ECAS progression score: a web-based model to predict progression of extracranial carotid artery stenosis

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ABSTRACT

**Background and purpose:** To develop and validate a risk model (Extracranial Carotid Artery Stenosis progression score, ECAS-PS) and to predict risk of ECAS progression.

**Methods:** The ECAS-PS was developed based on the Renqiu Stroke Screening Study (RSSS), in which eligible participants were randomly divided into derivation (60%) and validation (40%) cohorts. ECAS at baseline and follow-up was diagnosed by carotid duplex ultrasound according to the published criteria. ECAS progression was defined as an increase in ECAS >50% for those with a baseline of <50% or as an increase to a higher category of stenosis if the baseline stenosis was ≥50%. Independent predictors of ECAS progression were obtained using multivariable logistic regression. The area under the receiver operating characteristic curve (AUROC) and the Hosmer–Lemeshow test were used to assess model discrimination and calibration.

**Results:** A total of 4111 participants were included and the mean age was 64.3. A total number of 29 (0.7%), 24 (0.6%) and 48 (1.2%) patients progressed during 2-year follow-up for left, right and bilateral (either left or right) carotid artery, respectively. The ECAS-PS was developed from a set of predictors of ECAS progression. The ECAS-PS demonstrated good discrimination in both the derivation and validation cohorts (AUROC range: 0.824–0.917). The Hosmer–Lemeshow tests of ECAS progression score were not significant in the derivation and validation cohorts (all P > 0.05).

**Conclusion:** The ECAS progression score is a valid model for predicting the risk of ECAS progression. Further validation of the ECAS-PS in different populations and larger samples is warranted.

INTRODUCTION

Extracranial carotid artery stenosis (ECAS) is a well-documented and modifiable risk factor for ischemic stroke [1]. Its prevalence ranges from 0.1% to 7.5% in the general population and is highest in the older population [2,3].

Benefit from carotid endarterectomy (CEA) in ECAS was demonstrated in the North American Symptomatic Carotid Endarterectomy Trial [4], European Carotid Surgery Trial [5], Veterans Affairs Trials [6], Asymptomatic Carotid Atherosclerosis Study [7] and Asymptomatic Carotid Surgery Trial [8]. A pooled analysis of these trials has demonstrated an absolute risk reduction of 4.6% for symptomatic patients with moderate (>50%) ECAS and 16% for those with severe (≥70%) ECAS [9]. Meanwhile, SAPPHIRE [10] and CREST [11] trials showed that carotid angioplasty and stenting (CAS) was not inferior to CEA.

Studies indicated that ECAS progression increases steadily with time [12,13]. Thus, predicting the potential risk of ECAS progression is important for individualized stroke prevention, especially for those patients whose degree of stenosis does not initially warrant CEA or CAS. Previous studies have identified some risk factors of carotid atherosclerosis, such as age [14–18], gender [16,18], history of vascular disease [16–19], hypertension [14–16,19], hyperlipidemia [14,16–20], diabetes mellitus [16], cigarette smoking [14–17,19], height [18,21], C-reactive protein (CRP) [22,23], high-sensitivity CRP [20,24], cystatin C [25] and interleukin-23 [26]. In addition, some studies indicated that history of hypertension [27], cigarette smoking [27,28], blood pressure [27],...
LDL level [27,29], baseline ECAS status [13,27,30], interleukin-6 and interleukin-10 [31] and microRNAs [32] were significantly associated with ECAS progression. These risk factors could be used to establish a risk model for predicting the potential risk of ECAS progression.

In the study, we aimed to develop and validate a risk model (Extracranial Carotid Artery Stenosis Progression Score, ECAS-PS) to predict the potential risk of ECAS progression.

**Methods**

**Study population**

The derivation and validation cohorts originated from the Renqiu Stroke Screening Study (RSSS), which was a population-based prospective cohort study in Renqiu city (Hebei province, China) [18]. From May 2012 to October 2012, a random sample of subjects, age between 60 and 70 years, living in the Renqiu city was selected for the study. In the reference population, there are approximately 132,000 persons of this age. Subjects with severe chronic or terminal illnesses and those who were institutionalized were excluded. Each subject was assessed by physical examination, blood tests and carotid duplex ultrasound at baseline and annual follow-up for two years (Supplementary Figure 1). For this study, only those patients who completed a two-year follow-up were included. The study was performed according to the Guidelines of the World Medical Association Declaration of Helsinki and approved by the institutional review board at Kangji hospital (Renqiu city, Hebei Province, China). Informed consent was obtained from all participants.

