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Estimation of stroke severity with National Institutes of Health Stroke Scale grading and retinal features

A cross-sectional study

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Abstract

To estimate National Institutes of Health Stroke Scale (NIHSS) grading of stroke patients with retinal characteristics.

A cross-sectional study was conducted in Shenzhen Traditional Chinese Medicine Hospital. Baseline information and retinal photos were collected within 2 weeks of admission. An NIHSS score was measured for each patient by trained doctors. Patients were classified into 0 to 4 score group and 5 to 42 score group for analysis. Three multivariate logistic models, with traditional clinical characteristics alone, with retinal characteristics alone, and with both, were built.

For clinical characteristics, hypertension duration is statistically significantly associated with higher NIHSS score ($P=.014$). Elevated total homocysteine levels had an OR of 0.456 ($P=.029$). For retinal characteristics, the fractal dimension of the arteriolar network had an OR of 0.245 ($P<.001$) for the left eyes, and an OR of 0.417 ($P=.009$) for right eyes. The bifurcation coefficient of the arteriole of the left eyes had an OR of 2.931 (95% CI 1.573–5.46, $P=.001$), the nipping of the right eyes had an OR of 0.092 ($P=.003$) showed statistical significance in the model.

The area under receiver-operating characteristic curve increased from 0.673, based on the model with clinical characteristics alone, to 0.896 for the model with retinal characteristics alone and increased to 0.931 for the model with both clinical and retinal characteristics combined.

Retinal characteristics provided more information than clinical characteristics in estimating NIHSS grading and can provide us with an objective method for stroke severity estimation.

Abbreviations: AUC = area under receiver-operating characteristic curve, CI = confidence interval, OR = odds ratio, ROC = the receiver operating characteristic, TC = total cholesterol, TG = triglyceride.

Keywords: National Institutes of Health Stroke Scale, retinal features, stroke severity estimation

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1. Introduction

Stroke is the second leading cause of death and a major cause of disability, worldwide. In China, stroke is the leading cause of death. The incidence of the first stroke in adults aged 40 to 74 has increased from 189 per 100,000 in 2002 to 379 per 100,000 in 2013, with an annual increase of 8.3%.[1–3] The burden of stroke is still increasing due to the aging population.[4] The neurological impairments, emotional and social consequences, and the high risk for recurrence can cause great physical, social, and psychological burdens on stroke patients and their families.[5] Since the mortality and 5-year readmission rates were different for the severity of the different stroke patients, the measurement of stroke severity is critical for stroke management and secondary prevention.[6] Accurate and easy measurement of stroke severity can help with stroke management and secondary prevention since the mortality and 5-year readmission rates of stroke patients differ according to stroke severity.[6]

Originally developed in 1989, the National Institutes of Health Stroke Scale (NIHSS) is a 15-item impairment scale for stroke severity measurement[7] and is now widely used as a standardized evaluation of symptoms and signs for strokes.[8] The scoring range is 0 to 42 points, with higher numbers indicating greater severity. A score of <5 represents no stroke symptoms or a minor stroke, a score of 5 to 15 represents a moderate stroke, a score of 16 to 20 represents a moderate to severe stroke, and a score of 21 to 42 represents a severe stroke. Baseline NIHSS scores have been reported to strongly predict major clinical outcomes after stroke.[9] Stroke patients with a score of no >4 are highly likely to have good clinical outcomes.[10] A 1-point increase in a patient's baseline NIHSS score can lead to an increase in the probability of a poor 2-year postoperative outcome, by 28.5%.[11] It can also help with estimating the probability of each stroke subtype.[12]

Retinal vessels at the back of the eye are the only directly visible vessels in the whole body; they represent a unique site where the microcirculation can be imaged directly,[13] providing an opportunity to study, in vivo, the structure and pathology of the circulation. They can also help to detect changes in microvasculature relating to the development of cardiovascular disease.[14] Retinal vascular changes are a summary marker of a patient's lifetime exposure to risk factors,[15] and many retinal characteristics are related to strokes and show great value in stroke recurrence prediction.[16,17] Currently, no research has investigated the relationship between retinal characteristics and the NIHSS grading.

2. Materials and methods

2.1. Study population

We conducted a cross-sectional study in Shenzhen Traditional Chinese Medicine Hospital from September 2018 to March 2019. A total of 165 stroke patients were enrolled in our study. Inclusion criteria included the clear diagnosis of stroke with computed tomography or cranial magnetic resonance scan results, an age of 30 to 80 years, and an adequate sitting balance to carry out the retinal photography. Patients who were clinically unstable, required close monitoring, or who had an eye disease that had influenced the retinal vessel structures were excluded from our study.

