# Intracranial Artery Calcium Burden Predicts Recurrent Cerebrovascular Events in Transient Ischaemic Attack Patients

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*Background:* Patients with initial transient ischaemic attack (TIA) subsequently have a higher risk of recurrent TIA or acute ischemic stroke (AIS). The role of scoring intracranial arterial calcification (IAC) in predicting the prevalence of stroke remains unclear. We aim to evaluate if radiological CT calcium score measuring IAC burden could predict future ischemic events in a cohort of TIA patients. *Methods:* We studied consecutive patients from July 2014 to December 2015 who presented with first episode of TIA. All patients had noncontrasted CT or CT-angiogram of the brain on admission. CT calcium score (cm3) was quantified by measuring calcium deposition in the bilateral internal carotid arteries, middle cerebral arteries, and vertebrobasilar system. Patients were followed up for 2 years and ischemic events for either recurrent TIA or AIS were recorded. We compared patients in terms of clinical profile at presentation and CT calcium score using appropriate univariate and multivariable analyses. *Results:* Of 156 TIA patients studied, 22% (n = 35) had recurrent TIA or AIS within 2 years of follow-up. On univariate analyses, recurrent TIA/AIS was associated with gender (OR 0.61; 95%CI 0.40-0.95; $P = .038$), hypertension (mean difference 2.49; 95%CI 1.08-5.75; $P = .030$) and higher CT calcium score (mean difference 0.84 95%CI 0.16-1.52 $P = .016$). On multivariable logistic regression, a higher CT calcium score was significantly associated with recurrent TIA/AIS (adjusted OR 1.25 95%CI 1.01-1.55 $P = .042$). *Conclusions:* In TIA patients, higher IAC burden by measurement of a quantitative CT calcium score may be associated with recurrent ischemic events.
**Key Words:** Calcium—intracranial—stroke—transient ischemic attack—ABCD2


## Introduction

The accurate evaluation of acute ischemic stroke (AIS) risk is a key factor in successful primary and secondary prevention of stroke. AIS patients share similar cardiovascular risk factors as patients with ischemic heart disease, which has an established risk prediction scoring system. Coronary artery calcium scoring has been well-described as one of the major risk prediction models for acute coronary events, providing an incremental risk prediction value in addition to standard cardiovascular risk factors.[1] As atherosclerotic vasculopathy is a systemic process, vascular calcification may play a role in cerebrovascular events as well. In fact, previous studies had shown associations in both qualitative and quantitative calcium scoring with intracranial atherosclerosis and ischemic events.[2] However, the role of intracranial arterial calcification (IAC) scores in predicting ischemic events in symptomatic patients presenting with transient ischemic attack has never been evaluated. Therefore, we aim to investigate the role of scoring IAC using a quantitative CT calcium scoring method to predict future ischemic events (either recurrent TIA or AIS) in our cohort of patients who presented with an initial TIA episode.

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## Methods

All patients in our prospective TIA registry who were diagnosed with a first presentation of TIA at our tertiary care center between July 2014 and December 2015 were studied. Basic demographics, vascular risk factors, and outcomes of recurrent ischemic events – either a recurrent TIA episode or AIS within 2 years from initial presentation were recorded. Clinical risk factor stratification using the Age/Blood pressure/Clinical features of TIA/Duration of symptoms/History of diabetes (ABCD2) score was collected and tabulated.[3] Ethics approval was obtained from the local institutional review board and written informed consent was waived.

### *Neuroimaging Acquisition Protocol and Calcium Scoring*

All TIA patients who presented to the emergency department underwent a noncontrasted computed tomography (NCCT) of the brain and/or computed tomography angiography (CTA) of the brain, as part of workup. A standard 64-slice multidetector CT scanner from skull base to vertex was used to perform the scans. These studies were then retrieved to obtain 1 mm fine cut images for further processing and CT calcium scoring. As there is currently no automated software for CT calcium scoring available commercially, we adapted a manual scoring methodology using Siemens Syngo.via Calcium Scoring system for postprocessing of images for calcium scoring. CT calcium scoring was carried out manually by selecting the area of calcification using visual inspection by 2 trained readers, a neurologist and neuroradiologist, who were blinded for patient clinical data. CT calcium score ($cm^3$) was quantified by measuring calcium deposition in the bilateral internal carotid, middle cerebral artery, and vertebrobasilar system. Differences in scoring was settled by discussion (Figs. 1 and 2).

