Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# Multiverse analysis suggests that aneurysm location and admission condition modify the comparative effectiveness of clipping and coiling for ruptured aneurysms

**Jang Hun Kim**
Korea University Anam Hospital
**Jae-Wook Heo**
Korea University
**Eunji Moon**
Korea University Anam Hospital
**Min-Kyung Jung**
Korea University
**Dong-Joo Kim**
Korea University
**Hakseung Kim**
Korea University
**Dong-Hyuk Park**
doctorns@korea.ac.kr

Korea University Anam Hospital

**Article**

**Keywords:** Subarachnoid hemorrhage, Intracranial aneurysm, Microsurgical clipping, Endovascular coiling, Multiverse analysis, Propensity score

**Posted Date:** November 18th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-11436713/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

# Abstract

Whether a ruptured intracranial aneurysm is treated by microsurgical clipping or endovascular coiling is often decided by operator preference, and evidence from East Asian populations is limited. Because observational comparisons depend on many analytical choices, we applied a multiverse framework to a nationwide Korean registry of aneurysmal subarachnoid hemorrhage. Of 2,539 patients from 25 tertiary centers (2015–2017), 746 with anterior circulation aneurysms treated by a single modality were analyzed. We generated 8,964 analytical specifications combining missing-data strategies, propensity-score models and balancing methods, and summarized the 108 specifications that achieved covariate balance. Admission neurological severity and age were the most consistent predictors of unfavorable 1-year functional outcome. Coiling was directionally favored in 105 of 108 specifications (97.2%), but no specification showed a statistically significant overall difference. Interaction analyses suggested heterogeneity: clipping was favored for middle cerebral artery aneurysms, whereas coiling was favored for anterior cerebral and posterior communicating artery aneurysms and for patients with severely impaired consciousness or hypertension. These findings argue against a universal default and support individualized, data-driven selection of treatment modality.


# Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating cerebrovascular disease with high mortality and long-term disability. Global incidence is approximately 14 per 100,000 person-years,[1] and in the Republic of Korea more than 6,000 ruptured intracranial aneurysms are diagnosed each year, roughly 4,500 of which undergo microsurgical clipping or endovascular coiling.[2] Approximately 15% of patients die before reaching hospital and a further 20%–30% within the first 24 hours, and rebleeding without definitive aneurysm exclusion carries a mortality approaching 70%.[3,4] Prompt selection of the most appropriate treatment is therefore essential.

Outcomes and prognostic determinants of aSAH vary across regions, reflecting differences in ethnicity, healthcare infrastructure, and treatment culture.[1,2,5] Even within East Asia, aneurysm distribution and the relative use of clipping and coiling differ meaningfully from those of Western cohorts, so region-specific comparative-effectiveness evidence is needed rather than uncritical extrapolation of recommendations derived from Western populations.

To address this gap, the Korean Society of Cerebrovascular Surgery established a nationwide multicenter aSAH registry across 25 tertiary centers, enrolling patients over a 3-year window (2015–2017) with long-term outcome follow-up. To our knowledge, this is the first advanced multicenter ruptured-aneurysm cohort assembled in Korea and one of the few large, curated, real-world aSAH datasets in East Asia, complementing the recent Japanese registry-based comparative analysis by Ishikawa and colleagues.[6]

For a clinician facing a newly ruptured aneurysm, the decision between clipping and coiling remains one of the most consequential yet most subjective judgments in cerebrovascular practice. Current

international guidelines, including the 2023 American Heart Association/American Stroke Association recommendations,[7] provide broad guidance but no patient-tailored algorithm. In Korean practice, this decision is shaped largely by operator experience, institutional culture, and the availability of dual-trained neurovascular expertise. Whether one modality is preferable under specific anatomical and clinical conditions—and for whom—has not been rigorously characterized in Korean real-world data.

Observational comparative-effectiveness analyses are themselves vulnerable to methodological decisions: how missing data are handled, which propensity-score model is fit, which balancing strategy is applied, and which covariates are selected.[8] Any single analytical pipeline represents one of many defensible choices. Multiverse analysis addresses this problem by implementing many defensible specifications and quantifying the robustness of findings across them.[9] Applying this framework to the Korean multicenter aSAH cohort, we sought (i) to identify robust prognostic determinants of 1-year functional outcome and (ii) to characterize the conditions under which one treatment modality may be preferred.

## Results

# Participant characteristics

Of the 746 patients included, 286 (38.3%) underwent surgical clipping and 460 (61.7%) underwent endovascular coiling. None of the continuous variables met the assumption of normality (all $P < 0.05$). The distribution of aneurysm locations differed significantly between the two treatment groups. Significant between-group differences were also observed for ictus-to-obliteration interval, HH and WFNS severity grades, ruptured-aneurysm neck width and height, and dome size. The overall 1-year outcome distribution did not differ markedly between treatment groups (Table 1).

Table 1
Demographic and clinical characteristics of the study population.

| Variable | Clipping (n = 286) | Coiling (n = 460) | p-value |
|---|---|---|---|
| Age, years (mean ± SD) | 61.24 ± 11.69 | 59.94 ± 13.26 | 0.109 |
| Female sex, n (%) | 190 (66.43) | 298 (64.78) | 0.645 |
| Body mass index, kg/m² (mean ± SD) | 23.65 ± 3.15 | 23.54 ± 3.47 | 0.363 |
| Hypertension, n (%) | 118 (42.29) | 166 (36.32) | 0.106 |
| Diabetes mellitus, n (%) | 20 (7.33) | 44 (9.63) | 0.287 |
| Smoking, n (%) | 82 (28.77) | 140 (30.70) | 0.577 |
| Alcohol consumption, n (%) | 131 (46.29) | 187 (41.10) | 0.166 |
| Ictus to admission, h (median, IQR) | 3.00 (1.00–8.00) | 2.50 (1.00–5.00) | 0.138 |
| Ictus to obliteration, h (median, IQR) | 9.00 (5.00–23.00) | 5.50 (3.00–11.00) | < 0.001 |
| Glasgow Coma Scale at admission (median, IQR) | 14 (13–15) | 14 (12–15) | 0.322 |
| Hunt and Hess grade, n (%) I–II / III / IV–V | 156 (54.74) / 80 (28.07) / 49 (17.19) | 209 (45.43) / 145 (31.52) / 106 (23.04) | 0.035 |
| World Federation of Neurosurgical Societies grade, n (%) I–II / III / IV–V | 212 (74.39) / 24 (8.42) / 49 (17.19) | 308 (66.96) / 32 (6.96) / 120 (26.09) | 0.018 |
| Modified Fisher grade, n (%) 0–2 / 3–4 | 64 (22.54) / 220 (77.46) | 125 (27.23) / 334 (72.77) | 0.153 |
| Aneurysm location, n (%) | | | < 0.001 |
| Middle cerebral artery | 138 (48.25) | 52 (11.30) | |
| Anterior cerebral artery | 16 (5.59) | 32 (6.96) | |
| Anterior communicating artery | 81 (28.32) | 192 (41.74) | |
| Internal carotid artery–anterior choroidal artery | 15 (5.24) | 50 (10.87) | |
| Posterior communicating artery | 36 (12.59) | 134 (29.13) | |

*IQR, interquartile range; SD, standard deviation. Values are computed from the raw pre-imputation data using observed values only; the denominators for individual variables may therefore vary slightly.*

| Variable | Clipping (n = 286) | Coiling (n = 460) | p-value |
|---|---|---|---|
| Ruptured aneurysm neck width, mm (mean ± SD) | 3.57 ± 1.73 | 3.27 ± 1.36 | 0.040 |
| Ruptured aneurysm neck height, mm (mean ± SD) | 4.65 ± 2.51 | 5.21 ± 2.76 | 0.003 |
| Dome size, mm (mean ± SD) | 5.01 ± 3.19 | 5.25 ± 2.61 | 0.028 |
| Multiple aneurysms, n (%) | 41 (14.39) | 61 (13.26) | 0.664 |
| Unfavorable outcome (modified Rankin Scale 3–6) at 1 year, n (%) | 72 (25.17) | 116 (25.22) | 0.990 |

*IQR, interquartile range; SD, standard deviation. Values are computed from the raw pre-imputation data using observed values only; the denominators for individual variables may therefore vary slightly.*

## Propensity-score-based covariate balancing

The distribution of SMDs before and after adjustment is shown in Fig. 2. Before adjustment, the maximum SMD was 0.985, with three covariates exhibiting SMDs > 0.25, indicating substantial imbalance. Of the 8,964 candidate analyses, 3,240 met the criterion of a maximum weighted SMD < 0.25; after covariate adjustment, the median maximum SMD across analyses was 0.169 (IQR 0.136–0.201), indicating acceptable balance. Twelve analyses were then randomly sampled from each combination of balancing strategy and propensity-score model, yielding 108 specifications for the final pooled analysis.

