

RESEARCH ARTICLE

Predictors of activities of daily living outcomes after upper limb robot-assisted therapy in subacute stroke patients

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Abstract

Background

Upper limb recovery is one of the main goals of post-stroke rehabilitation due to its importance for autonomy in Activities of Daily Living (ADL). Although the efficacy of upper limb Robot-assisted Therapy (RT) is well established in literature, the impact of the initial status of the patient on the effects of RT is still understudied. This paper aims to identify whether demographic, clinical and motor characteristics of stroke patients may influence the ability to independently perform ADL after RT.

Methods

A retrospective study was conducted on sixty stroke patients who conducted planar upper limb goal-directed tasks with the InMotion 2.0 robot. The RT was administered 5 days/week for 4 weeks and each session lasted 45 minutes. The primary outcome measure was the Modified Barthel Index (BI), dichotomized into favourable (BI \geq 75) and unfavourable (BI <75) outcomes. The potential predictors were the demographic and clinical records, and the following clinical assessment scores: Modified Ashworth Scale-Shoulder (MAS-S); Modified Ashworth Scale-Elbow (MAS-E); Fugl-Meyer Assessment Upper Extremity (FMA-UE); upper limb section of the Motricity Index (MIul); total passive Range Of Motion (pROM); and Box and Block Test (BBT).

Results

Statistical analysis showed that the BBT, FMA-UE and MIul scores were significant predictors of a favourable outcome in ADL. The cut-off scores of the independent variables were calculated (FMA-UE = 32; MIul = 48; BBT = 3) with respect to the dichotomic BI outcome. Their robustness was assessed with the Fragility Index (FMA-UE = 2; MIul = 3; BBT = 7), showing that BBT is the most robust predictor of favourable BI outcome. Moreover, subjects

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with all predictors higher than the cut-off scores had higher probability to increase their independence in ADL at the end of the therapy. Demographic records, spasticity and pROM were not identified as predictors.

Conclusion

Stroke patients with greater manual dexterity and less impairment appear to have a higher probability of achieving clinically significant ADL outcomes after upper limb RT. The obtained results can help to optimise the management of RT treatment planning. Further studies on a larger number of patients with a long-term follow up are recommended in order to evaluate other potential predictors and to validate the results.

Introduction

Although declining stroke incidence and mortality are well documented, recent reports raised concerns that stroke incidence may be levelling off or increasing among younger adults [1,2,3,4]. Importantly, loss of arm function occurs in up to 85% of stroke survivors [5], with a significant long-term impact on Activities of Daily Living (ADL), leisure activities, and work [6]. Literature shows that only a small portion of stroke patients with upper limb motor impairment (12%) is able to regain full function, while the majority requires constant care from family or social services [7].

In order to autonomously perform ADL, the optimal restoration of arm and hand motor functions is extremely important. For this reason, many recent studies on innovative rehabilitation approaches focused on improving ADL and minimizing the hospital stay [8]. In this context, Robot-assisted Therapy (RT) could provide high-intensive, repetitive, task-specific, and interactive treatment of the impaired upper limb. Furthermore, RT is a solid, reproducible, and customizable practice for promoting motor learning [9,10]. Several RCTs and systematic reviews showed the effectiveness of upper limb RT, associated with conventional therapy, in improving the motor and functional outcomes in stroke patients, comparing it with conventional treatments [11,12,13,14]. However, despite the prominent role of RT in stroke rehabilitation, a limited number of studies aimed to identify which patient may benefit most from these innovative treatments [15,16,17,18,19]. A systematic review [16] on predictors of upper limb recovery after traditional arm therapy analysed several studies on this topic, and affirmed that measures of upper limb impairment and function were the most significant predictors (less impairment is associated with better recovery). However, literature on predictors of upper limb recovery after RT is limited and controversial [20,21,22,23,24].

Krebs *et al.* [25] analysed 208 stroke patients in order to assess if kinematic and kinetic data, automatically measured by InMotion 2.0 robot, could predict the clinical scales at the end of the RT. The results highlighted that robotic measures were able to predict the clinical measures and the recovery of patient's motor functions.

