pediatric stroke

Pediatric Cerebral Cavernous Malformations: A Systematic Review and Critical Evaluation of Clinical Features, Management Strategies and Outcomes

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Pediatr Stroke. 2025;11: 1-50
www.pediatricstrokejournal.com

ABSTRACT

Background: Pediatric studies investigating risk factors and treatment efficacy for cerebral cavernous malformations (CCM) are rare, characterized by small cohorts, heterogenous reporting, and limited postoperative follow-up. Consequently, pediatric and adolescent patients are frequently managed based on adult guidelines.

Objective: To examine the current literature to create an up to date, comprehensive summary of the management of CCM in pediatric patients, including risk factors, complications, and neurological morbidity following various treatment modalities.

Methods: A systematic review of the literature was conducted using PubMed, Google Scholar, and SCOPUS databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify retrospective studies detailing the use of conservative and/or surgical methods in the management of CCMs.

Results: 25 articles reported 1256 cases with studies ranging from 2 to 181 patients. Among the included patients, 719 were males and 537 females. The predominant symptoms were headache, predominantly attributed to hemorrhage, and sequelae of seizures. Patients were diagnosed based on CT or MRI. 532 lesions were supratentorial, and 432 were infratentorial, with average lesion size ranging from 2.1 cm to 22.5 cm with singular or multiple lesions. Patient management was based on an array of clinical and patient factors such as location, size, and nature of the CCM, with surgical treatment reported in 808 cases while the remainder were followed conservatively. Surgical resection proved to be the gold-standard therapy for patients with symptomatic CCM, particularly when lesions posed a substantial risk of morbidity. Conversely, lesions managed conservatively tended to be asymptomatic at diagnosis and smaller. The duration of follow-up varied across studies, ranging from 4 weeks to 29.7 years. Complications, including bleeding, infection, stroke, edema, and radiation-related morbidity, were reported in 67 cases. However, among the studies with available data, most patients demonstrated improvement in neurological outcomes, highlighting the overall positive response to both types of treatment interventions, regardless of surgical or conservative management.

Conclusions: CCMs in pediatric patients can present a diagnostic and treatment challenge due to their varying neurologic manifestations and clinical presentations. The primary treatment objective is to minimize complications and reduce rates of morbidity and mortality. The aggregate insights provided in this review serve as valuable guidance for tailoring individualized treatment plans in the context of pediatric CCM.

Keywords: Cavernous malformations; Cavernomas; Imaging; Management; Surgery; Conservative; Pediatrics

MANUSCRIPT

Introduction:

Cerebral cavernous malformations (CCM) are rare low-flow and low-pressure neurovascular lesions that commonly occur in the pediatric population, with a prevalence of 0.6%.[1-5] These malformations can present as solitary or multiple lesions. CCMs, which may be discovered incidentally, can occur sporadically or secondary to familial cavernomatosis or radiation therapy.[1] Pediatric CCMs have a higher risk of hemorrhage compared to adults[2-4] and often present with headaches, epileptic seizures, and focal neurological deficits.[5-11] Diagnosing these neurovascular lesions involves a comprehensive approach incorporating medical history, physical examination, neuroimaging through MRI/CT scans, electroencephalograms, blood testing, and genetic testing.

In its sporadic form, CCM presents as solitary or clustered lesions, often accompanied by developmental venous anomalies (DVA), though DVAs can occur independently of CCM.[12] In its inherited form, CCM is characterized by an autosomal dominant inheritance pattern, manifesting as multifocal lesions within the brain and spinal cord. Inherited CCM is primarily a result of a heterozygous germline loss-of-function mutation in either the *CCM1/KRIT1*, *CCM2/Malcavernin*, or *CCM3/PDCD10* genes.[12-20] Notably, a founder mutation (Q455X, involving *KRIT1*) and an associated preserved haplotype have been found to cause clustering of familial CCM in Hispanic/Latino patients of Mexican descent.[18] Clustering among patients of Ashkenazi Jew descendance is attributed to a deletion in *CCM2/Malcavernin*.[22]

Although intracerebral hemorrhage (ICH) is rare among young patients, CCMs carry an annual hemorrhage rate of up to 60%.[21] It has also been observed that a prior history of hemorrhage significantly raises the overall risk of hemorrhagic events in the pediatric population (11.3% per year).[3] Another factor associated with increased hemorrhage risk is the presence of familial forms of CCM.[2,3,19,22,23] Understanding such factors is crucial as recurrent hemorrhage can be devastating given the longer life expectancy of children and adolescents compared to adults.[23-25] The standard of care for young CCM patients involves neurosurgical resection or watchful waiting.[26] Evidence-based management of pediatric CCMs is limited by the lack of prospective multicenter databases[27,28] and the unique characteristics of the individual patient, including age, location of CCM, multiplicity of CCMs, and frequency of bleeding.[29]

Pediatric studies investigating risk factors and treatment efficacy for CCM are rare and are characterized by small cohorts, heterogenous reporting, and limited postoperative follow-up.[1,8,26] Consequently, pediatric and adolescent patients are frequently managed based on adult guidelines. In this study, we assess the existing literature to examine critical factors that guide management (surgical versus conservative) considerations in CCM. In addition, we present one illustrative case of solitary CCM in a pediatric patient from our institution to provide clinical context for existing evidence regarding CCM management.

Methods:

Search Strategy

A literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**).[24] The databases of PubMed, Web of Science, Google Scholar, Scopus, and Ovid Embase were queried on January 1st, 2023**.** The key search terms used included: "Pediatric cavernoma" OR "Pediatric Cavernous Hemangioma" OR "Pediatric Cavernous Angioma" OR "Pediatric Cerebral Cavernous Malformations." Exclusion criteria were as follows: adult patient population (>18 years old), articles not written in English, literature reviews, correspondences, commentaries, book chapters, animal studies, incomplete reporting of primary outcomes, and studies with overlapping pediatric and adult populations.

The primary objective of the study was to discuss and examine all original articles exploring management, recommendations, and outcomes in pediatric patients with cerebral cavernous malformations. Patient characteristics, risk factors, complications, and perioperative factors were also evaluated.

Data Extraction and Critical Summary of Evidence

Five authors (S.N., P.V., C.R., U.B., M.B.) independently conducted data extraction based on the search strategy. Inconsistencies were resolved through author consensus. Articles were screened by title, abstracts, and full texts. Relevant data, including research aim, population demographics, clinical characteristics, management, outcomes, and recommendations, were extracted from retrospective reviews. Information on patient demographics, presentation, underlying conditions, imaging, hemorrhage risk, management (conservative or surgical), and postoperative outcomes were examined, including age, gender, presenting signs and symptoms, family history, malformation characteristics, intervention type, and postoperative outcomes (length of stay, follow-up period, complications, modified Rankin Scores (mRS), and mortality).

Results:

Electronic Search Yield

A total of 593 studies were identified through the primary database search, and an additional 124 studies were found through manual review. Initially, 528 studies were selected, but only 25 papers met the inclusion criteria.[4,7,10,25-45] These included 23 retrospective studies, one cross-sectional study, and one prospective study. Of these, 16 studies did not compare surgical and conservative management[4,25,26,30-32,34-42,45] (**Table 1 and Table 2**) while nine articles directly compared the two treatment strategies in their populations (**Table 3 and Table 4**).[7,8,10,27-29,33,43,44]

Study and Patient Characteristics

In the included papers, a total of 1256 pediatric cases were discussed, with 719 male and 537 female patients. Demographics and patient characteristics of non-comparative studies are highlighted in **Table 1**. *Bigi et al.*[10] found that CCMs more commonly presented as seizures in younger patients while headache and focal deficits were more common in older

patients. In addition to seizures and headaches, other notable presenting characteristics included motor/sensory deficits, cranial nerve palsies, hydrocephalus, cerebellar symptoms, and increased intracranial pressure. Few cases were asymptomatic and found incidentally. The clinical course of brainstem cavernous malformations (BSCM) in children was highly variable, ranging from benign lesions to highly aggressive lesions with recurrent hemorrhages.[43] CT and/or MRI were the most common diagnostic tools. Studies involving patients with preoperative seizures also used electroencephalography while six studies[25,30,31,34,39,45] emphasized the use of cerebral angiography to rule out other diagnoses such as arteriovenous malformations (AVM) and to detect the existence of abnormal venous drainage associated with CCMs. One study required histological confirmation of the diagnosis for patients undergoing surgery whereas the presence of the near-pathognomonic "mulberry-like" lesions with signal susceptibility around the CCM (due to hemosiderin) on imaging was noted as a diagnostic feature critical to committing to conservative management.[33] Most of the lesions (532, 55.2%) were supratentorial while the remainder (432, 44.8%) were infratentorial, with average lesion diameter ranging from 2.1 cm to 22.5 cm. *Jaman et al*. provided the largest range for CCM lesions from 0.004 cm^3 to 38.44 cm^3.[35]

Management: Surgical and Conservative Approaches

Management and neurological outcomes of non-comparative studies are presented in **Table 2**. The management of CCMs in pediatric patients is influenced by various factors, including lesion location, size, symptom burden, epilepsy workup, and clinical course. Individualized assessment of risks and benefits remains the mainstay of management for pediatric CCMs.[7] When determining the appropriate treatment modality for CCM, it is essential to consider the individual needs of each patient and any clinical factors that could impact outcomes. A treatment algorithm proposed by *Santos et al.*[4] takes these factors into account and recommends conservative management for asymptomatic CCMs in pediatric patients while management of patients with symptomatic lobar CCMs should aim for gross total resection. For deep CCMs, subtotal resection may be an option to prevent neurological compromise and sustainably improve neurological outcome.

