[14,19]. Thus, changes in NIHSS scores within 1 h could be useful to predict patients with poor long-term outcome only by IV rt-PA.

Recanalization rate and clinical outcomes after IV rt-PA are highly dependent on the site of the arterial occlusion. Occlusion at the origin of the proximal portion (M1) of the middle cerebral artery (MCA) [20–22], or at the internal carotid artery (ICA) [20,22–24], predicts a low chance of recanalization and thus a higher risk of poor outcomes. In addition, NIHSS scores and their changes after IV rt-PA differ according to sites of arterial occlusion; patients with proximal carotid axis occlusion generally have higher NIHSS scores [21,23] and smaller changes in the score [25] than those with distal occlusion. Different strategies for determining the timing of additional thrombectomy based on NIHSS scores according to different sites of arterial occlusion may thus be needed.

The goal of the present study was to determine an index for predictors of unfavorable stroke outcomes based on the NIHSS scores during 1-h IV rt-PA therapy. Such predictors may be of help in choosing patients who would benefit from immediate addition of endovascular thrombectomy.

Patients and methods

The National Cerebral and Cardiovascular Center (NCVC) rt-PA Registry is a prospective single-center register for acute stroke patients treated using IV rt-PA. The register was initiated in October 2005 when IV rt-PA therapy was approved in Japan. The patients from the registry were studied retrospectively. Informed consent to receive IV rt-PA was obtained from all patients or from relatives if patients had communication problems preventing direct provision of consent. Consent to participate in the registration was then obtained using an opt-out approach by the demonstrating contents of the registration on the hospital bulletin board. The Research Ethics Committee of NCVC approved the study.

In the present study, potential subjects comprised all consecutive patients registered by December 2010, when the use of the MERCI Retriever for acute stroke patients was approved in our hospital. Thus, no patients in the present study underwent acute endovascular thrombectomy. The following patients were excluded from the study: (i) those with a pre-stroke modified Rankin Scale (mRS) score of 2–5; (ii) those with a baseline NIHSS score ≤7; (iii) those without performance of magnetic resonance imaging (MRI) before the administration of IV rt-PA due to contraindications or time constraints; and (iv) those without occlusion at the ICA or MCA on the initial MR angiography (MRA). The exclusion criterion of baseline NIHSS score ≤7 was set based on those used in major clinical trials on endovascular thrombectomy [3–7].

Patient eligibility for IV rt-PA therapy was decided principally according to the Japanese guidelines [26]. Each patient received a single alteplase dose of 0.6 mg/kg IV, with 10% given as a bolus within 3 h of stroke onset, followed by continuous IV infusion of the remainder over 1 h. During the initial 24 h, use of antithrombotic agents was prohibited in principle, blood pressure was maintained at 180/105 mmHg or lower, and neurological signs and symptoms were monitored frequently. Baseline data were collected for all eligible patients, including sex, age, comorbidities (hypertension, diabetes, dyslipidemia, atrial fibrillation), platelet count, glucose level on admission, and time from onset to treatment.

Before rt-PA therapy, MRI including diffusion-weighted imaging (DWI) and MRA were performed using a 1.5-T system (Magnetom Vision or Magnetom Sonata; Siemens, Germany). All initial DWI and MRA data were evaluated by two experienced stroke specialists. Early ischaemic changes were quantitatively assessed with the Alberta Stroke Program Early CT (ASPECTS) score using DWI [27,28]. Arterial occlusion sites were assessed on the initial MRA and were divided into two groups according to previous methods [20,22]: group P, proximal carotid axis occlusion at the ICA or proximal M1 with the residual length on anteroposterior view <5 mm; and group D, distal carotid axis occlusion at the distal M1 with residual length ≥5 mm or M2. Based on clinical, radiological and other information, the stroke subtype was assessed according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) categories [29].

NIHSS scores were assessed by experienced stroke specialists just before ($NIHSS_{baseline}$) and 30 min ($NIHSS_{30\ min}$) and 1 h ($NIHSS_{1\ h}$) after the initiation of rt-PA administration. The absolute inverse change of score from $NIHSS_{baseline}$ to $NIHSS_{30\ min}$ ($\Delta NIHSS_{30\ min} = NIHSS_{baseline} - NIHSS_{30\ min}$) and that from $NIHSS_{baseline}$ to $NIHSS_{1\ h}$ ($\Delta NIHSS_{1\ h} = NIHSS_{baseline} - NIHSS_{1\ h}$) were calculated. The mRS score was assessed at 3 months. Patients with mRS 0–1 were defined as having favorable outcomes and those with mRS 2–6 were defined as having unfavorable outcomes.

Statistical analysis

Baseline characteristics were compared between groups P and D using the χ^2 test, the unpaired t test and the Mann–Whitney U test. Because the NIHSS

Table 1 Baseline characteristics and outcomes at 3 months

	Total (N = 108)	Group P (N = 36)	Group D (N = 72)
Female	33 (30.6)	13 (36.1)	20 (27.8)
Age (years)	73.8 ± 11.1	74.7 ± 9.2	73.4 ± 11.9
Hypertension	77 (71.3)	28 (77.8)	49 (68.1)
Diabetes mellitus	17 (15.7)	2 (5.6)	15 (20.8)*
Dyslipidemia	25 (23.1)	9 (25.0)	16 (22.2)
Atrial fibrillation	62 (57.4)	22 (61.1)	40 (55.6)
Platelet count ($\times 10^4/\mu l$)	20.6 ± 6.6	19.7 ± 5.5	21.1 ± 7.2
Admitting glucose (mg/dl)	136 ± 42	121 ± 31	143 ± 45*
Onset to treatment time (min)	130 ± 28	130 ± 32	130 ± 26
Baseline NIHSS	17 (13–21)	20 (17–23)	16 (11–20)*
DWI-ASPECTS	7 (6–8.75)	7 (6–8.75)	7 (5–8.75)
Stroke subtype			
Cardioembolism	74 (68.5)	22 (61.1)	52 (72.2)
Large artery atherosclerosis	14 (13.0)	7 (19.4)	7 (9.7)
Small artery occlusion	0	0	0
Other determined/undetermeined	20 (18.5)	7 (19.4)	13 (18.1)
Modified Rankin Scale at 3 months			
0	14 (13.0)	2 (5.6)	12 (16.7)
1	16 (14.8)	1 (2.8)	15 (20.8)
2	11 (10.2)	3 (8.3)	8 (11.1)
3	12 (11.1)	3 (8.3)	9 (12.5)
4	28 (25.9)	12 (33.3)	16 (22.2)
5	18 (16.7)	12 (33.3)	6 (8.3)
6 (dead)	9 (8.3)	3 (8.3)	6 (8.3)

Values are given as mean ± SD for age, admitting glucose, platelet count and onset to treatment time; median (interquartile range) for baseline NIHSS and DWI-ASPECTS; and number of patients (%) for others. *$P < 0.05$ versus group P.

score was not normally distributed, the Mann–Whitney U test was chosen for the score. Statistical significance was established at the $P < 0.05$ level. Optimal cutoff scores of NIHSS and ΔNIHSS for predicting unfavorable outcome at 3 months were determined using receiver operating characteristic curves. To examine associations of NIHSS scores and ΔNIHSS scores with unfavorable outcome, multivariate analyses were performed. The NIHSS scores or ΔNIHSS scores were initially entered, and the baseline characteristics listed in Table 1, except for baseline NIHSS score, stroke subtype and mRS at 3 months, were chosen by a backward selection procedure using $P > 0.10$ on the likelihood ratio test as the exclusion criterion. For the NIHSS scores and ΔNIHSS, in consideration of the collinearity, multivariate analysis was performed separately for each variable. The predictive accuracy of NIHSS scores and ΔNIHSS scores for unfavorable outcome was assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Statistical analysis was performed using JMP version 8.0 statistical software (SAS Institute, Cary, NC, USA).

Results

A total of 219 consecutive patients were registered in our database. Of these, 18 patients were excluded due to pre-stroke mRS 2–5, 39 were excluded due to their baseline NIHSS ≤7, 23 were excluded because they did not undergo pre-treatment MRI or MRA (mainly due to the presence of a pacemaker) and 31 were excluded because the ICA or MCA was not occluded. Finally a total of 108 patients (33 women, aged 73.8 ± 11.1 years) were enrolled in this study.

