Overview of Cerebral Cavernous Malformations: Comparison of Treatment Approaches

A Systematic Review and Meta-Analysis

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Abstract

Objective: The comparison of treatment efficacy for cerebral cavernous malformations (CCMs) has not yet been well researched.

Methods: PubMed, Cochrane Library, Science Direct, ISI Web of Science, EMBASE and additional sources were searched to identify cohort studies about the treatment of CCMs published between 1990–2020. The PRISMA guidelines were followed, the Newcastle-Ottawa Scale was used to assess the risk of bias, and to evaluate limitations based on selection/outcome biases. The cumulative incidences with 95% confidence intervals (CIs) were calculated using the random effects model. The models of Poisson distribution were applied to evaluate risk factors of poorer treatment outcome by calculating rate ratios within 100 person-years with 95% CIs.

Results: A total of 100 cohorts yielding 8994 patients treated for CCM/CCMs within 41 098 person-years of follow-up were analysed. The efficacy of ensuring the prevention of haemorrhage was 97% in surgical, 86% in radiosurgical, 77% in the conservative treatment. The lowest mortality (1%) was after radiosurgery, and highest persistent morbidity (22%) was in natural history series. Deep-seated and brainstem CCMs were associated with higher bleeding rates. Lobar localization was a protective factor in all analyses. Patients with history of previous haemorrhage were exposed to higher risk of rebleeding. Male gender was a protective factor associated with lower risk of post-treatment haemorrhage.

Conclusions: Surgical resection of CCM is effective in ensuring the prevention of haemorrhage with acceptable morbidity and mortality, but conservative and radiosurgical management are justified treatment alternatives. Brainstem and deep-seated CCMs are predominantly associated with higher haemorrhage rates.

Keywords: Cerebral cavernous malformations; surgery; radiosurgery; natural history; haemorrhage rate; case fatality; systematic review; meta-analysis.

List of Abbreviations

CCM – cerebral cavernous malformation

CM – cavernous malformation

CT – computed tomography

Gy – gray

ICH – intracerebral haemorrhage

ISSVA – International Society for the Study of Vascular Anomalies

MRI – magnetic resonance imaging

mRS – modified Rankin Scale

NOS – Newcastle-Ottawa Scale

PICO – patient/population, intervention, comparison, outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RR – rate ratio

SRS – stereotactic radiosurgery

Introduction

Cavernous malformations (CMs) are dilated blood vessels with a typical mulberry-like appearance that occur in venous-capillary vascular bed without intervening brain parenchyma, muscular or elastic tissue [1, 2]. According to the newest ISSVA classification of vascular anomalies [3], CMs are defined as slow flow venous malformations.

There are two possible forms of cerebral cavernous malformations (CCMs): sporadic and familial. The latter is considered an autosomal dominant disease caused by a mutation in one of the three genes responsible for interendothelial cell junction integrity [4]. CCMs represent 10–15% of all vascular malformations in the CNS [5], the majority occur in supratentorial locations [6]. Clinical symptoms are typically seizures, consequences of intracerebral haemorrhage (ICH), and non-haemorrhagic focal neurological deficits [7].

The aim of CCM treatment is typically the prevention of haemorrhage but stabilization of neurological deficits or seizure control are other possible indications for the intervention. Several meta-analyses focusing on the treatment of CMs [8–13] have been published. However, none has been able to compare all three treatment approaches (i.e., surgery, radiosurgery, and observation) with a wider amount of analysed primary data. This meta-analysis was performed to unite outcomes of all possible treatment alternatives, clarify their efficacy and specify factors that are associated with CCMs' dynamic behaviour. The aim was to clearly define 1) haemorrhage, 2) mortality, and 3) morbidity rate within each treatment modality while simultaneously clarify what localizations (not only brainstem, but also lobar, deep-seated, and cerebellar CCM) localizations, and if gender, and prior history of bleeding are associated with higher/lower risk of haemorrhage.

Methods

We followed the PRISMA statement and its criteria when creating this meta-analysis. To formulate the basis of eligibility criteria, we used the PICO worksheet (eMethods1 and 2).

Organisation

Lobar, deep-seated (the area circumscribed by diencephalon, basal ganglia, insula, capsula interna), cerebellar and brainstem (mesencephalon, pons, medulla oblongata) CCMs are considered separately due to the significant difference in the treatment approach and its outcomes. The orbital CMs were excluded as they are not considered to be cerebral lesions in the context of their localization, similarly as spinal CMs.

