Natural history of brainstem cavernous malformations: prospective hemorrhage rate and adverse factors in a consecutive prospective cohort

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OBJECTIVE Given the paucity of data on the natural history of brainstem cavernous malformations (CMs), the authors aimed to evaluate the annual hemorrhage rate and hemorrhagic risk of brainstem CMs.

METHODS Nine hundred seventy-nine patients diagnosed with brainstem CMs were referred to Beijing Tiantan Hospital from 2006 to 2015; 224 patients were excluded according to exclusion criteria, and 47 patients were lost to follow-up. Thus, this prospective observational cohort included 708 cases (324 females). All patients were registered, clinical data were recorded, and follow-up was completed.

RESULTS Six hundred ninety (97.5%) of the 708 patients had a prior hemorrhage, 514 (72.6%) had hemorrhagic presentation, and developmental venous anomaly (DVA) was observed in 241 cases (34.0%). Two hundred thirty-seven prospective hemorrhages occurred in 175 patients (24.7%) during 3400.2 total patient-years, yielding a prospective annual hemorrhage rate of 7.0% (95% CI 6.2%–7.9%), which decreased to 4.7% after the 1st year. Multivariate Cox regression analysis after adjusting for sex and age identified hemorrhagic presentation (HR 1.574, $p = 0.022$), DVA (HR 1.678, $p = 0.001$), mRS score ≥ 2 on admission (HR 1.379, $p = 0.044$), lesion size > 1.5 cm (HR 1.458, $p = 0.026$), crossing the axial midpoint (HR 1.446, $p = 0.029$), and superficially seated location (HR 1.307, $p = 0.025$) as independent adverse factors for prospective hemorrhage, but history of prior hemorrhage was not significant. The annual hemorrhage rates were 8.3% and 4.3% in patients with and without hemorrhagic presentation, respectively; the rate was 9.9%, 6.0%, and 1.0% in patients with ≥ 2 , only 1, and 0 prior hemorrhages, respectively; and the rate was 9.2% in patients with both hemorrhagic presentation and focal neurological deficit on admission.

CONCLUSIONS The study reported an annual hemorrhage rate of 7.0% exclusively for brainstem CMs, which significantly increased if patients presented with both hemorrhagic presentation and focal neurological deficit (9.2%), or any other risk factor. Patients with a risk factor for hemorrhage needed close follow-up regardless of the number of prior hemorrhages. It should be noted that the referral bias in this study could have overestimated the annual hemorrhage rate. This study improved the understanding of the natural history of brainstem CMs, and the results are important for helping patients and physicians choose a suitable treatment option based on the risk factors and stratified annual rates.

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As the second most common intracranial vascular malformation,³⁷ cerebral cavernous malformations (CCMs) are composed of dilated sinusoidal channels, with a population prevalence of 0.4%–0.6%,¹⁵ approximately 19.1% (range 11%–30%) of which involve

the brainstem.^{1,4,7,9,13,15,19,20,28,29,31,32} The natural history of CCMs was extensively evaluated in prior studies,^{1–4,6–9,11–13,15–17,19,20,23,24,28,29,31,32} and particularly elaborated by Al-Shahi Salman et al.,^{3–5,16} Flemming et al.,⁹ and Gross et al.,^{11–13,15} but few studies focused on brainstem CMs that were

ABBREVIATIONS CCM = cerebral CM; CM = cavernous malformation; DVA = developmental venous anomaly; FND = focal neurological deficit; mRS = modified Rankin Scale; ROC = receiver operating characteristic; SRS = stereotactic radiosurgery.

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infrequently and separately reported or simply classified into deep location. There has been no consensus regarding the hemorrhagic predictors of CCMs (except prior hemorrhage),^{1,4,9,12,13,15–17,19,20,23,24,29,34} but deep,²⁹ nonlobar,⁷ and brainstem^{14,16,33} locations have been documented as significant risk factors for rehemorrhage, which was described as one of the top 10 research priorities for CCMs.⁵ Due to the high density of eloquent long-fiber tracts and vital nervous nuclei, the brainstem is vulnerable to hemorrhagic ictus or even minor bleeding that increases the chance of symptomatic hemorrhage with more severe disability compared to supratentorial counterparts.^{4,16} The estimated 5-year risk for a hemorrhagic event in brainstem CMs presenting with hemorrhage or focal neurological deficit (FND) was 30.8% in one meta-analysis.¹⁶ Therefore, we aimed to evaluate the adverse factors and hemorrhage rate of brainstem CMs based on a consecutive prospective cohort over a decade and to provide meaningful evidence for treatment selection.

Methods

Patient Population

This prospective cohort included patients with brainstem CMs referred to the outpatient department of Beijing Tiantan Hospital from January 2006 to December 2015. All clinical data were obtained from a prospective clinical trial (registration no. ChiCTR-POC-17011575; <http://www.chictr.org.cn/>). The Beijing Tiantan Hospital Research Ethics Committee approved this study, and written informed consent was obtained from all patients. The inclusion criteria were definitive diagnosis of a brainstem CM and provision of informed consent. The exclusion criteria included one of the following conditions: 1) prior resection or radiotherapy; 2) severe comorbidities involving the brainstem, peripheral nerves, or other hazardous lobes that might influence the evaluation of neurological function; 3) pregnancy and breastfeeding; 4) refusal to participate in follow-up; or 5) receiving resection immediately after diagnosis at our institute. Stereotactic radiosurgery (SRS) was not recommended in our institute, and the surgical indications have been described in our prior studies as follows:^{25–27,35} 1) multiple hemorrhages (≥ 2 ictuses), lesion size ≥ 2 cm, and severe or progressive neurological deficit; 2) lesion in the medulla oblongata; 3) acute or subacute hemorrhage with a significant mass effect; or 4) exophytic lesion or one abutting the pial surface accessible via the “safe entry zones.”