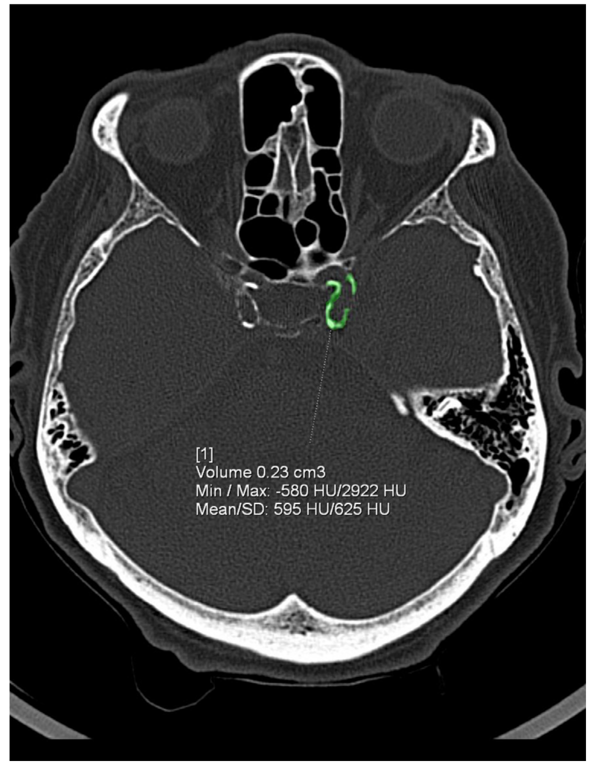


**Figure 1.** *Calcium scoring for left supraclinoid internal carotid artery. Images: Figure showing manual calcium scoring for intracranial arteries. (Color version of figure is available online.)*

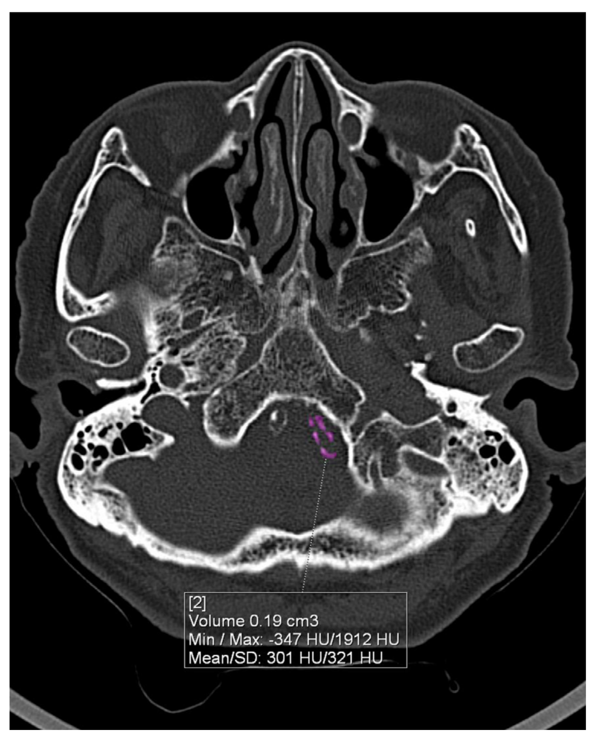


**Figure 2.** *Calcium scoring for left vertebral artery. (Color version of figure is available online.)*

### *Statistical Methods*

We present the numerical variables as mean and standard deviation. Categorical variables are presented as percentages. Numerical predictors were analyzed by using 2-sample *t*-test or Mann-Whitney *U* test where applicable. Categorical variables were evaluated using chi-square test or Fisher exact test where applicable. Variables that were found to have an association ($P \leq 0.1$) with recurrent ischemic events (recurrent TIA or AIS) were entered into the multivariable model to perform backward stepwise logistic regression to determine the independent predictors of recurrent ischemic events. Associations are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY).

## Results

A total of 156 patients who presented with a first episode of TIA were included. 35 patients (22%) had recurrence of TIA or AIS within the 2-years follow-up period. Baseline demographics of our TIA population are presented in Table 1. Mean age was 57.4 years (SD 13.8 years) and 65.6% of the cohort was male. Vascular risk factors

**Table 1.** *Descriptive statistics of study population (N = 156)*

| | Mean or frequency (±standard deviation, or percentage) |
|---|---|
| Age (y) | 57.4 (±13.8) |
| Gender (male) | 103 (65.6%) |
| Smoking | 45 (28.7%) |
| Diabetes mellitus | 26 (16.6%) |
| Hypertension | 91 (58.0%) |
| Hyperlipidaemia | 82 (52.2%) |
| Atrial fibrillation | 2 (1.3%) |
| Chronic kidney disease | 5 (3.2%) |
| Ischaemic heart disease | 15 (9.6%) |
| Systolic blood pressure (mmHg) | 149.6 (±24.8) |
| Diastolic blood pressure (mmHg) | 84.7 (±13.1) |
| HbA1c (%) | 6.2 (±1.5) |
| Corrected LDL (mmol/L) | 3.13 (±1.09) |

featured prominently amongst patients—28.7% smokers, 16.6% with diabetes, 58.0% with hypertension, and 52.2% with dyslipidemia. Mean ABCD2 score on presentation of the TIA cohort was 3.23 (SD 1.50).

