Florez-Perdomo *et al.*
Egyptian Journal of Neurosurgery (2024) 39:46
https://doi.org/10.1186/s41984-024-00307-3

Egyptian Journal of Neurosurgery

REVIEW

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Gamma knife radio surgery for cerebral arteriovenous malformation (AVM) in children: a systematic review and meta-analysis of clinical outcomes

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Abstract

This article aims to evaluate the safety and effectiveness of Gamma Knife radiosurgery as a treatment modality for pediatric cerebral arteriovenous malformations (AVMs) by assessing mortality rates, the rate of complete AVM obliteration, and the incidence of complications while exploring potential risk factors. A comprehensive search was conducted through multiple databases to identify relevant studies, including randomized controlled trials and observational studies. The studies were assessed for risk of bias using the ROBINS-I tool and methodological quality with the Newcastle–Ottawa Scale. Data on mortality, AVM obliteration rates, and complications were systematically extracted. Pooled rate analysis was performed to assess outcomes, and heterogeneity was evaluated. The analysis included 21 studies involving 2142 pediatric patients with cerebral AVMs. A low mortality rate of 0.75% (95% CI 0.09% to 2.71%) and a high rate of complete obliteration of AVMs was observed, with a rate of 71.64% (95% CI 65.716% to 77.211%). Complications, including new neurological deficits, post-radiosurgery intracranial hemorrhage, and other complications (such as seizures and radiation-related issues), were relatively low, with rates of 2.57%, 2.463%, and 4.784%, respectively. Gamma Knife radiosurgery demonstrates its potential as a safe and effective treatment option for pediatric cerebral AVMs. The low mortality rate and high rate of AVM obliteration suggest that this approach offers significant benefits. While some complications were observed, they were generally non-severe. However, further high-quality studies with extended follow-up periods are needed to better understand long-term efficacy and safety.

Keywords Cerebral arteriovenous malformations, Brain radiosurgery, Pediatrics, Systematic review, Outcome analysis

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Introduction

Cerebral arteriovenous malformations (AVMs) are intricate vascular anomalies of the central nervous system, characterized by a tangle of blood vessels where the arterial system is directly connected to the venous drainage without an interposed capillary network [1]. The underlying mechanisms behind the development of this condition continue to be enigmatic. Traditionally, they have been presumed to be congenital, although substantial empirical backing for this assertion is absent. Plausible explanations could involve errors or communication breakdowns during embryogenesis when arteries and veins come into direct contact without intervening capillaries [2]. Other possible etiologies are underlying genetic abnormalities that produce signaling errors during vascular development or traumatic injuries that disrupt normal vascular architecture and predispose to structural defects during angiogenesis [2, 3].

Although relatively rare, the impact of AVMs on affected individuals, particularly children, is substantial, both in terms of health and quality of life. Non-treated cerebral arteriovenous malformations in this population can increase the risk of cerebral hemorrhage and lead to significant neurological consequences such as cognitive deterioration, headaches, long-term disabilities, and so forth [4–7]. Cerebral AVMs in children present a unique clinical scenario, often requiring distinct diagnostic and therapeutic approaches compared to adults. The developmental stage of the child's brain, the long-term consequences of interventions, and the psychosocial impact on young patients and their families necessitate specialized investigation [5–7].

Over the years, the management of cerebral AVMs has evolved, introducing innovative techniques such as Gamma Knife radiosurgery into the clinical landscape [8–14]. This non-invasive procedure has shown promising results, especially for patients with high surgical risks or residual AVM after endovascular embolization [11, 15–17].

This systematic review and meta-analysis intend to comprehensively explore Gamma Knife radiosurgery as a therapeutic modality for pediatric cerebral AVMs, aiming to assess its safety and effectiveness by examining several clinical outcomes, including mortality, AVM obliteration rates, complications, and risk factors. This study seeks to answer critical questions that influence clinical decision-making. Is Gamma Knife radiosurgery a safe option for children with cerebral AVMs? What are the rates of AVM obliteration and associated complications? The findings of this study offer insights that can shape treatment strategies, inform healthcare practices, and ultimately enhance the lives of young patients grappling with this complex neurological condition.

This article was previously presented as a meeting abstract at the 2023 CNS Annual Scientific Meeting on September 13, 2023.

Methods

The scheme to follow will be in accordance with the recommendations of the meta-analysis and the systematic reviews of the MOOSE checklist for the presentation of the systematic reviews and the meta-analysis of observational studies, and the Cochrane Manual of Systematic Reviews and meta-analysis.

Primary Outcome: mortality and rate of complete obliteration rate at end of follow-up.

Secondary Outcomes: New Neurological deterioration, post-radiosurgery intracranial hemorrhage, and other complications (seizures, related radiation complications. Headache).

The protocol for this systematic review was registered with PROSPERO under registration number CRD42024518120.

Search

A search for RCT, not RCT, prospective and retrospective cohort studies will be carried out through PUBMED; SCOPUS; Central Cochrane Registry of Controlled Trials (The Cochrane Library); MEDLINE (Ovid); EMBASE (Ovid); CINAHL; in addition to the reference list of included studies and other relevant data in addition to potentially eligible studies.

The terms ("radiosurgery" OR "Gamma Knife" OR "stereotactic surgery") AND ("cerebral arteriovenous malformation" OR "brain arteriovenous malformation" OR "intracranial arteriovenous malformation") AND ("Mortality" OR "Death" OR "dead") AND ("Prognosis" OR "morbidity" OR "Complication") AND ("pediatric" OR "Child" OR "Children" OR "adolescent") NOT "Animals" were used to perform the search.

Inclusion criteria

The studies to be included are screened separately using the following inclusion criteria:

Randomized controlled trials (RCTs), quasi-randomized controlled studies, and prospective and retrospective observational studies that used Gamma Knife radiosurgery to treat cerebral Arteriovenous Malformations (AVMs).

The risk of bias assessment

The assessment of bias risk was conducted using the ROBINS-I tool, which appraises seven domains as follows: D1: "Potential for bias arising from confounding"; D2: "Bias related to participant selection"; D3: "Bias in the classification of interventions"; D4: "Potential bias

due to deviations from the intended intervention"; D5: "Bias stemming from missing data"; D6: "Bias associated with outcome measurement"; and D7: "Bias regarding the selection of reported results." This assessment categorizes the risk as "Low," "Moderate," "Serious," "Critical," or "No Information" based on the presence or absence of specific characteristics.

Evaluation of the quality of the studies included

The quality of included studies was through the Newcastle – Ottawa Quality Assessment Scale; studies with scores of 7 were considered of high methodological quality. Those with scores ranging from 5 to 6 were considered moderate quality and 5 or less as low quality.