## Average treatment effect

Comparative ATE estimates across the 108 final specifications are shown in Fig. 3. After covariate balancing, the median estimated ATE favored coiling by 0.033 (IQR 0.020–0.047). Coiling was directionally favored in 105 of 108 specifications (97.2%); however, all 95% CIs included zero, and no specification reached statistical significance.

## Univariate analysis

Figure 4a presents pooled univariate logistic regression results across the 108 final specifications. Markers of neurological severity (GCS, HH, WFNS, and modified Fisher grades), hypertension, diabetes, ruptured-aneurysm neck diameter, and older age were positively associated with unfavorable outcome, whereas alcohol consumption, male sex, BMI, and ictus-to-admission interval showed inverse associations. Treatment modality (coiling vs clipping) did not show a consistent association with outcome.

Univariate models incorporating neurological-severity scores had the highest explanatory power (pseudo-$R^2$ >0.20 and AUC > 0.70): WFNS (pseudo-$R^2$ 0.34, IQR 0.32–0.36; AUC 0.80, IQR 0.79–0.81), HH

(0.29, IQR 0.27–0.31; AUC 0.77, IQR 0.76–0.77), GCS (0.28, IQR 0.27–0.29; AUC 0.73, IQR 0.73–0.74), and modified Fisher grade (0.20, IQR 0.19–0.23; AUC 0.74, IQR 0.73–0.75). AUC values of the remaining univariate models were all below 0.67.

## Multivariate analysis

In multivariate models without interaction terms (Fig. 4b), WFNS grade (median OR 2.02, IQR 1.92–2.19), modified Fisher grade (OR 1.58, IQR 1.52–1.69), and older age (OR 1.06, IQR 1.05–1.07) were the most robust independent predictors of unfavorable outcome, reaching statistical significance in 107, 84, and 105 of 108 analyses, respectively. Ruptured-aneurysm neck diameter (OR 1.22, IQR 1.15–1.31) was included in 106 analyses and reached significance in 60, with a consistent adverse direction. Higher BMI showed a protective association, reaching significance in 37 of 98 analyses. Although GCS and HH grade were significant predictors in univariate analyses, their associations were attenuated in multivariate models, possibly owing to overlapping prognostic information captured by WFNS grade. Remaining covariates either lacked directional consistency or were non-significant in most analyses. Multivariate model performance improved over univariate models (AUC 0.87, IQR 0.86–0.87; pseudo-$R^2$ 0.46, IQR 0.45–0.48), with a median Hosmer–Lemeshow statistic of 8.00 ($P = 0.43$), indicating adequate calibration.

# Interaction analysis: treatment-effect heterogeneity

When interaction terms were included, the contrast between coiling and clipping varied substantially with aneurysm location and clinical condition (Fig. 5). Using ACoA as the reference location and prespecified baseline covariate values (defined below), the direction and magnitude of the coiling-versus-clipping OR were graded against the 0.67-to-1.5 equivalence range using both the median and the IQR (Table 2). Middle cerebral artery aneurysms strongly favored clipping (median OR 0.48, IQR 0.34–0.66; the entire IQR fell below 0.67 in 108 of 108 analyses). Anterior cerebral artery aneurysms (median OR 5.34, IQR 2.72–8.34) and posterior communicating artery aneurysms (OR 3.11, IQR 2.13–4.54) strongly favored coiling. Severe GCS at admission (OR 14.25, IQR 9.78–26.63; 26 analyses) and hypertension (OR 3.51, IQR 3.45–3.60; 14 analyses) also favored coiling, with the entire IQR above 1.5 in each case. Anterior communicating artery aneurysms favored coiling weakly (median OR 1.58, IQR 1.29–2.41; the IQR entered the equivalence range). Internal carotid artery–anterior choroidal artery aneurysms (median OR 0.91, IQR 0.60–1.25) and the severe HH grade interaction (median OR 0.80, IQR 0.48–0.93; 38 analyses) fell within the equivalence range and did not show a consistent preference.

Table 2
Multiverse-derived clipping-versus-coiling recommendation grade by aneurysm location and clinical condition.

| Interaction term | Retained (n/108) | Favored treatment | Median odds ratio (IQR) | Recommendation | Basis |
|---|---|---|---|---|---|
| Middle cerebral artery aneurysm | 108 | Clipping | 0.48 (0.34–0.66) | Strong | Entire IQR below 0.67 |
| Anterior cerebral artery aneurysm | 108 | Coiling | 5.34 (2.72–8.34) | Strong | Entire IQR above 1.5 |
| Posterior communicating artery aneurysm | 108 | Coiling | 3.11 (2.13–4.54) | Strong | Entire IQR above 1.5 |
| Severe Glasgow Coma Scale at admission | 26 | Coiling | 14.25 (9.78–26.63) | Strong | Entire IQR above 1.5 |
| Hypertension | 14 | Coiling | 3.51 (3.45–3.60) | Strong | Entire IQR above 1.5 |
| Anterior communicating artery aneurysm* | 108 | Coiling | 1.58 (1.29–2.41) | Weak | Median > 1.5, but IQR enters 0.67–1.5 |
| Severe Hunt and Hess grade | 38 | — | 0.80 (0.48–0.93) | Equipoise | Median within 0.67–1.5 |
| Internal carotid artery–anterior | 108 | — | 0.91 | Equipoise | Median within 0.67–1.5 |

*IQR, interquartile range. Odds ratio (coiling versus clipping) for unfavorable 1-year outcome (modified Rankin Scale 3–6), estimated from interaction-augmented multivariate weighted logistic regression across the 108 balance-passing multiverse specifications; an odds ratio below 1 favors clipping, and an odds ratio above 1 favors coiling. Each interaction term was graded by whether the median and the interquartile range of its odds ratio fell outside a conventional equivalence range (0.67–1.5): 'Strong' when both the median and the entire interquartile range fell outside the range; 'Weak' when only the median did; 'Equipoise' when the median itself fell within the range. Retained denotes the number of the 108 specifications in which the term was selected during Bayesian information criterion–based stepwise variable selection. *Anterior communicating artery aneurysm was used as the reference aneurysm location; the reported odds ratio represents the direct treatment effect at the reference condition.*

| Interaction term | Retained (n/108) | Favored treatment | Median odds ratio (IQR) | Recommendation | Basis |
|---|---|---|---|---|---|
| choroidal artery aneurysm | | | (0.60–1.25) | | |

*IQR, interquartile range. Odds ratio (coiling versus clipping) for unfavorable 1-year outcome (modified Rankin Scale 3–6), estimated from interaction-augmented multivariate weighted logistic regression across the 108 balance-passing multiverse specifications; an odds ratio below 1 favors clipping, and an odds ratio above 1 favors coiling. Each interaction term was graded by whether the median and the interquartile range of its odds ratio fell outside a conventional equivalence range (0.67–1.5): 'Strong' when both the median and the entire interquartile range fell outside the range; 'Weak' when only the median did; 'Equipoise' when the median itself fell within the range. Retained denotes the number of the 108 specifications in which the term was selected during Bayesian information criterion–based stepwise variable selection. *Anterior communicating artery aneurysm was used as the reference aneurysm location; the reported odds ratio represents the direct treatment effect at the reference condition.*

Interaction models showed slightly higher AUC and pseudo-$R^2$ than the base multivariate models (AUC 0.88, IQR 0.87–0.88; pseudo-$R^2$ 0.49, IQR 0.48–0.50), with a median Hosmer–Lemeshow statistic of 11.68 (P = 0.17). Reference conditions for the interaction models were defined as female sex, age 60 years, moderate GCS at admission, ictus-to-admission 3 hours, ictus-to-obliteration 6.5 hours, HH grade 3, WFNS grade 2, modified Fisher grade 3, ruptured-aneurysm neck diameter 3 mm, neck height 4.47 mm, dome size 4.55 mm, BMI 23.44 kg/$m^2$, and ACoA aneurysm location. For the remaining categorical covariates, the 'absent' category was used as the reference.

