

ORIGINAL CONTRIBUTION



Exoskeleton-Assisted Therapy Enhances Upper Limb Motor Recovery in Early Subacute Stroke: A Multicenter, Single-Blind Randomized Controlled Trial

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BACKGROUND: Robot-assisted therapy (RAT) with exoskeletons is believed to enhance motor recovery in stroke survivors. RAT offers intensive, feedback-based, task-oriented training to improve function. This study evaluated exoskeleton-based RAT integrated into usual rehabilitation care for individuals in early subacute stroke.

METHODS: This multicenter randomized controlled trial was conducted across 8 stroke neurorehabilitation units over a 3-year period (December 2020–March 2024). Inpatients with moderate-to-severe upper limb impairment postsubacute stroke (<3 months poststroke) were randomized (1:1) to 25 sessions (5/week for 5 weeks) of exoskeleton-assisted RAT (robotic group) or conventional rehabilitation (control group). Outcome assessors were blinded. The primary outcome was the change in the Fugl-Meyer Assessment for Upper Limb (motor section, 0–66) from baseline to treatment end. Secondary outcomes addressed body function, activity (capacity/performance), and participation. Clinical assessments were at baseline (T0), posttreatment (T1), and 6-month telephone follow-up (T2). Odds ratio for achieving a minimal clinically important difference (≥ 10 points) on the Fugl-Meyer Assessment for Upper Limb was calculated.

RESULTS: A total of 109 individuals with subacute stroke were screened. Of these, 94 (35% women; mean age 62.5 ± 13.5 years; mean onset 34 ± 28 days) were eligible and randomized, and 82 completed the intervention (12% dropout). No significant differences were observed at baseline, despite the median Fugl-Meyer score being 16 in the robotic group and 10 in the control group. The robotic group showed significantly greater improvement in Fugl-Meyer Assessment for Upper Limb motor score than the control group, with a median between-group difference of 22 points ($P < 0.001$). Minimal clinically important difference was reached by 68.4% in the robotic group versus 31.8% in the control group (odds ratio, 4.64 [95% CI, 1.83–11.8]; $P < 0.001$). All secondary outcomes improved significantly in both groups with no significant differences between groups, except for spasticity, which showed no significant change.

CONCLUSIONS: Exoskeleton-assisted RAT offers significant clinical benefits in early poststroke upper limb recovery, yielding higher minimal clinically important difference rates on impairment outcomes but not on specific functional measures compared with conventional therapy. Further research should evaluate long-term effects and optimize protocols based on patient characteristics.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: exoskeleton device ■ minimal clinically important difference ■ robotics ■ stroke ■ upper extremity

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Nonstandard Abbreviations and Acronyms

3D	3-dimensional
BoNT-A	botulinum toxin A
CG	control group
FMA	Fugl-Meyer Assessment
FM-UL	Fugl-Meyer Assessment for Upper Limb
MCID	minimal clinically important difference
RAT	robot-assisted therapy
RCT	randomized controlled trial
RG	robotic group
UL-RAT	upper limb robot-assisted therapy

Stroke remains a leading cause of disability worldwide, with ≈85% of survivors developing upper limb motor impairments, and up to 75% retaining functional deficits 6 months poststroke,¹ emphasizing the critical need for effective interventions. Motor recovery after stroke is variable and significantly influenced by initial impairment severity and timing of rehabilitation efforts. A systematic review highlighted that, while recovery is possible, its extent is often limited, particularly when rehabilitation is delayed or insufficiently intensive.² Reduced functional integration of the affected arm in daily activities is associated with further motor and functional decline over time,³ making recovery of hand function and arm strength a persistent priority for stroke survivors.⁴ One contributing factor is the increased energetic cost of movement with the impaired limb⁵ which promotes preferential use of the less affected arm.⁶

The early subacute phase—commonly defined as the first 3 months after stroke onset—is considered a critical window for functional recovery, during which neuroplasticity peaks.⁷ According to recommendations from the International Stroke Recovery and Rehabilitation Alliance Consensus, early and structured rehabilitation should be initiated whenever clinical stability allows,⁸ with interventions and strategies aimed at enhancing neuroplastic potential,⁹ including upper limb robot-assisted therapy (UL-RAT).¹⁰