Extraction, management, and statistical analysis of data

The following data is extracted: mortality, complete occlusion rate at end following, New Neurological deterioration, post-radiosurgery intracranial hemorrhage, and Other complications (seizures, related radiation complications. Headache) The authors of the included studies were contacted due to missing data. The doubts were clarified by consensus. Statistical analysis was performed through Pooled rate with the Mantel–Haenszel methodology for each variable MEDCALC software version 19.2. with a randomized effect analysis model calculated using. Heterogeneity was assessed by calculating Chi-square (I^2), categorized as very high heterogeneity I2 upper than 75%, High heterogeneity with an I2 between 60%-74,9%, Moderate heterogeneity with an I2 50–59.9, Low heterogeneity with an I2 lower than 50%.

Results

We identified 50 bibliographic citations based on the title, abstract, or both, and the full texts; 45 were potentially considered and were selected. After reviewing the complete text, 34 studies were considered eligible, 13 were ruled out because these did not meet the inclusion criteria [18–30], and only 21 met the inclusion criteria for the review [7, 31–50] (Fig. 1). Of the studies included, 17 were retrospective cohort observational studies, and 4 were prospective.

Risk of bias assessment

21 studies were chosen for the final analysis, involving 2142 patients. The risk of bias was evaluated for the different studies chosen using the described methodology, and it was found that in the global evaluation of bias, 85% had a low to moderate risk, which is expected for studies with adequate methodological quality; however, Foy et al. and Tamura et al. present serious overall risk of bias, Amendola et al. and Cohen-Gadol et al. present serious risk in domain 3 (D3) but being of moderate risk in the overall risk analysis, since when evaluating the intervention to be carried out, those who had received previous treatment with microsurgery or radiosurgery were not taken into account, which could influence the analysis, however, having a study protocol, and presenting low to moderate risk in the other domains, does not affect the meta-analysis. The funnel plots that value publication bias for the various clinical outcomes show us a graph with a mild asymmetry for most outcomes. However, Due to high heterogeneity among the included studies, it is possible to overestimate the effect of publication bias.

Quality assessment of included studies

Of the included studies, 6 studies (28.5%) obtained a score of 9/9 on the Newcastle–Ottawa Scale, 4 studies obtained 8 points (19.04%), only one study (Yen et al.) obtained 7 points on this scale (4.7%), 5 studies obtained 6 points, 4 studies obtained 5 points, and only Tamura et al. obtained a score lower than 5. According to this scale, 47.6% of the included studies were of high methodological quality, 47.6% were of moderate methodological quality, and only one study (4.8%) was of poor quality (Table 1). The latter study's protocol did not describe a concomitant disease or if the participant had been intervened by another method. Additionally, the study had a small sample size, and the method of follow-up was not clear.

Meta-analysis of included studies

The mortality rate in children treated with gamma knife surgery for cerebral arteriovenous malformations was 0.725% (95% CI 0.411% to 1,126%; I2 0.00%) (Fig. 2). The success of management through radiosurgery (gamma knife) was assessed by the rate of complete obliteration of the AV malformation, which was 71.64% (95% CI 65.716% to 77.211%; I2 = 88.13%) (Fig. 3) with high heterogeneity (Table 2). The rate of complications, including new neurological deficits, was 2.57% (1.43% to 3.89%; I2 = 66.78%) (Fig. 4). Most of these complications were visual deficits and sensory alterations; no severe motor deficits or vegetative states were reported. The postoperative intracranial bleeding rate was 2.463% (1.348% to 3.9%; I2 = 70.14%) (Fig. 5). Other complications, such as seizures, infectious complications, post-procedure headaches, and radiation-related complications, were reported at a rate of 4.784% (95% CI 3.170% to 6.708%; I2 = 70.5%) (Fig. 6) (Table 3).

Discussion

Cerebral arteriovenous malformations (AVMs) are rare but complex vascular connections without an intervening capillary network [51]. The potential etiology of this condition is believed to be congenital and has been studied

