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Article

Restoring Upper Limb Function by Combined Repetitive Transcranial Magnetic Stimulation and Occupational Therapy in Patients with Chronic Stroke: A Stratified Analysis Factoring the Severity of Motor Paralysis using a Multicenter Cohort Study Database

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Abstract: Repetitive transcranial magnetic stimulation (rTMS) with intensive occupational therapy improves upper limb motor paralysis and activities of daily living after stroke; however, amount of improvement according to paralysis severity remains unverified. Target activities for daily living using patients' upper limb functions can be established by predicting the amount of change after treatment for each severity level of upper limb motor paralysis and further aid practice planning. This study estimated post-treatment score changes for each severity level of motor paralysis (no, poor, limited, notable, and full) stratified according to Action Research Arm Test (ARAT) scores before combined rTMS and intensive occupational therapy. Severity of motor paralysis was the fixed factor for analysis of covariance, delta (post-pre) of the scores was the dependent variable. Ordinal logistic regression analysis was used to compare changes in ARAT subscores in patients, divided according to paralysis severity before treatment. A multicenter retrospective cohort dataset analyzed 907 patients with stroke hemiplegia. Largest treatment-related changes in scores were observed in the Limited recovery group for upper limb motor paralysis and Full recovery group for quality-of-life activities using paralyzed upper limb. These results will help predict treatment effects and determine exercises and goal movements for occupational therapy after rTMS.

Keywords: stroke; occupational therapy; activities of daily living; goal setting; transcranial magnetic stimulation: upper extremity; motor paralysis

1. Introduction

Motor paralysis after stroke limits patients' activities of daily living (ADL) and reduces their quality of life [1,2]. Recently, noninvasive brain stimulation therapy has been developed to improve patients' motor paralysis and ADL, and its effectiveness has been demonstrated [3,4]. The treatment of upper limb motor paralysis involves modulation of interhemispheric inhibition and induction of neuroplasticity in the cerebrum. Novel intervention using repetitive transcranial magnetic stimulation (rTMS) in combination with intensive occupational therapy (NEURO) has been used recently [5]. In patients with stroke hemiplegia, high-frequency rTMS has been applied to the hemisphere ipsilateral to the paralysis to increase excitability [6], and low-frequency rTMS has been applied to the contralateral hemisphere to decrease interhemispheric inhibitory connections [7,8] with the damaged cortex [9], or both high-frequency rTMS and low-frequency rTMS are applied [10]. Repetitive currents are induced in the brain cortex to produce long-term changes in cortical excitability. In acute patients, high-frequency (10 Hz) rTMS applied to the impaired motor cortex activates the motor cortex and improves paralysis [11,12]. In occupational therapy after rTMS, patients in whom the activation of the interhemispheric inhibitory motor cortex has been adjusted are prescribed repetitive joint movements to promote use-dependent plasticity in the brain, aiming to restore motor paralysis and improve ADL [13]. NEURO is an effective treatment for improving upper limb dysfunction and impairments in ADL in patients with chronic stroke 6 months after the onset of stroke, and its therapeutic effect has been shown to be unaffected by the type of stroke (cerebral hemorrhage or cerebral infarction) [14].

The goal of NEURO is to improve the quality of movement of the patient's paralyzed upper limb by allowing it to be used in ADL. Since the effectiveness of NEURO depends on the severity of motor paralysis, therapists set the exercises and target movements to be provided with reference to the patient's pre-treatment upper limb function assessment score. The Fugl–Meyer Assessment of the Upper Extremity (FMAUE) and the Action Research Arm Test (ARAT) are used for assessing upper limb motor function outcomes in NEURO [15]. These evaluation methods have been shown to have high measurement quality and clinical usefulness. A previous study has been conducted to estimate the post-treatment score from the pre-NEURO FMAUE score [16]. The ARAT is a functional upper limb assessment tool used in patients with post-stroke hemiplegia and is characterized by its ability to reflect the patient's activity [17]. Since the ARAT consists of object manipulation and reaching tasks, the occupational therapist (OT) plans exercises by estimating the ADLs in which the patient can use their hands based on the obtained assessment results. Since the ARAT score correlates with the Motor activity log, which investigates the use of the paralyzed limb in ADLs, OTs who help patients improve their activity limitations can use the score as a reference value for the content of exercises and goal setting [18,19]. If ARAT scores are predicted to improve with NEURO, it will be easier for OTs to pre-determine the content of ADL exercises and develop goals for ADLs that patients can achieve.

Patients with mild-to-moderate motor paralysis with FMAUE scores of ≥43 have higher interhemispheric inhibition from the healthy hemisphere to the sick hemisphere, and it is predicted that the therapeutic effect of upper limb practice in the presence of rTMS-induced changes in synaptic transmission efficiency is dependent on the severity of the patient's motor paralysis [20]. If the post-treatment effects according to the severity of motor paralysis can be predicted using pre-treatment ARAT scores, the target movements of patients with high accuracy can be set. In addition, shared goals between therapist and patient will promote treatment effectiveness [21]. Therefore, this study aimed to estimate the amount of change in ARAT scores for each level of severity of motor paralysis classified according to the ARAT score before NEURO.

2. Materials and Methods

2.1. Study design

This study was based on the database accumulated and managed by the Department of Rehabilitation, Tokyo Jikei University School of Medicine. In this multicenter retrospective cohort study, we reviewed the medical records of patients with stroke from February 2017 to March 2021 at six different hospitals certified as NEURO implementation facilities in Japan. These included Izumi Memorial Hospital, Shimizu Hospital, Nishi-Hiroshima Rehabilitation Hospital, General Tokyo Hospital, Kyoto O'Hara Memorial Hospital, and Tokyo Jikei University Hospital. We evaluated the therapeutic effect of NEURO on patients by providing a certain amount of selected functional exercises based on the severity of the patients' motor paralysis. We also attempted to define a research protocol in this study.

