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Clinical and imaging risk factors for early neurological deterioration and long-term neurological disability in patients with single subcortical small infarction

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Abstract

Introduction This study aims to evaluate the clinical and imaging risk factors for early neurological deterioration (END) and long-term neurological disability in patients with Single subcortical small infarction (SSSI).

Methods We retrospectively included SSSI patients hospitalized. Outcomes were defined as modified Rankin Scale (mRS) score > 2 at follow-up and the occurrence of END during hospitalization. Multivariate logistic regression identified independent predictors of END and long-term outcomes. Stepwise regression analysis was used to develop a predictive model for poor outcomes. The predictive performance of risk factors and the model was assessed using receiver operating characteristic (ROC) curves.

Results A total of 289 SSSI patients were included. During hospitalization, 18 patients (6.2%) experienced END, and 29 patients (10%) had neurological disability at a median follow-up of 21.4 (16.7–25.2) months. Multivariate analysis showed the National Institutes of Health Stroke Scale (NIHSS) score(OR 1.43, 95% CI 1.19–1.73, $P < 0.001$), and neutrophil to high-density lipoprotein cholesterol ratio (NHR) (OR 1.28, 95% CI 1.02–1.60, $P = 0.034$) were independently associated with END. Age (OR 1.08, 95% CI 1.01–1.15, $P = 0.028$), NIHSS (OR 1.60, 95% CI 1.29–1.98, $P < 0.001$), symptomatic intracranial artery stenosis (OR 5.26, 95% CI 1.56–17.71, $P = 0.007$), lacune number (OR 1.51, 95% CI 1.13–2.04, $P = 0.006$), the degree of brain atrophy (OR 2.03, 95% CI 1.19–3.46, $P = 0.01$), and mean hemoglobin concentration (MCHC) (OR 0.96, 95% CI 0.92–0.99, $P = 0.04$) were independently associated with neurological disability. The predictive model for END (included NIHSS score and NHR level) and long-term neurological disability (included age, NIHSS score, symptomatic intracranial artery stenosis, number of lacunes, and brain atrophy) showed areas under the ROC curve of 0.836 and 0.926, respectively.

Conclusion High NIHSS and NHR are independent risk factors for END. Age, NIHSS, symptomatic intracranial artery stenosis, the number of lacunes, and brain atrophy are predictors of neurological disability in SSSI patients.

Keywords Single subcortical small infarction, Cerebral small vessel disease, Magnetic resonance imaging, Early neurological deterioration, Prognosis

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Introduction

Single small subcortical infarction (SSSI), an infarction in the territory of penetrating arteries [1], accounts for approximately 20% of all ischemic strokes [2]. Due to the small size of the lesions and generally mild symptoms, clinicians may misjudge the prognosis of these patients. However, SSSI can still result in severe long-term neurological disabilities or even death. Additionally, despite adequate antithrombotic and lipid-lowering therapies, some patients with SSSI may experience early neurological deterioration (END) during hospitalization. END is characterized by sudden worsening of symptoms such as limb weakness, speech difficulties, and swallowing issues [3]. END can significantly impact long-term outcomes [4], and previous studies have reported END incidence rates ranging from 3% to 31.1% [5, 6]. Admission National Institutes of Health Stroke Scale (NIHSS) score, history of hypertension, and low-density lipoprotein cholesterol (LDL-C) levels are predictors of outcomes in SSSI patients [6]. Additionally, studies have suggested that systemic inflammation markers, such as the neutrophil-to-lymphocyte ratio (NLR), are associated with END [7]. However, studies focusing on risk factors for END and long-term neurological disability in SSSI patients is still limited. Some demographic and cardiovascular risk factors have not been thoroughly examined, and comprehensive models for predicting adverse outcomes are currently unavailable.

SSSI is closely related to cerebral small vessel disease (CSVD), and its major pathogenesis includes small vessel disease, with three main mechanisms: (1) Lipohyalinosis in the distal perforating arteries; (2) Micro-arteriosclerosis in the proximal perforating arteries; (3) Atherosclerosis of the parental artery obstructs the orifice of the perforating arteries [8]. The major imaging markers of CSVD include white matter hyperintensities (WMHs), lacunes, enlarged perivascular spaces (ePVS), cerebral microbleeds, and brain atrophy [9]. The SSSI lesions may convert to other CSVD imaging markers, such as lacunes and WMHs [10, 11]. Previous studies have also demonstrated that the overall burden of CSVD is associated with poor outcomes at discharge in SSSI patients [12, 13]. However, there is limited research on the differential impact of CSVD imaging marker types and locations on the END and long-term outcomes of SSSI. It remains unclear which combinations of markers are most predictive of SSSI prognosis. Additionally, the morphology and location characteristics of SSSI lesions may be related to outcomes. Lesion size and specific locations, such as the pons and internal capsule, have been shown to be associated with END in SSSI patients [4, 14, 15], but overall, the sample sizes in these studies have been limited.

Given the current insufficient exploration of factors influencing the occurrence of END during hospitalization and long-term neurological disability in SSSI patients, this study first aimed to evaluate potential risk factors for END and long-term prognosis. Clinical, neuroimaging (including CSVD features and the morphology and location of infarcts) and laboratory indicators were comprehensively considered. Furthermore, we aimed to develop predictive models for adverse outcomes (END and long-term disability) of SSSI to facilitate early identification and intervention for high-risk patients in clinical practice.

