Pretreatment Blood Pressure is a Simple Predictor of Hemorrhagic Infarction after Intravenous Recombinant Tissue Plasminogen Activator (rt-PA) Therapy

Ryo Ohtani, MD, PhD,* Michikazu Nakamura, MD, PhD,* Shinsuke Nirengi, PhD,† Osamu Kawakami, MD,‡ Jumpei Togawa, MD,* Kento Doi, MD,‡ Makoto Sainouchi, MD,* Yasuhiro Kuwata, MD,* Masaki Takata, MD,* Yuichi Masuda, MD,* Ryota Matsunari, MD,* Kiyoaki Takeda, MD,* Tetsuya Tsukahara, MD, PhD,‡ and Naoki Sakane, MD, PhD†

Background: Hemorrhagic infarction (HI) is among the most severe complications that can occur following the administration of intravenous recombinant tissue plasminogen activator (rt-PA). In the present study, we aimed to determine the optimal cut-off points of blood pressure (BP) for HI after rt-PA treatment, and to compare our findings with those for other prediction models. *Methods:* We analyzed data from 109 consecutive patients with stroke treated at our hospital between 2009 and 2016. HI was confirmed via computed tomography or magnetic resonance imaging. Patients were classified into a symptomatic HI group, an asymptomatic HI group, and a non-HI group. BP was measured on admission and before rt-PA treatment. Glucose Race Age Sex Pressure Stroke Severity (GRASPS) and Totaled Health Risks in Vascular Events (THRIVE) scores were also calculated. Receiver operating characteristic (ROC) analysis was used to determine factors associated with symptomatic and asymptomatic HI. *Results:* Among the 109 total patients, 25 patients developed symptomatic HI, while 22 patients developed asymptomatic HI. ROC analysis for predicting symptomatic and asymptomatic HI revealed that the area under the curve for pretreatment systolic BP (SBP) was .88 (95% confidence interval [CI]: .83-.94), while those for GRASPS and THRIVE scores were .75 (95% CI: .66-.85) and .69 (95% CI: .59-.79), respectively. We identified an optimal cut-off point of 160 mm Hg (sensitivity: 82.3%; specificity: 76.6%; diagnostic accuracy: 80.0%; positive predictive value: 76.6%; negative predictive value: 82.5%). *Conclusions:* Pretreatment SBP may be a simple predictor of symptomatic and asymptomatic HI in patients with stroke undergoing rt-PA treatment.

Key Words: Cerebral infarction—hemorrhagic infarction—tissue plasminogen activator—magnetic resonance imaging—acute stroke management

Introduction

Acute ischemic stroke (AIS) remains a leading cause of death and long-term disability worldwide. Intravenous recombinant plasminogen activator (rt-PA) was approved nearly 2 decades ago for the treatment of AIS.[1-3] Although treatment with rt-PA improves clinical outcomes in

From the *Department of Neurology, National Hospital Organization Kyoto Medical Center, Fukakusa, Kyoto, Japan; †Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Fukakusa, Kyoto, Japan; and ‡Department of Neurosurgery, National Hospital Organization Kyoto Medical Center, Fukakusa, Kyoto, Japan.

Received February 7, 2019; revision received March 7, 2019; accepted March 16, 2019.

Address correspondence to Ryo Ohtani, MD, PhD, Department of Neurology, National Hospital Organization Kyoto Medical Center, 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan. E-mail: ryoohtani@gmail.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.03.035

