Observation Versus Intervention for Low-Grade Intracranial Dural Arteriovenous Fistulas

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Observation Versus Intervention for Low-Grade Intracranial Dural Arteriovenous Fistulas

BACKGROUND: Low-grade intracranial dural arteriovenous fistulas (dAVF) have a benign natural history in the majority of cases. The benefit from treatment of these lesions is controversial.

OBJECTIVE: To compare the outcomes of observation versus intervention for low-grade dAVFs.

METHODS: We retrospectively reviewed dAVF patients from institutions participating in the CONsortium for Dural arteriovenous fistula Outcomes Research (CONDOR). Patients with low-grade (Borden type I) dAVFs were included and categorized into intervention or observation cohorts. The intervention and observation cohorts were matched in a 1:1 ratio using propensity scores. Primary outcome was modified Rankin Scale (mRS) at final follow-up. Secondary outcomes were excellent (mRS 0-1) and good (mRS 0-2) outcomes, symptomatic improvement, mortality, and obliteration at final follow-up.

RESULTS: The intervention and observation cohorts comprised 230 and 125 patients, respectively. We found no differences in primary or secondary outcomes between the 2 unmatched cohorts at last follow-up (mean duration 36 mo), except obliteration rate was higher in the intervention cohort (78.5% vs 24.1%, $P < .001$). The matched intervention and observation cohorts each comprised 78 patients. We also found no differences in primary or secondary outcomes between the matched cohorts except obliteration was also more likely in the matched intervention cohort ($P < .001$). Procedural complication rates in the unmatched and matched intervention cohorts were 15.4% and 19.2%, respectively.

CONCLUSION: Intervention for low-grade intracranial dAVFs achieves superior obliteration rates compared to conservative management, but it fails to improve neurological or functional outcomes. Our findings do not support the routine treatment of low-grade dAVFs.

KEY WORDS: Dural arteriovenous fistula, Radiosurgery, Surgery, Endovascular, Embolization, Cortical venous reflux, Intracranial

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Intracranial dural arteriovenous fistulas (dAVFs) are abnormal anastomoses between meningeal arteries and dural venous sinuses or cortical veins, and they comprise 10% to 15% of all intracranial vascular malformations.[1] Based on the presence of cortical venous reflux or lack thereof, dAVFs are classified into high- or low-grade dAVFs, respectively.[2,3] In contrast to their high-grade counterparts, low-grade dAVFs have a relatively benign natural history, with a 0% to 0.6% annual incidence of neurological events and absent mortality rate.[4-10] Current treatments for dAVFs comprise endovascular embolization, surgical ligation, and stereotactic radiosurgery (SRS) alone or in combination.[1,4,11-14] However, given generally quiescent course of untreated low-grade dAVFs, routine intervention for these patients remains controversial. Therefore, the aim of this multicenter, retrospective matched cohort study is to compare the outcomes of observation versus intervention for low-grade dAVFs.

ABBREVIATIONS: CONDOR, CONsortium for Dural arteriovenous fistula Outcomes Research; **CVD,** cortical venous drainage; **dAVF,** dural arteriovenous fistula; **NHND,** nonhemorrhagic neurological deficit

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METHODS

Patient Selection

The Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) is a collaborative clinical research effort among 12 participating institutions to investigate dAVF outcomes. Patients with an intracranial dAVF who presented to the participating institutions were identified, and their records were retrospectively reviewed. This study was approved by the institutional review board (IRB) of each individual institution, and it was exempt from patient consent by the IRBs. The collected data were de-identified and pooled by an independent third party, and the pooled data were transmitted to the institution of the first and senior authors for analysis. Verification and attestation of data accuracy were performed by each contributing institution.

The following inclusion criteria were used for this study: (1) no prior dAVF-related intracranial hemorrhage, (2) low-grade (Borden type I, or Cognard type I and IIa) intracranial dAVF confirmed by catheter digital subtraction cerebral angiography (DSA), and (3) availability of baseline data and management outcomes.[2] Eligible patients were subsequently categorized into observation or intervention cohorts.

Baseline Data and Variables

Baseline data comprised patient and dAVF characteristics. Patient variables included age, sex, and medical history. Alcohol use was defined as reported history of alcohol abuse, recent hospitalization for alcohol-related illness (≤6 mo before dAVF diagnosis) or liver disease, or >5 drinks within 24 h. Cigarette smoking status was categorized into current, past, and never smokers, as reported by the patient or designated proxy. Antiplatelet medication use was defined as the use of platelet inhibitors, including nonsteroidal anti-inflammatory drugs, at presentation. Anticoagulant use was defined as the use of vitamin K and nonvitamin K antagonists at presentation. Symptomatic presentation was defined as dAVF-related symptoms that led to its diagnosis. Baseline functional status was assessed using the modified Rankin Scale (mRS).[15] dAVF variables included Cognard classification, magnetic resonance imaging (MRI) hyperintensities (on fluid-attenuated inversion recovery or T2-weighted sequences that co-localized with the dAVF), and transverse/sigmoid sinus dAVF location.[3]

Follow-up and Outcomes

Radiological and clinical follow-up protocols were carried out at the discretion of the treating physicians and institutions. Follow-up durations were defined as the time period from diagnosis to last dAVF-related follow-up. Primary outcome was defined as mRS at final clinical follow-up.[15] Secondary outcomes were excellent (mRS 0-1) and good (mRS 0-2) outcomes, mortality, symptomatic improvement, and dAVF obliteration (confirmed on DSA) at final follow-up. Procedure-related complications (categorized into technical [no neurological sequelae, including vessel dissection, groin hematoma, and asymptomatic vessel perforation], transient with neurological sequelae, and permanent with neurological sequelae), dAVF-related hemorrhage, and dAVF-related nonhemorrhagic neurological deficits (NHND) during the follow-up period were also recorded.

