JOURNAL FOR INNOVATIVE DEVELOPMENT IN PHARMACEUTICAL AND TECHNICAL SCIENCE

Volume-2,Issue-6 (June-2019)
ISSN (O) :- 2581-6934

INTRACRANIAL ARTERIAL CALCIFICATION PREDICTS STROKE RECURRENCE: AN EMPIRICAL STUDY

Dr. Muhammad Bilal Ikram [1], Dr. Muhammad Waqas Rana [2], Dr. Anila Ishaque [3]

[1] Sharif Medical & Dental College, Lahore, Pakistan

[2] Demonstrator at AJK Medical College, Muzaffarabad Azad Kashmir, Pakistan

[3] Fatima Jinnah Medical University, Lahore, Pakistan

Abstract: This study presents some strengths. First, consecutive patients are studied on a prospective registry. Second, we use quantitative methods to evaluate arterial calcification, which contain both calcium volume and density information, and reflect the severity of intracranial arterial calcification most objectively and authentically. Third, we evaluate intracranial arterial calcification 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 followed up. On the other hand, one limitation in this study is the small sample size among different stroke subtypes. However, as a preliminary study it can provide considerable value for reference in future clinical research.

Keywords: brain CT, cerebral artery stenosis, intracranial micro-embolism

1.1 Background

Stroke is one of the leading causes of death globally18. Ischemic stroke is also a significant cause of disability in adults and has substantial economic consequences19. As is well documented, atherosclerosis is the major cause of ischemic stroke in industrialized countries10. In Asian, ICAS accounts for about 33–50% of stroke10,11. Strong evidence has been provided by clinical trials that effective prevention significantly reduces the rates of stroke recurrence and mortality12. Therefore, to establish an effective screen tool to find patients with high risk will be of great help for effective secondary prevention.

Unenhanced brain CT is a routine imaging investigation for every suspicious stroke patients, mainly to distinguish ischemic and hemorrhagic stroke. In recent years, increasing interest is directed towards intracranial arterial calcification and cerebrovascular diseases. intracranial arterial calcification has been noted closely associated with cerebral artery stenosis and intracranial micro-embolism12,11,. Recently a long-term population-based study in White individuals showed that IICA calcification volume is an independent risk factor for ischemic stroke14. It is noteworthy that intracranial arterial calcification was more frequent in stroke patients and found in more than 80% patients15. However, the association between intracranial arterial calcification and risk of stroke recurrence has received little attention, and the prognostic values of intracranial arterial calcification on different specific stroke subtypes are yet to be elusive. Based on a prospective study on the stroke registry, we aim to explore the effect of intracranial arterial calcification on the long-term stroke recurrence, to establish an effective screen tool for stratifying high risk patients and facilitate effective secondary prevention.

1.2 Methods

1.2.1 Studypopulation

This research study forms part of a prospective study on the stroke registry between 1 December 2014 and 31 March 2015. Patients admitted to the acute stroke unit were followed up using CMS, a territory-wide and networked clinical records system.

Clinical data of demographic characteristics, stroke risk factors, and stroke etiology of the patients were retrieved from the data-collection sheets of stroke registry collected on entry and obtained by record linkage to the CMS. Demographic characteristics included age and sex. Stroke risk factors for each patient were documented regarding the following: hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, ischemic heart disease, ischemic stroke history and smoking history. The stroke etiology (TOAST)13might be classified as large-artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined etiology, undetermined etiology, and two or more causes identified. All patients received cranialCT.

We excluded patients whose incident stroke was due to venous infarcts, intracranial hemorrhage, subdural hematoma or subarachnoid hemorrhage. Patients with other potential causes of intracranial arterial calcification, such as hyperparathyroidism or end-stage renal failure were excluded. Thirty patients were excluded due to obvious artifacts in the CT images that were not measurable for v. Four patients were excluded due to emigration outside the geographical area and could not be reached.

