Neuroimaging characteristics of ruptured aneurysm as predictors of outcome after aneurysmal subarachnoid hemorrhage: pooled analyses of the SAHIT cohort

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OBJECTIVE Neuroimaging characteristics of ruptured aneurysms are important to guide treatment selection, and they have been studied for their value as outcome predictors following aneurysmal subarachnoid hemorrhage (SAH). Despite multiple studies, the prognostic value of aneurysm diameter, location, and extravasated SAH clot on computed tomography scan remains debatable. The authors aimed to more precisely ascertain the relation of these factors to outcome.

METHODS The data sets of studies included in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository were analyzed including data on ruptured aneurysm location and diameter (7 studies, n = 9125) and on subarachnoid clot graded on the Fisher scale (8 studies; n = 9452) for the relation to outcome on the Glasgow Outcome Scale (GOS) at 3 months. Prognostic strength was quantified by fitting proportional odds logistic regression models. Univariable odds ratios (ORs) were pooled across studies using random effects models. Multivariable analyses were adjusted for fixed effect of study, age, neurological status on admission, other neuroimaging factors, and treatment modality. The neuroimaging predictors were assessed for their added incremental predictive value measured as partial R².

RESULTS Spline plots indicated outcomes were worse at extremes of aneurysm size, i.e., less than 4 or greater than 9 mm. In between, aneurysm size had no effect on outcome (OR 1.03, 95% CI 0.98–1.09 for 9 mm vs 4 mm, i.e., 75th vs 25th percentile), except in those who were treated conservatively (OR 1.17, 95% CI 1.02–1.35). Compared with anterior cerebral artery aneurysms, posterior circulation aneurysms tended to result in slightly poorer outcome in patients who underwent endovascular coil embolization (OR 1.13, 95% CI 0.82–1.57) or surgical clipping (OR 1.32, 95% CI 1.10–1.57); the relation was statistically significant only in the latter. Fisher CT subarachnoid clot burden was related to outcome in a gradient manner. Each of the studied predictors accounted for less than 1% of the explained variance in outcome.

CONCLUSIONS This study, which is based on the largest cohort of patients so far analyzed, has more precisely determined the prognostic value of the studied neuroimaging factors. Treatment choice has strong influence on the prognostic effect of aneurysm size and location. These findings should guide the development of reliable prognostic models and inform the design and analysis of future prospective studies, including clinical trials.

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KEY WORDS subarachnoid hemorrhage; intracranial aneurysm; outcome assessment; risk factors; meta-analysis; vascular disorders

Neuroimaging characteristics at hospital admission play an important role in the accurate diagnosis of subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysms. They help to identify the aneurysm causing bleeding and outline its anatomical configuration and that of adjoining structures to guide optimal choice of treatment modality for exclusion of the ruptured aneurysm from circulation. Neuroimaging parameters at hospital admission have been investigated for their value as predictors of outcome after SAH. Among these param...
ters, subarachnoid clot burden on CT and aneurysm diameter and location have been the focus of many studies. Despite multiple studies, their value as outcome predictors is, to a large extent, debatable. The Fisher scale or its modified version or the Hj德拉 scale is often used to semiquantitatively assess CT clot burden. These scales are considered predictors of risk of delayed cerebral ischemia, but no consensus exists as to their independent association with clinical outcomes after SAH. With advances in diagnostic and interventional neuroradiology, and increasing patient selection for endovascular coiling rather than surgical clipping, further queries could be raised regarding their value as outcome predictors in SAH. Prognostic studies investigating neuroimaging characteristics as predictors of outcome after SAH have scarcely accounted for differences in treatment modality, though such studies may be helpful to better understand and more accurately evaluate the value of these characteristics as predictors of outcome after SAH.

We analyzed patient information in the largest repository of prospectively collected data on SAH patients, the Subarachnoid Hemorrhage International Trialists (SAHIT) repository, to investigate the prognostic value of SAH CT clot burden graded on the Fisher scale and ruptured aneurysm diameter and location. Specifically, we sought to more precisely ascertain their relationship to outcome of patients with SAH and assess how much added predictive information they provide beyond other established prognostic factors.