# Discussion

The principal findings of this analysis, drawn from the first advanced Korean multicenter aSAH cohort, are twofold. First, admission neurological severity (WFNS grade and modified Fisher grade) and older age were the most robust predictors of unfavorable 1-year outcome across the 108 balance-passing analytical specifications, with higher BMI showing a protective association (Fig. 4b). Second, although coiling was directionally favored overall, treatment-effect heterogeneity emerged by aneurysm location and admission condition (Fig. 5): clipping was strongly favored for MCA aneurysms, and coiling was strongly favored for ACA and PCoA aneurysms. Coiling was also favored for patients presenting with severe GCS or hypertension and weakly favored for ACoA aneurysms, whereas no clear preference emerged for ICA-AChA aneurysms or in severe HH grade. Figure 6 consolidates these condition-specific preferences into a data-driven treatment-selection guide.

Surgical clipping was the historical standard for definitive treatment of ruptured intracranial aneurysms, but endovascular coiling has become widely adopted as a less invasive alternative.[7] Each modality carries well-recognized trade-offs: clipping affords higher complete-occlusion rates and lower rebleeding risk but is more invasive;[10,11] coiling offers fewer procedural complications and shorter hospitalization but is limited by concerns regarding incomplete occlusion, recanalization, and retreatment.[12] Most

contemporary comparative studies have found no significant difference in functional outcomes between the two modalities,[13,14] whereas some have shown short-term benefits favoring coiling in poor-grade patients[6] and others have documented durability advantages for clipping.[15,16] These inconsistencies are largely attributable to differences in study design, patient selection, aneurysm characteristics, and analytical approach.[17,18] Randomized controlled trials remain the gold standard, but ethical, logistical, and real-world heterogeneity considerations severely constrain their feasibility in aSAH;[8] rigorous observational analyses—particularly those minimizing researcher-degrees-of-freedom bias—therefore remain essential for informing modality selection.

**Coi**

ling was directionally favored in 105 of 108 ATE specifications (97.2%), consistent with the directional findings of early landmark trials favoring coiling.[19] However, CIs consistently spanned the null, indicating that any overall benefit, if real, is small in magnitude or is partially offset by effect heterogeneity across patient subgroups. These observations align with contemporary literature emphasizing the context-dependence of comparative effectiveness in aSAH.[20] Importantly, we found no evidence that either modality is uniformly and clinically meaningfully superior across all situations. Our findings complement the recent Japanese registry study by Ishikawa et al,[6] which reported a coiling advantage in poor-grade patients; our data extend that observation by mapping which specific anatomical and clinical conditions favor each modality in a Korean nationwide sample.

WFNS grade and modified Fisher grade were the strongest independent predictors of outcome. WFNS primarily reflects neurological status, whereas modified Fisher grade quantifies hemorrhage volume and distribution on computed tomography. These metrics capture key aspects of early brain injury and are well established as outcome predictors.[21] In our analysis they played a central role but, being admission-based, were unable to fully explain the variance in 1-year outcome. This argues for the development of richer, clinically actionable prognostic indices that integrate treatment strategy, detailed aneurysm morphology, and risk for complications such as delayed cerebral ischemia.

Higher BMI was associated with more favorable outcome, reaching statistical significance in a substantial minority of specifications. This is consistent with the well-described 'obesity paradox' observed across several acute and critical illnesses.[22] In older patients, low BMI often reflects unstable nutritional status and confers adverse prognosis. Because BMI does not fully capture body composition, the protective association is most appropriately interpreted as exploratory rather than causal.

The location- and condition-specific patterns visualized in Fig. 6 are concordant with established neurosurgical and neurointerventional rationales. MCA bifurcation aneurysms often harbor broad-necked or complex configurations that are technically more amenable to microsurgical reconstruction, and coincident hematomas can be evacuated at surgery. ACA and PCoA aneurysms are anatomically accessible to endovascular techniques and may afford less satisfactory surgical exposure, particularly in patients with elevated intracranial pressure or significant comorbidity. The strong coiling advantage in

severe-GCS and hypertensive patients is consistent with the lower physiological burden of endovascular treatment in poor-grade aSAH.[6] The weaker coiling signal in ACoA aneurysms and the equipoise for ICA-AChA aneurysms likely reflect anatomically heterogeneous configurations within these locations, in which case-by-case multidisciplinary decision-making remains warranted.

For variable selection, we used the BIC, a conservative criterion.[23] It prevents the selection of unnecessary variables, thereby reducing analytic noise and providing clinically interpretable models. Less frequently retained interaction terms can therefore be interpreted as lying at the borderline of model selection under this stringent criterion rather than as a direct indicator of clinical irrelevance.

Missingness was modest (< 5.8%) yet handled with multiple missing-data strategies to mitigate distortion from any single approach. To address confounding by indication in treatment allocation, we adopted both weighting-based (sIPTW and OW) and matching-based (PSM) approaches: sIPTW stabilizes weights by multiplying the inverse probability by the marginal treatment probability, mitigating instability arising from extreme propensity scores; OW similarly addresses extreme scores by assigning weights proportional to the probability of receiving the opposite treatment;[24,25] and PSM may offer additional protection against treatment-assignment bias.[26] An equal number of analyses was sampled from each strategy, enabling presentation of result distributions across diverse assumptions rather than a single deterministic estimate. These cross-specification distributions describe analytical variation rather than sampling uncertainty; accordingly, the reported IQRs should not be interpreted as CIs.

Beyond these safeguards, estimating the treatment effect across 108 defensible specifications rather than one allows the consistency of a finding to be quantified directly. The overall absence of a significant effect was consistent across all 108 specifications, suggesting that it reflects a small effect, or heterogeneity not resolved in this study, rather than an artifact of any single analytic choice. Likewise, the subgroup-specific preferences that recurred across specifications are unlikely to be incidental. Generalizability is supported by a multicenter design reflective of real-world Korean practice; restricting inclusion to single-modality treatment minimized treatment-crossover bias, and outcome assessment by multiple independent clinicians reduced single-rater bias.

Several important limitations should be acknowledged. First, 1,481 of the 2,539 initially identified patients were excluded because the 1-year mRS was missing or considered unreliable. Although the baseline characteristics of excluded patients who met the other eligibility criteria were broadly similar to those of the analytic cohort (Supplementary Table S3-5), the outcome analyses did not include the full cohort, and the direction and magnitude of resulting selection bias cannot be determined. Second, treatment allocation was likely influenced by aneurysm anatomy, clinical severity, institutional practice, operator expertise, and procedural availability, and center- and operator-level effects were not explicitly modeled in the primary analysis. In a sensitivity analysis using institution-clustered standard errors (Supplementary Tables S2-3–S2-5), statistical significance was reduced for some associations, but the overall results were broadly similar. However, because several centers contributed very few patients, this analysis could not be considered fully reliable, and residual confounding and clustering cannot be

excluded. Propensity-score methods adjust only for measured variables and cannot eliminate unmeasured confounding. Third, the analytical specifications were generated from the same cohort and overlapping model structures; they therefore constitute a distributed sensitivity analysis rather than independent replications. Furthermore, sIPTW, overlap weighting, and propensity-score matching may target different populations and estimands, limiting the interpretation of their estimates as repeated measures of a single treatment effect. The final 108 specifications were randomly selected from 3,240 balance-passing analyses, and this sampling procedure itself constitutes an analytical choice. The maximum SMD threshold of 0.25 was relatively permissive, and residual imbalance may have remained.