Statistical Analysis

All statistical analyses were performed using Stata (version 14.2, StataCorp, College Station, Texas). Baseline characteristics were compared between the observation and intervention cohorts. Student's *t*-test or Wilcoxon rank-sum tests were used to compare continuous variables, and Pearson's χ^2 or Fisher's exact tests were used to compare categorical variables, where appropriate. To minimize patient selection bias, the 2 cohorts were matched, without replacement in a 1:1 ratio with a caliper of 0.05, using propensity scores derived from baseline characteristics comparisons with $P < .10$. Matching was performed using the PSMATCH2 package developed for Stata.[16] Univariable ordinal and binary logistic regression analyses and Fisher's exact test were performed on both the unmatched and matched cohorts to assess the relationships between dAVF management (observation or intervention) and the primary and secondary outcomes. Likelihood-ratio tests were performed to assess proportional odds assumption for ordinal logistic regression. Subgroup analysis was performed comparing primary and secondary outcomes between symptomatic patients in the matched cohorts. Statistical significance was defined as $P < .05$, and all tests were 2-tailed. Missing data were not imputed.

RESULTS

Study Cohort Characteristics

From the CONDOR database of 1077 dAVF patients, the overall study cohort comprised 355 low-grade dAVFs. The intervention and observation cohorts comprised 230 and 125 patients, respectively (Figure 1). The treatments in the unmatched intervention cohort were embolization alone (n = 180), embolization and surgery (n = 5), embolization and SRS (n = 32), surgery alone (n = 2), surgery and SRS (n = 1), and SRS alone (n = 10). Table 1 compares the baseline characteristics between the unmatched observation and intervention cohorts. Symptomatic presentation was more frequent in the intervention cohort (88.3% vs 51.2%, $P < .001$), whereas coronary artery disease was more common in the observation cohort (8.3% vs 3.1%, $P = .034$). The distributions of baseline mRS ($P = .002$) and Cognard classifications ($P = .018$) were also different between the unmatched cohorts.

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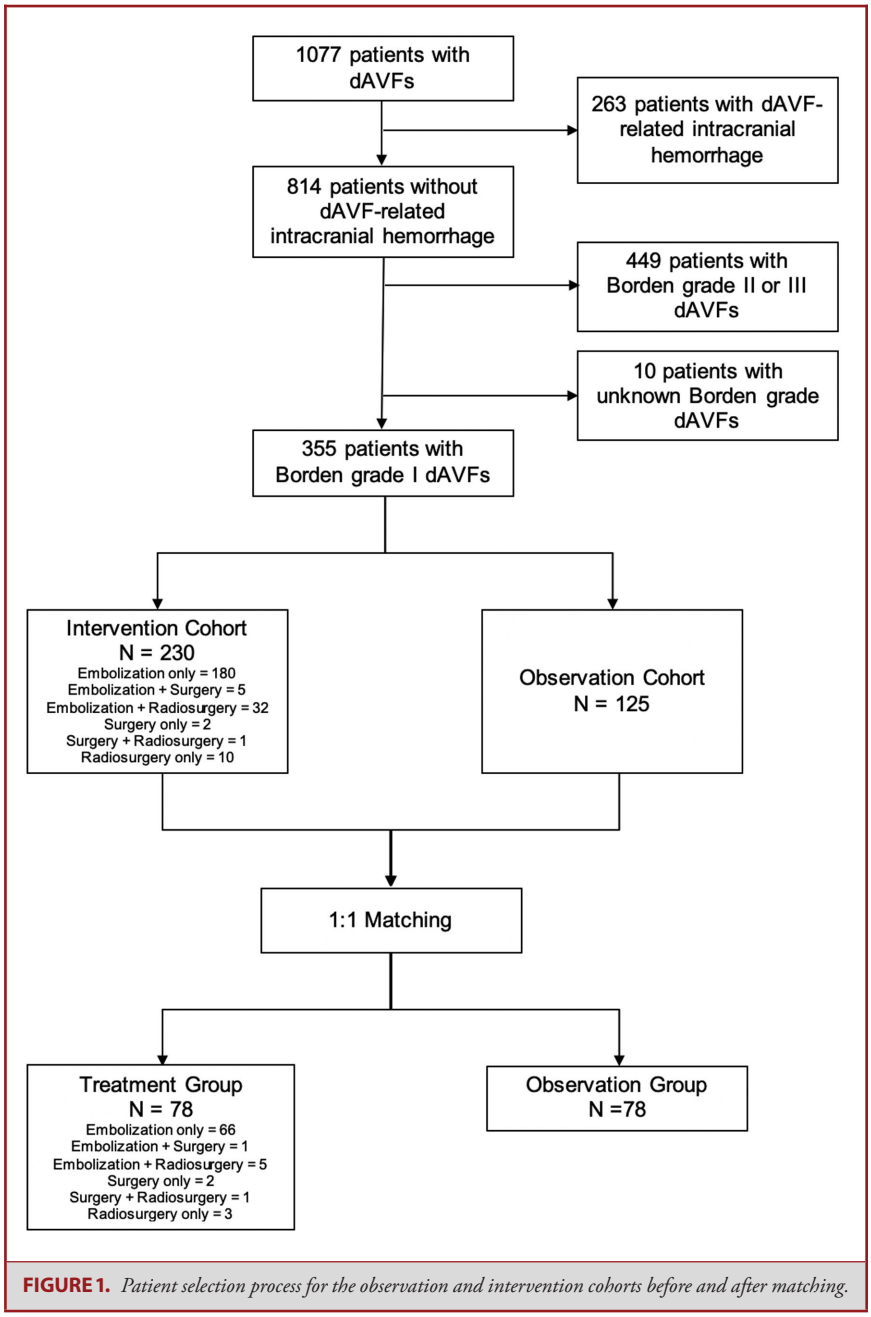