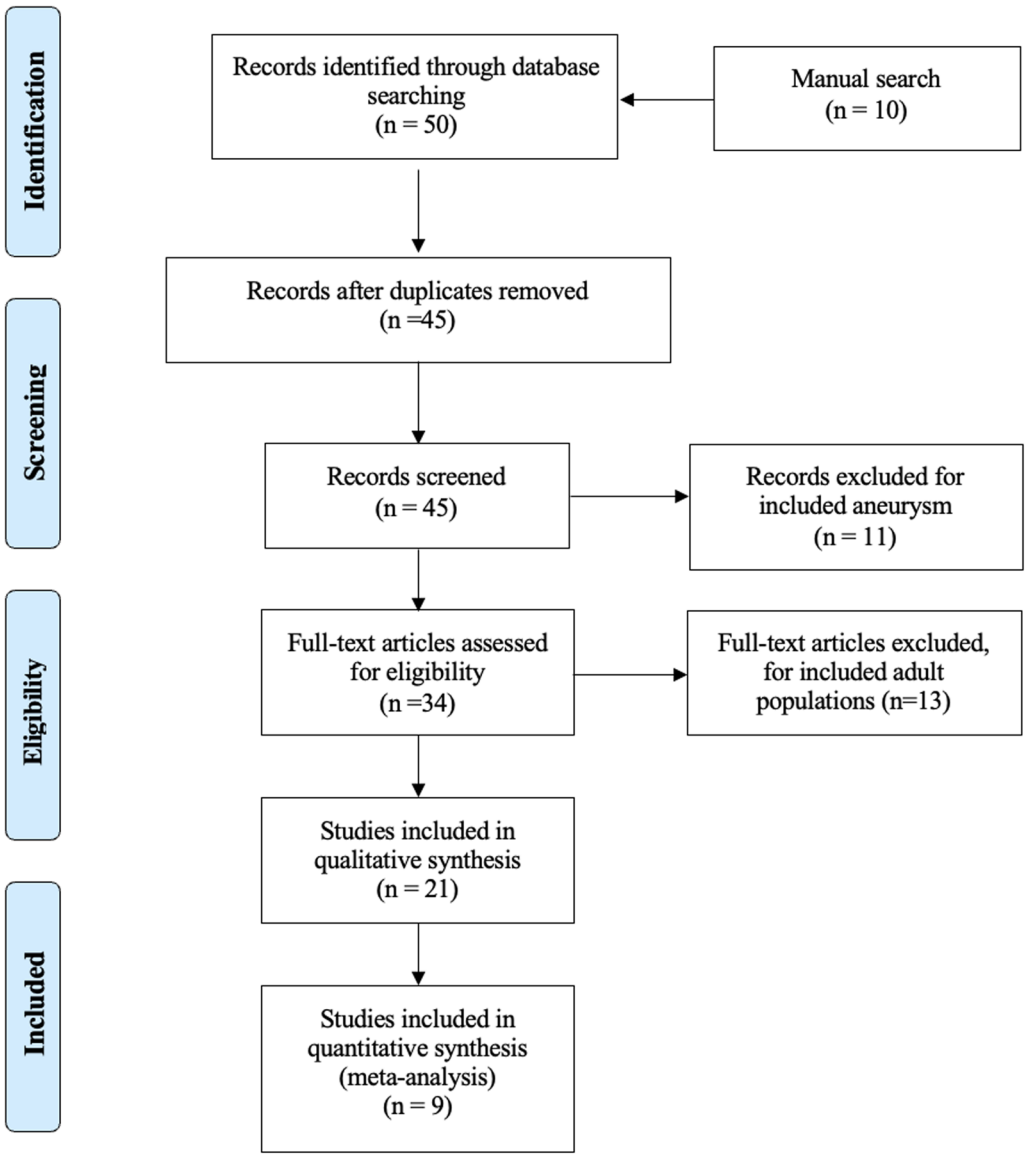

Fig. 1 Process of study selection – Flow chart of our search strategy and inclusion and exclusion criteria

for several years, as this malformation can disrupt blood flow and oxygen circulation and produce several complications, such as intracranial hemorrhage [52].

During normal vascular development, arteries carry oxygenated blood away from the heart and branch into smaller vessels, eventually leading to tiny capillaries where oxygen is exchanged with surrounding tissues. Veins then collect deoxygenated blood and return it to the heart [52]. However, in the case of AVMs, a crucial step is disrupted. Instead of the intricate capillary network connecting arteries to veins, an AVM forms a tangled cluster of blood vessels, bypassing the capillaries. Irregularities in vessel wall thickness, the absence of tight junctions and continuous endothelial lining, and the division of the elastic lamina have been described as cellular and molecular changes within the endothelium of AVMs [52, 53].

Although AVMs are often silent, the most common presentation in the pediatric population is intracerebral hemorrhage, and according to Smith ER et al., 25% of children will die from the initial rupture. Another common clinical presentation in this population is headaches and seizures, with a prevalence of 20% and 12%, respectively [54]. For this reason, it is essential to guide clinical decision-making by balancing the risks

Table 1 Quality assessment of included studies according to the Newcastle–Ottawa Scale

Study	Representativeness of sample	Size sample	Source of information	Demonstration that outcome was not present at study start	Confusion variable control	Assessment of outcome	Enough follow-up period	Newcastle Ottawa scale score
Aoki et al. [31]	★	★	★		★	★	★	6/9
Tanaka et al. [32]	★	★	★	★	★	★		6/9
Amendola et al. [33]	★★		★	★		★		5/9
Cohen-Gadol et al. [34]	★		★	★		★	★	5/9
Nicolato et al. [7]	★★	★★	★	★	★	★	★	9/9
Kiran et al. [35]	★★	★★	★	★	★	★	★	9/9
Pan et al. [36]	★★	★★	★	★	★	★		8/9
Foy et al. [37]	★			★	★	★	★	5/9
Yen et al. [38]	★★	★★	★		★	★		7/9
Yeon et al. [39]	★		★	★	★	★		5/9
Tamura et al. [40]	★		★		★	★		4/9
Borcek et al. [41]	★★	★★	★		★	★	★	8/9
Hanakita et al. [42]	★★	★★	★	★	★		★	8/9
Nicolato et al. [43]	★★	★★	★	★	★		★	8/9
Nerva et al. [44]	★	★	★	★	★		★	6/9
Zeiler et al. 2016 [45]	★	★	★	★	★		★	6/9
Park et al. [46]	★	★	★	★	★		★	6/9
Starke et al. [48]	★★	★★	★	★	★	★	★	9/9
Hasegawa et al. [47]	★★	★★	★	★	★	★	★	9/9
Kim et al. [49]	★★	★★	★	★	★	★	★	9/9
Eliava et al. [50]	★★	★★	★	★	★	★	★	9/9

★ Indicates that it meets criteria in Newcastle–Ottawa Scale 0/9

of treatment approaches and the natural course of this potentially life-threatening condition.

Several therapeutic approaches have been developed within the last decades, and surgical resection has shown significant results, with low rates of postoperative hemorrhage and recurrence [4, 7, 54]. However, new treatment options have been employed in many cases where surgical resection is not feasible, especially for those with inaccessible AVMs or high-risk factors like feeding artery aneurism.

Endovascular embolization is a minimally invasive technique that involves the insertion of a catheter, typically through the groin, into the arteries and navigating it to the AVM site in the brain. Once the catheter reaches the affected area, a special embolic material is injected into the abnormal blood vessels. These embolic materials obstruct the blood flow within the AVM, effectively closing off the tangled vessels [55]. This approach reduces the risk of bleeding, alleviates pressure within the AVM, and is particularly useful when the AVM is in a complex or deep location that is challenging to access surgically. However, it's important to note that endovascular embolization may not always lead to complete AVM obliteration, and multiple sessions may be necessary.

