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ORIGINAL REPORT

IMPACT OF REHABILITATION START TIME ON FUNCTIONAL OUTCOMES AFTER STROKE

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Objective: **To investigate the optimum rehabilitation start timing for improved functional outcomes after stroke in Japan.**

Design: **A retrospective database study.**

Subjects: **A total of 140,655 patients with stroke from 1,161 acute hospitals in Japan. Only data for those patients who were discharged alive was included in the analysis.**

Methods: **Activities of daily living were assessed. Comparisons were made using the rehabilitation start day after hospital admission. Reference day 2 was compared with days 1, 3, 4, 5, and 6 or later. Modified Rankin Scale at time of discharge was used as the primary outcome. In addition, cases of ischaemic stroke and haemorrhagic stroke were analysed as separate subgroups.**

Results: **Univariate and multivariate logistic regression analyses showed that starting rehabilitation on day 2 resulted in a better outcome than starting on day 3 or later. There was no significant difference in outcome between starting rehabilitation on days 1 or 2 in all cases and subgroup of patient with infarction stroke. For a subgroup of patients with haemorrhagic stroke, starting rehabilitation on day 2 resulted in a better outcome than starting on day 1.**

Conclusion: **Starting post-stroke rehabilitation on the day of admission or second day of hospitalization may be the optimum timing for functional outcomes. However, for haemorrhagic stroke, starting rehabilitation on the second day of hospitalization may be more effective than on the day of admission.**

Key words: early ambulation; recovery of function; stroke; time factor.

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LAY ABSTRACT

This study examined the effect on functional outcomes of the time after stroke of starting rehabilitation. A large national database was searched for eligible stroke patients, resulting in a total of 140,655 patients from 1,161 hospitals. Starting rehabilitation on the day of admission or second day of hospitalization after stroke was found to be associated with better functional outcomes at discharge than starting rehabilitation on the third day or later. For patients with haemorrhagic stroke, those who started rehabilitation on the second day of hospitalization had better functional outcome at discharge than those who started on the day of admission. Thus, starting rehabilitation on the day of admission or the second day of hospitalization after stroke may be the best timing for improved functional outcomes. However, among patients with haemorrhagic stroke, starting rehabilitation on the second day of hospitalization may result in better outcomes than starting on the day of admission.

Stroke is a major factor in causing functional impairment and often requires more resources for long-term care according to the Comprehensive Survey of Living Conditions in Japan (1). The number of people requiring nursing care and support in Japan's long-term care insurance system has been increasing every year, with more than 6 million elderly people in 2015. In recent years, there has been increasing emphasis on stroke prevention and quality stroke care to control the further expansion of the number of people requiring care (2).

For good-quality stroke care, early rehabilitation after stroke onset has been proposed in several Stroke Treatment Guidelines (3–5). Mechanism that may support the effectiveness of early rehabilitation include restoration of brain function, which promotes neuroplasticity (6), and reduction of bedridden syndrome, infections, deep vein thrombosis, and pressure sores (7). However, some researchers are concerned that starting too early rehabilitation may be harmful. One reason is that a head-up position reduces reperfusion of the penumbra region (8). Another reason is that the destabilization of blood pressure with exercise can inhibit the recovery of brain function (9). In addition, most stroke specialists have concerns about very early rehabilitation, especially in cases of haemorrhagic stroke. A possible reason is that patients with haemorrhagic stroke tend to die early after the attack, although the evidence regarding the timing of rehabilitation is insufficient (10).

Several randomized controlled trials (RCTs) have examined the effectiveness of early rehabilitation, but it remains a controversial topic. Two RCTs have provided evidence that early rehabilitation is effective for phys-

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ical functioning (11, 12), while other RCTs (13, 14) have not found such evidence. The latest multicentre RCT (14) concludes that very early rehabilitation leads to poor outcomes for physical functioning. However, some researchers have criticized the study design due to the short mean difference in rehabilitation start times between the intervention and control groups, being only 4 h. In addition, the variation in the timing of rehabilitation initiation in each RCT makes it difficult to interpret the effectiveness of early rehabilitation. For example, in the AKEMIS study (13), the mean time from stroke onset was set at 13.1 h in the intervention group and 33.3 h in the control group, compared with 18 and 22 h in the AVERT III study, and 27 and 32 h in the VERITAS study (12). Hence, the results of these RCTs may lead many clinicians to query when is the optimum time to start early rehabilitation after stroke.

