Effects of Preoperative Embolization on Spetzler–Martin Grade I and II Arteriovenous Malformations: A Propensity-Adjusted Analysis

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BACKGROUND: Cerebral arteriovenous malformations (AVMs) with low Spetzler–Martin grades (I and II) are associated with good neurological outcomes after microsurgical resection; however, the use of preoperative embolization for these lesions is controversial.

OBJECTIVE: To compare the neurological outcomes of preoperative embolization with no embolization in patients with low-grade AVMs.

METHODS: Patients with a Spetzler–Martin grade I or II AVM who underwent microsurgical resection during January 1, 1997, through December 31, 2019, were analyzed. Patients undergoing preoperative embolization were compared with patients not undergoing embolization. A propensity score was constructed from baseline characteristics and used to match intervention (embolization) and control (nonembolization) groups in a 1:1 ratio. The primary outcome was poor neurological status on last follow-up examination, defined as a modified Rankin Scale score >2 and a modified Rankin Scale score worse at follow-up than at the preoperative examination.

RESULTS: Of the 603 patients analyzed, 310 (51.4%) underwent preoperative embolization and 293 (48.6%) did not. Patients in the embolization cohort compared with those in the nonembolization cohort had a higher percentage of Spetzler–Martin grade II AVMs (71.6% vs 52.6%, $P < .001$) and a lower percentage of hemorrhage (41% vs 55%, $P = .001$). After propensity score matching, no differences were found between paired cohorts (each N = 203) for baseline characteristics with a significant reduction in absolute standardized mean differences. No significant differences were found in primary outcomes between treatment groups in the matched or unmatched cohorts.

CONCLUSION: Preoperative embolization of low-grade Spetzler–Martin AVMs is not associated with improved neurological outcomes after microsurgical resection.

KEY WORDS: Low-grade AVMs, Preoperative embolization, Spetzler–Martin grade I and II AVMs

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Spetzler–Martin grade I and II cerebral arteriovenous malformations (AVMs) are typically associated with favorable neurological outcomes after surgical resection.[1,2] The use of preoperative embolization for these low-grade lesions remains controversial, with a previous study of 232 surgical patients with Spetzler–Martin grade I or II AVMs reporting a 43% rate of the multimodal therapy.[3] Several studies have reported a lack of benefit in neurological outcomes from preoperative embolization in patients undergoing surgical resection for favorable AVMs.[4-15] Furthermore, embolization of these lesions is not without risk of complication and, although the complication rate is typically low, this risk benefit must be appropriately weighed.[5]

ABBREVIATIONS: BNI, Barrow Neurological Institute; **STROBE,** Strengthening the Reporting of Observation Studies in Epidemiology; **UCSF,** University of California, San Francisco

Our institution recently analyzed outcomes in 102 patients with Spetzler–Martin grade III AVMs and found that lack of preoperative embolization was a risk factor for a poor neurological outcome in patients undergoing surgical resection.[16] However, outcomes in patients with lower-grade AVMs have not been similarly analyzed. To our knowledge, this article presents the largest study yet reported to compare patient outcomes with and without preoperative embolization of Spetzler–Martin grade I and II AVMs, using a propensity-adjusted analysis. We hypothesize that the use of preoperative embolization does not have the same beneficial effect in low-grade AVMs that was observed in grade III AVMs, as measured by neurological outcome after resection.

METHODS

All patients who underwent microsurgical resection for a cerebral AVM from January 1, 1997, to June 1, 2017, at the University of California, San Francisco (UCSF), and from January 1, 2001, to December 31, 2019, at Barrow Neurological Institute (BNI) at St. Joseph's Hospital and Medical Center in Phoenix, Arizona, were retrospectively analyzed for the presence of a low-grade AVM (Spetzler–Martin grade I or II) using 2 prospectively maintained databases. A multi-institutional data agreement was established between the 2 facilities, and the St. Joseph's Hospital and Medical Center Institutional Review Board for Human Research in Phoenix, Arizona, approved the study protocol. Because of the low risk to the study subjects, a waiver for patient consent was granted. The Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines were used for reporting. Charts were analyzed for further data collection including treatments, outcomes, complications, Spetzler–Martin grade, Lawton–Young grade,[17] and supplemented Spetzler–Martin grading system score.[18] Embolizations were mainly performed by 4 interventionalists (including F.C.A. and A.F.D.) and surgical resections by 2 neurosurgeons (M.T.L. and R.F.S.).

