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# Intracranial Calcification is Predictive for Hemorrhagic Transformation and Prognosis After Intravenous Thrombolysis in Non-Cardioembolic Stroke Patients

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**Aim:** Hemorrhagic transformation is the major complication of intravenous thrombolysis. Calcification is used widely as an imaging indicator of atherosclerotic burden and cerebrovascular function. The relationship between intracranial calcification and hemorrhagic transformation has not been explored fully. We aimed to identify and quantify calcification in the main cerebral vessels to investigate the correlations between quantitative calcification parameters, hemorrhagic transformation, and prognosis.

**Methods:** Acute, non-cardiogenic, ischemic stroke patients with anterior circulation who received intravenous thrombolysis therapy in the First Hospital of Jilin University were retrospectively and consecutively included. All included patients underwent a baseline CT before intravenous thrombolysis and a follow-up CT at 24 hours. A third-party software, ITK-SNAP, was used to segment and measure the calcification volume. A vascular non-bone component with a CT value >130 HU was considered calcified. Hemorrhagic transformation was determined based on the ECASS II classification criteria.

**Results:** The study included 242 patients, 214 of whom were identified as having calcification. Thirty-one patients developed hemorrhagic transformation. The calcification volume on the lesion side (0.1ml) was associated with hemorrhagic transformation ($p=0.004$, OR=1.504, 95% CI: 1.140–1.985). Ninety-six patients had poor prognoses. The poor prognosis group had more calcified vessels than the good prognosis group ($p=0.014$, OR=1.477, 95% CI: 1.083–2.015).

**Conclusions:** The arterial calcification volume on the lesion side is associated with hemorrhagic transformation after thrombolysis. The higher the number of calcified vessels, the greater the risk of poor prognosis.

**Key words:** Vascular calcification, Thrombolysis, Hemorrhagic transformation, Prognosis, Stroke

## 1. Introduction

Intravenous thrombolysis is an effective approach for early reperfusion, significantly reducing disability and fatality in acute ischemic stroke patients[1, 2]. However, it is still accompanied by a 2-7% risk of symp-

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tomatic HT (hemorrhagic transformation), which can deteriorate clinical course and prognosis[3]. HT's underlying mechanism and pathophysiology are intricate, and the most likely reasons are ischemia reperfusion and damage of the blood–brain barrier[4]. Currently known HT risk factors include early imaging ischemic changes, higher baseline blood glucose level, higher baseline NIHSS (National Institute of Health Stroke Scale), time to treatment, and borderline-low platelet count[5].

Non-contrast CT is a simple, fast, and routine procedure recommended in the 2018 AHA/ASA guidelines before intravenous thrombolysis[6]. Because "Time is Brain", the earlier thrombolysis therapy began, the more likely patients were to achieve earlier reperfusion and better prognoses. Therefore, acquiring as much information as possible from the non-contrast CT before thrombolysis is crucial for clinical practice. Arterial calcification refers calcium salts deposited in one or more arterial wall layers[7]. Several studies showed that ICAC (intracranial arterial calcification) is associated with stroke[8] and poor prognosis[9]. ICAC suggests a heavier atherosclerosis burden and a higher risk of vessel stenosis, especially medial arterial calcification, which could affect the regulation of blood vessels[10-12]. Previous studies have explored the correlation between intracranial internal carotid artery calcification and HT or poor prognosis after thrombolysis, but the conclusions are inconsistent[13-15], and no quantitative study has been conducted. Also, a more thorough ICAC evaluation, not only in the intracranial internal carotid artery, but also the middle cerebral, vertebral, and basilar arteries, can help us better understand the whole picture of ICAC, HT, and prognosis.

## 2. Aim

A non-contrast CT scan to detect calcification is straightforward, convenient, and reliable. In this study, we used third-party quantitative software to investigate the quantification parameters of the vascular calcification, as well as its predictive value in HT and prognosis, for acute non-cardiogenic ischemic stroke patients receiving thrombolysis therapy.