Diagnosis and Clinical Data Collection

The patient's chart (sex, age, medical and family history, and other data) was recorded in our electronic medical system (Table 1). Radiological images were extensively reviewed, and 2 neuroradiologists independently reviewed MR images to confirm the diagnosis based on the accepted criteria.^{30,36} Radiographic data included lesion location (depth and side), crossing the axial midpoint,¹⁰ equivalent size, perilesional edema, Zabramski classification,³⁶ and developmental venous anomaly (DVA). The multiple cerebral CMs or brainstem CMs were recorded based on gradient-echo images and/or susceptibility-weighted im-

aging. Hemorrhage on admission was noted if an overt intralesional or extralesional hemorrhage was observed on the latest MRI at diagnosis. The prior hemorrhage was determined by the serial radiographic evidence before enrollment, combined with medical records; lesions without prior hemorrhage were usually asymptomatic or diagnosed incidentally due to other unrelated causes. To minimize recall bias, which introduced significant uncertainty, a clinically symptomatic event recalled by patients at enrollment was not considered a hemorrhagic event if it was not substantiated by concomitant radiographs. FND was defined as cranial neuropathy and/or long-tract deficit (motor and sensory deficit) pertinent to the anatomical location of the lesion. Non-FNDs included headache, dizziness, nausea, vomiting, and/or other symptoms not directly associated with the lesion. Two authors (Z.Y.W. and P.P.L.), blinded to radiographs and hemorrhagic status, evaluated neurological function using a modified Rankin Scale (mRS) score and completed the scheduled follow-up, with any discrepancies resolved by the senior author (J.T.Z.).

Follow-Up and Statistical Analysis

The inception point of enrollment in the study was the diagnosis of brainstem CM at our institute. Follow-up was performed at 3, 6, and 12 months after diagnosis and then annually afterward (via clinical visits, mailed questionnaires, telephone interviews, and/or contact with the family doctor), and MRI scans were recommended on the same schedule. Data were acquired, including treatment since enrollment inception, treatment effects, changes in neurological status, and mRS score. Prospective hemorrhage was defined as a clinically symptomatic event (acute or subacute, new onset or worsening of an FND, or severe headache) corresponding to the anatomical location of the brainstem CM, with the overt hemorrhage within or outside the lesion, and change in lesion size and signal intensity based on comparison of radiographs obtained at various periods.^{3,4,23} A hemorrhagic event was uncertain if a clinical event was suspicious without concomitant radiological evidence. An asymptomatic hemorrhage was defined as an overt hemorrhage with a change in lesion size and signal intensity but without a clinical event. Radiological examination was required following a questionable clinical event or hemorrhage to verify the hemorrhagic ictus.

The prospective annual hemorrhage rate was calculated as the number of hemorrhages divided by the duration (in years) of follow-up per patient and was further stratified by the adverse factors for hemorrhage (Table 2). Hemorrhage-free survival duration began at enrollment and ended on the date of the earliest rehemorrhage or the date of censoring (surgery, SRS, death, or most recent evaluation), whichever occurred first. The cutoff value of lesion size was determined using a receiver operating characteristic (ROC) curve. The hemorrhagic risk factors were evaluated by univariate Cox proportional hazards regression, and all univariate significant risk factors together with age and sex were entered into the multivariate Cox regression to confirm the independent risk factors. Survival curves were illustrated by the Kaplan-Meier method (univariate survival analysis). The analyses were performed us-

TABLE 1. Demographics of patients with brainstem CMs: total and stratified by number of prospective hemorrhages

Variable (%)	Overall, n = 708	No Ictus, n = 533	1 Ictus, n = 132	>1 Ictus, n = 43	p Value
Female, n (%)	324 (45.8)	244 (45.8)	61 (46.2)	19 (44.2)	0.973*
Mean age on admission (median), yrs	38.2 (38.0)	37.8 (38.0)	40.4 (40.5)	36.8 (39.0)	0.112†
Hypertension, n (%)	96 (13.6)	74 (13.9)	15 (11.4)	7 (16.3)	0.650*
Mean duration of symptoms (median), mos	21.5 (2.7)	20.6 (2.4)	23.5 (4.0)	26.1 (3.1)	0.623†
Patients w/ prior hemorrhages, n (%)	690 (97.5)	516 (96.8)	131 (99.2)	43 (100.0)	0.156*
Overall no. of prior hemorrhages	1021	743	203	75	
Mean no. of prior hemorrhages (median)	1.4 (1.0)	1.4 (1.0)	1.5 (1.0)	1.7 (1.0)	0.008†
Cumulative yrs of life	27,049	20,131	5335	1583	
Retrospective annual hemorrhage rate, %	3.8	3.7	3.8	4.7	
Mean mRS score on admission (median)	1.6 (1.0)	1.6 (1.0)	1.7 (1.0)	1.8 (1.0)	0.325‡
Hemorrhage on admission, n (%)	514 (72.6)	375 (70.4)	104 (78.8)	35 (81.4)	0.062*
FND on admission, n (%)	580 (81.9)	426 (79.9)	115 (87.1)	39 (90.7)	0.048*
Hemorrhage + FND on admission, n (%)	442 (62.4)	314 (58.9)	96 (72.7)	32 (74.4)	0.003*
CM location, n (%)					0.567*
Midbrain	155 (21.9)	110 (20.6)	34 (25.8)	11 (25.6)	
Pons	447 (63.1)	344 (64.5)	76 (57.6)	27 (62.8)	
Medulla	106 (15.0)	79 (14.8)	22 (16.7)	5 (11.6)	
Crossing axial midpoint, n (%)	176 (24.9)	122 (22.9)	45 (34.1)	9 (20.9)	0.024*
DVA, n (%)	241 (34.0)	162 (30.4)	57 (43.2)	22 (51.2)	0.001*
Multiple CCMs, n (%)	92 (13.0)	63 (11.8)	18 (13.6)	11 (25.6)	0.035*
Multiple brainstem CMs, n (%)	61 (8.6)	41 (7.7)	12 (9.1)	8 (18.6)	0.048*
Perilesional edema, n (%)	344 (48.6)	260 (48.8)	65 (49.2)	19 (44.2)	0.834*
Zabramski classification, n (%)					0.305*
I	192 (27.1)	140 (26.3)	41 (31.1)	11 (25.6)	
II	330 (46.6)	243 (45.6)	63 (47.7)	24 (55.8)	
III/IV	186 (26.3)	150 (28.1)	28 (21.2)	8 (18.6)	
Mean lesion size (median), cm	1.5 (1.4)	1.5 (1.4)	1.6 (1.7)	1.6 (1.6)	0.047†
Side, n (%)					0.759*
Lateral	183 (25.8)	144 (27.0)	30 (22.7)	9 (20.9)	
Ventral	218 (30.8)	161 (30.2)	44 (33.3)	13 (30.2)	
Dorsal	307 (43.4)	228 (42.8)	58 (43.9)	21 (48.8)	
Depth, n (%)					0.125*
Superficial	402 (56.8)	288 (54.0)	87 (65.9)	27 (62.8)	
Moderate	210 (29.7)	166 (31.1)	33 (25.0)	11 (25.6)	
Deep	96 (13.6)	79 (14.8)	12 (9.1)	5 (11.6)	
Disease-specific death, n (%)	13 (1.8)	0	11 (8.3)	2 (4.7)	<0.001*
Patients receiving surgery, n (%)	173 (24.4)	110 (20.6)	48 (36.4)	15 (34.9)	<0.001*
Patients receiving SRS, n (%)	15 (2.1)	8 (1.5)	5 (3.8)	2 (4.7)	