Literature Selection and Eligibility Criteria

We searched for relevant studies in the following databases: PubMed (MEDLINE), The Cochrane Library, ISI Web of Science, Science Direct, and EMBASE. Several combinations of keywords were used during the search (eMethods1). Twelve chapters from seven books [7, 14–18] were identified and included in the selection. We included meta-analyses and systematic reviews into the primary selection to search for studies cited in these publications. Through this step, we identified additional 33 studies that met our inclusion criteria.

Patients of all ages were included and cohorts of at least 20 patients presenting outcomes within conservative, surgical or radiosurgical treatment of CCM published between January 1990 and December 2020 were analysed. We searched only for retrospective and prospective studies officially published in English. In cases of multiple citations including the same patients, we analysed the largest/newest cohort. Each analysed study consisted of unique subjects who were not previously included in other series.

Assessment of Risk of Bias in Included Studies

After the identification of duplicate citations, two reviewers (A.B. and P.S.) independently excluded titles and abstracts which did not meet the predefined eligibility criteria. The Newcastle-Ottawa Scale (NOS) [19] was used to assess the risk of bias. Only studies rated with ≥ 6* according to the NOS were included. All discrepancies about exclusion or inclusion of specific studies were resolved at consensus meetings. Cohorts with insufficient follow-up data (rated with less than 2* within the evaluation of the study's outcomes) were excluded. The full length of follow-up was assessed when $\geq 80\%$ of patients per study were available at the final examination (eMethods3).

Data Extraction

Data on study design, patient demographics, CCM characteristics, lesion size, type of CCM treatment were collected. We looked for preoperative and postoperative outcomes, the length of follow-up, the marginal dose (mean gray; Gy), and the used modality of the stereotactic radiosurgery (SRS). For observation, we additionally extracted the total number of haemorrhages and the results of bleedings (eMethods4).

Statistical Analysis

The main outcome was to assess: (1) the haemorrhage rate following the treatment (in surgical and radiosurgical series, we calculated ruptures of primarily treated CCM, i.e., bleedings from partially resected or already irradiated CCMs), (2) the case fatality (any death attributed to CCM or conducted treatment), (3) the long-term morbidity, and to clarify (4) overall treatment efficacy (i.e., efficacy in ensuring the prevention of haemorrhage) and morbidity and mortality rates by calculating the cumulative incidences with corresponding 95% confidence intervals (CIs) for each outcome using the random effects model. The long-term morbidity was defined as any de novo persistent neurological deficit, new epilepsy onset or deteriorated patient's status determined by Engel classification worse than grade II [20]. We investigated associations between CCM localization, history of ICH, gender, and post-treatment haemorrhage with corresponding 95% CIs using Poisson regression models. The rate ratios (RRs) are expressed per 10% increase in the proportion of patients with post-treatment haemorrhage per 100 person-years. All computations were performed using MetaXL (Version 5.3, Epi Gear) and STATISTICA (Version 14.0.0.15, TIBCO Software Inc.) software.

For the conclusion, sensitivity analysis was performed in high-quality studies, i.e., those with prospective design and/or those in which the outcome of interest was not present at the start of the study.

Assessment of Heterogeneity

The test of heterogeneity of included cohorts was conducted by Cochran's Q and I-squared (I^2) statistics. For computations, we used measures of haemorrhage rates, case fatality, and long-term morbidity rates in our prespecified three treatment modalities.

Results

Study Characteristics and Cohort's Identification

A total of 98 primary studies with 100 cohorts including 8994 patients treated with one of three modalities were identified (eMethods2). Two publications [21, 22] presented outcomes of two treatment modalities separately on different patients' groups and thus we consider them individually (Table 1).

