ORIGINAL RESEARCH

DOI: 10.14744/globecc.2026.87059
Glob Emerg Crit Care 2026;5(2):61-70

Retrospective Study on the Impact of Neurovascular Calcifications on Increasing Intracranial Hemorrhage Risk in Acute Ischemic Stroke Patients Treated With Thrombolytic Therapy in the Emergency Department

Ömer Yasir Boz[1], Figen Coşkun[2], Serhat Akiş[3], Tuğçe Açıkgöz Özel[4], Yusuf Türker[5], Eren Bal[6], Şükran İdil Köstem Yayıcı[7]

[1]*Muğla Training and Research Hospital, Department of Emergency Medicine, Muğla, Türkiye*
[2]*Dokuz Eylül University Faculty of Medicine, Department of Emergency Medicine, İzmir, Türkiye*
[3]*University of Health Sciences, Bozyaka Training and Research Hospital, Department of Radiology, İzmir, Türkiye*
[4]*Uşak Training and Research Hospital, Department of Emergency Medicine, Uşak, Türkiye*
[5]*Kayseri City Hospital, Department of Radiation Oncology, Kayseri, Türkiye*
[6]*Soma State Hospital, Department of Emergency Medicine, Manisa, Türkiye*
[7]*Dokuz Eylül University Faculty of Medicine, Department of Neurology, İzmir, Türkiye*

Abstract

Objective: Intravenous thrombolysis with alteplase (IV tPA) is an established treatment for acute ischemic stroke, but hemorrhagic transformation remains an important complication. Although numerous parameters have been evaluated to minimize the risk of hemorrhagic transformation, no definitive predictor has yet been identified. This study primarily evaluated the association between CTA-detected neurovascular calcifications and hemorrhagic transformation in patients with acute ischemic stroke treated with intravenous alteplase and secondarily assessed their association with functional outcomes at discharge.

Materials and Methods: We retrospectively analyzed 243 patients with acute ischemic stroke who were treated with IV tPA and underwent computed tomography angiography (CTA) between 2018 and 2022. Intracranial internal carotid/carotid siphon calcifications were assessed on CTA by blinded radiologic review using the Kockelkoren calcification scoring system. The primary outcome was hemorrhagic transformation on follow-up CT, and the secondary outcome was poor functional outcome at discharge, defined as a modified Rankin Scale (mRS) score of 3–6.

Results: Calcifications were more common in older patients, those with hypertension, and those with higher red cell distribution width values. Calcification presence or pattern was not significantly associated with hemorrhagic transformation on follow-up CT. Contralateral calcification was independently associated with poor functional outcome at discharge (aOR 2.95, 95% CI 1.09–7.98). In subgroup analyses based on the CTA calcification score, non-intimal calcification was associated with poor functional outcome at discharge on both the ipsilateral and contralateral sides (p=0.03 and p=0.01, respectively). Because symptomatic hemorrhagic transformation occurred in only a small number of patients, hemorrhagic findings should be interpreted cautiously.

Conclusion: In this cohort of patients with acute ischemic stroke treated with intravenous alteplase, the overall presence of intracranial carotid calcification on CTA was not significantly associated with hemorrhagic transformation on follow-up CT. However, a pattern-specific exploratory analysis suggested an inverse association between ipsilateral non-intimal calcification and hemorrhagic transformation, which should be interpreted cautiously given the low number of hemorrhagic events. In contrast, contralateral calcification, particularly a non-intimal pattern, was associated with worse functional outcome at discharge, suggesting possible short-term prognostic value. These findings do not support withholding thrombolytic therapy on the basis of calcification alone, but they indicate that calcification pattern and laterality may merit further investigation in larger studies with 90-day outcomes. Intracranial ICA/carotid siphon calcifications on CTA should not be used in isolation to defer intravenous thrombolysis. In this cohort, calcification patterns appeared more relevant to short-term discharge outcomes than to hemorrhagic transformation risk. These findings are hypothesis-generating and require confirmation in larger multicenter studies.

Keywords: Acute ischemic stroke, alteplase, hemorrhagic transformation, intracranial arterial calcification, intravenous thrombolysis

Address for Correspondence: Ömer Yasir Boz, Muğla Training and Research Hospital, Department of Emergency Medicine, Muğla, Türkiye
E-mail: omeryasirboz@gmail.com **ORCID-ID:** 0000-0002-6268-6226

Received: 21.01.2026 **Revised Date:** 30.03.2026 **Accepted:** 15.04.2026

Cite this article as: Boz OY, Coşkun F, Akiş S, Açıkgöz T, Türker Y, Bal E, Kostem Yayici Şİ. Retrospective study on the ımpact of neurovascular calcifications on ıncreasing ıntracranial hemorrhage risk in acute ıschemic stroke patients treated with thrombolytic therapy in the emergency department. Glob Emerg Crit Care. 2026;5(2):61-70.

Introduction

Intravenous thrombolysis with alteplase (IV tPA) improves neurological outcomes in patients with ischemic stroke. However, intracranial hemorrhage occurs in 2–7% of patients treated with IV tPA. Although various scoring systems based on risk factors predictive of hemorrhagic transformation have been developed, these have not altered treatment protocols [1].

