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Management of Adult Unruptured Brain Arteriovenous Malformations: An Updated Network Meta-Analysis

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The management of unruptured brain arteriovenous malformations (ubAVMs) is a complex challenge to neurovascular practitioners. This meta-analysis aimed to identify the optimal management of ubAVMs comparing conservative management, embolization, radiosurgery, microsurgical resection, and multimodality. The search strategy was developed a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the Ovid Medline, Embase, Web of Science, and Cochrane Library databases to identify relevant papers. Using R version 4.1.1., a frequentist network meta-analysis was conducted to compare different management modalities for the ubAVMs. Overall, the conservative group had the lowest risk of rupture (P-score=0.77), and the lowest rate of complications was found in the conservative group (P-score=1). Among different interventions, the multimodality group had the highest rupture risk (P-score=0.34), the lowest overall complications (P-score=0.75), the best functional improvement (P-score=0.65), and the lowest overall mortality (P-score=0.8). However, multimodality treatment showed a significantly higher risk of rupture (odds ratio [OR]=2.13; 95% confidence interval [95% CI]=1.18–3.86) and overall complication rate (OR=5.56; 95% CI=3.37–9.15) compared to conservative management; nevertheless, there were no significant differences in overall mortality or functional independence when considered independently. Conservative management is associated with the lowest rupture risk and complication rate overall. A multimodal approach is the best option when considering mortality rates and functional improvement in the context of existing morbidity/symptoms. Microsurgery, embolization, and radiosurgery alone are similar to the natural history in terms of functional improvement and mortality, but have higher complication rates.

Key Words: Arteriovenous malformation; A Randomized Trial of Unruptured Brain Arteriovenous Malformations; Neurosurgery

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INTRODUCTION

The management of unruptured brain arteriovenous malformations (ubAVMs) is a complex challenge to neurovascular practitioners. It has been estimated that the prevalence of bAVMs is 15 per 100,000 adults and that 2% of hemorrhagic strokes are owed to this disease.[1-4] Although only 1.3–4.12% of these lesions present as hemorrhagic episodes, previous studies have estimated that the mortality rate of bAVM rupture can be up to 10% following the first hemorrhage.[2,5,6] Additionally, 20% of survivors will die after 3 months, and around one-third suffer moderate disability.[7] Accordingly, while prudent management of these patients is essential and may be lifesaving, the decision regarding appropriate management needs to be weighed against treatment complications to ensure good outcomes and quality of life.

Many treatment options, including medical management, embolization, microsurgical resection, radiosurgery, and multimodal combinations, have been reported and validated among studies in the literature. Over decades, many studies have been conducted to compare the safety and efficacy of these various approaches for the management of ubAVMs. Perhaps most notably, the results of A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) showed that after a median follow-up duration of 33.2 months, there was a significant difference in terms of mortality and symptomatic stroke between patients that were managed with interventions compared to those who were conservatively treated with medical management (30.7% *vs.* 10.1%, respectively). In addition, the clinical impairment rate was also significantly higher in the interventions group compared to medical treatment. Therefore, it has been maintained that conservative management is a better modality for managing ubAVMs than other interventional approaches.[8] However, significant criticism has arisen from many real-world studies which yielded contrary results.[9-13]

Based on many of these findings, numerous subsequent studies sought to validate the best modality for intervention in selected patients and lesions. Some authors have estimated the rates of clinical impairment and mortality or symptomatic stroke to be 4–12%, and 10.3–11.5%, respectively, in patients that were managed with stereotactic radiosurgery.[14,15] Other authors have also reported that the rates of clinical impairment and mortality or symptomatic stroke were 6–13.8%, and 12.2–16.1%, respectively, in patients that were managed with microsurgical resection.[11,16-18] As a result of this ongoing conflict among the different studies, we performed the current meta-analysis to furtherly compare the different treatment modalities and determine the optimal management for ubAVMs.

METHODS

Search Strategy

The search strategy was developed a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Ovid Medline, Embase, Web of Science, and Cochrane Library databases were searched electronically starting from January 1st, 2000. This time period was selected to capture contemporary management results of ubAVMs in the most recent decade. To maximize the sensitivity of the search strategy, the following terms were used in combination: "brain," "cerebral," "AVM," or "arteriovenous malformation." Specifically, we did not use any search terms related to types of treatment, so as not to miss any studies. The search was limited to the English language and human subjects. In addition, the references of included publications were searched manually for other relevant papers. The list of all retrieved articles was systematically assessed using the inclusion and exclusion criteria separately in parallel between 2 teams of 2 authors, and any disagreements were solved through discussion or third-party input.

Selection Criteria

Two reviewers independently screened titles, abstracts, and subject headings for eligible publications according to the predefined criteria. Studies were included if they were randomized or had an observational prospective or retrospective study design that reported primary, secondary, or tertiary outcomes specifically or separately for ubAVMs at any follow-up period. Studies with fewer than 15 patients with ubAVMs were excluded. Abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded. If institutions published multiple studies with accumulating numbers of patients and/or increased length of follow-up, the most complete study with the largest cohort was included for analysis.

Data Extraction and Outcomes of Interest

For each study, 2 independent reviewers extracted the data from the full text of eligible studies by using a Microsoft Excel

spreadsheet which was developed under pilot extraction. All conflicts were discussed, and a final decision was reached. The primary outcome of interest was the risk of rupture following treatment; this was averaged as rupture risk per year. We used the rupture risk per year provided by the included studies and excluded those with crude values from the analysis due to the considerable heterogeneity in follow-up duration. The secondary outcome was the functional outcome after treatment of an unruptured AVM, as measured by modified Rankin score (mRS), Glasgow Outcome Scale (GOS), or GOS Extended (GOSE). Due to discrepancies in reporting among the studies, functional outcomes were dichotomized as favorable (mRS 0–2, GOS 4–5, GOSE 5–8), or unfavorable (mRS 3–6, GOS 1–3, GOSE 1–4) at the latest reported follow-up.[19] Tertiary outcomes included radiographic occlusion rates, complication rates, and rate of improvement in presenting symptoms.

