NeuroImage: Clinical 35 (2022) 103050

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Silent brain infarction is associated with carotid siphon calcification in ischemic stroke patients

Jingjing Li [a,b,1], Yuhua Fan [a,b,1], Jian Zhang [a,b], Shihui Xing [a,b], Shujin Tang [a,b], Xiaoshuang Li [a,b], Chao Dang [a,b], Jinsheng Zeng [a,b,*]

[a] Department of Neurology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, China
[b] Guangdong Provincial Key Laboratory of Diagnosis and Treatment of Major Neurological Diseases, National Key Clinical Department and Key Discipline of Neurology, Guangzhou 510080, China

ARTICLE INFO

Keywords:
Silent brain infarction
Calcification pattern
Carotid siphon
Stroke

ABSTRACT

Background: Silent brain infarction (SBI) had a higher prevalence in ischemic stroke patients than healthy population. Intracranial artery calcification, as the important component of atherosclerosis, is a known risk factor of ischemic stroke. Whether it is also the risk factor of SBI is uncertain. We aimed to assess the association between SBI and carotid siphon calcification (CSC) in ischemic stroke patients.

Methods: We retrospectively collected consecutive data of acute ischemic stroke patients with and without SBI by Magnetic Resonance Imaging (MRI) and calcification using non-contrast Computerized Tomography (NCCT). We used a histopathologically validated method to score the circularity, thickness, and morphology of calcification. Clinical characteristics, prevalence and pattern (intimal and medial) of CSC were compared between patients with and without SBI. The association of CSC and SBI was investigated by logistic regression analysis.

Results: Totally, 303 acute ischemic stroke patients were enrolled, of whom 260 (85.8%) had CSC. Patients with SBI were older (64.5 ± 10.4 years vs. 61.3 ± 12.1 years, $P = 0.032$), had a higher proportion of hypertension (77.5% vs. 65.7%, $P = 0.035$). Of the 260 CSC patients, there's no significant difference except for hyperlipidemia between patients with SBI and without SBI. The prevalence of intimal pattern of CSC was higher in those with SBI (adjusted odds ratio 2.42, 95% CI 1.219–4.794).

Conclusions: Patients with SBI at acute phase of ischemic stroke have more risk factors than mentioned previously. SBI associated with the intimal pattern of CSC which relate to the atherosclerosis process in symptomatic ischemic stroke patients.

1. Introduction

Silent brain infarction (SBI) is defined as neuropathological evidence of cerebral infarction without a history of acute neurological dysfunction related to the lesion (Oh et al., 2010; Vermeer et al., 2007). Although called silent, SBI increased the risk of ischemic stroke and associated with subtle neurological deficits such as neurocognitive dysfunction (Fanning et al., 2014; Vermeer et al., 2007). SBI is commonly detected in patients with different subtypes of ischemic stroke, such as small artery occlusion (SAO) (32%-81.5%) (Adachi et al., 2002; Boon et al., 1994; Chen et al., 2017; Oh et al., 2010), large artery atherosclerotic(LAA) (23.3%-44.4%), and cardio-embolic (CE) (8.3%-42.1%) (Adachi et al., 2002; Boon et al., 1994; Chen et al., 2017; Cho et al., 2009; Escudero-Martinez et al., 2020; Oh et al., 2010).

SBI had many risk factors similar with symptomatic ischemic stroke such as hypertension, diabetes and smoking (Yi et al., 2011). As a major risk of stroke worldwide, intracranial atherosclerosis accounts for 30–50% of ischemic stroke events in Asians (Kim and Bonovich, 2014;

Abbreviations: SBI, silent brain infarction; TIA, transit ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale score; LAA, large artery atherosclerosis; SAO, small artery occlusion; CE, cardio-embolism; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; mRS, Modified Rankin Scale; CSC, carotid siphon calcification.

