Neurology Asia 2020; 25(4) : 447 – 451

Clinical predictors of early neurological deterioration in patients with acute minor ischemic stroke

[1,2]Yoon Jung Kang *MD*, [1,2,3]Sang Min Sung *MD Phd*, [1,2]Yuri Je *MD*, [1,2]Jaeseob Yun *MD*, [1,2]Nae Ri Kim *MD*, [1,2]Suk Min Lee *MD*, [1,2]Han Jin Cho *MD*

[1]Stroke Center, [2]Department of Neurology, [3]Biomedical Research Institute, Pusan National University Hospital, School of Medicine, Pusan National University, Busan, Republic of Korea

Abstract

Background: Early neurological deterioration is a critical determinant of functional outcome in patients with acute minor ischemic stroke. This study aimed to identify clinical predictors of early neurological deterioration in patients with acute minor ischemic stroke.
Methods: A total of 739 patients who experienced acute minor ischemic stroke symptoms between January 2014 and December 2018 were enrolled in this study. All patients were presented within a 4.5-hour time window of stroke symptom onset. Early neurological deterioration was defined as an increment of at least one point in motor power or total National Institute of Health Stroke Scale (NIHSS) score deterioration ≥ 2 points within 3 days after admission. Unfavorable functional outcome was defined as a modified Rankin Scale score of ≥ 2 at 90 days after stroke onset. Demographic characteristics, risk factors for vascular diseases, stroke severity, stroke subtypes, and neuroimaging parameters were analyzed. Regression analysis was used to determine clinical predictors of early neurological deterioration. *Results:* Of the 739 patients, 78 (10.5%) patients had early neurological deterioration. Among the 78 patients with early neurological deterioration, 61 (78.2%) had unfavorable functional outcome at 90 days after stroke onset. In contrast, 131 of the remaining 661 (19.8%) patients without early neurological deterioration had unfavorable functional outcome. Multivariate analysis identified hemorrhagic transformation (odds ratio, 3.8; 95% confidence interval, 1.4-10.5; P = 0.010), higher NIHSS score at admission (odds ratio, 1.4; 95% confidence interval, 1.1-1.7; P = 0.003), arterial stenosis (odds ratio, 2.0; 95% confidence interval, 1.2-3.5; P = 0.014) and occlusion (odds ratio, 2.6; 95% confidence interval, 1.4-4.8; P = 0.004) in the territory of stroke as significant predictors of early neurological deterioration.
Conclusions: The results of this study suggest that hemorrhagic transformation, higher NIHSS score at admission, and arterial steno-occlusive lesions in the territory of stroke are independent predictors of early neurological deterioration in patients with acute minor ischemic stroke.

Keywords: Predictor, early neurological deterioration, acute minor ischemic stroke, functional outcome

INTRODUCTION

A significant number of patients with ischemic stroke have mild neurological deficits at the time of stroke onset.[1,2] These patients are usually ineligible for a tissue plasminogen activator (tPA) due to mild stroke symptoms (NIHSS score of ≤ 3) even within the 4.5-hour time window. Despite initial mild neurological deficits, a large portion of patients with acute minor ischemic stroke become disabled or died.[3-8] Previous studies have shown that early neurological deterioration (END) is the main factor that contributes to disability or death after minor ischemic stroke.[5,7,9,10] END commonly follows acute minor ischemic stroke, occurring in up to one-quarter of patients.[9,11] Although there have been studies on risk factors related to END, there have been few studies integrating clinical information and imaging information. Besides, most of the studies were performed on ischemic stroke patients regardless of the severity of symptoms, and were not limited to acute minor stroke patients.[12-14] This study aimed to identify clinical predictors of END in patients with acute minor ischemic stroke based on clinical and neuroimaging information.