Intracranial arterial calcifications are established imaging markers of atherosclerotic burden and vascular remodeling. The biological significance of these calcifications may differ according to their dominant layer within the arterial wall, and computed tomography angiography (CTA)-based methods have been proposed to distinguish predominantly intimal patterns from predominantly medial/adventitial patterns [2,3]. This distinction may be relevant because plaque-related instability, arterial stiffness, impaired vasoreactivity, and reduced collateral capacity could influence both hemorrhagic transformation and post-stroke recovery [4–8].

The published literature remains inconsistent. Gocmen et al. [9] reported that non-intimal intracranial carotid calcifications were more common in patients with acute hemorrhagic complications after IV thrombolysis. Tábuas-Pereira et al. [10] and Yu et al. [11] also suggested that intracranial carotid calcification burden may be related to hemorrhagic transformation and prognosis after thrombolysis, although these studies differed in scoring strategy and patient selection. Kauw et al. [12] further suggested that the effect of intravenous thrombolysis may vary according to the calcification pattern. In contrast, other studies have not found a clear association between calcification scores and prognosis after IV thrombolysis [13,14]. These discrepancies likely reflect heterogeneity in calcification classification, the inclusion of endovascularly treated patients, stroke subtype selection, and outcome definition.

Accordingly, the present study evaluated whether intracranial carotid siphon calcifications and their CTA-based patterns, as classified using the Kockelkoren scoring system, are associated with hemorrhagic transformation after IV tPA and with short-term functional outcomes at hospital discharge in a CTA-selected acute ischemic stroke cohort [3].

Materials and Methods

The study protocol was approved by the Dokuz Eylul University Institutional Non-Interventional Clinical Research Ethics Committee of Blinded for peer review (Decision No: 2023/23-12; Date: 19.07.2023). The study was performed in compliance with the ethical principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of the study.

This retrospective observational cohort study was conducted using data from patients admitted to the emergency department of a tertiary university hospital, which serves as a stroke center, between January 1, 2018, and December 30, 2022. Eligible patients were those with acute ischemic stroke who were treated with IV tPA and evaluated with neurovascular CTA. The exclusion criteria were alternative final diagnoses, unavailable follow-up data, clear contraindications to thrombolysis identified during the treatment process, and incomplete vascular imaging due to technical limitations.

A total of 314 patients diagnosed with acute ischemic stroke on admission, treated with IV tPA, and evaluated with neurovascular CTA initially met the screening criteria. Thirteen patients were excluded because advanced evaluation revealed alternative diagnoses, 29 because outcome data were unavailable after transfer or treatment abandonment, 12 because clinically relevant hemorrhagic transformation risk factors were identified during or after IV thrombolysis, and 16 because carotid siphon thrombosis precluded complete evaluation of the vascular wall. Of the remaining 244 patients, one was excluded from the final statistical analysis because of incomplete data. Therefore, the final study cohort consisted of 243 patients (Fig. 1).

Clinical Management and Outcome Definitions

Admission National Institutes of Health Stroke Scale (NIHSS) scores, demographic characteristics, vascular risk factors, and laboratory

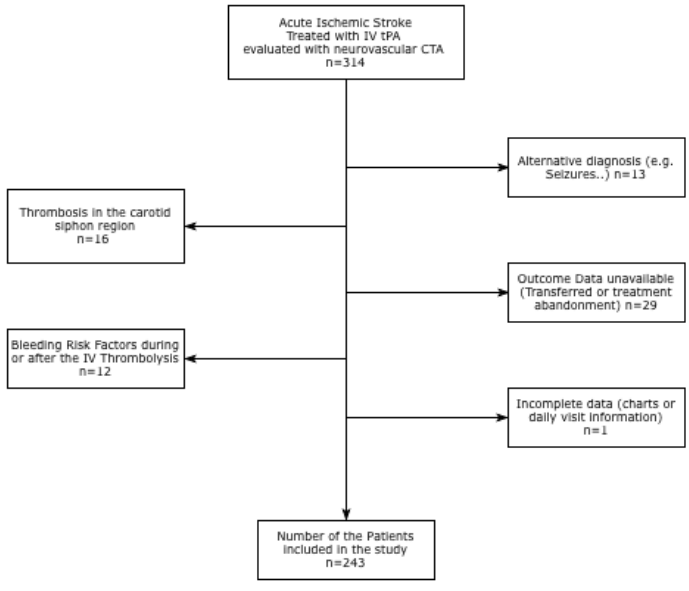

Figure 1. Flowchart of the study

data were recorded. Imaging was re-evaluated by a radiologist from the study team who was blinded to clinical information, prior reports, and outcomes. Discharge modified Rankin Scale (mRS) scores were derived from dependency information documented in the medical records.

All patients with suspected stroke underwent non-contrast head computed tomography (CT) on arrival. CTA was performed in patients considered likely to benefit from mechanical thrombectomy without waiting for creatinine results; in the remaining patients, CTA was obtained after creatinine results became available and before transfer from the emergency department to the stroke unit. IV tPA (Actilyse, Boehringer Ingelheim, Germany) was administered at 0.9 mg/kg in eligible patients after review of clinical findings and non-contrast CT.

Neurological examinations and vital signs were reassessed every 15 minutes during treatment. Although additional brain CT scans were performed in some patients because of clinical deterioration, hemorrhagic outcomes in this study were classified according to the routine 24-hour follow-up brain CT in all patients. Earlier CT scans, when available, were reviewed for clinical purposes but were not used for statistical outcome assessment; the routine 24-hour follow-up CT served as the reference scan in all patients.

