fit curve was applied in order to better understand distribution trends of the results. The software IBM SPSS Statistics version 19 (IBM Corp., Armonk, NY, USA) was used for this statistical analysis.

2.6 Ethical aspects

The project did not present any patient exposure or patient information to risks. It was carried out through a restricted analysis of the literature.

3. Results

Thirty one studies were selected for full text analysis. Sixteen of them were excluded due to lack of data (Figure 1). Fifteen studies were included in the analysis, with a total of 2.338 patients (Table 2). The number of patients in each study varied from 34 to 509 individuals. Mortality varied from 0 to 6.9%. All but one study were retrospective case series. The only prospective study in the analysis was the ARUBA trial. Three studies were multicentered and twelve were single centered (Table 2).

The frequency of treatment methods performed in the studies were 13,4% microsurgery, 73% radiosurgery, 2,7% endovascular embolization and 10% combination therapy. Most studies focused on one or two treatment techniques in their series, with fewer cases associating techniques or applying a combination of all techniques (Table 2).

Patient distribution according to SM classification was 1271 (54.3%) SM grade 1-2, 826 patients (35.3%) SM grade 3 and 241 patients (10.3%) SM grade 4-5 (Table 3). The frequency of lesions SM 1-2 varied from 43 to 76%, SM grade 3 varied from 19 to 48% and SM 4- 5 varied from 4,5 to 23% cases (Table 3).

Six studies did not include mRS scores in their analysis, or included an agglomerate of data that could not be filtered, and could not be used for long term neurologic outcome evaluations. The distribution of mRS grade 0-1 as reported at last follow up varied from 54 to 94%, and from 6 to 46% for grades of 2 or higher (Table 4). The incidence of stroke and neurologic deficit did not differ among treatment modalities, SM grade nor mortality (data not shown).

Data extracted from studies with clinical treatment groups is summarized in Table 5. Three studies reported outcomes in clinical treatment groups, including the ARUBA trial. Mortality rate was 1.8% in the ARUBA trial and varied from 0-8.3% in the other studies. Frequencies of lesions SM

1-2 varied from 47.4 to 55%, SM3 from 25 to 42.1% and SM4-5 from 10.5 to 25%. Stroke and deficit rates was 7.3% in the ARUBA trial and 15.8% in Maruyama study.

Proportion meta-analysis was performed to compare mortality and neurological deficit rates between subgroups in the studies. Mortality did not differ between interventional and clinical treatment groups (p=0.71, Table 6, Figure 2). No significant difference was identified in stroke and deficit rates between interventional and clinical treatment groups (p= 0.58, Table 7, Figure 3). Mortality and neurological deficit rates were compared between studies with lesions SM 1-2 ≥ 50% and SM 1-2<50%. The estimated mortality rate was significantly lower in studies with the proportion of lesions SM1-2 ≥ 50% (0.55%) when compared to studies with SM1-2 lesions in less than 50% (4.3%, Table 6, Figure 4, p=0.001). No significant difference was identified in stroke and deficit rates between studies with SM grade 1-2 ≥ 50% and SM1-2<50% (p= 0.47, Table 6, Figure 5).

Mortality was lower in studies with microsurgery ≥ 50% (0.43%, Table 6) compared to those using microsurgery in less than 50% (2.05%) but the differences were not significant (p= 0,36, Table 6, Figure 6). No significant difference was identified in stroke and deficit rates between studies using microsurgery in more or less than 50% cases (p= 0.85, Table 7, Figure 7).

Table 8 shows an inverse correlation between mortality and the proportion of AVM SM grade 1-2 (p=0,012, r=-0,628). A positive correlation was observed between AVM SM grade 3 (p=0,006, r=0,673) and no significant correlation was identified between AVM SM 4-5 and mortality (p=0,41).

Figure 8 shows graphic trends of mortality distribution among AVM SM grade fractions in the examined studies. The higher proportion of SM 1-2 in the studies was associated to low mortality rates (Figure 8-A). On the other hand, the higher proportion of SM 3 cases was associated to an

increase in mortality (Figure 8-B). The distribution of SM 4-5 proportions in the scattered plot did not present an obvious trend (Figure 8-C).

Figure 9 shows graphic trends of mortality among treatment techniques. No statistical significance was identified among microsurgical (9-A), endovascular embolization (9-B) and radiosurgery (9-C).

4. Discussion

This study highlights the association between bAVM grade and mortality in ARUBA eligible studies. The proportion meta-analysis have demonstrated that studies with bAVMs proportions of SM 1-2 $\geq$ 50% have smaller mortality rates when compared to those with SM1-2<50% (Table 6, Figure 4, $p<0.001$). Additionally, higher proportions of SM 1-2 lesions were associated with low mortality rates, while a higher proportion of SM 3 lesions was associated with high mortality. To the best of our knowledge, this is the first study to identify association between bAVMs grade proportions and mortality in ARUBA eligible studies. Previous studies have discussed the results obtained for treatment of low grade bAVMS (Han, Ponce et al. 2003, Korja, Bervini et al. 2014). The anatomy, vascular supply and low eloquence of the lesions tend to allow for complete microsurgical resection and anatomical cure with reduced morbidity. Other treatment modalities have also shown good results in the treatment of low grade bAVMs (Gami, Feghali et al. 2021, Catapano, Srinivasan et al. 2022).

Grade 3 bAVMs are subject to further discussion on the treatment modalities and objectives (Frisoli, Catapano et al. 2021). Our analysis identified that studies with larger proportions of lesions SM 3 bAVMs correlated to increased mortality rates ($p=0,006$, $r=0,673$). Several studies have suggested alternatives for treatment of these lesions. However SM 3 lesions remain as

challenging conditions (Catapano, Frisoli et al. 2021, Frisoli, Catapano et al. 2021). A recent study also reported a correlation between SM 3 lesions and worse mRS after 12 months (Sai Kiran, Vidyasagar et al. 2020).