Of the 108 patients, 23 had occlusion at the ICA, 13 at the proximal M1, 44 at the distal M1 and 28 at the M2 on the initial MRA. As a result, 36 patients were categorized to group P (13 women, 74.7 ± 9.2 years old) and 72 to group D (20 women, 73.4 ± 11.9 years old). Baseline patient characteristics and outcomes are presented in Table 1. Diabetes mellitus was less common (5.6% vs. 20.8%, $P = 0.039$), admitting glucose was higher (mean 121 ± 31 vs. 143 ± 45, $P = 0.011$), $NIHSS_{baseline}$ was higher (median 20 vs. 16, $P < 0.001$) and unfavorable outcome was more common (91.6% vs. 62.5%, $P = 0.001$) in group P than in group D.

Analysis for all patients

Patients with unfavorable outcome had higher $NIHSS_{baseline}$, $NIHSS_{30\ min}$ and $NIHSS_{1\ h}$ and lower $\Delta NIHSS_{1\ h}$ compared with patients with favorable outcome (Table 2). Each of the indices except for $NIHSS_{baseline}$ was independently related to unfavorable

Table 2 NIHSS scores and their change for patients with or without favorable outcome at 3 months

	Overall (N = 108)			Group P (n = 36)			Group D (n = 72)		
	mRS 0–1 (n = 30)	mRS 2–6 (n = 78)	P value	mRS 0–1 (n = 3)	mRS 2–6 (n = 33)	P value	mRS 0–1 (n = 27)	mRS 2–6 (n = 45)	P value
$NIHSS_{baseline}$	16 (10–19.25)	18 (14–22)	0.032	18 (13–23)	20 (17–23)	0.508	16 (10–19)	16 (12–20.5)	0.281
$NIHSS_{30\ min}$	10 (6–15.25)	15.5 (11–20)	<0.001	10 (10–18)	19 (14–21.5)	0.080	9 (6–15)	13 (10–19)	0.003
$NIHSS_{1\ h}$	8.5 (4–11.5)	15 (10–20)	<0.001	10 (2–13)	18 (14.5–21)	0.023	8 (4–11)	12 (8–19)	0.001
$\Delta NIHSS_{30\ min}$	1.5 (0–4.25)	0 (0–2)	0.058	3 (2–3)	0 (0–2)	0.031	1 (0–5)	1 (0–2)	0.379
$\Delta NIHSS_{1\ h}$	3 (0.75–8.25)	1 (0–2.25)	0.048	8 (3–10)	1 (0–2)	0.013	2 (0–8)	2 (0–3.5)	0.398

Values are given as median (interquartile range).

Table 3 Multivariable logistic regression of NIHSS scores and their change for predicting unfavorable outcome at 3 months

	Overall (N = 108)			Group D (n = 72)		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
$NIHSS_{baseline}$	1.05	0.96–1.16	0.286	1.00	0.89–1.12	0.967
$NIHSS_{30\ min}$	1.19	1.09–1.33	<0.001	1.14	1.02–1.30	0.016
$NIHSS_{1\ h}$	1.21	1.11–1.35	<0.001	1.15	1.04–1.30	0.007
$\Delta NIHSS_{30\ min}$	0.80	0.6–0.94	0.006	0.86	0.72–1.02	0.086
$\Delta NIHSS_{1\ h}$	0.84	0.74–0.94	0.003	0.90	0.79–1.02	0.087

Per 1-point increase for each score; in group P, multivariate analysis could not be performed because of a small number of favorable outcome patients (n = 3); adjusted with a backward selection procedure using the background characteristics listed in Table 1; the characteristics that were associated with unfavorable outcome were 'onset to treatment time' and 'female' and 'dyslipidemia' and 'DWI-ASPECTS' for all patients and 'onset to treatment time' and 'female' for group D.

Table 4 Diagnostic accuracy for unfavorable outcome using NIHSS scores and their change in overall patients

Variables	Cutoff score	Number of patients meeting the criterion	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Area under the curve
$NIHSS_{baseline}$	≥18	52	53.8 (48.0–58.8)	66.7 (51.5–79.5)	80.8 (72.0–88.2)	35.7 (27.6–42.6)	0.634
$NIHSS_{30\ min}$	≥11	72	80.8 (75.2–85.2)	70.0 (55.5–81.5)	87.5 (81.5–92.3)	58.3 (46.3–67.9)	0.769
$NIHSS_{30\ min}$	≥12	65	73.1 (67.4–77.4)	73.3 (58.6–84.7)	87.7 (80.9–92.9)	51.2 (40.9–59.1)	0.769
$NIHSS_{1\ h}$	≥11	66	73.1 (67.4–77.7)	70.0 (55.1–81.9)	86.4 (79.6–91.8)	50.0 (39.4–58.5)	0.789
$NIHSS_{1\ h}$	≥12	60	67.9 (62.3–72.1)	76.7 (61.9–87.4)	88.3 (81.0–93.7)	47.9 (38.7–54.7)	0.789
$\Delta NIHSS_{30\ min}$	≤2	82	82.1 (76.9–87.1)	40.0 (26.7–53.1)	78.0 (73.2–82.8)	46.2 (30.8–61.3)	0.613
$\Delta NIHSS_{1\ h}$	≤2	73	75.6 (70.0–80.8)	53.3 (38.8–66.9)	80.8 (74.8–86.4)	45.7 (33.2–57.3)	0.622

Data in parentheses represent 95% CI.

outcome after multivariate adjustment (Table 3). Optimal cutoff scores for $NIHSS_{baseline}$, $NIHSS_{30\ min}$ and $NIHSS_{1\ h}$ to predict unfavorable outcome were ≥18, ≥12 and ≥12 respectively, while those for $\Delta NIHSS_{30\ min}$ and $\Delta NIHSS_{1\ h}$ were both ≤2. The diagnostic accuracy of these cutoff scores is shown in Table 4; the accuracy of each cutoff based on the area under the curve (AUC) was fair (0.7–0.8) or poor (0.6–0.7).

Analysis for group P

Patients with unfavorable outcome displayed higher scores for $NIHSS_{1\ h}$ and lower scores for $\Delta NIHSS_{30\ min}$ and $\Delta NIHSS_{1\ h}$ than patients with favorable outcome (Table 2). Optimal cutoff scores for $NIHSS_{baseline}$, $NIHSS_{30\ min}$ and $NIHSS_{1\ h}$ to predict unfavorable outcomes were ≥19, ≥14 and ≥14, respectively, while those for $\Delta NIHSS_{30\ min}$ and $\Delta NIHSS_{1\ h}$ were ≤1 and ≤2, respectively. The diagnostic accuracies of these cutoff scores are shown in Table 5. AUCs for each cutoff exceeded 0.8 with the exception of that for $NIHSS_{baseline}$, indicating good accuracy. In particular, $NIHSS_{1\ h} \geq 14$ and $\Delta NIHSS_{30\ min} \leq 1$ and $\Delta NIHSS_{1\ h} \leq 2$ showed 100% specificity and 100% PPV, indicating that all the patients with $NIHSS_{1\ h} \geq 14$ or $\Delta NIHSS_{30\ min} \leq 1$ or $\Delta NIHSS_{1\ h} \leq 2$ showed unfavorable outcomes.

