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Long-Term Mortality According to the Characteristics of Early Neurological Deterioration in Ischemic Stroke Patients

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Purpose: Although early neurological deterioration (END) during the acute stroke period is known to be associated with poor functional outcomes, there is little data regarding the impact of END on long-term outcomes according to the characteristics of END. The aim of this study was to investigate whether there are differences in long-term mortality according to the characteristics of END among acute ischemic stroke or transient ischemic attack patients. **Materials and Methods:** END was defined as any increase (≥1) in National Institute of Health Stroke Scale score within 7 days after admission. We assessed the characteristics of END, such as the etiology and severity of END, as well as recovery after END. The relationship between 30-day or long-term mortality and each characteristic of END was investigated using multiple logistic analysis or Cox regression model. **Results:** Among 2820 patients, END was observed in 344 patients (12.2%). After adjustment for age, sex, underlying cardiovascular diseases, stroke severity, and stroke subtypes, END was associated with long-term mortality, whether it was mild or severe and whether or not it was followed by recovery. However, 30-day mortality was strongly related to the severity of END or the absence of recovery after END. Among the causes of END, recurrent stroke and medical illness were related to 30-day mortality, as well as long-term mortality, while brain herniation and intracranial hemorrhagic complications were only associated with 30-day mortality. **Conclusion:** The results of the present study demonstrated that END is associated with higher mortality and the effects of END on short-term and long-term mortality depend on END characteristics.

Key Words: Cerebral infarction, prognosis, early neurological deterioration

INTRODUCTION

Stroke is the leading cause of death worldwide. Previous studies have shown that the risk of early death during the acute stroke period is 7-20%, and death is caused by the direct impact of index stroke or its complications.[1-3] However, survivors after stroke are also at an increased risk for further strokes and death during long-term follow-up.[4] The risk of mortality for ischemic stroke patients is related to the initial stroke severity and stroke subtype, as well as cardiovascular disease burden.[2,5-8]

Early neurological deterioration (END) can occur in about 10-40% of ischemic stroke patients during the acute stage[8-13] and can be caused by brain herniation due to large cerebral infarction, poor collaterals, recurrent stroke, and medical illnesses, including infection, myocardial infarction, and gastrointestinal bleeding.[14] Although END is known to be associated with poor functional outcomes and higher mortality during short-term follow-up,[11,12,15] there are few data regarding the impacts of END on long-term outcomes, in particular mortality, according to its characteristics, such as etiology, severity, and recovery of neurological worsening, in a large stroke population.

The aim of this study was to investigate short-term and long-term mortality in ischemic stroke or transient ischemic attack (TIA) patients who exhibited deterioration during the acute stroke period. We also attempted to determine whether the characteristics of END have different effects on mortality.

MATERIALS AND METHODS

Study sample

From January 2000 to December 2008, a total of 4090 patients who experienced ischemic stroke or TIA were admitted to Yonsei University Hospital, Department of Neurology. During admission, all patients were thoroughly evaluated through our stroke care pathway, which includes previous medical history, neurological status, standard blood tests, brain CT/MRI, angiographic studies, and cardiac evaluations. All patient data were prospectively and consecutively registered with the Yonsei Stroke Registry.[16] For this study, we excluded data concerning re-admission for recurrent stroke (n=198), presentation to hospital later than 3 days after onset of stroke (n=717) or hospitalization for less than 2 days (n=6), those who received thrombolytic treatment (n=345), and those with missing National Institute of Health Stroke Scale (NIHSS) data (n=4). Finally, 2820 patients were included in this study. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine.

Early neurological course

During hospitalization, all patients were evaluated daily to assess neurological status. All patients were assessed by stroke specialists and senior residents to check for neurological impairment using the NIHSS scores. The baseline, 1-, 3-, and 7-day NIHSS scores were entered into the stroke registry, and these scores were used in this study. If a patient died or was discharged within 7 days after admission, we used the last NIHSS score immediately before death or discharge as the final NIHSS score. We also calculated delta NIHSS scores (baseline NIHSS-final NIHSS score).