Statistical Analysis

All analyses were performed using R version 4.1.1. A frequentist network meta-analysis was conducted using the "netmeta" package to compare different management modalities for the ubAVMs.[20] Random-effects or fixed-effects model network meta-analyses were used based on the heterogeneity levels, assessed using Q-statistics with I^2>50% or P-value<0.05 considered significant. Whenever heterogeneity was present, splitting of direct and indirect comparisons was done to explore any possible sources.[21] The ranking of treatment was based on P-score, which is the frequentist approach analog to surface under the cumulative ranking (SUCRA).[22] To assess the risk of bias and small-study effects (with ≥10 studies included), comparison-adjusted funnel plots were developed, and the funnel plot asymmetry was assessed with the Egger's regression test (P-value<0.1 considered significant).[21,23,24] Moreover, partial treatment ranking was used to order treatments based on the combined ranking of risk of rupture and complication rate (the 2 outcomes with statistically significant differences) and the combined ranking of mortality and mRS functional improvement.[25]

Risk of Bias Assessment

Three reviewers assessed the quality of included studies using a scoring system and quality rating, resolving conflicts by discussion. The tool for assessing risk of bias in non-random-

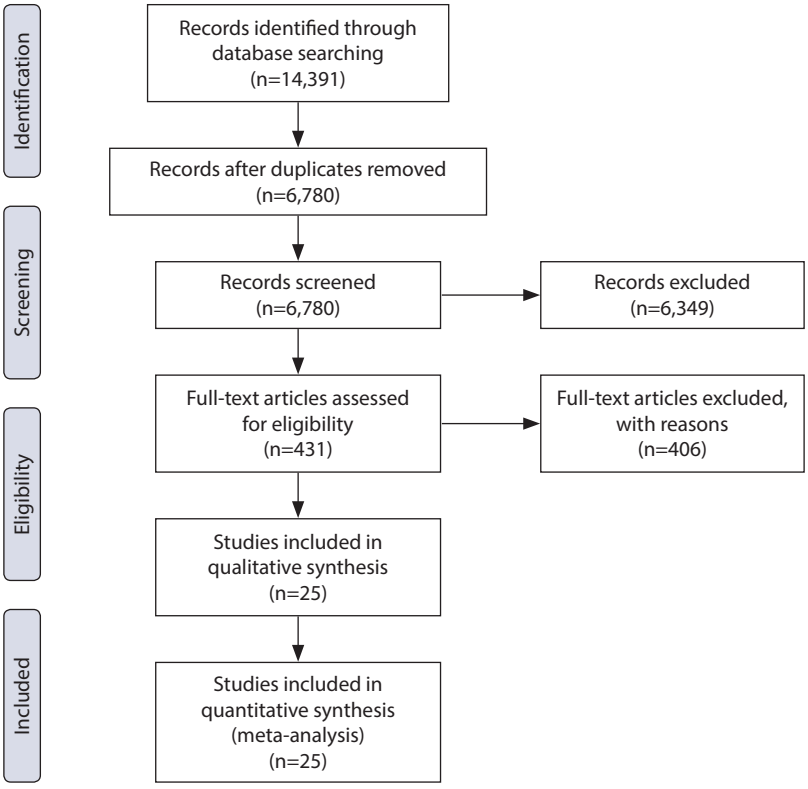

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

ized studies of interventions (ROBINS-I) was used to evaluate the observational studies.[26] Since 1 study[8] was a randomized controlled trial, it was assessed using the revised tool for assessing the risk of bias in randomized trials.[27]

RESULTS

Search Results

In total, 431 articles were eligible for full-text screening. An overall number of 25 articles were included after the full-text screening, excluding 406 articles as listed in the PRISMA flow chart (Fig. 1).

Study Characteristics and Risk of Bias

We listed the characteristics of the included studies in Supplementary Tables 1 and 2. The interventions of the studies were microsurgical resection, embolization, radiosurgery, and multimodality. Interventions were compared to conservative/medical treatment regarding the risk of rupture, functional outcome, complications, and mortality rates. The total sample size of the included studies had 9,662 patients; 24 articles were observational studies, while 1 study was a randomized control trial.

The overall risk of bias in most of the observational studies was moderate, with only 2 studies[28,29] showing a critical risk of bias (Supplementary Fig. 1). Most of the bias was identified due to possible cofounding factors and, to a much lesser extent, missing data. For the only randomized controlled trial (RCT) included,[8] there was a low risk of bias in all assessed domains.

Risk of Rupture

A total of 12 studies reported a risk of rupture; 263 of 2,862 patients experienced rupture. Each arm of the pairwise comparisons was composed of a different number of studies, giving an asymmetrical network plot (Supplementary Fig. 2A). The conservative group had the lowest risk of rupture (P-score=0.77), followed by microsurgical resection (P-score=0.54), radiosurgery (P-score=0.43), embolization (P-score=0.42), and multimodality group (P-score=0.34), respectively. Compared to conservative management, only multimodality treatment showed a significantly higher risk of rupture (odds ratio [OR]=2.13; 95% confidence interval [95% CI]=1.18–3.86) (Table 1). In addition, there was neither a risk of bias, as assessed by Egger's regression test (P-value=0.65), nor a heterogeneity/inconsistency among the included studies (tau^2=0.37, I^2=44.2%, P-value=0.11).

Table 1. Network analysis for risk of rupture (lower half) and mRS functional improvement (upper half), interventions compared to conservative treatment*

Microsurgical resection	0.96 (0.28–3.31)	1.01 (0.33–3.05)	1.27 (0.26–6.28)	0.43 (0.05–3.86)
0.86 (0.33–2.19)	Embolization	1.05 (0.49–2.26)	1.32 (0.17–10.00)	0.45 (0.04–4.84)
0.87 (0.34–2.26)	1.02 (0.46–2.25)	Radiosurgery	1.26 (0.18–8.84)	0.43 (0.04–4.24)
0.78 (0.08–7.79)	0.91 (0.08–9.96)	0.89 (0.09–9.29)	Multimodality	0.34 (0.02–5.13)
1.66 (0.18–15.36)	1.94 (0.19–19.68)	1.90 (0.20–18.33)	2.13 (1.18–3.86)†	Conservative

mRS, modified Rankin score.
*Treatment groups are reported in order of efficacy/safety ranking according to P-scores. Comparisons should be read from left to right. Odds ratio above one favors the row-defining treatment. †Statistically significant.