Method

Study population

The definition of SSSI is single acute ischemic infarct located in the corona radiata or centrum semiovale, thalamus, basal ganglia, or brainstem, showing hyperintensity on DWI with a diameter ≤ 20 mm [16]. We retrospectively included consecutive patients with SSSI who were hospitalized in the Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, and completed head MRI scans from April 2021 to June 2022. The inclusion criteria were: (1) admission within 72 h after symptom onset, (2) maximum lesion diameter ≤ 20 mm on diffusion-weighted imaging (DWI) sequence, and (3) age > 18 years. The exclusion criteria were: (1) receiving endovascular thrombectomy, (2) pre-stroke modified Rankin Scale score (mRS) > 1, (3) concurrent malignancy, vasculitis, systemic immune diseases, or hemorrhagic stroke, (4) multiple infarct lesions, and (5) current or previous cortical infarction and/or cerebellar infarction. The study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20210731). All patient information in this retrospective study was de-identified and anonymized, and written informed consent was obtained from each participant.

Outcome definition

Two neurologists who were blinded to the baseline data conducted follow-up assessments of SSSI patients independently. The NIHSS score on admission was used to assess the severity of symptoms of SSSI. END was defined as an increase in the NIHSS score by ≥ 2 points or in the limb weakness sub-score by ≥ 1 point after admission [7]. Long-term poor neurological outcomes were determined based on whether the mRS score > 2 at follow-up. The mRS scoring criteria range from 0 (no symptoms) to 6 (death).

Clinical assessment

We systematically collected demographic information (e.g., gender, age), medical history (e.g., hypertension, diabetes, hyperlipidemia, coronary artery disease,

stroke), laboratory test results (e.g.,LDL-C), time from onset to admission (OTT), diastolic blood pressure (DBP) and systolic blood pressure (SBP) on admission. Laboratory samples were collected on the day following admission. Hypertension was defined as a pre-admission or in-hospital systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications. Diabetes was defined as a pre-admission or in-hospital fasting blood glucose > 7 mmol/L and/or postprandial blood glucose ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5%, or current use of hypoglycemic medications. Hyperlipidemia was defined as total cholesterol (TC) ≥ 5.2 mmol/L and/or LDL-C ≥ 3.4 mmol/L and/or triglycerides (TG) ≥ 1.7 mmol/L, or current use of lipid-lowering medications. NLR and neutrophiltohigh-density lipoprotein cholesterol(HDL-C) ratio (NHR) were calculated by the formulas: NLR = neutrophil count (cells) / lymphocyte count (cells) [17] NHR = neutrophil count (10^9 cells) / HDL-C (mmol/L) [18].

Imaging evaluation

A 3 Tesla brain MRI was performed within 48 h of admission, including fluid-attenuated inversion recovery imaging (FLAIR), T2-weighted imaging, T1-weighted imaging, and DWI. (FLAIR: repetition time (TR): 8000 ms, echo time (TE): 150 ms, matrix size of 512 × 512. slice thickness: 5 mm, interslice gap:1.5 mm; DWI: TR of 3000 ms, TE: 65.3ms, slice thickness: 5 mm, interslice gap: 1 mm, a b-value: 1000 s/m^2). Two neuroradiologists, blinded to the clinical information and follow-up data, independently performed the imaging evaluations. In cases of disagreement, a senior neuroimaging expert made the final decision. The assessments included arterial stenosis, infarct lesion diameter, lesion location, degree of suspected vascular-original WMHs, extent of ePVS, number of chronic lacunar infarctions, and degree of brain atrophy.

The severity of arterial stenosis was assessed using digital subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Symptomatic extracranial arterial stenosis was defined as ≥ 50% stenosis of the cervical arteries (common carotid artery, extracranial internal carotid artery, and extracranial vertebral artery) with ipsilateral acute cerebral infarction or brain ischemic symptoms. Symptomatic intracranial arterial stenosis was defined as ≥ 50% stenosis of intracranial arteries with downstream acute cerebral infarction or brain ischemic symptoms.

SSSI lesion were identified as areas of hyperintensity on DWI, T2, and FLAIR, and hypointensity on apparent diffusion coefficient (ADC) maps. Suspected vascular-original WMHs were identified as hyperintensities in the white matter on FLAIR or T2-weighted images, categorized into periventricular WMHs and subcortical WMHs, and assessed using the Fazekas scale [19], scoring from 0 to 3 at each location. ePVS were identified as small (≤ 3 mm) round or linear hyperintensities in the basal ganglia and centrum semiovale on T2-weighted images and graded from 0 to 4 based on number: 0 = no ePVS, 1 = 1–10 ePVS, 2 = 11–20 ePVS, 3 = 21–40 ePVS, 4 = > 40 ePVS [20]. The distribution assessment of the two locations, with the total ePVS burden being the sum of the scores from the two locations. Lacunes were defined as lesions with cerebrospinal fluid intensity on T2, typically 3–15 mm in diameter, with a hyperintense rim on FLAIR. The degree of brain atrophy was assessed using a 0–3 grading scale based on comparisons of cortical sulcal depth and ventricular size with standard MRI images of age-matched elderly controls: 0 = no atrophy, 1 = mild atrophy (similar to the 95th percentile template image), 2 = moderate atrophy (greater than the 95th percentile but not exceeding twice the ventricular size and sulcal depth of the standard image), 3 = severe atrophy (ventricular size and sulcal depth more than twice the 95th percentile template image) [21]. Examples of SSSI and cerebral small vessel disease assessments in different regions are provided in the supplementary material.

