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CLINICAL ARTICLE

Clinical and prognostic features of venous hypertensive myelopathy from craniocervical arteriovenous fistulas: a retrospective cohort study

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OBJECTIVE Current knowledge about venous hypertensive myelopathy (VHM) is incomplete. This study was performed with the aim of clarifying the clinical features and outcomes of craniocervical VHM.

METHODS This retrospective, single-center cohort study included 65 patients with craniocervical junction arteriovenous fistulas resulting in VHM treated in Xuanwu Hospital from January 1, 2002, to December 30, 2020. All patients underwent microsurgery or endovascular treatment. The primary outcome was neurological function assessment using the Japanese Orthopaedic Association (JOA) scale, modified Aminoff-Logue Scale (mALS), and Venous Hypertensive Myelopathy Scale (VHMS). The secondary outcomes were recurrences and postoperative adverse events. Pearson linear regression and receiver operating characteristic curves were used to evaluate the relationships among the three scales. Kaplan-Meier and multivariate logistic regression analyses were performed to predict outcomes.

RESULTS The mean patient age was 57.4 ± 11.4 years, and 88% of patients were male. The 1-year follow-up rate was 83.1%, and the 5-year follow-up rate was 50.8%. The VHMS was correlated with the JOA (R^2 = 0.6722) and mALS (R^2 = 0.7399) and increased the assessment accuracy by approximately 20% when compared with the other two scales. Overall, 25.9% of patients experienced delayed neurological decline beyond the 1-year follow-up. Further logistic regression suggested that age > 65 years was an independent predictor (OR 7.831, 95% CI 1.090–56.266; p = 0.041). Embolic recanalization and new bilateral symmetry feeders were the major reasons for recurrence. Recurrence increased the risk of adverse events after the second surgery (OR 20.455, 95% CI 1.170–357.320; p = 0.039).

CONCLUSIONS CCJ AVFs resulting in VHM are a rare but deadly complication, and providers should be cautious of age-related delayed neurological decline and strive for a one-time anatomical cure.

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KEYWORDS craniocervical junction arteriovenous fistula; venous hypertensive myelopathy; spinal dural arteriovenous fistula; neurological deterioration; recurrence; vascular disorders

Venous hypertensive myelopathy (VHM) is rare and is often caused by a spinal arteriovenous fistula (AVF), especially a spinal dural AVF (SDAVF).[1] Some cohort studies have demonstrated that the thoracic and lumbar spinal cord are the most commonly affected sites of SDAVF.[2,3] However, it is indispensable to recognize and manage VHM arising from craniocervical junction (CCJ) AVFs. Scholars have supported that intracranial dural AVFs draining into the bridging vein of the medulla might be homologs of SDAVFs.[4] These have the same pathological mechanisms with different clinical features due to the various locations of the lesions. In recent

ABBREVIATIONS ALS = Aminoff-Logue Scale; APA = ascending pharyngeal artery; AVF = arteriovenous fistula; CCJ = craniocervical junction; DND = delayed neurological decline; DSA = digital subtraction angiography; END = early neurological deterioration; JOA = Japanese Orthopaedic Association; NIR = neurological improvement rate; ROC = receiver operating characteristic; SDAVF = spinal dural AVF; VA = vertebral artery; VHM = venous hypertensive myelopathy; VHMS = Venous Hypertensive Myelopathy Scale.

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decades, CCJ AVFs resulting in VHM have been reported in some case series that have described unique manifestations involving the brainstem and upper limbs.[5–7]

To date, researchers have illuminated the angioarchitecture and short-term prognosis of CCJ AVFs.[8–10] However, the clinical features and long-term prognosis of CCJ AVFs with VHM are unknown. We recently found a higher incidence (approximately 50%) of neurological deterioration in a 6-year follow-up of SDAVF patients with VHM.[11] This finding indicated that surgery might be the final treatment for SDAVFs but not for VHM. Equally important to surgery were long-term follow-up and rehabilitation after surgery. This current study was a single-center, retrospective cohort study of CCJ AVFs resulting in VHM that will improve the understanding of the clinical features and prognosis of VHM.

Methods

Participants

A CCJ AVF was defined as a subdural, dural, or epidural AVF without a nidus located at the jugular foramen, hypoglossal canal, foramen magnum, or C1 or C2 vertebral levels. The inclusion criteria for patients with a CCJ AVF resulting in VHM were as follows: 1) digital subtraction angiography (DSA) showing that the fistula drained into the spinal cord, medulla oblongata, paravertebral veins, or jugular vein; 2) the spinal cord or medulla showed a hyperintense signal on T2-weighted MRI; and 3) the clinical presentations were limb weakness and urination and defecation dysfunction. The first inclusion item was necessary, and the other two were optional. The exclusion criteria were as follows: 1) presence of hemorrhagic lesions on CT or MRI or the patient experienced a sudden unbearable headache; 2) MRI showing that there was a large expansion of drainage vessels and that there was resultant compression of the surrounding nerves; and 3) clinical presentation of single pulsatile tinnitus, headache, dizziness, and cranial nerve palsy without evidence of spinal cord and medulla edema. Two neurosurgeons (Y.M. and C.Y.) independently screened the medical records and resolved any disagreements through discussion. Following Hiramatsu et al., AVFs were divided into dural, radicular, epidural, and perimedullary AVFs.[8] The neurological function assessment was performed at admission, 7 days, and 1, 3, 5, and 7 years postoperatively through telephone or clinic visits. MRI and DSA reexaminations were conducted at 7 days and 1 year postsurgery. The follow-up physicians changed annually and were blinded to the previous records. This study was approved by the ethics committee of Xuanwu Hospital, and all patients signed informed consent forms. Flowcharts of the recruitment process are summarized in Supplementary Fig. 1.

Clinical Data Collection

A neurosurgeon (Z.S.) reviewed the medical records of the patients and extracted the following information: disease duration, clinical manifestation, physical and laboratory examination, history of misdiagnosis and steroid therapy, surgical procedure, neurological functional scoring, complications, and recurrence, among other factors. Disease duration was defined as the time from symptom onset to the last surgical treatment. Misdiagnosis was the experience of an ineffective surgical or medical treatment for other related diseases. The CSF was collected through lumbar puncture before treatment and was tested by our hospital laboratory. All patients underwent 1.5T or 3.0T MRI preoperatively, and 59 patients were available for complete sequences, including sagittal T1-weighted and T2-weighted and axial T2-weighted sequences. The "missing-piece" and "snake-eyes" signs were identified according to the literature description.[12,13] The imaging data from other hospitals were retained in JPG format through an X-ray scanner (Medi-6200, Microtek Corp.), and images obtained at our hospital were saved as DICOM files. All images were confirmed and analyzed by a neurosurgeon and a neuroradiologist.