**Physical examination and blood test**

All participants had a physical examination with the determination of height, weight, waist circumference (midway between the lowest rib and the iliac crest), heart rate and blood pressure (the mean of the last two measurements after three determinations 5 min apart). Standard laboratory tests were performed in all participants. Participants were scheduled in the outpatient clinic of Kangji hospital after an overnight fast. Blood samples were drawn by trained phlebotomists for measuring triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose and insulin by an autoanalyzer (Olympus, AU400, Japan). HOMA-insulin resistance (HOMA-IR) was calculated according to the formula: fasting insulin (uU/L) × fasting glucose (mmol/L)/22.5.

**Definition of ECAS progression**

ECAS was investigated by carotid duplex ultrasound scanning with a 5–12 MHz linear array transducer (Philips iU-22 ultrasound system, Philips Medical Systems, Bothell, WA). The initial and follow-up measurements were performed by the same certified sonographers who were blinded to the clinical data and laboratory findings of all participants. The scanning was performed on bilateral common carotid arteries, carotid bulb, carotid bifurcation and the origin of the internal carotid artery. ECAS was diagnosed by Doppler ultrasonography supported by B-mode ultrasound imaging according to the published criteria and was classified into (1) without stenosis, (2) mild stenosis (<50%), (3) moderate stenosis (50%–69%), (4) severe stenosis (70%–99%) and (5) total occlusion [33]. When determining ECAS progression, baseline status was used as the reference anchor. In accordance with previous studies [12,13], ECAS progression was defined as a transition from baseline status to ≥50% stenosis for those subjects without stenosis or with <50% stenosis or an increase of carotid artery stenosis to a higher category for those subjects with baseline stenosis ≥50%.

**Data collection and variable definition**

Standardized case report form (CRF) was used for data collection in the RSSS. Data from each CRF were manually checked for completeness and correct coding. In the present study, the following candidate variables were analyzed: (1) demographics (age and gender); (2) medical history: hypertension (history of hypertension or anti-hypertensive medication use), diabetes mellitus (history of diabetes mellitus or anti-diabetic medication use), dyslipidemia (history of dyslipidemia or lipid-lowering medication use), atrial fibrillation (history of atrial fibrillation or documentation of atrial fibrillation on presentation), coronary heart disease, stroke or transient ischemic attack, peripheral arterial disease (PAD) and current smoking (defined as a participant who had smoked continuously for 6 months with at least one cigarette per day); (3) physical examination: height, Waist, Weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate; (4) blood lipid: TG, TC, HDL and LDL; (5) blood glucose and (6) blood insulin and HOMA-IR index.

**Statistical analysis**

In the present study, we aimed to derive and validate a risk model to predict ECAS progression on left, right and bilateral (either left or right) carotid artery, respectively. In order to guarantee
the practicability of the model, we developed a web-based and user-friendly calculator, which can automatically provide a potential risk of ECAS progression.

The eligible participants were randomly divided into derivation (60%) and validation (40%) cohorts. Model building was performed exclusively in the derivation cohort. In univariate analysis, chi-square or Mann–Whitney test was used as appropriate. Multivariate logistic regression was used to determine independent predictors of ECAS progression on left, right and bilateral carotid artery, respectively. Candidate variables were those with the biologically plausible link to ECAS progression on the basis of prior publication or those associated with ECAS progression on univariate analysis (P ≤ 0.1). On multivariate analysis, backward stepwise method was used. To test collinearity between covariates of the final multivariable model, the tolerance and variance inflation factor (VIF) of each covariate were calculated. The resulting ECAS progression scores were then validated by assessing model discrimination and calibration in the validation cohort. Discrimination was assessed by calculating the area under the receiver operating characteristic curve (AUROC). Calibration was assessed by performing the Hosmer–Lemeshow goodness-of-fit test. In addition, model calibration was also graphically depicted in the plot of observed versus predicted risk according to 10 deciles of predicted risk. Furthermore, we calculated sensitivity, specificity, positive predict value (PPV) and negative predictive value (NPV) at each model’s maximum Youden Index.

All tests were two-tailed and statistical significance was determined at a level of 0.05. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC), SPSS 20.0 (SPSS Inc., Chicago, IL) and Medcalc software 12.3 (MedCalc, Ostend, Belgium).