2.2. Measurement and definition

Upon admission, baseline information including age, sex, medical history, physical examination result, and laboratory test results was collected by trained doctors. All patients underwent detailed radiographic evaluations, including a cranial magnetic resonance (MR) scan and a duplex color Doppler ultrasound or contrast-enhanced MR angiography. The NIHSS score was measured by their doctors in charge within 24 hours of admission.[8] Retinal photography was carried out within 2 weeks of admission.

Body mass index was calculated as weight (kg) divided by the square of height (m). Diabetes mellitus (DM) was defined as a fasting blood glucose concentration >7.0 mmol/L or an glycated hemoglobin value >6.5%; patients with a history of diabetes were also labeled as having DM. Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg, or patients with a history of hypertension. Dyslipidemia was defined as total cholesterol (TC) ≥240 mg/L, triglyceride (TG) ≥200 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, or as patients with a history of dyslipidemia. Details regarding measuring the characteristics of retinal imaging analysis have been documented elsewhere.[17] Briefly, characteristics related to arteriole-venous nicking, arteriole occlusion, hemorrhages, exudates, tortuosity, bifurcation coefficients, asymmetry of branches, and bifurcation angles were calculated automatically using the automatic retinal image analysis system. Retinal information for both eyes were used in our analysis.

2.3. Statistical analysis

Quantitative variables were expressed as the mean ± standard deviation, and categorical variables were expressed as counts with percentages. For univariate analysis, we conducted 2 independent samples *t* tests to compare continuous data and used chi-square tests for categorical data. Three multivariate logistic models were developed (namely: Model 1: including only clinical characteristics, Model 2: including only retinal characteristics, and Model 3: including both clinical and retinal characteristics) to further investigate the associations between retinal characteristics and NIHSS score grading. Classification accuracy and the area under the curve of the receiver operating characteristic (ROC) were measured for each model. The cut-off point for the NIHSS score was 4, and a value of no >4 was defined as being indicative of a minor stroke.[18]

All statistical analyses were performed using SPSS 24.0(SPSS Inc., IBM, Chicago, IL,USA). Two-tailed P values of <.05 were considered statistically significant.

3. Results

The general characteristics of the study participants are summarized in Table 1. The average age was 54.88 standard deviation: ±11.09) years; there were more men (83.03%) than women and more ischemic stroke patients (70.3%) than hemorrhage stroke patients (27.88%). The average NIHSS score was 4.92 (standard deviation: ±2.80), and nearly 53.33% of patients had an NIHSS score >4. A total of 138, 107, and 62 patients had hypertension, diabetes, and dyslipidemia, respectively. The majority of study participants were non-smokers (67.27%) and non-drinkers (76.97%).

In the univariate analysis, clinical characteristics such as age, body mass index, sex, stroke subtype, diabetes, smoking habit, and drinking habit, showed no statistical significance between the 2 groups ($P > .05$). Hypertension duration was positively associated with increasing NIHSS grade ($P = .014$), while elevated

Table 1

Baseline characteristics of the 165 patients.

	Baseline characteristics
Age	54.88 ± 11.09
NIHSS score	4.92 ± 2.80
NIHSS score group	
<5	77 (46.67%)
≥5	88 (53.33%)
Gender	
Female	28 (16.97%)
Male	137 (83.03%)
Stroke subtype	
Ischemic	116 (70.3%)
Hemorrhage	46 (27.88%)
Both	3 (1.82%)
Hypertension	
No	27 (16.36%)
Yes	138 (83.64%)
Diabetes	
No	107 (64.85%)
Yes	58 (35.15%)
Dyslipidemia	
No	103 (62.42%)
Yes	62 (37.58%)
Smoking	
No	111 (67.27%)
Former smoker	37 (22.42%)
Current smoker	17 (10.3%)
Drinking	
No	127 (76.97%)
Former drinker	29 (17.58%)
Current drinker	9 (5.45%)

total homocysteine (tHcy) levels were negatively associated with increasing NIHSS grade ($P = .006$) (Table 2).