Table 2. Network analysis for overall complications rate (lower half) and overall mortality rate (upper half), interventions compared to conservative treatment*

Microsurgical resection	0.57 (0.12–2.71)	0.54 (0.13–2.24)	1.33 (0.18–9.83)	0.40 (0.06–2.93)
1.61 (0.93–2.81)	Embolization	0.95 (0.33–2.77)	2.34 (0.24–22.80)	0.72 (0.08–6.69)
0.97 (0.55–1.70)	0.60 (0.33–1.10)	Radiosurgery	2.46 (0.30–20.43)	0.75 (0.09–5.95)
4.04 (2.23–7.30)†	2.50 (1.29–4.84)†	4.16 (2.32–7.46)†	Multimodality	0.31 (0.15–0.64)
22.44 (10.35–48.68)†	13.90 (6.08–31.78)†	23.12 (10.73–49.80)†	5.56 (3.37–9.15)†	Conservative

*Treatment groups are reported in order of efficacy/safety ranking according to P-scores. Comparisons should be read from left to right. Odds ratio above one disfavors the row-defining treatment . †Statistically significant.

Modified Rankin Score Functional Improvement

Eight studies reported the mRS as the primary assessed functional outcome, which reported an improvement in 1,626 out of 2,000 patients. The asymmetrical network plot of pairwise comparisons is shown in Supplementary Fig. 2B. The highest improvement rate was in the multimodality group (P-score=0.65), followed by radiosurgery (P-score=0.56), microsurgical resection (P-score=0.55), embolization (P-score=0.52) and conservative groups (P-score=0.23), respectively. However, there were no significant differences among different treatment groups, as shown in Table 1. There was no heterogeneity or inconsistency found in the conducted analysis (tau^2=0, I^2=0.0%, P-value=0.79).

Overall Rate of Complications

A total of 17 studies reported an overall rate of complications, in which 529 out of 3,163 patients were reported to have complications. The number of studies forming each arm of pairwise comparisons is shown in Supplementary Fig. 2C. The lowest rate of complications was found in the conservative group (P-score=1), followed by multimodality (P-score=0.75), embolization (P-score=0.48), microsurgical resection (P-score=0.15), and radiosurgery groups (P-score=0.13), respectively. As shown in Table 2, compared

Table 3. Availability of primary and secondary outcomes included in the analysis in the studies

Study	Intervention type	Outcomes			
		Primary outcomes		Secondary outcomes	
		mRS functional improvement	Overall rate of complications	Risk of rupture	Mortality rate
Al-Shahi Salman (2014; Scotland)[S1]	Multimodality	Yes	Yes	Yes	Yes
Bervini (2014; Australia)[S2]	Microsurgical resection	No	Yes	No	Yes
Ding (2016; USA)[14]	Radiosurgery	Yes	Yes	Yes	Yes
Ding (2017; USA, Canada)[35]	Radiosurgery	Yes	Yes	Yes	Yes
Halim (2004; USA)[S3]	Unknown	Yes	No	Yes	No
Hanakita (2016; Japan)[S4]	Radiosurgery	Yes	Yes	Yes	No
Javadpour (2016; UK)[17]	Microsurgical resection	N/A	Yes	No	Yes
Jiao (2018; China)[S5]	Microsurgical resection	N/A	No	No	No
Kim (2014; USA, Scotland)[5]	Conservative	Yes	No	Yes	No
Koltz (2013; USA)[S6]	Radiosurgery	N/A	Yes	No	Yes
Laakso (2011; Finland)[S7]	Conservative	Yes	No	Yes	No
Lang (2018; USA)[S8]	Multimodality	Yes	Yes	Yes	Yes
Link (2018; USA)[13]	Multimodality	N/A	Yes	No	Yes
Lv (2010; China)[S9]	Embolization	Yes	Yes	Yes	Yes
Lv (2012; China)[29]	Embolization	Yes	No	Yes	Yes
Mohr (2014; Germany)[8]	Multimodality	Yes	Yes	Yes	Yes
Nerva (2015; USA)[S10]	Microsurgical resection +/– embolization	Yes	Yes	Yes	Yes
Nerva (2018; USA)[S11]	Radiosurgery	Yes	Yes	Yes	Yes
Pollock (2013; USA)[15]	Radiosurgery	Yes	Yes	Yes	Yes
Potts (2015; USA)[28]	Microsurgical resection	N/A	No	No	Yes
Rutledge (2014; USA)[11]	Multimodality	Yes	No	Yes	Yes
Singfer (2017; Belgium)[51]	Embolization	Yes	Yes	Yes	Yes
Thenier-Villa (2017; Spain)[S12]	Radiosurgery	Yes	No	Yes	No
Yang (2009; South Korea)[S13]	Radiosurgery +/– embolization	Yes	Yes	Yes	No

mRS, modified Rankin score; N/A, not applicable.

to conservative treatment, the complication rate was higher in all other treatment modalities. Compared to multimodality management, microsurgical resection (OR=4.04; 95% CI=2.23–7.30), embolization (OR=2.50; 95% CI=1.29–4.84), and radiosurgery (OR=4.16; 95% CI=2.32–7.46) had higher complication rates. There was no significant risk of bias, as assessed by Egger's test (P-value=0.12), and no heterogeneity/inconsistency was found (tau^2=0.17, I^2=38%, P-value=0.12).