For our analysis of the NIHSS scores, END was defined as any increase (≥1) in NIHSS score within 7 days after admission compared with baseline NIHSS score. If patients experienced END, we determined the etiology and the severity of END. The causes of END were categorized into five groups of brain herniation, worsening of index stroke symptoms, recurrent stroke, intracerebral hemorrhage (ICH), and medical illness. Recurrent stroke was defined as exhibiting new neurologic symptoms with/without documentation of a new lesion in a different vascular territory on follow-up brain imaging. These classifications were mainly determined by a clinician based on additional results of brain imaging and medical condition. The severity of END was divided into three groups: severe END, with a worsening of ≥4 in NIHSS score; moderate END, with an increase of ≥2 and <4 in NIHSS score; and mild END, with an increase of 1 in NIHSS score, compared with baseline NIHSS score. We also investigated whether the patients with END recovered after they had experienced END. Recovery was defined as a final NIHSS score that was lower than or equal to the baseline NIHSS score for a given patient.

Long-term mortality

During follow-up, we collected patient data concerning death through nationwide death certificate data from the Korean National Statistical Office. The national death certification data are known to be reliable, according to previous studies,[17] because these data are collected based on a unique 13-digit identification code assigned to subjects at birth and the causes of death are coded according to the International Classification of Disease, 10th Revision. In this study, we defined the censoring date as December 31, 2008.

Statistical analysis

Numerical data are given as the mean±standard deviation and medians with interquartile range (IQR) for NIHSS scores. In this analysis, we investigated which variables were independently associated with short-term mortality (30-day mortality) in all ischemic stroke patients and long-term mortality in stroke survivors after 30 days. For comparison of 30-day mortality, we used multiple binary logistic regression anal-

ysis with adjustment for potential covariates, which exhibited a significant association in univariate analysis with a *p*-value <0.05. For analysis of long-term mortality in stroke survivors, we applied univariate and multivariate Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence intervals (CIs). The adjusted survival curves are presented after adjustment for all variables that were significant in the univariate Cox proportional hazards model.

In this study, all variables were investigated using the multicollinearity test. Based on this analysis, baseline NIHSS and other NIHSS scores, including final NIHSS score, had a strong association, while baseline NIHSS score was not statistically associated with the delta NIHSS score. Therefore, among the NIHSS scores measured at different times, the delta NIHSS score and baseline NIHSS score were entered into the multivariate model as covariates in the analysis of long term mortality.

Finally, all results with $p<0.05$ were considered statistically significant. All statistical analyses were conducted with the SPSS software package (version 18.0, SPSS Inc., Chicago, IL, USA) and the SAS software package (version 9.1.3, SAS Inc., Cary, NC, USA).

RESULTS

Overall baseline characteristics

Of the 2820 ischemic stroke patients enrolled for this analysis, the mean age was 63.9±11.9 years and 61.5% were male. Their median NIHSS score was 3 (IQR 1-6). Seventy-nine (2.8%) patients died within 1 month after index stroke, and a total of 500 (17.7%) patients were dead after a median follow-up of 3.1 years (range, 2 days-9 years). Baseline characteristics are presented in Table 1.

Characteristics of early neurologic deterioration

END was observed in 352 patients (12.5%). The frequency of END decreased as the interval from symptom onset to admission increased: the frequency of END was 13.4% (284/2126) within 24 hours, 10.4% (47/454) within 24-48 hours, and 8.8% (21/240) within 48-72 hours (p=0.012). Among the entire study population, TIA patients consisted of 9.8% and only 1.1% of TIA patients experienced END during hospitalization. Among patients with END, most patients worsened during the first 3 days (88.6%, 312/352) and did not recover during hospitalization (73.3%, 258/352). Of the causes of END, worsening of index stroke symptoms (59.9%, 211/352) was most common, followed by recurrent stroke (14.8%, 52/352), brain herniation (12.2%, 43/352), ICH (9.4%, 33/352), and medical illness (3.7%, 13/352). Patients who had experienced mild or moderate END were more likely to recover compared with those with severe END; the frequency of recovery after END was 51.1% (48/94) in mild END, 35.0% (35/100) in moderate END, and 7.0% (11/158) in severe END (p<0.001). Of the etiologies of END, neurological worsening caused by brain herniation, ICH, recurrent stroke, and medical illness were more frequently associated with severe END. The propor-

Table 1. Baseline Characteristics of the Study Population (n=2820)

