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Comparative outcomes of observation, stereotactic radiosurgery, and microsurgery for brainstem cavernous malformations: a systematic review and network meta-analysis

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ADMINISTRATIVE INFORMATION**Support** - Korea University grant (No. K2619631).**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100086**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2026 and was last updated on 20 October 2026.**INTRODUCTION**

Review question / Objective In patients with brainstem cavernous malformations (BSCMs), how do rebleeding, permanent neurological morbidity, and mortality differ among observation, stereotactic radiosurgery (SRS), and microsurgical resection? The review pooled event rates for each management strategy and compared strategies within multi-arm studies using direct within-study, Bucher-adjusted indirect, and frequentist network comparisons.

Rationale BSCMs carry a high risk of recurrent hemorrhage, and each management strategy carries distinct risks. No randomized trial has compared observation, SRS, and microsurgery, and previous meta-analyses either compared microsurgery with SRS or summarized each strategy separately.

Condition being studied Brainstem cavernous malformation (cerebral cavernous malformation

located in the midbrain, pons, or medulla oblongata).

METHODS

Search strategy PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials were searched from inception to February 6, 2026, using the same string adapted to each database: ("brain stem" OR brainstem OR midbrain OR pontine OR pons OR medulla OR cervicomedullary) AND (cavernoma* OR "cavernous malformation*" OR "cavernous hemangioma*" OR "cerebral cavernous malformation*") AND (observation* OR conservative OR "natural history" OR microsurgery OR surgery OR resection OR "stereotactic radiosurgery" OR radiosurgery OR "gamma knife") AND (hemorrhage OR haemorrhage OR rebleed* OR rehemorrhage OR outcome* OR morbidity OR mortality). Reference lists of retrieved articles were searched manually.

Participant or population Patients with BSCM managed by observation, SRS, or microsurgical resection; studies were required to include at least 10 patients with BSCM (counted per study, not per arm).

Intervention Stereotactic radiosurgery (Gamma Knife or linear accelerator-based) or microsurgical resection.

Comparator Observation (conservative management); interventions were also compared with each other.

Study designs to be included Original prospective or retrospective cohort studies, either comparative (multi-arm) or single-arm, reporting at least one primary outcome.

Eligibility criteria Included: original English-language articles reporting rebleeding, neurological morbidity, or mortality in ≥ 10 patients with BSCM managed by observation, SRS, or microsurgery. Excluded: reviews, case reports, studies without extractable primary outcomes, and duplicate reports of the same population (only one report retained). Series from the same institution with partially overlapping enrollment were retained and addressed in a sensitivity analysis.

Information sources PubMed, Embase, Web of Science, Cochrane CENTRAL, and manual searching of reference lists.

Main outcome(s) (1) Rebleeding: new symptomatic, imaging-confirmed hemorrhage after the index event (observation) or after treatment (SRS, microsurgery). (2) Permanent neurological morbidity: new or worsened deficit relative to baseline persisting at last follow-up (equivalent definitions accepted, e.g., new persistent deficit, mRS > 2 or mRS worsening, Glasgow Outcome Scale < 4 ; transient deficits excluded). (3) Mortality.

Additional outcome(s) Annualized rebleeding rate per 100 patient-years; lesion or hematoma size; pretreatment neurological status (proportion with mRS 0–2); new treatment-attributable deficits persisting at last follow-up; direction of change in neurological status (improved, unchanged, worsened); favorable outcome (mRS ≤ 2 or equivalent).

Data management Two reviewers independently screened and selected studies and extracted study characteristics and outcome data; disagreements were resolved by consensus or a third reviewer. Supplementary variables were extracted in

duplicate with verbatim source quotations, and discrepancies were adjudicated against the source text with an adjudication log. A generative AI tool was used to cross-check extracted data against source articles; all data were verified by the authors.

Quality assessment / Risk of bias analysis Newcastle–Ottawa Scale (scores ≥ 7 , 4–6, and ≤ 3 denoting low, moderate, and high risk of bias); multi-arm studies scored once. Certainty of evidence rated with GRADE.

Strategy of data synthesis Proportions pooled per strategy with DerSimonian–Laird random-effects models after logit transformation; heterogeneity quantified with I^2 . Within-study log odds ratios (0.5 continuity correction) pooled with the DerSimonian–Laird method; adjusted indirect comparisons by the Bucher method; direct and indirect estimates combined by inverse-variance weighting after consistency testing. A contrast-based frequentist network meta-analysis (metafor rma.mv, restricted maximum likelihood, observation as reference) was fitted to the multi-arm studies. Treatment rankings were not derived. Analyses used Python 3.11 and R 4.3.3 (metafor 4.4).

Subgroup analysis Stratification by study quality (NOS ≥ 5 vs < 5) and by publication era (2015 or later vs earlier).

Sensitivity analysis Institution-level deduplication (largest arm retained when arms of the same strategy came from the same institution with overlapping enrollment); annualized rebleeding rates per 100 patient-years. Three arms were excluded post hoc from pooling (cohort selected for ≥ 2 prior hemorrhages; mixed-location cohort; rebleeding reported only as an odds ratio).

Language restriction English only.

Country(ies) involved South Korea.

Other relevant information This registration was completed retrospectively, after completion of the review, at the request of the journal. Deviations and post hoc decisions are reported in the manuscript.

Keywords brainstem cavernous malformation; stereotactic radiosurgery; microsurgery; observation; network meta-analysis; systematic review.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

Author 1 - Minkyun Na - Conceptualization of the review; literature search and study selection; data extraction; risk-of-bias assessment; interpretation of data; drafting of the manuscript; approval of the final version. (Co-first author).

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Author 2 - Sae Min Kwon - Conceptualization of the review; literature search and study selection; data extraction; risk-of-bias assessment; interpretation of data; critical revision of the manuscript; approval of the final version. (Co-first author).

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