Three multivariate logistic models were built for stroke severity estimation. Model 1 included only clinical information, Model 2 included only retinal information, and Model 3 included both (Table 3). Both main effects and interaction effects were included in models. Both Model 1 and Model 3 showed that a hypertension duration was positively associated with NIHSS score. Compared with non-hypertension patients, patients with hypertension duration <5 years had an OR of 2.599 (95% CI 0.995–6.788, $P = .051$), patients with hypertension duration >5 years but <10 years had an OR of 3.747 (95% CI 1.127–12.458, $P = .031$), and patients with hypertension duration of >10 years had an OR of 1.309 (95% CI 0.498–3.442, $P = .583$). The elevated tHcy levels with an OR of 0.456 (95% CI 0.226–0.922, $P = .029$) showed a negative association with NIHSS score, which was consistent with the univariate results.

In Model 2, retinal characteristics including the fractal dimension of the arteriolar network (FDa) of both eyes (odds ratio [OR] = 0.245 [95% CI 0.13–0.459, $P < .001$]) for left eyes and 0.417 (95% CI 0.216–0.807, $P = .009$) for right eyes, and nipping of the right eyes (OR = 0.092 [95% CI 0.02–0.434, $P = .003$]) were negatively associated with NIHSS score. Several interactions (RAVR*RNipping, LCRVE*RNipping, RBCV*RNipping, RCRAE*RNipping, LAocclusion*RNipping) strengthened such negative association, while LCRAE*RNipping attenuated the negative association. The bifurcation coefficient of the arteriole of the left eyes (LBCA) with an OR of 2.931 (95% CI 1.573–5.46, $P = .001$) was positively associated with NIHSS score grading. Several other interactions between retinal characteristics (LAangle*LNipping, LNipping*RFDv, LCRAE*RFDv, LHemorrhage*RFDv, RBCA*RVangle, sLFDa*sRFDv) also showed statistical significance in Model 2.

Model 3 included both clinical and retinal characteristics. The specific OR and P values for each characteristic varied slightly, but the main results were consistent with the first 2 models.

Table 2

Comparison between 2 NIH stroke score groups.

Characteristics	NIHSS ≤ 4	NIHSS > 4	P
Age	55.23 ± 12.06	54.58 ± 10.24	.710
BMI	23.8 ± 2.93	23.11 ± 3.11	.146
Gender			.380
Female	11 (39.29%)	17 (60.71%)	
Male	66 (48.18%)	71 (51.82%)	
Stroke subtype			.403
Ischemic	57 (49.14%)	59 (50.86%)	
Hemorrhage	18 (39.13%)	28 (60.87%)	
Both	2 (66.67%)	1 (33.33%)	
Hypertension			0.063
No	17 (62.96%)	10 (37.04%)	
Yes	60 (43.48%)	78 (56.52%)	
Years of hypertension			0.014
0	17 (62.96%)	10 (37.04%)	
<5	22 (36.07%)	39 (63.93%)	
5–10	7 (30.43%)	16 (69.57%)	
>10	31 (57.41%)	23 (42.59%)	
Diabetes			0.338
No	47 (43.93%)	60 (56.07%)	
Yes	30 (51.72%)	28 (48.28%)	
Dyslipidemia			0.533
No	50 (48.54%)	53 (51.46%)	
Yes	27 (43.55%)	35 (56.45%)	
Elevated tHcy levels			0.006
No	44 (39.29%)	68 (60.71%)	
Yes	33 (62.26%)	20 (37.74%)	
Smoking			0.807
No	50 (45.05%)	61 (54.95%)	
Former smoker	18 (48.65%)	19 (51.35%)	
Current smoker	9 (52.94%)	8 (47.06%)	
Drinking			0.289
No	57 (44.88%)	70 (55.12%)	
Former drinker	17 (58.62%)	12 (41.38%)	
Current drinker	3 (33.33%)	6 (66.67%)	
LCRAE	14.8 ± 0.7	14.7 ± 0.63	0.334
LCRVE	21.24 ± 0.64	21.17 ± 0.64	0.485
Laangle	71.35 ± 1.81	71.55 ± 1.59	0.433
LBCA	1.62 ± 0.07	1.63 ± 0.08	0.196
LBCV	2.18 ± 7.75	2.07 ± 7.24	0.924
Lacclusion	0.1 ± 0.03	0.1 ± 0.04	0.908
LNipping	0.18 ± 1.01	–0.16 ± 0.97	0.026
LFDa	0.31 ± 1.02	–0.28 ± 0.9	<0.001
LFDv	0.12 ± 1.07	–0.11 ± 0.93	0.135
RCRAE	13.95 ± 0.62	13.91 ± 1.57	0.860
RCRVE	20.75 ± 0.73	20.76 ± 0.91	0.960
Raangle	70.39 ± 2.15	70.07 ± 2.02	0.334
RBCA	1.64 ± 0.06	2.44 ± 7.41	0.350
RBCV	1.28 ± 0.03	2.07 ± 7.38	0.349
Racclusion	0.11 ± 0.05	0.11 ± 0.06	0.837
RNipping	–0.09 ± 0.6	0.07 ± 1.25	0.307
RFDa	0.09 ± 0.09	–0.07 ± 1.36	0.304
RFDv	0.2 ± 1.09	–0.18 ± 0.87	0.016