Analysis for group D

Patients with unfavorable outcome showed higher scores of $NIHSS_{30\ min}$ and $NIHSS_{1\ h}$ than patients with favorable outcome (Table 2). These two indices were independently related to outcome after

Table 5 Diagnostic accuracy for unfavorable outcome using NIHSS scores and their change in patients with occlusion in the internal carotid or proximal M1 portion of the middle cerebral artery (group P)

Variables	Cutoff score	Number of patients meeting the criterion	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Area under the curve
$NIHSS_{baseline}$	≥19	23	66.7 (62.6–69.1)	66.7 (21.6–93.7)	95.8 (89.8–99.2)	15.4 (5.0–21.6)	0.616
$NIHSS_{30\ min}$	≥12	31	90.9 (86.9–93.3)	66.7 (22.4–93.5)	96.8 (92.5–99.4)	40.0 (13.5–56.1)	0.808
$NIHSS_{30\ min}$	≥13	30	87.9 (83.8–90.3)	66.7 (22.2–93.6)	96.7 (92.2–99.4)	30.0 (3.3–46.1)	0.808
$NIHSS_{30\ min}$	≥14	28	81.8 (77.7–84.3)	66.7 (21.9–93.7)	96.4 (91.6–99.3)	25.0 (8.2–35.1)	0.808
$NIHSS_{1\ h}$	≥12	29	84.8 (80.8–87.3)	66.7 (22.0–93.6)	96.6 (91.9–99.3)	28.6 (9.4–40.1)	0.898
$NIHSS_{1\ h}$	≥13	28	81.8 (77.7–84.3)	66.7 (21.9–93.7)	96.4 (91.6–99.3)	25.0 (8.2–35.1)	0.898
$NIHSS_{1\ h}$	≥14	26	78.8 (73.9–78.8)	100 (46.6–100)	100 (93.8–100)	30.0 (14.0–30.0)	0.898
$\Delta NIHSS_{30\ min}$	≤1	24	72.7 (67.8–72.7)	100 (46.3–100)	100 (93.3–100)	25.0 (11.6–25.0)	0.859
$\Delta NIHSS_{1\ h}$	≤2	28	84.8 (80.0–84.8)	100 (47.1–100)	100 (94.3–100)	37.5 (17.7–37.5)	0.929

Data in parentheses represent 95% CI.

Table 6 Diagnostic accuracy for unfavorable outcome using NIHSS scores and their change in patients with occlusion in the distal M1 portion or M2 portion of the middle cerebral artery (group D)

Variables	Cutoff score	Number of patients meeting the criterion	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Area under the curve
$NIHSS_{baseline}$	≥11	58	86.7 (79.7–92.9)	29.6 (18.0–40.0)	67.2 (61.8–72.1)	57.1 (34.7–77.1)	0.576
$NIHSS_{30\ min}$	≥11	41	73.3 (64.6–80.3)	70.4 (55.8–82.0)	80.5 (70.9–88.1)	61.3 (48.6–71.4)	0.712
$NIHSS_{30\ min}$	≥12	31	55.6 (46.8–62.0)	77.8 (63.2–88.5)	80.6 (68.0–90.0)	51.2 (41.6–58.3)	0.712
$NIHSS_{1\ h}$	≥11	36	62.2 (53.3–69.5)	70.4 (55.5–82.5)	77.8 (66.6–86.8)	52.8 (41.6–61.8)	0.730
$NIHSS_{1\ h}$	≥12	31	55.6 (46.8–62.0)	77.8 (63.2–88.5)	80.6 (68.0–90.0)	51.2 (41.6–58.3)	0.730
$\Delta NIHSS_{30\ min}$	≤2	53	80.0 (72.2–87.4)	37.0 (24.1–49.3)	67.9 (61.3–74.2)	52.6 (34.2–70.1)	0.560
$\Delta NIHSS_{1\ h}$	≤7	61	91.1 (84.7–96.1)	25.9 (15.2–34.3)	67.2 (62.5–70.9)	63.6 (37.3–84.1)	0.559

Data in parentheses represent 95% CI.

multivariate adjustment (Table 3). The optimal cutoff scores for $NIHSS_{baseline}$, $NIHSS_{30\ min}$ and $NIHSS_{1\ h}$ to predict unfavorable outcomes were ≥11, ≥12 and ≥12, respectively, and those of $\Delta NIHSS_{30\ min}$ and $\Delta NIHSS_{1\ h}$ were ≤2 and ≤7, respectively. The diagnostic accuracies of these cutoff scores are shown in Table 6; accuracy of each cutoff based on the AUC was fair or fail (0.5–0.6). $\Delta NIHSS_{1\ h} \leq 7$ showed >90% sensitivity.

Discussion

The present study sought to predict stroke outcome using the NIHSS scores during 1-h IV rt-PA therapy. The first major finding was that all the patients with proximal carotid axis occlusion showed unfavorable outcome (mRS 2–6) at 3 months if they showed $NIHSS_{1\ h} \geq 14$, $\Delta NIHSS_{30\ min} \leq 1$ or $\Delta NIHSS_{1\ h} \leq 2$. $\Delta NIHSS_{30\ min} \leq 1$ seems useful for quickly predicting outcomes. The second major finding was that 91.1% of patients with distal carotid axis occlusion who finally had favorable outcome (mRS 0–1) showed $\Delta NIHSS_{1\ h} \leq 7$. These simple clinical indices based on NIHSS score thus appear useful as a quick prognostic predictor when the site of arterial occlusion is identified prior to IV rt-PA. MRA was available for identification of the occlusion site in the present study as well as transcranial sonography [21,30].

Sensitivity, specificity, PPV and NPV are greatly influenced by the proportion of patients with favorable and unfavorable outcomes. In previous reports, mRS was 2–6 at 3 months in >90% of patients with occlusion at the ICA or proximal M1 [22,23,25]. The proportion of patients with unfavorable outcomes in group P (91.6%) was thus similar to previous findings. In contrast, patients with unfavorable outcomes in group D (62.5%) were relatively more common than the previously reported patients with distal M1 or M2 occlusion [22,23,25], partly because patients with baseline NIHSS ≤ 7 were excluded from the study.

Stunned brain syndrome with delayed recovery was proposed based on a finding that 10 of 27 patients without early clinical changes after IV rt-PA had returned to independent daily living at 3 months [31]. A contribution of delayed recanalization at 24 h to final favorable outcome has also been reported [32,33]. Thus, long-term outcomes cannot be perfectly predicted using indicators within the initial hours after

rt-PA therapy. Patients with stunned brain syndrome were reported to often have signs of compensatory flow diversion on transcranial Doppler indicating transcortical flow collateralization [31]. Such collateral flow is more common in patients with M2 occlusion than in those with proximal artery occlusion. This seems to be a reason for poor diagnostic accuracy of unfavorable outcome using ΔNIHSS in group D.

On the other hand, a decrease in NIHSS score immediately or 2 h after rt-PA therapy still represents a predictor of favorable outcome [19,34], mainly because a decrease in NIHSS is also an important indicator of recanalization after IV rt-PA [30]. Reduction in NIHSS score at 30 min of ≥40% from the baseline score indicates recanalization well. Thus, to maximize the effects of combination therapy of IV thrombolysis and endovascular thrombectomy, NIHSS-based indices seem practical and useful for quick prediction of prognosis after rt-PA and choosing candidates for additional thrombectomy. From the present results, the following strategies for additional thrombectomy are planned in our stroke team. Since >90% of patients in group P had unfavorable outcome after IV rt-PA alone, thrombectomy should be considered as an additional option for most of these patients. If NIHSS score does not decrease by more than 1 point within 30 min after initiation of rt-PA, quick puncture and endovascular procedures may be acceptable. In contrast, additional thrombectomy is not necessary at least for around 40% of patients in group D. Although it is not perfectly specific, an NIHSS score of ≥12 at 30 min after initiation of IV rt-PA seems to be a good indicator for scheduling additional thrombectomy. Of course, caution should be exercised about performing thrombectomy since its efficacy has not been proved yet [8–10].

Several limitations to this study should be considered. First, the single-center observational nature of the study and the relatively small number of patients could cause statistical bias, particularly in group P. Secondly, patients with a baseline NIHSS score ≤7 were excluded according to many clinical trials for endovascular thrombectomy [3–7]. If these patients with milder stroke were also included, three patients in group P and eight in group D would be added. The results are similar after the addition. Thirdly, our indicator is not simple because of separating patients into two groups based on the arterial occlusion site. In a study by the CLOTBUST investigators [27], relative changes in serial NIHSS scores reflected arterial status after thrombolysis regardless of arterial occlusion site. In our cohort, however, AUCs were not improved in the patients even using relative changes in NIHSS scores. Fourthly, all patients received 0.6 mg/kg of alteplase, the official dosage in Japan, within 3 h after stroke onset. The results might thus differ from those using 0.9 mg/kg of alteplase within 4.5 h, although post-marketing surveys from Japan and other countries using different dosages have shown similar efficacy [35–39]. Fifthly, associations between changes in NIHSS score and early recanalization were not studied. Although follow-up MRA was performed in 91 of 108 patients, most of these were done on the second day or later. After approval of the MERCI Retriever for clinical use in Japan in 2010, the patients in our registry principally underwent follow-up MRA at around 1 h [40]. ICA/M1 origin occlusion (i.e. group P) and the level of C-reactive protein were positively associated and the level of high density lipoprotein cholesterol was negatively associated with early recanalization failure after multivariate adjustment.