## 3. Methods

### 3.1 Patients

This study, retrospectively and consecutively, included patients diagnosed with acute non-cardiogenic ischemic stroke who received intravenous thrombolysis therapy in the Department of Neurology, First Hospital of Jilin University, from July 1st 2015 to June 30th 2018. All patients or immediate family members provided written informed consent. The Ethics Committee of the First Hospital of Jilin University approved the study protocol. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

We included patients who (1) met the inclusion criteria for intravenous thrombolysis in the 2018 AHA/ASA guidelines[6]; (2) received intravenous thrombolysis therapy less than 4.5 hours from onset; (3) were diagnosed with acute ischemic stroke in anterior circulation confirmed by diffusion weighted image or follow-up CT; (4) had complete baseline CT images, follow-up CT images, and clinical information; and (5) signed informed consent forms. The study excluded patients who (1) were classified into the cardioembolism stroke category according to the TOAST criteria[16, 17]; (2) had contraindications for intravenous thrombolysis according to 2018 AHA/ASA guidelines[6]; (3) received subsequent mechanical thrombectomy or other endovascular treatment; (4) had a mRS (modified Rankin Scale) score ≥ 2 before stroke onset; and (5) had incomplete clinical data or imaging information.

### 3.2 Intravenous Thrombolysis Therapy

The intravenous thrombolysis therapy was conducted with recombinant tissue plasminogen activator (rt-pa, Boehringer Ingelheim International, Germany). The dose was 0.9 mg/kg, of which 10% was intravenously injected within 1 minute, and the remaining dose was intravenously pumped in 1 hour[6].

### 3.3 Clinical Data Collection and Follow-Up

We collected demographic information (name, gender, age), lifestyle history (smoking, drinking), medical history (hypertension and diabetes mellitus, including both previous diagnosis and diagnosis during this hospitalization; previous stroke), baseline NIHSS scores (assessed by a professional neurologist before intravenous thrombolytic administration), ONT (onset-to-needle time), fingertip blood glucose and blood pressure (completed by thrombolysis specialized nurses before thrombolytic administration), laboratory results (fasting blood glucose, glycosylated hemoglobin, low density lipoprotein-cholesterol, and homocysteine). Regarding follow-up data, mRS was assessed 3 months after thrombolysis therapy. Good prognosis was defined as follow-up mRS ≤ 2 at 3 months, and poor prognosis was defined as follow-up mRS >2 at 3 months.