Characteristics	All Cohorts (n = 100)			Natural History (n = 25)			Surgery (n = 52)			Radiosurgery (n = 23)		
	N. of cohorts (%)	Sample size [a]	Mean [b] (range [c])	N. of cohorts (%)	Sample size [a]	Mean [b] (range [c])	N. of cohorts (%)	Sample size [a]	Mean [b] (range [c])	N. of cohorts (%)	Sample size [a]	Mean [b] (range [c])
Prospective design	15 (15)	2463	NA	12 (48)	2093	NA	2 (4)	72	NA	1 (4)	298	NA
Age (years)	95 (95)	8679	36.63 (7–58)	24 (96)	3455	38.27 (10–54)	50 (96)	3302	34.86 (7.1–58)	22 (95)	1922	38.95 (34–43.7)
Males	96 (96)	4436	46 (5–324)	24 (96)	1812	76 (11–324)	50 (96)	1672	33 (7–104)	22 (95)	952	43 (5–141)
CCM size (cm)	45 (45)	4808	1.78 (0.85–3.3)	13 (52)	2129	1.46 (0.85–2)	29 (56)	2256	1.96 (1.35–3.3)	3 (13)	423	1.4 (1.31–1.48)
Multiple CCMs	70 (70)	1194	17 (0–133)	19 (76)	678	36 (0–133)	38 (73)	308	8 (0–53)	16 (70)	208	16 (0–76)
Presentation												
Initial ICH	98 (98)	6314	64 (0–690)	25 (100)	2008	80 (0–690)	50 (96)	2502	50 (0–260)	23 (100)	1804	78.43 (0–261)
Localization												
Lobar	95 (95)	2921	31 (0–290)	21 (84)	1466	70 (0–290)	52 (100)	954	18 (0–168)	22 (95)	501	23 (0–115)
Deep-seated	94 (94)	1094	12 (0–121)	20 (80)	422	21 (0–121)	52 (100)	401	8 (0–72)	22 (95)	271	12 (0–55)

	Brainstem	95 (95)	4607	48 (0–708)	21 (84)	1560	74 (0–708)	52 (100)	1919	37 (0–260)	22 (95)	1128	51 (0–155)
	Cerebellum	93 (93)	344	4 (0–58)	19 (76)	115	6 (0–22)	52 (100)	106	2 (0–58)	22 (95)	123	5 (0–41)
Follow-up (months)		98 (98)	8856	49.15 (5–115.2)	25 (100)	3573	51.15 (11.2–104.4)	51 (98)	3339	43.9 (5–115.2)	22 (95)	1944	50.04 (23.6–112)

Table 1: Detailed characteristics of included cohorts. Used abbreviations: CCM, cerebral cavernous malformation; ICH, intracerebral haemorrhage; NA, not applicable. [a] A total number of patients with available requested data. [b] If mean was not available, median was used. [c] Data for the range in the following variables: age, CCM size, and follow-up, were derived from the mean values (and median, if mean was not available) within each study.

23% of studies described radiosurgical intervention (10 475 person-years of follow-up), 25% reported on the conservative treatment of CCM (17 452 person-years of follow-up), and 52% on surgery (13 171 person-years of follow-up). The majority (85%) of analysed studies were retrospective in design. A single randomized control study from authors Li et al. (2018) [23] was identified.

Technical and Clinical Outcome

The cumulative incidences (eFigure5) were calculated separately within each treatment modality. The percentage of haemorrhage rates was lowest after surgical intervention 3% (95% CI, 1–5%). The highest case fatality 4% (95% CI, 2–5%) and long-term morbidity 22% (95% CI, 16–28%) were reported within natural history series (Table 2). The final treatment efficacy was highest in the surgical (97% [95% CI, 95–99%]) and lowest within the conservative series (77% [95% CI, 75–83%]) (Table 3).

	Case fatality	Haemorrhage rate	Long-term morbidity
Natural history (n = 25)			
Sample size [a]	94	642	800
Rate (95% CI), %	4 (2–5)	23 (17–25)	22 (16–28)
Mean (range), %	2.34 (0–11.3)	21.96 (3–83.7)	20.9 (3–54.84)
Surgery (n = 52)			
Sample size [a]	39	77	397
Rate (95% CI), %	2 (1–2)	3 (1–5)	11 (9–13)
Mean (range), %	0.71 (0–4.7)	2. 56 (0–37.93)	10.48 (0.23–36)
Radiosurgery (n = 23)			
Sample size [a]	19	317	171
Rate (95% CI), %	1 (0–2)	14 (10–19)	10 (7–13)
Mean (range), %	0.61 (0–3.5)	13.81 (0–31.58)	9.37 (2–20)

Table 2: The overview of measured outcomes. Used abbreviations: CI, confidence interval. Haemorrhage rates are considered as bleedings following the surgical and radiosurgical management of initially treated CCMs or new bleedings within natural course of the disease. [a] Number of (1) deaths, (2) number of patients with haemorrhage after treatment, and (3) number of patients with persistent morbidity. For further details on the type of calculated data, see eFigure5.

	Efficacy	MM
Natural history	77% (95% CI 75–83%)	21% (95% CI 16–28%)
Surgery	97% (95% CI 95–99%)	11% (95% CI 9–12%)
Radiosurgery	86% (95% CI 81–90%)	9% (95% CI 7–12%)

Table 3: Efficacy and mortality/mortality rate within each treatment approach. The outcomes were measured by calculating the cumulative incidence with corresponding 95% confidence intervals (CIs). The random effects model was used. For further details and illustrative forest- plots, see eFigure5.