In conclusion, NIHSS scores and ΔNIHSS scores during 1 h of rt-PA infusion seems predictive of 3-month outcome after IV rt-PA when the site of arterial occlusion is identified prior to IV rt-PA and may be helpful in the selection of patients who would most benefit from immediate addition of endovascular thrombectomy.

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References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333:**1581–1588
2. Hacke W, Kaste M, Bluhmki E, *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359:** 1317–1329.
3. Smith WS, Sung G, Starkman S, *et al.* Safety and efficacy of mechanical embolectomy in acute ischemic

stroke: results of the MERCI trial. *Stroke* 2005; **36:** 1432–1438.
4. Smith WS, Sung G, Saver J, *et al.* Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke* 2008; **39:** 1205–1212.
5. Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009; **40:** 2761–2768.
6. Nogueira RG, Lutsep HL, Gupta R, *et al.* Trevo versus MERCI retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012; **380:** 1231–1240.
7. Saver JL, Jahan R, Levy EI, *et al.* Solitaire flow restoration device versus the MERCI Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; **380:** 1241–1249.
8. Broderick JP, Palesch YY, Demchuk AM, *et al.* Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368:** 893–903.
9. Ciccone A, Valvassori L, Nichelatti M, *et al.* Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013; **368:** 904–913.
10. Kidwell CS, Jahan R, Gornbein J, *et al.* A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; **368:** 914–923.
11. Marler JR, Tilley BC, Lu M, *et al.* Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000; **55:** 1649–1655.
12. Lees KR, Bluhmki E, von Kummer RD, *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *The Lancet* 2010; **375:** 1695–1703.
13. Becktepe JS, You SJ, Berkefeld J, Neumann-Haefelin T, Singer OC. Clinical outcome after mechanical recanalization as mono- or adjunctive therapy in acute stroke: importance of time to recanalization. *Cerebrovasc Dis* 2011; **32:** 211–218.
14. Felberg RA, Okon NJ, El-Mitwalli A, *et al.* Early dramatic recovery during intravenous tissue plasminogen activator infusion. *Stroke* 2002; **33:** 1301–1307.
15. Broderick JP, Lu M, Kothari R, *et al.* Finding the most powerful measures of the effectiveness of tissue plasminogen activator in the NINDS tPA stroke trial. *Stroke* 2000; **31:** 2335–2341.
16. Brown DL, Johnston KC, Wagner DP, Haley EC. Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. *Stroke* 2004; **35:** 147–150.
17. Nam HS, Lee K-Y, Han SW, *et al.* Prediction of long-term outcome by percent improvement after the first day of thrombolytic treatment in stroke patients. *J Neurol Sci* 2009; **281:** 69–73.
18. Mori M, Naganuma M, Okada Y, *et al.* Early neurological deterioration within 24 hours after intravenous rt-PA therapy for stroke patients: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. *Cerebrovasc Dis* 2012; **34:** 140–146.
19. Muresan I-P, Favrole P, Levy P, *et al.* Very early neurologic improvement after intravenous thrombolysis. *Arch Neurol* 2010; **67:** 1323–1328.
20. Lee K-Y, Han SW, Kim SH, *et al.* Early recanalization after intravenous administration of recombinant tissue plasminogen activator as assessed by pre- and post-thrombolytic angiography in acute ischemic stroke patients. *Stroke* 2007; **38:** 192–193.
21. Saqqur M, Uchino K, Demchuk AM, *et al.* Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007; **38:** 948–954.
22. Hirano T, Sasaki M, Mori E, *et al.* Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients. Exploratory analysis of Japan Alteplase Clinical Trial II. *Stroke* 2010; **41:** 2828–2833.
23. Derex L, Hermier M, Adeleine P, *et al.* Influence of the site of arterial occlusion on multiple baseline hemodynamic MRI parameters and post-thrombolytic recanalization in acute stroke: a multicenter study. *Neuroradiology* 2004; **46:** 883–887.
24. Kimura K, Iguchi Y, Shibazaki K, Aoki J, Uemura J. Early recanalization rate of major occluded brain arteries after intravenous tissue plasminogen activator therapy using serial magnetic resonance angiography studies. *Eur Neurol* 2009; **62:** 287–292.
25. Nakashima T, Toyoda K, Koga M, *et al.* Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0·6 mg/kg) alteplase therapy for ischaemic stroke. *Int J Stroke* 2009; **4:** 425–431.
26. Shinohara Y, Yanagihara T, Abe K, *et al.* II. Cerebral infarction/transient ischemic attack (TIA). *J Stroke Cerebrovasc Dis* 2011; **20:** S31–S73.
27. Nezu T, Koga M, Kimura K, *et al.* Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. *Neurology* 2010; **75:** 555–561.
28. Nezu T, Koga M, Nakagawara J, *et al.* Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry. *Stroke* 2011; **42:** 2196–2200.
29. Adams H, Bendixen B, Kappelle L, *et al.* Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24:** 35–41.
30. Mikulik R, Ribo M, Hill MD, *et al.* Accuracy of serial National Institutes of Health Stroke Scale scores to identify artery status in acute ischemic stroke. *Circulation* 2007; **115:** 2660–2665.
31. Alexandrov AV, Hall CE, Labiche LA, Wojner AW, Grotta JC. Ischemic stunning of the brain: early recanalization without immediate clinical improvement in acute ischemic stroke. *Stroke* 2004; **35:** 449–452.
32. von Kummer R, Holle R, Rosin L, Forsting M, Hacke W. Does arterial recanalization improve outcome in carotid territory stroke? *Stroke* 1995; **26:** 581–587.
33. Mori E, Minematsu K, Nakagawara J, *et al.* Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical

outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). *Stroke* 2010; **41:** 461–465.
34. Kharitonova T, Mikulik R, Roine RO, *et al.* Association of early National Institutes of Health Stroke Scale improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke. *Stroke* 2011; **42:** 1638–1643.
35. Albers GW, Bates VE, Clark WM, *et al.* Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA* 2000; **283:** 1145–1150.
36. Wahlgren N, Ahmed N, Dávalos A, *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; **369:** 275–282.
37. Toyoda K, Koga M, Naganuma M, *et al.* Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke* 2009; **40:** 3591–3595.
38. Nakagawara J, Minematsu K, Okada Y, *et al.* Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke* 2010; **41:** 1984–1989.
39. Shobha N, Buchan AM, Hill MD. Thrombolysis at 3–4.5 hours after acute ischemic stroke onset – evidence from the Canadian Alteplase for Stroke Effectiveness Study (CASES) Registry. *Cerebrovasc Dis* 2011; **31:** 223–228.
40. Koga M, Arihiro S, Miyashita F, *et al.* Factors associated with early recanalization failure following intravenous rt-PA therapy for ischemic stroke. *Cerebrovasc Dis* 2013; **36:** 299–305.

