

## Risk Factor Stratification for Intracranial Stenosis in Taiwanese Patients With Cervicocerebral Stenosis

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**Background**—Intracranial stenosis (ICS) is a major determinant of ischemic stroke in Asians. We determined the clinical significance of different risk factors and the role of ICS in Taiwanese patients with varied distributions of cervicocerebral stenosis.

**Methods and Results**—Presence of extracranial carotid stenosis (ECS,  $\geq 70\%$ ) and ICS ( $>50\%$ ) was examined in 13 539 patients using ultrasonography and magnetic resonance angiography, respectively. Seven hundred thirty-three patients with non-ECS/ICS ( $n=372$ ), isolated ICS ( $n=112$ ), isolated ECS ( $n=121$ ), or combined ECS/ICS (CEIS,  $n=128$ ) were selected. Prevalence of ischemic stroke in each group was compared, and risk factors for stenosis were determined. The area under the receiver operating characteristic curve for each risk factor was calculated. Prevalence of ischemic stroke was highest in patients with CEIS (odds ratio 15.86;  $P<0.001$ ), followed in decreasing order by those with isolated ICS (odds ratio 7.16;  $P<0.001$ ), isolated ECS (odds ratio 1.77;  $P=0.011$ ), and non-ECS/ICS. Multivariate logistic regression analysis revealed that hypertension, coronary artery disease, and smoking were risk factors for isolated ECS; hypertension, diabetes mellitus, coronary artery disease, and smoking were risk factors for isolated ICS; and diabetes mellitus, coronary artery disease, and smoking were risk factors for CEIS. Smoking, diabetes mellitus, and coronary artery disease were the greatest contributors to CEIS, isolated ICS, and isolated ECS, respectively.

**Conclusions**—CEIS was associated with higher odds of ischemic stroke compared with isolated ICS and isolated ECS. Smoking and diabetes mellitus, major determinants of CEIS and isolated ICS, should be targeted in therapeutic strategies to reduce the risk of ischemic stroke. (*J Am Heart Assoc.* 2015;4:e002692 doi: 10.1161/JAHA.115.002692)

**Key Words:** atherosclerosis • carotid arteries • risk factors • stenosis • stroke

Intracranial stenosis (ICS) is a well-known pathogenic factor for ischemic stroke. Previous studies have reported that the correlation of ICS and ischemic stroke is more prominent in Asians; in contrast, extracranial carotid stenosis

(ECS) is more prevalent in whites.<sup>1–3</sup> ICS is thought to be the cause of 33% to 84% of ischemic strokes in Asian populations<sup>4</sup> and 8% to 10% of strokes in North America.<sup>5,6</sup> Additionally, the annual stroke recurrence rate in patients with symptomatic ICS may be as high as 10% to 24%, even for patients receiving medical therapy<sup>7</sup>; on the other hand, the stroke recurrence rate is 7% to 13% in patients with symptomatic ECS who are treated with the appropriate medication.<sup>8,9</sup>

Variance in the distribution of cerebral atherosclerosis in different races is thought to be a result of differences in vascular risk factor profiles, lifestyles, and genetic susceptibility.<sup>6,10,11</sup> Improving our understanding of the risk factors contributing to ICS in Asians with ischemic stroke is critical for the development and implementation of appropriate treatment strategies. While several vascular risk factors have been identified in ICS,<sup>6,12–14</sup> these risk factors have varied among studies, possibly due to differences in study populations and methodologies. Therefore, in this study, we aimed to investigate the risk factor stratification of ICS in Taiwanese patients with different distributions of cervicocerebral stenosis.