2.2. Ethics statements

Patients were not required to provide informed consent because the analysis used anonymous clinical data that were obtained after each patient agreed to NEURO by providing written consent. This study was approved by the Jikei University School of Medicine Ethics Committee (approval number 24-295-7061).

2.3. Participants

Patients were blinded to their group assignment, the study hypothesis, and primary outcome measures. Patients receiving NEURO during the study period, those aged ≥18 years, diagnosed with stroke for >12 months, and those without cognitive impairment with a pre-treatment Mini Mental State Examination score >26 were included. The exclusion criteria were as follows: no data on the ARAT scores, subarachnoid hemorrhage, arteriovenous malformation, brain tumor, diagnosis of childhood paralysis, and bilateral motor paralysis.

2.4. Sample size

The ARAT score was used as a quantitative variable, and variation in the ARAT score among the five groups (see *Statistical analysis* for pre-treatment severity) was compared using G*power with analysis of covariance (ANCOVA) (F-test, main effects) using the following values: effect size f=0.25, α=0.05, 1-β=0.80, number of groups=5, and number of covariates=5. Therefore, the total number of patients required was 242 (49×5 groups).

2.5. rTMS combined with Occupational therapy

All patients were hospitalized for 15 days and received rTMS and occupational therapy [5]. Patients received a maximum of six sessions of occupational therapy per day, each session lasting 20 min. Physiotherapy was occasionally prescribed for two to three of the six sessions depending on the patient's complaints and state of physical function. The allocation of occupational therapy and physical therapy sessions was determined by the physician in charge. Occupational therapy was conducted as one-to-one training. The goal of occupational therapy was to regain the use of the paralyzed upper limb in daily life. The OT determined the target movements together with the patient based on the patient's wishes and the results of the physical function assessment. To achieve the goal, the OT prescribed the following to the patients: functional exercises for the proximal and distal parts of the upper limb, skillful movement exercises using objects, daily living exercises to use the paralyzed side, lifestyle guidance to promote the use of the paralyzed side, and self-guided exercises to improve the motor paralysis [13,22].

Patients received rTMS daily, excluding holidays [5,13,22]. A 70-mm figure-eight coil, attached to a MagPro R100 stimulator (MagVenture Company, Farum, Denmark) was used for rTMS during each session using one of the following methods: (1) focal 1-Hz rTMS applied to the contralesional hemisphere over the primary motor area, according to previous studies, (2) rTMS over the hand area of the ipsilesional primary motor cortex (M1) for a duration of 30 trains of 50 pulses with 25-s intervals at 10 Hz and 90% resting motor threshold (RMT) (total, 1500 pulses/day), (3) bilateral sequential stimulation involving low-frequency (1 Hz) contralesional stimulation followed immediately by high-frequency (10 Hz) stimulation in the ipsilesional primary motor cortex, or (4) theta-burst stimulation; the protocol consisted of bursts containing three pulses at 50 Hz, repeated at 5 Hz intervals (20 ms between each stimulus) but applied in 2-s trains repeated every 10 s for a total of 190 s (total, 600 pulses). The attending physician defined the stimulation intensity as the lowest intensity, which was set to 90% of the RMT for the first dorsal interosseous muscle.

2.6. Outcome

The change in ARAT scores was used to assess the primary outcome. The ARAT is an upper extremity function assessment developed based on the upper extremity function test [23]. The ARAT consists of four subtests—grasp, grip, pinch, and gross movement [24]. For the grasp subtest, a block, cricket ball, and grinding stone are used; for the grip subtest, a glass, cylinder, and washer are used; and for the pinch subtest, a metal ball and marble are used. In these subtests, the patient moves an object to a specified position or performs a movement with an object according to the instructions. In gross movement, patients reach toward the back of the head, the top of the head, and the mouth with their hands. The ARAT is scored on a 4-point ordinal scale, wherein 0=can perform no part of test, 1=performs test partially, 2=completes test but takes abnormally long time or has great difficulty, and 3=performs test normally. With reference to a 57-point scale, ARAT scores of 0-10, 11-21, 22-42, 43-54, and 55-57 are construed to represent no, poor, limited, notable, and full recovery capacity, respectively [25].

The change in Jikei Assessment Scale for Motor Impairment in Daily Living (JASMID) scores was used to assess the secondary outcome. The JASMID is a patient-reported measure to investigate the use of the upper limb on the paralyzed side in ADL among patients with stroke hemiplegia [26]. A similar assessment is the Motor activity log, but the JASMID has questions adapted to the Japanese lifestyle [27]. Patients are asked to respond to each question on a 5-point quantitative scale (0=never, 3=sometimes, and 5=always in terms of the amount of use of the paralyzed upper limb) and on another 5-point qualitative scale (0=almost no use, 3=feeling moderate difficulty, and 5=feeling no difficulty at all in terms of satisfaction with the use of the upper limb). The quantity and quality scores are calculated based on the scores of a total of 20 questions.

2.7. Statistical analysis

Patients' ARAT scores were divided into five groups (no, poor, limited, notable, and full) according to pre-treatment severity and used as fixed factors in ANCOVA. The severity of paralysis is a predictor of the ARAT score [25]. The ARAT score was converted from total and part A: grasp, B: grip, C: pinch, and D: gross movement subscores into a delta value (post-treatment minus pre-treatment), which was used as a dependent variable in ANCOVA. Ordinal logistic regression analysis was used to compare changes in ARAT subscores in patients categorized according to the pre-treatment severity of paralysis.