FIGURE 1. *Patient selection process for the observation and intervention cohorts before and after matching.*

Outcomes of Unmatched Observation Versus Intervention Cohorts

Table Table 2 compares the primary and secondary outcomes of the unmatched observation versus intervention cohorts. The mRS at final follow-up was similar between the 2 cohorts (Figure 2A). The dAVF obliteration rate was higher in the intervention cohort (78.5% vs 24.1%, $P < .001$). The remaining secondary outcomes were similar between the unmatched cohorts. Procedural complications occurred in 15.4% of the intervention cohort. All complications were attributed to embolization, including technical and asymptomatic, transiently symptomatic, and permanently symptomatic in 6.2% (n = 14/227), 6.6% (n = 15/227), and 2.6% (n = 6/227), respectively.

Matched Cohort Characteristics

The treatment and observation cohorts were matched using the covariates of coronary artery disease, symptomatic presentation, baseline mRS, Cognard classification, and radiological follow-up

TABLE 1. Comparison of Baseline Characteristics Between the Unmatched Observation and Intervention Cohorts

Characteristics	Total (n = 355)	Observation (n = 125)	Intervention (n = 230)	*P* value
Age, mean, yr (SD)	58.0 (15.6)	57.8 (14.7)	58.1 (16.1)	.849
Female, n (%)	217/355 (61.1)	74/125 (59.2)	143/230 (62.2)	.583
Myocardial infarction, n (%)	9/347 (2.6)	3/121 (2.5)	6/226 (2.7)	1.000
Coronary artery disease, n (%)	17/347 (4.9)	10/121 (8.3)	7/226 (3.1)	**.034**
Atrial fibrillation, n (%)	11/347 (3.2)	4/121 (3.3)	7/226 (3.1)	1.000
Ischemic stroke, n (%)	18/348 (5.2)	5/122 (4.1)	13/226 (5.8)	.506
Diabetes mellitus, n (%)	26/347 (7.5)	6/122 (4.9)	20/225 (8.9)	.180
Hypertension, n (%)	133/347 (38.3)	45/122 (36.9)	88/225 (39.1)	.684
Smoking, n (%)				.136
Never	205/284 (72.3)	56/87 (64.4)	149/197 (75.6)	
Past	58/284 (20.4)	22/87 (25.3)	36/197 (18.3)	
Current	21/284 (7.4)	9/87 (10.3)	12/197 (6.1)	
Alcohol use, n (%)	24/324 (7.4)	8/113 (7.1)	16/211 (7.6)	.869
Antiplatelet use, n (%)	64/341 (18.8)	24/120 (20.0)	40/221 (18.1)	.668
Anticoagulant use, n (%)	17/432 (5.0)	6/121 (5.0)	11/221 (5.0)	.994
Symptomatic, n (%)	267/355 (75.2)	64/125 (51.2)	203/230 (88.3)	**<.001**
Baseline mRS, n (%)				**.002**
0	139/350 (39.7)	79/226 (35.0)	60/124 (48.4)	
1	163/350 (46.6)	117/226 (51.8)	46/124 (37.1)	
2	29/350 (8.3)	22/226 (9.7)	7/124 (5.7)	
3	9/350 (2.6)	6/226 (2.7)	3/124 (2.4)	
4	1/350 (0.3)	0/226 (0)	1/124 (0.8)	
5	9/350 (2.6)	2/226 (0.9)	7/124 (5.7)	
Cognard classification, n (%)				**.018**
I	248/349 (71.1)	97/123 (78.9)	151/226 (66.8)	
IIa	101/349 (28.9)	26/123 (21.1)	75/226 (33.2)	
MRI T2/FLAIR hyperintensity, n (%)	33/305 (10.8)	9/113 (8.0)	24/192 (12.5)	.218
Transverse-sigmoid sinus location, n (%)	182/353 (51.6)	67/124 (54.0)	115/229 (50.2)	.494
Radiological follow-up, mean, mo (SD)	27.9 (35.7)	25.8 (34.6)	28.9 (36.3)	.439
Clinical follow-up, mean, mo (SD)	36.3 (42.0)	31.3 (39.5)	39.2 (43.2)	.091

FLAIR, fluid-attenuated inversion-recovery; SD = standard deviation.
They represent statistically significant values $p < 0.05$

(**Figure I, Supplemental Digital Content**). **Table I, Supplemental Digital Content** shows the reduction in standardized absolute bias for each propensity score matched covariate. The matched cohorts each comprised 78 patients (Figure 1). The treatments in the matched intervention cohort were embolization alone (n = 66), embolization and surgery (n = 1), embolization and SRS (n = 5), surgery alone (n = 2), surgery and SRS (n = 1), and SRS alone (n = 3). Table 3 shows that the baseline characteristics of the matched observation versus intervention cohorts were well balanced.

