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IAC PREDICTS LONG-TERM STROKE AND OTHER CARDIOVASCULAR EVENTS IN THE YOUNG AGE

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Abstract- Thus, this study aims to explore the long-term effects of quantitatively evaluated IAC on stroke, other cardiovascular events and related mortality in patients, to establish an effective screen tool for stratifying high risk patients and facilitate effective secondary prevention. The results of this study demonstrate that quantitative evaluated IAC score is strongly predictive of non-cardioembolic stroke, myocardial infarction and cardiovascular death in our hospital population in this prospective analysis. Further studies are warranted to evaluate the clinical implications of measuring IAC in screening subjects at high risk of vascular events.

Keywords:Intracranial arterial calcification,vascular events, clinical implications

1.1 Background

Stroke and ischemic heart disease are the leading causes of death globally[18, 19]. They share one major etiology, atherosclerosis, which causes clinical events through luminal narrowing or thromboembolisms that obstruct blood flow to the brain (ischemic stroke) or heart (CAD)[10, 11]. In recent years, increasing interest is directed towards arterial calcification measured by CT scanning and vascular risks. Histological studies documented three well-recognized patterns of arterial calcification: intimal calcification which is most often associated with atherosclerotic plaque burden, medial calcification described by Mönckeberg, and internal elastic lamina calcification which is associated with stiffening of the arterial wall and increased pulse pressure[1-4]. Although the latter two are considered non-atherosclerotic calcification, they could contribute to increased mechanical stress on atherosclerotic plaques and consequent plaque rupturepotentially.

IAC, which can be feasibly evaluated on unenhanced brain CT noninvasively, has been found closely associated with cerebral artery stenosis and intracranial micro-embolism[11, 12]. Recently a long-term prospective study in White individuals showed that IICA calcium volume is an independent risk factor for stroke[14]. However, previous studies involving Asians failed to find predictive value of IAC for a future stroke[11], and whether IAC associate with risk of stroke or other vascular events in Asian is still controversial.

Thus, this study aims to explore the long-term effects of quantitatively evaluated IAC on stroke, other cardiovascular events and related mortality in patients, to establish an effective screen tool for stratifying high risk patients and facilitate effective secondary prevention.

1.2 METHODS

1.2.1 STUDY POPULATION

This was a hospital-based cohort study. Participants came from our previous study, which aimed to identify the frequency and determinants of IAC[14]. In the previous study, 490 consecutive men and women referred for brain CT during Dec 2014 and Jan 2015 were included, regardless of their

different reasons for CT examination. In the present study, we excluded the patients who: (1) age <18 years (n=18); (2) lost baseline CT images or with obvious artifacts in the images that were not measurable for IAC (n=41); (3) were lost during follow-up period and could not be reached by the end of the study (n=24). This study provided a recruitment method that was almost identical to that of a population study. Age, sex, smoking habit and medical history (including hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, IHD, and ischemic stroke history) were recorded at baseline.

1.2.2 FOLLOW-UP AND ASCERTAINMENT OF CLINICAL OUTCOMES

All patients were followed up regularly till June 2016 for the development of related clinical events. The primary outcomes were ischemic stroke, non-cardioembolic stroke and myocardial infarction. Secondary outcomes were all-cause and cardiovascular mortality.

To determine the subtype of ischemic stroke, the criteria modified from the TOAST classification system were used[13]. Stroke subtype of cardioembolism was defined according to TOAST classification system. An acute brain infarction not due to cardioembolism was defined as a non-cardioembolic stroke.

1.2.3 STATISTICAL ANALYSIS

The impact of IAC characteristics (presence of IAC, IAC volume, and IAC Agatston score) and established vascular risk factors (age, sex, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, and smoking) on future clinical events were first evaluated by univariate analysis. Then multivariable Cox proportional hazards regression models were applied to determine whether IAC characteristics predicted future clinical events, by adjusting vascular risk factors which were determined significant in univariate analysis. Event-free survival for patients with and without IAC were compared with Kaplan-Meier curves and log-rank tests. A significance level of 0.05 was used for all analyses. All data were analyzed by the SPSS 16.0software.

