

# Effects of Early Neurological Deterioration in Acute Ischemic Stroke on Multiple Dimensions of Functional Outcomes using Propensity Score Matching Analysis

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## Research

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# Abstract

**Background:** Early neurological deterioration (END) is common in acute ischemic stroke (AIS), but its effect on functional outcomes is not well understood. Here, we explored the effects of END on multiple dimensions of functional outcomes.

**Methods:** 256 patients with AIS were analyzed. All patients were followed up for 1 year. We used the modified Rankin Scale (mRS) to assess body function impairment, the Lawton activities of daily living scale to assess activity limitations, and the reintegration to normal living index (RNLI) to assess participation restrictions. Brain MRI was performed to identify acute infarcts and preexisting abnormalities. To reduce the effects of a lack of randomization, we conducted a propensity score analysis.

**Results:** Among 256 patients with AIS, 61 (23.8%) patients had END. Before matching, patients with END had higher levels of small artery-type stroke, higher NIHSS scores on arrival, higher systolic blood pressure on admission, and larger infarct volumes. After matching, there were no significant differences between the two groups in any clinical or neuroimaging variables, except for stroke subtype and cortical region infarct. Logistic regression analysis revealed that END was a significant predictor of poor mRS (odds ratio [OR], 3.829; 95% confidence interval [CI], 1.367–10.723,  $p = 0.011$ ) and poor RNLI (OR, 2.777; 95% CI, 1.133–6.806,  $p = 0.026$ ) scores after adjusting for confounding factors.

**Conclusions:** END is relatively common in AIS. END might be a significant predictor of poor functional outcomes, including body function impairment and reduced social participation.

## Background

Stroke is a leading contributor to mortality and long-term morbidity in China, and the lifetime stroke risk in the Chinese population is estimated to be 39.3% [1, 2]. Early neurological deterioration (END) is common in a fraction of patients with acute ischemic stroke (AIS) [3, 4]. The reported frequency of END in AIS varies widely, ranging from 5–40% [5–8]. Previous studies have revealed some of the main clinical and radiological factors predicting END, including high blood glucose levels, older age, more severe stroke, history of diabetes, coronary heart disease, non-use of aspirin, high levels of high-sensitivity C-reactive protein, no recanalization, re-occlusion, brain swelling, and the presence of an infarction > 1/3 of the middle cerebral artery territory [9–12].

It has been reported that END may increase the probability of poor outcomes. For example, Liu et al. found that END was a predictor of poor modified Rankin scale (mRS) scores after 1 year [13]. Furthermore, Mori et al. reported that END after intravenous recombinant tissue plasminogen activator therapy was independently associated with death and dependency (mRS 3–6) [14]. However, evaluating the relationship between only these outcomes and END remains limited. The World Health Organization International Classification of Functioning, Disability, and Health (WHO-ICF) categorizes disease consequences into three different dimensions: body function impairments, activity limitations, and participation restrictions [15]. Despite these guidelines, which capture the complex nature of functioning, our understanding of functional outcomes after stroke combined with END is mainly limited to activities of daily living (ADL), which is often narrowly defined and evaluated using only the mRS [16]. However, functional status also involves the basic ADL and the instrumental ADL, which are both vital parameters to consider after stroke. In addition, stroke survivors often experience participation restrictions in the chronic phase [17]. However, few studies have identified the impact of END on these multiple functional domains. In the present study, we aimed to explore the effects of END on these multiple functional outcomes.

## Methods

### Participants and setting

The study was conducted at the Department of Neurology, Dongguan People's Hospital, between January 1, 2018, and December 30, 2018. The inclusion criteria for the study were: (1) aged over 18 years; (2) first AIS occurred within 7 days before admission and was diagnosed according to the American Heart Association Stroke Council criteria [18]; (3) had complete brain magnetic resonance imaging (MRI) examinations; and (4) had an mRS score < 3 before admission. The exclusion criteria were: (1) transient ischemic attack, cerebral hemorrhage, subdural hematoma, or subarachnoid hemorrhage; (2) incomplete clinical data (e.g., incomplete brain MRI); (3) died before discharge; (4) severe comorbidities (e.g., liver, kidney, heart, or respiratory failure, or malignant tumors); (5) unable to finish the assessment at follow-up because of severe hearing disabilities, visual disabilities, language disorders, or cognitive impairment; and (6) refused to sign a consent form.