From the clinician's point of view, it is important to determine whether rehabilitation should be provided very early after stroke, and when is the optimum time to start rehabilitation for good physical functioning outcomes. This study aimed to clarify these clinical questions, by investigating the impact of the timing of rehabilitation initiation after acute stroke on functional outcomes, using patient data from a Japanese multicentre database.

METHODS

Data source

Data were extracted from the Diagnose Procedure Combination (DPC), which represents the Japanese administrative claims data for inpatients. DPC data has been collected since 2003 and includes data from more than 1,000 hospitals in Japan (15). The number of beds included in the DPC system has been estimated to represent 63% of the total capacity for all acute care hospitals in Japan in 2014 (16). The DPC data summarize clinical information, such as age, sex, primary diagnosis, comorbidities at admission, Barthel Index scores at admission and discharge, modified Rankin Scale (mRS) scores before stroke onset and at discharge, and the date and details of clinical treatments, including injections and rehabilitation. All data for each patient is recorded at the time of discharge, and all doctors are required to record their diagnoses. In addition, qualified medical information managers and trained medical clerks are required to accurately record all daily procedures, including the use of any drugs or equipment. Each hospital is incentivized to maintain data quality because accurate data entry is mandatory for receiving DPC-based reimbursements of medical fees (17).

Study population, inclusion and exclusion criteria

Data on adult inpatients (aged 18 years or older) who were discharged from the hospital between 1 April 2012 and 31 March 2016 and whose primary diagnosis was haemorrhagic stroke or ischaemic stroke (International Classification of Diseases, 10th revision (ICD-10): I61x or ICD-63x) were selected for the study. For the analysis, inclusion criteria for the inpatients were: mRS of 0 before stroke; length of stay within 60 days; have undergone stroke rehabilitation; have not had surgery; and have not received tissue plasminogen activator. Exclusion criteria were: patients who transferred from acute care wards to rehabilitation wards in the same hospital, because they were patients in sub-acute care; inpatients who were discharged deceased; and those with missing mRS, Barthel Index, or rehabilitation data.

Baseline variables

Explanatory variables were: patients' age, sex, type of stroke (haemorrhagic stroke or ischaemic stroke), Barthel Index at admission, whether the admission date was a weekday, Japan Coma Scale (JCS) at admission (the JCS is simple coma scale similar to the Glasgow Coma Scale (18)), comorbidities, year of admission, total number of days of rehabilitation intervention, and the date of starting rehabilitation from the day of admission. Patients' age was classified as 18–64, 65–69, 70–74, 75–79, 80–84, and 85 years or older. Barthel Index at admission was classified as 0–24, 25–49, 50–79, and 80–100, as in a previous study (19). Weekdays were defined as days excluding Sunday, Saturday, public holidays including New Year holidays (December 29 to January 3), which were determined by the healthcare fee system in Japan. Comorbidities were obtained with reference to the Elixhauser Comorbidity Index (20) and stroke or stroke sequelae (ICD-10: I61×, I63×, I60×, I69×) were added as cerebrovascular disease. Cases with a suspected diagnosis were not counted as comorbidities. Rehabilitation start dates were classified as day 1, 2, 3, 4, 5, and 6 or later, counting from the date of admission day 1.

Outcome measures and statistical analysis

The primary outcome was modified Rankin Scale at discharge. The mRS is a commonly used scale for measuring the degree of disability in patients who have had a stroke, meaning more severe disability as it increases to 0, 1, 2, 3, 4, 5 and 6, where 0 means no disability and 6 means death (21). The other outcomes are total dose and days of rehabilitation, length of stay, Barthel Index at discharge. Inpatients characteristics and outcomes per day of initial rehabilitation were compared using Kruskal–Wallis test.

To examine the association between date of initial rehabilitation and mRS, univariate and multivariate logistic regression analyses were used. In these analyses, mRS 0–2 (patients who do not require any assistance in daily living) were considered "good" and mRS 3–5 (patients who require some assistance in daily living, but exclude mRS 6) were considered "poor" referring to the AVERT III study. The explanatory variables were the number of days of rehabilitation initiation, with basic characteristics, such as age and sex, as potential confounders. Finally, a subgroup analysis was also performed dividing into haemorrhagic and ischaemic stroke cases. In all the logistic regression models, odds ratios (ORs) and 95% confidential interval (95% CI) were calculated after controlling for basic characteristics. The analysis was examined using a 2-sided significance level of 0.05. Statistical analysis was performed using R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

A total of 187,668 patients with haemorrhagic stroke or ischaemic stroke from the DPC database were selected according to the inclusion criteria. After excluding death discharges and cases with missing data, 140,655

eligible patients from 1,161 hospitals were selected. A detailed flowchart of the patient selection is shown in Fig. 1.