Recovery of upper limb motor paralysis is affected by neuromodulation with rTMS and spasticity treatment [28]. Age, sex, side of paralysis, and time since onset were used as potential confounders when comparing the effects of NEURO between the groups in a previous study [29]. Thus, these factors were used as confounders in the covariates of ANCOVA and ordinal logistic regression analysis. JASP 0.16 (retrieved from https://jasp-stats.org/) was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Participants

In total, 2022 patients with stroke at all six hospitals who met the NEURO eligibility criteria were treated. ARAT data were unavailable for 1096 patients, and 19 patients who met the exclusion criteria were excluded. Therefore, the final analysis included 907 patients (Figure 1). Variations in the total ARAT score (mean±standard deviation) before and after NEURO for each severity group were as follows: hospital A, 3.6±4.2; hospital B, 1.7±4.9; hospital C, 3. 2±4.0; hospital D, 2.8±4.4; hospital E, 3. 4±5.1; and hospital F, 3.7±5.1.

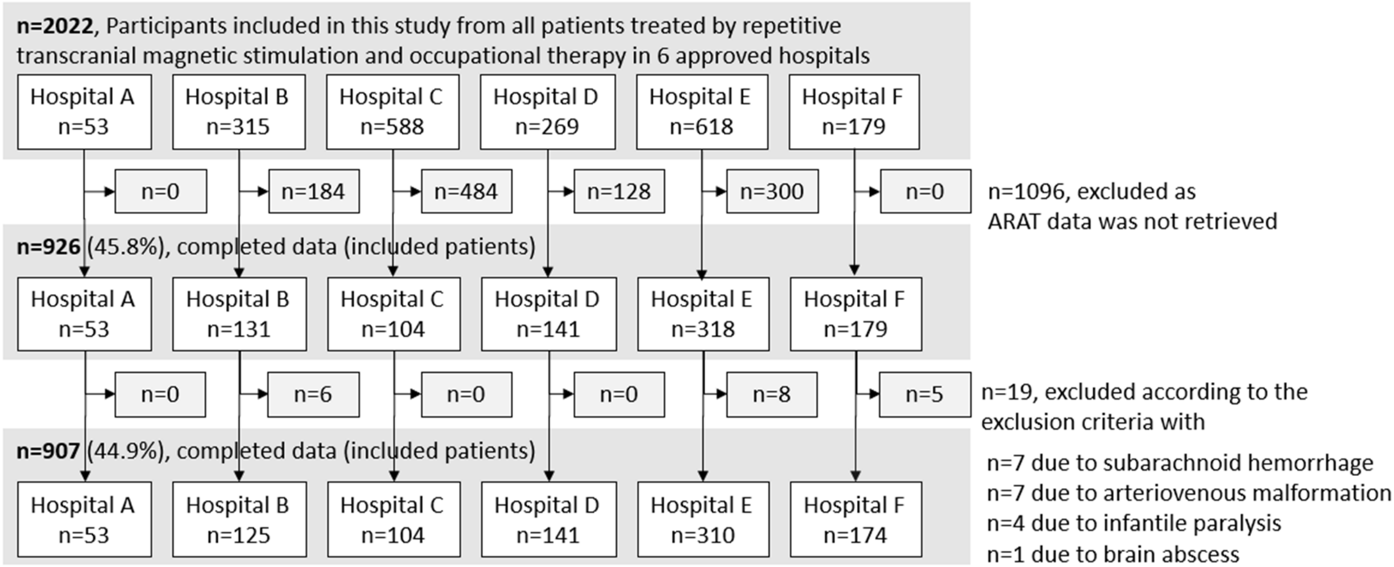

Figure 1. Selection procedure of patients. ARAT, Action Research Arm Test.

Table 1. Clinical characteristics of analyzed patients.

Characteristics		All (n=907)
Age (years)		63 [53, 70]
Sex	Female	297 (33)
	Male	610 (67)
Paralyzed hand	Left	395 (44)
	Right	512 (56)
Dominant hand	Left	44 (5)
	Right	861 (95)
Laterality in the paretic and dominant hand	Bilateral	2 (0.2)
	Ipsilateral side	411 (45)
	Contralateral side	496 (54)
Diagnosis	CI	465 (51)
	ICH	442 (49)
Time from onsets (months)		40 [22, 68]
rTMS stimulation methods	Low frequency	708 (78)
	High frequency	1 (0.1)
	Theta burst	198 (22)
Treatment by botulinum toxin A or xylocaine	Treatment	900 (99)
	No treatment	7 (0.8)
Pre-treatment ARAT score	Total	22 [8, 38]
Pre-treatment JASMID score	Quantity	34 [20, 57]
	Quality	31 [20, 50]

Values are presented as n (%) or median [25th, 75th percentile]. CI, cerebral infarction; ICH, intracranial hemorrhage; rTMS, repetitive transcranial magnetic stimulation; ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living. Repetitive transcranial magnetic stimulation was set at 1 Hz for low frequency, 10 Hz for high frequency, and theta burst for alternative methods. n=907.

3.2. Descriptive data

The clinical characteristics of patients are presented in Table 1. Patients were categorized into the “No” recovery group, 275 patients (30%); “Poor” recovery group, 167 patients (18%); “Limited” recovery group, 269 patients (30%); “Notable” recovery group, 84 patients (9%), and “Full” recovery group, 112 patients (12%). rTMS included low-frequency stimulation on the intact hemisphere of the brain in 708 patients (77.9%), high-frequency rTMS on the lesion side of the brain in one patient (0.1%), and theta burst stimulation on the intact side in 198 patients (21.8%). Seven patients (0.8%) were treated with botulinum toxin A or xylocaine during NEURO.