On the other hand bAVMs grade 4-5 have been extensively discussed and considered by many specialists as untreatable, with some even considering palliative treatment as inappropriate (Han, Ponce et al. 2003, Komatsu, Takagi et al. 2020). In this review, we could not find a significant correlation between the proportion of SM grade 4-5 lesions in studies and mortality ($p=0.411$, $r=0.229$). This may be explained by the small number lesions in this group, as well as the high frequency of non-curative treatment regimens.

Analysis of treatment modalities is difficult to assess since neither the ARUBA trial nor the ARUBA eligible studies randomized patients among treatment modalities. The studies display results over treatment preferences of the centers performed at the time (Mohr, Parides et al. 2014, Wong, Slomovic et al. 2017, Bokhari and Bokhari 2022). Therefore, conclusions about the efficacy of each treatment modality cannot be made. In the present study, we could not find association between a treatment modality and mortality or mRS outcomes. The general mortality calculated in this study with all treatment modalities was 2,6%, which was similar to the 3.1% reported in the ARUBA trial for all-cause mortality in the treatment group (Mohr, Parides et al. 2014). Additionally, we demonstrated that mortality and stroke or neurological deficit rates in the interventional groups were similar to clinical treatment data available in the studies (Figures 2-3). On the other hand, the rate of stroke and death for the ARUBA trial was 36%, while in our study it was 10.3%, which is closer to the 8% reported in the medical management group of the ARUBA trial (Mohr, Parides et al. 2014). If the ARUBA numbers are excluded from the analysis of the present study, the rate of stroke and death drops to 9.25%.

Deeper comparisons between the datasets are problematic due to the retrospective and metanalytical nature of this study, but questions over the criteria used to define an ischemic event have been raised. It is extremely difficult to distinguish transient neurologic deficit associated with an intervention from a definitive neurological deficit. If it is considered positive in the first medical encounter, the numbers might be inflated. The best variable to identify long term prognosis seems to be the mRS at the last follow up. Even small ischemic events, or small CT and MRI changes were considered as strokes and helped directing the outcomes in an unfavorable way. The fact is that ischemic events, as well as radiological changes are much more frequent in the intervention group than in clinical management groups. However, these events and changes are not certainly responsible for worsening functional status of the patients. A much more relevant outcome to take into account would be the long term functional status of the patients.

In the present study the rate of mRS grade ≥2 at last follow up was 13.5% as compared to 46.2% reported in the ARUBA trial. When the ARUBA trial is excluded from the analysis of our study, the value drops to 10.8%. Therefore, the results of the present study are closer to the 15.1% rate of mRS grade ≥2 reported in the clinical treatment group of the ARUBA trial.

The ARUBA trial presented 76% SM grade 1-2 lesions, 28% for SM grade 3 lesions and 8% SM grade 4-5 lesions. As compared to our study, which presented 54.3% lesions SM grade 1-2, 35.3% grade 3 and 10.3% grade 4-5. By the time of the ARUBA trial development, several groups have already questioned the benefits of treatment for most high grade bAVM cases, with many advocating that bAVMs grade 4 and 5 should be followed clinically (Ferch and Morgan 2002, Takagi, Takahashi et al. 2012). The vascular complexity involving high grade lesions is extremely challenging and it is even questioned if they do not have a smaller chance of rupture given the bigger size(Ferch and Morgan 2002).

Another subject to highlight is the distribution of treatment modalities in the studies. The ARUBA trial presented 5.3% of microsurgical treatment, 31.9% endovascular treatment, 32.9% of radiosurgery and 29% of combination therapy. Conversely, our study presented a 13.4% rate of microsurgical treatment, 2.7% of endovascular treatment, 73.3% radiosurgery and 10.5% of combination therapy. Of special note is the high frequency of radiosurgery in our review. This is explained by the large case series presented by Ding et al (Ding, Starke et al. 2016), Tonetti et al (Tonetti, Gross et al. 2018), Kim et al (Kim, Yeon et al. 2019) and Hak et al (Hak, Borius et al. 2021). These studies represent 1254 patients (53.6% of the whole series) treated by radiosurgery. In our study the microsurgical series have also increased almost threefold the amount of patients in comparison to the ARUBA trial (13.4% vs 5.3%). Few predominantly surgical series have been published with good clinical results and no cases of mortality in a total of 293 patients (Javadpour, Al-Mahfoudh et al. 2016, Schramm, Schaller et al. 2017, Wong, Slomovic et al. 2017). The most relevant decrease of treatment modality registered in our study was the endovascular approach intended as a single treatment modality. This is in agreement with several studies that have discussed the effectiveness and safety of endovascular procedures for unruptured bAVMs (Diaz and Scranton 2016, Mosimann and Chapot 2018, Lawton and Lang 2019, Pérez-Alfayate, Grasso et al. 2021). The conclusions presented in several studies, and shared by many specialists, seem to be that the endovascular embolization does not present a self-sufficient standard alternative for the treatment of bAVMs at this time (Diaz and Scranton 2016).

On the other hand, AVMs grade 1-2 have been discussed and agreed based on specialist opinion as of predominant surgical treatment strategy (Han, Ponce et al. 2003, Lawton and Lang 2019). These lesions are often small and more superficial, allowing good opportunity for a complete resection and anatomical cure of the lesion.

Grade 3 AVMs, conversely, are deemed as more complex yet treatable lesions by many authors (Han, Ponce et al. 2003, Chen, Li et al. 2020). This group is often considered for multidisciplinary treatment, as it often involves the evaluation of microsurgeons, endovascular surgeons and radiosurgeons (Han, Ponce et al. 2003, Kato, Dong et al. 2019, Chen, Li et al. 2020).