The first letter "L," "R" indicates the characteristics of left eyes or right eyes. Aangle = bifurcation angles of arterioles; AVR = arteriolar-to-venular diameter ratio; BCA = bifurcation coefficient of arteriole, BMI = body mass index; CRVE = central retinal venular equivalent; CRAE = central retinal artery equivalent; FDa = fractal dimension of arteriolar network; FDv = fractal dimension of venular network.

Table 3

Multivariate logistic model of NIHSS grading.

	Model 1		Model 2		Model 3	
Characteristics	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
No Hypertension_	Ref	.054	Ref	/	Ref	.083
Hypertension_Years<5	2.599 (0.995,6.788)	.051	/	/	4.67 (1.013,21.529)	.048
Hypertension_Years<10	3.747 (1.127,12.458)	.031	/	/	5.468 (0.857,34.875)	.072
Hypertension_Years>=10	1.309 (0.498,3.442)	.583	/	/	1.361 (0.316,5.848)	.679
Elevated tHcy levels	0.456 (0.226,0.922)	.029	/	/	0.178 (0.055,0.577)	.004
LFDa	/	/	0.245 (0.13,0.459)	<.001	0.253 (0.129,0.496)	<.001
LBCA	/	/	2.931 (1.573,5.46)	.001	3.849 (1.834,8.076)	<.001
RNipping	/	/	0.092 (0.02,0.434)	.003	0.061 (0.009,0.418)	.004
RFDa	/	/	0.417 (0.216,0.807)	.009	0.437 (0.214,0.895)	.024
RAVR*RNipping	/	/	0.558 (0.414,0.754)	<.001	0.549 (0.392,0.769)	<.001
LCRVE*RNipping	/	/	0.485 (0.333,0.706)	<.001	0.476 (0.313,0.724)	.001
RBCV*RNipping	/	/	0.036 (0.005,0.277)	.001	0.02 (0.002,0.249)	.002
LCRAE*RNipping	/	/	2.945 (1.678,5.167)	<.001	3.034 (1.615,5.699)	.001
RCRAE*RNipping	/	/	0.012 (0.001,0.19)	.002	0.008 (0,0.229)	.005
LAocclusion*RNipping	/	/	0.338 (0.124,0.927)	.035	0.315 (0.098,1.02)	.054
LAangle*LNipping	/	/	0.199 (0.096,0.413)	<.001	0.144 (0.061,0.342)	<.001
LNipping*RFDv	/	/	0.293 (0.151,0.568)	<.001	0.231 (0.109,0.49)	<.001
LCRAE*RFDv	/	/	6.133 (2.863,13.138)	<.001	7.34 (3.106,17.347)	<.001
LHemorrhage*RFDv	/	/	3.865 (1.793,8.331)	.001	3.798 (1.653,8.727)	.002
RBCA*RVangle	/	/	0.617 (0.483,0.787)	<.001	0.545 (0.409,0.726)	<.001
sLFDa*sRFDv	/	/	0.35 (0.192,0.638)	.001	0.347 (0.181,0.664)	.001
Constant		.585		<.001		.1

Aangle=bifurcation angles of arterioles; AVR=arteriolar-to-venular diameter ratio; BCA=bifurcation coefficient of arteriole; CRAE=central retinal artery equivalent; CRVE=central retinal venular equivalent; FDa=fractal dimension of arteriolar network; FDv=fractal dimension of venular network.

Further diagnostic testing was performed to investigate the prediction accuracy of the 3 models. The area under the ROC (AUC) curve for the multivariate logistic regression with traditional characteristics alone was 0.673 (95% CI 0.591–0.755), with a sensitivity of 49.4% and specificity of 72.7%; the AUC for the multivariate logistic regression with retinal characteristics alone was 0.896 (95% CI 0.850–0.942), with a sensitivity of 76.6% and specificity of 86.2%; and the AUC curve for the multivariate logistic regression with both clinical and retinal characteristics was 0.931 (95% CI 0.894–0.967) with a sensitivity of 80.5% and specificity of 88.5% (Fig. 1).