Surgical Procedure

All patients received intervention, including microsurgical disconnection and endovascular treatment, at our center. Surgery was the first-line therapy. In brief, the fistula was exposed by a C1–2 laminectomy and an occipital craniotomy. Then, the fistula was excised through bipolar electrocoagulation and microscissors. Embolization was considered when the fistula was difficult to expose from a posterior approach or if the patient did not tolerate open surgery.

Outcomes

The primary outcomes were evaluation of the patient's neurological function using the modified Aminoff-Logue Scale (mALS),[2] Japanese Orthopaedic Association (JOA) scale,[14] and Venous Hypertensive Myelopathy Scale (VHMS). The VHMS was developed based on the patient's clinical presentations and physical examination, the mALS (lower limb function, urination, and defecation), and JOA (upper limb and sensory function). More details are provided in Supplementary Table 1. We refer to Kato et al. for details on data processing.[15] The neurological improvement rate (NIR) was calculated as follows: NIR = (preoperative score − postoperative score)/preoperative score × 100%. The NIRs were categorized as deteriorated (NIR < 0%), ineffective (NIR < 25%), effective (25% ≤ NIR < 60%), notable improvement (NIR ≥ 60%), and cure (NIR = 100%). Early neurological deterioration (END) was defined as an NIR < 0 within 7 days postoperatively. Delayed neurological decline (DND) was defined as an NIR decrease of at least one grade after a 1-year follow-up that was maintained or even worsened until the end of follow-up. The secondary outcomes were recurrence and adverse events comprising surgical complications and END. The time to recurrence was calculated from the date of initial surgery to rediagnosis by DSA.

Statistical Analysis

In this study, all statistics were performed using GraphPad Prism (version 9.0.0) or R (version 3.6.3) software. Continuous variables were described as the mean (SD) for data with a normal distribution or the median [IQR] for nonnormally distributed data. The trend of NIR was not

normally distributed at different time points, so a Friedman test was used. Fisher's exact test was used to compare the distributions of adverse events and recurrence between the two treatments. Pearson linear regression was used to evaluate the correlation among the three neurological scales. Receiver operating characteristic (ROC) curves were used to compare the prediction efficiency of postoperative neurological deterioration among the three scales. The independent variables were END calculated from each neurological function scale, and the outcome variable was judged by two senior neurosurgeons. Recurrence was analyzed using Kaplan-Meier survival curves. The DND and adverse events were analyzed by multivariable logistic regression.

Results

Demographic and Clinical Features

The clinical characteristics of the 65 patients included in this study are presented in Table 1. The 1- and 5-year follow-up rates were 83.1% (54/65) and 50.8% (33/65), respectively. The mean age was 57.4 (SD 11.4) years, and the male/female ratio was 8:1. Most patients developed symptoms slowly and insidiously with a median duration of 7.2 months. The minimum length of disease duration was 1 week, and the maximum was 5 years. Unfortunately, 46.2% (30/65) of patients were misdiagnosed with other diseases, such as myelitis, and were treated accordingly. Twenty-six patients received steroid therapy before the surgery, of whom 65.4% worsened and 11.5% experienced temporary remission. CSF laboratory examinations suggested that elevated proteins were common among the patients (71.4%, 5/7), and the patients' cell counts were occasionally increased. However, immunological evidence is lacking.

The imaging characteristics of CCJ AVF resulting in VHM are shown in Fig. 1. The fluid-void sign, a specific presentation on the T2-weighted sequence, was found in 73.3% of patients (Fig. 1A). Meanwhile, the majority of patients had a long segment of hyperintensity on sagittal T2-weighted MRI, and the lesions could involve the region from the medulla to the lumbar area. Interestingly, the axial T2-weighted sequence revealed irregular features, including transverse, gray matter–specific, or unilateral hyperintensity (Fig. 1B, E, and I). Approximately 75% of the patients had enhanced lesions (29/40) and abnormal vessels (31/40) on the enhanced T1-weighted sequences, and some patients had snake-eye signs (Fig. 1F) and missing-piece signs (Fig. 1G). Ten patients showed neither fluid-void signs on T2-weighted sequences nor abnormally enhanced vasculature on enhanced T1-weighted sequences (Fig. 1J and K). These patients often were suspected of having VHM due to exacerbations after steroid therapy, which was eventually confirmed by angiography. DSA showed that CCJ AVFs resulting in VHM were more likely to occur at the C1 level (72.3%). The most common feeding artery was the dural branch of the vertebral artery (VA; 86.2%), followed by the ascending pharyngeal artery (APA) and occipital artery. Two patients had fistulas that mainly drained into the epidural venous plexus, and the rest of the fistulas were predominantly

TABLE 1. Clinical characteristics of CCJ AVF resulting in VHM

Characteristic	Value
Sex ratio (male/female)	8:1 (58/7)
Mean age, yrs	57.4 ± 11.4
Median disease duration, mos	7.2 (2–10.5)
Hx misdiagnosis*	30 (46.2)
Myelitis	19
Spinal degenerative disease	7
Other	4
Steroid therapy	26 (40.0)
Exacerbated symptoms	17
Reduced symptoms	3
CSF lab tests (n = 7)	
Median total blood cell count, 10^6/L	4 (1–200)
Median WBC count, 10^6/L	2 (0–4)
Median protein level, mg/dL	73.8 ± 48.6
T2WI (n = 60)†	
Fluid-void sign	49 (81.7)
Hyperintensity	
Involved brainstem	9 (15.0)
Involved brainstem & spinal cord	29 (48.3)
Involved spinal cord	22 (36.7)
T1WI enhancement (n = 31)	
Intramedullary enhancement	24 (77.4)
Drainage vessel enhancement	24 (77.4)
Missing-piece sign	6 (19.4)
Snake-eye sign	3 (9.7)
Angiography	
Location	
Jugular foramen	2 (3.1)
Hypoglossal canal	1 (1.5)
Foramen magnum	9 (13.8)
C1	47 (72.3)
C2	6 (9.2)
Feeding arteries‡	
VA dural branch	56 (86.2)
APA	11 (16.9)
Occipital artery	4 (6.2)
Meningohypophyseal trunk	3 (4.6)
Anterior spinal artery	3 (4.6)
Other	2 (3.1)
Drainage veins	
Perimedullary	50 (76.9)
Intracranial	3 (4.6)
Both perimedullary & intracranial	10 (15.4)
Epidural & paravertebral	2 (3.1)

Hx = history of; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; WBC = white blood cell.
Values are presented as the number of patients (%), median (IQR), or mean ± SD.
* All misdiagnosed patients were treated accordingly with poor therapeutic effects. "Other" includes prostatic hyperplasia, hemorrhoids, and cerebral infarction.
† The original MRI data were lost in 5 patients.
‡ Some cases had multiple feeding arteries. "Other" involves the posterior inferior cerebellar artery and middle meningeal artery.