Risk Factors

Within surgical series (Table 4), patients with brainstem CCM and with a history of previous haemorrhage were exposed to a higher risk of postoperative bleeding (RR 1.016 [95% CI, 1.01–1.023]; $p < 0.001$, and RR 1.017 [95% CI, 1.005–1.028]; $p = 0.005$, respectively). Lobar CCMs had lower bleeding rates when compared to other localizations and were in all analyses considered as a protective factor (Table 4 and 5).

	All cohorts (n=100)			Surgical series (n=52)		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Males	0.993	0.985–1.002	.149	1.001	0.974–1.029	.932
Initial ICH	1.004	1.002–1.006	<.001	1.017	1.005–1.028	.005
CCM						
Lobar	0.997	0.995–0.998	<.001	0.975	0.964–0.986	<.001
Deep	1.002	0.998–1.005	.284	0.993	0.981–1.005	.234
Brainstem	1.006	1.004–1.008	<.001	1.016	1.010–1.023	<.001
Cerebellum	0.995	0.986–1.003	.190	0.997	0.975–1.020	.843

Table 4: Post-treatment haemorrhage rate and associations with patients and study characteristics in all cohorts and surgical series. Used abbreviations: CCM, cerebral cavernous malformation; CI, confidence interval; ICH, intracerebral haemorrhage; RR, rate ratio.

	Radiosurgical series (n=23)			Conservative series (n=25)		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Males	0.977	0.961–0.993	.006	0.979	0.966–0.993	.003
Initial ICH	1.009	1.002–1.017	.013	1.014	1.012–1.016	<.001
CCM						
Lobar	0.997	0.991–0.999	.154	0.995	0.938–0.997	<.001
Deep	1.012	1.001–1.024	.036	1.002	0.998–1.005	.334
Brainstem	1.002	0.997–1.006	.461	1.008	1.006–1.010	<.001
Cerebellum	1.006	0.992–1.020	.387	0.953	0.939–0.968	<.001

Table 5: Post-treatment haemorrhage rate and associations with patients and study characteristics within radiosurgical and conservative treatment series. Used abbreviations: CCM, cerebral cavernous malformation; CI, confidence interval; ICH, intracerebral haemorrhage; RR, rate ratio.

The analysis of radiosurgical treatment outcomes (Table 5) proposed that deep, cerebellar, and brainstem CCMs are associated with a higher risk of post-treatment haemorrhage. Only deep CCMs were considered as statistically significant (RR 1.012 [95% CI, 1.001–1.024]; p = 0.036). Initial ICH also correlated with a higher risk of bleeding after radiosurgical intervention (RR 1.009 [95% CI, 1.002–1.017]; p = 0.013). Male gender was considered as a protective factor (RR 0.977 [95% CI, 0.961–0.993]; p = 0.006). From all radiosurgical cohorts, 20 studies (87%) reported on using Gamma Knife (GK), one study on Linear Accelerator (LINAC) [24], and two publications on various modalities of LINAC/GK [25], and LINAC/helium ion [26].

Male gender, lobar and cerebellar CCMs were associated with a lower risk of bleeding in conservative treatment series (Table 5), while brainstem CCMs correlated with a higher risk of haemorrhage (RR 1.008 [95% CI, 1.006–1.013]; p < 0.001). Initial ICH also correlated with a higher risk of bleeding (RR 1.014 [95% CI, 1.012–1.016]; p < 0.001).

Sensitivity Analysis

Sensitivity analysis (eTable6) was performed in predefined high-quality studies (n = 37) using the same models of Poisson distribution. The analysis revealed the same results as the primary analysis, with deep and brainstem CCMs being the risk factors of haemorrhage (RR 1.005 [95% CI, 1.001–1.008]; p = 0.008, and RR 1.006 [95% CI, 1.004–1.009]; p < 0.001, respectively).

History of ICH was associated with a higher risk of bleeding (RR 1.005 [95% CI, 1.002–1.008] p = 0.002).

