SVN | Stroke and Vascular Neurology

Neurological outcomes of untreated brainstem cavernous malformations in a prospective observational cohort and literature review

Da Li,[1] Jing-Jie Zheng,[2] Jian-Cong Weng,[1] Pan-Pan Liu,[1] Ze-Yu Wu,[1] Li-Wei Zhang,[1] Jun-Ting Zhang,[1] Liang Wang,[1] Zhen Wu ORCID [1]

Check for updates

[1]Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Obstetrics and Gynecology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Correspondence to
Professor Zhen Wu;
ttyywuzhen@sina.com

Professor Liang Wang;
ttyywangliang@sohu.com

ABSTRACT

Background Haemorrhages of brainstem cavernous malformations (CMs) can lead to neurological deficits, the natural history of which is uncertain. The study aimed to evaluate the neurological outcomes of untreated brainstem CMs and to identify the adverse factors associated with worsened outcomes.

Methods From 2009 to 2015, 698 patients (321 women) with brainstem CMs were entered into the prospective cohort after excluding patients lost to follow-up (n=43). All patients were registered, clinical data were collected and scheduled follow-up was performed.

Results After a median follow-up of 60.9 months, prospective haemorrhages occurred in 167 patients (23.9%). The mean modified Rankin Scale scores at enrolment and at censoring time were 1.6 and 1.2. Neurological status was improved, unchanged and worsened in 334 (47.9%), 293 (42.0%) and 71 (10.2%) patients, respectively; 233 (33.4%) recovered to normal levels. Lesions crossing the axial midpoint (relative risk (RR) 2.325, p=0.003) and developmental venous anomaly (DVA) (RR 1.776, p=0.036) were independently significantly related to worsened outcomes. The percentage of worsened outcomes was 5.3% (18 of 337) in low-risk patients (neither DVA nor crossing the axial point) and increased to 26.0% (13 of 50) in high-risk patients (with both DVA and crossing the axial point). The percentage of worsened outcomes significantly increased as the number of prospective haemorrhages increased (from 1.5% (8 of 531, if 0 prospective ictus) to 37.5% (48 of 128, if 1 ictus) and 38.5% (15 of 39, if >1 ictus)).

Conclusions The neurological outcomes of untreated brainstem CMs were improved/unchanged in majority of patients (89.8%) with a fatality rate of 1.7% in our cohort, which seemed to be favourable. Radiological features significantly predicted worsened outcomes. Our results provide evidence for clinical consultation and individualised treatment. The referral bias of our cohort was underlined.

INTRODUCTION

Cerebral cavernous malformations (CCMs) account for 10%–15% of intracranial vascular malformations, with a population incidence ranging from 0.4% to 0.8%.[1] Due to their sluggish blood flow, they are often considered clinically quiescent and angiographically occult, and up to 40% of patients are asymptomatic. In a population-based cohort,[2] the 5-year risk of a composite outcome (haemorrhage or focal neurological deficit (FND)) was approximately 57.1% for brainstem cavernous malformations (CMs), which was in accordance with the rate of 50.7% with haemorrhage/FND presentation in our recent meta-analysis.[3] Due to the presence of vital and dense neurostructures, the eloquent site with a small volume and the high susceptibility to minor haemorrhage,[4] the brainstem has been confirmed to be associated with symptomatic haemorrhage.[3 5–7] The natural history of CCMs and favourable surgical outcomes of brainstem CMs have been extensively delineated,[2 3 5 6 8–21] but there is a paucity of data regarding the neurological outcome of untreated brainstem CM, which has otherwise been poorly individually reported. Haemorrhage of brainstem CMs can result in severe neuropathies, impairments in quality of life and even unexpected death relevant to patients. Therefore, we aimed to describe the neurological status of untreated brainstem CMs in a prospective cohort and to review the literature regarding the untreated disease in order to contribute to improving our understanding of the natural history of the disease, to distinguish between patients who might suffer from worsened outcomes and subsequently become surgical candidates, and to facilitate clinical decision-making.

PATIENTS AND METHODS
Patient population

Patients diagnosed with brainstem CMs in our institute from January 2009 to December 2015 were registered and enrolled in the consecutive prospective cohort according to the inclusion and exclusion criteria. The inclusion criteria were (1) a definitive diagnosis of an untreated brainstem CM and (2)

BMJ

provision of informed consent. Patients were excluded if they met one of the following criteria: (1) the diagnosis was questionable/undefined; (2) they did not consent to follow-up; (3) they received treatment (radiation or surgery) before enrolment; (4) they had severe comorbidities involving the eloquent location, which might potentially influence the accuracy of neurological evaluation; (5) they were pregnant or breast feeding; and (6) they underwent surgery immediately following diagnosis. Surgical indications have been described in prior studies,[15–19 22 23] and stereotactic radiosurgery (SRS) was not recommended. Surgical treatment was recommended if as follows: (1) multiple haemorrhages and poor or progressively aggravated neurological status; (2) lesion size ≥2 cm or enlarged with a significant mass effect; and (3) lesion grew exophytically or became abutting the pial surface after haemorrhagic ictus. All clinical data were obtained from a prospective clinical trial (no. ChiCTR-POC-17011575). Written informed consent was obtained from all participants and their parents or caregivers.

Procedures and neurological evaluation

The inception point of the study was the date of the first medical consultation or clinical visit that led to the diagnosis of a brainstem CM at our institute. Two neuroradiologists independently reviewed the MRI scans to verify the diagnosis according to the accepted criteria (online supplemental figure 1).[13] In patients with MRI scans obtained more than 2 weeks prior, MRI re-examination was prescribed at enrolment to check the radiological features because haematomas evolve over time. The characteristics of MRI, including (but not limited to) an equivalent lesion size, crossing the axial midpoint,[16] the Zabramski classification[13] and developmental venous anomalies (DVAs), were extensively reviewed. If there were multiple CMs involving the brainstem, the symptomatic haemorrhagic CM took precedence for analysis; otherwise, the larger CM was preferred since both were postulated to be predictors of haemorrhage or FND.[2] Brainstem CMs often encompassed different compartments, and we classified each CM only to one compartment according to the location of the maximal axial cross-sectional area of the lesion regardless of the number of anatomical compartments involved by the lesion (online supplemental figure 2). If the maximal axial cross-sectional area of a CM was located in the thalamus, the lesion would be classified as a thalamic CM even if it concurrently encompassed the midbrain. Neither the anatomical compartment within the brainstem nor the number of compartments involved by a brainstem CM had been proven to be related to the worsened outcome that had been observed in prior studies.[15 16 18–22] Our classification was easily understandable, practicable and repeatable in clinical practice that conformed to the gross anatomy of the brainstem and facilitated statistical analysis.