The study protocol was approved by the Ethics Committee of Dongguan People's Hospital. The consent of all subjects was obtained in accordance with the Declaration of Helsinki.

### Data collection

Information about demographic variables (e.g., age, sex) and vascular risk factors (e.g., hypertension, diabetes mellitus, atrial fibrillation) was collected. We also recorded clinical data, including stroke severity, blood pressure, stroke subtype, lesion location, in-hospital treatment (antiplatelet, anticoagulation, and statins), and laboratory data. The severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) [19]. The subtype of ischemic stroke was evaluated using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype system [20]. Laboratory data included fasting blood glucose, glycosylated hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, homocysteine, white blood cells, hemoglobin, fibrinogen, prothrombin time, and creatinine. Blood pressure was measured and recorded shortly after admission, and the laboratory data were tested within 24 hours after admission.

### Definition of END

We evaluated NIHSS scores on the day of admission, and then daily over the

following 7 days after admission. We defined END as an increase in NIHSS score  $\geq 2$  points within 72 h after admission [21].

### Patient follow-up

All follow-up assessments were completed by the patients. We assessed multiple outcomes at 12–15 months after the index stroke. Based on the WHO-ICF (2002) [15], we selected one measure to evaluate each level of functioning: body function impairment was assessed using the mRS, activity limitation was assessed using the Lawton ADL scale [22], and participation restriction was evaluated using the Chinese version of the reintegration to normal living index (RNLI) [23].

ADL is composed of basic ADL and instrumental ADL. The components of basic ADL include six different levels of abilities for toilet activity, feeding, dressing, grooming, physical ambulation, and bathing. The total basic ADL score is calculated by summing up the points for each item, with a maximum score of 24. The Lawton instrumental ADL score is composed of eight different domains: using a telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and handling finances. The total instrumental ADL score

is calculated by summing up the points for each item, with a maximum of 32. Therefore, the total ADL score ranges from 14 to 56. A higher ADL score reflects poorer ADL performance [22].

The RNLI is an 11-item questionnaire that targets nine domains affected by incapacitating events: mobility, self-care ability, daily activities, recreational activities, general coping skills, family roles, social activities, personal relationships, and presentation of self to others. Each item is scored from 1 (minimal reintegration) to 10 (complete reintegration), with a total scale range of 11–110. A lower RNLI score reflects poorer participation in normal living [23].

Poor outcome was defined as follows: body function, mRS score  $\geq 3$ ; activity limitation, ADL score > the 75% quartile; and participation restriction, RNLI score < the 25% quartile.

## **MRI assessments**

Each participant underwent brain MRI, including T1-weighted imaging, T2-weighted imaging, and diffusion-weighted imaging (DWI), within 7 days of admission using a 3.0 T system (Sonata, Siemens Medical, Erlangen, Germany). DWI spin echo-planar imaging (EPI) (TR/TE/excitation = 2162/76/1, matrix = 128 × 128, field of view [FOV] = 230 mm, slice thickness/gap = 6 mm/1 mm, EPI factor = 47, acquisition time = 25.9 s) with three orthogonally applied gradients was used, with a b value of 0 and 1000. Axial SE T1 (TR/TE/excitation = 488/15/1, FOV = 230 mm, slice thickness/gap = 6 mm/1 mm, matrix = 256 × 256, time of acquisition = 1 min 24.8 s) and TSE T2 (TR/TE/excitation = 3992/110/2, turbo factor = 15, FOV = 230 mm, slice thickness/gap = 6 mm/1 mm, matrix = 512 × 512, time of acquisition = 1 min 55.8 s) images were also acquired.