Methods

Details about the SAHIT repository have been published previously. In brief, the repository accures data of randomized clinical trials (RCTs) and prospective cohort studies and hospital registries of SAH. For the present study, we pooled data on ruptured aneurysm diameter and location, which was available in 7 studies, and data on CT clot burden measured on the Fisher scale, which was available in 8 of the 14 studies in the repository. Fisher CT clot burden was estimated from the modified Fisher grade in the Columbia University Subarachnoid Hemorrhage Outcomes Project (SHOP) data set and from CT clot size (classified as thick or thin) and location (localized or diffused), with or without the presence of intraventricular hemorrhage in the tirilazad and Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After SAH (CONSCIOUS-I) trials data sets. Ruptured aneurysm diameter was available as a continuous variable in 5 studies and as a categorical variable in the tirilazad and CONSCIOUS-I data sets. We analyzed aneurysm diameter primarily as a continuous predictor, and secondarily as a categorical variable to include patients for whom data were dichotomized a priori, and examined for consistency in the results of both analyses. For the latter, we categorized aneurysm diameter as small (1–12 mm), large (13–24 mm), and giant (≥ 25 mm). Ruptured aneurysm location was categorized broadly into anterior cerebral artery (ACA); internal carotid artery (ICA), including posterior communicating region; middle cerebral artery (MCA); and posterior circulation, inclusive of ruptured vertebral and basilar artery aneurysms. This categorization is identical to that used in the International Subarachnoid Aneurysm Trial (ISAT). The outcome measure was the score on the Glasgow Outcome Scale (GOS; with 1 = death and 5 = good recovery) at 3 months, which was imputed from the 2-month GOS score in the ISAT data and from the 6-month GOS score in the University of Washington Database of Subarachnoid Treatment (D-SAT). This technique is acceptable to minimize loss of data points, and it has been used previously in similar studies such as those of the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) database.

Statistical Analysis

The distribution of baseline characteristics was summarized by frequency tables for categorical variables and by the median and 25th and 75th percentiles or mean with standard deviation for continuous variables. Restricted cubic splines were used to study the relation between aneurysm diameter and GOS score. Splines are flexible polynomial functions that are very useful to demonstrate the shape of the relation of a continuous predictor to an outcome variable, where such relationship is anticipated to be nonlinear or complex. Analysis of variance (1-way ANOVA) was performed to test whether aneurysm diameter differed significantly with treatment modality. The unadjusted effect of the neuroimaging predictors was quantified using the technique of meta-analysis of individual participant data. First, proportional odds logistic regression models were fitted to obtain unadjusted odds ratios (ORs) with 95% confidence intervals by study. Next, the unadjusted ORs were pooled with a random effects model. Their consistency was illustrated across studies using forest plots and statistically tested using a test of heterogeneity. The adjusted effects of the neuroimaging parameters were assessed in a set of successive adjustment models using proportional odds logistic regression analysis, correcting for the fixed effect of study (Model A), age and World Federation of Neurosurgical Societies (WFNS) grade of neurological status at admission (Model B), other neuroimaging factors (Fisher CT clot burden, ruptured aneurysm location and diameter as applicable) (Model C), and treatment modality—whether ruptured aneurysm was repaired by clipping or coiling or treated conservatively (Model D, full adjustment model). We first illustrated relative prognostic strength with ORs. For aneurysm diameter, the OR was expressed as the change in interquartile range (IQR) (75th vs 25th percentile of aneurysm diameter), so we could directly compare the prognostic strength to those of categorical variables such as the Fisher grade. Second, we estimated the unique contribution of each variable in a model to outcome with partial R² statistics. This statistic reflects the increase in explained variability and has been recommended as a means of assessing added incremental predictive value.