**Results**

**Baseline characteristics**

Baseline characteristics of the derivation and validation cohorts are shown in Table 1. A total number of 4111 subjects were included for the present study (Figure 1). The mean age was 64.3 (SD = 3.0) and 42.1% were male. The eligible participants were randomly divided into derivation (60%, n = 2465) and validation cohort (40%, n = 1646), which were

| Table 1. Baseline characteristics. | Overall cohort (N = 4111) | Derivation cohort (N = 2465) | Validation cohort (N = 1646) | P-value |
|-----------------------------------|--------------------------|-----------------------------|-------------------------------|---------|
| Demographics                      |                          |                             |                               |         |
| Age, y, mean (SD)                 | 64.3 (3.0)               | 64.3 (3.1)                  | 64.4 (3.0)                    | 0.24    |
| Gender (male), n (%)              | 1729 (42.1)              | 1017 (41.3)                 | 712 (43.3)                    | 0.20    |
| Married, n (%)                    | 3652 (88.8)              | 2192 (88.9)                 | 1460 (88.7)                   | 0.84    |
| Medical history                   |                          |                             |                               |         |
| Hypertension, n (%)               | 1036 (25.2)              | 622 (25.2)                  | 414 (25.2)                    | 0.95    |
| Diabetes mellitus, n (%)          | 399 (9.7)                | 247 (10.0)                  | 152 (9.2)                     | 0.40    |
| Dyslipidemia, n (%)               | 544 (13.2)               | 321 (13.0)                  | 223 (13.5)                    | 0.63    |
| Atrial fibrillation, n (%)        | 70 (1.7)                 | 38 (1.5)                    | 32 (1.9)                      | 0.33    |
| Coronary artery disease, n (%)    | 595 (14.5)               | 346 (14.0)                  | 249 (15.1)                    | 0.33    |
| Stroke/TIA, n(%)                  | 563 (13.7)               | 357 (14.5)                  | 206 (12.5)                    | 0.07    |
| Peripheral artery disease, n (%)  | 248 (6.0)                | 160 (6.5)                   | 88 (5.3)                      | 0.13    |
| Current smoking, n (%)            | 2189 (53.2)              | 1289 (52.3)                 | 900 (54.7)                    | 0.13    |
| Medications                       |                          |                             |                               |         |
| Antiplatelet therapy, n (%)       | 1677 (40.8)              | 1007 (40.9)                 | 670 (40.7)                    | 0.93    |
| Anticoagulation therapy, n (%)    | 59 (1.4)                 | 36 (1.5)                    | 23 (1.4)                      | 0.87    |
| Statins, n (%)                    | 732 (17.8)               | 438 (17.8)                  | 294 (17.9)                    | 0.97    |
| Physical examination              |                          |                             |                               |         |
| Height, cm, median (IQR)          | 160.0 (154.1–166.0)      | 160.0 (154.2–166.0)         | 160.0 (154.0–166.0)           | 0.49    |
| Waist, cm, median (IQR)           | 87.0 (80.2–94.0)         | 87.0 (80.2–94.0)            | 87.1 (80.0–94.0)              | 0.95    |
| Weight, kg, median (IQR)          | 63.5 (56.4–71.3)         | 63.5 (56.5–71.3)            | 63.5 (56.3–71.3)              | 0.73    |
| BMI, median (IQR)                 | 24.8 (22.4–27.2)         | 24.8 (22.4–27.3)            | 24.9 (22.4–27.2)              | 0.97    |
| SBP (mm Hg), median (IQR)         | 149 (134–166)            | 149 (134–166)               | 150 (134–167)                 | 0.60    |
| DBP (mm Hg), median (IQR)         | 81 (73–89)               | 81 (73–88)                  | 81 (73–89)                    | 0.88    |
| Heart rate/min, median (IQR)      | 72 (65–79)               | 72 (65–79)                  | 72 (65–80)                    | 0.45    |
| Blood tests                       |                          |                             |                               |         |
| TG, (mmol/L), median (IQR)        | 1.39 (0.98–2.01)         | 1.39 (0.97–2.01)            | 1.40 (0.98–2.01)              | 0.90    |
| TC, (mmol/L), median (IQR)        | 4.77 (4.20–5.36)         | 4.76 (4.18–5.38)            | 4.79 (4.22–5.34)              | 0.55    |
| LDL, (mmol/L), median (IQR)       | 2.74 (2.27–3.21)         | 2.73 (2.27–3.21)            | 2.75 (2.28–3.21)              | 0.87    |
| HbA1c, (mmol/L), median (IQR)     | 1.45 (1.24–1.69)         | 1.44 (1.24–1.68)            | 1.46 (1.25–1.71)              | 0.14    |
| Glucose, (mmol/L), median (IQR)   | 4.72 (4.38–5.27)         | 4.74 (4.39–5.29)            | 4.70 (4.37–5.24)              | 0.22    |
| Insulin, (µIU/ml), median (IQR)   | 7.04 (4.31–11.7)         | 7.08 (4.28–11.7)            | 6.99 (4.33–5.24)              | 0.66    |
| HOMA-IR index                     | 1.54 (0.90–2.68)         | 1.53 (0.90–2.70)            | 1.55 (0.91–2.66)              | 0.63    |

SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; UA, urine acid; ECAS, extracranial carotid artery stenosis.
matched well with respect to baseline characteristics and blood test (Table 1).

**Proportion of ECAS progression**

The proportion of ECAS at baseline and 2-year follow-up stratified by laterality is shown in Table 2. Significant difference is indicated between ECAS at baseline and at follow-up in derivation, validation and overall cohort (all \( P < 0.001 \)). A total number of 29 (0.7%), 24 (0.6%) and 48 (1.2%) patients progressed during 2-year follow-up for left, right and bilateral (either left or right) carotid artery, respectively. The derivation and validation cohort were matched well with respect to the proportion of ECAS at baseline and 2-year follow-up (Table 2).

**Derivation of the ECAS progression score**

The multivariate analysis for predictors of ECAS progression stratified by laterality is shown in Table 3. Gender, present history of hypertension and stroke/TIA, SBP, DBP, weight, HDL, LDL and baseline carotid artery stenosis were identified as independent predictors of ECAS progression on left, right or bilateral (either left or right) carotid artery. The tolerance of covariates in the final multivariable model ranged 0.794–0.992 and the VIF 1.008–1.259. The potential risk of ECAS progression can be estimated for an individual subject by a web-based calculator (Figure 1) (www.ecas-ps.com).

**Validation of the ECAS progression score**

ECAS progression score showed good discrimination for predicting ECAS progression on left, right and bilateral (either left or right) carotid artery in the derivation, validation, and overall cohort (AUROC range: 0.824–0.917) (Table 4). Sensitivity, specificity, PPV and NPV at each model's maximum Youden Index are shown in Table 5. The Hosmer–Lemeshow tests of ECAS progression score were not significant in the derivation, validation and overall cohort (all \( P > 0.05 \)). Meanwhile, a graph of observed versus predicted risk of ECAS progression showed good correlation in the derivation, validation and overall cohorts (\( r \) range: 0.996–0.999, all \( P < 0.001 \)) (Supplementary Figure 2 and 4).

**Sensitivity analysis**

We completed pre-specified subgroup analyses by age, gender, medical history of hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, stroke/TIA, peripheral artery disease, vascular disease, current smoking and HOMA-IR index. Similar good discrimination was seen in these subgroups (AUROC range: 0.801–0.987) (Table 4).