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## Methods

This retrospective cohort study was carried out within the certified Neurovascular Ultrasound Laboratory at Tri-Service General Hospital, Taipei, Taiwan. Between January 1, 2006, and December 31, 2012, a total of 13 539 consecutive patients were referred to the Neurovascular Ultrasound Laboratory due to stroke-related symptoms in 7191 (53.1%), dizziness or syncope in 5205 (38.4%), coronary artery disease (CAD) or high risk for stroke in 842 (6.2%), cancer in 29 (0.2%), and other conditions or symptoms in 272 (2.0%). All patients were screened for carotid stenosis by 3 certified sonographers. Each individual underwent color-coded duplex ultrasonography of the cervical and retrobulbar vessels with the use of an ATL HDI 5000 ultrasound system (Philips) with an L12-5 linear 38-mm transducer. Degree of stenosis was determined according to the laboratory's ultrasound criteria,<sup>15</sup> which have been validated to correspond to the degree of stenosis on cerebral angiography measured by using the European Carotid Surgery Trial method,<sup>16</sup> along with carotid endarterectomy findings. The entire process for each patient was recorded by using a digital video system, and examination data were reviewed by 2 neurovascular specialists. Written consent was provided by every patient before the examinations. The study was approved by the Institutional Review Board for Human Studies of the Tri-Service General Hospital (approval No. 2-101-05-030).

## Selection of Study Patients With ECS or ICS

Among the 13 539 patients screened in this study, 9408 had <30% stenosis of the extracranial carotid artery (ECA), including the common carotid and internal carotid arteries (ICAs) on both sides, while 353 had  $\geq 70\%$  stenosis of the ECA, including unilateral or bilateral lesions. After exclusion of patients who did not undergo magnetic resonance imaging/magnetic resonance angiography (MRI/MRA), 2606 patients with stenosis of the ECA of <30% and 264 patients with stenosis of the ECA of  $\geq 70\%$  remained. Based on propensity scores that used age, sex, and examination dates as covariates, 528 patients were selected from the 2606 patients with stenosis of the ECA of <30%, with a ratio of 2:1, to match the 264 patients with stenosis of the ECA of  $\geq 70\%$ . All patients received detailed structural surveys for vascular risk factors in the neurovascular examination laboratory. After the exclusion of patients with incomplete data or risk factors that were not associated with atherosclerosis, such as cardiogenic embolism, coagulopathy, dissection, Takayasu disease, cancer, and extracranial-to-intracranial bypass, a total of 733 patients (484 with stenosis of the ECA of <30% and 249 with stenosis of the ECA of  $\geq 70\%$ ) were

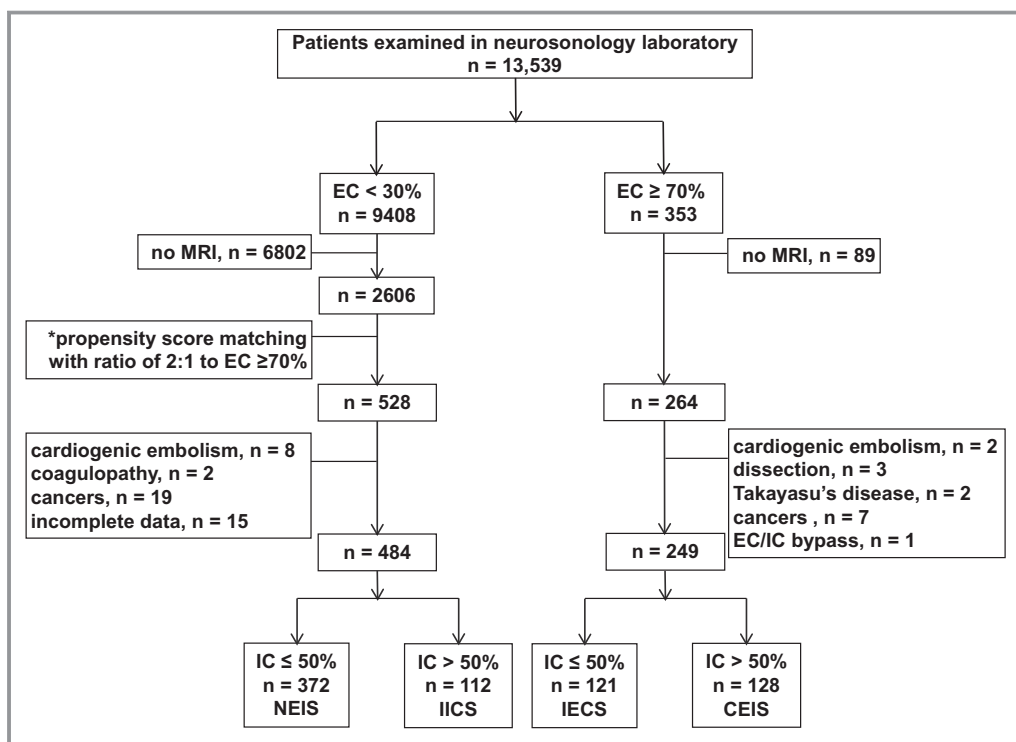
recruited for investigation of stenosis of the ICA (Figure 1). Grade of ICS was determined by using brain MRA. All intracranial vessels were evaluated, and severity of ICS was classified as normal to mild stenosis ( $\leq 50\%$ ) or moderate stenosis to occlusion ( $>50\%$ ), as described in previous reports.<sup>15,17,18</sup> Consequently, a total of 733 patients were classified into 4 subgroups: non-ECS/ICS (NEIS; ECS <30% and ICS  $\leq 50\%$ ; n=372), isolated ICS (IICS; ECS <30% and ICS  $>50\%$ ; n=112), isolated ECS (IECS; ECS  $\geq 70\%$  and ICS  $\leq 50\%$ ; n=121), and combined ECS/ICS (CEIS; ECS  $\geq 70\%$  and ICS  $>50\%$ ; n=128).

