

# A Whole-Scope Evaluation of Cervicocephalic Atherosclerotic Burden is Essential to Predict 90-Day Functional Outcome in Large-Artery Atherosclerotic Stroke

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**Aim:** Cervicocephalic atherosclerosis (AS) of patients with large-artery atherosclerotic (LAA) stroke might be more closely correlated to the functional outcome than patients with stroke of other etiologies. We aimed to investigate whether a whole-scope evaluation of cervicocephalic AS condition was better at predicting the 90-day functional outcome of LAA stroke than evaluation of intracranial or cervical AS condition alone.

**Methods:** Patients with LAA stroke were consecutively enrolled in this study. Computed tomography angiography was performed to evaluate AS condition of various cervicocephalic arterial segments. AS conditions ranging from no AS plaque to complete arterial occlusion scored 0–4 points. Intracranial atherosclerotic burden (IAB) and cervical atherosclerotic burden (CAB) were in respective the sums of AS scores of all intracranial arterial segments and all cervical arterial segments. And the sum of them was intracranial and cervical atherosclerotic burden (ICAB). Relationships of these three scores with the 90-day unfavorable functional outcome (modified Rankin Scale[mRS] score > 2 points) were compared.

**Results:** Of 172 patients who finished 90-day follow-up, only ICAB (adjusted odds ratio[OR]=1.10, 95% confidence interval[CI]:1.00–1.21,  $p=0.044$ ) predicted 90-day unfavorable functional outcome independently of clinical factors, National Institutes of Health Stroke Scale (NIHSS) and mRS scores at admission. ICAB (adjusted hazard ratio[HR]=1.16, 95%CI:1.02–1.32,  $p=0.029$ ) was related to 90-day recurrent ischemic stroke/death independently of clinical factors and was independently, positively correlated with NIHSS score at admission ( $r=0.16$ ,  $p=0.047$ ), whereas IAB and CAB were not.

**Conclusion:** A whole-scope evaluation of cervicocephalic AS condition using ICAB outperformed evaluation of intracranial or cervical AS condition alone in predicting 90-day functional outcome of patients with LAA stroke.

**Key words:** Cervicocephalic atherosclerosis, Atherosclerotic burden, Large-artery atherosclerotic stroke, 90-day functional outcome, Whole-scope atherosclerosis evaluation

## Introduction

A major cause of acute ischemic cerebral vascular diseases (AICVD) is atherosclerosis (AS)<sup>1, 2</sup>, which also affects the functional outcome of patients with AICVD<sup>3-7</sup>. Functional outcome is the ability of a

patient to carry out daily activities after a stroke, and the modified Rankin Scale (mRS) evaluates the functional outcome of patients with stroke in clinical practice<sup>8</sup>. AS condition of intracranial and/or cervical arteries were able to predict functional outcome of patients with AICVD independently of other

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predictors, including age, previous stroke, neurological deficit severity, hyperglycemia<sup>9)</sup>, recanalization therapy<sup>7)</sup>, recurrent vascular events or death, and so forth.

Smith WS *et al.* demonstrated that intracranial large arterial occlusion caused by AS was an independent predictor for six-month unfavorable functional outcomes of patients with AICVD<sup>3)</sup>. However, this study merely evaluated intracranial AS condition of patients with AICVD. AS commonly affects multiple vascular beds as a systemic disease, and AS lesions on different vascular beds share common risk factors<sup>10)</sup>. Li D *et al.* evaluated AS condition of intracranial and extracranial carotid arteries and aortic arch. They found that combined evaluation of AS condition on these three vascular beds showed stronger predictive value for the presence of an acute infarcted lesion in patients with AICVD (including ischemic stroke and transient ischemic attack[TIA]) than evaluation of AS condition on single vascular bed<sup>11)</sup>. Compared with transient cerebral ischemia without infarction, an acute infarcted lesion would lead to poorer neurological functional outcomes. This study implied that an overall evaluation of AS condition on stroke-related arteries might outperform the evaluation of a single vascular bed in predicting the functional outcome of patients with AICVD. However, whether a whole-scope evaluation of cervicocephalic AS condition is advantageous for evaluating intracranial or cervical AS condition alone in predicting the functional outcome of patients with AICVD has not been directly certified.

Luminal moderate-severe stenosis or occlusion caused by AS on cervicocephalic large arterial segments are arterial pathological features of large-artery atherosclerotic (LAA) stroke. They are likely to decrease the perfusion of the infarcted region in patients with LAA stroke. Therefore, cervicocephalic AS condition of patients with LAA stroke, compared with that of patients with stroke of other etiologies, might be more likely to affect the functional outcome. Our previous study found that both severity and extent of AS lesions should be considered to reflect the “AS burden” of cervicocephalic arteries<sup>12)</sup>. In the present study, we quantified the cervicocephalic AS burden of patients with LAA stroke based on this idea with computed tomography angiography (CTA).

### Aim

We aimed to investigate whether a whole-scope evaluation of cervicocephalic AS burden was better at predicting the 90-day functional outcome of patients

with LAA stroke than evaluation of intracranial or cervical AS burden alone.

### Methods

The hospital ethics committee approved the study, and all participants provided written informed consent. Patients admitted to the hospital stroke unit from January 01, 2019, to January 31, 2020, and diagnosed as acute ischemic stroke by cranial computed tomography or magnetic resonance image were consecutively enrolled in this study. The inclusion criteria were age between 18 and 80 years, within 7 days after symptom onset, diagnosed as LAA subtype according to Trial of Org 10172 in Acute Stroke Treatment<sup>13)</sup>, and successfully finished the cervicocephalic CTA examination. Patients with cerebral ischemic symptoms lasting less than 24 hours, other potential causes of the stroke, e.g., atrial fibrillation, poor organ functions, contraindications or intolerance for CTA and mRS score >2 points before the index stroke were excluded.