Mortality Rate

A total of 10 studies reported a mortality rate with a reported 120 deaths out of 2,967 individuals. The number of studies forming each arm of pairwise comparisons is shown in Supplementary Fig. 2D. The lowest rate of mortality was found in the multimodality group (P-score=0.8), followed by microsurgical resection (P-score=0.69), embolization (P-score=0.4), radiosurgery (P-score=0.37) and conservative groups (P-score=0.24), respectively. Nevertheless, no significant differences in mortality rates were found among any of the compared groups (Table 2). Additionally, there was no significant risk of bias as assessed by Egger's test (P-value=0.10), and no heterogeneity/inconsistency was found among the included studies (tau^2=0.49, I^2=30.4%, P-value=0.22).

Combined Ranking of Treatments

Ranking of the combined risk of overall complications and risk of rupture in different treatment groups showed that conservative treatment was the best, followed by the multimodality group, embolization, microsurgical treatment, and radiosurgery, respectively (Supplementary Fig. 3A). In contrast, the combined ranking of treatments based on mortality and mRS functional improvement showed that the multimodality group was associated with the best outcome, followed by microsurgical treatment, embolization, radiosurgery, and conservative management, respectively (Supplementary Fig. 3B). In Table 3, we listed the primary and secondary outcomes included in the analysis and the availability of each item from the studies.

DISCUSSION

In the present meta-analysis, we aimed to determine the optimal management for ubAVMs by comparing conservative embolization, radiosurgery, and microsurgical resection based on the results of the included studies in the literature. Our results indicate that conservative management has the lowest risk of rupture, followed by microsurgical resection, radiosurgery, embolization, and multimodal management, respectively. It also has the lowest rate of overall complications. On the other hand, the results were comparable among all groups in terms of functional improvement and overall mortality, differing from the conclusions reported from the ARUBA trial.[9-13,30,31]

Evidence in the literature shows that unruptured lesions are associated with higher treatment-related morbidity rates compared to ruptured lesions.[8,32] This may be related to their asymptomatic course and, thus, difficulty in choosing a definitive management option. Therefore, adequate assessment of the benefit/risk ratio of the different management modalities compared with the risk of the spontaneous course of the disease is essential in cases of ubAVMs before initiating management approaches. The complication rates for the different treatment modalities might be associated with the initial presentation of the included patients in a certain study. For instance, it has been reported that having seizures and epilepsy might be attributed to post-treatment complications. Moreover, prior research also indicates that lower frequencies of new neurological deficits post-treatment might be associated with younger patients (<40 years old), type 3A lesions, small-sized AVMs (<3 cm), and having an initial presentation with hemorrhage. Type 3A or "III-", as described by Lawton et al.,[33] refers to small, eloquent lesions with deep venous drainage (S1E1V1). However, it was also reported that the size is not important, and the reported association of type 3A lesions with worsened surgical outcomes lacks further evidence.[34] Accordingly, it has been suggested that unruptured type 3A lesions, especially those involving the cerebellum, should be managed using radiation therapy.[34,35]

It is now well known that surgical resection, radiosurgery, or embolization might not be suitable options for large and highly eloquent (thalamic, basal ganglia, or brain stem) AVMs, and therefore, multimodal management can be the best option in such cases.[36] Although it has been reported that hypofractionated stereotactic radiotherapy, or stereotactic radiotherapy alone or in combination with surgical resection or embolization are validated for the management of difficult-to-manage AVMs, many studies have demonstrated that the obtained obliteration rate usually did not exceed 50%.[37-42] In contrast, it has been indicated in the ARUBA study that the rates of complications were higher in the combined non-mi-

crosurgical management modalities.[8] It has also been suggested that using multimodal approaches should be avoided because of the high rates of complications and mortality, and instead, a single moderately effective approach should be used, although complete obliteration rates may not be obtained using such modalities.[8,43,44] In the current study, the multimodal treatment group experienced the lowest complications among interventions, but it was significantly higher compared to conservative treatment. Therefore, the decision to use a multimodal approach should be carefully weighed due to the risk of rupture and comparable functional outcomes compared to conservative management.

There is also contradicting evidence regarding whether surgical resection should be used for managing silent or ubAVMs. Abla et al.[45] previously suggested that surgical resection in these patients might halt the development of rupture and, therefore, might be associated with more beneficial outcomes. However, some patients might suffer from post-treatment neurological deficits despite presenting as neurologically intact. Accordingly, it has been suggested that surgical approaches should be used with caution, and clinicians should carefully assess each case.[46] It has been reported that a 2% bleeding rate per year is an acceptable rate to recommend surgery in patients with unruptured AVMs.[47,48] Considerations should be given to the angioarchitecture and eloquence to avoid the potential development of complications.[49,50]

Embolization agents Onyx and N-butyl cyanoacrylate (NBCA) demonstrate promising yet differing outcomes in the management of ubAVMs, as NBCA was found to have a lower cure rate compared to Onyx.[29] High occlusion rates are noted with Onyx, used alone or in combination with stereotactic radiosurgery.[39,51] Utilizing combined embolization and stereotactic radiosurgery was found to be more efficacious than radiosurgery alone for large AVMs.[38,39] However, the presence of complications, like minor post-embolization recanalization and transient neurological deficits, necessitate caution and further research.[38]

The findings of the current meta-analysis may be limited by the non-randomized design of most of the included studies. There is a risk of selection bias, as some of the included patients within the intervention groups might have been younger in age, presented with smaller AVMs, or been more likely to present with seizures. There were some limitations in the meta-analysis. Although there was no statistical risk of bias, limitations related to patients' enrollment capacity and associated selection bias should be considered. Secondly, according to the Spetzler and Martin grading, subgroup analysis was not possible due to the absence of proper stratification of different outcomes according to Spetzler and Marting grading in their cohort.