The initial presentation, number of prior haemorrhages, and symptoms and neurological status following each ictus were collected and identified according to the

medical records combined with available radiographic evidence that facilitated judgement of the presence of haemorrhagic events. Cranial nerve palsy, long tract deficits (motor and sensory abnormalities) and/or extrapyramidal symptoms specifically pertinent to the anatomical location of the lesion were classified as FNDs. Headache, dizziness, nausea, vomiting and/or other symptoms not directly associated with the lesion were classified as non-FNDs (non-specific symptoms). The definition of haemorrhage according to that advocated by Al-Shahi Salman *et al*[24] is as follows: a clinically symptomatic event (an acute or subacute, new-onset or worsening FND corresponding to the anatomical location of the brainstem CM, impaired consciousness, or severe headache) with recent overt haemorrhage within or outside the lesion leading to changes in lesion size and/or signal intensity based on serial radiographs.[2 22] The first 3 days since onset of a clinically symptomatic event was defined as acute, and after that the interval ranging from the fourth day to 3 weeks was defined as subacute. Symptomatic events, provided by patients' impression, recall or only medical records but without concomitant radiographs, were not enough to conclude a haemorrhagic event, which was considered uncertain to reduce recall bias and to avoid overestimating prior haemorrhages. Acute-onset symptoms or worsened deficits, anatomically consistent with the CM location, likely raised the suspicion of a haemorrhage, but other causes (ischaemic attack, infarction or secondary perilesional oedema) were not precluded in the absence of timely radiographs.

Follow-up

At enrolment, at least three phone numbers from the patients and their relatives were registered, along with information on home address, email address and social media account (Tencent Messenger and WeChat) if available. Two authors (PPL and ZYW), blinded to the results of the radiographs and haemorrhagic status, independently evaluated the neurological status at enrolment using modified Rankin Scale (mRS) scores and then completed the scheduled follow-up by clinical revisits (in person) 3, 6 and 12 months after enrolment and then annually after that or by telephone interviews, with visual contact according to structured question approaches or mailed questionnaires with digital photos sufficient for clinical evaluation. Home visits or connections with family doctors from community health services or community hospitals were alternative approaches to obtain follow-up information, with any discrepancy resolved by the senior author (JTZ). Since 2009, with the economic development, few patients would change their phone numbers, and these three phone numbers were less likely to change at the same time. These phone numbers and information for contacting the patients would be updated at each scheduled clinical revisit, and if clinical revisits were unavailable telephone interviews were performed annually to check the availability of these contact methods. MRI was recommended at the same time, but MRI at any time was

Table 1 Baseline and clinical data of brainstem cavernous malformations stratified by neurological outcome

Variable (%)	Overall, N=698	Improved (mRS=0), n=334	Unchanged, n=293	Worsened, n=71	P value
Female	321 (46.0)	154 (46.1)	132 (45.1)	35 (49.3)	0.811†
Mean age at enrolment, years	38.3±13.8	36.8±13.3	39.5±13.8	40.6±15.2	**0.017*‡**
Hypertension	96 (13.8)	50 (15.0)	38 (13.0)	8 (11.3)	0.625†
Mean duration of symptoms, months	21.3±44.7	16.4±37.9	24.5±46.3	30.8±62.5	**0.013*‡**
Patients with prior haemorrhage	680 (97.4)	322 (96.4)	288 (98.3)	70 (98.6)	0.267†
Mean number of prior haemorrhage	1.4±0.8	1.3±0.8	1.5±0.9	1.6±0.8	**0.003*‡**
Haemorrhage at enrolment	508 (72.8)	228 (68.3)	223 (76.1)	57 (80.3)	**0.029*†**
FND at enrolment	589 (84.4)	265 (79.3)	262 (89.4)	62 (87.3)	**0.002*†**
Midbrain location	154 (22.1)	69 (20.7)	65 (22.2)	20 (28.2)	0.699†
Pontine location	442 (63.3)	216 (64.7)	186 (63.5)	40 (56.3)	
Medullary location	102 (14.6)	49 (14.7)	42 (14.3)	11 (15.5)	
Crossing axial midpoint	174 (24.9)	70 (21.0)	71 (24.2)	33 (46.5)	**<0.001*†**
Developmental venous anomaly	237 (34.0)	106 (31.7)	98 (33.4)	33 (46.5)	0.057†
Perilesional oedema	342 (49.0)	172 (51.5)	132 (45.1)	38 (53.5)	0.198†
Zabramski type I	190 (27.2)	97 (29.0)	70 (23.9)	23 (32.4)	**0.010*†**
Zabramski type II	326 (46.7)	135 (40.4)	156 (53.2)	35 (49.3)	
Zabramski type III/IV	182 (26.1)	102 (30.5)	67 (22.9)	13 (18.3)	
Mean lesion size, cm¶	1.5±0.7	1.4±0.6	1.6±0.6	1.9±0.7	**<0.001*‡**
Size >1.5 cm	299 (42.8)	116 (34.7)	135 (46.1)	48 (67.6)	**<0.001*†**
Superficial-seated	395 (56.6)	173 (51.8)	171 (58.4)	51 (71.8)	**0.003*†**
Moderate-seated	208 (29.8)	102 (30.5)	93 (31.7)	13 (18.3)	
Deep-seated	95 (13.6)	59 (17.7)	29 (9.9)	7 (9.9)	
mRS score at enrolment					0.363§
0	47 (6.7)	41 (12.3)	0	6 (8.5)	
1	400 (57.3)	153 (45.8)	210 (71.7)	37 (52.1)	
2	104 (14.9)	52 (15.6)	38 (13.0)	14 (19.7)	
3	66 (9.5)	39 (11.7)	17 (5.8)	10 (14.1)	
4	68 (9.7)	38 (11.4)	26 (8.9)	4 (5.6)	
5	13 (1.9)	11 (3.3)	2 (0.7)	0	
mRS score at censored					**<0.001*§**
0	233 (33.4)	233 (69.8)	0	0	
1	283 (40.5)	70 (21.0)	210 (71.7)	3 (4.2)	
2	71 (10.2)	17 (5.1)	38 (13.0)	16 (22.5)	
3	44 (6.3)	10 (3.0)	17 (5.8)	17 (23.9)	
4	49 (7.0)	4 (1.2)	26 (8.9)	19 (26.8)	
5	6 (0.9)	0	2 (0.7)	4 (5.6)	
6	12 (1.7)	0	0	12 (16.9)	
Mean follow-up duration, months	56.9±35.3	69.0±28.5	49.8±37.6	29.4±31.3	**<0.001*‡**
Haemorrhage-free survival time, months	48.7±36.0	61.4±32.2	41.9±36.6	17.0±21.0	**<0.001*‡**
Patients with prospective bleeding	167 (23.9)	48 (14.4)	56 (19.1)	63 (88.7)	**<0.001*†**
Mean number of prospective bleeding	0.3±0.7	0.2±0.5	0.3±0.6	1.2±0.8	**<0.001*‡**
Patients under observation	514 (73.6)	301 (90.1)	188 (64.2)	25 (35.2)	**<0.001*†**
Patients receiving radiosurgery	14 (2.0)	5 (1.5)	7 (2.4)	2 (2.8)	
Patients receiving surgery	170 (24.4)	28 (8.4)	98 (33.4)	44 (62.0)	

