Factors associated with unfavorable outcome in minor ischemic stroke

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ABSTRACT

Objectives: The purpose of this study was to elucidate the factors that correlate with unfavorable outcomes and to develop a simple validated model for assessing risk of unfavorable outcomes in patients with minor ischemic stroke.

Methods: The derivation cohort included 1,313 patients hospitalized within 72 hours after onset with an initial NIH Stroke Scale score of 0 to 3 enrolled in a prospective, multicenter, observational study. Unfavorable outcome was defined as dependency (modified Rankin Scale score of 3–5) or death at 90 days. The predictive values of factors related to unfavorable outcome were evaluated. External validation was performed in 879 patients from a single-center stroke registry.

Results: In the derivation cohort, a total of 203 patients (15%) had unfavorable outcomes. On multivariable analysis, women (odds ratio [OR] 1.95, 95% confidence interval [CI] 1.30–2.94), age ≥ 72 years (OR 2.80, 95% CI 1.83–4.36), intra/extracranial vascular occlusive lesion (OR 2.80, 95% CI 1.82–4.28), leg weakness (OR 1.72, 95% CI 1.06–2.82), and extinction/inattention (OR 5.55, 95% CI 1.30–21.71) were independently associated with unfavorable outcome. Patients having both a vascular lesion and either leg weakness or extinction/inattention showed 4.63 (95% CI 2.23–9.33) times the risk of unfavorable outcome compared with those having neither. In the validation cohort, the risk was similar, at 3.77 (95% CI 1.64–8.37).

Conclusions: Intra- and extracranial vascular imaging, NIH Stroke Scale items such as leg weakness and extinction/inattention, and their combination, as well as female sex and advanced age, may be useful for predicting unfavorable outcomes in patients with minor stroke. *Neurology*® 2014;83:174–181

GLOSSARY

CI = confidence interval; **mRS** = modified Rankin Scale; **NCVC** = National Cerebral and Cardiovascular Center; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **rt-PA** = recombinant tissue-type plasminogen activator; **SUMO** = Stroke Unit Multicenter Observational.

Minor strokes account for approximately 30% of all strokes.^{1,2} Although the outcomes of most patients with minor symptoms, epitomized by a low NIH Stroke Scale (NIHSS) score, are favorable, a small but significant number of such patients become disabled.^{3–7} Thus, it is important to identify the patients at risk of unfavorable functional outcomes in the early stage in the clinical setting.

It has been reported that abnormal CT or MRI findings such as acute infarction and vascular stenosis or occlusion are associated with functional dependency at 90 days in patients with minor stroke and TIA.^{8–11} Although the baseline NIHSS score is also associated with functional outcome in overall patients with stroke,³ it has a significant weakness regarding capturing lesion-specific neurologic deficits, such as those with right-sided and posterior circulation lesions.^{12,13} There is limited information about the clinical significance of using NIHSS scores with minor stroke.

The purpose of the present study was to elucidate the factors that correlate with unfavorable outcomes and to develop a simple validated model for assessing risk of unfavorable outcomes in patients with minor stroke.

Supplemental data
at *Neurology.org*

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SUMO Study coinvestigators are listed on the *Neurology*® Web site at *Neurology.org*.

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METHODS Derivation cohort. The derivation cohort was selected from the Stroke Unit Multicenter Observational (SUMO) Study, a prospective, observational, cohort study conducted between December 2004 and December 2005 in Japan.¹⁴ Its aim was to clarify diagnostic and therapeutic processes of acute stroke care that are effective for improving clinical outcomes. Eighty-four representative acute institutes participated in the SUMO Study. A total of 6,815 consecutive patients with ischemic and hemorrhagic stroke admitted within 72 hours after symptom onset were registered. Of these, patients with minor

ischemic strokes, defined as a baseline total NIHSS score ≤ 3 , were enrolled as the derivation cohort (figure 1A).

Validation cohort. The National Cerebral and Cardiovascular Center (NCVC) Stroke Registry^{15,16} is a prospective database of patients with acute stroke treated in our stroke care unit. Data of 3,439 patients with ischemic and hemorrhagic stroke who were admitted within 7 days after onset between January 2006 and December 2012 were extracted from this database. Of these, patients with minor ischemic strokes, defined as a baseline total NIHSS score ≤ 3 , were registered as the derivation cohort (figure 1B).