Comparison of Outcomes Between the Matched Treatment Versus Observation Cohorts

Table 4 compares the primary and secondary outcomes of the matched observation versus intervention cohorts. The mRS at final follow-up was similar between the matched cohorts (Figure 2B). The dAVF obliteration rate was higher in the matched intervention cohort (72.2% vs 25.4%, $P < .001$). The remaining secondary outcomes were similar between the matched cohorts. Of the 52 patients who had dAVF obliteration in the matched intervention cohort, 29 patients (55.8%) had symptomatic improvement. Of the 15 patients who had dAVF obliteration in the matched observation cohort, 13 patients (86.7%) had symptomatic improvement ($P = .029$). Procedural complications occurred in 19.2% of the matched intervention cohort. All complications were attributed to embolization, including technical and asymptomatic, transiently symptomatic, and permanently symptomatic in 7.7% (n = 6/78), 7.7% (n = 6/78), and 3.9% (n = 3/78), respectively.

Subgroup Analysis of Symptomatic Patients in the Matched Treatment vs Observation Cohorts

Symptomatic patients comprised 109 (70%) of the 156 patients in the matched cohorts, including 55 and 54 in the observation and intervention cohorts, respectively. Table 5 compares the primary and secondary outcomes of the symptomatic patients in the matched observation versus intervention cohorts. The mRS at final follow-up was similar between symptomatic patients in the matched cohorts (Figure 2C). The dAVF obliteration rate was higher in the symptomatic subgroup of the matched

TABLE 2. Comparison of Primary and Secondary Outcomes Between the Unmatched Observation and Intervention Cohorts

	Observation (n = 125)	Intervention (n = 230)	OR [95% CI]	*P* value
Primary outcome				
mRS, median (IQR)	0 (0-1)	1 (0-1)	0.978 [0.636-1.503]	.919
Secondary outcomes				
Excellent outcome, n (%)	98/115 (85.2)	183/215 (85.1)	0.992 [0.524-1.876]	.980
Good outcome, n (%)	105/115 (91.3)	204/215 (94.9)	1.766 [0.727-4.293]	.209
Mortality, n (%)	2/115 (1.7)	2/215 (0.9)	0.531 [0.074-3.816]	.529
Symptomatic improvement, n (%)	45/114 (39.5)	103/218 (47.3)	1.373 [0.867-2.176]	.177
dAVF obliteration, n (%)	19/79 (24.1)	168/214 (78.5)	11.533 [6.264-21.234]	**<.001**
Procedural complication, n (%)	–	35/227 (15.4)	–	–
Hemorrhage, n (%)	0/112 (0)	2/220 (0.9)	–	.552[a]
NHND, n (%)	0/114 (0)	6/214 (2.8)	–	.096[a]

CI, confidence interval; IQR, interquartile range; OR, odds ratio.
[a] Fisher's exact test.
Excellent outcome = mRS 0-1; good outcome = mRS 0-2.
They represent statistically significant values p < 0.05

intervention cohort (68.8% vs 22.2%, $P < .001$). The remaining secondary outcomes were similar between symptomatic patients in the matched cohorts. Procedural complications occurred in 20.4% of symptomatic patients in the matched intervention cohort. All complications were attributed to embolization, including technical and asymptomatic, transiently symptomatic, and permanently symptomatic in 11.1% (n = 6/54), 3.7% (n = 2/54), and 5.6% (n = 3/54), respectively.

DISCUSSION

The pathological mechanisms of dAVF formation remain elusive. While most dAVFs are acquired idiopathically, a subset of these lesions have been reported to arise from venous sinus thrombosis, infection, traumatic head injury, craniotomy, or tumors.[17-20] These anomalous anastomoses result in arteriovenous shunting between arteries that perfuse the dura and venous sinuses or cortical veins.[1] Presence of cortical venous drainage (CVD), either from direct connections or reflux through adjacent venous sinuses, is often associated with an aggressive clinical course (eg, hemorrhage, NHND) that can lead to substantial neurological morbidity and mortality.[2,3,17,21,22] dAVF-related hemorrhage is thought to arise from the rupture of fragile arterialized veins that have been progressively weakened from by persistent CVD and venous hypertension.[1,17,23] Venous congestion due to CVD can also contribute to NHND by precluding adequate arterial oxygen delivery and toxic waste product removal.[24,25] Hence, the primary goals of dAVF treatment are to reduce initial or recurrent hemorrhage risk and ameliorate or prevent NHND, and these risks are largely confined to high-grade dAVFs.

In contrast to high-grade dAVFs, low-grade lesions have direct arteriovenous anastomoses between meningeal arteries and dural venous sinuses without CVD. As such, low-grade dAVFs have a benign natural history which is rarely associated with hemorrhage or NHND.[4-6] Patients with low-grade dAVFs often present with headaches, tinnitus, and/or ocular symptoms. In a retrospective cohort study of 112 low-grade dAVFs that were managed conservatively or incompletely treated, Satomi et al[4] reported one hemorrhage and no NHND over a period of 28 mo, which translates to annual neurological event and mortality rates of 0.6% and 0%, respectively. Shah et al[5] observed 0% neurological event and mortality rates in 19 conservatively managed or incompletely treated low-grade dAVFs with 5.6 yr of follow-up. Gross and Du[6] also reported no neurological events or deaths in 24 low-grade dAVFs that were managed conservatively over 60.9 lesion-years. Taken together, low-grade dAVFs appear to harbor a very low neurological morbidity (0%-0.6% per year) and negligible mortality rates.