Statistical analysis

Statistical analyses were performed using SPSS version 26 and STATA version 14. Continuous variables with a normal distribution were presented as mean ± standard deviation, while non-normally distributed continuous variables and ordinal variables were presented as median (interquartile range). Categorical variables were expressed as counts (percentages). Group comparisons for normally distributed variables were performed using the independent samples t-test, while non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were compared using the chi-square test, with or without continuity correction and Fisher's exact test. Spearman correlation analysis was used to assess the degree of association between two variables. Binary logistic regression analysis was conducted to identify clinical, imaging, and laboratory factors associated with long-term poor neurological outcomes and END. Variables with $P < 0.1$ in univariate analysis were included in the multivariate logistic regression model. A stepwise regression method was used to sequentially include variables with $P < 0.05$ in the multivariate logistic regression model, eliminating irrelevant factors to develop the final prediction model. The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity, specificity, and predictive value (area under curve, AUC) of risk factors and the final model. The cut-off value was determined based on the maximum Youden's index on the curve. Youden's index

was calculated by the formula: Youden's Index = Sensitivity + Specificity − 1. The comparison of AUC values between predictive models was performed using the DeLong test. A two-sided p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics of study subjects

During the study period, 1,329 acute ischemic stroke patients were hospitalized. Among them, 304 patients met the inclusion and exclusion criteria. Excluding patients with missing baseline information, loss to follow-up, and incomplete MRI examinations (15/304), a final total of 289 patients with SSSI were included in the analysis (Fig. 1). The clinical information of the subjects is summarized in Table 1. The mean age of the patients was 60 years (60.2 ± 10.3), with 216 (74.7%) males. During hospitalization, 18 patients (6.2%) experienced END. After a median follow-up of 21.4 (16.7–25.2) months, 29 patients (10%) had a mRS score > 2, while 260 patients