Factors Associated with Proximal Carotid Axis Occlusion in Patients with Acute Stroke and Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) are more likely to exhibit proximal carotid axis occlusion than those without AF. However, clinical characteristics associated with proximal arterial occlusion (PAO) in acute stroke patients with AF are not fully known. This study was aimed to elucidate the factors correlated with PAO. *Methods:* Consecutive patients with acute ischemic stroke developed in the middle cerebral artery (MCA) territory and AF who underwent magnetic resonance angiography (MRA) within 24 h from onset were retrospectively enrolled. Prior users of warfarin were excluded. Patients were divided into 3 groups based on the site of arterial occlusion: occlusion at the internal carotid artery (ICA), at the horizontal segment of the MCA (M1), and at the MCA branch or no identifiable occlusion. Clinical characteristics were compared between the 3 groups, and the factors associated with proximal vessel occlusion were evaluated with ordinal logistic regression analysis. All variables identified on univariable analyses with *P* values less than .1 were entered into the model. *Results:* A total of 244 patients (124 women, median 80 years old [interquartile range 72-87], median National Institutes of Health Stroke Scale [NIHSS] score 16 [7-22]) were studied. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Occlusion site was the ICA in 34 patients, M1 in 78, and MCA branch or no occlusion in the remaining 132. As the occlusion site was more proximal, patients were older and more female, the initial NIHSS score was higher, levels of D-dimer and brain natriuretic peptide (BNP) were higher, and histories of heart failure and systemic embolism were more common. On multivariable ordinal logistic regression analysis, female sex (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.03-3.26), advanced age (OR 1.37, 95% CI 1.02-1.84 for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75), and higher BNP level (OR 1.03, 95% CI 1.01-1.07 for every 100 pg/mL) were independent factors associated with the risk of occlusion at more proximal arteries. The risk was 2.68-fold higher (95% CI 1.28-5.61) in patients having 2 of the following factors: female sex, age more than 80 years, systemic embolism, and BNP greater than 250 pg/mL; and 4.50-fold (2.11-9.59) higher in those having 3 or 4 of the 4 factors compared with those without any of these factors. *Conclusions:* Female sex, advanced age, history of systemic embolism, and higher BNP level were independently associated with more proximal carotid axis occlusion. Patients with AF having

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these factors may be prone to have relatively large thrombi in the heart. **Key Words:** Acute ischemic stroke—magnetic resonance angiography—atrial fibrillation—arterial occlusion.

Introduction

The site of arterial occlusion plays a key role in neurologic severity and outcome in patients with acute ischemic stroke. Patients with proximal arterial occlusion (PAO) show more severe symptoms,[1,2] poorer outcomes,[3] and more limited response to intravenous tissue plasminogen activator therapy than those with distal artery occlusion.[4,5] The factors associated with PAO are not fully known, and related factors are considered to differ according to the etiologies. Embolic PAO seems to be correlated with embolus size. Patients with atrial fibrillation (AF) often develop severe ischemic stroke and poor outcomes,[6,7] even after thrombolytic therapy,[8] mainly because they are more likely to have PAO on admission than patients without AF.[8] However, clinical factors associated with PAO in patients with AF are not well known.

The aim of this study was to clarify the clinical characteristics related to PAO in acute stroke patients with AF.

Methods

A prospective database of consecutive patients with acute stroke treated in the Stroke Care Unit in the National Cerebral and Cardiovascular Center was created (National Cerebral and Cardiovascular Center Stroke Registry).[9] From April 2006 to May 2012, consecutive acute stroke patients (<24 h from onset) with AF who fulfilled the following criteria were retrospectively enrolled from the registry: (1) underwent magnetic resonance imaging (MRI) examinations including diffusion-weighted imaging (DWI) and time-of-flight magnetic resonance angiography (MRA) on admission and (2) developed ischemic stroke in the middle cerebral artery (MCA) territory confirmed on initial DWI with compatible acute neurologic deficits. Patients with contraindications to MRI (eg, cardiac pacemakers or mechanical heart valve replacements) were excluded. Stroke patients having concomitant etiology other than AF (eg, >50% stenosis on the responsible artery) and patients on anticoagulant therapy were also excluded because anticoagulant therapy could reduce intracardiac thrombi and then affect the site of arterial occlusion in subjects with AF.[10] The institutional ethics committee approved this study.

Clinical Background Characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and medical history, were obtained on admission. Cardiovascular risk factors were defined as: (1) hypertension, history of using antihypertensive agents, systolic blood pressure of 140 mm Hg or more, or diastolic blood pressure of 90 mm Hg or more before or 2 or more weeks after stroke onset; (2) diabetes mellitus, use of hypoglycemic agents, random glucose level of 200 mg/dL or more, or glycosylated hemoglobin of 6.5% or more on admission; (3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level of 220 mg/dL or more; and (4) current smoking habit. Routine blood biochemistry examinations were performed on admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcome was estimated by the modified Rankin scale[11] score at hospital discharge or 30 days from onset. AF was diagnosed on 12-lead electrocardiogram or a history of AF was confirmed.

Neuroimaging

MRI studies including DWI and time-of-flight MRA were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Siemens MAGNETOM Vision or MAGNETOM Sonata scanner, Erlangen, Germany). DWI was obtained using the following parameters: repetition time/echo time, 4000/100 ms; *b* values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 96 × 128; and slice thickness, 4.0 mm, with a 1.0-mm intersection gap. The occluded vessel was determined on initial MRA. All patients were divided into 3 groups based on the occluded site: at the internal carotid artery (ICA) group, at the MCA horizontal segment (M1 group), and at the MCA branch occlusion or no identifiable occlusion (Branch group).

Statistical Analysis

First, clinical background characteristics were compared among the 3 groups. Univariable analyses were performed using the chi-square test, Fisher exact test, or the Kruskal–Wallis test, as appropriate. The data are presented as median values (interquartile range) or frequencies (%). Next, multivariable ordinal logistic regression analysis was performed to identify independent factors associated with more proximal arterial occlusion. This model allows the outcome variable to have more than 2 categories and estimates a proportional odds ratio (OR) for each predictor of shifting to a more proximal arterial occlusion category (eg, the ICA group versus the M1 and Distal groups or the ICA and M1 groups versus the Distal group). Sex, age, and all clinical characteristics identified on univariable analyses with P values less

than .1 were entered into the model. Receiver operating characteristic (ROC) curve analyses were conducted to obtain the practical cutoff value of continuous variables. All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL). Results were considered significant at P less than .05.

Results

Overall, 503 patients with both acute ischemic stroke and AF were admitted to our stroke center during the study period. Of these, 61 patients were excluded because of absent or incomplete MRI, 29 were excluded because the site of the index stroke was outside the MCA territory, 14 were excluded because of concomitant etiology, and 155 were excluded for taking prestroke anticoagulant therapy. Finally, 244 patients (124 women, median age 80 [interquartile range 72-87] years, median NIHSS score 16 [7-22]) were enrolled in the present study.

Table 1 shows the clinical background characteristics of the included patients. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Of the 244 patients, 34 (14%) had ICA occlusion (ICA group), 78 (32%) had M1 occlusion (M1 group), and 132 (54%) had MCA branch occlusion or no arterial occlusion (Branch group) on initial MRA. As the occlusion site was more proximal, patients were older ($P < .001$), the initial NIHSS score was higher ($P < .001$), levels of D-dimer ($P = .002$) and brain natriuretic peptide (BNP, $P = .029$) were higher, and female sex ($P = .004$) and histories of heart failure ($P = .047$) and systemic embolism ($P = .001$) were more common.

The results of multivariable ordinal logistic regression analysis are shown in Table 2. Female sex (OR 1.83, 95% confidence interval [CI] 1.03-3.26, $P = .039$), advanced age (OR 1.37, 95% CI 1.02-1.84, $P = .037$ for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75, $P = .025$), and higher BNP level (OR 1.03, 95% CI 1.01-1.07, $P = .048$ for every 100 pg/mL) were independent factors associated with increased risk of more proximal arterial occlusion. The practical cutoff values for age and BNP to predict ICA or M1 occlusion were 80 years (sensitivity, 57%; specificity, 64%; area under the ROC curve, .645) and 250 pg/mL (sensitivity, 57%; specificity, 61%; area under the ROC curve, .578), respectively. Having more of the following 4 factors, female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL was also independently related to more proximal arterial occlusion ($P = .001$, chi-square test, Fig 1). The risk of more proximal arterial occlusion was 2.68-fold higher (95% CI 1.28-5.61) in patients having

