BALNEO RESEARCH Balneo and PRM Research Journal
English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

Research article

Toward a morphology-based rupture risk score in middle cerebral artery aneurysms: an exploratory retrospective study

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Citation: Paslaru F.G., Brehar F.M., Stanoaia O.E., Iliescu A., Gorgan R.M. - Toward a morphology-based rupture risk score in middle cerebral artery aneurysms: an exploratory retrospective study
Balneo and PRM Research Journal **2026**, *17(1): 971*

Academic Editor(s):
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Production Officer:
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Received: 29.01.2026
Published: 31.03.2026

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Publisher's Note: Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: Accurate rupture risk stratification remains a major challenge in the management of unruptured intracranial aneurysms, particularly given the non-negligible risks associated with prophylactic treatment. Morphological characteristics reflecting aneurysm geometry and complexity have been increasingly implicated in rupture status, yet their integration into practical risk models remains limited. We conducted a retrospective single-center cohort study including 61 consecutive patients with middle cerebral artery (MCA) aneurysms diagnosed at a tertiary referral center between 2015 and 2025. The cohort comprised 23 ruptured and 38 unruptured aneurysms. Clinical and morphological variables were assessed, including patient demographics, rupture status, dome and neck dimensions, bottleneck factor, presence of a daughter dome, and vascular risk factors. Univariate analyses were performed to identify associations with rupture status. Multiple predefined bottleneck factor thresholds were evaluated. An exploratory rupture risk score was constructed by summing three binary variables (bottleneck factor >1.6, daughter dome presence, and arterial hypertension). Score performance was assessed using trend testing, logistic regression, receiver operating characteristic analysis with bootstrap confidence intervals, and permutation testing. Among the 61 aneurysms (23 rupture events), bottleneck factor thresholds between 1.4 and 2.0 were significantly associated with rupture status. Daughter dome presence demonstrated the strongest univariate association. The composite score showed a monotonic increase in rupture proportion across score categories (0–3 points). Higher scores were significantly associated with rupture in dichotomized analyses and per-point logistic regression. Discriminative performance was high (AUC = 0.876), and permutation testing indicated that this performance was unlikely to be due to chance. In this exploratory retrospective single-center cohort, morphological features reflecting aneurysm shape and complexity were strongly associated with rupture status. The proposed rupture risk score integrates morphological and clinical information and demonstrated robust internal performance. Although not intended as a validated clinical decision tool, this score provides a biologically plausible, hypothesis-generating framework for future validation in larger, independent, prospective cohorts..

Keywords: unruptured, cerebral, intracranial, aneurysm, rupture, risk

1. Introduction

Saccular aneurysms, focal outpouchings of an arterial wall, are thought to be acquired lesions present in about 3% of the world population, diagnosed with increasing frequency due to the larger availability of cerebral imaging [1], [2], [3]. While relatively rare, with an estimated incidence of 9 per 100,000 patients, cerebral aneurysm rupture with the resulting subarachnoid hemorrhage (aSAH) can be a devastating occurrence, with approximately one third of the aSAH patients dying in days to weeks following aneurysm rupture and only about 5% of those who survive being

able to return to their pre-morbid activity level [4], [5], [6]. However, prophylactic treatment of unruptured intracranial aneurysms is also associated with notable risks [7], [8], [9], [10], making accurate discrimination between aneurysms at high risk of rupture and those with a low rupture risk imperative for informed treatment decisions.

Our purpose was to investigate an exploratory rupture risk score based on aneurysm morphology and clinical factors, aimed at supporting risk stratification in patients with middle cerebral artery aneurysms. Accordingly, the specific aim of this study was to explore whether selected morphological characteristics of MCA aneurysms, in combination with relevant clinical factors, could be integrated into a simple composite score associated with rupture status. We hypothesized that geometric indices reflecting aneurysm shape complexity—particularly bottleneck factor and daughter dome presence—together with vascular risk factors such as arterial hypertension, would demonstrate additive discriminatory value for rupture status in a retrospective single-center cohort.

2. Materials and Methods

This retrospective single-center cohort study included 61 consecutive patients diagnosed with middle cerebral artery (MCA) aneurysms at a tertiary referral center between 2015 and 2025.

Inclusion and exclusion criteria

Inclusion criteria were:
(1) confirmed diagnosis of saccular MCA aneurysm by digital subtraction angiography (DSA);
(2) complete clinical documentation regarding rupture status;
(3) availability of high-quality angiographic images permitting accurate morphological measurements.