In conclusion, in this Korean multicenter aSAH cohort, admission neurological severity was the most consistent predictor of poor functional outcome. No overall superiority was demonstrated for either clipping or coiling, but interaction analyses suggested location- and condition-dependent heterogeneity: clipping was strongly favored for MCA aneurysms, whereas coiling was strongly favored for ACA and PCoA aneurysms. Coiling was also favored for severely obtunded or hypertensive patients. These findings argue against a universal default and support individualized, data-driven modality selection.

## Methods

# Study design and patient population

This multicenter retrospective cohort study was conducted as a secondary analysis of an existing nationwide aneurysmal subarachnoid hemorrhage registry established by the Korean Society of Cerebrovascular Surgery (KSCVS), comprising data from 25 participating tertiary medical centers.The present secondary analysis was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No. 2019AN073). The participating institutions of the original registry are listed in the Acknowledgements section.

All methods were performed in accordance with relevant guidelines and regulations and the Declaration of Helsinki. The requirement for informed consent for the present retrospective secondary analysis was waived by the Institutional Review Board of Korea University Anam Hospital.

The study is reported in accordance with the STROBE guideline. Data on patients with aSAH admitted to 25 tertiary medical centers in the Republic of Korea between January 1, 2015, and December 31, 2017 (a 3-year enrollment window; outcome ascertainment extended through subsequent follow-up) were retrospectively collected using a standardized electronic case report form (eCRF). The eCRF was specifically designed for this study, and data were entered through a centralized web-based system and subsequently curated for analysis (Supplementary Figs. S1-1–S1-13). All patients were managed according to standard clinical practice at each institution. A total of 2,539 patients were initially identified.

Patients with incomplete or unreliable data in the eCRF, particularly those with missing or indeterminate 1-year modified Rankin Scale (mRS) outcomes—a key variable for prognostic assessment—were

excluded (n = 1,481). An additional 12 patients were excluded due to missing or indeterminate ruptured-aneurysm location. To minimize confounding by indication for combined or hybrid procedures, only patients who underwent a single, clearly defined treatment modality (surgical clipping or endovascular coiling) were retained; 244 patients who received additional or non-classifiable interventions (eg, flow-diversion or salvage stent placement, external ventricular drainage alone as the index procedure) were excluded. Because the primary objective was to evaluate prognostic factors and treatment effects in anterior circulation aneurysms, patients with vertebrobasilar aneurysms were excluded (n = 56); these lesions had a small sample size with marked treatment imbalance favoring endovascular therapy, reflecting limited variability in clinical decision-making and a high risk of biased comparative inference. After applying these criteria, 746 patients were included in the final analysis (Fig. 1).

# Variables and outcome definition

The variables considered for analysis were sex, age, body mass index (BMI), diabetes mellitus, hypertension, hyperlipidemia, alcohol consumption, smoking status, prior anticoagulant or lipid-lowering medication use, ictus-to-admission interval, ictus-to-obliteration interval, Hunt and Hess (HH) grade, World Federation of Neurosurgical Societies (WFNS) grade, modified Fisher grade at admission, Glasgow Coma Scale (GCS) score at admission, presence of multiple aneurysms, ruptured aneurysm neck width and height, dome size, and aneurysm location (middle cerebral artery [MCA], anterior cerebral artery [ACA], anterior communicating artery [ACoA], internal carotid artery–anterior choroidal artery [ICA-AChA], and posterior communicating artery [PCoA]).

The primary outcome was functional status at 1 year after aSAH, assessed with the mRS and dichotomized as favorable (mRS 0–2) versus unfavorable (mRS 3–6). Sensitivity analyses using alternative dichotomization thresholds (0 vs 1–6, 0–1 vs 2–6, 0–3 vs 4–6, 0–4 vs 5–6, and 0–5 vs 6) are reported in Supplementary Tables S2-1 and S2-2.

# Missing data and bias management

Missing covariate data were handled using three alternative approaches: median imputation, multiple imputation by chained equations (MICE), and complete-case analysis. The maximum proportion of missingness for any variable was less than 5.8%, and the overall impact of the imputation strategy on the analysis was considered minimal. To address potential confounding by indication in treatment allocation, propensity-score-based methods were applied, including stabilized inverse probability of treatment weighting (sIPTW), overlap weighting (OW), and propensity score matching (PSM). Propensity scores were estimated using logistic regression, random forest, and gradient boosting classifiers, each with hyperparameters optimized via grid search, yielding 90, 216, and 192 trained models, respectively (498 propensity-score models in total per missing-data condition).

# Multiverse analysis framework

To avoid dependence on a single analytical pipeline, we constructed a multiverse of analytical specifications by combining missing-data strategies, propensity-score estimation models, covariate-

balancing strategies, and variable-selection directions (forward and backward stepwise selection using the Bayesian information criterion [BIC]), yielding 8,964 candidate specifications. Following a principled multiverse approach, adequate covariate balance—defined as a maximum weighted standardized mean difference (SMD) < 0.25—was applied as an inclusion criterion so that only specifications achieving acceptable confounding control contributed to the pooled inference; 3,240 specifications met this criterion. To ensure that each stratum contributed equally to the pooled inference, 12 specifications were randomly sampled from the 9 strata defined by covariate-balancing strategy × propensity-score model class, yielding 108 final specifications. Details of the multiverse analysis framework and propensity model training are provided in Supplementary Tables S3-1–S3-4 and Supplementary Fig. S3-1.

Two complementary analyses were performed. First, the average treatment effect (ATE) of coiling versus clipping was estimated as the difference in weighted mean outcomes between groups. Second, prognostic factors and treatment-effect heterogeneity were examined through a sequence of weighted logistic regressions: (1) univariate models to screen candidate predictors, (2) multivariate models for independent covariate effects, and (3) interaction-augmented models for the differential effect of clipping versus coiling across conditions. The multivariate models included variables with $P < 0.20$ in univariate analysis, together with treatment modality and aneurysm location. The interaction models used the same base inputs as the multivariate models, with the interaction terms retained through the stepwise variable selection. Whereas the univariate and multivariate odds ratios (ORs) express each covariate's association with unfavorable outcome, the interaction analysis derived the conditional OR of an unfavorable outcome for clipping versus coiling within each condition. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), the Nagelkerke pseudo-$R^2$, and the Hosmer–Lemeshow goodness-of-fit test. Results are reported as median with interquartile range (IQR).

# Statistical analysis

The normality of continuous variables was assessed with the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as frequencies and percentages. Group comparisons used the Mann–Whitney U test for continuous and ordinal variables and the $\chi^2$ test for categorical variables. The GCS score was categorized as mild (13–15), moderate (9–12), and severe (3–8). Continuous and ordinal variables were normalized using min–max scaling and centered at the median. A two-sided $P < 0.05$ was considered statistically significant. All analyses were conducted in Python 3.11.

# Use of large language models

Claude (Anthropic) was used for English-language editing, for condensing the text to journal length, and for generating plotting code used to format the figures. It was not used for data analysis or interpretation. The authors reviewed all output and take full responsibility for the content.

## Declarations

# Additional information

**Competing interests:**

The authors declare no competing interests.

# Funding

This work was supported by the Korean Fund for Regenerative Medicine (KFRM) grant funded by the Korean government (MSIT, MHW) (No. 22A0204L1); the Korea University Grant (K2614871, K2426661); and the National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (No. 2022R1A2C1013205 and No. RS-2024-00336744). The funders had no role in the design, conduct, analysis, or reporting of the study.

# Author Contribution

JH Kim and J-W Heo contributed equally to this work as co-first authors. H Kim and D-H Park contributed equally to this work as co-corresponding authors.