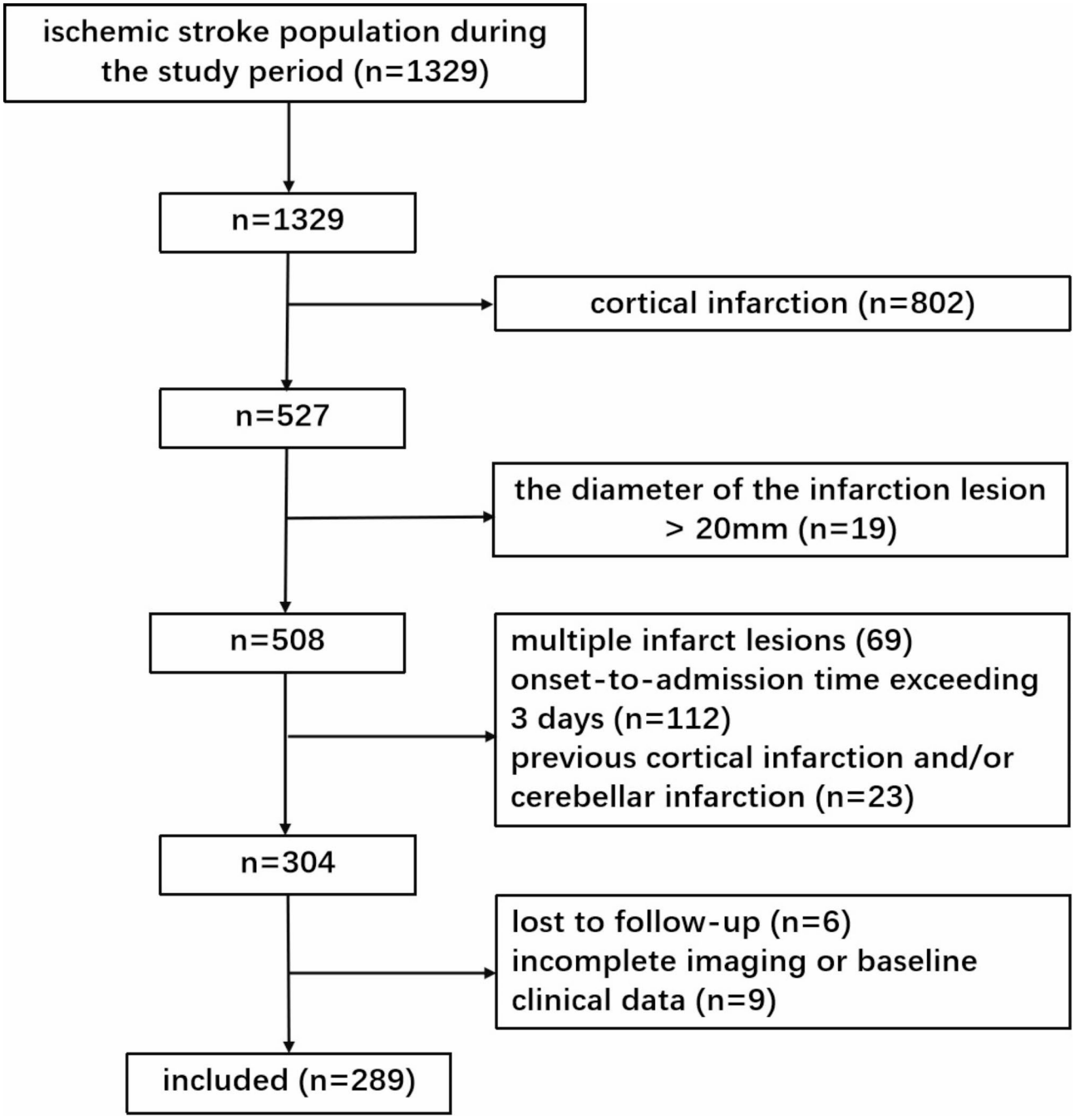

Fig. 1 Selection of study subjects

Table 1 Characteristics of the study population

Characteristics	Total *N* = 289	mRS>2 *N* = 29	mRS ≤ 2 *N* = 260	*P* value	END *N* = 18	without END *N* = 271	*P* value
Age	60.2 ± 10.3	68.4 ± 9.1	59.3 ± 10.1	*< 0.001*	60.3 ± 13.2	60.2 ± 10.1	0.965
Sex, male	216(74.7)	21(72.4)	195(75)	0.761	12(66.7)	204(75.3)	0.593
mRS score	0(0∼1)	3(3∼4.5)	0(0∼1)	*< 0.001*	2(1∼3)	0(0∼1)	*< 0.001*
Follow-up duration, months	21.4(16.7∼25.25)	20.9(15.35∼26.7)	21.45(16.83∼25.18)	0.767	21.8(17.95∼23.35)	21.4(16.7∼25.3)	0.915
Onset-to-admission, days	2(1∼3)	2(1∼2.5)	1.625(1∼3)	0.876	2(0.9∼2)	1.25(1∼3)	0.844
Thrombolytic therapy	18(6.2)	2(6.9)	16(6.2)	1	2(11.1)	16(5.9)	0.703
Admission SBP mmHg	153 ± 21.2	158.1 ± 18.6	152.4 ± 21.4	0.173	162.3 ± 14.2	152.4 ± 21.5	*0.011*
Admission DBP mmHg	88 ± 12.5	83.4 ± 11.8	88.5 ± 12.5	*0.033*	88.5 ± 14.1	88 ± 12.4	0.867
Risk factors							
Hypertension	222(76.8)	26(89.7)	196(75.4)	0.084	14(77.8)	208(76.8)	1
Diabetes	107(37)	13(44.8)	94(36.2)	0.359	7(38.9)	100(36.9)	0.866
Dyslipidemia	171(59.2)	17(58.6)	154(59.2)	0.949	11(61.1)	160(59)	0.863
Smoke	118(40.8)	12(41.4)	106(40.8)	0.949	6(33.3)	112(41.3)	0.504
Alcohol use	80(27.7)	9(31)	71(27.3)	0.671	6(33.3)	74(27.3)	0.778
History of Coronary artery disease	29(10)	6(20.7)	23(8.8)	0.091	1(5.6)	28(10.3)	0.804
History of stroke or TIA	33(11.4)	5(17.2)	28(10.8)	0.464	0(0)	33(12.2)	0.234
Admission NIHSS	3(1∼5)	7(4∼9)	3(1∼4)	*< 0.001*	7(5∼8)	3(1∼4)	*< 0.001*
Symptomatic extracranial artery stenosis	10(3.5)	1(3.4)	9(3.5)	1	0(0)	10(3.7)	1
Symptomatic intracranial artery stenosis	61(21.1)	11(37.9)	50(19.2)	*0.019*	4(22.2)	57(21)	1
Infarct location							
Brainstem	93(32.2)	12(41.4)	81(31.2)	0.264	7(38.9)	86(31.7)	0.529
Thalamus	36(12.5)	0(0)	36(13.8)	0.065	1(5.6)	35(12.9)	0.584
Basal ganglia	56(19.4)	4(13.8)	52(20)	0.422	3(16.7)	53(19.6)	1
Corona radiata or centrum Semiovale	97(33.6)	13(44.8)	84(32.3)	0.176	7(38.9)	90(33.3)	0.621
Other locations	7(2.4)	0(0)	7(2.7)	1	0(0)	7(2.6)	1
Radiological features							
Lesion diameter mm	13.13(9.22∼17.80)	15.74(10.20∼19.77)	12.52(9.16∼17.31)	0.08	16.8(12.87∼19.45)	12.52(9.04∼17.3)	*0.044*
Periventricular WMHs	1(1∼1)	1(1∼2)	1(1∼1)	*0.008*	1(0.75∼1)	1(1∼1)	0.241
Subcortical WMHs	1(1∼1)	1(1∼2)	1(1∼1)	*0.032*	1(0∼1)	1(1∼1)	0.232
ePVS burden	3(2∼4)	3(2∼4)	3(2∼4)	0.946	3(2∼4)	3(2∼4)	0.725
Lacune number	0(0∼2)	2(0∼3.5)	0(0∼1.75)	*0.001*	0(0∼1)	0(0∼2)	0.113
Cerebral atrophy	0(0∼1)	1(0∼2)	0(0∼1)	*< 0.001*	0(0∼1.25)	0(0∼1)	0.818
Laboratory data							
TC mmol/L	4.73(4.1∼5.31)	4.87(4.15∼6.18)	4.68(4.08∼5.28)	0.172	5.275(4.53∼6.26)	4.66(4.08∼5.26)	*0.035*
LDL-C mmol/L	2.76(2.22∼3.24)	2.84(2.32∼3.48)	2.76(2.18∼3.22)	0.363	2.93(2.41∼3.38)	2.76(2.21∼3.25)	0.341
MCHC g/L	337(328∼347)	332(322∼344)	338(329∼348)	*0.01*	336.5(327.75∼347)	337(328∼347)	0.793
NLR	2.65(1.98∼3.81)	3.7(2.54∼4.57)	2.59(1.93∼3.71)	*0.005*	3.94(2.61∼5.36)	2.60(1.93∼3.75)	*0.009*
NHR	4.76(3.47∼6.25)	5.79(3.81∼7.08)	4.67(3.46∼6.10)	0.098	6.40(4.22∼8.61)	4.68(3.46∼6.13)	*0.02*