### 3.4 CT Scanning Protocol and HT Interpretation

Brain CT scans were performed at baseline and

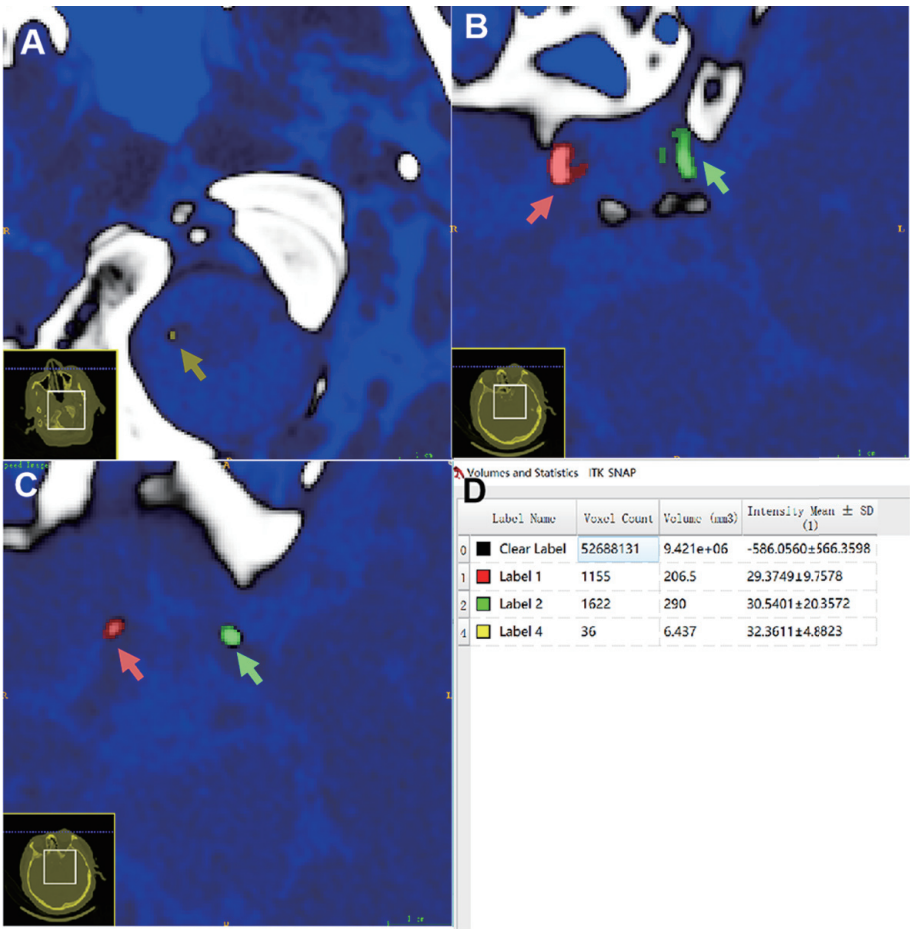


**Fig. 1.** Calcification Segmentation and Quantification

The ITK-SNAP can identify areas with CT values above 130 HU (the blue region is where the CT value less than 130HU) semi-automatically and use different colors to mark the calcification range of different blood vessels to quantify the specific volume value. In this case, the calcifications in the right vertebral artery, the right internal carotid artery, and the left internal carotid artery were marked as yellow, red, and green, respectively.

24 ± 2 hours after intravenous thrombolysis. A brain CT would be re-performed, if necessary, because of a change of the patient's condition. All CT scans were performed on a 64-slice Philips CT scanner (Philips Healthcare, Best, The Netherlands) with a slice thickness of 1.5 mm and a slice gap of 0.75 mm. All images were interpreted by two experienced neuroimaging physicians blinded to the clinical information and final diagnosis. HT determination and classification were undertaken according to the ECASS II classification criteria[18].

### 3.5 Intracranial Calcification Quantification

We assessed and quantified intracranial calcification of seven main vessels (bilateral internal carotid artery C2–C7 segments, bilateral middle cerebral artery, bilateral vertebral artery V4 segments, and basilar artery), shown by baseline CT scan before intravenous thrombolysis. We used the ITK-SNAP Medical Image Segmentation Tool, which is third-party image semi-quantitative segmentation measurement software developed by the National Institutes of Health and the National Center for Biomedical Imaging and Bioengineering[19, 20]. Intracranial calcification was defined as a CT value >130 HU within the vessel regions[21, 22]. The calcification region was segmented by ITK-SNAP and then delineated manually on each successive layer to obtain the exact number of pixels and the volume of the region of interest, thereby obtaining each blood vessel's calcification volume (typical case shown in Fig. 1). The CT images can be reconstructed in sagittal, coronal, and axial positions by ITK-SNAP, thus better differentiating between calcification and bone. The calcification parameters were ICAC (qualitative determination), NCV (number of calcified vessels), CV-L (calcification volume on the lesion side, 0.1 ml),

