Retrospective Cohort Study

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Association of hemorrhage-to-treatment time with outcomes in patients with brainstem cavernous malformations: a nationwide cohort study

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Background: Brainstem cavernous malformations (BSCMs) often present with haemorrhage, but the optimal timing for microsurgical intervention remains unclear. This study aims to explore how intervention timing relates to neurological outcomes in haemorrhagic BSCM patients undergoing microsurgery, offering insights for clinical decisions.

Methods: A total of 293 consecutive patients diagnosed with BSCMs, who underwent microsurgery were identified between March 2011 and January 2023 at two comprehensive centres in China, with a postoperative follow-up duration exceeding 6 months. Utilizing logistic regression models with restricted cubic splines, distinct time groups were identified. Subsequently, matching weight analysis compared these groups in terms of outcomes, new haemorrhage rates, cranial nerve deficits, and perioperative complications. The primary outcome was an unfavourable outcome, which was defined as a mRS score greater than 2 at the latest follow-up.

Results: Among the 293 patients, 48.5% were female, median age was (39.9 ± 14.3) years, and median haemorrhage-to-treatment time was 42 days. Patients were categorized into acute ($\leq$21 days), subacute (22–42 days), and delay ($>$42 days) intervention groups. After matching, 186 patients were analyzed. Adjusted analysis showed lower unfavourable outcome rates for acute [adjusted odds ratio (OR), 0.73; 95% CI, 0.65–0.82; $P<0.001$] and subacute (adjusted OR, 0.83; 95% CI, 0.72–0.95; $P=0.007$) groups compared to the delay group. Subacute intervention led to fewer cranial nerve deficits (adjusted OR, 0.76; 95% CI, 0.66–0.88, $P<0.001$). New haemorrhage incidence didn't significantly differ among groups.

Conclusions: For haemorrhagic BSCMs patients, delayed microsurgical intervention that exceeded 42 days after a prior haemorrhage were associated with an increased risk of unfavourable neurological outcomes.

Keywords: Brainstem cavernous malformations, microsurgery, neurological outcomes, optimal timing

Introduction

Brainstem cavernous malformations (BSCMs) account for 19–30% of cerebral cavernous malformations (CCMs), and they are characterized by higher rates of haemorrhage compared to CCMs in other brain regions[1,2]. The higher tendency to haemorrhage is probably due to the fact that even minor haemorrhages in the brainstem are more noticeable than in supratentorial lesions. Ninety percent of patients with BSCMs present with symptomatic haemorrhage[3,4]. A temporal clustering of re-haemorrhage has been observed in the first 1 or 2 years after a symptomatic haemorrhage, and new bleeding may lead to deterioration or even disability of neurological function[5,6].

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:2217–2225

Received 31 October 2023; Accepted 9 January 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 18 January 2024

http://dx.doi.org/10.1097/JS9.0000000000001111

Surgical intervention is primarily recommended following haemorrhagic events in BSCMs[7,8]. Advancements in surgical techniques have rendered the brainstem no longer an untouchable territory, making surgical intervention feasible and safer. However, the ideal time for treatment initiation in such cases remains unclear, as different studies offer varying recommendations. The Lawton–Garcia (LG) grading system categorized the timing of a haemorrhagic event to surgical treatment as acute (within 3 weeks), subacute (3–8 weeks), and chronic (over 8 weeks) based on clinical experience, and suggested that early surgery treatment is associated with good postoperative prognoses[9]. Contrary studies posit that intervention during the chronic period is an independent adverse factor contributing to unfavourable postoperative outcomes in cases of BSCMs. Nonetheless, substantial debate remains regarding the precise timing of the interventions[10–12]. The existing data on the timing of treatment for BSCMs have yielded ambiguous results, partly due to diverse study designs and potential patient exclusions, creating a need for more robust evidence.

Despite previous studies attempting to assess the role of various factors on outcomes, such as patient age, disease severity, lesion features, and complications, there is still a lack of robust evidence regarding the optimal timing of surgery[13–16]. Expert opinions suggest that performing surgical resection early yields better results than delayed intervention; however, this concept and the precise timing have not been definitively established through a comprehensive analysis of real-world data[8]. Understanding the ideal haemorrhage-to-treatment time for BSCMs could significantly improve patient outcomes, including lower rates of unfavourable functional outcome, reduced recurrent haemorrhage after surgery, and fewer complications.

This study aims to address the existing gaps in current knowledge by investigating the association between haemorrhage-to-treatment time and neurological function outcomes in patients with BSCM; and identifying the optimal treatment window associated with better outcomes. By conducting a thorough analysis of a diverse set of factors and outcomes, we strive to provide valuable insights that can aid clinicians in optimizing treatment strategies for BSCMs patients.

HIGHLIGHTS

- This study contributes by highlighting the potential advantages of early intervention for haemorrhagic brainstem cavernous malformations (BSCMs). Furthermore, interventions performed more than 42 days after the haemorrhage exhibit poorer outcomes.
- Restricted cubic splines: The initial application of cubic spline statistical method was employed to statistically investigate the significance of different time nodes for surgical intervention in BSCMs and assess their impact on outcomes.
- Clinical significance: This study may offer more robust evidence that can guide clinical decision-making regarding the timing of interventions for patients with BSCMs. This may lead to enhanced patient management strategies and potentially impact clinical practice and policy decisions in this field.