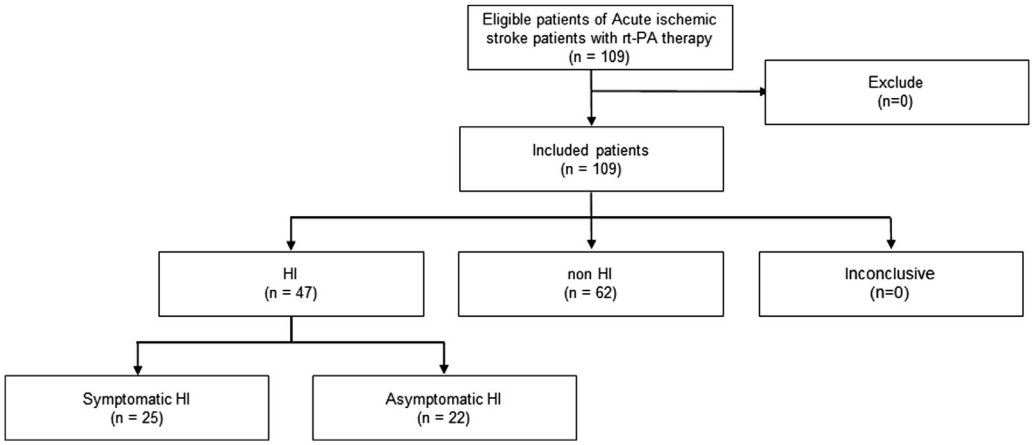

Figure 1. *Flow chart showing the selection of patients for inclusion in the study.*

carefully selected patients with AIS, intracerebral hemorrhagic infarction (HI) is among the most severe complications of this treatment.[4-6] Several clinical prediction models for symptomatic HI in patients with AIS have been developed, exhibiting fair predictive value.[7] However, there is currently no prediction model for asymptomatic HI after treatment with rt-PA.

Elevated blood pressure (BP) is observed in over 60% of patients presenting to the emergency department with stroke.[8] Increased BP is a risk factor for HI.[9-11] Based on the National Institute of Neurological Disorders and Stroke t-PA study protocol, those with a systolic BP (SBP) greater than or equal to 185 mm Hg and a diastolic BP (DBP) greater than or equal to 110 mm Hg are ineligible for thrombolytic therapy.[12] In such cases, hypertension is treated using intravenous labetalol or nicardipine. However, current recommendations do not specifically address the optimal level of BP reduction for HI. In the present study, we aimed to determine the optimal cut-off points for symptomatic and asymptomatic HI after treatment with rt-PA, and to compare our findings with those for other prediction models.

Materials and Methods

Study Design and Setting

A retrospective cohort design was used to analyze single-center stroke registry data collected from consecutive patients with AIS who had been treated with a .6 mg/kg dose of intravenous rt-PA within 4.5 hours from stroke onset between January 2009 and June 2016. All patients were prospectively identified, and their data were entered into a computerized stroke registry. The study was approved by the Kyoto Medical Center Ethics Committee (Japan; approval number: 18-084).

Patients with a clinical diagnosis of ischemic stroke causing measurable neurologic deficit with symptom onset less than 3.0 hours (2009-2012)[13] and less than 4.5 hours (2012-2016)[14] before beginning treatment were included. Patients who had experienced intracranial hemorrhage or serious head trauma within the preceding 3 months, had undergone major surgery within 14 days, had a SBP greater than or equal to 185 mm Hg or DBP greater than or equal to 110 mm Hg, hypoglycemia (blood glucose < 50 mg/dL) or severe hyperglycemia (>400mg/dL), thrombocytopenia (PLT < 100,000), PT-INR greater than 1.7, serious liver injury, or acute pancreatitis were excluded (Fig 1).

The study was performed and reported in accordance with the STARD reporting guidelines.[15] BP on admission and pretreatment BP were measured by trained nurses in accordance with our in-hospital manual for acute stroke. BP was measured at the level of the axillary line with the patient in the supine position, with his/her head tilted slightly downward. A manual, solar, oscillometric device was used to measure BP (Omron HEM 4500-SOL; Omron Healthcare, Kyoto, Japan). BP was measured 3 times during each session, and the median value was used for analysis. Patients with BP levels exceeding Japan Stroke Society recommendations were treated with nicardipine (continuous infusion of 5 mg/h, titration up to the desired effect in increments of 2.5 mg/h at intervals of 5-15 minutes; maximum dose: 15 mg/h) at the discretion of the attending physician The onset-to-treatment time was defined as the time from stroke onset to rt-PA bolus. Treatment with rt-PA was performed in patients with an SBP less than 185 mm Hg and a DBP less than 110 mm Hg, in accordance with Japan Stroke Society criteria. We managed BP with nicardipine for 20 patients with a SBP greater than or equal to 180 mm Hg on admission, and there were no uncontrolled patients. After rt-PA administration, we also controlled BP with nicardipine. We also evaluated Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography (scores[16] and National Institutes of Health Stroke Scale (NIHSS) scores[17] for each patient before and after treatment. Outcomes after treatment with rt-PA were evaluated based on modified Rankin Scale score[18] 30 days after stroke onset.