A neurologist (JFQ) who was blinded to the patients' clinical information measured the MRI variables. The MRI measurements included acute infarcts and preexisting abnormalities, as follows:

(1) Acute infarction. Both the site and volume of acute lesions in the DWI sequence were recorded. The sites of the acute infarcts were classified into cortical regions, subcortical regions, and infratentorial regions. Cortical regions included the frontal, temporal, parietal, and occipital lobes; subcortical regions included the white matter, basal ganglia, and thalamus; and infratentorial regions included the brainstem and cerebellum. Acute infarcts were defined as areas of restricted water diffusion identified on DWI with b values of 1000, together with hypointensity on the corresponding apparent diffusion coefficient map. The total area of acute infarcts on DWI was measured using manual outlines. The total volume was calculated by multiplying the total area by the sum of the slice thickness and the gap.

1. White matter lesions (WMLs). WML severity was graded using the four-point scale described by Fazekas et al [24]. WMLs included periventricular hyperintensities and deep white matter hyperintensities, which were scored separately on fluid-attenuated inversion recovery images.
2. Medial temporal lobe atrophy (MTLA). MTLA was evaluated using the Scheltens scale [25]. The MRI rater judged the severity of MTLA based on standard images of the coronal section of the MRI (range 0–4), with 0 representing no atrophy and 4 representing severe atrophy.
3. Microbleeds. These were defined as small (2–10 mm) hypointense lesions with a clear margin in susceptibility-weighted imaging [26]. Symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded.
4. Silent lacunae. These were visible as focal lesions (diameter > 3 mm), with approximately the same intensity as cerebrospinal fluid on MRI [27].

Intra-rater reliability (kappa) tests were carried out on 20 stroke patients with the same MRI rater. The intra-rater agreements for the MRI measurements were good to excellent: volume of infarction-ICC: 0.82; WMLs: 0.86; MTLA: 0.86; microbleeds: 0.80; silent lacunae: 0.83.

## Statistical analysis

Statistical analyses were performed using SPSS for Windows (v24.0, SPSS Inc., Chicago, IL, USA). Descriptive data are presented as proportions, means, or medians, as appropriate. To reduce the lack of randomization, we conducted a propensity score analysis using the SPSS custom dialog. Before matching, we performed a univariate analysis to compare variables between patients with and without END. The propensity score was then developed using a logistic regression model in which the variables with  $p < 0.05$  in the univariate analysis were entered. After estimating the propensity score, we matched participants using a simple 1:1 matching. After matching was completed, the two matched groups with and without END were compared. Logistic regression models were performed to analyze the relationship between multiple outcomes and END, based on the matched data. In the multivariate logistic regression analyses, the poor outcomes served as dependent variables, while END and other confounding factors served as independent variables. The odds ratio (OR) of END was interpreted as the risk of poor outcomes. The significance level was set at  $p < 0.05$  (two-sided).

## Results

In this study, 465 patients with first-ever AIS were consecutively admitted. Of these, 55 patients were excluded because they had no MRI data, and 42 were excluded because their MRI data were incomplete. Nine patients were excluded because they died before discharge, 29 patients were excluded because of severe complications, and 13 patients refused to sign their informed consent. During the follow-up, 4 patients died, 54 patients were lost to follow-up, and 3 patients were unable to finish the RNLI assessment. Hence, 256 patients were finally included in the analysis (Fig. 1).

Compared with the excluded patients, the included patients did not differ significantly in terms of sex (men, 71% vs. 67.6%,  $p = 0.455$ ), but differed significantly in age ( $59.9 \pm 11.25$  vs.  $63.63 \pm 12.76$ ,  $p = 0.002$ ) and NIHSS score on admission (2 [1–3] vs. 3 [2–5],  $p < 0.001$ ).