## Demographic Features and Clinical Characteristics

Ischemic stroke was evaluated by using brain MRI. All ischemic stroke types were included except for cardioembolism and nonatherosclerotic etiologies. Acute, recurrent, and old ischemic stroke were defined by using different MRI modalities, including T1/T2-weighted imaging, diffusion-weighted imaging, apparent diffusion coefficient, and fluid-attenuated inversion recovery. Patients were diagnosed as having acute first-ever stroke, recurrent stroke, or old stroke according to the presence of typical stroke symptoms and positive brain MRI findings. Demographic features and risk factors were recorded using a structured checklist that included hypertension (HTN), diabetes mellitus (DM), CAD, hypercholesterolemia, and hyperuricemia, defined as described previously.<sup>17</sup> Smoking habit was defined as being a current smoker or having quit smoking <6 months earlier, while alcohol drinking was classified as either nonheavy (<1 drink per day for women or <2 drinks per day for men) or heavy (>1 drink per day for women or >2 drinks per day for men).

## Statistical Analysis

Continuous variables were presented as mean $\pm$ SD values, while categorical variables were expressed as numbers and percentages. Univariate logistic regression was performed to determine the risk of ischemic stroke in patients with IECS, IICS, and CEIS compared with that in patients with NEIS and to estimate unadjusted odds ratios (ORs) and corresponding 95% CIs. Multivariate logistic regression was performed to identify significant independent risk factors for IECS, IICS, and CEIS compared with NEIS and to estimate ORs and corresponding 95% CIs. Discrimination of significant risk factors for IECS, IICS, and CEIS was assessed by using area under the receiver operating characteristic (ROC) curves (AUC). An ROC curve area of 0.5 indicated no discrimination, whereas an ROC curve area of 1.0 indicated perfect discrimination. Statistical analyses were performed with SPSS



**Figure 1.** Study patient selection. \*Age, sex, and examination dates were used as covariates to compute propensity score. CEIS indicates combined extracranial/intracranial stenosis; EC, extracranial carotid artery; IC, intracranial artery; IECS, isolated extracranial stenosis; IICS, isolated intracranial stenosis; MRI, magnetic resonance imaging; NEIS, nonextracranial/intracranial stenosis.

version 19 (SPSS). Values were considered statistically significant at  $P < 0.05$ .

