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Estimating a two-year recurrence risk of ischemic stroke based on Essen Stroke Risk Score and retinal characteristics

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Abstract

Objectives: Prediction of recurrence risk after initial ischemic stroke helps improve patient outcomes. We estimated the validity of combining the Essen Stroke Risk Score (ESRS) with retinal characteristics to predict the two-year recurrent risk of ischemic stroke. *Methods:* A prospective cohort study was conducted at Shenzhen Traditional Chinese Medicine Hospital. Patients with initial ischemic stroke were recruited. ESRS was measured, and fundus photographs were taken by trained physicians. All patients were followed up for 2 years to determine the outcome of recurrent stroke. Logistic models were built using ESRS alone and combined with ESRS and retinal characteristics. The prognostic value of recurrence risk was evaluated by calculating the area under the receiver operating characteristic curve. *Results:* The total recurrence rate of ischemic events within 2 years was 20%. The risk of recurrence was significantly higher in patients with an ESRS score of >2. Regarding retinal characteristics, patients with recurrent stroke had a lower mean asymmetry index of venules (0.76 vs. 0.77, P=0.00) and bifurcation coefficient of venules (1.29 vs. 1.28, P=0.03) but a higher mean occlusion of arterioles (0.11 vs. 0.13, P=0.01). The area under the curve was 0.5985 based on the logistic regression model with ESRS alone to 0.7294 for the model with both ESRS and retinal characteristics. This study was registered in the Chinese Clinical Trial Registry (registration no. ChiCTR1800019648).
Conclusion: A model combining ESRS with retinal characteristics can accurately predict the risk of recurrent stroke.

Keywords: ESRS; recurrent stroke; ischemic stroke; stroke prediction; retinal characteristics

INTRODUCTION

Stroke, with a death rate of 149.49 per 100 000 in 2018, is the third leading cause of death in China, after malignant tumors and heart disease.[1] The clinical endpoints include re-hospitalization and long-term disability, with stroke recurrence as the leading cause of death. Approximately 80–85% of patients survive after the first ischemic stroke (IS), and 15–30% experience recurrence within the first 2 years.[2] Therefore, the reduction of stroke recurrence is of great importance.

Many tools can be used to predict the risk of recurrent IS. The Essen Stroke Risk Score (ESRS)[3], originally developed in 1996, is widely used to predict stroke recurrence in patients with IS. The ESRS is a 10-item scale for stroke prediction, including risk factors such as age, hypertension, diabetes, previous myocardial infarction (MI), other cardiovascular diseases, peripheral arterial disease, smoking, and previous transient ischemic attack (TIA)/strokes. The scoring range is 0–9 points, with higher scores indicating greater risk. It has been demonstrated that patients with high ESRS should be candidates for intensified secondary prevention strategies.[4] The ESRS has demonstrated external validity for long-term recurrence risk prediction.[5] However, few studies have reported the value of the ESRS in Chinese patients. A study evaluated the predictive accuracy of ESRS using data from a prospective cohort of patients in China, and the results showed that the ESRS could accurately predict the occurrence of 1-year stroke recurrence in patients with acute IS.[6] However, the area under the curve (AUC) of the prediction model values was 0.59, showing no high prediction performance.

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Cerebral vascular changes are a major pathological cause of stroke—retinal vessel circulation shares similar morphology, function, and pathological changes with the cerebral vascular system. Studies have shown that the common pathological basis of fundus blood vessels and stroke is microvascular lesions, and observing the changes in the fundus blood vessels provides a theoretical basis for the early diagnosis and prediction of cerebrovascular disease risk.[7] In our previous study, we observed that retinal vessel characteristics could be used to predict the risk of recurrent stroke.[8] This study aimed to evaluate the value of recurrent risk estimation of IS using the ESRS or combining ESRS and retinal characteristics.

METHODS

Ethics

This study was approved by the Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital (approval number: 2018–75) and was performed in accordance with the guidelines of the Declaration of Helsinki (1964). All patients provided written informed consent to participate in the study. This study was registered in the Chinese Clinical Trial Registry (registration no. ChiCTR1800019648).

Study population

This prospective cohort study was conducted at Shenzhen Traditional Chinese Medicine Hospital from January 2019 to December 2021. Patients who experienced an initial IS were included in the study. The inclusion criteria were stroke onset within 3 months, age >18 years, and adequate sitting balance to perform retinal photography. The exclusion criteria were patients who were clinically unstable, required close monitoring, or had an eye disease that influenced the retinal image.