Exclusion criteria included:
(1) fusiform, dissecting, or mycotic aneurysms;
(2) aneurysms located outside the MCA territory;
(3) previously treated aneurysms;
(4) incomplete imaging or clinical data.

Imaging protocol and measurement procedure

All aneurysms were evaluated using digital subtraction angiography (DSA), which served as the reference imaging modality for morphological assessment.

Morphological measurements were independently performed by two neurosurgeons (Francesca Gabriela Paslaru and Oana Elena Stanoaia). Continuous measurements were obtained independently by each evaluator, and the final values used in the analysis represent the arithmetic mean of the two measurements.

Binary variables, including the presence of a daughter dome, were initially assessed independently. In cases of disagreement, a consensus decision was reached after joint image review.

Formal inter-rater reliability statistics (e.g., intraclass correlation coefficient or Cohen's kappa) were not calculated, given the exploratory nature of the study. However, standardized measurement criteria were applied to enhance reproducibility.

Variables assessed

We examined factors previously reported in the literature to be associated with rupture status. The following variables were recorded: patient age, sex, rupture status, dome width, neck width, bottleneck factor, presence of a daughter dome, history of arterial hypertension, and type 2 diabetes mellitus.

The bottleneck factor (BNF) was defined as the ratio between dome width and neck width.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation and range, while categorical variables were expressed as absolute counts and percentages. Normality of continuous variables was not assumed due to the limited sample size.

Associations between individual variables and aneurysm rupture status were assessed using univariate analyses. For categorical variables, Fisher's exact test was applied due to small cell counts. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated from 2×2 contingency tables. When zero cell counts were encountered, a Haldane–Anscombe correction was applied.

For continuous variables, univariate logistic regression was used to estimate the association with rupture status, reporting ORs per one-unit increase of the predictor.

Multiple predefined bottleneck factor thresholds (1.2–2.0, increment 0.2) were evaluated using Fisher's exact test to explore their association with rupture status. Threshold selection for score construction was based on statistical performance, biological plausibility, and consistency with previously published literature, with a value of 1.6 retained for further analyses. The threshold selection was not data-driven for optimal statistical separation but was predefined based on biological plausibility and consistency with previously published literature to reduce the risk of overfitting.

An exploratory rupture risk score was constructed by summing three binary variables identified as clinically and morphologically relevant in univariate analysis: bottleneck factor >1.6, presence of a daughter dome, and history of arterial hypertension. The resulting score ranged from 0 to 3 points.

Score performance was evaluated using complementary descriptive and inferential approaches appropriate for exploratory analyses in small cohorts. The distribution of ruptured and unruptured aneurysms across score categories was examined, and rupture proportions were calculated for each score level.

For inferential assessment, the score was analyzed:

1. As an ordinal variable using the Cochran–Armitage trend test.
2. As a continuous predictor in univariate logistic regression (OR per one-point increase).
3. As a dichotomized variable (low risk: score 0–1; high risk: score 2–3) using Fisher's exact test.

Discriminative performance was evaluated using receiver operating characteristic (ROC) analysis, with calculation of the area under the curve (AUC). Confidence intervals were estimated using bootstrap resampling (5,000 iterations). A permutation test (10,000 permutations) was performed to assess robustness by comparing the observed AUC against the distribution obtained under random reassignment of rupture status.

All statistical tests were two-sided. Results were interpreted as exploratory and hypothesis-generating, given the sample size and absence of external validation. Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

The cohort included 61 patients (15 men and 46 women), with a mean age of 56.0 ± 10.2 years (range 32–72 years). Twenty-three aneurysms were ruptured and 38 unruptured.

All evaluated bottleneck factor thresholds demonstrated significant associations with rupture, with stronger discrimination at higher thresholds (Table 1).

Table 1. Bottleneck factor thresholds and rupture risk association.

Bottleneck threshold	OR	95% CI	p-value
> 1.2	3.45	0.98-12.13	0.0546
> 1.4	9.13	2.57-32.51	0.000449
> 1.6	7.37	2.31-23.52	0.00101
> 1.8	10	2.94-33.99	0.000188
> 2.0	4.89	1.48-16.16	0.00940

Univariate analysis identified bottleneck factor >1.6 and daughter dome presence as the strongest morphological predictors of rupture, while hypertension was retained as a clinically relevant covariate (Table 2). The very large odds ratio observed for daughter dome presence likely reflects sparse data and small cell counts, resulting in inflated effect size estimates and wide confidence intervals.