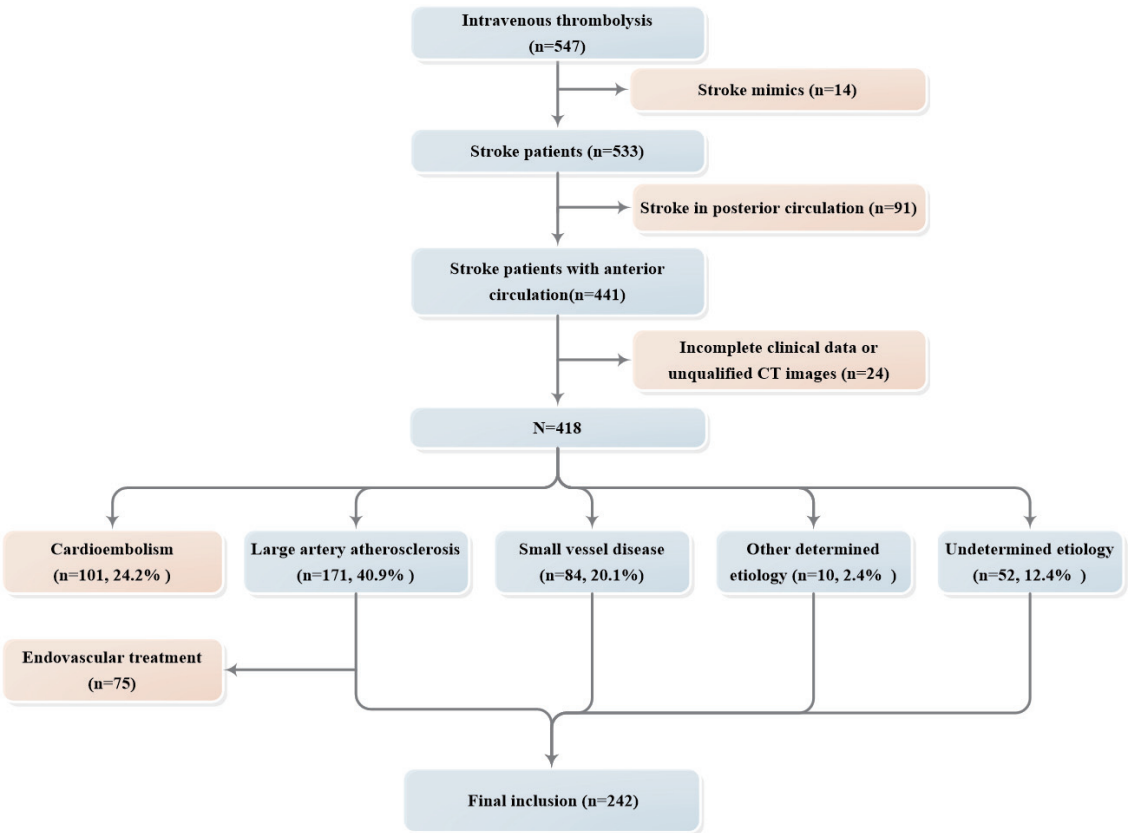


**Fig. 2.** Flow chart of patient inclusion

and CV-O (overall calcification volume, 0.1 ml). All measurements were performed by two experienced neuroimaging researchers, and both investigators were blinded to the patient's clinical data.

### 3.6 Statistical Analysis

Statistical analysis was completed with SPSS 22.0 (International Business Machine, West Grove, PA, USA). A $p$ value of $<0.05$ was considered statistically significant. Measurement data were expressed as mean ± standard deviation or median and quartile according to the normality test, and the categorical variables were presented as frequency (percentage). Kappa was used to test inter and intra-rater reliability for detecting ICAC and HT. The two groups of measurement data were tested by $t$ test or Mann–Whitney test according to their normality tests. The comparison between the two sets of categorical variables was assessed by the chi-square test, corrected chi-square test, or Fisher's exact probability method.

Correlations between HT or poor prognosis and calcification were performed by logistic regression analysis, and sensitivity analysis was also applied to test correlation stability. We applied four different logistic regression models to do the sensitivity analysis: model 1 (adjusted for age and gender); model 2 (adjusted for age, gender, smoking, and drinking); model 3 (adjusted for age, gender, smoking, drinking, hypertension, diabetes mellitus, and previous stroke); model 4: (adjusted for age, gender, smoking, drinking, hypertension, diabetes mellitus, previous stroke, previous antithrombotic agents, TOAST criteria, ONT, baseline NIHSS, fingertip blood glucose, systolic pressure). Only statistical results that were consistent in all the four models would be considered conclusive.

## Results

### 4.1 Overall Characteristics

Ultimately, 242 patients were included. The sample selection framework is presented in Fig. 2. The median age was 61(53–67) years, and 61(25.2%) patients were female. The median baseline NIHSS was 9(5–13). Excellent inter and intra-observer reliability was seen in distinguishing the presence of ICAC (Kappa = 0.875, 0.866) and HT (Kappa = 0.903, 0.921). The inter-observer agreements (intraclass correlation coefficient) for NCV, CV-L, and CV-O were 0.902, 0.870, and 0.863. The patients' baseline information is shown in Table 1.

