Observational Study

Medicine

OPEN

Effects of tissue plasminogen activator on medium-term functional independence

A propensity score-matched analysis

Tomohiro Kakinuma, PhD[a,*], Takaaki Fujita, OTR, PhD[b], Tetsuya Iwamoto, PhD[c], Tsuyoshi Mizushiri, MD[d], Yukako Yazawa, MD, PhD[e]

Abstract

This study revealed the effects of tissue plasminogen activator (tPA) on medium-term functional independence in patients with stroke. We retrospectively examined 240 patients from April 2016 to March 2019 and selected 68 who met our criteria. After adjusting the functional status at the onset by propensity score matching, the functional independence measure (FIM) on admission to and discharge from the convalescent rehabilitation wards was compared between the groups classified by the presence or absence of tPA. Twelve pairs were derived by propensity score matching. Upon admission to the convalescent rehabilitation ward, the median score of the FIM was significantly higher in the tPA group than in the non-tPA group (P = .028). Patients in the tPA group had higher median FIM scores at discharge than those in the non-tPA group (P = .060). The difference in the independence level of activities of daily living (ADL) between the groups with and without tPA may gradually decrease with continuous inpatient rehabilitation. However, the tPA group tended to have high levels of independence in ADL at the time of discharge.

Abbreviations: ADL = activities of daily living, FIM = functional independence measure, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale, tPA = tissue plasminogen activator.

Keywords: activities of daily living, functional independence, rehabilitation, stroke, tissue plasminogen activator

1. Introduction

Stroke is now one of the leading causes of disabilities rather than death. For patients with stroke, outcomes after discharge from the hospital are important for their daily life. In Japan, cerebral infarction accounts for more than half of all strokes.[1,2] Recently, the efficacy of tissue plasminogen activator (tPA) for acute stroke has been validated in Japan[3–7] and other parts of the world.[8–16]

However, few reports have examined the efficacy of tPA on medium- and long-term functional statuses using patient matching. Long-term efficacy has been reported to reduce the risk of long-term mortality[17] and improve functional independence.[18]

Regarding the medium-term efficacy of tPA, within 6 months of onset, activities of daily living (ADL) independence at discharge from the rehabilitation department was higher in the tPA group than in the non-tPA group.[19] It is important to confirm the efficacy of tPA on functional status during this period was because many patients are discharged from the hospital after active rehabilitation within 6 months of onset. However, in this report, the functional status of the two groups at the time of onset was not strictly matched. Therefore, it is desirable to verify tPA's middle and long-term efficacy in improving ADL after strictly controlling background factors by propensity score matching or other methods.

In this study, we investigated the medium-term effectiveness of tPA in improving ADL, which has rarely been reported, from the aspect of functional improvement and resource input of patients with stroke who received intensive rehabilitation in a convalescent rehabilitation ward after treatment in an acute care ward. Detailing the medium-term functional improvement of tPA is meaningful for patients in terms of their life after discharge and healthcare professionals in terms of rehabilitation.

2. Methods

This study was a retrospective observational study. Participants were 240 patients with stroke who were discharged from an acute care hospital (Kohnan Hospital) between April 2016 and March 2019 and transferred to a convalescent rehabilitation

This work was supported by a grant from the Japanese Society for the Promotion of Science Grants-in-Aid for Scientific Research (grant no. 19K10490).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Department of Health and Welfare Services, National Institute of Public Health, Wako City, Saitama, Japan, [b] Department of Occupational Therapy, School of Health Sciences, Fukushima Medical University, Fukushima City, Fukushima, Japan, [c] Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health, Wako City, Saitama, Japan, [d] Department of Rehabilitation Medicine, Koeki Zaidan Hojin Miyagi Kosei Kyokai Nagamachi Hospital, Sendai City, Miyagi, Japan, [e] Department of Stroke Neurology, Kohnan Hospital, Sendai City, Miyagi, Japan.