CONCLUSION

Our analysis indicates that among the different treatment modalities for ubAVMs, conservative management is associated with the lowest risk of rupture and overall complications. However, a multimodal approach is the best option when considering mortality rates and functional improvement in the context of existing morbidity/symptoms. Microsurgery, embolization, and radiosurgery are similar to conservative management in terms of functional improvement and mortality, but have higher complication rates. Therefore, the optimal treatment modality, between multimodal or conservative management, is contingent upon individual patient characteristics and clinical judgment, carefully weighing the risk of rupture, potential for functional improvement, and risk of complications. If only one treatment modality is available (i.e., no multimodal option), results are likely to be inferior to natural history. Further RCTs are necessary to strengthen these findings and establish more definitive treatment guidelines for ubAVMs.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.5469/neuroint.2023.00171.

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Conflicts of Interest
The authors have no conflicts to disclose.

Author Contributions

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Supplementary Table 1. Baseline characteristics of the included studies

Study	Intervention type	Control/ comparison type	Study design	Study setting (for observational studies)	Inclusion criteria described	Exclusion criteria described	Overall sample size	Average/ last follow-up (mo)
Al-Shahi Salman (2014; Scotland)[S1]	Multimodality	Conservative/ medical	Observational	Prospective	Yes	Yes	204	82.8
Bervini (2014; Australia)[S2]	Microsurgical resection	Conservative/ medical	Observational	Prospective	Yes	Yes	377	9
Ding (2016; USA)[14]	Radiosurgery	N/A	Observational	Retrospective	Yes	Yes	509	86
Ding (2017; USA, Canada)[35]	Radiosurgery	N/A	Observational	Retrospective	Yes	Yes	232	90.5
Halim (2004; USA)[S3]	Unknown	Ruptured	Observational	Retrospective	No	No	793	120
Hanakita (2016; Japan)[S4]	Radiosurgery	N/A	Observational	Retrospective	No	No	292	62
Javadpour (2016; UK)[17]	Microsurgical resection	Multimodality	Observational	Retrospective	Yes	Yes	143	69
Jiao (2018; China)[S5]	Microsurgical resection	N/A	Observational	Retrospective	No	No	201	14.2
Kim (2014; USA, Scotland)[5]	Conservative	Ruptured	Observational	Mixed	Yes	Yes	5,050	Variable
Koltz (2013; USA)[S6]	Radiosurgery	Ruptured	Observational	Retrospective	No	No	102	102
Laakso (2011; Finland)[S7]	Conservative	Ruptured	Observational	Prospective	Yes	No	63	132
Lang (2018; USA)[S8]	Multimodality	Radiosurgery+ embolization	Observational	Retrospective	Yes	Yes	105	43
Link (2018; USA)[13]	Multimodality	N/A	Observational	Prospective	Yes	Yes	86	At least 6 months
Lv (2010; China)[S9]	Embolization	Ruptured	Observational	Retrospective	No	No	144	82.8
Lv (2012; China)[29]	Embolization	Ruptured	Observational	Retrospective	No	No	147	67.2
Mohr (2014; Germany)[8]	Multimodality	Conservative/ medical	RCT	Prospective	Yes	Yes	223	32.9
Nerva (2015; USA)[S10]	Microsurgical resection +/– embolization	Radiosurgery +/– embolization	Observational	Retrospective	Yes	Yes	61	15.6
Nerva (2018; USA)[S11]	Radiosurgery	Ruptured	Observational	Retrospective	Yes	No	70	51.6
Pollock (2013; USA)[15]	Radiosurgery	N/A	Observational	Prospective	Yes	Yes	174	64
Potts (2015; USA)[28]	Microsurgical resection	Ruptured	Observational	Prospective	No	No	232	20.4
Rutledge (2014; USA)[11]	Multimodality	Conservative/ medical	Observational	Prospective	Yes	Yes	74	21
Singfer (2017; Belgium)[51]	Embolization	N/A	Observational	Prospective	Yes	No	61	60
Thenier-Villa (2017; Spain)[S12]	Radiosurgery	Ruptured	Observational	Retrospective	Yes	No	195	121.91
Yang (2009; South Korea)[S13]	Radiosurgery +/– embolization	Ruptured	Observational	Prospective	Yes	No	46	66.5
Yang (2012; South Korea)[S14]	Radiosurgery	N/A	Observational	Prospective	Yes	Yes	78	92.5

N/A, not applicable; RCT, randomized controlled trial.