Table 2. Univariate analysis of the variables associated with aneurysm rupture.

Variable	OR	95% CI	p-value
BNF > 1.6	7.37	2.31-23.52	0.00101
daughter-dome presence	117.53	6.42-2151.55	3.63×10^{-8}
arterial hypertension	1.88	0.64-5.46	0.295
diabetes mellitus type 2	0.13	0.0068-2.46	0.147
side (right = 1 vs left = 0)	0.92	0.33-2.58	1.000
male sex	1.64	0.50-5.35	0.541
BNF (continuous, per 1 unit)	2.52	1.22-5.19	0.0123
dome width (per 1 unit)	1.11	0.98-1.26	0.0960
neck width (per 1 unit)	0.97	0.76-1.23	0.795
age (per 1 year)	1.01	0.96-1.06	0.719

An exploratory rupture risk score (range 0–3) was constructed by summing three binary variables: bottleneck factor >1.6, presence of a daughter dome, and hypertension status. The selection of variables for inclusion in the exploratory rupture risk score, along with the rationale for inclusion or exclusion, is summarized in Table 3. Although the threshold of 1.8 yielded the lowest p-value, a cutoff of 1.6 was retained for score construction to ensure consistency with previously published morphological thresholds and to favor external interpretability over maximal statistical separation within this cohort. The proportion of ruptured aneurysms increased stepwise with increasing score values: 0.0% for score 0 (0/14), 23.1% for score 1 (6/26), 75.0% for score 2 (12/16), and 100% for score 3 (5/5) (Table Z). When dichotomized into low (0–1) versus high (2–3) score categories, high scores were strongly associated with rupture status (Fisher exact test: OR = 24.08, 95% CI 5.98–96.95, $p = 6.36\times10^{-7}$) (Table 4). A significant positive trend across ordered score categories was confirmed using the Cochran–Armitage trend test ($Z = 5.22$, $p = 1.75\times10^{-7}$). In univariate logistic regression, each 1-point increase in score was associated with increased odds of rupture (OR = 13.56, 95% CI 3.85–47.72, $p = 4.86\times10^{-5}$). Discriminative performance was high (AUC = 0.876, bootstrap 95% CI 0.793–0.948), and permutation testing supported that this performance was unlikely by chance ($p < 0.0001$) (Table 5).

Table 3. Variable selection and rationale for inclusion in the rupture risk score.

Variable	Included in the rupture risk score	Rationale
BNF > 1.6	yes	Selected based on strong univariate association, biological plausibility related to inflow concentration, and consistency with previously published morphological thresholds.
daughter-dome presence	yes	Included as a marker of aneurysm morphological complexity and irregularity, features associated with disturbed hemodynamics and wall instability.
arterial hypertension	yes	Retained as a clinically relevant covariate reflecting systemic vascular risk, improving the generalizability of the score despite a weaker individual association.
diabetes mellitus type 2	no	Excluded due to lack of meaningful association with rupture and absence of consistent biological support in this cohort.
side (right = 1 vs left = 0)	no	Excluded due to lack of biological plausibility and no observed association with rupture status.
male sex	no	Excluded as no meaningful association with rupture was observed in univariate analysis.
BNF (continuous, per 1 unit)	no	Excluded to avoid redundancy, as a dichotomized bottleneck threshold was retained for score construction.
dome width (per 1 unit)	no	Excluded due to collinearity with the bottleneck factor and lack of additional discriminatory value.
neck width (per 1 unit)	no	Excluded because it showed a weak and inconsistent association with rupture when analyzed as a standalone parameter.
age (per 1 year)	no	Excluded as age appeared to influence aneurysm prevalence rather than rupture risk in this cohort.

Table 4. Distribution of rupture status across score categories.

Score	Ruptured (n)	Unruptured (n)	Total (n)	Rupture proportion
0	0	14	14	0
1	6	20	26	0.231
2	12	4	16	0.750
3	5	0	5	1

Table 5. Exploratory validation metrics (4 methods).

Method	Metric	Result
Cochran–Armitage trend test	Z; p for trend	$Z = 5.22$; $p = 1.75\times10^{-7}$
Logistic regression (score ordinal)	OR per +1 point; 95% CI; p	OR = 13.56; 95% CI 3.85–47.72; $p = 4.86\times10^{-5}$
ROC / AUC + bootstrap	AUC; 95% CI	AUC = 0.876; 95% CI 0.793–0.948
Permutation test (AUC-based, 10,000 perm.)	p-value	$p < 0.0001$ (0/10,000 ≥ observed)

4. Discussion

In this retrospective single-center cohort of 61 MCA aneurysms (23 ruptured), an exploratory rupture risk score integrating bottleneck factor >1.6, daughter dome presence, and arterial hypertension demonstrated a stepwise increase in rupture proportion across score categories. Higher score values were associated with rupture status in univariate analyses and showed good internal discrimination (AUC 0.876). These findings suggest that combining morphology-derived and clinical parameters may capture relevant features of aneurysm instability.