**Discussion**

In the study, we developed and validated a web-based score to predict the risk of ECAS progression by...
|                      | Derivation cohort (N = 2465) | Validation cohort (N = 1646) | Overall cohort (N = 4111) |
|----------------------|-----------------------------|-------------------------------|--------------------------|
|                      | ECAS at baseline | ECAS at follow-up | P-value | ECAS at baseline | ECAS at follow-up | P-value | ECAS at baseline | ECAS at follow-up | P-value | ECAS progression |
| Left carotid artery  |                           |                              |          |                           |                              |          |                           |                              |          |                     |
| Without stenosis, n (%) | 2385 (96.8) | 2260 (91.7) | <0.001 | 1598 (97.1) | 1502 (91.3) | <0.001 | 3983 (96.9) | 3762 (91.5) | <0.001 | 29 (0.7) |
| Mild stenosis, n (%)    | 67 (2.7)     | 181 (7.3)    |          | 37 (2.2)     | 127 (7.7)    |          | 104 (2.5)   | 308 (7.5)    |          |                     |
| Moderate stenosis, n (%)| 6 (0.2)      | 17 (0.7)     |          | 2 (0.1)      | 4 (0.2)      |          | 8 (0.2)     | 21 (0.5)     |          |                     |
| Severe stenosis, n (%)  | 3 (0.1)      | 4 (0.2)      |          | 7 (0.4)      | 11 (0.7)     |          | 10 (0.2)    | 15 (0.4)     |          |                     |
| Total occlusion, n (%)  | 4 (0.2)      | 3 (0.1)      |          | 2 (0.1)      | 2 (0.1)      |          | 6 (0.1)     | 5 (0.1)      |          |                     |
| Right carotid artery   |                           |                              |          |                           |                              |          |                           |                              |          |                     |
| Without stenosis, n (%) | 2397 (97.2) | 2274 (92.3) | <0.001 | 1596 (97.0) | 1562 (92.7) | <0.001 | 3993 (97.1) | 3800 (92.4) | <0.001 | 24 (0.6) |
| Mild stenosis, n (%)    | 52 (2.1)     | 167 (6.8)    |          | 38 (2.3)     | 104 (6.3)    |          | 90 (2.2)    | 271 (6.6)    |          |                     |
| Moderate stenosis, n (%)| 9 (0.4)      | 15 (0.6)     |          | 5 (0.3)      | 8 (0.5)      |          | 14 (0.3)    | 23 (0.6)     |          |                     |
| Severe stenosis, n (%)  | 4 (0.2)      | 3 (0.1)      |          | 1 (0.1)      | 1 (0.1)      |          | 5 (0.1)     | 4 (0.1)      |          |                     |
| Total occlusion, n (%)  | 3 (0.1)      | 6 (0.2)      |          | 6 (0.4)      | 7 (0.4)      |          | 9 (0.2)     | 13 (0.3)     |          |                     |
| Bilateral carotid artery|                           |                              |          |                           |                              |          |                           |                              |          |                     |
| Without stenosis, n (%) | 2329 (94.5) | 2142 (86.9) | <0.001 | 1559 (94.7) | 1427 (86.7) | <0.001 | 3888 (94.6) | 3569 (86.8) | <0.001 | 48 (1.2) |
| Mild stenosis, n (%)    | 110 (4.5)    | 280 (11.4)   |          | 66 (4.0)     | 190 (11.5)   |          | 176 (4.3)   | 470 (11.4)   |          |                     |
| Moderate stenosis, n (%)| 12 (0.5)     | 27 (1.1)     |          | 6 (0.4)      | 10 (0.6)     |          | 18 (0.4)    | 37 (0.9)     |          |                     |
| Severe stenosis, n (%)  | 7 (0.3)      | 7 (0.3)      |          | 7 (0.4)      | 10 (0.6)     |          | 14 (0.3)    | 17 (0.4)     |          |                     |
| Total occlusion, n (%)  | 7 (0.3)      | 9 (0.4)      |          | 8 (0.5)      | 9 (0.5)      |          | 15 (0.4)    | 18 (0.4)     |          |                     |

ECAS, extracranial carotid artery stenosis; SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; UA, uric acid.
Table 3. Multivariable predictors of ECAS progression by laterality in the derivation cohort (n = 2465).