Methods

Data sources and study design

The Clinical Study of BSCMs Prognosis Trial is a retrospective cohort study that includes all cases ($N = 736$) of BSCM in patients admitted to two comprehensive cerebrovascular centres in China from 1 March 2011, and 31 March 2023 (Fig. 1). In this study, we conducted an observational cohort study using a database obtained from the clinical trial based on specific inclusion and exclusion criteria. The inclusion criteria were as follows: patients who were 18 years of age or older, with a confirmed diagnosis of BSCMs based on MRI showing evidence of acute blood within or around the BSCMs on computed tomography (CT) imaging, and who underwent microsurgery within 365 days after the prior haemorrhagic event (first or multiple times). All included patients who underwent surgical excision of brainstem lesions were pathologically diagnosed with cavernous malformation. Patients were excluded if they had prior microsurgery or radio-surgery for cranial CM, if they had insufficient follow-up duration (less than six months), or if they had incomplete clinical assessments or missing imaging data.

The study received approval from the institutional review boards at both hospitals. Informed consent was waived as this study involved the use of anonymized retrospective data. All patient data were deidentified to ensure confidentiality and protect the privacy of the participants. The reporting of this study has been conducted in accordance with the STROCSS criteria[17], Supplemental Digital Content 1, http://links.lww.com/JS9/B733, Supplemental Digital Content 2, http://links.lww.com/JS9/B734.

Clinical parameters

We used electronic medical records to extract demographic information, data on comorbidities, and clinical details. Haemorrhage-to-treatment time was defined as the duration in days between the onset of the most recent symptomatic haemorrhage event and the commencement of neurosurgical treatment for BSCMs. Symptomatic haemorrhage events were characterized by the presence of new focal neurological dysfunction or new headache symptoms, and confirmed by head imaging examinations indicating cerebral haemorrhage, which involved head CT and/or MRI displaying new intracranial haemorrhage attributed to BSCMs[18]. In cases where precise time estimates for the onset of symptoms were unavailable, the time of the first CT scan at the initial hospital visit was utilized as a proxy to approximate the symptomatic event's occurrence. This approach allowed us to account for any missing data and ensure a comprehensive analysis of the haemorrhage-to-treatment time parameter in our study. "Preoperative multiple bleedings" was defined as the manifestation of symptomatic haemorrhage events on more than one occasion prior to surgical intervention.

Covariates that affect the prognosis of BSCM and time to treatment were selected from the literatures and clinical experience[13–16]. One index of severity based on first in-hospital assessments conducted before any procedures were performed included the modified Rankin Scale (mRS) score. For the purpose of statistical analysis, the continuous variables of age and lesion size were discretized into categorical variables using the most widely used LG grading system[9]. MRI scans for BSCMs were acquired using 3T MR scanners, encompassing T1-weighted, T2-weighted, SWI(susceptibility-weighted images), and T1-weighted contrast-enhanced imaging. The BSCMs imaging features, such as the Zabramski classification, location, size, and the presence of