1.3 RESULTS

Patients characteristics

Total 407 patients were recruited and followed up in our study, with the age 64.4±17.7 years and 205 males (50.4%). The median (range) time between baseline CT scan and last contact date was 8.1 years (0 to 11.7 years). Table 5-1 provides the vascular risk factors and IAC characteristics of all individuals. Of the 407 enrolled patients, presence of IAC was found in 275 patients (67.6%). Median IAC volume was 46 mm^3, and median Agatston score was 15.0. The direct reasons for CT examination were shown in Table 2. IAC was mainly observed in large arteries, including IICA in 274 (67.3%) patients, VA in 110 (27.0%) patients, BA in 10(2.5%)patients, and MCA in 9 (2.0%) patients (Table 3).

Table 1. Baseline characteristics

Variable	Total (n=407)
Vascular risk factors	
Age (years) (mean/SD)	64.4 (17.72)
Sex (male), %	205 (50.4)
Hypertension, %	185 (45.5)
Diabetes mellitus, %	79 (19.4)
Hyperlipidaemia, %	63 (15.5)
Smoking history, %	98 (24.1)
Atrial fibrillation, %	44 (10.8)
Ischemic heart disease, %	40 (9.8)
Ischemic stroke history, %	100 (24.6)
IAC characteristics	
Presence of IAC, %	275 (67.6)
IAC volume (mm^3) (median / IQR)	46.0 (0-257.1)
IAC Agatston score (median / IQR)	15.0 (0-118.8)

Table 2. Direct reasons for CT screen

Reason for CT screen	Number, %
Ischemic stroke	98 (24.1)
Head and neck tumor	65 (16.0)
Head injury	43 (10.6)
Dizziness or vertigo	38 (9.3)
Hemorrhagic stroke	32 (7.9)
Confusion or syncope	28 (6.9)
Headache	23 (5.7)
Convulsion or seizure	17 (4.2)
Memory loss	14 (3.4)
Intracranial inflammatory diseases	12 (2.9)
Psychiatric disease	12 (2.9)
Hydrocephalus	8 (2.0)
Parkinsonism	3 (0.7)
Demyelination diseases	2 (0.5)
Non-specific symptoms (numbness, tremor or diplopia)	12 (2.9)

Table 3. Prevalence of IAC in 407 patients

IICA	ACA	MCA	PCA	BA	VA	All intracranial arteries
274 (67.3%)	0 (0%)	9 (2.0%)	0 (0%)	10 (2.5%)	110 (27.0%)	275 (67.6%)

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Table 4. Multivariate Cox proportional hazard model for predictive value of IAC on ischemic stroke or myocardial infarction

	Ischemic stroke (n=35)		Non-cardioembolicstroke (n=27)		Myocardialinfarction (n=27)	
IAC characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Presence of IAC						
Crude estimate	3.021 (1.251, 7.294)	0.014	2.699 (1.019, 7.146)	0.046	16.14 (2.188, 119.13)	0.006
Adjusted estimate	1.332 (0.463, 3.831)	0.595	1.378 (0.423, 4.486)	0.595	5.535 (0.676, 45.341)	0.111
IAC volume, per 1-SD increment						
Crude estimate	1.622 (1.127, 2.333)	0.009	1.707 (1.118, 2.605)	0.013	3.507 (1.937, 6.350)	0.000
Adjusted estimate	0.985 (0.607, 1.598)	0.950	1.227 (0.693, 2.174)	0.483	3.507 (1.937, 6.350)	0.000

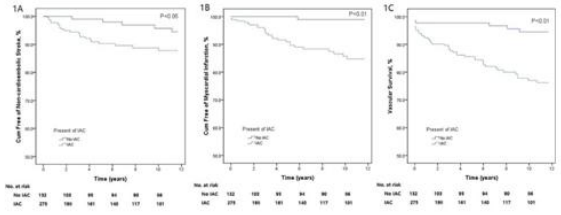
Adjusted for age, hypertension and diabetes mellitus. For ischemic stroke, atrial fibrillation was additionally adjusted.

Table 5. Long-term predictive factor for all-cause and cardiovascular mortality

	All-cause death (n=231)		Cardiovascular death (n=54)	
IAC characteristic	HR (95% CI)	*P value*	HR (95% CI)	*P value*
Presence of IAC				
Crude estimate	2.124 (1.551, 2.908)	0.000	4.669 (1.995, 10.93)	0.000
Adjusted estimate	0.869 (0.592, 1.275)	0.473	1.057 (0.406, 2.751)	0.909
IAC volume, per 1-SD increment				
Crude estimate	1.573 (1.364, 1.814)	0.000	2.702 (1.865, 3.915)	0.000
Adjusted estimate	1.057 (0.867, 1.287)	0.584	1.632 (1.026, 2.596)	0.039
IAC Agatston score, per 1-SD increment				
Crude estimate	1.569 (1.369, 1.798)	0.000	2.608 (1.856, 3.663)	0.000
Adjusted estimate	1.114 (0.923, 1.344)	0.260	1.698 (1.107, 2.605)	0.015

Adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidaemia, smoking history, and atrial fibrillation.