Address correspondence to: Sang Min Sung, M.D., Ph.D. Stroke Center, Department of Neurology, Pusan National University, School of Medicine, Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-Ro, Seo-Gu, Busan, 602-739, Republic of Korea. Tel. 82-51-240-7317, E-mail: aminoff@hanmail.net

Date of Submission: 10 July 2020; Date of Acceptance 5 October 2020

METHODS

We reviewed 739 consecutive patients with acute minor ischemic stroke who presented to our stroke center within a 4.5-hour time window between January 2014 and December 2018. Minor ischemic stroke was defined as the National Institute of Health Stroke Scale (NIHSS) score of ≤ 3 on admission. END was defined as an increment of at least one point in motor power or total NIHSS score deterioration ≥ 2 points within 3 days after admission. The same trained neurologists assessed the NIHSS score of the patients on a daily basis during hospitalization. Functional outcome was assessed by a neurologist blinded to the presence of END, who rated the modified Rankin Scale (mRS) score at 90 days after stroke onset. Unfavorable functional outcome was defined as an mRS score of ≥ 2. We identified demographic characteristics (age and sex), risk factors for vascular diseases (hypertension, diabetes, hyperlipidemia, smoking, coronary heart disease, and atrial fibrillation), neuroimaging information (location and arterial territory), subtypes of stroke, hemorrhagic transformation, initial NIHSS scores, and arterial steno-occlusive lesions in the territory of stroke. Etiological subtypes of ischemic stroke were classified by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.[15] All patients underwent magnetic resonance imaging, including a diffusion-weighted image (DWI) with vessel imaging such as computed tomographic angiography (CTA) or magnetic resonance angiography (MRA). DWI lesion pattern was categorized into anterior, posterior, or both circulations. Hemorrhagic transformation was defined as any hemorrhage including petechial hemorrhage in the area of infarction. Hemorrhagic transformation was determined by brain computed tomography or magnetic resonance imaging at 3 days after admission or the day of END. Arterial stenosis or occlusion in the territory of stroke was assessed using initial CTA or MRA. We excluded the patients who had a premorbid mRS score of ≥ 1, mechanical thrombectomy or emergent carotid artery stenting, missing mRS score at 90 days, and new neurological symptoms after hospital discharge. Enrolled patients were divided into two groups: those with and those without END. Demographic characteristics, risk factors for vascular diseases, subtypes of stroke, neuroimaging information, hemorrhagic transformation, initial NIHSS scores, arterial steno-occlusive lesions in the territory of stroke and functional outcome were compared between the two groups using the chi-square test or Fisher's exact test for categorical variables, and an independent t-test or the Wilcoxon rank-sum test for continuous variables. Logistic regression was used to analyze independent predictors of END. $P < 0.05$ was considered statistically significant. All statistical analyses were completed with SPSS for Windows 5. This study was approved by the Institutional Review Board of our hospital with a waiver of informed consent due to the retrospective nature of the study.

RESULTS

Clinical characteristics

A total of 739 patients (499 men and 240 women, mean age 64.55 ± 11.81) were included in this study. There was no difference between patients with END and those without END in age, gender, vascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, coronary heart disease, and atrial fibrillation), location of the lesion, arterial territory and TOAST classification (Table 1).

Predictors of early neurological deterioration

Among the 739 patients, 78 (10.55%) patients had END. In univariate analysis, patients with END were more likely to have a hemorrhagic transformation, higher NIHSS score at admission, and arterial stenosis or occlusion in the territory of stroke compared with those without END (Table 1). In multivariate analysis, hemorrhagic transformation (odds ratio [OR] = 3.80; 95% confidence interval [CI] = 1.38-10.45), initial NIHSS score (OR = 1.40; 95% CI = 1.13-1.73), arterial stenosis (OR = 2.01; 95% CI = 1.15-3.49), and occlusion (OR = 2.56; 95% CI = 1.36-4.82) in the territory of stroke were the independent predictors of END in acute minor ischemic stroke (Table 2).