### Demographics and Clinical Characteristics

We collected patients' demographic and clinical information through face-to-face interviews, including age, sex, hypertension history, diabetes mellitus history, hyperlipidemia history, smoking, alcohol consumption, obesity, and previous ischemic stroke or TIA history. The definitions of smoking and obesity were in line with our previous study<sup>14)</sup>. Neurological deficit severity of all patients were evaluated at admission based on National Institute of Health Stroke Scale (NIHSS) score<sup>15)</sup> and mRS score (0 points for without any neurological deficit symptom; 1 point for being able to carry out all daily activities despite with symptoms independently; 2 points for unable to carry out previous activities but able to fulfill own affairs without assistance; 3 points for requiring assistance but able to walk independently; 4 points for unable to walk or attend to own bodily needs without assistance; 5 points for bedridden, incontinent, and requiring constant nursing care<sup>8, 16)</sup>). All patients underwent routine exams and laboratory tests during hospitalization. The medical treatment during hospitalization and after discharge was in accordance to the acute ischemic stroke management and secondary prevention guidelines<sup>17)</sup>.

### Cervicocephalic CTA and the Quantification of AS Condition

Cervicocephalic CTA was performed to evaluate various intracranial and cervical arterial segments. In specific, cervical arterial segments included bilateral

common carotid, extracranial internal carotid, and extracranial vertebral arteries. In contrast, intracranial arterial segments included bilateral anterior cerebral, middle cerebral, posterior cerebral, intracranial internal carotid, intracranial vertebral arteries, and basilar artery. The petrous part of the internal carotid artery had an external elastic lamina, which characterized the extracranial arteries<sup>18</sup>). Thus, it was categorized as a cervical arterial segment, as previously reported<sup>4, 19</sup>). Cervical arterial stenoses were evaluated with North American Symptomatic Carotid Endarterectomy Trial method<sup>20</sup>), while intracranial arterial stenoses were evaluated by Warfarin-Aspirin Symptomatic Intracranial Disease Study Trial method<sup>21</sup>). The details of CTA scanning mode and parameters were described in our previous study<sup>14, 22</sup>). AS condition of cervicocephalic arterial segments were respectively evaluated by two independent and experienced radiologists blinded to patients' demographic and clinical information. If there were disagreements in the evaluations of these two radiologists, a third practitioner would participate in the evaluation, and a final consent was reached. The relevant artery was an artery with symptomatic stenosis, i.e., with stenosis  $\geq 50\%$  and downstream acute infarction lesions.

Cohen's kappa<sup>11</sup>) was used to determine the intraobserver and interobserver agreement in the atherosclerotic burden evaluation. The grade of the AS condition on each large cervicocephalic arterial segment was scored as follows: 0 for no AS plaque; 1 for  $< 50\%$  stenosis or AS plaque with no stenosis; 2 for  $50\%$ – $69\%$  stenosis; 3 for  $70\%$ – $99\%$  stenosis; 4 for occlusion<sup>23</sup>). If there were multiple stenoses on one intracranial or cervical arterial segment, this segment was scored according to the grade of the severest stenosis. Intracranial atherosclerotic burden (IAB) was calculated as the sum of intracranial arterial AS severity scores and cervical atherosclerotic burden (CAB) as the sum of cervical arterial AS severity scores. Then intracranial and cervical atherosclerotic burden (ICAB) was calculated by summing IAB and CAB. The  $\kappa$  values of the intraobserver agreement for both IAB and CAB were 1.00, while the  $\kappa$  values of the interobserver agreement were 0.866 for IAB and 0.873 for CAB (all  $p < 0.001$ ).

### Follow-Up

An independent stroke neurologist contacted patients or surrogates through telephone follow-up on 30, 60, and 90 days after index stroke to assess patients' daily activities and monitor whether patients experienced new ischemic stroke or death. Patients' daily activities were evaluated by mRS score (0–6

points). Unfavorable functional outcome was defined as mRS  $> 2$  points.

### Grouping of Study Subjects

According to telephone follow-up, patients were divided into 90-day favorable functional outcome group (mRS  $\leq 2$  points) and 90-day unfavorable functional outcome group (mRS  $> 2$  points).