Boldface type indicates statistical significance.

* Chi-square test.

† One-way ANOVA.

‡ Kruskal-Wallis test.

ing IBM SPSS statistical package software (version 25.0; IBM Corp.) with the significance set at $p < 0.05$ and using confidence interval (CI) analysis software.

Results

Patient Demographics

During the 10 years, 979 patients diagnosed with brain-

stem CMs were referred to our institute, and 224 patients were excluded due to the study exclusion criteria, including 125 patients receiving resection immediately after diagnosis (Fig. 1). The prospective cohort included 755 patients, and 47 (6.2%) were lost to follow-up after enrollment. In 708 patients (324 females, 45.8%) with available follow-up, the mean and median ages on admission were 38.2 and 38.0 years (range 3–76 years), respectively, with a mean

TABLE 2. Annual rate of prospective hemorrhage stratified by risk factors in patients with brainstem CMs

Risk Factor	Years						Overall
	0 to <0.5	0.5 to <1	0 to <1	1 to <2	2 to <5	5 to <10	
Overall	21.8 (17.4–26.9)	13.0 (9.4–17.6)	17.5 (14.6–20.9)	7.2 (5.3–9.8)	4.8 (3.8–6.1)	2.9 (1.9–4.4)	7.0 (6.2–7.9)
DVA	34.7 (25.7–44.7)	17.0 (10.3–26.5)	26.3 (20.4–33.1)	9.9 (6.1–15.4)	6.4 (4.5–9.2)	4.5 (2.5–7.8)	10.1 (8.4–12.1)
No DVA	15.2 (10.7–21.0)	11.0 (7.1–16.5)	13.2 (10.1–17.0)	5.9 (3.8–9.0)	4.1 (3.0–5.6)	2.2 (1.2–3.9)	5.5 (4.6–6.5)
mRS score 2 on admission	32.6 (23.7–43.0)	17.6 (10.5–27.8)	25.6 (19.6–32.7)	10.4 (6.3–16.3)	5.3 (3.4–8.0)	5.4 (3.2–9.1)	9.8 (8.1–11.9)
mRS <2 on admission	16.7 (12.0–22.6)	11.0 (7.2–16.4)	13.9 (10.8–17.8)	5.9 (3.9–8.9)	4.6 (3.5–6.2)	1.8 (0.9–3.4)	5.8 (4.9–6.8)
Hemorrhage on admission	28.2 (22.5–35.0)	14.6 (10.1–20.7)	21.8 (17.9–26.2)	7.9 (5.4–11.2)	5.7 (4.4–7.4)	3.2 (1.9–5.1)	8.3 (7.2–9.5)
No hemorrhage on admission	7.4 (3.3–15.1)	9.6 (4.7–17.8)	8.5 (5.1–13.6)	6.0 (3.2–10.7)	3.1 (1.8–5.1)	2.3 (0.9–5.2)	4.3 (3.2–5.7)
Size >1.5 cm	35.1 (26.6–44.7)	13.5 (7.7–22.4)	25.2 (19.6–31.7)	10.4 (6.6–16.1)	7.7 (5.5–10.7)	7.1 (4.4–11.1)	11.3 (9.5–13.4)
Size 1.5 cm	13.9 (9.5–19.8)	12.7 (8.5–18.5)	13.4 (10.2–17.3)	5.7 (3.6–8.7)	3.5 (2.5–4.9)	0.9 (0.3–2.3)	4.9 (4.1–5.9)
Crossing axial midpoint	39.8 (28.7–52.4)	19.1 (10.6–31.3)	30.1 (22.6–38.7)	9.4 (5.0–16.4)	4.6 (2.6–7.8)	2.9 (1.1–7.0)	9.6 (7.6–12.1)
Not crossing axial midpoint	16.4 (12.1–21.9)	11.2 (7.6–16.4)	13.9 (11.0–17.5)	6.7 (4.6–9.6)	4.9 (3.8–6.4)	2.9 (1.8–4.6)	6.2 (5.4–7.3)
>1 prior ictus	26.9 (18.5–37.2)	19.3 (11.8–29.7)	23.3 (17.4–30.4)	10.7 (6.5–16.8)	6.5 (4.4–9.5)	4.9 (2.6–8.9)	9.9 (8.1–12.0)
1 prior ictus	20.4 (15.2–26.7)	10.9 (7.0–16.4)	15.8 (12.4–19.8)	5.9 (3.8–8.9)	4.4 (3.2–5.9)	2.2 (1.2–3.8)	6.0 (5.1–7.1)
No prior ictus	0	0	0	5.6 (0.3–29.4)	0	0	1.0 (0.1–6.2)
Hemorrhage + FND	31.1 (24.6–38.5)	15.5 (10.5–22.2)	23.7 (19.4–28.7)	8.7 (5.9–12.5)	6.3 (4.8–8.3)	3.5 (2.0–5.8)	9.2 (8.0–10.6)
Either hemorrhage or FND	10.0 (5.2–18.1)	12.5 (6.9–21.3)	11.3 (7.3–16.7)	4.3 (2.0–8.6)	2.8 (1.6–4.8)	2.6 (1.2–5.3)	4.4 (3.3–5.7)
Neither hemorrhage nor FND	3.6 (0.2–20.2)	0	1.8 (0.1–10.8)	9.0 (3.4–20.5)	3.5 (1.3–8.4)	0	3.5 (1.9–6.3)