Data collection

Baseline data for ESRS measurements were collected through face-to-face interviews with trained physicians within 24 hours of admission. The ESRS was calculated according to Diener as follows[9]: 2 points for age >75 years and 1 point each for ages between 65 and 75 years, arterial hypertension, diabetes mellitus, previous MI, other cardiovascular diseases (except MI and atrial fibrillation), peripheral arterial disease (PAD), smoking, and previous TIA or IS in addition to the qualifying event.

Retinal image collection

Retinal photography was performed within 2 days of admission. Retinal images were taken using a Digital Retinal Camera CR-2 AF (Canon, Japan). To ensure the compatibility of the parameters, all retinal images were scaled to 1365 × 1024 pixels and saved in the "JPEG" format. Characteristics related to arteriole-venous nipping, arteriole occlusion, hemorrhages, exudates, tortuosity, bifurcation coefficients, asymmetry of branches, and bifurcation angles were calculated automatically using the 'automatic retinal image analysis system' (Arias), as reported by Zee.[10]

The characteristics of retinal images, such as the central retinal artery equivalent (CRAE), central retinal venous equivalent (CRVE)[11], arteriole occlusions (Aocclusion)[12], bifurcation coefficient of arterioles (BCA), bifurcation coefficient of venules (BCV)[13,14], asymmetry index of arterioles (Aasym), asymmetry index of venules (Vasym), bifurcation angles of arterioles (Aangle) and bifurcation angles of venules (Vangle), arteriole-venous nipping (Nipping), arteriole occlusions (Occlusion)[12], status of hemorrhage and exudates[12,15,16], tortuosity[17], dimension of the venular network (FDv), fractal dimension of the arterioles network (FDa) were recorded.

Follow-up and outcome assessment

Patients were followed up by physicians by phone or in-person interviews 2 years after stroke onset. Recurrent stroke was defined as a new cerebrovascular event. Additionally, deterioration of the original neurological dysfunction to a score of ≥4 points on the NIHSS was defined as a recurrent event.

Statistical analyses

Qualitative variables were expressed as absolute frequencies and percentages. Continuous variables were described using the mean and standard deviation. Significant risk factors for IS recurrence were identified using univariate analysis. For univariate analysis, two independent sample t-tests were conducted to compare continuous data, and chi-square tests were conducted for categorical data. Two multivariate logistic models were developed (Model 1: including only ESRS, Model 2: including both ESRS and retinal characteristics) to evaluate the value of recurrent risk prediction.

Classification accuracy and area under the curve (AUC) of the receiver operating characteristic (ROC) were measured for each model. All data were analyzed using STATA15.0 (Stata Corp., College Station, TX, USA). Two-tailed p-values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 612 patients with IS were enrolled in our study; 450 patients finished a two-year follow-up, of which 90 (20%) had more than one recurrent event. The general clinical characteristics of patients are presented for two groups in Table 1. Compared to patients with no recurrent events, those who experienced recurrent stroke had a higher proportion of hypertension (76.67% vs. 92.22%, P=0.00), prior MI (1.11% vs. 4.44%, P=0.03), other heart diseases (except MI and atrial fibrillation) (19.17% vs. 28.89%, P=0.04), PAD (0.00% vs. 3.33%, P=0.00), and prior TIA or IS (2.22% vs. 12.22%, P=0.00). Furthermore, patients with recurrent stroke had a higher mean ESRS (2.06 vs. 2.53, P=0.00).

Retinal characteristics

Retinal characteristics of the patients are presented for two groups in Table 2. Compared to patients with no recurrence, patients with recurrent stroke had a lower mean asymmetry index of venules (0.76 vs. 0.77, P=0.00) and BCV (1.29 vs. 1.28, P=0.03); however, they had a higher mean occlusion of arterioles (0.11 vs. 0.13, P=0.01).

Essen Stroke Risk Score

Survival free of IS stratified by ESRS is shown in figure 1. The risk of recurrent stroke was significantly higher in patients with an ESRS score of >2 (P=0.00; log-rank test). The distribution of stroke recurrence according to the ESRS is shown in Table 3. The ESRS score of the admitted patients ranged from 0 to 6. The recurrent stroke percentage was mainly in the range of 1–4 points on the ESRS.

