JNS

CLINICAL ARTICLE

J Neurosurg 144:20–24, 2026

Risk factors of wall calcification in unruptured intracranial aneurysms

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OBJECTIVE Wall calcification in unruptured intracranial aneurysms (UIAs) increases the risk of complications of microsurgical aneurysm treatment. Therefore, information on wall calcification is important in deciding on the indication and modality of preventive treatment. However, wall calcification is often not visible on MR angiography. The authors studied risk factors for aneurysm wall calcifications to identify patients who should undergo preprocedural CT imaging to detect wall calcifications.

METHODS From two international cohorts of patients with single or multiple UIAs, data were collected on age, sex, smoking status, hypertension, aneurysm location, aneurysm size, and morphological parameters associated with increased risk for rupture (i.e., at-risk morphology = aspect ratio > 1.6, size ratio > 3, presence of lobulations, and/or irregular shape). Logistic regression was used to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to investigate risk factors for wall calcification. Using receiver operating characteristic analysis in one cohort, a size cutoff value was determined for ruling out aneurysm wall calcification, which was validated in the other cohort.

RESULTS Two hundred fifty-five patients with 306 UIAs were included. In univariable analyses, risk factors of aneurysm wall calcification were aneurysm size (OR 1.2, 95% CI 1.1–1.3), hypertension (OR 2.1, 95% CI 1.1–4.5), and at-risk morphology (OR 2.4, 95% CI 1.3–4.4). In multivariable analysis, independent risk factors for wall calcification were aneurysm size (OR 1.2, 95% CI 1.1–1.3) and hypertension (OR 2.8, 95% CI 1.2–6.6), but not at-risk morphology (OR 1.3, 95% CI 0.7–2.7). Aneurysm wall calcification could be ruled out in more than 90% of aneurysms smaller than 6 mm in both the derivation and validation cohorts.

CONCLUSIONS Aneurysm size and hypertension are independent risk factors of aneurysm wall calcification. The authors recommend preprocedural CT imaging in patients with a UIA ≥ 6 mm.

https://thejns.org/doi/abs/10.3171/2025.5.JNS25144

KEYWORDS calcification; computed tomography; hypertension; intracranial aneurysm; risk factors; smoking; diagnostic technique; skull base; vascular disorders

The increasing use of brain imaging has led to an increase in the diagnosis of incidental unruptured intracranial aneurysms (UIAs).[1] In newly detected UIAs, the risk of rupture must be weighed against the risk of complications from preventive endovascular or microsurgical treatment.[2] Approximately 10%–25% of UIAs have visible wall calcifications on clinical CT imaging.[3–5] Aneurysm calcification makes preventive treatment more challenging[2,3,6] and increases the risk of complications from microsurgical treatment.[2,3] Thus, aneurysm wall calcification is a factor to consider when balancing the risks and benefits of preventive treatment of UIAs, but the presence or absence of calcification is often not considered in daily clinical practice. UIAs are diagnosed using various imaging modalities.[7] Aneurysm wall calcification, however, is only visible on CT imaging, and performing additional CT imaging in all patients with UIAs is inefficient.

In a previous study, aneurysm size was found to be a

ABBREVIATIONS ACA = anterior cerebral artery; AComA = anterior communicating artery; AUC = area under the ROC curve; CI = confidence interval; DSA = digital subtraction angiography; ICA = internal carotid artery; MCA = middle cerebral artery; MRA = MR angiography; OR = odds ratio; PComA = posterior communicating artery; ROC = receiver operating characteristic; UIA = unruptured intracranial aneurysm.

SUBMITTED January 19, 2025. **ACCEPTED** May 14, 2025.

INCLUDE WHEN CITING Published online September 19, 2025; DOI: 10.3171/2025.5.JNS25144.

risk factor for aneurysm wall calcification.[4] However, due to the large sizes of the aneurysms included in that study, the cutoff value for a high risk of calcifications was 10 mm. Because most aneurysms are smaller than 10 mm,[8] such a cutoff level is clinically not very relevant. Thus, we need better tools to identify patients at high risk of aneurysm calcification.

We aimed to assess risk factors for the presence of wall calcifications in UIAs, and to identify which patients with a UIA should undergo CT imaging to assess the presence of aneurysm wall calcifications.