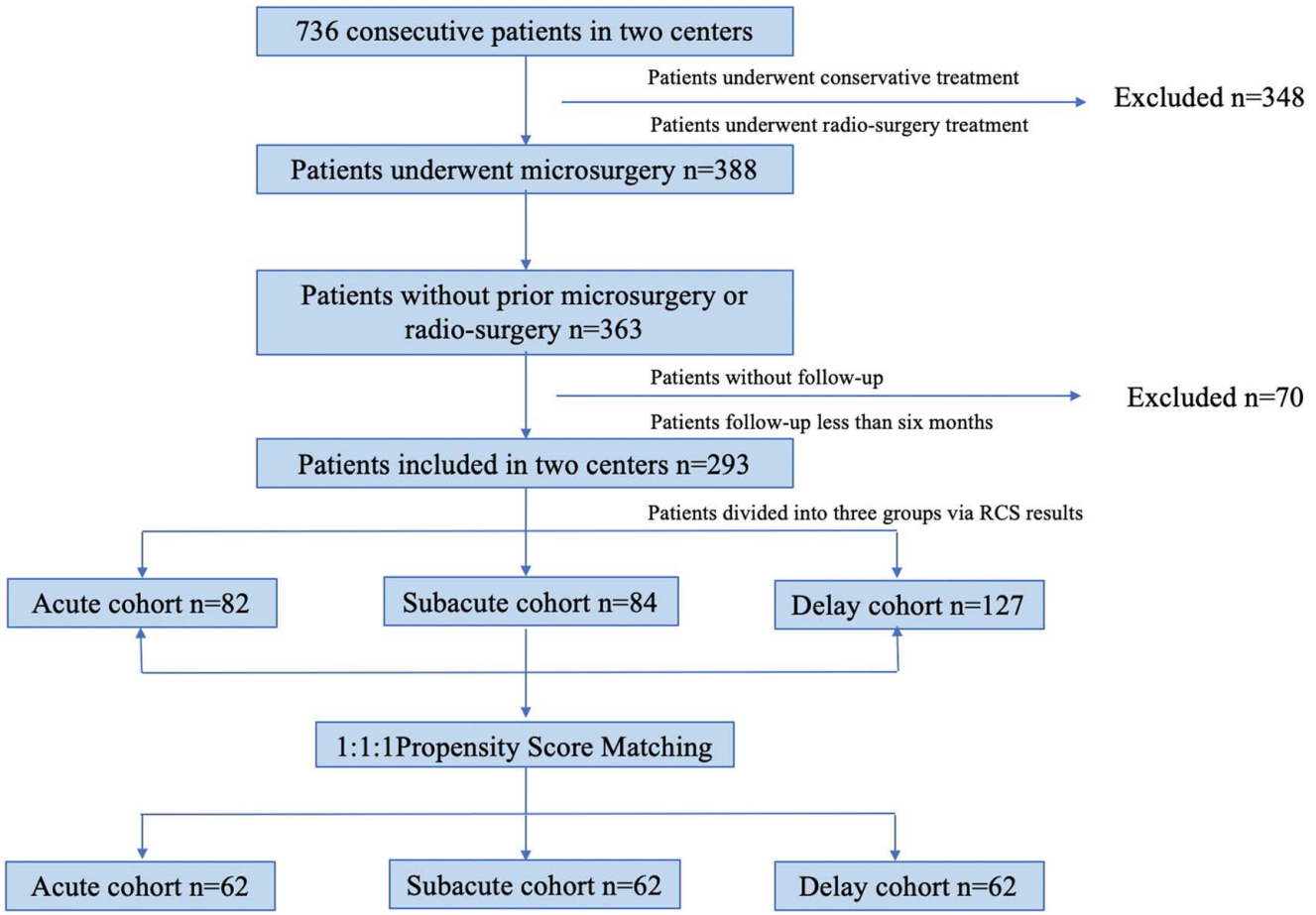

Figure 1. Flow diagram of the brainstem cavernous malformation study population.

associated developmental venous anomaly (DVA), were assessed following consensus recommendations for reporting variables in CCM research[19]. Zabramski classification is a grading system based on the MRI features of cavernous malformations. It categorizes lesions into three types: Type I involves subacute haemorrhage, Type II manifests as popcorn-like microhemorrhages and thrombi, and Type III is characterized by chronic staining with hemosiderin[20]. Since the Zabramski classification is correlated with bleeding time, it was excluded from the statistical analysis[21]. The location of each lesion was classified as mesencephalic, pontine, or medullary. Lesions extending across the pontomidbrain or pontomedullary junctions were classified based on their predominant location.

Outcomes

The primary outcome measure of this study was an unfavourable outcome, which was defined as a mRS score greater than 2 at the latest follow-up. The secondary outcomes included neurological deterioration and cranial nerve (CN) deficit (cranial nerve deficit) at the latest follow-up and recurrent haemorrhage events during the follow-up period. Neurological deterioration was quantified by calculating the difference between the mRS score at follow-up and the preoperative mRS score, with a positive value indicating worsened neurological function compared to the baseline. If any of the twelve pairs of cranial nerves have dysfunction during follow-up, it will be considered as CN deficit. Recurrent haemorrhage events were identified when new-onset or aggravated symptoms were observed, accompanied by evidence of acute bleeding related to the location of previous surgery on CT imaging. The occurrence of recurrent haemorrhage is believed to be associated with incomplete resection of the BSCMs.

Neurological function and radiographic films were evaluated at regular intervals, specifically at 3–6 months post-surgery, and subsequently on an annual or biennial basis during clinic visits.

Statistical analysis

Considering that haemorrhage-to-treatment time is a continuous variable, we initially investigate whether it exhibits a linear or nonlinear relationship with the unfavourable outcome. Restricted cubic splines confirmed the significant nonlinear, continuous association between haemorrhage-to-treatment and outcomes. A logistic regression model that adjusted for other clinical, imaging variables and follow-up time was used to determine independent risk features for unfavourable outcome. Subsequently, we found the inflection points by examining the confidence intervals of the estimated spline coefficients in the restricted cubic spline (RCS).

According to the time points obtained from RCS analysis, we classified the continuous haemorrhage-to-treatment time into three distinct groups. Baseline characteristics between different groups were compared using the *t*-test for continuous variables, chi-square

test for categorical variables, and Mann–Whitney U-test for ordinal variables. To address potential confounding and selection biases, we employed matching weight (MW) as a method to compensate for differences in baseline characteristics among the three groups[22]. Covariate balance was evaluated using the absolute standardized mean difference (ASMD), and an ASMD less than 0.1 was considered indicative of acceptable matching[23].

Considering the impact of follow-up time on outcomes, adjusted logistic regression was conducted after MW to assess the associations between the haemorrhage-to-treatment time and the primary and secondary outcomes. The results are presented as odds ratio (OR), along with their corresponding 95% CI. Furthermore, to estimate the influence of unmeasured confounders on the observed treatment-outcome association, the E value was calculated[24].

Data analysis and visualization were conducted using IBM SPSS Statistics version 22.0 (IBM Corp.) and R version 4.2.0 GUI 1.78 (The R Foundation for Statistical Computing). A significance level of P less than 0.05 was considered statistically significant throughout the analysis.