Given the modest risks of hemorrhage and NHND associated with low-grade dAVFs, their treatment is controversial. Management of low-grade dAVFs based on symptoms has been recommended, and intervention requires one to consider the risk to benefit profile of each therapeutic modality.[1] Furthermore, it remains unknown whether treatment alters the natural history of low-grade dAVFs, as neither spontaneous obliteration nor symptom resolution is uncommon with these lesions. In a study comprising 54 patients harboring 55 low-grade dAVFs, Davies et al[26] observed symptom resolution or improvement in 81% of untreated patients. In the same study, 86% of treated patients, most of whom underwent transarterial embolization, had symptom resolution or improvement, and 2 had procedural complications. Satomi et al[4] reported tolerable, stable symptoms in 98.5% of conservatively managed low-grade dAVF patients (n = 68) versus 97.7% of treated patients (n = 43) who primarily underwent embolization. Shah et al[5] found complete symptom resolution in 53.8% of endovascularly treated low-grade dAVFs patients (n = 13) at a mean follow-up of 3.6 yr, resulting in mean mRS and Barthel Index of 0.5 and 99.6, respectively. In the same study, 80% of conservatively managed low-grade dAVF patients (n = 10) had no new symptoms at a mean follow-up of 6.5 yr, resulting in mean mRS and Barthel Index of 0.2

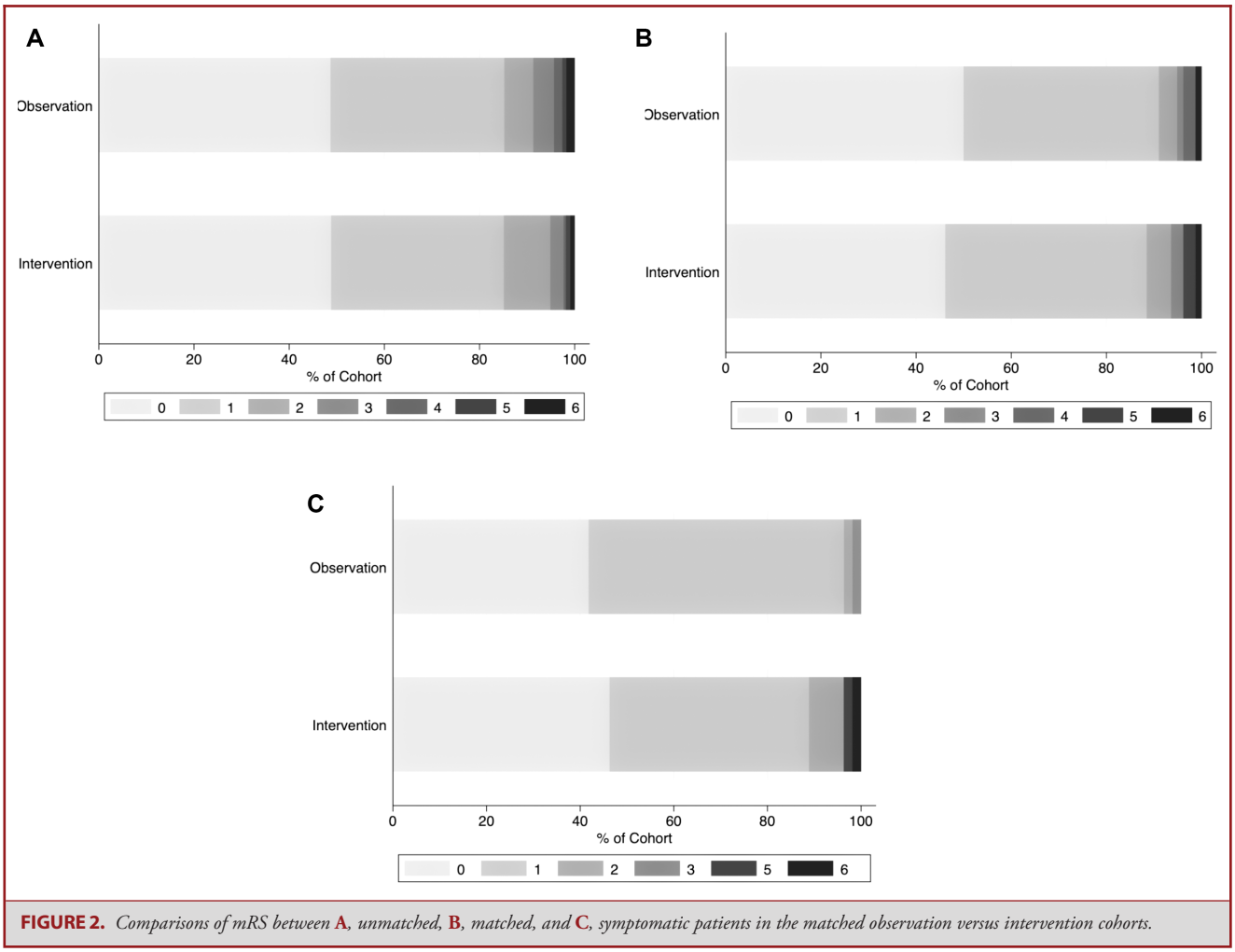

FIGURE 2. *Comparisons of mRS between* **A**, *unmatched,* **B**, *matched, and* **C**, *symptomatic patients in the matched observation versus intervention cohorts.*

and 94.3, respectively. However, direct comparisons between the intervention and observation cohorts could not be made in these aforementioned studies due to selection bias and small cohort sizes.