Any hemorrhagic transformation on follow-up CT was treated as the primary radiological outcome. Symptomatic hemorrhagic transformation was defined as hemorrhage on follow-up CT accompanied by a ≥2-point worsening in NIHSS without another clear cause. Hemorrhagic transformations without corresponding NIHSS worsening were classified as asymptomatic hemorrhagic transformations. Poor short-term functional outcome was defined as a discharge mRS score ≥3; a discharge mRS score ≤2 was considered a good outcome.

CTA Acquisition and Calcification Assessment

All patient images were acquired using a commercially available 160-slice multidetector CT scanner (Aquilion Prime, Canon Medical Systems, Otawara, Japan) located in the emergency department. A tube voltage of 120 kVp was used for all scans. A total of 100 cc of contrast agent was injected via an antecubital vein using an auto-injector. Sequential regions of interest (ROIs) placed in the aortic arch triggered axial-plane imaging once the contrast threshold was reached, followed by the creation of angiographic reformatted images in three planes.

CTA examinations were reviewed for calcifications in the intracranial internal carotid artery and carotid siphon. Calcifications were categorized as ipsilateral or contralateral according to the clinically affected hemisphere and, when available, MRI lesion laterality. Calcium scoring followed the method of Kockelkoren et al. [3] circularity was scored as 0 for no calcification, 1 for punctate calcification, 2 for calcification spanning <90 degrees, 3 for 90–270 degrees, and 4 for >270 degrees. Thickness ≥1.5 mm received 1 point, and thickness <1.5 mm received 3 points. Morphology was scored as 0 for indistinct, 1 for irregular, and 4 for regular and continuous calcification. Total scores <7 were classified as dominant intimal calcification, and scores ≥7 were classified as non-intimal (medial/adventitial) calcification.

Statistical Analysis

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Numerical variables were assessed for normality using the Kolmogorov–Smirnov test and are presented as mean ± standard deviation or median (interquartile range [IQR]) according to distribution. Comparisons of numerical variables were performed using Student's t-test, the Mann–Whitney U test, or the Kruskal–Wallis test, as appropriate.

Binary logistic regression was used to evaluate factors associated with any hemorrhagic transformation on follow-up CT and with poor functional outcome at discharge. Variables with $p<0.20$ in univariable analyses were considered eligible for multivariable modeling, and clinically relevant covariates were additionally retained based on guideline recommendations and prior literature. To limit overfitting, separate multivariable models were constructed for any hemorrhagic transformation (43 events) and poor functional outcome at discharge, whereas symptomatic hemorrhagic transformation (9 events) was analyzed descriptively and not modeled separately.

Each multivariable model included the calcification variable of interest together with age, sex, hypertension, diabetes mellitus, atrial fibrillation, infarction on admission CT, admission NIHSS score, dense artery sign, and mechanical thrombectomy status; poor-outcome models also included any hemorrhagic transformation on follow-up CT. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported for multivariable models. A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

Results

The cohort consisted of 243 patients who received IV tPA and underwent neurovascular CTA. Calcifications were more frequent in older patients and in patients with hypertension, and patients with calcifications had higher red cell distribution width values at admission. No significant sex-based difference was observed in calcification presence or pattern (Table 1).

Table 1. Baseline characteristics according to calcification status and pattern

Panel A. Any calcification

Characteristic	Absent (n=32)	Present (n=211)	*p*
Age, years	59.1±14.7	72.6±10.7	<0.001
Sex, female, n (%)	14 (43.7%)	88 (41.7%)	0.827
Diabetes mellitus, n (%)	6 (18.8%)	72 (32.1%)	0.083
Hypertension, n (%)	16 (50.0%)	144 (68.2%)	0.043
Atrial fibrillation, n (%)	2 (6.3%)	20 (9.5%)	0.423*
Large-vessel occlusion, n (%)	11 (34.4%)	59 (28.0%)	0.455
Infarction on admission CT, n (%)	3 (9.4%)	34 (16.1%)	0.242*
Mechanical thrombectomy, n (%)	5 (15.6%)	24 (11.4%)	0.328*
Any hemorrhagic transformation on follow-up CT, n (%)	7 (21.9%)	36 (17.1%)	0.506
Symptomatic hemorrhagic transformation, n (%)	0 (0.0%)	9 (4.3%)	0.274*
Poor functional outcome at discharge (mRS ≥ 3), n (%)	9 (28.1%)	100 (47.4%)	0.041
RDW, median (IQR)	13.6 (13.1–14.2)	14.6 (13.7–15.9)	<0.001

Panel B. Ipsilateral calcification pattern

Characteristic	No calcification (n=39)	Intimal (n=87)	Non-intimal (n=117)	*p*
Age, years	59.9±14.6	69.9±9.99	75.1±10.2	<0.001
Sex, female, n (%)	14 (35.8%)	30 (34.4%)	58 (49.5%)	0.068
Diabetes mellitus, n (%)	9 (23.1%)	26 (29.9%)	43 (36.8%)	0.245
Hypertension, n (%)	21 (53.8%)	50 (57.5%)	89 (76.1%)	0.005
Atrial fibrillation, n (%)	2 (5.1%)	8 (9.2%)	12 (10.3%)	0.626
Large-vessel occlusion, n (%)	13 (33.3%)	27 (31.0%)	30 (25.6%)	0.557
Infarction on admission CT, n (%)	6 (15.4%)	11 (12.6%)	20 (17.1%)	0.682
Mechanical thrombectomy, n (%)	6 (15.4%)	12 (13.8%)	11 (9.4%)	0.486
Any hemorrhagic transformation on follow-up CT, n (%)	10 (25.6%)	15 (17.2%)	18 (15.4%)	0.344
Symptomatic hemorrhagic transformation, n (%)	0 (0.0%)	5 (5.7%)	4 (3.4%)	0.280
Poor functional outcome at discharge (mRS ≥ 3), n (%)	12 (30.8%)	35 (40.2%)	62 (53.0%)	0.030
RDW, median (IQR)	13.7 (13.1–14.2)	14.6 (13.6–15.5)	14.6 (13.8–16.1)	<0.001