**Table 1.** Baseline Information

| | Total ($n$ = 242) | ICAC ($n$ = 214) | Without ICAC ($n$ = 28) | $P$ Value |
|---|---|---|---|---|
| Gender (female) | 61 (25.2) | 51 (23.8) | 10 (35.7) | 0.173 |
| Age (years old) | 61.00 (53.00–67.00) | 61.00 (53.00-67.00) | 59.00 (51.75–69.50) | 0.833 |
| Life history | | | | |
| Smoking ($n$, %) | 155 (64.0) | 134 (62.6) | 21 (75.0) | 0.199 |
| Drinking ($n$, %) | 110 (45.5) | 99 (46.3) | 11 (39.3) | 0.486 |
| Previous history | | | | |
| Hypertension ($n$, %) | 149 (61.6) | 130 (60.7) | 19 (67.9) | 0.467 |
| Diabetes mellitus ($n$, %) | 67 (27.7) | 62 (29.0) | 5 (17.9) | 0.216 |
| Previous stroke ($n$, %) | 59 (24.4) | 53 (24.8) | 6 (21.4) | 0.699 |
| Previous antithrombotic agents ($n$, %) | 30 (12.4) | 27 (12.6) | 3 (10.7) | 0.774 |
| Baseline clinical data | | | | |
| ONT (min) | 180.00 (146.00-226.50) | 179.00 (146.50-225.00) | 210.00 (122.75-233.75) | 0.679 |
| NIHSS | 9 (5–13) | 9.00 (5.00–13.25) | 6 (4–10) | 0.009* |
| Fingertip blood glucose (mmol/l) | 7.40 (6.40-8.80) | 7.40 (6.40–8.97) | 7.20 (6.23–8.14) | 0.383 |
| Systolic pressure (mmHg) | 156.50 (137.75-177.25) | 157.00 (138.00–178.00) | 154.00 (132.00–173.25) | 0.714 |
| TOAST criteria | | | | |
| Large artery atherosclerosis ($n$, %) | 96 (39.7) | 85 (39.7) | 11 (39.3) | |
| Small vessel disease ($n$, %) | 84 (34.7) | 76 (35.5) | 8 (28.6) | 0.344 |
| Other determined etiology ($n$, %) | 10 (4.1) | 10 (4.7) | 0 (0) | |
| Undetermined etiology ($n$, %) | 52 (21.5) | 43 (20.1) | 9 (32.1) | |
| Lab tests | | | | |
| High LDL-C ($n$, %) | 92 (38.0) | 86 (40.2) | 6 (21.4) | 0.052 |
| High homocysteine ($n$, %) | 69 (28.5) | 60 (28.0) | 9 (32.1) | 0.696 |

Abbreviations: ICAC: Intracranial Arterial Calcification; ONT: onset-to-needle time; NIHSS: National Institute of Health Stroke Scale; LDL-C: Low Density Lipoprotein-Cholesterol. Notes: *: $p<0.05$.

### 4.2 Relationship between ICAC and Post-Thrombolysis HT

Among the 242 patients, 31(12.8%) had HT. In univariate analysis, the baseline NIHSS, NCV, CV-L and CV-O of the HT group were all higher than otherwise (12.32 vs 9.16, $p=0.003$; 2.42 vs 1.91, $p=0.002$; 1.70 vs 0.83, 0.1ml, $p<0.001$; 3.08 vs 1.78, 0.1ml, $p<0.001$). An illustration of the CV-L Quartiles, CV-O Quartiles and HT is shown in **Fig. 3 A, B**. A binary logistic analysis and sensitivity analysis were performed by four different models. The OR values and 95% confidence intervals are shown in **Table 2**. CV-L was significantly associated with HT ($p=0.004$, OR=1.504, 95% CI: 1.140–1.985). The sensitivity analysis indicated this correlation was stable in all four models.