The annual rate of prospective hemorrhage was stratified by the risk factors during the specified yearly intervals. The period "0 to <0.5" refers to the first 6-month interval since the inception; "0.5 to <1" refers to the second 6-month interval since the inception; "0 to <1" refers to the 1st year interval since the inception; and "1 to <2," "2 to <5," and "5 to <10" refer to the interval of the 2nd year, the interval from the 3rd year to the 5th year, and the interval from the 6th year to the 10th year, respectively. All data given as percentage (95% CI).

duration of symptoms of 21.5 months (range 1 day–358.5 months). Family history, hypertension, and hemorrhages following occasional alcohol ingestion were recorded in 9 (1.3%), 96 (13.6%), and 10 (1.4%) patients, respectively.

Overall, 690 patients (97.5%) suffered a total of 1021 prior hemorrhages during 27,049 cumulative years of life, and the retrospective annual hemorrhage rate was estimated to be 3.8% (Table 1). The numbers of prior hemorrhage were

FIG. 1. Patient flow diagram showing the inclusion and exclusion process for the analysis.

FIG. 2. Sankey diagram showing the distribution and changes of mRS scores at different periods. Most mRS scores gradually improved during the follow-up period, and some worsened due to rehemorrhage. The horizontal axis of the figure was the time of follow-up from the date of initial diagnosis retrospectively to the date of enrollment, the censoring event, and the recent follow-up evaluation prospectively. The figure consists of 6 bars and 5 flows in between. The 4 bars in orange show the distributions of mRS scores at each time point of neurological evaluation. Both bars in gray show important intermediate events after inception between the date of enrollment and the time of censoring, and between the date of censoring and the recent follow-up evaluation, respectively. The width and value of each flow was calculated according to the sample size showing the dominant or subordinate contributions to the overall flow. The charts below the bars show the transition of the mRS score at different time points, categorized based on the mRS score at initial diagnosis. F/U = follow-up. Figure is available in color online only.

1, 2, and > 2 in 455 (64.3%), 165 (23.3%), and 70 (9.9%) patients, respectively, and 18 patients (2.5%) did not have prior hemorrhage.

On admission, 514 patients (72.6%) presented with acute ($n = 190$, 26.8%) or subacute ($n = 324$, 45.8%) hemorrhage. FND ($n = 580$, 81.9%), including cranial neuropathy ($n = 473$, 66.8%) and long-tract deficit ($n = 435$, 61.4%), was the most common symptom, followed by nonspecific symptoms (headache, dizziness, nausea, and vomiting; $n = 198$, 28.0%) and other deficits (ataxia, disequilibrium, dystonia, and tremor) mimicking extrapyramidal symptoms ($n = 180$, 25.4%). Seven patients (1.0%) were diagnosed incidentally due to brain injury ($n = 1$), intracranial tumor ($n = 1$), or routine health examination ($n = 5$). The mean and median mRS scores were 1.6 and 1.0, respectively (Fig. 2).

Radiological Characteristics

The pons ($n = 447$, 63.1%) was the predominant CM location, followed by the midbrain ($n = 155$, 21.9%) and medulla ($n = 106$, 15.0%; Table 1). The mean lesion size was 1.5 cm (range 0.2–4.0 cm). Multiple CCMs, multiple brainstem CMs, and DVAs were observed in 92 (13.0%), 61 (8.6%), and 241 (34.0%) patients, respectively; 176 lesions (24.9%) were crossing the axial midpoint, and perilesional edema was evident in 344 lesions (48.6%) on the latest T2-weighted MR images before enrollment. Most lesions ($n = 307$, 43.4%) were dorsally located, and the remaining were either ventral ($n = 218$, 30.8%) or lateral ($n = 183$, 25.8%). Four hundred two lesions (56.8%) were superficial, 210 (29.7%) were moderate, and 96 (13.6%) were deep seated. The Zabramski classification types I, II, and

FIG. 3. Radiographic characteristics of brainstem CMs. **A and B:** Both contrast-enhanced T1-weighted axial MR images show associated DVAs. **C and D:** Axial T1-weighted MR images show 1 lesion (C) crossing the axial midpoint, but not the other (D). **E–G:** Axial T1-weighted MR images demonstrating the depth of the lesion according to the thickness of the parenchyma between the lesion and the pial/ependymal membrane, as follows: superficial = 1 lesion abutting the pial/ependymal membrane with a thickness of the parenchyma < 1 mm (E); moderate = thickness of the parenchyma was 1–2 mm (F); and deep = thickness of the parenchyma was > 2 mm (G). **H–M:** Case illustration of sagittal T1-weighted MR images (H–L) and an axial CT scan (M) showing a patient suffering 3 repeat hemorrhages within 60 months since the first ictus, with a stepwise decline in neurological function. The lesion size experienced repeated decreases followed by increases due to the vanishing of the hematoma and rehemorrhage.