The limitations of this study consist of those for reviews and meta-analytical data compilations. No individual patient data was collected, therefore no causative conclusion should be drawn from the results herein presented. The correlations presented should serve as a reflection on the state of the bAVM treatment strategies and how it should be improved in the future. Of note are the large heterogeneity estimators (I^2), that can be identified in the forest plots and in tables 6-7. However, proportion meta-analysis usually have higher I^2 values and they should not suggest inconsistent data(Barker, Migliavaca et al. 2021). This is also in accordance to what is expected in a study attempting to aggregate data from several independent sources. As a predominantly retrospective study, risk of bias should be considered high.

5. Conclusion

In this review, we have shown that studies with rates of bAVM SM grade 1-2 greater than 50% had lower mortality rates when compared to those with lesions SM grade 1-2 less than 50%. We also present a correlation between larger fractions of lesions SM 1-2 in the studies and low mortality as well as increased mortality for studies with larger fractions of bAVMs grade 3. These correlations have been hypothesized in many previous studies, but this is the first time they are demonstrated in ARUBA eligible case series. The analysis presented in this study should be considered for choice of treatments offered for patients with unruptured bAVMs. More studies ON

bAVM management are needed o confirm these findings and to keep improving the standards of bAVM treatments.

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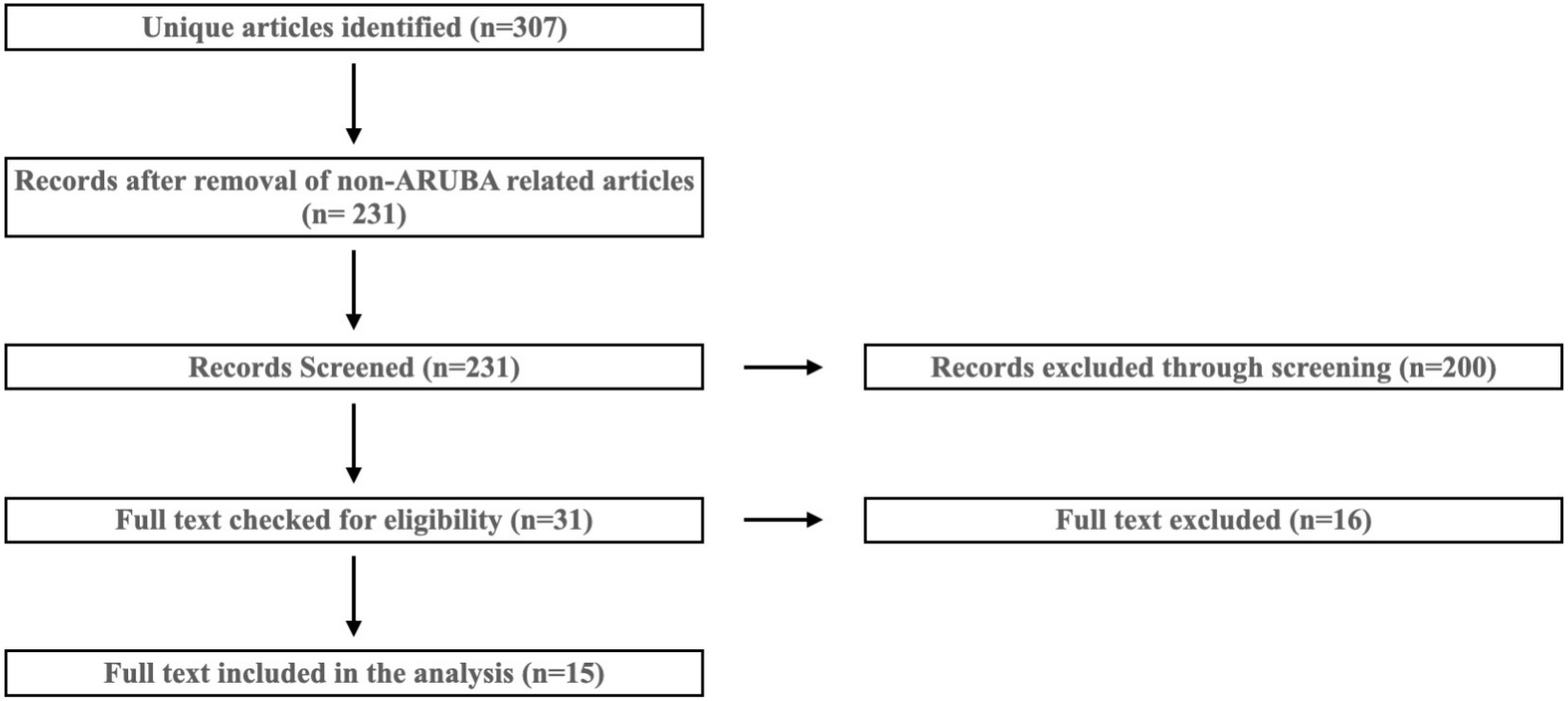

Figure 1: Article screening and inclusion flowchart.