* Corresponding author at: Department of Neurology and Stroke Center, The First Affiliated Hospital of Sun Yat-Sen University, No. 58 Zhongshan Road 2, Guangzhou 510080, China.
E-mail address: zengjsh@mail.sysu.edu.cn (J. Zeng).

[1] These authors contributed equally to this study.

https://doi.org/10.1016/j.nicl.2022.103050
Received 6 February 2022; Received in revised form 4 May 2022; Accepted 15 May 2022
Available online 18 May 2022

Qureshi et al., 2009). Intracranial artery calcification is the important component of atherosclerosis, and is also an independent risk factor of ischemic stroke (Bos et al., 2014; Bugnicourt et al., 2011; Chen et al., 2006; Chen et al., 2019). Previous data proved the relationship between carotid siphon calcification (CSC) and SBI in the stroke-free community-dwelling old adults without differentiating the calcification pattern (Del Brutto et al., 2016). CSC can be categorized into intimal calcification and medial calcification in postmortem studies (Kockelkoren et al., 2017). Distinguishing the distinct morphological CSC patterns (intimal and medial) may reflect different pathological processes and clinical effects. The relationship between CSC and SBI has not been analyzed in ischemic stroke patients. Therefore, this study aimed to investigate the association between CSC and SBI in patients with symptomatic acute ischemic stroke and analyze the etiology of SBI.

2. Materials and methods

2.1. Participants

This retrospective cross-sectional study was approved by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University. We retrospectively analyzed the clinical and radiological characteristics of ischemic stroke patients who were admitted to our neurology department from June 1, 2016, to June 1, 2017. Inclusion criteria were as follows: (1) age 18–80 years; (2) <14 days since stroke onset at the time of assessment; (3) diagnosis of ischemic stroke confirmed by magnetic resonance imaging (MRI) with the updated definition of acute ischemic stroke as an acute episode of focal dysfunction of the brain or retina lasting longer than 24 h, or for any duration if CT, MRI, or autopsy shows focal infarction relevant to the symptoms; (Sacco et al., 2013) MRI sequencing included T-1 weighted image, T-2 weighted image, fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI). (4) having performed brain CT for the measurement of calcification. The exclusion criteria were: (1) poor brain imaging quality; (2) insufficient data or artifacts in the images. Stroke subtypes were classified into LAA, SAO, CE, stroke of other determined etiology (SOE), and stroke of undetermined etiology (SUE) according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria (Adams and Biller, 2005). We also compared the percentage of vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus (DM), cigarette smoking, and alcohol drinking) between different groups. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic pressure $\geq$ 90 mmHg or a history of hypertension or drug treatment. DM was determined using a 75 g oral glucose tolerance test, or as HbA1c $\geq$ 6.0%, or a medical history of diabetes or drug treatment. Dyslipidemia was defined as a level of cholesterol $>$ 5.7 mmol/L, triglyceride $>$ 1.7 mmol/L, low-density lipoprotein (LDL) $>$ 3.62 mmol/L, high-density lipoprotein (HDL) $<$ 1.03 mmol/L, or a history of hypercholesterolemia or drug treatment. Smoking was defined as smoking at the time of stroke onset. Alcohol consumption was considered habitual if the patient had consumed at least 30 g of alcohol a day for at least 1 year.