Panel C. Contralateral calcification pattern

Characteristic	No calcification (n=43)	Intimal (n=88)	Non-intimal (n=112)	*p*
Age, years	60.3±13.6	70.8±10.3	74.8±10.4	<0.001
Sex, female, n (%)	20 (46.5%)	30 (34.0%)	52 (46.4%)	0.172
Diabetes mellitus, n (%)	8 (18.6%)	29 (33.0%)	41 (36.6%)	0.097
Hypertension, n (%)	18 (41.9%)	60 (68.2%)	82 (73.2%)	<0.001
Atrial fibrillation, n (%)	2 (4.7%)	8 (9.1%)	12 (10.7%)	0.500
Large-vessel occlusion, n (%)	14 (32.6%)	31 (35.2%)	25 (22.3%)	0.113
Infarction on admission CT, n (%)	4 (9.3%)	14 (15.9%)	19 (17.0%)	0.481
Mechanical thrombectomy, n (%)	7 (16.3%)	13 (14.8%)	9 (8.0%)	0.216
Any hemorrhagic transformation on follow-up CT, n (%)	8 (18.6%)	17 (19.3%)	18 (16.1%)	0.824
Symptomatic hemorrhagic transformation, n (%)	1 (2.3%)	5 (5.7%)	3 (2.7%)	0.467
Poor functional outcome at discharge (mRS ≥ 3), n (%)	11 (25.6%)	39 (44.3%)	59 (52.7%)	0.010
RDW, median (IQR)	13.8 (13.2–14.7)	14.6 (13.6–15.5)	14.5 (13.7–16.1)	0.011

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. For binary variables, only the presence of the characteristic is reported; percentages were calculated within columns. P values were calculated using the Pearson chi-square test or Fisher's exact test for categorical variables and the Student t test or Mann–Whitney U test for continuous variables, as appropriate. An asterisk (*) indicates Fisher's exact test. CT: Computed tomography; IQR: Interquartile range; mRS: modified Rankin Scale; RDW: Red cell distribution width; SD: Standard deviation.

Poor functional outcome at discharge was more frequent among patients with calcification than among those without calcification (47% vs. 28%, p=0.041). When calcification laterality and pattern were considered, poor functional outcome at discharge was more common in patients with ipsilateral non-intimal calcification and in those with contralateral non-intimal calcification. In contrast, discharge NIHSS differed significantly only across ipsilateral Kockelkoren categories, with the highest median NIHSS observed in the non-intimal group (Tables 2 and 3).

Any hemorrhagic transformation was detected in 43 patients (17.7%), whereas symptomatic hemorrhagic transformation occurred in only 9 patients (3.7%). Baseline infarction on admission CT, large-vessel occlusion, and mechanical thrombectomy were associated with any hemorrhagic transformation on follow-up imaging. Because symptomatic hemorrhagic transformation was infrequent, symptomatic hemorrhagic transformation results are presented descriptively and should be interpreted as exploratory (Table 4).

In multivariable analysis, contralateral calcification presence was associated with poor functional outcome at discharge (aOR 2.95, 95% CI 1.09–7.98; p=0.033), and contralateral non-intimal calcification was also associated with poor functional outcome at discharge (aOR 3.32, 95% CI 1.16–9.49; p=0.025). Calcification presence was not consistently associated with hemorrhagic transformation. However, ipsilateral non-intimal calcification showed an inverse association with any hemorrhagic transformation (aOR 0.31, 95% CI 0.10–0.95; p=0.040). Given the limited number of hemorrhagic transformation events across subgroups and the number of related comparisons, this apparently protective association should be interpreted cautiously rather than as definitive evidence of a biologically protective effect (Table 5).

Table 2. Distribution of calcification status according to functional outcome at discharge and discharge NIHSS score

Calcification category	Good outcome (mRS ≤2; n=134)	Poor outcome (mRS ≥3; n=109)	*p*	Discharge NIHSS median (IQR)	*p*
No calcification	23 (17.2%)	9 (8.3%)	0.041	4 (2–7)	0.307
Any calcification	111 (82.8%)	100 (91.7%)		5 (3–9)	
No ipsilateral calcification	27 (20.1%)	12 (11.0%)	0.054	4 (2–7)	0.181
Any ipsilateral calcification	107 (79.9%)	97 (89.0%)		5 (3–9)	
No contralateral calcification	32 (23.9%)	11 (10.1%)	0.005	4 (2–7)	0.166
Any contralateral calcification	102 (76.1%)	98 (89.9%)		5 (3–9)	

Data are presented as n (%) unless otherwise stated. Percentages were calculated within outcome columns and should not be interpreted as event rates within calcification categories. Discharge NIHSS scores are presented as median (IQR). P values for categorical variables were calculated using the Pearson chi-square test, and discharge NIHSS scores were compared using the Mann-Whitney U test. IQR: Interquartile range; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 3. Distribution of Kockelkoren calcification categories according to discharge functional outcome and discharge NIHSS score