**Correspondence: Tomohiro Kakinuma, Department of Health and Welfare Services, National Institute of Public Health, Wako City, Saitama 351-0197, Japan (e-mail: kakinuma.t.aa@niph.go.jp).*

How to cite this article: Kakinuma T, Fujita T, Iwamoto T, Mizushiri T, Yazawa Y. Effects of tissue plasminogen activator on medium-term functional independence: A propensity score-matched analysis. Medicine 2022;101:41(e31108).

Received: 11 June 2022 / Received in final form: 9 September 2022 / Accepted: 13 September 2022

http://dx.doi.org/10.1097/MD.0000000000031108

hospital (Nagamachi Hospital) in Miyagi Prefecture, which are in the Tohoku region of Japan's main island. Of these, 31 were patients administered tPA. The patients were treated with intravenous alteplase at 0.6 mg/kg (with 10% bolus administration and 90% by 60-minute infusion) within 4.5 hours after symptom recognition.

We excluded patients in the cautious group who were ≥81 years old and had the National Institute of Health Stroke Scale (NIHSS) of ≥26 on admission and selected patients who were ≤80 years with the NHISS of ≤25 on admission, referring to the Japanese guideline.[20] Additionally, we excluded patients with a history of stroke and those who required assistance in daily living (patients with modified Rankin Scale [mRS] before stroke >2), dead, and with missing data.

As a result, the number of patients was 68. Of these, 14 were patients with tPA. Figure 1 shows the patients' selection flow. The Research Ethics Committees of National Institute of Public Health and Kohnan Hospital and Nagamachi Hospital reviewed and approved the study (NIPH-IBRA #12290, 20200311,2019-03), which was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

We collected the data from the acute care hospital and the convalescent hospital. First, we collected gender, date of birth, the functional independence measure (FIM), date of admission, date of discharge, and total rehabilitation time from the convalescent rehabilitation hospital. The main outcomes were total FIM scores, an index of ADL. The follow-up period was up to the time of discharge from the convalescent rehabilitation hospital, and FIM scores were measured on admission to and discharge from the convalescent rehabilitation hospital. The FIM is a reliable tool used to assess the ability to perform ADL.[21] The FIM consists of 18 items, 13 motor items, and 5 cognitive items. All 18 items of the FIM consist of seven levels ranging from 1 to 7 points, and the total score ranged from 18 to 126 points. The FIM used was the Japanese version of the FIM, 3rd edition.[22] Next, we traced the data back to the acute care ward for 240 patients. The data obtained from the acute care hospital were gender, year of birth, NHISS on admission, NIHSS at discharge, mRS before stroke, mRS at discharge, presence of tPA treatment, date of admission, and date of discharge.

We conducted an intergroup comparison of 68 patients in the tPA and non-tPA groups. Of these, 14 patients were classified into the tPA group, 54 patients were classified as the non-tPA group. The items we compared were age, gender, NIHSS on admission, mRS before stroke, NHISS and mRS at discharge, the total FIM score on admission and discharge at the convalescent rehabilitation, length of stay at the acute care wards, length of stay at the convalescent rehabilitation wards, total length of stay at the acute care wards and convalescent rehabilitation wards, and total rehabilitation time of the convalescent rehabilitation wards.

The independent variables used to calculate the propensity score were those that showed statistically significant differences among the above functional status of the patients in terms of gender, age, NIHSS on admission, and mRS before stroke at the acute care wards.

We used propensity score matching to control for the effects of applicable variables and implemented rigorous between-group comparisons. As gender, age, NIHSS on admission, and mRS before stroke are established prognostic indicators in patients with stroke,[23–25] we used these factors.

Propensity score matching is a robust method to equalize background factors. The appropriate variables above were used as independent variables, and the propensity score was calculated using logistic regression analysis. In this study, 1:1 matching was implemented for subjects with similar propensity scores. The caliper used for this matching was a quarter of a standard deviation of the propensity score. We used the c-statistics to discriminate the models and the Hosmer–Lemeshow test to determine the goodness of fit.