| Variables                        | Progression of left ECAS | Progression of right ECAS | Progression of bilateral ECAS |
|----------------------------------|--------------------------|---------------------------|-------------------------------|
|                                  | β-coefficients | Adjusted OR* | 95% CI | P-value | β-coefficients | Adjusted OR* | 95% CI | P-value | β-coefficients | Adjusted OR* | 95% CI | P-value |
| Model intercept                  | −5.271          | 3.261         | 1.405–7.567 | 0.006   | −12.334       | 3.261         | 1.405–7.567 | 0.006   | −6.441       | 3.261         | 1.405–7.567 | 0.006   |
| Male gender (yes)                | 1.182           | 3.261         | 1.405–7.567 | 0.006   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| History of hypertension (yes)    | 1.158           | 3.261         | 1.405–7.567 | 0.006   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| History of stroke/TIA (yes)      | ...             | ...           | ...       | ...     | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| Current smoking (yes)            | ...             | ...           | ...       | ...     | 1.285         | 3.261         | 1.405–7.567 | 0.006   | 1.017       | 3.261         | 1.405–7.567 | 0.006   |
| SBP (per mmHg increase)          | 0.029           | 1.030         | 1.013–1.047 | 0.001   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| DBP (per mmHg increase)          | −0.050          | 0.951         | 0.919–0.984 | 0.004   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| Weight (per kg increase)         | ...             | ...           | ...       | ...     | 0.037         | 1.038         | 1.003–1.074 | 0.034   | ...           | ...           | ...       | ...     |
| HDL (per mmol/L increase)        | −1.254          | 0.285         | 0.085–0.962 | 0.043   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| LDL (per mmol/L increase)        | ...             | ...           | ...       | ...     | 0.489         | 1.631         | 1.004–2.639 | 0.046   | ...           | ...           | ...       | ...     |
| Baseline left carotid stenosis   | ...             | ...           | ...       | ...     | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| Without stenosis                 | ...             | ...           | ...       | ...     | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| <50% stenosis                    | 2.724           | 15.23         | 6.468–35.89 | <0.001  | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| ≥50% stenosis                    | 2.002           | 7.40          | 1.407–38.95 | 0.018   | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| Baseline right carotid stenosis  | ...             | ...           | ...       | ...     | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| Without stenosis                 | ...             | ...           | ...       | ...     | ...           | ...           | ...       | ...     | ...           | ...           | ...       | ...     |
| <50% stenosis                    | ...             | ...           | ...       | ...     | 1.974         | 7.197         | 2.285–22.63 | 0.001   | ...           | ...           | ...       | ...     |
| ≥50% stenosis                    | ...             | ...           | ...       | ...     | 2.066         | 7.892         | 1.576–39.52 | 0.012   | ...           | ...           | ...       | ...     |

* Multivariable logistic regression adjusted for demographics (age and gender), medical history (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease, history of stroke/TIA, current smoking), physical examination (height, waist, weight, systolic blood pressure, diastolic blood pressure, heart rate/min), blood tests (TG, TC, LDL, HDL, blood glucose).

Predicted risk of extracranial carotid artery stenosis = e^{b_0 + b_1x_1 + b_2x_2 + b_3x_3 + ... + b_nx_n}.

ECAS, extracranial carotid artery stenosis; SE, standard error; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
using information routinely available or easily obtained at presentation. Gender, present history of hypertension and stroke/TIA, SBP, DBP, weight, HDL, LDL and baseline carotid artery stenosis were identified as independent predictors of ECAS progression. Based on these risk factors, ECAS progression score was developed and showed good discrimination and calibration in large derivation

| Table 4. Sensitivity analysis of the ECAS progression score in the overall cohort (n = 4111). |
|---------------------------------|---------------------------------|---------------------------------|
|                                 | ECAS progression Score-L | ECAS progression Score-R | ECAS progression Score-B |
|                                 | AUROC 95% CI              | AUROC 95% CI              | AUROC 95% CI              |
| **Cohort**                      |                           |                           |                           |
| Derivation cohort               | 0.917 0.851–0.982         | 0.868 0.791–0.945         | 0.860 0.787–0.933         |
| Validation cohort               | 0.842 0.740–0.973         | 0.832 0.707–0.957         | 0.824 0.729–0.918         |
| Overall cohort                  | 0.886 0.828–0.944         | 0.854 0.786–0.922         | 0.846 0.788–0.904         |
| **Age**                         |                           |                           |                           |
| ≤65                            | 0.897 0.805–0.990         | 0.821 0.726–0.917         | 0.856 0.768–0.943         |
| ≥66                            | 0.873 0.795–0.950         | 0.896 0.806–0.986         | 0.832 0.754–0.910         |
| **Gender**                      |                           |                           |                           |
| Male                           | 0.837 0.736–0.938         | 0.843 0.741–0.945         | 0.838 0.766–0.910         |
| Female                         | 0.920 0.848–0.992         | 0.859 0.772–0.947         | 0.833 0.731–0.935         |
| **Hypertension**               |                           |                           |                           |
| Yes                            | 0.841 0.741–0.940         | 0.838 0.744–0.931         | 0.817 0.724–0.909         |
| No                             | 0.879 0.791–0.966         | 0.836 0.733–0.939         | 0.818 0.725–0.911         |
| **Diabetes mellitus**          |                           |                           |                           |
| Yes                            | 0.882 0.783–0.981         | 0.810 0.648–0.971         | 0.892 0.785–1.000         |
| No                             | 0.882 0.816–0.948         | 0.857 0.781–0.932         | 0.836 0.771–0.902         |
| **Dyslipidemia**               |                           |                           |                           |
| Yes                            | 0.976 0.958–0.994         | 0.895 0.790–1.000         | 0.886 0.794–0.979         |
| No                             | 0.887 0.828–0.946         | 0.827 0.741–0.913         | 0.836 0.770–0.903         |
| **Coronary heart disease**     |                           |                           |                           |
| Yes                            | 0.924 0.862–0.985         | 0.987 0.977–0.996         | 0.954 0.893–1.000         |
| No                             | 0.869 0.795–0.943         | 0.846 0.775–0.917         | 0.825 0.756–0.891         |
| **History of stroke/TIA**      |                           |                           |                           |
| Yes                            | 0.831 0.712–0.951         | 0.802 0.662–0.942         | 0.836 0.745–0.926         |
| No                             | 0.894 0.805–0.964         | 0.845 0.754–0.936         | 0.817 0.738–0.896         |
| **History of PAD**             |                           |                           |                           |
| Yes                            | 0.957 0.929–0.986         | 0.987 0.977–0.996         | 0.954 0.893–1.000         |
| No                             | 0.881 0.819–0.943         | 0.854 0.786–0.922         | 0.840 0.780–0.901         |
| **History of vascular disease**|                           |                           |                           |
| Yes                            | 0.885 0.809–0.961         | 0.890 0.814–0.966         | 0.900 0.848–0.951         |
| No                             | 0.865 0.769–0.962         | 0.848 0.758–0.938         | 0.801 0.714–0.889         |
| **Current smoking**            |                           |                           |                           |
| Yes                            | 0.873 0.797–0.949         | 0.825 0.734–0.916         | 0.817 0.738–0.896         |
| No                             | 0.895 0.797–0.992         | 0.907 0.826–0.987         | 0.865 0.760–0.979         |
| **HOMA-IR index**              |                           |                           |                           |
| Below median (<1.54)           | 0.881 0.803–0.959         | 0.880 0.793–0.967         | 0.857 0.770–0.943         |
| Above median (≥1.54)           | 0.898 0.817–0.979         | 0.828 0.727–0.928         | 0.832 0.754–0.911         |