Conservative versus Surgical Management

Table 3 and **Table 4** highlight the 9 studies that directly compared surgical and conservative management in CCMs. Demographics of these studies are presented in **Table 3**, and management and outcomes are presented in **Table 4**. Surgical resection is considered the gold standard for patients with symptomatic CCMs, especially if lesions do not pose excessive surgical risk.[7,10,26,32,34,37,44] One study found that patients treated with surgical resection had significantly higher rates of ICH at presentation (OR: 6.30; 95% CI: 2.70–14.74; p<0.001) and were less likely to be asymptomatic at diagnosis compared to those managed conservatively (OR: 0.11; 95% CI: 0.04–0.35; p<0.001).[4] *Bhardwaj et al*.[28] recommended conservative management of BSCMs in asymptomatic patients with smaller lesions (mean size=10.6mm) while patients with larger lesions (mean size=21.0 mm), pial presentation, and symptomatic presentation at a younger age were more likely to undergo surgical management. Complete microsurgical excision must be preceded by careful anatomical and functional evaluation, and risk reduction can be achieved with the help of neuronavigational

and intraoperative ultrasonography.[44] Surgical planning must be individualized for each patient to reduce the risk of morbidity, and complete resection should be attempted to reduce the rebleed risk.[38]

Samanci et al. reported that prior radiation treatment or CCM multiplicity did not influence the decision to perform surgery.[42] Given the increased likelihood for functional recovery and longer life expectancy in children, surgical treatment in high-volume centers should be considered for young patients with surgically accessible lesions and an aggressive clinical course. Asymptomatic lesions or those in critical areas are monitored with serial MRI scans, and surgery is considered if there are clinical changes or lesion growth.[7,32] It is crucial to note that the estimated annual hemorrhage risk from natural studies of CCM according to a review by *Washington et al.* ranges from 0.7% to 6% per patient-year.[46] Given this risk, early management is strongly considered to monitor growth of the cavernoma and determine risk for hemmorhage.[36]

Functional and Neurological Outcomes

Although improvements in neurological outcomes, reduction in seizure incidence, and control of hemorrhage risk can be achieved with surgery for pediatric BSCMs, only a few patients may achieve full neurologic recovery.[32,38,47,48] *Acciari et al*. reported improvement in neurological status with surgical treatment in 69% of cases (defined as complete resolution of presenting symptoms), unchanged deficits in 23.8% of cases, and surgical complications in 7.1%.[25] Mortality was absent in this series, with data confirming surgical treatments as yielding favorable results at long-term follow-up. Following complete excision of lobar CCMs in pediatric patients, there appears to be both excellent symptom relief and durable radiographic cure rates.[7] Two studies discussed clinical outcomes in children suffering from epileptic seizures before surgery,[27,34] and two additional studies reported that seizure control improved in all patients who underwent cavernoma resection.[26,31] *Di Rocco et al.* went on to describe that in these cases, lesionectomy alone may be sufficient to resolve epilepsy.[31] Additionally, two papers investigated the natural history of CCMs, with emphasis on recurrent bleeding and hemorrhage.[4,21] Much of early surgical morbidity tends to improve over time.[28] Certain factors such as age, number of preoperative hemorrhages, and mRS have demonstrated utility in predicting postoperative outcomes and can be used to further guide treatment decisions.

Illustrative Case

A 6-year-old female presented to the emergency department with left facial droop, left-sided weakness, numbness (most pronounced in the left upper extremity), ataxia, dizziness, anisocoria (left 3 mm, right 1 mm), and worsening headaches for 3 days. CT head revealed a hemorrhagic pontine lesion eccentric to the right with surrounding edema that nearly presented to the ependymal surface of the floor of the fourth ventricle. The lesion measured 2.5 x 2.4 x 2.5 cm, and MRI identified several other smaller lesions consistent with cavernomas (**Figure 2A,B**). Due to the location in the brainstem and potential morbidity of surgery, she was initially managed conservatively. On the evening of her 9th hospital day, she had several body spasms, an increase in left-sided weakness, with loss of coordination and

balance. She was drowsy and did not respond to verbal commands. CT identified and MRI confirmed new hemorrhage within the lesion and worsening ventriculomegaly (**Figure 2C,D**) . She was admitted to the ICU, intubated, and an external ventricular drain (EVD) was placed. A pentobarbital coma was initiated for sedation and cerebral protection, and levetiracetam was started. She underwent surgery one week later (32 days after admission). A midline suboccipital craniotomy was performed after which the cavernoma was approached through a non-eloquent location in the floor of the fourth ventricle based on intraoperative neurophysiologic mapping. Cranial nerves (VI, VII, X, and XII) were monitored. The patient's left facial nerve and lateral rectus were paretic but functional after surgery. The EVD was removed on postoperative day 2, and she was extubated on postoperative day 5.

During her hospitalization, the patient experienced several infections including a *H. influenzae* respiratory infection, possible CSF infection with Bacillus spp., and a urinary tract infection. Prior to surgery, she also suffered from severe constipation, which was resolved through sigmoidoscopy and disimpaction. After 68 days of admission, she was discharged. At neurosurgical follow-up 14 months later, MRI revealed further reduction in both the size of the resection cavity and the surrounding edema in the pons (**Figure 2E,F)**. The other cavernous malformations remained stable. She was free from headaches and seizures, exhibited normal running and walking gaits, and had symmetric extremity motor function with mild dysmetria on finger-to-nose testing. Mild left facial weakness persisted. She excelled in school and was the top reader in her first-grade class. Genetic testing confirmed a de novo pathological mutation in the *KRIT1* gene.

Discussion:

Cerebral cavernous malformations are rare in pediatric populations with an estimated prevalence of 0.6%, accounting for possibly one fourth of all CCM patients.[4] However, the exact prevalence is not known because many are asymptomatic.[6,36] CCM is characterized by dilated low-flow venous sinusoids without intervening brain tissue. They can be diagnosed at any age and present with a wide range of symptoms, from asymptomatic to hemorrhagic with seizures or focal neurological deficits. Younger age at diagnosis is associated with a higher risk of long-term neurologic injury due to recurrent hemorrhage or seizures.[21,37,38] Patients can present with single or multiple lesions that can be sporadic or associated with genetic mutations.[49] Lesions can produce symptoms due to hemorrhage or seizures, and neurologic deficits depend on anatomic location. Some lesions are found incidentally on workup of unrelated issues.

CCMs are angiographically occult. Reports of hemorrhage rates in CCM have varied due to variability in the definition or recognition of hemorrhage and differences in study methodologies. Hemorrhage in CCM has been defined as any acute clinical symptom (headache, seizure, or focal neurologic deficit) that refers to the region of the CCM lesion and must be supported by imaging evidence.[11] Recurrent hemorrhage risk is increased in CCMs that initially presented with a hemorrhagic event[5,50,51] and less for lesions without such an event.[52-54] However, reports often fail to make the distinction between incidentally found/asymptomatic patients and symptomatic patients, which can impact management

and risk assesment.[51] For solitary CCM lesions in all ages without initial hemorrhage, the estimated hemorrhage risk is 0.7-4.2% per patient-year.[11] The annual risk of hemorrhage per year for BSCM significantly escalates, reaching a five-year hemorrhage risk of 8%, and approximately 30% if hemorrhage or a focal neurological deficit was identified at initial presentation.[23,55]

Primary assessment of a suspected symptomatic CCM often involves computed tomography (CT), although microcalcifications detected through CT can be a non-specific finding. CT imaging is not the first-line diagnostic tool for CCM, but it is commonly used in acute settings where MRI is unavailable. It is recommended to perform CT imaging within one week of symptom onset, followed by MRI within two weeks and a two-month follow-up to assess hemorrhage resolution.[56] MRI is preferred over CT when possible due to its superior ability to visualize soft tissues and vascular structures with greater detail. It can also distinguish CCMs from other brain neoplasms due to their characteristic anatomic appearance and the presence of hemosiderin.[56-58] The susceptibility-weighted sequence (a gradient-echo MRI technique) confers high sensitivity for blood breakdown products[59] and has demonstrated high sensitivity in detecting multiple small CCM lesions in familial cases. The T1- and T2-weighted sequences also provide valuable information about the presence and age of the blood products associated with the lesion. Both sequences may exhibit the characteristic reticulated or “popcorn” appearance, surrounded by a hypointense hemosiderin rim.[56,60] The Angioma Alliance recommends that MRI protocols for CCM should at the minimum include T2-weighted gradient sequences or SWI.[56] The presence of DVA should also be assessed as these have been found to occur in about 30% of all CCM cases. However, presence of DVA has been shown to have no effect on hemorrhage risk and also does not affect surgical decision making.[3]