Key Findings and Secondary Outcomes

In this multicenter, retrospective matched cohort analysis of the CONDOR database, we compared functional outcomes, angiographic results, and adverse events between observation and intervention for low-grade dAVFs. The present study represents the largest cohort of low-grade dAVFs to date. To control for selection bias, the observation and intervention cohorts were propensity score matched using baseline characteristics. Functional outcomes and the rates of mortality, symptomatic improvement, hemorrhage, and NHND were similar between the matched cohorts, although obliteration was achieved in a higher proportion of treated low-grade dAVFs. A subgroup analysis of symptomatic patients in the matched observation versus intervention cohorts showed similar findings. Among patients with dAVF obliteration, symptomatic improvement rates were lower in those who underwent treatment compared to observation, which may signify potential negating effects of treatment on outcome. Despite procedural complications in 19% of the matched intervention cohort, treatment of low-grade dAVFs did not appear to worsen functional disability compared to conservative management. Although the intervention cohort's complication rate appears high, procedure-related complications that resulted in permanently symptomatic deficits occurred in only 3.9%. However, since low-grade dAVFs harbor low risks of hemorrhage or progressive neurological symptoms, tolerance for any interventional complications is similarly modest.

Interpretation

Overall, the benefits of low-grade dAVF treatment may be negated by procedural complications in the intervention cohort and spontaneous symptomatic improvement in the observation

TABLE 3. Comparison of Baseline Characteristics Between the Matched Observation and Intervention Cohorts

Characteristics	Observation (n = 78)	Intervention (n = 78)	*P* value
Age, mean, yr (SD)	56.7 (15.0)	57.6 (16.7)	.744
Female, n (%)	48/78 (61.5)	39/78 (50.0)	.147
Myocardial infarction, n (%)	2/78 (2.6)	2/78 (2.6)	1.000
Coronary artery disease, n (%)	3/78 (3.9)	4/78 (5.1)	1.000[a]
Atrial fibrillation, n (%)	2/78 (2.6)	2/78 (2.6)	1.000
Ischemic stroke, n (%)	1/78 (1.3)	4/78 (5.1)	.367
Diabetes mellitus, n (%)	5/78 (6.4)	6/77 (7.8)	.765
Hypertension, n (%)	24/78 (30.8)	31/78 (40.3)	.217
Smoking, n (%)			.851
Never	36/52 (69.2)	48/68 (70.6)	
Past	11/52 (21.2)	12/68 (17.7)	
Current	5/52 (9.6)	8/68 (11.8)	
Alcohol use, n (%)	4/72 (5.6)	8/70 (11.4)	.241
Antiplatelet use, n (%)	11/77 (14.3)	18/74 (24.3)	.117
Anticoagulant use, n (%)	5/77 (6.5)	4/74 (5.4)	1.000
Symptomatic, n (%)	55/78 (70.5)	54/78 (69.2)	.861[a]
Baseline mRS, n (%)			.319[a]
0	38/78 (48.7)	50/78 (64.1)	
1	31/78 (39.7)	20/78 (25.6)	
2	4/78 (5.1)	4/78 (5.1)	
3	1/78 (1.3)	2/78 (2.6)	
4	1/78 (1.3)	0/78 (0)	
5	3/78 (3.9)	2/78 (2.6)	
Cognard classification, n (%)			.493[a]
I	55/78 (70.5)	51/78 (65.4)	
IIa	23/78 (29.5)	27/78 (34.6)	
MRI T2/FLAIR hyperintensity, n (%)	6/71 (8.5)	7/66 (10.6)	.667
Transverse-sigmoid sinus location, n (%)	42/77 (54.6)	37/78 (47.4)	.376
Radiological follow-up, mean, mo (SD)	28.4 (33.9)	22.8 (33.0)	.301[a]
Clinical follow-up, mean, mo (SD)	32.6 (36.5)	38.5 (46.9)	.379

FLAIR, fluid-attenuated inversion-recovery; SD, standard deviation.
[a]Matched covariates.
They represent statistically significant values $p < 0.05$

cohort. Therefore, we found no evidence to support routine treatment of low-grade dAVFs.

Limitations

It is important to note the limitations of the current study. The results are contingent upon the accuracy and reliability of data provided by each participating institution, and the data may be subject to reporting bias. In addition, the balance of both measured and unmeasured covariates between the observation and intervention cohorts may be constrained by the modest dataset available for propensity score matching and the nonrandomized study design. Therefore, we presented both the unmatched and matched analyses. The specific indication for treatment of each low-grade dAVF could not be ascertained from the CONDOR database, and as such, we acknowledge that the results may be confounded by variations in goals of intervention. Furthermore, the capture of specific symptoms was not complete in the database, and hence presence of symptoms and symptomatic improvement was broadly categorized. Consequently, subgroup analyses of specific symptoms could not be performed. The specific treatment techniques and respective follow-ups were left to the discretion of the treating physician to provide the most appropriate management strategy. The range and severity of presenting symptomatology could influence management decisions. Despite being categorized as low-grade dAVFs, these lesions have heterogeneous angioarchitecture, and our matched analysis may not fully account for such variations. Furthermore, the modality of standalone or combined therapies was based on the experience of the treating physician and patient preference, and this lack of dAVF treatment standardization contributes to heterogeneity of the intervention cohort. Defining patient- and DAVF-specific criteria for intervention will be important in future prospective studies of these lesions. The modest number of low-grade dAVFs treated with each approach precludes subgroup analysis by interventional modality.