Discussion

To the best of our knowledge, this study is the largest meta-analysis about the treatment of CCMs. We have investigated relationships among factors associated with the lower (or higher) post-treatment haemorrhage rate following each treatment modality of CCM. Our results are suggestive that brainstem and deep-seated CCMs are predominantly associated with higher haemorrhage rates when compared to other localizations [27]. Although we aimed to illustrate correlations between the risk of poor treatment outcome and CCM size, 55% of cohorts did not reveal enough relevant data for us to study this factor. The lower case fatality within observation might be attributed to the significant number of patients (11%) who subsequently underwent (radio)surgical intervention and therefore could not be included in the final examination within the conservative treatment. The higher postoperative mortality may be attributed to the patients' selection bias. Surgery, when compared to SRS, is more often performed in an acute fashion when symptomatic CCM bleeding is present and therefore may be associated with a higher probability of poor clinical outcome [7].

Treatment Outcomes

The best therapy decision-making may be challenging, especially in eloquent CCMs or those with aggressive nature [5, 12]. The haemorrhage does not have to be symptomatic and may spontaneously resolve while in some cases may cause severe neurological deficit or epilepsy onset. In this meta-analysis, the evaluation of clinical outcomes was conducted within a single treatment modality so we could not provide details on multimodality therapy management.

Natural History

Observation is a justified treatment approach especially in asymptomatic patients, patients with lesions considered too risky for surgical resection or those with non-aggressive behaviour [7, 28]. Among many factors, the localization of the CCM seems to be an important determinant of disease behaviour. However, Gross et al. [28] proposed that the haemorrhage rate does not have to be attributed to the localization of CCM. Our findings showed significant lower bleeding rates of lobar lesions and conversely higher haemorrhage rates of brainstem CCMs in all analyses. This might be to a certain degree explained by unique treatment policy – higher surgical risks of brainstem CMs management (when compared to lobar CMs) may lead to initial conservative treatment. On the other hand, lobar CMs are more likely to be directly managed by surgery, ensuring the prevention of haemorrhage.

Other reports suggested a possible link between gender and haemorrhage until our results revealed that male gender might very likely be a protective factor associated with lower risk of haemorrhage [29. Male gender was a risk factor only in surgical series, but this result was not statistically significant (RR 1.001 [95% CI, 0.985–1.002]; p = 0.932).

A phenomenon of haemorrhage clustering was investigated by Barker et al. [30] by using several statistical models. Within the first year after the initial haemorrhage, a cumulative rebleeding rate was 14%, within 5-years the rebleeding increased to 56%. During the first 2.5 years, the probability of bleeding was 2% per month, but only 0.8% per month afterwards. A recent meta-analysis [31] demonstrated that individuals with a history of previous bleeding(s) are exposed to a higher probability of (re)bleeding when compared to patients who did not initially present with ICH. Our analysis revealed similar results, also previously verified by other authors [12, 31].

Surgical Management

Surgery is generally considered as first-line treatment. According to the long-accepted threshold, patients with a history of two and more bleedings, neurological deficit or uncontrolled epilepsy may be considered for surgical intervention. Pial and ependymal projection of the lesion should be one of the determinative factors when it comes to the decision-making of active treatment policy especially in eloquent areas [32].

One of the largest studies consisting of 1390 surgically treated brainstem CCMs from the literature [8] did not prove a direct association between brainstem localization and subsequent haemorrhage. Our results outline a higher risk of symptomatic haemorrhage of brainstem CCMs, since these lesions are within eloquent regions. It remains to be a surgical challenge and complete resection may not be accomplished in all cases. However, the outcomes are highly favourable and series with low morbidity/mortality rates are present.

The number of reports devoted to deep-seated CCMs remains low. In a recent meta-analysis [33], the mortality from surgical management of basal ganglia and thalamic CMs was 1.3% and the morbidity was 10%, which are comparable results with our findings. Pandey et al. [34] found out that patients with basal ganglia CCMs postoperatively presented better when compared to other deep seated CCMs – 73.3% of patients with resected thalamic CCMs and 100% of patients with basal ganglia CCMs had favourable postoperative outcome in terms of neurological function and Modified Rankin Scale (mRS). Although our analysis described a trend of the proneness of deep CCMs to bleeding, our results were in most cases statistically non-significant due to a lack of studies in the field.

Lobar CCMs are associated with lower morbidity and mortality rates, especially in non-eloquent areas. Our results show that possible risks of subsequent bleeding from lobar CCMs are lowest after surgical intervention when compared to other treatment approaches ($p < 0.001$). Moreover, aforementioned results suggest that lobar CMs are a protective factor in haemorrhage. Nevertheless, of note is that surgical series including supratentorial cases primarily deal with epilepsy. Therefore, there might be a possible outcome bias in terms of lower postoperative bleeding because the primary outcome of these publications was not to evaluate haemorrhage rate, but to study efficacy of surgery in ensuring epilepsy freedom postoperatively.