## Results

A total of 13 539 patients were screened for ECS in the neurosonology laboratory (Figure 1). Of these patients, 9408 (69.5%) were found to have no stenosis (ECA <30%), whereas 353 (2.6%) had ECS. Patients with ECS had higher rates of concomitant ICS compared with patients without ECS (51.4% [128/249 patients] versus 23.1% [112/484 patients]). According to brain MRA findings in patients with ICS (CEIS, n=128; IICS, n=112), 123 patients (96.1%) with CEIS had ICS in the anterior circulation; 81 (63.3%) had an isolated lesion in the anterior circulation, and 42 (32.8%) had lesions in both the anterior and posterior circulation. Eighty-three patients (74.1%) with IICS had ICS in the anterior circulation; 46 (41.1%) had an isolated lesion in the anterior circulation, and 37 (33.0%) had lesions in both the anterior and posterior circulation. Patients with CEIS had a significantly higher incidence of ICS in the anterior circulation compared with those with IICS ( $P < 0.001$ ).

Table 1 and Figure 2 show that the prevalence of total ischemic stroke was highest in the CEIS group (95.3%, OR 15.86, 95% CI, 6.81 to 36.91,  $P < 0.001$ ), followed in

decreasing order by the IICS (90.2%, OR 7.16, 95% CI, 3.72 to 13.79,  $P < 0.001$ ), IECS (69.4%, OR 1.77, 95% CI, 1.14 to 2.74,  $P = 0.011$ ), and NEIS (56.2%, reference) groups.

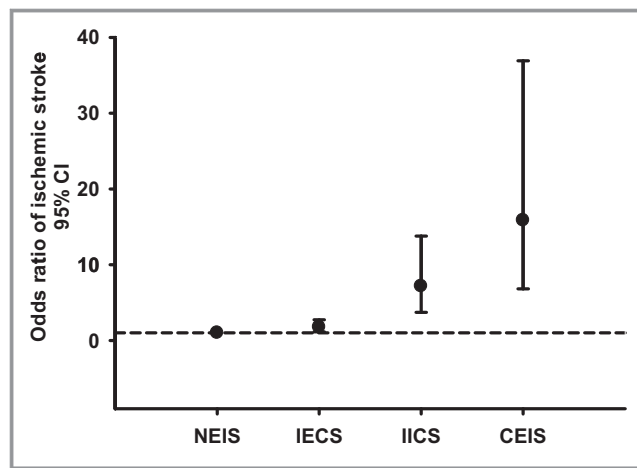
Risk factors for different distributions of cervicocerebral stenosis are shown in Table 2. Multivariate logistic regression analysis revealed that CAD (OR 3.32, 95% CI, 2.01 to 5.51,  $P < 0.001$ ), HTN (OR 2.40, 95% CI, 1.34 to 4.29,  $P = 0.003$ ), and smoking (OR 1.75, 95% CI, 1.05 to 2.92,  $P = 0.033$ ) were significant risk factors for IECS. DM (OR 2.50, 95% CI, 1.59 to 3.96,  $P < 0.001$ ), smoking (OR 2.26, 95% CI, 1.34 to 3.82,  $P = 0.002$ ), HTN (OR 2.21, 95% CI, 1.24 to 3.94,  $P = 0.007$ ), and CAD (OR 2.03, 95% CI, 1.14 to 3.60,  $P = 0.016$ ) were significant risk factors for IICS. Smoking (OR 4.41, 95% CI, 2.70 to 7.22,  $P < 0.001$ ), CAD (OR 3.30, 95% CI, 1.92 to 5.69,  $P < 0.001$ ), and DM (OR 1.77, 95% CI, 1.10 to 2.83,  $P = 0.018$ ) were significant risk factors for CEIS.