1.2.2 STATISTICALANALYSIS

Intracranial arterial calcification volume and intracranial arterial calcification Agatston score were natural logarithm (Ln) transformed to reduce skewness and 1.0 mm^3 or 1 score was added to the nontransformed values to deal with zero calcium [Ln (IAC + 1.0)]. Univariate Cox proportional hazards regression models were used to determine whether presence of IAC, IAC volume and IAC Agatston score predicted stroke recurrence and mortality. MultivariableCox proportional hazards regression models were used for multivariate analysis ofstrokerisk factors (IAC scores, age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidaemia, IHD, ischemic stroke history and smoking history) pertaining to the stroke outcomes. Cox proportional hazards model was also performed to test whether IAC Agatston score predicted recurrent stroke among patient subgroups with index TIA or different major stroke subtypes (large-artery atherosclerosis, small-vessel occlusion, cardioembolism). We used Kaplan-Meier curves and log-rank tests for estimation of stroke recurrence and mortality for patient groups with higher (>median score) or lower (<median score) IAC Agatston scores.

1.3 RESULTS

Demographics and stroke mechanism

The characteristics and prognosis of stroke or TIA was evaluated in 694 patients, with a mean age of 72 years (28–101 years) and female ratio of 49.7%. The median follow-up period was 8.83 years (IQR 3.17-11.08 years). Baseline characteristics of patients are given in table 1. According to the TOAST criteria, large-artery atherosclerosis was the most important underlying etiology (40.0%, 233/582). Small-vessel occlusion was found in 167 patients (28.7%), cardioembolic stroke in124 patients (21.3%), other determined etiology in 10 patients (1.7%), and cryptogenic causes in 5 patients (0.9%). Two or more causes were identified in 43 patients (7.4%). For IAC characteristics, presence of IAC was found in 643 patients (92.7%). Median IAC volume was 169.3 mm^3, and median total IAC Agatston score was 64.8. Calcification in anterior circulation account for majority of that in whole cerebral vasculature, with median calcium volume 161.9 mm^3, and median Agatston score 49.9. In posterior circulation, median calcium volume and median Agatston score were both 0. IAC was mainly observed in large arteries such as IICA (92.4%), VA (39.2%), MCA (3.6%), and BA (2.9%) (table 2).

COX REGRESSION MODEL OF STROKE RECURRENCE AND STROKE DEATH

We evaluated 694 patients prospectively for 11 years starting in December 2004, and 156 patients with recurrent ischemic stroke were identified. The incidence of recurrent ischaemic stroke was 22.5%. Table 3 reports the associations between intracranial arterial calcification characteristics and risks of stroke recurrence. Univariate analysis showed that higher IAC Agatston score was associated with a higher risk of stroke recurrence (HR per 1-SD increment, 1.397; 95%

ISSN:-2581-6934|www.jidps.com

CI,1.171-1.665, p<0.001). This result was similar for IAC volume. After adjustments for established stroke risk factors, multivariate Cox proportional hazard model showed IAC Agatston score (HR per 1-SD increment, 1.301; 95% CI,1.084-1.561, p=0.005) and IAC volume (HR per 1-SD increment, 1.265; 95% CI,1.051-1.521, p=0.013) both remained independently predictive for recurrent stroke,respectively.

During the long-term follow-up period, 84 patients (12.1%) died of stroke cause. Univariate analysis showed that higher IAC Agatston score was predictive of higher risk of stroke death, which were similar to presence of IAC and IAC volume. After adjustments for a total of 9 variables (age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidaemia, ischemic heart diseases, ischemic stroke history, and smoking history) in a multivariate Cox proportional hazard model, IAC Agatston score (HR per 1-SD increment, 1.441; 95% CI, 1.061-1.956) and IAC volume (HR per 1-SD increment, 1.705; 95% CI, 1.271-2.286) remained significantly predictive for stroke death.