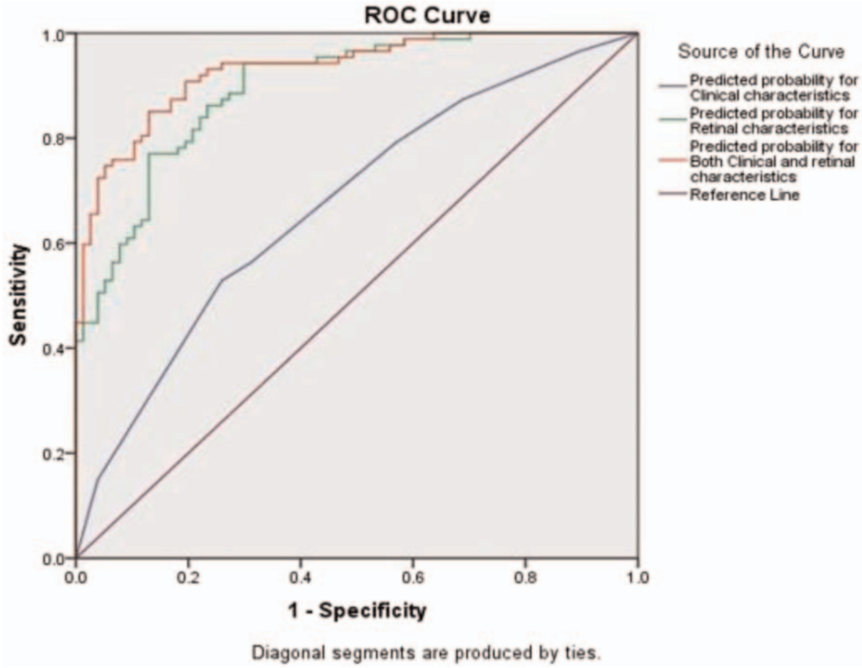

Figure 1. The ROC curve of the 3 multivariate logistic models. ROC=the receiver operating characteristic.

4. Discussion

Since acute stroke severity diagnosis remains problematic due to frequently inaccurate clinical estimates,[19] and because required diagnostic ancillary tests may be time-consuming or unavailable on an emergent basis,[20] objective novel measurement methods that are easy and accurate should be developed to help with clinical diagnosis. To our knowledge, this is the first study considering the value of retinal characteristics in estimating stroke severity with an NIHSS score.

These results showed that using clinical variables alone would not have enough of a discriminate capability to separate patients with high NIHSS scores from patients with low NIHSS scores. Only hypertension duration and elevated tHcy levels showed statistical significance in both the univariate and multivariate analyses; no other traditional clinical characteristics showed statistical significance. Patients with a hypertension duration >5 years had a greater probability of higher NIHSS score grading compared with those with a hypertension duration ≤ 5 years, which is consistent with previous studies.[21–26] It was surprising to find that elevated tHcy levels were negatively associated with NIHSS score grading. The effect of elevated tHcy levels on stroke has been debated in previous studies. Several studies showed that elevated tHcy levels are an independent risk factor for ischemic stroke, while others reached a contrary conclusion.[27–32] The reason that no other traditional clinical characteristics were statistically significant may be due to the high prevalence of these risk factors in both groups. As a result, although these common risk factors are of great importance in developing stroke, they provide little information in estimating the severity of the disease.

For the models involving retinal characteristics, we included not only the main effects of retinal characteristics but also several interaction effects to improve the ability of the models. The model with only retinal characteristics performed better than the model with only clinical characteristics, and the model with both clinical and retinal characteristics performed best. This implies that retinal characteristics provided more information than clinical characteristics in the classification of NIHSS score grading. Thus, it is essential to incorporate retinal image information in the risk assessment models to increase their discrimination power for specific events.

Our research had several limitations. First, due to the relatively small sample size, we did not separate data for the model validation, which needs to be addressed in future studies. Second, the NIHSS scores were classified into only 2 groups in our analysis because few patients had a score >16. Finally, this is a cross-sectional study, and the results can only reveal the potential relationship; therefore, a prospective cohort is needed to confirm the relationship in the future.

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Author contributions

All authors participated in the study design. Yuanyuan Zhuo and Weiqu Yuan acquired the data. Jack Lee and Benny Zee calculated the retinal characteristics using ARIA system. Benny Zee revised the manuscript. All authors read and approved the final manuscript.

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