Methods

Patient Cohort

Patients were retrieved from the full cohort of patients with one or more UIAs who were seen at the Department of Neurosurgery of Mannheim University Hospital from 2012 to 2019. We included a similar number of UIAs from a cohort of patients with single or multiple UIAs seen at the Department of Neurology and Neurosurgery of University Medical Centre Utrecht from 2015 to 2018.

Inclusion and Exclusion Criteria

We included patients in whom a UIA was detected on CT imaging performed for other reasons (such as ischemic stroke or trauma) or for screening for aneurysms in patients with contraindications for MRI. During the study period, CT imaging was not additionally performed in patients who were referred with an aneurysm found on MR angiography (MRA) or digital subtraction angiography (DSA). We excluded patients with previous aneurysmal subarachnoid hemorrhage; previously treated aneurysms; fusiform, traumatic, or mycotic aneurysms; aneurysms associated with arteriovenous malformations; and patients younger than 18 years. This study followed the STROBE guideline for cross-sectional studies.[9]

Data Collection

Information on age, sex, smoking status, and hypertension was retrieved from the patients' medical records. Smoking status was divided into current, former (stopped smoking > 3 months ago), and never smokers. Hypertension was defined as a previous diagnosis of arterial hypertension by a physician or the use of antihypertensive medication.

Aneurysm Characteristics

We evaluated CT scans in all patients. Aneurysm size was determined by measuring the maximal intraluminal diameter (from DSA or MRA for the Mannheim cohort, and CT angiography for the Utrecht cohort). The time interval between CT scans and DSA or MRA was < 3 months. Aneurysms were also categorized into one of the following locations: internal carotid artery (ICA), middle cerebral artery (MCA), anterior communicating artery (AComA), posterior communicating artery (PComA), anterior cerebral artery (ACA), and posterior circulation.

Morphological parameters associated with an increased risk for rupture (at-risk morphological configuration) were defined according to the Unruptured Intracranial Aneurysm Treatment Score as one or more of the following: 1) aspect ratio > 1.6 or size ratio > 3, 2) presence of lobulations, and/or 3) irregular aneurysm configuration.[10]

Aneurysm wall calcifications were identified using CT images as hyperdense structures along the aneurysm wall. The cohort from Mannheim consisted of 156 aneurysms and was reviewed for calcification by a neurosurgery resident (L.F.C.). To reduce interobserver variance, 20 aneurysms were reviewed by the neurosurgery resident and a PhD candidate in radiology (M.J.K.) to ensure the assessment of calcifications was similar in both cohorts. Subsequently, the cohort from Utrecht, consisting of 150 aneurysms, was reviewed for calcification by M.J.K. In cases of uncertainty, the images were reviewed by both investigators and the presence of aneurysm wall calcification was determined by consensus.

Ethics Approval

This research project was approved by the ethics committee at University Hospital Mannheim. Due to the retrospective nature of this research project, patient consent was not required, and no formal approval was necessary from an ethics committee for the Utrecht cohort, according to the Medical Research Ethics Committee NedMec. Data analysis was performed at University Hospital Mannheim.

Statistical Analysis

Statistical analysis was performed using JMP statistical software (version 16.0.0, SAS Institute Inc.). All analyses were aneurysm-based. We used logistic regression to calculate crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to determine whether patient age, sex, hypertension, smoking status, aneurysm location, aneurysm size, and at-risk morphology were risk factors for the presence of aneurysm wall calcification. Multivariable logistic regression was then performed with the variables that reached statistical significance. For continuous variables (aneurysm size, patient age), we calculated unit ORs (OR per unit change).

Finally, receiver operating characteristic (ROC) analysis was used to determine a cutoff value for aneurysm size in millimeters in the Mannheim cohort. The size of the cutoff value for ruling out aneurysm wall calcification was determined by selecting the size in millimeters with the highest sum of sensitivity and specificity in the Mannheim cohort. Subsequently, the cutoff value was validated in the Utrecht cohort. The performance of the ROC model was defined as good when the area under the ROC curve (AUC) was ≥ 0.8. Lastly, positive and negative predictive values were calculated for both cohorts.