Data are presented as mean ± standard deviation, median (interquartile range), or n (%)

mRS modified rankin scale, SBP systolic blood pressure, DBP diastolic blood pressure, NIHSS national institutes of health stroke scale, TIA transient ischemic attack, WMHs white matter hyperintensities, ePVS enlarged perivascular spaces, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, MCHC mean hemoglobin concentration, NLR neutrophil to lymphocyte ratio, NHR neutrophil to high-density lipoprotein cholesterol ratio

(90%) had an mRS score ≤ 2. The kappa value between the two neuroradiologists was 0.83.

Univariate and multivariate analysis of END

Compared to patients without END during hospitalization, those with END had higher SBP and NIHSS scores on admission, larger lesion diameters, and higher values of TC, NLR, and NHR. After adjusting for confounding factors, multivariate logistic regression analysis showed that NIHSS score (OR = 1.43, 95% CI = 1.19–1.73, $P < 0.001$), and NHR (OR = 1.28, 95% CI = 1.02–1.60, $P = 0.034$) were independent predictors of END (Table 2).

Table 2 Multivariable logistic regression and stepwise regression of early neurological deterioration

Variables	Univariate regression	*P* value	Model 1	*P* value	Model 2	*P* value	stepwise regression	*P* value
	OR (95%CI)		OR (95%CI)		OR (95%CI)		OR (95%CI)	
Admission SBP	1.02 (1.00–1.04)	0.057						
NIHSS	1.45 (1.23–1.71)	*< 0.001*	1.46 (1.24–1.74)	*< 0.001*	1.43(1.19–1.73)	*< 0.001*	1.46 (1.23–1.73)	*< 0.001*
Lesion diameter	1.07 (1.00–1.16)	0.065						
TC	1.43 (1.04–1.96)	*0.028*	1.41 (1.03–1.95)	*0.035*				
NLR	1.26 (1.07–1.48)	*0.005*	1.26 (1.07–1.48)	*0.006*				
NHR	1.25 (1.04–1.51)	*0.018*	1.26 (1.05–1.52)	*0.014*	1.28(1.02–1.60)	*0.034*	1.26 (1.02–1.55)	*0.029*

Model 1: age, sex; Model 2: age, sex, NIHSS, lesion diameter, admission SBP, TC. SBP systolic blood pressure, NIHSS national institutes of health stroke scale, TC total cholesterol, NLR neutrophil to lymphocyte ratio, NHR neutrophil to high-density lipoprotein cholesterol ratio

Table 3 ROC curve parameters for predictors of unfavorable outcomes at follow-up and early neurological deterioration

outcome	Variables	AUC	95%CI	*P* value	cut-off value	Sensitivity	Specificity	DeLong test
mRS>2	Age	0.746	0.654–0.838	*< 0.001*	67.5	0.655	0.792	0.0001*
	NIHSS	0.804	0.723–0.885	*< 0.001*	3.5	0.862	0.65	0.0018*
	Lacune number	0.675	0.564–0.786	*0.002*	1.5	0.552	0.75	< 0.0001*
	Cerebral atrophy	0.747	0.643–0.85	*< 0.001*	0.5	0.724	0.708	< 0.0001*
	Predictive mode 1	0.926	0.889–0.964	*< 0.001*	-	0.897	0.815	-
END	NIHSS	0.833	0.754–0.911	*< 0.001*	4.5	0.833	0.76	0.9094^
	NHR	0.664	0.524–0.804	*0.02*	5.28	0.667	0.657	0.0026^
	Predictive mode 2	0.836	0.744–0.927	*< 0.001*	-	0.722	0.875	-

*Compared with prediction model 1; ^compared with prediction model 2

AUC Area Under the Curve, NIHSS national institutes of health stroke scale, MCHC Mean Hemoglobin Concentration, NHR neutrophil to high-density lipoprotein cholesterol ratio