Figure 3 shows ROC curves demonstrating the sensitivity and specificity of different risk factors with respect to prediction of IECS, IICS, and CEIS. For prediction of IECS, the AUCs of CAD, HTN, and smoking were 0.619, 0.586, and 0.552, respectively. DM was the best factor for predicting IICS, with an AUC of 0.618, followed by HTN, smoking, and CAD (AUCs of 0.580, 0.566, and 0.548, respectively). Smoking was the best factor for predicting CEIS, with an

**Table 1.** Odds Ratios of Ischemic Stroke in Patients With Different Distributions of Cervicocerebral Stenosis

	NEIS (n=372)	IECS (n=121)	OR (95% CI)	P Value	IICS (n=112)	OR (95% CI)	P Value	CEIS (n=128)	OR (95% CI)	P Value
Ischemic stroke	209 (56.2)	84 (69.4)	1.77 (1.14–2.74)	0.011	101 (90.2)	7.16 (3.72–13.79)	<0.001	122 (95.3)	15.86 (6.81–36.91)	<0.001
Acute, first-ever	113 (30.4)	29 (24.0)	0.72 (0.45–1.16)	0.177	59 (52.7)	2.55 (1.66–3.93)	<0.001	64 (50.0)	2.29 (1.52–3.46)	<0.001
Recurrent	53 (14.2)	12 (9.9)	0.66 (0.34–1.29)	0.224	26 (23.2)	1.82 (1.08–3.08)	0.026	31 (24.2)	1.92 (1.17–3.17)	0.010
Old	43 (11.6)	43 (35.5)	4.22 (2.59–6.88)	<0.001	16 (14.3)	1.28 (0.69–2.36)	0.440	27 (21.1)	2.05 (1.20–3.48)	0.008

Values are expressed as n (%). Statistically significant differences were determined using univariate logistic regression. CEIS indicates combined extracranial/intracranial stenosis; IECS, isolated extracranial stenosis; IICS, isolated intracranial stenosis; NEIS, nonextracranial/intracranial stenosis, OR odds ratio.



**Figure 2.** Odds ratio of ischemic stroke in IECS, IICS, and CEIS groups. The odds ratio of ischemic stroke was highest in the CEIS group (OR 15.86, 95% CI 6.81 to 36.91), followed in decreasing order by the IICS (OR 7.16, 95% CI 3.72 to 13.79), IECS (OR 1.77, 95% CI 1.14 to 2.74), and NEIS (reference) groups. CEIS indicates combined extracranial/intracranial stenosis; IECS, isolated extracranial stenosis; IICS, isolated intracranial stenosis; NEIS, nonextracranial/intracranial stenosis, OR odds ratio.

AUC of 0.657, followed by CAD and DM (AUCs of 0.589 and 0.560, respectively).

### Discussion

Our study demonstrated that CEIS was more strongly associated with odds of ischemic stroke than were IICS and IECS in Taiwanese patients. Patients with IECS had lower odds of ischemic stroke compared with patients with IICS or CEIS. Moreover, while CAD was significantly associated with IECS, DM was the major determinant of IICS. Smoking, being a common risk factor for IECS, IICS, and CEIS, was the most important contributor to CEIS. These data provide important insights into the risk factors associated with ICS in Taiwanese patients.

Angiographic and pathologic evidence has shown that racial and ethnic differences exist in the distribution of cervicocerebral stenosis in patients with ischemic stroke.<sup>1</sup> ICS is the most common vascular lesion in Asians with ischemic stroke.<sup>2–4</sup> The estimated prevalence of middle cerebral artery stenosis among asymptomatic Asian patients ranges from 7.2% to 29.6%, while Asian patients with ischemic stroke have a higher ICS incidence of 33% to 84%.<sup>4,19</sup> Further, concurrent atherosclerosis of intracranial and extracranial vessels is not uncommon in Asian populations<sup>13,20–22</sup>; in fact, ≈20% to 50% of patients with ECS are reported to also have ICS.<sup>22–24</sup> In this study, we found that 51.4% of patients with ECS had concurrent ICS. Compared with the IICS and IECS groups, the CEIS group had the highest prevalence of

**Table 2.** Multivariate Logistic Regression Analysis for Vascular Risk Factors in Patients With Different Distributions of Cervicocerebral Stenosis