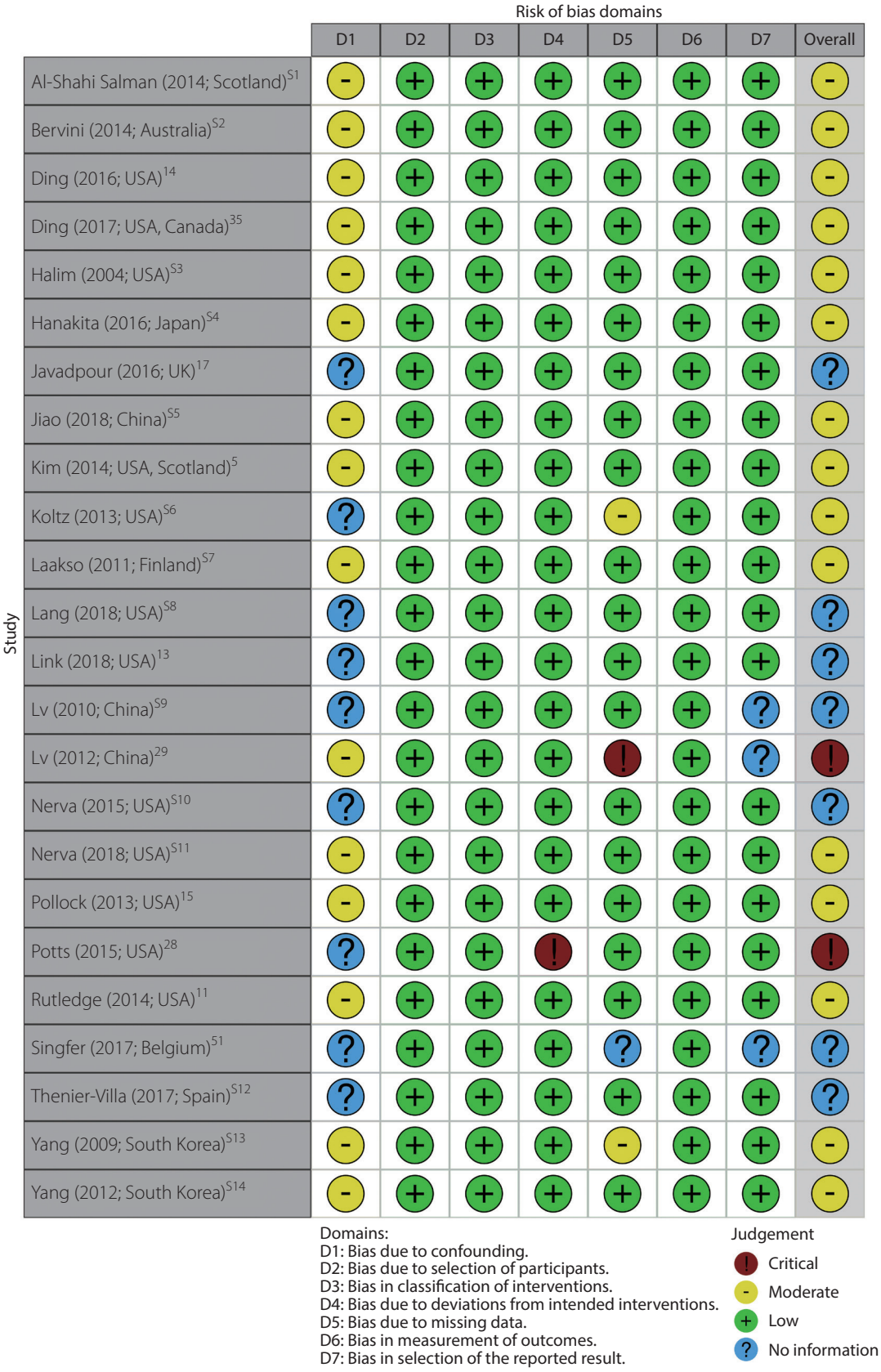
Supplementary Table 2. Demographics of the included studies

Study	Age		Sex (%)		Initial presentation/events (%)				Associated aneurysms (%)	Drainage		Location				Size			Spetzler–Martin Grade				
	Mean	SD	Male	Female	Hemorrhage	Seizure	Headache	Other		Superficial (%)	Deep (%)	Supratentorial, lobar (%)	Thalamus or basal ganglia (%)	Brain stem (%)	Cerebellum (%)	<3 (%)	3–6 (%)	>6 (%)	I (%)	II (%)	III (%)	IV (%)	V (%)
Al-Shahi Salman (2014; Scotland)[S1]	46.9	15.7	121 (59.3)	83 (40.7)	N/A	85 (41.7)	N/A	18 (8.8)	46 (22.5)	99 (48.5)	10 (4.9)	187 (91.7)	10 (4.9)	4 (2.0)	3 (1.5)	95 (46.6)	79 (38.7)	8 (3.9)	30 (14.7)	51 (25.0)	41 (20.1)	18 (8.8)	2 (1.0)
Bervini (2014; Australia)[S2]	37.4	15.6	198 (52.5)	179 (47.5)	N/A	196 (52.0)	N/A	63 (16.7)	119 (31.6)	N/A	42 (11.1)	354 (93.9)	N/A	N/A	N/A	126 (33.4)	217 (57.6)	34 (9.0)	N/A	N/A	N/A	N/A	N/A
Ding (2016; USA)[14]	39.7	13.7	238 (46.8)	271 (53.2)	N/A	103 (20.2)	86 (16.9)	46 (9.0)	50 (9.8)	N/A	350 (68.8)	226 (44.4)	134 (26.3)	60 (11.8)	48 (9.4)	N/A	N/A	N/A	49 (9.6)	183 (36.0)	245 (48.1)	32 (6.3)	N/A
Ding (2017; USA, Canada)[35]	41.8	14.2	111 (47.8)	121 (52.2)	N/A	49 (21.1)	41 (17.7)	23 (9.9)	25 (10.8)	N/A	85 (36.6)	142 (61.2)	15 (6.5)	13 (5.6)	35 (15.1)	N/A	N/A	N/A	49 (21.1)	183 (78.9)	N/A	N/A	N/A
Halim (2004; USA)[S3]	37	20	382 (49)	390 (51)	367 (46.3)	190 (24)	114 (14)	119 (15)	N/A	N/A	89 (20)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hanakita (2016; Japan)[S4]	N/A	N/A	187 (64)	105 (36)	N/A	177 (40)	54 (18)	32 (11)	N/A	N/A	N/A	245 (83.9)	17 (5.8)	8 (2.7)	11 (3.8)	N/A	N/A	N/A	84 (29)	115 (39)	69 (24)	15 (5)	N/A
Javadpour (2016; UK)[17]	39	13	16 (47)	18 (53)	N/A	23 (68)	7 (21)	N/A	N/A	N/A	8 (23)	N/A	N/A	N/A	N/A	23 (68)	N/A	N/A	8 (23)	16 (47)	8 (23)	2 (6)	N/A
Jiao (2018; China)[S5]	28.8	12.9	127 (63.2)	74 (36.8)	48 (23.9)	N/A	N/A	N/A	N/A	178 (88.6)	23 (11.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kim (2014; USA, Scotland)[5]	37.2	17.8	2,502 (50)	2,548 (50)	2,272 (45)	N/A	N/A	N/A	864 (17)	N/A	736 (15)	2,442 (48)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Koltz (2013; USA)[S6]	38	N/A	44 (43)	58 (57)	41 (40)	21 (21)	18 (18)	4 (4)	N/A	N/A	N/A	N/A	N/A	4 (4)	4 (4)	54 (53)	N/A	N/A	5 (5)	28 (27)	43 (42)	22 (21)	4 (4)
Laakso (2011; Finland)[S7]	32.1	16.8	40 (63)	23 (37)	32	N/A	3 (5)	25 (40)	N/A	N/A	24 (38)	N/A	N/A	N/A	N/A	N/A	29 (46)	34 (54)	N/A	N/A	N/A	50 (79)	13 (21)
Lang (2018; USA)[S8]	43	13	43 (41)	62 (59)	N/A	35 (33)	57 (54)	45 (43)	N/A	65 (62)	40 (38)	71 (68)	17 (16)	2 (2)	14 (13)	55 (52)	48 (46)	2 (2)	15 (14)	31 (30)	35 (33)	23 (22)	1 (1)
Link (2018; USA)[13]	43.6	14.6	45 (52.3)	41 (47.7)	N/A	35 (40.7)	44 (51.2)	44 (51.2)	15 (17.4)	N/A	23 (26.7)	N/A	N/A	N/A	6 (7)	52 (61.9)	31 (36.9)	1 (1.2)	16 (18.6)	35 (40.7)	29 (33.7)	6 (7)	N/A
Lv (2010; China)[S9]	27.9	12	92 (63.9)	52 (36.1)	62 (43.1)	45 (29.2)	25 (17.4)	12 (8.3)	N/A	N/A	25 (17.4)	134 (90.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lv (2012; China)[29]	27.5	11.1	87 (59.2)	60 (40.8)	69 (46.9)	N/A	N/A	N/A	14 (9.5)	N/A	48 (32.6)	135 (91.8)	N/A	N/A	N/A	N/A	N/A	N/A	5 (3.4)	19 (12.9)	53 (36.1)	47 (32)	23 (15.6)