3.3. Outcome data

The clinical characteristics of patients according to ARAT severity classifications are presented in Table 2. The total ARAT scores (median [first to third quarter]) before treatment were 4 [3, 6] in the No recovery group, 16 [13, 18] in the Poor recovery group, 30 [26, 36] in the Limited recovery group, 48 [45, 51] in the Notable recovery group, and 57 [56, 57] in the Full recovery group. The JASMID quantity and quality scores were the highest in the Full recovery group and the lowest in the No recovery group. The results of changes in ARAT and JASMID scores for patients classified by ARAT severity are shown in Table 3.

Table 2. Characteristics of analyzed patients according to ARAT severity classification.

Characteristics		Recovery capacity on the ARAT				
		No	Poor	Limited	Notable	Full
Patients (n)		275 (30)	167 (18)	269 (30)	84 (9)	112 (12)
Age (years)		63 [53, 70]	66 [54, 71]	61 [52, 69]	64 [55, 70]	63 [54, 69]
Sex	Female	109 (40)	58 (35)	75 (28)	29 (35)	26 (23)
	Male	166 (60)	109 (65)	194 (72)	55 (65)	86 (77)
Paralyzed hand	Left	129 (47)	74 (44)	108 (40)	39 (46)	45 (40)
	Right	146 (53)	93 (56)	161 (60)	45 (54)	67 (60)
Dominant hand	Left	19 (7)	3 (2)	9 (3)	5 (6)	5 (6)
	Right	256 (93)	163 (98)	259 (96)	79 (94)	79 (94)
	Bilateral	0 (0)	1 (1)	1 (0.4)	0 (0)	0 (0)
Laterality in the paretic and dominant hand	Ipsilateral side	136 (49)	76 (46)	112 (42)	40 (48)	47 (42)
	Contralateral side	139 (51)	91 (54)	157 (58)	44 (52)	65 (58)
Diagnosis	CI	145 (53)	89 (53)	138 (51)	47 (56)	46 (41)
	ICH	130 (47)	78 (47)	131 (49)	37 (44)	66 (59)
Time from onsets (months)		45 [27, 70]	40 [24, 63]	34 [19, 66]	37 [21, 78]	39 [18, 63]
rTMS stimulation methods	Low frequency	222 (81)	124 (74)	206 (77)	67 (80)	89 (79)
	High frequency	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
	Theta burst	52 (19)	43 (26)	63 (23)	17 (20)	23 (20)
Treatment by botulinum toxin A or xylocaine	Treatment	2 (0.7)	1 (0.6)	2 (0.7)	1 (1)	1 (1)
	No treatment	273 (99)	166 (99)	267 (99)	83 (99)	111 (99)
Pre-treatment ARAT score	Total	4 [3, 6]	16 [13, 18]	30 [26, 36]	48 [45, 51]	57 [56, 57]
Pre-treatment JASMID score	Quantity	20 [19, 26]	28 [20, 38]	41 [28, 58]	60 [40, 77]	73 [59, 91]
	Quality	20 [20, 25]	26 [20, 35]	25 [37, 51]	48 [36, 63]	63 [48, 78]

Values are presented as n (%) or median [25th, 75th percentile]. ARAT, Action Research Arm Test; CI, cerebral infarction; ICH, intracranial hemorrhage; rTMS, repetitive transcranial magnetic stimulation; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living. Repetitive transcranial magnetic stimulation was set at 1 Hz for low frequency, 10 Hz for high frequency, and theta burst for alternative methods. Pre-treatment ARAT scores of 0-10 represent no upper limb capacity, scores of 11-21 represent poor capacity, scores of 22-42 represent limited capacity, scores of 43-54 represent notable capacity, and scores of 55-67 represent full upper limb capacity. n=907.

3.4. Main results

Delta values of the total ARAT score before and after NEURO were analyzed using ANCOVA according to the severity of paralysis. The results are displayed in Table 4. Delta values (mean±standard deviation) were 2.4±4.2 in the No recovery group, 3.9±4.8 in the Poor recovery group, 4.6±5.8 in the Limited recovery group, 3.0±4.2 in the Notable recovery group, and 0.3±1.3 in the Full recovery group (Table 3), indicating a significant main effect by group (F=18.677, p<0.001, η^2=0.077; age, sex, laterality in the paretic and dominant hand, and time since onset were adjusted for as covariates). This main effect remained unchanged when adjusted for the pre-treatment ARAT total score, indicating a significant main effect (F=18.545, p<0.001, η2=0.076). A post-test for the change in total ARAT scores showed that the Limited and Notable recovery groups displayed a more significant change in total ARAT scores than the Full recovery group (p=0.024 and p=0.022).

Table 3. Outcome scores of analyzed patients according to ARAT severity classification.

Index of measurements		ARAT severity classification				
		No	**Poor**	**Limited**	**Notable**	**Full**
Δ ARAT	Total	2.4±4.2	3.9±4.8	4.6±5.8	3.0±4.2	0.3±1.3
	A. grasp	0.9±2.4	1.2±2.2	1.2±2.2	0.5±1.6	0.0±0.5
	B. grip	0.6±1.4	1.0±1.7	0.9±1.8	0.5±1.8	0.0±0.3
	C. pinch	0.3±0.9	1.2±2.1	2.0±3.0	1.6±2.9	0.2±1.1
	D. gross movement	0.5±1.1	0.6±1.2	0.6±1.3	0.3±1.1	0.1±0.5
Δ JASMID	Quantity	2.2±10.9	3.3±14.7	4.6±12.0	5.1±15.6	4.4±15.5
	Quality	1.6±10.5	3.6±11.8	4.5±10.0	5.5±11.2	7.2±12.9

Values are presented as mean±standard deviation. ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living. Pre-treatment ARAT scores of 0-10, 11-21, 22-42, 43-54, and 55-57 represented no, poor, limited, notable, and full recovery capacity, respectively. n=907.

