Microsurgery versus Microsurgery With Preoperative Embolization for Brain Arteriovenous Malformation Treatment: A Systematic Review and Meta-analysis

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Received, March 3, 2022.
Accepted, July 29, 2022.
Published Online, October 26, 2022.

BACKGROUND: Preoperative embolization has traditionally been regarded as a safe and effective adjunct to microsurgical treatment of brain arteriovenous malformations (bAVM). However, there is currently no high-level evidence to ascertain this presumption.
OBJECTIVE: To compare the outcomes of microsurgery (MS) vs microsurgery with preoperative embolization (E + MS) in patients with bAVM through systematic review.
METHODS: We searched MEDLINE, PubMed, and Embase. The primary outcome was bAVM obliteration. Secondary outcomes were intraoperative bleeding (mL), complications, worsened modified Rankin Scale (mRS), and mortality. The pooled proportions of outcomes were calculated through the logit transformation method. The odds ratio (OR) of categorical data and mean difference of continuous data were estimated through the Mantel-Haenszel and the inverse variance methods, respectively.
RESULTS: Thirty-two studies met the eligibility criteria. One thousand eight hundred twenty-eight patients were treated by microsurgery alone, and 1088 were treated by microsurgery with preoperative embolization, respectively. The meta-analysis revealed no significant difference in AVM obliteration (94.1% vs 95.6%, OR = 1.15 [0.63-2.11], $P = .65$), mortality (1.7% vs 2%, OR = 0.88 [0.30-2.58], $P = .82$), procedural complications (18.2% vs 27.2%, OR = 0.47 [0.19-1.17], $P = .10$), worsened mRS (21.2% vs 18.5%, OR = 1.08 [0.33-3.54], $P = .9$), and intraoperative blood loss (mean difference = 182.89 [−87.76, 453.55], $P = .19$).
CONCLUSION: The meta-analysis showed no significant difference in AVM obliteration, mortality, complications, worse mRS, and intraoperative blood loss between MS and E + MS groups. For AVMs where MS alone has acceptable results, it is reasonable to bypass unnecessary preoperative embolization given higher postoperative complication risk.

KEY WORDS: Arteriovenous malformation, Surgery, Embolization, Obliteration, Morbidity, Mortality, Meta-analysis

Neurosurgery 92:27–41, 2023 https://doi.org/10.1227/neu.0000000000002171

Brain arteriovenous malformations (bAVMs) are vascular lesions comprised feeding arteries shunted to draining veins without intervening capillary networks.[1-3] The prevalence of bAVM is 10 to 18 patients per 100 000 persons, and the annual incidence is 1.1 to 1.3 cases per 100 000 individuals.[4-7] Symptomatic bAVMs may present with intracranial hemorrhage, seizure, headache, and ischemic deficits.[8-11] The annual rupture risk ranges from 2.1% to 4.3%, leading to devastating ICHs, which are associated with morbidity and mortality of 25% to 60% and 10% to 30%, respectively.[2,5,6,9,12,13] The risk factors of hemorrhage are prior AVM rupture, aging, exclusively deep venous drainage, deep-seated AVM, venous outflow stenosis, and feeding artery aneurysm.[1,2,9,14] Provided intracranial hemorrhage as the most common debilitating manifestation, bAVM treatment goal is total obliteration.[15-17]

Treatments included conservative management, microsurgical resection, stereotactic radiosurgery, endovascular embolization, and multimodality approach.[4,9] Given the interventions are not risk-free, surgeons should weigh interventions against the natural history on an individualized approach.[9,18]

ABBREVIATIONS: bAVM, brain AVM; **ICH,** intracranial hemorrhage; **MD,** mean difference; **MS,** microsurgery; **NBCA,** N-butyl cyanoacrylate; **PI,** prediction interval; **PVA,** Polyvinyl alcohol; **SMG,** Spetzler-Martin grade.

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To elucidate the optimal management for unruptured bAVMs, Mohr et al[19] published A Randomized Trial of Unruptured Brain AVM trial in 2014. However, this study has been largely criticized for selection bias, poor allocation, use of nonstandard care, and short-term follow-up.[20] To date, high-level evidence suggesting the best strategy is lacking. The consensus is that patients with high-risk features should undergo treatment if the risk profile is favorable.[9,21,22]

Surgery is an option when the risk is acceptable.[23,24] Continued effort to advance surgical techniques has been made to increase safety and effectiveness in achieving obliteration. Preoperative embolization has been a long-standing surgical adjunct with presumed advantage in mitigating high-risk features, reducing bleeding, and delineating lesion margin.[9,21,22,25] However, embolization risks include periprocedural bleeding, resulting in overall 16% morbidity, 2% to 4% mortality, and new neurological deficits up to 14%.[12,26] Therefore, physicians should meticulously weigh the risk and benefit of preoperative embolization.

Evidence has been scarce regarding the efficacy and safety of preoperative embolization compared with microsurgery alone. This study seeks to perform a comprehensive literature search on this topic to assess whether there is a significant difference in bAVM obliteration, intraoperative blood loss, morbidities, and mortalities in patients with bAVM who underwent microsurgery (MS) vs patients who underwent microsurgery with preoperative embolization (E + MS). We hypothesized that, in recent decades, preoperative embolization did not lead to an improved chance of bAVM obliteration.

METHODS

Search Strategy

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[27] We searched the MEDLINE/PubMed with [("AVMs" OR "AVM" OR "Arteriovenous Malformations" OR "Arteriovenous Malformation") AND ("Brain" OR "Cerebral" OR "Intracranial") AND ("Microsurgery" OR "Surgery" OR "Resection" OR "Surgical") AND ("Embolization")] and the Embase with [("arteriovenous malformation"/exp and "surgery"/exp and "embolization"/exp and "brain"/exp)], from inception to the May 17, 2021. We consider only English-written articles.

Study Selections

Studies that met the following criteria were considered eligible for inclusion: (1) adult patients with brain AVM, (2) presence of at least 10 patients in either MS or E + MS groups, and (3) these studies had to report at least the overall obliteration rate. The exclusion criteria were (1) reviews, (2) letters, and (3) studies without countable outcomes report. In the case of more than 1 publication from the same cohort, we considered only the 1 with the larger study population.

Two reviewers (SAS and AS) independently screened the titles and abstracts of all retrieved records. The relevant studies were reviewed in full text by the same 2 reviewers separately, and the articles were either included or excluded based on the eligibility criteria. In the case of unresolved discordance, the corresponding author (J.H.) would adjudicate.

Data Extraction

Two reviewers (S.A.S. and A.S.) separately extracted data in 2 Excel sheets, and then, the sheets were crossed checked against each other and the source material. We gathered the following data: first author name, publication year, the country of study, study design, sample size, patients age and sex, AVM size, Spetzler-Martin grade (SMG), the proportion of eloquent and rupture bAVMs, embolic material, follow-up duration in months or years, the proportion of AVM obliteration, complications, worse modified Rankin scale (mRS), intraoperative bleeding volume (mL), and mortality. In the case of unresolved discordance, the corresponding author (J.H.) would adjudicate.

Study Outcomes

The primary outcome was AVM obliteration confirmed by intraoperative or postoperative imaging. The secondary outcomes were intraoperative bleeding (mL), procedural-related complications (defined as total complication events divided by the patient number and included new neurological deficit, vessel rupture, hemorrhage, hematoma, seizure, stroke, and meningitis), worse mRS, and mortality.

Bias Assessment

Two reviewers (S.A.S. and A.S.) blindly assessed the risk of bias of the included studies using the "risk of bias in nonrandomized studies of interventions (ROBINS-I) tool."[28] Then, the risk of bias summaries was crossed checked, and in the case of unresolved discordance, the corresponding author (J.H.) would adjudicate.

Statistical Analysis

We demonstrated the baseline characteristics of the included studies using descriptive statistics. The proportions of the outcomes were pooled through the logit transformation method using R Studio (R Foundation) version 4.1.2. In the case of substantial heterogeneity in the meta-analysis of proportion, the prediction interval (PI) was reported. Studies reporting the outcomes in both the MS and E + MS groups were included in the comparative quantitative analysis using Review Manager (RevMan International), version 5.4.1. The odds ratio (OR) of categorical data and mean difference (MD) of continuous data with associated 95% CI were calculated by using the Mantel-Haenszel and the inverse variance methods, respectively. Considering the clinical diversities and the methodological differences between the included studies, the random effect model was applied. The heterogeneities between studies were detected using the I^2 statistic test. All statistical tests were 2-sided, and a P value <.05 was considered statistically significant.