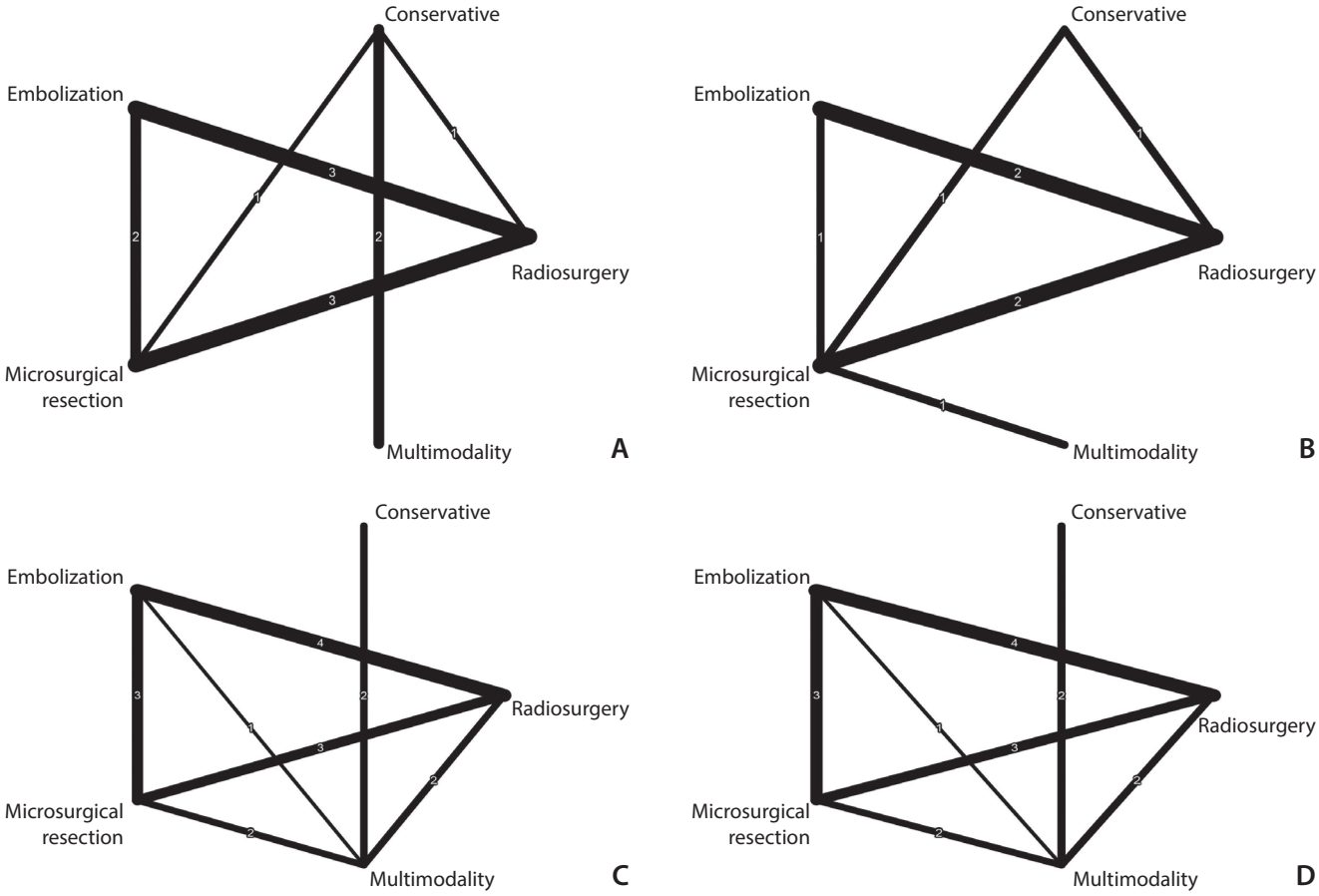
Supplementary Table 2. Continued

Study	Age		Sex (%)		Initial presentation/events (%)				Associated aneurysms (%)	Drainage		Location				Size			Spetzler–Martin Grade				
	Mean	SD	Male	Female	Hemorrhage	Seizure	Headache	Other		Superficial (%)	Deep (%)	Supratentorial, lobar (%)	Thalamus or basal ganglia (%)	Brain stem (%)	Cerebellum (%)	<3 (%)	3–6 (%)	>6 (%)	I (%)	II (%)	III (%)	IV (%)	V (%)
Mohr (2014; Germany)[8]	44.5	12.3	131 (59)	92 (41)	N/A	95 (43)	115 (52)	42 (19)	36 (16)	147 (66)	74 (33)	203 (91)	N/A	N/A	N/A	138 (62)	N/A	N/A	65 (29)	71 (32)	62 (28)	23 (10)	N/A
Nerva (2015; USA)[S10]	40	15	32 (52)	29 (48)	N/A	24 (39)	27 (44)	12 (20)	15 (25)	36 (59)	25 (41)	54 (89)	N/A	N/A	4 (7)	N/A	N/A	N/A	6 (10)	25 (41)	0 (33)	7 (12)	3 (5)
Nerva (2018; USA)[S11]	37	18.9	42 (60)	28 (40)	29 (41)	N/A	N/A	N/A	21 (30)	30 (43)	40 (53)	48 (69)	N/A	N/A	7 (10)	36 (51)	29 (41)	5 (7)	5 (7)	21 (30)	23 (33)	17 (24)	4 (6)
Pollock (2013; USA)[15]	N/A	N/A	80 (45.9)	94 (54)	N/A	70 (40.2)	77 (44.3)	N/A	N/A	100 (57.5)	74 (42.5)	151 (86.8)	8 (4.6)	2 (1.1)	8 (4.6)	101 (58.1)	72 (41.4)	1 (0.6)	N/A	N/A	55 (31.6)	N/A	N/A
Potts (2015; USA)[28]	38.1	17	101 (44)	131 (56)	120 (52)	37 (16)	40 (17)	35 (15)	N/A	N/A	N/A	180 (78)	N/A	1 (<1)	35 (15)	N/A	N/A	N/A	76 (33)	156 (67)	N/A	N/A	N/A
Rutledge (2014; USA)[11]	44.2	N/A	42 (57)	32 (43)	N/A	32 (43)	23 (31)	19 (26)	N/A	49 (66)	24 (32)	N/A	N/A	N/A	N/A	30 (41)	39 (53)	4 (5)	10 (14)	26 (35)	24 (32)	10 (14)	3 (4)