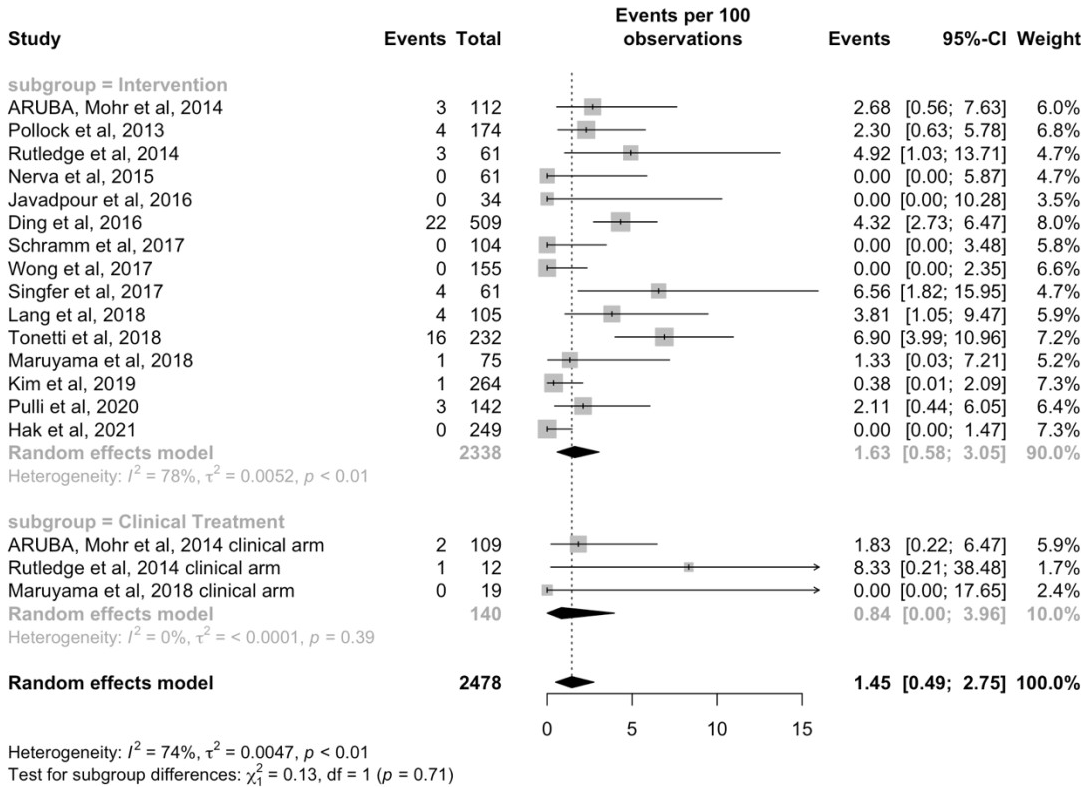

Figure 2: Forest plot comparing mortality between clinical interventional and clinical treatment groups. No significant difference in mortality was identified (p=0.71)

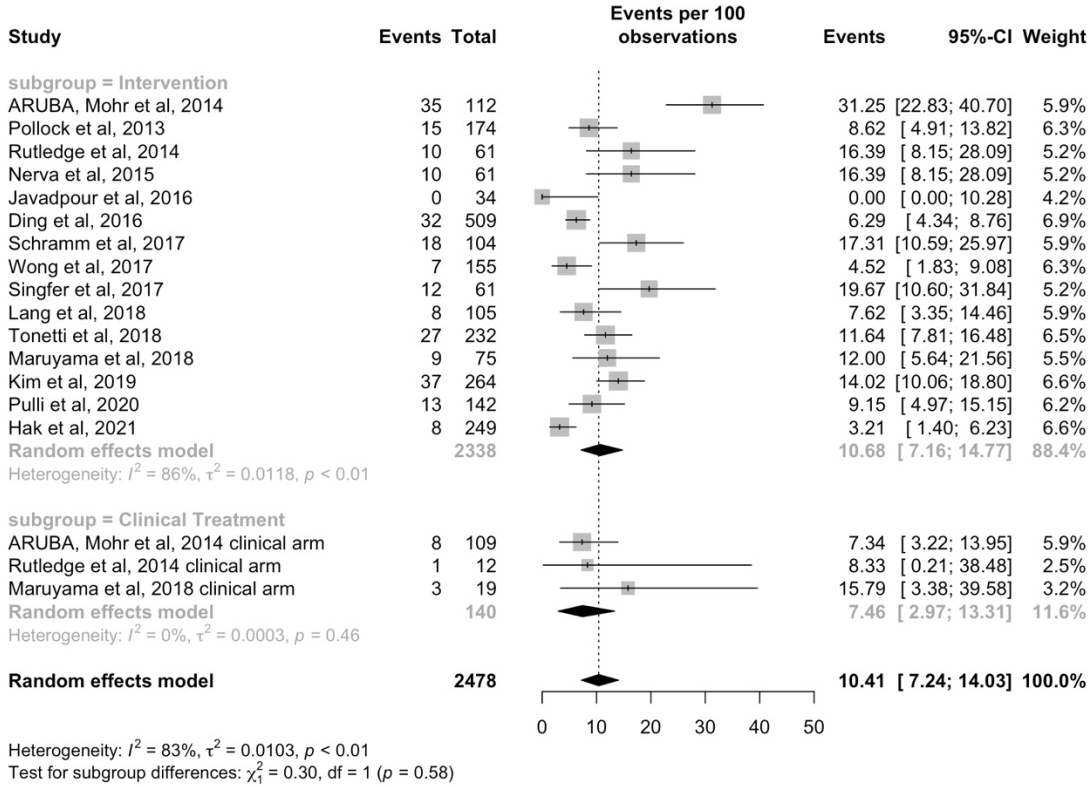

Figure 3: Forest plot comparing stroke and deficit incidence between clinical interventional and clinical treatment groups. No significant difference was identified (p=0.58)