Table 1. Baseline Characteristics

Characteristic	Total (n=694)
Vascular risk factors	
Age (years) (mean/SD)	71.6 (12.4)
Sex (male), %	349 (50.3)
Hypertension, %	503 (72.5)
Diabetes mellitus, %	232 (33.4)
Hyperlipidaemia, %	360 (51.9)
Atrial fibrillation, %	148 (21.3)
Ischemic heart diseases, %	98 (14.1)
Ischemic stroke history, %	170 (24.5)
Smoking history, %	195 (28.1)
TIA	112 (16.1%)
Ischemic stroke	582 (83.9%)
TOAST classification	
Large-artery atherosclerosis	233 (40.0%)
Small-vessel occlusion	167 (28.7%)
Cardioembolism	124 (21.3%)
Other determined etiology	10 (1.7%)
Undetermined etiology	5 (0.9%)
Two or more causes identified	43 (7.4%)
IAC characteristics	
Presence of IAC, %	643 (92.7)
IAC volume (mm³) (median / IQR)	169.3 (40.9-431.7)
IAC volume in anterior circulation (mm³) (median / IQR)	161.9 (38.2-407.7)
IAC volume in posterior circulation (mm³) (median / IQR)	0 (0-10.5)
IAC Agatston score (median / IQR)	64.8 (14.8-180.7)
Agatston score in anterior circulation (median / IQR)	49.9 (10.8-120.4)
Agatston score in posterior circulation (median / IQR)	0 (0-61.9)

Table 2. Prevalence of IAC in 694 patients

IICA	ACA	MCA	PCA	BA	VA	All intracranial arteries
641 (92.4%)	1 (0.1%)	25 (3.6%)	0 (0%)	20 (2.9%)	272 (39.2%)	643 (92.7%)

Table 3. Multivariate Cox proportional hazard model for predictive value of IAC score on ischemic stroke or stroke death

IAC characteristic	Ischemic stroke (n=156) HR (95% CI)	*P value*	Stroke death (n=84) HR (95% CI)	*P value*
Presence of IAC				
Crude estimate	1.797 (0.882, 3.661)	0.107	7.492 (1.043, 53.831)	0.045
Adjusted estimate	1.229 (0.569, 2.655)	0.599	3.170 (0.422, 23.793)	0.262
IAC volume, per 1-SD increment				
Crude estimate	1.363 (1.140, 1.629)	0.001	1.855 (1.391, 2.475)	0.000
Adjusted estimate	1.265 (1.051, 1.521)	0.013	1.705 (1.271, 2.286)	0.000
IAC volume in anterior circulation, per 1-SD				
Crude estimate	1.356 (1.135, 1.620)	0.001	1.889 (1.409, 2.532)	0.000
Adjusted estimate	1.255 (1.044, 1.509)	0.016	1.727 (1.282, 2.327)	0.000
IAC volume in posterior circulation, per 1-SD				
Crude estimate	1.229 (1.062, 1.422)	0.006	1.209 (0.994, 1.472)	0.058
Adjusted estimate	1.189 (1.024, 1.382)	0.024	1.082 (0.877, 1.335)	0.461
IAC Agatston score, per 1-SD increment				
Crude estimate	1.397 (1.171, 1.665)	0.000	1.756 (1.342, 2.298)	0.000
Adjusted estimate	1.301 (1.084, 1.561)	0.005	1.441 (1.061, 1.956)	0.019
Agatston score in anterior circulation, per 1-SD increment				
Crude estimate	1.387 (1.163, 1.654)	0.000	1.828 (1.385, 2.415)	0.000
Adjusted estimate	1.289 (1.075, 1.545)	0.006	1.665 (1.255, 2.209)	0.000
Agatston score in posterior circulation, per 1-SD increment				
Crude estimate	1.275 (1.093, 1.487)	0.002	1.253 (1.019, 1.540)	0.032
Adjusted estimate	1.231 (1.053, 1.439)	0.009	1.093 (0.881, 1.355)	0.418

Adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidaemia, ischemic heart diseases, ischemic stroke history and smoking history.