Results

From the Mannheim cohort consisting of 384 UIAs, 156 UIAs were selected according to the inclusion and exclusion criteria. As described in the *Methods* section, we included a similar number of UIAs from the Utrecht cohort. In total, we included 255 patients with 306 UIAs (Mannheim cohort, 131 patients with 156 UIAs; Utrecht cohort, 124 patients with 150 UIAs). Patient and aneurysm

TABLE 1. Patient and aneurysm characteristics

	Total		Mannheim Cohort		Utrecht Cohort	
	Calc+, n = 46	Calc−, n = 209	Calc+, n = 19	Calc−, n = 112	Calc+, n = 27	Calc−, n = 97
Patient characteristic						
Mean age (SD), yrs	64 (10)	60 (12)	61 (10)	60 (12)	65 (9)	61 (13)
Female sex, n (%)	31 (67)	153 (73)	11 (58)	88 (79)	20 (74)	65 (67)
Smoking status, n (%)						
Current smoker	17 (37)	86 (41)	8 (42)	52 (46)	9 (33)	34 (35)
Never smoker	7 (15)	44 (21)	1 (5)	16 (14)	6 (22)	28 (29)
Former smoker	17 (37)	55 (26)	6 (32)	22 (20)	11 (41)	33 (34)
Hypertension, n (%)	37 (80)	133 (64)	19 (100)	72 (64)	18 (67)	61 (63)
	Total		Mannheim Cohort		Utrecht Cohort	
	Calc+, n = 49	Calc−, n = 257	Calc+, n = 20	Calc−, n = 136	Calc+, n = 29	Calc−, n = 121
Aneurysm characteristic						
Median aneurysm size, mm	10.0	5.0	9.5	4.8	10.0	5.3
Mean aneurysm size (SD), mm	13.0 (8.3)	6.0 (4.4)	11.4 (7.7)	5.8 (4.5)	14.2 (8.7)	6.3 (4.4)
At-risk morphology, n (%)*	24 (49)	74 (29)	12 (60)	50 (37)	12 (41)	24 (20)
Aneurysm location, n (%)						
ICA	17 (35)	51 (20)	6 (30)	30 (22)	11 (38)	21 (17)
MCA	15 (31)	91 (35)	7 (35)	56 (41)	8 (28)	35 (29)
AComA	5 (10)	48 (19)	3 (15)	21 (15)	2 (7)	27 (22)
PComA	3 (6)	24 (9)	1 (5)	12 (9)	2 (7)	12 (10)
ACA	2 (4)	8 (3)	1 (5)	4 (3)	1 (3)	4 (3)
Posterior circulation	7 (14)	35 (14)	2 (10)	13 (10)	5 (17)	22 (18)

Calc+ = aneurysm wall calcification present; Calc− = aneurysm wall calcification not present.
* At-risk morphology = aspect ratio > 1.6 or size ratio > 3, presence of lobulations, and/or irregular aneurysm configuration.

characteristics are shown in Table 1. The mean patient age was 61 (SD 12) years and 184 patients (72%) were female. In the total cohort, 49 UIAs (16%) showed wall calcification.

In univariable analysis, risk factors for the presence of wall calcification were UIA size (OR 1.2, 95% CI 1.1–1.3), at-risk morphology (OR 2.4, 95% CI 1.3–4.4), and hypertension (OR 2.1, 95% CI 1.1–4.5; Fig. 1, Table 2). In the multivariable analysis, independent risk factors for aneurysm wall calcification were UIA size (OR 1.2, 95% CI 1.1–