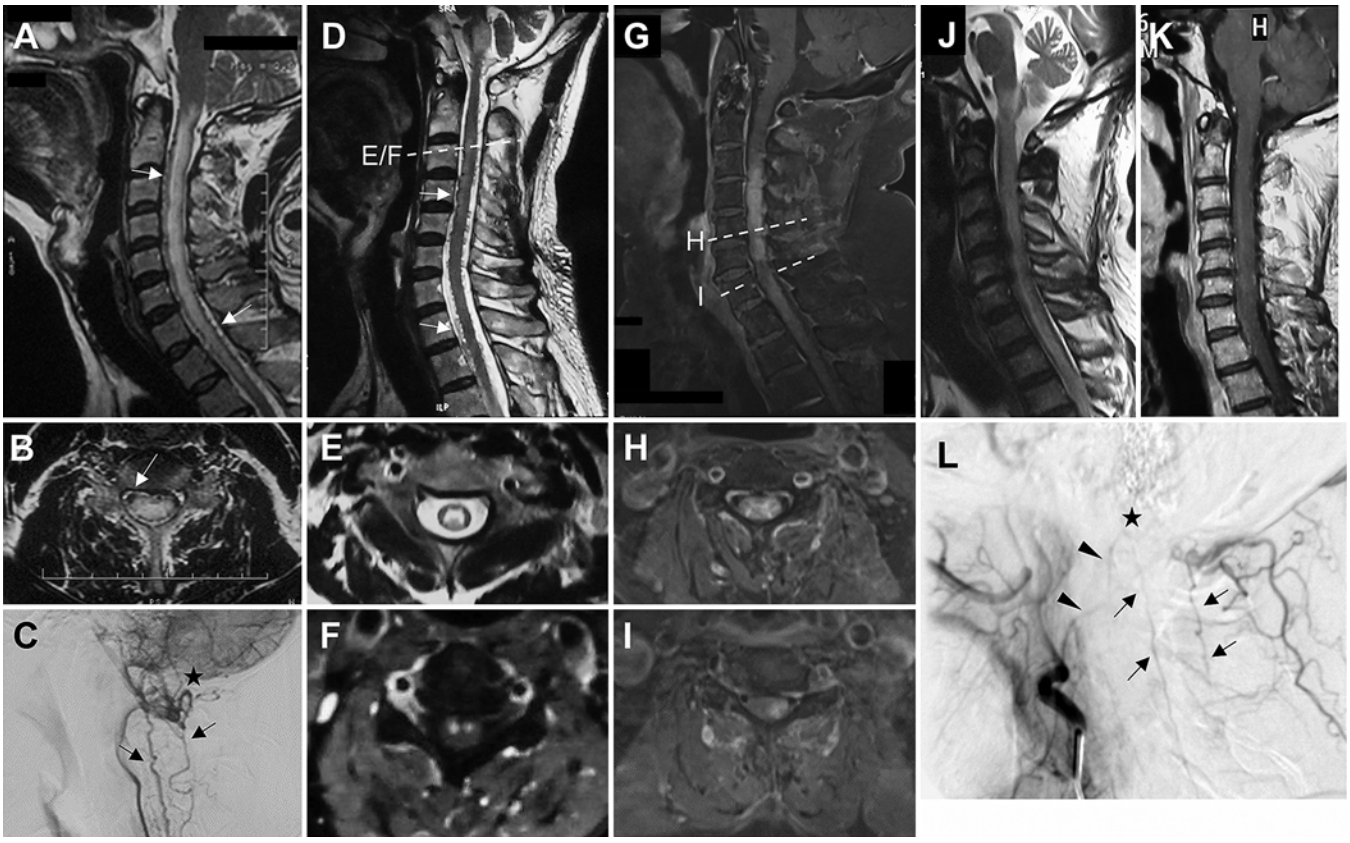

FIG. 1. Diverse imaging findings before surgery. **A–C:** Images with typical imaging features obtained in a middle-aged male who reported lower-extremity weakness and difficulty with urination and defecation. Sagittal and axial T2-weighted MR images showing multisegment (A) and transverse (B) intramedullary hyperintensity was found with spinal cord surface abnormal vascular shadowing. An angiogram showed that the fistula was fed by the dural branch of the VA and drained along the ventral and dorsal spinal cord (C). **D–F:** Images obtained in a middle-to-older-aged male who reported nausea, numbness in both hands, and lower-limb weakness. Sagittal T2-weighted image showing involvement of the medulla and spinal cord were (D). Axial images showing gray matter T2 hyperintensity (E) and T1-weighted Gd enhancement of the anterior horn (F). **G–I:** Images obtained in a patient in his mid-70s who reported neck and back pain and paresthesia of the right upper limb. Sagittal Gd-enhanced T1-weighted image revealing a "missing-piece" sign, that is, one nonenhancing area within a long segment (> 2 vertebrae) of enhancement (G). Axial images of different segments showing irregular enhancement (H and I). **J–L:** Images obtained in a patient in his 60s with neck and back pain and appendicular weakness at 1 week who was misdiagnosed with acute myelitis. Sagittal T2-weighted image showing hyperintensity and swelling of the spinal cord and medulla oblongata (J). Gd-enhanced image examination showing a few abnormal vessels in the ventral spinal cord (K). However, the neurologist ignored the abnormality, and the patient developed paralysis and urinary incontinence due to methylprednisolone pulse therapy. Subsequent angiography revealed a fistula at the jugular foramen region fed by the APA and drainage into the spinal cord (L). *White* and *black arrows* indicate abnormal draining veins. *Stars* indicate abnormally connecting arteries and veins. *Arrowheads* indicate arterial feeding vessels. *Dashed lines* indicate the location of the corresponding axial images.

DAVFs that drained along the surface of the spinal cord and medulla.