The study sample consisted of 185 men (72.3%) and 71 women (27.7%). Sixty-one patients underwent END, with an incidence of 23.8%. The baseline characteristics of patients with and without END, before and after propensity score matching, are summarized in Table 1. Before matching, patients with END had higher levels of small artery-type stroke, higher NIHSS scores on arrival, higher systolic blood pressure on admission, and larger infarct volumes. After matching, there were no significant differences between the two groups in any clinical or neuroimaging variables, except for stroke subtype and cortical region infarct.

Table 1  
Comparison of clinical and neuroimaging characteristics of END and non-END patients

	Prematched			Postmatched		
	END(n = 61)	non-END(n = 195)	<i>P</i> -value	END(n = 60)	non-END(n = 60)	<i>P</i> -value
Clinical						
Age(years) <sup>a</sup>	59.21(11.38)	59.71(10.67)	0.756	59.28(11.46)	61.37(10.6)	0.303
Male <sup>b</sup>	45(73.8%)	140(71.8%)	0.764	45(75%)	48(80%)	0.512
Hypertension <sup>b</sup>	52(85.2%)	149(76.4%)	0.143	51(85%)	47(78.3%)	0.345
Diabetes mellitus <sup>b</sup>	22(36.1%)	68(34.9%)	0.865	22(36.7%)	25(41.7%)	0.575
Atrial fibrillation <sup>d</sup>	1(1.6%)	10(5.1%)	0.241	1(1.7%)	4(6.7%)	0.364
Stroke subtype			0.08			0.02
Large artery	30(49.2%)	57(29.3%)		29(48.3%)	44(73.3%)	
Small artery	20(32.8%)	97(49.7%)		20(33.3%)	16(26.7%)	
Cardioembolism	4(6.6%)	5(2.6%)		4(6.7%)	0	
Unknown etiologies	7(11.5%)	36(18.5%)		7(11.7%)	0	
Onset to arrival time(hour) <sup>a</sup>	10.85(5.74)	10.63(6.04)	0.796	10.85(5.79)	10.99(5.62)	0.892
NIHSS on arrival <sup>c</sup>	3(2–4)	2(1–3)	< 0.001	3(2–4)	3(2–4)	0.221
I.V. thrombolysis <sup>d</sup>	2(3.3%)	5(2.6%)	0.765	2(3.3%)	1(1.7%)	1
Laboratory information						
SBP, mmHg <sup>a</sup>	164.16(25.91)	156.35(22.39)	0.023	163.42(25.45)	157.07(21.58)	0.143
DBP, mmHg <sup>a</sup>	95.67(15.88)	93.06(15.12)	0.246	95.23(15.64)	93.97(14.5)	0.646
Fast glucose, mmol/L <sup>a</sup>	6.99(3.3)	6.55(2.91)	0.313	7.03(3.31)	7.36(4.03)	0.626
HbA1c, % <sup>a</sup>	6.93(2.02)	6.85(2.07)	0.811	6.95(2.03)	7.16(2.32)	0.602

Note: END, early neurological deterioration; <sup>a</sup> Mean (SD), *t*-test; <sup>b</sup> *n* (%), chi-squared test; <sup>c</sup> M (Qu–QL), Mann–Whitney *U* test; <sup>d</sup> *n* (%), Fisher’s exact test; SBP, systolic blood pressure; DBP, diastolic blood pressure; MTLA, medial temporal lobe atrophy; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities.

