A model for predicting carotid instability plaque in high risk group of stroke individuals

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Abstract

Objective: To establish a predictive model of carotid vulnerable plaque through systematic screening of high-risk population for stroke. Patients and methods: All community residents who participated in the screening of stroke high-risk population by the China National Stroke Screening and Prevention Project (CNSSPP). A total of 19 risk factors were analyzed. Individuals were randomly divided into Derivation Set group and Validation Set group. According to carotid ultrasonography, the derivation set group patients were divided into instability plaque group and non-instability plaque group. Univariate and multivariable logistic regression were taken for risk factors. A predictive model scoring system were established by the coefficient. The AUC value of both derivation and validation set group were used to verify the effectiveness of the model.

Results: A total of 2841 high-risk stroke patients were enrolled in this study, 266 (9.4%) patients were found instability plaque. According to the results of Doppler ultrasound, Derivation Set group were divided into instability plaque group (174 cases) and non-instability plaque group (1720 cases). The independent risk factors for carotid instability plaque were: male (OR 1.966, 95%CI 1.406-2.749), older age (50-59, OR 6.012, 95%CI 1.410-25.629; 60-69, OR 13.915, 95%CI 3.381-57.267; ≥70, OR 31.267, 95%CI 7.472-130.83), married (OR 1.780, 95%CI 1.186-2.672), LDL-c (OR 2.015, 95%CI 1.443-2.814), and HDL-C (OR 2.130, 95%CI 1.360-3.338). A predictive scoring system was created, range 0-10. The cut-off value of prediction model score is 6.5. The AUC value of derivation and validation set group were 0.738 and 0.737.

Conclusion: For a high risk group of stroke individual, We provide a model that could distinguishing those who have a high probability of having carotid instability plaque. When resident's predictive model score exceeds 6.5, the incidence of carotid instability plaque is high, carotid artery Doppler ultrasound would be checked immediately. This model can be helpful in the primary prevention of stroke.

Background

Stroke is the third leading cause of lost disability adjusted life years (DALYS) worldwide [1]. It is well-known that atherosclerosis is the main risk factor of cardiovascular and cerebral vascular disease. Asymptomatic carotid artery diseases are very common among the residents. It would be helpful to screening carotid for primary prevention of Cardiovascular diseases (CVD) and stroke in selected population, although it still has controversy. The USPSTF recommended against screening for asymptomatic carotid artery stenosis (CAS) in the general adult population both in 2007 and 2014 [2,3]. The American Society of Neuroimaging has concluded that screening for CAS is appropriate if the prevalence is greater than 20% [4].

Several researches [5,6] demonstrated older age, smoking, high blood pressure, diabetes and others were independent risk factors for carotid stenosis (>50% stenosis), yet they were ignored that people with lower levels of stenosis (≥50% or carotid plaque, especially instability plaque) who may benefit from early risk-reducing medications, such as statins, antiplatelet drugs.
In order to better understand the risk factors about carotid instability plaque, we analyzed China National Stroke Screening and Prevention Project (CNSSPP) Database, including information about carotid duplex scans, demographic data, lifestyle risk factors, medical history, family history of stroke and blood tests. Therefore, the purpose of this research was to discover residents with a high probability of having carotid instability plaque for whom primary prevention therapy may be beneficial.

Methods

2.1 Ethical statement

The study was performed according to the declaration of Helsinki and approved by the Ethics Committee of the Nanjing Brain Hospital Institutional Review Board, Nanjing Medical University (Nanjing, China). All participants received information on the study and provided written informed consent to participate.

2.2 High risk group of stroke individuals

Screening records between 2012 and 2016 were provided by China National Stroke Screening and Prevention Project (CNSSPP), a nationally ongoing community-based study, which was conducted by the National Project Office of Stroke Prevention and Control. Screenings were performed throughout the city of Nanjing at 21 communities.

Individuals were selected cluster sampling. They should meet these criterions: Age ≥ 40 years old, living in the community above 9 month per year, and above 85% population were included.

According to the standard which is defined by The China National Stroke Prevention Project Committee[7], high risk group of stroke were interpreted at least 40 years of age and had at least three of the following risk factors: hypertension, atrial fibrillation, smoking, dyslipidemia, diabetes mellitus, physical inactivity, obese or overweight (BMI ≥ 26 kg/m²), and family history of stroke. People who has the history of stroke or transient ischemic attack also equivalent to high-risk population management.