Clinical Manifestations and Venous Hypertensive Myelopathy Scale

The clinical presentations of CCJ AVFs resulting in VHM were various neurological disturbances involving the motor system, sensation, urination, defecation, and brainstem (see Supplementary Table 2 for detailed statistics). At the onset of the disease, approximately half of the patients had motor and sensory dysfunction, which was progressively present in more than 90% of the patients before admission (Fig. 2A). The involvement of motor and sensory dysfunction was predominant in the lower limbs compared with the upper limbs. In addition, 27.7% (18/65) of the patients presented with hemiplegia. It was noteworthy that approximately one-quarter (16/62) of the patients had limb weakness or decreased motor endurance with no evidence of decreased muscle strength. Moreover, the abnormal sensation level was often lower than the lesion level (56.8%, 25/44). Urinary and bowel disorders accounted for only 20% of the initial symptoms in all patients. However, deficits arose in 67.7% of the patients as the disease progressed, which could partly indicate the severity of the disease. Brainstem and cranial nerve nuclei involvement were the most unique and dangerous manifestations of CCJ AVF with VHM compared with thoracolumbar VHM. Overall, 41.5% (27/65) of patients had brainstem

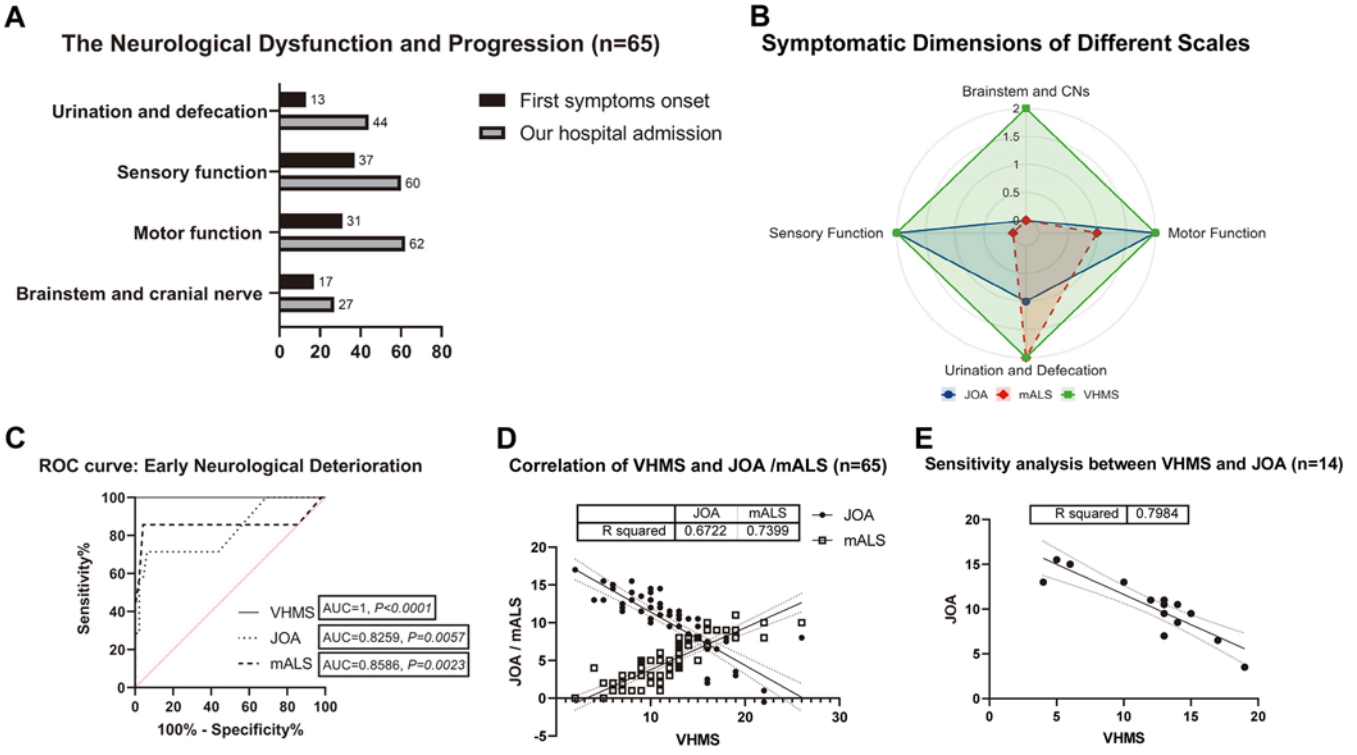

FIG. 2. Comparison of clinical presentation and scales. **A:** Frequency distribution graphs of symptom onset in patients with CCJ AVFs resulting in VHM. A patient might have multiple symptoms at initial onset. **B:** Comparison of evaluation dimensions across the three scales. CN = cranial nerve. **C:** The outcome variable was END, and the test variables were the scoring changes of each scale (i.e., postoperative score − preoperative score). **D:** Correlation analysis of different preoperative scores in all patients through simple linear regression. **E:** The sensitivity analysis was also a simple linear regression conducted in 14 patients who were satisfied with the standard JOA scales. Figure is available in color online only.

and nuclei disturbances at admission. Three patients presented with Wallenberg syndrome. Five patients had dyspnea, with 3 progressing to severe respiratory depression after steroid treatment.

Based on the aforementioned symptoms, neurological assessment was found to be most accurate according to the VHMS score, followed by the JOA and the mALS scores (Fig. 2B). Hence, we constructed an ROC analysis to predict the incidence of END and found that the areas under the curve for JOA and mALS scores were approximately 80% of the area under the curve for VHMS (Fig. 2C). This implied that the two scales could not accurately reflect the neurological changes in patients with CCJ AVF resulting in VHM. Of course, the correlation was relatively good between the VHMS and JOA/mALS scores (n = 65, Fig. 2D). We also performed a sensitivity analysis by excluding the patients in whom the JOA score could not be used. The linearity of JOA and VHMS scores fit better, in which R^2 increased from 0.6722 to 0.7984 (n = 14, Fig. 2E). The sensitivity analysis was not performed for the mALS scores because only one patient could be included.

Postoperative Neurological Function in the Long-Term Follow-Up

Although all three scales were used in the follow-up, we eventually adopted the VHMS score to analyze neurological function outcomes. The postoperative neurological function of two-thirds of the patients (23/33) showed dynamic changes at the 5-year follow-up. Most of the patients improved effectively within the 1st year after surgery (median NIR 30.0% [95% CI 16.7%–46.2%], p = 0.0075) (Fig. 3A). Overall, 63.6% (21/33) of the patients had no obvious neurological improvement 7 days postoperatively, and 5 had symptoms that suddenly worsened (Fig. 3B). One patient experienced a new onset of respiratory rhythm abnormalities after anesthesia resuscitation, which might be associated with ischemia–reperfusion injury of the medulla oblongata but recovered 1 month later following mechanical ventilation. The number of improved patients (NIR ≥ 25%) peaked at the 1-year follow-up (54.5%, 18/33), and 1 patient achieved a complete cure. However, an upward trend in the annual proportion of patients was shown with a decline in neurological function, with a cumulative DND incidence of 24.2% (8/33). The chi-square trend test did not show statistical significance, indicating a positive long-term efficacy of the surgical intervention in all patients (p = 0.3918) (Fig. 3B).