After propensity score matching, the same items were compared as before propensity score matching to examine differences in patients' functional status and resource inputs.

Before propensity score matching, we adopted Student's *t* test, Mann–Whitney *U* test, and chi-square test to compare groups. In particular, age, FIM, length of hospital stay, and total rehabilitation time were examined by Student's *t* test if both groups were significant by Shapiro–Wilk test and Mann–Whitney *U* test if $P < .05$ in one group.

After propensity score matching, we adopted the paired *t* test, Wilcoxon signed-rank test, and chi-square test for comparison between groups, depending on the characteristics of the variables.

For the same items as before matching, we used the Shapiro–Wilk test with a paired *t* test if both groups were significant, and the Wilcoxon signed-rank test if $P < .05$ for one group. The statistical analysis was implemented using the statistical software SPSS, version 25.0. We decided the level of significance as $P < .05$.

3. Results

Table 1 summarizes the patients' characteristics and functional status. The median age of the 68 patients was 68.5 (58.3–76.0) years, men (48.5%). The median NIHSS on admission in the

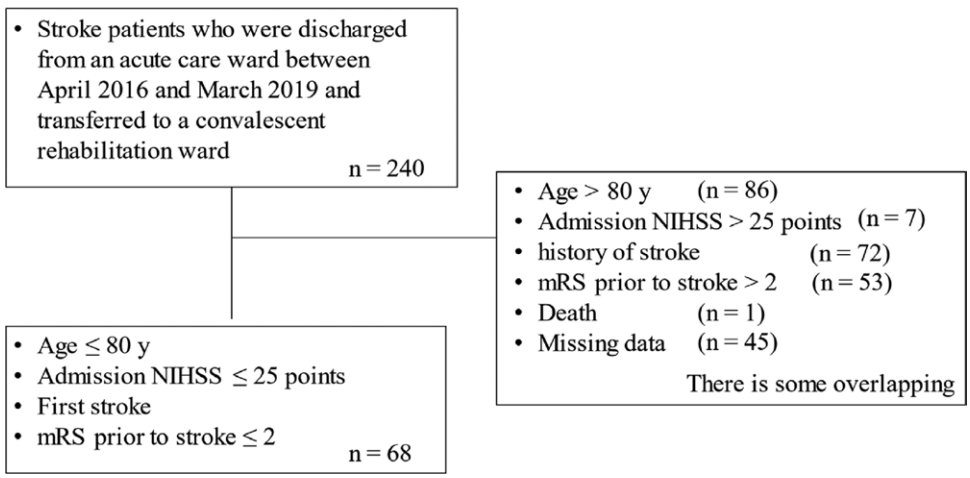

Figure 1. The flow of patients' selection.

Table 1

Patients' characteristics and functional status.