Table 1. *Clinical characteristics*

Variables	HI (n = 47)			Non-HI (n = 62)	*P* value*	*P* value†
	Symptomatic + asymptomatic (n = 47)	Symptomatic (n = 25)	Asymptomatic (n = 22)			
Age, years	75.0 ± 10.5	78.6 ± 8.0	71.0 ± 11.6	72.4 ± 10.8	.21	<.05
Female, %	38.3	60.0	63.6	43.5	.36	1.00
Current smoking, %	48.9	60.0	36.4	46.8	.49	.15
Alcohol intake, %	27.7	28.0	27.3	33.9	.32	1.00
Atrial fibrillation, %	83.0	80.0	86.4	50.0	<.01	.71
Hypertension, %	76.6	92.0	59.1	75.8	.55	<.05
Diabetes mellitus, %	25.5	32.0	18.2	24.2	.52	.33
Dyslipidemia, %	23.4	28.0	18.2	30.6	.27	.51
Renal disease, %	19.1	28.0	9.1	17.7	.52	.14
Hepatic disease, %	8.5	12.0	4.5	4.8	.35	.61
Heart failure, %	63.8	72.0	55.5	32.4	<.01	.24

*HI versus non-HI.
†Symptomatic HI versus asymptomatic HI + non-HI.

Symptomatic and Asymptomatic HI

Symptomatic HI was defined as evidence of intracranial hemorrhage on brain imaging and clinical worsening of NIHSS scores (increase of ≥4 points) within 36 hours from rt-PA bolus. Asymptomatic HI was defined as evidence of intracranial hemorrhage on brain imaging without clinical worsening of NIHSS scores. We evaluated the intracranial hemorrhage using computed tomography (CT scan) in 3 patients with implanted the pace maker, and 106 patients were evaluated using magnetic resonance imaging with T2* sequence.[19]

Glucose Race Age Sex Pressure Stroke Severity (GRASPS) Score

The following data were recorded for each patient to calculate GRASPS scores: age, NIHSS score, SBP, casual blood glucose on admission, race, and sex.[20,21] GRASPS scores were calculated by assigning 8 points for an age less than or equal to 60, 11 points for an age of 61-70, 15 points for an age of 71-80, 17 points for an age greater than 80, 25 points for an NIHSS score of 0-5, 27 points for an NIHSS score of 6-10, 34 points for an NIHSS score of 11-15, 40 points for an NIHSS score of 16-20, 42 points for an NIHSS greater than 20, 10 points for an SBP less than 120 mm Hg, 14 points for an SBP of 120-149 mm Hg, 18 points for an SBP of 150-179 mm Hg, 21 points for an SBP greater than or equal to 180 mm Hg, 9 points for Asian race, 0 points for non-Asian race, 4 points for male sex, and 0 points for female sex. Thus, total GRASPS scores ranged from 45 to 100.

Totaled Health Risks in Vascular Events (THRIVE) Scores

The following data were recorded for each patient to calculate THRIVE scores: age; initial stroke severity as determined using NIHSS scores; and the presence or absence of hypertension, diabetes mellitus, or atrial