Demographics	
Age, yr	63.9±11.9
Sex, male	1735 (61.5)
Risk factors	
Hypertension	2101 (74.5)
Diabetes mellitus	921 (32.7)
Hyperlipidemia	303 (10.7)
Smoking	1218 (43.2)
Atrial fibrillation	472 (16.7)
Previous ischemic stroke	483 (17.1)
Previous ischemic heart diseases	412 (14.6)
Peripheral arterial occlusive diseases	37 (1.3)
TOAST classification*	
Small vessel occlusion	380 (13.5)
Large artery atherosclerosis	606 (21.5)
Cardioembolism	518 (18.4)
Stroke of other determined etiology	49 (1.7)
Undetermined	992 (35.2)
Medication during admission	
Antiplatelet	2466 (87.4)
Statin	2020 (71.6)
Anticoagulation (including intravenous)	1295 (45.9)
NIHSS score during admission	
Baseline NIHSS score	3 [1-6]
NIHSS score at 1 day	2 [1-5]
NIHSS score at 3 days	2 [0-5]
NIHSS score at 7 days (or final NIHSS score)	1 [0-4]
Delta: baseline-7 days (or final NIHSS score)	0 [0-2]

TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale.
Data are expressed as mean±SD, number (%), or median [interquartile range].
*Stroke mechanism was determined among 2545 ischemic stroke patients with acute ischemic lesion in brain imaging.

tion of patients who did not recover during hospitalization was greater in patients with brain herniation or medical illness compared to those with other causes (Fig. 1).

Short-term (30-day) mortality

With respect to 30-day mortality, age (p<0.001), previous ischemic heart disease (p=0.039), peripheral arterial occlusive disease (p=0.006), atrial fibrillation (p<0.001), and baseline NIHSS score (p<0.001), as well as final NIHSS score (p<0.001) or delta NIHSS score (p<0.001), were associated with short-term mortality. With adjustment for these potential confounders, the presence of END was an independent predictor of mortality at 30 days (odds ratio 3.185, 95% CIs 1.522-6.664, p=0.002) (Table 2). However, END with recovery was not associated with mortality within 30 days. Compared with no END, the development of severe END was more strongly associated with short-term mortality. Among the causes of END, brain herniation, recurrent stroke, ICH, and medical illness were associated with 30-day mortality, while worsening of the index stroke

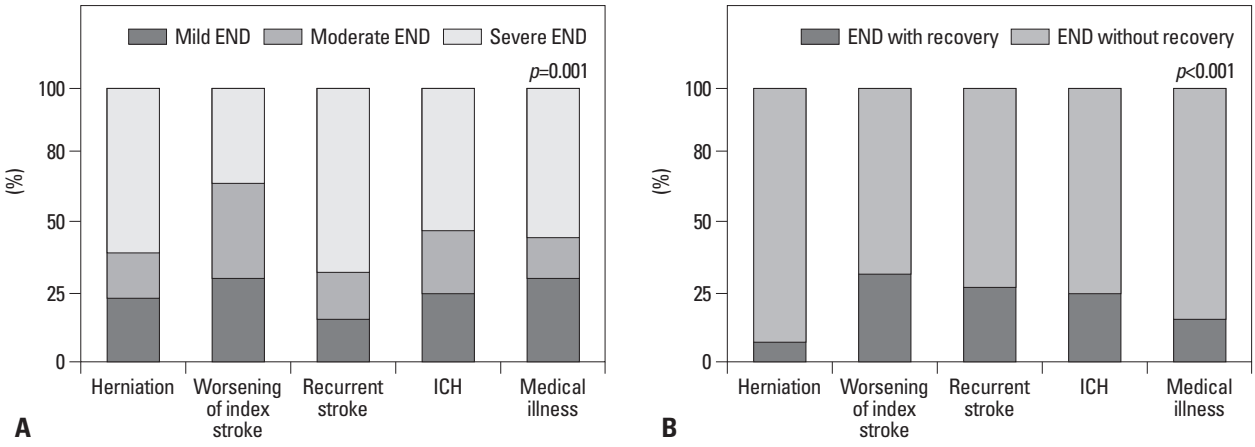

Fig. 1. Frequency of (A) early neurologic deterioration (END) conditions and (B) END with recovery according to the causes of END. ICH, intracerebral hemorrhage.

