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Factors Independently Associated With Hemorrhagic Presentation in Brain Arteriovenous Malformations: A Systematic Review and Meta-Analysis of Adjusted Estimates

Alsalama, A; McCarthy, F; Emara, M; Muqsith, MA; Ghaith, AK; Alaraj, A.

Corresponding author:
Ali Alaraj

alaraj@uic.edu

Author Affiliation:
Department of Neurosurgery, University of Illinois Chicago.

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INTRODUCTION

Review question / Objective To identify, through systematic review and meta-analysis of adjusted (multivariable) estimates, the demographic and angioarchitectural factors independently associated with hemorrhagic presentation in brain arteriovenous malformations (bAVMs). Population: patients with confirmed intracranial AVMs from studies enrolling at least 50 patients. Exposures: demographic and angioarchitectural/hemodynamic features (e.g., sex, age, race/ethnicity, venous drainage pattern, nidus location and size, feeding artery pattern, AVM-associated aneurysms). Comparators: harmonized reference categories for each predictor. Outcome: hemorrhagic presentation or rupture at diagnosis. Study designs: observational studies reporting adjusted odds ratios from multivariable models.

Rationale Previous hemorrhage is the most consistently validated predictor of subsequent AVM rupture, but the independent contribution of other reported demographic and angioarchitectural features to hemorrhagic presentation is less certain and estimates vary across cohorts. Because intracranial hemorrhage is the leading cause of AVM-related disability and death, and treatment decisions balance projected hemorrhage risk against procedural risk, systematically pooling adjusted multivariable estimates may help clarify which features carry independent value beyond univariable associations reported in individual cohorts.

Condition being studied Brain arteriovenous malformations (bAVMs) are dysplastic vascular networks connecting arteries directly to veins without an intervening capillary bed, exposing the nidus and draining veins to abnormal hemodynamic stress. They are uncommon, with an estimated prevalence of 10-18 per 100,000 adults. Intracranial hemorrhage is their most frequent and clinically important presentation, occurring in roughly half of affected patients, and accounts for a substantial proportion of hemorrhagic strokes in younger adults and children.

METHODS

Search strategy PubMed, Embase, and Web of Science were searched on June 1, 2026, without date or language restrictions, using Medical Subject Headings and free-text terms for intracranial, cerebral, or brain arteriovenous malformation; hemorrhage or rupture; and bleeding risk factors. Reference lists of eligible full-text articles and relevant systematic reviews were also manually screened for additional eligible studies.

Participant or population Patients with confirmed intracranial arteriovenous malformations, from studies enrolling at least 50 patients, that reported hemorrhagic presentation or rupture; cohorts could be adult-only, pediatric-only, or mixed-age.

Intervention Not applicable in the traditional sense, as this is a review of prognostic/risk factors rather than an intervention. Exposures assessed included demographic and angioarchitectural/hemodynamic features such as venous drainage pattern, number of draining veins, venous stenosis or dilation, nidus location and diameter, feeding artery pattern, and AVM-associated aneurysms, evaluated as predictors of hemorrhagic presentation.

Comparator Harmonized reference categories specific to each predictor (e.g., presence versus absence of a feature, or an opposite category such as deep versus superficial venous drainage), aligned across studies using a prespecified harmonization protocol for differing reference categories and predictor scales.

Study designs to be included Observational studies (single-institution cohorts, multicenter registries, and population-based databases) enrolling at least 50 patients with confirmed intracranial AVMs that reported an adjusted odds ratio, or sufficient data to derive one, from a multivariable model for hemorrhagic presentation or rupture.

Eligibility criteria Included: studies with confirmed intracranial AVMs; evaluating hemorrhagic presentation or rupture; reporting an OR with 95% CI (or sufficient data to derive one) for at least one demographic, angioarchitectural, or hemodynamic predictor; and including at least 50 patients. Excluded: studies focused exclusively on post-treatment outcomes, noncerebral AVM subtypes, conference abstracts, and reports unavailable in English.

Information sources PubMed, Embase, and Web of Science electronic databases, supplemented by manual screening of reference lists of eligible full-text articles and relevant systematic reviews.

Main outcome(s) Hemorrhagic presentation (or rupture) at diagnosis, expressed as adjusted odds ratios with 95% confidence intervals for demographic and angioarchitectural predictors, pooled with random-effects models using restricted maximum likelihood estimation and the Hartung-Knapp-Sidik-Jonkman correction, accompanied by prediction intervals.

Additional outcome(s) Age-group subgroup estimates (adult-only, mixed adult-pediatric, pediatric-only); leave-one-out sensitivity analyses for outcomes with significant heterogeneity; risk of bias (QUIPS) and methodological quality (JBI) appraisals; and assessment of small-study effects via contour-enhanced funnel plots for analyses with at least 10 contributing studies.

Data management Two reviewers independently extracted each reported OR and 95% CI, predictor definition and reference category, study design, age group, enrolling institution or registry, and model type (univariable vs multivariable); disagreements were resolved by discussion or a third reviewer. A prespecified harmonization protocol aligned reference categories and predictor units across studies, and enrollment periods were reviewed to assess possible patient overlap between publications from the same institution or registry.

Quality assessment / Risk of bias analysis Risk of bias was assessed with the Quality In Prognosis Studies (QUIPS) tool, and methodological quality with the revised Joanna Briggs Institute (JBI) analytical cross-sectional checklist, with judgments tailored to hemorrhagic presentation at diagnosis; no numerical score or exclusion threshold was applied.

Strategy of data synthesis Random-effects meta-analyses were performed in R (meta package) using restricted maximum likelihood estimation of between-study variance and the Hartung-Knapp-Sidik-Jonkman correction for confidence intervals; fixed-effect pooling was not performed. Prediction intervals accompanied summary estimates, and heterogeneity was assessed with I2 and Cochran's Q (significance threshold $p<0.10$).

Subgroup analysis Prespecified subgroups by age group (adult-only, mixed adult-pediatric, pediatric-only), with between-subgroup

heterogeneity tested using chi-square; analyses with three or fewer contributing studies, or only one study per subgroup, were interpreted cautiously.

Sensitivity analysis For outcomes with significant heterogeneity, leave-one-out analysis omitted each study sequentially and re-estimated the pooled odds ratio; the study whose removal produced the greatest reduction in I2 was identified, and when a directionally discordant study's exclusion substantially improved homogeneity, the resulting estimate was reported as the primary result for that outcome.

Language restriction No restrictions were applied during the electronic search; however, reports not available in English were excluded during eligibility screening.

Country(ies) involved United States; United Arab Emirates.

Keywords brain arteriovenous malformation; hemorrhagic presentation; intracranial hemorrhage; angioarchitecture; risk factors; meta-analysis.

Contributions of each author

Author 1 - Abdulrhman Alsalama - Contributed equally to this work (co-first author).
Author 2 - Finn McCarthy - Contributed equally to this work (co-first author).
Author 3 - Mohamed Emara - The author contributed to.
Author 4 - Mohammed Abdul Muqsith.
Author 5 - Abdul Karim Ghaith.
Author 6 - Ali Alaraj - Corresponding author; guarantor for the accuracy of the registered protocol.
Email: alaraj@uic.edu