Robot-assisted therapy (RAT) has emerged as a promising neuromotor strategy to improve motor and functional recovery of the arm, particularly in individuals with severe impairments.¹¹ It provides intensive, task-oriented training derived from sensory feedback that engages motor-related brain networks and complements conventional therapy in promoting functional recovery dependent on adaptive plasticity.^{10,11} Rehabilitation robots can be classified as exoskeletons or end-effector devices. Exoskeletons, attached at multiple points, allow precise multijoint control and 3-dimensional (3D) movements, whereas end-effector devices provide distal-only, planar control.¹²

The advantage of exoskeletons is their ability to facilitate 3D, functional training, overcoming limitations of 2-dimensional planar exercises.^{10,12,13} The inclusion of 3D movement patterns allows individuals to perform functional tasks within a workspace volume (eg, reaching, grasping) more naturally, supporting functional task training, a key strategy for promoting adaptive plasticity and encouraging the active use of the affected limb in daily contexts.^{11,14,15} Despite these advances, most research has focused on end-effectors, developed decades earlier.^{10,12}

Growing evidence suggests that individuals with moderate-to-severe impairments in the subacute phase may particularly benefit from robotic-assisted training delivered through 3D exoskeletons, with promising effects on sensorimotor recovery.^{10,12,13} However, despite the expanding body of research in this field, important methodological limitations still characterize the existing literature. Many studies and reviews combine heterogeneous populations (different stroke phases, impairment severities, and device types, including 2-dimensional end-effectors and 3D exoskeletons), limiting interpretation and clinical applicability.^{2,10,16} Furthermore, most available trials are monocentric or underpowered, few have specifically targeted the early subacute period, when neuroplastic potential is greatest, and standardized high-dose protocols embedded into routine clinical practice have rarely been evaluated.

Thus, this multicenter randomized controlled trial (RCT), as one of the first attempts to address these gaps, aimed to examine the efficacy of RAT using a 3D exoskeleton to improve upper limb motor recovery in inpatients with subacute stroke and moderate-to-severe arm deficits. We hypothesized that UL-RAT, integrated into the standard multidisciplinary rehabilitation program and stratified by time since stroke onset and severity of motor impairment, would yield better motor and functional recovery compared with conventional therapy alone.¹⁷

METHODS

Data Availability

Deidentified individual participant data and statistical code will be made available from the corresponding author on reasonable request, after publication, for researchers who provide a methodologically sound proposal for purposes of replicating results or conducting a meta-analysis.

Participants and Study Design

The study was a multicenter RCT, designed and conducted in accordance with the Consolidated Standards of Reporting Trials guidelines for nonpharmacological interventions (Consolidated Standards of Reporting Trials checklist reported).¹⁸ Ethical approval was obtained from the ethics committees of all participating centers. The coordinating center (IRCCS [Istituto di Ricovero e Cura a Carattere Scientifico - Scientific Institute

for Research, Hospitalization and Healthcare] San Raffaele Roma) received primary approval (Prot. Power UPS REHAB-RP20/08, March 25, 2020), and each collaborating site received local authorization in compliance with national and institutional requirements. The study adhered to the principles of the Declaration of Helsinki. All data were anonymized or pseudonymized and processed in accordance with applicable data protection regulations (eg, European Union General Data Protection Regulation - EU GDPR 2016/679), with access limited to authorized study personnel. Inpatients were consecutively recruited from 8 stroke neurorehabilitation units over ≈ 3 years (December 2020–March 2024) and were approached within the first days of admission. The protocol was explained by the site principal investigators, and written information was provided to patients and relatives as needed. Written informed consent was obtained from all participants before enrollment.

Patients were randomly assigned to 1 of the 2 groups using a web-based platform (www.randomization.com) with a fixed block size of 4 to ensure balanced group sizes over time. Stratified randomization was applied based on time since stroke onset (distance since stroke onset ≤ 30 days; distance since stroke onset > 30 days) and baseline severity of upper limb impairment (Fugl-Meyer Assessment [FMA] for Upper Limb [FM-UL] ≤ 22 ; $22 < \text{FM-UL} \leq 44$). No specific age- or sex-matching strategy was applied across centers.