In patients with complete 1-year follow-up, 25.9% (14/54) experienced DND and 13.0% (7/54) had END. For patients with END, 3 improved after the 1-year follow-up, but 2 had DND. The detailed clinical information for patients with postoperative neurological deterioration is listed in Table 2. Furthermore, a multivariate logistic regression was built to identify prognostic factors for DND.

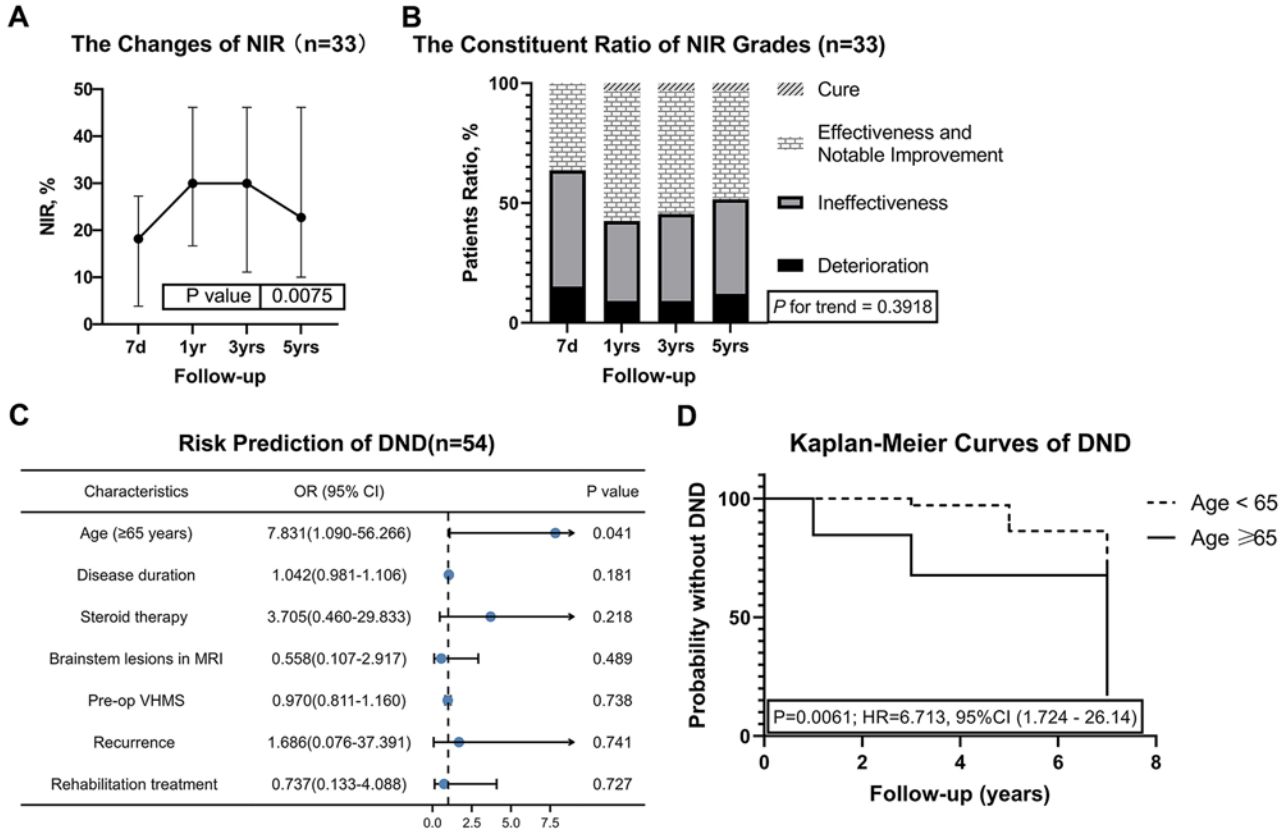

FIG. 3. Analysis of postoperative neurological function. **A and B:** Dynamic NIR in patients with more than 5 years of follow-up. The changes in the NIR plateaued at 1–3 years. The statistics are described as the median and 95% CI and tested by the nonparametric Friedman method (A). The proportions of ineffective and deteriorated patients (NIR < 25%) increased after the 1-year follow-up. The chi-square test for trend was used between patients with NIR ≥ 25% and < 25% (B). **C and D:** Prediction of DND in patients with more than 1 year of follow-up. Multivariate logistic regression identified age as an independent prognostic factor (C). The results of Kaplan-Meier analysis revealed a high DND risk in elderly patients (median time to DND 7 years; D); $p < 0.05$ was considered statistically significant. Figure is available in color online only.

The results supported that age was an independent predictor (OR 7.831, 95% CI 1.090–56.266) (Fig. 3C). The risk of DND occurrence increased by approximately eightfold for patients older than 65 years. Similar results were seen on Kaplan-Meier analysis. Elderly patients had a higher risk of DND (HR 6.713, 95% CI 1.724–26.14) (Fig. 3D). The median time to DND for the elderly cohort was 7 years, and freedom from DND at 3, 5, and 7 years was 76%, 61%, and 30% respectively.

Recurrence and Postoperative Adverse Events

All 9 patients (13.8%) who experienced recurrence had DAVFs, and the two patterns of recurrence are shown in Fig. 4. One reason for recurrence was vascular recanalization (Fig. 4A–L). Eight patients underwent transarterial embolization at the first treatment. Five patients had Onyx injected as the embolization material, and 3 patients underwent reoperation because of poor durability of the embolic agent. The recurrence rate of the embolization group was higher than that of the surgery group ($p = 0.007$) (Table 3). Kaplan-Meier analysis showed that the recurrence hazard was increased 11-fold in the embolization group (median recurrence time 34 months, $p < 0.0001$) (Fig. 5A). The other recurrence pattern was a new contralateral feeder in 4 patients (3 patients who underwent surgery and 1 patient who underwent embolization), in which the drainage structure could be identical (Fig. 4O and S, n = 3) or different (Fig. 4I and J, n = 1) compared with the initial onset. The reason for recurrence in the remaining patients (1 patient who underwent surgery and 2 patients who underwent embolization) could not be accurately judged because the initial angiography data were missing. Most of the patients with recurrence (8/9, 88.9%) were treated by microsurgery in our hospital.