The proportion of missing data were small (1.6% for analysis of the effect of aneurysm location and effect of aneurysm size, and 3% for analysis of the effect of Fisher
grade). To fill in missing data, we did multiple imputations by chained equations, generating 20 imputed data sets for analysis. The imputation models were specified on all covariates and GOS score and stratified by study. The following secondary analyses were performed. 1) Interactions: we tested a limited number of prespecified interaction effects including those of aneurysm diameter and location with patient age, neurological grade, and treatment modality to evaluate differential effects by these clinical characteristics; and 2) consistency over outcome splits: we fitted binary logistic models to assess the association between the predictor variables and outcome at each dichotomization split of the GOS (GOS 1 vs GOS 2–5, GOS 1–2 vs GOS 3–5, etc.) to examine comparability of prognostic associations at each split point of the GOS. The proportional odds analysis provided a summary estimate over all splits rather than focusing on 1 specific split. The level of statistical significance was set at 5%. The meta-analysis was performed in Stata version 12 (Statacorp). Other analyses were executed in the R platform (R Foundation for Statistical Computation) using the rms and MICE libraries.

Results

Patient and Aneurysm Characteristics

The study cohort consisted of 9125 patients (derived from 5 RCT data sets and 2 hospital registry data sets) for the analysis of the effect of ruptured aneurysm diameter and location, and 9452 patients (from 4 RCT data sets and 2 hospital registry data sets) for the analysis of the effect of Fisher CT clot burden. The median age of patients was 52 years (IQR 43–61 years). Median aneurysm diameter was 6 mm (IQR 4–9 mm). Mean aneurysm diameter significantly varied by treatment modality, with smaller aneurysms preferentially treated by clipping (clipping: 6.5 ± 3.4 mm; coiling: 6.5 ± 3.4 mm; none: 9.32 ± 10.2 mm; ANOVA p < 0.001). Most aneurysms were in the anterior circulation (89%). The distributions of Fisher CT clot burden and aneurysm diameter and location across studies are shown in Table 1. Small aneurysms were relatively more frequent in RCT studies than observational studies (73%–96% vs 47%–67%), whereas the converse was the case with respect to large diameter aneurysms (3%–23% vs 9%–51%). Posterior circulation aneurysms were relatively fewer in RCT data sets (3%–14%) than observational studies (18%–19%). Aneurysms of the ACA and MCA were preferentially treated by clipping while aneurysms of the posterior circulation were preferentially treated conservatively or with endovascular coiling (Table 2). A greater proportion of patients were classified as Fisher Grade 3 (42%–80% across studies; Table 1).

Prognostic Associations

The distribution of ruptured aneurysm diameter, location, and Fisher CT clot burden by 3-month GOS score is as shown in Table 3. Spline plots demonstrated a U-shaped relationship between aneurysm diameter and GOS score, with the inflection point at a diameter of 5.5 mm (Fig. 1). The unadjusted OR associated with the effect of aneurysm diameter and the effect of location was borderline across studies in the SAHIT repository, suggesting a weak relationship with outcome (Fig. 2). The pooled unadjusted OR for aneurysm diameter was 1.17 (95% CI 0.97–1.41). Adjusting for the fixed effect of study, age, neurological status, aneurysm location, and Fisher grade had a slight effect on the OR (reduced from 1.13 to 1.09). On further accounting for treatment modality in the full adjustment model, the OR was 1.03, which was statistically not significant (95% CI 0.98–1.09). Table 4 shows that compared with ACA aneurysms, posterior circulation aneurysms were associated with 23% higher odds of poor outcome (OR 1.25, 95% CI 1.08–1.44), adjusting for study effect, age, and WFNS grade. The effect was attenuated on further adjusting for treatment modality (OR 1.10, 95% CI 0.95–1.28). We noted an interaction effect between aneurysm diameter and patient neurological status (p < 0.001) and treatment modality (p = 0.005) but not between aneurysm diameter and age (p = 0.226). We also noted a strong interaction between aneurysm location and treatment modality (p = 0.0002) but none between aneurysm location