To ensure allocation concealment and minimize selection bias, the randomization sequence was generated and managed by a central study coordinator not involved in patient recruitment, treatment administration, outcome evaluation, or data analysis. Clinical investigators at each site had no access to the randomization list or allocation sequence, preventing prediction of group assignment during enrollment.

Regarding blinding, outcome evaluators were blinded to group allocation, whereas blinding of therapists delivering the interventions and of patients receiving them was not feasible due to the nature of the intervention.

Participants were allocated to either the robotic group (RG), receiving UL-RAT, or to the control group (CG), receiving conventional upper limb rehabilitation. Both interventions were delivered as add-on therapies to standard stroke rehabilitation, which included intensive neuromotor, occupational, speech, and cognitive therapy for ≈ 3 hours per day.

Inclusion criteria were participants of both sexes; age between 18 and 85 years; first-ever ischemic stroke confirmed by brain imaging (computed tomography or magnetic resonance imaging); moderate-to-severe upper limb hemiparesis according to the FM-UL motor score (FM-UL ≤ 22 or $22 < \text{FM-UL} \leq 44$)¹⁹; stroke in the early subacute phase (within 90 days from onset); Modified Ashworth Scale score < 3 at the shoulder, elbow, and wrist²⁰; and sufficient cognitive and linguistic abilities to understand instructions and provide informed consent.

Exclusion criteria were stroke located in the brainstem or cerebellum, unstable general medical conditions, severe visual impairment, recent or planned injection of BoNT-A (botulinum toxin A) to the upper limb during the study period, including follow-up, other orthopedic or neurological conditions affecting the paretic upper limb, interruption of treatment (both conventional and UL-RAT) for 1 week or 5 consecutive sessions, and participation in other experimental upper limb rehabilitation protocols.

All participants were assessed at baseline (T0), at the end of treatment (T1), and at 6 months after stroke onset (T2). All

outcome assessments were performed by independent, trained physical therapists who were not involved in patient recruitment, treatment administration, or data analysis, and were blinded to group allocation. To address potential attrition, an intention-to-treat approach was applied: participants who were reassessed at follow-up (T1 or T2) were analyzed in their originally allocated groups, even if the number of sessions was reduced due to clinical reasons (eg, fever, medical checks). Only participants completely lost to reassessment at both T1 and T2 for long-term clinical conditions (eg, COVID-19) were considered true dropouts.

Functional and Motor Performance Assessments

A set of specific functional scales was administered before (T0) and after (T1) the experimental and control interventions. The primary outcome measure was the motor component of the FMA for the Upper Limb (FM-UL),²¹ with a minimal clinically important difference (MCID) set at 10, based on Arya et al²². The FM-UL is a stroke-specific, performance-based impairment index designed to assess motor functioning, balance, sensation, and joint functioning in individuals with poststroke hemiplegia. It is widely applied both clinically and in research to evaluate disease severity, describe motor recovery, and guide treatment planning and outcome assessment. In this study, we considered only the motor performance items of the upper extremity, which range from 0 (minimum performance) to 66 (maximum performance),²¹ excluding the sensory, joint range of motion, and joint pain components.

Secondary outcomes, aligned with the domains of the International Classification of Functioning, Disability and Health,²³ included the following.

Body Function

The Modified Ashworth Scale, which assesses spasticity levels at the shoulder, elbow, and wrist by grading resistance during passive muscle stretching. It provides a cumulative measure of muscle tone alterations following upper motor neuron lesions.

Activity (Capacity/Performance)

The Box and Block Test, the Nine-Hole Peg Test, the Frenchay Arm Test, and the modified Barthel Index. The Box and Block Test evaluates gross manual dexterity by measuring the number of blocks moved from one compartment to another using the affected limb, while the Nine-Hole Peg Test assesses fine motor coordination and finger dexterity by timing how quickly pegs are inserted into holes. The Frenchay Arm Test is a brief, functional test of upper limb use in daily activities. The modified Barthel Index quantifies independence in basic activities of daily living.