### 4.3 Relationship between ICAC and Prognosis

Of the 242 included patients, 96(39.7%) had poor prognoses. In univariate analysis, the baseline NIHSS of the poor prognosis group was higher than otherwise (11.99 vs 7.97, $p<0.001$). Regarding the calcification parameters, patients with ICAC were more likely to have a poor prognosis (96.9% vs 82.9%, $p=0.001$). NCV, CV-L, and CV-O in the poor prognosis group were all higher than otherwise in univariate analysis(2.30 vs 1.75, $p<0.001$; 1.15 vs 0.81, 0.1ml, $p=0.017$; 2.33 vs 1.70, 0.1ml, 0.015). An illustration of the ICAC, NCV and prognosis is shown in **Fig. 3 C, D**. OR values and 95% confidence intervals are shown in **Table 2**. Patients with ICAC were more likely to have poor prognoses ($p=0.015$, OR=5.002, 95%CI: 1.365-18.330). NCV in the poor prognosis group was higher than otherwise ($p=0.014$, OR=1.477, 95% CI: 1.083–2.015). The sensitivity analysis indicated this correlation was stable in all four models.

## 5. Discussion

Arterial calcification is common in atherosclerosis, chronic kidney disease, and diabetes mellitus, especially in the elderly[7]. Previous studies showed that more than 80% of the community group that older than 55 had CT visible ICAC[23]. ICAC is associated with increased risk of ischemic stroke[24], poor prognosis[9] and leukoaraiosis[25], which is related to HT. There are two calcification types most associated with isch-

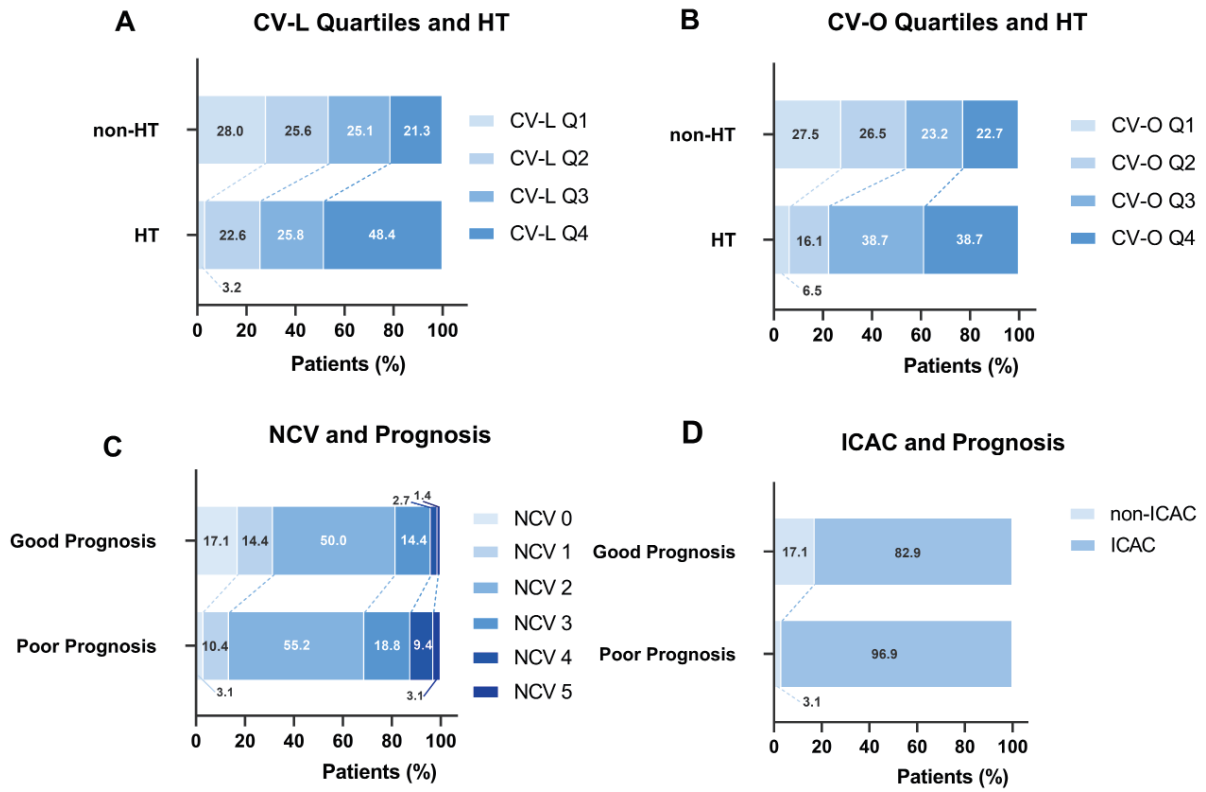


**Fig. 3.** Stacked percentage diagram

A, B: CV-L and CV-O in HT group were all higher otherwise. C: The NCV in the poor prognosis group was higher than otherwise. D: Patients with ICAC were more likely to have higher mRS and poor prognosis.