Kockelkoren category	Good outcome (mRS ≤2; n=134)	Poor outcome (mRS ≥3; n=109)	*p*	Discharge NIHSS median (IQR)	*p*
Panel A. Ipsilateral calcification pattern					
No calcification	27 (20.1%)	12 (11.0%)	0.030	4 (2–7)	0.033
Intimal calcification	52 (38.8%)	35 (32.1%)		4 (2–7)	
Non-intimal calcification	55 (41.0%)	62 (56.9%)		5.5 (3–9.75)	
Panel B. Contralateral calcification pattern					
No calcification	32 (23.9%)	11 (10.1%)	0.010	4 (2–7)	0.312
Intimal calcification	49 (36.6%)	39 (35.8%)		5 (2–10)	
Non-intimal calcification	53 (39.6%)	59 (54.1%)		5 (3–9)	

Data are presented as n (%) unless otherwise stated. Percentages were calculated within outcome columns and should not be interpreted as event rates within calcification categories. Discharge NIHSS scores are presented as median (IQR). P values for categorical variables were calculated using the Pearson chi-square test, and discharge NIHSS scores were compared using the Kruskal-Wallis test. No post hoc pairwise comparisons were performed. IQR: Interquartile range; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 4. Characteristics according to hemorrhagic transformation on follow-up CT

Panel A. Any hemorrhagic transformation on follow-up CT

Characteristic	Absent (n=200)	Present (n=43)	*P*
Age, years, mean±SD	70.4±12.2	72.3±12.0	0.234
Sex, female, n (%)	87 (43.5%)	15 (34.8%)	0.299
Diabetes mellitus, n (%)	66 (33.0%)	12 (27.9%)	0.516
Hypertension, n (%)	133 (66.5%)	27 (62.8%)	0.642
Atrial fibrillation, n (%)	19 (9.5%)	3 (7.0%)	0.430*
Large-vessel occlusion, n (%)	49 (24.5%)	21 (48.8%)	<0.001
Infarction on admission CT, n (%)	23 (11.5%)	14 (32.6%)	<0.001
Time to IV tPA, min, mean±SD	163±57	164±52	0.963
Mechanical thrombectomy, n (%)	17 (8.5%)	12 (27.9%)	<0.001
Any calcification, n (%)	175 (87.5%)	36 (83.7%)	0.506
Ipsilateral calcification, n (%)	171 (85.5%)	33 (76.7%)	0.156
Contralateral calcification, n (%)	165 (82.5%)	35 (81.4%)	0.863
Ipsilateral calcification pattern			
No calcification, n (%)	29 (14.5%)	10 (23.3%)	0.185
Intimal calcification, n (%)	72 (36.0%)	15 (34.9%)	
Non-intimal calcification, n (%)	99 (49.5%)	18 (41.9%)	
Contralateral calcification pattern			
No calcification, n (%)	35 (17.5%)	8 (18.6%)	0.824
Intimal calcification, n (%)	71 (35.5%)	17 (39.5%)	
Non-intimal calcification, n (%)	94 (47.0%)	18 (41.9%)	

CT: Computed tomography.

Panel B. Symptomatic hemorrhagic transformation on follow-up CT

Characteristic	Absent (n=234)	Present (n=9)	*P*
Age, years, mean±SD	70.6±12.2	75.9±9.7	0.169
Sex, female, n (%)	99 (42.3%)	3 (33.3%)	0.432*
Diabetes mellitus, n (%)	75 (32.1%)	3 (33.3%)	0.595*
Hypertension, n (%)	157 (67.1%)	3 (33.3%)	0.045*
Atrial fibrillation, n (%)	21 (9.0%)	1 (11.1%)	0.581*
Large-vessel occlusion, n (%)	66 (28.2%)	4 (44.4%)	0.240*
Infarction on admission CT, n (%)	36 (15.4%)	1 (11.1%)	0.590*
Time to IV tPA, min, mean±SD	162±56	180±55	0.353
Mechanical thrombectomy, n (%)	27 (11.5%)	2 (22.2%)	0.292*
Any calcification, n (%)	202 (86.3%)	9 (100.0%)	0.274*
Ipsilateral calcification, n (%)	195 (83.3%)	9 (100.0%)	0.201*
Contralateral calcification, n (%)	192 (82.1%)	8 (88.9%)	0.506*
Ipsilateral calcification pattern			
No calcification, n (%)	39 (16.7%)	0 (0.0%)	0.280
Intimal calcification, n (%)	82 (35.0%)	5 (55.6%)	
Non-intimal calcification, n (%)	113 (48.3%)	4 (44.4%)	

Table 4. Continue

Panel B. Symptomatic hemorrhagic transformation on follow-up CT			
Characteristic	**Absent (n=234)**	**Present (n=9)**	***P***
Contralateral calcification pattern			
No calcification, n (%)	42 (17.9%)	1 (11.1%)	0.467
Intimal calcification, n (%)	83 (35.5%)	5 (55.6%)	
Non-intimal calcification, n (%)	109 (46.6%)	3 (33.3%)	

Data are presented as mean ± SD or n (%), as appropriate. Percentages were calculated within columns. P values for categorical variables were calculated using the Pearson chi-square test, except where indicated by an asterisk (*), for which Fisher's exact test was used. Continuous variables were compared using the independent-samples t-test. CT: Computed tomography; IV tPA: intravenous tissue plasminogen activator.