Accurate rupture risk stratification remains a central challenge in the management of unruptured intracranial aneurysms, particularly given the risks associated with prophylactic treatment [4], [8], [10]. Existing models such as PHASES primarily integrate clinical and anatomical variables [11], whereas the present exploratory score places greater emphasis on morphology-derived features. Conceptually, the proposed score differs from PHASES in scope and intent. The PHASES score was developed from large prospective cohorts to estimate long-term rupture probability across multiple aneurysm locations [11]. In contrast, the present score is location-specific (MCA), exploratory in nature, and focused primarily on morphology-derived features assessed by high-resolution angiography. Rather than competing with established models, it is intended to complement existing clinical frameworks by highlighting geometry-related characteristics that may not be fully captured by broader epidemiologic scores.

The presence of a daughter dome demonstrated the strongest univariate association with rupture in our cohort, consistent with prior studies linking aneurysm irregularity to adverse hemodynamic conditions and focal wall degeneration [1], [12], [13]. Morphological irregularity has repeatedly been associated with rupture status across different aneurysm locations, suggesting a plausible biological substrate related to wall stress heterogeneity and structural vulnerability.

Similarly, bottleneck factor thresholds between 1.4 and 2.0 were significantly associated with rupture. Although a threshold of 1.8 yielded the lowest p-value in our dataset, a value of 1.6 was retained to ensure comparability with prior studies and to favor external interpretability. Previous investigations have shown that higher aspect ratios and complex geometries are associated with altered inflow patterns, increased wall stress, and rupture status [14]–[16].

Methodological literature supports the development of composite models integrating biologically plausible predictors when clearly framed as exploratory and appropriately validated [17], [18]. In this context, the present score should be viewed as a structured synthesis of morphology-derived and clinical information rather than as a finalized predictive instrument.

A key strength of this study is the structured evaluation of morphology-based parameters using DSA as the reference imaging modality, along with independent

measurements performed by two experienced neurosurgeons. The use of complementary statistical approaches—including trend testing, ROC analysis with bootstrap confidence intervals, and permutation testing—provides internal validation within the study sample, although this does not substitute for external validation.

However, several limitations must be acknowledged. First, the study is retrospective and single-center, limiting generalizability. Second, although the overall cohort size (n=61) is moderate, the number of rupture events (n=23) restricts statistical power and precludes multivariable modeling. The score was therefore derived and evaluated within the same dataset, raising the possibility of optimism bias despite bootstrap and permutation procedures. Third, external validation was not performed. Fourth, morphological assessment, particularly binary features such as daughter dome presence, may be subject to measurement variability, although standardized criteria and dual independent review were applied.

These limitations indicate that the present findings should be interpreted as hypothesis-generating rather than confirmatory.

The exploratory score presented here provides a biologically plausible framework integrating morphology-derived and clinical variables for rupture risk stratification in MCA aneurysms. Future studies should aim to validate this model in independent, preferably multi-center cohorts with larger sample sizes and event counts.

Prospective investigations incorporating high-resolution imaging, standardized geometric measurements, and advanced analytical approaches—including machine learning-based modeling—may further refine the role of morphology in rupture risk assessment. Ultimately, robust external validation and calibration will be required before any morphology-based score can be considered for clinical implementation.

5. Conclusions

In this exploratory cohort of MCA aneurysms, morphological features reflecting aneurysm shape and complexity demonstrated the strongest association with rupture status. The proposed rupture risk score integrates morphological and clinical variables and showed a clear stepwise increase in rupture probability with strong internal performance. While not intended as a validated clinical decision tool, it provides a biologically plausible framework for future validation.

6. Patents

Author Contributions:

Conceptualization, Paslaru Francesca Gabriela and Iliescu Adrian;

Methodology, Brehar Felix Mircea;

Validation, Gorgan Radu Mircea;

Formal analysis, Paslaru Francesca Gabriela, Stanoaia Oana Elena;

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Supervision, Brehar Felix Mircea and Gorgan Radu Mircea;

All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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