Patient characteristics

Table I shows the patient characteristics at the time of admission for each starting rehabilitation date after

Table I. Patient characteristics

Characteristics	Overall *n* = 140,655	Day 1 *n* = 20,101	Day 2 *n* = 66,247	Day 3 *n* = 23,834	Day 4 *n* = 13,039	Day 5 *n* = 6,826	Day 6 or later *n* = 10,608	*p*-value
Female, *n* (%)	53,032 (37.7)	7,117 (35.4)	24,737 (37.3)	9,124 (38.3)	5,027 (38.6)	2,686 (39.3)	4,341 (40.9)	< 0.001
Age, years, mean (SD)	70.6 (12.4)	70.5 (12.1)	70.5 (12.4)	70.3 (12.6)	70.8 (12.4)	70.6 (12.5)	71.2 (13.0)	< 0.001
Age, years, *n* (%)								
18–64 years	40,785 (29.0)	5,776 (28.7)	19,289 (29.1)	7,147 (30.0)	3,697 (28.4)	1,925 (28.2)	2,951 (27.8)	< 0.001
65–69 years	20,441 (14.5)	3,038 (15.1)	9,746 (14.7)	3,487 (14.6)	1,800 (13.8)	973 (14.3)	1,397 (13.2)	< 0.001
70–74 years	21,378 (15.2)	3,172 (15.8)	10,094 (15.2)	3,547 (14.9)	2,037 (15.6)	1,035 (15.2)	1,493 (14.1)	0.002
75–79 years	21,623 (15.4)	3,127 (15.6)	10,211 (15.4)	3,530 (14.8)	2,028 (15.6)	1,080 (15.8)	1,647 (15.5)	0.158
80–84 years	19,096 (13.6)	2,653 (13.2)	8,913 (13.5)	3,255 (13.7)	1,786 (13.7)	929 (13.6)	1,560 (14.7)	0.01
≥85 years	17,332 (12.3)	2,335 (11.6)	7,994 (12.1)	2,868 (12.0)	1,691 (13.0)	884 (13.0)	1,560 (14.7)	< 0.001
Barthel Index at admission, median (IQR)	50 (0–90)	50 (10–95)	50 (5–95)	45 (0–90)	45 (0–90)	45 (0–85)	30 (0–80)	
80–100, *n* (%)	43,007 (30.6)	6,455 (32.1)	21,164 (31.9)	6,955 (29.2)	3,806 (29.2)	1,935 (28.3)	2,692 (25.4)	< 0.001
50–79, *n* (%)	28,381 (20.2)	4,438 (22.1)	13,969 (21.1)	4,564 (19.1)	2,388 (18.3)	1,315 (19.3)	1,707 (16.1)	< 0.001
25–49, *n* (%)	17,909 (12.7)	2,854 (14.2)	8,399 (12.7)	3,054 (12.8)	1,583 (12.1)	838 (12.3)	1,181 (11.1)	< 0.001
0–24, *n* (%)	51,358 (36.5)	6,354 (31.6)	22,715 (34.3)	9,261 (38.9)	5,262 (40.4)	2,738 (40.1)	5,028 (47.4)	< 0.001
Stroke type								
Haemorrhagic	34,074 (24.2)	3,884 (19.3)	15,596 (23.5)	6,377 (26.8)	3,412 (26.2)	1,794 (26.3)	3,011 (28.4)	< 0.001
Ischaemic	106,581 (75.8)	16,217 (80.7)	50,651 (76.5)	17,457 (73.2)	9,627 (73.8)	5,032 (73.7)	7,597 (71.6)	< 0.001
Japan Coma Scale score at admission, *n* (%)								
JCS0	77,143 (54.8)	11,652 (58.0)	37,162 (56.1)	12,769 (53.6)	6,940 (53.2)	3,627 (53.1)	4,993 (47.1)	< 0.001
JCS1	50,034 (35.6)	7,001 (34.8)	23,658 (35.7)	8,554 (35.9)	4,641 (35.6)	2,380 (34.9)	3,800 (35.8)	0.144
JCS2	10,679 (7.6)	1,211 (6.0)	4,487 (6.8)	2,026 (8.5)	1,126 (8.6)	625 (9.2)	1,204 (11.3)	< 0.001
JCS3	2,799 (2.0)	237 (1.2)	940 (1.4)	485 (2.0)	332 (2.5)	194 (2.8)	611 (5.8)	< 0.001
Admission on a weekday, *n* (%)	99,526 (70.8)	16,510 (82.1)	51,400 (77.6)	10,850 (45.5)	8,098 (62.1)	4,936 (72.3)	7,732 (72.9)	< 0.001
Fiscal year, *n* (%)								
2012	28,817 (20.5)	3,748 (18.6)	12,712 (19.2)	5,051 (21.2)	2,884 (22.1)	1,553 (22.8)	2,869 (27.0)	< 0.001
2013	30,629 (21.8)	4,267 (21.2)	14,213 (21.5)	5,151 (21.6)	2,896 (22.2)	1,573 (23.0)	2,529 (23.8)	< 0.001
2014	40,499 (28.8)	5,826 (29.0)	19,328 (29.2)	6,910 (29.0)	3,711 (28.5)	1,925 (28.2)	2,799 (26.4)	< 0.001
2015	40,710 (28.9)	6,260 (31.1)	19,994 (30.2)	6,722 (28.2)	3,548 (27.2)	1,775 (26.0)	2,411 (22.7)	< 0.001