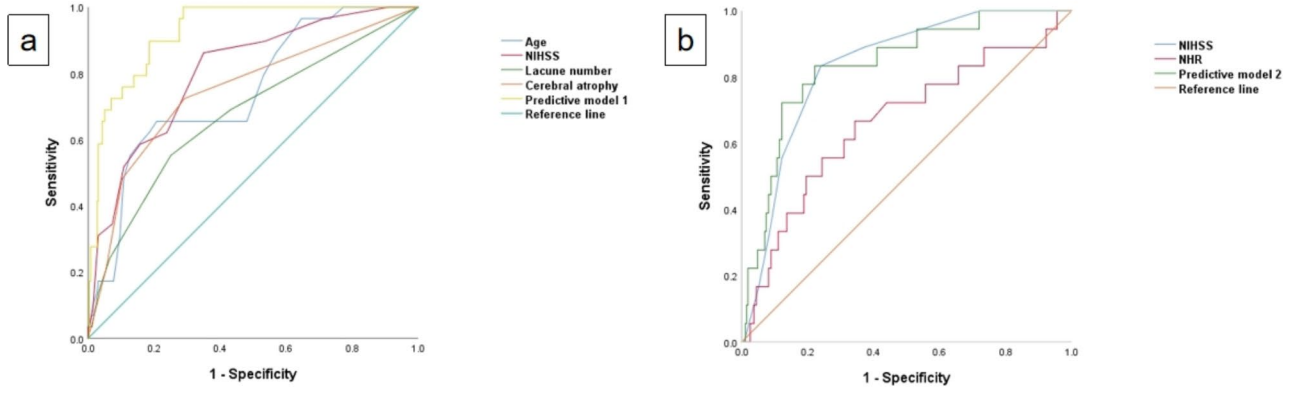

Fig. 2 The ROC curve of independent risk factors and predictive model associated with poor long-term prognosis (mRS > 2) (**a**) and early neurological deterioration (**b**). mRS modified rankin scale, NIHSS national institutes of health stroke scale, NHR neutrophil to high-density lipoprotein cholesterol ratio

A predictive model for END in SSSI was constructed using stepwise regression, which included NIHSS score and NHR on admission (Table 2), with an area under the ROC curve of 0.836 (95% CI = 0.744–0.927). ROC analysis for the independent predictive factors indicated that the optimal cut-off value for NIHSS score in predicting END was 4.5, with a sensitivity of 83.3% and specificity of 76%. The cut-off value for NHR was 5.28, with a sensitivity of 66.7% and specificity of 65.7% (Table 3; Fig. 2).

Univariate and multivariate analysis of poor neurological outcomes (mRS > 2)

Univariate analysis indicated that age, DBP and NIHSS score on admission, responsible intracranial artery stenosis, periventricular and subcortical WMHs, number of lacunes, degree of brain atrophy, Mean Corpuscular Hemoglobin Concentration (MCHC), and NLR were associated with long-term poor outcomes in SSSI patients. Multivariate logistic regression models adjusted for age, gender, imaging evaluations, and laboratory results showed that age (OR = 1.08, 95% CI = 1.01–1.15, $P = 0.028$), NIHSS score on admission (OR = 1.60, 95% CI = 1.29–1.98, $P < 0.001$), number of lacunes (OR = 1.51,

Table 4 Multivariable logistic regression and stepwise regression of unfavorable outcomes at follow-up

Variables	Univariate regression	*P* value	Model 1	*P* value	Model 2	*P* value	stepwise regression	*P* value
	OR (95%CI)		OR (95%CI)		OR (95%CI)		OR (95%CI)	
age	1.10 (1.06–1.15)	*< 0.001*	1.11 (1.06–1.16)	*< 0.001*	1.08 (1.01–1.15)	*0.028*	1.07 (1.01–1.13)	*0.015*
Admission DBP mmHg	0.97 (0.94–1.00)	*0.035*						
Hypertension	2.83 (0.83–9.66)	0.097						
Coronary artery disease	2.69 (1.00–7.27)	0.051						
Symptomatic intracranial artery stenosis	2.57 (1.14–5.78)	*0.023*	2.66 (1.12–6.33)	*0.027*	5.26 (1.56–17.71)	*0.007*	5.19 (1.75–15.43)	*0.003*
NIHSS	1.49 (1.29–1.73)	*< 0.001*	1.48 (1.27–1.73)	*< 0.001*	1.60 (1.29–1.98)	*< 0.001*	1.64 (1.35–1.98)	*< 0.001*
Lesion diameter	1.06 (1.00–1.13)	0.058						
Periventricular WMHs	2.24 (1.29–3.88)	*0.004*						
Subcortical WMHs	1.75 (1.10–2.80)	*0.019*						
Lacune number	1.35 (1.12–1.64)	*0.002*	1.32 (1.08–1.62)	*0.008*	1.51 (1.13–2.04)	*0.006*	1.35 (1.07–1.69)	*0.01*
Cerebral atrophy	2.39 (1.69–3.39)	*< 0.001*	1.86 (1.23–2.83)	*0.003*	2.03 (1.19–3.46)	*0.01*	1.80 (1.12–2.88)	*0.015*
MCHC	0.97 (0.94–0.99)	*0.008*	0.97 (0.94–0.99)	*0.015*	0.96 (0.92–0.99)	*0.04*		
NLR	1.18 (1.02–1.37)	*0.023*						
NHR	1.14 (0.98–1.34)	0.097						

Model 1: age, sex; Model 2: age, sex, admission DBP, hypertension, coronary artery disease, follow-up time, NIHSS, lesion diameter, symptomatic intracranial artery stenosis, subcortical WMHs, lacune number, cerebral atrophy, MCHC, NLR

DBP diastolic blood pressure, NIHSS national institutes of health stroke scale, WMHs white matter hyperintensities MCHC mean hemoglobin concentration, NLR neutrophil to lymphocyte ratio, NHR neutrophil to high-density lipoprotein cholesterol ratio

95% CI = 1.13–2.04, $P = 0.006$), grading of brain atrophy (OR = 2.03, 95% CI = 1.19–3.46, $P = 0.01$), MCHC (OR = 0.96, 95% CI = 0.92–0.99, $P = 0.04$), and symptomatic intracranial artery stenosis (OR = 5.26, 95% CI = 1.56–17.71, $P = 0.007$) were independently associated with poor outcomes at follow-up (Table 4).

