Official Title: Early neurological deterioration in recent small subcortical infarction：a multicenter prospective study

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Background and objectives

Recent small subcortical infarction (RSSI) is defined as a small deep infarction in the territory of a perforating artery with maximum axial diameters (MAD) of less than 20 mm. Although RSSI is generally considered to be of a relatively favorable prognosis, about 13.5% to 43% of RSSI patients experience early neurological deterioration (END) in the acute phase, which often bring adverse effects on long-term outcomes. Although a number of risk factors for END have been identified previously, however, the risk factors of END and the underlying etiological mechanism are still ambiguous, and also the relevant intervention measures lack sufficient evidences, which is a thorny problem that clinicians have to face.

In this multicenter, large-sample prospective registry study, the primary objective is to investigate the natural course of END in patients with RSSI. Exploring the risk factors and potential mechanism of its development, and trying to establish a comprehensive predictive model for END that integrates multi-dimensional information including clinical symptom, demographic data, biochemical biomarker and image data, and so as to provide a valuable tool for clinical evaluation and early management. Secondary objective is to figure the long term outcome of the patients with RSSI and its risk factors.

Methods

Study design

This study is a multicenter, consecutive, prospective, observational, cohort study recruiting RSSI patients within 72 hours after symptom onset. This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. The anticipated duration of the study will be about 2 years from June 1, 2022 to June 1, 2024.

Study population

Inclusion criteria.

1. Age ≥ 18 years;
2. Time from the last seen normal to enrollment ≤ 72 h;
3. Completion of brain MRI (T1/T2/Flair/DWI/ADC sequences). The lesion belonged to the territory of the penetrating artery (lenticulostriate area and pons) on the DWI sequence and at least one of the vascular examinations such as MRA, CTA or DSA was completed.

Exclusion criteria.

1. Patients with low imaging quality affecting the evaluation of the results;
2. Intracranial hemorrhagic diseases, vascular malformations, aneurysms, brain abscesses, malignant space occupying lesions or other non-ischemic intracranial lesions observed by baseline head imaging;

3. Patients with combined malignancy, hematological disease and other systemic diseases with possible hypercoagulable state;
4. mRS score prior to the onset of the disease was≥2 points;
5. Patients with symptom progression or TIA before completion of cranial MRI after admission;
6. Received or plan to receive acute endovascular treatment after onset of the disease;
7. Pregnant or lactating women;
8. Participation in another ongoing study;
9. Those who refused to participate in the study.

Data collection

RSSI patients within 72 hours of stroke onset were prospectively and consecutively enrolled from June 2022 to June 2023. After enrollment, Clinical data will be collected using an online electronic case report Form (e-CRF) at baseline and follow-up. Baseline data including demographic, first blood pressure, past and family history, past medications use, pre-stroke modified Rankin Scale score (mRS), assessment of mRS and NIHSS score on admission were recorded. After admission, NIHSS score was evaluated twice a day by two certified physicians, who were blinded to the study. laboratory tests including routine blood/biochemistry/renal function, etc.) Transthoracic echocardiogram, 24-hour Holter and neuroimages data including brain MRI/MRA/CTA/DSA, etc. were all

collected. During hospitalization, the drug therapy (antiplatelet/anticoagulation, lipid-lowering, glucose lowering, antihypertensive, etc.) were also recorded. Early neurological deteriorations (END) were monitored by two certified physicians, who were blinded to the imaging, and the primary outcome of our study was the occurrence of END, which was defined as any increase of ⩾ 2 points in the total NIHSS score or ⩾ 1 point on the motor items of the NIHSS within 7 days of hospital admission with blind evaluation. And any new cerebrovascular events confirmed during hospitalization were recorded. By face-to face or telephone interviews, we extended the follow up to 1 year for our secondary outcome as follow. The outcomes will be assessed by the neurologists blinded to study images. The quality control of all data will be held dynamically by the central center.

Outcome measures

Primary outcome

Any increase of ≥ 2 points in the total NIHSS score or ≥ 1 point on the motor items of the NIHSS within 7 days of hospital admission with blind evaluation.

Secondary outcome

1. percentage of patients with favorable functional recovery, defined as an mRS ⩽1;
2. Percentage of patients with new vascular events, defined as any

stroke (ischemic or hemorrhage);

3. Percentage of patients with the new clinical vascular events (ischemic stroke/ hemorrhagic stroke/ TIA/ MI/ vascular death) as a cluster and evaluated individually；
4. Severe bleeding incidence (GUSTO definition), including fatal bleeding and symptomatic intracranial hemorrhage;
5. Incidence of symptomatic and asymptomatic intracranial hemorrhagic events;
6. All-cause mortality;
7. cognitive function (MOCA/MMSE score).

Sample size

In out cohort study, no specific hypothesis for the primary outcome is set, the sample size is estimated based on the number of variables, using the method recommended for registry study (10 times number of variable). The sample size is estimated as 500 , and increases to 550 for 10% loss during follow-up.

Statistical analysis

Categorical variables will be presented as frequencies and percentages, Continuous variables with non-normal distributions will be shown as median and interquartile range (IQR), while continuous variables with normal distributions as mean and 95% confidence interval (CI). For the statistical significance analysis of different

groups and outcomes, Pearson χ 2 or Fisher's exact test, Wilcoxon tests, and t-tests will be used, where appropriate, with statistical uncertainty expressed by means of 95% CI. Cox proportional hazards model, Logistic regression model, and Poisson regression model will be used to assess the association between outcomes and predictors, where appropriate. All associated variables in the univariate analysis that reached P <0 .10 were included in the multinomial logistic analysis as candidate variables and then removed by a forward conditional selection. A two-sided P P<0.05 was considered statistically significant. The good prognosis is defned as 0–2 mRS score, and poor prognosis as 3–6 mRS score on 12 mon. All analysis will be performed using SPSS 26.0 (SPSS, Inc., Chicago, IL).