2.2. Diagnosis of SBI

We screened MRI and DWI data of all the acute ischemic stroke patients. SBI was defined as cerebral infarction observed on MRI scans without any corresponding clinically apparent cerebrovascular ischemic event (Sacco et al., 2013). The presence of SBI was concluded by one of three types of lesions on MRI: (1) a focus demonstrating restricted diffusion (DWI-positive; new onset SBI), (2) a cavitary lesion, or (3) T2 hyperintense/T1 hypointense lesions (chronic SBI) (Fanning et al., 2014). To distinguish SBI from dilated perivascular spaces, the lesions were required to be 3 mm or larger in size (Fanning et al., 2014). Acute ischemic stroke patients with SBI were included in the with SBI group, and those without SBI were included in the without SBI group. SBI were divided into cortical infarction and subcortical infarcts (lacunar infarctions and larger subcortical infarction) (Smith et al., 2017). Transversal T2-weighted images: repetition time (TR)/ echo time (TE), 4200 ms/109 ms; field of view (FOV), 230 mm $\times$ 230 mm; slice thickness, 6 mm; slice gap, 1.2 mm; Transversal T1-weighted images: repetition time (TR)/ echo time (TE), 2000 ms/17 ms; FOV, 230 mm $\times$ 230 mm; slice thickness, 6 mm; slice gap, 1.2 mm. Axial fluid-attenuated inversion recovery images (FLAIR): TR/TE, 9000 ms/110 ms; FOV, 220 mm $\times$ 220 mm; slice thickness, 6 mm; slice gap, 1.2 mm. DWI was performed using an axial echo-planar spin-echo sequence: TR/TE, 8700 ms/88 ms; slice thickness, 3 mm; FOV 260 $\times$ 260 mm; voxel resolution: 1.2 mm $\times$ 1.2 mm $\times$ 6.0 mm. Diffusion was measured in 3 orthogonal directions using of 3b-values (0, 500, and 1000 s/mm2). Apparent Diffusion Coefficient (ADC) maps were automatically generated.

2.3. Assessment of CSC

Non-contrast Computed Tomography (NCCT) is the most accessible and direct method to evaluate intracranial artery calcification (Bos et al., 2011). All patients were scanned on an 80-slice spiral CT scanner (Aquilion Prime, Toshiba Medical Systems, Tokyo, Japan) from the skull base to the vertex. Tube voltage was 120 kV and tube current ranged between 200 and 250 mA with a slice thickness of 1 mm. A senior neurologist and a senior radiologist who were blinded to the clinical data independently analyzed the images and made the diagnoses. Images were assessed in the bone setting (center: 500 Hounsfield Units [HU] $\pm$ width: 1500 HU) in all planes (axial, sagittal, and coronal). Calcification was defined as the presence of hyperdense foci along the artery with a peak intensity above 130 HU. Intracranial large arteries such as the middle cerebral artery (MCA), internal carotid artery (ICA), vertebral artery (VA), and basilar artery (BA) were evaluated from the horizontal part of the petrous segment of the artery to its top (circle of Willis). Calcification of the ICA is commonly referred to as the carotid siphon due to the tortuous shape (Kockelkoren et al., 2017). The percentage of CSC was recorded and compared between the with SBI and the without SBI groups. CT scans showed good reproducibility in being able to differentiate these patterns (Kockelkoren et al., 2017; Vos et al., 2016; Yang et al., 2018).

2.4. Calcification pattern

According to the histopathologically validated method using plain CT, calcification are of two types: intimal calcification and medial calcification (Kockelkoren et al., 2017). This scoring model has been proved and used in many researches (Compagne et al., 2018; Kauw et al., 2021; Yang et al., 2018; Yu et al., 2021). The circularity, thickness, and morphology of calcification were recorded. Two different observers blinded to clinical data measured the scores. Points were awarded for different morphological aspects of calcification: 0–4 points for circularity, 0–3 points for the thickness of calcification, and 0–4 points for continuity of calcification over a longer arterial segment. Intimal calcification (score $<$ 7 points) is more clustered and often grow intraluminally, while medial calcification (score $\geq$ 7 points) is identified as a thin, continuous, and almost circular calcification (Kockelkoren et al., 2017).

We calculated the points of calcification in bilateral carotid siphons and there were three conditions: intimal/ medial calcification can be detected in one siphon or bilateral siphons or at least one side siphon. The intimal pattern of CSC was defined as intimal calcification in at least one carotid siphon. The medial pattern of CSC was defined as medial calcification in at least one carotid siphon. The percentage of CSC pattern was compared between the with SBI and without SBI group.