	Prematched			Postmatched		
Total cholesterol, mmol/L <sup>a</sup>	5.35(0.99)	5.17(1.21)	0.269	5.34(0.99)	1.13(0.27)	0.39
Triglycerides, mmol/L <sup>a</sup>	2(1.82)	1.79(1.27)	0.305	2(1.83)	1.93(1.4)	0.798
HDL cholesterol, mmol/L <sup>a</sup>	1.1(0.19)	1.22(1.52)	0.524	1.1(0.19)	1.13(0.27)	0.448
LDL cholesterol, mmol/L <sup>a</sup>	3.55(0.77)	3.44(0.86)	0.366	3.54(.078)	3.46(0.91)	0.57
Homocysteine, ug/ml <sup>a</sup>	15.43(5.06)	17.05(14.41)	0.391	15.48(5.09)	16.54(5.55)	0.277
WBC (× 10 <sup>9</sup> /L) <sup>a</sup>	7.91(1.81)	8.22(3.91)	0.541	7.88(1.81)	8.55(4.4)	0.279
Hemoglobin (g/L) <sup>a</sup>	143(17.49)	139.44(17.13)	0.159	143.13(17.61)	138.78(16.37)	0.164
Fibrinogen (g/L) <sup>a</sup>	3.44(0.73)	3.44(0.87)	0.969	3.42(0.73)	3.55(0.88)	0.371
Prothrombin time (INR) <sup>a</sup>	0.99(0.97)	1.05(0.7)	0.551	1(0.98)	1.18(1.26)	0.266
Creatinine (umol/L) <sup>a</sup>	71.46(20.77)	75.07(25.5)	0.316	71.8(20.76)	77.15(30.64)	0.266
Neuroimaging information						
Location of infarcts						
Cortical region <sup>b</sup>	18(29.5%)	80(41%)	0.106	18(30%)	35(58.3%)	0.002
Subcortical region <sup>b</sup>	52(85.2%)	144(73.8%)	0.067	51(85%)	51(85%)	1
Infratentorial region <sup>b</sup>	6((9.8%)	33(16.9%)	0.179	6(10%)	5(8.3%)	0.752
Infarct volume <sup>c</sup>	2.28(1.14–2.25)	0.91(0.42–2.94)	< 0.001	2.31(1.13–5.29)	2.44(0.92–7.34)	0.929
MTLA <sup>c</sup>	0(0–1)	0(0–1)	0.272	0(0–1)	0(0–2.75)	0.146
PVH <sup>c</sup>	1(0–2)	1(0–2)	0.509	1(0–2)	1(0–2)	0.333
DWMH <sup>c</sup>	1(0–1)	1(0–1)	0.616	1(0–1)	1(0–2)	0.929
Note: END, early neurological deterioration; <sup>a</sup> Mean (SD), <i>t</i> -test; <sup>b</sup> <i>n</i> (%), chi-squared test; <sup>c</sup> <i>M</i> (Qu–QL), Mann–Whitney <i>U</i> test; <sup>d</sup> <i>n</i> (%), Fisher's exact test; SBP, systolic blood pressure; DBP, diastolic blood pressure; MTLA, medial temporal lobe atrophy; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities.						

	Prematched			Postmatched		
Microbleed <sup>c</sup>	17(27.9%)	59(30.3%)	0.722	17(28.3%)	28(46.7%)	0.038
Lacunae <sup>c</sup>	26(42.6%)	94(48.2%)	0.446	26(43.3%)	33(55%)	0.201

Note: END, early neurological deterioration; <sup>a</sup> Mean (SD), *t*-test; <sup>b</sup> *n* (%), chi-squared test; <sup>c</sup> M (Qu–QL), Mann–Whitney *U* test; <sup>d</sup> *n* (%), Fisher’s exact test; SBP, systolic blood pressure; DBP, diastolic blood pressure; MTLA, medial temporal lobe atrophy; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities.

Multiple stepwise regression models were used to analyze the effects of END on multiple outcomes (Table 2). END was revealed to be a significant predictor of poor mRS (OR, 3.829; 95% confidence interval [CI], 1.367–10.723, *p* = 0.011) and RNLI (OR, 2.777; 95% CI, 1.133–6.806, *p* = 0.026) scores, after adjusting for confounding factors.

Table 2  
Multiple dimensions of poor outcome according to the presence of END, following matching by PSM<sup>a</sup>

Variables	END	Non-END	$\beta$	OR (95% CI)	<i>P</i> -value
ADL	25(41.7%)	16(26.7%)	0.848	2.335(0.967–5.641)	0.059
mRS	19(31.7%)	8(13.3%)	1.343	3.829(1.367–10.723)	0.011
RNLI	26(43.3%)	16(26.7%)	1.021	2.777(1.133–6.806)	0.026

Note: END, early neurological deterioration; PSM, propensity score matching; ADL: activities of daily living; mRS, modified Rankin scale; RNLI, reintegration to normal living index; <sup>a</sup> adjusted for age, NIHSS on admission, and infarct volume.