Functional outcome and early neurological deterioration

Of 739 minor stroke patients, 192 (25.98%) patients had unfavorable functional outcome. The median 90-day mRS score was higher in patients with END than in those without END (2.45 vs. 0.83; $P < 0.001$). When an unfavorable functional outcome at 90 days was defined as an mRS score of ≥ 2, the patients with END were more likely to have unfavorable functional outcome than those without END. In total, 61 of 78 (78.2%) patients

Table 1: Univariate comparison of clinical characteristics between patients with END and patients without END

Variables	Overall (n =739)	END (n=78)	No END (n=661)	*P-value
Age, mean (SD)	64.55 (11.81)	66.23 (11.08)	64.35 (11.89)	0.183
Female (%)	240 (32.48)	32 (41.03)	208 (31.47)	0.115
Hypertension (%)	477 (64.55)	45 (57.69)	432 (65.36)	0.225
Diabetes (%)	218 (29.5)	23 (29.49)	195 (29.5)	1.000
Hyperlipidemia (%)	198 (26.79)	16 (20.51)	182 (27.53)	0.234
Smoking (%)	317 (42.9)	29 (37.18)	288 (43.57)	0.338
Coronary heart disease (%)	70 (9.47)	7 (8.97)	63 (9.53)	1.000
Atrial fibrillation (%)	117 (15.83)	11 (14.1)	106 (16.04)	0.781
Location of Lesion (%)				
Right	313 (42.35)	32 (41.03)	281 (42.51)	
Left	335 (45.33)	39 (50)	296 (44.78)	0.537
Bilateral	91 (12.31)	7 (8.97)	84 (12.71)	
Arterial territory of Lesion (%)				
Anterior circulation	369 (49.93)	42 (53.85)	327 (49.47)	
Posterior circulation	333 (45.06)	34 (43.59)	299 (45.23)	0.510
Both	37 (5.01)	2 (2.56)	35 (5.3)	
TOAST classification (%)				
LAA	113 (15.29)	13 (16.67)	100 (15.13)	
CE	168 (22.73)	12 (15.38)	156 (23.6)	
SAO	145 (19.62)	18 (23.08)	127 (19.21)	0.219
OD	17 (2.3)	4 (5.13)	13 (1.97)	
UD	296 (40.05)	31 (39.74)	265 (40.09)	
Hemorrhagic transformation (%)	21 (2.84)	6 (7.69)	15 (2.27)	0.017
Initial NIHSS score, mean (SD)	1.25 (1.09)	1.60 (1.09)	1.21 (1.08)	0.002
Arterial stenosis in the territory of stroke (%)	164 (22.19)	24 (30.77)	140 (21.18)	0.003
Arterial occlusion in the territory of stroke (%)	98 (13.26)	17 (21.79)	81 (12.25)	
mRS at 90 days, mean (SD)	1.00 (1.02)	2.45 (1.26)	0.83 (0.84)	<0.001

Abbreviations: END, Early neurological deterioration; TIA, Transient ischemic attack; TOAST, Trial of Org 10172 in acute stroke treatment; LAA, Large-artery atherosclerosis; CE, Cardioembolism; SAO, Small artery occlusion; OD, Other determined causes; UD, Undetermined causes; NIHSS, National institutes of health stroke scale; mRS, modified Rankin Scale; SD, Standard deviation.
*P < 0.05 was considered statistically significant.

with END had unfavorable functional outcome at 90 days after stroke onset. In contrast, 131 of the remaining 661 (19.81%) patients without END had unfavorable functional outcome.

DISCUSSION

Our study revealed that about 1 in 10 of acute minor ischemic stroke patients have neurological deterioration within 3 days after stroke onset, and

Table 2: Multivariate analysis of predictors of END in acute minor ischemic stroke*

Variables	OR	95% CI	P-value
Hemorrhagic transformation	3.80	1.38-10.45	0.010
Initial NIHSS score	1.40	1.13-1.73	0.003
Arterial stenosis in the territory of stroke	2.01	1.15-3.49	0.014
Arterial occlusion in the territory of stroke	2.56	1.36-4.82	0.004

Abbreviations: OR, Odds ratio; CI, Confidence interval; NIHSS, National institutes of health stroke scale
*Multivariate analysis included predictors of END on univariate analysis.

the incidence of END was lower than previous similar studies.[11,13] Hemorrhagic transformation, the severity of the initial neurological deficit (as measured by the NIHSS), and arterial stenosis or occlusion in the territory of stroke were significant predictors of END in acute minor ischemic stroke.