**Table 2.** Odds Ratios (95% Confidence Interval) of the Association between ICAC, HT and prognosis

| | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|
| ICAC and HT | | | | |
| ICAC | | | | |
| Yes | 4.695 (0.609–36.196) | 4.871 (0.611-38.819) | 4.802 (0.600-38.419) | 3.554 (0.431-29.341) |
| No | 1 | 1 | 1 | 1 |
| NCV (per 1 count) | 1.644*(1.133–2.386) | 1.655*(1.127-2.430) | 1.636*(1.104-2.426) | 1.592*(1.032-2.455) |
| CV-L (per 0.1 ml) | 1.523*(1.194–1.942) | 1.508*(1.176–1.934) | 1.529*(1.184–1.976) | 1.504*(1.140-1.985) |
| CV-O (per 0.1 ml) | 1.167*(1.038–1.313) | 1.154*(1.025–1.300) | 1.155*(1.020–1.308) | 1.151*(1.006-1.316) |
| ICAC and Poor Prognosis | | | | |
| ICAC | | | | |
| Yes | 6.216*(1.817-21.269) | 5.707*(1.656-19.671) | 5.544*(1.600-19.213) | 5.002*(1.365-18.330) |
| No | 1 | 1 | 1 | 1 |
| NCV (per 1 count) | 1.655*(1.264-2.167) | 1.621*(1.233-2.132) | 1.602*(1.213-2.114) | 1.477*(1.083-2.015) |
| CV-L (per 0.1 ml) | 1.227*(1.003–1.502) | 1.227*(1.002–1.504) | 1.213 (0.987–1.490) | 1.139 (0.907-1.432) |
| CV-O (per 0.1 ml) | 1.093 (0.992–1.204) | 1.092 (0.990–1.203) | 1.084 (0.981–1.198) | 1.057 (0.947-1.180) |

Abbreviations: ICAC: Intracranial Arterial Calcification, Yes vs No; HT: hemorrhagic transformation; NCV: Number of Calcified Vessels, per 1 count; CV-L: Calcification Volume on the Lesion Side, per 0.1 ml; CV-O: Overall Calcification Volume, per 0.1 ml. Notes: *: $p<0.05$; Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, smoking, and drinking; Model 3: adjusted for age, gender, smoking, drinking, hypertension, diabetes mellitus, and previous stroke; Model 4: adjusted for age, gender, smoking, drinking, hypertension, diabetes mellitus, previous stroke, previous antithrombotic agents, TOAST criteria, ONT, baseline NIHSS, fingertip blood glucose, systolic pressure.

emic events: medial calcification and atherosclerotic calcification (often occurs in the intima). Intimal calcification is mainly related to plaque stability, while medial calcification can obstruct the vessels' function. Due to the worsening of vascular compliance and elasticity, vascular regulation could be damaged[26]. Also, calcification could impede the positive remodeling process[27]. Several studies focused on the correlation between ICAC and post-thrombolysis HT, but the conclusions were not completely consistent. In 2013, a study categorized 297 post-thrombolysis patients into a mild calcification group and a moderate-to-severe calcification group by morphological assessment. The risk of HT in the moderate-to-severe calcification group was significantly higher[14]. This study explored the relationship between ICAC and HT for the first time. Inevitably, the qualitative two-category classification could have overlooked some detailed information. Later, another study enrolled 396 post-thrombolysis patients and performed a calcification burden assessment by calcification thickness and spread angle of the most severe slice on CT. They found that the increased calcification score would not lead to a higher risk of HT, but was associated with increased mortality[13]. In 2017, Kockelkoren published a calcification evaluation score, which consisted of the calcification angle, layer thickness, and morphology to differentiate between intimal and medial calcification, and the results were verified by pathology[28]. In 2018, a research used the Kockelkoren score to analyze the calcification of 91 post-thrombolysis patients. They found that patients with medial calcification had a higher risk of HT, and worse reactivity to thrombolytic drugs[15]. Methodologically, these above studies did not investigate the quantitative patterns of ICAC volume among thrombolysis patients, as well as a classification of the lesion side or total burden. Also, previous studies mainly focused on intracranial internal carotid artery calcification. Although it was the most common type of ICAC, the vertebral artery was the second most common artery affected by calcification (3%-20% in general patients[29], 70% in stroke patients[30]), followed by the middle cerebral artery (5% in general patients) and basilar artery (5% in general patients)[31]. By evaluating ICAC more thoroughly, we can get a more comprehensive understanding of the correlation between ICAC, HT and prognosis.