After stepwise regression to exclude irrelevant variables, we developed a predictive model for poor prognosis, which consisting of age, NIHSS score at admission, symptomatic intracranial artery stenosis, number of lacunes, and brain atrophy (Table 4). Subsequent ROC curve analysis showed that the model had good predictive performance (AUC 0.926, 95% CI = 0.889–0.964). ROC analysis for the independent predictive factors indicated that the optimal cut-off value for NIHSS in predicting poor outcomes was 3.5, with a sensitivity of 86.2% and specificity of 65%. The cut-off value for age was 67.5 years, with a corresponding sensitivity of 65.5% and specificity of 79.2%. The cut-off value for the number of lacunes was 1.5, with a sensitivity of 55.2% and specificity of 75%. The cut-off value for the degree of brain atrophy was 0.5, with a sensitivity of 72.4% and specificity of 70.8% (Table 3; Fig. 2).

Discussion

Previous study focusing on minor ischemic stroke (NIHSS ≤ 3) showed that age, NIHSS score, large artery atherosclerosis, non-culprit vessel stenosis, and lesion diameter were associated with poor outcomes at 3 months [22]. Other studies have identified NIHSS score, culprit artery stenosis, and branch atheromatous disease as independent predictors of END in acute lacunar stroke patients [7, 16]. Consistent with previous findings, ROC analysis showed that even lower NIHSS scores at admission could predict END and long-term poor outcomes (cut-off values of 4.5 and 3.5, respectively). This suggests that despite the small lesion size and relatively mild symptoms, patients can still develop significant neurological disability, emphasizing the need for adequate clinical attention in these patients. The AUC and Youden index for prediction model of END did not show a substantial improvement over that of the independent variable NIHSS, suggesting that the NIHSS holds dominant predictive value in this model.

Previous studies have shown that the total burden of CSVD is the risk factor for in-hospital worsening of mRS and lack of improvement in NIHSS scores in patients with acute lacunar infarction [13]. Helenius et al. conducted a study involving 80 patients with small subcortical infarction (SSI) and found that the severity of WMHs was related to lesion volume and poor outcomes at three months [23]. Another study, which included 119 patients with acute ischemic stroke, demonstrated that brain atrophy and lacunes were associated with poor outcomes at three months [24]. Our findings are consistent with these results but with a longer follow-up period. We provided a detailed classification and localization of CSVD imaging characteristics, finding differences in periventricular and subcortical WMHs between different outcome group. Lacunes and brain atrophy were independent predictors of poor prognosis. The different relationships between CSVD subtypes and outcomes suggest distinct

underlying mechanisms and risk factors, highlighting the varying importance of CSVD markers when assessing prognosis in SSSI patients. The extent of CSVD may represent "brain frailty [25]," affecting post-stroke functional recovery by reducing cerebral functional reserve or collateral compensation [24, 26, 27]. The ROC curve cut-off values for brain atrophy and lacunes suggest that few lacunes and mild brain atrophy can predict adverse outcomes. However, whether the relationship between brain atrophy and outcomes differs based on the vascular or neurodegenerative origin of brain atrophy remains to be further studied.

Previous studies have demonstrated that red blood cell-related tests such as hemoglobin or hematocrit are independently associated with ischemic stroke outcomes [28, 29]. However, there are few reports on the relationship between MCHC and ischemic stroke prognosis. Huang et al. found that MCHC is independently associated with mortality during hospitalization and within one year post-discharge in acute myocardial infarction patients [30]. Inflammatory responses play a crucial role in the pathogenesis and progression of ischemic stroke. Various inflammatory markers, such as D-dimer, C-reactive protein, and the widely recognized inflammation index NLR, have been shown to be independently associated with ischemic stroke outcome [12, 31], which suggested that inflammation might mediate the relationship between MCHC and SSSI by impairing iron metabolism [30]. Additionally, red blood cells may influence cerebral atherosclerosis by regulating vascular function and maintaining vascular integrity [32]. The relationship between red blood cell parameters and ischemic stroke warrants further investigation.