Results

Baseline characteristics

This study encompassed a cohort of 293 patients with BSCMs who underwent microsurgery. Among these individuals, 48.5% were female, and the overall mean age of the participants was (39.9 ± 14.3) years. Prior to microsurgery, a favourable preoperative neurological status was evident in 58.3% (171/293) of patients. Notably, 116 patients encountered multiple haemorrhagic events prior to their inclusion in the study, highlighting the recurrent nature of bleeding episodes in certain BSCM cases. Regarding the location of BSCMs lesions, the majority (69.9%) were found in the pons, followed by 15.7% in the mesencephalic, and 14.7% in the medulla (Table 1). Furthermore, 91 patients had BSCMs with a maximal diameter exceeding 20 mm, and 169 (57.7%) of the lesions crossed the axial midpoint. Detection of a DVA on preoperative MRI scans was observed in 46 patients (15.7%). Concerning the Zabramski classification, 225 (76.8%) of the BSCMs were categorized as Zabramski I features, which are typically associated with acute or subacute haemorrhage. The median haemorrhage-to-treatment time for the entire cohort was 42 days, with an interquartile range (IQR) of 21.0–66.5 days (Supplemental Figure 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B735).

Table 1

Cohort characteristics.

Characteristic	Patients, *N* (%)
Age at treatment, mean (SD), year	39.9 ± 14.3
≤ 40	160 (54.6)
> 40	133 (45.4)
Sex	
Female	142 (48.5)
Male	151 (51.5)
mRS score on admission	
0	0
1	69 (23.5)
2	102 (34.8)
3	77 (26.3)
4	26 (8.9)
5	19 (6.5)
Preop CN deficit	174 (59.4)
Preop multiple bleedings	116 (39.6)
Size, cm	
≤ 2	202 (68.9)
> 2	91 (31.1)
DVA	46 (15.7)
Crossing axial midpoint	169 (57.7)
Location	
Mesencephalic	46 (15.7)
Pontine	204 (69.6)
Medullary	43 (14.7)
Zabramski classification	
I	225 (76.8)
II	45 (15.4)
III	23 (7.8)
IV	0 (0)
Haemorrhage-to-treatment time, days	
Mean (SD)	60.2 ± 63.4
Median (IQR)	42.0 (21.0–66.5)
Follow-up time, median (IQR), y	2.33 (1.17–3.83)

CN, cranial nerve; DVA, developmental venous anomaly; IQR, interquartile range; mRS, modified Rankin Scale score.

Haemorrhage-to-treatment time as a continuous variable and outcomes

Overall, 92 patients (31.4%) experienced unfavourable outcomes after a median [interquartile range (IQR)] clinical follow-up of, 2.33 [1.17–3.83] years. Our analysis revealed a significant and highly nonlinear association between the unfavourable outcomes OR and the haemorrhage-to-treatment time, as indicated by an effective degrees of freedom (df) of 3 in the generalized additive model ($P < 0.001$ for the 5-df cubic spline). The results showed that there was a progressive increase in the odds of unfavourable outcomes when treatment was received within 21 days after haemorrhage onset, but it remained beneficial to favourable outcomes until 42 days (OR = 1). Subsequently, the odds of unfavourable outcomes decreased with treatment after 21 days, hitting their nadir at 42 days (OR = 1). Beyond 42 days, it increased until ~42 days after haemorrhage onset (Fig. 2A). On adjustment for covariates (age, sex, multiple bleedings, size, crossing axial midpoint, location, and the presence of DVA), the nonlinear association of haemorrhage-to-treatment time was attenuated (likelihood ratio test: df = 3, $P < 0.001$). The shape of the association of treatment delay with the odd of unfavourable outcomes from the adjusted model was similar to the shape of the unadjusted model (Fig. 2B).

Outcomes measured by categorical haemorrhage-to-treatment time

Based on the aforementioned results, we categorized the patients into three groups: the acute group (haemorrhage-to-treatment time ≤ 21 days), the subacute group (21 days < haemorrhage-to-treatment time ≤ 42 days), and the delay group (42 days < haemorrhage-to-treatment time)(Fig. 2). This categorization allows us to better understand the impact of different intervention times on the likelihood of unfavourable outcomes in patients with BSCMs. Baseline characteristics of patients among the three groups were presented in Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/B735: 82 patients (28.0%) were in the acute group, 84 patients (28.7%) were in the subacute group, and 127 patients (43.3%) were in the delay