In our study, the frequency (2.84%) of hemorrhagic transformation was lower than in previous studies of ischemic stroke.[14-19] One possible explanation for this difference is that we analyzed only acute minor ischemic stroke patients who were expected to have a small-sized infarction; also, our patients had not received acute reperfusion therapies. We also found that hemorrhagic transformation was significantly associated with END, even in patients with minor ischemic stroke. This finding is in line with previous studies that have reported the association of hemorrhagic transformation with neurological deterioration in stroke patients with moderate to severe neurological deficits or large infarctions.[14-18]

We found the association of END with the severity of initial neurological deficit rated by the NIHSS scores, as in the previous study.[20] These findings might be explained by focal cerebral edema, the main etiology of neurological deterioration. Minor ischemic stroke patients with higher NIHSS scores may have more extensive infarction than patients with lower NIHSS scores, and cerebral edema is more likely to be severe in large infarction.

Several studies have shown the association of unfavorable outcomes with occlusive lesions in the intracranial or extracranial arteries.[5] Our study found that arterial stenosis or occlusion in the territory of stroke were independent predictors of END. These findings suggest that arterial steno-occlusive lesions contribute to unfavorable functional outcome without a recurrence of stroke.

Several studies have reported predictors for END; however, different factors were suggested in each study, such as diabetes, occlusion of the middle cerebral artery, and the stenosis of the carotid artery.[12,21,22] However, there was no significant association with diabetes in our study. Also, some studies have reported biomarkers related to END, such as homocysteine, factor VIII, and D-dimer. We did not analyze these biomarkers because we have focused on clinical and neuroimaging information in this study.[23-25] Our study, like previous studies, showed that the outcomes of patients with acute minor ischemic stroke are not benign.[9,26,27] We found that about one-quarter of patients with acute minor ischemic stroke have unfavorable functional outcome at 90 days after stroke onset. In particular, patients with END after acute minor ischemic stroke were more likely to have unfavorable functional outcome than those without END.

Our study had some limitations. First, it was a retrospective analysis of patients at a single stroke center. Second, the incidence of END is relatively low. As our study excluded acute minor ischemic stroke patients who underwent acute reperfusion therapies (mechanical thrombectomy or emergent carotid artery stenting), the incidence of END may have been underestimated. Also, we did not completely rule out the silent infarction. It may have been helpful to take follow-up images at 90 days after stroke onset to rule out the recurrence of a new ischemic stroke during the 90-day follow-up period. However, as we excluded the patients who experienced new neurological symptoms after hospital discharge, follow-up imaging of all patients in this study was unnecessary. Third, we did not consider the volume of infarction and the collateral status. Fourth, we did not continuously monitor the change of blood pressure and glucose. Even small changes in blood pressure and blood sugar may have a significant effect on the occurrence of END. Also, a previous medication history of antiplatelet or anticoagulant was not determined.

In conclusion, our findings demonstrated that hemorrhagic transformation, higher NIHSS score at admission, and arterial steno-occlusive lesions in the territory of stroke were independent predictors of END in patients with acute minor

ischemic stroke. Furthermore, END contributed to unfavorable functional outcome in patients with acute minor ischemic stroke.

DISCLOSURE

Financial support: This work was supported by clinical research grant from Pusan National University Hospital in 2020.