Recurrence prediction by combining ESRS with retinal characteristics

The stepwise logistic regression method was used to build classification models that included only ESRS, and combination of both ESRS and retinal variables together. For the ESRS model, statistical significance was set at P=0.001. The area under the ROC curve of the logistic regression model was calculated. The AUC was 0.5985. For the ESRS combining with retinal characteristics model, the significant variables included ESRS (P=0.000), Aocclusion (P=0.001), BCA (P=0.010), Fractal dimension of the venular network (P=0.000), Fractal dimension of arterioles

Table 1: Baseline characteristics of the patients with the no recurrent and recurrent stroke

Risk factors	No recurrent stroke (N=360)	Recurrent stroke (N=90)	X^2	P
Male	265	66	0.00	0.96
Age <65 years	257	63	0.06	0.80
Age 65–70 years	85	21	0.00	0.96
Age >75 years	18	6	0.40	0.53
Hypertension	276	83	10.80	0.00
Diabetes mellitus	145	39	0.28	0.60
Prior MI	4	4	4.58	0.03
other heart disease (except MI and atrial fibrillation)	69	26	4.09	0.04
PAD	0	3	12.08	0.00
Smoking	108	27	0.00	1.00
Prior TIA or IS	8	11	17.80	0.00
ESRS	2.06±1.09	2.53±1.29	-3.52	0.00

MI: myocardial ischemia, PAD: peripheral arterial disease, TIA: transient ischemic attack, IS: ischemic stroke, ESRS: Essen Stroke Risk Score.

Table 2: Retinal characteristics of the patients with the no recurrent and recurrent stroke

Risk factors	No recurrent stroke (N=360)	Recurrent stroke (N=90)	t	P
CRAE	14.00±1.01	13.95±1.01	0.41	0.69
CRVE	20.59±.97	20.53±.99	0.56	0.58
AVR	0.68±.02	0.68±.02	-0.05	0.96
Vasym	0.77±.02	0.76±.02	2.65	0.01
Aasym	0.83±.01	0.83±.01	0.03	0.97
Vangle	68.96±2.23	68.68±2.25	1.08	0.28
Aangle	70.98±2.09	70.90±2.03	0.33	0.74
BCV	1.29±.03	1.28±.02	2.24	0.03
BCA	1.64±.07	1.64±.06	-0.55	0.58
Tortuosity	0.36±.07	0.38±.06	-1.90	0.06
Nipping	0.30±.08	0.30±.07	-0.22	0.83
Hemorrhage	0.22±.06	0.24±.07	-1.92	0.06
Aocclusion	0.11±.05	0.13±.08	-2.72	0.01
FDa	1.18±.02	1.18±.01	1.55	0.12
FDv	1.17±.07	1.18±.01	-1.01	0.31

CRAE: central retinal artery equivalent, CRVE: central retinal vein equivalent, AVR: arteriole-to-venule ratio, Vasym: asymmetry index of venules, Aasym: asymmetry index of arterioles, Vangle: bifurcation angles of venule, Aangle: bifurcation angles of arterioles, BCV: bifurcation coefficient of venule, BVA: bifurcation coefficient of arterioles, Nipping: arteriole-venous nipping, Aocclusion: arteriole occlusion, FDa: fractal dimension of the retinal arterioles, FDv:fractal dimension of the retinal vasculature.