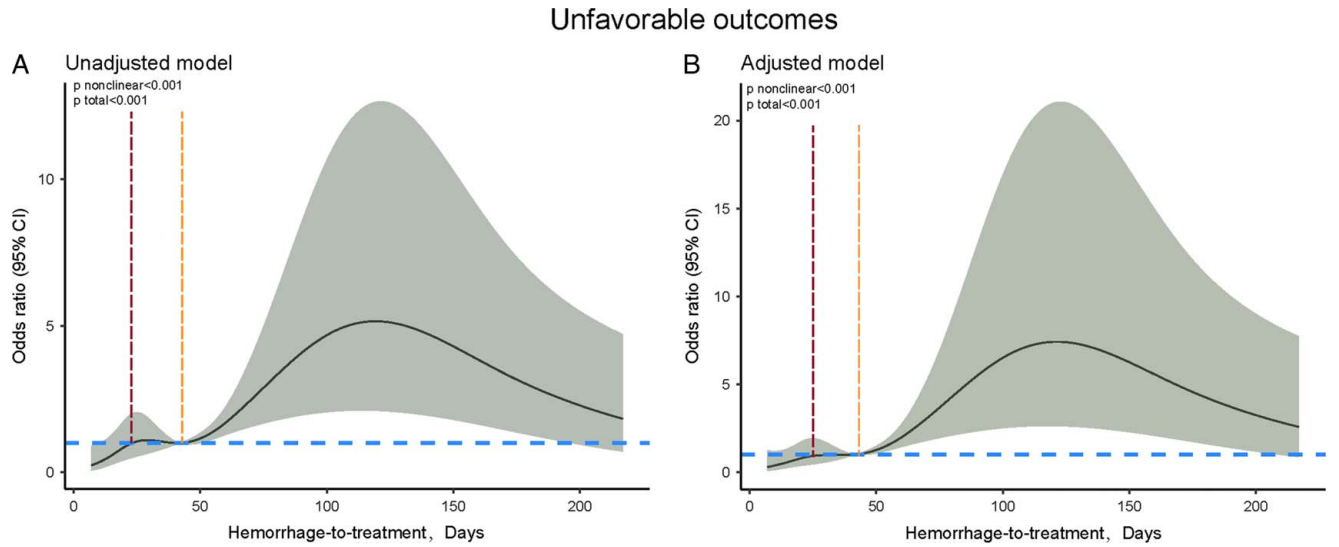

Figure 2. Association of haemorrhage-to-treatment with unfavourable outcomes in participants with brainstem cavernous malformations. Odds ratios with 95% CIs (red and yellow lines) for the association of haemorrhage-to-treatment time with unfavourable outcomes in a restricted cubic spline model. (A) Unadjusted model showed treatment within 21 days and 42 days were associated with beneficial to favourable outcomes (odds ratio = 1). (B) Adjusted for covariates (age, sex, multiple bleedings, size, crossing axial midpoint, location, and the presence of developmental venous anomaly), the model also showed treated exceeded 42 days after a prior haemorrhage were associated with an increased risk of unfavourable neurological outcomes. Shaded areas indicate 95% CIs.

group. As depicted in Supplemental Figure 2, Supplemental Digital Content 3, http://links.lww.com/JS9/B735, the likelihood of favourable neurological outcomes at the last follow-up was highest in the acute group, relatively lower in the subacute group, and lowest in the delay group (86.6% vs. 70.2% vs. 55.9%, $P < 0.001$). Preoperative mRS and Zabramski classification significantly differed among the three groups ($P < 0.001$). The most unfavourable outcomes were observed in the delay group, accounting for 44.1%, followed by the subacute group (29.8%), and the acute group (13.4%). Instances of mRS deterioration were more prevalent in the delay group (31.5%). Intriguingly, CN deficits were least frequent in the subacute group. Furthermore, the occurrence of new haemorrhages, linked to subtotal resection, exhibited correlation with acute interventions (8.5%) (Table 2).

Following MW approach, the 3 cohorts of microsurgical treated BSCM patients were comparable for all observed features, with no ASMD exceeding 0.1 (Table 3, Supplemental Figure 3, Supplemental Digital Content 3, http://links.lww.com/JS9/B735). Notably, we observed significant differences in unfavourable outcome rates between the acute, subacute, and delay groups (Fig. 3). A preoperative mRS score of 5 (adjusted OR 1.55, 95% CI 1.24–1.95) and multiple haemorrhage times (adjusted OR 1.16, 95% CI 1.04–1.30) were also associated with unfavourable outcomes in multivariable proportional odds regression (Supplemental figure 4, Supplemental Digital Content 3, http://links.lww.com/JS9/B735). After adjusting for the impact of follow-up time among groups, the acute group demonstrated a significantly lower likelihood of unfavourable outcomes (adjusted OR, 0.73; 95% CI, 0.65–0.82, $P < 0.001$) and neurological deterioration (adjusted OR, 0.87; 95% CI, 0.78–0.98, $P = 0.02$) at the last follow-up when compared to the delay group. Similarly, the subacute group exhibited a reduced risk of unfavourable outcomes (adjusted OR, 0.83; 95% CI, 0.72–0.95, $P = 0.007$) and CN deficits (adjusted OR, 0.76; 95% CI, 0.66–0.88, $P < 0.001$) at the last follow-up when compared to the delay group. However, no significant difference was observed in the occurrence rate of recurrent haemorrhage among the three groups. To assess the strength of any unmeasured confounder, we calculated the E value. Our findings suggest that the presence of such a confounder is unlikely, as all estimated ORs were lower than the calculated E value (Table 4).

Discussion

Currently, neurological surgery stands as the primary therapeutic approach for managing haemorrhagic BSCMs, aiming to mitigate the risk of re-haemorrhage and associated neurological debilitation[6]. Nonetheless, a dispute persists regarding the most suitable timing for surgical intervention in cases of haemorrhage-related BSCMs. Despite the prevailing viewpoint that delay interventions are correlated with unfavourable outcomes, this perspective predominantly originates from clinical experience and lacks comprehensive statistical substantiation. This large cohort study represents the first attempt, to our knowledge, to characterize the nonlinear relationship between the time from haemorrhage to treatment for BSCM and the subsequent risk of recurrent haemorrhage and prognosis. Our analysis reveals that the ideal window for microsurgical treatment of BSCM is approximately within 42 days following the haemorrhage onset. Notably, only 30% of BSCM patients in our study received treatment within this critical period, underscoring the potential need for expedited access to medical care for such patients presenting with haemorrhage symptoms at the hospital. While we recognize the potential limitations in our study design, our findings provide valuable insights that can contribute to refining clinical guidelines.