Hisieh *et al.* [26] investigated the predictors of minimal clinically important changes on outcome measures after RT. 55 stroke patients received 20 sessions of upper limb RT with the Bi-Manu-Track (Reha-Stim, Berlin, DE) and the main outcome measures were the Fugl-Meyer Assessment Upper Extremity (FMA-UE), and the Motor Activity Log (MAL). The potential predictors were age, sex, side of lesion, time since stroke onset, finger extension, Box and Block Test (BBT) score, and FMA-UE distal score. The results revealed that greater manual dexterity (from BBT) increased the probability of achieving clinically significant

motor functional improvements after RT. Furthermore, being a female was a significant predictor of MAL. Subsequently, the same group of researchers published a study [27] assessing both clinical and kinematic measures at baseline as predictors of improved motor function (FMA-UE & Wolf Motor Function Test—WMFT) and ADL (MAL & Stroke Impact Scale—SIS) after RT. Results from 66 stroke patients who conducted upper limb RT partially confirmed the previous one [26]: the manual dexterity (from BBT) was a valuable predictor of improvements at motor function and ADL. Moreover, reduced shoulder flexion synergy (measured with motion capture) was predictive of WMFT; and MAS–distal was predictive of WMFT and SIS.

Conversely, Duret *et al.* [28] reported that severely motor impaired patients may benefit more from RT. These results were obtained from a retrospective study on 17 patients, who conducted 20 sessions of upper limb RT with InMotion 2.0 robot. The correlation analysis showed that the mean value of the number of movements per robotic session decreased together with motor impairment and disability at baseline, while no correlation was found with age, aphasia and neglect. However, the improvement of the Motricity Index (MI) score and of the number of repeated movements correlated negatively with the MI at baseline and with the number of movements performed at the end of the rehabilitation period, respectively.

Therefore, considering the heterogeneity of published results on predictors of outcome measures after upper limb RT in subacute stroke patients, further studies on this topic are needed. Moreover, the efficacy of RT should be contextualised in everyday life, as suggested by the existing literature on the importance of arm function recovery in ADL [29,30,31].

The aim of this study is to identify how the characteristics of stroke patients may influence the degree of independence in ADL after upper limb RT. The identification of predictors of ADL outcomes after RT will help to identify individuals who can benefit more from this kind of therapy, and to optimise the management of treatment planning.

Materials and methods

Patients and experimental setup

A retrospective study was conducted on a database of 327 inpatients who were treated with the InMotion 2.0 robot (Interactive Motion Technologies, Inc., Cambridge, MA, USA) at the IRCCS San Raffaele Pisana of Rome between January 2010 and December 2016. The upper limb RT was systematically administered as part of usual care to both moderately and severely motor impaired inpatients. All subjects underwent conventional physiotherapy sessions according to the standardised rehabilitative protocol for subacute stroke patients. Inclusion criteria for the patients selection were: age between 18 and 80 years; first event of unilateral hemiparetic stroke; subacute phase (RT started within 30 ± 7 days poststroke); upper limb Chedoke-McMaster scores between 2 and 5; RT for 17 ± 3 sessions. Exclusion criteria were: bilateral impairment; chronic phase (RT started after $30+7$ days poststroke); RT for less than 14 sessions; RT interruption for more than 3 consecutive days; incomplete data in the database.

The patients' data had been extracted from the electronic medical records of our health care institute's database. The following demographic and clinical records were exported from the database: age; sex; aetiology; stroke location; time between stroke and the date on which the RT began.

The following assessments were extracted at the beginning (T1) and at the end (T2) of the therapy: Modified Ashworth Scale at Shoulder (MAS-S) and Elbow (MAS-E); Modified Barthel Index (BI); Fugl-Meyer Assessment Upper Extremity (FMA-UE); Motricity Index upper limb (MIul), which assesses limbs motor impairment, and ranges from 0 to 100 per limb [32]; total passive Range Of Motion (pROM), as sum of shoulder and elbow movements

(shoulder flexion/extension, abduction, intra/extra rotation and elbow extension); and Box and Block Test (BBT). All these clinical indexes were applied as routine clinical practice in our health care institute and all of them were considered as potential predictors of autonomy in ADL after RT.

The BI was defined as the primary outcome. The BI is a measure of ADL, which shows the degree of independence of a patient from any assistance.

Patients' anonymity was preserved by identifying each record in the database with an alphanumeric code.