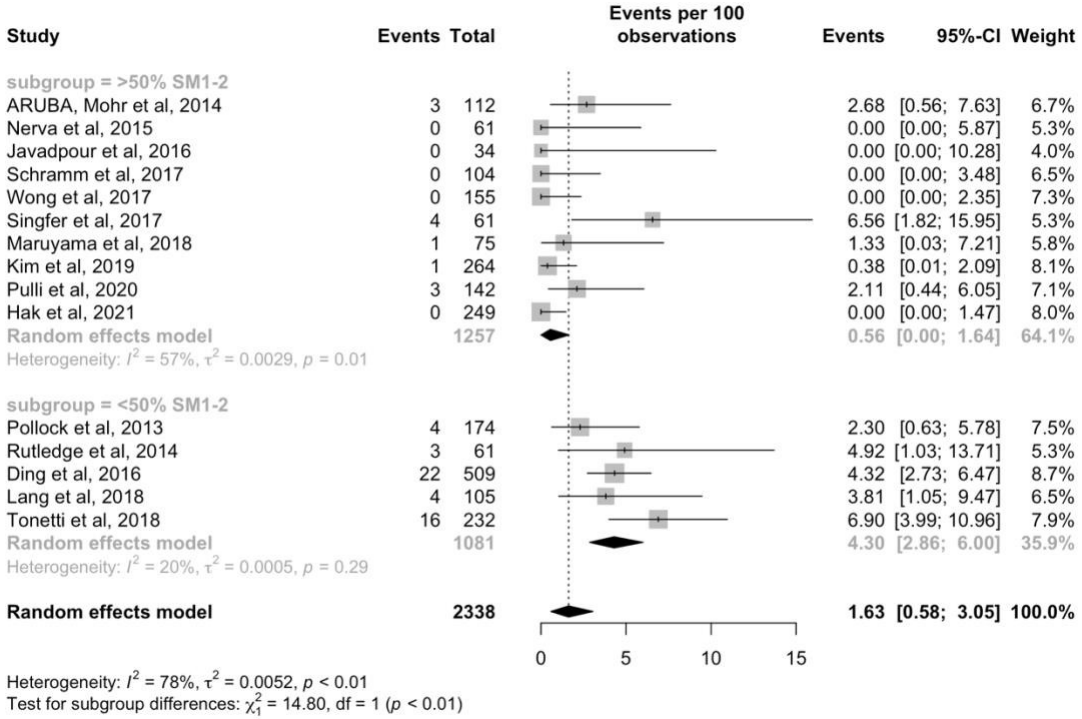

Figure 4: subgroup analysis of the interventional group. Mortality is statistically higher in studies with SM1-2 less than 50% (p<0,01)

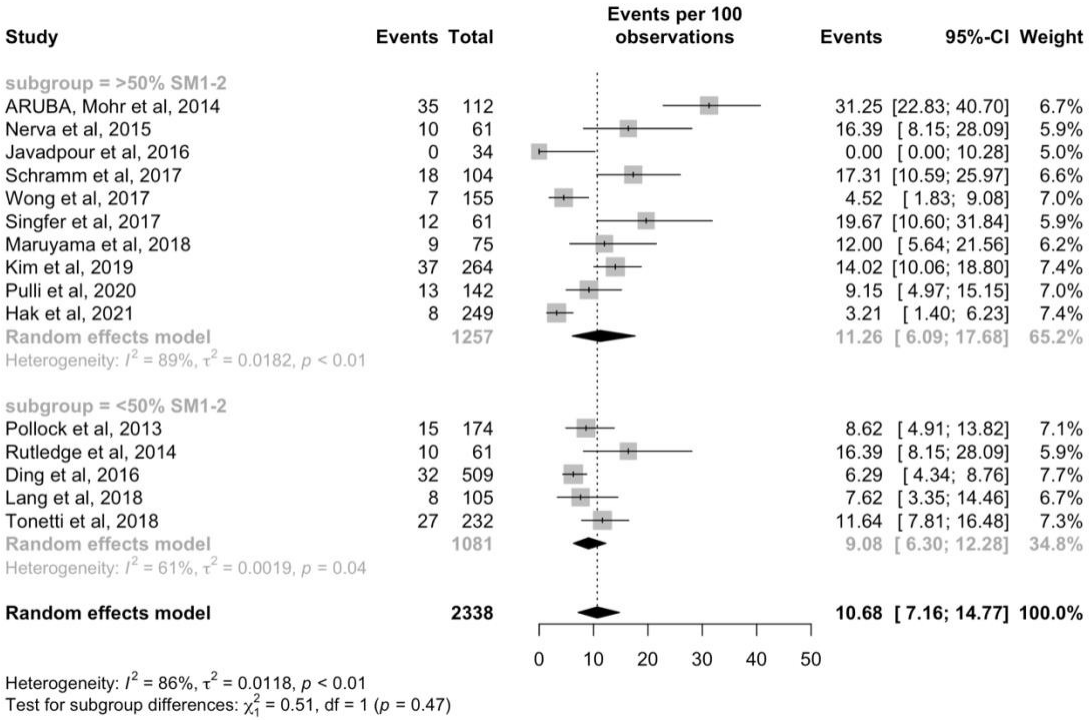

Figure 5: subgroup analysis of the interventional group. Incidences of stroke and deficit were similar in both groups.