Lyne et al. found that biomarkers including sCD14, VEGF, IL-1β, and sROBO-4 have shown promise in predicting the risk of hemorrhage in the following year with high sensitivity (83%) and specificity (93%) (p=0.001).[61] Thrombomodulin has also been proposed as a potential indicator of CCM presence and hemorrhage risk.[62] Biomarkers could be useful in assessing hemorrhage morbidity during long-term CCM patient follow-up as vascular permeability within CCM lesions is hypothesized to play a significant role in hemorrhage. MRI techniques such as quantitative susceptibility mapping (QSM) and dynamic contrast-enhanced quantitative permeability (DCEQP) have shown great diagnostic potential.[63]

The genetic basis of CCM is well established: familial CCM is due to loss of function mutations in genes *CCM1* (*KRIT1*), *CCM2* (*MGC4607*), and *CCM3* (*PDCD10*).[64-67] These genes regulate junctional integrity between neighboring vascular endothelial cells,[68,69] and 20% of cases are familial with autosomal dominant inheritance. Counseling families is difficult as risk estimation is complicated by incomplete penetrance and variability in presentation.[70] Sporadic CCMs generally lack an association with genetic components in contrast to familial CCMs.

The Angioma Alliance (www.angioma.org) recommends the following approach to genetic testing and counseling: 1) obtain a 3-generation family history focused on symptoms of headache, stroke, abnormal MRI scan, or other neurological complication (Class I, Level C); 2) consider genetic testing of CCM1-3 genes by Sanger or NextGen sequencing followed by deletion/duplication analysis in cases of multiple CCM without associated DVA or in cases with known history of brain radiation or positive family history (Class I, Level B); and 3) if there is a positive mutation in a proband, counsel the patient and family about autosomal dominant inheritance and identifying at-risk individuals through pedigree. While genetic screening of asymptomatic family members is controversial due to the psychological effect it can have on these patients, genetic testing of at-risk adult family members should be offered with appropriate discussion and education about psychological consequences (Class I, Level C).[56]

Conservative versus Surgical Management

Conservative management can be considered for incidentally-discovered, non-progressive, or asymptomatic lesions, lesions that carry a high risk of surgical morbidity, and when seizures are adequately controlled with medications.[71] While patients with supratentorial CCM in the frontal lobe carry the lowest annual risk of rebleeding,[2] the risk of rebleed increases after the first hemorrhage, with reported rates of 7.0-8.9% per year.[72,73] Other studies report patients 23.3-42.4% rate of recurrent bleed.[5,52,56,74] Several factors are associated with a low hemorrhage risk such as location, absence of prior hemorrhages, moderate lesion size, no prior radiation or family history of CCM, no associated DVA, and seizure without hemorrhage,[71] making conservative medical management potentially more attractive.

Positive aspects of surgical management include alleviation of mass effect, potential resolution of seizures, and a reduction (or elimination) of the hemorrhage risk. Early operative intervention may improve seizure outcome. Cons of surgical management include the invasiveness of cranial neurosurgery and perioperative morbidity.[25,38,47,75] In a systemic pooled analysis, *Gross et al.* demonstrated that patients with CCM who present incidentally or with seizure have a 9.3% 5-year risk of developing epilepsy.[3] Balancing the risks and benefits of surgery in CCM is challenging. Delaying intervention may result in long-term deficits or structural damage. However, surgical excision can lead to complete resolution of deficits and prevent future neurological complications. Watchful waiting may increase the risk of needing future surgery and can allow further significant neurological damage due to re-hemorrhage. In cases of BSCM, allowing the lesion to hemorrhage multiple times until it reaches the pial surface can decrease operative morbidity by reducing the length of the operative corridor through normal tissue, though neurologic damage accumulates due to recurrent hemorrhage.

Gamma knife radiosurgery may also be considered as a therapeutic alternative for pediatric CCMs. In a study by *Pollock et al*., the annual hemorrhage rate during the 51 months preceding radiosurgery was 40.1%, compared with 8.8% in the first 2 years following radiosurgery and 2.9% thereafter.[76] However, it does entail inherent risks, including

radiation-induced toxicity to the adjacent normal tissue.[42] Its efficacy is controversial, due to its safety profile, delayed therapeutic effects, side effects, and radiation exposure; therefore, radiation is not the recommended first-line treatment for CCM.[42] Moreover, this treatment option may not be suitable for all patients, especially those with large or deep CCMs. In addition, there is a lack of consensus regarding the indications, contraindications, safe dosages, and long-term outcomes associated with this procedure. Laser Interstitial Thermal Therapy (LITT) offers a minimally invasive stereotactic approach for treating CCM by heating the lesion with a laser whose energy is transmitted through a stereotactically-placed fiberoptic catheter. *Ogasawara et al.* reviewed five studies with a total of 32 patients whose CCMs were treated with LITT.[77] 93% of patients had an improvement in symptoms with no new recurrence after a mean follow up of 21.4 months. LITT has also been shown to be effective and safe, particularly in cases involving deep, delicately located CCMs as well as lesions that are prone to hemorrhage or causing seizures.[77,78] In conclusion, while gamma knife radiosurgery and LITT present promising therapeutic alternatives for pediatric CCMs, each modality comes with its own set of risks, limitations, and considerations, underscoring the importance of an individualized treatment approach.

Clinical trials, like the AT CASH EPOC trial, are exploring treatments for CCM hemorrhage, including atorvastatin (80 mg daily) to reduce re-bleeding[79]. Chen et al. found no effect of statins, beta-blockers, or other medications on hemorrhage risk in 1,116 CCM patients over five years[74]. Similarly, Wildi et al. reported no difference in hemorrhage risk for 428 CCM patients on statins compared to untreated patients, though antiplatelet or anticoagulant therapies appeared to reduce hemorrhage risk.[80] The CARE pilot trial studied 72 patients with symptomatic CCMs, comparing medical management with and without surgery (resection or radiosurgery).[81] Participants (median age 50.6) were mostly adults, with 78% having prior hemorrhage and 39% with seizures. Six-month follow-up showed 93% retention, with new or recurrent neurological deficits in 6% of both groups and no serious adverse events. While feasible, this study is not representative of pediatric patients and does not endorse a specific treatment based on symptoms or lesion characteristics.

While no treatment has been proven to be more effective in familial or sporadic cases of CCMs in pediatrics, it is crucial to identify symptoms and their progression early. Our study reviewed 14 articles noting family history, with five specifically addressing familial CCMs, finding no difference in symptoms. Limited genetic testing and follow-ups might explain this. Management is symptom-based, with conservative care for asymptomatic patients and symptomatic treatments like antiepileptics and beta-blockers as needed.[72,82] Surgery or radiosurgery is considered only if symptoms progress and all other treatments fail, based on clinical presentation, lesion characteristics, and surgical risks.[83-85]. Lesion factors to consider include location, size, recent bleeds, and weighing the risks of surgery against the natural history of the lesion.

Future Direction and Recommendations

This review highlights several important future directions and recommendations for improving the understanding and management of CCMs in the pediatric population. First, establishment of prospective, multicenter registries and cohort studies with standardized data collection is critically needed to better characterize natural history, risk factors for hemorrhage/re-bleeding, and comparative outcomes between surgical and conservative management approaches. Additionally, long-term follow-up will be essential to further our understanding and outcomes. Development of evidence-based, pediatric-specific clinical guidelines tailored to the unique challenges and longer life expectancies of children and adolescents with CCMs is also warranted to provide clear strategies for screening, surveillance, genetic counseling, treatment selection, and follow-up. Additional research should focus on fully elucidating the genetic underpinnings, penetrance, and expressivity of familial CCM syndromes as well as further validation and longitudinal study of promising circulation and imaging biomarkers for risk prediction and early therapeutic intervention. While microsurgery remains the mainstay, the role of emerging therapies like stereotactic radiosurgery, LITT, and other minimally invasive approaches requires head-to-head comparison versus surgery and conservative management, especially for high-risk locations. Given the complexities of care, establishment of comprehensive, multidisciplinary CCM treatment centers with concentrated experience may optimize outcomes through coordinated multispecialty approaches, imaging, treatment planning, and sponsorship of clinical trials. Finally, most studies have prioritized radiographic, clinical, and safety outcomes, but dedicated qualitative and quantitative assessment of patient/parent-reported outcomes and quality of life in pediatric CCM patients is still needed to better determine quality-adjusted life expectancies and guide family counseling. In summary, this review reveals key gaps in evidence that highlight an urgent need for dedicated, prospective, multicenter studies to optimally care for pediatric CCM patients through accurate risk stratification, biomarker development, improved therapies, and coordinated multidisciplinary treatment paradigms.