Figure 1. Kaplan-Meier survival plots for 275 patients with IAC and 132 patients without IAC. Patients with IAC had significantly poorer outcomes (non-cardioembolic stroke, myocardial infarction and vascular death) than those without. 1A. Kaplan-Meier survival plot for non-cardioembolic stroke-free survival. 1B. Kaplan-Meier survival plot for myocardial infarction-free survival. 1C. Kaplan-Meier survival plot for cardiovascular survival.



IAC and occurrence of further stroke or other cardiovascular events

During the long-term follow-up period, 67 patients (16.5%) suffered further stroke or other cardiovascular events, of which 46 were stroke (11.3%, including 32 patients suffered ischemic strokes, 11 suffered hemorrhagic strokes, and 3 suffered both), and 27 were myocardial infarction (6.6%) (6 patients suffered both stroke and myocardial infarction). Among the 35 patients who suffered further ischemic stroke, 27 were classified as non-cardioembolic stroke patients (6.6%).

Univariate analysis on established vascular risk factors (age, sex, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, and smoking) showed that older age (HR 1.039; 95%CI 1.015-1.063), hypertension (HR 2.625; 95%CI 1.305-5.284), diabetes mellitus (HR 2.423; 95%CI 1.204-4.877), and atrial fibrillation (HR 2.759; 95%CI 1.198-6.353) were all associated with higher risks of ischemic stroke; among them older age (HR 1.032; 95%CI 1.006-1.058), hypertension (HR 2.717; 95%CI 1.219-6.058), and diabetes mellitus (HR 2.727; 95%CI 1.247-5.964) also indicated higher risks of non-cardioembolic stroke. In addition, older age (HR 1.065; 95%CI 1.033-1.098), hypertension (HR 3.211; 95%CI 1.404-7.343), and diabetes mellitus (HR 2.722; 95%CI 1.245-5.948) were associated with higher risk of myocardialinfarction.

Table 4 reports the associations between IAC characteristics and risks of ischemic stroke or myocardial infarction. Univariate analysis showed that higher IAC Agatston scores were associated with higher risks of ischemic stroke (combined cardioembolic and non-cardioembolic), non-cardioembolic ischemic stroke alone, and myocardial infarction, respectively (HRs per 1-SD increment, 1.569-3.195, $p<0.05$). These results were similar for presence of IAC and IAC volume. After adjustments for established vascular risk factors, multivariate Cox proportional hazard model showed IAC Agatston score remained independently predictive for both non-cardioembolic stroke (HR per 1-SD increment, 1.747; 95% CI, 1.162-2.626) andmyocardialinfarction(HRper1SDincrement,3.195;95%CI,1.891-5.396)

Besides, IAC volume (HR per 1-SD increment, 3.507; 95% CI, 1.937-6.350) was also an independent predictor for myocardial infarction. The Kaplan-Meier curves showed significantly

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higher rates of occurrence of non-cardioembolic stroke and myocardial infarction in patients with than in those without IAC (Figure 1, 1A, 1B).

IAC AND OCCURRENCE OF DEATH

A total of 231 patients (56.8%) died of any cause during follow-up, including 54 patients (6.6%) died of cardiovascular cause, and 177 patients died of other causes.

Table 5 indicates the associations between IAC and all-cause as well as cardiovascular mortality. Univariate analysis showed that higher IAC Agatston scores were associated with higher risks of all-cause death and cardiovascular death, which were similar to presence of IAC and IAC volumes. After adjustments for a total of 7 variables (age, sex, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, and smoking) in a multivariate Cox proportional hazard model, IAC volume (HR per 1-SD increment, 1.632; 95% CI, 1.026-2.596) and IAC Agatston score (HR per 1-SD increment, 1.698; 95% CI, 1.107-2.605) remained significantly predictive for cardiovascular death. The Kaplan-Meier curves showed significantly higher rates of cardiovascular survival in patients without IAC (Figure 1,1C).

1.4 DISCUSSION

This long-term study demonstrated that quantitatively evaluated IAC score is a strong and independent predictor of non-cardioembolic stroke, myocardial infarction and cardiovascular mortality in hospital patients referred for brain CT scanning, even after adjustment for other possible predictors. This finding indicates that evaluation of IAC on unenhanced head CT allow identification of Asian individuals at high risk of ischemic stroke and other cardiovascular events.