**Hypertension** was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-reported hypertension diagnosed by a physician, or use of antihypertensive medications. **Atrial fibrillation** was defined as ECG examination indicates atrial fibrillation, self-reported diagnosis of atrial fibrillation, or use of anticoagulant medications. **Smoking** status was classified as smoking(current smoking or had a history of smoke for more than one year) and never smoking(never smoking or had a history of smoke for less than one year) . **Dyslipidemia** was defined as having one or more of the following results: triglyceride ≥ 2.26 mmol/L, total cholesterol ≥ 6.22 mmol/L, high-density lipoprotein cholesterol < 1.04 mmol/L, low-density lipoprotein cholesterol ≥ 4.14 mmol/L, self-reported diagnosis of dyslipidemia, or taking cholesterol-lowering medications. **Diabetes mellitus** was defined as fasting plasma glucose ≥ 7.0 mmol/L, self-reported diagnosis of diabetes mellitus, or use of oral hypoglycemic
agents or insulin injection. **Physical activity** was defined as regular physical exercise >3 times/week for at least 30 minutes per session. Body mass index was calculated as body weight (in kg) divided by the square of height (in m; kg/m$^2$). **Obesity** was defined as body mass index $\geq$28kg/m$^2$, **Overweight** was defined as body mass index $\geq$26kg/m$^2$, according to the guidelines of the Working Group on Obesity in China[8]. **A family history of stroke** was defined as the occurrence of stroke in a participant's parents, brothers, or sisters.

Before carotid duplex scans, candidates were asked to complete a standardized CNSSPP questionnaires, providing demographic information, lifestyle risk factors, medical history, and a family history of stroke, which were collected through face-to-face interviews by trained staff. Individuals fasting blood were obtained to test for fasting plasma glucose (FPG), homocysteine (Hcy), Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Hemoglobin A1C (HbA1C), triglyceride (TG).

### 2.3 Blood test

Venous blood (5mL) was collected from all patients before breakfast. Serum samples were obtained by centrifugation for 10 min at 3000g, placed in freezing tubes, and preserved at -80°C until subsequent analysis. Serum FPG, HCY and blood lipids levels were determined using OLYMPUS AU5400 (OLYMPUS, Japan). EDTA anticoagulated whole blood samples (2ml) from the same patients were used to measure HbA1c expression by TOSOH G8 (TOSOH, Japan).

### 2.4 Carotid artery ultrasound screening protocol

According to Chinese stroke vascular ultrasound examination guidelines[9], the duplex scan consisted of ultrasound imaging of the distal common carotid artery, bulb, and proximal internal and external carotid arteries, with evaluation of a Doppler signal for 3 to 5 beats in each location on both sides. Plaque was interpreted as greater than 1.5mm of IMT based on Doppler-derived[10]. Color Doppler ultrasonography of the carotid artery indicates plaque with hypoechoic, mixed echoes, or plaque indicating ulceration, defined as instability plaque. Carotid duplex examinations were performed by four experienced registered vascular technicians in Nanjing Brain Hospital, which is a Stroke Screening and Training Base Hospital. All of the vascular technicians were independent of other clinical information. Screening work has to comply with the criteria established by CNSSPP Committee.

### 2.5 Predictive model evaluation

Continuous variables were presented as mean (Standard deviation, SD), and categorical variables were presented as percentages. The whole sample was randomly divided into a model derivation set and a model validation set, which consisted of approximately two-thirds and one-third of the sample, respectively. A comparison was performed between the two groups with t-test of derivation set for continuous variables and with $\chi^2$ tests for categorical variables. Univariate logistic regression was taken for each risk factors. When the value of P is less than 0.1, the variable was entered into the multivariable
logistic regression model (Stepwise forward). Those variables which P less than 0.05 were kept in. According to the previous study[5], we also created a scoring system based on the regression coefficients. The lowest coefficient in absolute value was used as denominator. The coefficient of each independence risk factor was divided by the absolute value of the lowest coefficient and then rounded to the nearest integer. The sum of the scores from each individual was taken into receiver operator characteristic (ROC) curve, generated to determine the prediction power of carotid instability plaque, and the best cutoff scores by Youden index.