### Statistical Analysis

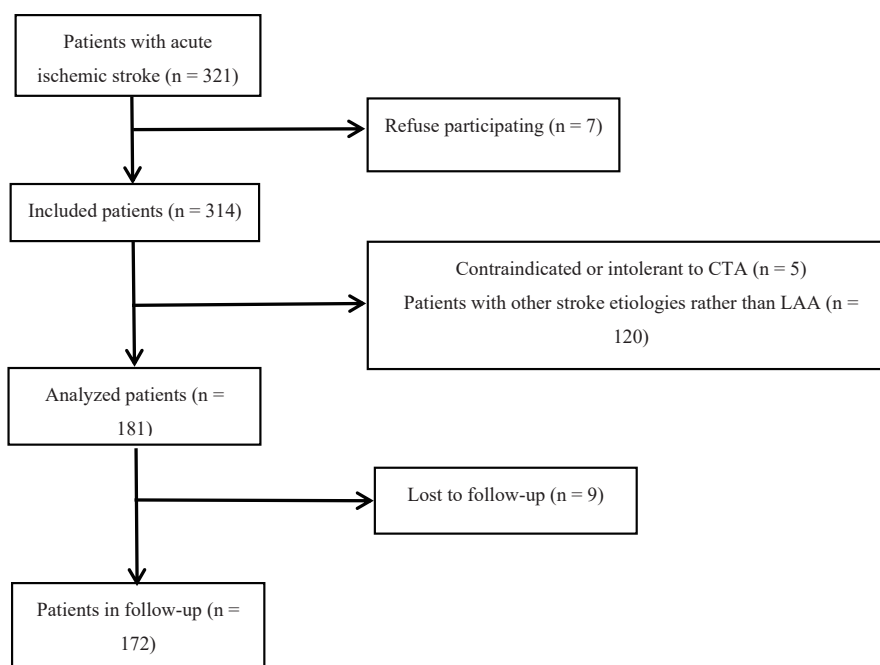
All statistical analyses were performed using SPSS software (v25.0; IBM, Armonk, NY, United States). All tests were two-sided, and the  $p$ -value  $< 0.05$  was considered statistically significant. Categorical variables were compared using the Chi-square test or Fisher's exact test. Continuous variables were compared in two groups using independent sample  $t$ -test or Mann–Whitney  $U$  test and were compared in multiple groups using one-way analysis of variance test or Kruskal–Wallis test.

In univariate analysis, age, sex, and clinical factors with  $p < 0.1$  were included in multivariate logistic regression analysis to test relationships of AS burden indices and 90-day unfavorable functional outcome. Multivariate Cox proportional hazards regression analysis was used to analyze the predictive value of each AS burden index for the risk of recurrent ischemic stroke or all-cause death after adjusting for age, sex, and clinical factors with  $p < 0.1$  in univariate Cox regression analysis. Pearson or Spearman correlation analysis and partial correlation analysis were used to evaluate the relationships between each AS burden index and 90-day mRS score and NIHSS score at admission.

## Results

A total of 321 consecutive patients with acute ischemic stroke were admitted to a hospital stroke unit. Among them, 7 patients refused to participate in our study, 5 patients were contraindicated or intolerant to CTA, 120 patients were diagnosed as an ischemic stroke of other etiologies rather than LAA, and mRS scores of 8 patients were  $> 2$  points before this index stroke. All these patients were excluded from this study. Finally, 181 patients with LAA stroke were enrolled in the cohort (Fig. 1). There were 150 (82.9%) patients with concurrent intracranial and cervical AS. By median, these patients had 9 (6, 13) cervicocephalic arterial segments with AS lesion and had 2 (1, 4) arterial segments with  $\geq 50\%$  stenosis.

Among the 181 enrolled patients, 9 (5.0%) patients were lost to follow-up, 7 (3.9%) had recurrent ischemic stroke, and 1 (0.6%) died of stroke



**Fig. 1.** Flowchart of patient's enrollment and follow-up  
None.

complications within 90-days after index stroke. Among 172 patients who finished 90-day follow-up, 37 (21.5%) had 90-day unfavorable functional outcomes (mRS > 2 points) (Table 1), 124 (72.1%) had symptomatic intracranial stenoses, 27 (15.7%) had symptomatic cervical stenoses, and 21 (12.2%) patients had both intracranial and cervical symptomatic stenoses (Table 2).

### Correlations between AS Burden Indices and Functional Outcome of Patients with LAA Stroke

Patients with 90-day unfavorable functional outcome had elder age ( $64.5 \pm 9.3$  vs.  $58.9 \pm 11.4$  years,  $p=0.007$ ), had higher NIHSS score ( $8.3 \pm 4$  vs.  $2.8 \pm 3.2$  points,  $p < 0.001$ ) and mRS score ( $3.5 \pm 0.7$  vs.  $1.4 \pm 1.1$  points,  $p < 0.001$ ) at admission, and had higher IAB ( $12.2 \pm 4.7$  vs.  $9.2 \pm 4.4$  points,  $p < 0.001$ ), CAB ( $4.8 \pm 3.1$  vs.  $3.2 \pm 2.7$  points,  $p=0.004$ ) and ICAB ( $17 \pm 6.2$  vs.  $12.4 \pm 5.5$  points,  $p < 0.001$ ) than those with 90-day favorable functional outcome. The hypertension history proportion ( $64.9\%$  vs.  $80.7\%$ ,  $p=0.041$ ), uric acid level ( $285.40 \pm 99.53$  vs.  $322.74 \pm 97.92$  mmol/L,  $p=0.048$ ) and posterior circulation stroke proportion ( $27.0\%$  vs.  $48.1\%$ ,  $p=0.022$ ) of patients with 90-day unfavorable functional outcome were lower than that of patients with 90-day favorable functional outcome (Table 1). In multivariate logistic regression analysis, only ICAB (adjusted odds ratio [OR]=1.10, 95% confidence interval [CI]:1.00–1.21,

$p=0.044$ ) was an independent predictor for 90-day unfavorable functional outcome after adjusting for age, sex, hypertension history, uric acid level, posterior circulation stroke proportion, NIHSS and mRS scores at admission (Table 3).

In Pearson correlation analysis, ICAB ( $r=0.302$ ,  $p < 0.001$ ), IAB ( $r=0.277$ ,  $p < 0.001$ ), CAB ( $r=0.182$ ,  $p=0.017$ ) was positively associated with 90-day mRS score, respectively. Partial correlation analysis showed that the positive correlation of ICAB and IAB with 90-day mRS score remained statistically significant after controlling age, sex, hypertension history, uric acid level, posterior circulation stroke proportion, NIHSS, and mRS scores at admission (Table 4).