RESULTS

Study Selection

The search strategy yielded 2763 publications, of which duplicated records (n = 256) and non-English articles (n = 257) were removed. We screened the remaining 2241 publications by title and abstracts and excluded the 2164 unrelated publications. Then, the remaining 77 publications were reviewed in detail for the potential eligibilities, from which 45 publications were excluded because of review articles (n = 3), studies with less than 10 cases in the interest groups (n = 9), unclear data reports (n = 15),

and studies without primary outcome report (n = 18). Finally, 32 studies were included in this systematic review (Figure 1).[18,29-59]

Characteristics of the Included Studies

The 32 included studies were published between 1993 and 2021, and apart from the prospective Natarajan et al,[34] the remaining publications were retrospective observational studies and were at unavoidable risk of bias per the ROBINS-I tool (Figure 2).[28]

The included studies were performed in the United States (n = 13), Canada (n = 1), United Kingdom (n = 2), United Kingdom and Ireland (n = 1), France (n = 2), Germany (n = 1), Australia (n = 1), Turkey (n = 2), India (n = 1), China (n = 5), Japan (n = 1), Vietnam (n = 1), and Malaysia (n = 1). These studies included 3455 patients of which 84.3% (n = 2916) underwent either MS or E + MS, and the remaining 539 patients were treated by other modalities. In the included studies, the mean age ranges from 30.8 to 65 years, the mean AVM size ranges from 1.2 to 4.7 cm, 42.2% (n = 1432) were moderate to high grade AVM, 52.1 % (n = 1501) were in eloquent regions, and 49.3% (n = 1644) were ruptured.

Within the surgery group (n = 2916), 62.6% (n = 1828) underwent MS only strategy. Various embolic agents were used in these studies, including Avitene powder, Coil, Glubran, polyvinyl alcohol, n-butyl cyanoacrylate, Onyx, silk suture, and Squid. Follow-up duration ranges from postoperative discharge date to a mean of 5.7 years. All studies confirmed postoperation AVM obliteration by either digital subtraction angiography or MR angiography (Table 1). Nine studies reported the interval time between the endovascular embolization and surgical resection, which were single stage (i.e., endovascular embolization followed by surgical resection on the same day with no interval) in Kocer et al,[48] Chen et al,[52] Song et al,[55] Brown et al[57]; 1 day in Conger et al,[39] and Schramm et al[46]; 2.5 days in Catapano et al[58]; 1 week in Hongo et al[30]; and 2 weeks in Hartmann et al.[32] As the outcomes of surgery with and without

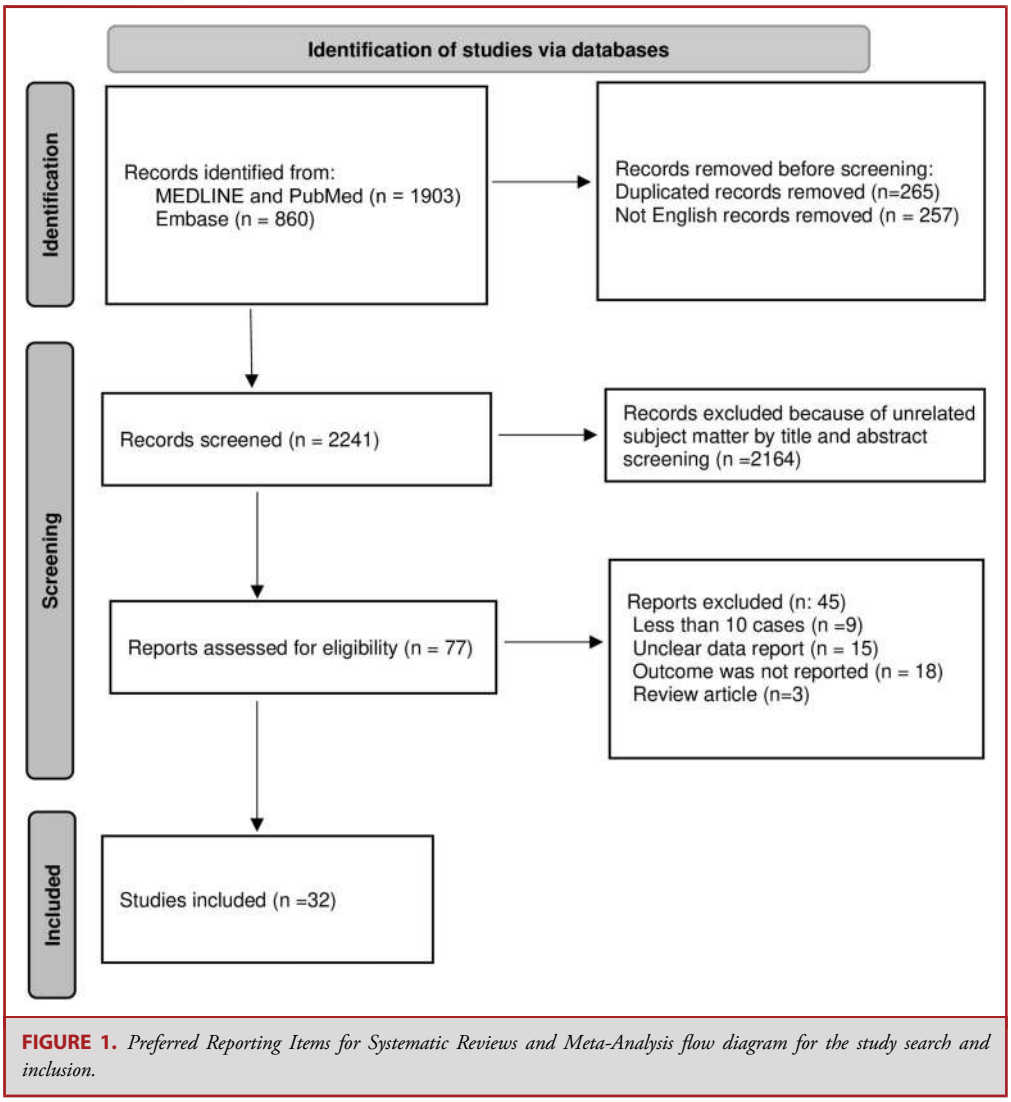

FIGURE 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for the study search and inclusion.*