Atherosclerosis of the subcortical perforating arteries and parent arteries is the important pathogenic mechanism of SSSI [8]. Neutrophil contribute to the formation of atherosclerotic plaques by accumulating at the plaque site [33], releasing myeloperoxidase [34], inducing platelet activation [35], and hindering the cholesterol-clearing function of HDL-C [36]. HDL-C, on the other hand, exerts anti-inflammatory and atherosclerosis-inhibiting effects through reverse cholesterol transport, anti-oxidation of LDL-C [37], and inhibition of neutrophil activation and migration [38, 39]. The interaction between inflammation and lipid metabolism abnormalities plays a critical role in the formation and progression of atherosclerotic plaques. Therefore, as a comprehensive indicator of these two pathological mechanisms, the NHR has attracted attention from researchers of cardio-cerebral vascular disease. Studies have shown that elevated NHR is associated with the degree of coronary artery stenosis [40]. Additionally, multiple studies have supported its correlation with adverse prognoses in patients with acute coronary syndrome and ischemic stroke [41, 42]. To our knowledge, no study has yet focused on the relationship between NHR and SSSI outcomes. Beyond its role in promoting atherosclerosis progression, the elevation of neutrophils also contributes to plaque instability and rupture [33, 43]. Moreover, neutrophils involved in the neuroinflammatory response triggered by infarcted tissue may exacerbate brain damage and delay functional recovery [44, 45]. The reduction of HDL-C, which reflects the decline in anti-inflammatory capacity, further exacerbates this process [38]. Finally, studies have shown that elevated NHR may also reflect the presence of metabolic syndrome [46]. A cohort study involving 2,684 middle-aged and elderly Iranians indicated a significant association between elevated NHR and the presence of metabolic syndrome and central obesity, with NHR levels being able to predict the occurrence of metabolic syndrome (AUC = 0.61) [46]. Metabolic syndrome has already been established as a risk factor for poor stroke prognosis [47].

Compared to NHR, NLR is a widely accepted classic indicator focusing on the overall level of inflammation. Lymphocyte-released cytokines play a dual role in inducing both the progression and repair of infarct lesion damage [48]. During acute stage of stroke, lymphocytopenia also reflects the elevation of pro-inflammatory factors caused by the stress response [49]. NLR has been extensively validated in predicting the severity and prognosis of cardio-cerebral vascular disease [50]. Nam et al. reported that NLR is associated with END in a study involving 438 SSSI patients [7]. Our study observed elevated NLR and NHR in patients with END, but NLR lost its statistical significance in predicting END after adjusting for admission NIHSS or lesion diameter. This suggests that, compared to NHR, the association of NLR with END is primarily mediated by stroke severity and lesion size (Spearman correlation analysis: NLR: NIHSS: correlation coefficient 0.208, $P < 0.001$; lesion diameter: correlation coefficient 0.141, $P = 0.016$; NHR: NIHSS: correlation coefficient 0.157, $P = 0.008$; lesion diameter: correlation coefficient 0.013, $P = 0.826$). NHR can reflect both metabolic abnormalities and inflammation levels, and may be a better independent marker than NLR for predicting inpatient outcomes in stroke patients. This requires further validation through large-scale prospective studies.

The limitations of this study include: 1. The relatively small sample size and outcome events led to wide confidence intervals for some predictive factors and might have masked certain risk factors. 2.The retrospective method of the study may introduce bias due to record inaccuracies and missing information. 3. The long follow-up period means that the health status of patients might have been influenced by other comorbidities. 4. The lack of susceptibility-weighted imaging in most patients

precluded an assessment of cerebral microbleeds, limiting the comprehensiveness of our analysis regarding the impact of CSVD on stroke outcomes.

Conclusion

Our study reveals that the severity of symptoms at admission, elevated NHR are risk factors for END during hospitalization. the severity of symptoms at admission, presence of symptomatic intracranial arterial stenosis, lacune, and brain atrophy are associated with poor long-term prognosis in SSSI patients. This study provides a predictive model for the END and long-term adverse outcomes of SSSI. The findings have potential value for stratifying high-risk patients and evaluating therapeutic efficacy, offering clues for patient and risk factor selection in future prospective studies.

Abbreviations

ADC	Apparent Diffusion Coefficient
AUC	Area Under Curve
CSVD	Cerebral Small Vessel Disease
CTA	Computed Tomography Angiography
DBP	Diastolic Blood Pressure
DSA	Digital Subtraction Angiography
DWI	DiffusionWeighted Imaging
END	Early Neurological Deterioration
ePVS	Enlarged Perivascular Spaces
FLAIR	Fluid-Attenuated Inversion Recovery
HDL-C	High-Density Lipoprotein Cholesterol
LDL-C	Low-Density Lipoprotein Cholesterol
MCA	Middle Cerebral Artery
MCHC	Mean Corpuscular Hemoglobin Concentration
mRS	Modified Rankin Scale
MRA	Magnetic Resonance Angiography
NHR	Neutrophil to High-Density Lipoprotein Cholesterol Ratio
NIHSS	National Institutes of Health Stroke Scale
NLR	Neutrophil-to-Lymphocyte Ratio
OTT	Onset to Admission Time
ROC	Receiver Operating Characteristic
SBP	Systolic Blood Pressure
SSSI	Single Subcortical Small Infarction
TC	Total Cholesterol
TE	Echo Time
TIA	transient ischemic attack
TR	Repetition Time
WMHs	White Matter Hyperintensities

Supplementary Information

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Supplementary Material 1

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Author contributions

FX: Responsible for study design, drafting the manuscript, data collection, and data analysis. MH, MT, DJY: Responsible for data collection and analysis. ZWH, XSB: Responsible for study design, data analysis, data interpretation, and manuscript revision. All authors have commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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Data availability

Upon reasonable request, the corresponding author will provide access to the datasets generated and/or analyzed during this study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20210731). The patient information in this retrospective study was de-identified and anonymized, and written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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