Comorbidities, *n* (%)								
Cerebrovascular disease	9,942 (7.1)	1,307 (6.5)	4,621 (7.0)	1767 (7.4)	919 (7.0)	505 (7.4)	823 (7.8)	< 0.001
Congestive heart failure	6,439 (4.6)	836 (4.2)	2,835 (4.3)	1141 (4.8)	663 (5.1)	361 (5.3)	603 (5.7)	< 0.001
Cardiac arrhythmias	19,785 (14.1)	2,869 (14.3)	9,242 (14.0)	3,263 (13.7)	1,734 (13.3)	945 (13.8)	1,732 (16.3)	< 0.001
Valvular disease	1,456 (1.0)	227 (1.1)	670 (1.0)	238 (1.0)	145 (1.1)	63 (0.9)	113 (1.1)	0.535
Pulmonary circulation disorders	105 (0.1)	10 (0.0)	43 (0.1)	20 (0.1)	10 (0.1)	3 (0.0)	19 (0.2)	0.002
Peripheral vascular disorders	1,505 (1.1)	202 (1.0)	687 (1.0)	247 (1.0)	139 (1.1)	90 (1.3)	140 (1.3)	0.035
Hypertension	84,881 (60.3)	12,176 (60.6)	40,667 (61.4)	14,426 (60.5)	7,650 (58.7)	3,939 (57.7)	6,023 (56.8)	< 0.001
Paralysis	17,421 (12.4)	2,843 (14.1)	8,335 (12.6)	2,925 (12.3)	1,506 (11.5)	715 (10.5)	1,097 (10.3)	< 0.001
Other neurological disorders	5,501 (3.9)	722 (3.6)	2,459 (3.7)	940 (3.9)	530 (4.1)	301 (4.4)	549 (5.2)	< 0.001
Chronic pulmonary disease	2,787 (2.0)	415 (2.1)	1,347 (2.0)	461 (1.9)	225 (1.7)	138 (2.0)	201 (1.9)	0.238
Diabetes, uncomplicated	25,957 (18.5)	3,978 (19.8)	12,392 (18.7)	4,188 (17.6)	2,362 (18.1)	1,207 (17.7)	1,830 (17.3)	< 0.001
Diabetes, complicated	6,653 (4.7)	815 (4.1)	3,061 (4.6)	1,176 (4.9)	645 (4.9)	391 (5.7)	565 (5.3)	< 0.001
Hypothyroidism	806 (0.6)	107 (0.5)	385 (0.6)	123 (0.5)	79 (0.6)	42 (0.6)	70 (0.7)	0.566
Renal failure	3,380 (2.4)	406 (2.0)	1,489 (2.2)	595 (2.5)	373 (2.9)	200 (2.9)	317 (3.0)	< 0.001
Liver disease	2,727 (1.9)	401 (2.0)	1,303 (2.0)	451 (1.9)	235 (1.8)	124 (1.8)	213 (2.0)	0.706
Peptic ulcer disease excluding bleeding	9,020 (6.4)	1,125 (5.6)	4,165 (6.3)	1,486 (6.2)	955 (7.3)	505 (7.4)	784 (7.4)	< 0.001
AIDS/HIV	13 (0.0)	2 (0.0)	5 (0.0)	3 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)	0.816
Lymphoma	198 (0.1)	20 (0.1)	80 (0.1)	41 (0.2)	21 (0.2)	17 (0.2)	19 (0.2)	0.022
Metastatic cancer	340 (0.2)	41 (0.2)	150 (0.2)	53 (0.2)	34 (0.3)	20 (0.3)	42 (0.4)	0.018
Solid tumour without metastasis	3,644 (2.6)	468 (2.3)	1,656 (2.5)	645 (2.7)	356 (2.7)	221 (3.2)	298 (2.8)	< 0.001
Rheumatoid arthritis/collagen vascular diseases	1,104 (0.8)	131 (0.7)	504 (0.8)	204 (0.9)	118 (0.9)	63 (0.9)	84 (0.8)	0.057
Coagulopathy	488 (0.3)	57 (0.3)	202 (0.3)	87 (0.4)	55 (0.4)	34 (0.5)	53 (0.5)	0.001
Obesity	138 (0.1)	13 (0.1)	71 (0.1)	27 (0.1)	9 (0.1)	9 (0.1)	9 (0.1)	0.356
Weight loss	23 (0.0)	3 (0.0)	11 (0.0)	3 (0.0)	2 (0.0)	1 (0.0)	3 (0.0)	0.947
Fluid and electrolyte disorders	3,260 (2.3)	410 (2.0)	1,532 (2.3)	544 (2.3)	308 (2.4)	199 (2.9)	267 (2.5)	0.001
Blood loss anaemia	28 (0.0)	4 (0.0)	16 (0.0)	6 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0.532
Deficiency anaemia	860 (0.6)	102 (0.5)	414 (0.6)	148 (0.6)	70 (0.5)	44 (0.6)	82 (0.8)	0.085
Alcohol abuse	584 (0.4)	82 (0.4)	277 (0.4)	89 (0.4)	55 (0.4)	28 (0.4)	53 (0.5)	0.717
Drug abuse	10 (0.0)	0 (0.0)	5 (0.0)	3 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.549
Psychoses	915 (0.7)	113 (0.6)	398 (0.6)	159 (0.7)	99 (0.8)	46 (0.7)	100 (0.9)	0.001
Depression	1,246 (0.9)	168 (0.8)	585 (0.9)	204 (0.9)	127 (1.0)	58 (0.8)	104 (1.0)	0.676