	Before matching				After matching			
	Total (n = 68)	tPA group (n = 14)	non-tPA group (n = 54)	*P* value	Total (n = 24)	tPA group (n = 12)	Non-tPA group (n = 12)	*P* value
Age, yr (IQR)	68.5 (58.3–76.0)	71.5 (59.0–77.5)	68.0 (57.8–75.3)	.471	71.0 (62.8–76.0)	71.5 (60.5–76.8)	70.0 (62.8–75.5)	.574
Gender, men, n (%)	33 (48.5)	8 (57.1)	25 (46.3)	.469	13 (54.2)	7 (58.3)	6 (50.0)	.682
NIHSS on admission of acute care ward, points (IQR)	4.0 (2.0–13.8)	13.5 (4.8–20.8)	4.0 (2.0–9.0)	.002	10.5 (4.0–18.8)	11.0 (4.3–18.8)	10.0 (4.0–19.5)	.052
mRS before stroke, points (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.840	0.0 (0.0–0.8)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	.480
NIHSS at discharge of acute care ward, points (IQR)	2.0 (1.0–5.8)	2.5 (1.8–7.8)	2.0 (1.0–4.3)	.457	4.0 (2.0–9.8)	2.5 (2.0–7.0)	4.5 (3.0–13.8)	.090
mRS at discharge of acute care ward, points (IQR)	3.0 (2.0–4.0)	4.0 (2.0–4.0)	3.0 (2.0–4.0)	.453	4.0(3.0–4.0)	4.0 (2.3–4.0)	4.0 (3.3–4.0)	.084
Total FIM at admission of convalescent rehabilitation ward, points (IQR)	83.0 (52.8–96.0)	79.0 (45.0–96.0)	83.5 (54.5–97.3)	.444	62.0(36.0–83.8)	79.0 (52.8–93.8)	49.5 (28.5–75.5)	.028
Total FIM at discharge of convalescent rehabilitation ward, points (IQR)	111.0 (90.3–120.8)	112.0 (73.5–123.5)	111.0 (95.5–120.3)	.994	109.5 (76.5–114.8)	112.0 (76.5–121.3)	103.0 (59.5–111.8)	.060
Length of stay at acute care ward of Konan hospital, days (±SD)	40.7 ± 11.6	40.4 ± 7.9	40.7 ± 12.4	.929	37.8 ± 9.6	39.6 ± 8.0	35.9 ± 11.0	.382
Length of stay at convalescent rehabilitation ward of Nagamachi hospital, days (IQR)	72.0 (37.3–111.8)	88.0 (37.8–155.8)	64.0 (36.8–98.3)	.237	95.1 ± 50.5	93.4 ± 53.8	96.8 ± 49.3	.850
Length of stay at Konan hospital and Nagamachi hospital, days (±SD)	77.2 ± 46.7	93.6 ± 54.9	72.9 ± 44.0	.167	132.9 ± 52.8	133.0 ± 56.2	132.8 ± 51.7	.991
Total rehabilitation time, hours (IQR, ±SD)	157.7 (86.0–258.5)	202.9 (90.5–341.3)	152.9 (84.8–246.0)	.255	222.6 ± 122.9	214.7 ± 125.1	230.6 ± 125.7	.715

FIM = the fuctional independence measure, IQR = interquartile range, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale, SD = standard deviation, tPA = tissue plasminogen activator.

acute care wards was 4.0 (2.0–13.8), while the median mRS before stroke was 0.0 (0.0–0.0).

We compared gender, age, NIHSS on admission at the acute care wards, and mRS before stroke to adjust for background factors. As a result, the median NIHSS on admission in the acute care wards was 13.5 (4.8–20.8) in the tPA group, but 4.0 (2.0–9.0) in the non-tPA group, and there was a significant difference between the groups (P = .002). There were no significant differences in the other variables.

We then used propensity score matching to adjust for NHISS on admission at the acute care wards as a background factor to determine whether there was a difference in functional improvement with tPA treatment. After propensity score matching, 12 pairs were derived from each group. The c-statistic was 0.77, and the Hosmer–Lemeshow test result was P = .81, which indicates that the model is good. There was no difference between groups in NHISS on admission at the acute care wards, reducing the impact of background factors.

The results of the comparison of outcomes after propensity score matching were as follows. The median total FIM on admission at the convalescent rehabilitation wards was 79.0 (52.8–93.8) in the tPA group and 49.5 (28.5–75.5) in the non-tPA group (P = .028). The median total FIM at discharge from the convalescent rehabilitation wards was 112.0 (76.5–121.3) in the tPA group and 103.0 (59.5–111.8) in the non-tPA group (P = .060). The total rehabilitation time was 214.7 ± 125.1 hours in the tPA group and 230.6 ± 125.7 hours in the non-tPA group (P = .715).

4. Discussion

This study included patients who were ≤80 years old, NIHSS ≤25 on admission at the acute care wards, first onset, and with mRS ≤2. We analyzed the medium-term functional status of tPA-treated patients from admission to discharge after adjusting for background factors using propensity score matching.