Generalizability

We are unable to make recommendations regarding observation algorithm (eg, interval and frequency of radiological and

TABLE 4. Comparison of Primary and Secondary Outcomes Between the Matched Observation and Intervention Cohorts

	Observation (n = 78)	Intervention (n = 78)	OR [95% CI]	*P* value
Primary outcome				
mRS, median (IQR)	0.5 (0-1)	1 (0-1)	1.192 [0.653-2.177]	.567
Secondary outcomes				
Excellent outcome, n (%)	71/78 (91.0)	69/78 (88.5)	0.756 [0.267-2.142]	.599
Good outcome, n (%)	74/78 (94.9)	73/78 (93.6)	0.789 [0.204-3.056]	.732
Mortality, n (%)	1/78 (1.3)	1/78 (1.3)	1.000 [0.061-16.277]	1.000
Symptomatic improvement, n (%)	35/77 (45.5)	36/78 (46.2)	1.029 [0.547-1.935]	.930
dAVF obliteration, n (%)	15/59 (25.4)	52/72 (72.2)	7.627 [3.494-16.647]	**<.001**
Procedural complication, n (%)	–	15/78 (19.2)	–	–
Hemorrhage, n (%)	0/74 (0)	0/78 (0)	–	–
NHND, n (%)	0/76 (0)	3/76 (4.0)	–	.245

CI, confidence interval; IQR, interquartile range; OR, odds ratio.
Excellent outcome = mRS 0-1; good outcome = mRS 0-2.
They represent statistically significant values $p < 0.05$

TABLE 5. Comparison of Primary and Secondary Outcomes Between Symptomatic Patients in the Matched Observation and Intervention Cohorts

	Observation (n = 55)	Intervention (n = 54)	OR [95% CI]	*P* value
Primary outcome				
mRS score, median (IQR)	1 (0-1)	1 (0-1)	1.001 [0.483-2.074]	.997
Secondary outcomes				
Excellent outcome, n (%)	53/55 (96.4)	48/54 (88.9)	0.302 [0.058-1.568]	.154
Good outcome, n (%)	54/55 (98.2)	52/54 (96.3)	0.481 [0.042-5.472]	.556
Mortality, n (%)	0/55 (0)	1/54 (1.9)	–	.495[a]
Symptomatic improvement, n (%)	23/54 (42.6)	26/54 (48.2)	1.252 [0.586-2.673]	.562
dAVF obliteration, n (%)	10/45 (22.2)	33/48 (68.8)	7.700 [3.036-19.532]	**<.001**
Procedural complication, n (%)	–	11/54 (20.4)	–	–
Hemorrhage, n (%)	0/51 (0)	0/54 (0)	–	–
NHND, n (%)	0/53 (0)	3/52 (5.8)	–	.118[a]

CI, confidence interval; IQR, interquartile range; OR, odds ratio.
[a]Fisher's exact test.
Excellent outcome = mRS 0-1; good outcome = mRS 0-2.
They represent statistically significant values $p < 0.05$

clinical assessments, neuroimaging modality, outcome metrics). The findings of this study may not be generalizable to all low-grade dAVFs, as most patients presented with a baseline mRS 0 to 1, harbored dAVFs located at the transverse-sigmoid sinus, and were symptomatic. Additionally, all low-grade dAVFs patients with ocular symptoms (ie, chemosis, ophthalmoplegia, diplopia, and visual deficit) were treated, and therefore our results are likely inapplicable to this subset of cases. Lastly, the overall mean clinical follow-up duration of 36 mo may not be sufficient to comparatively assess the long-term outcomes of observation versus intervention. Further longitudinal analysis is required to clarify the optimal management algorithm for patients with low-grade dAVFs.

CONCLUSION

Intervention for low-grade intracranial dAVFs improves the likelihood of obliteration compared to conservative management, but it does not appear to reduce symptomatic burden or functional disability. Symptomatic presentation did not alter the comparative effectiveness of observation versus intervention for low-grade dAVFs. The potential benefits of low-grade dAVF treatment may be negated by procedure-related complications in the intervention cohort and spontaneous obliteration and symptomatic improvement in the observation cohort. Therefore, our findings do not support the routine treatment of low-grade dAVFs. Future studies are necessary to justify the treatment of appropriately selected low-grade dAVFs.