Table 2. *Time, ASPECT-DWI, blood pressure and neurological findings*

Variables	HI (n = 47)			Non-HI (n = 62)	*P* value*	*P* value†
	Symptomatic + asymptomatic (n = 47)	Symptomatic (n = 25)	Asymptomatic (n = 22)			
Onset-treatment time, min	140.7 ± 43.6	138.8 ± 34.4	142.8 ± 53.0	126.3 ± 42.6	.09	.41
ASPECT-DWI	5.4 ± 2.2	4.6 ± 1.9	6.4 ± 2.3	8.2 ± 1.9	<.05	<.05
Blood pressure						
SBP (on admission), mm Hg	170.8 ± 22.2	181.4 ± 19.3	158.7 ± 19.1	143.1 ± 20.1	<.05	<.05
DBP (on admission), mm Hg	94.7 ± 22.3	102.3 ± 23.1	86.0 ± 18.4	75.6 ± 11.1	<.05	<.05
SBP (before rt-PA), mm Hg	163.2 ± 14.4	170.2 ± 9.6	155.3 ± 14.9	135.9 ± 17.5	<.05	<.05
DBP (before rt-PA), mm Hg	87.8 ± 11.5	91.4 ± 9.3	83.8 ± 12.6	70.5 ± 10.0	<.05	<.05
NIHSS (before rt-PA), point	17.7 ± 7.6	20.8 ± 6.7	14.3 ± 7.1	12.9 ± 7.6	<.05	<.05
NIHSS (after rt-PA), point	16.2 ± 7.5	19.4 ± 6.4	12.6 ± 7.0	9.4 ± 7.1	<.05	<.05

*HI versus non-HI.
†Symptomatic HI versus asymptomatic HI + non-HI.

Table 3. *Comparison of blood pressure, GRASPS score, and THRIVE score for predicting symptomatic hemorrhagic infraction*

Variables	Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Diagnostic accuracy, %	Likelihood ratio of a positive test	Likelihood ratio of a negative test	AUC (95% CI)	*P* value*	*P* value†
SBP (on admission)	160	100	69.0	49.0	100	76.1	3.2	0	.90 (.85-.96)	.60	.05
DBP (on admission)	85	76.0	72.6	45.2	91.0	73.4	2.8	.3	.83 (.75-.91)	.40	.56
SBP (before rtPA)	160	100	73.4	53.2	100	79.8	3.8	0	.92 (.87-.96)	.42	<.05
DBP (before rtPA)	85	76.0	83.3	57.6	92.1	81.7	4.6	.29	.87 (.80-.93)	.86	.18
GRASPS	89	76.0	85.7	61.3	92.3	83.5	5.3	.28	.88 (.80-.96)	-	<.01
THRIVE	7	64.0	84.5	55.2	88.8	79.8	4.1	.43	.79 (.70-.88)	<.01	-

AUC, area under the curve; DBP, diastolic blood pressure; GRASPS, Glucose Race Age Sex Pressure Stroke Severity; NPV, negative predictive value; PPV; positive predictive value; SBP, systolic blood pressure; THRIVE, Totaled Health Risks in Vascular Events.

*versus GRASPS.

†versus THRIVE.

fibrillation.[22] THRIVE scores were calculated by assigning 1 point for an age of 60-79 years; 2 points for an age greater than or equal to 80 years; 2 points for an NIHSS score of 11-20; 4 points for an NIHSS score greater than or equal to 21; and 1 point each for hypertension, diabetes mellitus, and atrial fibrillation. Thus, total THRIVE scores ranged from 0 to 9.

Sample Size

Sample size was estimated using easyROC, a web-tool for receiver operating characteristics (ROC) curve analysis (ver. 1.3) (http://www.biosoft.hacettepe.edu.tr/easyROC/). We estimated that a sample size of 90 participants would allow us to compare area under the curve (AUC) values between .9 and .7 with 90% power.

Statistical Analysis

ROC curve analysis was used to determine the optimal cut-off points of the parameters for predicting HI.[23] AUC values are presented with confidence intervals (CI). AUC values greater than or equal to .90 are considered excellent, values between .80 and .89 are considered good, values between .70 and .79 are considered fair, and those less than .70 are considered poor.[24] The Youden index was used to identify the optimal cut-off value for predicting HI.[25] Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were also calculated.[26] Diagnostic accuracy measures tell us about the ability of a test to discriminate between and/or predict disease and health. Diagnostic accuracy express as the proportion of correctly classified subjects (True Positive + True Negative) among all subjects (True Positive + True Negative+ False Positive + False Negative).[27] The distributions of the different variables were examined for normality using the Kolmogorov-Smirnov test. Data are expressed as the mean and standard deviation or as percentages. Variables with non-normal distributions are expressed as the geometric mean (95% C]). All normally distributed data were analyzed using Student's *t* test to evaluate differences in mean values and chi-square tests to evaluate differences in proportions. Non-normally distributed data were analyzed using Mann-Whitney *U* tests for independent subgroups and Wilcoxon tests for dependent subgroups. In order to identify significant differences between groups after chi-square tests, we consecutively performed a residual error analysis. *P* values less than .05 were considered statistically significant.