Our study found a 31.4% rate of unfavourable outcomes at final follow-up, similar to a multi-centre study in the United States[2,5], confirming the representativeness of our study

Table 2

Comparison of baseline characteristics between the unmatched different interventional cohorts.

Characteristics	Haemorrhage-to-treatment time (≤3 weeks) (*n* = 82), *n* (%)	Haemorrhage-to-treatment time (>3–6 weeks) (*n* = 84), *n* (%)	Haemorrhage-to-treatment time (>6 weeks) (*n* = 127), *n* (%)	*P* *
Age at treatment, mean (SD), year	36.7 ± 15.0	40.6 ± 14.2	41.6 ± 13.7	0.09
≤40	48 (58.5)	46 (54.8)	66 (52.0)	
>40	34 (41.5)	38 (45.2)	61 (48.0)	
Sex				0.59
Female	36 (43.9)	41 (48.8)	65 (51.2)	
Male	46 (56.1)	43 (51.2)	62 (48.8)	
mRS on admission				**0.02**
0	0	0	0	
1	26 (31.7)	16 (19.0)	27 (21.3)	
2	20 (24.4)	27 (32.1)	55 (43.3)	
3	20 (24.4)	23 (27.4)	34 (26.8)	
4	10 (12.2)	12 (14.3)	4 (3.1)	
5	6 (7.3)	6 (7.1)	7 (5.5)	
Preop CN deficit	52 (63.4)	42 (50.0)	80 (63.0)	0.12
Preop multiple bleedings	30 (36.6)	34 (40.5)	52 (40.9)	0.81
Size, cm				0.51
≤2	55 (67.1)	55 (65.5)	92 (72.4)	
>2	27 (32.9)	29 (34.5)	35 (27.6)	
DVA	13 (15.9)	12 (14.3)	21 (16.5)	0.91
Crossing axial midpoint	48 (58.5)	52 (61.9)	69 (54.3)	0.56
Location				0.48
Mesencephalic	10 (12.2)	15 (17.9)	21 (16.5)	
Pontine	62 (75.6)	53 (63.1)	89 (70.1)	
Medullary	10 (12.2)	16 (19.0)	17 (13.4)	
Zabramski classification				**<0.001**[a]
I	74 (90.2)	70 (83.4)	81 (63.7)	
II	6 (7.3)	8 (9.5)	31 (24.4)	
III	2 (2.4)	6 (7.1)	15 (11.8)	
IV	0	0	0	
Outcomes				
Unfavourable outcome	11 (13.4)	25 (29.8)	56 (44.1)	**<0.001**
mRS deterioration	14 (17.1)	13 (15.5)	40 (31.5)	**0.009**
CN deficit	49 (61.3)	28 (33.3)	71 (55.9)	**0.001**
New haemorrhage	7 (8.5)	1 (1.2)	5 (3.9)	0.06[b]

P value in boldface indicates statistical significance.

CN, cranial nerve; DVA, developmental venous anomaly; mRS, modified Rankin Scale score.

[a]*P* values are from Fisher's exact test.

[b]*P* values are from Yates' correction for continuity.

*Statistical significance ($P < 0.05$).

population. By employing the generalized additive model with RCS, we identified the critical time intervals of 21 days and 42 days, both associated with the outcomes of microsurgery for BSCMs. The patients treated within 21 days after haemorrhage onset generally had a better prognosis, consistent with the LG grading system. However, we identified a critical intervention window within 42 days, earlier than the 8-week period mentioned by the LG grading system. A potential rationale for our earlier time window, could stem from the intricate nuclei present within the brainstem, along with confined space and relatively limited haematoma volume in the brainstem tissue, might necessitate early intervention, defying the conventional 8-week timeline. Moreover, the intricate nature of brainstem surgery, coupled with variations in surgical techniques, could significantly impact prognosis, it is conceivable that the advanced surgical centres may observe a delay in the critical postoperative outcome window. This suggests that a timeframe of 42 days might be more appropriate for a broader range of neurosurgical centres. This underscores the importance of timely surgical intervention in cases of BSCMs, potentially leading to enhanced outcomes. Significantly, a subset of 127 patients (43.3%) underwent treatment after the 42-day threshold, thereby highlighting the potential imperative to enhance timely access to microsurgery for patients with BSCMs following haemorrhagic events.

Notably, our study uncovered an intriguing inconsistency in unfavourable outcomes, encompassing mRS deterioration, CN deficits, and new haemorrhage occurrences, within acute and subacute intervention groups. Furthermore, we identified a significant variance in preoperative mRS scores across the three groups. This phenomenon might originate from a selective deviation in the timing of surgical intervention in patient management. Based on our experience, we frequently tailor treatment timing recommendations to align with individual patients' distinct preoperative neurological functional statuses. In situations

Table 3

Comparison of baseline characteristics between the weighed different interventional cohorts.