Table 1. *Clinical background characteristics*

Variables	Total, n = 244	ICA group, n = 34	M1 group, n = 78	Distal group, n = 132	P
Female sex, n (%)	124 (51)	24 (71)	45 (58)	55 (42)	.004
Age, y, median (IQR)	80 (72-87)	85 (74-88)	82 (74-89)	79 (69-84)	<.001
Onset to MRI, h, median (IQR)	2.7 (1.5-8.9)	2.3 (1.7-6.6)	2.4 (1.4-4.8)	3.8 (1.6-11.4)	.193
Vascular risk factors, n (%)					
Hypertension	171 (70)	24 (71)	52 (68)	95 (72)	.794
Diabetes mellitus	34 (14)	4 (12)	8 (10)	22 (17)	.400
Hyperlipidemia	62 (25)	8 (24)	18 (23)	36 (27)	.768
Current smoking	43 (18)	5 (15)	10 (13)	28 (21)	.286
History, n (%)					
Ischemic stroke	53 (22)	8 (24)	16 (21)	29 (22)	.934
Hemorrhagic stroke	10 (4)	1 (3)	2 (3)	7 (5)	.586
Ischemic heart disease	21 (9)	4 (12)	7 (9)	10 (8)	.732
Heart failure	44 (18)	10 (29)	17 (22)	17 (13)	.047
Peripheral artery disease	10 (4)	2 (6)	2 (3)	6 (5)	.662
Systemic embolism	4 (2)	3 (9)	1 (1)	0 (0)	.001
Prior antiplatelet therapy, n (%)	99 (41)	12 (35)	29 (37)	58 (44)	.500
Initial NIHSS score, median (IQR)	16 (7-22)	22 (18-26)	18 (16-23)	10 (4-17)	<.001
Biochemistry sign at admission, median (IQR)					
Leukocyte count, /μL	6700 (5400-8900)	6700 (4800-9300)	7100 (5600-8600)	6400 (5500-8900)	.580
Blood glucose, mg/dL	124 (107-152)	126 (109-152)	129 (109-152)	119 (106-153)	.467
Total cholesterol, mg/dL	182 (161-206)	172 (164-202)	176 (155-204)	186 (167-211)	.191
D-dimer, μg/mL	2.1 (1.4-3.3)	2.6 (2.0-3.1)	2.1 (1.4-3.5)	1.8 (1.2-3.3)	.002
Brain natriuretic peptide, pg/mL	236 (127-437)	340 (197-666)	266 (130-409)	215 (104-409)	.029

Abbreviations: Distal group: patients with more distal occlusion or no identifiable occlusion; ICA group: patients with internal carotid artery occlusion; IQR, interquartile region; M1 group: patients with middle cerebral artery horizontal segment occlusion; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

Table 2. *Result of multivariate ordinal logistic regression analysis for factors associated with larger vessel occlusion*

Variables	OR	95% CI	*P*
Female sex	1.83	1.03-3.26	.039
Age (for every 10 y)	1.37	1.02-1.84	.037
History of heart failure	1.11	.54-2.28	.773
History of systemic embolism	14.9	1.41-158	.025
D-dimer (for every 1.0 μg/mL)	1.01	.91-1.11	.887
BNP (for every 100 pg/mL)	1.03	1.01-1.07	.048

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio.

2 of the above 4 factors, and 4.50-fold (95% CI 2.11-9.59) higher in those with 3 or 4 of the 4 factors compared with those without any of these factors on ordinal logistic regression analysis (Fig 2).

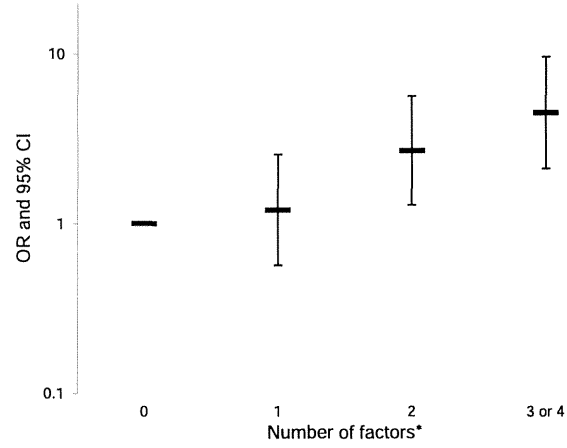

Figure 2. *OR and 95% CI of the risk of more proximal arterial occlusion according to the number of factors independently associated with larger arterial occlusion on ordinal logistic regression analysis. Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

Discussion

The first major finding of the present study was that 46% of the patients with both acute ischemic stroke and AF without prior anticoagulant therapy had ICA or M1 occlusion on initial MRA. This percentage was between that of patients within 3 h from onset (75%)[8] and that of patients within 7 days from onset (33%)[12] because the percentage decreases with spontaneous recanalization as onset-to-imaging time increases.[13]

The second major finding was that female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with the risk of more proximal arterial occlusion. In addition, coexistence of 2 or more of these 4 factors clearly increased the risk. This finding is partly in line with the previous reports that showed that advanced age,[14-16] history of systemic embolism,[17] and elevated BNP level[18] were correlated with the presence of intracardiac thrombi in AF patients. However, there is no study investigating the relationships between intracardiac clot size and patients' characteristics. It is possible that a prothrombotic state and large intracardiac thrombi are induced by these factors and cause PAO.

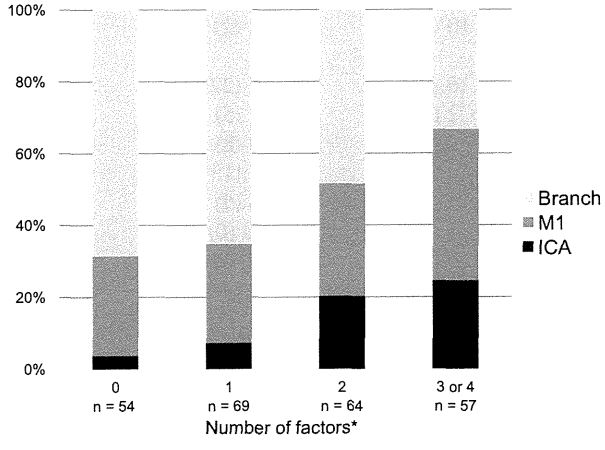

Figure 1. *The site of arterial occlusion based on the number of factors independently associated with larger arterial occlusion. Abbreviations: BNP, brain natriuretic peptide; Branch, middle cerebral artery branch or no identifiable occlusion; ICA, internal carotid artery; M1, middle cerebral artery horizontal segment. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

The female hormone, estrogen, increases fibrinolytic potential[19] and accelerates the recovery of injured endothelial cells.[20] Estrogen production is reduced after menopause, and elderly women with AF have a higher clot formation marker level[21] and worse outcomes after stroke[12] than men. Most women in the present study were considered to be postmenopausal because the median age of the included women was 84 years.

Advanced age may represent a longer period with a pathologic condition, such as hypertension, heart failure, and AF. Prolonged exposure to these pathologic conditions leads to cardiac remodeling, including left atrial enlargement and reduced atrial contractility.[22-24] This remodeling causes blood stasis in the left atrium and left atrial appendage and could contribute to form large thrombi. Furthermore, advanced age itself may be associated with a prothrombotic state.[25]

BNP is proven to be well correlated with heart failure,[26] though a high BNP level remained an independent predictor for PAO in the present patients using the regression model containing both heart failure and BNP as variables. The association of BNP with PAO independently from heart failure was because a high BNP level also stands for high left ventricular filling pressure,[27] which leads to left atrial enlargement[28] and left atrial appendage dysfunction[29]; all these cause formation of large thrombi. A history of systemic embolism may also indicate that the patients were prothrombotic.

This study had some limitations. First, the retrospective design might have contributed to some selection bias. Second, PAO might be overestimated because distal arterial occlusion and slow flow velocity in the proximal arteries are sometimes difficult to distinguish from PAO on MRA. On the other hand, the inclusion criteria of less than 24 h of onset might lead underestimation of the presence of PAO because of spontaneous recanalization, despite the MRI examinations were performed 2.7 h (median) from onset in the present study. Third, only the internal validity of the present results was assessed. The present findings should be confirmed with a prospective cohort.

In conclusion, nearly half of acute stroke patients with AF who did not receive anticoagulant therapy had ICA or MCA horizontal segment occlusion. Female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with PAO. Patients having these factors may be prone to having larger thrombi in the heart than those without these factors.