Means are given with SD.
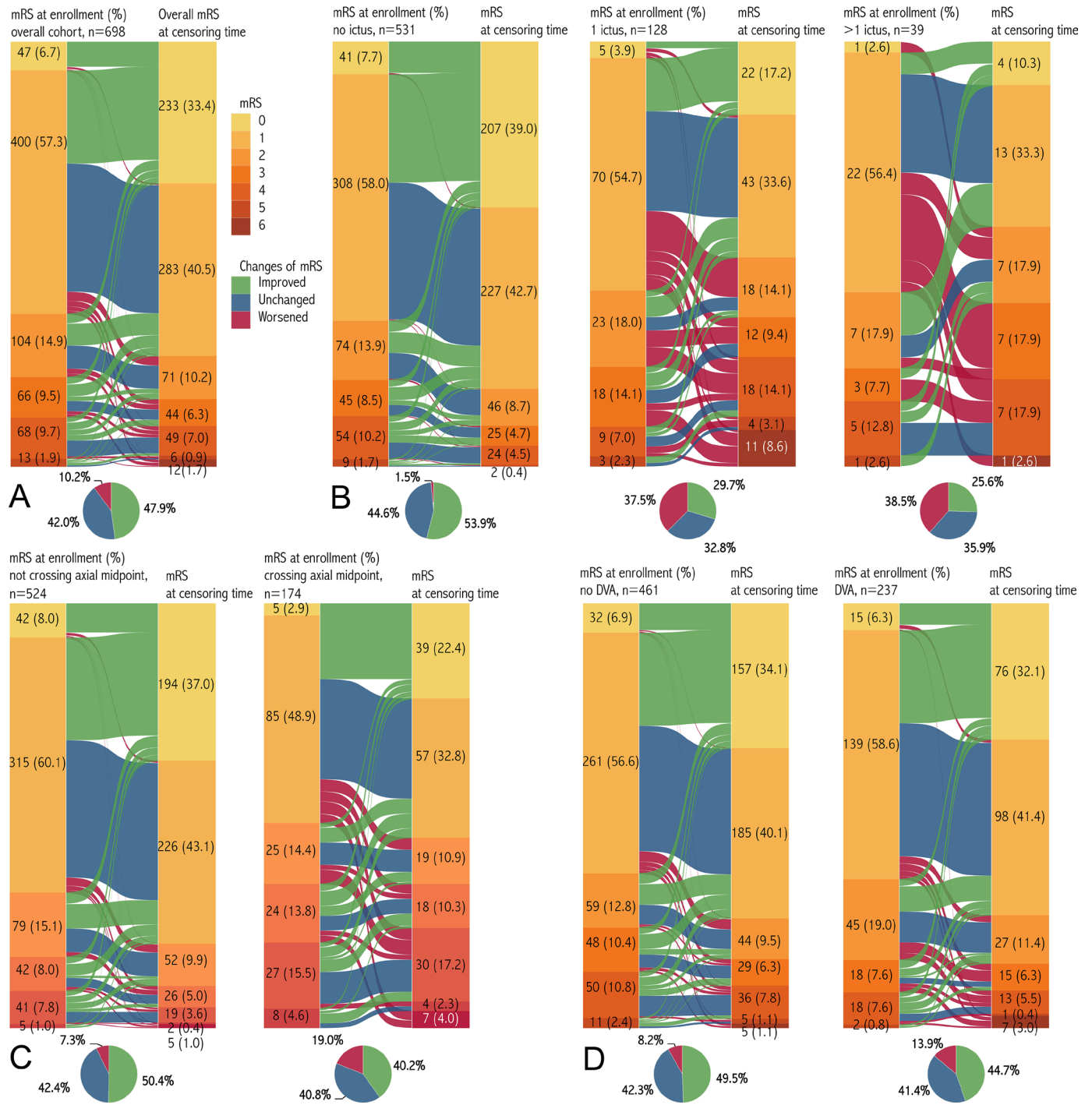Bold indicates statistical significance.
*P<0.05.
†χ^2 test.
‡One-way analysis of variance.
§Kruskal-Wallis test.
¶Lesion size was expressed as the lesion equivalent diameter $(abc)^{1/3}$, where a, b and c represent the maximal diameters (length, width and height) measured on axial, sagittal and coronal MRI scans.
FND, focal neurological deficit; mRS, modified Rankin Scale.