Figure 1 Flowchart of patient selection in the derivation (A) and validation (B) cohorts

A. The derivation cohort

B. The validation cohort

mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

Clinical characteristics. Baseline data including sex, age, onset to admission time, comorbidities, and risk factors (hypertension, diabetes, dyslipidemia, arrhythmia including atrial fibrillation, and previous all strokes/TIA) were collected from both cohorts.

An intra/extracranial vascular occlusive lesion was defined as a $\geq 50\%$ narrowing in diameter or occlusion verified by imaging modalities such as magnetic resonance angiography, conventional digital subtraction angiography, or carotid duplex sonography.

Each NIHSS item was dichotomized as normal (subscore of 0) or abnormal (subscore ≥ 1). The sum of the right and left scores was used for motor arm and motor leg items.¹⁷

Patients who were disabled before the stroke (corresponding to a modified Rankin Scale [mRS] score ≥ 2) were excluded from the analysis. An unfavorable outcome was defined as an mRS score of 3 to 6 (dependency or death) at 90 days.¹⁸ The outcome corresponding to an mRS score of 2 to 6 at 90 days was also assessed.

Statistical analysis. Statistical analysis was performed using JMP 10.0.2 (SAS Institute Inc., Cary, NC). Baseline characteristics were compared between favorable and unfavorable outcomes using χ^2 tests, unpaired t tests, Fisher exact tests, or Wilcoxon/Kruskal-Wallis tests. To identify the cutoffs of variables that could be used for discriminating between favorable and unfavorable outcomes, receiver operating characteristic curves were constructed. The odds ratios (ORs) for variables associated with unfavorable outcomes were determined using multivariable logistic regression analyses by the forced entry method adjusted for variables with $p < 0.05$ on univariate analyses. A value of $p < 0.05$ was considered significant for all results.

Standard protocol approvals, registrations, and patient consents. Each institutional Ethics and Hospital Management Committee approved the studies from the SUMO Study database. Written informed consent to participate in the study was obtained from the patient whenever possible; acceptance from a relative was obtained if patients could not consent themselves. The Regional Ethics and Hospital Management Committees of NCVC approved the studies from the NCVC Stroke Registry. The Ethics Committee waived consent because this was a registry study.

RESULTS A total of 1,313 patients were included in the analysis as the derivation cohort. Their mean age was 69 years, and 433 (33%) were women. Of these patients, 203 (15%) had unfavorable outcomes at 90 days, and 54 (4%) had recurrent stroke (ischemic or hemorrhagic) before 28 days or discharge. Magnetic resonance angiography, digital subtraction angiography, and carotid duplex sonography were performed in 1,208 (92%), 105 (8%), and 945 (72%) patients within 7 days of hospitalization, respectively.

The patients' characteristics were compared between patients with and without unfavorable outcomes in the derivation cohort (table 1). Patients with unfavorable outcomes were older ($p < 0.001$), more frequently female ($p < 0.001$), had a higher percentage of onset to admission time ≤ 12 hours ($p = 0.001$), less frequently had dyslipidemia ($p = 0.015$), and more often had an intra/extracranial vascular occlusive lesion ($p < 0.001$) than those with favorable outcomes. The median total NIHSS score

was 1 (interquartile range 0–2) in patients with unfavorable outcomes and 2 (interquartile range 1–3) in those with favorable outcomes ($p < 0.001$). Patients with unfavorable outcomes more frequently had leg weakness ($p = 0.002$) and extinction/inattention ($p = 0.024$) and less frequently had facial palsy ($p = 0.013$) and sensory ($p = 0.027$) manifestations than those with favorable outcomes. Figure 2 shows the distribution of mRS scores according to baseline total NIHSS score in the derivation cohort.

The optimal cutoff age for an unfavorable outcome was ≥ 72 years, with a sensitivity of 67%, a specificity of 58%, and an area under the receiver operating characteristic curve of 0.666. Table 2 shows the results of the multivariable analysis for unfavorable outcome (mRS score of 3–6) at 90 days in the derivation cohort. Female sex (OR 1.95, 95% CI 1.30–2.94), age ≥ 72 years (OR 2.80, 95% CI 1.83–4.36), intra/extracranial vascular occlusive lesion (OR 2.80, 95% CI 1.82–4.28), leg weakness (OR 1.72, 95% CI 1.06–2.82), and extinction/inattention (OR 5.55, 95% CI 1.30–21.71) were independently associated with unfavorable outcome after adjusting for baseline total NIHSS score. In contrast, the baseline total NIHSS score was not independently associated with unfavorable outcome.