2.5. Statistical analysis

Continuous variables were compared using Student's *t*-test if

normally distributed or the Mann-Whitney *U* test if not normally distributed. Categorical variables were compared using the Chi-squared test or Fisher's exact test. Multivariate regression analysis was further used to investigate the independent variables. Multivariable logistic regression analysis was performed in the 260 CSC patients. Covariates selected for multivariate logistic regression were the variables with significant differences between the two groups in the clinical analysis and other published risk factors. Cohen's kappa values and proportions of the agreement were calculated to define the level of interobserver agreement in grading CSC percentage and pattern. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 22.0, IBM Corp, Armonk, NY, USA).

3. Results

3.1. Clinical characteristics

We assessed 575 patients with acute ischemic stroke obtained within 14 days of the onset. Totally, 303 acute ischemic stroke patients were enrolled, of whom 260 (85.8%) had CSC. The clinical data of the 303 patients were compared between SBI group and without SBI group. The other patients were excluded for the following reasons: 182 patients were excluded for lack of brain MRI and/or CT imaging in our hospital for detecting cerebral infarction and calcification; 58 patients for being over 80 years of age and 32 patients for insufficient data or artifacts in the images (Fig. 1). Of the 260 CSC patients, the data of 93 patients with SBI and 167 CSC patients without SBI were analyzed.

The mean age was 62.3 ± 11.6 years and 213 patients (70.3%) were male of the enrolled 303 patients. Table 1 shows the clinical data (demographic characteristics, risk factor variables) of with SBI and without SBI groups. Patients with SBI were older (mean age: 64.5 ± 10.4 years vs. 61.3 ± 12.1 years, $P = 0.032$; Table 1) and a higher percentage of hypertension (77.5% vs. 65.7%, $P = 0.035$; Table1) compared to those without SBI. When analyzing the 260 CSC patients, we found that there was no significant difference in clinical data except for hyperlipidemia. The percentage of hyperlipidemia was higher in the without SBI group than in the with SBI group in these 260 CSC patients (24.7% vs. 12.8%, $P = 0.038$; Table 2).

3.2. Percentage and CSC pattern

Cohen's kappa value was 0.88 of the interobserver agreement in grading CSC percentage and pattern. The percentage of intimal pattern of CSC was significantly higher in patients with SBI (86.0% vs. 72.5%, $P = 0.012$; Table 2). There's no statistically difference of medial pattern of CSC between patients with SBI and without SBI (26.9% vs. 34.7%, $P = 0.193$; Table 2).

Multivariate-adjusted logistic regression analysis was used to analyze the association between CSC pattern and SBI. We measured and calculated the scores of calcifications using the mentioned method. The clustered intimal and continuous medial calcification were shown in Fig. 2. The percentage of intimal pattern of CSC in the with SBI group was higher than that in the without SBI group (adjusted odds ratio 2.42, 95% CI 1.219–4.794) after adjusting for variables (age, gender, hypertension, smoking and hyperlipidemia). Age, hypertension and hyperlipidemia were derived from the analysis between with SBI group and without SBI group in the 303 acute stroke patients. Meanwhile, gender and smoking are from published paper as the risk factors of SBI.

3.3. SBI pattern and its relationship with CSC pattern

Among the 93 CSC patients with SBI in our study, 16 (17.2%) patients had silent cortical infarction while 72 (77.4%) patients had silent lacunar infarction, and 5 (5.4%) patients have both. The number of patients with intimal pattern of calcification was 13, 62, and 4 in the above mentioned SBI patterns. That of medial pattern of CSC was 3, 26, and 1 separately. There is no statistical relationship between SBI pattern and CSC pattern by Fisher's exact test.