Patients who underwent preoperative embolization were compared with patients who did not undergo embolization. The primary outcome analyzed was neurological status on last follow-up examination. Patients who were followed for fewer than 30 d were excluded. Poor outcomes were defined as a modified Rankin Scale (mRS) score >2 and a worse mRS score compared with the preoperative score. Secondary outcomes analyzed included both complications and residual AVMs after surgery.

SPSS version 27 (IBM Corp) with Python Essentials (Python Software Foundation) and R Essentials (The R Foundation) were used for statistical analysis. Means and standard deviation (SD), percentages, independent *t* tests, and χ^2 analysis were initially performed to compare the unmatched cohorts. A propensity score was computed to account for measurable differences between treatment groups. Variables known to impact outcomes after cerebral AVM surgery were included: patient age, preoperative mRS score, AVM location, AVM size, eloquence of surrounding brain, presence of deep venous drainage, AVM rupture status, nidus diffuseness, and presence of associated aneurysm. Additional variables included year of treatment, geographic location (UCSF or BNI), and duration of follow-up. Year of treatment was treated as a categorical variable, with patients binned into 4 equal quartiles, where the first quartile included the years 1997 to 2003, the second quartile included 2004 to 2007, the third quartile included 2008 to 2013, and the fourth quartile included 2014 to 2019. The dependent variable in propensity score construction was treatment group. Matching was conducted using the 1:1 nearest neighbor technique with a caliper of 0.1 (maximum tolerance of 0.1 SDs from logits). The success of matching was evaluated by comparing the absolute standardized mean difference of baseline covariates before and after matching. In addition, we compared the pseudo R^2 in the logistic regression model for the exposure group before and after matching. A decrease in this value toward <0.001 suggests that the propensity score is no longer predictive of a difference in treatment group assignment.

The primary outcomes of mRS score >2 and average final mRS score were compared in both unmatched and matched cohorts. The outcomes were compared in univariate analysis with independent *t* tests and χ^2 analysis. Binary logistic regression analysis was conducted in the unmatched and matched populations to analyze treatment effect against primary outcomes. In the unmatched data set, a standard logistic regression model was used with adjustment for propensity score. In the matched data set, a conditional logistic regression model was used to account for clustering of pairs.

RESULTS

Study Population Characteristics

Of 704 patients treated for low-grade AVMs during the study period, 603 had complete records and ≥30 d of follow-up. Of these 603 patients, 310 (51.4%) underwent preoperative embolization and 293 (48.6%) did not undergo embolization before resection. A flow diagram describing inclusion and exclusion criteria is displayed in Figure. Baseline characteristics of the unmatched intervention (embolization) and control (nonembolization) cohorts are presented in Table 1. The proportion of patients embolized decreased significantly over time (from the first through the fourth quartiles, $P < .001$). Patients at UCSF were slightly more likely to be embolized ($P = .03$, Table 1). The unmatched cohorts were significantly different in terms of Spetzler–Martin grade, with the embolization cohort having a greater percentage of Spetzler–Martin grade II lesions than the nonembolization cohort (71.6% [222/310] vs 52.6% [154/293], $P < .001$). Patients in the embolization cohort had larger AVM niduses (mean [SD] size 2.4 [1.0] cm) compared with the nonembolization cohort (mean size 1.8 [0.9] cm; $P < .001$). Patients in the embolization cohort also had a lower percentage of patients with a previous hemorrhage (41% [127/310]) compared with the nonembolization cohort (55% [161/293]; $P = .001$). The unmatched cohorts were not significantly different regarding patient age, AVM location, eloquence, deep venous drainage, associated aneurysm, or diffuseness, preoperative mRS scores, or follow-up months ($P > .43$). There were 6 symptomatic complications from embolization (1.7%), including 1 femoral occlusion, 3 cerebrovascular accidents, and 2 intraparenchymal hemorrhages.