Table 4. Cox proportional hazard model for predictive value of IAC Agatston score on patient groups with index TIA or different major stroke subtypes

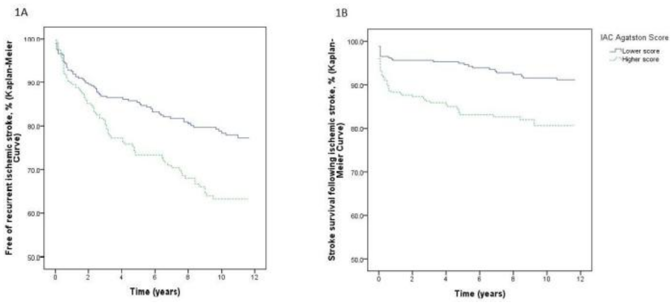
Category	NO.	Re-stroke during follow-up	Crude HR (per 1-SD increment)	*P* value	Adjusted HR (per 1-SD increment)	*P* value
All patients	694	156 (22.5%)	1.397 (1.171, 1.665)	0.000	1.327 (1.101, 1.674)	0.004
TIA	112	23 (20.5%)	1.271 (0.854, 1.890)	0.237	1.202 (0.758, 1.906)	0.435
Ischemic stroke	582	133 (22.9%)	1.413(1.159, 1.723)	0.000	1.385(1.092, 1.757)	0.007
Stroke subtype	582					
Large-artery atherosclerosis	233	54 (23.2%)	1.298(0.944, 1.784)	0.108	1.198(0.834, 1.721)	0.328
Small-vessel occlusion	167	34 (20.4%)	1.484(1.018, 2.162)	0.040	1.674(1.061, 2.639)	0.027
Cardioembolism	124	27 (21.8%)	1.574(0.919, 2.696)	0.099	1.063(0.580, 1.951)	0.842

Adjusted for age and hypertension

Figure 1. Kaplan-Meier survival plots of stroke recurrence and stroke death. Patients with higher IAC Agatston score had significantly poorer outcomes (recurrent

ISSN:-2581-6934|www.jidps.com

stroke or stroke death) than those with lower score. A. Kaplan-Meier survival plot for patients free of recurrent stroke. B. Kaplan-Meier survival plot for stroke survival



SUBGROUP ANALYSIS: CALCIFICATION IN DIFFERENT CIRCULATIONS AND ASSOCIATION WITH CLINICAL OUTCOME

Among different cerebral circulations, multivariance Cox proportional model showed that calcification Agatston score in both anterior (HR per 1-SD increment, 1.289; 95% CI, 1.075-1.545, p=0.006) and posterior (HR per 1-SD increment, 1.231; 95% CI, 1.053-1.439, p=0.009) circulations are individually predictive for recurrent stroke (table 3).

SUBGROUP ANALYSIS: PATIENTS WITH DIFFERENT STROKE ETIOLOGICAL SUBTYPES OR TIA

A subgroup analysis of the prognosis of patients with ischemic stroke (n=582) or TIA (n=112) showed that another ischemic stroke was documented in 22.9% patients with ischemic stroke, and 20.5% patients with TIA (table 4). Among different stroke mechanisms, 54 stroke recurrence cases were found in patient with index large-artery atherosclerotic stroke (23.2%), 34 in index small-vessel occlusive stroke (20.4%), and 27 in index cardioembolic stroke (21.8%). Univariate Cox proportional model showed that among different mechanisms, IAC Agatston score was only significantly predictive for stroke recurrence in patients with index small-vessel occlusive stroke (HR per 1-SD increment, 1.484; 95% CI, 1.018-2.162, p=0.040). However, there were also statistical trends that IAC Agatston score predict stroke recurrence in patients with index large-artery atherosclerotic stroke (HR per 1-SD increment, 1.298; p=0.108) or index cardioembolic stroke (HR per 1-SD increment, 1.574; p=0.099). After adjustment for age and hypertension, multivariate analysis showed IAC Agatston score was independent risk factor of stroke recurrence for index small-vessel occlusive stroke patients (HR per 1-SD increment, 1.674; 95% CI, 1.061-2.639, p=0.027).