Interestingly oppositely, two European research teams find IAC associate with recurrence in stroke patients[18,13]. Although heterogeneous in methodology, these studies all use visual scales to evaluate IAC, which are not efficient in reflecting either real calcium volume or density information. Recently, a prospective, population-based study reporting quantified IICA calcification volume and the risk of stroke in 2323 patients with 6 years of follow-up is published[14]. The authors find that both presence and severity of IICA calcification are associated with higher risks of all stroke (combined hemorrhagic and ischemic) and ischemic stroke, which are independent of conventional cardiovascular risk factors. Inconsistently, we do not find IAC volume to be the same independently predictive for ischemic stroke. However, roughly a quarter of new ischemic stroke were categorized as cardioembolic source in this study, which is similar to previous report in Asian[15]. Since no causal relationship has been established between IAC and brain hemorrhage as well as IAC and ischemic stroke caused by cardiac embolism[16], we turn into specifically investigate the association between IAC and non-cardioembolic stroke. Our study found IAC Agatston score to be an independent indicator for a future non-cardioembolic stroke. This result again demonstrated intracranial atherosclerosis to be a major risk factor for ischemic stroke in Asian population.

In coronary disease, CAC is considered as an indicator of atherosclerosis burden[17]. However, how cerebral artery calcification affects the relevant artery and subsequent stroke mechanism is not yet settled. A neuroimaging study shows that severe carotid siphon calcification is correlated with a coexistent stenosis of greater than 50% on angiography, and the positive predictive value of which is 86%[12]. Previously we find extensive carotid artery calcification is associated with a higher rate of microembolism occurrence detected in downstream MCA[12]. These results involving coexistent stenosis and unstable plaque feather can partially explain the causalmechanismlinkingIAC andrisk for stroke, but exact patho physiological process still need to be confirmed in more specifically designed studies.

As part of the extensive systemic atherosclerosis process, IAC is suggested to be a potential marker of more broadly vascular outcomes, including extracranial events. Recently in a group of stroke patients after hospital discharge, Bugnicourt et al reports that IAC is associated with a combination future events including ischemic stroke, cardiac and peripheral diseases[18]. Ahn et al finds that quantified IAC scores on unenhanced CT correlate significantly with CAC scores and may serve as an independent predictor of asymptomatic CAD in ischemic stroke patients[19]. More recently, a subgroup analysis based on the Rotterdam Study in the general community shows that IICA

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calcification volume is related to higher risks of all-cause mortality, cardiovascular, and noncardiovascular mortality, independent of cardiovascular risk factors[17]. Our study also demonstrates that IAC is predictive of myocardial infarction and cardiovascular death observed in this population, which is consistent with the current evidences, and indicates that the utility of imaging the cerebral arteries on unenhanced head CT alone is expectedly suboptimal for estimating the total burden of vascular eventrisk.

This study presents some limitations. First, study subjects are recruited from hospital patients with unselected admission causes, which are not able to provide as powerful evidences as community-based participants. However, this study consecutively recruited all subjects in total two months, and with adequate sample size, which as a preliminary study can provide considerable value for reference in future clinical research. Second, nearly 14% of patients lose IAC data or are not regularly followed. Nevertheless, this study also presents a number of strengths. First, consecutive patients are studied on a prospective registry. Second, we use quantitative methods to evaluate arterial calcification, which concern both calcium volume and density information, and most objectively and authentically reflect the severity of IAC. Third, we evaluate IAC on unenhanced head CT, which is noninvasive and easily available in general hospitals. Finally, this is a very long-term study and the majority of patients are successfully followedup.

References

1. Babiarz LS, Yousem DM, Wasserman BA, Wu C, Bilker W, Beauchamp NJ, Jr. Cavernous carotid artery calcification and white matter ischemia. *AJNR Am J Neuroradiol*.2003;24:872-877

2. Babiarz LS, Yousem DM, Bilker W, Wasserman BA. Middle cerebral artery infarction: Relationship of cavernous carotid artery calcification. *AJNR Am J Neuroradiol*.2005;26:1505-1511