In the ARAT subscore analysis, there was a significant main effect of the group on delta values for subscores A-D (p<0.05, adjusted for all covariates; Table 4). The post-test results showed that in terms of the ARAT total score, the change in the Poor and the Limited recovery groups was significantly greater than that in the No recovery group (p=0.034 and p<0.001, Figure. 2-a). Regarding the ARAT grasp score, the change in the No, Poor, and Limited recovery groups was significantly greater than that in the Full recovery group (p=0.005, p<0.001, and p<0.001, respectively, Figure 2-b). Further, in terms of the ARAT grip score, the change in the Poor and Limited recovery groups was significantly greater than that in the Full recovery group (p<0.001 and p<0.001, respectively, Figure. 2-c). In terms of the ARAT pinch score, the change in the Limited recovery group was significantly greater than that in the No, Limited, and Full recovery groups (p<0.001, p=0.002, and p<0.001, respectively Figure 2-d). Regarding the ARAT gross movement scores, the change in the No, Poor, and Limited recovery groups was significantly greater than that in the Full recovery group (p=0.014, p=0.012, and p=0.004, respectively, Figure 2-e). In terms of the post-test ARAT subscores, the change in the Notable recovery group was not significantly different from that in the Poor and Limited recovery groups. The JASMID score of hand usage (quantity, F=2.02, p=0.089, η2=0.009) had no main effect of the group on the delta value. The JASMID score of satisfaction had a main effect of group on the delta values (quality, F=6.66, p<0.001, η2=0.028, Table 4). According to the multiple comparison test, the JASMID score of quality had a significantly greater main effect of group on the delta value in the Limited and Full recovery groups than in the No recovery group (p=0.032 and p<0.001, respectively, Figure. 2-f).

Next, stratified analysis was performed using ordinal logistic regression analysis to factor the change in ARAT and JASMID scores into the severity of motor paralysis prior to treatment—Akaike's Information Criterion (AIC)=4792, grasp (x^2=56.0, p<0.001, AIC=3161), grip (x^2=58.2, p<0.001 , AIC=2728), pinch (x^2=135, p<0.001, AIC=3082), gross movement (x^2=31.1, p<0.001 , AIC=2192), JASMID quantity (x^2=36.8, p<0.001, AIC=6072), and quality (x^2=35.5, p<0.001, AIC=5935) were significantly model fit by severity of motor paralysis. The coefficients of variation and odds ratios were calculated for the ARAT total score and subscores A-D and for the change in JASMID quantity and quality scores with respect to the data of the no recovery group for each level of severity (Table 5).

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Table 4. Differences between pre- and post-treatment ARAT and JASMID scores using analysis of covariance.

Index of measurements		F	*p*	η2
Δ ARAT	Total	18.68	<0.001	0.077
	A. grasp	7.48	<0.001	0.032
	B. grip	7.27	<0.001	0.031
	C. pinch	29.41	<0.001	0.116
	D. gross movement	4.82	<0.001	0.021
Δ JASMID	Quantity	2.02	0.089	0.009
	Quality	6.66	<0.001	0.028

Analysis of covariance was used. Statistical significance was set at 0.05 (n=907). ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living.