We used validation set to evaluate the ability of the classification scheme to discriminate between persons with and without carotid instability plaque, which was also assessed using a ROC curve with SYSSTAT (SPSS Inc, Chicago, IL). A ROC curve plots the true-positive rate (test sensitivity) for a given threshold on the y-axis and the corresponding false-positive rate (one-test specificity) on the x-axis. The area under the resulting fitted curve represents the discriminating ability of that particular screening method and is assumed to be normally distributed. An area of 50% represents a non-discriminant screening test in which the true-positive rate equals the false-positive rate. The area under the ROC curve for excellent test and poor test approximates 100% and 50%, respectively.

All statistical analyses were performed using the SPSS version 20.0 software for Windows (SPSS, Inc, Chicago, IL, USA). In all Statistical analyses, a P value <0.05 was considered statistically significant

Results

During 2012-2016, more than 34000 residents were enrolled the CNSSPP. According the risk factors screening, 5250 persons were high risk, checking Carotid artery ultrasound. A total of 2309 persons were excluded because of previous stroke or transient ischemic attack, 100 persons were excluded because of incomplete data. Of the total 2841 participants included in this study, the prevalence of carotid plaque was 35.2% (n=1000), the prevalence of carotid instability plaque was 9.4% (n=266). All the 2841 residents were randomly divided into the derivation set group (n=1894) and the validation set group (n=947). Participant characteristic are provided in Table 1.

The derivation set included 1894 participants (mean age =60.7±8.6 years) of whom 174 (9.2%) had carotid instability plaque. The clinical characteristics of this set are provided in Table 2. Men were more likely to have carotid instability plaque. A higher proportion of persons older than 60 had carotid instability plaque. People who is married or had a history of diabetes mellitus would had more chance to get carotid instability plaque. Residents with instability carotid plaque were more likely to be a higher FPG, Hcy, TC, LDL-C, and a lower HLD-C, overweight chance. No significant differences were showed between groups with regard to education level, atrial fibrillation, hypertension, hypercholesterolemia, smoking, lack of physical activity, family history of strok, HbA1c, or TG.

Table 3 shows the results of multivariable logistic regression analysis. Five variables were significantly associated with Carotid instability Plaque: male (OR 1.966, 95%CI 1.406-2.749) older age (50-59, OR
6.012, 95%CI 1.410-25.629; 60-69, OR 13.915, 95%CI 3.381-57.267; ≥70, OR 31.267, 95%CI 7.472-130.83), married (OR 1.780, 95%CI 1.186-2.672), LDL-c (OR 2.015, 95%CI 1.443-2.814), and HDL-C (OR 2.130, 95%CI 1.360-3.338). According to the probability obtained in the multivariable logistic regression analysis, ROC curves are plotted. The area under the ROC curve was 0.741, as shown in Figure 1.

For these 5 risk factors, marriage (married) had the lowest regression coefficients 0.577, we scored it 1 point. Other 4 factors score was calculated by coefficients divided by 0.577 and then rounded to the nearest integer. Using this scoring system, we got a score for each Derivation Set person. The sum of the scores was taken into ROC curve with carotid artery ultrasound results, generated to determine the prediction power of carotid instability plaque, and the best cutoff scores by Youden index. The area under the ROC curve was 0.738. The Youden index of score was calculated by sensitivity plus specificity. The best predictive value of score was 6.5, sensitivity was 71.8%, specificity was 63.0%, as shown in Figure 1.

The ability of the classification scheme to discriminate between patients with and without carotid instability plaque was evaluated in a separate validation set comprising 947 persons (mean age = 60.4±8.7 years) of whom 92 (9.7%) had carotid instability plaque. The area under the ROC curve was 0.743. According to the scoring system, we got a score for each validation Set individuals. The sum of the scores and carotid artery ultrasound results were taken into ROC curve. The area under the ROC curve was 0.737. The Youden index of score was calculated by sensitivity plus specificity. The best predictive value of score was still 6.5, sensitivity was 76.1%, specificity was 63.6%, as shown in Figure 2.