For the first treatment, the complication rate in the surgery group tended to be higher than that in the embolization group, but the difference was not statistically significant ($p = 0.5810$) (Table 3). A patient in his 70s with central respiratory depression in the perioperative period died following surgical treatment within 14 days. A multivariate logistic regression was conducted to predict the postoperative adverse events at the last treatment. This finding supported that the recurrence history would increase the risk of adverse events (OR 20.455, 95% CI 1.170–357.302; $p = 0.039$) (Fig. 5B) rather than the initial treatment strategies. Overall, 55.6% (5/9) of the patients with recurrence had ad-

TABLE 2. Characteristics of patients with postoperative neurological deterioration

Case No.	Sex	Age, yrs	Duration, mos	Hx Steroid Therapy	Feeding Artery	Location	Classification	Lesion Range on MRI	Preop VHMS	1st Treatment (time to recurrence, mos)	Last Treatment	Postop Complications & END	DND (time to DND, yrs)
1	M	62	4	No	Rt VA	C1	DAVF	MO–C3	10		Op		Yes (3)
2	M	66	12	No	Rt VA	C1	RAVF	C1–7	9		Op		Yes (5)
3	M	70	13	Yes	Lt VA	C1	DAVF	C3–T1	16		Op		Yes (1)
4	M	51	48	Yes	Lt VA	C1	DAVF	Pons–C4	12		Op		Yes (1)
5	M	56	24	Yes	Rt VA	C1	RAVF	C1–T2	22		Op		Yes (5)
6	M	48	3	Yes	Lt VA	C1	DAVF	MO–C4	19		Op	END	
7	M	48	2	No	Rt VA	C1	DAVF	MO–C4	10	Embolization (1)	Op	END	Yes (5)
8	M	65	4	No	Lt VA	C2	DAVF	None	4	Embolization (3)	Op	END	Yes (1)
9	M	59	3	No	Rt VA, lt VA	C1	DAVF	MO	2	Embolization (8)	Op	END	
10	M	53	3	No	Rt VA	C2	EDAVF	None	10		Op	VA occlusion, END	
11	M	62	24	Yes	Rt VA	C1	DAVF	C3–T2	16		Op		Yes (3)
12	M	67	15	No	Lt VA	C1	DAVF	MO–C4	11		Op		Yes (1)
13	M	58	2	Yes	Rt VA	Foramen magnum	DAVF	MO–T1	15		Op		Yes (3)
14	M	59	17	No	Rt VA	C1	DAVF	C4–6	10	Op (6)	Op	Intracranial infections, END	
15	M	81	4	No	Lt VA	C1	DAVF	C1–6	14		Op		Yes (1)
16	M	63	2	Yes	Rt VA	C1	DAVF	MO	12		Op		Yes (3)
17	M	48	4	No	Lt VA	C1	DAVF	Pons–C5	7		Op	END	
18	M	69	6	Yes	Lt APA, rt MMA	Foramen magnum	DAVF	MO–T2	13		Op	Intracranial infections	Yes (1)
19	M	66	2	No	Bilat MHT, rt APA	Jugular foramen	DAVF	None	5	Embolization (8)	Embolization		Yes (1)

DAVF = dural AVF; EDAVF = epidural AVF; MHT = meningohypophyseal trunk; MMA = middle meningeal artery; MO = medulla oblongata; RAVF = radicular AVF.

verse events after the second treatment. Acute neurological deterioration occurred in 4 patients, of whom 3 were initially treated by embolization. Two patients, who were first treated by surgery, developed an intracranial infection.

Discussion

As the main cause of VHM, SDAVF has been the subject in some large studies that illustrate its clinical features, anatomy, and prognosis,[3,16] but the proportion of cervical SDAVF cases was less than 6%. On the other hand, the latest research has shown that 11%–27% of the patients with CCJ AVFs had VHM, while it accounted for 34% (65/192) of the cases in our center. The previous studies that focused on CCJ AVFs resulting in VHM were case reports or case series.[5–7] Given the underlying risk of brainstem injuries in CCJ AVFs resulting in VHM, the current research was prone to underestimate the severity of VHM.

Correlation Between CCJ AVFs Resulting in VHM and SDAVF

In this study, we found that the clinical features of CCJ AVFs resulting in VHM were similar to those of SDAVFs. Both etiologies have a chronic insidious onset with a predilection for older males. Steroid therapy aggravated patients' conditions. CSF exhibited mild protein and cell count elevation. Although specific fluid-void vasculature was found in approximately 70% of the patients, the misdiagnosis rate was greater than 50%. The fluid-void sign might be imperceptible in the early stage of VHM. As a common disease in elderly people, cervical spinal stenosis also increases the difficulty of the differential diagnosis.[17] We also observed the missing-piece sign (reported by Zalewski et al.[12]) on Gd-enhanced MRI and speculated that it was caused by irregular disruption of the blood-brain barrier at different levels (Fig. 1C). In addition, lesions largely confined to gray matter and enhanced in the anterior horn (snake-eye sign) have not been previously reported. This might be explained by the fact that CCJ AVFs had more ventral drainage patterns than SDAVFs. Both snake-eye and missing-piece signs indicated that VHM was not a simple transverse spinal injury. The complexity of imaging findings also made differential diagnosis more difficult, especially in patients with nonobvious abnormal vessels on MRI.

