Early neurological deterioration during the acute phase as a predictor of long-term outcome after first-ever ischemic stroke

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Abstract

Early neurological deterioration (END) is associated with increased risk of functional disability and mortality. However, data are limited regarding the long-term risk of poor functional outcomes. Thus we explored the association between END and long-term outcomes in patients with acute ischemic stroke.

A total of 1064 patients were enrolled with acute ischemic stroke who were consecutively admitted to the 3 stroke units of Huai-He Hospital, Kaifeng, China. END was defined as an increment change of at least one point in motor power or total National Institute of Health Stroke Scale (NIHSS) score deterioration ≥2 points within the first week after admission. We retrospectively assessed the risk factors of END and prospectively explored the relationship between END and the long-term outcomes by multivariable regression models after adjusting the potential confounding factors. Outcomes were evaluated at 18 months based on modified Rankin scale (MRS) scores.

Approximately 32% of first-ever ischemic stroke patients experienced END during the acute phase. END was associated with diabetes (odds ratio [OR], 2.218; 95% confidence interval [CI] 1.619–3.037), NIHSS score at admission (OR, 1.052; 95% CI 1.023–1.082), C-reactive protein (CRP) levels (OR, 1.224; 95% CI 1.066–1.406]), and homocysteine (HCY) levels (OR, 1.203; 95% CI 1.061–1.365) after adjusting related factors, such as hypertension, diabetes, NIHSS at admission, and some blood laboratory values, including direct bilirubin, total cholesterol, low-density lipoprotein, glucose, CRP, HCY, and D-dimer levels. During the follow-up period, 52 (4.9%) patients died, 160 (15.0%) recrudesced, and 317 (29.8%) suffered poor outcomes. Multivariate logistic regression analyses revealed that poor outcome was associated with END (OR, 3.366; 95% CI 2.495–4.542), age (OR, 1.028; 95% CI 1.015–1.041), body mass index (OR, 1.096; 95% CI 1.051–1.144), coronary heart disease (OR, 1.637; 95% CI 1.108–2.416), and CRP (OR, 2.474; 95% CI 1.840–3.326).

The risk factors of END are multifaceted. Diabetes, NIHSS score at admission, CRP, and HCY are independent predictors of END. In addition, the results of this study indicate that END is an important predictor of poor functional outcome.

Abbreviations: BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, END = early neurological deterioration,, HCY = homocysteine, HDL = high-density lipoprotein, HOD = hospitalization day, LDL = low-density lipoprotein, MRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale, OR = odds ratio, SD = standard deviation.

Keywords: acute ischemic stroke, early neurological deterioration, follow-up, outcome

1. Introduction

Worldwide, Asia, Russia, and Eastern Europe experience the highest rates of mortality and disability-adjusted life years lost, as a result of stroke.[1] Furthermore, it reported that, the incidence rate of ischemic stroke increased by an average of 8.7% annually between 1984 and 2004 in China.[2] The consequences of stroke-related disability and death are significant for both society and individuals. Therefore, all measures capable of decreasing disability are therefore extremely important.

Early neurological deterioration (END), also known as "stroke progression,', "early stroke progression," "stroke-in-progression," and "stroke-in-evolution," has been observed in approximately 5% to 40% of patients with acute ischemic stroke,[3–5] and is frequently associated with increased risk of functional disability and mortality.[6–11]

The majority of studies have focused on the early risk of END[5,7,12] and short-term assessments (up to 6 months),[8,11,13,14,15] but data regarding the long-term risk of poor functional outcomes are limited. Despite Millikan and Siekert[16] first proposed the concept of progressive stroke 50 years ago, the effects of prognosis are still not clear. Our current study aimed to explore the risk factors of END in patients with acute ischemic stroke, as well as stroke recurrence, stroke disability, and all-cause death after END during a follow-up period of approximately 18 months.