# Acknowledgement

The authors gratefully acknowledge the Multicenter Clinical Trial Committee of the Korean Society of Cerebrovascular Surgery (KSCVS) for organizing and supporting the nationwide multicenter subarachnoid hemorrhage registry from which the study data were derived, and thank the clinical and research staff at the 25 participating tertiary institutions for their contributions to patient enrollment, data collection, and quality assurance. Participating institutions (alphabetical order): Chonnam National University Hospital; Chungnam National University Hospital; Dong-A University Hospital; Eulji University Hospital; Gachon University Gil Medical Center; Hanyang University Guri Hospital; Hanyang University Seoul Hospital; Inha University Hospital; Inje University Busan Paik Hospital; Inje University Sanggye Paik Hospital; Keimyung University Dongsan Medical Center; Korea University Anam Hospital; Kyungpook National University Hospital; Pusan National University Yangsan Hospital; Seoul National University Bundang Hospital; Soonchunhyang University Cheonan Hospital; Sungkyunkwan University Kangbuk Samsung Hospital; Sungkyunkwan University Samsung Medical Center; The Catholic University Bucheon St. Mary's Hospital; The Catholic University Incheon St. Mary's Hospital; Ulsan University Hospital; Wonkwang University Hospital; Yeungnam University Hospital; Yonsei University Gangnam Severance Hospital; and Yonsei University Severance Hospital. Figure 6 was drawn by the authors.

# Data Availability

The datasets analysed during the current study are not publicly available because of data-sharing restrictions of the multicenter registry, but are available from the corresponding author on reasonable request.

## References


1. Ding, P. F. et al. Analysis and prediction of subarachnoid hemorrhage burden in global, China, and Japan. *BMC Public. Health*. **25**, 27 (2025).
2. Kim, T. et al. Incidence and risk factors of intracranial aneurysm: a national cohort study in Korea. *Int. J. Stroke*. **11**, 917–927 (2016).
3. Mori, S. et al. Fatal intracranial aneurysms and dissections causing subarachnoid hemorrhage: an epidemiological and pathological analysis of 607 legal autopsy cases. *J. Stroke Cerebrovasc. Dis.* **27**, 486–493 (2018).
4. Datar, S. *Aneurysmal subarachnoid hemorrhage. in Neurological Emergencies: A Practical Approach 231–244* (Springer, 2019).
5. Etminan, N. et al. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. *JAMA Neurol.* **76**, 588–597 (2019).
6. Ishikawa, T. et al. Superiority of endovascular coiling over surgical clipping for clinical outcomes at discharge in patients with poor-grade subarachnoid hemorrhage: a registry study in Japan. *Neurosurgery* **94**, 1051–1060 (2024).
7. Hoh, B. L. et al. 2023 guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* **54**, e314–e370 (2023).
8. Monti, S., Grosso, V., Todoerti, M. & Caporali, R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatol. (Oxford)*. **57**, vii54–vii58 (2018).
9. Moore, M. J. & Demeyere, N. Multiverse to inform neurological research: an example using recovery outcome of neglect. *J. Neurol.* **269**, 233–242 (2022).
10. Hammed, A. et al. Preventive clipping versus coiling in unruptured intracranial aneurysms: a comprehensive meta-analysis and systematic review to explore safety and efficacy. *Neurol. Sci.* **46**, 2499–2522 (2025).
11. Broderick, J. Clipping or coiling: the first step for ruptured aneurysms. *Lancet Neurol.* **8**, 414–415 (2009).
12. Spetzler, R. F. et al. The Barrow Ruptured Aneurysm Trial: 6-year results. *J. Neurosurg.* **123**, 609–617 (2015).
13. Bakker, N. A., Veeger, N. & van Dijk, J. M. C. Clipping comparable to coiling in intracranial aneurysm. *Ned Tijdschr Geneeskd*. **159**, A8601 (2015).

14. Zanaty, M. et al. Short-term outcome of clipping versus coiling of ruptured intracranial aneurysms treated by dual-trained cerebrovascular surgeon: single-institution experience. *World Neurosurg.* **95**, 262–269 (2016).
15. Wach, J., Vychopen, M., Kühnapfel, A., Seidel, C. & Güresir, E. A long-term comparative analysis of endovascular coiling and clipping for ruptured cerebral aneurysms: an individual patient-level meta-analysis assessing rerupture rates. *J. Clin. Med.* **13**, 1778 (2024).
16. Li, H. et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. *Stroke* **44**, 29–37 (2013).
17. Lindgren, A. et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst. Rev.* **8**, CD003085 (2018).
18. Lindgren, A. et al. Outcome after clipping and coiling for aneurysmal subarachnoid hemorrhage in clinical practice in Europe, USA, and Australia. *Neurosurgery* **84**, 1019–1027 (2019).
19. Molyneux, A. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* **360**, 1267–1274 (2002).
20. Zhu, W. et al. Clipping versus coiling for aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis of prospective studies. *Neurosurg. Rev.* **45**, 1291–1302 (2022).
21. Al-Mufti, F. et al. Prognostication following aneurysmal subarachnoid hemorrhage: the modified Hunt and Hess grading scale. *Stroke Vasc Interv Neurol.* **4**, e001349 (2024).
22. Hainer, V. Aldhoon-Hainerová, I. Obesity paradox does exist. *Diabetes Care*. **36**, S276–S281 (2013).
23. Vrieze, S. I. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). *Psychol. Methods*. **17**, 228–243 (2012).
24. Pezzi, A., Cavo, M., Biggeri, A., Zamagni, E. & Nanni, O. Inverse probability weighting to estimate causal effect of a singular phase in a multiphase randomized clinical trial for multiple myeloma. *BMC Med. Res. Methodol.* **16**, 150 (2016).
25. Thomas, L. E., Li, F. & Pencina, M. J. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. *JAMA* **323**, 2417–2418 (2020).
26. Kush, J. M., Konold, T. R. & Bradshaw, C. P. Covariate balance for observational effectiveness studies: a comparison of matching and weighting. *J. Res. Educ. Eff.* **16**, 189–212 (2023).