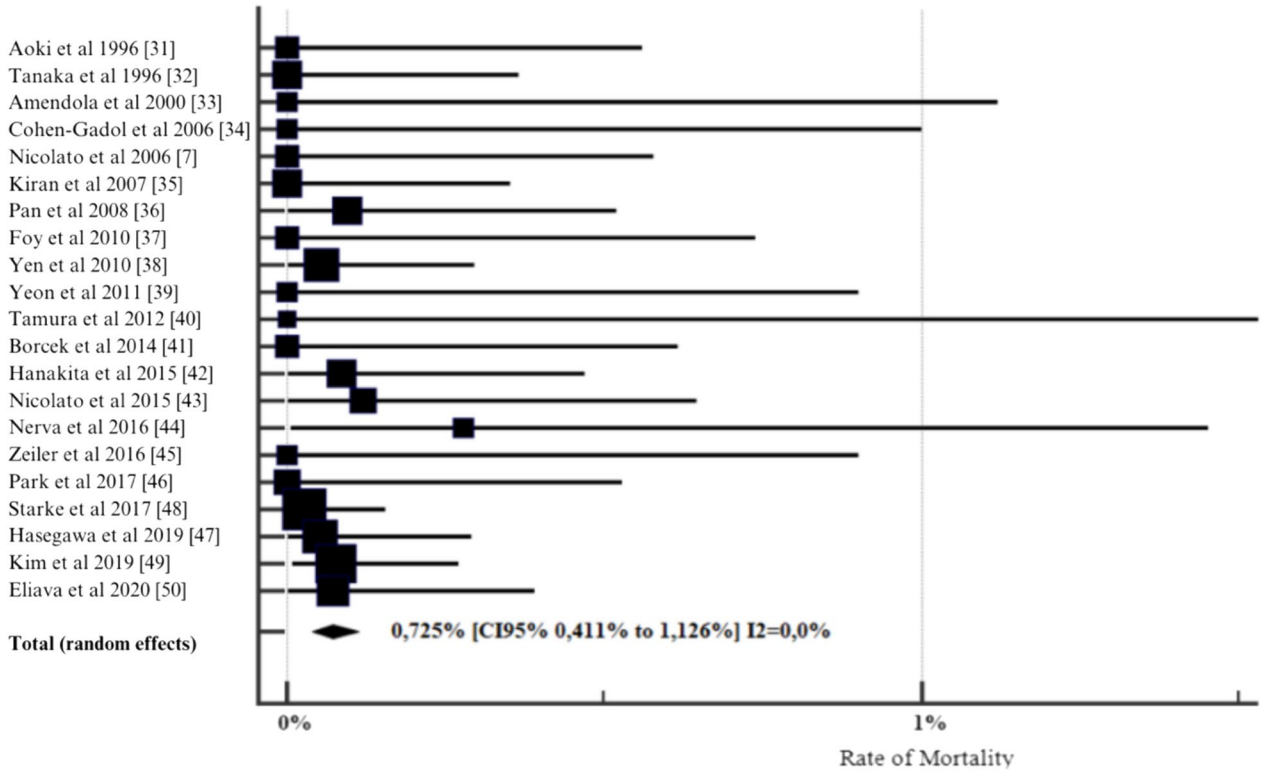

Fig. 2 Meta-analysis for cerebral AVMs treatment primary outcomes: mortality rate

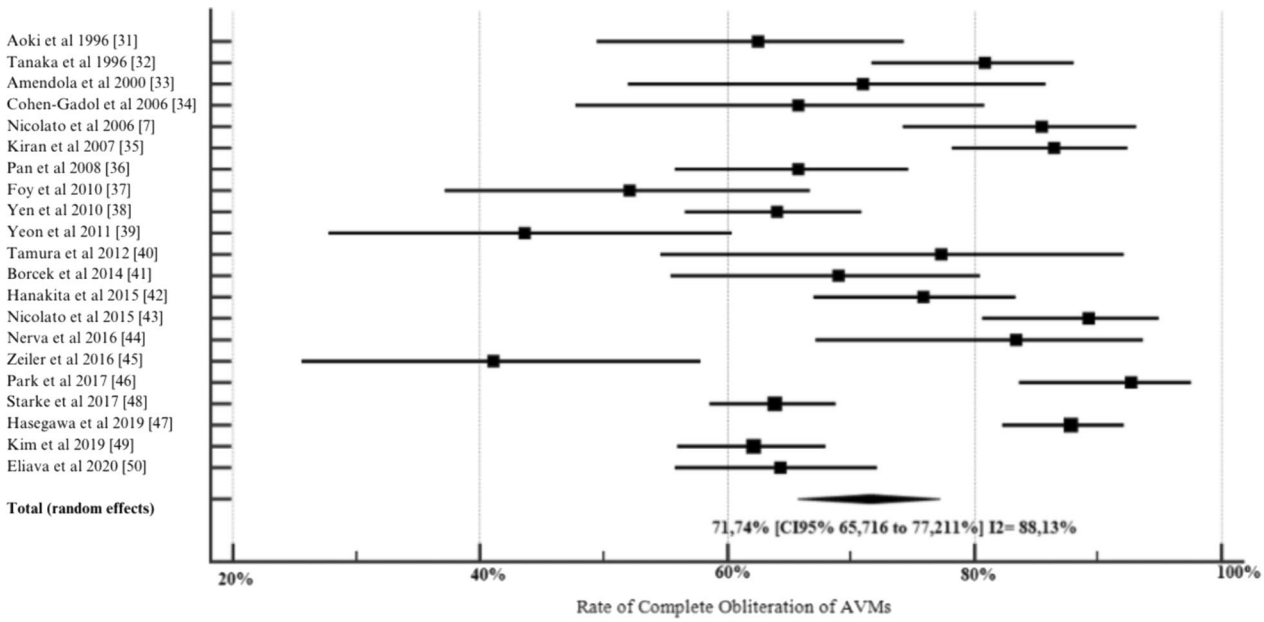

Fig. 3 Meta-analysis for cerebral AVMs treatment primary outcomes: complete obliteration rate

Table 2 Metanalysis: GKS as AVMs in Children Treatment Primary Outcomes: Mortality and Rate of Complete Obliteration OF AVMs

Study	Sample size	Mortality		Rate of complete obliteration OF AVMs	
		Proportion (%)	95% CI	Proportion (%)	95% CI
Aoki et al. [31]	64	0.00	0.00 to 5.60	62.50	49.50 to 74.29
Tanaka et al. [32]	99	0.00	0.00 to 3.65	80.80	71.66 to 88.03
Amendola et al. [33]	31	0.00	0.00 to 11.21	70.96	51.96 to 85.77
Cohen-Gadol et al. [34]	35	0.00	0.00 to 10.00	65.71	47.78 to 80.86
Nicolato et al. [7]	62	0.00	0.00 to 5.77	85.48	74.22 to 93.14
Kiran et al. [43]	103	0.00	0.00 to 3.51	86.40	78.24 to 92.36
Pan et al. [36]	105	0.95	0.02 to 5.19	65.71	55.81 to 74.70
Foy et al. [37]	48	0.00	0.00 to 7.39	52.08	37.18 to 66.71
Yen et al. [38]	186	0.53	0.01 to 2.95	63.97	56.63 to 70.87
Yeon et al. [39]	39	0.00	0.00 to 9.02	43.59	27.81 to 60.37
Tamura et al. [40]	22	0.00	0.00 to 15.43	77.27	54.63 to 92.17
Borcek et al. [41]	58	0.00	0.00 to 6.16	68.96	55.45 to 80.46
Hanakita et al. [42]	116	0.86	0.02 to 4.71	75.86	67.03 to 83.32
Nicolato et al. [43]	84	1.19	0.03 to 6.45	89.28	80.63 to 94.98
Nerva et al. [44]	36	2.77	0.07 to 14.52	83.33	67.18 to 93.62
Zeiler et al. [45]	39	0.00	0.00 to 9.02	41.02	25.56 to 57.90
Park et al. [46]	68	0.00	0.00 to 5.28	92.64	83.66 to 97.56
Starke et al. [48]	354	0.28	0.00 to 1.56	63.84	58.59 to 68.85
Hasegawa et al. [47]	189	0.52	0.01 to 2.91	87.83	82.30 to 92.12
Kim et al. [49]	264	0.75	0.09 to 2.71	62.12	55.97 to 67.99
Eliava et al. [50]	140	0.71	0.01 to 3.91	64.28	55.75 to 72.19
Total (random effects)	2142	0.72	0.41 to 1.12	71.64	65.71 to 77.21
		Heterogeneity	$I^2 = 0.0\%$	Heterogeneity	$I^2 = 88.13\%$

On the other hand, Gamma Knife radiosurgery is an innovative and non-invasive medical technique that delivers precisely highly focused beams of gamma radiation to the AVM, targeting the abnormal blood vessels while sparing surrounding healthy tissue [55]. The treatment effect is based on achieving gradual AVM closure by causing damage to the blood vessels, leading to eventual occlusion. This approach is advantageous for AVMs in critical or deep brain regions that may be challenging to reach through surgery, as it offers an excellent balance between treatment effectiveness and safety.