TABLE 1. Studies Design and Baseline Characteristics

References[a]	Study duration	Country	Total no. of patients	Age (y), mean or median or range	Men no. (%)	AVM size (cm), mean or median or range	Eloquent no. (%)	SMG no. (%)					Rupture no. (%)
								I	II	III	IV	V	
Sisti et al[29]	1971-1991	United States	67	34[b]	40 (59.7)	<3	NR	NR	NR	NR	NR	NR	63 (94)
Hongo et al[30]	1994-1998	Japan	27	36.9[b]	20 (74.07)	NR	NR	5 (18.5)	8 (29.6)	10 (37)	3 (11.1)	1 (3.7)	21 (77.7)
Pik et al[31]	1989-1998	Australia	110	38[b]	46 (41.8)	<3	46 (41.8)	43 (39)	47 (42.7)	20 (18.1)	0	0	69 (62.7)
Hartmann et al[32]	1991-1999	United States	119	34[b]	61 (51.2)	3.5[b]	72 (61)	10 (8)	32 (27)	48 (40)	26 (22)	3 (3)	41 (35)
Nataf et al[33]	1984-1998	France	39	35.7[b]	19 (48.7)	3.1[b]	14 (35.8)	11 (28.2)	16 (41)	9 (23)	3 (7.6)	0	27 (69%)
Natarajan et al[34]	2005-2006	United States	28	45.6[b]	16 (57.1)	3.5[b]	14 (50)	2 (7.1)	11 (39.2)	8 (28.5)	4 (14.2)	3 (10.7)	14 (50)
Nataraj et al[35]	1980-2008	United Kingdom	290	40.8[b]	156 (54)	NR	NR	30 (10.3)	71 (24.4)	82 (28.2)	54 (18.6)	40 (13.7)	150 (51.7)
Theofanis et al[36]	1994-2010	United States	264	<55	124 (46.9)	NR	173 (65.5)	27 (10.2)	101 (38.3)	96 (36.4)	31 (11.7)	9 (3.4)	120 (45.4)
Aboukaïs et al[37]	2002-2012	France	139	30.8[b]	67 (40.1)	NR	49 (35.2)	64 (46)	52 (37.4)	13 (9.3)	10 (7.1)	0	139 (100)
Nerva et al[18]	2005-2012	United States	61	40[b]	32 (52.4)	NR	42 (68.8)	6 (9.8)	25 (40.9)	20 (32.7)	7 (11.4)	3 (4.9)	0
Tong et al[38]	1990-2012	China	98	65[b]	72 (73.4)	3.9[b]	36 (36.7)	16 (16.3)	41 (41.8)	20 (20.4)	17 (17.3)	4 (4)	47 (47.9)
Conger et al[39]	2000-2013	United States	11	32[c]	3 (27.2)	2.4[c]	7 (63.6)	0	7 (63.6)	2 (18.1)	2 (18.1)	0	5 (45.4)
Javadpour et al[40]	2004-2014	Ireland & United Kingdom	34	39[b]	16 (47)	NR	19 (55.9)	8 (23.5)	16 (47)	8 (23.5)	2 (6)	0	0
Rosli et al[41]	2008-2011	Malaysia	30	27.5[c]	15 (50)	1.2[b]	7 (23.3)	15 (50)	10 (33.3)	5 (16.7)	0	0	19 (63.3)
Wong et al[42]	1994-2014	Canada	155	38.5[b]	67 (43.2)	NR	62 (40)	52 (33.5)	66 (42.6)	30 (19.4)	7 (4.5)	0	0
Lang et al[43]	2001-2014	United States	44	39[b]	21 (47.7)	3.2[b]	28 (63.6)	9 (20.4)	13 (29.5)	14 (31.8)	8 (18.1)	0	0
Luksik et al[44]	1990-2015	United States	96	35.6[b]	41 (42.7)	2.5[b]	31 (32.3)	30 (31.3)	41 (42.7)	18 (18.8)	6 (6.3)	1 (1)	36 (37.5)
Ren et al[45]	2008-2014	China	445	32.5[b]	285 (64)	3.3[b]	206 (46.3)	83 (18.6)	156 (35.1)	132 (29.7)	61 (13.7)	13 (2.9)	298 (67)
Schramm et al[46]	1983-2012	Germany	288	35.3[b]	154 (53.5)	NR	164 (56.9)	53 (18.4)	114 (39.6)	90 (31.3)	28 (9.7)	3 (1.0)	144 (50)
Chen et al[47]	2001-2013	United States	59	38.6[b]	29 (49.2)	2.3[b]	NR	10 (17)	31 (52.5)	12 (20.3)	6 (10.2)	0	44 (74.5)
Kocer et al[48]	2006-2018	Turkey	31	38.5[b]	18 (58)	NR	26 (83.8)	0	0	25 (80.6)	5 (16.1)	1 (3.2)	17 (54.8)
Link et al[49]	2004-2017	United States	86	43.6[b]	45 (52.3)	2.7[b]	59 (68.6)	16 (18.6)	35 (40.7)	29 (33.7)	6 (7.0)	0	0
Jean et al[50]	2015-2017	Vietnam	86	35.2[b]	50 (58.1)	NR	46 (53.4)	18 (20.9)	38 (44.1)	22 (25.5)	7 (8.1)	1 (1.1)	53 (61.6)
Wang et al[51]	2002-2017	United States	258	38.3[b]	123 (47.6)	NR	95 (36.8)	93 (36)	165 (63.9)	0	0	0	125 (48.4)
Chen et al[52]	2016-2018	China	100	30.1[b]	59 (59)	4.7[b]	80 (80)	0	0	59 (59)	36 (36)	5 (5)	53 (53)
Kiran et al[53]	2013-2016	India	42	32.2[b]	32 (76.2)	NR	24 (57.1)	6 (14.3)	22 (52.4)	14 (33.3)	0	0	19 (45.2)
Pulli et al[54]	2003-2015	United States	142	39.7[b]	67 (47.1)	2.5[b]	76 (53.5)	33 (23.2)	55 (38.7)	40 (28.2)	14 (9.9)	0	0
Song et al[55]	2016-2018	China	54	32.6[b]	32 (59.2)	NR	NR	22 (40.7)	16 (29.6)	8 (14.7)	7 (13)	1 (2)	32 (59.2)
Chen et al[56]	2011-2019	China	71	64.7[b]	52 (73.2)	2.9[b]	41 (57.7)	15 (21.1)	22 (31)	24 (33.8)	7 (9.9)	3 (4.2)	45 (76)
Brown et al[57]	2016-2018	United Kingdom	19	40[b]	NR	NR	NR	4 (21)	10 (52.6)	4 (21)	1 (5.2)	0	12 (63.1)
Catapano et al[58]	2011-2018	United States	102	34[b]	52 (50.9)	NR	84 (82.3)	0	0	102 (100)	0	0	51 (50)
Kaya et al[59]	2011-2019	Turkey	60	38.4[b]	38 (63.3)	NR	NR	19 (31.7)	22 (36.7)	14 (23.3)	5 (8.3)	0	NR
Total			3455		1855 (53.9)		1501 (52.1)	700 (20.6)	1243 (36.6)	978 (28.8)	363 (10.7)	91 (2.6)	1644 (49.3)

NR, not reported; SMG, Spetzler-Martin Grade.

[a]All studies were retrospective observational studies. The only prospective study was by Nataraj et al.[35]

[b]Mean.

[c]Median.

preoperative embolization were comparable in these studies, it seems that the reported interval did not affect the outcome.

Study Outcomes

AVM Obliteration

Table 2 presents a detailed systematic review and meta-analysis of the outcomes. The pooled proportion (95% CI) of the AVM obliteration after all treatment modalities, MS, and E + MS were 91.84 (88.24-94.41), 92.72 (89.08-95.21), and 94.81 (91.49-96.87), respectively. Of the 12 studies reporting the obliteration in both groups, the meta-analysis showed that the OR was not significantly different between MS and E + MS (94.1% vs 95.6%, OR = 1.15 [0.63-2.11], P = .65, I^2 = 0, P = .77; Figure 3).

Complications

The pooled proportion (95% CI) of the complications after all treatment modalities, MS, and E + MS were 24.93 (18.79-32.27), 18.59 (10.01-31.90), and 39.18 (25.77-54.45), respectively. The PI ranged from 2.4 to 67.6 and 6.9 to 84.6 in MS and E + MS groups, respectively. Of the 7 studies reporting the complications in both groups, the meta-analysis showed that the risk of complication was similar between MS and E + MS groups (18.2% vs 27.2%, OR = 0.47 [0.19-1.17], P = .10). The heterogeneity was moderate (I^2 = 58%, P = .03; Figure 4).

Worse mRS

The pooled proportion (95% CI) of the worse mRS after all treatment modalities, MS, and E + MS were 22.25 (14.48-32.59), 13.43 (3.85-37.52), and 22.37 (13.97-33.83), respectively. The PI ranged from 0.9 to 71.7 and 6.1 to 55.7 in MS and E + MS groups, respectively. Of the 3 studies reporting worse mRS in both groups, the meta-analysis showed that the OR of worse mRS was not significantly different (21.2% vs 18.5%, OR = 1.08 [0.33-3.54], P = .9). The heterogeneity was moderate (I^2 = 49%, P = .14; Figure 5).

Mortality

The pooled mortality (95% CI) after all treatment modalities, MS, and E + MS were 3.81 (2.64-5.47), 3.91 (2.13-7.08), and 3.49 (1.98-6.09), respectively. Of the 8 studies reporting mortality in both groups, the meta-analysis showed that the OR of mortality was not significantly different (1.7% vs 2%, OR = 0.88 [0.30-2.58], P = .82, I^2 = 0, P = .54; Figure 6).

Intraoperative Blood Loss (mL)

Chen et al,[52] Catapano et al,[58] and Kaya et al[59] reported intraoperative blood loss, yielding 128 and 134 patients in MS and E + MS groups, respectively. Although intraoperative blood loss was lower in the E + MS group, the MD was not statistically significant (MD = 182.89 [−87.76, 453.55], P = .19; Figure 7). Heterogeneities between studies were substantial (P < .001, I^2 = 95%). Kaya et al[59] contributed notably to the identified heterogeneity. If this study would exclude because of high heterogeneity, the MD remained statistically nonsignificant between the 2 groups (MD = 64.24 [−73.98, 202.35], P = .36) while the heterogeneity decreased considerably (P = .15, I^2 = 52%).

Subgroup Analysis

In this article, we conducted a subgroup analysis on studies reporting the treatment outcomes of the SMG III-V. The meta-analysis showed that the odds of obliterations (OR = 1.35 [0.57-3.23], P = .49) and complications (OR = 0.73 [0.41-1.33], P = .31) were not significantly different between MS vs E + MS groups (Figure 8). Furthermore, the subgroup analysis of studies using only the Onyx as the embolic agent revealed that the odds of obliteration (OR = 2.11 [0.27-16.76], P = .48) and complications (OR = 0.73 [0.41-1.33], P = .31) were not significantly different between MS vs E + MS groups (Figure 9).

DISCUSSION

Brief Summary of the Study Results

Some scholars presumed that preoperative embolization eases the bAVM resection by reducing bleeding and delineating the AVM border, thereby potentially decreasing morbidity and mortality[9,22,54,58]; however, existing evidence was not able to establish this presumption.[44,60,61] To date, no randomized controlled trial compared the safety and efficacy of E + MS vs MS. To the best of our knowledge, this is the first systematic review and meta-analysis comparing the outcomes of the 2 approaches.