	NEIS (n=372)	IECS (n=121)	aOR (95% CI)	P Value	IICS (n=112)	aOR (95% CI)	P Value	CEIS (n=128)	aOR (95% CI)	P Value
Male	301 (80.9)	97 (80.2)			88 (78.6)			99 (77.3)		
Age, mean±SD, y	71.1±13.4	73.1±11.3			72.4±11.6			70.9±11.6		
HTN	253 (68.0)	103 (85.1)	2.40 (1.34–4.29)	0.003	94 (83.9)	2.21 (1.24–3.94)	0.007	99 (77.3)	1.44 (0.85–2.43)	0.176
DM	98 (26.3)	36 (29.8)	1.03 (0.63–1.68)	0.912	56 (50.0)	2.50 (1.59–3.96)	<0.001	49 (38.3)	1.77 (1.10–2.83)	0.018
CAD	47 (12.6)	44 (36.4)	3.32 (2.01–5.51)	<0.001	25 (22.3)	2.03 (1.14–3.60)	0.016	39 (30.5)	3.30 (1.92–5.69)	<0.001
H/C	106 (28.5)	51 (42.1)	1.51 (0.95–2.39)	0.080	32 (28.6)	0.80 (0.48–1.33)	0.392	46 (35.9)	1.09 (0.68–1.76)	0.714
Hyperuricemia	41 (11.0)	27 (22.3)	1.65 (0.92–2.96)	0.093	8 (7.1)	0.48 (0.21–1.12)	0.089	29 (22.7)	1.74 (0.96–3.16)	0.070
Smoking	84 (22.6)	40 (33.1)	1.75 (1.05–2.92)	0.033	40 (35.7)	2.26 (1.34–3.82)	0.002	69 (53.9)	4.41 (2.70–7.22)	<0.001
Alcohol drinking										
Nonheavy	35 (9.4)	22 (18.2)	1.73 (0.90–3.34)	0.102	15 (13.4)	1.06 (0.51–2.22)	0.872	29 (22.7)	1.45 (0.77–2.73)	0.245
Heavy	20 (5.4)	3 (2.5)	0.50 (0.14–1.81)	0.291	5 (4.5)	0.66 (0.23–1.95)	0.455	8 (6.3)	0.90 (0.36–2.25)	0.820

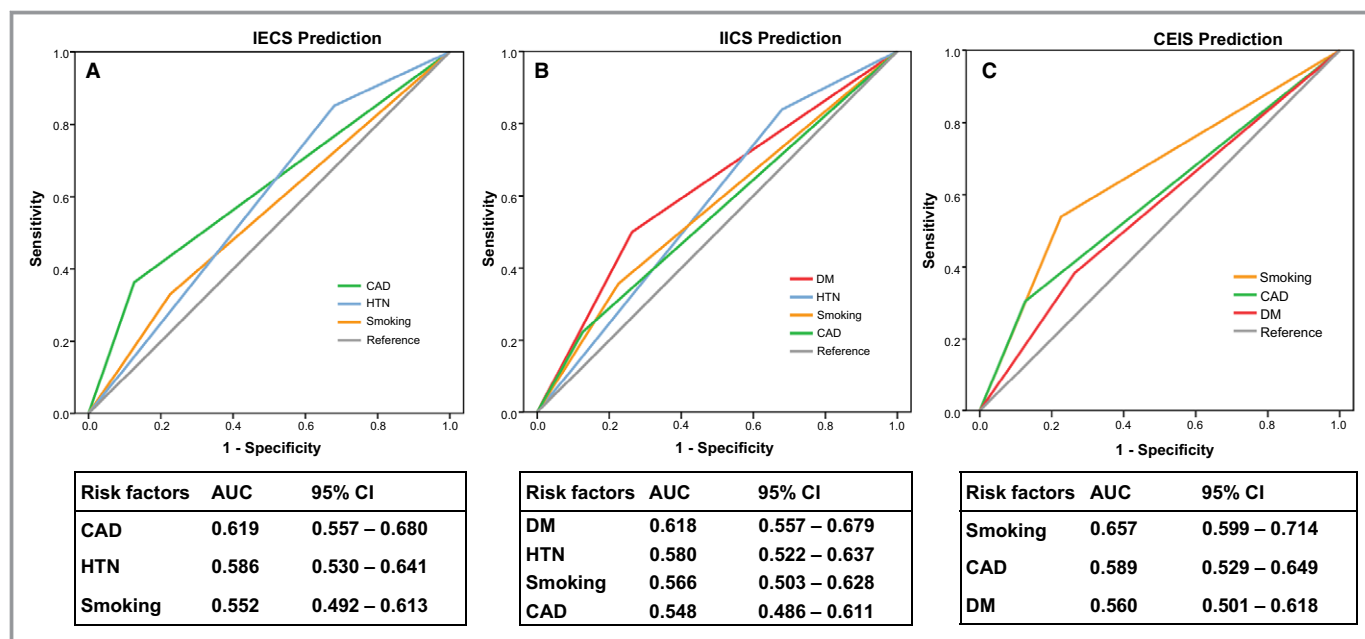
Values are expressed as n (%) unless otherwise noted. Statistically significant differences were determined using multivariate logistic regression after adjusting for other factors. aOR indicates adjusted odds ratio; CAD, coronary artery disease; CEIS, combined extracranial/intracranial stenosis; DM, diabetes mellitus; H/C, hypercholesterolemia; HTN, hypertension; IECS, isolated extracranial stenosis; IICS, isolated intracranial stenosis; NEIS, nonextracranial/intracranial stenosis.