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References

1. Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36:2121-2125.
2. Nakajima M, Kimura K, Ogata T, et al. Relationships between angiographic findings and National Institutes of Health stroke scale score in cases of hyperacute carotid ischemic stroke. AJNR Am J Neuroradiol 2004; 25:238-241.
3. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40:3834-3840.
4. Lee KY, Han SW, Kim SH, et al. Early recanalization after intravenous administration of recombinant tissue plasminogen activator as assessed by pre- and post-thrombolytic angiography in acute ischemic stroke patients. Stroke 2007;38:192-193.
5. Nakashima T, Toyoda K, Koga M, et al. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. Int J Stroke 2009; 4:425-431.
6. Kimura K, Minematsu K, Yamaguchi T. Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76: 679-683.
7. Tu HT, Campbell BC, Churilov L, et al. Frequent early cardiac complications contribute to worse stroke outcome in atrial fibrillation. Cerebrovasc Dis 2011; 32:454-460.
8. Kimura K, Iguchi Y, Shibazaki K, et al. IV t-PA therapy in acute stroke patients with atrial fibrillation. J Neurol Sci 2009;276:6-8.
9. Tomii Y, Toyoda K, Suzuki R, et al. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. Stroke 2011;42:3511-3517.
10. Ren JF, Marchlinski FE, Callans DJ, et al. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. J Cardiovasc Electrophysiol 2005;16:474-477.
11. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
12. Sato S, Yazawa Y, Itabashi R, et al. Pre-admission CHADS2 score is related to severity and outcome of stroke. J Neurol Sci 2011;307:149-152.
13. Molina CA, Montaner J, Abilleira S, et al. Timing of spontaneous recanalization and risk of hemorrhagic transformation in acute cardioembolic stroke. Stroke 2001; 32:1079-1084.
14. Fukuda S, Watanabe H, Shimada K, et al. Left atrial thrombus and prognosis after anticoagulation therapy in patients with atrial fibrillation. J Cardiol 2011;58: 266-277.
15. Scherr D, Dalal D, Chilukuri K, et al. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2009; 20:379-384.
16. Yamashita E, Takamatsu H, Tada H, et al. Transesophageal echocardiography for thrombus screening prior to left atrial catheter ablation. Circ J 2010;74: 1081-1086.
17. Habara S, Dote K, Kato M, et al. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. Eur Heart J 2007;28:2217-2222.
18. Sugiura S, Fujii E, Senga M, et al. Clinical features of patients with left atrial thrombus undergoing anticoagulant therapy. J Interv Card Electrophysiol 2012;34:59-63.
19. Gebara OC, Mittleman MA, Sutherland P, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. Circulation 1995;91:1952-1958.
20. Krasinski K, Spyridopoulos I, Asahara T, et al. Estradiol accelerates functional endothelial recovery after arterial injury. Circulation 1997;95:1768-1772.
21. Feinberg WM, Macy E, Cornell ES, et al. Plasmin-alpha2-antiplasmin complex in patients with atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. Thromb Haemost 1999;82:100-103.
22. Cuspidi C, Meani S, Fusi V, et al. Prevalence and correlates of left atrial enlargement in essential hypertension: role of ventricular geometry and the metabolic syndrome: the Evaluation of Target Organ Damage in Hypertension study. J Hypertens 2005; 23:875-882.
23. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003;108:1461-1468.
24. Sun H, Gaspo R, Leblanc N, et al. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia. Circulation 1998;98:719-727.
25. Starr ME, Ueda J, Takahashi H, et al. Age-dependent vulnerability to endotoxemia is associated with reduction of anticoagulant factors activated protein C and thrombomodulin. Blood 2010;115:4886-4893.
26. Doust JA, Glasziou PP, Pietrzak E, et al. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med 2004;164: 1978-1984.

27. Baba O, Izuhara M, Kadota S, et al. Determinant factors of plasma B-type natriuretic peptide levels in patients with persistent nonvalvular atrial fibrillation and preserved left ventricular systolic function. J Cardiol 2009;54:402-408.
28. Tsang TS, Barnes ME, Gersh BJ, et al. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284-1289.
29. Tamura H, Watanabe T, Nishiyama S, et al. Elevated plasma brain natriuretic peptide levels predict left atrial appendage dysfunction in patients with acute ischemic stroke. J Cardiol 2012;60:126-132.

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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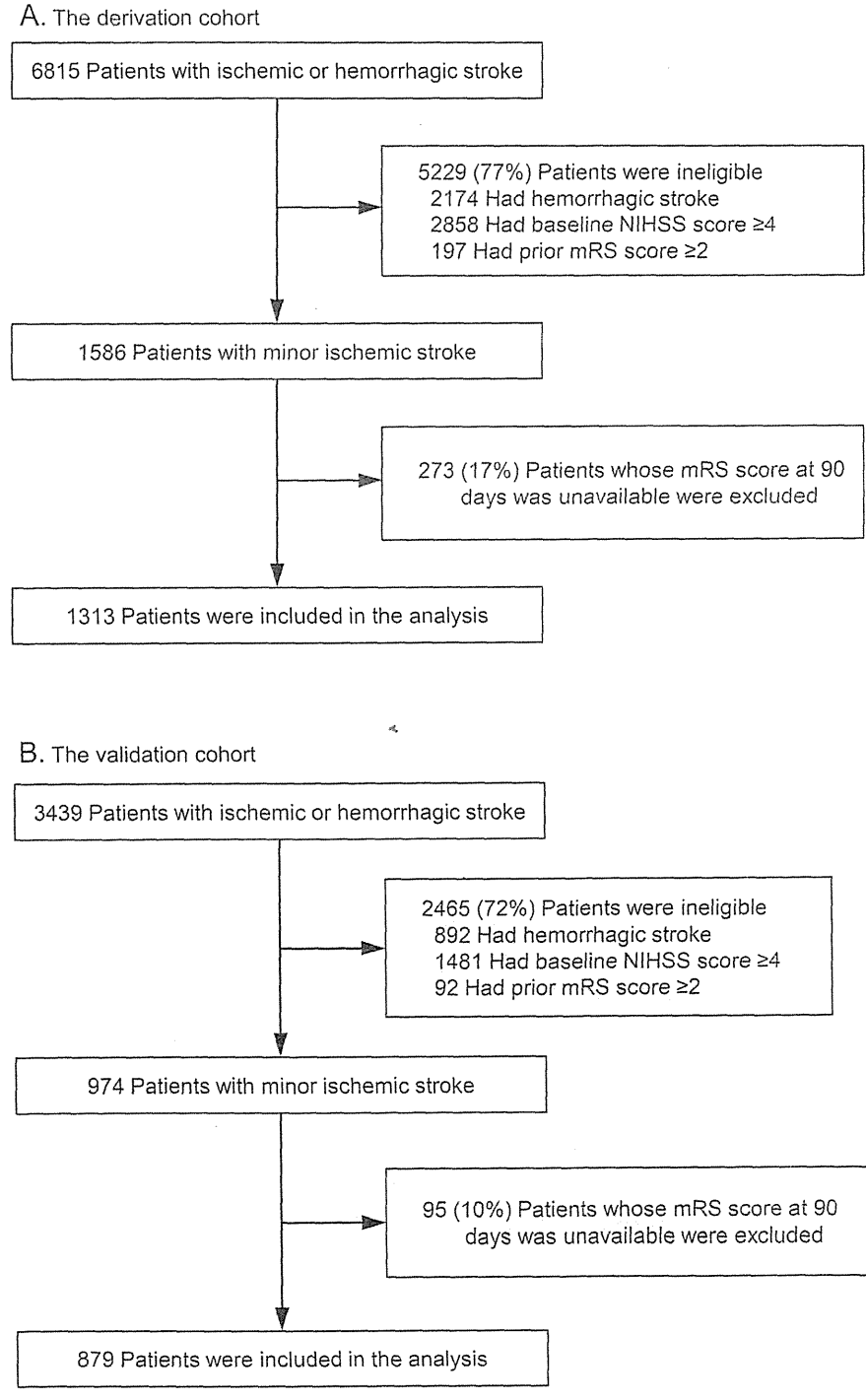
METHODS Derivation cohort. The derivation cohort was selected from the Stroke Unit Multicenter Observational (SUMO) Study, a prospective, observational, cohort study conducted between December 2004 and December 2005 in Japan.[14] Its aim was to clarify diagnostic and therapeutic processes of acute stroke 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