This review demonstrated that AVM obliteration, morbidity, and mortality rates were comparable between MS and E + MS. These findings are consistent with the review by van Beijnum et al[21] reporting 96% obliteration rate after surgical approach, with risk of postprocedural complication at a median of 29% and case fatality at a median of 0.67%.

Overview of Effectiveness in AVM Obliteration for Preoperative Embolization

Given the hemorrhage risk, the goal of bAVMs treatment is complete obliteration.[9,21] Some reports assumed that presurgical embolization might facilitate bAVM resection.[34,44] However, this meta-analysis showed that 2 strategies are comparable. This finding might be due to selection bias, in which complex lesions underwent adjunctive embolization. Contradictory to the selection bias assumption in the study by Catapano et al,[58] surgery achieved higher obliteration relative to adjunctive embolization strategy in grade III AVMs (82% vs 79%, P = .68). Although the nonembolized group was smaller (P = .01), they were more eloquent (P = .02) and more diffuse (P = .01).[58] Furthermore, our subgroup analysis of SMG III-V revealed higher obliteration after microsurgery vs the preoperative embolized group (92% vs 87%, P = .49). In fact, for low-grade AVMs, the obliteration rates after surgery were 90% for the ruptured cohort[37] and 100% for the

TABLE 2. Systematic Review and Meta-Analysis Outcomes

References	Total patients no.	Treatment modalities no.		Used embolic agent (s)	Obliteration rate no. (%)			Complication rate no. (%)			Worsen mRS rate no. (%)			Mortality rate no. (%)		
		MS	E + MS		Total	MS	E + MS	Total	MS	E + MS	Total	MS	E + MS	Total	MS	E + MS
Sisti et al[29]	67	65	2	NR	63 (94.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hongo et al[30]	27	14	7	Aviten powder	20 (74)	13 (92.8)	6 (85.7)	6 (22.2)	2 (14.2)	4 (57.1)	NR	NR	NR	2 (7.4)	0	2 (28.5)
Pik et al[31]	110	101	9	NR	109 (99)	NR	NR	12 (10.9)	NR	NR	NR	NR	NR	NR	NR	NR
Hartmann et al[32]	119	NA	119	NBCA	115 (96)	NA	115 (96)	96 (80.6)	NA	96 (5)	56 (47)	NA	56 (47)	0	NA	0
Nataf et al[33]	39	25	14	NR	36 (92)	NR	NR	17 (43.5)	NR	NR	NR	NR	NR	1 (2.5)	NR	NR
Natarajan et al[34]	28	NA	28	Onyx	26 (92.8)	NA	26 (92.8)	12 (42.8)	NA	12 (42.8)	7 (25)	NA	7 (25)	1 (3.5)	NA	1 (3.5)
Nataraj et al[35]	290	57	101	NBCA & Onyx	233 (88)	56 (98.2)	100 (99)	58 (20)	1 (1.75)	25 (24.7)	NR	NR	NR	17 (6)	1 (1.7)	1 (1)
Theofanis et al[36]	264	162	102	NBCA & Onyx	257 (97.3)	157 (96.9)	100 (98)	19 (7.1)	NR	NR	NR	NR	NR	7 (2.6)	5 (3)	2 (1.9)
Aboukaïs et al[37]	139	139	NA	NA	123 (89.7)	123 (89.7)	NA	11 (7.9)	11 (7.9)	NA	NR	NR	NA	2 (1.4)	2 (1.4)	NA
Nerva et al[18]	61	NA	28	Onyx	45 (73.7)	NA	28 (100)	20 (32.7)	NA	14 (50)	15 (24.4)	NA	9 (32.1)	2 (3.2)	NA	1 (3.2)
Tong et al[38]	98	43	20	NR	93 (94.1)	41 (95.3)	19 (95)	14 (14.2)	NR	NR	NR	NR	NR	3 (3)	NR	NR
Conger et al[39]	11	NA	11	Silk Suture & PVA	11 (100)	NA	11 (100)	11 (100)	NA	11 (100)	2 (18.1)	NA	2 (18.1)	1 (9)	NA	1 (9)
Javadpour et al[40]	34	26	8	NR	34 (100)	26 (100)	8 (100)	6 (17.6)	NR	NR	NR	NR	NR	0	0	0
Rosli et al[41]	30	30	NA	NA	25 (83.3)	25 (83.3)	NA	7 (23.3)	7 (23.3)	NA	NR	NR	NR	4 (13.3)	4 (13.3)	NA
Wong et al[42]	155	107	39	NR	152 (98)	NR	NR	72 (46.4)	NR	NR	NR	NR	NR	NR	NR	NR
Lang et al[43]	44	14	28	NR	42 (95.4)	NR	NR	17 (38.6)	NR	NR	NR	NR	NR	2 (4.5)	NR	NR
Luksik et al[44]	96	48	48	NR	89 (92.7)	45 (93.8)	44 (91.7)	NR	NR	NR	10 (10.4)	3 (6.2)	7 (14.5)	1 (1)	0	1 (2)
Ren et al[45]	445	334	29	NR	388 (87.2)	NR	NR	148 (33.2)	NR	NR	NR	NR	NR	35 (7.9)	NR	NR
Schramm et al[46]	288	244	39	NR	285 (99)	NR	NR	35 (12.2)	NR	NR	NR	NR	NR	5 (1.7)	NR	NR
Chen et al[47]	59	35	24	NR	56 (94.9)	NR	NR	18 (30.5)	NR	NR	NR	NR	NR	NR	NR	NR
Kocer et al[48]	31	NA	22	NBCA & Onyx & Squid	30 (96.8)	NA	21 (95.4)	12 (38.7)	NA	11 (50)	NR	NA	NR	1 (3.2)	NA	1 (4.5)
Link et al[49]	86	NA	54	NR	81 (94.1)	NA	54 (100)	16 (18.6)	NA	13 (24)	16 (18.6)	NA	13 (24)	1 (1.2)	NA	0
Jean et al[50]	86	84	2	NR	80 (97.5)	NR	NR	NR	NR	NR	NR	NR	NR	6 (7)	NR	NR
Wang et al[51]	258	54	164	NBCA & Onyx	241 (93.4)	54 (100)	164 (100)	19 (7.3)	NR	NR	NR	NR	NR	1 (0.3)	NR	NR
Chen et al[52]	100	53	47	Onyx	98 (98)	53 (100)	45 (96.2)	52 (52)	26 (49)	26 (55.3)	NR	NR	NR	1 (1)	1 (1.8)	0
Kiran et al[53]	42	42	NA	NA	37 (88)	37 (88)	NA	15 (35.7)	15 (35.7)	NA	NR	NR	NA	3 (7.4)	3 (7.4)	NA
Pulli et al[54]	142	15	19	NBCA& Onyx	80 (56.3)	15 (100)	19 (100)	9 (6.3)	1 (6.6)	1 (5.2)	13 (9.1)	1 (6.6)	1 (5.2)	3 (2.1)	0	1 (5.2)
Song et al[55]	54	31	18	Onyx	52 (96.2)	31 (100)	16 (89)	5 (9.2)	1 (3.2)	4 (22.2)	NR	NR	NR	0	0	0
Chen et al[56]	71	30	NA	NA	32 (45)	28 (93.3)	NA	20 (28.1)	18 (60)	NA	18 (25.3)	7 (23.3)	NA	12 (16.9)	4 (13.3)	NA
Brown et al[57]	19	NA	19	Glubran & Squid	17 (89)	NA	17 (89)	9 (47.3)	NA	9 (47.3)	NR	NA	NR	1 (5.2)	NA	1 (5.2)
Catapano et al[58]	102	45	57	NBCA& Onyx & PVA	82 (80.3)	37 (82.2)	45 (78.9)	23 (22.5)	9 (20)	14 (24.5)	34 (33.3)	19 (42.2)	15 (26.3)	NR	NR	NR
Kaya et al[59]	60	30	30	Onyx	54 (90)	26 (86.6)	28 (93.3)	7 (11.6)	5 (16.6)	2 (6.6)	NR	NR	NR	NR	NR	NR
Total patients no. and pooled proportion (95% CI)	3455	1828	1088		91.84 (88.24-94.41)	92.72 (89.08-95.21)	94.81 (91.49-96.87)	24.93 (18.79-32.27)	18.59 (10.01-31.90)	39.18 (25.77-54.45)	22.25 (14.48-32.59)	13.43 (3.85-37.52)	22.37 (13.97-33.83)	3.81 (2.64-5.47)	3.91 (2.13-7.08)	3.49 (1.98-6.09)

E + MS, microsurgery with preoperative embolization; mRS, modified Rankin Scale; MS, microsurgery; NA, not applicable; NBCA, N-butyl cyanoacrylate; NR, not reported; PVA, polyvinyl alcohol.