Patients were divided according to quartiles (9, 13, 17 points, respectively) of ICAB. The proportion of patients with 90-day unfavorable functional outcomes increased along with the increase of ICAB grades ( $p=0.002$ ), which was as high as 40.0% in the group with the top quartile of ICAB (ICAB > 17 points) (Fig. 2).

### Correlations between AS Burden Indices and 90-Day Recurrent Ischemic Stroke/Death

Among all 181 patients, Kaplan–Meier survival analysis showed that the rate of recurrent stroke and death was higher in patients with ICAB above mean (13 points) than that in patients with ICAB  $\leq 13$  points (log-rank test,  $p=0.021$ ) (Fig. 3). In multivariate

**Table 1.** Comparisons of patients with favorable and unfavorable 90-day functional outcome

Clinical factors	Total (n=172)	mRS ≤ 2 points (n=135)	mRS > 2 points (n=37)	P value
Age (year, $\bar{x} \pm s$ )	60.1 ± 11.2	58.9 ± 11.4	64.5 ± 9.3	0.007*
Male (n, %)	123 (71.5)	99 (73.3)	24 (64.9)	0.31
Onset to arrival (day, $\bar{x} \pm s$ )	3.6 ± 2.1	3.7 ± 2.1	3.3 ± 1.8	0.26
Hypertension (n, %)	133 (75.1)	109 (80.7)	24 (64.9)	0.041*
Diabetes mellitus (n, %)	71 (41.3)	55 (40.7)	16 (43.2)	0.78
Hyperlipidemia (n, %)	94 (54.7)	77 (57.0)	17 (45.9)	0.23
History of AIS or TIA (n, %)	36 (20.9)	28 (20.7)	8 (21.6)	0.91
Smoking (n, %)	76 (44.2)	62 (45.9)	14 (37.8)	0.38
Alcohol consumption (n, %)	66 (38.4)	51 (37.8)	15 (40.5)	0.76
Obesity (n, %)	22 (12.8)	17 (12.6)	5 (13.5)	1.00
SBP (mmHg, $\bar{x} \pm s$ )	146.2 ± 20.1	145.1 ± 20.2	150 ± 19.6	0.19
DBP (mmHg, $\bar{x} \pm s$ )	84.5 ± 12.3	84.4 ± 12.3	84.9 ± 12.6	0.84
HbA1c (% , $\bar{x} \pm s$ )	6.79 ± 1.71	6.75 ± 1.70	6.94 ± 1.73	0.56
FBG (mmol/L, $\bar{x} \pm s$ )	6.42 ± 2.47	6.27 ± 2.45	6.99 ± 2.50	0.12
TC (mmol/L, $\bar{x} \pm s$ )	3.90 ± 1.00	3.93 ± 1.01	3.81 ± 0.95	0.54
TG (mmol/L, $\bar{x} \pm s$ )	1.67 ± 1.05	1.71 ± 1.05	1.52 ± 1.03	0.35
LDL-C (mmol/L, $\bar{x} \pm s$ )	2.30 ± 0.83	2.32 ± 0.84	2.24 ± 0.83	0.62
HDL-C (mmol/L, $\bar{x} \pm s$ )	1.05 ± 0.29	1.06 ± 0.30	0.98 ± 0.25	0.15
Hcys (mmol/L, $\bar{x} \pm s$ )	16.36 ± 9.78	16.28 ± 9.27	16.67 ± 11.79	0.84
Uric acid (mmol/L, $\bar{x} \pm s$ )	314.77 ± 99.15	322.74 ± 97.92	285.40 ± 99.53	0.048*
NIHSS score at admission (point, $\bar{x} \pm s$ )	4 ± 4	2.8 ± 3.2	8.3 ± 4	<0.001*
mRS score at admission (point, $\bar{x} \pm s$ )	1.9 ± 1.4	1.4 ± 1.1	3.5 ± 0.7	<0.001*
IAB (point, $\bar{x} \pm s$ )	9.9 ± 4.6	9.2 ± 4.4	12.2 ± 4.7	<0.001*
CAB (point, $\bar{x} \pm s$ )	3.6 ± 2.9	3.2 ± 2.7	4.8 ± 3.1	0.004*
ICAB (point, $\bar{x} \pm s$ )	13.4 ± 6	12.4 ± 5.5	17 ± 6.2	<0.001*
posterior circulation stroke (n, %)	75 (43.6)	65 (48.1)	10 (27.0)	0.022*
Thrombolysis (n, %)	6 (3.5)	4 (3.0)	2 (5.4)	0.83
Antiplatelet (n, %)	166 (96.5)	131 (97.0)	35 (94.6)	0.83
Anticoagulation (n, %)	11 (6.4)	8 (5.9)	3 (8.1)	0.92
Statins (n, %)	166 (96.5)	129 (95.6)	37 (100)	0.42

\* $P < 0.05$  was considered statistically significant.

Abbreviations: mRS=modified Rankin Scale; AIS=acute ischemic stroke; TIA=transient ischemic attack; SBP=systolic blood pressure; DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; FBG=fasting blood glucose; TC=total cholesterol; TG=triglyceride; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Hcys=homocysteine; NIHSS=National Institutes of Health Stroke Scale; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.