III/IV were noted in 192 (27.1%), 330 (46.6%), and 186 (26.3%) lesions, respectively (Table 1, Fig. 3).

Follow-Up

The mean and median follow-up durations were 57.6 and 61.2 months (range 0.2–152.9 months), respectively, and MRI reexaminations during follow-up were available in 619 patients (87.4%). Overall, 15 patients (2.1%) received SRS due to rehemorrhage ($n = 7$), poor neurological status ($n = 5$), and unknown reasons ($n = 3$), and 5 patients received a second SRS. One hundred seventy-three patients (24.4%) underwent resection primarily due to multiple prior hemorrhages ($n = 61$), severe neuropathy ($n = 22$), large lesion size ($n = 24$), progressively worsened symptoms ($n = 3$), and rehemorrhage ($n = 63$). One patient received a second surgery due to the failure of the first surgery. The baseline and outcomes of patients receiving SRS, surgery, or observation are detailed in Table 3. The untreated observation interval from the inception of the study to the censoring date in patients receiving SRS or resection was 75.7 months (range 15.8–114.5 months) and 7.9 months (range 0.2–83.4 months), respectively. The mean and median mRS scores at the time of censoring were 1.2 and 1.0, respectively (range 0–6; score 0, $n = 236$, 33.3%; score 1–2, $n = 359$, 50.7%; score 3–5, $n = 100$, 14.1%; and score 6, $n = 13$, 1.8%; Fig. 2). Compared to mRS score on admission, the scores of 297 patients (41.9%) improved, 336 (47.5%) were unchanged, and 75 (10.6%) worsened. Nineteen patients (2.7%) died of rehemorrhage ($n = 13$, 1.8%), other unrelated causes ($n = 3$, 0.4%), and unknown causes ($n = 3$, 0.4%). The disease-specific survival at 1, 3, 5, and 10 years was 98.6%, 98.0%, 97.8%, and 97.4%, respectively.

Prospective Hemorrhage and Risk Factors

A total of 237 prospective hemorrhages occurred in 175 patients (24.7%) during 3400.2 total patient-years (1 ictus, $n = 132$; 2 ictuses, $n = 29$; 3 ictuses, $n = 9$; 4 ictuses, $n = 5$) yielding a prospective annual hemorrhage rate of 7.0% (95% CI 6.2%–7.9%) per patient-year (Table 2). Forty-three patients (6.1%) experienced multiple hemorrhages (≥ 2 ictuses). Overall, 104 (43.9%) and 144 (60.8%) hemorrhages occurred within 1 and 2 years after enrollment, respectively; for the first hemorrhage ($n = 175$), 89 (50.9%) and 118 (67.4%) hemorrhages occurred within 1 and 2 years. The mean intervals from the date of inception to the first ictus, from the first to the second ictus, and from the second to the third ictus were 18.7, 14.9, and 12.0 months, respectively. The overall hemorrhage-free survival estimated by Kaplan-Meier analysis at 6 months and at 1, 3, 5, and 10 years was 90.4%, 86.1%, 75.9%, 72.3%, and 68.7%. The annual hemorrhage rates during the first and the second 6 months were 21.8% (total 67 ictuses occurring in 62 patients divided by 307.6 patient-years; 95% CI 17.4%–26.9%) and 13.0% (95% CI 9.4%–17.6%; Table 2), which decreased greatly over time to 4.7% (95% CI 4.0%–5.6%; 133 ictuses during 2807.5 patient-years) after the 1st year. These rates were reflective of significant radiographic hemorrhage.

Regarding the clinical baseline, compared to patients with < 2 prospective ictuses (Table 1), patients with ≥ 2 prospective ictuses had significantly more prior hemorrhages ($p = 0.008$), larger lesion size ($p = 0.047$), and a higher proportion of FND on admission ($p = 0.048$) and DVAs ($p = 0.001$). In the univariate Cox regression analysis (Fig. 4), prior ictus ($p < 0.001$), DVA ($p < 0.001$), mRS score ≥ 2 on admission ($p < 0.001$), FND on admission (p

TABLE 3. Patient demographics categorized by treatment/observation during follow-up