Limitations

This study has several important limitations that should be considered. First, as a systematic review, our study was restricted to published studies written in English, which may have led to language bias and the exclusion of potentially relevant papers. Additionally, most included studies were retrospective in nature, which are prone to bias and confounding compared to prospective studies. The lack of prospective, controlled clinical trials severely limits the strength of evidence regarding optimal management of pediatric CCMs. Several of the studies included mixed populations of pediatric and adult patients, which complicated extraction of pediatric-specific data. Outcomes were often not stratified based on patient age at diagnosis or lesion characteristics, making it difficult to tease out unique risk factors and prognostic indicators for the pediatric population. Furthermore, there was substantial heterogeneity across studies in terms of data collected, definitions used (e.g. for hemorrhage), and duration of follow-up, limiting the ability to perform quantitative meta-analyses. Our illustrative case highlights the challenges and nuances in pediatric CCM management but represents just a single patient's experience. Finally, the literature search was conducted in January 2023, so more recent publications were not

captured. Despite these limitations, this review synthesizes the most comprehensive evidence to date on this rare pediatric condition and highlights critical knowledge gaps that require further dedicated prospective research.

Conclusions:

CCMs present with a diverse array of neurologic symptoms, and the management approach is influenced by factors such as lesion size, location, and multiplicity. In pediatric patients, treatment decisions should consider these factors as well as consider overall health status and hemorrhage risk. Cases that are asymptomatic or exhibit minimal symptoms may be best managed conservatively. Microsurgery, facilitated by imaging and frameless stereotactic navigation, presents an effective treatment avenue with limited morbidity for many CCMs. Each approach carries inherent limitations and associated risks.

Acknowledgements:

We would like to express our sincere gratitude to Children's Health and University of Texas Southwestern Medical Center's Neurosurgery Department for their invaluable contributions to this research project. Their support, guidance, and expertise have been instrumental in shaping the direction and outcomes of this work.

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Conflict of interest Statement:

The authors have no personal or institutional interest with regards to the authorship and/or publication of this manuscript.

Funding Disclosures:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

IRB compliance statement and ethical adherence:

This study was written in compliance with our institutional ethical review board. IRB approval was waived given the de-identified nature of the information presented.

Acknowledgments

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Figure and Table Legends

Figure 1: PRISMA Flow diagram showcasing the methodology employed in conducting the systemic review. Created with BioRender.com.

Figure 2: **(A,B)** Axial T1W and coronal T2W MRI imaging identifying a hemorrhagic lesion located in the right hemipons. **(C,D)** Axial T1W and coronal T2W MRI imaging showing re-hemorrhage of the cavernous malformation. **(E,F)** Axial FLAIR and coronal T2W MRI imaging taken at last follow-up showing complete resection of the cavernoma with mild surrounding edema.

Table 1. Demographics and patient characteristics of non-comparative retrospective studies included in the systematic review.

Table 2. Management and neurological outcome of non-comparative retrospective studies included in the systematic review.

Table 3. Demographics and patient characteristics of retrospective studies comparing surgical versus conservative management in pediatric cavernomas.

Table 4. Management and neurological outcomes of retrospective studies comparing surgical versus conservative management in pediatric cavernomas.

Table 1. Demographics and patient characteristics of non-comparative retrospective studies included in the systematic review.

#	*Author . Year*	Study Aim	Patient Info	Age in Years	Family History or Medical History	Presenting Signs and Symptoms	Time From Symptoms to Management in months	Diagnostic Modality	Location of Cavernoma	Size of Lesion in cm	Isolated vs. Multiple
1	*Jaman et al. 2023*[35]	To classify and characterize differences in the clinical presentation, characteristics, and outcomes of CCMs between familial and sporadic cases within the pediatric population.	N 131 M 71 F 60	Mean (SD) 8.4 (5.93) Range .16 to 20	Familial CCMs 35 Sporadic CCMs 96 Family History of CCMs 20 DVA 34 Previous Hemorrhage 73	Seizure 39 Nonspecific symptoms 42 Asymptomatic 34 CN deficits 5 Motor deficits 5 Developmental deficits 4 Syncope 2 Hemorrhage at DX 42	N/A	MRI CT	Supratentorial 97 Infratentorial 34	Mean (SD): 1.37 (1.84) Range 0.15 to 3.37	Multiple 41 Isolated 90 Mean No. of CCMs 3.5 Range 1 to 33
2	*Samanci et al. 2022.*[42]	Reported experience in managing pediatric CCMs with GKRS.	N 46 M 27 F 19	Median 13 Range 2 to 17	Previous hemorrhage 35 Previous resection 7 DVA 5 Sporadic 46 Craniotomy 1	Symptomatic hemorrhages 35 Neurological symptoms 22 Seizure 13 Headache 12 Motor deficit 6 Syncope 5 CN deficits 3 Dizziness 3 Hemisensory deficit 2	Median 12 Range 0.5 to 180	MRI	Supratentorial superficial 34 Supratentorial deep 13 Brainstem 10 Cerebellum 7	Median 0.62 Range 0.46 to 2.18	Multiple 8 Isolated 38 Median No. of CCMs 1 Range 1 to 5

						Incidental 2					
3	*Santos et al. 2022.*[86]	Investigated the course of cerebral cavernous malformations (CCM) in the pediatric population, with emphasis on the risk of first and recurrent bleeding over a 5-year period.	N 129 M 73 F 56	Mean (SD) 10.7 (5.78)	DVA 18 Family History of CCMs 35	ICH 72 Asymptomatic 42 Cavernoma-related Epilepsy 46	N/A	MRI	Brain stem 25	N/A	Multiple 53 Isolated 76
4	*Prolo et al. 2020.*[41]	Studied the clinical course and recurrence rate following surgery for a cohort of CMs in children.	N 53 M 32 F 21	Mean 10.5 Range 0.3 to 18	DVA 23 AVM 2 Prior radiation 1 Family history of CMs 13	Seizures 24 Neurological deficit 18 Severe/Mild headache 4 Somnolence 3 Incidental 4 Hemorrhage at DX 34	N/A	MRI CT	Supratentorial cortical 43 Brainstem 13 Basal ganglia/thalamus 7 Cerebellar 6 Mixed 4 Spinal cord 1	N/A	Multiple 22 Isolated 30 Unknown 1 No. of CCMs 74
5	*Knerlich-Lukoschus et al. 2015.*[36]	Described the clinical, radiological, and surgical features of CCM in children.	N 5 M 4 F 1	Mean (SD) 7 (4.6) Range 2.5 to 14	Family history of CMs 1 DVA 3	Hydrocephalus 3 Headaches 5 Nausea 1 Ataxia 2 Vomiting 1 CN VI palsy 1 Syncopal episode 1 Hemorrhage at DX 5	N/A	MRI CT Angiography	Infratentorial 5	Mean (SD): 3.03 (2.88) Range 1.16 to 4.25	Multiple 4 Isolated 1

6	*Noh et al. 2014.*[40]	Investigated the clinical course of pediatric CMs treated with resection using neuronavigational systems, intraoperative neuromonitoring, and TTRS.	N 29 M 18 F 11	Mean 9.4 Range .75 to 18	N/A	Seizures 13 Mild neurological symptoms (headache, dizziness, nausea, and vomiting) 8 Focal neurological deficits (weakness and delayed speech) 2 Incidental 6 Hemorrhage at DX 7	N/A	MRI CT US	Supratentorial 26 Supra- and infratentorial 3 Eloquent areas 10	N/A	Multiple 10 Isolated 19
7	*Li et al. 2014.*[21]	Investigated the appearance of untreated pediatric brainstem cavernous malformations (CMs) and identified the hemorrhagic risks and functional outcomes.	N 85 M 59 F 26	Mean (SD) 12.7 (4.0) Range .83 to 17.9	Family history of CMs 2 Previous hemorrhage 67 DVA 13 Edema at DX 38 Neurological comorbidity 1 Previous surgical resection 2 Ventriculoperitoneal shunt 4	Asymptomatic 3 Hydrocephalus 8 CN deficits 61 Motor deficits 42 Neuropathic pain 35 Sensory Deficit 34 Ataxia 15 Walking Deficit 31 Incidental 6	N/A	MRI	Midbrain 15 Pons 53 Medulla 17	Mean (SD): 1.9 (0.7) Range 0.4 to 3.4	Multiple 14 (Cerebral 10, Brainstem 4) Isolated 71
8	*Hugelshofer et al. 2011.*[34]	Compared the outcomes with respect to the location of lesions in children who preoperatively	N 79 M 41 F 38	Mean 9.7 Range .3 to 17	Multiple and Familial CCMs 1	Epileptic seizures 36 Seizures following other symptoms 5 Hemorrhage at DX 18 Focal neurological deficits 14 Headache 8	N/A	MRI CT Electroencephalography	Frontal lobe 25 Temporal lobe 10 Parietal lobe 6 Occipital lobe 5	Mean 1.96 Range 0.5 to 6	Multiple 3 Isolated 76 No. of CCMs