# Figures

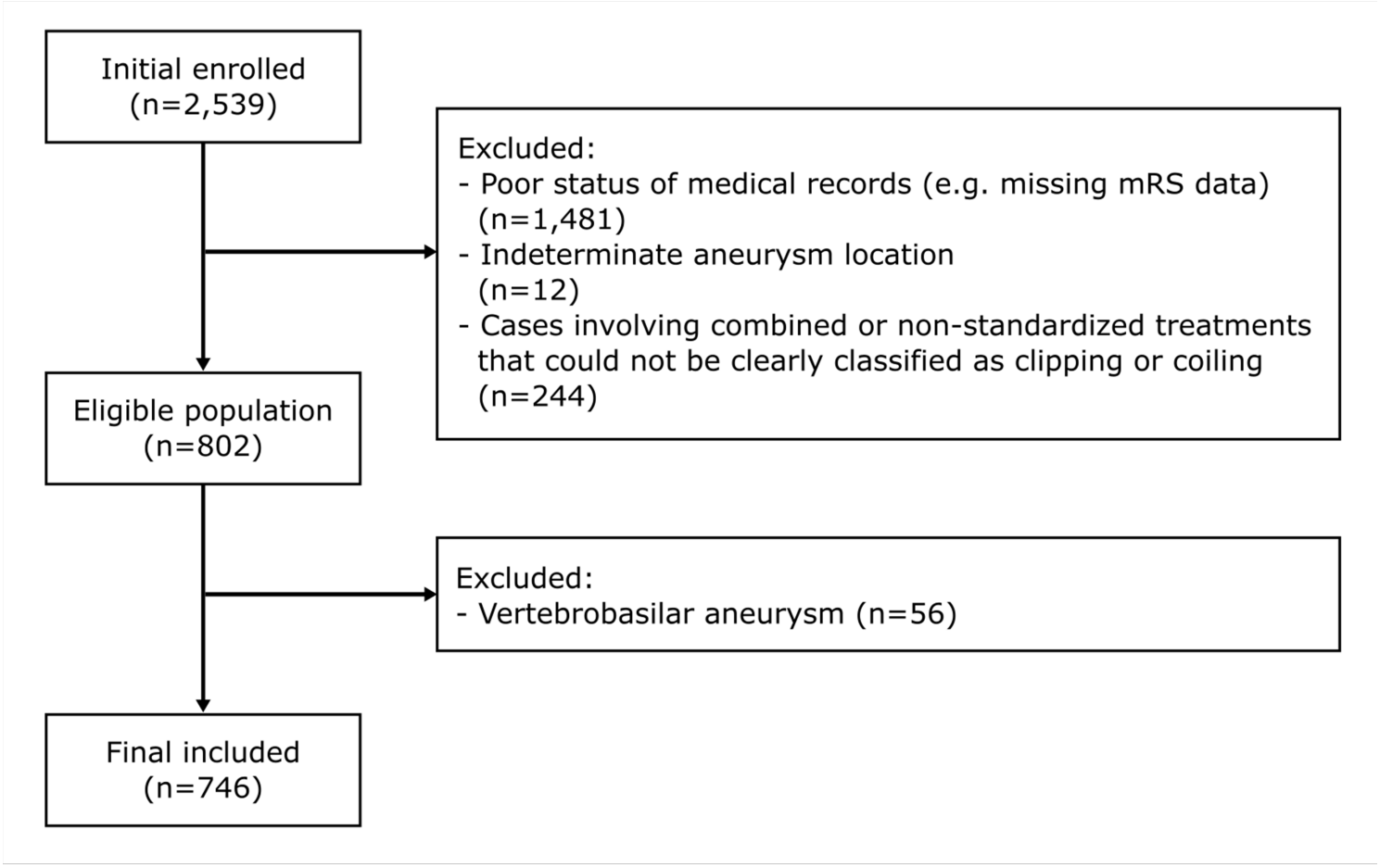
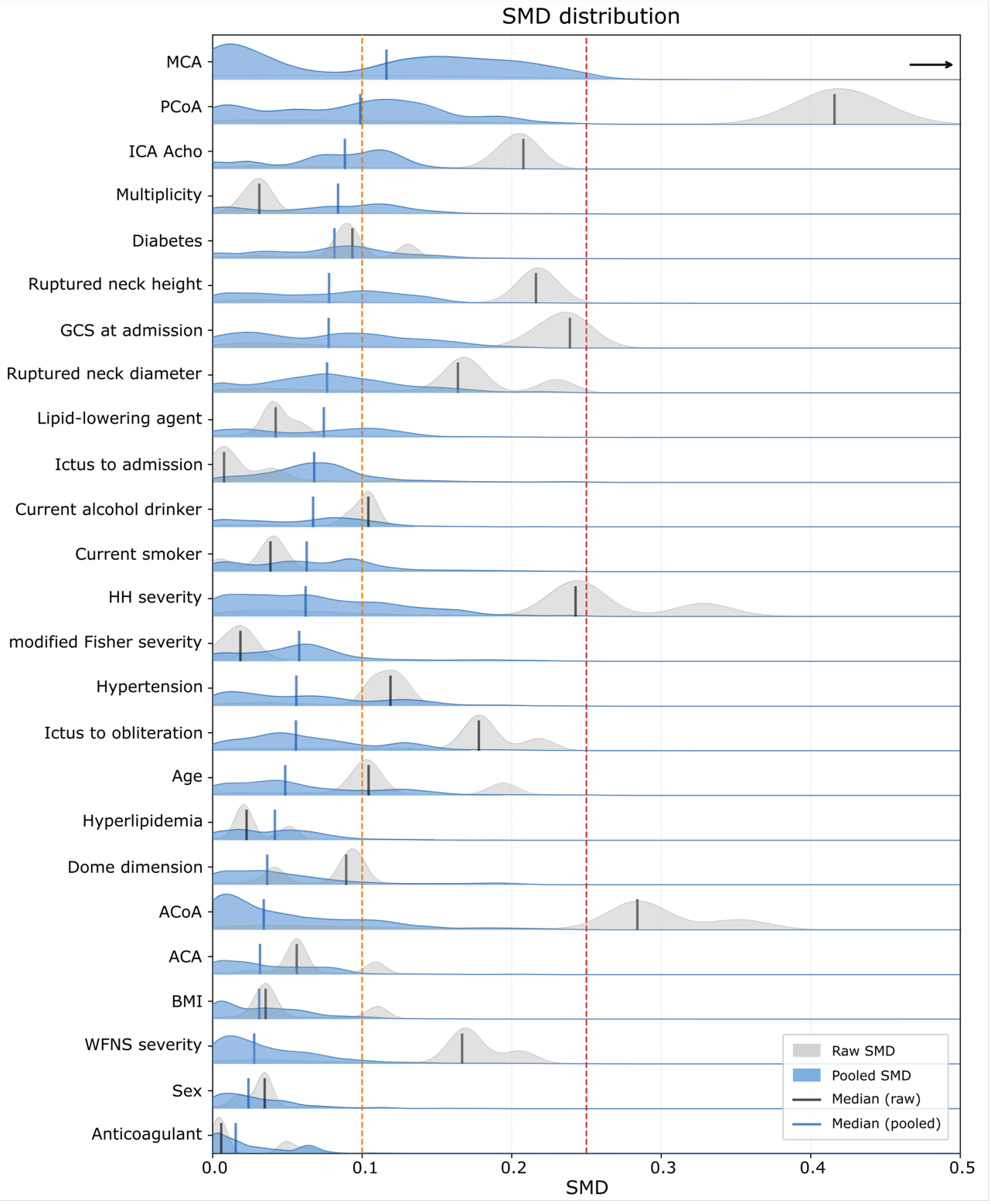



**Figure 1**

Patient selection flow diagram. Of 2,539 patients with aneurysmal subarachnoid hemorrhage identified at 25 Korean tertiary institutions (2015–2017), 746 patients with anterior circulation aneurysms treated by a single modality were included after exclusion of patients with a missing 1-year modified Rankin Scale score (n = 1,481), missing rupture location (n = 12), combined or non-classifiable interventions (n = 244) and vertebrobasilar aneurysms (n = 56).




## Figure 2

Covariate balance across the multiverse. Distribution of standardized mean differences (SMDs) for each covariate before (grey) and after (blue) covariate balancing across the candidate specifications; vertical lines indicate medians. Dashed lines mark SMDs of 0.1 and 0.25. Before adjustment the maximum SMD was 0.985; 3,240 of 8,964 specifications met the balance criterion (maximum SMD < 0.25), with a median maximum post-adjustment SMD of 0.169 (interquartile range [IQR], 0.136–0.201).