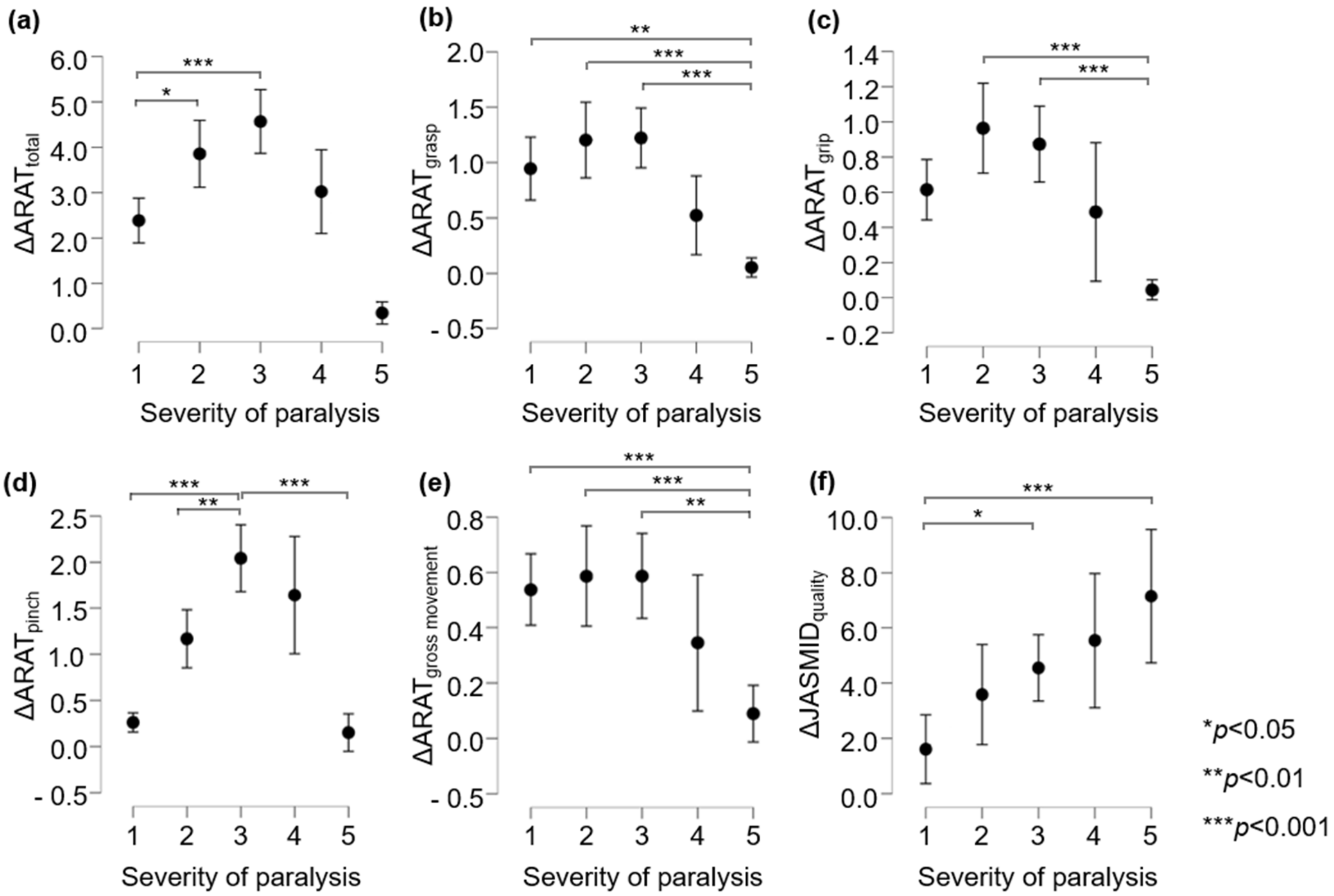

Figure 2. Comparison of change in upper extremity function according to ARAT scores. Statistical significance was set at $p<0.05$ for Scheffé's multiple comparisons (n=907). ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living.

Regarding total ΔARAT, when the coefficient of variation of the No recovery group was 1, that of the Poor recovery group was 0.9, that of the Limited recovery group was 1.1, and that of the Notable recovery group was 0.8, the odds ratio was estimated to be 2.53 times of No recovery group for the Poor recovery group, 3.08 times of No recovery group for the Limited recovery group, and 2.22 times of No recovery group for the Notable recovery group. The coefficient of variation for the Full recovery group was -0.9, and the odds ratio was 0.42. Regarding ΔJASMID, when the coefficient of variation of the No recovery group was 1, that of the Limited recovery group was 0.6, that of the Notable recovery group was 0.8, and that of the Full recovery group was 0.8, the odds ratio was estimated to be 1.84 times of No recovery group for the Limited recovery group, 2.30 times of No recovery group for the Notable recovery group, and 2.23 times of No recovery group for the Full recovery group.

Table 5. Comparison of post-treatment change in ARAT and JASMID scores using ordinal logistic regression analysis.

Index of measurements		Predictors	Coefficient	*p*	Odds ratio	95% confidence interval	
						Lower	Upper
ARAT	Total	Poor	0.9	<0.001	2.53	1.79	3.56
		Limited	1.1	<0.001	3.08	2.26	4.21
		Notable	0.8	<0.001	2.22	1.45	3.40
		Full	-0.9	<0.001	0.42	0.29	0.61
	A. grasp	Poor	0.6	0.002	1.80	1.25	2.59
		Limited	0.6	<0.001	1.79	1.30	2.47
		Notable	0.1	0.734	1.08	0.69	1.70
		Full	-0.8	<0.001	0.44	0.29	0.67
	B. grip	Poor	0.6	0.001	1.86	1.28	2.70
		Limited	0.6	<0.001	1.82	1.31	2.53
		Notable	0.2	0.382	1.24	0.76	1.99
		Full	-0.8	<0.001	0.45	0.29	0.69
	C. pinch	Poor	1.0	<0.001	2.75	1.90	3.99
		Limited	1.7	<0.001	5.43	3.86	7.67
		Notable	1.5	<0.001	4.52	2.80	7.26
		Full	-0.1	0.600	0.89	0.57	1.38
	D. gross movement	Poor	0.2	0.344	1.21	0.82	1.77
		Limited	0.3	0.120	1.31	0.93	1.84
		Notable	-0.3	0.325	0.77	0.46	1.28
		Full	-1.0	<0.001	0.38	0.23	0.61
JASMID	Quantity	Poor	0.3	0.047	1.40	1.00	1.96
		Limited	0.5	0.001	1.64	1.22	2.20
		Notable	0.8	<0.001	2.16	1.38	3.36
		Full	0.3	0.173	1.32	0.89	1.99
	Quality	Poor	0.3	0.055	1.39	0.99	1.96
		Limited	0.6	<0.001	1.84	1.37	2.47
		Notable	0.8	<0.001	2.30	1.49	3.55
		Full	0.8	<0.001	2.23	1.49	3.34

Ordinal logistic regression analysis was used. Statistical significance was set at 0.05 (n=907). Data from the No recovery group was used as a reference for the other groups. ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living. Pre-treatment ARAT scores of 0-10 represent no upper limb capacity; scores of 11-21 represent poor capacity; scores of 22-42 represent limited capacity; scores of 43-54 represent notable capacity; and scores of 55-67 represent full upper limb capacity.

4. Discussion

In this study, the amount of change in ARAT was calculated for each level of severity of motor paralysis classified according to the ARAT score before NEURO. The results indicated that patients in the Limited recovery group showed the most significant improvement in upper limb motor paralysis with NEURO. In a previous study, patients with FMAUE scores of ≥43 had higher interhemispheric inhibition from the healthy hemisphere to the sick hemisphere [20]. In the present study, rTMS was applied to the intact hemisphere in 99% of patients. The higher interhemispheric inhibition in the Limited recovery group and higher excitability of the primary motor cortex or supplementary motor cortex on the lesion side using rTMS may be the reasons for the more significant improvement of upper limb motor paralysis by the subsequent occupational therapy [20,30].