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REFERENCES

1. Reynolds MR, Lanzino G, Zipfel GJ. Intracranial dural arteriovenous fistulae. *Stroke*. 2017;48(5):1424-1431.
2. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. *J Neurosurg*. 1995;82(2):166-179.
3. Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. *Radiology*. 1995;194(3):671-680.
4. Satomi J, van Dijk JM, Terbrugge KG, Willinsky RA, Wallace MC. Benign cranial dural arteriovenous fistulas: outcome of conservative management based on the natural history of the lesion. *J Neurosurg*. 2002;97(4):767-770.
5. Shah MN, Botros JA, Pilgram TK, et al. Borden-Shucart type I dural arteriovenous fistulas: clinical course including risk of conversion to higher-grade fistulas. *J Neurosurg*. 2012;117(3):539-545.
6. Gross BA, Du R. The natural history of cerebral dural arteriovenous fistulae. *Neurosurgery*. 2012;71(3):594-603; discussion 602-593.
7. van Dijk JM, terBrugge KG, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. *Stroke*. 2002;33(5):1233-1236.
8. Duffau H, Lopes M, Janosevic V, et al. Early rebleeding from intracranial dural arteriovenous fistulas: report of 20 cases and review of the literature. *J Neurosurg*. 1999;90(1):78-84.
9. Soderman M, Pavic L, Edner G, Holmin S, Andersson T. Natural history of dural arteriovenous shunts. *Stroke*. 2008;39(6):1735-1739.
10. Strom RG, Botros JA, Refai D, et al. Cranial dural arteriovenous fistulae: asymptomatic cortical venous drainage portends less aggressive clinical course. *Neurosurgery*. 2009;64(2):241-248; discussion 247-248.
11. Chen CJ, Buell TJ, Diamond J, et al. Stereotactic radiosurgery for high-grade intracranial dural arteriovenous fistulas. *World Neurosurg*. 2018;116:e640-e648.
12. Chen CJ, Lee CC, Ding D, et al. Stereotactic radiosurgery for intracranial dural arteriovenous fistulas: a systematic review. *J Neurosurg*. 2015;122(2):353-362.
13. Gross BA, Du R. Surgical treatment of high grade dural arteriovenous fistulae. *J Clin Neurosci*. 2013;20(11):1527-1532.
14. Sadeh-Gonike U, Magand N, Armoiry X, et al. Transarterial onyx embolization of intracranial dural fistulas: a prospective cohort, systematic review, and meta-analysis. *Neurosurgery*. 2018;82(6):854-863.
15. Rankin J. Cerebral vascular accidents in patients over the age of 60: II. Prognosis. *Scott Med J*. 1957;2(5):200-215.
16. Leuven E, Sianesi B. PSMATCH2: Stata Module to Perform Full Mahalanobis and Propensity Score Matching, Common Support Graphing, and Covariate Imbalance Testing. 2003; 4.0.11: http://ideas.repec.org/c/boc/bocode/s432001.html. Accessed October 10, 2020.
17. Brown RD Jr, Wiebers DO, Nichols DA. Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients. *J Neurosurg*. 1994;81(4):531-538.
18. Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML. Natural history, evaluation, and management of intracranial vascular malformations. *Mayo Clin Proc*. 2005;80(2):269-281.
19. Bulters DO, Mathad N, Culliford D, Millar J, Sparrow OC. The natural history of cranial dural arteriovenous fistulae with cortical venous reflux—the significance of venous ectasia. *Neurosurgery*. 2012;70(2):312-319; discussion 318-319.
20. Vellimana AK, Daniels DJ, Shah MN, Zipfel GJ, Lanzino G. Dural arteriovenous fistulas associated with benign meningeal tumors. *Acta Neurochir*. 2014;156(3):535-544.
21. Zipfel GJ, Shah MN, Refai D, Dacey RG Jr, Derdeyn CP. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. *Neurosurg Focus*. 2009;26(5):E14.
22. Awad IA, Little JR, Akarawi WP, Ahl J. Intracranial dural arteriovenous malformations: factors predisposing to an aggressive neurological course. *J Neurosurg*. 1990;72(6):839-850.
23. Lasjaunias P, Chiu M, ter Brugge K, Tolia A, Hurth M, Bernstein M. Neurological manifestations of intracranial dural arteriovenous malformations. *J Neurosurg*. 1986;64(5):724-730.
24. Kuroda S, Furukawa K, Shiga T, et al. Pretreatment and posttreatment evaluation of hemodynamic and metabolic parameters in intracranial dural arteriovenous fistulae with cortical venous reflux. *Neurosurgery*. 2004;54(3):585-592; discussion 591-582.
25. Iwama T, Hashimoto N, Takagi Y, et al. Hemodynamic and metabolic disturbances in patients with intracranial dural arteriovenous fistulas: positron emission tomography evaluation before and after treatment. *J Neurosurg*. 1997;86(5):806-811.
26. Davies MA, Saleh J, Ter Brugge K, Willinsky R, Wallace MC. The natural history and management of intracranial dural arteriovenous fistulae. Part 1: benign lesions. *Interv Neuroradiol*. 1997;3(4):295-302.

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Supplemental Digital Content. Figure I. Standardized percentage bias across matched covariates before and after propensity score matching. mRS = modified Rankin Scale. **Table I.** Propensity score matched variables before and after matching and reduction in standardized bias. mRS = modified Rankin Scale; std. = standardized.

COMMENT

The authors query a multi-center registry (CONDOR) for data on Borden type I or Cognard type I and IIa intracranial dAVFs without prior hemorrhage to compare observation to intervention. While no data is provided on why certain lesions were treated, there is a higher rate of "symptomatic" lesions (88% vs 51%) and Cognard IIa lesions (33% vs 21%) in the intervention cohort. Outcomes data are provided for an unmatched cohort and, importantly, a propensity score-matched cohort of 109 patients. Mean follow-up was 36 m.

Some key observations include: (1) a 25% rate of spontaneous obliteration with observation, (2) a 15-20% complication rate (~2-4% permanent deficits) with intervention (mostly endovascular was used), and (3) a 70-75% obliteration rate with attempted intervention. While the authors reiterate that the risks outweigh the benefits when treating these lesions to reduce hemorrhage rate, which is essentially already known, they further attempt to address effect on symptoms, which is why low grade lesions are typically treated. Interestingly, when treatment is attempted, there is no difference in general symptom improvement, just a higher risk of complications. In the matched observation cohort, 86.7% of obliterated dAVFs had symptomatic improvement compared to only 55.8% in the matched intervention cohort. However, neither specific symptoms nor criteria for improvement are defined, which is a notable limitation in the strength of the findings. Future studies are tasked with providing further granular data on specific symptoms and criteria for improvement in order to better define a role for intervention in selected subgroups.

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