Results

Baseline Characteristics

Among the 109 total patients, 25 patients (22.9%) developed symptomatic HI, while 22 patients (20.2%) developed asymptomatic HI. Patients in the HI group had a

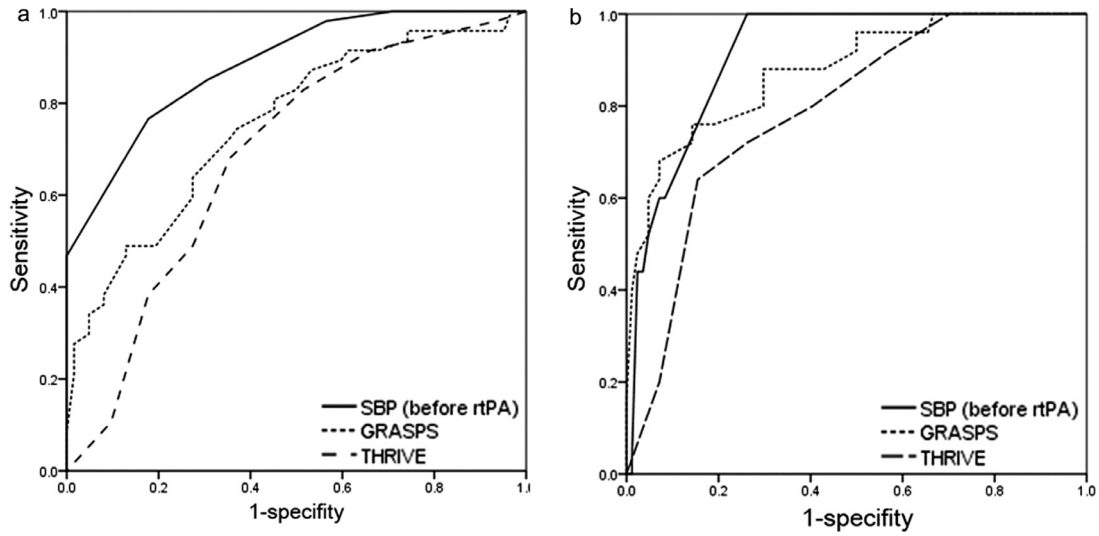

Figure 2. *Receiver operating characteristic (ROC) curve of blood pressure versus other score in predicting symptomatic and asymptomatic or symptomatic HI for patients with rt-PA therapy. (a) Predicting symptomatic and asymptomatic HI. SBP (before trPA) versus GRASPS or THRIVE. (b) Predicting symptomatic HI. SBP (before trPA) versus GRASPS or THRIVE.*

significantly higher incidence of atrial fibrillation and heart failure ($P < .05$). In contrast, patients in the symptomatic HI group were significantly older and had a higher incidence of hypertension than those in the asymptomatic HI and non-HI groups ($P < .05$) (Table 1).

Admission and pretreatment SBP/DBP and NIHSS scores were significantly higher in the HI group than in the non-HI group, while Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography scores were significantly lower. No significant differences in onset-to-treatment time were observed between the groups (Table 2). Significant differences in modified Rankin Scale scores were observed between the HI and non-HI groups (4.0 ± 1.9 versus 1.6 ± 1.8 points; $P < .05$) and between the symptomatic HI and asymptomatic HI/non-HI group (5.0 ± .9 versus 1.9 ± 1.9 points; $P < .05$).