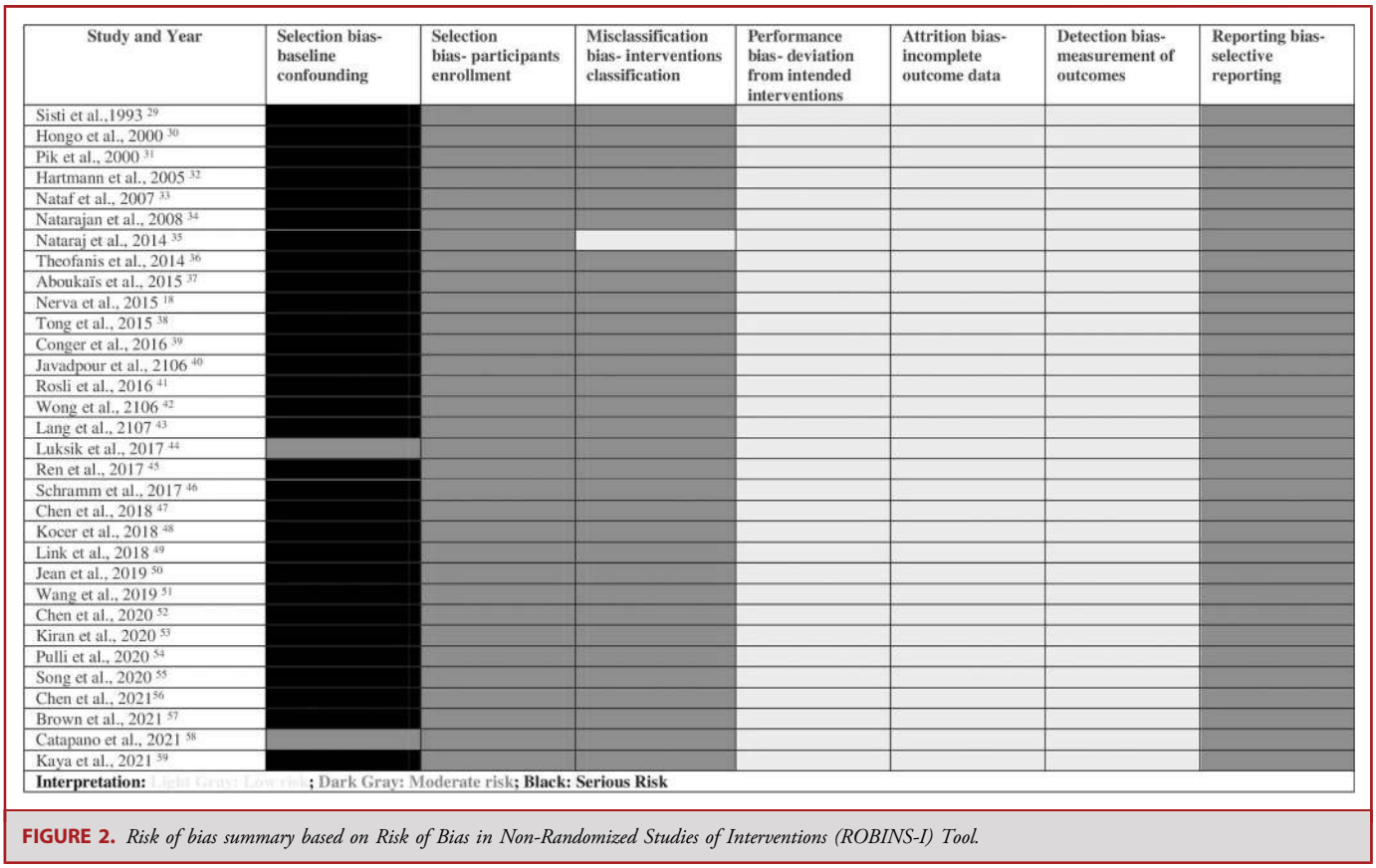

FIGURE 2. *Risk of bias summary based on Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) Tool.*

mixed (un) ruptured cohort and A Randomized Trial of Unruptured Brain AVM eligible patients.[18,40,49] Therefore, by existing evidence, preoperative embolization has not added more obliteration to the surgery strategy.

Of note, angiography may overestimate embolization efficacy because residual fillings were identified in AVMs with angiographically established obliteration. Furthermore, recanalization can occur in embolized AVMs. Both the recanalization and residual fillings account for incomplete obliteration, which can paradoxically increase bleeding risk relative to no treatment.[34,35,48] Therefore, even AVMs deemed angiographically cured after embolization should undergo surgery.

Morbidity and Mortality

Some studies postulated that preoperative embolization decreases postoperative complications by mitigating the high-risk features.[44,58,59] However, no difference was noted in complications between the groups, and the odds of worsening mRS and mortality were the same. One factor explaining the heterogeneity of outcome for preoperative embolization is the embolization strategies, including "intention to treat" and "mitigate the risk" approaches. For the latter, surgery determined the outcome. However, in the intention to treat strategy, the patients underwent multiple embolizations, which might pass the safety boundaries, and surgery was a salvage procedure. In such an approach, adverse outcomes may already occur before surgery.

Of note, the safety threshold for bAVMs embolization can be ambiguous in definition, and the ambiguity may result in significant practice variations. For example, Natarajan et al[34] stopped the embolization in case of complete AVM obliteration, recurrent opacification of draining vein, exceeding the safe reflux threshold, or no forward movement of Onyx despite a moderate injection pressure. In addition, even many low-grade AVMs underwent intention to treat embolization strategy in the study by Nataraj et al.[35] To prevent nonarterial, delayed phase bleeding after embolization, Kocer et al[48] and Chen et al[52] adopted a hybrid approach; however, both series applied the intention to treat strategy, resulting in a higher risk of complications. Conversely, studies that used embolization to mitigate the risk before surgery noted a similar procedural risk to the nonembolized group.[44,58] The number of preoperative embolization was a predictor of postoperative complications.[36,58] Therefore, there are bleeding and neurological deficit risks per embolization cycle. Respecting such a risk per each embolization cycle, it is worth considering a definitive safety threshold for embolization.