Participation

The modified Rankin Scale,²⁴ a widely used global disability scale that evaluates the degree of dependence or independence in daily life.

These outcome measures were selected to comprehensively assess the effects of the interventions across the International Classification of Functioning, Disability and Health dimensions, capturing changes in impairment, functional ability, and social participation.

Experimental Intervention: Robot-Assisted Upper Limb Therapy

The RG, in addition to multidisciplinary standard rehabilitation, underwent 1 daily session of exoskeleton-assisted upper limb therapy using the Armeo Power robotic system (Hocoma AG, Switzerland; Figure S1), delivered by qualified and experienced physical and/or occupational therapists specialized in robotic and neurorehabilitation. Each participant performed a total of 25±3 treatment sessions with a frequency of 5× a week for 5 consecutive weeks, each session lasting 45 minutes.

During the first session, the device was adjusted to the patient's arm size and the angle of suspension and other parameters (eg, level of assistance). Exercises and working space were selected based on the patient's neuromotor residual ability, with difficulty level (eg, the suspension rate, the level of assistance, and the complexity of movement) gradually increased over training. Physiotherapist chose the modality according to the patient's motor skills, combining standardized and personalized exercises.

All therapists received standardized training on the ArmeoPower system to ensure consistent delivery, focusing on device calibration, progressive task difficulty, and adherence to treatment protocols aligned with routine clinical practice.

UL-RAT accounted for ≈25% of the total weekly regular rehabilitation, in addition to the remaining 75% of the tailored multidisciplinary rehabilitation program, including occupational therapy, speech therapy, and cognitive-neuropsychological therapy. A detailed list of examples of Armeo Power exercises delivered as part of a single RAT session is provided in the Supplemental Material (Table S1).

Control Intervention: Upper Limb Neuromotor Training

The CG, in addition to multidisciplinary standard rehabilitation, was submitted to 40 min of conventional upper limb rehabilitation. Each participant performed a total of 25±3 conventional upper limb treatment sessions with a frequency of 5× a week for 5 weeks. Each session consisted of passive, active-assisted, and active exercises tailored for shoulder, arm, and hand motor rehabilitation. A detailed list of conventional upper limb exercises, including passive, active-assisted, active, and proprioceptive activities, is provided in the Supplemental Material (Table S2). Overall, total therapy time per session and weekly intensity were equivalent between the robotic and CGs, ensuring comparability of treatment dosage. Total therapy time and frequency were consistent with current stroke rehabilitation recommendations for intensity and frequency of upper limb practice.^{25,26}

A complete description of the scheduled exercises is also available in the Template for Intervention Description and Replication,²⁷ in the Supplemental Material (Table S3), as reported in the published study protocol.¹⁷

Sample Size Calculation

The primary outcome was planned to detect a between-group difference of 10 points on the FM-UL motor score, corresponding to the MCID established by Arya et al²². Assuming a SD of 10 points, we calculated that 82 participants (41 per group) would provide 80% statistical power ($\beta=0.20$) at a 2-sided significance level of $\alpha=0.05$. To account for potential dropouts, the target sample size was increased to 94 participants. The general analytic approach was informed by the methodology

described in Calabrò et al²⁸. With 8 sites involved, each was expected to recruit ≈10 to 12 participants.

Statistical Analysis

Data were reported as mean±SD, median (interquartile range), or relative frequency (%), depending on whether the variables were continuous, ordinal, or nominal. The statistical analyses were performed using IBM SPSS Statistics (Version 26.0; IBM Corp, Armonk, NY). Due to the non-normal distribution of most clinical scale scores, as determined by the Shapiro-Wilk test (eg, $P<0.001$ for FMA, Modified Ashworth Scale, and Frenchay Arm Test at T0; similar results at T1), nonparametric tests were used. Specifically, the Mann-Whitney *U* test was used for between-group comparisons, the Wilcoxon signed-rank test for within-group comparisons, and the χ^2 test for frequency comparisons. To handle missing data, complete-case analyses were performed to confirm the robustness of the results. Participants lost to follow-up at both T1 and T2 were considered true dropouts.

