Effects of tissue plasminogen activator on medium-term functional independence
A propensity score-matched analysis

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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) 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 ward from the hospital. 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.

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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 NIHSS 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 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 and at 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] The 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 and at 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] 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, NIHSS 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, NIHSS 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.

For the same items as before matching, we used the Shapiro–Wilk test with a 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

| Stroke patients who were discharged from an acute care ward between April 2016 and March 2019 and transferred to a convalescent rehabilitation ward | n = 240 |
|---|---|
| Age ≤ 80 y | (n = 86) |
| Admission NIHSS ≤ 25 points | (n = 7) |
| First stroke | (n = 72) |
| mRS prior to stroke ≥ 2 | (n = 53) |
| Death | (n = 1) |
| Missing data | (n = 45) |

There is some overlapping

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 (69.0–77.5) | 68.0 (57.8–75.3) | .471 | 71.0 (62.8–76.0) | 71.5 (60.5–76.0) | 70.0 (62.8–75.5) | .574 |
| Gender, men, n (%) | 33 (48.5) | 8 (57.1) | 25 (46.3) | .469 | 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 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | .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 (3.0–4.0) | 4.0 (3.0–4.0) | .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 (75.5–114.8) | 112.0 (75.5–118.5) | 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 | 226.2 ± 122.9 | 214.7 ± 125.1 | 230.6 ± 125.7 | .715 |

- **FIM** = the functional 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 NIHSS 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 NIHSS 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. 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.

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.
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 of 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.

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