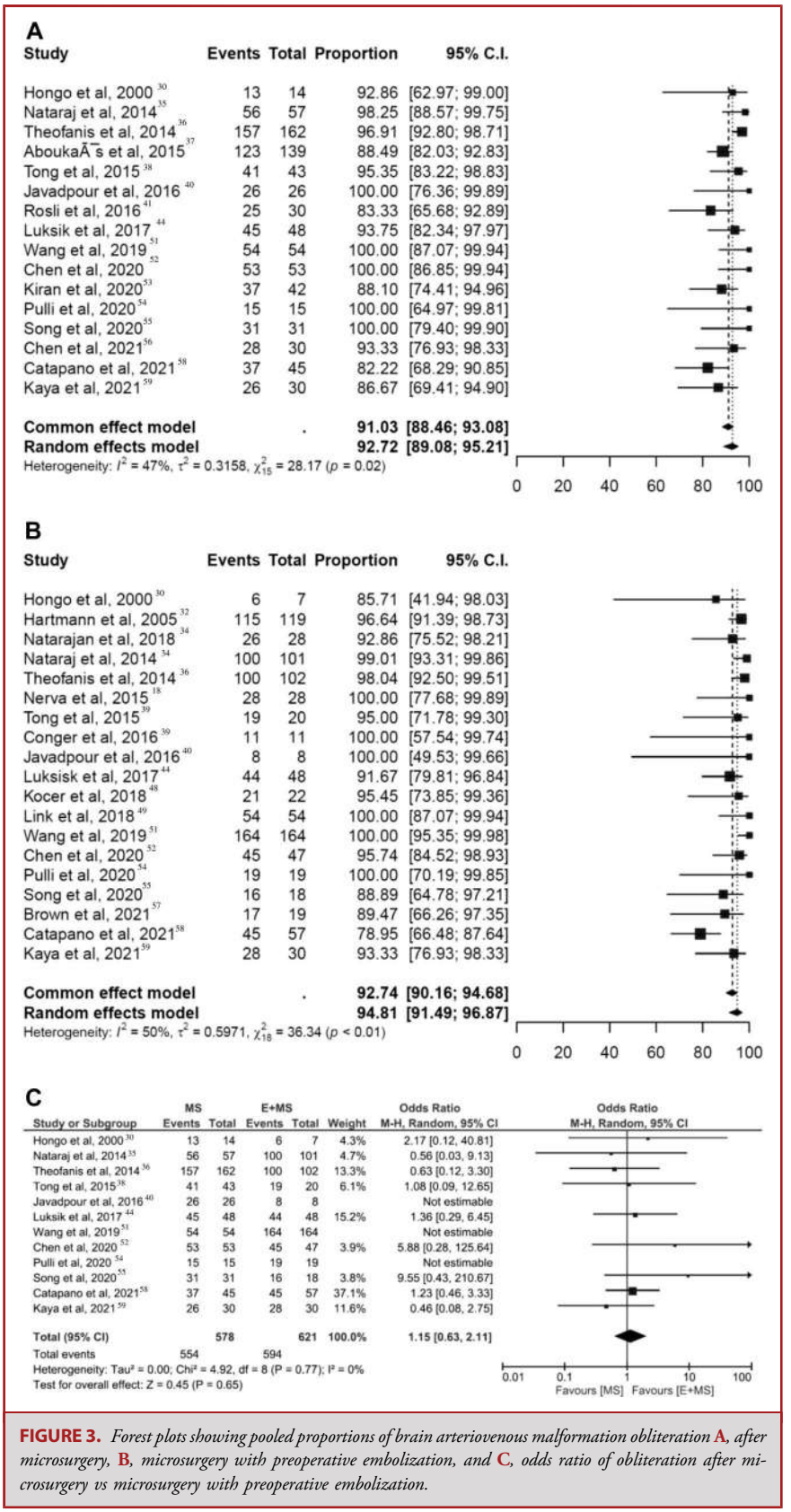

FIGURE 3. *Forest plots showing pooled proportions of brain arteriovenous malformation obliteration* **A**, *after microsurgery,* **B**, *microsurgery with preoperative embolization, and* **C**, *odds ratio of obliteration after microsurgery vs microsurgery with preoperative embolization.*

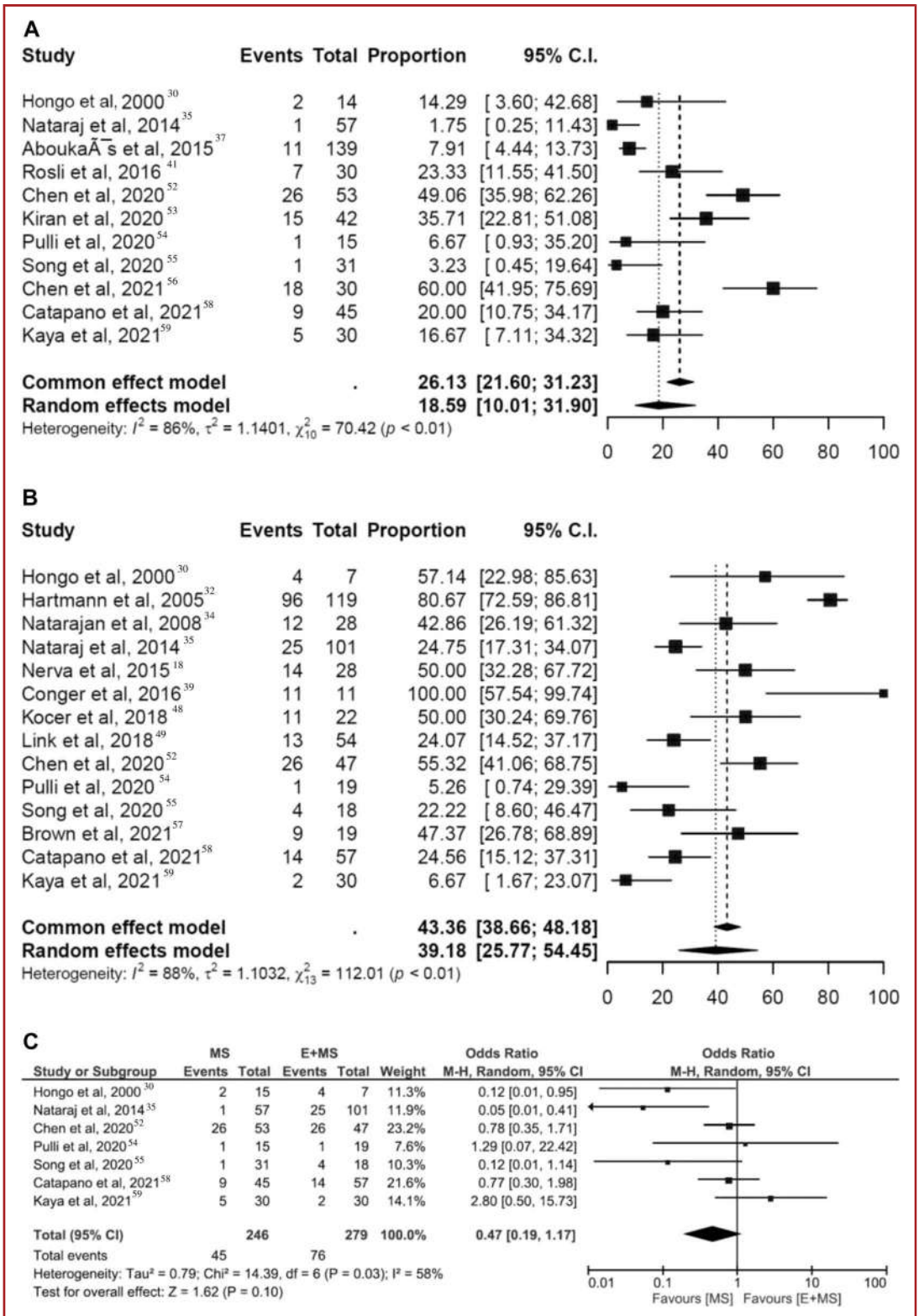

FIGURE 4. *Forest plots showing pooled proportions of complications* **A**, *after microsurgery,* **B**, *microsurgery with preoperative embolization, and* **C**, *odds ratio of complications after microsurgery vs microsurgery with preoperative embolization.*

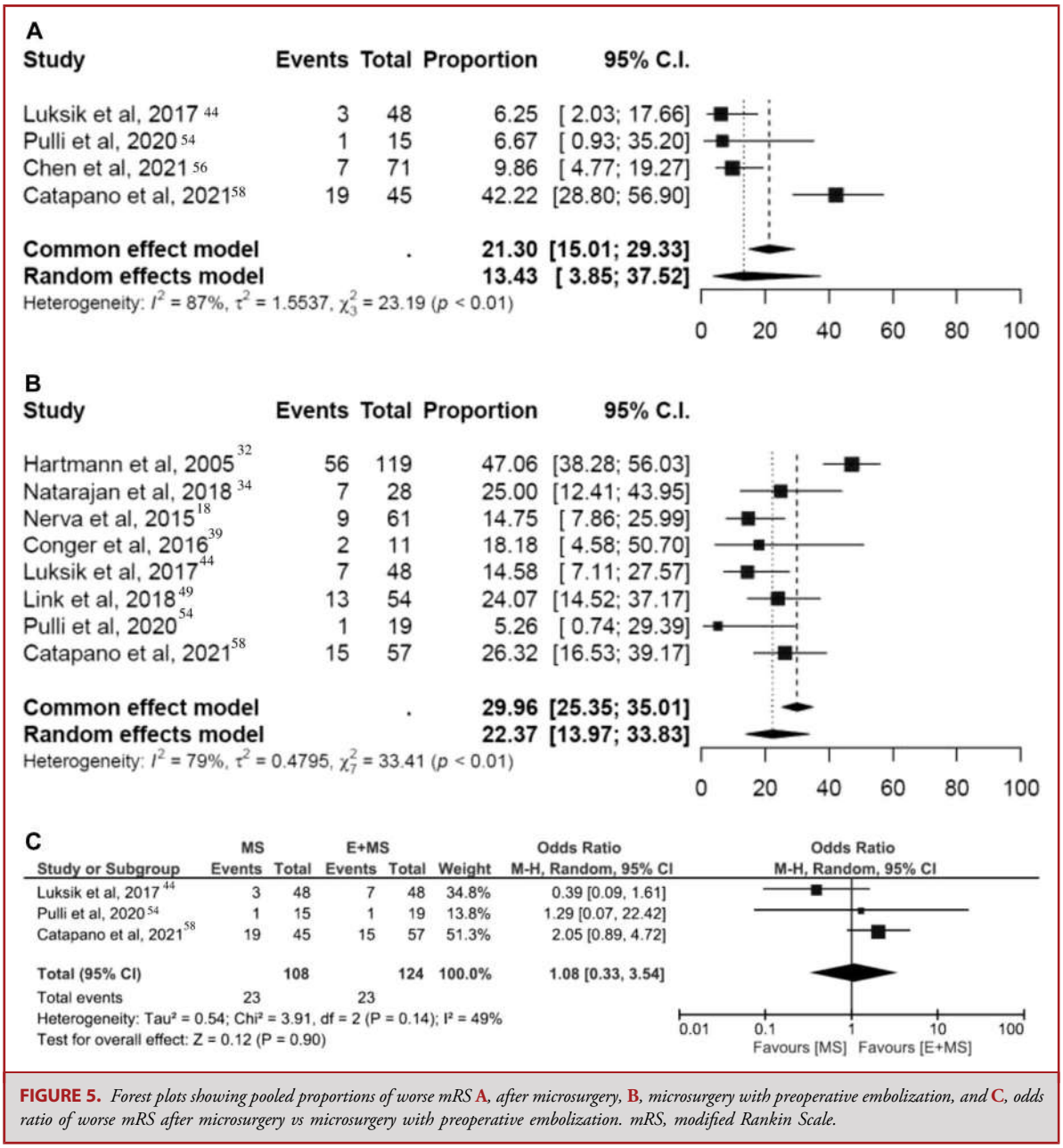

FIGURE 5. *Forest plots showing pooled proportions of worse mRS* **A**, *after microsurgery,* **B**, *microsurgery with preoperative embolization, and* **C**, *odds ratio of worse mRS after microsurgery vs microsurgery with preoperative embolization. mRS, modified Rankin Scale.*