THE KAPLAN–MEIER RISK OF STROKE RECURRENCE AND STROKE DEATH

The Kaplan-Meier curves and log-rank tests showed significantly higher rates of stroke recurrence (P=0.001) and lower rates of stroke survival (P<0.001) in patients with higher IAC Agatston score (figure 1). For patient group with lower IAC Agatston score, the risk of developing recurrent stroke was 6.9% at 1 year, 13.5% at 5 years, and 18.7% at 10 years. While for patients with higher IAC Agatston score, the risk was much higher, with 9.2% at 1 year, 21.0% at 5 years, and 25.6% at 10 years. The mortality rate following stroke for patients with lower IAC Agatston score was 4.3% at 1 year, 4.9% at 5 years, and 7.5% at 10 years. Interestingly, the risk of stroke death did not increase substantially after first years from the index stroke or TIA in both groups. In patient group with higher IAC Agatston score, the risk was 11.5% at 1 year, 15.3% at 5 years, and 16.4% at 10years.

1.4 DISCUSSION

Quantitative-evaluated IICA calcification volume has been identified as an independent risk factor for all stroke and ischemic stroke in community population in recent literatures. With a IAC score that reflected both volume and density information, our study prospectively followed up a group of stroke or TIA patient for more than 10 years, and recognized that IAC is also independently predictive for recurrent stroke, especially in patients with index etiological subtype of small-vessel occlusion. In addition, IAC is also an independent predictor for death due tostroke.

In the term of IAC impact on recurrent stroke, Mak et al. 2009 in a prospective study involving 60 stroke patients failed to verify the association between IAC

ISSN:-2581-6934|www.jidps.com

and stroke recurrence, though partly due to the small sample size of the study (only 60 patients recruited)[15]. Our results are in agreement with the two Western studies as we also show the prognostic value of IAC on ischemic events. What is more is that we also demonstrated precise predictive values of IAC score on recurrent stroke alone, as well as related death alone, respectively, which may help secondary stroke prevention by stratifying high risk patients in stroke units.

A cross-sectional subgroup analysis based on the Rotterdam Study showed that compared to lacunar ischemic strokes (small vessel disease), nonlacunar strokes is associated with a larger aortic arch calcification volume[15], whichimplicated that the roles of arterial calcification might differ on different causes of stroke. Our study found that among different stroke etiological subtypes, IAC was independently predictive for stroke recurrence in patients with index small-vessel occlusive stroke.

Altogether, our data demonstrates that IAC is frequently identified in acute ischemic stroke patients and that quantitative-evaluated IAC scores can predict both long-term stroke recurrence and stroke death in this prospective analysis. In addition, among different stroke etiological subtypes, IAC Agatston score is independent risk factor for stroke recurrence in index small-vessel occlusive stroke patients