## Discussion

In the current study, END affected multiple functional outcomes, including participation restriction and body function impairment. Because END is common in AIS, our results provide insights into the multifaceted nature of functioning after AIS combined with END.

In the present study, the incidence of END was 23.8%, which is consistent with results from previous studies. Current estimates of END incidence after AIS vary widely, and may depend on the definition, type of stroke scales, and time frame used to define this deterioration [5–8].

END may lead to an elevated probability of mortality and poor functional outcomes. As expected, the present results revealed that END was a significant predictor of poor mRS scores (OR = 3.829)—indicating more severe body function impairments—as reported in previous studies [13, 14, 28]. END also correlated with many clinical factors, such as age, stroke severity, systolic blood pressure, diabetes, and atrial fibrillation [13]. Because mRS scores reflect the overall degree of disability, including both physical function and prognosis [29], it is important to understand and emphasize the role of END in AIS.

END is an important problem in AIS and is correlated with poor functional outcomes. However, previous studies of functional outcomes after stroke combined with END have mainly focused on body function impairments alone, which are often narrowly defined and evaluated only using the mRS [16]. The WHO-ICF categorizes the consequences of disease into three different dimensions: body function impairments, activity limitations, and

participation restrictions [15]. In the present study, patients with END had a higher risk for poor participation (OR = 2.777) after adjusting for confounding factors using a propensity score analysis. Few previous studies have explored the relationship between END and participation restriction. Stroke survivors often experience participation restrictions in the chronic phase, despite having favorable basic ADLs [17]. Several factors contribute to participation restriction after stroke, including cognitive impairment, emotional deficits, stroke severity, functional dependency, and older age [30, 31]. We hypothesize that the contribution of END to impaired participation may be influenced by comprehensive risk factors.

Surprisingly, in our study, END was not an independent risk factor for poor ADL after adjusting for confounding factors. The complete ADL requires both dependent basal ADL and satisfactory memory and executive functions. Thus, impairment in ADL is likely influenced by dysfunction in multiple aspects, such as memory and executive function, which may not be related to END.

Our study had some advantages: we assessed the relationship between END and multiple aspects of functional outcomes, and we used propensity score analysis to adjust for confounding factors. Furthermore, we assessed comprehensive MRI variables, which included acute infarct and preexisting brain abnormalities. However, there were also some limitations to our study. First, the sample size was relatively small. Second, we did not assess the NIHSS score at follow-up after stroke, which led to an inadequate evaluation of post-stroke residual neurological deficits. Third, at the follow-up, we did not assess mental function, such as cognitive function, depression, or anxiety, which might be mediators between END and participation restriction.

In conclusion, END is common in AIS, with an incidence of 23.8%. END might be able to predict poor functional outcomes, including impaired body function and restricted social participation.

## Abbreviations

END, early neurological deterioration

AIS, acute ischemic stroke

mRS, modified Rankin Scale

RNLI, reintegration to normal living index

ADL, activities of daily living

NIHSS, National Institutes of Health Stroke Scale

DWI, diffusion-weighted imaging

WMLs, white matter lesions

MTLA, Medial temporal lobe atrophy

WHO-ICF, World Health Organization International Classification of Functioning, Disability, and Health

## Declarations

### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Not applicable.

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## Contributions

Study concept and design: JQ, SW. Acquisition of data: JQ, HZ, WL, YC, YL, Analysis and interpretation of data: HZ, WL, YL, Drafting of the manuscript: JQ. Critical revision of the manuscript for important intellectual content: YC. Statistical analysis: JQ.