| TABLE 1. Distribution of ruptured aneurysm location, diameter, and Fisher grade by study* |
|-----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Variable        | C-1     | HHU     | IMASH   | IHAST   | ISAT    | TIRILAZAD | D-SAT   | SHOP    |
|                 | (n = 433) | (n = 60) | (n = 327) | (n = 998) | (n = 2143) | (n = 3552) | (n = 439) | (n = 1500) |
| Location        |         |         |         |         |         |         |         |         |
| ACA             | 174 (42)| 20 (33)| —       | 391 (40)| 1085 (51)| 1256 (36)| 137 (31)| 395 (32) |
| ICA             | 118 (29)| 11 (18)| —       | 309 (31)| 697 (32)| 1046 (30)| 130 (30)| 412 (33) |
| MCA             | 76 (18)| 21 (35)| —       | 205 (21)| 303 (14)| 711 (20)| 88 (20)| 209 (17) |
| PCQ             | 46 (11)| 8 (14)| —       | 83 (8)| 58 (3)| 474 (14)| 84 (19)| 218 (18) |
| Diameter in mm, median (IQR) |         |         |         |         |         |         |         |         |
| —               | 5 (4–8)| —       | 7 (5–10)| 5 (4–7)| —       | 16 (3–22)| 7 (5–10) |
| Fisher grade    |         |         |         |         |         |         |         |         |
| 1               | 3       | 0       | 2 (1)   | 53 (5)  | 114 (5)  | 338 (9)  | 68 (16)  | 210 (15)  |
| 2               | 68 (16)| 2 (3)   | 24 (7)  | 342 (34)| 360 (17)| 455 (13) | 47 (11)  | 315 (22)  |
| 3               | 348 (80)| 9 (15) | 262 (80)| 473 (47)| 902 (42)| 2315 (66)| 184 (41)| 695 (48)  |
| 4               | 17 (4) | 49 (61)| 39 (12)| 130 (13)| 753 (35)| 420 (12)| 142 (32)| 218 (15)  |

C-1 = CONSCIOUS 1 trial; HHU = Heinrich Heine University Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation After Severe Subarachnoid Hemorrhage Trial; IHAST = Intracerebral Hypothermia for Aneurysm Surgery Trial; IMASH = Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage trial; PCQ = posterior circulation aneurysm; — = data not available.

* Values are number (%) unless otherwise indicated.
and neurological status (p = 0.52) or age (p = 0.85). Motivated by the significant interaction effects, the full model (Model D) was stratified by treatment modality to obtain adjusted OR of aneurysm diameter and location for each treatment modality. We found that aneurysm diameter had no significant effect on outcome in patients who had undergone endovascular coiling (OR 0.92, 95% CI 0.81–1.04), nor in those who had undergone surgical clipping (OR 1.04, 95% CI 0.98–1.09). However, in patients who had neither (conservatively treated), the effect of aneurysm diameter was significant, with increasing diameter associated with poorer outcome (OR 1.17, 95% CI 1.02–1.35).

Compared with ACA aneurysms, those of the posterior circulation tended to result in poorer outcomes in patients who had undergone clipping (OR 1.32, 95% CI 1.10–1.57) than in those who had undergone coiling (OR 1.13, 95% CI 0.82–1.57), though the relationship was significant only in the former group. In patients who were treated conservatively, the outcome of posterior circulation aneurysms appeared better than that of ACA aneurysms (OR 0.37, 95% CI 0.23–0.60).

In the unadjusted analysis, increasing Fisher grade of SAH on CT scan was associated with poorer outcome across studies (Fig. 3). The effect of Fisher grade varied significantly between studies, in particular the effects of Fisher Grades 3 and 4. In adjusted analysis (Table 4), increasing Fisher grade was independently related to poorer outcome in a gradient manner (p < 0.001). In the full adjustment model (Model D), the OR associated with the effect of Fisher Grade 2 was 1.26, Fisher Grade 3 was 1.77, and Fisher Grade 4 was 1.86, relative to Fisher Grade 1 as baseline category.

Figure 4 compares the relative prognostic strength of all predictors in the fully adjusted model (D), expressed as partial $R^2$. We noted, that of all covariates, WFNS grade had the highest added predictive value, whereas the location of aneurysm had the least value. The value of treatment modality for predicting outcome was highest in patients with a poor grade. Aneurysm diameter, location, and Fisher grade had only small added value for predicting outcome (partial $R^2 < 1\%$ in each case). Secondary analysis showed prognostic effects were comparable at each dichotomization split point of the GOS.