**Table 2.** Sites of symptomatic stenoses on relevant arteries of patients finished 90-day follow-up

Sites of symptomatic stenoses	Total (n=172)
Intracranial segments (n, %)	124 (72.1)
Cervical segments (n, %)	27 (15.7)
Both intracranial and cervical segments (n, %)	21 (12.2)

**Table 3.** Correlations of atherosclerotic burden indices with 90-day unfavorable functional outcome in logistic regression analysis

Atherosclerotic burden indices	Crude OR (95% CI)	p value	Adjusted OR <sup>§</sup> (95% CI)	p value
IAB	1.16 (1.06-1.26)	0.001*	1.12 (0.99-1.27)	0.07
CAB	1.19 (1.06-1.35)	0.005*	1.15 (0.96-1.38)	0.14
ICAB	1.14 (1.07-1.22)	<0.001*	1.10 (1.00-1.21)	0.044*

\* $P < 0.05$  was considered statistically significant.

Abbreviations: OR=odds ratio; CI=confidence interval; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.

<sup>§</sup> Adjusting for age, sex, hypertension history, uric acid level, posterior circulation stroke proportion, NIHSS and mRS scores at admission.

**Table 4.** Correlations of atherosclerotic burden indices with NIHSS score at admission and 90-day mRS score

Atherosclerotic burden indices	NIHSS score at admission		90-day mRS score	
	<i>r</i> ( <i>p</i> value)	Partial <i>r</i> ( <i>p</i> value) <sup>§</sup>	<i>r</i> ( <i>p</i> value)	Partial <i>r</i> ( <i>p</i> value) <sup>§</sup>
IAB	0.219 (0.003)*	0.11 (0.16)	0.277 (<0.001)*	0.16 (0.045)*
CAB	0.137 (0.065)	-	0.182 (0.017)*	0.087 (0.28)
ICAB	0.236 (0.001)*	0.16 (0.047)*	0.302 (<0.001)*	0.17 (0.037)*

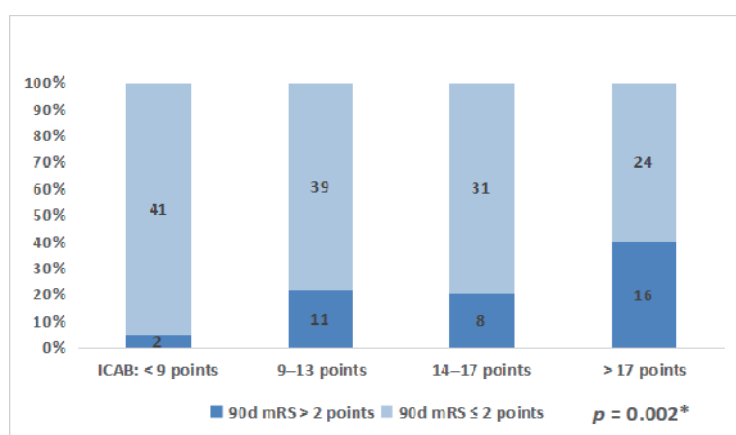
\**P*<0.05 was considered statistically significant.

Abbreviations: NIHSS=National Institutes of Health Stroke Scale; mRS=modified Rankin Scale; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.

The Pearson correlation analysis was used to calculate the correlation coefficient.

<sup>§</sup>The controlling factors included age, sex, hypertension and hyperlipidemia history, triglyceride and uric acid level, mRS score at admission, posterior circulation stroke proportion.

<sup>§</sup>The controlling factors included age, sex, hypertension history, uric acid level, NIHSS and mRS scores at admission, posterior circulation stroke proportion.

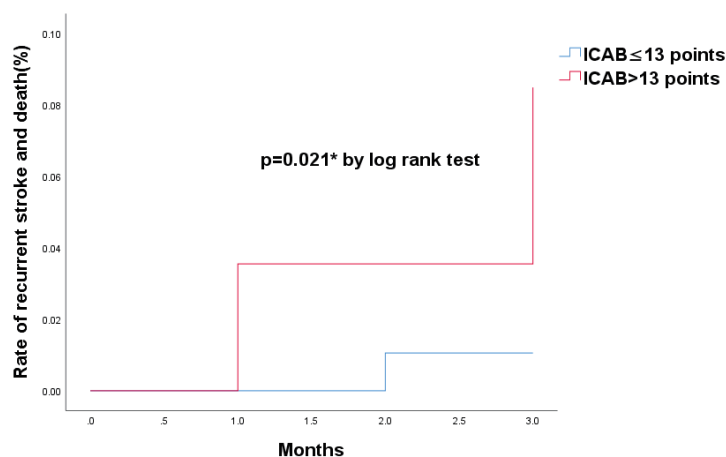


**Fig. 2.** Proportions of patients with 90-day unfavorable functional outcome in groups divided based on quartiles of ICAB

*p*-value was calculated by Chi-square test.

\**p*<0.05 was considered statistically significant.

Abbreviations: mRS=modified Rankin Scale; ICAB=intracranial and cervical atherosclerotic burden.



**Fig. 3.** Kaplan–Meier curves for recurrent stroke and death within 90-days in groups divided based on the mean of ICAB

\**p*<0.05 was considered statistically significant.

Abbreviation: ICAB=intracranial and cervical atherosclerotic burden.