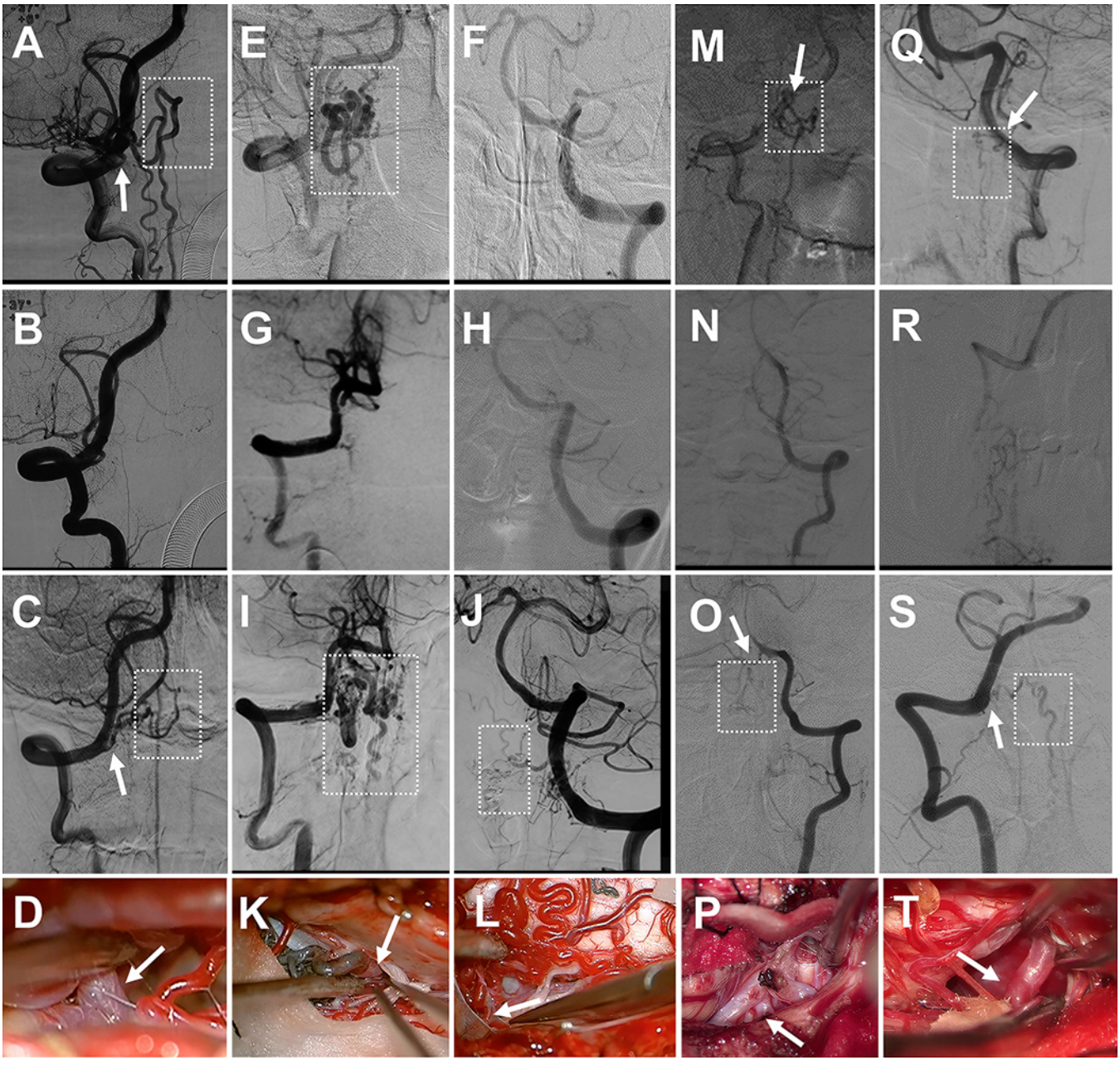

FIG. 4. Angiograms and intraoperative images obtained in 2 patients with recurrence after liquid embolization treatment (A–D and E–L) and in 2 patients with a symmetric contralateral recurrence pattern after microsurgical surgery (M–P and Q–T). **A–D:** The fistula was confirmed to be feeding on the right dural branch of the VA and was occluded by Onyx (A). The abnormal vasculature disappeared immediately postembolization (B). Three months later, the angiogram showed recanalization with drainage similar to that seen preoperatively (C). The fistula was unobstructed, and no embolic residue was found under the operating microscope (D). **E–L:** The initial angiogram showed extramedullary tortuous vessels fed by the V4 segment of the right VA (E), and no abnormalities were present on the other side (F). The 1-month follow-up angiograms were satisfactory (G and H). The 4-month follow-up angiogram showed recanalization of the original location (I) and a new fistula from the contralateral V4 segment (J). The two drainage systems were relatively independent. Intraoperative views showing that the primary fistula communicated with the embolized vascular mass (K), and the new contralateral fistula was slender (L). **M–T:** Symmetric contralateral recurrence pattern after microsurgical surgery. The initial preoperative angiograms showed that the fistula arose from one side of the V4 segment (M and Q), with negative changes on the other side (N and R). The 6-month (O) and 3-month (S) postoperative angiograms suggested a new feeding artery derived from the contralateral V4 segment, and the drainage venous shapes were the same as before. The fistulas were recurrent near the previous incision (P, the *charred black* was the previous residual vein) or on the medial wall of the contralateral dura mater (T). *White arrow*s indicate the feeding artery, and the *white dotted boxes* frame the drainage veins.

TABLE 3. Clinical classification and secondary outcomes of CCJ AVF resulting in VHM

	Microsurgery (n = 57)*	Endovascular Therapy (n = 8)	p Value
Classification			
DAVF	53	8	
RAVF	2	0	
EDAVF	2	0	
PAVF	2	0	
Complications	8 (14.0)	0	0.5810
Death	1	0	
CSF leakage	2	0	
Intracranial infection	2	0	
Central respiratory failure	1	0	
Deep vein thrombosis	1	0	
VA occlusion†	1	0	
Recurrence	4 (7.0)	5 (62.5)	0.0007

PAVF = perimedullary AVF.
Values are presented as the number of patients (%) unless stated otherwise. The data were grouped and organized according to the initial surgical strategy and medical records. Most patients with recurrence (8/9) underwent microsurgical disconnection at the second surgery.
* Two patients underwent hybrid surgery.
† One patient had spinal cord infarction for VA occlusion during transvenous retrograde embolism of the hybrid operation.

Corresponding to the imaging performance, individual heterogeneity of the clinical presentation was found in patients with CCJ AVFs resulting in VHM. If the spinal cord had a transverse injury, the injury was manifested by varying degrees of bilateral inferior motor neuron paralysis, hypotonia, loss of tendon reflexes, inability to elicit pathological signs, and urinary and bowel retention or incontinence. If the spinal cord is incompletely injured, it often manifests as hemiplegia or Brown-Séquard syndrome. If the medulla was involved, various types of brainstem syndromes appeared, such as Wallenberg syndrome. As a disease with low morbidity and high disability rates, it is particularly important to evaluate the neurological function of VHM patients. The primary tools used in previous SDAVF studies were the ALS or mALS.[3,18] However, the scales do not evaluate sensory impairment, which greatly affects patients' quality of life. Subsequently, several clinical teams used combined strategies of multiple scales (including sensation and defecation) to improve the evaluation methods,[2,19] but these methods still ignored disorders of the medulla oblongata and upper extremities. In a few case reports of CCJ AVF resulting in VHM, the authors adopted the JOA scale or modified Rankin Scale;[10,17] the former scale only applied to particular patients and the latter was overly general in assessment. Here, we introduced the VHMS in-house based on the clinical features of CCJ AVFs resulting in VHM and SDAVFs.