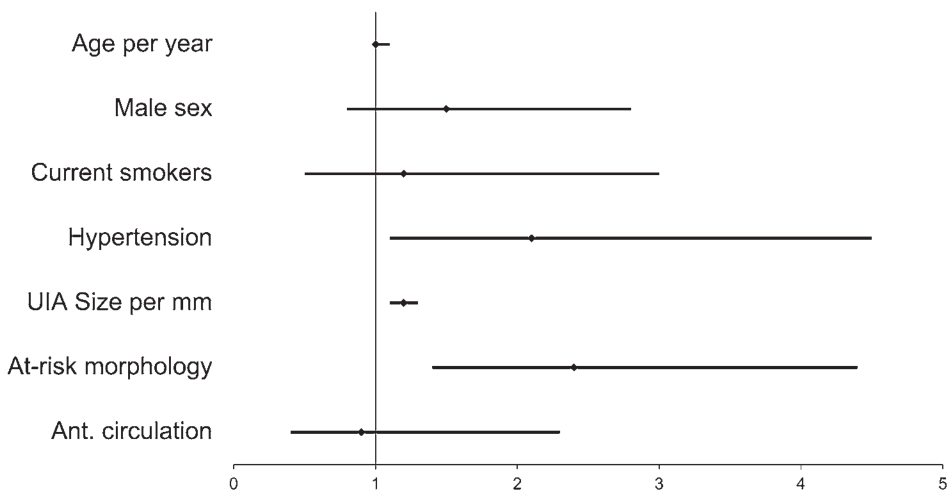

FIG. 1. Forest plot depiction of the univariable analysis of risk factors for aneurysm wall calcification. Hypertension, aneurysm size, and at-risk morphology (aspect ratio > 1.6 or size ratio > 3, presence of lobulations, and/or irregular aneurysm configuration) were significant risk factors. The control group for smoking status was never smokers. Ant. = anterior.

TABLE 2. Results of uni- and multivariable analyses showing the OR for UIA calcification

Variable	Univariable Analysis	Multivariable Analysis
Age, per year	1.0 (1.0–1.1)	—
Sex, male vs female	1.5 (0.8–2.8)	—
Smoking status, current vs never smokers	1.2 (0.5–3.0)	—
Hypertension	2.1 (1.1–4.5)	2.8 (1.2–6.6)
UIA size, per mm	1.2 (1.1–1.3)	1.2 (1.1–1.3)
At-risk morphology	2.4 (1.3–4.4)	1.3 (0.7–2.7)
Location, anterior vs posterior circulation	0.9 (0.4–2.3)	—

1.3) and hypertension (OR 2.8, 95% CI 1.2–6.6), but not at-risk morphology (OR 1.3, 95% CI 0.7–2.7; Fig. 2, Table 2).

In the derivation cohort (Mannheim), a size cutoff value of 6 mm for assessing the absence of aneurysm wall calcification had an AUC of 0.80. A cutoff value of 6 mm had a negative predictive value for aneurysm calcification of 94% and a positive predictive value of 23%. A cutoff level of 6 mm in the validation cohort had an AUC of 0.82. A cutoff value of 6 mm had a negative predictive value of 97% and a positive predictive value of 33%.

Discussion

In this study, we showed that aneurysm size and hypertension are independent risk factors for aneurysm wall calcification. In both cohorts, calcification in UIAs smaller than 6 mm could be ruled out in > 90% of aneurysms.

Our observation that aneurysm size is associated with the presence of wall calcification is consistent with those in previous studies.[3,4] Both previous studies, however, included large aneurysms, resulting in a cutoff size for a high risk of aneurysm calcification of > 10 mm in one of the studies.[4] The aneurysm sizes in our cohorts are comparable with those from recent meta-analyses of patients undergoing treatment or follow-up of a UIA,[11] which increases the clinical relevance of our findings and the applicability of our cutoff level. At-risk morphology was a risk factor, but not an independent one for aneurysm calcification. This observation is explained by the association between aneurysm size and at-risk morphology,[12,13] as larger aneurysms are more likely to have at-risk morphology. We could not find other studies on at-risk morphology and risk of intracranial aneurysm calcification, so we could not compare our results to those from previous research. In UIAs, hypertension is an established independent risk factor for aneurysm rupture.[11] In our study, hypertension was also an independent risk factor for aneurysm calcification. Because wall calcification in UIAs is associated with a reduced risk of aneurysm rupture,[5,14] hypertension appears to have opposing effects on UIA rupture risk. In contrast to the divergent effects on risk of rupture, aneurysmal calcification and hypertension are both associated with an increased risk for perioperative complications after microsurgical treatment of UIAs.[2] Thus, part of the increased risk of hypertension for perioperative complications may be explained by the simultaneous presence of wall calcification in these UIAs. Smoking was not a statistically significant risk factor for aneurysm wall calcification, whereas it is associated with calcification of the intracranial ICA.[15–17] These discrepant findings may be explained by the different constitution of the aneurysm and ICA wall. In the ICA, smoking was associated with calcifications found in the tunica media, which is lacking in the wall of UIAs.[17,18] Although our study shows hypertension to be an independent risk factor for the presence of aneurysm wall calcification, the wide 95% CI indicates that the extent of this effect is uncertain. For this reason, we did not draw any clinical implications from this observation.