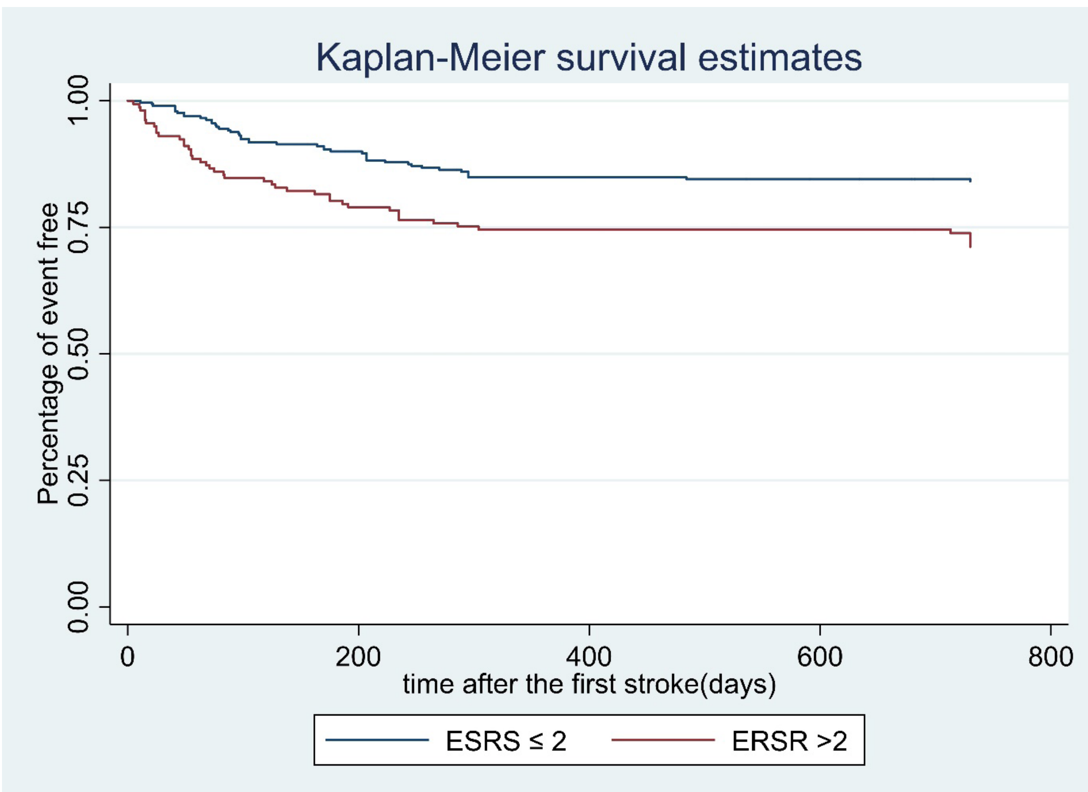

Figure 1. Kaplan–Meier curve of survival free of ischemic stroke stratified by ESRS >2 vs. ESRS ≤2 (n = 450).

Table 3: Stroke recurrences for each ESRS

ESRS	Numbers of recurrent stroke patients	Percentage of recurrent stroke patients	Total number of patients
0	2	2.22	25
1	22	24.44	110
2	21	23.33	158
3	22	24.44	94
4	18	20.00	54
5	4	4.44	8
6	1	1.11	1
Total	90	100.00	450

ESRS: Essen Stroke Risk Score.

network (P=0.000), and bifurcation angles of venular (P=0.021)(Table 4). The area under the ROC curve of the multivariate logistic regression model was calculated to evaluate the predictive ability of significant factors. The AUC was 0.7294. The goodness-of-fit was 0.9891 (Figure 2).

DISCUSSION

Stroke risk scales are widely used to evaluate the risk of recurrent strokes. Reportedly, the ESRS validates the prediction of recurrent risk for many types of IS.[18-20] Patients with an ESRS of 1–4 have a low to moderate risk of recurrence; clear trends towards higher stroke recurrence have been seen in patients with a higher ESRS. However, our study revealed that approximately 75% of the patients with recurrent ischemic events scored less than three points on the ESRS scale. The area under the ROC curve was 0.59, which proved not to have a high predictive value for recurrent IS within 2 years. This may be because the recurrence rates were based on the population from the Reduction of Atherothrombosis for Continued Health (REACH) registry[4], and there is still a lack of in-depth research on whether the tool is suitable for Chinese patients. Hence, we are committed to developing a tool that can improve the effectiveness of predicting the recurrence risk of IS.

The validity of predicting the risk of IS recurrence based on clinical risk factors is limited. However, the development of imaging has enabled the visualization and quantification of vascular structures to supply a more accurate prediction tool for recurrent stroke. Nam[21] built a predictive model composed of demographic, clinical, and radiological findings to predict long-term IS recurrence and showed good discrimination. Therefore, vascular imaging can more accurately reflect the differences between each patient in clinical settings and improve the understanding of cerebrovascular disease from multiple dimensions such as lesion nature, vascular condition, cerebral hemodynamics, collateral circulation, and plaque vulnerability, to improve recurrent IS prediction.

Table 4: Logistic regression for the recurrence of IS by combining ESRS with retinal characteristics

Recurrent stroke	Coef.	Std.Err	Z	P	95% Confidence interval	
					Lower	Upper
ESRS	.4420	.1140	3.88	0.000	.2186	.6655
Aocclusion	7.1232	2.0562	3.46	0.001	3.0933	11.1533
BCV	-13.7535	5.3686	-2.56	0.010	-24.2759	-3.2313
FDv	96.4774	20.6078	4.68	0.000	56.0869	136.8679
FDa	-80.7218	18.4839	-4.37	0.000	-116.9497	-44.4938
Vangle	-.1490	.0646	-2.31	0.021	-.2756	-.0224
Constant	5.7966	15.5796	0.37	0.710	-24.7388	36.3321

ESRS: Essen Stroke Risk Score, Aocclusion: arteriole occlusion, BCV: bifurcation coefficient of venule, FDv:fractal dimension of the retinal vasculature, FDa:fractal dimension of the retinal arterioles, Vangle: bifurcation angles of venule.