Intraoperative Blood Loss

Another presumed benefit of preoperative embolization was blood loss reduction. Although this benefit was not universally observed in the existing literature, Kaya et al[59] reported a significantly lower intraoperative bleeding in the preoperative embolization group (578 ± 52 mL vs 978 ± 124 mL, P < .05). However, this study did not observe a significant difference in postoperative hemoglobin and hematocrit, even with comparable transfusion between the 2 treatment groups.[59] Conversely, the study by Chen et al[52] reported lesser operative bleeding in the embolized group, but the difference was not statistically significant. The authors in this study defined 3 stratifications of embolization degree (A: minimal, B: moderate, and C: excessive) and observed that the bleeding volume was not predictable as a linear equation of embolization degree, while bleeding decreased from point A to B, it increased from point B to C (grade A, 916.7 ± 482.2 mL vs grade B, 488.9 ± 347.5 mL vs grade C, 640 ± 373.3 mL, P = .03).[52] Interestingly, Catapano et al[58] noted a

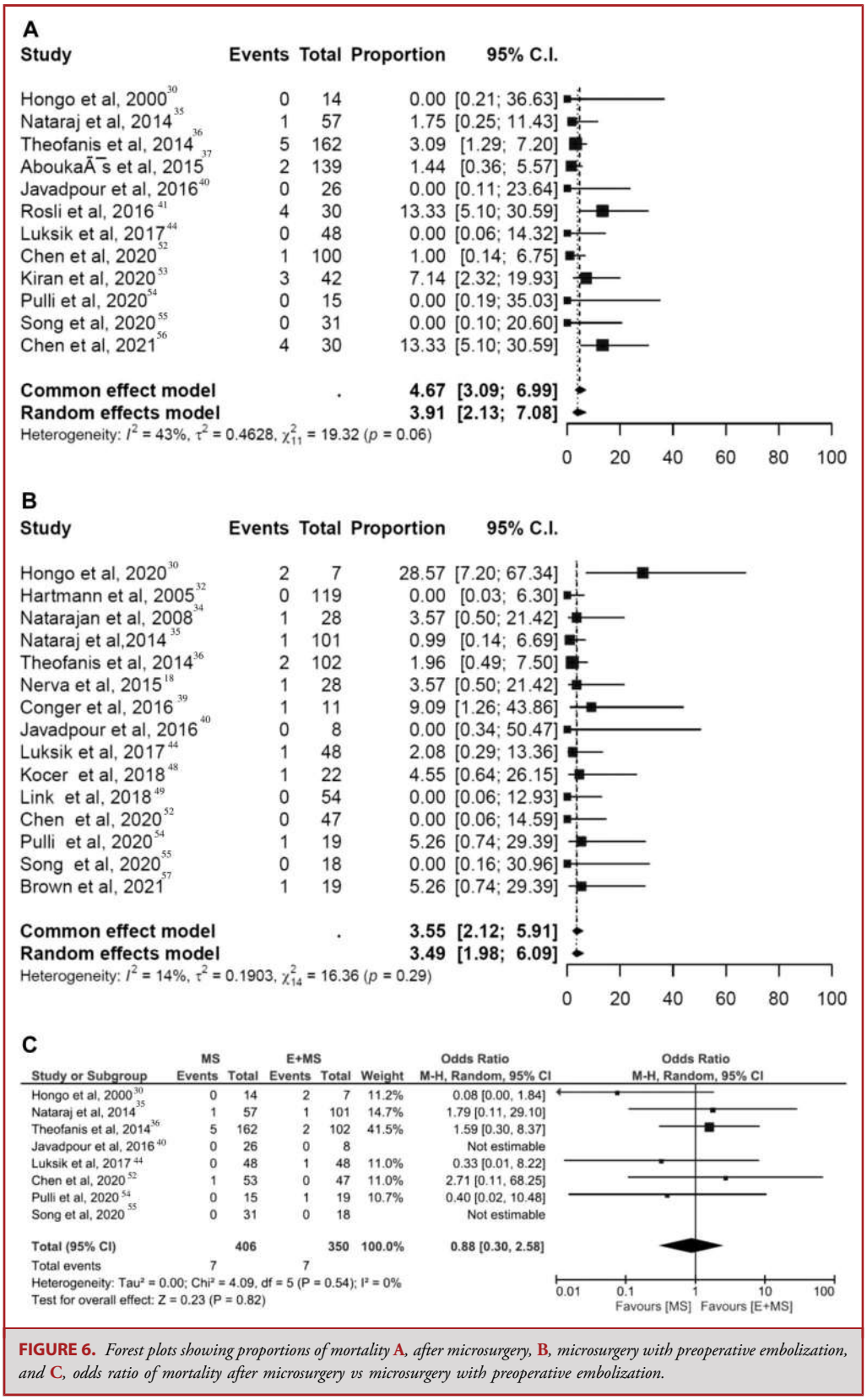

FIGURE 6. *Forest plots showing proportions of mortality* **A**, *after microsurgery,* **B**, *microsurgery with preoperative embolization, and* **C**, *odds ratio of mortality after microsurgery vs microsurgery with preoperative embolization.*

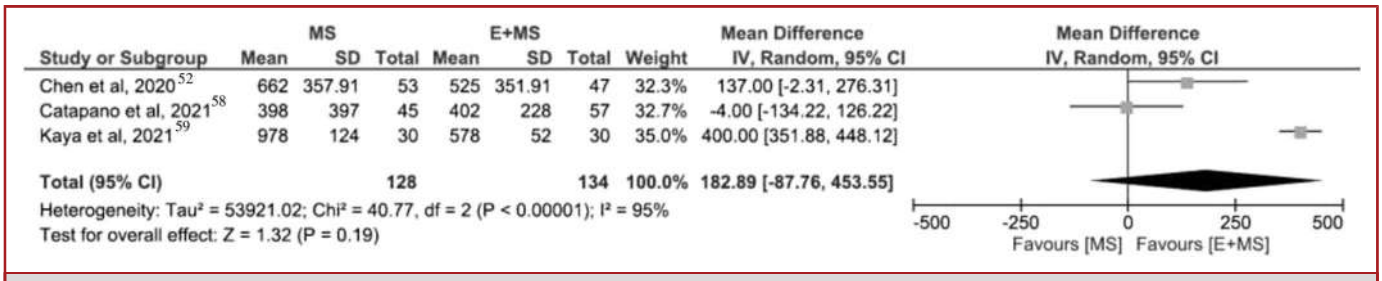

FIGURE 7. *Forest plot showing pooled mean difference of intraoperative bleeding volume (mL) in microsurgery vs microsurgery with preoperative embolization.*

lower intraoperative bleeding volume in the microsurgery-alone group (398 ± 397 mL vs 402 ± 228 mL, $P = .95$). The conflicting reports on intraoperative blood loss rendered an initiation for investigation of this parameter in our study, and this meta-analysis concluded no significant difference in the mean of intraoperative bleeding between the 2 groups.