## Discussion

This study investigated the risk factors of carotid instability plaque in asymptomatic patients with high risk group of strokes and created a scoring system. It showed that carotid instability plaque was associated with male (OR 1.966, 95%CI 1.406-2.749), older age (50-59, OR 6.012, 95%CI 1.410-25.629; 60-69, OR 13.915, 95%CI 3.381-57.267; ≥70, OR 31.267, 95%CI 7.472-130.83), married (OR 1.780, 95%CI 1.186-2.672), LDL-c (OR 2.015, 95%CI 1.443-2.814), and HDL-C (OR 2.130, 95%CI 1.360-3.338). In this study, married was actually associated with an increased prevalence of carotid instability plaque by univariate and multivariate analysis. It is the first time that marriage is associate with carotid instability plaque. Yue W et al investigate potential associations between carotid artery stenosis and cognitive impairment among patients with acute ischemic stroke, one subgroup analysis of the relationship between marriage and severity of left and right carotid stenosis. The results show that married persons are closely related to severe stenosis of carotid artery, and there is statistical difference between them (P=0.0471) [11]. We noticed that this study is based on data from Tianjin, China. This may be related to Chinese tradition, the improvement of living standards after marriage, especially in terms of food and housing. Another possible reason is that people fill out questionnaires themselves, which may not be very accurate.

Previous studies [12,13] founded that advanced age, smoking, peripheral arterial disease, hypercholesterolemia, hypertension, Diabetes mellitus, and coronary artery disease were associated with
occult carotid stenosis of >50% or 60%. Moderate to severe stenosis may benefit from carotid endarterectomy and carotid artery stenting, but they are few. Focused on carotid instability plaque, it can identify more people with lower levels of stenosis who may benefit from aggressive primary prevention, such as healthy lifestyle, control of chronic diseases, risk-reducing medications [14].

The carotid intima-media thickness (IMT) was not recommended for use in clinical practice as a routine measurement of risk assessment for a first atherosclerotic cardiovascular disease (ASCVD) event assessment designated in 2013 by American College of Cardiology/American Heart Association (ACC/AHA) [15]. Although it has controversial, researchers believe that carotid artery plaque is better than MIT in predicting cardiovascular and cerebrovascular diseases [16-18], because it can provide more information, such as plaque size, surface ulcer, echo properties, etc.

Hill [19] reported that the prevalence of Asymptomatic Carotid Artery Stenosis (ACAS) is estimated to range from 2% to 8% for stenosis 50% or greater and from 1% to 2% for stenosis 80% or greater in the general population. Due to the low prevalence of carotid artery disease, numerous cost-evaluation models have failed to demonstrate a benefit in screening the general population [12]. On the other hand, Jones [20] reported a total of 173 Middle-Aged participants group, the prevalence of carotid plaque is 21.0%, which is similar to our findings. In this study, our participant’s average age is 60 years old, and the prevalence of carotid plaque is 35.2%, the unstable plaque is 9.4%.

The effectiveness of carotid stenting and endarterectomy has been well established for stroke primary and secondary prevention. For the reason of cost-effective, unselected population screening for carotid stenosis has not been accepted [21-22]. Checking the high-risk groups may be the best choice, but how to define high-risk population is still not uniform. CNSSPP defined high risk of stroke person was elder than 40 years old and have more than 3 of 8 risk factors, which content Hypertension, Diabetes Mellitus, Dyslipidemia, Smoking, lack of Physical activity, Overweight, Family history of stroke, were similar to previous research [23], and which is convenient for large population screening. Our research has established a simple and easy scoring system, when high risk of stroke person has more than 6.5 points, a carotid artery ultrasound screening would be needed. Previous prediction models[5,6] were obtained only through medical history inquiry. In this study, objective blood indicators were included in the prediction model, which reduced subjective bias and made it more accurate.

However, certain inadequacies of this study cannot be ignored. First, although this study was based on a 21 Communities in Nanjing, it stills a single-center cross-sectional study, which is failed to show the national level and the progression of instability carotid plaque. Second, for the lack of time and staff, the size of the plaque was not measured energetically, and the plaque characteristics was also not be analyzed by 3D probe. Lastly, Follow-up data for the above population are being compiled, especially for interventions (medication and surgery) and the occurrence of stroke. The above work will be perfected and supplemented in the next step.