Variable (%)	Observation, n = 520	SRS, n = 15	Surgery, n = 173	p Value
Female, n (%)	239 (46.0)	6 (40.0)	79 (45.7)	0.900*
Mean age on admission (median), yrs	39.2 (39.5)	41.5 (45.0)	34.9 (35.0)	0.001†
Patients w/ prior hemorrhages, n (%)	502 (96.5)	15 (100.0)	173 (100.0)	0.035*
Mean no. of prior hemorrhages (median)	1.4 (1.0)	1.5 (1.0)	1.7 (1.0)	<0.001†
Overall no. of prior hemorrhages	706	22	293	
Cumulative yrs of life	20,389	623	6037	
Retrospective annual hemorrhage rate, %	3.5	3.5	4.9	
Mean lesion size (median), cm	1.4 (1.3)	1.6 (1.5)	2.0 (2.0)	<0.001†
Crossing axial midpoint, n (%)	109 (21.0)	3 (20.0)	64 (37.0)	<0.001*
DVA, n (%)	170 (32.7)	7 (46.7)	64 (37.0)	0.340*
Superficial seated, n (%)	272 (52.3)	8 (53.3)	122 (70.5)	<0.001*
Moderate seated, n (%)	163 (31.3)	5 (33.3)	42 (24.3)	
Deep seated, n (%)	85 (16.3)	2 (13.3)	9 (5.2)	
Hemorrhage on admission, n (%)	344 (66.2)	12 (80.0)	158 (91.3)	<0.001*
FND on admission, n (%)	410 (78.8)	15 (100.0)	155 (89.6)	0.001*
Mean mRS score on admission (median)	1.5 (1.0)	2.0 (1.0)	2.1 (2.0)	<0.001‡
Mean mRS score at censoring (median)	0.9 (1.0)	1.8 (1.0)	2.3 (2.0)	<0.001‡
Patients w/ prospective hemorrhage, n (%)	105 (20.2)	7 (46.7)	63 (36.4)	<0.001*
Mean no. of prospective hemorrhages (median)	0.3 (0.0)	0.7 (0.0)	0.5 (0.0)	0.001†
Overall no. of prospective hemorrhages	146	10	81	
Cumulative yrs of observation	3191.4	94.6	114.2	
Prospective annual hemorrhage rate, %	4.6	10.6	70.9	
Disease-specific death, n (%)	11 (2.1)	2 (13.3)	0	0.001*
Mortality, n (%)	15 (2.9)	2 (13.3)	2 (1.2)	0.017*

Boldface type indicates statistical significance.

* Chi-square test.

† One-way ANOVA.

‡ Kruskal-Wallis test.

= 0.005), hemorrhage on admission ($p < 0.001$), size > 1.5 cm ($p < 0.001$), crossing the axial midpoint ($p = 0.003$), and superficially seated location ($p = 0.001$) significantly predicted prospective hemorrhage. However, in the multivariate Cox regression analysis including all univariate significant risk factors with adjustment for sex and age, DVA (HR 1.678, 95% CI 1.240–2.269, $p = 0.001$), mRS score ≥ 2 on admission (HR 1.379, 95% CI 1.009–1.886, $p = 0.044$), hemorrhage on admission (HR 1.574, 95% CI 1.068–2.320, $p = 0.022$), lesion size > 1.5 cm (HR 1.458, 95% CI 1.046–2.032, $p = 0.026$), crossing the axial midpoint (HR 1.446, 95% CI 1.039–2.013, $p = 0.029$), and superficially seated location (HR 1.307, 95% CI 1.034–1.651, $p = 0.025$) were independent adverse factors for prospective hemorrhage (Fig. 5). Prior ictus ($p = 0.230$) and FND on admission ($p = 0.309$) were no longer risk factors.

Discussion

No previous evidence has verified that the hemorrhagic risk factors of brainstem CMs are necessarily similar to those of supratentorial CMs. Even in studies of CCMs, there was a wide spectrum of hemorrhage rates and risk factors due to diverse study designs that remained debat-

able. Hemorrhage of brainstem CMs tended to be more symptomatic with low complete functional recovery,^{23,24} would produce considerable neuropathies, and subsequently impair the quality of life. Before the study by Li et al.²³ reporting 331 cases of brainstem CMs, there were only 182 total cases enrolled in 8 prior natural history studies, without detailed information.^{1,4,7,19,21,28,29,31} In our series, we mainly focused on symptomatic hemorrhage, because asymptomatic hemorrhage usually cannot be easily detected via scheduled radiographic reexamination (hematoma might vanish within the reexamination interval), the nonhemorrhagic event would be overestimated due to the psychological burden, and the mild nonhemorrhagic event did not justify surgical intervention. From a neurosurgical perspective, an accurate symptomatic hemorrhage rate endorsed by radiology was useful for patient counseling, who eagerly inquired about the hemorrhage risk if presented with symptomatic hemorrhage and/or other risk factors on admission. In our institute, treatment of brainstem CMs was conducted using either resection, or observation until the next hemorrhage accompanied by stepwise neurological decline. To avoid this deterioration, we aimed to qualitatively identify patients who would potentially suffer future hemorrhage based on the risk factors and the

FIG. 4. Forest plot showing HRs for prospective hemorrhage. The *black squares* indicate the HR values, and *error bars* represent 95% CIs. * $p < 0.05$; †univariate Cox's proportional hazards regression model; ‡multivariate Cox's proportional hazards regression model adjusted for age and sex; §Zabramski grade recorded as type I or II. BSCMs = brainstem CMs; Syx = symptoms.

stratified rates (Table 2). Overall, we identified several independent risk factors (Fig. 5), an annual hemorrhage rate of 7.0% that was within the limits of prior studies, and an acceptable mortality rate of 1.8%, with a disease-specific survival rate at 10 years of 97.4%.

Hemorrhagic Risk Factors

Both female^{1,4,23,28,31} and male⁹ sex were each once considered risk factors for rehemorrhage, but other studies as well as our cohort failed to identify this significance.^{7,20,29} There has been speculation about the association between hormone levels and consequent hemorrhage, but this association was questionable due to lack of pathophysiological evidence and the fact that pregnancy did not increase hemorrhage rates.^{9,18} Furthermore, in 3 recent meta-analyses, sex did not add independent prognostic information.^{13,16,33}

Prior hemorrhage had been acknowledged as a less-controversial risk factor that has been consistent throughout most studies.^{4,9,14,17,20,21,23} The rehemorrhage risk usually doubled or greatly increased in patients with prior hemorrhage (Jeon et al.,¹⁷ HR 7.13, and Gross et al.,¹⁴ HR 4.63) or hemorrhagic presentation (Flemming et al.,⁹ HR 5.26) compared to patients without hemorrhage, and the subdivided annual rates without this risk factor were only