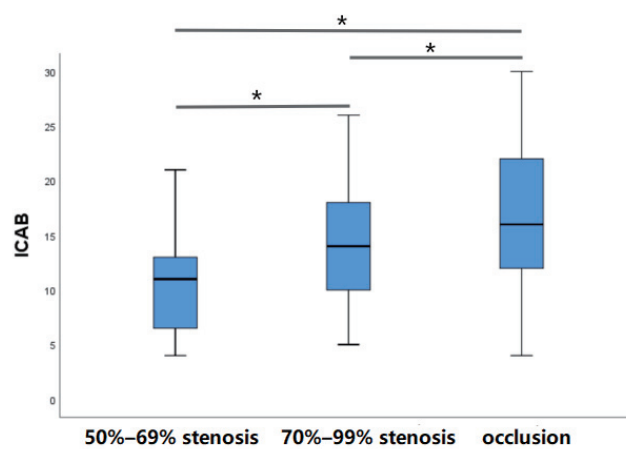
**Table 5.** Correlations of atherosclerotic burden indices and 90-day recurrent ischemic stroke/death in Cox regression analysis

Atherosclerotic burden indices	Adjusted HR <sup>§</sup> (95% CI)	<i>p</i> value
IAB	1.18 (0.99-1.39)	0.056
CAB	1.22 (0.94-1.59)	0.14
ICAB	1.16 (1.02-1.32)	0.029*

\* $P < 0.05$  was considered statistically significant.

Abbreviations: HR=hazard ratio; CI=confidence interval; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.

<sup>§</sup>Adjusted HR were calculated by adjusting for age, sex, fasting blood glucose level.

**Fig. 4.** ICAB of groups with different grades of the severest stenoses

The middle line of the box was the median. The upper and lower limits of the box were 25% and 75% quartile, respectively. The top bar was the maximum value, and the bottom bar was the minimum value.

\* $p < 0.05$  was considered statistically significant.

Abbreviation: ICAB=intracranial and cervical atherosclerotic burden.

Cox regression analysis, only ICAB (adjusted hazard ratio[HR]=1.16, 95%CI:1.02–1.32,  $p=0.029$ ) could independently predict recurrent ischemic stroke and death in 90-days after index stroke, after adjusting for age, sex, and clinical factor with  $p < 0.1$  in univariate Cox regression analysis (fasting blood glucose level, **Supplemental Table 1**) (**Table 5**).

### Correlations between AS Burden Indices and NIHSS Score at Admission

In the Pearson correlation analysis, ICAB ( $r=0.236$ ,  $p=0.001$ ) and IAB ( $r=0.219$ ,  $p=0.003$ ) were positively correlated with NIHSS score at admission, respectively. After controlling age, sex, and clinical factors with  $p < 0.1$  in comparisons between patients with mild stroke (NIHSS  $\leq 4$  points) and moderate-severe stroke (NIHSS  $> 4$  points) (hypertension and hyperlipidemia history, triglyceride and uric acid level, posterior circulation stroke proportion, mRS score at admission, **Supplemental Table 2**), only ICAB was positively correlated with

NIHSS score at admission ( $r=0.16$ ,  $p=0.047$ ) in partial correlation analysis (**Table 3**).

### Relationship of ICAB with the Severity and Extent of Cervicocephalic AS Lesions

All 181 patients were divided into three groups according to the grades of their severest stenoses: group 1 with 50%–69% stenosis, group 2 with 70%–99% stenosis, and group 3 with occlusion. ICAB significantly increased from group 1 to group 3 (**Fig. 4**).

The 181 patients were further dichotomized according to the mean (13 points) of ICAB. Patients with ICAB  $> 13$  points had more arterial segments with various grades of AS lesion than patients with ICAB  $\leq 13$  points (**Table 6**).

## Discussion

The present study found that ICAB could independently predict 90-day unfavorable functional

**Table 6.** Comparison of extent of cervicocephalic AS lesions in groups with different ICAB

Extent of cervicocephalic AS lesions	ICAB ≤ 13 points (n=95)	ICAB > 13 points (n=86)	P value
Number of segments with AS lesions [n, M (Q25, Q75)]	6 (4,8)	13 (10.8,14)	<0.001*
Number of segments with only AS plaque or < 50% stenosis [n, M (Q25, Q75)]	4 (2,7)	9 (6,11)	<0.001*
Number of segments with 50-69% stenosis [n, M (Q25, Q75)]	1 (0,1)	1 (0,2)	0.006*
Number of segments with 70-99% stenosis [n, M (Q25, Q75)]	0 (0,1)	1.5 (0,2)	<0.001*
Number of segments with occlusion [n, M (Q25, Q75)]	0 (0,0)	0 (0,1)	<0.001*

Abbreviations: AS=atherosclerosis; ICAB=intracranial and cervical atherosclerotic burden.

\*P<0.05 was considered statistically significant.

outcomes of patients with LAA stroke, whereas IAB and CAB had poorer predictive values than ICAB.

Previous studies merely focused on the effects of atherosclerotic steno-occlusive arteries on the functional outcome of patients with AICVD. We evaluated cervicocephalic AS condition in a semiquantitative method (AS condition ranging from no AS plaque to complete arterial occlusion were respectively scored 0–4 points), which might provide more information. Similarly, Sun P *et al.* quantified AS condition of all intracranial large arterial segments and found that the final score was associated with 1-year recurrent ischemic stroke in patients with AICVD<sup>24</sup>. However, this study did not evaluate AS condition of cervical arteries in the scoring. It did not analyze the correlation of the score with the functional outcome of study subjects. In the present study, both severity and extent of intracranial and cervical AS lesions were taken into account when “AS burden” of overall intracranial and cervical arteries (ICAB) was calculated, thereby leading to a relatively complete evaluation of overall cervicocephalic AS condition.

Lau AY *et al.* reported that the presence of multiple intracranial and concurrent cervical arterial steno-occlusion caused by AS were independently associated with the unfavorable 180-day functional outcome of patients with AICVD, respectively<sup>4</sup>. Lei C *et al.* also found that the presence of intracranial and coexisted intracranial and cervical arterial moderate-severe stenosis or occlusion caused by AS were independently associated with 90-day and 1-year unfavorable functional outcomes of patients with ischemic stroke, respectively<sup>6</sup>. These two studies demonstrated that cervicocephalic AS condition could independently predict the functional outcome of patients with AICVD. However, whether a whole-scope evaluation of cervicocephalic AS condition would be better at predicting the functional outcome of patients with AICVD than evaluation of intracranial or cervical AS condition alone was still unknown, especially in patients with LAA stroke.