Conclusions
The incidence of carotid artery plaque is high in the high-risk population of stroke, especially vulnerable plaque, so it is necessary to screen carotid artery by color Doppler ultrasonography. Elder age, marriage, male, high LDL-c and low HDL-c are the independent risk factors. Among all these risk factors, advanced age has the largest proportion. We created a scoring system by assigning values to various risk factors. The total score is 0-10. When a resident's predictive model score exceeds 6.5, the incidence of carotid artery instability plaque is high. It is necessary to accomplish the color Doppler ultrasound examination of the carotid artery as soon as possible, and to prevent stroke as early as possible according to the guidelines.

Declarations

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Disclosures

The authors have no conflicts of interest to disclose.

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Tables

Table 1. Demographic and Risk Factor Profiles in the Derivation and Validation Sets
| Variable                              | Derivation Set | Validation Set | P  |
|--------------------------------------|----------------|----------------|----|
|                                     | n=1894         | n=947          |    |
| Sex (male)                           | 874 (46.1%)    | 451 (47.6%)    | 0.457 |
| Mean age (years)                     | 60.7±8.6       | 60.4±8.7       | 0.321 |
| Education level (Primary school or below) | 730 (38.5%)   | 402 (42.4%)    | 0.045 |
| Marriage (married)                   | 1330 (70.2%)   | 699 (73.8%)    | 0.102 |
| Atrial fibrillation                  | 130 (6.9%)     | 57 (6.0%)      | 0.392 |
| Diabetes mellitus                    | 457 (24.1%)    | 251 (26.5%)    | 0.168 |
| Hypertension                         | 1503 (79.4%)   | 743 (78.5%)    | 0.579 |
| Hypercholesterolemia                 | 741 (39.1%)    | 349 (36.9%)    | 0.241 |
| Overweight and obesity               | 847 (44.7%)    | 408 (43.1%)    | 0.408 |
| Smoking                              | 634 (33.5%)    | 339 (35.8%)    | 0.219 |
| Lack of Physical activity            | 1443 (76.2%)   | 727 (76.8%)    | 0.731 |
| Family history of stroke             | 602 (31.8%)    | 282 (29.8%)    | 0.276 |
| FPG (mmol/L)                         | 6.1±1.8        | 6.2±2.0        | 0.079 |
| HbA1c (%)                            | 6.6±2.5        | 6.6±1.9        | 0.872 |
| Hcy (mmol/L)                         | 12.2±7.5       | 12.0±6.6       | 0.611 |
| TC (mmol/L)                          | 5.1±1.0        | 5.1±1.0        | 0.386 |
| LDL-C (mmol/L)                       | 3.0±0.8        | 3.0±0.8        | 0.944 |
| HDL-C (mmol/L)                       | 1.6±0.8        | 1.5±0.7        | 0.600 |
| TG (mmol/L)                          | 1.7±1.3        | 1.7±1.4        | 0.699 |
| Carotid plaque                       | 660 (34.8%)    | 340 (35.9%)    | 0.579 |
| Carotid instability plaque           | 174 (9.2%)     | 92 (9.7%)      | 0.649 |