Table 2 compares patients with recurrence and no recurrence of TIA or AIS. On univariate analyses, recurrent TIA or AIS was associated with gender (OR 0.61; 95%CI 0.40-0.95; $P = .038$), hypertension (mean difference 2.49; 95%CI 1.08-5.75; $P = .030$), and higher CT calcium score (mean difference 0.84; 95%CI 0.16-1.52; $P = .016$). ABCD2 scores were similar across both groups (mean difference 0.03; 95%CI 0.55-0.62; $P = .907$). On multivariate analyses (Table 3), only subjects with a higher CT calcium score were associated with a higher risk of developing recurrent TIA or AIS. (OR 1.25; 95%CI 1.01-1.55; $P = .042$).

**Table 3.** *Multivariate analysis of TIA population with recurrence of TIA/stroke*

| | Adjusted OR (95% CI) | *p* value |
|---|---|---|
| Ct calcium score | 1.25 (1.01-1.55) | 0.042 |
| Hypertension | 0.514 (0.196-1.347) | 0.176 |
| Gender | 0.44 (0.19-1.02) | 0.055 |
| LDL-C | 1.011 (0.679-1.506) | 0.956 |
| DM | 0.40 (0.15-1.06) | 0.065 |

Abbreviations: LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; TIA, transient ischaemic attack.

## Discussion

Our study shows that higher intracranial artery calcium burden by measurement of a quantitative CT calcium score is associated with recurrent TIA or AIS in patients who were diagnosed with an initial TIA episode.

**Table 2.** *Univariate analysis of TIA population with recurrence of TIA/Stroke and no recurrence*

| | Recurrence of TIA or Stroke (n = 35) | No Recurrence (n = 121) | Mean difference/Odds Ratio (95%CI) | *p* value |
|---|---|---|---|---|
| *Clinical background* | | | | |
| Age (y) | 59.9 (±13.5) | 56.7 (±13.8) | 3.3 (-2.0-8.5) | 0.219 |
| Gender (male) | 18 (51.4%) | 85 (70.2%) | 0.61 (0.40-0.95) | **0.038** |
| Smoking | 11 (31.4%) | 34 (28.1%) | 1.17 (0.52-2.65) | 0.702 |
| Diabetes mellitus | 9 (25.7%) | 17 (14.0%) | 2.12 (0.85-5.29) | 0.103 |
| Hypertension | 26 (74.3%) | 65 (53.7%) | 2.49 (1.08-5.75) | **0.030** |
| Hyperlipidaemia | 20 (57.1%) | 62 (51.2%) | 1.27 (0.59-2.71) | 0.569 |
| Atrial fibrillation | 0 (0.0%) | 2 (1.7%) | - | 1.000 |
| Chronic kidney disease | 5 (14.3%) | 0 (0.0%) | - | <**0.001** |
| Ischaemic heart disease | 4 (11.4%) | 11 (9.1%) | 1.29 (0.38-4.34) | 0.679 |
| *Clinical presentation* | | | | |
| Systolic blood pressure (mmHg) | 151.4 (±27.8) | 149.0 (±23.9) | 2.4 (−7.0-11.8) | 0.617 |
| Diastolic blood pressure (mmHg) | 84.9 (±13.0) | 84.6 (±13.2) | 0.3 (−4.7-5.3) | 0.910 |
| *Clinical Score* | | | | |
| ABCDD Score | 3.26 (±1.52) | 3.22 (1.50) | 0.03 (−0.55-0.62) | 0.907 |
| Laboratory parameters | | | | |
| HbA1c (%) | 6.7 (±2.0) | 6.1 (±1.4) | 0.5 (−0.2-1.2) | 0.148 |
| Corrected LDL (mmol/L) | 2.45 (±1.18) | 2.80 (±1.14) | 0.94 −0.20-2.07) | 0.096 |
| Therapy | | | | |
| Single antiplatelet therapy (aspirin or clopidogrel) | 26 (74.3%) | 60 (49.6%) | 1.25 (0.55-2.84) | 0.593 |
| Aspirin and clopidogrel | 11 (31.4%) | 38 (31.4%) | 1.001 (0.445-2.251) | 0.998 |
| No antiplatelet therapy | 4 (15.4%) | 7 (7.4%) | 2.260 (0.607-8.413) | 0.214 |
| *Imaging* | | | | |
| CT Calcium score ($cm^3$) | 1.384 (±3.175) | 0.548 (±1.107) | 0.839 (0.161-1.517) | **0.016** |

Abbreviations: TIA, transient ischaemic attack.
Bold value represents the mean difference/odds ratio is statistically significant $p < 0.05$.