2. Subjects and methods

We studied 3015 subjects who were consecutively admitted to 3 Stroke Units (2 of them were from the Department of Neurology and the other was from the Department of Rehabilitation) of Huai-He Hospital, Kaifeng, China between January 1, 2014 and November 30, 2015. All of the patients with first-ever ischemic stroke during the acute phase (symptoms occurring within 7 days[17]) were diagnosed by a neurologist according to the fourth Chinese National Conference's recommendations for the diagnosis of cerebrovascular diseases.[18] All potentially eligible patients were screened. The inclusion criteria were as follows: (1) 18 years of age or older, (2) ischemic stroke diagnosed via computed tomography and/or magnetic resonance imaging, (3) and first-ever ischemic stroke occurring within 7 days before admission. The exclusion criteria were as follows: (1) diagnosis of transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, brain tumors or unspecified stroke; (2) history of more serious medical disease other than ischemic stroke, such as cancer, renal failure, and Parkinson's disease; (3) the interference of the C- reaction protein (CRP) level by any disorder, including asthma, arthritis, liver disease, bronchitis, sinus infection, aspiration pneumonia or urinary tract infection on acute stroke phase; (4) death during the hospital admission; (5) incomplete clinical data; and (6) lack of follow-up data, including no information and refusal to participate. Finally, 1064 patients met the inclusion criteria and provided informed consent for their participation. A flowchart illustrating the selection of study subjects is presented in Figure 1.

2.1. Study protocol

Data were collected including patients' demography, medical history, stroke risk factors, and blood samples. Risk factors were defined according to protocol. Body mass index (BMI) was calculated by dividing measured weight in kilograms by the square of measured height in meters. Hypertension was defined as treatment with antihypertensive drugs before stroke onset or introduction of antihypertensive drugs before discharge. Diabetes was defined as treatment with glucose-lowering medications or diet prior to stroke onset, or a fasting serum glucose level > 7.7 mmol/L and / or 2-hour postprandial blood glucose > 11.1 mol/L according to the WHO and the International Diabetes Federation standard during the hospitalization. Coronary heart disease was documented by using previous history of myocardial infarction >6 months but <5 years before enrollment in the study, or angina pectoris confirmed by positive coronary angiography, nuclear scintigraphy, or exercise test.[19] Smoking was defined as the use of at least 1 cigarette per day prior to stroke onset. Alcohol drinkers were defined as those who drank alcohol on average more than once per week over the past year. Blood samples were obtained from all patients within 24 hours of admission, after an overnight fast of 12 to 14 hours. Blood samples, that is, the peripheral venous blood, were drawn from the antecubital vein of the patients, and then placed into plasma separator tubes with ethylene diamine tetraacetic acid and serum separator tubes for centrifugation. Levels of direct bilirubin, total bilirubin, albumin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, C-reactive protein (CRP), homocysteine (HCY), fibrinogen, and D-dimer were measured within 2 hours of collection.
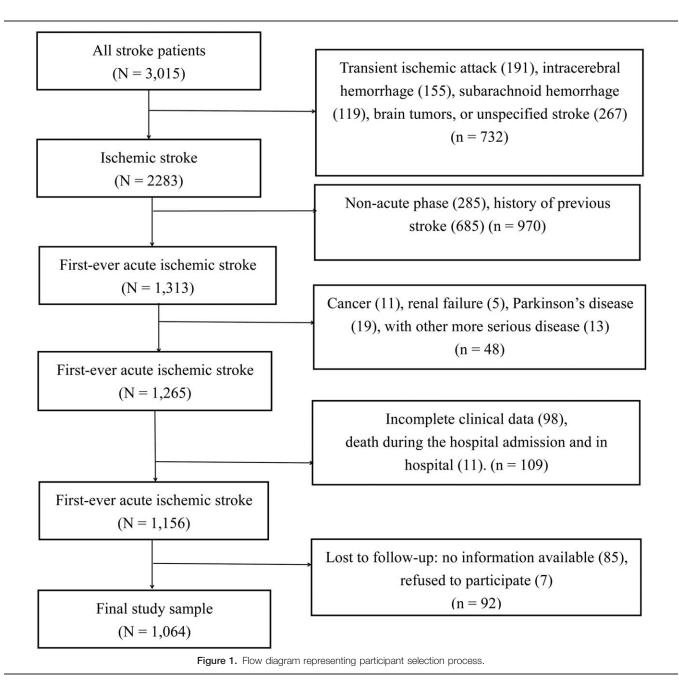
2.2. Neurological assessment and definition of END

Stroke severity was assessed at admission by a certified neurologist using the National Institutes of Health Stroke Scale (NIHSS).[20] In our study, END was defined as an increment of at least one point in motor power or total NIHSS score deterioration ≥2 points within the first week after admission.[10,17,21–24] Trained neurologists assessed the neurological status of the patients on a daily basis.