Conflict of interest: None

REFERENCES

1. Reeves M, Khoury J, Alwell K, *et al*. Distribution of national institutes of health stroke how scale in the Cincinnati/northern Kentucky stroke study. *Stroke* 2013;44:3211-3.
2. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20:1407-31.
3. Yaghi S, Rostanski SK, Boehme AK, *et al*. Imaging parameters and recurrent cerebrovascular events in patients with minor stroke or transient ischemic attack. *JAMA Neurol* 2016;73:572-8.
4. Wu L, Wang A, Wang X, *et al*. Factors for short-term outcomes in patients with a minor stroke: results from China National Stroke Registry. *BMC Neurol* 2015;15:253.
5. Coutts SB, Modi J, Patel SK, *et al*. What causes disability after transient ischemic attack and minor stroke? Results from the CT and MRI in the Triage of TIA and minor Cerebrovascular Events to Identify High Risk Patients (CATCH) Study. *Stroke* 2012;43:3018-22.
6. Wang X, Zhao X, Johnston SC, *et al*. CHANCE Investigators. Effect of clopidogrel with aspirin on functional outcome in TIA or minor stroke: CHANCE Substudy. *Neurology* 2015;85:573-9.
7. Smith EE, Abdullah AR, Petkovska I, *et al*. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. *Stroke* 2005;36:2497-9.
8. Barber PA, Zhang J, Demchuk AM, *et al*. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology* 2001;56:1015-20.
9. Rajajee V, Kidwell C, Starkman S, *et al*. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. *Neurology* 2006;67:980-4.
10. Khatri P, Conaway MR, Johnston KC, Acute Stroke Accurate Prediction Study (ASAP) Investigators. Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke* 2012;43:560-2.
11. Kim JT, Heo SH, Yoon W, *et al*. Clinical outcomes of patients with acute minor stroke receiving rescue IA therapy following early neurological deterioration. *J Neurointerv Surg* 2016;8:461-5.
12. Cuadrado-Godia E, Jimena S, Ois A, *et al*. Factors associated with early outcome in patients with large-vessel carotid strokes. *J Neurol Neurosurg Psychiatry* 2013;84:305-9.
13. Hellbert BH, Ellekjaer H, Indredavik B. Outcomes after early neurological deterioration and transitory deterioration in acute ischemic stroke patients. *Cerebrovasc Dis* 2016;42:378-86.
14. Kranendonk KR, Treurniet KM, Boers AMM, *et al*. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *J Neurointerv Surg* 2019;11:464-8.
15. Ay H, Furie KL, Singhal A, *et al*. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005;58:688-97.
16. Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction–a prospective study. *Stroke* 1986;17:179-85.
17. Fiorelli M, Bastianello S, von Kummer R, *et al*. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 1999;30:2280-4.
18. Berger C, Fiorelli M, Steiner T, *et al*. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001;32:1330-5.
19. Kablau M, Kreisel SH, Sauer T, *et al*. Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011;32:334-41.
20. Siegler JE, Boehme AK, Albright KC, et al. A proposal for the classification of etiologies of neurologic deterioration after acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2013;22:e549-e556.
21. Siegler JE, Samai A, Semmes E, Martin-Schild S. Early neurologic deterioration after stroke depends on vascular territory and stroke etiology. *J Stroke* 2016;18:203-10.
22. Tanaka R, Ueno Y, Miyamoto N, *et al*. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. *J Neurol Sci* 2013;332:45-50.
23. Kwon HM, Lee YS, Bae HJ, Kang DW. Homocysteine as a predictor of early neurological deterioration in acute ischemic stroke. *Stroke* 2014;45:871-3.
24. Kuo CY, Lin CH, Kuo YW, *et al*. Factor VIII levels are associated with ischemic stroke, stroke subtypes and neurological worsening. *Curr Neurovasc Res* 2015;12:85-90.
25. Krarup LH, Sandset EC, Sandset PM, Berge E. D-dimer levels and stroke progression in patients with acute ischemic stroke and atrial fibrillation. *Acta Neurol Scand* 2011;124:40-4.
26. Kim DH, Lee DS, Nah HW, *et al*. Clinical and radiological factors associated with unfavorable outcome after intravenous thrombolysis in patients with mild ischemic stroke. *BMC Neurol* 2018;18:30.
27. Smith EE, Fonarow GC, Reeves MJ, *et al*. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: Findings from Get With The Guidelines–Stroke. *Stroke* 2011;42:3110-5.