In the derivation cohort, outcomes for 17 of 65 patients (26%) having both an intra/extracranial vascular occlusive lesion and abnormal NIHSS items for either leg weakness or extinction/inattention were unfavorable. Patients with both factors had 4.63 (95% CI 2.23–9.33, $p < 0.001$) times the risk of an unfavorable outcome compared with those having neither after adjustment for sex, age, and other essential characteristics (figure 3A). The foregoing model was also applied to patients with baseline NIHSS scores of 0 to 4 ($n = 1,941$) and 0 to 5 ($n = 2,233$) in the SUMO Study cohort. Patients with both factors had 7.53 (95% CI 4.47–12.66, $p < 0.001$) and 6.96 (95% CI 4.39–11.02, $p < 0.001$) times the risk of an unfavorable outcome, respectively (figure e-1 on the *Neurology*® Web site at Neurology.org). The analysis was also performed for the outcome corresponding to mRS scores of 2 to 6. Patients with both factors had 2.72 (95% CI 1.50–4.86, $p = 0.001$) times the risk of having mRS scores of 2 to 6 at 90 days compared with those having neither after adjustment for the same factors. In addition, sensitivity analysis including missing follow-up patients as having an “unfavorable outcome” was performed. Patients having both factors showed 3.15 (95% CI 1.97–5.06) times the risk for an unfavorable outcome compared with those having neither.

The patients' characteristics included in the derivation and validation cohorts ($n = 879$) are shown in table e-1. In the validation cohort, the frequency of

Table 1 Patients' characteristics in the derivation cohort

	Total (n = 1,313)	Unfavorable (mRS score 3-6) (n = 203)	Favorable (mRS score 0-2) (n = 1,110)	p
Demographics				
Female sex, %	33.0	44.3	30.9	<0.001
Age, mean $\bar{y} \pm$ SD	69 $\pm$ 11	75 $\pm$ 10	68 $\pm$ 11	<0.001
Onset to admission time $\leq$ 12 h, %	50.2	61.5	48.2	0.001
Comorbidities and risk factors, %				
Hypertension	61.8	57.1	62.6	0.140
Diabetes	23.7	28.6	22.8	0.075
Dyslipidemia	23.4	16.8	24.6	0.015
Arrhythmia including atrial fibrillation	16.9	21.2	16.1	0.077
Previous all strokes/TIA	22.2	25.6	21.5	0.198
Intra- or extracranial vascular occlusive lesion, %	25.3	42.4	22.2	<0.001
Baseline total NIHSS score, median (IQR)	2 (1-3)	1 (0-2)	2 (1-3)	<0.001
Abnormal NIHSS items, %				
1a. Level of consciousness	1.4	2.3	1.3	0.426
1b. Questions	4.5	6.8	4.2	0.178
1c. Commands	0.2	0	0.2	1.000
2. Gaze	2.3	4.5	2.0	0.077
3. Visual fields	6.1	3.0	6.5	0.125
4. Facial palsy	14.7	7.5	15.7	0.013
5. Motor arm	36.0	37.6	35.8	0.678
6. Motor leg	32.5	44.4	30.9	0.002
7. Ataxia	12.4	9.8	12.8	0.328
8. Sensory	20.0	12.8	20.9	0.027
9. Language	4.8	7.5	4.5	0.126
10. Dysarthria	30.0	26.3	30.6	0.318
11. Extinction/inattention	0.9	3.0	0.6	0.024
IV thrombolytic therapy, %	0.2	0.5	0.1	0.285

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

hypertension ($p < 0.001$), diabetes mellitus ($p = 0.037$), dyslipidemia ($p < 0.001$), previous all strokes/TIA ($p = 0.040$), intra- or extracranial vascular occlusive lesion ($p < 0.001$), and IV thrombolytic therapy ($p = 0.018$) were significantly higher than in the derivation cohort. Baseline total NIHSS score ($p < 0.001$) was also higher in the validation cohort than in the derivation cohort. The frequencies of NIHSS item abnormalities also differed between the cohorts. Level of consciousness questions ($p = 0.005$), motor arm ($p < 0.001$), motor leg ($p = 0.002$), and ataxia ($p = 0.033$) were higher in the derivation cohort. Facial palsy ($p < 0.001$), sensory ($p < 0.001$), and dysarthria ($p < 0.001$) were higher in the validation cohort. Fewer patients had unfavorable outcomes at 90 days in the validation cohort than in the derivation cohort ($p < 0.001$). Outcomes for

12 of 64 patients (19%) having both an intra/extracranial vascular occlusive lesion and abnormal NIHSS items for either leg weakness or extinction/inattention were unfavorable. Patients with both factors had 3.77 (95% CI 1.64–8.37, $p = 0.002$) times the risk of an unfavorable outcome compared with those having neither after adjustment for the same factors as the derivation cohort (figure 3B).