Limitations

We acknowledged several limitations in this study. First, owing to the rarity of bAVMs, almost all existing literatures were observational studies, and therefore, included studies were limited by sample, confounders, and selection bias. Second, apart from the prospective study by Nataraj et al,[35] other studies were retrospective, which were limited by the heterogeneity of data reports and follow-up protocols. Third, the details of AVMs angioarchitecture, such as venous drainage pattern, degree of shunting, and nidal-related aneurysm, were not reported by most of the studies. Fourth, the AVMs size was below 3 cm in 9 studies and in the range of 3 to 4.7 cm in 7 studies and was not reported by other studies. Fifth, most studies did not stratify the outcomes, and we could not conduct subgroup analysis per SM grades. However, we conducted a subgroup analysis on studies reporting the treatment outcome of SMG III-V, which were consistent with the primary findings. Sixth, other studies are needed to determine which AVM characteristics significantly benefit from the preoperative embolization relative to surgery only strategy. Seventh, the method of intraoperative blood loss collection was not reported by the included studies. Eighth, we excluded the studies with lesser than 10 patients because the small studies are less precise and known to be the major source

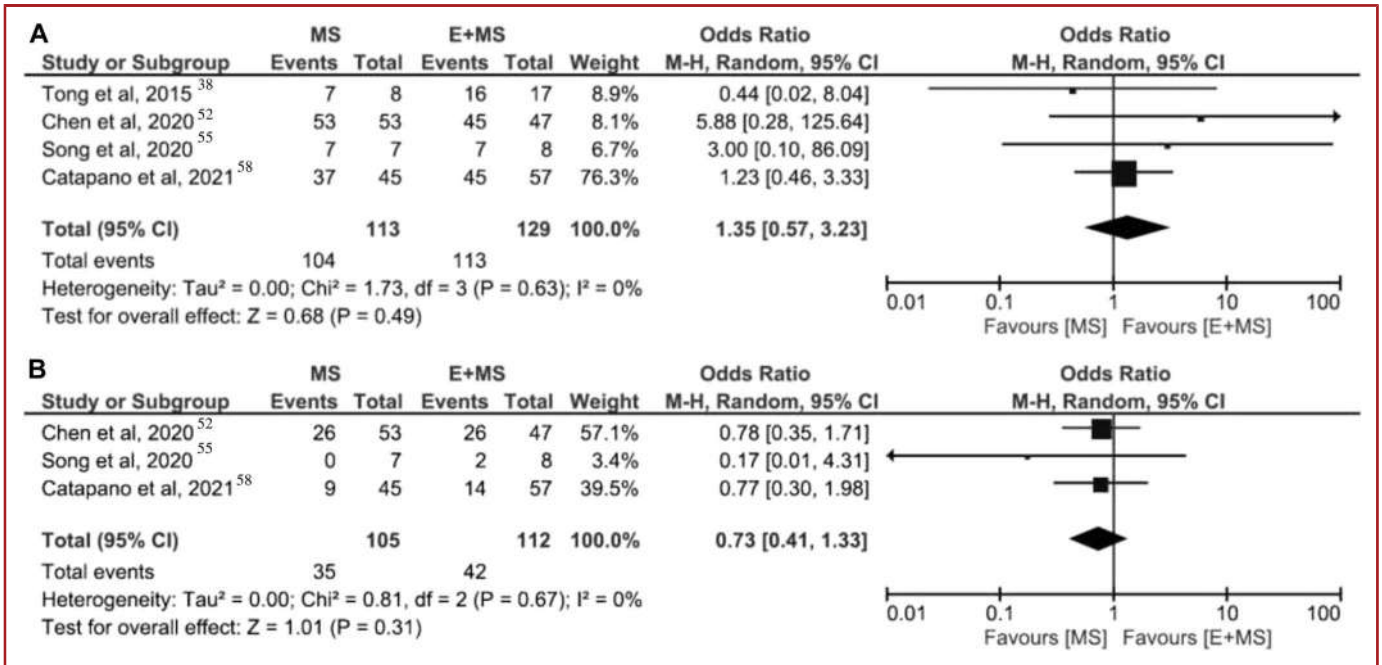

FIGURE 8. *Forest plots showing odds ratio of* A*, obliteration and* B*, complication after microsurgery vs microsurgery with preoperative embolization in the subgroups of Spetzler-Martin grade* III-V *arteriovenous malformation.*

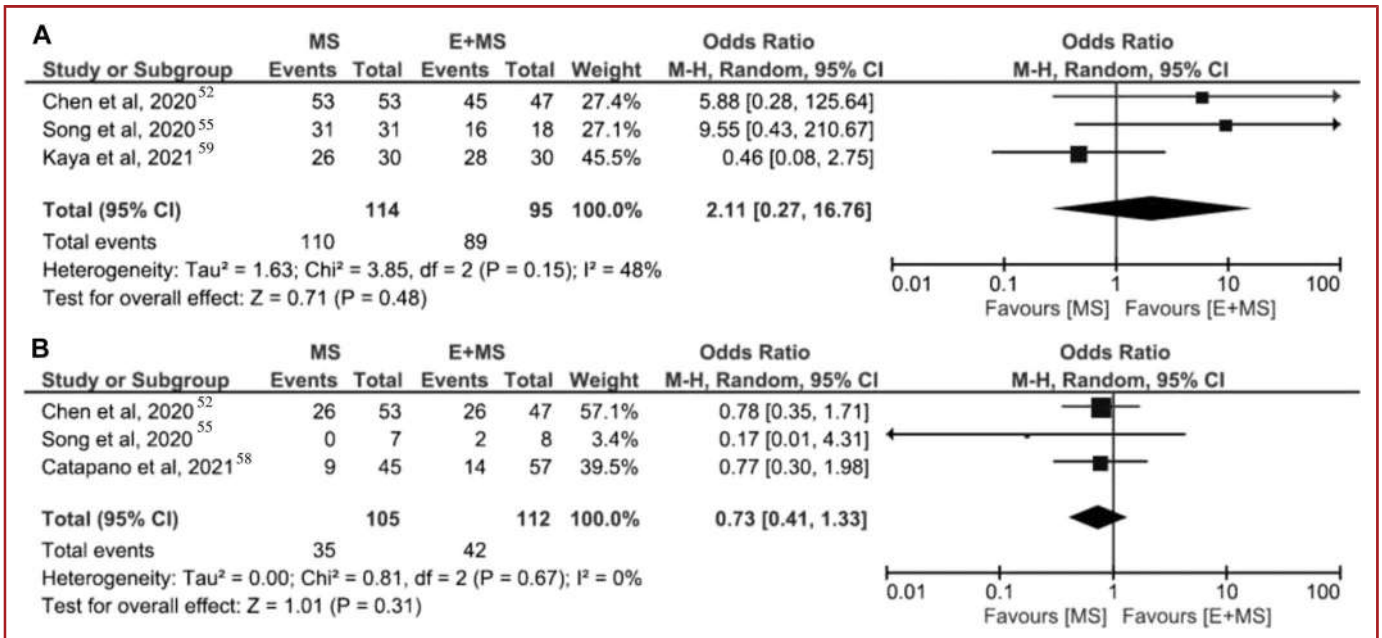

FIGURE 9. *Forest plots showing odds ratio of* **A**, *obliteration and* **B**, *complication after microsurgery vs microsurgery with preoperative embolization in the subgroups of only Onyx embolized arteriovenous malformation.*

of heterogeneity in the systematic review. Considering the outcome proportion (p) in the included study by Luksik et al,[44] $p1 = 0.937$, $p2 = 0.916$, $\alpha = 0.05$, and $\beta = 0.8$, the sample size would be 501 patients in each arm (i.e., 1002 patients in total). This systematic review included 2916 patients in total and therefore reached the optimal information size and had adequate statistical power. Finally, owing to the severity and acuity nature of bAVMs hemorrhage, the random assignment of patients to treatment arms seems challenging because of ethical underpinning.[62]

CONCLUSION

The current evidence synthesis demonstrates that, as currently applied in practice, microsurgery with and without embolization seem to achieve comparable outcomes. This meta-analysis concluded that preoperative embolization neither decreased intraoperative bleeding, morbidity, and mortality nor increased the odds of AVM obliteration significantly. There was no observed benefit in outcome improvement to undergo preoperative embolization. Surgery can achieve excellent outcomes, especially in the low-grade AVMs, and preoperative embolization can be eschewed if it is deemed unnecessary.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The increasing use of preoperative embolization to mitigate risk and enhance surgical resection of bAVMs remains poorly understood in the literature. The authors are to be commended for an excellent systematic review of the current literature to clarify this issue. Although they were not able to conclude that the use of preoperative embolization improved resection/cure rates, their research highlights the deficiencies that exist in the current literature including heterogeneity in study design and intervention. As the authors have correctly emphasized, the existing literature is almost all retrospective in design and is subject to inherent selection bias. The lack of details concerning bAVM angioarchitecture (SMG, pattern of venous drainage, degree of AV shunting) is a significant weakness of the published studies.

Our group has made use of preoperative embolization in the majority of high-grade AVMs routinely (SMG III-V), but only occasionally in selected lower grade AVMs that exhibit significant arteriovenous shunting or have deep feeders. Prior research has demonstrated the safety of this approach. From this and similar reports it is likely that there exists a subgroup of bAVMs where preoperative embolization has a role.

The authors conclude correctly that the indiscriminate use of preoperative embolization is unlikely to provide clinical benefit. The more challenging focus for future study is not whether embolization should be used as routine in bAVMs, but what features would identify an AVM that would benefit from preoperative embolization. It is this subgroup that additional research in bAVM preoperative embolization should delineate further.

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