Predictors of Symptomatic HI versus Asymptomatic HI and Non-HI

The ROC curve for predicting symptomatic HI revealed that the AUC value for pretreatment SBP was .92 (95% CI .87-.96), while those for GRASPS and THRIVE scores were .88 (95% CI .80-.96) and .79 (95% CI .70-.88), respectively. Our analysis identified an optimal cut-off point of 160 mm Hg before rt-PA (sensitivity: 100%; specificity: 73.4%; over all diagnostic accuracy: 79.8%; PPV: 53.2%; and NPV: 100%). For predicting the risk of symptomatic HI after rt-PA, the ROC curve for pretreatment SBP yielded the highest value (.92) (Table 3).

The prevalence of symptomatic HI was higher in patients with both an admission SBP less than 160 mmHg and a pretreatment SBP greater than 160 mm Hg than in those without such SBP values (82.9% (34/41) versus 33.3% (2/6), respectively). Thus, 43.1% (47/109) exhibited uncontrolled BP values.

Predictors of Symptomatic and Asymptomatic HI versus Non-HI

The ROC curve for predicting symptomatic and asymptomatic HI revealed that the AUC value for pretreatment SBP was .88 (95% CI .83-.94), while those for GRASPS and THRIVE scores were .75 (95% CI .66-.85) and .69 (95% CI .59-.79), respectively (Fig 2). Our analysis identified an optimal cut-off point of 160 mm Hg (sensitivity: 82.3%; specificity: 76.6%; diagnostic accuracy: 80.0%; PPV: 76.6%; and NPV: 82.5%). For predicting the risk of symptomatic and asymptomatic HI after rt-PA, the ROC curve for pretreatment SBP yielded the highest value (.88) (Table 4).

Discussion

Main Findings

The present study is the first to determine cut-off values for admission and pretreatment BP for predicting symptomatic and asymptomatic HI following rt-PA treatment. Our findings might be indicated that the diagnostic accuracy of BP was superior to that of GRASPS or THRIVE scores. Symptomatic HI after rt-PA treatment is associated with neurological prognosis and mortality among patients with stroke.[28,29] Taken together, these findings indicate that strict BP management is required to prevent HI in high-risk patients with ischemic stroke.[30]

Previous studies have reported that BP protocol violations (e.g., pretreatment SBP greater than 185 or DBP greater than 110 mmHg) are more frequent among patients with symptomatic HI.[31] However, in the present study, SBP and DBP levels were managed within less

Table 4. *Comparison of blood pressure, GRASPS score, and THRIVE score for predicting symptomatic and asymptomatic hemorrhagic infraction*

Variables	Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Diagnostic accuracy, %	Likelihood ratio of a positive test	Likelihood ratio of a negative test	AUC (95% CI)	*P* value*	*P* value†
SBP (on admission)	170	59.6	91.9	84.8	75.0	78.0	7.4	.44	.83 (.75-.91)	.17	<.05
DBP (on admission)	85	68.1	83.9	76.2	77.6	77.1	4.2	.38	.79 (.71-.88)	.48	.10
SBP (before rtPA)	160	76.6	82.3	76.6	82.5	80.0	4.4	.28	.88 (.83-.94)	<.01	<.01
DBP (before rtPA)	75	91.5	66.1	67.2	91.1	77.1	2.7	.13	.87 (.80-.93)	<.05	<.01
GRASPS	83	74.5	62.9	60.3	76.5	67.9	2.0	.41	.75 (.66-.85)	-	<.05
THRIVE	5	68.1	64.5	59.3	72.7	66.1	1.9	.50	.69 (.59-.79)	<.05	-

AUC, area under the curve; DBP, diastolic blood pressure; GRASPS, Glucose Race Age Sex Pressure Stroke Severity; NPV, negative predictive value; PPV, positive predictive value; SBP, systolic blood pressure; THRIVE, Totaled Health Risks in Vascular Events.
*versus GRASPS.
†versus THRIVE.