Propensity Score Matching

The propensity score matched cohort was composed of 406 patients matched 1:1 with 0.1% accuracy. Table 2 shows a comparison of baseline characteristics and the reduction in absolute standardized mean difference for each covariate. After matching, there were no statistically significant differences between the intervention and control groups for baseline covariates (Table 2). The pseudo R^2 for the logistic regression model of the

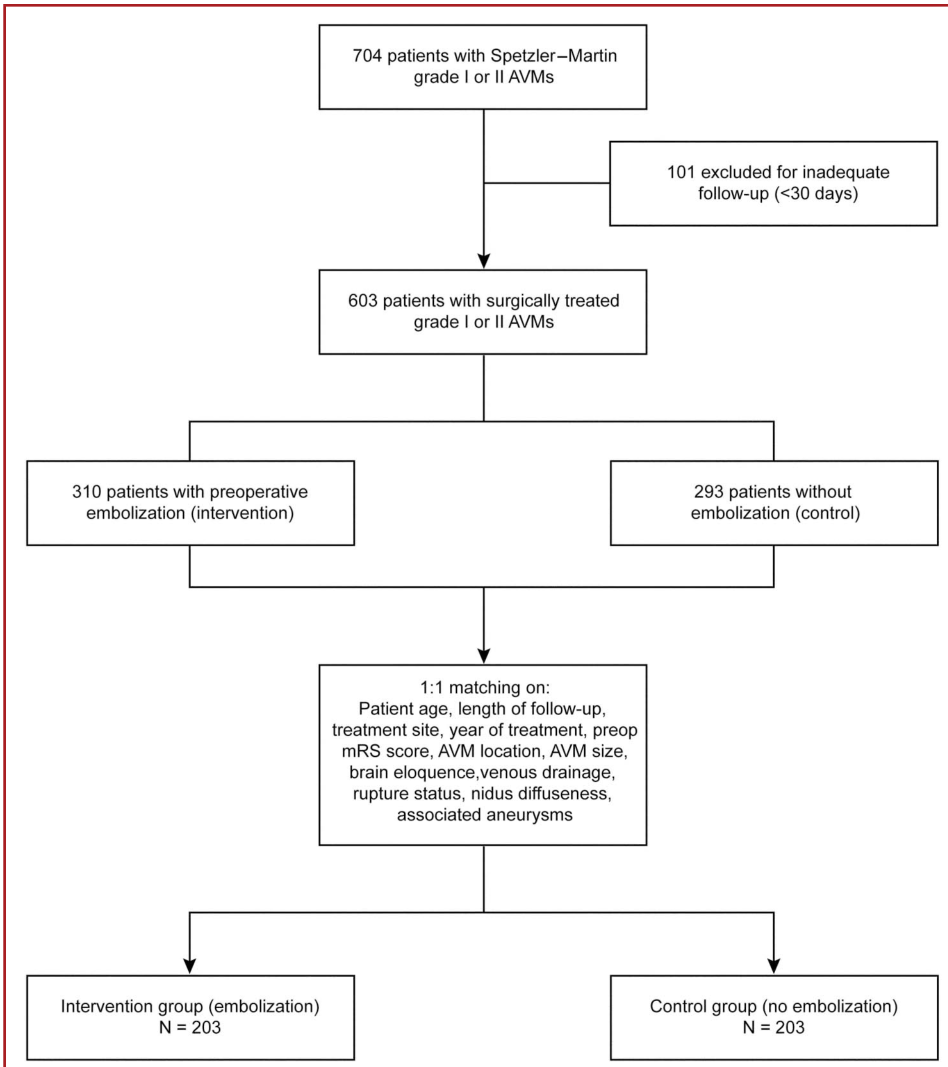

FIGURE. *Flow diagram for inclusion/exclusion criteria in patients with Spetzler–Martin grade I or II AVMs who were propensity score matched (1:1). AVM, arteriovenous malformation; mRS, modified Rankin Scale. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.*

exposure group decreased from 0.271 in the unmatched data set to <0.0001 in the 1:1 matched cohort.

Outcomes

For both the unmatched (N = 603) and matched (N = 406) cohorts, no differences were found between treatment groups for any of the primary or secondary outcome measures (Table 3). Outcomes remained similar after subgroup analysis for Spetzler–Martin grade and treatment site (UCSF or BNI) (Table 3). The results from the matched-pair logistic regression demonstrated no difference in the odds of having an mRS score >2 or worse mRS score at follow-up between patients with and without embolization (Table 4).