Ethical considerations

Since March 2012, the Italian Data Protection Authority (Garante per la protezione dei dati personali) declared that IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico—Institute for scientific research and health care) can perform retrospective studies without the approval of the local Ethical Committee [33] since only a formal communication is needed (S2 and S3 Files). Such communication has been registered by the Ethical Committee of the IRCCS San Raffaele Pisana of Rome (date: 22/02/2017; code number: 06/17) that waived the need for participant consent.

Rehabilitative protocol

Between T1 and T2, all selected patients performed 20 sessions (5 days/week for 4 weeks) of goal-directed, planar reaching tasks involving shoulder and elbow movements. The upper limb conducted robot-assisted movements from a central target to each of the 8 peripheral targets, equally spaced on a 0.14 m radius circumference, and viceversa, using the InMotion 2.0 robot (Interactive Motion Technologies, Inc., Cambridge, MA, USA). During each session, a series of 16 unassisted clockwise repetitions to each target followed by 3 series of 320 assisted (using an adaptive control technique) clockwise repetitions were performed by patients. At the end of each assisted series, an additional series of 16 unassisted clockwise movements was performed. After 45 minutes the session was stopped.

Furthermore, all patients underwent conventional physiotherapy sessions according to the standardised rehabilitative protocol for subacute stroke patients of IRCCS San Raffaele Pisana of Rome. Treatments were provided by senior physiotherapists and included: assisted stretching, shoulder and arm exercises, and functional reaching tasks.

Sample size and statistical analysis

The sample size calculation (power analysis by logistic regression and by using the guidelines of Lipsey & Wilson [34] and G*Power 3.1.7 software [35]), estimated that 58 subjects would provide 80% power with 5% α and an odd-ratio of 2.5.

The primary outcome (BI at T2) was dichotomized into favourable and unfavourable. The BI cut-off scores were defined as $BI \geq 75$ for favourable outcome and as $BI < 75$ for unfavourable outcome, as suggested by Uyttenboogaar *et al.* (2005) for severe stroke patients [36].

Sensitivity and specificity were defined as the rate of unfavourable and favourable outcomes, correspondingly. To investigate the relationship between sensitivity and specificity, Receiver Operator Characteristic (ROC) curves were obtained by plotting sensitivity versus 1-specificity and allowed to assess the cut-off points for each independent variable. FMA-UE, MI, pROM and BBT were dichotomized in order to find the best cut-off values at T1. MAS-S and MAS-E, on the other hand, were analysed with the Analysis Of Variance (ANOVA) because their scores were composed by 6 levels only.

Age, gender, and the clinical scales (MAS-S, MAS-E, FMA-UE, MIUL, pROM, BBT) were considered as independent variables. A multivariate analysis was performed by using logistic binary regression models in order to identify multiple relations between the dichotomized BI at T2 and the independent variables. If appropriate, the individual variables were reported with their Odds Ratio, and the significance of each coefficient in the model was examined.

We used the Fragility Index (FI), as Ridegón *et al.* suggests [37], to evaluate the robustness (or fragility) in statistically significant clinical trial results [38]. The FI number indicates how many patients would be required to convert a trial from being statistically significant to not significant ($p \geq 0.05$). The larger the FI the better (more robust) a trial's data are [39].

The BI Absolute Functional Gain (BI_{AFG}) and the BI gain through the Montebello Rehabilitation Factor Score (BI_{MRFS}) [40] were calculated for each patient as follow:

$$BI_{AFG} = BI(T2) - BI(T1)$$

$$BI_{MRFS} = \frac{BI(T2) - BI(T1)}{\max(BI) - BI(T1)} \cdot 100$$

where $BI(T1)$ and $BI(T2)$ are the BI scores at T1 and T2 respectively, and $\max(BI)$ is the maximum value of the BI (i.e. 100).

Results

Population characteristics

From the 327 patients, 60 satisfied the inclusion criteria and were included in the study (S1 File, Fig 1). The mean age was 65.82 years (SD 15.40 years) and 25 (41.70%) patients were female. Half subjects were affected by stroke on the right side and half on the left one.

Table 1 shows the demographic and clinical characteristics of the sample at baseline. The BI scores at T1 are showed in Table 1: the median BI score at T1 was 24.50 with an interquartile range from 14 to 39.75.

No subject had $BI \geq 75$ at T1, while 27 patients had $BI \geq 75$ at T2.