References

1. Kassab MY, Gupta R, Majid A, Farooq MU, Giles BP, Johnson MD, Graybeal DF, Rappard G. Extent of intra-arterial calcification on head ct is predictive of the degree of intracranial atherosclerosis on digital subtraction angiography. *Cerebrovasc Dis*.2009;28:45-48
2. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation*.2001;103:1051-1056
3. Kitagawa T, Yamamoto H, Horiguchi J, Ohhashi N, Tadehara F, Shokawa T, Dohi Y, Kunita E, Utsunomiya H, Kohno N, Kihara Y. Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography.*JACC Cardiovasc Imaging*. 2009;2:153-160
4. Nicholls SJ, Tuzcu EM, Wolski K, Sipahi I, Schoenhagen P, Crowe T, Kapadia SR, Hazen SL, Nissen SE. Coronary artery calcification and changes in atheroma burden in response to established medical therapies. *J Am Coll Cardiol*.2007;49:263-270
5. Otsuka F, Finn AV, Virmani R. Do vulnerable and ruptured plaques hide in heavily calcified arteries? *Atherosclerosis*.2013;229:34-37
6. Shaalan WE, Cheng H, Gewertz B, McKinsey JF, Schwartz LB, Katz D, Cao D, Desai T, Glagov S, Bassiouny HS. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg*. 2004;40:262-269
7. Chen XY, Wong KS, Lam WW, Zhao HL, Ng HK. Middle cerebral artery atherosclerosis: Histological comparison between plaques associated with and not associated with infarct in a postmortem study. *Cerebrovasc Dis*. 2008;25:74-80
8. Pletcher MJ, Sibley CT, Pignone M, Vittinghoff E, Greenland P. Interpretation of the coronary artery calcium score in combination with conventional cardiovascular risk factors: The multi-ethnic study of atherosclerosis (mesa). *Circulation*.2013;128:1076-1084
9. Alexopoulos N, Raggi P. Calcification in atherosclerosis. *Nat Rev Cardiol*. 2009;6:681-688
10. Chen XY, Lam WW, Ng HK, Fan YH, WongKS. Intracranial artery calcification: A newly identified risk factor of ischemic stroke. *J Neuroimaging*.2007;17:300-303

ISSN:-2581-6934|www.jidps.com

11. Ovesen C, Abild A, Christensen AF, Rosenbaum S, Hansen CK, Havsteen I, Nielsen JK, Christensen H. Prevalence and long-term clinical significance of intracranial atherosclerosis after ischaemic stroke or transient ischaemic attack: A cohort study. *BMJ Open*.2013;3:e003724

12. Bos D, Portegies ML, van der Lugt A, Bos MJ, Koudstaal PJ, Hofman A, Krestin GP, Franco OH, Vernooij MW, Ikram MA. Intracranial carotid artery atherosclerosis and the risk of stroke in whites: The rotterdam study. *JAMA Neurol*.2014;71:405-411

13. van Dijk AC, Fonville S, Zadi T, van Hattem AM, Saiedie G, Koudstaal PJ, van der Lugt A. Association between arterial calcifications and nonlacunar and lacunar ischemic strokes. *Stroke*.2014;45:728-733

14. Hong NR, Seo HS, Lee YH, Kim JH, Seol HY, Lee NJ, Suh SI. The correlation between carotid siphon calcification and lacunar infarction. *Neuroradiology*.2011;53:643-649

15. Chung PW, Park KY, Kim JM, Shin DW, Ha SY. Carotid artery calcification is associated with deep cerebral microbleeds. *Eur Neurol*.2014;72:60-63

16. Bos D, Vernooij MW, Elias-Smale SE, Verhaaren BF, Vrooman HA, Hofman A, Niessen WJ, Witteman JC, van der Lugt A, Ikram MA. Atherosclerotic calcification relates to cognitive function and to brain changes on magnetic resonance imaging. *Alzheimers Dement*.2012;8:S104-111

17. Bos D, Vernooij MW, de Bruijn RF, Koudstaal PJ, Hofman A, Franco OH, van der Lugt A, Ikram MA. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. *Alzheimers Dement*. 2015;11:639-647 e631

18. Ptak T, Hunter GH, Avakian R, Novelline RA. Clinical significance of cavernous carotid calcifications encountered on head computed tomography scans performed on patients seen in the emergency department. *J Comput Assist Tomogr*.2003;27:505-509

19. Wu XH, Chen XY, Wang LJ, Wong KS. Intracranial artery calcification and its clinical significance. *J Clin Neurol*.2016;12:253-261

20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*.1990;15:827-832

21.Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G. User-guided 3d active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuro image*. 2006;31:1116-1128