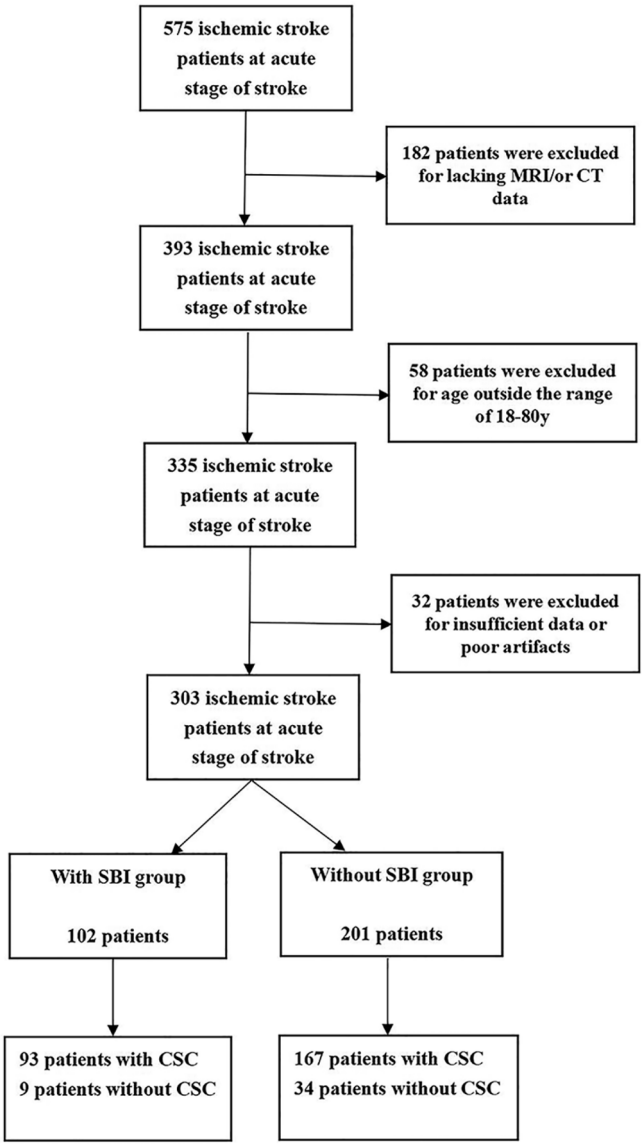

Fig. 1. Flow chart of patient inclusion (Abbreviations: SBI = silent brain infarction; CSC = carotid siphon calcification).

4. Discussion

Our data demonstrated that acute ischemic stroke patients with SBI are older with a significantly higher percentage of hypertension. After adjusting for variables, the proportion of intimal pattern of CSC is higher in patients with SBI. This suggested that SBI is associated with the intimal patternof CSC which relates to atherosclerosis.

As the most widely accepted risk factors (Chen et al., 2017; Fanning et al., 2014; Oh et al., 2010; Putaala et al., 2009), the average age and percentage of hypertension were higher in patients with SBI and the prevalence of SBI was 33.7% in the whole 303 patients. In acute ischemic stroke patients, the frequency of SBI is significantly higher in those of SAO subtype while it is also common in those of LAA and CE subtypes (Chen et al., 2017; Oh et al., 2010). In this study which did not define leukoaraiosis as SAO stroke presentation, there's no significant difference of TOAST subtypes between two groups. In 260 patients with CSC, the percentage of hyperlipidemia was higher in the without SBI group. This might be explained by the prevalence of stroke subtypes. The

Table 1
Clinical data of the patients with and without SBI.

