Research letter

Neurology

Intracranial arterial calcification and recurrent stroke and mortality: clinical associations and AI-based detection

Sandra Elsheikh[1,2,3], Jianyang Xie[1,4], Yuankai Wang[1,4], Greg J. Irving[1,3,5], Andrew M. Hill[1,3], Yalin Zheng[1,4], Gregory Y. H. Lip[1,2,6,7]*, Azmil H. Abdul-Rahim[1,2,3]

[1]Institute of Life Course and Medical Sciences, University of Liverpool, UK
[2]Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, Faculty of Health and Life Sciences, University of Liverpool, UK
[3]Mersey and West Lancashire Teaching Hospitals NHS Trust, Prescot, UK
[4]Department of Eye and Vision Sciences, University of Liverpool, UK
[5]Health Research Institute, Edge Hill University, Ormskirk, UK
[6]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[7]Department of Cardiology, Lipidology and Internal Medicine with Intensive Coronary Care Unit, Medical University of Bialystok, Poland

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***Corresponding author:**
Prof. G.Y.H. Lip
Institute of Life Course and Medical Sciences
Cardiovascular and Metabolic Medicine
Institute of Life Course and Medical Sciences
Faculty of Health and Life Sciences
University of Liverpool, UK
Department of Clinical Medicine
Aalborg University
Aalborg, Denmark
Department of Cardiology, Lipidology and Internal Medicine with Intensive Coronary Care Unit
Medical University of Bialystok, Poland
E-mail: gregory.lip@liverpool.ac.uk

Intracranial arterial calcification (IAC) is a common radiological finding detected incidentally on computed tomography (CT) scans in the general population. Such arterial calcification measured on CT scans can serve as a reliable marker of atherosclerosis. In a study of 2,495 White participants from the Rotterdam Study, over 80% had intracranial carotid artery calcification [1]. Calcification of the internal carotid artery has been associated with stroke risk; greater calcification has been associated with a higher stroke risk [2]. Given that substantial numbers of IS patients are at high risk of stroke recurrence (41% within 5 years) and death (17% within 5 years) [3], it is crucial to accurately identify high-risk patients and optimise stroke prevention strategies.

Currently, head computed tomography angiography (CTA) is a commonly used clinical stroke imaging tool that can detect intracranial large-vessel occlusion (LVO) and cervical carotid or vertebral artery disease, as well as intravascular calcification [4]. The presence of IAC involving the intima (known as intimal calcification) is associated with atherosclerosis, while medial calcification (affecting the internal elastic lamina) may result in impaired vessel physiology and changes in pulse pressure, and ultimately increased rupture risk [5]. A recent meta-analysis found that the presence of IAC was associated with an increased risk of stroke (OR = 1.54, 95% CI: 1.06-2.24, p = 0.001) [6]. Compared to non-contrast CT, head CTA offers improved vessel delineation and contrast resolution, enabling more accurate identification and localisation of intracranial arterial calcifications, but it remains unclear whether IAC assessed by CTA predicts recurrent IS and all-cause mortality in post-IS patients.

Meanwhile, the conventional assessment of IAC mainly relies on manual interpretation, which can pose challenges such as subjectivity. The existing methods for assessing IAC severity vary widely and lack consistency, and a more objective method is required to enhance comparisons between studies involving different populations [7]. With the rapid advancement of artificial intelligence (AI) technology, deep learning (DL) has

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made breakthroughs in a wide range of applications in the field of stroke research [8, 9]. Therefore, the development of DL-driven automated IAC detection models for head CTA may improve both the accuracy and efficiency of IAC identification and assessment, as well as provide new imaging tools for risk stratification and individualised treatment for patients after IS.

In this pilot proof-of-concept study, we investigated the prognostic significance of IAC in patients with IS, and developed a DL model for automated detection of IAC based on AI.

Methods. Detailed methods are provided in the online Supplementary Material.

Thirty-seven patients were included. Among those, 21 (56.8%) had IAC, while 16 (43.2%) had no calcification. The mean age ± SD of the study population was 58.08 ±18.20 years, with a significantly older mean age in the IAC group (70.10 ±10.84 years vs. 42.31 ±13.07 years, $p < 0.001$). The proportion of females and mean BMI was comparable between the two groups.

In terms of comorbidities, patients with calcification had a significantly higher prevalence of hypertension, a history of atrial fibrillation (AF) and coronary artery disease, compared to those without calcification. Other comorbidities showed no significant differences between the two groups. Regarding medication use, direct oral anticoagulant (DOAC) and antiplatelet agent use were numerically higher in the calcification group, although statistical significance was not reached. Warfarin use was also higher in the calcification group, but the difference did not reach statistical significance. The detailed results are shown in Supplementary Table SI.

Study outcomes. During a median follow-up period of 0.62 [IQR 0.03–2.64] years, 19 patients experienced recurrent IS, with a higher proportion observed in the calcification group than in the non-IAC group (66.7% vs. 31.2%, $p = 0.071$). The difference suggests a potential association between IAC and risk of recurrent IS, although it was not statistically significant. Regarding all-cause mortality, a total of 5 patients died during the follow-up period. The mortality rate was numerically higher in the calcification group than in the non-calcification group. Details are shown in Figure 1.