		suffered from epileptic seizures.				Behavioral changes 3		Angiography	Brainstem 33		Range 1 to 5
9	*Consales et al. 2010.*[30]	Reported on CCs prospectively followed at the Gaslini Children's Hospital, Genoa, Italy and compared with literature data to define surgical indications and strategies in the management of children with CCs.	N 32 M 17 F 15	Mean (SD) 7.1 (5.3) Median 7 Range .005 to 17	Family History of CMs 3 Brain cancer 2	Macrohemorrhage 21 Diffuse headache 6 Intracranial HTN 10 Epilepsy 5 Seizures 7 Hemiparesis 2 Loss of consciousness 2 CN deficits 4 Nystagmus 1 Ataxia 1	N/A	MRI CT Angiography	Supratentorial 24 Infratentorial 8	N/A	Multiple 8 Isolated 24
10	*Acciarri et al. 2009.*[25]	Described the main clinico-diagnostic features, risk factors and associated diseases of cavernous malformations (CMs) focusing on the management of pediatric patients harboring cranial and spinal CMs.	N 42 M 21 F 21	Mean (SD) 11.30 (5.04) Median 12.5 Range .03 to 17	Familial CCMs 1 Klinefelter's syndrome 1 Brain cancer 2	Seizures 28 Epilepsy 15 Previous Hemorrhage 1 Recurrent headaches 11 Intracranial hypertension 11 Rapidly progressive paraparesis 1 Insidious clinical progression 1	Mean (SD) 16.99 (26.84) Median 6 Range .03 to 138	MRI CT MR Angiography Electroencephalography X-ray	Supratentorial 35 Infratentorial 5 Spinal cord 2	Mean (SD): 1.10 (3.32)	Multiple 5 Isolated 37 No. of CCMs Range 1 to 10
11	*Alexiou et al. 2009.*[26]	Analyzed a series of patients surgically treated for cavernomas.	N 16 M 6	Mean 10	Family History of CMs 3	Seizures 12 Intracranial hemorrhage 3 CN paresis 2	N/A	MRI CT	Supratentorial 14 Infratentorial 2	N/A	Multiple 3 Isolated 13

			F 10	Range 4 to 14							
12	*Lee et al. 2008.*[37]	Focused on the clinical and therapeutic features of CMs with emphasis on their specificities in the pediatric age group.	N 33 M 18 F 15	Mean 11.1 Range 1 to 20	No family history of CMs	Intracranial hemorrhage and seizures 11 Intracranial hemorrhage only 14 Seizures 8	N/A	MRI CT Angiography	Supratentorial 27 Infratentorial 6	N/A	Isolated 33
13	*Di Rocco et al. 1996.*[31]	Described the surgical treatment and outcomes of patients with CNS cavernomas.	N 22 M 10 F 12	< 15	No family history of CMs Previous hemorrhage 22	Seizures 14 Impaired consciousness 6 Intracranial hypertension 13 Hemiparesis 6 Focal neurological deficits 9 Hemorrhage at DX 17	Mean 3.5 Range 0 to 24	CT Angiography	Supratentorial 19 Infratentorial 3	N/A	Multiple 2 Isolated 20
14	*Giulioni et al. 1994.*[32]	Analyzed the surgical management in pediatric patients with CNS symptomatic cavernous angiomas, treated in a period of 16 years at the	N 18 M 8 F 10	Range .83 to 17	No familial occurrence Brain cancer 1 DVA 1	Headache 1 Seizures 11 Cerebellar deficits 2 Hemiparesis 3 Hemianopsia 1 Paraparesis 1 Expansive lesion 14 Hemorrhage at DX 6	Range 1 to 72	MRI CT Angiography Myelography	Supratentorial 15 Infratentorial 2 (cerebellar) Thoracic subdural-extra medullary space 1	Range 1.5 to 3	Isolated 18

		Neurosurgical Department of Bellaria Hospital in Bologna.									
15	*Mazza et al. 1991.*[39]	Described pediatric cases of cavernous malformations seen at their institution.	N 17 M 9 F 8	Range 18 to 16	Family History of CMs 4	Hemorrhage only 12 Epilepsy only 2 Epilepsy plus hemorrhage 2 Expansive lesion 1 Asymptomatic 5	N/A	MRI CT Angiography	Supratentorial 11 Infratentorial 6	N/A	Multiple 2 Isolated 15
16	*Zimmerman et al. 1991.*[45]	Follow the surgical versus conservative treatment for brainstem CMs.	N 2/16 F 2	14 and 7	N/A	Nausea Vomiting Weakness Left hemiparesis Hemiatrophy Headache Diplopia deconjugate gaze	30 and 84	MRI CT Angiography	Upper spine Brainstem	N/A	N/A

Abbreviations

AVM: Arteriovenous Malformation
CC: cerebral cavernomas
CCM: cerebral cavernous malformations
CN: cranial nerve
CNS: central nervous system
CT: computed tomography
DX: Diagnosis
F: Female
GKRS: gamma knife radiosurgery
HTN: Hypertension

ICH: Intracerebral hemorrhage
MRI: magnetic resonance imaging
N/A: Data is not available
SD: Standard deviation
US: Ultrasound

Table 2. Management and neurological outcome of non-comparative retrospective studies included in the systematic review.

#	*Author. Year.*	Study Aim	Patient Info	Management	Immediate Outcome Post-surgery: Complications?	Last Follow-up in months	Neurological Outcome at Last Follow-Up	Conclusions	Recommendation
1	*Jaman et al. 2023.*[35]	To classify and characterize differences in the clinical presentation, characteristics, and outcomes of CCMs between familial and sporadic cases within the pediatric population.	N 131 M 71 F 60	Surgery 33 Conservative 98	Surgery patients demonstrated overall better trends in symptom resolution	Mean 46.9	Seizures 14 Generalized 35 Asymptomatic 55 CN deficits 3 Motor deficits 1 Developmental deficits 3 Syncope 2	Familial and sporadic CCMs tend to present with similar characteristics within the pediatric population. Patients with the familial form of the disease have an increased risk of progressive disease in terms of further hemorrhagic events.	This study suggests that patients with familial disease or large lesions should be monitored more closely to identify recurrent or symptomatic hemorrhage that may lead to a recommendation for resection.
2	*Samanci et al. 2022.*[42]	Reported management of pediatric CCMs with GKRS.	N 46 M 27 F 19	Gamma Knife Radiosurgery	Re(hemorrhage) 2	Median 79 Range 19 to 175	Improved seizure control 11 Favorable outcome (Engel class I and II) 8 Engel class III 3 No Improvements (Engel class IV) 2	Low annual hemorrhage rate following GKRS with no radiation-induced toxicity makes GKRS a therapeutic alternative for pediatric CCMs.	This study revealed that the ARH remains low even 6 years following GKRS. No adverse radiation events were observed. Regarding these results, GKRS might be a treatment alternative for pediatric CCMs.

3	*Santos et al. 2022.*[86] *Cross-Sectional Study*	Investigated the course of cerebral cavernous malformations (CCM) in the pediatric population, with emphasis on the risk of first and recurrent bleeding over a 5-year period.	N 129 M 73 F 56	Surgery 48 Conservative 81 (11 required surgery)	Hemorrhage 17 (11 requiring surgery)	Mean (SD) Surgery 22.9 (26.48) Conservative 39.6 (23.21)	The risk of (re)hemorrhage per year per patient during the maximum available follow-up in all patients was 4.1% for the entire cohort, 8.1% for patients with ICH, 7.1% for patients with BSCM, 6.2% for patients with a familial accumulation of CCM, 4.8% for patients with multiple CCM, and 0.4% for asymptomatic patients. Additionally, participants with DVA had a risk of 3.6%, and patients with CCM-related epilepsy were 4.2%.	Pediatric patients with BSCM, ICH at diagnosis, and familial history of CCM are prone to develop (re)bleeding. During untreated 5-year follow-up, pediatric and adult patients carry an equal susceptibility for (re)hemorrhage. The probability of ICH tends to increase over time, particularly in cases with ICH at presentation or brain stem localization.	Prospective multicenter studies are needed to validate our assumptions and to examine new predictors of patient outcome.
4	*Prolo et al. 2020.*[41]	Studied the clinical course and recurrence rate following surgery for a cohort of CMs in children.	N 53 M 32 F 21	Surgical Resection	No. of Operations Two operations 4 Three operations 3	Median 67.8	Dead 1 Infection 1 CSF leak 2 Pseudo-meningocele 1 Right thalamic/internal capsule venous infarct 1	Pediatric patients presenting with CMs requiring surgical intervention have differential future risks of requiring subsequent surgery based on the number of lesions present on initial imaging and the	Postoperative patients are considered low risk for requiring subsequent surgery if they present with a single CM on initial MRI and without acute hemorrhage. Postoperative patients are considered medium risk if they present with either

					Four operations 2 Six operations 1 Subtotal resection 13 Revision Reason Original CMs 8 Remnant CMs 6 De Novo CMs 5 Recurrence CMs 2			presence of acute hemorrhage.	multiple CMs or acute hemorrhage. Postoperative patients are considered high risk for requiring additional surgeries in the future if they present with multiple CMs and acute hemorrhage on initial imaging.
5	*Knerlich-Lukoschus et al. 2015.*[36]	Described the characteristic clinical, radiological, and surgical features of CCM in children.	N 5 M 4 F 1	Surgery Suboccipital craniotomy approach	No mortality No deficits No seizures Growing remnant 1	Mean (SD) 28.4 (15.23 Range 10 to 72	Excellent 4 Good 1	Cerebellar CMs occur in all pediatric age groups and display characteristic clinical and imaging features. In children, CCMs reach large sizes and can result in massive hemorrhage, often leading to a possible diagnosis of hemorrhage into a tumor. An associated DVA is quite common.	Cerebellar CM should be considered when the MRI characteristics suggest hemorrhage of varying age and the coexistence of a DVA. Surgery is a safe treatment option providing excellent clinical outcome in pediatric patients who are treated in a timely fashion.