JCS: Japan Coma Scale (JCS0: alert JCS1: possible eye-opening, but not lucid, JCS2: possible eye-opening by stimulation JCS3: no eye-opening and coma); SD: standard deviation; IQR: interquartile range.

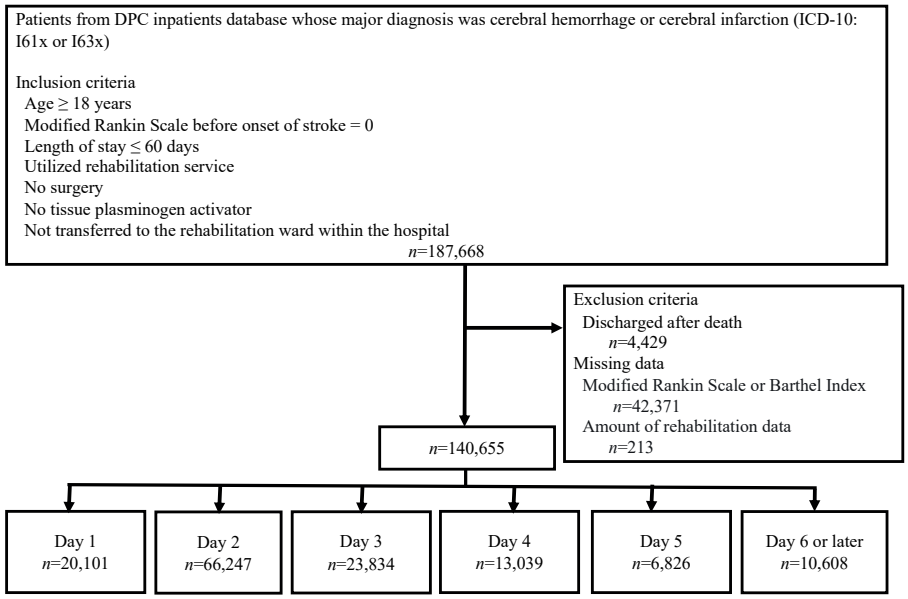

Fig. 1. Patient selections from Diagnosis Procedure Combination (DPC) data. ICD-10: International Classification of Diseases, 10th revision

admission. The mean age of patients was 70.6 years, median Barthel Index at admission 50, and proportion of females 37.5%. The number of patients in whom rehabilitation was initiated on the second day was 66,247, the highest among the 6 categories of rehabilitation start days. Higher age at admission or lower Barthel Index tended to result in a later start to rehabilitation. The proportion of haemorrhagic and ischaemic stroke cases were 24.2% and 75.8%, respectively; the proportion of patients with JCS 0 (alert state) 54.8%. The lower the JSC, the earlier the timing of start of rehabilitation. More than half (54.5%) of patients who started rehabilitation on day 3 were admitted at the weekend. As the year progressed, the trend toward early rehabilitation became stronger.