ischemic stroke. Moreover, IICS was more significantly associated with ischemic stroke compared with IECS. All of these findings are in agreement with those of previous studies showing that CEIS is associated with the highest rate of stroke and poor prognoses<sup>20</sup> and that ICS has worse prognoses than ECS in Asian populations.<sup>2,10–12,14</sup> Recently, one study found a much higher prevalence of ICS in Europeans,<sup>25</sup> suggesting that ICS-related stroke is a major problem worldwide and is likely the most common stroke subtype.

Several risk factors, such as age, HTN, hyperlipidemia, metabolic syndrome, smoking, and DM, are regarded as major contributors to ICS.<sup>1,6,12–14</sup> In particular, DM has been identified as a common vascular risk factor for ICS, even in different races.<sup>6,14,21,25,26</sup> After multivariate logistic regression analysis, our study showed that DM was the most important determinant of IICS and an independent risk factor for both IICS and CEIS but not for IECS (Table 2, Figure 3). The mechanisms through which DM contributes preferentially to the pathogenesis of ICS rather than ECS remain unclear. However, the distinct structures between extracranial and intracranial arteries may be involved. Intracranial arteries are muscular-type arteries with few elastic fibers and greater antioxidant enzyme activity.<sup>27</sup> Risk factors for ICS, such as DM, may be associated with reduced antioxidant capacity and increased oxidative stress, resulting in endothelial dysfunction and increased inflammation to accelerate atherogenesis.<sup>27</sup> However, further research is needed to investigate the pathologic mechanisms responsible for the differential effects of DM on ICS and ECS. Given the poor prognoses in patients with ICS,<sup>28</sup> particularly in Asian populations, aggressive control of DM is very important for the prevention of IICS- and CEIS-related ischemic stroke.

We demonstrated that smoking was a common risk factor for IECS, IICS, and CEIS (Table 2). Moreover, smoking was the most important contributor to CEIS (Figure 3). A previous study demonstrated that both past and current smoking (passive and active) are associated with carotid atherosclerosis.<sup>29</sup> Additionally, there is a significant dose–response relationship between pack-years of smoking and severity of stenosis.<sup>30</sup> Given the high smoking rates in Asian countries,<sup>31</sup> immediate action is needed to increase public and political awareness of this issue for better tobacco control.