2.3. Follow-up and outcome assessment

Follow-up was performed by telephone interview. Patients who were unable to answer orientation questions had a proxy interview. Trained research personnel making the phone calls were blinded to patients' baseline clinical status. Patients were asked standardized follow-up questions approximately 18 months after stroke onset. The collected outcome data included stroke recurrence, stroke disability, and all-cause death. Recurrent cerebrovascular events included ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage. Cases of recurrent stroke were cross-checked with the treating hospitals to ensure the accuracy of diagnosis. In case of suspected stroke recurrence without hospitalization, the case was adjudicated by the trial executive committee. Stroke disability was defined as modified Rankin scale (MRS) of 3 to 6 at approximately 18 months after stroke onset. All-cause mortality was defined as death from any cause confirmed by either a death certificate from the local citizen registry or records from the treating hospital. When no official documentation was available, case fatality was determined if death was reported on 2 consecutive follow-up periods by different proxies.

2.4. Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the

Figure 1. Flow diagram representing participant selection process.

Ethics Committee of Henan University, China. Oral consent for use of clinical records was obtained from patients during follow-up. Written consent was not required due to the retrospective nature of the study. All patient data were anonymized prior to analysis.

2.5. Statistical analyses

Categorical variables were reported as proportions, while continuous variables were reported as median values or means ±standard deviations (SD). We examined the differences in continuous variables between patients with good and poor outcomes using Student's t- and nonparametric tests for normally and non-normally distributed data, respectively. Categorical variables were compared using Pearson's chi-square tests.

Multivariate logistic regression models were used to investigate the risk factors of functional outcome with a forward, stepwise selection strategy. A parsimonious final logistic regression model was fitted by retaining all predictor variables with $P < .05$. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Two-tailed P values $<.05$ were considered statistically significant. All statistical analyses were performed using SPSS software package, version 17.0 (SPSS, Inc., Chicago, IL).

3. Results

A total of 3015 patients were recruited between January 1, 2014 and November 30, 2015. Of these, 732 with other types of stroke or brain tumors, 685 with history of previous stroke, and 285 in the nonacute phase at admission were excluded. In addition, 48 patients

Table 1

Univariate comparison of demographic and clinical characteristics between first-ever ischemic stroke patients who showed early neurological deterioration and patients who did not.