Figure 1 Sankey diagrams showing the distribution and changes in mRS score at enrolment and at censoring time. (A) The figure consisted of two bars and one flow in between. These two bars show the distribution of mRS scores at enrolment and at censoring time in orange. The width and value of each flow were calculated according to the sample size showing the dominant or subordinate contributions to the overall flow that were similar in other panels. (B–D) The mRS scores at enrolment and at censoring time were stratified by the number of prospective haemorrhages (B), crossing the axial midpoint or not (C), and presence of DVA or not (D). The Sankey diagrams are illustrated using Tableau Desktop (V.8.3). DVA, developmental venous anomaly; mRS, modified Rankin Scale.

necessary once the patient perceived severe headache or new/worsened pre-existing symptoms. Provided changes in neurological function, we were fully aware of a new haemorrhage, but it would be noted as questionable without radiological evidence.

The follow-up duration began at enrolment and ended on the date of surgery, SRS, death or the most recent evaluation, whichever occurred first. The cause of death was enquired from their relatives if the patient has passed away.

Statistical analysis and literature review

The clinical and baseline data stratified by neurological outcomes were compared (table 1). The risk factors for worsened outcomes were evaluated by univariate and multivariate binary logistic regression (method: Enter). Statistical analyses were performed using SPSS statistical package software (V.25.0), with significance set at p<0.05. A systematic review of the literature was performed regarding neurological outcomes in untreated brainstem CMs. Studies were reviewed and screened by two independent review authors using the terms 'cavernoma', 'cavernous malformation' and 'cavernous hemangioma' in the following databases from January 1984 to December 2019: EMBASE, PubMed, Cochrane, Ovid/Medline, Web of Science and EBSCO. We further reviewed all of the references provided in the identified studies and incorporated all pertinent citations. Studies that did not provide neurological outcomes were excluded.

RESULTS

Patient demographics

During the period from 2009 to 2015, after excluding 43 patients lost to follow-up, 698 patients (321 women, 46.0%) with brainstem CMs referred to our institute were entered into the consecutive prospective cohort, with a mean age of 38.3±13.8 years. Nine patients (1.3%) had a family history and 96 patients (13.8%) had a history of hypertension. The mean duration of symptoms before enrolment was 21.3±44.7 months, and 680 patients (97.4%) had a prior haemorrhage.

At enrolment, 508 patients (72.8%) presented with a recent haemorrhage (188 acute and 320 subacute haemorrhage), 589 patients (84.4%) complained of FNDs, including cranial nerve deficits (n=466, 66.8%), long tract impairments (n=428, 61.3%) and extrapyramidal symptoms (n=177, 25.4%), and 197 patients (28.2%) had non-specific symptoms. The mRS scores at enrolment were 0, 1, 2, 3, 4 and 5 in 47 (6.7%), 400 (57.3%), 104 (14.9%), 66 (9.5%), 68 (9.7%) and 13 (1.9%) patients, respectively. The mean and median mRS scores were 1.6 and 1.0. Overall, 447 patients (64.0%) were able to perform usual activities, 104 (14.9%) had self-care abilities without the need for assistance, and 147 (21.1%) were unable to carry out self-care and required assistance. Radiologically, the pons (n=442, 63.3%) was the most common lesion location, followed by the midbrain (n=154, 22.1%) and medulla (n=102, 14.6%). The mean lesion size was 1.5±0.7 cm. The details of other radiographic parameters are described in table 1.

Follow-up

During a mean follow-up of 56.9±35.3 months (median 60.9 months), 167 patients (23.9%) suffered prospective haemorrhages. The censoring events (n=199, 28.5%) included SRS (n=14, 2.0%), surgical resection (n=170, 24.4%), disease-specific deaths (n=11, 1.6%) and deaths due to unrelated/unknown causes in the observation group (n=4, 0.6%).

Primary results: neurological status and risk factors for worsened outcomes

The mRS scores at censoring time were 0, 1, 2, 3, 4, 5 and 6 in 233 (33.4%), 283 (40.5%), 71 (10.2%), 44 (6.3%), 49 (7.0%), 6 (0.9%) and 12 (1.7%) patients, respectively. The mean and median mRS scores were 1.2 and 1.0. Compared with the mRS scores at enrolment, those in 334 patients (47.9%) improved, unchanged in 293 patients (42.0%) and worsened in 71 patients (10.2%) at censoring time (Z=−9.134, p<0.001) (table 1, figures 1 and 2). In 169 patients who were recommended surgery but at first refused, 52 (30.8%) suffered a prospective haemorrhage, 88 (52.1%) finally received surgery, and overall neurological status at censoring time was improved,
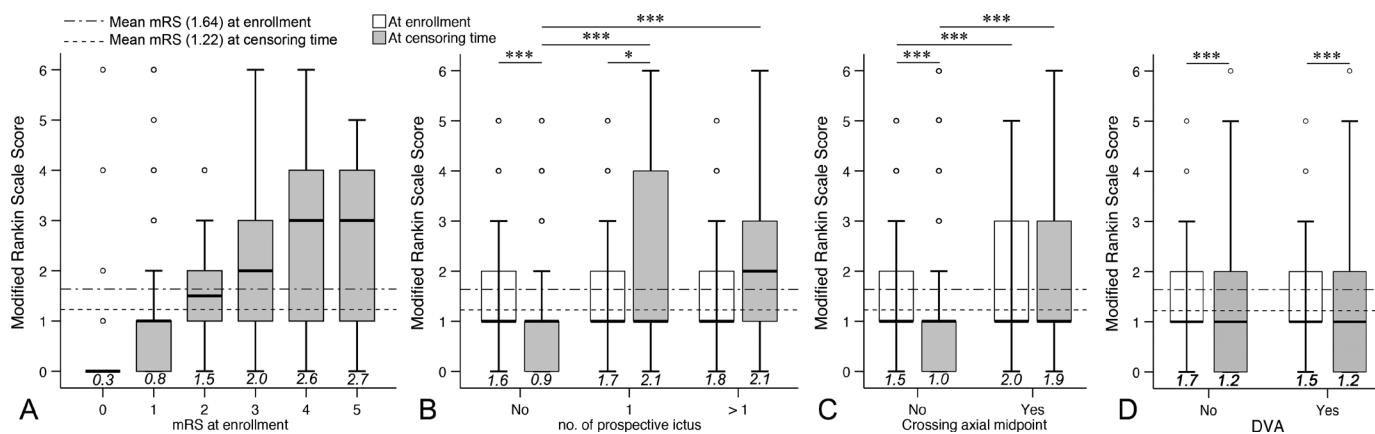
Figure 2 Boxplots showing the distribution of mRS scores at enrolment and at censoring time based on risk factors. (A) The boxplot shows the mRS score at censoring time stratified by mRS score at enrolment. (B–D) The outcome was significantly better in patients without prospective ictus than in patients with one (Z=−7.398, p<0.001) or more (Z=−5.414, p<0.001) ictus (B). Patients without lesions crossing the axial midpoint had significantly better outcomes than patients with lesions crossing the axial midpoint (Z=−6.352, p<0.001) (C). However, there was no significance between the outcomes in patients with or without DVA (Z=−0.384, p=0.701) (D). *P<0.05, ***P<0.001. Circles indicate the outliers; values in italic above the horizontal axis indicate the mean values of each boxplot. DVA, developmental venous anomaly; mRS, modified Rankin Scale.