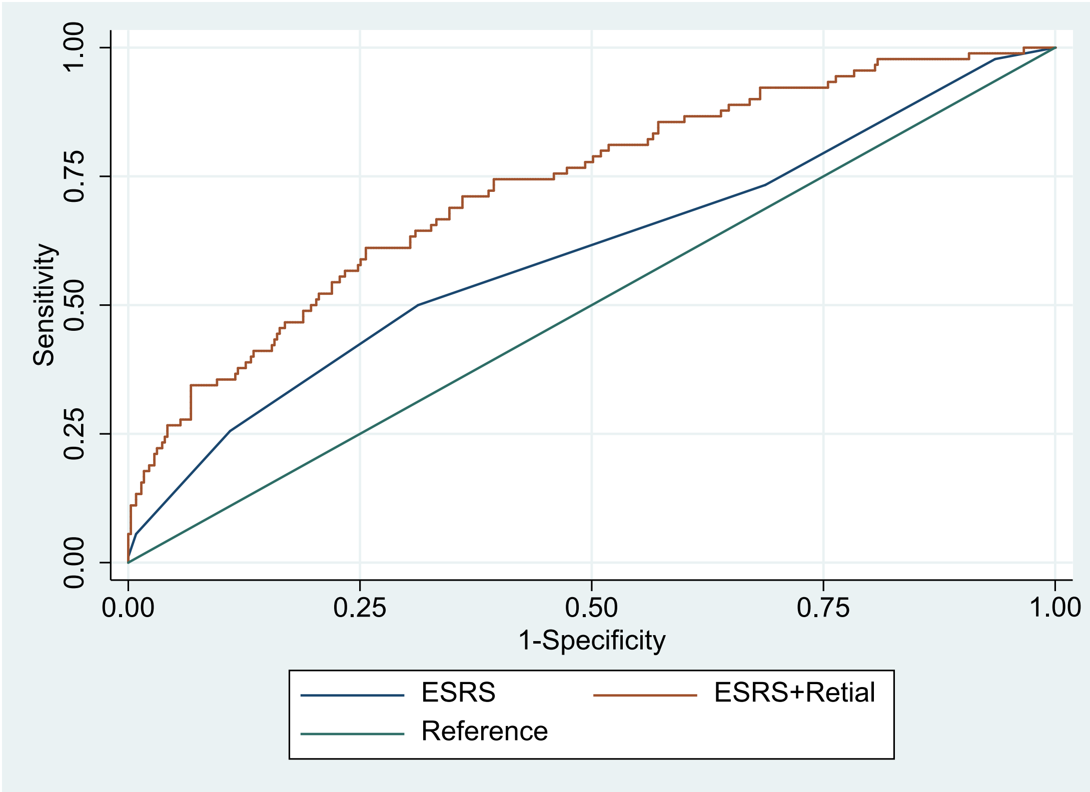

Figure 2. ROC curve for the model based on different sets of characteristics

Fundus vessels, such as microvessels *in vivo*, can reflect pathological changes in intracranial vessels. Many studies have been conducted on the correlation between retinal vessels and stroke and provided a theoretical basis for the early diagnosis and prediction of the risk of cerebrovascular diseases by observing the changes in retinal vessels.[7] In our previous study, we observed a relationship between retinal characteristics and risk factors of IS recurrence and established a prediction model of IS recurrence, which can be used to screen high-risk groups of IS patients.[8,22] In this study, we observed that the combination of retinal characteristics with the ESRS could better predict the recurrence of IS.

Our study had limitations. We did not separate the data for model validation due to the relatively small sample size. For future studies, we can add more predictors to improve the effectiveness of the model prediction. Also, machine learning can be used to discover the characteristics of retinal images to make a more accurate classification of stroke recurrences.

In conclusion, compared with the model built with the ESRS alone, the model built by combining ESRS with retinal characteristics can more accurately predict the risk of recurrent stroke.

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DISCLOSURE

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Conflict of interest: None

Data availability: All data generated or analyzed during this study are included in this article. Fundus images of all patients and further inquiries regarding the data can be obtained by contacting the corresponding author.

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