Characteristic	Non-END (n=724)	END (n=340)	P
Age, (mean±SD, years)	63.65±12.42	64.20±12.96	.505
Sex			.461
Male	405 (55.9%)	182 (53.5%)	
Female	319 (44.1%)	158 (46.5%)	
BMI (mean±SD, kg/m^2)	25.04±3.51	25.37±3.69	.166
Residence			.433
Rural	386 (53.3%)	190 (55.9%)	
Urban	338 (46.7%)	150 (44.1%)	
Working status			.608
Unemployed	490 (67.7%)	225 (66.2%)	
Retired	175 (24.2%)	81 (23.8%)	
Employed	59 (8.1%)	34 (10.0%)	
Marital status			.951
Single	80 (11.0%)	38 (11.2%)	
Married	644 (89.0%)	302 (88.8%)	
Smoking			.187
Yes	179 (24.7%)	97 (28.5%)	
No	545 (75.3%)	243 (71.5%)	
Alcohol drinking			.338
Yes	111 (15.3%)	60 (17.6%)	
No	613 (84.7%)	280 (82.4%)	
NIHSS score at admission	10.14±4.75	11.46±5.07	**.000**
Time to hospital arrival, hours	88.76±68.21	90.47±67.12	.702
HOD (mean±SD, days)	17.12±10.22	17.66±10.15	.420
Hypertension			**.044**
Yes	391 (54.0%)	206 (60.6%)	
No	333 (46.0%)	134 (39.4%)	
Diabetes			**.000**
Yes	117 (16.2%)	98 (28.8%)	
No	607 (83.8%)	242 (71.2%)	
Coronary heart disease			.062
Yes	102 (14.1%)	63 (18.5%)	
No	622 (85.9%)	277 (81.5%)	
Blood Samples			
Total bilirubin, μmol/L	12.99±5.52	13.09±5.93	.788
Direct bilirubin, μmol/L	4.34±2.01	4.58±2.34	**.030**
Total protein, g/L	67.34±5.20	67.23±5.63	.746
Albumin, g/L	39.00±3.51	38.53±3.72	.060
Total cholesterol, mmol/L	4.75±1.01	4.59±1.04	**.006**
Triglyceride, mmol/L	1.69±0.95	1.75±1.22	.383
HDL, mmol/L	1.07±0.29	1.04±0.23	.165
LDL, mmol/L	3.10±0.87	2.96±0.89	**.016**
Glucose, mmol/L	6.51±2.67	6.84±2.87	**.031**
CRP, mg/L	6.61±12.05	9.72±15.79	**.000**
HCY, μmol/L	19.10±12.93	21.37±15.18	**.015**
Fibrinogen, mg/dL	309.91±244.90	317.78±82.00	.564
D-dimer, ng/mL	509.86±872.45	638.23±948.30	**.030**
Functional prognosis			
Recurrence — n (%)	101 (14.0%)	59 (17.4%)	.148
Death — n (%)	26 (3.6%)	26 (7.6%)	**.004**
Poor outcome — n (%)	151 (20.9%)	166 (48.8%)	**.000**

Data presented are n (%) or mean±SD (standard deviation)
BMI=body mass index, END=early neurological deterioration; single marital status included unmarried, divorced, and widowed participants; CRP=C- reactive protein, HCY=homocysteine, HDL=high-density lipoprotein, HOD=hospitalization day, LDL=low-density lipoprotein, NIHSS=National Institute of Health Stroke Scale.

with more serious disease and 109 patients with incomplete clinical data and death before discharge were excluded, and 85 patients without available content information and 7 patients who refused to participate were also excluded. Finally, 1064 patients participated in

Table 2

Multivariate logistic regression analysis of significant risk factors for early neurological deterioration in acute ischemic stroke patients.

Factor	OR*	95%CI	P
Diabetes			**.000**
Yes	2.218	1.619–3.037	
No	Reference		
NIHSS at admission	1.052	1.023–1.082	**.000**
CRP (increase per unit)	1.224	1.066–1.406	**.004**
HCY (increase per unit)	1.203	1.061–1.365	**.004**

CI=confidence interval, CRP=C- reactive protein, HCY=homocysteine, NIHSS=National Institute of Health Stroke Scale, OR=odds ratio.
* Adjusted for NIHSS score at admission, hypertension, diabetes, direct bilirubin, total cholesterol, LDL, glucose, CRP, HCY, and D-dimer level.

the follow-up study, and 92.0% completed the follow-up at 18 months after stroke onset (Fig. 1).

To examine the effect of early neurological deterioration, the patients were classified into 2 groups: those with (1) early neurological deterioration (END), and (2) nonearly neurological deterioration (non-END). Table 1 shows the baseline characteristics of patients in 2 groups. The END group contained 340 (32.0%) patients. The patients' ages ranged from 18 to 96 (63.82 ±12.59), and their BMI ranged from 17.7 to 36.3 kg/m^2 (25.15 ± 3.57). Univariate analyses revealed that END was significantly associated with the increasing hypertension, diabetes, NIHSS at admission, and some blood laboratory values such as direct bilirubin, total cholesterol, LDL, glucose, CRP, HCY, and D-dimer level (Table 1). During the follow-up time of 18 months, 52 (4.9%) patients died, 160 (15.0%) patients recrudesced, and 317 (29.8%) patients had poor outcomes (Table 1). In addition, Table 1 showed that END was significantly associated with death and poor outcomes, but was not associated with recurrence.