ROC curves and cut-off scores

The sensitivity and specificity for the cut-off scores of the independent variables (FMA-UE, MIul, BBT) in relation to the dichotomic outcome of BI (≥ 75 or < 75) were calculated (Table 2) and plotted as ROC curves (Fig 2). The optimal cut-off score at T1 of FMA-UE was 32 (with a sensitivity of 59.3% and a specificity of 75.8%), and 27 patients were over such cut-off score; of MIul was 48 (with a sensitivity of 77.8% and a specificity of 60.5%), and 34 patients were over such cut-off score; of pROM was 760 (with a sensitivity of 70.4% and a specificity of 54.5%), and 34 patients were over such cut-off score; and of BBT was 3 (with a sensitivity of 66.7% and a specificity of 78.8%), and 25 patients were over such cut-off score.

Fig 3 shows the logistic regression and depicts that FMA-UE, MIul and BBT data which are higher than the cut-off scores can significantly predict the favourable outcome (i.e. $BI \geq 75$ at T2). In particular, a BBT score higher than 3, multiplies by 7 the probability to have $BI \geq 75$ at T2. Conversely, pROM, MAS-S, MAS-E, age and gender are not significant predictors of the favourable BI at T2.

In Table 3, the number of subjects in each subgroup (e.g. 17 subjects had $FM-UE > 32$ and $BI \geq 75$, while 10 subjects had $FM-UE \leq 32$ and $BI < 75$, etc.) and the corresponding FI (indicating the number of patients required to lose the statistical significance) are showed. These figures have been calculated for all predictors. The robustness of BBT (FI = 7) is greater than those obtained by dichotomising FM-UE (FI = 2) and MIul (FI = 3). Moreover, having

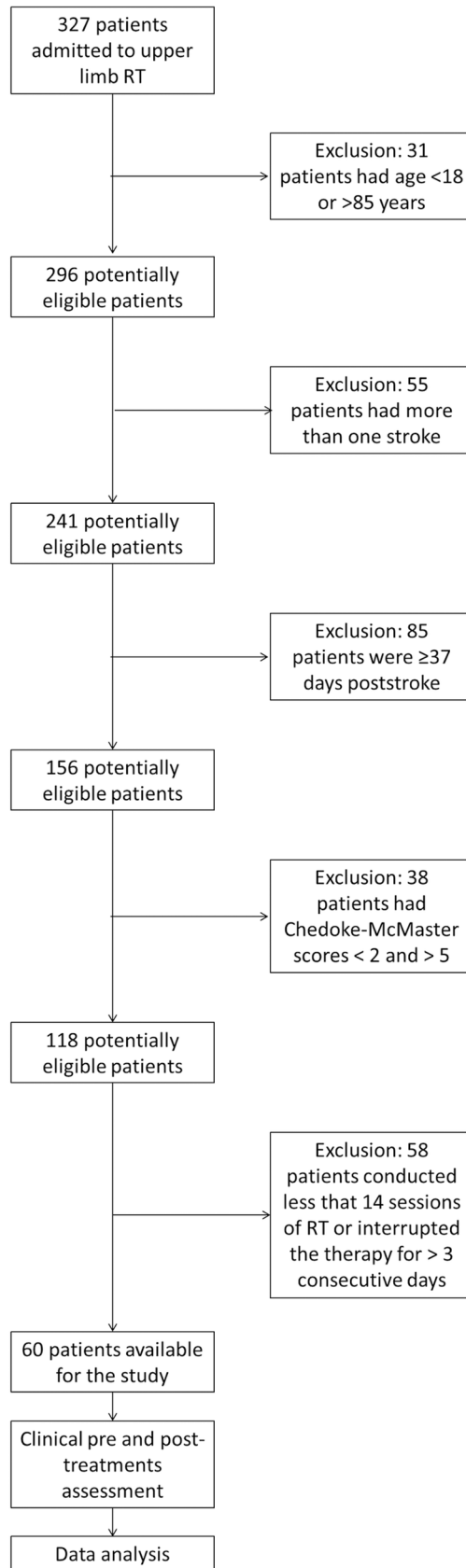


Fig 1. Flow chart of the step-by-step selection procedure of stroke patients included in the retrospective study.

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FM-UE > 32, MIul > 48, and BBT > 3 together at T1, makes their predictive impact stronger (FI = 8).