In the Kaplan-Meier survival analysis, patients with IAC had a significantly lower survival proba-

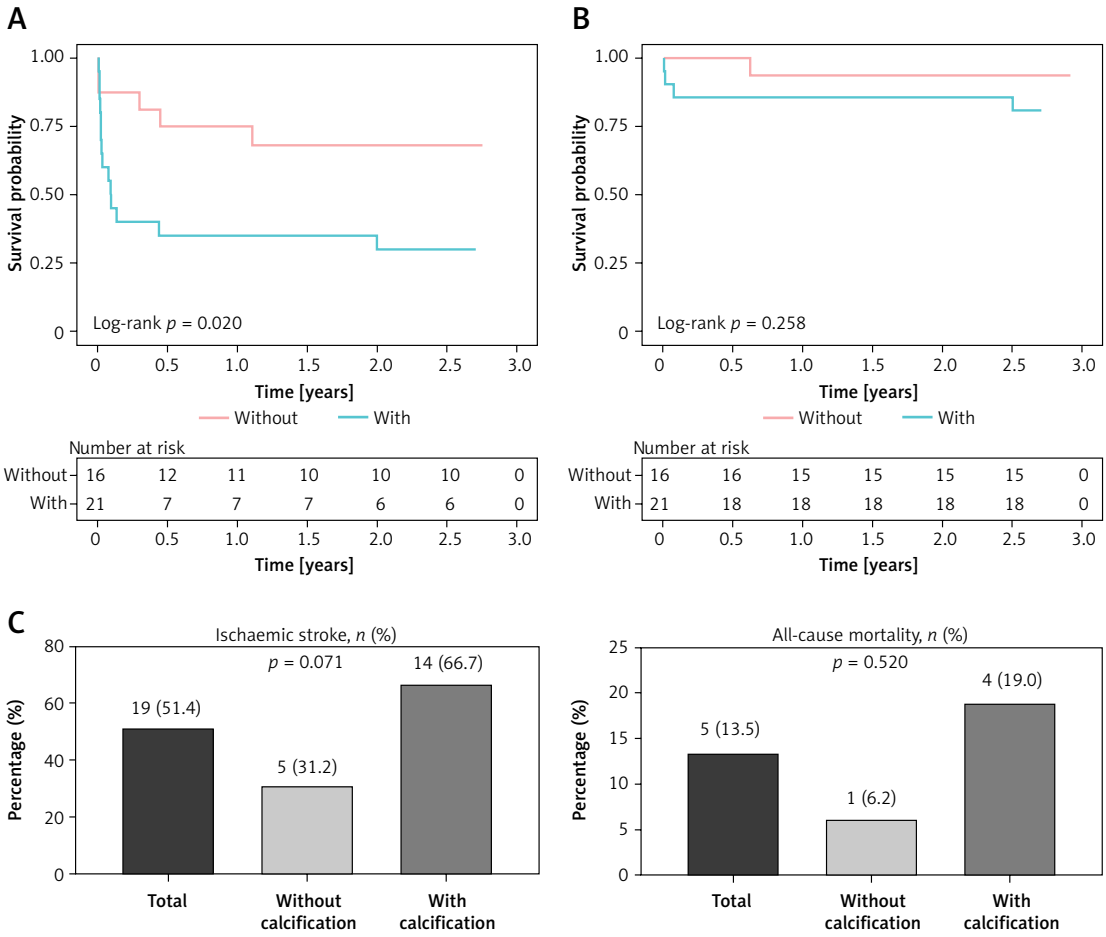

Figure 1. Study outcomes in patients with and without ICA. Kaplan-Meier survival analysis for recurrent ischaemic stroke (**A**) and all-cause mortality (**B**). Detailed data for ischaemic stroke and all-cause mortality are shown in (**C**)

bility for recurrent IS compared to those without IAC (log-rank p = 0.020) (Figure 1). The survival curves demonstrated an early and sustained divergence, indicating a higher risk of recurrent IS in patients with calcification. Although the survival curve of the IAC group for all-cause mortality showed a slight trend toward lower survival probability, this was not statistically significant (log-rank p = 0.258).

Associations of calcification and study outcomes. In an unadjusted Cox proportional hazards model, patients who had IAC had a significantly higher hazard of IS recurrence than those without IAC (HR = 3.17, 95% CI: 1.13–8.88, p = 0.029); see Supplementary Table SII. This association was further strengthened after adjusting for age and sex (HR = 16.52, 95% CI: 2.50–109.30, p = 0.004), suggesting that IAC may be an independent prognostic factor for IS recurrence. For the risk of all-cause mortality, the HR in the unadjusted model was 3.30 (95% CI: 0.37–29.53, p = 0.286) in the IAC group. The association was not statistically significant after adjustment for age and sex.