	with SBI group (n=102)	without SBI group (n=201)	p value
Age, years, mean ± SD	64.5 ± 10.4	61.3 ± 12.1	0.032*
Male, n (%)	70(68.6)	143(71.1)	0.651
Hypertension(%)	79(77.5)	132(65.7)	0.035*
Diabetes mellitus (%)	35(34.3)	76(37.8)	0.550
Atrial fibrillation (%)	10(9.8)	19(9.5)	0.922
Hyperlipidemia	19(18.6)	54(26.9)	0.113
Myocardial infarction (%)	12(6.0)	7(3.5)	0.762
History of stroke or TIA (%)	12(11.8)	36(17.9)	0.166
Smoking(%)	46(45.1)	84 (41.8)	0.632
heavy smoking (%)	36(35.3)	65(32.8)	0.712
Heavy drinking (%)	14(13.7)	20(10.0)	0.348
TOAST (%)			0.805
LAA	45(44.1)	98(48.8)	
SAO	34(33.3)	57(28.4)	
CE	8(7.8)	19(9.5)	
SOE	4(3.9)	10(5.0)	
SUE	11(10.8)	17(8.5)	
NIHSS on admission median (IQR)	8(5-12)	7(4-12)	0.843
mRS > 2 when discharged(%)	32(31.4)	66(32.8)	0.797

Abbreviations: SBI = silent brain infarction; TIA = transit ischemic attack; TOAST = Trial of Org 10172 in Acute Stroke Treatment ; NIHSS = National Institutes of Health Stroke Scale score; LAA = large artery atherosclerotic; SAO = small artery occlusion; CE = cardio-embolism; SOE = stroke of other determined etiology; SUE = stroke of undetermined etiology; mRS = Modified Rankin Scale.

Table 2
Clinical data of the patients with CSC.

	with SBI group (n=93)	without SBI group (n=167)	*p* value
Age, years, mean ± SD	65.0 ± 9.8	63.8 ± 10.5	0.367
Male, n (%)	64(68.1)	112(67.5)	0.920
Hypertension(%)	72(72.6)	113(68.1)	0.145
Diabetes mellitus (%)	34(36.2)	67(40.4)	0.505
Atrial fibrillation (%)	9(9.6)	17(10.2)	0.863
Hyperlipidemia (%)	12(12.8)	41(24.7)	0.038*
Myocardial infarction (%)	5(5.3)	12(7.2)	0.550
History of stroke or TIA (%)	12(12.8)	33(19.9)	0.145
Smoking(%)	42(45.2)	67(40.1)	0.549
Heavy Smoking(%)	33(35.1)	52(31.3)	0.647
Heavy drinking(%)	14(15.0)	17(10.8)	0.274
TOAST(%)			0.405
LAA	40(42.6)	86(51.8)	
SAO	32(34.0)	47(28.3)	
CE	7(7.45)	17(10.2)	
SOE	4(4.26)	4(2.4)	
SUE	11(11.7)	13(7.8)	
NIHSS on admission median (IQR)	8(5-12)	7(4-12)	0.605
mRS > 2 when discharged (%)	29(30.9)	56(33.7)	0.634
Intimal pattern CSC	80(86.0)	121(72.5)	0.012*
Medial pattern CSC	58(26.9)	25(34.7)	0.193

Abbreviations: SBI = silent brain infarction; TIA = transit ischemic attack; TOAST = Trial of Org 10172 in Acute Stroke Treatment; NIHSS = National Institutes of Health Stroke Scale score; LAA = large artery atherosclerotic; SAO = small artery occlusion; CE = cardio-embolism; SOE = stroke of other determined etiology; SUE = stroke of undetermined etiology; mRS = Modified Rankin Scale; CSC = carotid siphon calcification.

association of cholesterol with stroke varies in stroke subtypes and patients' subgroups (Tirschwell et al., 2004). A mendelian randomization study of lipid genetics suggested an increased risk of large artery ischemic stroke with increased LDL and a lower risk of small-vessel ischemic stroke with increased HDL (Hindy et al., 2018). Although there's no statistically significant difference, the percentage of LAA was higher in patients without SBI. Recently, researchers have found that the triglyceride/HDL cholesterol ratio was positively associated with the prevalence of SBI in a neurologically healthy population (Nam et al., 2019). Similar with the previous data, majority of SBIs located in the subcortical area (Smith et al., 2017).