**Discussion**

Increasing aneurysm size and lesion location in the posterior circulation were only weakly associated with outcome in this study. Their effects were strongly influenced

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**Table 2. Distribution of aneurysm location by treatment modality**

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Location</th>
<th>Clipping</th>
<th>Coiling</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>2617 (38.9)</td>
<td>716 (44.7)</td>
<td>125 (28.5)</td>
<td>3458 (39.5)</td>
<td></td>
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<tr>
<td>ICA</td>
<td>2096 (31.2)</td>
<td>501 (31.3)</td>
<td>126 (28.7)</td>
<td>2723 (31.1)</td>
<td></td>
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<tr>
<td>MCA</td>
<td>1358 (20.2)</td>
<td>203 (12.7)</td>
<td>52 (11.9)</td>
<td>1613 (18.4)</td>
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<tr>
<td>PCQ</td>
<td>653 (9.7)</td>
<td>182 (11.4)</td>
<td>136 (30.9)</td>
<td>971 (11.1)</td>
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</table>

*Values are number (%).
Neuroimaging factors and SAH outcomes by treatment modality. Previous studies have identified aneurysm location as a predictor of periprocedural complication with MCA aneurysms at increased risk of intraoperative rupture.\textsuperscript{29} Some studies reported posterior circulation aneurysms to be associated with poorer outcomes than anterior circulation aneurysms,\textsuperscript{34,35} but these studies only included patients whose aneurysms were treated by surgical clipping. Studies in patients who had undergone coil embolization are scarcely available. Some researchers analyzed patients who had undergone coil clipping and found no significant relationship between aneurysm location and outcomes of patients with SAH.\textsuperscript{24,32,42} Some showed larger aneurysms correlated with higher risk of rebleeding\textsuperscript{9,22} and a higher risk of poor outcome,\textsuperscript{9,12,18,24,31,33,34} though at least 1 study\textsuperscript{38} found no relationship between aneurysm size and outcome at 6 months on the GOS. A recent study involving 534 Japanese patients with data in a prospective registry also found no relationship between aneurysm size and outcome on the modified Rankin Scale after 12-months of follow-up.\textsuperscript{42} The inconsistent results of previous studies may be explained, in part, by the fact that they did not account for treatment modality. In the present analysis, the effects of aneurysm size and location varied with and was dependent on treatment modality. The prognostic effect of aneurysm size was only significant in patients who were treated conservatively, which suggests that appropriate selection of patients for treatment mitigates the effect of aneurysms size. The effect of posterior circulation aneurysms was less pronounced in patients who had undergone clipping than those who had undergone clipping, probably because these aneurysms were preferentially treated by clipping. In contrast, in their study of 914 patients, Ogilvy et al.\textsuperscript{28} noted a significant effect of posterior lesions relative to anterior lesions in patients who had undergone clipping but none in those who underwent coiling. That patients with posterior lesions who were treated conservatively in the present study seemed to experience better outcome relative to those with ACA lesions most likely reflects a treatment selection bias, as most posterior lesions with potentially poor outcomes would have had definitive intervention either by coiling or clipping, which further reinforces the need to account for treatment effect.

Comparing the prognostic strength of aneurysm size across previous studies is challenging as aneurysm size has been dichotomized differently with different threshold values applied in different studies, including the use of 10 mm,\textsuperscript{9,18,20,23,31,33,34} 13 mm,\textsuperscript{24} or the use of different multiple categories.\textsuperscript{34,38} We showed that aneurysm diameter has a

\textbf{FIG. 2.} Forest plots depicting unadjusted effect of ruptured aneurysm diameter and location across studies. C-1 = CONSCIOUS-1; HHU = Heinrich Heine University Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation after Severe Subarachnoid Hemorrhage Trial; IHAST = Intraoperative Hypothermia for Aneurysm Surgery Trial.
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U-shaped relationship with outcome, a finding which suggests worse outcomes at extremes of size. Though this may be somewhat counterintuitive, it is not unlikely. Previous studies have reported that very small aneurysms are associated with more extensive hemorrhage,30,33,37,43 are more difficult to treat, are associated with a relatively higher risk of periprocedural complications, particularly when treated endovascularly, and have relatively higher morbidity and mortality.1,27,30,40 Giant aneurysms may present similar challenges.2,4,6 Furthermore, some researchers have suggested the possibility of an aggressive subset of small aneurysms that grow rapidly and rupture at very small size.14 If they exist, such aneurysms could represent a prognostically distinct group of intracranial aneurysms that theo-