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 ≥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

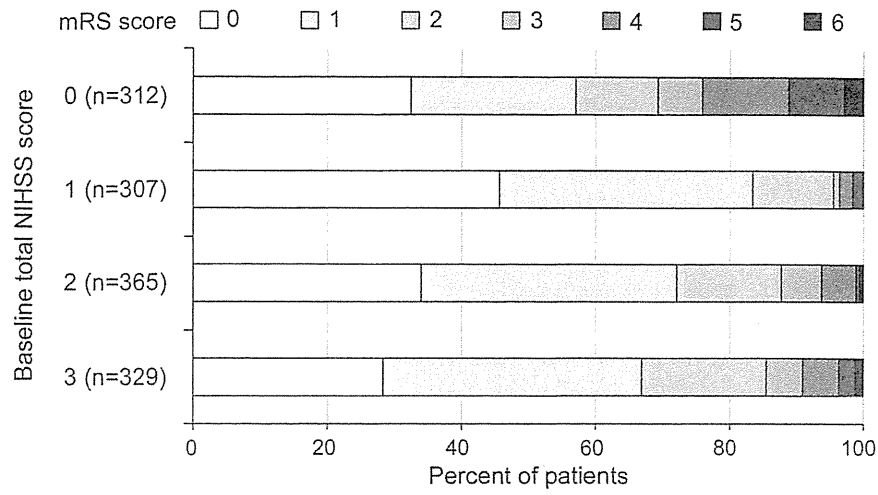
	Total (n = 1,313)	Unfavorable (mRS score 3-6) (n = 203)	Favorable (mRS score 0-2) (n = 1,110)	p
Demographics				
Female sex, %	33.0	44.3	30.9	<0.001
Age, mean y ± SD	69 ± 11	75 ± 10	68 ± 11	<0.001
Onset to admission time ≤12 h, %	50.2	61.5	48.2	0.001
Comorbidities and risk factors, %				
Hypertension	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.

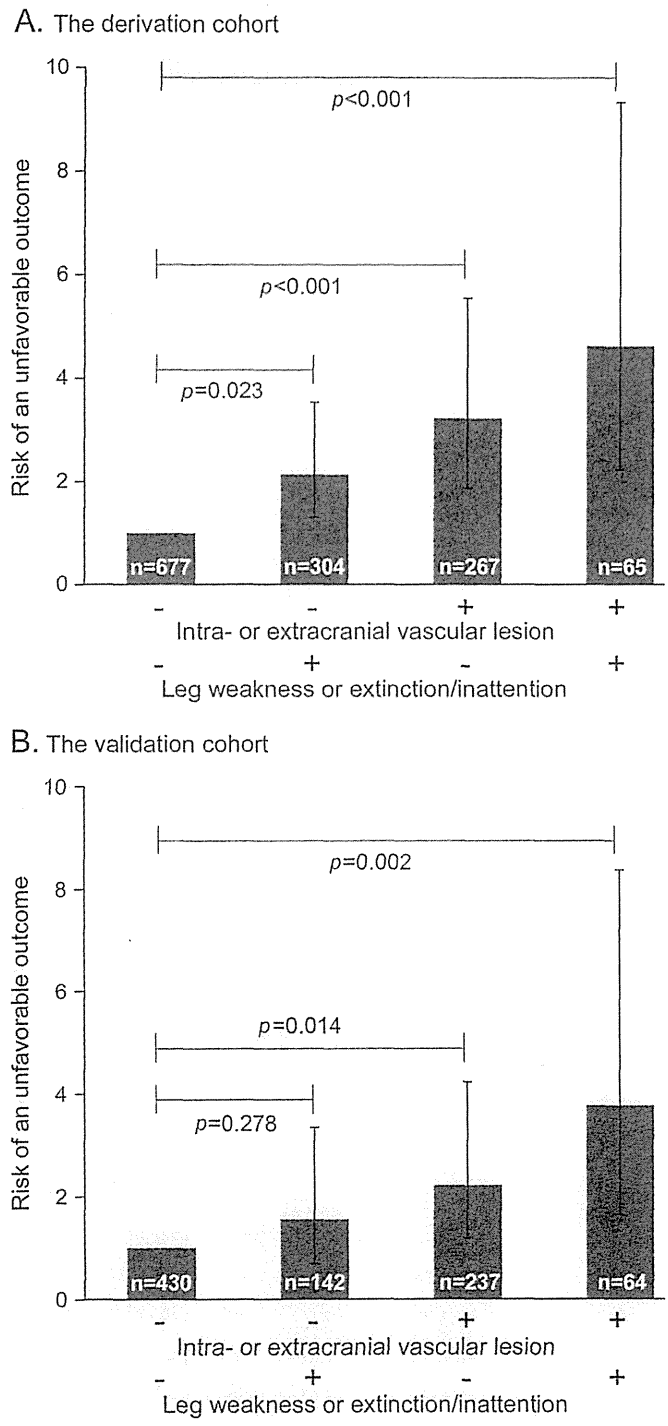
It has been reported that advanced age,[6,10] female sex,[6,11] diabetes mellitus,[11] and intra- or extracranial vascular occlusive lesion[8,9,23] were the factors related to unfavorable outcomes in patients with minor strokes. The present results are generally in line with the previous reports. However, 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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DISCLOSURE

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REFERENCES

1. Ferrari J, Knoflach M, Kiechl S, et al. Early clinical worsening in patients with TIA or minor stroke: the Austrian Stroke Unit Registry. Neurology 2010;74:136–141.
2. Ayis SA, Coker B, Rudd AG, Dennis MS, Wolfe CD. Predicting independent survival after stroke: a European study for the development and validation of standardised stroke scales and prediction models of outcome. J Neurol Neurosurg Psychiatry 2013;84:288–296.
3. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126–131.
4. Kimura K, Kazui S, Minematsu K, Yamaguchi T. Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan: a hospital-based prospective registration study. Cerebrovasc Dis 2004;18:47–56.
5. Smith EE, Abdullah AR, Petkovska I, Rosenthal E, Koroshetz WJ, Schwamm LH. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. Stroke 2005;36:2497–2499.
6. 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;42:3110–3115.
7. Sucharew H, Khoury J, Moomaw CJ, et al. Profiles of the National Institutes of Health Stroke Scale items as a predictor of patient outcome. Stroke 2013;44:2182–2187.
8. Coutts SB, Simon JE, Eliasziw M, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol 2005;57:848–854.
9. Nedeltchev K, Schwegler B, Haefeli T, et al. Outcome of stroke with mild or rapidly improving symptoms. Stroke 2007;38:2531–2535.
10. Coutts SB, O'Reilly C, Hill MD, et al. Computed tomography and computed tomography angiography findings predict functional impairment in patients with minor stroke and transient ischaemic attack. Int J Stroke 2009;4:448–453.
11. 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;43:3018–3022.
12. Woo D, Broderick JP, Kothari RU, et al. Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? NINDS t-PA Stroke Study Group. Stroke 1999;30:2355–2359.
13. Sato S, Toyoda K, Uehara T, et al. Baseline NIH Stroke Scale score predicting outcome in anterior and posterior circulation strokes. Neurology 2008;70:2371–2377.
14. Sato S, Uehara T, Toyoda K, et al. Impact of the approval of intravenous recombinant tissue plasminogen activator therapy on the processes of acute stroke management in Japan: the Stroke Unit Multicenter Observational (SUMO) Study. Stroke 2009;40:30–34.
15. Sakamoto Y, Sato S, Kuronuma Y, Nagatsuka K, Minematsu K, Toyoda K. Factors associated with proximal carotid axis occlusion in patients with acute stroke and atrial fibrillation. J Stroke Cerebrovasc Dis Epub 2013 Oct 5.
16. Sato S, Uehara T, Hayakawa M, Nagatsuka K, Minematsu K, Toyoda K. Intra- and extracranial atherosclerotic disease in acute spontaneous intracerebral hemorrhage. J Neurol Sci 2013;332:116–120.