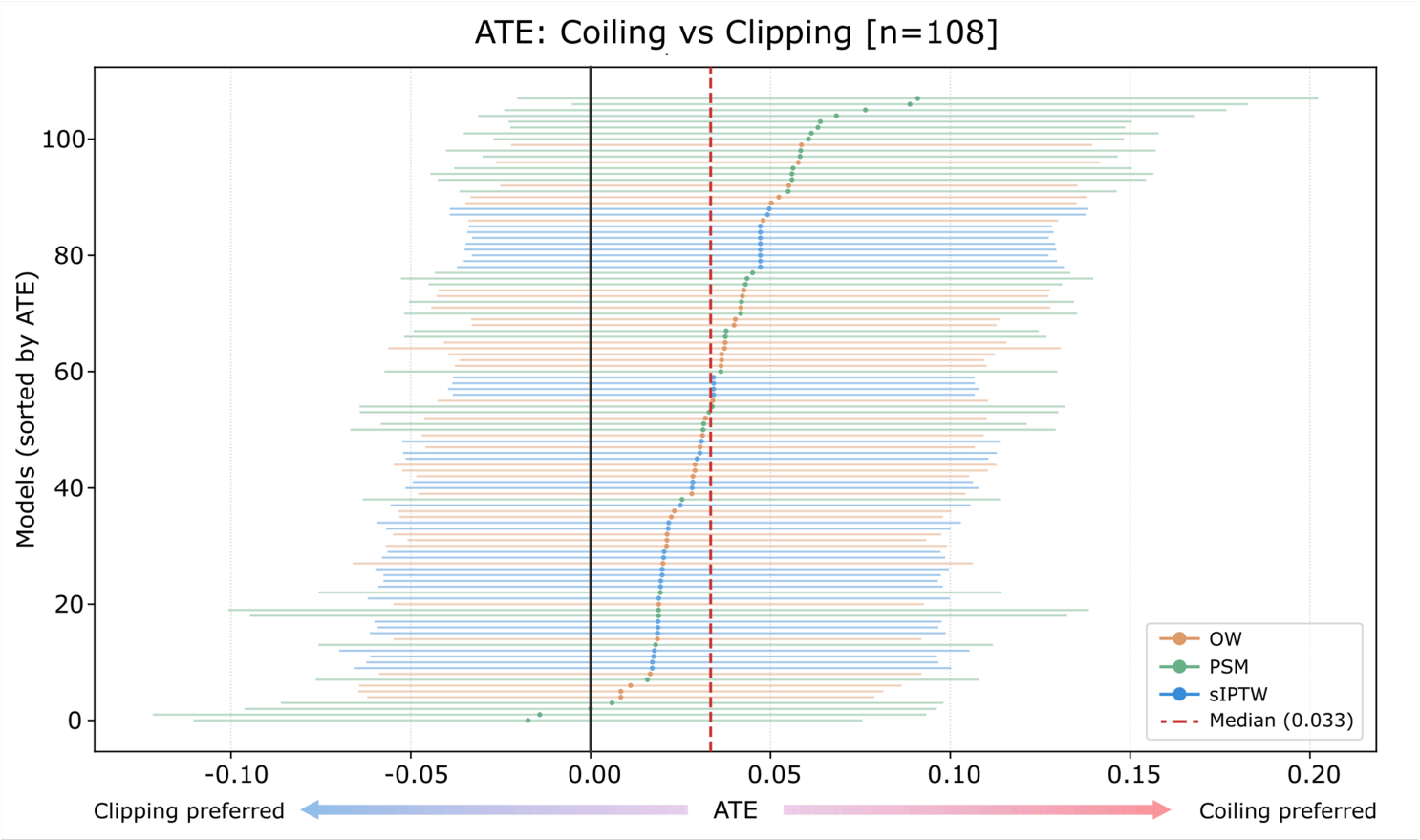
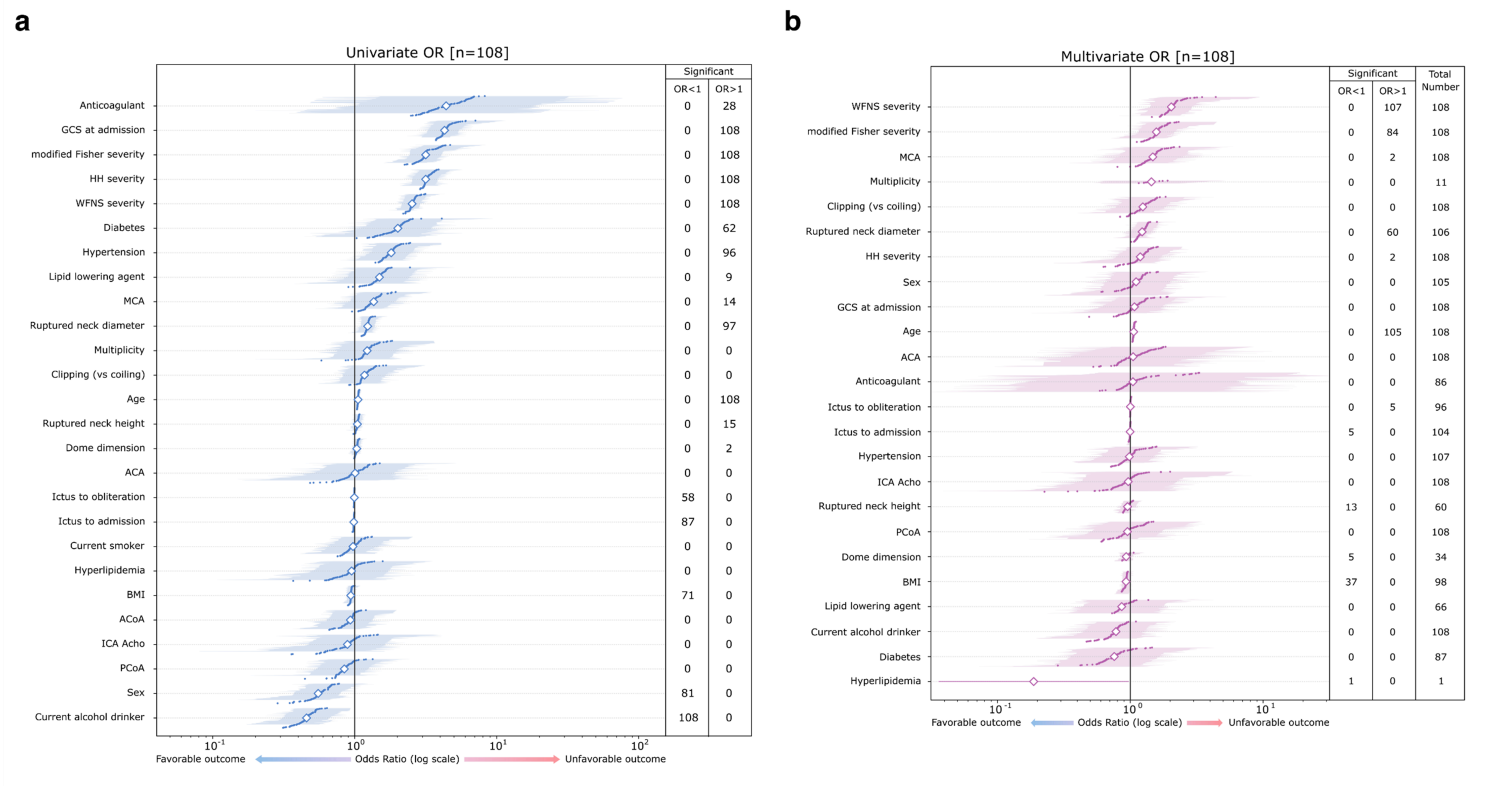