Notably, CAD was found to be significantly associated with IECS, IICS, and CEIS and was the best predictor for IECS. CAD is thought to be associated with the same pathologic mechanism of atherosclerosis as that seen in cervicocerebral vessel stenosis. Previous studies have shown that the degree of carotid stenosis is significantly related to the extent of CAD.<sup>32,33</sup> Although our study showed that the association between IECS and ischemic stroke was far less significant than that between IICS or CEIS and ischemic stroke, the



**Figure 3.** Receiver operating characteristic curve, demonstrating the associations of risk factors and prediction of IECS, IICS, and CEIS. A, CAD was the most predictive factor (highest AUC value) for IECS, followed in decreasing order by HTN and smoking. B, DM was the most predictive factor for IICS, followed in decreasing order by HTN, smoking, and CAD. C, Smoking was the most predictive factor for CEIS, followed in decreasing order by CAD and DM. AUC indicates area under the receiver operating characteristic curve; CAD, coronary artery disease; CEIS, combined extracranial/intracranial stenosis; DM, diabetes mellitus; HTN, hypertension; IECS, isolated extracranial stenosis; IICS, isolated intracranial stenosis.

significance of IECS in clinical practice is still relevant. Based on our results, which showed a close correlation between CAD and IECS, patients with ECS should undergo detailed examinations for presence of CAD to facilitate early diagnosis and treatment, potentially reducing CAD-related morbidity and mortality.

This study provided strong evidence in a large patient pool ( $n=13\ 539$ ), and all included patients were strictly evaluated by using color-coded duplex ultrasonography and brain MRI/MRA. Additionally, we enrolled 4 distinct patient groups: CEIS, IICS, IECS, and NEIS. This allowed for clear identification of the risk factors for each distribution of atherosclerosis. However, when interpreting data from an institutional series, the limitations of a retrospective analysis, such as patient selection biases as well as lack of a temporal relationship and adequate outcome assessment, must be considered. We used propensity scores with age and sex as covariates to match the patients. Therefore, the impact of age and sex on distribution of atherosclerosis could not be evaluated. Most of the patients referred for color-coded duplex ultrasonography were symptomatic suspect of relating to a vascular lesion, which may reflect the high prevalence of ischemic stroke in our population. Moreover, patients who did not undergo an MRI/MRA study were excluded, which could influence the results regarding prevalence of ICS and ischemic stroke. Meanwhile, it is possible that some patients experienced a stroke after

ECS or ICS, and then a new lesion developed after the stroke. However, duration from onset of stroke to date of examination was not recorded in this study.

Some diseases have been proved to be independent predictors for cardiovascular disorders<sup>34,35</sup> but were not discussed in this study. For example, obstructive sleep apnea and chronic obstructive pulmonary disease are related to a systemic inflammatory condition and are significantly associated with cardiovascular events.<sup>34</sup> Dolicho-carotids, an anatomic variation of cervical ICA, are also a relative risk factor for stroke.<sup>35</sup> Some medications have been linked to risk control against atherosclerotic progression. Therefore, history of medication use, including drug types and treatment durations, may be an influential factor for the varied distribution of cervicocranial vessel lesions. Future clinical trials are warranted to test the benefit of medication against vascular progression and for better clinical outcomes. This study population was hospital based rather than community based; thus, generalization of the results may be limited. In addition, MRA may overestimate stenosis of the major arteries. Conventional digital subtraction angiography is still the gold standard for confirming cervicocerebral stenosis. Finally, embolic disease could not be completely excluded in this study. Embolic occlusion with partial recanalization can angiographically resemble stenosis.

## Conclusion

In this study, we found that patients with CEIS had the highest odds of ischemic stroke. Moreover, patients with CEIS or IICS had higher odds of ischemic stroke than those with IECS. The identification of risk factors contributing to the varied distribution of cervicocerebral stenosis in this study may provide important insights into appropriate clinical practices and methods. Patients with newly diagnosed DM may benefit from undergoing advanced neuroimaging or neurosonology tests to screen for ICS. Smoking, which was a common risk factor for CEIS, IICS, and IECS, should be strictly controlled. Patients with ECS should undergo detailed examinations for the presence of CAD. Early identification of these risk factors and aggressive management are essential for reducing the risk of ischemic stroke and improving outcomes.

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## Disclosures

None.

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