DISCUSSION In the analysis of patients with minor stroke in the derivation cohort, it was found that (1) NIHSS leg weakness and inattention/extinction items were independently related to unfavorable outcomes; (2) advanced age, female sex, and intra/extracranial vascular occlusive lesion were independently associated with unfavorable outcomes after adjusting for NIHSS items; and (3) baseline total NIHSS score

Figure 2 mRS score according to baseline total NIHSS score in the derivation cohort

mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

was not independently associated with outcomes in patients with minor stroke. A simple model based on the analysis of the derivation cohort was developed; the combination of intra/extracranial vascular occlusive lesion and leg weakness or extinction/inattention could be used to assess risk of unfavorable outcomes, even after adjusting for other significant factors including sex and advanced age. Predictability of this simple model was validated using our single-center cohort. Although several outcome prediction models for ischemic stroke patients, especially those receiving IV thrombolysis, have been reported,^{19–22} this study is unique in that an outcome prediction model for minor ischemic stroke patients was proposed.

It has been reported that advanced age,^{6,10} female sex,^{6,11} diabetes mellitus,¹¹ and intra- or extracranial vascular occlusive lesion^{8,9,23} were the factors related to unfavorable outcomes in patients with minor strokes. The present results are generally in line with the previous reports. However, individual NIHSS items were not included in these reports. A recent study involving patients with minor stroke, defined as retrospectively assessed NIHSS scores ≤ 5 , showed that patients with an NIHSS profile represented by signs of slurred speech and language deficit had the worst outcome.⁷ The study did not analyze each NIHSS item. In addition, the total baseline NIHSS score was reported to be inversely related to favorable outcome without significant associations between

Table 2 Multivariable analysis for unfavorable outcome (mRS score 3–6) at 90 days in the derivation cohort

	Crude			Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Female sex	1.78	1.31–2.41	<0.001	1.95	1.30–2.94	0.001	1.95	1.30–2.94	0.001
Age ≥ 72 y	2.91	2.13–4.02	<0.001	2.81	1.84–4.36	<0.001	2.80	1.83–4.36	<0.001
Onset to admission time ≤ 12 h	1.72	1.25–2.40	0.001	1.44	0.97–2.16	0.074	1.44	0.97–2.16	0.073
Dyslipidemia	0.62	0.41–0.90	0.012	0.84	0.51–1.37	0.496	0.85	0.51–1.37	0.502
Intra- or extracranial vascular occlusive lesion	2.58	1.89–3.53	<0.001	2.79	1.82–4.28	<0.001	2.80	1.82–4.28	<0.001
Baseline total NIHSS score	0.73	0.64–0.84	<0.001				1.03	0.79–1.32	0.844
Abnormal NIHSS items									
4. Facial palsy	0.44	0.21–0.81	0.007	0.50	0.24–0.96	0.036	0.49	0.22–0.97	0.042
6. Motor leg	1.78	1.23–2.58	0.002	1.77	1.17–2.67	0.007	1.72	1.06–2.82	0.029
8. Sensory	0.55	0.31–0.92	0.021	0.65	0.35–1.13	0.131	0.64	0.34–1.13	0.131
11. Extinction/inattention	4.99	1.26–17.70	0.024	5.68	1.35–21.78	0.020	5.55	1.30–21.71	0.023

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; NIHSS = NIH stroke scale; OR = odds ratio.

Model 1: adjusted for variables with $p < 0.05$ on univariate analyses excluding the baseline total NIHSS score. Model 2: adjusted for variables with $p < 0.05$ on univariate analyses including the baseline total NIHSS score.

Figure 3 Combined effects of intra/extracranial vascular occlusive lesion and leg weakness or extinction/inattention on unfavorable outcome

Risk of an unfavorable outcome was calculated using “patients without both” as the reference, adjusting for female sex, age ≥ 72 years, onset to admission time ≤ 12 hours, dyslipidemia, facial palsy, and sensory items of the NIH Stroke Scale in both cohorts.

individual NIHSS items and outcome in a small study involving 194 patients with minor stroke with NIHSS scores ≤ 6 ,²⁴ whose vascular status was not assessed.