Table 2 Risk factors for worsened neurological function in brainstem cavernous malformations

Variable (%)	n	Worsened (n=71, %)	Univariate† RR (95% CI)	P value	Multivariate†‡ RR (95% CI)	P value
Male	377	36 (9.5)	Reference		Reference	
Female	321	35 (10.9)	1.159 (0.709 to 1.894)	0.555	1.074 (0.634 to 1.819)	0.792
Age (per 1 year)			1.014 (0.995 to 1.032)	0.145	1.020 (1.000 to 1.041)	0.051
Without hypertension	602	63 (10.5)	Reference			
Hypertension	96	8 (8.3)	0.778 (0.360 to 1.679)	0.522		
Duration of symptoms (per 0.1 months)			1.004 (1.000 to 1.008)	0.064	1.004 (0.999 to 1.009)	0.101
Without prior haemorrhage	18	1 (5.6)	Reference			
With prior haemorrhage	680	70 (10.3)	1.951 (0.256 to 14.882)	0.519		
Without haemorrhage at enrolment	190	14 (7.4)	Reference			
Haemorrhage at enrolment	508	57 (11.2)	1.589 (0.863 to 2.924)	0.137		
Without FND at enrolment	109	9 (8.3)	Reference			
FND at enrolment	589	62 (10.5)	1.307 (0.629 to 2.715)	0.473		
mRS score at enrolment (per one score)			0.939 (0.756 to 1.168)	0.573		
Lesion size (per 1 mm)			**2.343 (1.643 to 3.341)**	**<0.001***	1.263 (0.806 to 1.979)	0.309
Not crossing axial midpoint	524	38 (7.3)	Reference		Reference	
Crossing axial midpoint	174	33 (19.0)	**2.993 (1.811 to 4.948)**	**<0.001***	**2.325 (1.332 to 4.060)**	**0.003***
Without venous anomaly	461	38 (8.2)	Reference		Reference	
Developmental venous anomaly	237	33 (13.9)	**1.801 (1.097 to 2.955)**	**0.020***	**1.776 (1.037 to 3.041)**	**0.036***
Depth (superficial-seated)	395	51 (12.9)	**1.595 (1.074 to 2.367)**	**0.021***	1.194 (0.774 to 1.841)	0.423
Without oedema	356	33 (9.3)	Reference			
Perilesional oedema	342	38 (11.1)	1.223 (0.748 to 2.001)	0.422		
Zabramski classification			1.313 (0.935 to 1.846)	0.116		
Type III/IV	182	13 (7.1)	Reference			
Type II	326	35 (10.7)	1.564 (0.805 to 3.038)	0.187		
Type I	190	23 (12.1)	1.790 (0.878 to 3.652)	1.790		

Bold indicates statistical significance.
*P<0.05.
†Binary logistic regression (method: Enter); risk factors, entered into the multivariate binary logistic regression, included gender, age, duration of symptoms, lesion size, crossing axial midpoint, developmental venous anomaly and depth of the lesion.
‡Adjustment for duration of follow-up.
FND, focal neurological deficit; mRS, modified Rankin Scale; RR, relative risk.

unchanged and worsened in 59 (34.9%), 79 (46.7%) and 31 (18.3%) patients, respectively.

The univariately significant risk factors for worsened outcome are lesion size (per 1 mm) (relative risk (RR) 2.343, p<0.001), crossing the axial point (RR 2.993, p<0.001), DVA (RR 1.801, p=0.020) and depth (RR 1.595, p=0.021) (table 2). In the multivariate analysis (Enter method) with adjustment for duration of follow-up, crossing the axial point (RR 2.325, 95% CI 1.332 to 4.060, p=0.003) and DVA (RR 1.776, 95% CI 1.037 to 3.041, p=0.036) were significantly related to worsened neurological outcomes (figures 1 and 2), and other factors were no longer significant. The percentage of worsened outcomes was 5.3% (18 of 337) in low-risk patients (neither DVA nor crossing the axial point), 12.9% (40 of 311) in mid-risk patients (either DVA or crossing the axial point) and 26.0% (13 of 50) in high-risk patients (with both DVA and crossing the axial point).