Characteristics	Haemorrhage-to-treatment time (≤3 weeks) (*n* = 62), *n* (%)	Haemorrhage-to-treatment time (>3–6 weeks) (*n* = 62), *n* (%)	Haemorrhage-to-treatment time (>6 weeks) (*n* = 62), *n* (%)	SMD[a]
Age at treatment, mean (SD), year				0.035
≤40	34 (54.8)	34 (54.8)	35 (56.5)	
>40	28 (45.2)	28 (45.2)	27 (43.5)	
Sex				0.047
Female	27 (43.5)	29 (46.8)	29 (46.8)	
Male	35 (56.5)	33 (53.2)	33 (53.2)	
mRS on admission				0.032
0	0	0	0	
1	16 (25.8)	16 (25.8)	16 (25.8)	
2	19 (30.6)	20 (32.3)	19 (30.6)	
3	18 (29.0)	18 (29.0)	19 (30.6)	
4	5 (8.1)	4 (6.3)	4 (6.3)	
5	4 (6.3)	4 (6.3)	4 (6.3)	
Preop multiple bleedings	24 (38.7)	23 (37.1)	23 (37.1)	0.020
Size, cm				0.018
≤2	42 (67.7)	43 (66.1)	42 (67.7)	
>2	20 (32.3)	21 (33.9)	20 (32.3)	
DVA	10 (16.1)	10 (16.1)	9 (14.5)	0.030
Crossing axial midpoint	37 (59.7)	38 (61.3)	36 (58.1)	0.043
Location				0.036
Mesencephalic	9 (14.5)	8(12.9)	8 (12.9)	
Pontine	45 (72.6)	45 (72.6)	45 (72.6)	
Medullary	8 (12.9)	9 (14.5)	9 (14.5)	

ASMD, absolute standardized mean difference; DVA, developmental venous anomaly; mRS, modified Rankin Scale score.
[a]ASMD < 0.1.

Table 4

Comparison of follow-up outcomes between the weighed cohorts.

Outcomes	Acute group	Subacute group	Delay group
Unfavourable outcome			
Case number	9	17	26
Adjusted OR (95% CI)	**0.73 (0.65–0.82)**	**0.83 (0.72–0.95)**	Reference
Adjusted *P* value	**<0.001**	**0.007**	Reference
E value	2.08	1.70	Reference
mRS deterioration			
Case number	10	12	18
Adjusted OR (95% CI)	**0.87 (0.78–0.98)**	0.91 (0.80–1.03)	Reference
Adjusted *P* value	**0.02**	0.13	Reference
E value	1.56	1.43	Reference
CN deficit			
Case number	37	20	37
Adjusted OR (95% CI)	1.00 (0.87–1.16)	**0.76 (0.66–0.88)**	Reference
Adjusted *P* value	1.00	**<0.001**	Reference
E value	1.00	1.96	Reference
New haemorrhage			
Case number	3	1	2
Adjusted OR (95% CI)	1.00 (0.95–1.06)	0.98 (0.94–1.02)	Reference
Adjusted *P* value	0.89	0.23	Reference
E value	1.00	1.16	Reference

Adjusted for the follow-up time.
CN, cranial nerve; mRS, modified Rankin Scale score; OR, odds ratio.
OR and *P* value in boldface indicates statistical significance.

where patients exhibit poor conditions (mRS > 2), our practice often entails advocating for subacute microsurgery after an initial four weeks of rehabilitative treatment. This strategy aims to grant patients time for neurological recovery and enhancement, thereby rendering them better equipped to withstand perioperative complications and optimize microsurgical outcomes. In situations where patients exhibit severe disability or are bedridden due to a significantly compromised overall neurological condition, especially when coupled with respiratory dysfunction, our recommendation leans towards early surgical intervention. This course of action is intended to alleviate symptoms arising from brainstem compression and effectively manage potential life-threatening complications. Differences in patient distribution could plausibly contribute to the divergent outcomes observed between the acute and subacute groups. Additionally, we noted that the prevalence of CN deficits was lower in the subacute intervention group when compared to the acute group. This discrepancy might be attributed to an extended period of cranial

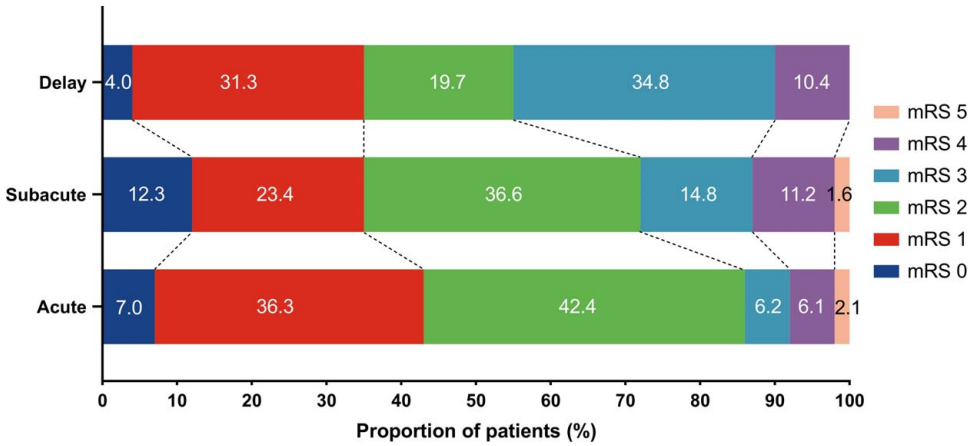

Figure 3. Proportions of patients stratified by modified Rankin Scale (mRS) score between the weighed cohorts. Percentage of mRS scores at preoperative time point and at final follow-up clinical evaluation for the weighed cohorts.