Similarly to previous studies focused on the adult population [11, 12], this study provides a comprehensive investigation regarding Gamma Knife radiosurgery as a treatment modality for cerebral arteriovenous malformations (AVMs) in the pediatric population and its implications and significance regarding the safety and effectiveness of this innovative approach.

Safety and effectiveness of gamma knife radiosurgery

The primary outcome (mortality and rate of complete obliteration of AVMs), as well as the secondary outcomes (new neurological deficit, post-GKS bleeding, and other Complications), were systematically reviewed.

Starke et al. [48] included a total of 357 pediatric patients with a mean age of 12.6 years, and they were distributed in two cohorts: the unruptured (112) and ruptured (245) pediatric AVM patients. Previously, AVMs were managed through embolization, resection, and fractionated external beam radiation therapy in 22%, 6%, and 13% of cases, respectively [48]. After stereotactic radiosurgery, a 63% AVM obliteration rate was achieved, with significantly higher rates of obliteration (68% vs. 53%, $p = 0.005$) in ruptured AVMs and positive outcome (63% vs 51%, $p = 0.033$) [48]. The annual rate of post-radiosurgery hemorrhage stood at 1.4% over a cumulative latency period of 2748 years, with annual post-radiosurgery hemorrhage rates of 0.8% for unruptured and 1.6% for ruptured AVMs. Symptomatic radiation-induced changes were experienced by 8%, while permanent changes affected 3% [48].

Kim et al. [25] retrospectively reviewed 264 ARU5BA-eligible patients treated with GKS and compared them against those in the ARUBA (A Randomized trial of Unruptured Brain Arteriovenous malformations) study

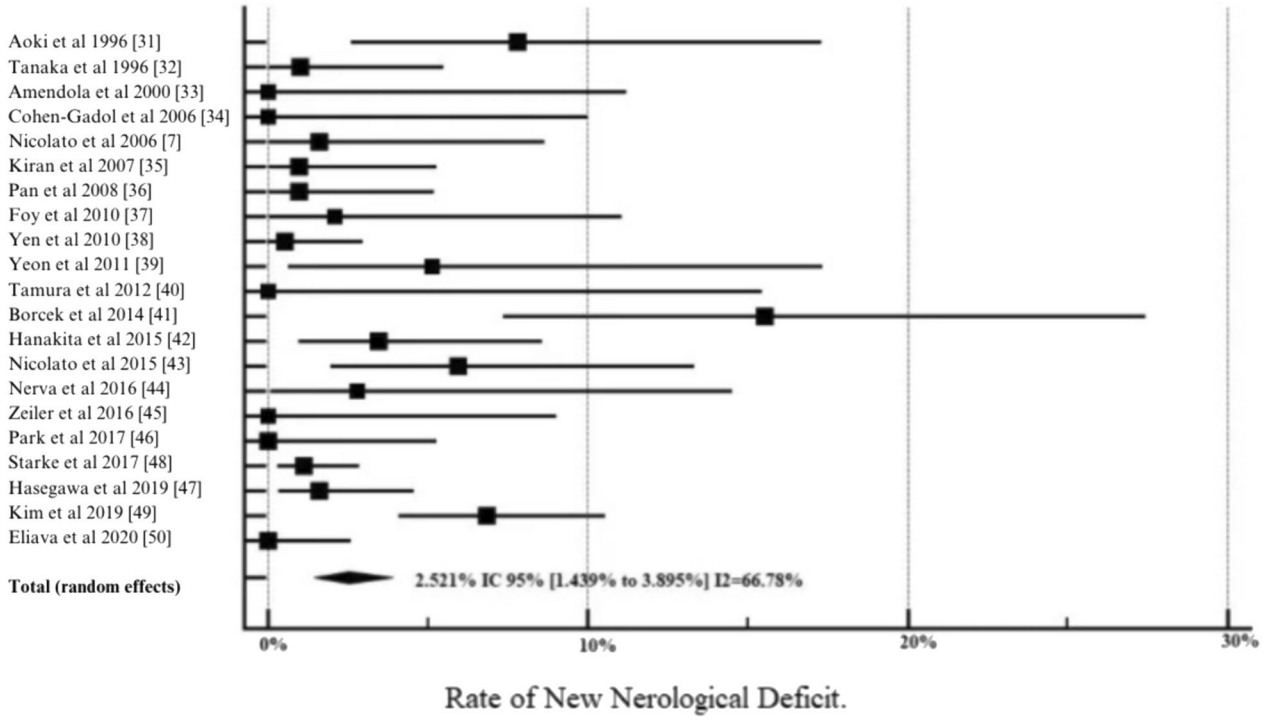

Fig. 4 Meta-analysis for cerebral AVMs treatment secondary outcomes: the new neurological deficit