Secondary results: prospective haemorrhages and worsened outcomes

Overall, the numbers of patients experiencing 1, 2, 3 and 4 prospective haemorrhages were 128 (18.3%), 27 (3.9%), 8 (1.1%) and 4 (0.6%), respectively. The percentage of worsened outcomes significantly increased as the number of prospective haemorrhages increased (from 1.5% (8 of 531, if 0 ictus) to 37.5% (48 of 128, if 1 ictus) and 38.5% (15 of 39, if >1 ictus)), while the percentage of complete recovery significantly decreased from 39.0% (207 of 531, if 0 ictus) to 17.2% (22 of 128, if 1 ictus) and 10.3% (4 of 39, if >1 ictus) (χ^2=31.965, p<0.001) (figures 1 and 2).

DISCUSSION

The natural history of CMs has been elaborately demonstrated,[1–3 5 6 8–13] but in prior studies brainstem CMs were often reported together with CMs of other locations

rather than as a distinct entity, and the neurological outcomes of brainstem CMs were often not detailed or not described separately with limited sample size. Overall, the 5-year risk of a composite outcome (haemorrhage or FND) is 44.5% for brainstem CMs and 8.8% for CMs in other locations,[3] the posthaemorrhage full recovery is 38.8%/person-years, and the haemorrhage-associated mortality is 2.2%.[6] Due to the crucial anatomical location of the brainstem and unpredictable haemorrhage, the outcome of brainstem CMs is considerably poor. In our cohort, after a median follow-up of 5.1 years, we found that 233 patients (33.4%) recovered to an asymptomatic status, 334 (47.9%) improved and 71 (10.2%) worsened; additionally, DVA and crossing the axial midpoint had substantial effect on worsened outcomes. These results indicated that neurological status most likely trended towards improved/unchanged if without risk factors during the remaining lifetime of the patients.

Neurological outcomes of untreated brainstem CMs

Due to the relative rarity of brainstem CMs, they are often reported along with other locations with various outcomes. Given the aggressive features in surgical candidates, the preoperative complete recovery rate of 16.7% (6 of 36)[25] was lower than that of observational series (25.9%–43.3%)[22 23 26] and our cohort (33.4%). The complete recovery rate further declines following repeated haemorrhage.[22 23 25] Across 16 prior studies and 1 meta-analysis with available data regarding the outcomes of untreated brainstem CMs (table 3),[2 3 5 8 12 14 20–23 26–32] 9 studies reported the evolution of neurological status compared with the initial status,[12 20 22 23 27–29 31 32] 6 studies only described the final status,[2 5 14 21 26 30] and the remaining 2 studies did not describe the outcome.[3 8] Several studies reported relatively poor outcomes, with a worsened proportion up to 41.7%,[20] 48.1%[27] and 53.3%.[28] Furthermore, Gross et al[5] observed a permanent neurological morbidity rate of 45% for brainstem, thalamic and basal ganglia CMs; Al-Shahi Salman et al[2] reported that 57.1% (8 of 14) of patients suffered a second composite outcome (haemorrhage or FND), and the worst outcome was underlined with an observational mortality rate of 20.0% (6 of 30).[26] In contrast, three studies exclusively dedicated to the natural history of brainstem CMs reported fairly high percentages of improved outcomes, ranging from 38.8% to 59.8%[12 22 23]; our result (47.9%) was within this interval and was in accordance with that of a prior study (48.6%).[12] In addition, Zimmerman et al,[30] Kupersmith et al,[12] Esposito et al[32] and Bhardwaj et al[31] reported favourable outcomes, with worsened percentages of only 12.5%, 8.1%, 5.9% and 7.7%, respectively. Overall, we performed a pooled analysis of nine studies,[12 20 22 23 27–29 31 32] and the proportion of improved/unchanged and worsened outcomes was 85.2% (465 of 546) and 14.3% (78 of 546), respectively, which was analogous to our series and appeared more benign than previously thought.[26–28] In 16 prior studies (n=685),[2 5 8 12 14 20–23 26–32] disease-specific deaths occurred in 12 patients (1.8%),[20 22 26 27 30] which

was comparable with our series (1.7%, 12 of 698) and seemed to be acceptable. For censoring events, 24.4% of our patients underwent surgery, which was similar to a prior study (23.6%, 69 of 292)[10] but higher than another cohort (17.2%, 23 of 134).[2] The variation and wide spectrum of these outcomes might be attributed to the small sample size, selection and referral biases, different study designs, and diverse radiological parameters, which were also substantially vulnerable to prospective haemorrhages. Data on brainstem subsets extracted from prior studies were less convincing, but the results of pooled analysis would improve the level of evidence.

Adverse factors for worsened/poor outcomes in brainstem CMs

The risk factors for outcomes were arguable and inconsistent in prior studies. In surgical series, larger lesion size,[15 33] older age (eg, ≥12 years,[17] >40 years[19] per 5 years,[16] and increased age),[18] multiple haemorrhages,[17–19] DVA[16] and poor preoperative status[17–19] were demonstrated to predict poor outcomes. However, opposing findings were occasionally reported in that multiple haemorrhages did not significantly lead to worsened outcomes.[15 21 33] Parenchyma transgression, manipulation of circumferential tissue, poor postoperative neural plasticity and unfavourable baseline data might account for the variation.

Among untreated series, Kupersmith et al[12] stated that the total number of episodes or rebleeding had little effect on neurological status. Conversely, Samii et al[25] declared a lower chance of neurological recovery following multiple haemorrhages (6.25%) compared with only one episode (25.0%). A similar result reported by Li et al[17] showed full recovery rates of 26.9%, 13.0% and 0% after 1, 2 and 3 haemorrhages, respectively. A new haemorrhagic episode would interrupt the course of recovery or would further lead to clinical deterioration. Our univariably significant risk factors were consistent with three of five predictors from the proposed grading scale (size, crossing the axial midpoint and DVA) advocated by Garcia et al.[16] In our multivariable analysis, DVA and crossing the axial midpoint were independently significant. Lesions crossing the axial midpoint with mass effect, involving bilateral neurostructures and producing more morbidities, might restrain recovery after haemorrhagic ictus. DVA was found to be related to the genesis of CM and was also identified as a predictor of prospective haemorrhage; meanwhile, DVA might affect perilesional venous drainage followed by brainstem oedema, thrombosis or ischaemia, which jeopardised neurological function.[5 34] Our results seemed to be applicable to clinical practice because both factors could be evaluated at enrolment.