Model performance of IAC segmentation and score calculation. To evaluate the segmentation performance, a five-fold cross-validation approach was applied. Our model achieved a Dice Similarity Coefficient (DSC) of 0.73, with a standard deviation of 0.01, indicating consistent segmentation performance across the cross-validation folds. Supplementary Figures S1 and S2 present examples of IAC segmentation, demonstrating the model's ability to delineate calcifications. The output of the score calculation in this study is shown in Supplementary Table SIII. These results provide a preliminary basis for future IAC score calculations, although further validation is needed before clinical application.

Discussion. Our study demonstrated that patients with IAC had a higher incidence of recurrent stroke than those without IAC, and Cox proportional hazards models showed that IAC was independently associated with a higher hazard of IS recurrence. However, no significant association was observed between IAC and all-cause mortality. In addition, we developed an IAC segmentation model for the automatic detection of IAC on head CTA images. This model achieved a DSC of 0.73 ±0.01. These results provide a preliminary basis for future IAC score calculations, although further validation is needed before clinical application.

IAC may contribute to the risk of IS through several interrelated mechanisms. Arterial calcification can impair cerebral haemodynamics and lead to arterial stiffness [10]. Moreover, intimal IAC is more closely linked to luminal stenosis, eccentric plaques and increased plaque burden, as well as intraplaque haemorrhage, which increases plaque vulnerability and risk of plaque rupture, leading to thrombosis and embolism [11]. As shown by Fujimoto *et al*., vascular calcification burden is strongly associated with inflammation, with areas of early to intermediate calcification showing higher inflammatory activity and plaque vulnerability [12]. These findings suggest the hypothesis that IAC increases the risk of IS by promoting an inflammatory and thrombotic environment.

Several studies have examined the relationship between IAC (evaluated on plain CT) and the risk of stroke recurrence and death in post-stroke populations. Wu *et al*. found that higher IAC (measured using Agatston method) was significantly associated with an increased risk of stroke recurrence (HR per 1-SD increase = 1.30, 95% CI: 1.08–1.56, p = 0.005) and post-stroke death (HR per 1-SD increase = 1.44, 95% CI: 1.06–1.96, p = 0.019) [13]. Magdič *et al.* reported vertebrobasilar arterial calcification to be significantly associated with higher risk of stroke recurrence (HR = 3.13, 95% CI: 1.35–7.20), while no significant association was observed with all-cause mortality [14]. Similarly, Lee *et al*. showed that severe IAC was associated with an increased risk of early (within 14 days) stroke recurrence compared with no IAC (HR = 2.00, 95% CI: 1.07–3.71, p = 0.029), but no association with all-cause mortality was observed (HR = 0.54, 95% CI: 0.19–1.53, p = 0.224) [15]. Koton *et al.* also found no association between IAC and mortality after IS (at 1 month and 1 year) in the model adjusted for age and stroke severity [16]. Our findings are broadly in line with those of previous studies, in which IAC was significantly associated with an increased risk of stroke recurrence, but not with all-cause mortality.

When looking at other studies using AI to assess IAC, Mahdian *et al.* used cone-beam CT to identify intracranial carotid calcification (DSC: 0.46 ±0.11) [17]. Our model achieved a higher DSC on CTA. The detection of IAC using AI can be of great value in overcoming the limitations of manual assessment. One clinical application of our DL model will be to facilitate early identification of patients with IAC, which may in turn aid decision-making in terms of appropriate primary and secondary prevention measures. In addition, the automated IAC identification and grading could be integrated into the automated diagnostic process for head CTA, providing extra clinical value without additional cost. If integrated into the clinical workflow, the model may improve efficiency and facilitate the early identification of high-risk post-stroke patients. Our automated IAC model could potentially be integrated into hospital medical systems.

This study provides new insights into the prognostic value of IAC in patients with IS, contributing to the current debate about its clinical significance. By combining clinical outcome analysis with an AI-driven approach, we were able to gather information on both the association between IAC and clinical outcomes and automated detection of IAC, potentially improving the efficiency of clinical workflows and reducing inter-observer variability. However, this study has several limitations. First, unmeasured confounders such as inflammatory markers and dynamic changes in disease status may have affected the results. Second, the limited sample size restricted the statistical power of the study. Third, while all 7 AF patients in our study had evidence of IAC, we were not able to explore the potential link between IAC and AF due to the small sample size. Fourth, the approach used to quantify IAC burden in our study was exploratory in nature, aiming to provide a preliminary framework for assessing calcification severity. While this method facilitated initial risk stratification, it has not yet been standardised or externally validated. Further refinement of the IAC quantification method and scoring system, as well as external validation of the DL model, is essential.

In conclusion, IAC may be an independent predictor of recurrent IS in patients with IS. Our AI-based automated IAC detection model achieved preliminary segmentation performance, but further validation is needed to establish its accuracy and clinical utility.

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Ethical approval

Ethical approval was obtained from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) [REC reference: 23/NW/0310] and from the Confidentiality Advisory Group (CAG) [CAG reference:24/CAG/0023].

Conflict of interest

The authors declare no conflict of interest.

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