Furthermore, these two studies only focused on the presence of steno-occlusive arteries in evaluating cervicocephalic AS conditions of patients with AICVD. However, different stenotic degree of arteries with AS, which were not evaluated in these two studies, were also correlated with functional outcomes of patients with AICVD<sup>25</sup>. Hence, these two studies might less completely evaluate the cervicocephalic AS condition of their study subjects, compared with our “AS burden” method that simultaneously reflected the severity and extent of AS. In the present study, ICAB were able to provide a stronger predictive value for 90-day unfavorable functional outcomes of patients with LAA stroke than IAB and CAB. The possible reasons were discussed as follows.

First, the present study found that only ICAB could independently predict 90-day recurrent ischemic stroke and death in multivariate Cox regression (Table 5). This result indicated that ICAB was more closely correlated with the risk of recurrent ischemic stroke and death within 3 months after the index stroke. This would lead to a 90-day unfavorable functional outcome, thus ICAB could provide stronger predictive value than IAB and CAB for 90-day unfavorable functional outcomes of patients with LAA stroke. Second, we found that only ICAB was independently, positively correlated with NIHSS score at admission (Table 4), which was also an independent predictor for the functional outcome of patients with stroke, as shown by previous research<sup>26</sup> and the present study. These results suggested that ICAB was more closely associated with early neurological deficit severity of patients with LAA stroke than IAB and CAB. These might partly help to explain the stronger relationship of ICAB with 90-day functional outcome. Finally, we analyzed the distribution of symptomatic stenoses of all patients who finished a 90-day follow-up. We found that intracranial and cervical symptomatic stenosis proportions were 72.1% and 15.7%, respectively, and 12.2% of patients had both intracranial and cervical symptomatic stenoses (Table



2). With luminal moderate-severe stenosis or occlusion, these symptomatic AS lesions would significantly affect the functional outcome of patients with LAA stroke in theory by decreasing the perfusion for infarct regions. Thus, an AS burden index that could fully incorporate the AS condition of all symptomatic stenoses might be better at predicting the functional outcome. Considering the aforementioned intra- and extracranial distribution patterns of these symptomatic stenoses, measuring ICAB would have a greater chance to take the AS condition of all symptomatic stenoses into account, compared with evaluating intracranial or cervical AS burden alone. It might provide a further reason why ICAB had some superiority in the functional outcome prediction of LAA stroke.

In our AS severity scoring, both severity and extent of cervicocephalic AS lesions were taken into account when ICAB was calculated. Patients with higher ICAB had more arterial segments with various grades of AS lesion than patients with lower ICAB (Table 6). We found that ICAB significantly increased with the increase of the grade of patients' severest stenoses (Fig. 4). These results indicated that ICAB could reflect both severity and extent of cervicocephalic AS condition as we expected.

The present study preliminarily demonstrated that ICAB could be considered a score for predicting the 90-day functional outcome of patients with LAA stroke. ICAB could predict the functional outcome more accurately than IAB and CAB. A whole-scope evaluation of cervicocephalic AS burden was essential for predicting the functional outcome of patients with LAA stroke and could help screen patients who had a higher risk of unfavorable functional outcome thus might need intensive monitoring and medical therapy.

The present study had some certain limitations. First, this study was a single-center study with relatively small sample size. Thus, our results are generalized to other populations with caution. Second, all patients' neurological deficits were relatively minor (mean NIHSS score at admission was 4 points). The majority (78.5%, 135/172) of patients had 90-day favorable functional outcomes. Therefore, the results of this study might not be applicable for patients with LAA stroke with severe neurological deficits. Third, this study mainly focused on the short-term functional outcome of patients with LAA stroke, and extended follow-up of these patients for their long-term prognosis should be administered.

## Conclusion

ICAB could independently predict 90-day

unfavorable functional outcomes of patients with LAA stroke, whereas IAB and CAB could not. ICAB could be used to reflect both severity and extent of cervicocephalic AS condition of patients with LAA stroke. A whole-scope evaluation of cervicocephalic AS burden might be essential for screening patients with LAA stroke who were more likely to have unfavorable functional outcomes.

## Acknowledgements

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## Conflict of Interest

None.

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**Supplemental Table 1.** Correlations of clinical factors with recurrent ischemic stroke/death in univariate Cox regression analysis

Clinical factors	Crude HR	95% CI	P value
Age, year	1.06	0.98-1.14	0.17
Male	1.55	0.37-6.48	0.55
Hypertension history	0.42	0.05-3.45	0.42
Diabetes mellitus history	0.70	0.18-2.81	0.62
Hyperlipidemia history	1.17	0.29-4.66	0.83
History of AIS or TIA	0.51	0.12-2.13	0.35
Smoking	5.55	0.68-45.13	0.11
Alcohol consumption	0.66	0.16-2.62	0.55
Obesity	0.32	0.08-1.34	0.12
SBP, mmHg	1.02	0.98-1.05	0.35
DBP, mmHg	1.00	0.95-1.06	0.98
HbA1c, %	0.90	0.55-1.46	0.66
FBG, mmol/L	1.22	0.99-1.50	0.059
TC, mmol/L	0.70	0.30-1.60	0.39
TG, mmol/L	0.69	0.25-1.90	0.48
LDL-C, mmol/L	0.49	0.16-1.49	0.21
HDL-C, mmol/L	0.24	0.01-5.23	0.37
Hcys, mmol/L	0.98	0.89-1.09	0.72
Uric acid, mmol/L	1.00	0.99-1.01	0.53
NIHSS score at admission, point	1.01	0.86-1.19	0.89
posterior circulation stroke	0.82	0.20-3.44	0.79
IAB, point	1.21	1.04-1.41	0.016*
CAB, point	1.18	0.96-1.44	0.12
ICAB, point	1.16	1.04-1.31	0.009*
Thrombolysis	21.15	0.00- >1000.00	0.73
Antiplatelet agent	0.05	0.00- >1000.00	0.73
Anticoagulation agent	0.43	0.05-3.51	0.43
Statins	0.05	0.00- >1000.00	0.73