For the primary outcome (FMA), the number of patients achieving a clinically meaningful improvement (MCID≥10 points) from T0 to T1 was calculated and compared between groups. Where applicable, odds ratios with 95% CIs were also reported. Statistical significance was set at an α level of 0.05 for all analyses.



RESULTS

Main Analysis

We screened 109 individuals with subacute stroke and enrolled 94 participants at T0. Of these, 82 participants were reassessed at T1; all had completed the treatment. The attrition rate at T1 was 12% (11 in the RG: 3 due to transfer to other stroke units for a new acute event, 3 due to clinical deterioration or complications, such as urinary/pulmonary infections, and 5 due to COVID-19 infection; 1 in the CG due to COVID-19 infection). At the 6-month follow-up (T2), 49 participants were available for reassessment, reflecting a long-term attrition of 52%. Therefore, the analysis at T2 was performed separately. Figure 1 presents the Consolidated Standards of Reporting Trials flow chart of the study. Table 1 shows the demographic and clinical parameters recorded at baseline for the 2 groups. Although no specific age- or sex-matching strategy was applied across centers, the age distribution between groups appeared comparable as a coincidental outcome of the overall recruitment process (see Table 1).

Table 2 presents the median and interquartile range values for the clinical assessments measured at baseline (T0) and posttreatment (T1). The table includes the results of the Wilcoxon signed-rank test to compare changes within each group (T0 versus T1) and Mann-Whitney *U* test results to assess differences between groups at both T0 (*P* value at baseline) and T1 (*P* value at posttreatment). These analyses highlighted the within-group improvements over time and the between-group

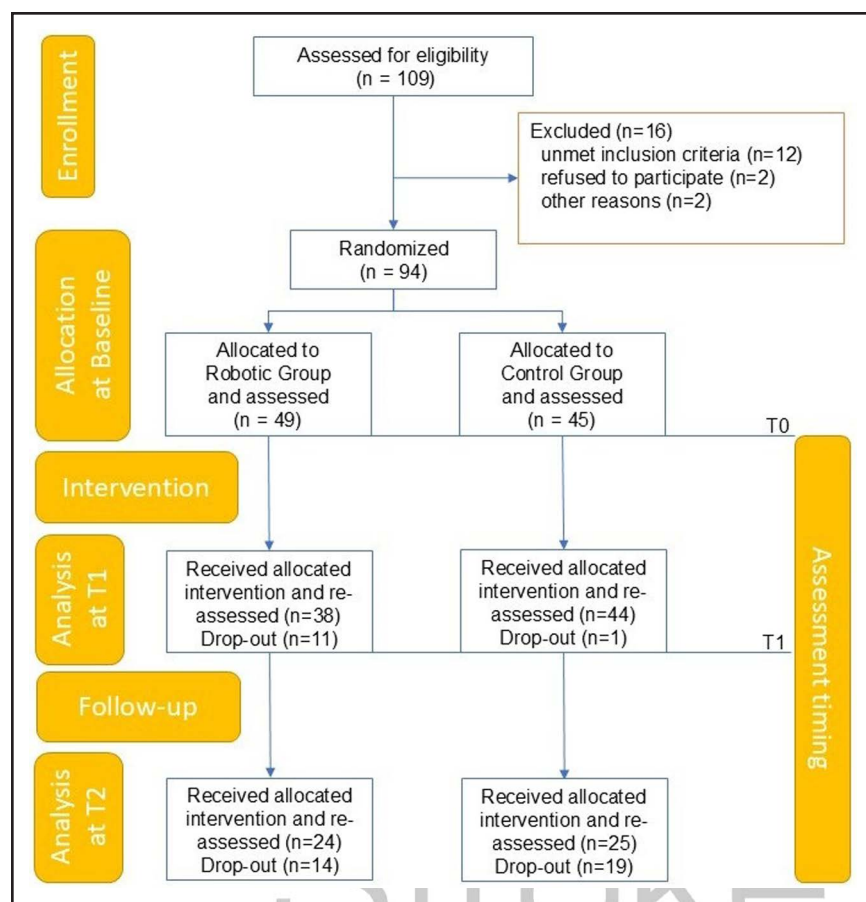


Figure 1. Consort flow chart of the study participants.