Table 2 showed the results of the multivariate logistic regression analysis for determination of the predictors of END. Diabetes (OR, 2.218; 95% CI 1.619–3.037), NIHSS score at admission (OR, 1.052; 95% CI 1.023–1.082), CRP (OR, 1.224; 95% CI 1.066–1.406]), and HCY (OR, 1.203; 95% CI 1.061–1.365) were significantly independent predictors of END.

As shown in Table 3, poor outcome by the 18-month follow-up was not associated with sex, residence, marital status, smoking, alcohol drinking, hypertension, or time from onset of stroke to admission, but was significantly related to working status (P=.033), hospitalization day (HOD; P=.006), END (P<.001), diabetes (P=.008), coronary heart disease (P<.001), and NIHSS score at admission (P=.001). Compared to patients with good outcomes, those who with poor outcomes were elderly (67.03±12.60 vs. 62.46±12.34 years, P<.001), with higher BMI (25.77±3.41 vs. 24.88±3.61 kg/m^2, P<.001), higher direct bilirubin level (4.61±2.52 vs. 4.33±1.92 umol/L, P=.014), lower albumin level (37.98±3.93 vs. 39.22±3.36 g/L, P<.001), lower total cholesterol level (4.58±1.07 vs. 4.75± 1.00 mmol/L, P=.013), lower LDL level (2.96±0.90 vs. 3.09± 0.86 mmol/L, P=.023), higher CRP level (13.64±20.99 vs. 5.03 ±6.95 mg/L, P<.001), and higher D-dimer level (739.24± 1144.29 vs. 470.95±758.51 ng/mL, P<.001). The other blood values did not differ significantly between the 2 groups.

A number of independent predictors of poor outcome after acute ischemic stroke were revealed in multivariate logistic regression analyses (Table 4). It showed that poor outcome was

Table 3

Comparison of baseline demographic and clinical characteristics between patients with poor and good outcomes.

Characteristic	Good outcome (MRS ≤2) (n = 747)	Poor outcome (MRS >2) (n = 317)	P
Age (mean ± SD, years)	62.46 ± 12.34	67.03 ± 12.60	.000
Sex			.231
Male	421 (56.4%)	166 (52.4%)	
Female	326 (43.6%)	151 (47.6%)	
BMI (mean ± SD)	24.88 ± 3.61	25.77 ± 3.41	.000
Residence			.958
Rural	404 (54.1%)	172 (54.3%)	
Urban	343 (45.9%)	145 (45.7%)	
Working status			.033
Unemployed	498 (66.7%)	217 (68.5%)	
Retired	173 (23.2%)	83 (26.2%)	
Employed	76 (10.2%)	17 (5.4%)	
Marital status			.301
Single	78 (10.4%)	40 (12.6%)	
Married	669 (89.6%)	277 (87.4%)	
Smoking			.733
Yes	196 (26.2%)	80 (25.2%)	
No	551 (73.8%)	237 (74.8%)	
Alcohol drinking			.577
Yes	117 (15.7%)	54 (17.0%)	
No	630 (84.3%)	263 (83.0%)	
HOD (mean ± SD, day)	16.76 ± 9.95	18.52 ± 10.68	.006
END			.000
Yes	174 (23.3%)	166 (52.4%)	
No	573 (76.7%)	151 (47.6%)	
Hypertension			.577
Yes	415 (55.6%)	182 (57.4%)	
No	332 (44.4%)	135 (42.6%)	
Diabetes			.008
Yes	135 (18.1%)	80 (25.2%)	
No	612 (81.9%)	237 (74.8%)	
Coronary heart disease			.000
Yes	87 (11.6%)	78 (24.6%)	
No	660 (88.4%)	239 (75.4%)	
NIHSS score at admission	10.17 ± 4.67	11.49 ± 5.07	.000
Time to hospital arrival, hours	86.78 ± 67.54	95.25 ± 68.27	.063
Blood samples			
Total bilirubin, μmol/L	12.89 ± 5.35	13.32 ± 6.29	.251
Direct bilirubin, μmol/L	4.33 ± 1.92	4.61 ± 2.52	.014
Total protein, g/L	67.39 ± 5.39	67.12 ± 5.24	.450
Albumin, g/L	39.22 ± 3.36	37.98 ± 3.93	.000
Total cholesterol, mmol/L	4.75 ± 1.00	4.58 ± 1.07	.013
Triglyceride, mmol/L	1.74 ± 1.03	1.64 ± 1.06	.164
HDL, mmol/L	1.06 ± 0.28	1.04 ± 0.24	.324
LDL, mmol/L	3.09 ± 0.86	2.96 ± 0.90	.023
Glucose, mmol/L	6.53 ± 2.69	6.82 ± 2.84	.106
CRP, mg/L	5.03 ± 6.95	13.64 ± 20.99	.000
HCY, μmol/L	19.94 ± 14.31	19.56 ± 12.24	.182
Fibrinogen, mg/dL	304.38 ± 240.38	331.40 ± 86.93	.052
D-dimer, ng/mL	470.95 ± 758.51	739.24 ± 1144.29	.000