								Surgery is a safe and efficient treatment option with excellent outcomes in patients.	Subtotal resection should prompt ongoing clinical and imaging monitoring, as growth of residual CCM with repeat hemorrhage is possible.
6	*Noh et al. 2014.*[40]	Investigated the clinical course of pediatric CMs treated with resection using neuronavigational systems, intraoperative neuromonitoring, and TTRS.	N 29 M 18 F 11	Surgery Craniotomy and lesionectomy Transparent tubular retraction system 7	Complete resection 26 Deep Seated CMs 2 Subtotal resection 1 Mild disabilities 2 Transient weakness or sensory changes recovered completely 3	Mean 27 Range 1 to 96	Seizures 3 Mild weakness 1 No signs or Symptoms 25	Based on the satisfactory seizure outcome achieved, complete microsurgical excision in children is recommended for CMs presenting with seizures but removal of hemosiderin-stained areas seems to be unnecessary.	For a symptomatic solitary CM, the treatment of choice is complete microsurgical excision preceded by careful anatomical and functional evaluation. If the lesion is located in the eloquent area, surgical intervention may be very challenging for surgeons.
7	*Li et al. 2014.*[21]	Investigated the appearance of untreated pediatric brainstem cavernous	N 85 M 59 F 26	Resection 51 Gamma Knife 4 CyberKnife 1	Multiple hemorrhage 6 Hemorrhages 37 (47 episodes)	Mean (SD) 56.43 (80.45) Range 1.20	Improved 33 Stabilized 32 Worsen 20 Complete recovery 22 Independently and mild deficits 41	Hemorrhage rate was relatively high in pediatric brainstem CMs, although the functional outcome was acceptable. The decline in hemorrhage risk and the identified adverse	Recommended conservative management for pediatric patients who did not have severe neurological deterioration with only a single hemorrhage or had small

		malformations (CMs) and identified the hemorrhagic risks and functional outcomes.				to 348.23	Dependent and moderate to severe disability 22 Deficits 63	predictors in this study are helpful for clinicians and patients when deciding on treatment. Referral bias and the insufficient follow-up period of the study were highlighted as limitations.	(< 1 cm), deeply located, and inaccessible lesions. Surgery was recommended for pediatric patients presenting with a large lesion size (≥ 2 cm) accompanied by significant mass effect, severe or progressive neurological dysfunction, or exophytic lesions or lesions abutting the pial membrane, which is accessible via safe entry zones, occasionally even if patients had only a single hemorrhage. A multiple hemorrhage event was an important surgical indication.
8	*Hugelshofer et al. 2011.*[34]	Compared the outcomes with respect to the location of lesions in children who preoperatively suffered from epileptic seizures.	N 79 M 41 F 38	Surgery Lesionectomy	Recurrent Hemorrhage 2	Mean (SD) 36.1 (31.1) Range 1 to 192	Seizure free 26 Rare seizure 4 Worthwhile improvement 3 No Worthwhile improvement 3 Hemorrhage at DX Unchanged 9	Found favorable outcome for surgically treated children with symptomatic CCMs.	Recommended that resection should be the gold-standard therapy for patients with lesions that do not cause an excessive surgical risk such as localization in a highly eloquent area.

							Improved Hemorrhage symptoms 6 Worsen 1		
9	*Consales et al. 2010.*[30]	Report on CCs prospectively followed at the Gaslini Children's Hospital, Genoa, Italy and compare with literature data to better define surgical indications and strategies in the management of children with CCs.	N 32 M 17 F 15	Surgery 28 Craniotomy Conservative 4	New transient neurological deficit 2 Intense headache 1 Hematoma 1	Mean (SD) 53.15 (34.8) Median 48 Range 12 to 132	Surgery Patients Good condition and no focal neurological deficits 22 Same as pre-surgical deficit (left hemiparesis) 1 Seizure-free without antiepileptic 4 Conservative patients Persisted seizures despite polytherapy 1 Asymptomatic 3	Data confirmed the high risk of macrohemorrhage in children with CCs. In general, recommended surgical treatment in most surgically accessible CCs, whereas an accurate monitoring policy can be proposed for small, asymptomatic, deep-located lesions or for minute, punctuate lesions, without signs of bleeding.	Additional studies on larger series are needed to better delineate the natural history of CCs in pediatric age.
10	*Acciarri et al. 2009.*[25]	Described the main clinico-diagnostic features, risk factors and associated diseases of	N 42 M 21 F 21	Surgery	Unchanged 10	Mean (SD) 53.80 (38.88) Median 48	Excellent 9 Good 20 Fair 10 Poor 3	Surgical treatment produced excellent or good results in 69% of our 42 children. Unchanged neurological deficits were observed in 23.8% of cases, while morbidity from	Symptomatic patients who are operated on early, before they develop severe neurological deficits or long-standing seizures, may achieve the best clinical outcome. Radiosurgery does not

		cavernous malformations (CMs) focusing on the management of pediatric patients harboring cranial and spinal CMs.				Range 12 to 192		surgical procedures was 7.14%.	seem to be advisable in children as an alternative treatment for deep CMs or those causing epilepsy.
11	*Alexiou et al. 2009.*[26]	Analyzed a series of patients surgically treated for intracranial cavernomas.	N 16 M 6 F 10	Surgery Complete resection	Revision 2 Hemorrhage 1	Mean 5.9 Range 1 to 17	Seizure free 11 Rare seizures 3 Slight Ataxia 1 Chorea 1	Symptomatic CMs should be treated surgically to minimize the risk of rebleeding. Total resection is associated with patients' clinical improvement and seizure control.	With the improvement of microsurgical techniques and modern neuroimaging, nearly all cavernomas can be safely removed. Total resection is associated with patients' clinical improvement and seizure control.
12	*Lee et al. 2008.*[37]	Focused on the clinical and therapeutic features of intracranial CMs with emphasis on their specificities in	N 33 M 18 F 15	Microsurgery 25 Radiosurgery 8	Microsurgery Transient dysphasia 1 Remnant lesions 2 Radiosurgery Rebleeding 1	Mean (SD) 69.59 (45.6) Range 24 to 204	Dead 1 Complete recovery 29 Seizure free 16 Antiepileptics continued use 3	Our results suggest that pediatric patients with symptomatic CMs should be treated surgically because of the risk of recurrent hemorrhaging and general benefits of CM removal.	In our series, the microsurgical removal of CMs prevented recurrent hemorrhage and controlled seizure disorders in all cases.

		the pediatric age group.							
13	*Di Rocco et al. 1996.*[31]	Described the surgical treatment and outcomes of patients with CNS cavernomas.	N 22 M 10 F 12	Surgery Craniotomies	Hydrocephalus and CSF shunt 2 Persistence of pre-surgical neurological signs 4 Transient dysphagia 1	Mean 53.9 Range 6 to 168	Dead 1 No neurological deficit 14 Unchanged or partially ameliorated 7 Seizure and drug free 9 Seizure free with drugs 5	The removal of cavernomas was always able to control the seizure disorders of our patients, proving that in these cases lesionectomy alone may be sufficient to resolve epilepsy.	In our experience surgery was very effective, with a relatively low surgical risk.
14	*Giulioni et al. 1994.* [32]	Analyzed the surgical management in pediatric patients with CNS symptomatic cavernous angiomas, treated in a period of 16 years at the Neurosurgical Department of Bellaria Hospital in Bologna.	N 18 M 8 F 10	Surgery Microsurgery Open Guided Surgery	All the 18 patients had an uneventful postoperative course	Mean 84 Range 1 to 192	Seizure control 11 Seizure and drug free 1 Seizure free with decrease drug 1 Seizure-free with the same preoperative therapy 8 Focal neurologic deficits 5 (Unchanged 3, Improvement 2)	In conclusion, it's our opinion that all accessible, symptomatic CNS cavernomas have to be treated surgically; asymptomatic lesions, especially those in critical areas, might be periodically controlled on MRI--surgery being considered only for those causing a clinical change.	The surgical management in epileptic patients may be considered not only for intractable or longstanding seizures, but also to prevent the following risks: Spreading and autonomization of the epileptogenic area; Gross hemorrhage; Lesion growth.