Table 2. Comparison of Demographic and Risk Factor Profiles in Participants with and Without Carotid Instability Plaque in the Derivation Set
| Variable                        | With Carotid Vulnerable Plaque | Without Carotid Vulnerable Plaque | P     | OR 95%CI |
|--------------------------------|--------------------------------|-----------------------------------|-------|---------|
| Sex (male)                     | 109 (62.6%)                    | 765 (44.5%)                       | 0.001 | 2.093(1.518-2.887) |
| Mean age (years)               |                                |                                   |       |         |
| 40-49                          | 14 (8.0%)                      | 207 (12.0%)                       | 0.001 | 1.00(Reference) |
| 50-59                          | 35 (20.1%)                     | 512 (29.8%)                       | 0.018 | 5.686(1.340-24.117) |
| 60-69                          | 87 (50.0%)                     | 765 (44.5%)                       | 0.001 | 12.933(3.160-52.934) |
| ≥70                            | 38 (21.8%)                     | 236 (13.7%)                       | 0.001 | 27.500(6.626-114.142) |
| Education level                | 67 (38.5%)                     | 663 (38.5%)                       | 0.992 | 0.998(0.725-1.375) |
| (Primary school or below)      |                                |                                   |       |         |
| Marriage(married)              | 141 (81.0%)                    | 1189 (69.1%)                      | 0.001 | 1.908(1.289-2.826) |
| Atrial fibrillation            | 13 (7.5%)                      | 117 (6.8%)                        | 0.740 | 1.106(0.610-2.007) |
| Diabetes mellitus              | 54 (31.0%)                     | 403 (23.4%)                       | 0.026 | 1.471(1.047-2.066) |
| Hypertension                   | 145 (83.3%)                    | 1358 (79.0%)                      | 0.175 | 1.333(0.880-2.019) |
| Hypercholesterolemia           | 67 (38.5%)                     | 674 (39.2%)                       | 0.861 | 0.972(0.705-1.339) |
| Overweight and obesity         | 61 (35.1%)                     | 786 (45.7%)                       | 0.008 | 0.641(0.463-0.888) |
| Smoking                        | 68 (39.1%)                     | 566 (32.9%)                       | 0.101 | 1.308(0.949-1.803) |
| Condition                          | Cases   | Controls | OR     | 95% CI   |
|-----------------------------------|---------|----------|--------|----------|
| Lack of Physical activity         | 134     | 1309     | 0.789  | 0.652-1.923|
| Family history of stroke          | 54      | 548      | 0.824  | 0.708-1.067|
| FPG (mmol/L)                      |         |          |        |          |
| ≤6.1                              | 101(58.0%) | 1192(69.3%) | 0.007 | 1.0-Reference |
| 6.11-6.99                         | 29(16.7%) | 235(13.7%) | 0.091 | 1.456-0.942- |
| ≥7.0                              | 44(25.3%) | 293(17.0%) | 0.003 | 1.772-1.216- |
| HbA1c (≤6.5%)                     | 14(8.0%) | 125(7.3%) | 0.959  | 1.109-0.496- |
| Hcy (≤15mmol/L)                   | 30(17.2%) | 212(12.3%) | 0.122 | 1.393-0.915- |
| TC (≤5.2mmol/L)                   | 91(52.3%) | 716(41.6%) | 0.007 | 1.537-1.125- |
| LDL-C (≤3.12mmol/L)               | 97(55.7%) | 704(40.9%) | 0.001 | 1.467-1.223- |
| HDL-C                             | 32(18.4%) | 194(11.3%) | 0.006 | 1.773-1.175- |
| TG (≤1.7mmol/L)                   | 59(33.9%) | 574(33.4%) | 0.886 | 1.024-0.737- |

Table 3. Determinants of Carotid Plaque Derived from Stepwise multivariable Logistic Regression Analysis
| Variable          | B     | Odds Ratio (95% CI) | P Value | Score |
|-------------------|-------|---------------------|---------|-------|
| Sex              | 0.676 | 1.966               | 1.406-2.749 | 0.001 | 1     |
| age              | NA    | 1.0                 | Reference | 0.001 | 0     |
| 40-49            | 1.794 | 6.012               | 1.410-25.629 | 0.015 | 3     |
| 50-59            | 2.633 | 13.915              | 3.381-57.267 | 0.001 | 5     |
| ≥70              | 3.443 | 31.267              | 7.472-130.83 | 0.001 | 6     |
| marriage (married) | 0.577 | 1.780               | 1.186-2.672 | 0.005 | 1     |
| LDL-C            | 0.701 | 2.015               | 1.443-2.814 | 0.001 | 1     |

(3.12mmol/L)

HDL-C            | 0.756 | 2.130               | 1.360-3.338 | 0.001 | 1     |

(1.04mmol/L)

Figures

![ ROC Curve of risk factors of carotid instability plaque in Derivation Set group ](image1)

![ ROC Curve of predictive model score in Derivation Set group ](image2)

Figure 1
The receiver operating characteristic curve of Derivation Set group for risk factors and predictive model Scoring in high risk group of strokes.

Figure 2

The receiver operating characteristic curve of Validation Set group for risk factors and predictive model Scoring in high risk group of strokes.