ICA was considered as the most prevalent Intracranial large artery calcification, followed by VA, MCA, and BA in Chinese population (Chen et al., 2006). Calcification of ICA is commonly referred to CSC due to the tortuous shape of carotid siphon. The percentage of CSC equaled to the percentage of ICA calcification. Analyzing CSC can reflect the calcification of intracranial large artery and the atherosclerosis burden. Numerous researches have investigated the relationship between CSC and symptomatic cerebral infarction (Bos et al., 2014; Gocmen et al., 2018; Hong et al., 2011; Tábuas-Pereira et al., 2018). Few research analyzes that of CSC and SBI.

We described the characteristics of calcification and its relationship with SBI in the 260 patients with CSC. Intracranial artery calcification can reflect atherosclerosis burden of acute ischemic stroke (Kim et al., 2019). In addition to large artery atherosclerosis, small lacunes and SBIs may be caused by atherosclerosis of small penetrating arteries (Adachi et al., 2002; Baradaran et al., 2016; Kong et al., 2019). Intimal calcification is most often associated with atherosclerotic plaque burden, while medial calcification is considered non-atherosclerotic calcification (Sanz and Fayad, 2008; Vos et al., 2016). Intimal calcification was seen in approximately 70% of random autopsies of patients with stroke (Kockelkoren et al., 2017; Vos et al., 2016; Yang et al., 2017). In a cohort of stroke patients from the Dutch acute stroke study (DUST) study, the prevalence of intimal calcification was higher than that of the medial calcification on both sides of symptomatic cerebral infarction (Vos et al., 2018). The higher prevalence of intimal pattern of CSC in patients with SBI in our study suggested that the existence of SBI associated with intimal pattern of CSC in stroke patients. In addition, intracranial atherosclerosis may play an important role in the pathological process of SBI in these patients. We should differentiate the more clustered and intraluminal intimal pattern of CSC on NCCT which may suggest the existence of SBI.

There are some limitations to our study. First, it excluded several patients because of a lack of complete neuroimaging data. Additionally, because of the retrospective nature of the study, a selection bias might be present such as the higher percentage of male patients. Second, our results may not be valid in Caucasians, because stroke subtypes differed between Chinese population and Caucasians. The percentage of included cardioembolic stroke patients is lower than the other studies. Third, we scored the calcification without quantitative measurements. It would be interesting to investigate the association between the CSC pattern and vulnerable plaque elements with high-resolution vessel wall MRI scans in the future. In addition, SBI pattern should be analyzed intensively when we have more patients in the future.

5. Conclusions

Our study analyzed the relationship between SBI and CSC in patients at acute stage of stroke. We demonstrated that patients with SBI at acute phase of stroke have more risk factors than mentioned previously. SBI associated with the intimal pattern of CSC which relate to the atherosclerosis process in symptomatic ischemic stroke patients. It emphasized the need to identify the CSC on non-contrast CT which relate to the existence of SBI.

CRediT authorship contribution statement

Jingjing Li: Conceptualization, Methodology, Writing – original draft. **Yuhua Fan:** Data curation, Writing – original draft. **Jian Zhang:**