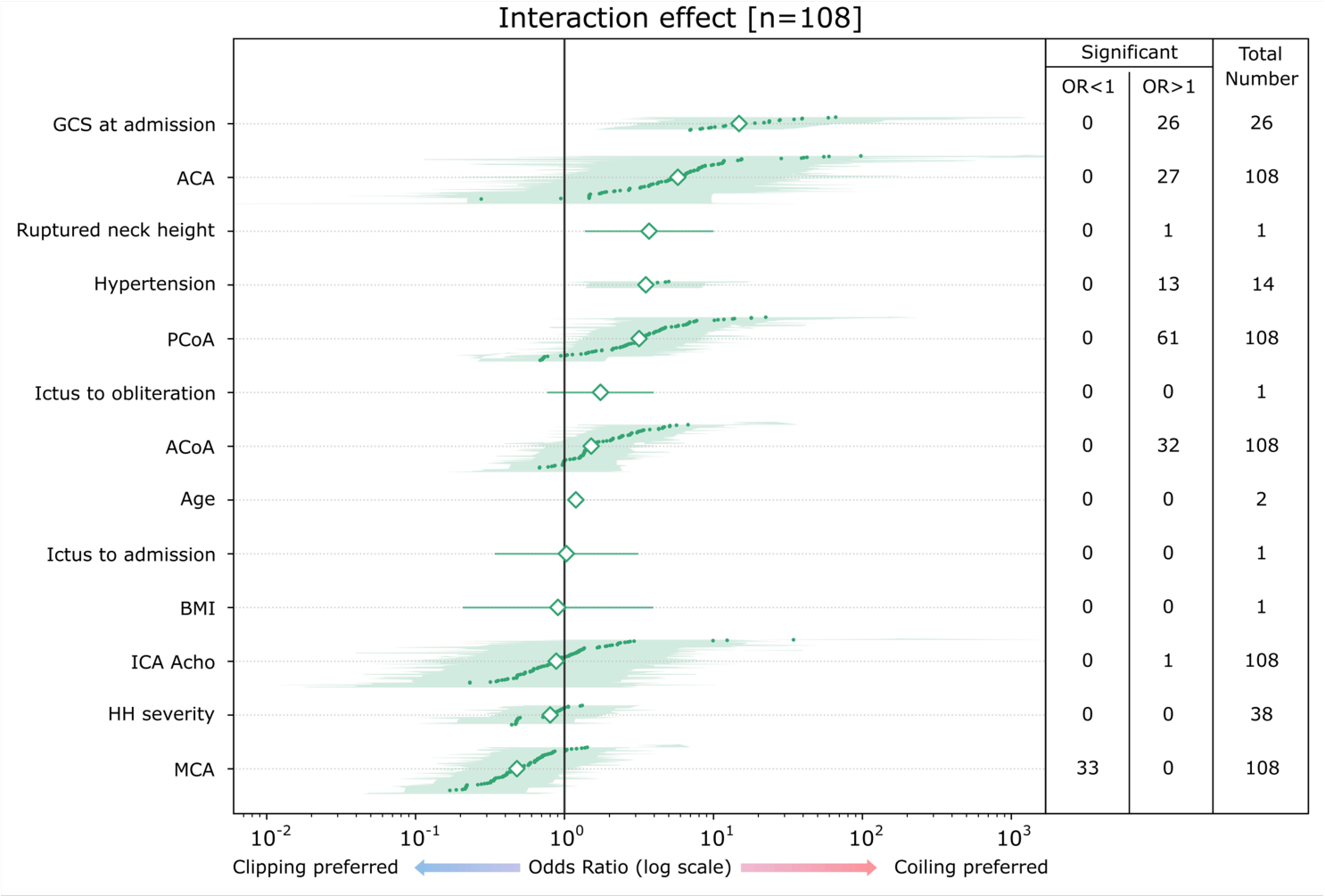

**Figure 3**

Average treatment effect of coiling versus clipping across the 108 final specifications. Each horizontal line shows one specification (point estimate and 95% confidence interval), sorted by estimate and coloured by balancing strategy (OW, overlap weighting; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting). The dashed red line marks the median (0.033; IQR, 0.020–0.047). Coiling was directionally favored in 105 of 108 specifications (97.2%); no specification reached statistical significance.




## Figure 4

Prognostic factors for unfavorable 1-year outcome (modified Rankin Scale 3–6) across the 108 final specifications. (a) Odds ratios from univariate weighted logistic regression. (b) Odds ratios from multivariate weighted logistic regression without interaction terms. Diamonds indicate median odds ratios and shaded areas the distribution across specifications; columns give the number of specifications in which each term reached significance ($P < 0.05$) in either direction and the number in which it was retained.




## Figure 5

Treatment-effect heterogeneity. Odds ratios of unfavorable 1-year outcome for coiling versus clipping from interaction-augmented multivariate weighted logistic regression across the 108 final specifications, by aneurysm location and clinical condition; odds ratios < 1 favor clipping and > 1 favor coiling. Clipping was strongly favored for middle cerebral artery aneurysms, and coiling for anterior cerebral and posterior communicating artery aneurysms; coiling was also favored for severe Glasgow Coma Scale at admission and hypertension, terms retained in a subset of specifications. ACA, anterior cerebral artery; ACoA, anterior communicating artery; BMI, body mass index; GCS, Glasgow Coma Scale; HH, Hunt and Hess; ICA Acho, internal carotid artery–anterior choroidal artery; MCA, middle cerebral artery; PCoA, posterior communicating artery.

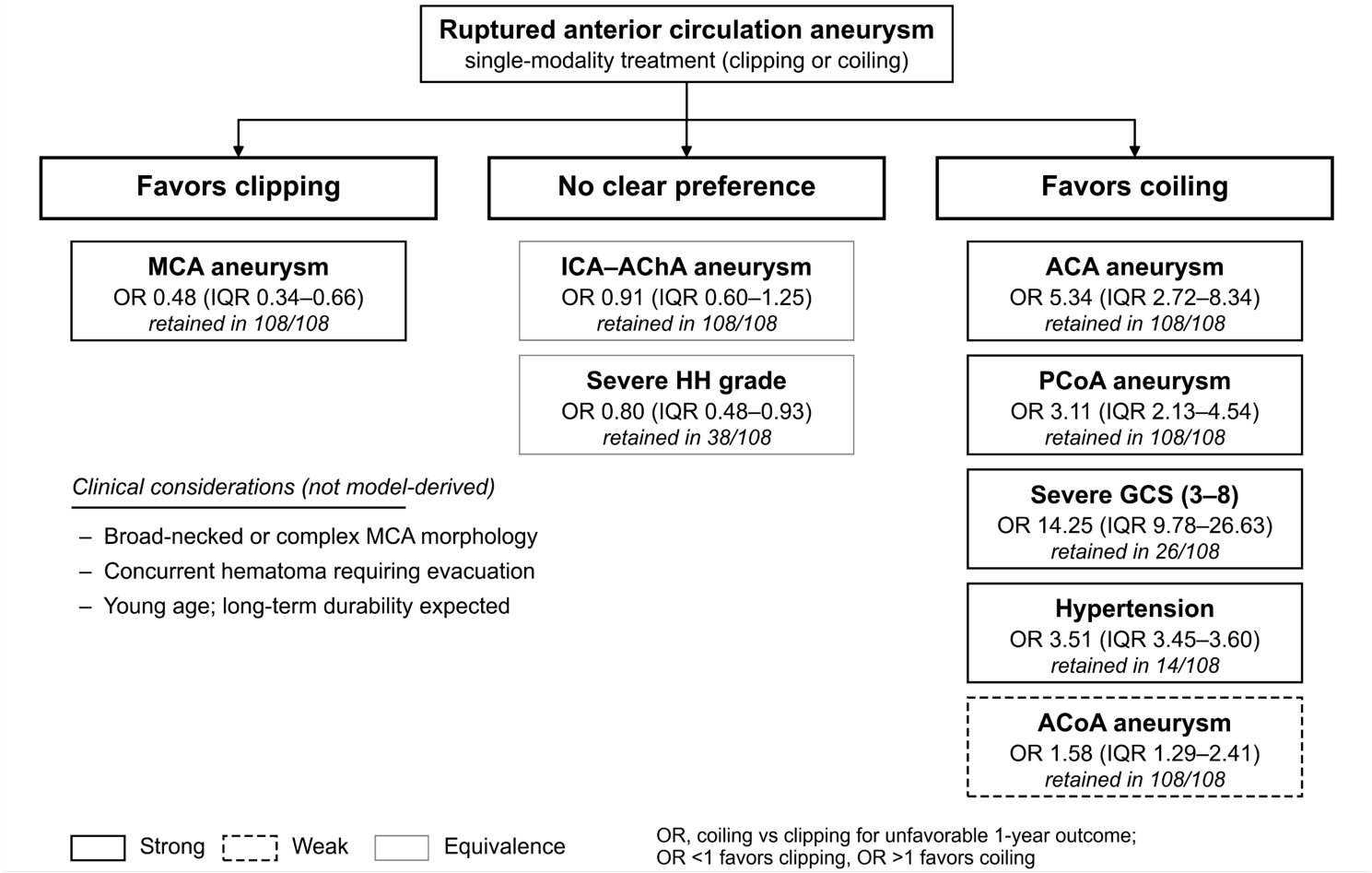



**Figure 6**

Data-driven treatment-selection guide for ruptured anterior circulation aneurysms, derived from the interaction analyses in Fig. 5. Each box gives the median odds ratio (IQR) of unfavorable 1-year outcome for coiling versus clipping across the 108 final specifications and the number of specifications in which the term was retained. Solid boxes indicate strong evidence (median and entire IQR outside the 0.67–1.5 equivalence range), the dashed box weak evidence (only the median outside) and grey boxes no clear preference. Clinical considerations listed under clipping are not model-derived. Full grading is given in Table 2.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.docx