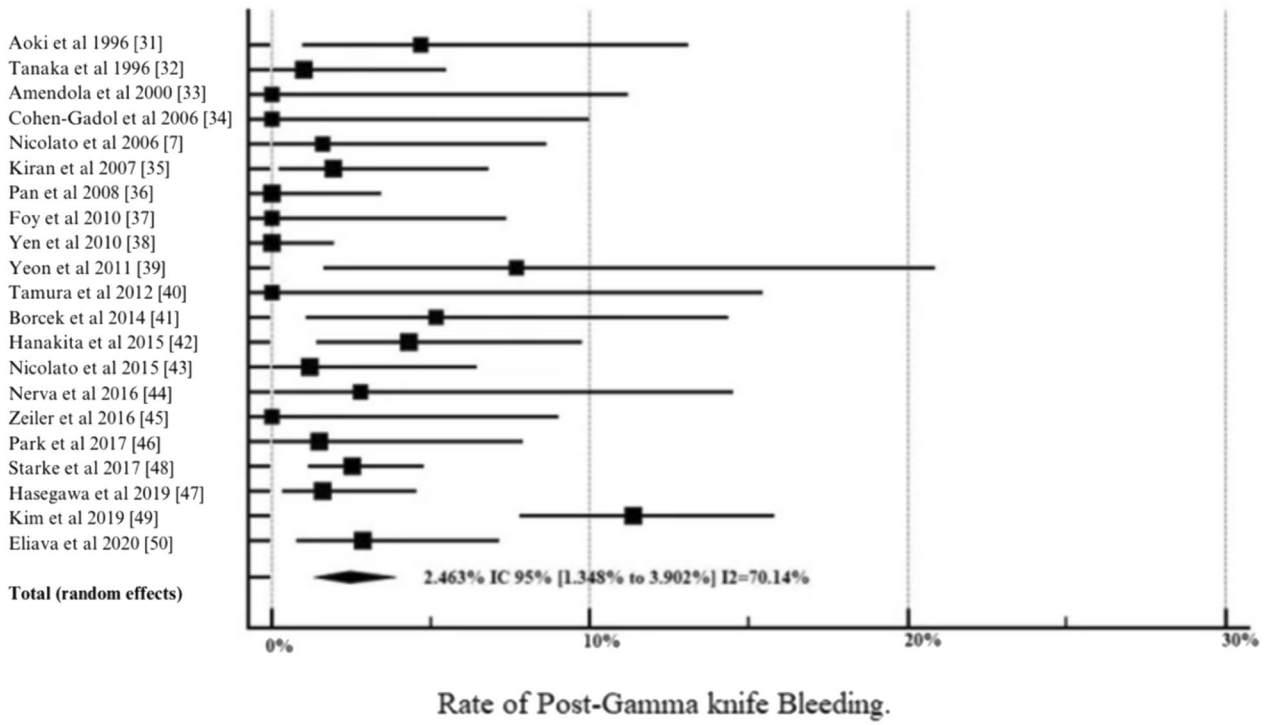

Fig. 5 Meta-analysis for cerebral AVMs treatment secondary outcomes: post gamma knife surgery bleeding rate

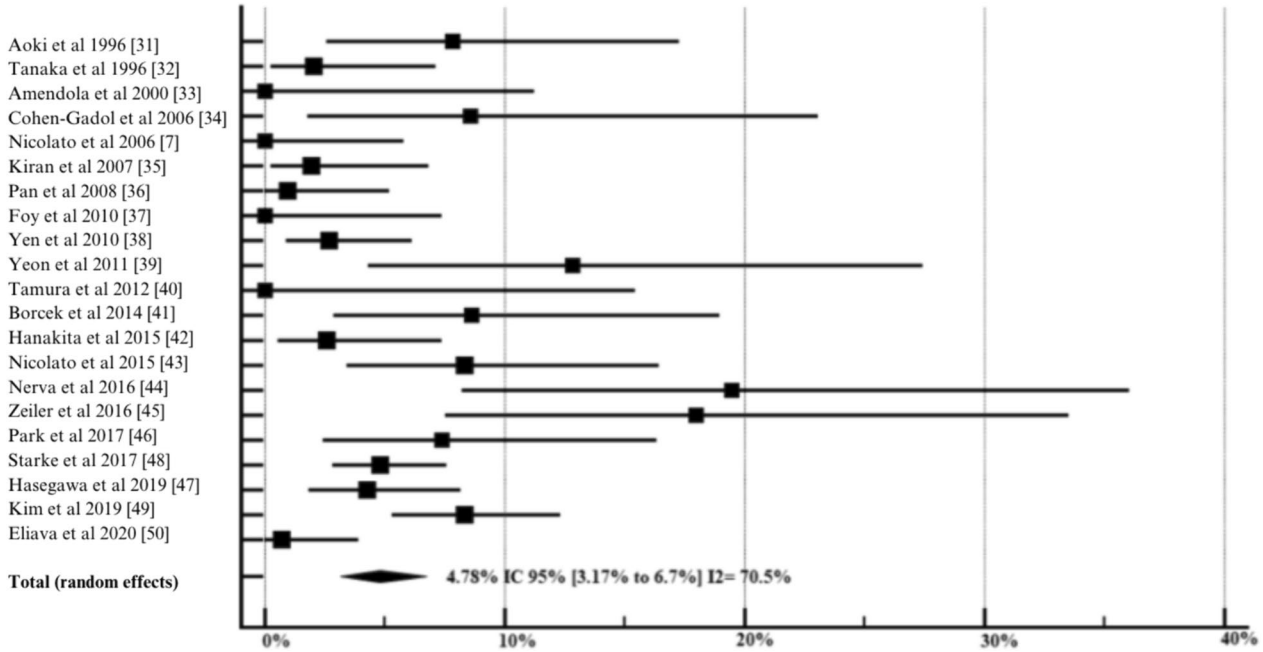

Fig. 6 Meta-analysis for cerebral AVMs treatment secondary outcomes: other complications

Table 3 Metanalysis: GKS as AVMs in Children Treatment Secondary Outcomes: New Neurological Deficit, Post-procedure Bleeding and other complications

Study	Sample size	New neurological deficit		Post GKS bleeding		Another complications	
		Proportion (%)	Proportion (%)	Proportion (%)	95% CI	Proportion (%)	95% CI
Aoki et al. [31]	64	7.81	4.68	4.68	0.97 to 13.09	7.81	2.58 to 17.29
Tanaka et al. [32]	99	1.01	1.01	1.01	0.02 to 5.50	2.02	0.24 to 7.10
Amendola et al. [33]	31	0.00	0.00	0.00	0.00 to 11.21	0.00	0.00 to 11.21
Cohen-Gadol et al. [34]	35	0.00	0.00	0.00	0.00 to 10.00	8.57	1.80 to 23.05
Nicolato et al. [7]	62	1.61	1.61	1.61	0.04 to 8.66	0.00	0.00 to 5.77
Kiran et al. [43]	103	0.97	1.94	1.94	0.23 to 6.83	1.94	0.23 to 6.83
Pan et al. [36]	105	0.95	0.00	0.00	0.00 to 3.45	0.95	0.02 to 5.19
Foy et al. [37]	48	2.08	0.00	0.00	0.00 to 7.39	0.00	0.00 to 7.39
Yen et al. [38]	186	0.53	0.00	0.00	0.00 to 1.96	2.68	0.87 to 6.16
Yeon et al. [39]	39	5.12	7.69	7.69	1.61 to 20.87	12.82	4.29 to 27.43
Tamura et al. [40]	22	0.00	0.00	0.00	0.00 to 15.43	0.00	0.00 to 15.43
Borcek et al. [41]	58	15.51	5.17	5.17	1.08 to 14.38	8.62	2.85 to 18.98
Hanakita et al. [42]	116	3.44	4.31	4.31	1.41 to 9.77	2.58	0.53 to 7.37
Nicolato et al. [43]	84	5.95	1.19	1.19	0.03 to 6.45	8.33	3.41 to 16.41
Nerva et al. [44]	36	2.77	2.77	2.77	0.07 to 14.52	19.44	8.19 to 36.02
Zeiler et al. [45]	39	0.00	0.00	0.00	0.00 to 9.02	17.94	7.53 to 33.53
Park et al. [46]	68	0.00	1.47	1.47	0,0372 to 7,923	7.35	2.43 to 16.33
Starke et al. [48]	354	1.13	2.54	2.54	1.16 to 4.77	4.80	2.82 to 7.57
Hasegawa et al. [47]	189	1.58	1.58	1.58	0.32 to 4.56	4.23	1.84 to 8.17
Kim et al. [49]	264	6.81	11.36	11.36	7.80 to 15.82	8.33	5.29 to 12.34
Eliava et al. [50]	140	0.00	2.85	2.85	0.78 to 7.15	0.71	0.01 to 3.91
Total (random effects)	2142	2.38	2.46	2.46	1.34 to 3.90	4.78	3.17 to 6.70
		Heterogeneity	$I^2 = 66.78\%$	Heterogeneity	$I^2 = 70.14\%$	Heterogeneity	$I^2 = 70.5\%$