**Fig. 3.** Forest plots depicting unadjusted effect of Fisher grade across studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>C-1</th>
<th>IHAST</th>
<th>ISAT</th>
<th>TIRILAZAD</th>
<th>D-SAT</th>
<th>SHOP</th>
<th>Overall (I-squared = 36.6%, p = 0.163)</th>
<th>Odds ratio (95% CI)</th>
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<td></td>
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*Analyses were done separately for each neuroimaging factor. Values are OR (95% CI).**
Neuroimaging factors and SAH outcomes

The effect of age may be because of declining compensatory capacity of the aging brain to tolerate injury and the greater comorbid burden in older populations. Admission neurological status most likely reflects the severity of the primary injury and evolving secondary insults from multiple physiological mechanisms. Studies presenting prognostic models for SAH often include neuroimaging variables such as aneurysm size, location, and Fisher grade in addition to age and admission neurological status, but with little or no information as to how much incremental value was achieved to justify the added complexity of including the neuroimaging predictors. The limitations of this study include the fact that patient enrollment for some studies occurred prior to the adoption of endovascular coiling as first-line treatment modality in many centers, though the overall pattern of treatment is comparable to what is obtainable in many centers with expertise to treat SAH by surgical clipping or endovascular coiling. The generalizability of the findings may be affected by the preferential inclusion of RCT data sets, and potentially could have been improved had we included more data from all possible primary studies considering neuroimaging parameters and outcome after SAH. We also recognize that specific correlations and interactions between some variables may exist that we could not reliably evaluate, even with our large sample size. Despite the limitations, the study has a number of advantages: the large volume of prospectively collected data from multiple centers enhances the generalizability, and refined statistical analyses including proportional odds analysis recognize the ordinal nature of the GOS rather than loses information by dichotomizing the GOS as favorable and unfavorable outcome.

In the present study, we have attempted a detailed analysis of the prognostic value of aneurysm size, location, and the Fisher grade in the SAHIT cohort, which far exceeds that of any previous studies. We envision that our data, in addition to helping us better understand the prognostic relevance of the studied variables, should be helpful to guide the development of reliable prognostic models and risk assessment tools for unruptured and ruptured aneurysms causing SAH. Such tools have potential to assist clinical practice and guide future trial design, particularly with respect to patient enrollment and data analysis. Though studies have inconsistently identified aneurysm size, location, and Fisher grade as prognostic factors after SAH, most studies and our analysis of the SAHIT cohort agree that age and admission neurological status are the key prognostic factors among all factors studied to date.

The considerable between-study heterogeneity in the effect of Fisher CT clot burden, seen particularly for Fisher Grade 3 and 4, could be due to measurement variability associated with the subjective nature of the scale. This finding may also reflect our approximation of the Fisher grade in some studies from a simple categorization of clot thickness and location or from the modified Fisher scale. Nonetheless, in some respects, the results further underscore the need for better methods for grading subarachnoid blood volume, density, and distribution as seen on modern CT images.

In the present study, we have attempted a detailed analysis of the prognostic value of studied neuroimaging predictor. Bars represent the difference in Nagelkerke’s $R^2$ values of adjustment models with and without the predictor.

**FIG. 4.** Bar graph showing the relative prognostic value of studied neuroimaging predictor. Bars represent the difference in Nagelkerke’s $R^2$ values of adjustment models with and without the predictor.
Conclusions

In conclusion, this study provides empirical evidence that choice of treatment should be considered in evaluating the prognostic effect of aneurysm size and location. The effect is such that aneurysm size is associated with the outcome only in patients who are conservatively treated. Aneurysm location has a weak effect on outcome in patients who are treated by clipping but no effect in patients who have undergone coilings. These findings should guide the development of reliable prognostic models and inform the design and analysis of future prospective studies, including clinical trials.

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**Author Contributions**

Conception and design: all authors. Acquisition of data: Macdonald, Jaja. Analysis and interpretation of data: Jaja, Lingsma, Steyerberg. Thorpe. Drafting the article: Jaja. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Macdonald. Statistical analysis: Jaja. Administrative/technical/material support: Jaja, Schweizer. Study supervision: Macdonald, Steyerberg, Thorpe.

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