## Ethics declarations

### Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Dongguan People's Hospital. The consent of all subjects was obtained in accordance with the Declaration of Helsinki.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

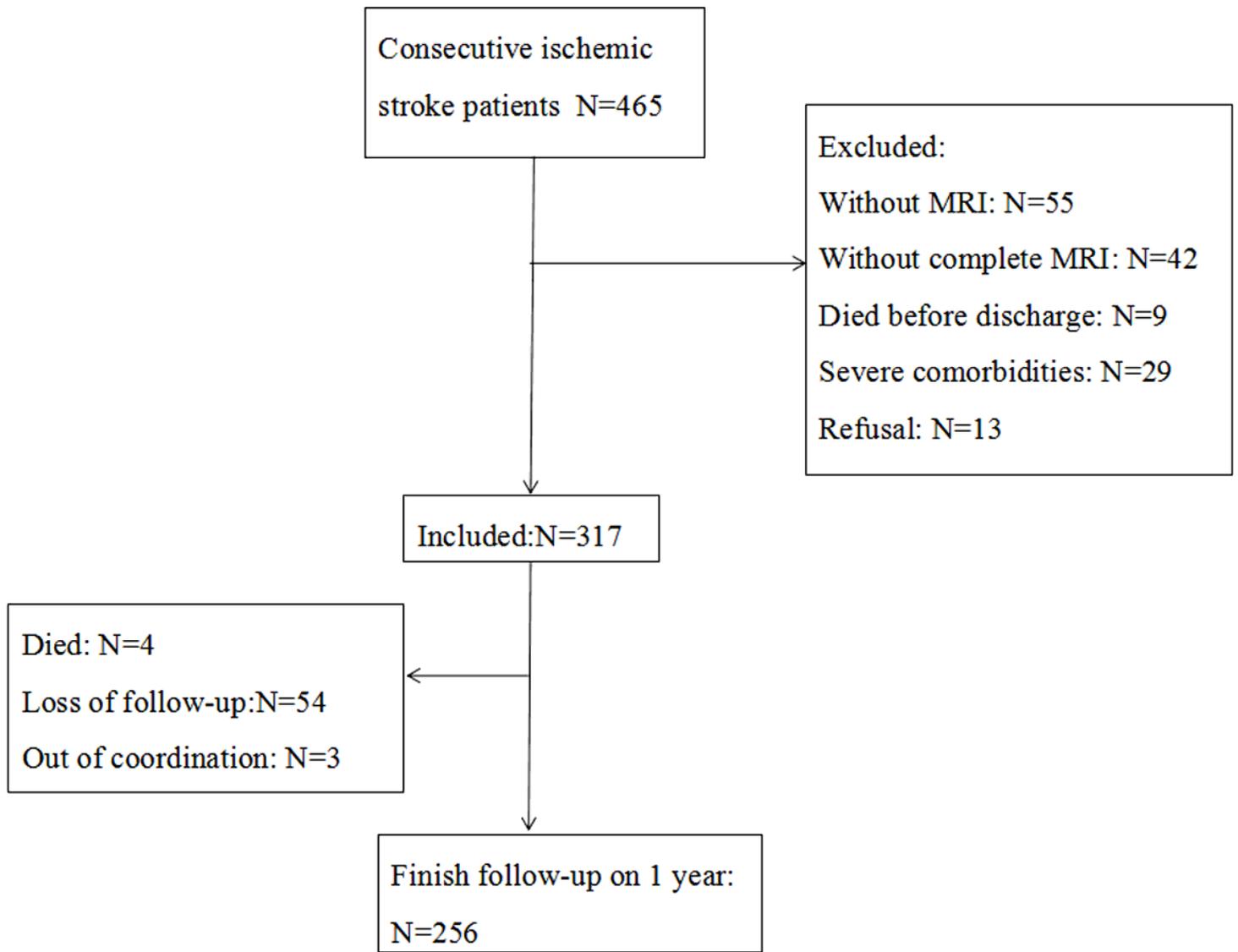
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## Figures



**Figure 1**

Flow chart of participants.