DISCUSSION

AVMs with low Spetzler–Martin grade are associated with a 4% risk of a stroke or death within 33 mo if left untreated.[19] Because the majority of patients with low-grade AVMs have good neurological outcomes after resection, these lesions are typically treated microsurgically to eliminate the risk associated with rupture.[1-3] The utility of preoperative embolization for AVMs continues to be debated, as embolization is thought to facilitate resection by decreasing nidal volume and blood loss during surgery; however, studies have mostly shown no benefit in neurological outcomes.[1,8,9,20-25] Our group recently found that the absence of preoperative embolization is associated with

TABLE 1. Standardized Difference Between Embolization and Nonembolization Cohorts of Baseline Characteristics in Unmatched Patients (N = 603) Who Underwent Resection of Spetzler–Martin Grade I or II AVMs[a]

Characteristic	Embolization cohort (N = 310)[b]	Nonembolization cohort (N = 293)	Absolute standardized mean difference	P value
Treatment year by quartile			0.378	<.001
First (1997-2003)	84 (66.7)	42 (33.3)		
Second (2004-2007)	83 (55.7)	66 (44.3)		
Third (2008-2013)	80 (45.7)	95 (54.3)		
Fourth (2014-2019)	63 (41.2)	90 (58.8)		
Treatment site			0.174	.03
BNI	96 (31.0)	115 (39.2)		
UCSF	214 (69.0)	178 (60.8)		
AVM nidus location			0.069	.77
Frontal	96 (31.0)	101 (34.5)		
Parietal	56 (18.1)	58 (19.8)		
Temporal	67 (21.6)	58 (19.8)		
Occipital	29 (9.4)	18 (6.1)		
Deep (basal ganglia, internal capsule, corpus callosum, and ventricle)	14 (4.5)	12 (4.1)		
Brainstem	3 (1.0)	2 (0.7)		
Cerebellum/other posterior fossa	45 (14.5)	44 (15.0)		
Spetzler–Martin grade			0.400	<.001
I	88 (28.4)	139 (47.4)		
II	222 (71.6)	154 (52.6)		
Patient age, mean (SD), yr	38.4 (17.5)	39.0 (18.9)	0.035	.67
Deep venous drainage present	67 (21.6)	56 (19.1)	0.062	.45
Eloquence present	92 (29.7)	82 (28.0)	0.037	.65
Associated aneurysm present	17 (5.5)	12 (4.1)	0.065	.43
AVM size, mean (SD), cm	2.4 (1.0)	1.8 (0.9)	0.695	<.001
Associated hemorrhage present	127 (41.0)	161 (55.0)	0.282	.001
Nidus diffuse	37 (11.9)	33 (11.3)	0.021	.80
Preoperative mRS score, mean (SD)	1.5 (1.4)	1.6 (1.4)	0.051	.53
Follow-up duration, median, mo	12.2	12.2		
25th percentile	1.2	1.0		
75th percentile	24.3	12.2		
Minimum	1.0	1.0		
Maximum	129.5	122.9		
Surgical complications[c]	12 (3.9)	7 (2.4)	0.085	.30
Residual present after resection	4 (1.3)	6 (2.0)	0.059	.47
Follow-up duration, mean (SD), mo	18.1 (22.8)	17.8 (20.6)	0.023	.88
Follow-up mRS score >2	39 (12.6)	31 (10.6)	0.062	.44
Follow-up mRS score worse	57 (18.4)	54 (18.4)	0.001	.99

AVM, arteriovenous malformation; BNI, Barrow Neurological Institute; mRS, modified Rankin Scale; SD, standard deviation; UCSF, University of California, San Francisco.
[a]Data are presented as No. (%) unless otherwise indicated. Total percentages may not equal 100 because of rounding.
[b]Symptomatic complications from embolization occurred in 6 patients (1.7%; 1 femoral occlusion, 3 cerebrovascular accidents, and 2 intraparenchymal hemorrhages).
[c]Complications included 4 (1.4%) intraoperative and postoperative hemorrhages in the nonembolization cohort and 5 (1.6%) in the embolization cohort.

an 8-fold increase in the odds of a poor neurological outcome in patients with Spetzler–Martin grade III lesions.[16] However, in our propensity score matched analysis, we found no difference in neurological outcome (follow-up mRS score >2 or worse mRS score on follow-up than preoperatively) after resection in patients with low-grade lesions with preoperative embolization compared with those with no embolization. The propensity score was applied to effectively match the control and intervention groups on baseline characteristics. Similarly, Morgan et al[9] analyzed 297 patients with low-grade AVMs and found no difference in adverse outcomes (mRS score >2) for patients who underwent preoperative embolization compared with patients who did not undergo embolization. The authors concluded that the temptation of preoperative embolization should be resisted because of the lack of neurological benefit and risk of a serious complication.[9] Although the risk of a serious complication from embolization is small (1.9% in this study and 0.34% as reported by Morgan et al[9]), our results further support a lack of neurological benefit from preoperative embolization of low-grade AVMs.