where patients were directed towards either medical management combined with interventional therapies (such as neurosurgery, embolization, or stereotactic radiotherapy, used individually or in combination) or exclusive medical management (involving pharmacological therapy for neurological symptoms as required) [25]. It was found an AVM obliteration rate of 62.1% was successfully attained and following GKS, the annual hemorrhage rate stood at 3.4%. [25]. Additionally, a total of 14.0% experienced a stroke or death and the overall stroke or death rate within the ARUBA-eligible cohort was notably lower than in the treated group of the ARUBA study ($P < 0.001$) [25].

Hasegawa et al. assessed a total of 189 pediatric patients with AVM, all of whom had a minimum follow-up period of 12 months with a mean of 136 months [47]. The authors addressed the incidence of late adverse radiation effects, such as cyst formation (CF), chronic encapsulated hematoma (CEH), and radiation-induced tumor, in pediatric patients with AVM treated with GKS[47]. Throughout the follow-up duration, five patients (3%) exhibited symptomatic perilesional edema induced by radiation, while seven patients (4%) experienced radiation-induced cystic formations (CFs), seven patients (4%) developed cystic edema headaches (CEHs), and two patients (1%) developed radiation-induced tumors. The cumulative incidences were 1.2% at 5 years, 5.2% at 8 years, 6.1% at 10 years, 7.2% at 15 years, and 17.0% at 20 years [47]. Based on these findings, it can be inferred that Gamma Knife radiosurgery represents a viable treatment choice for pediatric AVMs, effectively mitigating the risk of future intracranial hemorrhages.

Yen et al. 2010 reviewed the long-term imaging and clinical outcomes of intracranial arteriovenous malformations (AVMs) in 186 children treated with Gamma Knife surgery (GKS) [38]. Regarding obliteration rates following the first GKS procedure, complete angiographic obliteration was attained in 49.5% of patients [38]. Subsequently, 41 patients, whose AVM nidus persisted, underwent additional GKS sessions and therefore achieved an obliteration rate of 58.6% whereas, in 9 patients (4.8%), only partial obliteration was achieved [38]. In a multivariate analysis, factors significantly associated with an increased obliteration rate were a lack of pre-GKS embolization history ($p = 0.042$), a small nidus volume ($p = 0.001$), and a high prescription dose ($p = 0.025$) [38]. According to hemorrhagic events, ten patients experienced a total of 17 events during the follow-up period and the hemorrhage rate was 5.4% within the initial 2 years after GKS and reduced to 0.8% between 2 and 5 years [38]. Neurological deficits were present in six patients in conjunction with the observed radiation-induced changes and after an average clinical follow-up duration of 98 months, fewer than 4% of patients faced challenges in attending school or pursuing a career [38]. Additionally, two patients developed asymptomatic meningiomas at 10 and 12 years post-GKS [38].

This systematic review and meta-analysis reveal promising outcomes regarding the safety and efficacy of Gamma Knife radiosurgery in treating pediatric cerebral AVMs. Notably, the observed mortality rate (0.75%) suggests this treatment modality carries a relatively low mortality risk. This finding underscores the potential advantages of radiosurgery compared to conventional surgical interventions, particularly in reducing the risks associated with open surgery.

Moreover, the high rate of complete obliteration of AVMs (71.64%) is a standout result. This high success rate in achieving complete obliteration is a testament to the technical precision of Gamma Knife radiosurgery and holds substantial clinical significance. Complete AVM obliteration can mitigate the risk of AVM-related complications, offering the prospect of a significantly improved long-term quality of life for affected children.

Complication rates and heterogeneity

While this study demonstrates favorable outcomes regarding mortality and AVM obliteration, it is crucial to acknowledge the complications associated with Gamma Knife radiosurgery. The rates of complications, including new neurological deficits (2.57%) and post-radiosurgery intracranial hemorrhage (2.463%), were relatively low in our analysis. Importantly, the nature of these complications was predominantly non-severe, with reports primarily consisting of visual deficits and sensory alterations. Notably, we found no severe motor deficits or patients entering a vegetative state. This suggests that, overall, Gamma Knife radiosurgery is well-tolerated by pediatric patients.

However, it is essential to contextualize these complication rates within the broader landscape of treatment options for pediatric AVMs. While the rates are generally low, the potential for complications remains, and clinicians must carefully weigh the risks and benefits when considering radiosurgery as a treatment option.

The presence of significant heterogeneity among the included studies should also be acknowledged. Heterogeneity is a common challenge in meta-analyses due to variations in patient populations, AVM characteristics, and treatment protocols across different institutions. While the pooled analysis provides valuable insights, the variations between studies should be considered when interpreting our findings.

Quality assessment and future directions

This study supports that Gamma Knife radiosurgery is a safe and effective treatment option for pediatric cerebral AVMs. The combination of a low mortality rate, a high AVM obliteration rate, and a manageable complication profile positions this approach as a promising therapeutic avenue for improving patient outcomes.

Nonetheless, our study emphasizes the need for further research, especially high-quality case–control studies with extended follow-up periods. These studies will provide more comprehensive insights into Gamma Knife radiosurgery's long-term efficacy and safety in pediatric patients with cerebral AVMs.

Our findings contribute significantly to the growing evidence supporting radiosurgery as a viable therapeutic option. This research offers hope for enhanced outcomes and improved quality of life for pediatric patients grappling with the challenging diagnosis of cerebral AVMs. As this field evolves, ongoing research endeavors will be pivotal in refining treatment protocols and optimizing patient care.