In the present study, the amount of change in the frequency of hand use did not differ according to the severity of motor paralysis, but the quality of movement was the most improved in the Full recovery group. A phenomenon termed "Learned non-use hand" affecting the paretic arm or hand occurs in patients with stroke paraplegia due to the continuous disuse of the paralyzed upper limb in their daily lives [31,32]. In the present study, the Full recovery group had the highest scores in the pre-treatment evaluation and had less functional impairment of the upper limb than the other groups. In the intensive inpatient rehabilitation program, in which OTs provide appropriate practice and instruction in ADL, the amount of improvement in the frequency of hand use did not differ by severity, yet the Full recovery group was presumably more satisfied with the use of their hands and improved qualitatively than the other groups. In particular, the rehabilitation of these patients was more effective than that of patients in the other groups. The effectiveness of rehabilitation is enhanced when patients themselves are aware of the motor functions they need to perform to acquire the ADL set by them and the therapist [33,34]. The use of the results obtained in this study as a reference value for determining the content of occupational therapy exercises and goals of ADL to be used in conjunction with rTMS is summarized in Appendix.

The No recovery group was predicted to improve the ARAT grasp and gross movement scores by NEURO more significantly than the other groups. However, the quality of movement with the paralyzed upper limb was predicted to be less improved. Our results are consistent with the findings of previous studies reporting that patients with severe motor paralysis regained function in the proximal part of the upper limb in previous studies [35,36]. Regarding occupational therapy included in NEURO, it can be inferred that ADL exercises that frequently use shoulder and elbow movements are suitable for patients with severe motor paralysis because they improve the function of the proximal part of the upper limbs. In addition, it is recommended to practice movements with the paralyzed upper limb considering the patient's wishes and set up target movements to improve the quality of hand use. In the ARAT, the grasp task includes the rotation of the forearm, and the gross movement task includes reaching the patient's own body. For the target daily activities, it is suggested to use the function of the proximal part of the upper limb to press a plate, paper, or a book on a desk, a task that includes inward movement of the forearm. Similarly, even in the case of reduced hand dexterity, if patients can reach their own body, they can aim to acquire movements such as pressing an upper garment when opening and closing a zipper, washing the upper limb and fingers of the non-paralyzed side, stretching wrinkles of clothes, and removing dust from clothes [37,38].

The Poor recovery group was more likely to show improvement in ARAT grasp and grip scores using NEURO. However, it was less likely to show improvement in ARAT pinch scores. It is assumed that improvement in hand function is necessary to improve the use of the paralyzed upper limb and the quality of movement of the patients in the Poor recovery group. The ARAT grip task includes the task of holding the forearm in the middle position or from the medial to the external rotation position. In occupational therapy, we expect that the grip score will improve. The target movements include grasping a plastic bottle with the paralyzed limb, opening and closing a sliding door, holding a

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toothbrush with the paralyzed limb when applying toothpaste, flipping a switch or pressing an elevator button within reach using the paralyzed limb, and grasping a cellphone with the paralyzed hand [39,40].

Since the Limited recovery group showed the most promising improvement in ARAT scores using NEURO, the target movement practice items should be defined by estimating the amount of improvement in grasp, grip, gross movement, and pinch. In rehabilitation, an improvement in motor function score does not always directly lead to an improvement in the amount of use or quality of movement of the paralyzed upper limb [41]. This may be because patients perform compensatory movements of the paralyzed fingers and upper limbs and do not use the improved hand functions properly. Therefore, daily living exercises are essential in occupational therapy provided to patients. Learned bad-use of the paretic limb is the reinforcement of abnormal compensatory movement strategies at the expense of normal movement patterns, making it challenging to improve movement performance [42,43]. In occupational therapy, it is important to provide appropriate feedback to abnormal joint movements during movement and inhibit learned bad-use so that patients can use their paralyzed upper limbs in an appropriate manner in their daily lives. Although this point has not been tested, the patient's target movements should be incorporated into the practice. The patient should be motivated to practice using the paralyzed upper limb for ADLs thoroughly so that the patient can exercise the function when their hand motor function improves. The suggested target activities include manipulating a spoon or fork, unzipping and closing clothes, fastening and unbuttoning clothes, putting on socks, tying shoelaces, washing one's face, signing, and other activities requiring fine motor skills [44,45].

The Notable recovery group had fewer ARAT and JASMID subscores that showed significant improvement than the other groups. Use-dependent plasticity is a phenomenon in which the same pattern of activity tends to occur when specific neurons are repeatedly activated, and repetitive practice in rehabilitation is intended to enhance this plasticity [46,47]. In recent years, the practice time and the number of joint movements required to achieve recovery of motor function have been verified [48,49]. In occupational therapy included in NEURO, it is important to promote use-dependent plasticity and improve motor function and ADL by providing a sufficient amount of challenging movement exercises for the Notable recovery group. For patients in the Notable recovery group with good proximal and distal function, we propose the following ADL as goals: drinking water from a cup, drying laundry, washing hair, tying hair, manipulating chopsticks, and tying a neck tie [38,50,51].

In the Full recovery group, the change in the ARAT score was small, but the change in JASMID quality was expected to be high. The recovery process of motor paralysis after stroke improved in terms of motor speed and coordination after the emergence of joint movements, weakening of spasticity, and gaining the ability to perform isolated movements. Studies examining the difficulty level of detailed items in FMAUE also support this recovery process [52-54]. A method using a motion analyzer that can detect angular and velocity changes in joints is recommended for evaluating functional impairment and determining treatment effects in patients with mild hemiplegia [55]. The Box and Block Test and the Wolf motor function test can assess the coordination of movement and speed of joint movement based on the number of pieces carried and the time required to perform the task [56-58]. However, the ARAT is a test that is scored on an ordinal scale, and it is difficult to evaluate these factors in detail. In other words, the Full recovery group is expected to show improved quality of movement by improving the speed of movement and coordination of joint movements, which are expected to be difficult to be evaluated by the ARAT. Therefore, it is recommended that occupational therapy in NEURO should provide more challenging exercises, such as exercises to adjust the speed of joint movements, exercises for complex movements that require multiple joints, and resistance exercises. Regarding ADL, it is possible to aim at acquiring activities, such as cooking, that require hand dexterity and upper limb motor coordination, brushing teeth, operating smartphones and PCs, and putting on and taking off necklaces and earrings [59,60]. In addition, it can be expected to improve the quality of ADLs that patients desire.