Table 5. Multivariable associations of calcification parameters with hemorrhagic transformation on follow-up CT and poor functional outcome at discharge

Panel A. Any hemorrhagic transformation on follow-up CT				
Calcification parameter	**aOR**	***P***	**95% CI**	
			CI Lower	**CI Upper**
Any calcification	0.45	0.160	0.144	1.38
Ipsilateral calcification	0.37	0.055	0.136	1.02
Contralateral calcification	0.59	0.330	0.205	1.69
Ipsilateral intimal calcification	0.44	0.130	0.15	1.28
Ipsilateral non-intimal calcification	0.31	0.040	0.102	0.95
Contralateral intimal calcification	0.63	0.420	0.208	1.92
Contralateral non-intimal calcification	0.54	0.290	0.17	1.71
Panel B. Poor functional outcome at discharge (mRS ≥3)				
Any calcification	2.31	0.130	0.78	6.79
Ipsilateral calcification	2.31	0.110	0.82	6.44
Contralateral calcification	2.95	0.033	1.09	7.98
Ipsilateral intimal calcification	1.88	0.253	0.64	5.55
Ipsilateral non-intimal calcification	2.84	0.060	0.96	8.38
Contralateral intimal calcification	2.59	0.080	0.89	7.47
Contralateral non-intimal calcification	3.32	0.025	1.16	9.49

Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were derived from multivariable binary logistic regression analyses using the enter method. Each calcification parameter shown in the table was entered into a separate model adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, presence of infarction on admission CT, admission NIHSS score, dense artery sign, and mechanical thrombectomy status. Because of the low number of hemorrhagic transformation events, estimates for hemorrhagic transformation should be interpreted cautiously. aOR: Adjusted odds ratio; CI: Confidence interval; CT: Computed tomography; NIHSS: National Institutes of Health Stroke Scale.

Discussion

This study evaluated whether intracranial carotid siphon calcifications on CTA were associated with hemorrhagic transformation after IV tPA and with short-term functional outcome at hospital discharge. The main findings were that calcification presence and pattern were not consistently related to post-thrombolytic hemorrhagic transformation, whereas contralateral calcification, particularly contralateral non-intimal calcification, was associated with poorer discharge status. Because only nine patients experienced symptomatic hemorrhagic transformation, all hemorrhagic transformation results should be regarded as exploratory.

Interest in intracranial arterial calcifications in ischemic stroke has increased in recent years. Prior studies have shown that

intracranial arterial calcifications are common in patients with cerebrovascular disease and may reflect different forms of vascular injury depending on their morphology and distribution [15–17]. In addition, CTA-based morphologic classification systems have provided a structured framework for distinguishing predominantly intimal from predominantly medial/adventitial calcification patterns in the intracranial internal carotid artery [3].

In our cohort, calcifications were more common in older patients and in patients with hypertension, which is consistent with the broader vascular literature and supports the interpretation that intracranial arterial calcification is better understood as a marker of chronic vascular burden than as an isolated imaging phenomenon [17,18]. Whether intracranial carotid calcification is associated with hemorrhagic transformation after intravenous alteplase remains uncertain. From a biological perspective, different calcification patterns may plausibly correspond to different vascular properties. Intimal calcification is generally discussed in relation to atherosclerotic plaque burden and plaque-related instability, whereas medial or non-intimal calcification has been associated with arterial stiffening, impaired vasomotor function, and reduced vascular compliance [2,4,6–8]. Based on these concepts, it is reasonable to examine whether the calcification pattern may be related to reperfusion-related hemorrhagic transformation in ischemic tissue. However, the available clinical literature has been inconsistent, and our results add to that heterogeneous body of evidence rather than resolving it.

Several previous studies suggested that intracranial carotid calcification burden or pattern may be associated with hemorrhagic transformation or post-thrombolysis prognosis. A higher frequency of acute hemorrhagic complications in patients with non-intimal calcifications was reported in one thrombolysis cohort [9]. Other studies also suggested that calcification burden or calcification pattern may carry prognostic information in patients with ischemic stroke treated with IV tPA [10–12]. In contrast, other reports did not identify a clear and consistent association between intracranial carotid artery calcification scores and post-thrombolysis prognosis [13,14]. Taken together, the prior literature is better characterized as heterogeneous than directional, which was also the rationale for the present study. This framing is important because it clarifies that the current work was not designed to confirm a universally established effect, but rather to examine a question that remains unresolved across different cohorts and methodologies.

In the present cohort, neither overall calcification presence nor most calcification subcategories showed a stable association with hemorrhagic transformation. Although ipsilateral non-intimal calcification showed an inverse association with any hemorrhagic transformation in one adjusted model, this isolated finding should not be overinterpreted. It was not supported by a broader pattern of consistently lower hemorrhagic transformation risk across calcification variables, and symptomatic hemorrhagic transformation was too infrequent for a robust separate regression analysis. For this reason, this result is better viewed as an exploratory signal than as evidence of a biologically protective relationship.

The discrepancy across published studies likely reflects genuine methodological heterogeneity rather than a simple contradiction. Calcification assessment is not standardized across the literature. Some studies relied on burden-based or semiquantitative scores, whereas others used morphologic classifications designed to distinguish intimal from non-intimal calcification [3,14]. Study populations also differ substantially. Some cohorts excluded patients undergoing thrombectomy, some focused on selected stroke subtypes such as non-cardioembolic stroke, and some did not evaluate all patients with CTA [11,12]. Endpoints also vary, ranging from any hemorrhagic transformation to symptomatic hemorrhage, discharge status, and later functional outcome. These differences complicate direct comparison and may explain why one study identifies an apparent association while another does not.