Amount of rehabilitation and patient outcomes

The amount of rehabilitation and patient outcomes are shown in Table II. The mean total dose was 49.2 units (one unit was defined as 20 min) and the mean length of rehabilitation was 13.5 days. The earlier the rehabil-

Table II. Amount of rehabilitation and patient outcomes

	Overall *n* = 140,655	Day 1 *n* = 20,101	Day 2 *n* = 66,247	Day 3 *n* = 23,834	Day 4 *n* = 13,039	Day 5 *n* = 6,826	Day 6 or later *n* = 10,608	*p*-value
Total dose of rehabilitation, units, mean (SD)	49.2 (47.5)	59.2 (53.7)	52.1 (49.6)	45.8 (43.5)	42.1 (40.1)	38.3 (37.3)	35.9 (36.0)	< 0.001
Total days of rehabilitation intervention, days, mean (SD)	13.5 (9.3)	14.8 (9.7)	13.7 (9.4)	13.2 (9.0)	12.8 (8.8)	12.3 (8.5)	12.0 (8.6)	< 0.001
Length of stay, mean (SD)	20.8 (12.0)	19.4 (11.6)	19.8 (11.7)	21.2 (12.0)	22. 0 (12.2)	22.4 (11.9)	26.6 (12.9)	< 0.001
Barthel Index at discharge, median (IQR)	100 (50–100)	100 (55–100)	100 (55–100)	100 (50–100)	95 (50–100)	95 (50–100)	85 (25–100)	
Barthel Index change, median (IQR)	20 (0–50)	20 (0–50)	20 (0–50)	20 (0–50)	15 (0–50)	15 (0–50)	15 (0–50)	
Modified Rankin Scale at discharge, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–4)	2 (1–4)	2 (1–4)	
Modified Rankin Scale at discharge, *n* (%)								
0	22,777 (16.2)	3,343 (16.6)	10,975 (16.6)	3,778 (15.9)	2,008 (15.4)	1,082 (15.9)	1,591 (15.0)	< 0.001
1	43,435 (30.9)	6,698 (33.3)	21,426 (32.3)	7,003 (29.4)	3,777 (29.0)	1,924 (28.2)	2,607 (24.6)	< 0.001
2	26,403 (18.8)	3,625 (18.0)	12,543 (18.9)	4,529 (19.0)	2,492 (19.1)	1,320 (19.3)	1,894 (17.9)	0.004
3	15,012 (10.7)	2,067 (10.3)	6,882 (10.4)	2,698 (11.3)	1,456 (11.2)	777 (11.4)	1,132 (10.7)	< 0.001
4	23,480 (16.7)	3,201 (15.9)	10,614 (16.0)	4,193 (17.6)	2,324 (17.8)	1,192 (17.5)	1,956 (18.4)	< 0.001
5	9,548 (6.8)	1,167 (5.8)	3,807 (5.7)	1,633 (6.9)	982 (7.5)	531 (7.8)	1,428 (13.5)	< 0.001

Barthel Index change: Barthel Index at discharge minus Barthel Index at admission
Rehabilitation, units: 1 unit equals 20 min of rehabilitation; SD: standard deviation; IQR: interquartile range

Table III. Logistic regression analysis for a favourable outcome (modified Rankin Scale) at discharge

Total number of patients, $n = 140,655$	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Timing of initial rehabilitation						
Day 1	1.01	0.97–1.04	0.849	1.00	0.95–1.04	0.801
Day 2	ref			ref		
Day 3	0.85	0.83–0.88	<0.001	0.90	0.86–0.93	<0.001
Day 4	0.82	0.79–0.86	<0.001	0.85	0.81–0.90	<0.001
Day 5	0.85	0.78–0.86	<0.001	0.82	0.77–0.88	<0.001
Day 6 and later	0.64	0.61–0.67	<0.001	0.71	0.68–0.75	<0.001

OR: odds ratio; 95% CI: 95% confidence interval.

itation day, the more exposure and rehabilitation days were introduced. The mean length of stay was 20.8 days, median Barthel Index at discharge 100, and median mRS at discharge 2. When rehabilitation was introduced earlier, the length of stay tended to be shorter, and the Barthel Index and mRS at discharge higher.