Table 4 depicts the BI_{AFG} and the BI_{MRFS} by dividing the patients accordingly to their BBT score (BBT cut-off score criteria). These figures allow to understand if the gain in ADL is different between moderately and severely motor impaired subjects. Data are shown as mean, standard deviation, median value, and 25th and 75th percentiles and confirms that all patients increased their ability to perform ADL at the end of the therapy. However, moderately impaired patients (BBT > 3) have a higher improvement of their autonomy.

Discussion

This retrospective study analysed the demographic, clinical and motor characteristics of 60 subacute stroke patients at baseline comparing them with their degree of independence in ADL after upper limb RT. Patients with a limited body function (FMA-UE, MIul) and discrete conserved dexterity (BBT) are more likely to achieve a good degree of autonomy in ADL at the end of the therapy.

A BBT score (dexterity) greater than 3 appears to raise significantly the opportunity of becoming more independent after this kind of rehabilitation. Therefore, the dexterity could be considered as a potential predictor to increase the probability of regaining independence in ADL. The results on manual dexterity are in accordance with the predictors of ADL obtained by Hisieh *et al.* [26] and Huang [27] on stroke patients who used the Bi-Manu-Track. Furthermore, our findings are in line with Kwakkel *et al.* [5], who pointed out the importance of manual dexterity in upper limb motor improvement for stroke patients, highlighting that individuals who do not show functional dexterity at stroke onset seem to have poor upper limb motor function six months after stroke. Moreover, the obtained values of BI_{AFG} and BI_{MRFS} confirm that all patients increased their ability to independently perform ADL after RT. However, subjects with a BBT score at T1 higher than the cut-off value have a higher increase of BI at T2. This finding is associated with the correlation between the ability to use hands and

Table 1. Characteristics of the sample at T1 (n = 60).

Variables	n (%)	Mean (SD)	Median (IQR)
Age, years		65.82 (15.40)	70.00 (60.00–75.00)
Gender, Male/Female	35 (58.30)/25 (41.70)		
Etiology, Ischemic/Haemorrhagic	48 (80.00)/12 (20.00)		
Lesion Side, Left/ Right	30 (50.00)/30 (50.00)		
MAS-S, 0-2/3-4	47 (78.30)/13 (21.70)		
MAS-E, 0-2/3-4	49 (81.70)/11 (18.30)		
BI		26.30 (16.50)	24.50 (14.00–39.75)
FMA-UE		28.95 (11.15)	30.00 (21.00–37.75)
MIul		47.15 (23.24)	51.00 (30.00–65.75)
pROM		781.70 (95.48)	785.00 (720.00–863.80)
BBT		6.73 (9.90)	.00 (.00–10.75)

Abbreviation: SD, Standard Deviation; IQR, Interquartile Range; MAS-S, Modified Ashworth Scale Shoulder; MAS-E, Modified Ashworth Scale Elbow; BI, Modified Barthel Index; FMA-UE, Fugl-Meyer Assessment Upper Extremity; MIul, Motricity Index upper limb; pROM, passive Range Of Motion; BBT, Box and Block Test.

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Table 2. Characteristics of the predictive to Barthel Index at T2 \geq 75 (using ROC curve optimal criterion); n = 60.

Variables	Youden Index J	Associated Criterion	# Subjects above the Criterion at T1	SE (95% CI)	SP (95%CI)	AUC (95% CI)
FMA-UE	.350	> 32	27	59.30 (38.80–77.60)	75.80 (57.70–88.90)	.704 (.572 - .815)
MIul	.384	> 48	34	77.80 (57.70–91.40)	60.60 (42.10–77.10)	.698 (.565 - .809)
pROM	.249	> 760	34	70.40 (49.80–86.20)	54.60 (36.40–71.90)	.633 (.499 - .754)
BBT	.455	> 3	25	66.70 (46.00–83.50)	78.80 (61.10–91.00)	.742 (.613 - .846)

Abbreviation: CI, confidence interval; SE, sensitivity; SP, specificity; ROC, Receiver Operating Characteristic; AUC, Area Under the ROC curve (maximum = 1.0); FMA-UE, Fugl-Meyer Assessment Upper Extremity; MIul, Motricity Index upper limb; pROM, passive Range Of Motion; BBT, Box and Block Test.