TABLE 2. Standardized Difference Between Embolization and Nonembolization Cohorts of Baseline Characteristics in Matched Patients (N = 406) Who Underwent Resection of Spetzler–Martin Grade I or II AVMs[a]

Characteristic	Embolization cohort (N = 203)	Nonembolization cohort (N = 203)	Absolute standardized mean difference	*P* value
Treatment year by quartile			0.206	.17
First (1997-2003)	46 (22.7)	36 (17.7)		
Second (2004-2007)	53 (26.1)	46 (22.7)		
Third (2008-2013)	58 (28.6)	56 (27.6)		
Fourth (2014-2019)	46 (22.7)	65 (32.0)		
Treatment site			0.101	.30
BNI	64 (31.5)	74 (36.5)		
UCSF	139 (68.5)	129 (63.5)		
AVM nidus location			0.052	.54
Frontal	64 (31.5)	68 (33.5)		
Parietal	39 (19.2)	38 (18.7)		
Temporal	35 (17.2)	41 (20.2)		
Occipital	22 (10.8)	12 (5.9)		
Deep (basal ganglia, internal capsule, corpus callosum, and ventricle)	8 (3.9)	11 (5.4)		
Posterior fossa	35 (17.2)	33 (16.3)		
Spetzler–Martin grade			0.158	.13
I	73 (36.0)	88 (43.3)		
II	130 (64.0)	115 (56.7)		
Patient age, mean (SD), yr	38.1 (17.9)	39.8 (18.2)	0.075	.36
Deep venous drainage present	46 (22.7)	42 (20.7)	0.050	.63
Eloquence present	64 (31.5)	58 (28.6)	0.068	.52
Associated aneurysm present	9 (4.4)	11 (5.4)	0.044	.65
AVM size, mean (SD), cm	2.1 (0.8)	2.0 (0.9)	0.135	.18
Associated hemorrhage present	96 (47.3)	95 (46.8)	0.015	.92
Nidus diffuse	26 (12.8)	21 (10.3)	0.079	.44
Preoperative mRS score, mean (SD)	1.5 (1.4)	1.6 (1.4)	0.033	.70
Follow-up duration, mean (SD), mo	3.1 (1.8)	2.9 (1.6)	0.151	.15

AVM, arteriovenous malformation; BNI, Barrow Neurological Institute; mRS, modified Rankin Scale; SD, standard deviation; UCSF, University of California, San Francisco.
[a]Data are presented as No. (%) unless otherwise indicated. Total percentages may not equal 100 because of rounding.

As mentioned previously, preoperative embolization is thought to facilitate surgical resection and potentially lead to fewer surgical complications. However, after adjustment, our results showed no difference in surgical complications comparing preoperative embolization to nonembolization cohorts with low-grade AVMs. Furthermore, the risk of an intraoperative or postoperative hemorrhage was nearly the same in both groups (1.6% in the embolization cohort vs 1.4% in the nonembolization cohort). Similarly, in our recent analysis of patients with grade III AVMs, no difference in surgical complication rates was found between the embolization and nonembolization groups.[16] Morgan et al[9] commented that a comparison of complication rates of surgery with or without embolization is lacking in the literature; however, their analysis similarly found no difference in complications. Furthermore, in our study, we found a low overall residual rate in low-grade lesions (1.7%, 11/603), with no difference between the embolization and nonembolization cohorts ($P = .47$). Because preoperative embolization is thought to facilitate surgical resection, the lack of difference in residual between the 2 cohorts further supports the argument against the notion that embolization assists in resection of low-grade lesions.

Limitations

This analysis is limited by the retrospective nature of the study and several significant variables that were not obtainable for any patients, including the type of embolysate used, number of feeding arteries embolized, and number of deep arterial feeders embolized. Propensity score analysis is a robust method for adjusting for measured covariates and confounders. However, we cannot account for potential unmeasurable differences between the treatment groups. Although the samples were matched and no statistically significant differences were noted between the embolization and nonembolization groups, a few of the variables still had a standardized mean difference that exceeded 0.15 or even 0.2, which indicates a slight covariate imbalance. Furthermore, the cerebrovascular and endovascular surgeons performing the procedures have substantial experience; thus, the results may not be generalizable to less experienced centers. Another limitation of this study is that patients in our cohort were treated by surgeons over a period of

TABLE 3. Comparison of Primary and Secondary Outcomes in Matched Intervention (Embolization) and Control (No Embolization) Groups (N = 406), With Subgroup Analysis by Spetzler–Martin Grade and Treatment Site