In a population of 68 patients before controlling for background factors, the outcome of the 14 patients in the tPA group was not necessarily better than that of the 54 patients in the non-tPA group. This is because the analysis did not control for the neurological severity of the background factors.

However, in a population of 24 patients adjusted for background factors, 12 patients in the tPA group had significantly better total FIM at transfer to the convalescent wards compared with the non-tPA group. The total FIM is slightly better when discharged from the convalescent rehabilitation wards, although the difference is not significant at the 5% significance level. As for the medium-term effectiveness of tPA because of intensive rehabilitation within 6 months of onset, the difference in ADL independence between the tPA and non-tPA groups may be small, although the tPA group tends to have higher ADL independence.

To the authors' knowledge, there are currently two studies using propensity score matching for the tPA and non-tPA groups.[17,18] One of them is monitoring functional status over time, including perspectives up to rehabilitation. However, the impact of factors other than tPA treatment on the outcome must be considered in the long term, though they are difficult to identify. As for tPA, one study showed an increased incidence of fatal intracranial hemorrhage in the days following treatment regardless of age or severity but reports that alteplase significantly improves the overall odds of a good outcome if given within 4.5 hours of stroke onset.[26]

On the other hand, this study used the age of ≤80 years as one of the criteria, referring to the Japanese guidelines for appropriate treatment. However, one study has shown that the mRS of the tPA treatment group aged ≥81 years at 3 months is not as good as that of the group aged ≤80 years.[27]

Therefore, this study's results were based on patients aged ≤80 years of age and patients with NIHSS ≤25 at the time of admission at the acute care ward.

This study was able to follow one patient for >4 months. The follow-up period was short compared to previous studies.[17,18] However, the medium-term functional status of stroke patients, adjusted for background factors, has not been sufficiently studied.

Especially in Japan, it is difficult to follow the functional status of a single patient after discharge from an acute care hospital among different hospitals due to insufficient database information. This rare study revealed the functional status of tPA-treated patients in rehabilitation over a medium-term.

There are some limitations to this study. The first is that it is an observational study. For this reason, we used propensity score matching to adjust for the effects of observable background factors to reduce bias as much as possible and compared the functional status of patients in the tPA and non-tPA groups. Another limitation, unmeasured background factors need to be examined and measured.

Additionally, there are issues with the reproducibility of the results and generalization. This is because the current study included 68 of the 240 participants who met the criteria for this study. Therefore, future work should include expanding the sample size, but in this study, we were able to make rigorous comparisons.

The medium-term functional improvement of tPA may be favorable for the tPA-treated patients included in this study. In Japan, equalization of tPA treatment is currently underway based on the law. Clarifying the outcomes until the rehabilitation phase should help raise awareness among patients to enable earlier treatment and the overall healthcare delivery system, including life in the community after discharge.

Author contributions

Conceptualization: Tomohiro Kakinuma, Takaaki Fujita.
Data curation: Tomohiro Kakinuma.
Formal analysis: Tomohiro Kakinuma, Takaaki Fujita.
Funding acquisition: Tomohiro Kakinuma.
Investigation: Tsuyoshi Mizushiri, Yukako Yazawa.
Methodology: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.
Project administration: Tomohiro Kakinuma.
Resources: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.
Software: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.
Supervision: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.
Validation: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.
Visualization: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto.
Writing – original draft: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto.
Writing – review & editing: Tomohiro Kakinuma, Takaaki Fujita, Tetsuya Iwamoto, Tsuyoshi Mizushiri, Yukako Yazawa.

References

[1]Iihara K, Nishimura K, Kada A, et al. Effects of comprehensive stroke care capabilities on in-hospital mortality of patients with ischemic and hemorrhagic stroke: J-ASPECT study. PLoS One. 2014;9:e96819.

[2]Ishikawa S, Kayaba K, Gotoh T, et al. Incidence of total stroke, stroke subtypes, and myocardial infarction in the Japanese population: the JMS cohort study. J Epidemiol. 2008;18:144–50.