Limitations of the study

Referral and selection biases were the main limitations of the study, which might overestimate the worsened outcomes and limit extrapolation of our findings to patients from other institutes. Patients with haemorrhagic CM with serious deficits were more likely referred

Table 3 Neurological outcome of untreated brainstem CMs

Study and year	Study type	Patients (n)	Mean age, years	Mean follow-up, years	Patients with prospective ictus (%)	Total number of ictus	Annual haemorrhage rate, %	Neurological outcome (%)
Zimmerman et al 1991[30]	Retrospective	8	NA	3–60 months	1 (12.5)	1	NA	7 (87.5) minor symptoms or asymptomatic; 1 (12.5) died of haemorrhage.
Fritschi et al 1994[26]	Retrospective	30	NA	3.0	NA	NA	NA	13 (43.3) normal; 7 mildly, 2 moderately and 2 severely disabled; 6 (20.0) died of CMs.
Bouillot et al 1996[29]	Retrospective	7	NA	5.6	NA	NA	11.7	1 (14.3) improved; 4 (57.1) same; 2 (28.6) worsened.
Porter et al 1999[20]	Retrospective	12	NA	NA	NA	NA	NA	7 (58.3) improved/ same; 5 (41.7) worsened; 1 (8.3) died of rebleeding.
Kupersmith et al 2001[12]	Retrospective	37	37.5	4.9	7 (18.9)	8	5.1	18 (48.6) improved; 14 (37.8) same; 3 (8.1) worsened; 2 (5.4) died of myocardial infarction.
Esposito et al 2003[32]	Retrospective	17	NA	NA	NA	NA	2.5	11 (64.7) favourable; 5 (29.4) same; 1 (5.9) worsened.
Tarnaris et al 2008[28]	Retrospective	15	37.9	6.1	4 (26.7)	4	4.4	2 (13.3) improved; 5 (33.3) same; 8 (53.3) worsened; mean mRS score 2.07.
Bhardwaj et al 2009[31]	Retrospective	13‡	12.7	4.4	1 (7.7)	1	≈1.7	4 (30.8) improved; 8 (61.5) same (6 asymptomatic, 2 symptomatic); 1 (7.7) died.
Chen et al 2011[21]	Retrospective	20	38.1	3.7	7 (35.0)	≥11	NA	Mean NIHSS score 1.7.
Menon et al 2011[27]	Retrospective	29†	NA	4.0	17 (63.0)	≥41	≥35.3	14 (51.9) improved/ same; 13 (48.1) worsened; 1 (3.7) died of haemorrhage.
Al-Holou et al 2012[8]	Retrospective	15 les	NA	≈3.5	5 les (33.3)	8	≈15.2 per les	NA
Al-Shahi Salman et al 2012[2]	Prospective	14	NA	5.0	NA	NA	NA	8 patients (57.1) had a second haemorrhage or focal neurological deficit.
Li et al 2014[17]	Prospective	85	12.7	4.7	37 (43.5)	47	11.7	22 (25.9) normal; 33 (38.8) improved; 32 (37.6) same; 20 (23.5) worsened.

Continued

Table 3 Continued

Study and year	Study type	Patients (n)	Mean age, years	Mean follow-up, years	Patients with prospective ictus (%)	Total number of ictus	Annual haemorrhage rate, %	Neurological outcome (%)
Li et al 2014[17]	Prospective	331	36.2	6.5	131 (39.6)	185	13.6	95 (28.7) normal; 198 (59.8) improved; 109 (32.9) same; 24 (7.3) worsened; 3 (0.9) deaths.
Gross et al 2016[5]	Retrospective	18 lesion	NA	3.3	NA	10	16.7 per lesion	Permanent neurological morbidity of 45% for brainstem, thalamic and basal ganglia CMs.
Horne et al 2016[3]	Meta-analysis	575	NA	NA	139 (24.2)	139	NA	NA
Zuurbier et al 2019[14]	Prospective	34	NA	NA	NA	15	NA	15 events of haemorrhage or persistent or progressive focal neurological deficit.
Present series	Prospective	698	38.3	4.7	167 (23.9)	222	6.7	233 (33.4) normal; 334 (47.9) improved/ mRS=0, 293 (42.0) same; 71 (10.2) worsened.

*Two patients were lost to follow-up; 5 had one haemorrhage and 12 had more than two haemorrhages during follow-up.
†Seven patients had previous radiotherapy and one patient died of medulloblastoma.
CMs, cavernous malformations; les, lesions; mRS, modified Rankin Scale; NA, not available; NIHSS, National Institutes of Health Stroke Scale.

for medical consultation due to survival instinct and the significantly unbalanced surgical techniques within our country. Despite the size of our cohort, this was not a true natural history because some patients already had a known diagnosis, while many others eventually underwent surgical treatment. Our findings were meaningful for patients who suffered from ruptured brainstem CMs but did not require immediate surgery or experienced hesitation regarding the selection of surgery. To minimise referral bias, a multicentre study or a population-based cohort is recommended based on the true natural history being theoretically more benign than in our cohort.

CONCLUSION

The neurological outcomes of untreated brainstem CMs were improved/unchanged in majority of patients (89.8%) and seemed to be favourable, and radiological features significantly predicted worsened outcomes. Our results provide updated evidence for clinical consultation and help to individualise patient treatment. Patients with risk factors require close follow-up. The referral bias in our study should be stressed.

ORCID iD
Zhen Wu http://orcid.org/0000-0002-4985-4889

REFERENCES

1 Gross BA, Lin N, Du R, et al. The natural history of intracranial cavernous malformations. *Neurosurg Focus* 2011;30:E24.
2 Al-Shahi Salman R, Hall JM, Horne MA, et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol* 2012;11:217–24.
3 Horne MA, Flemming KD, Su I-C, et al. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol* 2016;15:166–73.