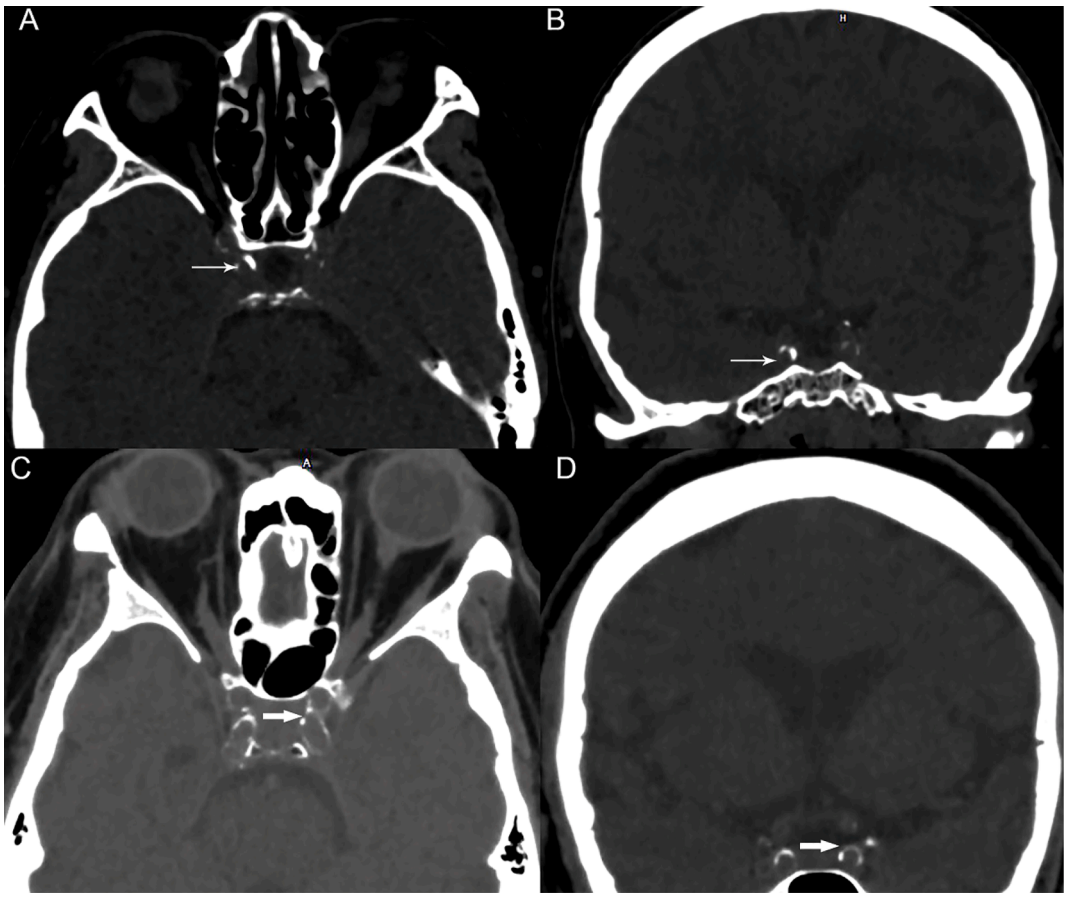

Fig. 2. The transverse section and coronal section of the carotid siphon calcification (CSC). A and B are the transverse section and coronal section of intimal calcification; C and D are the transverse section and coronal section of the medial calcification.

Data curation, Visualization, Validation. **Shihui Xing:** Software, Methodology. **Shujin Tang:** Visualization, Investigation. **Xiaoshuang Li:** Project administration, Resources. **Chao Dang:** Project administration, Software. **Jinsheng Zeng:** Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from the Guangzhou Science and Technology Program Key Projects (202007030010), Guangdong Provincial Key Laboratory of Diagnosis and Treatment of Major Neurological Diseases (2020B1212060017), Guangdong Provincial Clinical Research Center for Neurological Diseases (2020B1111170002), Southern China International Joint Research Center for Early Intervention and Functional Rehabilitation of Neurological Diseases (2015B050501003 and 2020A0505020004), Guangdong Provincial Engineering Center for Major Neurological Disease Treatment, Guangdong Provincial Translational Medicine Innovation Platform for Diagnosis and Treatment of Major Neurological Disease, Guangzhou Clinical Research and Translational Center for Major Neurological Diseases (201604020010). National Natural Science Foundation of China (81571107, 81771137, 81971103) and Natural Science Foundation of Guangdong Province (2017A030313660, 2017A030313575).

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