IAC has been described both quantitatively and qualitatively to predict ischemic events.[4−6] Large population-based studies have shown a significant association between calcification of the carotid artery or intracranial arteries and vascular events in asymptomatic patients and ischemic stroke patients respectively. However, this association is still controversial as other studies have reported conflicting results finding no association between calcium scores and vascular events.[7,8] Differences in the study population, calcium scoring methods, and detection of vascular events may have contributed to this discrepancy. Larger population-based prospective studies with improved quantitative calcium scoring method may be needed to identify the specific subgroups of patients where this technique is effective to determine recurrent ischemic events.

In contrast to previous studies, we elected to select a more stringent selection criteria by including only a TIA population. First, it is difficult to ethically justify exposing asymptomatic persons to radiation risk from a CT brain. For our TIA population, NCCT and/or a CTA was done on presentation as part of the usual workup protocol for such patients, hence they were not subjected to additional radiation. By using their initial scan on presentation and following up these patients up for 2 years, we were able to establish a significant association between higher IAC and recurrence of ischemic events, even after adjusting for other potential confounders in the multivariate model.

Interestingly, the commonly used ABCD2 score was not predictive of recurrence of TIA/stroke in our population. The performance of the ABCD2 score for long-term prognostication and prediction of recurrence of stroke had been debated extensively. The ABCD2 score was developed to stratify short-term stroke risk. In a systematic review, the AUC for both ABCD and ABCD2 scores in predicting 7 days stroke risk in TIA population was 0.72.[9] Another study comparing ABCD3 and ABCD2 showed higher AUC for ABCD3 (0.61) than ABCD2 (0.54) in predicting stroke risk at 7 days.[10] The same study described superiority of ABCD3-I (ABCD3 and presence of carotid stenosis) in predicting stroke risk in longer term up to 3 years. Our study suggests that IAC score may have a distinct role from the ABCD2 clinical score to predict long-term recurrent of ischemic events in patients with TIA.

We choose to use an operator-dependant manual determination of intracranial artery calcium score, via a pre-existing volume-calculation enabled software. Although equal correlation between visual scoring method and quantitative calcium volume using the Agatston scoring has been described,[6] the same studies acknowledge the limitation of Agatston in identifying vascular calcification at the petrous part of the ICA. We are able to more precisely delineate the calcium volume near this area by manually adjusting the area of interest.

## Limitations

This is a single center retrospective study with all its inherent bias. Of note is the high ABCD2 score in this cohort indicating a higher risk population. Siemens Syngo.via is an operator dependant semiautomated scoring method, which has previously been used to measure intracranial calcium score and its inherent limitations have been described.[11] Although we were able to more precisely measure the calcium volume near the petrous bone and clivus, as mentioned, there is still a possibility of oversampling of calcium in this area. This is largely due to inclusion of nearby bony calcification in volume sampling, especially for NCCT. For NCCT, we based our measurements on the assumption that the carotid siphon must be a smooth canal and any calcium disrupting the smoothness of the canal is within the vessel. A correlation study between NCCT and CTA is crucial and will be performed in a separate study with sufficient sample size of patients with both imaging modalities. We did not investigate the correlation between IAC and intracranial plaque burden and stenosis, which has already been described in several studies.[12,13] We were unable to correlate IAC location with TIA location. In our study, IAC is measured as a total summation score of all IA in all vascular territories, as most patients with high IAC burden has diffuse vascular calcification. Moreover, in view of the fact that different TIA from vascular territory can manifest with similar symptoms, we were unable to correlate location of ischemia convincingly with vascular territories without MRI DWI sequences. Our multivariate analysis is also limited by the moderate sample size. The strengths of our study are the 2-year follow-up duration and, as previously mentioned, the accurate manual delineation of the areas of calcification.

## Conclusion

Our study suggests the potential role of quantitative intracranial artery CT calcium scoring as an independent radiological biomarker to predict long-term TIA or AIS recurrence risk in high-risk patients presenting with TIA.

## Conflict of Interest

I, Wan Yee Kong, hereby declare no conflict of interest , on behalf of all of my co-authors, including Benjamin YQ Tan, Eide Sterling Ellis, Nicholas JH Ngiam, Wilson GW Goh, Vijay K Sharma, Bernard PL Chan, Leonard LL Yeo.

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