15	*Mazza et al. 1991.*[39]	Described pediatric cases of cavernous malformations seen at their institution.	N 17 M 9 F 8	Radical surgery 15 Conservative 2	There was no surgical mortality and results were considered excellent in 11 cases.	N/A	No surgical mortality Excellent 11 Hemiparesis 2 Handicapped 1 Unchanged 1	Concluded from their study that cavernous malformations have to be considered a relatizy frequent pathological lesion in the pediatric age-group with tendency to hemorrhage, but easily diagnosed with modern neuroradiological equipment; and that most cases can be treated surgically, with excellent results in a high percentage of cases.	MRI offers the most conclusive means of diagnosis and, considering the possibility of family predispositions, this is also the method to be used in screening a patient's family members. The operation is easy, at least for the most frequent location, and is justified in view of the risk of hemorrhage and relapses.
16	*Zimmerman et al. 1991.*[45]	Follow the surgical versus conservative treatment for brainstem CMs.	N 2/16 F 2	Surgery	Both required revision	Range 3 to 60	Stable hemiparesis Transient CN VII weakness Lateral gaze paresis Transient quadriparesis	However, the 24 patients reported here present a unique subset of cavernous malformation pathology that suggests progressive neurological deterioration once the lesions become symptomatic.	Superficial symptomatic cavernous malformations of the brain stem can be removed safely with careful planning and microsurgical technique. This option is important because symptomatic cavernous malformations of the brain stem probably have a worse prognosis than asymptomatic ones in other locations.

Abbreviations

ARH: Annual Re-hemorrhage

BCSM: brainstem cavernous malformation
CC: cerebral cavernomas
CCM: cerebral cavernous malformations
CM: cavernous malformations
CN: cranial nerve
CNS: central nervous system
CSF: Cerebrospinal Fluid
CT: computed tomography
DVA: developmental venous anomaly
F: Female
GKRS: gamma knife radiosurgery
M: Male
MRI: magnetic resonance imaging
N/A: Not applicable
SD: Standard deviation

Table 3. Demographics and patient characteristics of retrospective studies comparing surgical versus conservative management in pediatric cavernomas.

#	*Author. Year.*	Study Aim	Patient Info	Age in years	Family History or Medical History	Presenting Signs and Symptoms	Time from Symptoms to Management	Diagnostic Modality	Location of Cavernoma	Size of Lesion in cm	Isolated vs. Multiple
1	*Velz et al. 2022.*[43]	Evaluated the clinical behavior of BSCMs in childhood and the long-term outcome in children managed conservatively and surgically.	N 40 M 27 F 13	Mean (SD) 11.4 (5.4) Range 1.4 to 19.4	Familial CMs 14 Brain cancer 2 DVA 19	Sensory deficits 20 Motor deficits 21 Gait ataxia 24 CN palsy 25 CN I–XII 46 Speech disturbance 3 Dysphagia 8 Respiratory disturbance 2 Nystagmus 7 Internuclear ophthalmoplegia 3 Increased intracranial pressure 3 Vertigo 18 Hydrocephalus 3 Decreased level of consciousness 4 Seizures 6 Incidental 9	N/A	MRI	Supratentorial superficial 34 Supratentorial deep 13 Brainstem 10 Cerebellum 7	Mean 1.06 Range 0.2 to 2.9	Multiple 15 (Multiple BSCMs 8) Isolated 25 No. of BSCMs 76

2	*Hirschmann et al. 2022.*[33]	Provided a treatment algorithm for pediatric patients with intracranial cavernous malformations (CMs).	N 61 M 34 F 27	Surgery Median 7 Range 1 to 17 Conservative Median 13 Range 1 to 17	Familial CMs 16	Seizures 24 Headache 19 Hemiparesis 10 Other neurological deficits (CN palsy, gait disorder, vertigo, and reduced state of consciousness) 23 Asymptomatic 6 Incidental 5 Hemorrhage at DX 38	Median .56 Range .03 to 38.82	MRI CT Diffusion tensor imaging Functional MRI	Supratentorial 45 Infratentorial 16	Surgical Median2.4 Range 0.7 to 5.8 Conservative Medias 0.9 Range 0.5 to 2.6	Multiple 23 Isolated 38
3	*Bilginer et al. 2014.*[29]	Retrospectively analyzed demographic, clinical, radiological, management, and follow-up data of pediatric patients with CMs from a single institution	N 36 M 21 F 15	Mean (SD) 8.7 (5.7) Range .75 to 17	Family History of CMs 7 DVA 7	Seizure 14 Neurological deficits (headache, intracranial hypertension signs, and/or neurological deficits) 8 Focal neurological deficits 15 Intracranial hypertension (headache, nausea and vomiting, altered mental status, diplopia) 11 Quadriparesis 1 Acute/subacute hemorrhage (or intracerebral hematoma) 23	Range .06 to 48 Median .80	MRI CT	Supratentorial 26 Infratentorial 5 Infra and Supratentorial 4 Supratentorial and spinal 1	Largest 4x2.2x1.5 CMs (≥2.5) 15	Multiple 10 Isolated 26

						Intraventricular hemorrhage 1 Transient lower extremity monoparesis and ataxia 1					
4	*Amato et al. 2013.*[27]	Evaluate clinical and surgical data in a single-centered pediatric series of CMs.	N 30 M 18 F 12	Mean 8.7 Range .5 to 17	Family History of CMs 5	Seizures 16 Headaches 15 Focal neurological deficits 11 Behavior disturbance 1 Acute intracranial hemorrhage 16	N/A	MRI CT	Supratentorial 23 Infratentorial 7	N/A	Multiple 5 Isolated 25
5	*Gross et al. 2013.*[7]	Reviewed data obtained in a large cohort of children with lobar CMs, comparing those selected for surgery with those managed nonoperatively.	N 181 Surgery M 42 F 41 Observed M 59 F 39	Surgery Mean 11.8 Median 12.1 Range 0.7 to 22 Conservative Mean 9.8	Family History of CMs 35 Prior radiation 21 DVA 24	Asymptomatic 64 Hemorrhagic lesions 77 Seizure 68 Headaches 33 Focal neurological deficits 10 Asymptomatic 3	N/A	MRI	Frontal 87 Temporal 41 Parietal 34 Occipital 19 Eloquent cortex (motor, sensory, speech, or calcarine cortex) 45	Surgery Mean 2.2 Conservative Mean 1	No. of CMs 238
6	*Gross et al. 2013.*[8]	Studied children who had undergone	N 11 M 7 F 4	Mean (SD) 9.3 (5.5)	Family History of CMs 2	Hemorrhage 8 Incidental 2 Seizures 1	N/A	MRI	Putamen 7 Caudate 4	Mean (SD): 1.83 (1.21)	N/A

		surgery or conservative treatment for this cerebral vascular malformation.		Range 1 to 15	Prior radiation 1	Choreiform movements 2 Hemiparesis 2				Median 1.7	
7	*Bigi et al. 2011.*[10]	Describe the clinical presentation, neuroimaging, treatment, and outcome in children with CM in the central nervous system (CNS) and discuss the value of newer neuroimaging techniques.	N 20 M 7 F 13	Mean 8.5 Range .58 to 16	No Family History of CMs	Seizure 9 Headache 3 Hemiparesis 3 Paraparesis 1 Acute Blindness 1 Incidental Findings 3 Focal Symptoms 5	N/A	MRI CT EEG	Supratentorial 15 Infratentorial 2 Supra and infratentorial 2 Spinal 1	Large (> 2 to < 6) 11 Small (<2) 9	Multiple 5 Isolated 15 No. of CM Range 1 to 46
8	*Xia et al. 2009.*[44]	Investigate the clinical features and treatment outcome of pediatric cavernous malformation (CM) in the central	N 66 M 40 F 26	Mean 11.6 Range 1.25 to 17.8	Family history of CMs 1 Prior radiation 4	Seizures 31 Headache 30 Intracranial hemorrhage 13 Focal neurological deficits 8 Behavioral abnormality 2	N/A	MRI CT digital substract angiography	Supratentorial 55 Infratentorial 6 supra- and infratentorial 4 Spinal 1	Mean 1.9 Range 0.5 to 5.0	Multiple 7 Isolated 59 No. of CM Range 1 to 5

		nervous system.				Accidental discovery without symptoms 2 Paraplegia 1 Asymptomatic 2					
9	*Bhardwaj et al. 2009.*[28]	Reviewed experience with the management of pediatric brainstem CMs at the Hospital for Sick Children.	N 20 M 13 F 7	Mean (SD) 10.1 (5.4) Range .03 to 17	Family history of CMs 3 Prior radiation 7 DVA 2	Failure to thrive 2 Headache 5 Dysphagia 1 Hemiparesis 3 Hemisensory loss 1 CN deficits 4 Diplopia 6 Ataxia 4 Irritability and hydrocephalus 1 Coma 1 Asymptomatic 7	N/A	MRI	Midbrains 4 Pontine 13 Medullary 3	Mean (SD): 1.43 (1.12)	Multiple 9 Isolated 11

Abbreviations

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CC: cerebral cavernomas
CCM: cerebral cavernous malformations
CM: cavernous malformations
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CNS: central nervous system
CT: computed tomography
DVA: developmental venous anomaly
F: Female
GKRS: gamma knife radiosurgery
M: Male
MRI: magnetic resonance imaging

N/A: Not applicable
SD: Standard deviation

Table 4. Management and neurological outcomes of retrospective studies comparing surgical versus conservative management in pediatric cavernomas.