ECAS, extracranial carotid artery stenosis; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; TIA, transient ischemic attack; PAD, peripheral artery disease; L, left side; R, right side; B-bilateral side (either left or right).

| Table 5. Sensitivity, specificity, PPV, NPV and accuracy of ECAS progression score at Youden index. |
|---------------------------------|---------------------------------|---------------------------------|
|                                 | AUROC 95% CI | P-value | Youden index | Sensitivity | Specificity | PPV | NPV |
| **Derivation cohort (n = 2465)**|                           |         |              |             |             |     |     |
| ECAS progression score-L        | 0.917 0.851–0.982 | <0.001 | 0.750 | 0.824 | 0.927 | 0.072 | 0.999 |
| ECAS progression score-R        | 0.868 0.791–0.945 | <0.001 | 0.541 | 0.600 | 0.941 | 0.059 | 0.997 |
| ECAS progression score-B        | 0.860 0.787–0.933 | <0.001 | 0.550 | 0.690 | 0.860 | 0.055 | 0.996 |
| **Validation cohort (n = 1646)**|                           |         |              |             |             |     |     |
| ECAS progression score-L        | 0.842 0.740–0.973 | <0.001 | 0.573 | 0.833 | 0.740 | 0.023 | 0.998 |
| ECAS progression score-R        | 0.832 0.707–0.957 | <0.001 | 0.633 | 0.889 | 0.744 | 0.019 | 0.999 |
| ECAS progression score-B        | 0.824 0.729–0.918 | <0.001 | 0.457 | 0.526 | 0.931 | 0.082 | 0.994 |
| **Overall cohort (n = 4111)**   |                           |         |              |             |             |     |     |
| ECAS progression score-L        | 0.886 0.828–0.944 | <0.001 | 0.580 | 0.655 | 0.925 | 0.058 | 0.997 |
| ECAS progression score-R        | 0.854 0.786–0.922 | <0.001 | 0.565 | 0.833 | 0.732 | 0.018 | 0.999 |
| ECAS progression score-B        | 0.846 0.788–0.904 | <0.001 | 0.506 | 0.646 | 0.860 | 0.052 | 0.995 |

ECAS, extracranial cervical atherosclerotic stenosis; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; L, left side; R, right side; B-bilateral side.
and validation cohorts. In addition, the ECAS progression score demonstrated to be effective and stable for subjects with various baseline characteristics.