Postoperative Neurological Deterioration

Recently, several cohort studies have indicated that the majority of patients with VHM remained disabled after surgery, but no disease-related death was found.[2,3] In this study, only 1 patient was asymptomatically cured. Two patients had central respiratory depression after surgery, one of whom recovered by mechanical ventilation in 1 month, and the other died of multiorgan system failure triggered by respiratory failure. In addition, this study also revealed age-related neurological decline. Approximately 26% of the patients developed symptomatic worsening from 1 year postoperatively to the end of follow-up, which was consistent with our recent research about the long-term outcomes of SDAVF.[11] As we now know, VHM is a congestive neural injury caused by increased intramedullary pressure.[20] Many preclinical experiments illuminated that there was

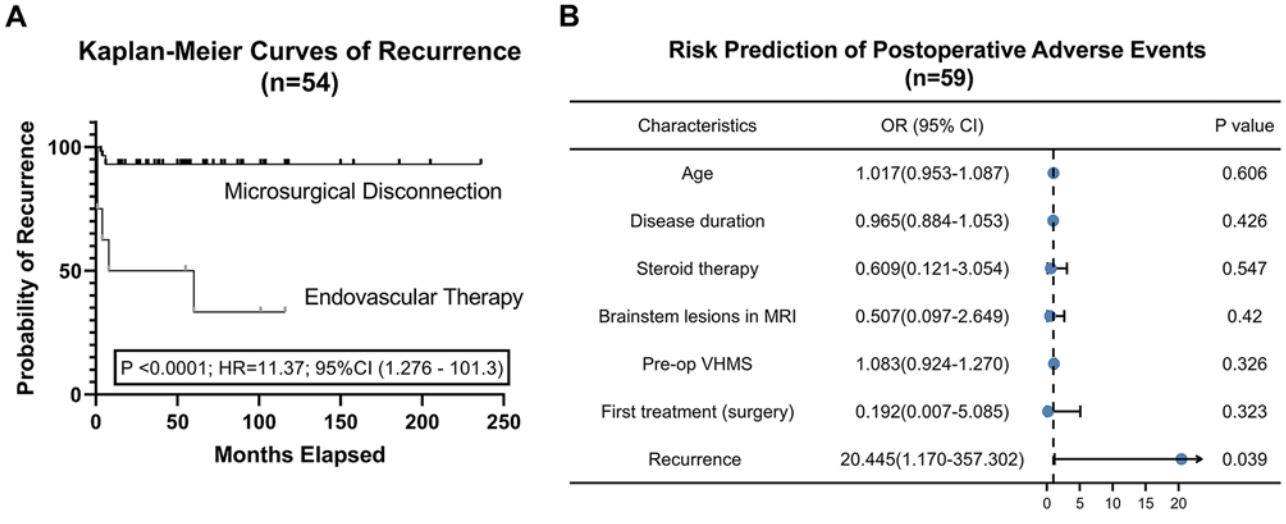

FIG. 5. Analysis of recurrence and adverse events. **A:** Kaplan-Meier analysis of recurrence was conducted in patients with 1-year follow-up. The results supported a higher risk of endovascular treatment (median time to recurrence 34 months). **B:** Multivariate logistic regression was used to predict the risk of postoperative adverse events. Recurrence was an independent risk factor; $p < 0.05$ was considered statistically significant. Figure is available in color online only.

an age-dependent decline in nerve repair.[21] Meanwhile, investigators found that proinflammatory microglia and oxidative neuronal cell bodies in the rim surrounding human traumatic spinal cord injury lesions remained significantly elevated up to months or years.[22] These factors might be responsible for delayed neurological deterioration in some VHM patients.

Potential Reasons for and Types of Recurrence

The surgical goal was complete occlusion of the fistula, whether for CCJ AVF or SDAVF. The underlying mechanisms of recurrence are very complex and involve multiple factors. First, recanalization might occur because of incomplete durability of the Onyx agent, especially in high-flow fistulas.[23] For most patients, open surgery was more appropriate than embolization. Second, this study presented a recurrence pattern of bilateral symmetry fed by the V4 segment of the VA, which was similar to the mirror-site CCJ AVF reported by Oshita et al.[24] However, the drainage systems of the two fistulas were relatively independent in their study while they were the same (Fig. 4O and S) or independent (Fig. 4I and J) in our patients. We hypothesized three reasons for the symmetric recurrence. 1) Small-caliber flow fistulas in the early stage of the disease were hard to opacify and gradually appeared with disease progression or hemodynamic changes after embolization.[23,25] 2) In Fig. 4P, no other fistulas were found on the first preoperative angiogram and intraoperative exploration, and the recurrent fistula was adjacent to the previous surgical incisions on the spinal dural. These clues led to the suspicion of neovascularization due to surgical intervention. 3) The blood flow from bilateral symmetric feeders might counteract each other, resulting in a low flow in the nondominant side and nonvisualization on conventional angiography. When bilateral symmetrical feeders are suspected, a balloon might be attempted to temporarily obstruct the feeding artery of the dominant side and then angiography is performed on the other side. Meanwhile, we reiterated the importance of postoperative angiography of the bilateral VAs to avoid missing the contralateral occult fistula, regardless of what treatments were used. Above all, the risk of postoperative adverse events increased 20-fold in the patients who experienced a recurrence, which also suggested the importance of the initial diagnosis and treatment.

Study Limitations

Our study has some limitations. First, the retrospective study design might have introduced selection bias. The definition of VHM was still vague, and we defined the criteria according to images and symptoms. Some patients, whose disease manifested as simple tinnitus and headache, had fistula drainage into the spinal cord, but no hyperintensity was found on T2-weighted MRI. There was controversy within our teams as to whether these patients should be included in the study, and these patients were finally excluded after a discussion with all authors. Second, systematic errors might arise because of the large time span and the different physicians involved with the follow-up. Moreover, CSF analysis and standardized rehabilitation, which might affect DND, were lacking in most patients. Finally, the study had potential selection bias between treatment options. Our results supported that surgery was the first-line treatment. However, patients should receive individualized treatment according to vascular architecture. Endovascular therapy might be more suitable for complicated cases, such as perimedullary MAVF with anterior spinal artery feedings, which are not treatable for microsurgery.

Conclusions

This study is an important update of the clinical features and long-term follow-up for venous hypertension myelopathy. We summarized the unique clinical features of CCJ AVFs resulting in VHM and proposed the VHMS. The primary results suggested that more than one-quarter of patients had age-related DND. Patients older than 65 years demonstrated an eightfold increased risk of DND. Embolic recanalization is one reason for recurrence, but new contralateral feeders should be evaluated. Importantly, the risk of postoperative complications increased 20-fold for the second treatment, regardless of the initial treatment options. It is reasonable to strive for a one-time anatomical cure at an experienced center.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zhang, Ma, Hu. Acquisition of data: Wang, Song, C Yang, Tu, K Yang. Analysis and interpretation of data: Wang, C Yang, K Yang, Hu. Drafting the article: Wang. Critically revising the article: Tu, Li, Hu. Reviewed submitted version of manuscript: Ma, C Yang, He, Li, Hu. Approved the final version of the manuscript on behalf of all authors: Zhang. Statistical analysis: K Yang. Administrative/technical/material support: Tu, He, Li, Sun, Ye. Study supervision: He, Li, Sun, Ye.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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