#	*Author. . Year.*	Study Aim	Patient Info	Management	Immediate Outcome Post-surgery: Complications?	Last Follow-up in months	Neurological Outcome at Last Follow-up	Conclusions	Recommendation
1	*Velz et al. 2022.*[43]	Evaluated the clinical behavior of BSCMs in childhood and the long-term outcome in children managed conservatively and surgically.	N 40 M 27 F 13	Surgery 17 Conservative 23	Worsen 3 Single hemorrhage 20 Multiple hemorrhages 13 No hemorrhage 7 Incomplete resection 4 Revision 3	Mean (SD) 88 (92.6)	None or only minor neurological deficits 22 Severe neurological deficits 18 Favorable outcome 36 Unfavorable outcomes 4	Given the greater life expectancy and the known higher functional recovery in children, surgical treatment should be considered early in young patients presenting with surgically accessible lesions and an aggressive clinical course, and it should be performed in a high-volume center.	Maximizing functional outcome for children is necessary. Individual plans should be completed for each case of cavernous malformation.
2	*Hirschmann et al. 2022.*[33]	Provided a treatment algorithm for pediatric patients with intracranial cavernous malformations (CMs).	N 61 M 34 F 27	Surgery 42 Conservative 19	Complications 4 Subgaleal pseudomeningocele 1 Epidural hematoma 1 Subdural hematoma 1 Worsen 1 Recurrence CMs 5	Median 65 Range 1 to 356	Surgery Favorable outcome 32 Unfavorable outcomes 2 Conservative Favorable outcome 18	Proposed a treatment algorithm according to lesion location and size, burden of symptoms, epilepsy workup, and further clinical course during observation.	Conservative management is safe in pediatric patients with asymptomatic CMs. Gross total resection should be the aim in patients with symptomatic lobar CMs. A less aggressive approach

					New CMs 3 One revision 34 Two revisions 6 Three revisions 1 Six revisions 1		Hemorrhage 34 Seizure free 14		with subtotal resection, when required to prevent neurological compromise, sustainably improves neurological outcome in patients with deep CMs.
3	*Bilginer et al. 2014.*[29]	Retrospectively analyze demographic, clinical, radiological, management, and follow-up data of pediatric patients with CMs from a single institution	N 36 M 21 F 15	Surgery 31 Conservative 5	No deficits 23 Improved 5 Unchanged 6 Worsen 1 N/A 1	Mean (SD) 82.79 (6.9)	Excellent (GOS 5) 24 Good (GOS 4) 10 Fair (GOS 3) 2 Rare seizures 2	While cavernous malformations that are asymptomatic, small in size, and located in eloquent areas can be followed conservatively, microsurgical resection should be the choice of treatment in symptomatic and accessible CMs. Intraoperative guidance of neuronavigation and ultrasonography could aid the accurate excision of the lesions.	Younger children tend to harbor larger CMs and present with hemorrhage more frequently than older ones. Microsurgical resection should be the treatment of choice in symptomatic and accessible CMs.
4	*Amato et al. 2013.*[27]	Evaluate clinical and surgical data in a single-centered pediatric series of CMs.	N 30 M 18 F 12	Surgery 26 Conservative 4	No postoperative deaths or significant complications Recurrence 1 Revision 1	Mean 49.19 Range 6 to 156	No deficits 13 Seizure free 14 Epilepsy 1 Permanent monopoiesis 1 Transit CN VI palsy 1	For symptomatic solitary cavernous malformation, the treatment of choice is complete microsurgical excision preceded by careful anatomical and functional evaluation. For multiple cavernous malformation or	Extended surgery associated with CM lesionectomy for long-term epilepsy or high frequency of seizures should be considered after proper investigation

								asymptomatic patients, the treatment modalities must be cautiously considered.	and failure of drug therapy. Conservative treatment may be considered for asymptomatic patients, multiple CMs, critical lesion location (brainstem, thalamus, and basal nuclei) and in cases of small lesions that are not associated with hemorrhage.
5	*Gross et al. 2013.*[7]	Reviewed data obtained in a large cohort of children with lobar CMs, comparing those selected for surgery with those managed nonoperatively.	N 181 Surgery M 42 F 41 Observed M 59 F 39	Surgery 83 Conservative 98	Complete resection 81 Remnant CMs 2 Hemorrhage 1 Recurrence 1	Mean 55.19 Median 32.4 Range 1.2 to 267.59	Left upper-extremity paresis and medically controlled seizures 1 De Novo seizures 1 Seizure-free 46 New or worsening neurological deficits 6 Permanent complication 4	The resection of symptomatic supratentorial lobar CMs is a safe and effective procedure with high complete resection rates, rewarding long-term seizure outcomes, and low complication rates. Asymptomatic lesions or those in eloquent cortex may be better candidates for observation, although individualized assessment of risks and benefits remains critical.	Pediatric patients with symptomatic supratentorial lobar CMs are ideal candidates for surgery, for which there are high complete resection rates, rewarding long-term seizure outcomes, and low operative morbidity. Observation may be warranted in smaller asymptomatic lesions located within eloquent cortex.

6	*Gross et al. 2013.*[8]	Studied children who had undergone surgery or conservative treatment for this cerebral vascular malformation.	N 11 M 7 F 4	Surgery 6 Conservative 5	Transient hemiparesis 2 Permeant hemiparesis 1 Transient speech deficits 1	Mean (SD) 88.31(54.59) Median 92.39	No new or worsening neurological deficits No hemorrhage or delayed morbidity	The children with large (> 1.5 cm) symptomatic lesions underwent excision; neurological impairment was apparently minimal, and no hemorrhage or neurological deterioration occurred later.	In this patient population, the natural history of small and asymptomatic CMs of the basal ganglia was benign.
7	*Bigi et al. 2011.*[10]	Describe the clinical presentation, neuroimaging findings, treatment, and outcome in children with CM in the central nervous system (CNS) and discuss the value of newer neuroimagin	N 20 M 7 F 13	Microsurgical resections 10 Conservative 10	Revision 1 Expanding CMs 2	Mean 48 Range 6 to 120	Neurological sequelae 6 Underwent surgery 2 No deficits 11	Microsurgical resection appears to be a safe intervention that should be the first choice in cases of symptomatic CM. Newer MRI techniques such as SWI re able to detect even small lesions and define their real extent.	The regular application of newer neuroimaging techniques such as susceptibility weighted imaging will detect more lesions but not necessarily resolve problems concerning optimum treatment.

		g techniques.							
8	*Xia et al. 2009.*[44]	Investigate the clinical features and treatment outcome of pediatric cavernous malformation (CM) in the central nervous system.	N 66 M 40 F 26	Microsurgery 62 Conservative 4	Complications 3 Remnant CMs 6 Revision 2	Mean 39.1 Range 5 to 112	Free of Symptoms 34 Improvement 9 No change 1 Worsen 2 Lost to follow up 16 Conservative Spontaneous symptom resolution 3 Stable lesion 1	For symptomatic solitary CM, the treatment of choice is complete microsurgical excision preceded by careful anatomical and functional evaluation, and the risk of operation can be decreased to lower level with the help of neuronavigation and intraoperative ultrasonography. For multiple CM, the treatment modalities must be considered cautiously. A much longer follow-up remains mandatory for appropriate treatment strategies.	The first treatment of choice is complete microsurgical excision preceded by careful anatomical and functional evaluation, and the risk of operation can be decreased to a lower level with the help of neuronavigation and intraoperative ultrasonography.
9	*Bhardwaj et al. 2009.*[28]	Reviewed experience with the management of pediatric brainstem CMs at the Hospital for Sick Children.	N 20 M 13 F 7	Surgery 7 Conservative 13	No. of Events CSF leak 3 Strabismus repair 2 Facial paralysis repair 1 Partial resection 1 Could not locate lesion 1 Hemiparesis 1 Dysmetria 1	Follow-ups until they reached the age of 18 years	Dead (medulloblastoma) 1 All improved	Larger brainstem CMs with pial contact that are diagnosed in younger, symptomatic patients are more likely to be managed surgically. Neither prior radiation treatment nor CM multiplicity influenced management toward surgery. Conservative management was associated with new deficits	The majority of patients received conservative management and tended to be asymptomatic with smaller lesions. Patients with larger lesions and direct pial contact, in whom symptoms arose at a younger age were

								arising in children, some of which improved with time.	more likely to undergo surgical management. A history of familial CM was also a predictor for receiving surgical treatment.

Abbreviations

BCSM: brainstem cavernous malformations
CC: cerebral cavernomas
CCM: cerebral cavernous malformations
CN: cranial nerve
CNS: central nervous system
CT: computed tomography
GKRS: gamma knife radiosurgery
GOS: Glasgow Outcome Scale
MRI: magnetic resonance imaging

Pediatr Stroke. 2025;11: 1-50
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