Logistic regression analysis

Table III presents the results of univariate and multivariate logistic regression analyses for favourable mRS at discharge. Referring to day 2, the crude odds ratio (OR) for day 1 was 1.01 (95% CI 0.97–1.04) and the adjusted OR was 1.00 (95% CI 0.95–1.04), which was not significantly different between day 1 and day 2. On the other hand, after day 3, both the crude and adjusted ORs were all significantly below 1, meaning that the outcomes were worse than on day 2. After day 2, the adjusted OR values decreased with later rehabilitation start dates. The c-statistic of the model was 0.85 (95% CI 0.84–0.85).

Subgroup analysis

Table IV shows the result of the same multivariate logistic regression analysis as in Table III, divided into haemorrhagic and ischaemic stroke cases. In the haemorrhagic stroke group, compared with day 2, days 1, 3, and day 6 and later were associated with a significant reduction in adjusted ORs; adjusted ORs on days 4 and 5 were also associated with a reduction in OR, but this was not significant. In the ischaemic stroke group, the adjusted OR on day 1 was 1.04 (95% CI 0.99–1.09), but all other starting rehabilitation days (day 3, 4, 5 and 6, and later) were significantly associated with a reduction in OR. The c-statistics of the models were 0.84 (95% CI 0.84–0.85) in haemorrhagic stroke and 0.79 (95% CI: 0.79–0.80) in ischaemic stroke.

DISCUSSION

This study analysed the effect of initiation of rehabilitation on functional outcomes after stroke. Patients who started rehabilitation on the day of admission and day 2 of hospitalization were found to have better mRS at discharge from hospital than those who started rehabilitation on day 3 or later after hospitalization of hospitalization. Subgroup analysis of the haemorrhagic stroke group found that the mRS at discharge may be best when rehabilitation is started on day 2 of hospitalization.

An earlier RCT study of 42 patients compared the effects of rehabilitation initiated 52 h after onset of the acute phase of ischaemic stroke with rehabilitation initiated 6 days later (22). The results showed that the proportion of favourable outcomes (ranking score 0–2 at 3 months from onset of stroke) was 40% in the early rehabilitation group, and 35% in the late rehabilitation group, but the difference was not significant due to the small number of patients eligible. The results were largely consistent with the trend in the current study, in which the proportion of favourable outcomes (mRS 0–2 at discharge) was 67.8% at day 2 and 57.5% after day 6.

There may be no difference in the association of initial rehabilitation between the day of admission and day 2 of hospitalization. Although there are no previous studies using the same methods, there is

Table IV. Multivariable logistic regression analysis for a favourable outcome (modified Rankin Scale) at discharge as a subgroup analysis

Total number of patients, $n = 140,655$	Haemorrhagic stroke $n = 34,074$			Ischaemic stroke $n = 10,6581$		
	Adjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Timing of initial rehabilitation						
Day 1	0.89	0.82–0.95	0.004	1.04	0.99–1.09	0.136
Day 2	ref			ref		
Day 3	0.91	0.85–0.98	0.008	0.90	0.85–0.94	<0.001
Day 4	0.92	0.85–1.01	0.078	0.83	0.78–0.88	<0.001
Day 5	0.95	0.85–1.07	0.405	0.77	0.71–0.83	<0.001
Day 6 and later	0.87	0.80–0.96	0.005	0.65	0.61–0.69	<0.001

OR: odds ratio; 95% CI: 95% confidence interval.

a study which is similar to the current study in the comparison of rehabilitation start timing: the AKEMIS study (13), which examined outcomes for mRS at 3 months, comparing starting rehabilitation within 24 h of stroke with starting within 24–48 h. No significant difference in outcome was found, which is consistent with the results of the current study. Although not statistically significant, the outcome tended to be worse in the group starting rehabilitation within 24 h. However, this result may be due to the fact that the within 24-h group included patients with more serious stroke and haemorrhagic stroke than the within 24-h group. This previous study did not limit the analyses to cases of ischaemic stroke, whereas the AVERT III trial (14) performed subgroup analyses of ischaemic stroke and haemorrhage. The study found that very early intervention was associated with a better prognosis in cases of ischaemic stroke than in haemorrhagic stroke, which is consistent with the current study. There may be less harm from very early rehabilitation in ischaemic stroke than in haemorrhagic stroke, which justifies the need to consider the timing of initiation of rehabilitation separately in cases of ischaemic stroke and haemorrhagic stroke.