In our study, the inclusion of only patients who underwent CTA improved the reliability of calcification morphology assessment and reduced the risk of mistaking adjacent calcified structures for true arterial wall calcification. At the same time, this requirement may have preferentially selected patients with more severe stroke, suspected large-vessel occlusion, or possible thrombectomy candidacy, thereby limiting generalizability to the broader population of intravenous alteplase-treated stroke patients.

Another notable finding in our cohort was the association between calcification presence and higher RDW values. RDW has traditionally been used in the evaluation of anemia, but it is increasingly discussed as a nonspecific biomarker linked to inflammation, oxidative stress, and adverse cardiovascular profiles [19,20]. In addition, potential links between RDW, vascular calcification, and stroke prognosis have been suggested in previous studies [21–23]. Within this context, the higher RDW values observed in patients with intracranial calcifications in our cohort may indicate that these imaging findings coexist with a broader systemic vascular or inflammatory profile. This interpretation remains tentative, but it is clinically interesting because RDW is inexpensive, routinely measured, and rapidly available in emergency settings.

The association between contralateral calcification and poor functional outcome at discharge also deserves careful interpretation. The biological basis of this association is not straightforward, and our data do not allow causal inference. One possibility is that contralateral calcification functions as a marker of diffuse intracranial vascular disease rather than a lesion-specific characteristic. This interpretation is compatible with prior work suggesting that arterial calcification may accompany chronic vascular damage, altered hemodynamics, and downstream embolic or prognostic burden [24,25]. In that framework, contralateral non-intimal calcification may identify patients with an adverse cerebrovascular profile, reduced vascular reserve, or more extensive systemic vascular disease. However, this interpretation should remain hypothesis-generating. The current data do not show that contralateral calcification itself causes poor functional outcome; rather, they suggest that calcification may serve as an imaging marker of an adverse vascular profile.

The laterality finding should also be interpreted conservatively. A simple lesion-centered assumption would be that ipsilateral calcification should be more relevant to tissue-level events in the affected hemisphere, whereas contralateral calcification might be less informative. Our results did not follow that simple pattern. Instead, contralateral calcification showed the more consistent association with poor functional outcome at discharge. This may indicate that laterality in this setting reflects asymmetry in overall intracranial vascular burden, collateral pathways, or chronic arterial remodeling rather than purely local plaque behavior. Because collateral imaging, perfusion parameters, and long-term follow-up were not available in the present study, this interpretation should be regarded as hypothesis-generating rather than definitive.

These findings may also have practical implications for the interpretation of imaging findings in patients with acute ischemic stroke treated with IV tPA. Based on the present results, intracranial carotid calcifications on CTA should not be used in isolation to infer a high risk of post-thrombolytic hemorrhagic transformation or to discourage otherwise guideline-concordant alteplase treatment. At the same time, the observed association between contralateral calcification, especially contralateral non-intimal calcification, and poor functional outcome at discharge raises the possibility that calcification pattern and laterality may contribute to early short-term risk stratification. At present, however, this possible prognostic role should be viewed as preliminary and should not be considered practice-changing.

Conclusion

In this CTA-selected cohort of patients with acute ischemic stroke treated with IV tPA, intracranial arterial calcifications were not consistently associated with post-thrombolytic hemorrhagic transformation. Some calcification patterns, particularly contralateral and contralateral non-intimal calcifications, were associated with poor short-term functional outcome at discharge. These findings should be interpreted cautiously because symptomatic hemorrhagic transformation was uncommon, and functional outcome was assessed only at discharge.

Limitations

This retrospective single-center study is subject to residual confounding and limited external validity.

The cohort included only patients who underwent CTA, which may have selected for more severe stroke and limited the generalizability of the findings to all patients treated with IV thrombolysis.

Symptomatic hemorrhagic transformation occurred in only 9 patients, which limited statistical power and precluded a reliable separate multivariable model for symptomatic hemorrhagic transformation.

Functional outcome was measured at discharge rather than at 90 days, so the reported associations apply only to short-term hospital outcomes.

Ethics

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylul University Institutional Non-Interventional Clinical Research Ethics Committee of Blinded for peer review (Decision No: 2023/23-12; Date: 19.07.2023).

Informed Consent: The requirement for informed consent was waived because of the retrospective design of the study.

Conflict of Interest: None declared.

Financial Disclosure: The author declared that this study has received no financial support.

Use of AI for Writing Assistance: None declared.

Authorship Contributions: Concept: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Design: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Supervision: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Resource: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Materials: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Data collection and/or processing: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Analysis and/or interpretation: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Literature review: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Writing: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.; Critical review: Ö.Y.B., F.C., S.A., T.A.Ö., Y.T., E.B., Ş.İ.K.Y.

Peer-review: Externally peer-reviewed.