3. Taoka T, Iwasaki S, Nakagawa H, Sakamoto M, Fukusumi A, Takayama K, Wada T, Myochin K, Hirohashi S, Kichikawa K. Evaluation of arteriosclerotic changes in the intracranial carotid artery using the calcium score obtained on plain cranial computed tomography scan: Correlation with angiographic changes and clinical outcome. *J Comput Assist Tomogr*. 2006;30:624-628

4. Erbay S, Han R, Baccei S, Krakov W, Zou KH, Bhadelia R, Polak J. Intracranial carotid artery calcification on head ct and its association with ischemic changes on brain mri in patients presenting with stroke-like symptoms: Retrospective analysis. *Neuroradiology*.2007;49:27-33

5. Chung PW, Park KY, Moon HS, Kim YB, Youn YC, Byun JS, Kwon OS. Intracranial internal carotid artery calcification: A representative for cerebral artery calcification and association with white matter hyperintensities. *Cerebrovasc Dis*.2010;30:65-71

6. Bleeker L, Marquering HA, van den Berg R, Nederkoorn PJ, Majoie CB. Semi-automatic quantitative measurements of intracranial internal carotid artery stenosis and calcification using ct angiography. *Neuroradiology*. 2012;54:919-927

7. Ahn SS, Nam HS, Heo JH, Kim YD, Lee SK, Han K, Kim EY. Quantification of intracranial internal carotid artery calcification on brain unenhanced ct: Evaluation of its feasibility and assessment of the reliability of visual grading scales. *Eur Radiol*.2013;23:20-27

8. Marquering HA, Nederkoorn PJ, Bleeker L, van den Berg R, Majoie CB. Intracranial carotid artery disease in patients with recent neurological symptoms: High prevalence on cta. *Neuroradiology*.2013;55:179-185

9. Yilmaz A, Akpinar E, Topcuoglu MA, Arsava EM. Clinical and imaging features associated with intracranial internal carotid artery calcifications in patients with ischemic stroke. *Neuroradiology*.2015;57:501-506

10. Katada K, Kanno T, Sano H, Shinomiya Y, Koga S. Calcification of the vertebral artery. *AJNR Am J Neuroradiol*.1983;4:450-453

11. Pikija S, Magdic J, Hojs-Fabjan T. Calcifications of vertebrobasilar arteries on ct: Detailed distribution and relation to risk factors in 245 ischemic stroke patients. *Biomed Res Int*.2013;2013:918970

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12. Higgins CL, Marvel SA, Morrisett JD. Quantification of calcification in atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*.2005;25:1567-1576

13. Schoenhagen P, Halliburton SS, Stillman AE, Kuzmiak SA, Nissen SE, Tuzcu EM, White RD. Noninvasive imaging of coronary arteries: Current and future role of multi-detector row ct. *Radiology*.2004;232:7-17

14. Koton S, Tashlykov V, Schwammenthal Y, Molshatzki N, Merzeliak O, Tsabari R, Tanne D. Cerebral artery calcification in patients with acute cerebrovascular diseases: Determinants and long-term clinical outcome. *Eur J Neurol*.2012;19:739-745

15. Bugnicourt JM, Chillon JM, Tribouilloy C, Canaple S, Lamy C, Massy ZA, Godefroy O. Relation between intracranial artery calcifications and aortic atherosclerosis in ischemic stroke patients. *J Neurol*.2010;257:1338-1343

16. Bugnicourt JM, Leclercq C, Chillon JM, Diouf M, Deramond H, Canaple S, Lamy C, Massy ZA, Godefroy O. Presence of intracranial artery calcification is associated with mortality and vascular events in patients with ischemic stroke after hospital discharge: A cohort study. *Stroke*.2011;42:3447-3453

17. Coutinho T, Turner ST, Kullo IJ. Aortic pulse wave velocity is associated with measures of subclinical target organ damage. *JACC Cardiovasc Imaging*. 2011;4:754-761

18. Zhang J, Li Y, Wang Y, Niu W, Zhang Y, Gao P, Zhang L, Lin H, Chen K, Zhu D. Arterial stiffness and asymptomatic intracranial large arterial stenosis and calcification in hypertensive chinese. *Am J Hypertens*.2011;24:304-309

19. Park KY, Kim YB, Moon HS, Suh BC, Chung PW. Association between cerebral arterial calcification and brachial-ankle pulse wave velocity in patients with acute ischemic stroke. *Eur Neurol*.2009;61:364-370

20. Park KY, Chung PW, Kim YB, Moon HS, Suh BC, Yoon WT. Increased pulsatility index is associated with intracranial arterial calcification. *Eur Neurol*.2013;69:83-88