Strengths and Limitations of the Study

Strengths of our study are the large sample size and the validation in a separate cohort. The results were comparable between the two study cohorts from two different

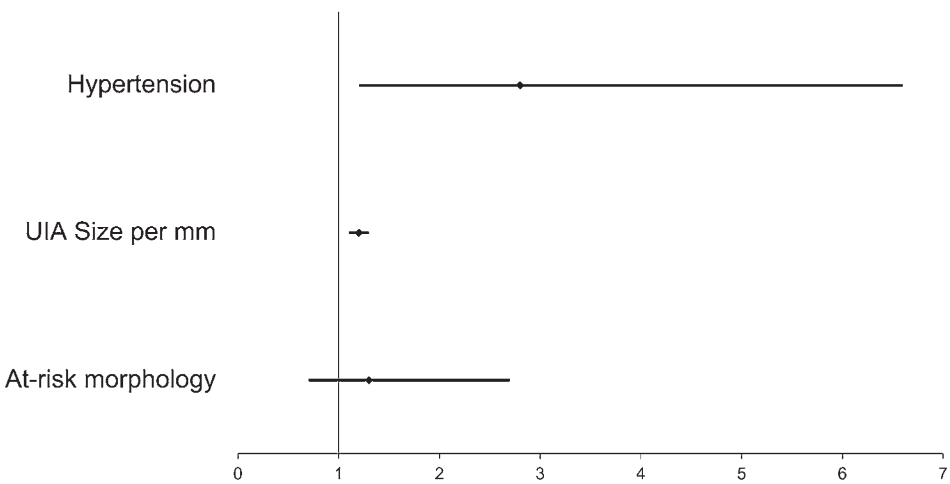

FIG. 2. Forest plot depiction of the multivariable analysis of risk factors for aneurysm wall calcification. Hypertension and aneurysm size were independent risk factors, while at-risk morphology was not.

institutions, which supports the external validity of our findings. Another strength is that the characteristics of the aneurysms included in our study are comparable with those in prevalence studies of UIAs, which supports the clinical applicability of our results.

We also need to address some limitations. The evaluation of calcification in CT imaging was not performed by certified radiologists, but both cohorts showed similar percentages of calcified aneurysms, underscoring the external validity of our results. Furthermore, evaluation of calcification could not be performed blinded to other aneurysm characteristics such as size, morphology, and location. In addition, our study assessed the presence and absence of aneurysm wall calcification, without considering whether the calcification was in the neck or the dome of the aneurysm. Further research is necessary to elucidate the effect of the location of wall calcification on the natural history and surgical decision-making of UIAs.

Conclusions

Aneurysm size and hypertension are independent risk factors of aneurysm wall calcification. Based on our findings, we recommend additional CT imaging in the preprocedural workup of patients with UIAs ≥ 6 mm in diameter to assess the presence of aneurysm wall calcifications, because this information is an important additional factor when deciding on the indication and modality of preventive treatment.

Acknowledgments

Dr. Vergouwen was supported by a Clinical Established Investigator grant from the Dutch Heart Foundation (no. 2018T076) and received grant support from Bayer BV.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Costa, Rinkel. Acquisition of data: Costa, Kamphuis, Akanji. Analysis and interpretation of data: Costa, Kamphuis, Vergouwen, Rinkel. Drafting the article: Costa. Critically revising the article: Kamphuis, Akanji, van der Schaaf, van der Kamp, Vergouwen, Etminan, Rinkel. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Costa. Statistical analysis: Costa. Study supervision: Rinkel.

Supplemental Information

Previous Presentations

This material was presented orally at the 2024 Annual Meeting of the German Society of Neurosurgery in Göttingen, Germany, June 9–12, 2024, and at the 2024 Annual Meeting of the European Association of Neurosurgery in Sofia, Bulgaria, October 13–17, 2024.

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