Table 2. Multivariate Analysis According to END Characteristics

	30-day mortality (n=2820)		Long-term mortality (n=2741)	
	Adjusted OR (95% CIs)	p value*	Adjusted HR (95% CIs)	p value†
The presence of END	3.185 (1.522-6.664)	0.002	1.571 (1.165-2.119)	0.003
Degree of END				
No END	1		1.000	
END with increase in 1 NIHSS	5.300 (1.991-14.106)	0.001	1.759 (1.109-2.787)	0.016
END with increase in 2-3 NIHSS	3.141 (1.014-9.735)	0.047	1.396 (0.882-2.209)	0.154
END with increase in ≥4 NIHSS	24.556 (13.213-45.635)	<0.001	1.592 (1.022-2.480)	0.040
Presence of recovery after END				
No END	1		1.000	
END with recovery	1.638 (0.357-7.523)	0.525	1.611 (1.039-2.496)	0.033
END without recovery	16.427 (9.288-29.054)	<0.001	1.546 (1.069-2.234)	0.020
Causes of END				
No END	1		1.000	
Herniation	32.135 (13.828-74.677)	<0.001	1.383 (0.576-3.320)	0.468
Worsening of index stroke sx	0.981 (0.225-4.272)	0.980	1.379 (0.975-1.950)	0.069
Recurrent stroke	15.156 (5.478-41.933)	<0.001	2.787 (1.589-4.888)	<0.001
Intracranial hemorrhage	26.483 (10.806-64.902)	<0.001	1.341 (0.617-2.913)	0.458
Medical problem	39.187 (10.746-142.910)	<0.001	4.704 (1.838-12.041)	0.001

END, early neurological deterioration; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

*Binary logistic regression model for the analysis of 30-day mortality adjusted for age, sex, previous ischemic heart disease, peripheral arterial occlusive disease, atrial fibrillation, and baseline NIHSS score in the study population.

†Cox proportional hazard model for the analysis of long-term mortality adjusted for age, sex, hypertension, diabetes, smoking, previous ischemic stroke, ischemic heart disease, peripheral arterial occlusive disease, stroke subtype, and baseline NIHSS score, as well as delta NIHSS score in stroke survivors.

was not. In multivariate analyses, according to each characteristic of END, baseline NIHSS score was a significant and independent predictor of short-term mortality (data not shown).

Long-term mortality in stroke survivors

Univariate Cox proportional hazard model revealed that age (p<0.001), hypertension (p=0.031), diabetes (p=0.001), smoking (p=0.009), previous ischemic stroke (p<0.001), ischemic heart disease (p=0.001), peripheral arterial occlusive disease (p<0.001), stroke subtype (p<0.001), baseline NIHSS (p<0.001), and final NIHSS score (p<0.001) were related to long-term mortality among stroke survivors. In multivariate Cox proportional hazard model, END itself was an independent predictor of long-term mortality (HR 1.571, 95% CIs 1.165-2.119). In contrast to the results for short-term mortality, the long-term risk of mortality was not different according to the severity of END or the presence of recovery after END (Table 2). Among the causes of END, recurrent stroke and medical illness remained independent, while brain herniation and ICH were not associated with long-term mortality. On multivariate analysis of the relationship between each characteristic of END and long-term mortality, baseline NIHSS score and delta NIHSS score remained independent and significant predictors of long-term morality (data not shown).

Fig. 2 shows the adjusted survival curves for all-cause mortality in stroke survivors. Survival was similar between patients who did not recover after END and those who recovered after END and between the patients who developed mild END and those who developed severe END. However, among the etiologies of END, patients with medical illness and recurrent stroke showed poorer survival.

DISCUSSION

Previous studies have shown that initial stroke severity and functional status at discharge have a strong association with long-term mortality.[2,5,18] Those associations were consistently observed in our study in that the initial NIHSS score as well as delta NIHSS score were independent predictors of long-term mortality. Furthermore, we showed that patients who experienced neurologic deterioration while they were admitted due to acute ischemic stroke encompassed higher risks of short-term and long-term mortality, irrespective of initial stroke severity.

In our study, short-term and long-term mortality differed according to the characteristics of END. END followed by recovery was not associated with short-term mortality, but was associated with long-term mortality, while severe END with an increase of ≥4 in NIHSS score was more associated with short-term mortality. Compared to END without recovery, END with recovery during the acute stage resulted in milder neurological disability at discharge. However, the risk of long-term mortality was similar regardless of whether the END was followed by recovery, although patients without recovery were more severely disabled at discharge. Previous studies showed that patients with TIA or recovery within 24 hours after ischemic stroke had a greater risk of subsequent stroke or neurological deterioration.[19,20] Our results along with previous findings suggest that END, with or without recovery in the acute stage, is a surrogate marker of recurrent vascular events and future mortality.