4   Gross BA, Batjer HH, Awad IA, *et al*. Brainstem cavernous malformations. *Neurosurgery* 2009;64:E805–18. discussion E818.

5   Gross BA, Du R, Orbach DB, *et al*. The natural history of cerebral cavernous malformations in children. *J Neurosurg Pediatr* 2016;17:123–8.

6   Taslimi S, Modabbernia A, Amin-Hanjani S, *et al*. Natural history of cavernous malformation: systematic review and meta-analysis of 25 studies. *Neurology* 2016;86:1984–91.

7   Akers A, Al-Shahi Salman R, A Awad I, *et al*. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the angioma alliance scientific Advisory board clinical experts panel. *Neurosurgery* 2017;80:665–80.

8   Al-Holou WN, O'Lynnger TM, Pandey AS, *et al*. Natural history and imaging prevalence of cavernous malformations in children and young adults. *J Neurosurg Pediatr* 2012;9:198–205.

9   Barker FG, Amin-Hanjani S, Butler WE, *et al*. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. *Neurosurgery* 2001;49:15–24.

10 Flemming KD, Link MJ, Christianson TJH, *et al*. Prospective hemorrhage risk of intracerebral cavernous malformations. *Neurology* 2012;78:632–6.

11 Jeon JS, Kim JE, Chung YS, *et al*. A risk factor analysis of prospective symptomatic haemorrhage in adult patients with cerebral cavernous malformation. *J Neurol Neurosurg Psychiatry* 2014;85:1366–70.

12 Kupersmith MJ, Kalish H, Epstein F, *et al*. Natural history of brainstem cavernous malformations. *Neurosurgery* 2001;48:47–53. discussion 53-54.

13 Zabramski JM, Wascher TM, Spetzler RF, *et al*. The natural history of familial cavernous malformations: results of an ongoing study. *J Neurosurg* 1994;80:422–32.

14 Zuurbier SM, Hickman CR, Tolias CS, *et al*. Long-term antithrombotic therapy and risk of intracranial haemorrhage from cerebral cavernous malformations: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol* 2019;18:935–41.

15 Abla AA, Lekovic GP, Turner JD, *et al*. Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. *Neurosurgery* 2011;68:403–14. discussion 414-415.

16 Garcia RM, Ivan ME, Lawton MT. Brainstem cavernous malformations: surgical results in 104 patients and a proposed grading system to predict neurological outcomes. *Neurosurgery* 2015;76:265–77. discussion 277-278.

17 Li D, Hao S-Y, Tang J, *et al*. Surgical management of pediatric brainstem cavernous malformations. *J Neurosurg Pediatr* 2014;13:484–502.

18 Li D, Yang Y, Hao S-Y, *et al*. Hemorrhage risk, surgical management, and functional outcome of brainstem cavernous malformations. *J Neurosurg* 2013;119:996–1008.

19 Pandey P, Westbroek EM, Gooderham PA, *et al*. Cavernous malformation of brainstem, thalamus, and basal ganglia: a series of 176 patients. *Neurosurgery* 2013;72:573–89. discussion 588-589.

20 Porter RW, Detwiler PW, Spetzler RF, *et al*. Cavernous malformations of the brainstem: experience with 100 patients. *J Neurosurg* 1999;90:50–8.

21 Chen L, Zhao Y, Zhou L, *et al*. Surgical strategies in treating brainstem cavernous malformations. *Neurosurgery* 2011;68:609–21. discussion 620-621.

22 Li D, Hao S-Y, Jia G-J, *et al*. Hemorrhage risks and functional outcomes of untreated brainstem cavernous malformations. *J Neurosurg* 2014;121:32–41.

23 Li D, Hao S-Y, Tang J, *et al*. Clinical course of untreated pediatric brainstem cavernous malformations: hemorrhage risk and functional recovery. *J Neurosurg Pediatr* 2014;13:471–83.

24 Al-Shahi Salman R, Berg MJ, Morrison L, *et al*. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. angioma alliance scientific Advisory board. *Stroke* 2008;39:3222–30.

25 Samii M, Eghbal R, Carvalho GA, *et al*. Surgical management of brainstem cavernomas. *J Neurosurg* 2001;95:825–32.

26 Fritschi JA, Reulen HJ, Spetzler RF, *et al*. Cavernous malformations of the brain stem. A review of 139 cases. *Acta Neurochir* 1994;130:35–46.

27 Menon G, Gopalakrishnan CV, Rao BRM, *et al*. A single institution series of cavernomas of the brainstem. *J Clin Neurosci* 2011;18:1210–4.

28 Tarnaris A, Fernandes RP, Kitchen ND. Does conservative management for brain stem cavernomas have better long-term outcome? *Br J Neurosurg* 2008;22:748–57.

29 Bouillot P, Dufour H, Roche PH, *et al*. [Angiographically occult vascular malformations of the brain stem. Apropos of 25 cases]. *Neurochirurgie* 1996;42:189–200.

30 Zimmerman RS, Spetzler RF, Lee KS, *et al*. Cavernous malformations of the brain stem. *J Neurosurg* 1991;75:32–9.

31 Bhardwaj RD, Auguste KI, Kulkarni AV, *et al*. Management of pediatric brainstem cavernous malformations: experience over 20 years at the hospital for sick children. *J Neurosurg Pediatr* 2009;4:458–64.

32 Esposito P, Coulbois S, Kehrli P, *et al*. [Place of the surgery in the management of brainstem cavernomas. Results of a multicentric study]. *Neurochirurgie* 2003;49:5–12.

33 Zaidi HA, Mooney MA, Levitt MR, *et al*. Impact of timing of intervention among 397 consecutively treated brainstem cavernous malformations. *Neurosurgery* 2017;81:620–6.

34 Li D, Wu Z-Y, Liu P-P. Natural history of brainstem cavernous malformations: prospective hemorrhage rate and adverse factors in a consecutive prospective cohort. *J Neurosurg* 2020:1–12.