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manipulating objects, and independence in ADL. Since a good ability to perform ADL depends on both fine (e.g. grasping) and coarse (e.g. reaching) motor abilities, and since the RT with the InMotion 2.0 robot aims to recover coarse motor abilities and do not train the fine ones, subjects who had greater level of fine motor skills at baseline have a higher probability to increase autonomy in ADL [41]. Such findings confirm the results that subjects with greater manual dexterity, and moderate impairment, appear to have a higher ability to independently perform ADL after upper limb RT.

The results earned by analysing the functional outcomes (FMA-UE and MIul) can not be compared with the studies by Hisieh *et al.* [26] and Huang [27] since they considered the motor functions as primary outcomes. The predictive power of FMA-UE and MIul are in accordance with studies on constraint-induced therapy or bilateral arm training [5,18] and with the meta-analysis by Coupar *et al.* [16]. On the other hand, our findings are in disagreement with Duret *et al.* [24], who found a negative correlation between MIul at T2 and MIul at T1. The reasons of such discrepancy can be found in the different sample sizes and in the different nature of the primary outcomes (our primary outcome is ADL, Duret’s primary outcome was motor function).

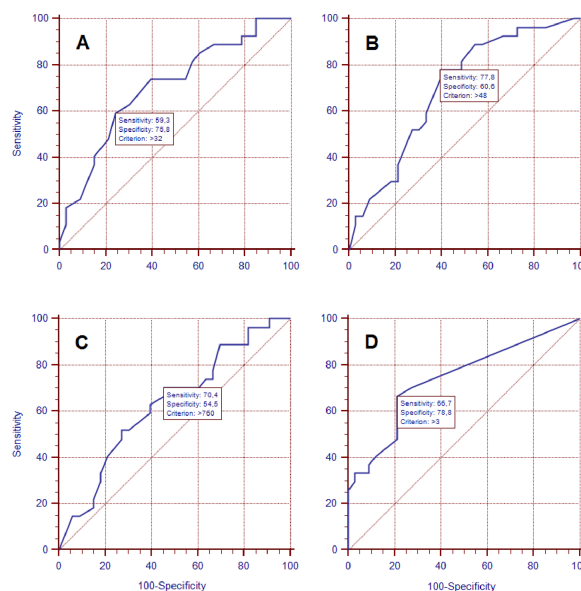


Fig 2. ROC curve to identify optimal criterion for variables at baseline, using characteristics of the predictive to Barthel Index at T2 \geq 75 (A: FMA-UE; B: MIul; C: pROM; D: BBT).

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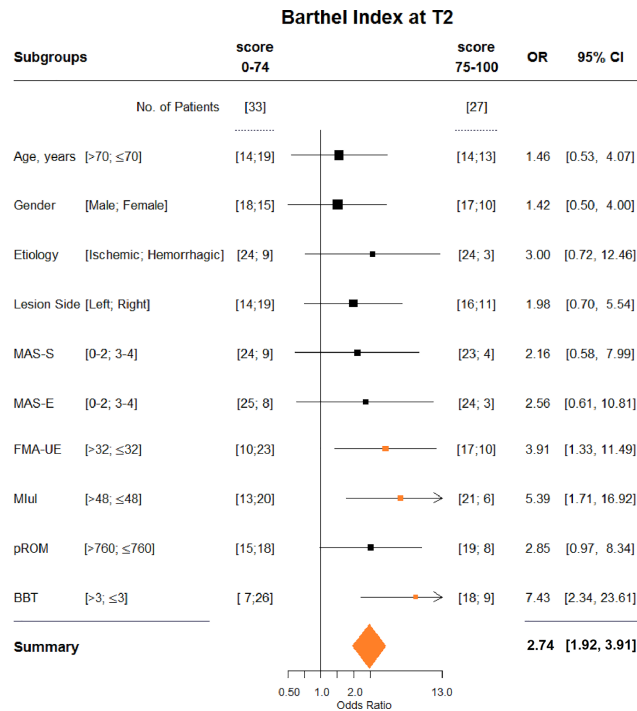


Fig 3. Forest-plot for predictor of independence in ADL (Barthel Index at T2 ≥ 75) for dichotomic variables; univariate analysis.

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Table 3. Robustness for prediction of independence in ADL (Barthel Index at T2 ≥ 75) reporting Fragility Index (FI).