We further demonstrated that the risk of future mortality varies according to the etiology of END. Among the etiologies of END, brain herniation and ICH were associated

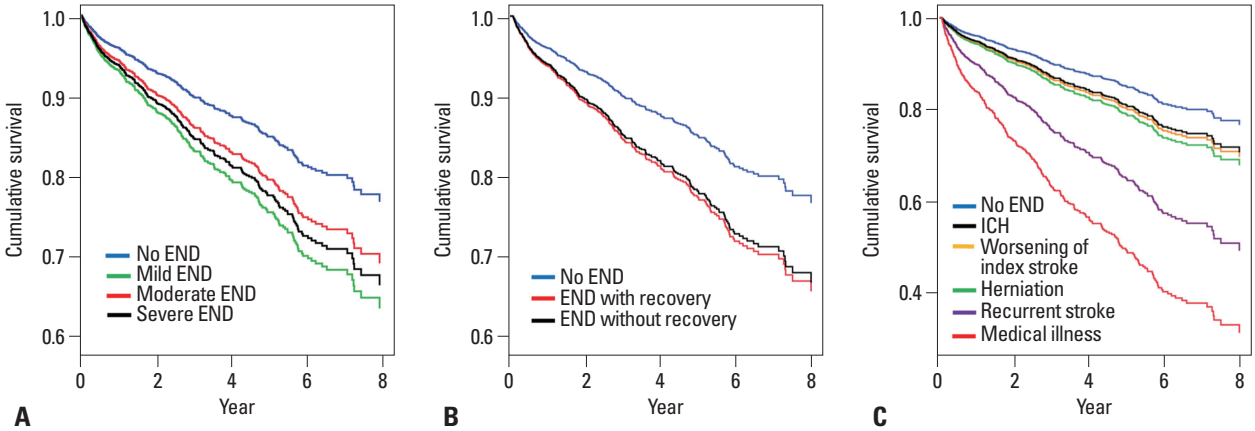

Fig. 2. Adjusted survival curves for long-term mortality in stroke survivors according to (A) severity of early neurologic deterioration (END), (B) presence of recovery after END, and (C) causes of END. ICH, intracerebral hemorrhage.

with 30-day mortality, while these were not associated with long-term mortality. In contrast, END caused by recurrent stroke or medical illness was associated with a higher risk of long-term mortality, as well as 30-day mortality. An increased risk of short-term mortality in patients with END due to brain herniation and ICH is expected because they are the most severe and devastating complications that usually develop during the acute stage of stroke with large infarction.[21] A risk of stroke recurrence during the acute period depends on underlying vascular status, including unstable atherosclerotic plaques, intracardiac conditions, inflammatory markers, and procoagulable/prothrombotic conditions. Because these are also surrogates for future risk of vascular events, patients who experience early recurrence would have a higher risk of recurrent vascular events.[22-25] Patients with recurrent ischemic lesions on MRI during the acute stroke period are more likely to have had late radiological or clinical recurrences.[26] In this context, subjects with early clinical recurrence may be important targets for more aggressive treatment for stroke prevention. Likewise, END caused by medical illness was associated with short-term and long-term mortality in our study. Previous studies also showed that in-hospital medical complications in acute stroke influenced both short-term and long-term mortality.[3,27,28] These data suggest that the prevention and early assessment of medical complications are essential to prevent both long-term and short-term fatality.

Our study has some limitations. First, this was a retrospective study, although all patients were consecutively registered and reliable mortality data were used. Second, not all patients with END underwent repeated diffusion weighted MRI to confirm recurrent stroke, although follow-up brain CT had performed in nearly all cases of END for exclusion of hemorrhagic complications in our center. However, documentation of new symptoms was required to diagnose recurrent stroke in this study, since neurological symptoms are well correlated with new ischemic recurrent lesions during the acute stroke stage.[24] Third, treatment effects were not considered. Although all patients were managed through our stroke care pathway and treatment protocol during admission, the patient's long-term compliance to treatment was unknown, which might affect patient outcomes.

In conclusion, END has a negative impact on the long-term and short-term mortality regardless of whether it is mild or severe or whether it is followed by recovery. Our findings also suggest that the prediction of mortality differs depending on the etiology of END. Physicians should concern about patients with END in order to prevent devastating events.

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