than 185 mm Hg and less than 110 mm Hg before treatment with rt-PA, respectively. Moreover, the relationships between BP and symptomatic HI remain controversial.[32] In the Safe Implementation of Treatments in Stroke registry, higher SBP after treatment with rt-PA was independently associated with worse outcomes and an increased risk of symptomatic HI.[33] However, in a USA study of 351 patients who had undergone rt-PA treatment, higher pretreatment SBP was not independently associated with outcomes.[34] The reasons for these discrepancies remain unknown. In most Asian countries, stroke is among the major causes of mortality,[35] and high BP is a major risk factor for adult mortality in Japan.[36] Japanese individuals consume high quantities of salt.[37]

Although the reasons remain unclear, mean age was higher in our study (mean age: 73.5 years versus 65.6 years) than in previous studies performed in other countries.[38] Life expectancy is known to be high among the Japanese population,[39] which may indicate that relatively older Japanese patients have the opportunity to receive rt-PA therapy. Older age may be associated with a higher prevalence of symptomatic HI.

BP is elevated in 75% or more of patients with acute stroke and is associated with poor outcomes.[40] Researchers have long debated whether high BP should be treated in patients with acute stroke.[41] There are 2 main theoretical concerns associated with the loss of normal cerebral autoregulation: high BP can lead to cerebral edema, hematoma expansion, or hemorrhagic transformation. However, low BP can lead to an increased risk of cerebral infarction or perihematomal ischemia.[42] Pretreatment SBP values less than 160 mm Hg are recommended to prevent HI in patients undergoing rt-PA treatment. However, in the present study, 43% of patients exhibited SBP values that exceeded this range. Further studies involving more strict BP control are required to clarify these issues.

Strengths and Limitations

Our study possesses several strengths, including the use of manual, in-hospital BP measurements; its real-world setting, and the inclusion of patients with both symptomatic and asymptomatic HI confirmed via MRI or computed tomography. A total of 106 patients (97.2%) were confirmed using MRI except 3 patients with the implanted pace maker However, there are also several limitations. First, this was a single center study with a relatively small sample size. Thus, further studies involving larger samples of patients are required to verify our findings. Nonetheless, our findings indicate that pretreatment BP may be a simple predictor of symptomatic and asymptomatic HI in patients with stroke undergoing rt-PA treatment.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number 17K19871 and Innovation, SIP (Project ID 14533567),

Technologies for creating next-generation agriculture, forestry and fisheries (Bio-oriented Technology Research Advancement Institution, NARO). We thank Kana Kuroda and Natsuko Nakajyo for collecting data.

Conflict of Interest

The authors have no conflict of interest to report.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.03.035.