Data presented are n (%) or mean ± SD (standard deviation); BMI = body mass index, MRS, modified Rankin scale; single marital status included unmarried, divorced, and widowed participants; CRP = C-reactive protein, END = early neurological deterioration, HCY = homocysteine, HDL = high-density lipoprotein, HOD = hospital day, LDL = low-density lipoprotein, NIHSS = National Institute of Health Stroke Scale.

Table 4

Factors related to poor outcome in acute ischemic stroke patients, based on multivariate logistic regression models.

Factor	OR*	95%CI	P
END			.000
Yes	3.366	2.495–4.542	
No	Reference		
Age	1.028	1.015–1.041	.000
BMI	1.096	1.051–1.144	.000
Coronary heart disease			.013
Yes	1.637	1.108–2.416	
No	Reference		
CRP (increase per unit)	2.474	1.840–3.326	.000

BMI = Body mass index, CI = confidence interval, CRP = C-reactive protein, END = early neurological deterioration, OR = odds ratio.
* Adjusted for age, BMI, working status, HOD, END, diabetes, coronary heart disease, NIHSS score at admission, direct bilirubin, albumin, total cholesterol, LDL, CRP, and D-dimer level.

admission, direct bilirubin, albumin, total cholesterol, LDL, and D-dimer levels were not statistically significant, and were therefore not included in the final parsimonious regression model.

4. Discussion

In our work, the most important finding was that END was a strong predictor of long-term unfavorable outcome during the acute phase in the first-ever ischemic stroke patients. In addition, older age, higher BMI and CRP level, and concomitant coronary heart disease were all associated with the long-term clinical unfavorable outcomes. It suggests our findings might provide new etiological factors as well as practical implications for stroke patients.

It also revealed that 32% of the first-ever ischemic stroke patients have experienced END during the acute phase. The proportion of patients with END was ranging from 5% to 40% which was consistent with the previous studies.[3–5] The incidence of END after acute ischemic stroke may vary widely in previous studies, depending on the definition used (i.e., different stroke scales and time frames used to assess deterioration). In fact, because some patients may be going trough their "natural" worsening in the early stage, the time of evaluation after first acute ischemic stroke is an important influencing factor on the incidence of END. Dávalos et al[7] reported a 20.3% incidence rate of patients with relatively late neurological deterioration after 3 to 7 days. In addition, Siegler et al[25] reported that NIHSS scores ≥2 points is a sensitive indicator of poor outcome compared to NIHSS scores ≥4 points. However, regardless of the definition used, END is consistently associated with poor three-month clinical outcomes.[26]