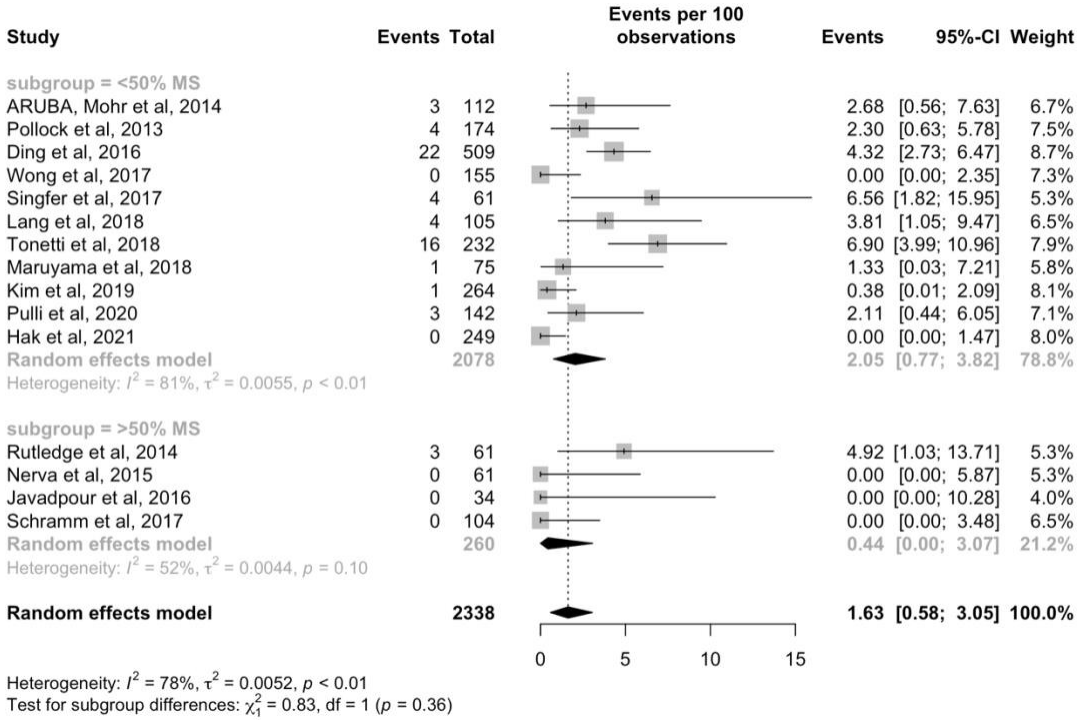

Figure 6: Subgroup analysis of the interventional group. Studies with more than 50% of microsurgery cases compared with studies with less than 50% of microsurgery cases. No statistically significant difference in mortality was identified. (p=0.36).

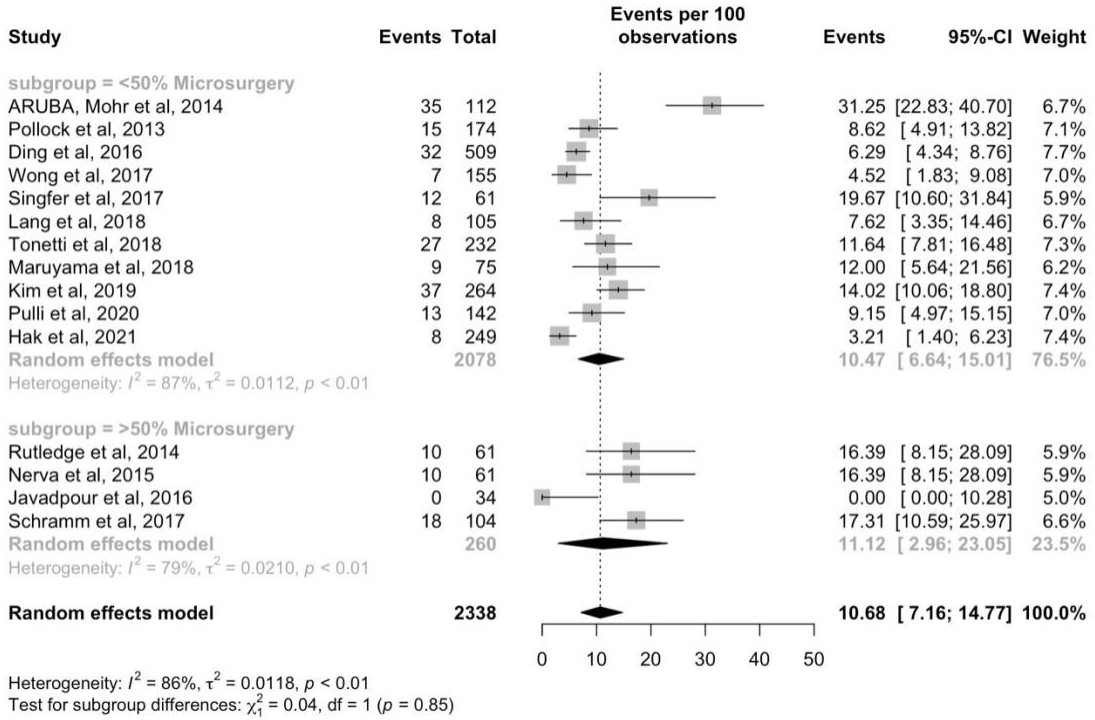

Figure 7: Subgroup analysis of the interventional group. Studies with more than 50% of microsurgery cases compared with studies with less than 50% of microsurgery cases. No statistically significant difference in stroke and deficit incidence was identified. (p=0.85).

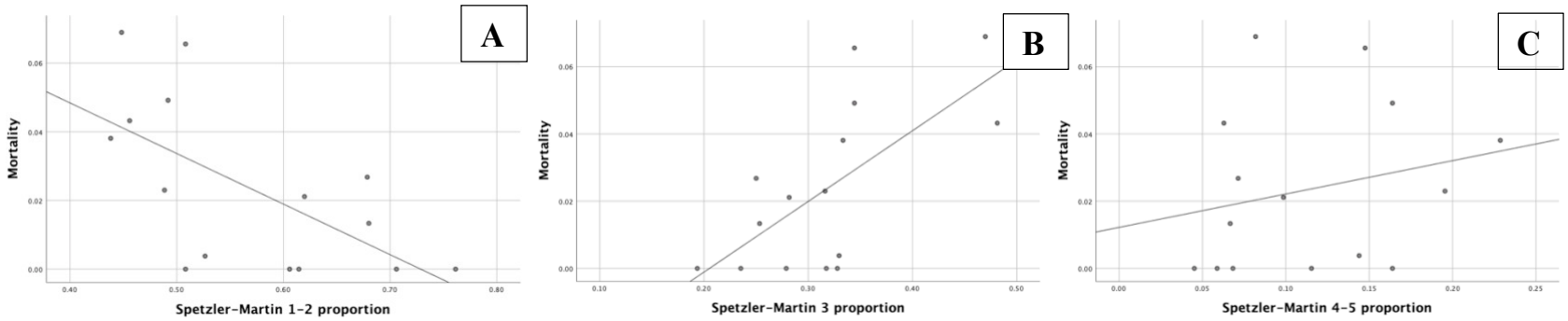

Figure 8: Graphic trends of mortality and SM classification: A) SM grade 1-2; B) grade 3 and C) grade 4-5.