This study has several limitations. The ARAT used for the main outcome has been reported to have a ceiling effect, and it is inferred that patients with mild motor paralysis underestimate changes [61]. Sensory perception, muscle tone, and joint range of motion are involved in the ability to manipulate objects [62-65]. The present study does not clarify the effects of the presence or absence of these symptoms on the amount of change in ARAT scores. Since the JASMID questionnaire was designed for the Japanese lifestyle, it is unclear whether the same results would be obtained if it is administered to patients from other countries [26]. Occupational therapy in NEURO was provided by therapists affiliated with NEURO-accredited facilities based on a defined concept. The generalization of the results is limited because the treatment effect will not be the same if the therapy is provided outside of a NEURO-accredited facility. The content and amount of exercises provided to patients influence the recovery of motor paralysis [48,49]. In the present study, we could not investigate the specific content and amount of exercises provided by the therapists. This should be clarified in future studies. In the present study, brain imaging data were not examined in detail. Given that some previous studies have shown that stroke subtype is a confounding factor for recovery, a detailed analysis of the neurological characteristics of patients receiving NEURO should be conducted to understand this issue [66].

5. Conclusion

This study estimated the hand and upper limb functions restored as a result of NEURO according to the severity of motor paralysis using pre-treatment ARAT scores. The results of the present study can be used to propose the patients' desired ADL exercises in occupational therapy after rTMS, in accordance with the functional recovery of the paralyzed upper limb. The benefits to the patients when the functional recovery of the paralyzed upper limb is estimated, and the ADL exercises that are appropriate for that functional recovery need to be verified in future studies.

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Informed Consent Statement: Patients were waived because the analysis used anonymous clinical data that were obtained after each patient agreed to undergo NEURO by written consent.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Appendix

Goal setting and practice content according to severity of motor paralysis for patients undergoing combined repetitive transcranial magnetic stimulation and occupational therapy

Recovery capacity	Scores predicted to change significantly	Goals for ADLs using the paralyzed upper limb and fingers	Main required joint movements
No: 0-10	ARAT: Grasp, Gross movement	Pressing a plate on a desk.	Shoulder flexion, adduction and internal rotation, forearm pronation.
		Pressing paper or a book on a desk.	Shoulder flexion, adduction, and internal rotation, forearm pronation.
		Pressing an upper garment when opening and closing a zipper.	Shoulder adduction and internal rotation, elbow extension, forearm pronation.
		Washing the upper limb and fingers of the non-paralyzed side.	Shoulder flexion, adduction, abduction, elbow flexion, elbow extension.
		Stretching wrinkles of clothes. Removing dust from clothes.	Shoulder flexion, adduction, abduction, elbow flexion, elbow extension.
Poor: 11-21	ARAT: Grasp, Grip	Grasping a plastic bottle with the paralyzed limb.	Elbow flexion, Forearm supination, finger flexion.
		Opening and closing a sliding door.	Shoulder flexion, extension, adduction, abduction, elbow extension.
		Holding a toothbrush with the paralyzed limb when applying toothpaste.	Elbow flexion, forearm supination, finger flexion.
		Flipping a switch or pressing an elevator button within reach using the paralyzed limb.	Shoulder flexion and extension, elbow flexion and extension.
		Grasping a cellphone with the paralyzed hand.	Elbow flexion, forearm rotation, finger flexion.
Limited: 22-42	ARAT: Grasp, Grip, Pinch, Gross movement	Manipulating a spoon or fork.	Forearm rotation, wrist flexion/extension, finger dexterity exercises.
		Unzipping and closing clothes. Fastening and unbuttoning clothes.	Forearm rotation, wrist flexion/extension, finger dexterity exercises.
		Putting on socks. Tying shoelaces.	Forearm rotation, wrist flexion/extension, finger dexterity exercises.
		Washing one's face.	Elbow flexion, forearm external rotation, wrist extension, finger extension.
		Signing.	Wrist flexion, wrist extension, finger dexterity exercises.

Notable: 43-54	None	Drinking water from a cup.	Shoulder flexion/extension, elbow flexion, forearm rotation, finger flexion.
		Drying laundry.	Shoulder flexion, elbow extension, forearm rotation, finger flexion and extension.
		Washing hair. Tying hair.	Shoulder flexion, rotation, forearm rotation, finger dexterity exercises.
		Manipulating chopsticks.	Wrist flexion/extension, forearm rotation, finger dexterity exercises.
		Tying a neck tie.	Wrist flexion/extension, forearm rotation, finger dexterity exercises.
Full: 55-57	JASMID: Quality	Cooking.	Wrist flexion/extension, forearm rotation, hand dexterity exercises.
		Brushing teeth.	Elbow flexion/extension, forearm rotation, hand dexterity exercises.
		Operating smartphones and PCs.	Forearm rotation, wrist flexion/extension, hand dexterity exercises.
		Putting on and taking off necklaces and earrings.	Shoulder flexion/rotation, forearm rotation, hand dexterity exercises.
		To improve the quality of ADLs that patients desire.	Complex movements that require multiple joints.

ARAT, Action Research Arm Test; JASMID, Jikei Assessment Scale for Motor Impairment in Daily Living; ADL, activities of daily living; rTMS, repetitive transcranial magnetic stimulation. Pre-treatment ARAT scores of 0-10, 11-21, 22-42, 43-54, and 55-57 represent no, poor, limited, notable, and full recovery capacity, respectively.

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