\* $P < 0.05$  was considered statistically significant.

Abbreviations: HR=hazard ratio; CI=confidence interval; AIS=acute ischemic stroke; TIA=transient ischemic attack; SBP=systolic blood pressure; DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; FBG=fasting blood glucose; TC=total cholesterol; TG=triglyceride; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Hcys=homocysteine; NIHSS=National Institutes of Health Stroke Scale; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.

**Supplemental Table 2.** Comparisons between patients with mild stroke and moderate-severe stroke

Clinical factors	Total ( <i>n</i> =181)	NIHSS ≤ 4 points ( <i>n</i> =125)	NIHSS > 4 points ( <i>n</i> =56)	<i>P</i> value
Age (year, $\bar{x} \pm s$ )	60 ± 11	60.1 ± 10.6	59.8 ± 12	0.87
Male ( <i>n</i> , %)	130 (71.8)	91 (72.8)	39 (69.6)	0.66
Onset to arrival (day, $\bar{x} \pm s$ )	3.6 ± 2.1	3.7 ± 2.1	3.3 ± 1.9	0.17
Hypertension ( <i>n</i> , %)	136 (75.1)	103 (82.4)	33 (58.9)	0.001*
Diabetes mellitus ( <i>n</i> , %)	75 (41.4)	53 (42.4)	22 (39.3)	0.69
Hyperlipidemia ( <i>n</i> , %)	98 (54.1)	73 (58.4)	25 (44.6)	0.086
History of AIS or TIA ( <i>n</i> , %)	43 (23.8)	28 (22.4)	15 (26.8)	0.52
Smoking ( <i>n</i> , %)	79 (43.6)	54 (43.2)	25 (44.6)	0.86
Alcohol consumption ( <i>n</i> , %)	72 (39.8)	48 (38.4)	24 (42.9)	0.57
Obesity ( <i>n</i> , %)	30 (16.6)	20 (16.0)	10 (17.9)	0.76
SBP (mmHg, $\bar{x} \pm s$ )	145.9 ± 20.4	145.3 ± 20.2	147.2 ± 21.1	0.57
DBP (mmHg, $\bar{x} \pm s$ )	84.7 ± 12.5	84.6 ± 11.9	84.8 ± 14	0.92
HbA1c (% , $\bar{x} \pm s$ )	6.77 ± 1.69	6.80 ± 1.75	6.71 ± 1.57	0.76
FBG (mmol/L, $\bar{x} \pm s$ )	6.36 ± 2.45	6.29 ± 2.52	6.52 ± 2.28	0.57
TC (mmol/L, $\bar{x} \pm s$ )	3.92 ± 1.00	3.95 ± 1.02	3.83 ± 0.96	0.44
TG (mmol/L, $\bar{x} \pm s$ )	1.68 ± 1.05	1.77 ± 1.09	1.48 ± 0.95	0.098
LDL-C (mmol/L, $\bar{x} \pm s$ )	2.31 ± 0.83	2.33 ± 0.84	2.27 ± 0.82	0.69
HDL-C (mmol/L, $\bar{x} \pm s$ )	1.05 ± 0.29	1.07 ± 0.28	1.01 ± 0.30	0.25
Hcys (mmol/L, $\bar{x} \pm s$ )	16.24 ± 9.60	16.53 ± 9.58	15.58 ± 9.70	0.56
Uric acid (mmol/L, $\bar{x} \pm s$ )	313.3 ± 98.7	329.35 ± 97.05	277.25 ± 93.52	0.001*
mRS score at admission (point, $\bar{x} \pm s$ )	1.9 ± 1.4	1.3 ± 0.9	3.3 ± 1.1	<0.001*
posterior circulation stroke ( <i>n</i> , %)	76 (42)	61 (48.8)	15 (26.8)	0.006*
IAB (point, $\bar{x} \pm s$ )	10 ± 4.6	9.2 ± 4.3	11.8 ± 4.8	0.001*
CAB (point, $\bar{x} \pm s$ )	3.5 ± 2.9	3.3 ± 2.6	4.1 ± 3.4	0.073
ICAB (point, $\bar{x} \pm s$ )	13.6 ± 5.9	12.5 ± 5.3	15.9 ± 6.6	<0.001*

\**P*<0.05 was considered statistically significant.

Abbreviations: NIHSS=National Institutes of Health Stroke Scale; AIS=acute ischemic stroke; TIA=transient ischemic attack; SBP=systolic blood pressure; DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; FBG=fasting blood glucose; TC=total cholesterol; TG=triglyceride; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Hcys=homocysteine; mRS=modified Rankin Scale; IAB=intracranial atherosclerotic burden; CAB=cervical atherosclerotic burden; ICAB=intracranial and cervical atherosclerotic burden.