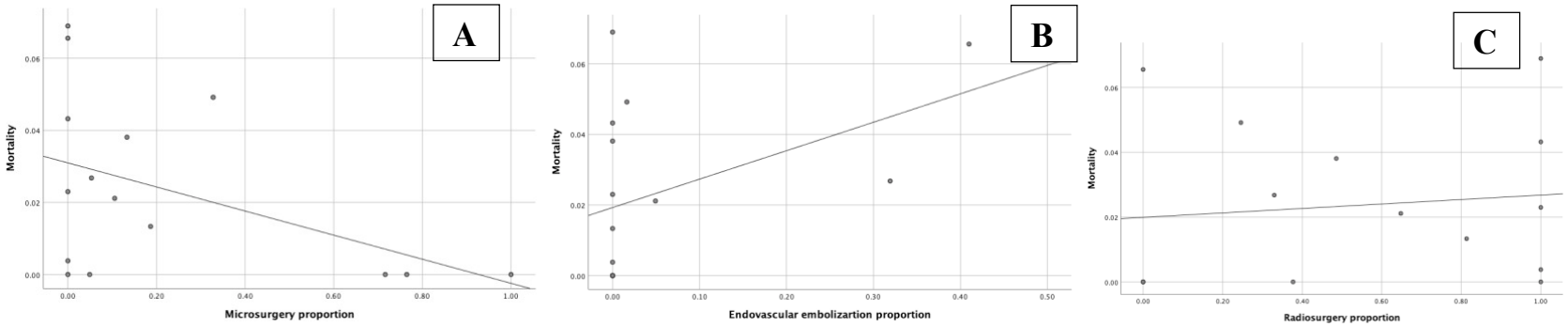

Figure 9: Graphic trends of mortality related to treatment technique applied. A best fit curve was applied to each of the scattered dot representation. A) Microsurgery; B) Endovascular Embolization; C) Radiosurgery

Table 1: Complete ARUBA eligibility criteria (Mohr, Parides et al. 2014)

Inclusion Criteria
1. Patient must have unruptured BAVM diagnosed by MRI/MRA, CTA and/or angiogram
2. Patient is 18 years of age or older
3. Patient has signed Informed Consent and Release of Medical Information and Health Insurance Portability and Accountability Act (HIPPA, US-only) Forms
Exclusion Criteria
1. Patient has BAVM presenting with evidence of recent or prior hemorrhage
2. Patient has received prior BAVM therapy (endovascular, surgical, radiotherapy)
3. Patient has BAVM deemed untreatable by local team, or has concomitant vascular or brain disease that interferes with/or contraindicates any interventional therapy type (stenosis/occlusion of neck artery)
4. Patient has baseline Rankin of ≥2
5. Patient has concomitant disease/ life expectancy to less than 10 years
6. Patient has thrombocytopenia (<100,000/μL)
7. Patient has uncorrectable coagulopathy (INR>1.5)
8. Patient is pregnant or lactating
9. Patient has known allergy against iodine contrast agents
10. Patient has known multiple-foci BAVMs
11. Patient has any form of arteriovenous or spinal fistulas
12. Patient has a diagnosed Vein of Galen type malformation
13. Patient has a diagnosed cavernous malformation
14. Patient has a diagnosed dural arteriovenous fistula
15. Patient has a diagnosed developmental venous anomaly
16. Patient has a diagnosed neurocutaneous syndrome such as cerebro-retinal angiomatosis (von Hippel-Lindau), encephalo-trigeminal syndrome (Sturge-Weber), or Wyburn-Mason syndrome
17. Patient has diagnosed BAVMs in context of moya-moya-type changes
18. Patient has diagnosed hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)

Table 2: Summary of the ARUBA eligible studies analyzed.

	Patients	MS (%)	EE(%)	RS(%)	MSEE(%)	RSMS(%)	EERS(%)	EERSMS(%)	Study	Design
ARUBA, Mohr et al, 2014	112	5	32	33	13	0	16	1	Multicenter	Prospective
Pollock et al, 2013	174	0	0	100	0	0	0	0	Multicenter	Retrospectiv
Rutledge et al, 2014	61	33	2	25	38	0	0	3	Single	Retrospectiv
Nerva et al, 2015	61	5	0	38	46	0	11	0	Single	Retrospectiv
Javadpour et al, 2016	34	76	0	0	24	0	0	0	Single	Retrospectiv
Ding et al, 2016	509	0	0	100	0	0	0	0	Multicenter	Retrospectiv
Schramm et al, 2017	104	100	0	0	0	0	0	0	Single	Retrospectiv
Wong et al, 2017	155	72	0	0	25	3	0	1	Single	Retrospectiv
Singfer et al, 2017	61	0	41	0	2	2	56	0	Single	Retrospectiv
Lang et al, 2018	105	13	0	49	27	0	7	5	Single	Retrospectiv
Tonetti et al, 2018	232	0	0	100	0	0	0	0	Single	Retrospectiv
Maruyama et al, 2018	75	19	0	81	0	0	0	0	Single	Retrospectiv
Kim et al, 2019	264	0	0	100	0	0	0	0	Single	Retrospectiv
Pulli et al, 2020	142	11	5	65	13	1	5	0	Single	Retrospectiv
Hak et al, 2021	249	0	0	100	0	0	0	0	Single	Retrospectiv