Previous studies have shown that a variety of risk factors are associated with carotid atherosclerosis and progression [15–26]. In accordance with these studies, we found that gender, present history of hypertension and stroke/TIA, SBP, DBP, weight, HDL, LDL and baseline carotid artery stenosis were independently associated with ECAS progression. In order to preserve the clinical utility of the model for clinical decision-making, we used only information available or easily obtained at presentation. We chose not to include variables related to long-term stroke prevention, such as smoking cessation, dietary modification, physical exercise and persistence of evidence-based secondary prevention medications (antithrombotic agents, statins, antihypertensive agents and diabetic agents, etc.) [34,35], despite the fact that these interventions could influence ECAS progression. This model therefore predicts the risk of ECAS progression at presentation.

To the best of our knowledge, we are the first to establish models for predicting the risk of ECAS progression. For a risk model to become effective and widely used, it must be accurate, reliable and practicable. For accuracy, the ECAS progression score was proven to be accurate in risk stratification for ECAS progression on left, right and bilateral (either left or right) carotid artery in both derivation and validation cohorts. For reliability, the ECAS score was developed based on large derivation and validation cohorts; in addition, in sensitivity analysis, the ECAS score demonstrated to be effective and stable for patients with various baseline characteristics, such as age, gender, medical history of hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, stroke/TIA, PAD, vascular disease, smoking status and HOMA-IR index. For practicability, the ECAS score consists of factors that are routinely available or easily obtained at presentation. In addition, by a web-based and user-friendly calculator, users could obtain predictive information without doing a complex calculation.

Different degrees of carotid stenosis progress at different rates and therefore should be followed at different intervals [30,36]. Thus, patients with asymptomatic and mild ECAS are generally followed with periodic carotid duplex ultrasounds with the intent of identifying those who progress to severe disease. Such patients might be offered CEA or CAS in addition to optimal medical therapy. As a result, clinicians caring for patients with asymptomatic and mild ECAS face a clinical conundrum regarding the ideal frequency of follow-up carotid duplex studies. Performing them too often increases cost unnecessarily, whereas performing them too infrequently risks missing the ideal window for revascularization. ECAS progression score could provide useful and objective information on optimal frequency of ultrasound examinations for surveillance of untreated ICA stenosis.

Although carotid artery stenosis is a risk factor for stroke, not every carotid stenosis carries the same risk and clinicians should strive to assess and treat them accordingly [37]. With some investigators already calling for more targeted strategies for intervention in severe asymptomatic disease and randomized trials in revascularization [38,39], upstream evaluation of asymptomatic carotid artery disease will likely need to follow suit [37]. We recommend to evaluate the potential risk of stroke for patients with ECAS by combined parameters rather than the only degree of stenosis. Although some emerging modalities are not currently part of routine practice, they could be promising tools used to estimate the individual risk of stroke in the coming future. For example, neovascularization of carotid plaque can be identified with contrast-enhanced ultrasound [40,41], which was shown to be associated with a higher risk of ipsilateral stroke. Microembolic signals detected by transcranial Doppler have been shown to discriminate patients at higher risk of stroke [42]. High-resolution magnetic resonance imaging can accurately demonstrate lipid-rich necrotic core, intra-plaque hemorrhage and thinning or rupture of the fibrous cap [43,44]. Integrating relevant information on degree of stenosis, risk of progression, plaque texture, neovascularity and microembolic signals might be helpful for identifying higher risk patients for either more intensive surveillance or even earlier intervention.

Our study has limitations that deserve comment. First, like all observational studies, we cannot rule out the possibility that additional variable (unmeasured confounders) might have some impact on ECAS progression, such as cystatin C [25], interleukin-23 [26], interleukin-6 [31], interleukin-10 [31] and microRNAs [32]. However, given our emphasis on prediction using information routine or easily obtained at presentation, the ECAS progression score might be easier to be applied in clinical practice or clinical trials. Second, our study only included participants with age of 60–70 years and those younger and elder subjects were not included. Meanwhile, like most registries, our registry required informed consent and selection bias was inevitable [45]. Finally, both the derivation and validation cohorts originated from the Asian population, and therefore, the ECAS score needed to be further validated in non-Asian populations.

**Conclusion**

In conclusion, the ECAS progression score is a valid model for predicting ECAS progression. Further
validation of the ECAS progression score in different populations and larger samples is warranted.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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