Examining findings with other studies

Börcek et al. 2019 presented 20 studies with 1212 patients who underwent single-session Gamma Knife Radiosurgery that resulted in complete obliteration in 65.9% (95% CI 60.5%-71.1%; I2 = 66.5%) patients [56]. The complication rate (new hemorrhage, new neurodeficit, and mortality) was 8.0% (95% CI 5.1%-11.5%; I2 = 66.4%) [56]. Post-SRS new neurological deficit rate was 3.1% (95% CI 1.3%-5.4%; I2 = 59.7%), and post-SRS hemorrhage rate was 4.2% (95% CI 2.5%-6.3%; I2 = 42.7%) [56].

Zhu et al. assessed six retrospective studies and the outcomes were the rate of AVM obliteration on 3-year follow-up 2069 patients: 637 had undergone embolization followed by GKS, and 1432 had undergone GKS alone. According to their results, the obliteration rate of AVMs in patients who had undergone embolization followed by GKS was 49.5%, and for patients with GKS performed alone was 70.4% (OR 2.29, 95% CI 1.55–3.38, $p < 0.00001$) [11]. However, the rates of new hemorrhage (8.9% vs. 4.2%, OR 0.59, 95% CI 0.23–1.57, $p = 0.29$) and permanent neurological deficits rate (3.6% vs. 4.6%, OR 0.51, 95% CI 0.57–3.12, $p = 0.51$) [11]. It is important to note that this study included an adult population.

Hak et al. conducted a systematic review and meta-analysis of studies investigating AVM recurrence in children between 2000 and 2020 to explore the overall recurrence rates across treatment modalities by analyzing surgery versus other treatments. Seventy children with obliterated AVMs were included. AVM recurrences (n = 10) were more commonly treated with EVT as the final treatment (60% in the recurrence vs 13.3% in the no-recurrence group, $p =$ $p = 0.018$) [57]. The presence of infratentorial locations was related to earlier and more frequent recurrences (adjusted relative risk = 4.62, 95% CI 1.08 to 19.04; $p = 0.04$) [57]. The rate of AVM recurrence was 10.9% (95% CI 8.7% to 13.5%) [57].

Jiang et al. 2021 aimed to assess the efficacy and safety of stereotactic radiosurgery (SRS) with and without prior endovascular embolization in patients with IAVMs. Nineteen studies (two prospective and 17 retrospective studies) involving a total of 3,454 patients with IAVMs were selected for the final meta-analysis [58]. The authors noted that prior embolization and SRS were associated with a lower obliteration rate compared with SRS alone (OR, 0.57; 95% CI, 0.44–0.74; $P < 0.001$) [58]. However, prior embolization and SRS were not associated with the risk of rebleeding (OR, 1.05; 95% CI, 0.81–1.34; $p = 0.729$) and permanent neurological deficits (OR, 0.80; 95% CI, 0.48–1.33; $p = 0.385$) compared with SRS alone [58].

Starke et al. conducted a retrospective observational cohort study with a cohort comprised of 357 patients with a mean age of 12.6 years (range 2.8–17.9 years) with AVMs. Patients with a history of prior AVMs were treated with embolization, resection, and fractionated external beam radiation. A cohort of 112 patients corresponded to unruptured pediatric AVM and a group of 245 patients were categorized as ruptured pediatric AVM. Ruptured AVMs had dramatically higher rates of obliteration (68% vs 53%, $p = 0.005$) and better outcomes (63% vs 51%, $p = 0.033$), with a trend toward a major presence of post-procedure hemorrhage (10% vs 4%, $p = 0.07$) [48]. Regarding post-radiosurgery hemorrhage after a year the intervention has been performed, rates were 0.8% for unruptured and 1.6% for ruptured AVMs [48].

Another study developed by Aziz et al. included fifty-two AVMs, with forty of them (805) ruptured, and only 8 (16%) required emergency intervention [59]. Regarding the type of surgery, 17 (35%) required elective procedures, 15 (30%) underwent endovascular embolization, and 15 (30%) patients were treated with stereotactic radiosurgery [59]. There was an 88% overall obliteration rate, two (4%) patients rebled, and there were no mortalities [61]. In total, the average time from diagnosis to definitive treatment was 144 days (median 119; range 0–586) [59]. Quality of life outcomes were collected for 26 (51%) patients [59]. Ruptured pAVM presentation was associated with worse QoL ($p = 0.0008$) and location impacted psychosocial scores significantly (71.4, 56.9, and 46.6 for right supratentorial, left supratentorial, and infratentorial, respectively; $p = 0.04$) [59].

Similar to these studies, this systematic review demonstrates that radiosurgery is a reasonable treatment option for pediatric AVMs as obliteration and favorable outcomes are achieved in the majority of patients. This

information can guide decision-making, particularly for patients who may have comorbidities or are at a higher risk for complications. The positive outcomes and safety profile associated with Gamma Knife radiosurgery may lead to increased adoption of this technique in the management of cerebral AVMs. This can expand access to effective treatment options for a wider range of patients and potentially reduce the burden on healthcare resources.

Limitations

17 of the included studies were retrospective observational studies, and there was high heterogeneity both within and between the included studies. It is important to note that, like any other meta-analytical study that relies on pooled data without access to original patient data, this study has its limitations.

Conclusion

Pediatric patients with AVMs can be affected by devastating consequences derived from this complex neurological condition such as intracranial hemorrhage, cognitive impairment, long-term disabilities, and even mortality. The therapeutic approach for this population can be challenging and requires a multidisciplinary team that can guide young patients and their families throughout the course of the treatment. Gamma Knife radiosurgery is a safe and effective treatment option for cerebral arteriovenous malformations, with high surgical success rates, low mortality, and low complication rates. This approach emerges as a promising therapeutic option for children, with favorable results encouraging the adoption of this technique that can minimize secondary effects derived from conventional surgery. However, further high-quality case–control studies are needed to evaluate its long-term efficacy and safety.

Abbreviations

AVMs	Arteriovenous malformations
ARUBA	A randomized trial of unruptured brain arteriovenous malformations
D3	Domain 3
RCTs	Randomized controlled trials
SRS	Stereotactic radiosurgery

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by William Andrés Florez-Perdomo, Juan Sebastián Reyes Bello, Luis Rafael Moscote Salazar, Amit Agrawal, Tariq Janjua, Vishal Chavda, Ezequiel García-Ballestas, Ebtesam Abdulla. The first draft of the manuscript was written by William Andrés Florez-Perdomo, Juan Sebastián Reyes Bello, Luis Rafael Moscote Salazar, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability

Available from the corresponding author on reasonable request.

Declarations

Ethical approval

Ethical committee approval was not required for this review, as it involved the analysis of previously published data and did not involve any direct interaction with human subjects or animals. All data utilized in this review were obtained from publicly available sources and were analyzed following established guidelines and principles of scientific rigor and integrity.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Received: 1 April 2024 Accepted: 11 June 2024
Published online: 05 July 2024

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