Treatment type: MS: microsurgery; EE: endovascular Embolization; RS: Radiosurgery

Table 3: Spetzler-Martin (SM) classification, neurologic deficit and mortality

Author, year	SM 1-2 (%)	SM 3 (%)	SM 4-5 (%)	Stroke-deficit (%)	Mortality (%)
ARUBA, Mohr et al, 2014	68	25	7	31	3
Pollock et al, 2013	49	32	20	9	2
Rutledge et al, 2014	49	34	16	16	5
Nerva et al, 2015	51	33	16	16	0
Javadpour et al, 2016	71	24	6	0	0
Ding et al, 2016	46	48	6	6	4
Schramm et al, 2017	61	28	12	17	0
Wong et al, 2017	76	19	5	5	0
Singfer et al, 2017	51	34	15	20	7
Lang et al, 2018	44	33	23	8	4
Tonetti et al, 2018	45	47	8	12	7
Maruyama et al, 2018	68	25	7	12	1
Kim et al, 2019	53	33	14	14	0
Pulli et al, 2020	62	28	10	9	2
Hak et al, 2021	61	32	7	3	0

Table 4: Modified Rankin Scale (mRS) distribution for each study

	Patients	MRS 0 or 1 (%)	MRS 2 to 6 (%)
ARUBA, Mohr et al, 2014	52	54	46
Pollock et al, 2013	174	91	9
Rutledge et al, 2014	61	87	13
Nerva et al, 2015	61	87	13
Javadpour et al, 2016	34	94	6
Ding et al, 2016	UA	UA	UA
Schramm et al, 2017	104	92	8
Wong et al, 2017	UA	UA	UA
Singfer et al, 2017	61	77	23
Lang et al, 2018	UA	UA	UA
Tonetti et al, 2018	UA	UA	UA
Maruyama et al, 2018	75	91	9
Kim et al, 2019	UA	UA	UA
Pulli et al, 2020	59	92	8
Hak et al, 2021	UA	UA	UA

UA: unavailable

Table 5: Summary of data for studies which presented clinical or non-intervention arm data

	Patients	SM1-2 (%)	SM3 (%)	SM4-5 (%)	Stroke-deficit (%)	Mortality (
ARUBA, Mohr et al, 2014	109	60 (55.0)	34 (31.2)	15 (13.7)	8 (7.3)	2 (1.8)
Rutledge et al, 2014	12	6 (50.0)	3 (25.0)	3 (25.0)	1 (8.3)	1 (8.3)
Maruyama et al, 2018	19	9 (47.4)	8 (42.1)	2 (10.5)	3 (15.8)	0 (0)

Table 6: Mortality per 100 cases. Comparison between groups.

	n	Estimated mortality	CI	I^2 (%)	p
Interventional	15	1.62	[0.5844; 3.0539]	77.7	0.7146
Clinical treatment	3	0.8408	[0.0000; 3.9569]	0	
SM1-2≥50%	10	0.55	[0.0049; 1.6439]	56.9	0.0001
SM1-2<50%	5	4.3	[2.8584; 5.9977]	19.6	
MS≥50%	4	0.43	[0.0000; 3.0712]	51.8	0.3632
MS<50%	11	2.05	[0.7669; 3.8162]	81.4	

n: number of studies; SM1-2≥50%: studies with 50% or more cases of Spetzler-Martin classification 1 or 2 (SM1-2); SM1-2<50%: studies with SM1-2 less than 50%; MS≥50: studies with 50% or more cases treated with microsurgery; MS<50%: studies with less than 50% cases treated with microsurgery. CI: 95% confidence interval; I^2: estimate of the fraction of variance due to heterogeneity

Table 7: Stroke and deficit per 100 cases. Comparison between groups.

	n	Estimated stroke-deficit	CI	I^2 (%)	p
Interventional	15	10.7	[7.1630; 14.7653]	85.6	0.5849
Clinical treatment	3	7.45	[2.9710; 13.3103]	0	
SM≥50%	10	11.2	[6.0890; 17.6759]	89.1	0.4736
SM<50%	5	9.1	[6.3005; 12.2821]	61.0	
MS≥50%	4	11.1	[2.9631; 23.0484]	78.8	0.8503
MS<50%	11	10.4	[6.6444; 15.0068]	87.1	

n: number of studies; SM1-2≥50%: studies with 50% or more of Spetzler-Martin classification 1 or 2 (SM1-2); SM1-2<50%: studies with SM1-2 less than 50%; MS≥50: studies with 50% or more of cases treated with microsurgery; MS<50%: studies with less than 50% of patients treated with microsurgery. CI: 95% confidence interval; I^2: estimate of the fraction of variance due to heterogeneity

Table 8: Pearson correlation coefficients for mortality and SM classification, stroke and deficit incidence, treatment modalities and mRS.

Mortality	SM1-2	SM3	SM4-5	Stroke and deficit	MS	EE	RS	MS+EE	RS+MS	EE+RS	EE+RS+MS	mRS 0-1	mRS
Pearson Correlation	-.628	.673	.229	.267	-.452	.423	.118	-.148	.017	.444	.289	-.386	.38
p	.012	.006	.411	.336	.091	.116	.675	.599	.952	.098	.295	.305	.30
N	15	15	15	15	15	15	15	15	15	15	15	9	9

SM: Spetzler-Martin classification; MS: microsurgery; EE: endovascular Embolization; RS: Radiosurgery