nerve function neurological recovery in the subacute phase group. Moreover, our study indicated that subacute intervention confers a protective effect against re-haemorrhage rates during the final follow-up when contrasted with both the acute and delay groups. In our perspective, the rationale behind this observation is that while the evacuation of a haematoma creates a surgical workspace, lesions in the acute bleeding phase tend to be relatively fragile. The limited size of the brainstem surgical area coupled with potential visual field blind spots may lead to incomplete resections. Conversely, lesions in the subacute phase tend to exhibit greater resilience and possess a clear capsule, facilitating easier separation and complete en-bloc resection. This improved visibility and en-bloc resection might be associated with a reduced risk of re-haemorrhage.

Furthermore, our study identified a significant association between prior multiple bleedings and unfavourable neurological outcomes. Repeated bleeding of the lesion can lead to adhesion with surrounding brain tissue, making the resection of the lesion more challenging and potentially damaging the brainstem function. Additionally, patients with prior multiple bleedings may have already experienced unfavourable neurological dysfunction before the surgery, which can complicate the postoperative recovery process and contribute to unfavourable outcomes. Similarly, patients with a preoperative mRS score of 5 were also found to be associated with unfavourable neurological outcomes. It is not surprising that patients with such severe preoperative neurological impairment may have higher risks of unfavourable outcomes following microsurgery.

The surgical intricacies associated with BSCMs predominantly revolve around the strategic selection of surgical approaches and the precise execution of intraoperative microsurgical techniques. In recent years, the extensive publications by Professor Lawton detailing the surgical experience with BSCMs, particularly emphasizing the nuances of surgical approach selection, have played a pivotal role in advancing neurosurgical techniques across various centres[26–30]. A notable development addressing a longstanding challenge in brainstem surgery is the introduction of the Surgical Entry Zone (SEZ) concept[13]. In contrast to lesions in more superficial locations, the removal of deep-seated lesions carries an elevated risk of compromising brainstem nuclei and fibre tracts, potentially resulting in residual neurological impairments. At present, many neurosurgeons are embracing the SEZ concept based on anatomical studies illustrating access paths between or around critical nuclei and tracts, despite the absence of definitive evidence regarding safety. With the ongoing advancement of surgical techniques, the radiological evaluation of BSCMs is poised to play a progressively significant role in predicting surgical prognosis outcomes.

Limitation

This study has several limitations. Firstly, the retrospective design of our study may introduce certain biases, as it relies on historical data and medical records. Secondly, treatment preference and decision-making by clinicians may have influenced the timing of interventions, leading to significant deviations in the distribution of patients across different interventional time periods. Third, given the intricacy and difficulty of brainstem surgery, the varying surgical techniques employed by different surgeons in two centres may impact the outcomes of the patients.

However, the utilization of MW analysis substantially mitigated the confounding impacts associated with preoperative mRS variations among the groups, thus facilitating a more dependable and impartial comparison of neurological outcomes across the three groups. Consequently, although not entirely analogous in characteristics, the method accounts for the cumulative effect of multiple factors while maintaining a relatively comparable baseline among each group. To achieve a more comprehensive resolution, further prospective randomized controlled studies are warranted. These studies should encompass advanced model construction, a larger and more diverse study population, and validation through collaborative efforts across multiple medical centres.

Conclusions

This cohort study highlights the potential benefits of early intervention for haemorrhagic BSCMs and interventions performed after 42 days post-haemorrhage demonstrate poorer outcomes. This may provide more comprehensive evidence to inform clinical decision-making and optimize patient management strategies for BSCMs patients.

Ethical approval

The study protocol was reviewed and approved by the ethics committee of West China Hospital, Sichuan University; and the approval number given by the ethical board was 2023-498.

Sources of funding

None.

Author contribution

Z.L. and J.L. conceived the idea, designed the paper, wrote and revised the manuscript. M.L. and K.Q. performed the statistical analysis, Y.S., P.L., H.Z. and X.D. collected the data. W.Z. and R.T. funded the study, critically revised the manuscript and approved the final manuscript as submitted. Z.L. is the guarantor. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinical Study of Brainstem Cavernous Malformations Prognosis.
2. Unique Identifying number or registration ID: ChiCTR230 0070907.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): URL: https://www.chictr.org.cn/.

Guarantor

Zongze Li.

Data statement

The data used in this study are available upon request from the corresponding author, subject to any applicable ethical or legal restrictions. Access to the data may require approval from the ethics committee or institutional review board of the participating institutions. Any data sharing will be conducted in accordance with relevant data protection and privacy laws.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

The authors acknowledge all individuals for their participation in this study.

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