References

1. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, et al. Treatment and outcome of hemorrhagic transformation after ıntravenous alteplase in acute ıschemic stroke: a scientific statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2017;48:e343–e61.
2. Lanzer P, Hannan FM, Lanzer JD, Janzen J, Raggi P, Furniss Det al. Medial arterial calcification: JACC state-of-the-art review. J Am Coll Cardiol. 2021;78:1145–65.
3. Kockelkoren R, Vos A, Van Hecke W, Vink A, Bleys RL, Verdoorn D, et al. Computed tomographic distinction of ıntimal and medial calcification in the ıntracranial ınternal carotid artery. PLoS One. 2017;12:e0168360.
4. Du H, Li J, Yang W, Bos D, Zheng L, Wong LKS, et al. Intracranial arterial calcification and ıntracranial atherosclerosis: close but different. Front Neurol. 2022;13:799429.
5. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical ındications. Vascul Pharmacol. 2016;77:1–7.
6. Du H, Yang W, Chen X. Histology-verified ıntracranial artery calcification and ıts clinical relevance with cerebrovascular disease. Front Neurol. 2022;12:789035.
7. Li X, Du H, Li J, Li X, Gao Q, Chen X. Cerebral arterial stiffness as measured based on the pulse wave velocity is associated with ıntracranial artery calcification in patients with acute stroke. J Clin Neurol 2023;19:338–43.
8. Vasan RS, Pan S, Xanthakis V, Beiser A, Larson MG, Seshadri S, et al. Arterial stiffness and long-term risk of health outcomes: the framingham heart study. Hypertension 2022;79:1045–56.
9. Gocmen R, Arsava EM, Oguz KK, Topcuoglu MA. Atherosclerotic intracranial internal carotid artery calcification and intravenous thrombolytic therapy for acute ischemic stroke. Atherosclerosis. 2018;270:89–94.
10. Tábuas-Pereira M, Sargento-Freitas J, Silva F, Parra J, Mendes P, Seara V, et al. Intracranial ınternal carotid artery wall calcification in ıschemic strokes treated with thrombolysis. Eur Neurol. 2018;79:21–6.
11. Yu Y, Zhang FL, Qu YM, Zhang P, Zhou HW, Luo Y, et al. Intracranial calcification is predictive for hemorrhagic transformation and prognosis after ıntravenous thrombolysis in non-cardioembolic stroke patients. J Atheroscler Thromb. 2021;28:356–64.
12. Kauw F, de Jong PA, Takx RAP, de Jong HWAM, Kappelle LJ, Velthuis BK, et al. Effect of intravenous thrombolysis in stroke depends on pattern of ıntracranial ınternal carotid artery calcification. Atherosclerosis. 2021;316:8–14.
13. Shen Y, Dong Z, Xu G, Zhong J, Pan P, Chen Z, et al. Correlation between ıntracranial carotid artery calcification and prognosis of acute ıschemic stroke after ıntravenous thrombolysis. Front Neurol. 2022;13:740656.
14. He XW, Zhao R, Li GF, Zheng B, Wu YL, Shi YH, et al. Lack of correlation between ıntracranial carotid artery modified woodcock calcification score and prognosis of patients with acute ıschemic stroke after ıntravenous thrombolysis. Front Neurol. 2019;10:696.
15. Zhang F, Yang L, Gan L, Fan Z, Zhou B, Deng Z, et al. Spotty calcium on cervicocerebral computed tomography angiography associates with ıncreased risk of ıschemic stroke. Stroke. 2019;50:859–66.
16. Mazzacane F, Del Bello B, Ferrari F, Persico A, Rognone E, Pichiecchio A, et al. Intracranial carotid artery calcification morphology differs in patients with lacunar and nonlacunar acute ischemic strokes. Eur J Neurol 2023;30:963–9.
17. Bartstra JW, van den Beukel TC, Van Hecke W, Mali WPTM, Spiering W, Koek HL, et al. Intracranial arterial calcification: prevalence, risk factors, and consequences: JACC review topic of the week. J Am Coll Cardiol. 2020;76:1595–604.
18. Gutierrez J, Turan TN, Hoh BL, Chimowitz MI. Intracranial atherosclerotic stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2022;21:355–68.
19. Horta-Baas G, Romero-Figueroa MDS. Clinical utility of red blood cell distribution width in inflammatory and non-inflammatory joint diseases. Int J Rheum Dis. 2019;22:47–54.
20. Khan HA, Haseeb Khan S, Tayyab Z, Saif S, Khan SN, Musaddiq S. Association of red cell distribution width and mean platelet volume with disease activity in rheumatoid arthritis patients. Cureus. 2024;16:e56908.
21. den Harder AM, de Jong PA, de Groot MCH, Wolterink JM, Budde RPJ, Išgum I, et al. Commonly available hematological biomarkers are associated with the extent of coronary calcifications. Atherosclerosis. 2018;275:166–73.
22. Pan J, Borné Y, Gonçalves I, Persson M, Engström G. Associations of red cell distribution width with coronary artery calcium in the general population. Angiology 2022;73:445–52.
23. Shen H, Shen L. Red blood cell distribution width as a predictor of mortality and poor functional outcome after acute ischemic stroke: a meta-analysis and meta-regression. BMC Neurol. 2024;24:122.
24. Lee SJ, Hong JM, Lee M, Huh K, Choi JW, Lee JS. Cerebral arterial calcification is an imaging prognostic marker for revascularization treatment of acute middle cerebral arterial occlusion. J Stroke. 2015;17:67–75.
25. Wu XH, Chen XY, Fan YH, Leung TWH, Wong KS. High extent of ıntracranial carotid artery calcification ıs associated with downstream microemboli in stroke patients. J Stroke Cerebrovasc Dis. 2017;26:442–7.