We explored the correlation between ICAC and HT after intravenous thrombolysis. Since the number of patients with HT was relatively small, we applied sensitivity analysis to test logistic regression analysis stability. Compared with other calcification parameters, CV-L can better reflect the calcification burden of the diseased vessel itself. A heavier calcification burden suggests a basis of chronic vascular disease and may also be accompanied by more risk factors for atherosclerosis[32, 33]. In addition, ICAC can impede vascular elasticity and vascular compliance. Because blood vessels surrounding the smooth muscle are involved, the blood vessels' flow regulation ability could also be damaged[34]. For acute ischemic stroke patients treated by thrombolysis, if the responsible vessel's calcification burden is heavy, the damage would be two-sided. On one hand, the vessel elasticity is worse; hence, the self-regulation and compensatory ability are relatively poorer[34]. When faced with the occurrence of ischemic lesions, the disrupted autoregulatory capability could lead to higher hydrostatic pressure across the capillary bed, thus facilitating the blood–brain barrier leakage, which could lead to HT[35, 36]. On the other hand, after recanalization of the blood vessel, its capability to maintain a stable hemodynamic status is relatively poorer because of impaired vascular regulation ability. This factor along with elevated permeability, also facilitate HT. Meanwhile, it is worth noting that NCV and CV-O were also associated with HT in model 1-model 4. It is reasonable that large NCV or CV-O may indicate a spread and severe intracranial vascular endothelial damage[37], which could increase the risk of remote parenchymal hemorrhage after intravenous thrombolysis. Due to the sample size limitation, we cannot draw any conclusion about the NCV by now, but it is an interesting phenomenon that calls for future investigation.

We also investigated the correlation between ICAC and prognosis. Compared with other calcification parameters, the NCV can better reflect the overall distribution of ICAC. Patients with a wider distribution of calcification tend to have more systematic risk factors for atherosclerosis, such as hypertension, diabetes mellitus, and smoking[32, 33]. The spread distribution of ICAC also suggested more systematic atherosclerosis[29]. It also indicated diffuse vascular lesions and functional impairment[26]. For post-thrombolysis patients, if there is an extensive distribution of ICAC, patients may have a poor response to thrombolytic drugs due to impaired endothelial function[37], and the vessel recanalization rate is relatively lower. Furthermore, wide distribution of calcification may affect the positive remodeling of blood vessels as well as the formation of new capillary vessels[38]. As a result, the collateral circulation would be relatively poorer, which, in turn, affects the patient's brain tissue perfusion and functional prognosis.

Our study has several limitations, especially its retrospective analysis. In addition, the number of HT cases is relatively small; therefore, the statistical model

may be unstable. However, the sensitivity analysis's main conclusions are consistent, so the results are still of clinical significance.

## 6. Conclusion

This study's primary finding is that, for every increased 0.1 ml of CV-L, the risk of HT increased for 50.4%. The risk of poor prognosis at 3 months increased by 47.7% for each additional NCV. For future clinical practice, we do not suggest ruling out the all patients with ICAC for intravenous thrombolysis, but as an early warning mechanism. If the patient has an accompanying significant burden of CV-L, the acute management and observation should be stricter.

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None.

## Conflicts of Interest

None.

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