0.33%–1.2%,^{9,14,34} but increased to 6.19%–11.7% if this risk factor was included.^{9,14,34} Aiba et al.¹ reported a remarkably high annual hemorrhage rate of 22.9% for patients with prior hemorrhage. Porter et al.²⁹ and Moriarity et al.²⁸ initially failed to confirm the significance of prior hemorrhage, but the effect of prior hemorrhage became significant in the subgroup analysis if combined with FND presentation²⁹ or if restricted to extralesional hemorrhage.²¹ We evaluated both the effect of prior hemorrhage and the effect of hemorrhagic presentation on future hemorrhage, and both were significant in the univariate model (Fig. 4); however, only hemorrhagic presentation remained independently significant in the multivariate model, and the effect of prior hemorrhage was no longer significant, which suggested more statistical validity and weight favoring hemorrhagic presentation, directly reflecting the current hemorrhagic activity and indicating patients' early stage of "temporal clustering."⁶ It was easier and more accurate to judge the hemorrhagic presentation based on radiographs. Prior hemorrhage, which is subject to recall bias, seemed to be a confounding factor versus hemorrhagic presentation, which might be attributable to the small cohort without prior hemorrhage ($n = 18$, 2.5%).

DVA has been associated with CM development,¹³ pretreatment hemorrhage,¹⁴ and postoperative rehemor-

FIG. 5. Kaplan-Meier survival curves showing the risk factors for hemorrhage. DVA, crossing the axial midpoint, hemorrhage on admission, mRS score ≥ 2 on admission, more superficial location, and lesion size > 1.5 cm all increased the chance of rehemorrhage. These factors were independent adverse factors in multivariate Cox proportional hazards regression models. The chi-square and p values were estimated by Kaplan-Meier survival analysis. Figure is available in color online only.

rhage,^{11,27} but conversely numerous studies confirmed the insignificance of DVA in predicting hemorrhage, probably due to all CMs containing DVAs.^{4,9,13,14,17,23} The percentage of trackable radiographic DVAs, ranging from 9% to 27.7%, was considered an underestimation on conventional radiological sequences. Given the assumption of the existence of occult DVA with minor vessels, the blood flow volume was smaller compared to trackable DVA, and the trackable DVA with relatively greater vessel and slower blood flow took charge of the venous drainage surrounding CMs and had a proclivity for thrombus formation.³⁷ The venous drainage obstruction due to occlusion of a trackable DVA could not be easily compensated via shunting to adjacent veins followed by hemorrhagic infarcts, and these catastrophic events might be less likely to occur after occlusion of a minor vessel, which had minor responsibility for drainage. Therefore, the morphology of DVAs and the spatial relationship between DVAs and CMs should be taken into account as potential risk factors that require further study to validate the hypothesis.

Jeon et al.¹⁷ reported that Zabramski type I/II CMs increased the chance of rehemorrhage compared to type III.³⁶ However, in other studies, the MR signal appearance did not have an impact on rehemorrhage.^{9,23,24,34} Gross and Du¹³ argued that the Zabramski grade, almost by definition, was confounded by hemorrhage and subject to interobserver variability.²⁶ Otherwise, the MR signal quite depended on the period between symptoms and MRI, which would change over time. Lesion size (≥ 10 mm²¹ and 20 mm²⁴) was significant in only 2 prior studies, and we found that size > 1.5 cm based on the ROC curve,

which produced mass effect given the small volume of the brainstem, predicted rehemorrhage ($p = 0.026$). Lesions crossing the axial midpoint and mRS scores ≥ 2 , which were associated with lesion size ($p < 0.001$) via bivariate correlation analysis (Fig. 4), were independent risk factors in our cohorts due to the considerable lesion size and poor neurological status on admission, respectively, that conformed to surgical indications.

Hemorrhage Rate

The annual hemorrhage rate of CCMs was reported to be 0.25%,⁸ 1.7%,⁷ and 2.3%–2.5%¹⁹ in retrospective studies, and 0.5%,⁴ 1.6%–3.1%,^{9,20,28,29,32} and 10.0%¹ in prospective studies. Gross and Du¹³ pooled 7 prior prospective studies^{1,4,9,20,28,29,32} and calculated an annual hemorrhage rate of 2.5% per patient-year for CCMs (136 bleeds/5081.2 patient-years). These annual rates were susceptible to the composition of the patient population,²⁴ and we found that studies with the lowest annual rates of 0.5%,⁴ 0.6%,²² and 0.7% per lesion-year³¹ had the longest mean observation duration (8.8 years), the highest proportion of asymptomatic patients (100%), and the lowest proportion of patients with hemorrhagic presentation (9.1%), respectively. Taslimi et al.³³ suggested brainstem location as a source of heterogeneity, and the percentage of brainstem CMs should account for the diversity of hemorrhage rates.

In a retrospective study by Kupersmith et al.²¹ including 37 cases of brainstem CMs, the annual bleeding and rebleeding rates were 2.46% and 5.1%, respectively. Similar results were also cited by Cantu et al.⁷ (2.33% in 25 pa-