Very early rehabilitation on the day of admission for haemorrhagic stroke may be detrimental. In the AVERT III trial, in the subgroup analysis for haemorrhage cases, the very early rehabilitation group had poorer physical outcomes than the usual care group, which is consistent with the current study. Starting rehabilitation on day 2 seemed to have the best outcome in haemorrhage cases, but the prognosis was not always significantly better than starting on day 3 or later and there was no dose-response relationship between rehabilitation start date and outcomes, as seen in ischaemic stroke. A possible reason for this is that intracranial pressure tends to be higher in haemorrhagic stroke, which leads to a worse prognosis, and stricter blood pressure control is required (23). A 30° bed tilt or systolic blood pressure of 140 mmHg or less was recommended to reduce intracranial pressure (24). Further studies are needed to examine the effects of ultra-early rehabilitation under such strict blood pressure control.

The results of the current study suggest that the optimum time to start rehabilitation after haemorrhagic stroke or ischaemic stroke is on the second day after admission. However, there are several challenges in applying these finding to real-life medical practice. For example, in Japan, some acute care hospitals do not offer rehabilitation on weekends, and stroke patients admitted on a Friday cannot receive rehabilitation within 2 days of admission. This incomplete system of provision of rehabilitation may be due not only to the practice of not providing holiday treatment except for urgent care, but also to a lack of penetration of standards of care, such as the Clinical Path, in hospitals. A questionnaire report (25) from the Japanese Society of Clinical Pathology in 2018 indicates that the percentage of facilities actively using the clinical path is low (9.95% (40/402) in neurology and 27.7% (131/473) in neurosurgery), suggesting that the standardization of stroke care has not progressed. It is hoped that the results of the current study will lead to the introduction of a system for the provision of daily rehabilitation, including weekends, and the active use of the clinical path to improve the quality of care.

Strengths

A major strength of this study was to analyse the optimum timing of starting rehabilitation on functional outcomes (mRS) on a daily basis after admission, which was not explored in previous studies. In addition, this study used real-world large datasets to analyse 140,655 patients over the last 4 years (2012–2016), including weekend hospitalization, which would be less feasible in RCT studies.

Limitations

There are several limitations to this study. First, the DPC data did not include information on details of the rehabilitation. It was not clear whether early rehabilitation meant "out-of-bed", as defined in the AVERT studies (16). Secondly, the current study assessed mRS at discharge (mean length of stay 20.8 days), whereas some several previous studies (13, 14, 26, 27) evaluated mRS in 3 months after stroke onset. In general, physical function after stroke recovers rapidly for the first 3 months (28), then recovers gradually for the next 3 months and reaches a plateau after 6 months (29, 30). Therefore, the result of this study might not reflect long-term functional outcomes. Thirdly, the lack of adequate adjustments for patient severity may represent a confounding factor due to the limitation of the data. The timing of initial rehabilitation is often delayed in patients with severe stroke, which can result in poor functional outcomes (31). Age, JCS, and Barthel Index scores at admission were used to perform severity adjustments; however, additional clinical information, such as stroke severity (NIHSS score (32, 33)), is necessary to perform appropriate severity adjustments. Fourthly, the results of the current study may be biased if death at discharge is included; however, an additional analysis, including cases of death, showed almost the same estimated results and conclusions (Table SI[1]). Fifthly, selection bias could occur due to the exclusion of patients with

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2775

tissue plasminogen activator (tPA) and missing mRS or Barthel Index data, which may indicate that these results are more applicable to acute stroke patients who do not use tPA or who are measured for mRS. Sixthly, the results of the current study were derived from an observational database study and, therefore, can only show an association without providing evidence of causation. Finally, outcomes were examined on each day from hospitalization to the start day of rehabilitation, whereas previous studies examined the outcomes based on hours of starting rehabilitation from onset of stroke; the difference between these might bias interpretation of the results.

Conclusion

This study analysed the impact of the timing of start of rehabilitation on functional outcomes in patients after stroke in Japan. The results suggest that the optimal timing of initial rehabilitation after stroke may be on the day of admission or day 2 of hospitalization. In haemorrhagic stroke, starting rehabilitation on the day of admission may result in a less favourable functional outcome compared with starting on day 2 of hospitalization.

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