Singfer (2017; Belgium)[51]	38	11	32 (53)	29 (47)	N/A	25 (41)	19 (31)	5 (8)	N/A	N/A	20 (33)	52 (85)	N/A	N/A	N/A	26 (43)	N/A	N/A	11 (18)	20 (33)	21 (34)	8 (13)	1 (2)
Thenier-Villa (2017; Spain)[S12]	37.64	15.17	110 (56.4)	85 (43.6)	87 (44,62)	47 (24.10)	17 (8.72)	9 (4.62)	N/A	113 (57.9)	82 (42.1)	123 (63)	20 (10)	10 (5)	12 (6)	N/A	N/A	N/A	30 (15.39)	57 (29.23)	78 (40)	26 (13.33)	4 (2.05)
Yang (2009; South Korea)[S13]	32.3	13	27 (59)	19 (41)	17 (37)	16 (35)	7 (15)	2 (4)	N/A	N/A	27 (59)	N/A	N/A	N/A	N/A	N/A	32 (70)	14 (30)	N/A	N/A	6 (13)	27 (59)	13 (28)
Yang (2012; South Korea)[S14]	34.5	12.6	48 (42)	30 (38)	N/A	78 (100)	N/A	N/A	N/A	N/A	N/A	58 (74)	N/A	N/A	N/A	N/A	N/A	N/A	15 (19)	28 (36)	26 (33)	7 (9)	2 (3)

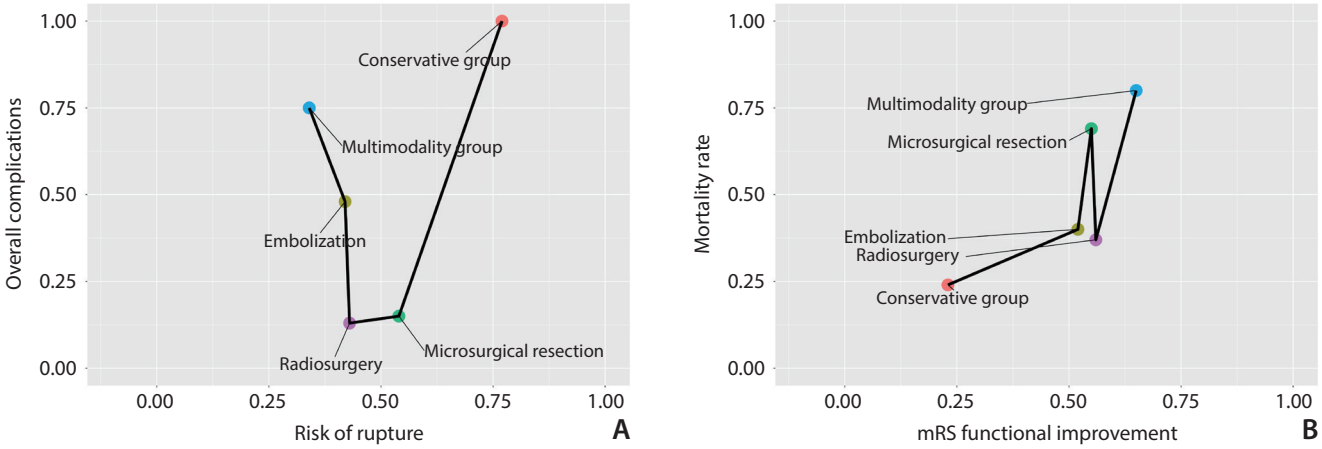
SD, standard deviation; N/A, not applicable.



Supplementary Fig. 1. Risk of bias in non-randomized studies of interventions (ROBINS-I) risk of bias assessment.



Supplementary Fig. 2. Network plot for comparisons of the eligible studies. (**A**) Risk of rupture. (**B**) mRS functional improvement. (**C**) Overall rate of complications. (**D**) Mortality rate. mRS, modified Rankin score.



Supplementary Fig. 3. Scatter plots for partial treatment ranking. (**A**) Overall complications and rupture risk. (**B**) Mortality rates and mRS functional improvement. mRS, modified Rankin score.

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