Characteristic	Embolization cohort (N = 203)	Nonembolization cohort (N = 203)	*P* value
Preop mRS score, mean (SD)	1.5 (1.4)	1.6 (1.4)	.74
Follow-up mRS score >2, No. (%)	25 (12.3)	19 (9.4)	.34
Follow-up mRS score worse, No. (%)	37 (18.2)	37 (18.2)	>.99
Final mRS score, mean (SD)	1.2 (1.3)	1.1 (1.3)	.23
Spetzler–Martin grade I (N = 160)	N = 72	N = 88	
Preop mRS score, mean (SD)	1.3 (1.2)	1.6 (1.5)	.14
Follow-up mRS score >2, No. (%)	7 (9.6)	5 (5.7)	.35
Follow-up mRS score worse, No. (%)	6 (8.2)	7 (8.0)	.95
Final mRS score, mean (SD)	1.0 (1.3)	0.8 (1.1)	.44
Spetzler–Martin grade II (N = 245)	N = 130	N = 115	
Preop mRS score, mean (SD)	1.7 (1.5)	1.6 (1.3)	.54
Follow-up mRS score >2, No. (%)	18 (13.8)	14 (12.2)	.70
Follow-up mRS score worse, No. (%)	31 (23.8)	30 (26.1)	.69
Final mRS score, mean (SD)	1.3 (1.3)	1.2 (1.4)	.52
Treatment site UCSF (N = 267)	N = 138	N = 129	
Preop mRS score, mean (SD)	1.4 (1.4)	1.4 (1.5)	.91
Follow-up mRS score >2, No. (%)	16 (11.5)	12 (9.3)	.56
Follow-up mRS score worse, No. (%)	30 (21.6)	32 (24.8)	.53
Final mRS score, mean (SD)	1.1 (1.4)	1.1 (1.3)	.75
Treatment site BNI (N = 138)	N = 64	N = 74	
Preop mRS score, mean (SD)	1.8 (1.5)	1.9 (1.3)	.64
Follow-up mRS score >2, No. (%)	9 (14.1)	7 (9.5)	.40
Follow-up mRS score worse, No. (%)	7 (10.9)	5 (6.8)	.39
Final mRS score, mean (SD)	1.4 (1.2)	1.0 (1.2)	.07

BNI, Barrow Neurological Institute; mRS, modified Rankin Scale; Preop, preoperative; SD, standard deviation; UCSF, University of California, San Francisco.

22 yr, which may have affected the results. We attempted to mitigate experience bias by including year of treatment in our propensity score. Reduced blood loss during surgery is sometimes mentioned as another benefit to preoperative embolization, but this factor was not assessed in this study. In addition, the decision for preoperative embolization was made by the primary cerebrovascular surgeon, and no algorithm for the use of embolization was used in the study. However, both senior authors (R.F.S. and M.T.L.) who performed the surgical resections opt for the use of preoperative embolization when AVMs have deep and/or high-flow arteries and/or when AVMs are associated with aneurysms that may be difficult to access during resection. However, the frequency of associated aneurysms was similar between the treatment groups. Selection bias may still be present, for which patients underwent embolization based on these criteria, but other factors were controlled for as much as possible. Our clinical experience in the context of these results suggests that these limitations are unlikely to change the primary results of our study.

CONCLUSION

Low-grade Spetzler–Martin AVMs are associated with good neurological outcomes after resection. Preoperative embolization of these low-grade lesions does not seem to decrease the rate of a symptomatic surgical complication or the frequency of a residual

TABLE 4. Propensity-Adjusted[a] Predictors of Outcomes for Embolization (vs No Embolization) in Spetzler–Martin Grade I and II AVMs, Before and After 1:1 Matching

	Before matching		After matching	
Outcome	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Follow-up mRS score >2	1.25 (0.71-2.21)	.45	1.35 (0.73-2.54)	.35
Follow-up mRS score worse	0.81 (0.51-1.30)	.38	0.93 (0.56-1.55)	.79

AVM, arteriovenous malformation; CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.
[a]Adjusted for patient age, AVM size, AVM location, presence of associated aneurysm, rupture status, diffuse nidus, eloquence of surrounding brain, presence of deep draining vein, Spetzler–Martin grade, treatment site, treatment year, and duration of follow-up.

nidus. Furthermore, our results suggest that preoperative embolization is not associated with improved neurological outcomes after microsurgical resection in these patients. Although severe complications from embolization are rare, there seems to be little to no benefit in preoperative embolization of low-grade AVMs.

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