[3]Yamaguchi T, Mori E, Minematsu K, et al. Japan Alteplase Clinical Trial (J-ACT) group. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke. 2006;37:1810–5.

[4] Nakagawara J, Minematsu K, Okada Y, et al; J-MARS Investigators. 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.

[5]Mori E, Minematsu K, Nakagawara J, et al; Japan Alteplase Clinical Trial II Group. 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;41:461–5.

[6]Toyoda K, Koga M, Naganuma M, et al; Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke. 2009;40:3591–5.

[7]Aoki J, Kimura K, Sakamoto Y. Early administration of tissue-plasminogen activator improves the long-term clinical outcome at 5 years after onset. J Neurol Sci. 2016;362:33–9.

[8]National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.

[9]Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017–25.

[10]Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study investigators. Lancet. 1998;352:1245–51.

[11]Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke. JAMA. 1999;282:2019–26.

[12]Albers GW, Thijs VN, Wechsler L, et al; DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol. 2006;60:508–17.

[13]Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.

[14]Davis SM, Donnan GA, Parsons MW, et al; EPITHET investigators. Effects of alteplase beyond 3 h after stroke in the echoplanar imaging thrombolytic evaluation trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7:299–309.

[15]Sandercock P, Wardlaw JM, Lindley RI, et al; IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial (IST-3)): a randomised controlled trial. Lancet. 2012;379:2352–63.

[16]Anderson CS, Robinson T, Lindley RI, et al; ENCHANTED Investigators and Coordinators. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med. 2016;374:2313–23.

[17]Schmitz ML, Simonsen CZ, Hundborg H, et al. Acute ischemic stroke and long-term outcome after thrombolysis: nationwide propensity score-matched follow-up study. Stroke. 2014;45:3070–2.

[18]Muruet W, Rudd A, Wolfe CDA, et al. Long-term survival after intravenous thrombolysis for ischemic stroke: a propensity score-matched cohort with up to 10-year follow-up. Stroke. 2018;49:607–13.

[19]Meiner Z, Sajin A, Schwartz I, et al. Rehabilitation outcomes of stroke patients treated with tissue plasminogen activator. PM R. 2010;2:698–702; quiz 792.

[20]Toyoda K, Koga M, Iguchi Y, et al. Guidelines for intravenous thrombolysis (recombinant tissue-type plasminogen activator), the Third Edition, March 2019: a guideline from the Japan stroke society. Neurol Med Chir (Tokyo). 2019;59:449–91.

[21]Hamilton BB, Laughlin JA, Fiedler RC, et al. Interrater reliability of the 7-level functional independence measure (FIM). Scand J Rehabil Med. 1994;26:115–9.

[22]The data management service of the uniform data system for medical rehabilitation and the center for functional assessment research: guide for use of the uniform data set for medical rehabilitation (Ver.3.0). New York: State University of New York at Buffalo. 1990.

[23]Veerbeek JM, Kwakkel G, van Wegen EE, et al. Early prediction of outcome of activities of daily living after stroke: a systematic review. Stroke. 2011;42:1482–8.
[24]Qu JF, Chen YK, Luo GP, et al. Severe lesions involving cortical cholinergic pathways predict poorer functional outcome in acute ischemic stroke. Stroke. 2018;49:2983–9.
[25]Franceschini M, Fugazzaro S, Agosti M, et al; Italian Study Group on Implementation of Stroke Care (ISC Study). Acute phase predictors of 6-month functional outcome in Italian stroke patients eligible for in-hospital rehabilitation. Am J Phys Med Rehabil. 2018;97:467–75.
[26]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;384:1929–35.
[27]Koga M, Shiokawa Y, Nakagawara J, et al. Low-dose intravenous recombinant tissue-type plasminogen activator therapy for patients with stroke outside European indications: stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry. Stroke. 2012;43:253–5.