Radiosurgical Management

SRS and its benefits in CCM treatment algorithm are widely discussed but remain controversial. Generally, radiosurgery is a method of choice for poorly accessible CCMs where surgical resection might be unsafe, and it gives a better haemorrhage control after a latency period than observation alone [35]. However, the postradiosurgical bleeding rates are higher when compared to surgical interventions considering the latency period when the risk of bleeding is still present [11].

General Issues

Recent meta-analysis comparing outcomes from surgical and radiosurgical treatment of CCMs [13] proposed the urge to perform randomized control trials and prospective studies on the topic. In 2018, a nationwide multicentre prospective cohort study involving 24 hospital departments in China started and is currently ongoing for 5 years (to 2023) [36]. The authors should follow approximately 1200 patients for at least a 3-year period and their results may provide valuable results.

In relation to recently published population-based studies, the 5-year risk of recurrent haemorrhage is typically higher when compared to first haemorrhage [37]. Interestingly the annual risk of recurrent bleeding was higher in female patients when compared to males ($p = 0.01$), therefore revealing results comparable to our meta-analysis. However, there was statistically non-significant difference between adults with brainstem CCMs and those with CCMs in different localizations, in terms of annual risk of rebleeding ($p = 0.17$) [37]. Moreover, since we studied risk factors of haemorrhage separately, possible mixes of different risk factors within treatment modalities might be responsible for higher rates of haemorrhage.

Study Strengths and Limitations

The main limitation of this study is the retrospective design of most analysed studies and the fact that we searched only for studies officially published in English. Only 15 prospective cohorts were entered into the final analysis. With respect to the majority of retrospective studies, we reduced possible bias via detailed independent bias assessment and setting strict inclusion criteria into the final statistical analysis. However, we may have excluded publications with relevant treatment outcomes, but not fulfilling eligibility criteria. The heterogeneity was evaluated as moderate in most cases, significant heterogeneity was measured in analyses of all cohorts since we combined outcomes of three unique treatment modalities. The main issue, however, is the lack of randomized control trials and related risk of selection of outcome biases that might have influenced our results. Additionally, there is a potential bias based on conclusive values of mortality rates. Since we evaluated only CCM/treatment-related mortality, these values might vary according to what the authors consider to be CCM-related death.

One of the most important priorities in this analysis was to differentiate the localizations of brain CMs as being predictive factors of lesions' behaviour, treatment approach and its clinical outcome. The fact that we included almost 9000 patients in the analysis offers relevant results applicable in decision-making in cavernoma-related treatment.

Implications of Future Research

The lack of high-quality studies with a wider population sample and longer follow-up is the main field of implications of our results in the future. The conduction of randomized control trials and population-based studies that might clarify treatment outcomes related not only to specific localizations, but also to individual patients who are (un)suitable for specific treatment, would be helpful in prospective research.

Conclusion

Our findings suggest that brainstem and deep-seated CCMs are associated with higher risk of haemorrhage. Surgical interventions for CCMs are highly effective in ensuring the prevention of haemorrhage with an acceptable risk of morbidity/mortality. Radiosurgery is a method of choice predominantly in poorly accessible CCMs or those with a less aggressive nature. The active treatment policy for CCMs is justified but needs to be individually set for each patient in order to deliver the best clinical outcome. The natural course of the disease is dynamic and conservative treatment is favourable when higher risk of bleeding, new onset of neurological deficits or seizures is not present or when (radio)surgical intervention may be unsafe and therefore unbeneficial. These conclusions should be considered when deciding the best treatment modality for CCM management.

Authors Contributions

A. Bubeníková, P. Skalický, and O. Bradáč had full access to all of the data in the meta-analysis and take responsibility for the integrity of the data. A. Bubeníková and P. Skalický screened titles and abstracts for eligible studies. Discrepancies were resolved on consensus meetings or by discussion with O. Bradáč. A. Bubeníková and P. Skalický extracted data from the identified articles, and O. Bradáč was a second reviewer. A. Bubeníková and O. Bradáč performed the statistical analysis and take responsibility for the accuracy of the data analysis. All authors interpreted the data. A. Bubeníková drafted the manuscript which was critically reviewed and revised for important intellectual content by all authors.

Competing Interests

All authors report no disclosures or conflicts of interest.

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Data Availability

All datasets are available from the corresponding author on reasonable request.

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