References

1. Mendez AA, Samaniego EA, Sheth SA, et al. Update in the early management and reperfusion strategies of patients with Acute Ischemic Stroke. Crit Care Res Pract 2018;28:916873. https://doi.org/10.1155/2018/9168731. eCollection 2018.
2. Bhaskar S, Stanwell P, Cordato D, et al. Reperfusion therapy in acute ischemic stroke: dawn of a new era? BMC Neurol. 2018;18:8.
3. Khandelwal P, Yavagal DR, Sacco RL. Acute Ischemic Stroke intervention. J Am Coll Cardiol 2016;67:2631-2644.
4. Kaesmacher J, Kaesmacher M, Maegerlein C, et al. Hemorrhagic transformations after thrombectomy: risk factors and clinical relevance. Cerebrovasc Dis 2017;43:294-304.
5. Seet RC, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. Cerebrovasc Dis 2012;34:106-114.
6. Emberson J, Lees KR, Lyden P, et al. Stroke thrombolysis trialists' collaborative group: effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-1935.
7. Van Hooff RJ, Nieboer K, De Smedt A, et al. Validation assessment of risk tools to predict outcome after thrombolytic therapy for acute ischemic stroke. Clin Neurol Neurosurg 2014;125:189-193.
8. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 2007;25:32-38.
9. 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;333:1581-1587.
10. Larrue V, von Kummer RR, Müller A, et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke 2001;32:438-441.
11. Lager K, Mistri AK. Current status of blood pressure management after stroke. Expert Rev Cardiovasc Ther 2010;8:1587-1598.
12. Jauch EC, Saver JL, Adams Jr HP, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology: guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
13. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
14. 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.
15. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.
16. McTaggart RA, Jovin TG, Lansberg MG, et al. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography and MRI: reader agreement, modality agreement, and outcome prediction. Stroke 2015;46:407-412.
17. Lyden PD, Lu M, Levine SR, et al. NINDS rtPA stroke study group: a modified National Institutes of Health Stroke Scale for use in stroke clinical trials: preliminary reliability and validity. Stroke 2001;32:1310-1317.
18. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
19. Vymazal J, Rulseh AM, Keller J, et al. Comparison of CT and MR imaging in ischemic stroke. Insights Imaging 2012;3:619-627.
20. Li M, Wang-Qin RQ, Wang YL, et al: Symptomatic intracerebral hemorrhage after intravenous thrombolysis in Chinese patients: comparison of prediction models. J Stroke Cerebrovasc Dis 2015;24:1235-1243.
21. Menon BK, Saver JL, Prabhakaran S, et al. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. Stroke 2012;43:2293-2299.
22. Flint AC, Gupta R, Smith WS, et al. The THRIVE score predicts symptomatic intracerebral hemorrhage after intravenous tPA administration in SITS-MOST. Int J Stroke 2014;9:705-710.
23. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
24. Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978;8:283-298.
25. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J 2005;47:458-472.
26. Eusebi P. Diagnostic accuracy measures. Cerebrovasc Dis 2013;36:267-272.
27. Cheng HM, Sung SH, Chuang SY, et al. Am J Hypertens 2014;27:382-391.
28. Tan S, Wang D, Liu M, et al. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol 2014;261:905-912.
29. Al-Khaled M, Matthis C, Eggers J. Predictors of in-hospital mortality and the risk of symptomatic intracerebral hemorrhage after thrombolytic therapy with recombinant tissue plasminogen activator in acute ischemic stroke. J Stroke Cerebrovasc Dis 2014;23:7-11.
30. Tsai HH, Kim JS, Jouvent E, et al. Updates on prevention of hemorrhagic and lacunar strokes. J Stroke 2018;20:167-179.
31. Tsivgoulis G, Frey JL, Flaster M, et al. Pre-tissue plasminogen activator blood pressure levels and risk of symptomatic intracerebral hemorrhage. Stroke 2009;40:3631-3634.

32. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for Acute Ischemic Stroke. Neurohospitalist 2015;5:110-121.
33. Ahmed N, Wahlgren N, Brainin M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009;40:2442-2449.
34. Tsivgoulis G, Saqqur M, Sharma VK, et al. CLOTBUST Investigators: association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. Stroke 2007;38:961-966.
35. Toda A, Ishizaka Y, Tani M, et al. Current dietary salt intake of Japanese individuals assessed during health check-up. Hypertens Res 2015;38:163-168.
36. Ikeda N, Inoue M, Iso H, et al. Adult mortality attributable to preventable risk factors for non-communicable diseases and injuries in Japan: a comparative risk assessment. PLoS Med 2012;9:e1001160.
37. Jayedi A, Ghomashi F, Zargar MS, et al. Dietary sodium, sodium-to-potassium ratio, and risk of stroke: a systematic review and nonlinear dose-response meta-analysis. Clin Nutr 2018;1. https://doi.org/10.1016/j.clnu.2018.05.017. pii: S0261-5614(18)30202-4. [Epub ahead of print].
38. Xu X, Li C, Wan T, et al. Risk factors for hemorrhagic transformation after intravenous thrombolysis in acute cerebral infarction: a retrospective single-center study. World Neurosurg 2017;101:155-160.
39. Tokudome S, Hashimoto S, Igata A. Life expectancy and healthy life expectancy of Japan: the fastest graying society in the world. BMC Res Notes 2016;9:482.
40. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. Stroke Vasc Neurol 2016;1:72-82.
41. Bath PM, Appleton JP, Krishnan K, et al. Blood pressure in acute stroke: to treat or not to treat: that is still the question. Stroke 2018;49:1784-1790.
42. Maida C, Tuttolomondo A, Di Raimondo D, et al. Management of blood pressure and heart rate in patients with acute stroke. Curr Pharm Des 2017;23:4538-4597.