tients) and Kondziolka et al.²⁰ (2.4% in 43 patients, which increased to 5.0% if restricted to brainstem location with prior hemorrhage), and a relatively higher annual hemorrhage rate reported by Gross et al.¹⁴ (16.7%). It should be noted that the annual rebleeding rate in patients with extracerebral bleeding could increase to 14.2%,²¹ and Aiba et al.¹ reported an annual hemorrhage rate up to 21.5% in 15 cases of brainstem CMs with hemorrhagic presentation. In our patients with prior hemorrhage ($n = 690$), the annual hemorrhage rate within the 1st year was 18.1% (95% CI 15.1%–21.6%; 104 bleeds/574.7 patient-years), remarkably similar to the 18.3% rate in 74 patients presenting with acute hemorrhage reported by Flemming et al.⁹ notwithstanding location. In patients with 1 prior hemorrhage ($n = 455$), the annual hemorrhage rate was 6.0% (141 bleeds/2342.0 patient-years), which was also similar to the overall annual hemorrhage rate for patients with hemorrhagic presentation (6.19%).⁹ Our overall annual hemorrhage rate (7.0%) was close to that of thalamic CMs (9.7%) in a previous study.³⁴ Temporal clustering of hemorrhage within the first 2 years has been observed in several studies^{4,6,9,13} and the hemorrhage risk decreased thereafter, comparable to our overall cohort with a 17.5%/patient-year rate within the 1st year and 4.7%/patient-year rate thereafter. If patients were followed up for the rest of their lives, the annual hemorrhage rate would decrease even if the CM involved eloquent locations. Given the phenomenon of temporal clustering of hemorrhage and that the majority of the patients presented with hemorrhage, the true hemorrhage rate was likely overestimated in our study. The annual hemorrhage rate of patients with or without hemorrhagic presentation was 8.3% and 4.3%, and the annual hemorrhage rates of patients with > 1, 1, or no prior ictus were 9.9%, 6.0%, and 1.0%, respectively (Table 2). These results indicate that the hemorrhage rate was vulnerable to patient composition and clinical presentation models.

Implications for Clinical Management

There were several significantly different clinical parameters between the subgroups of surgery and SRS, which might lead to the large disparity in untreated observation intervals between both groups (Table 3). The surgery subgroup had significantly younger age, higher retrospective annual hemorrhage rate, larger lesion size, more lesions crossing the axial midpoint and being superficially seated, and worse mRS score at censoring than that of the SRS subgroup. Remarkably, the surgery subgroup had a significantly higher annual prospective hemorrhage rate (70.9% vs 10.6%), worse hemorrhage-free survival by Kaplan-Meier analysis (log-rank test, chi-square = 17.161, $p < 0.001$), and shorter estimated median hemorrhage-free survival time (10.7 months), which was not reached in the SRS subgroup and mainly contributed to the large disparity.

We focused on symptomatic hemorrhage, which was easily detected with pertinent radiographs, and because new or aggravated symptoms would remind patients to undergo immediate radiological examination to obtain the radiological evidence and definitively confirm the hemorrhage. This convincing information helped to adjust the individualized patient management strategy. Clinical exacerbation due to hemorrhage rather than ischemia justi-

fied resection. However, asymptomatic hemorrhage, which almost always was unnoticed with a small volume of hematoma, was less likely detected unless it occurred just before a scheduled radiological examination. Because it was asymptomatic, we were less likely to detect and record all asymptomatic hemorrhage, even with real-time radiological monitoring; therefore, the number of asymptomatic hemorrhages was usually underestimated. It would significantly increase medical costs to find all asymptomatic hemorrhages via frequent radiological examinations. Most importantly, given the assumption of asymptomatic hemorrhage, for which the management strategy (observation) was likely unchanged, resection was controversial and seemed to be excessive treatment if the risk outweighed the benefit. In addition, the surgical morbidity might be less acceptable because the preoperative neurological status was normal. Therefore, the evaluation of the incidence of asymptomatic hemorrhage appeared to be a paradox, because it was barely possible to capture all asymptomatic ones, and the incorrect questionable hemorrhage rate would misguide the clinical consultation. It was reasonable for us to wait for the asymptomatic hemorrhage to become a symptomatic one that would convince the patient to shift his/her attitude toward treatment.

We would recommend surgery to patients meeting surgical indications but would not suggest prophylactic resection to eliminate future hemorrhage in nonsurgical candidates, because of the potential surgical morbidity and because we could not guarantee the absolute accuracy of predicting future hemorrhage at enrollment. The aggressive attitude became less feasible in routine clinical practice if the surgeon could not accurately judge whether rehemorrhage was possible or not. Repeated hemorrhages with new FND within a short period of time implied clinical progression and the aggressive nature of the lesions that to a certain extent warranted surgical intervention; however, other parameters (e.g., location, depth, accessibility, and size) should be considered as well, and it remained important to distinguish aggressive ones from occult/silent ones.

Study Limitations

This study was a hospital-based consecutive cohort with significant systematic referral bias and was susceptible to random sampling of patients from the general population. The selection bias was unavoidable given that severe brainstem CMs with a more aggressive course justifying surgery were excluded from the study and the management strategy for these lesions was less debatable, but the remaining patients in the present cohort with weaker indications for surgery or who declined surgery were precisely those requiring our attention to investigate their hemorrhagic risk and determine a reasonable treatment. As a national medical referral center, our results might overestimate the hemorrhage rate compared to that of the general population,²⁴ but they may be useful to a certain degree for other tertiary hospitals that often encounter patients with hemorrhagic presentation transferred from primary care providers or secondary hospitals. A population-based multicenter study is needed to reduce these biases and improve the generalization and extrapolation to a broader patient population.^{4,5}

Conclusions

In this study, we reported an annual hemorrhage rate of 7.0% exclusively for brainstem CMs, which significantly increased if patients presented with other risk factors. Patients with hemorrhagic presentation needed close follow-up regardless of the number of prior hemorrhages. Our results are useful for patients and physicians in helping to select a personalized treatment in other referral centers. The referral bias and the composition of the patient population of our cohort should be noted, and a population-based multicenter study is suggested to reduce these limitations. Further studies are required to verify our findings.

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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: all authors. Acquisition of data: Li, Ze-Yu Wu, Liu, Ma, Huo, Wang. Analysis and interpretation of data: all authors. Drafting the article: Li, Ze-Yu Wu, Liu, Wang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: JT Zhang. Statistical analysis: Li, Ze-Yu Wu, Liu, Ma, Huo, Zhen Wu. Administrative/technical/material support: all authors. Study supervision: JT Zhang, Li, Ze-Yu Wu, Liu, Wang, LW Zhang, Zhen Wu.

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