In recent years, many investigators have reported diabetes and NIHSS score at admission could be independent predictors of END.[7,13,27,28,29] Similarly, we also found these factors were related to END in the acute phase, even after adjusting for other significant covariates. A recently published cohort study also reported NIHSS score at admission to be independently associated with an increased risk of END in the acute phase.[30] Nevertheless, Zhang et al[21] found that the NIHSS score at admission was not associated with END. The probable causes may be not only their sample size was 208, relatively small, but also the object of their study included mild neurological disorder

associated with END (OR, 3.366; 95% CI 2.495–4.542), age (OR, 1.028; 95% CI 1.015–1.041), BMI (OR, 1.096; 95% CI 1.051–1.144), coronary heart disease (OR, 1.637; 95% CI 1.108–2.416), and CRP (OR, 2.474; 95% CI 1.840–3.326). The associations with working status, HOD, diabetes, NIHSS score at

(the average NIHSS score at admission was 3). The NIHSS score represents the degree of neurological deficits. The NIHSS score at admission may be an important predictor of END in the acute phase.

CRP level is an important prognostic indicator for ischemic stroke.[31,32] Nevertheless, Seo et al[33] found that CRP level at admission was significantly associated with END in acute ischemic stroke. The increasing of CRP level may be related to END. Our results also support these findings.

In this study, we found that elevated HCY levels at admission are also an important predictor of END, but are not associated with poor prognosis. Many researchers found that HCY levels were associated with END and prognosis.[19,24] The reason of springy structure damage, endothelial dys-function, and basal lamina injury of microvessels was elevated HCY levels. This potential mechanism may be the impairment of vessel wall integrity and break of cerebrovascular permeability.[34] That acute hyperhomocysteinemia causes endothelial dysfunction, which might affect cerebrovascular reactivity and promote atheroma development.[19,35] However, the mechanisms underlying these associations are not yet completely understood and require further study.

To the best of our knowledge, this is the first report of END in acute ischemic stroke as an independent predictor of poor outcomes during a follow-up period of approximately 18 months. Previous studies only reported that END was associated with short-term poor functional outcomes.[8–10,11–15] In our study, 29.8% of patients had poor outcomes, a lower rate than those reported in other studies.[23,36,37] The results of our study also revealed that END was associated with long-term death, similar to the results reported by Kim et al.[22] The underlying mechanism may be explained by decreased perfusion and/or decreased potential for rapid development during adequate collateral blood flow to ischemic zones.[38,39] Furthermore, the platelets are activated and formed blood clots, and then they further develop the thrombus, thus causing ischemic stroke symptoms to become worse.[40] However, we found no association of END in acute ischemic stroke and recurrence. The reason for this observation is unclear at present. Finally, older age and high BMI were independent predictors of long-term outcome in our study. Similarly, Helbok et al[41] and Wang et al[42] also reported older age is an independent predictor of disability and death. However, Tanaka et al[27] observed no relationship between BMI and outcome. This may be partly related to their relatively small sample size (n=242), and shorter time to assess outcome (30 days).

In this study, we found an important connection between coronary heart disease and poor outcomes. A previous study[43] also showed that coronary heart disease was associated with poor long-term outcomes. These data suggest that prevention and early assessment of medical complications are essential to prevent poor functional outcomes.

This study also have several limitations. First, this is a retrospective study. Unknown but potentially important factors might have confounded our results. Retrospective identification of patients might cause a selection bias. However, to minimize this error, we restricted the inclusion and exclusion criteria to avoid potential confounding factors. Second, we did not record the cause and time of death. It remains unclear whether the outcomes are affected after adjusting for cause and time of death. Finally, we defined END as an increment of at least one point in motor power or total NIHSS score ≥2 points. However, an increment of NIHSS ≤1 is easy to occur in clinical. The score may

have changed because of uncertainty factors rather than neurological impairment. Therefore, further prospective studies are required.

5. Conclusions

Our study demonstrated that diabetes, NIHSS score at admission, CRP, and HCY are independent predictors of END. During the follow-up period, it showed that END was an important predictor of poor functional outcome and was associated with death. In addition, we also revealed that older age, high BMI, coronary heart disease, and high CRP levels were also associated with poor functional outcomes. Further research into this topic is warranted to reduce the burden of unfavorable outcomes.

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