Previous studies reported that leg weakness and extinction/inattention were major determinants of

worse outcome.^{25–27} One possible reason for the leg weakness outcome is that the mRS, which is highly focused on walking ability, was used for outcome assessment.^{18,28} In a study that examined angiographic occlusion in the first hours after onset of stroke, leg weakness and extinction/inattention were related to major vessel occlusion.²⁹ The presence of these items might indicate large hemispheric ischemia resulting only from proximal major vessel occlusion, not from peripheral vessel occlusions. In the present study, it was not possible to capture the percentage of each individual arterial occlusive lesion, because individual angiographic data were not collected in the derivation cohort. It seems paradoxical that facial palsy was inversely associated with unfavorable outcome. A potential reason for this may be that patients with facial palsy less frequently had leg weakness (34% vs 25%, $p = 0.030$) in the derivation cohort, because the total NIHSS score of the studied patients was limited to 3 or less.

The results suggest that a combination of NIHSS items and assessment of vascular status could help predict unfavorable outcomes in patients with minor stroke. A large-scale observational study reported that 31% of 93,517 acute stroke patients with rapidly improving or mild symptoms as the only reason for avoiding recombinant tissue-type plasminogen activator (rt-PA) were unable to be discharged home.⁶ Recently, it has been reported that 890 rt-PA-treated patients with mild symptoms corresponding to NIHSS scores of 0 to 5 had better outcomes at 3 months than matched controls without rt-PA.³⁰ In these studies, onset to admission time was shorter than in the present study. In addition, NIHSS subscores and vascular status were not described. However, patients with both factors might be highly appropriate candidates for acute intensive management, such as recanalization therapy, if they appear within the therapeutic time window, regardless of age, sex, or low total NIHSS score.

One of the strengths of the present study is that it included multicenter and single-center prospective databases of minor ischemic stroke patients, excluding patients with TIA. Data such as individual NIHSS items and vascular imaging findings were systematically collected and analyzed using multivariable models. The validation cohort was from a single, highly specialized stroke center. Although there were significant differences between the cohorts in risk factors, vascular status, severity, and outcome, the model was successfully validated. That is another strength of the study.

The present study had some limitations. First, the mRS score at 90 days was not available for all patients. The follow-up rate of 83% does not preclude a possible bias. Patients’ characteristics were generally similar

between patients with available mRS scores at 90 days ($n = 1,313$) and those without ($n = 273$). When the mRS score at acute hospital discharge (median 17 days after onset) or at 28 days was used instead of the 90-day mRS score for these 273 patients, the results were almost identical; for example, patients having both a vascular occlusive lesion and either of the abnormal NIHSS items showed 4.43 (95% CI 2.36–8.13) times the risk of unfavorable outcome compared with those having neither. Second, the current population consisted mostly of Asian patients. It is known that there are differences in the distribution of occlusive vascular disease between Asian and other populations. Intracranial artery atherosclerosis is a common cause of ischemic stroke in Asian, African, and Hispanic patients, while extracranial carotid artery atherosclerosis develops frequently in Caucasians.³¹ Unfortunately, the present database did not include detailed information on the location of vascular lesions, so it was impossible to assess the distribution of occlusive vascular disease. Racial differences might affect the results and limit the generalizability. Third, the rate of rt-PA use was extremely low in the present 2 cohorts. One possible reason for this is that the use of rt-PA as a therapy for acute ischemic stroke within 3 hours of onset was approved on October 11, 2005, when registration in the SUMO Study was almost completed.¹⁴ Another reason is that the Japanese Guidelines for IV Application of rt-PA (alteplase), October 2005, stated that most patients with NIHSS scores of 4 or less were considered ineligible for rt-PA therapy.³² The model was not validated in an rt-PA–treated cohort, but this should be considered for future studies.

Several independent factors that could be assessed at the time of initial presentation were found to be associated with unfavorable outcome at 90 days in patients with minor stroke. The combination of intra- and extracranial vascular imaging and NIHSS items such as leg weakness and extinction/inattention appears to provide valuable information related to outcomes.

AUTHOR CONTRIBUTIONS

Dr. Sato conceived and designed the study, drafted the manuscript, and performed the statistical analyses. Dr. Uehara, Dr. Ohara, Dr. Suzuki, and Dr. Toyoda made critical revisions to the manuscript for important intellectual content. Dr. Minematsu supervised and obtained study funding.

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