		BI at T2		OR (95% CI)	p-value	FI
		(75–100)	(0–74)			
FMA-UE				3.910 (1.331, 11.487)	0.0131	2
	> 32	17	10			
	≤ 32	10	23			
MIul				5.385 (1.714, 16.919)	.0039	3
	> 48	21	13			
	≤ 48	6	20			
BBT				7.429 (2.338, 23.607)	0.0007	7
	> 3	18	7			
	≤ 3	9	26			
Summary				7.808 (2.151, 28.349)	.0018	8
FMA-UE	> 32					
MIul	> 48	14	4			
BBT	> 3					
FMA-UE	≤ 32					
MIul	≤ 48	13	29			
BBT	≤ 3					

Abbreviation: OR, Odds Ratio; CI, confidence interval; FI, Fragility Index; FMA-UE, Fugl-Meyer Assessment Upper Extremity; MIul, Motricity Index upper limb; BBT, Box and Block Test.

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Table 4. BI Absolute Functional Gain (BI_{AFG}) and BI Montebello Rehabilitation Factor Score (BI_{MRFS}) for patients with BBT score ≤ 3 and >3.

BBT score	N	BI _{AFG}					BI _{MRFS}				
		Mean	SD	25th perc.	Median	75th perc.	Mean	SD	25th perc.	Median	75th perc.
≤3	35	38.77	21.20	18.00	43.00	51.00	51.8%	25.1%	37.5%	55.7%	71.6%
>3	25	50.68	22.05	38.00	49.00	64.00	71.3%	27.9%	51.9%	80.7%	88.3%

Abbreviation: SD, Standard Deviation; BI_{AFG}, BI Absolute Functional Gain; BI_{MRFS}, BI Montebello Rehabilitation Factor Score.

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We did not find any relationship between MAS and pROM, and the improvements in daily function. The initial level of spasticity and pROM does not influence the outcome. In this context, some authors affirmed that there is a low correlation between spasticity and disabilities using the MAS and BI, as in our study [42]. Other studies on pROM and MAS showed that spasticity significantly decreases in the EG (RT) rather than in the CG (no RT), demonstrating positive effects of the RT delivered in the early phase of rehabilitation in subacute stroke patients [11,43]. Moreover, the reduction of spasticity correlates with the increase of pROM. In our study, patients were recruited within 30+7 days from the acute event and observed for about 20 days: in such period of time the spasticity may not have developed completely [44], and the muscular tone could decrease (in case of flaccidity) or increase (in case of an initial spasticity). These statements support our results on the non predictive nature of MAS and pROM in ADL outcome after RT.

The FI analysis showed that the cut-off values obtained in this study are sufficiently robust and that the subjects with FM-UE, MIul and BBT higher than such cut-off values, may be more likely to improve their independence in ADL at the end of the therapy.

Limitations of our study are correlated with the retrospective nature of the research: the presence of potential confounding factors, and a limited number of subjects. In our study, the environmental influences are minimized because all subjects were inpatients and underwent additional conventional physiotherapy sessions according to the standardised rehabilitative protocol for subacute stroke patients. However, a more controlled observational prospective study on a larger sample with a long-term follow up (6/12 months from acute event) is suggested in order to confirm our results and to study the phenomenon more accurately. In addition, other potential factors that might affect RT outcomes, such as muscle activity and kinematic parameters, need further investigation.

Conclusions

This study reports that patients with less impairment and disability could benefit more from an upper limb rehabilitation program composed of RT and traditional therapy. Conversely, gender, age, spasticity and passive range of motion do not considerably influence the effects of such therapy on autonomy in ADL.

The obtained results can help to optimise the management of RT treatment planning, giving higher priority to patients who have more segmental motor activities and dexterity. Nevertheless, our findings confirms that patients with more severe impairment can also benefit from upper limb RT for improving their ability to perform ADL.

Supporting information

S1 File. Database (n = 60). Original data. (XLSX)

S2 File. Official documentation Italian Data Protection Authority ITA. Italian version of the Data Protection Authority (01 March 2012, Official Gazette No.72 of March 26, 2012). (PDF)

S3 File. Summary Official documentation Italian Data Protection Authority ENG. English version of the Data Protection Authority (01 March 2012, Official Gazette No.72 of March 26, 2012). (PDF)

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Writing – review & editing: Sanaz Pournajaf, Federico Posteraro.

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