differences before and after the intervention. No significant between-group differences were observed at T0. At T1, both groups demonstrated higher values in all clinical assessments compared with baseline, except for the Modified Ashworth Scale score, which remained stable. The difference in terms of BI only approached the statistical significance ($P=0.057$). The between-group

analysis revealed a significant difference only regarding the FM-UL motor part, which resulted in higher values at T1 in RG ($P<0.001$).

The distribution of FM-UL motor part scores for both groups is illustrated in Figure 2.

About the other FM subscores, sensory score significantly increased at T1 with respect to baseline, both in RG and CG ($P<0.001$). Joint passive range of motion did not significantly vary in RG ($P=0.888$), it did in CG ($P=0.005$), but with a not important clinical difference (on average: $0.8\pm 2.6^\circ$). No significant changes were found in joint pain (RG: $P=0.378$, CG: $P=0.798$). According to these findings, despite the sensory impairment was not significantly different at baseline between the 2 groups (RG: 10 [6] versus CG: 6 [4]; $P=0.060$), but its change could play a significant role, a mixed ANOVA (which is considered robust even for not normally distributed data) was performed on the primary outcome measure (functional score of FM) with sensory impairment score included as a covariate. Two other factors could be considered as influencing the outcome: sex (included as between-subject factor) and cognitive impairment (assessed by MOCA and included as covariate variable). The time-by-group remained statistically significant ($F[1,71]=5.736$, $P=0.019$, partial eta squared=0.075), whereas the sensibility-by-time interaction was not ($F[1,71]=0.555$, $P=0.459$, partial eta squared=0.008).

Table 1. Demographic and Clinical Characteristics

Variables	Robotic group (n=38)	Control group (n=44)	P value
Age, y	62±15	63±12	0.893
DSO, d	34±28	34±29	0.874
MOCA	21±5	22±5	0.222
Gender (females)	31% (n=12)	36% (n=16)	0.649
Right side hemiparesis	45% (n=16)	41% (n=18)	0.783
Bamford class: LACI	34% (n=13)	10% (n=4)	0.239
Bamford class: PACI	27% (n=10)	43% (n=19)	
Bamford class: POCI	8% (n=3)	9% (n=4)	
Bamford class: TACI	31% (n=12)	38% (n=17)	

Mean±SD or percentage of relative frequencies of demographic and clinical parameters of participants at baseline compared between groups (P values refer to Mann-Whitney U test for age, DSO, and MOCA; and to χ^2 test for percentages). DSO indicates distance since stroke onset; LACI, lacunar anterior circulation infarct; MOCA, Montreal Cognitive Assessment; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; and TACI, total anterior circulation infarct.

Table 2. Median Values (IQR) of Clinical Outcomes at Baseline (T0) and Posttreatment (T1) in the RG and CG

	RG			CG			RG vs CG	
	T0	T1	<i>P</i> value	T0	T1	<i>P</i> value	<i>P</i> value (T0)	<i>P</i> value (T1)
FMA	16 (28)	41 (38)	<0.001	10 (9)	19 (21)	<0.001	0.082	<0.001
MAS	0 (3)	1 (3)	0.267	1 (8)	1 (5)	0.102	0.138	0.393
BBT	0 (12)	9 (29)	<0.001	0 (6)	5 (16)	<0.001	0.893	0.487
FAT	0 (1)	3 (4)	<0.001	0 (2)	3 (3)	<0.001	0.600	0.791
BI	43 (39)	77 (43)	<0.001	30 (30)	63 (29)	<0.001	0.162	0.057
mRS score	4 (1)	3 (2)	<0.001	5 (1)	3 (1)	<0.001	0.067	0.718

Median (IQR) for the variables assessed at the beginning (T0) and at the end of treatment (T1), with *P* values (*p*) of Wilcoxon test within group (between T0 and T1), *p*(T0) and *p*(T1) as results of Mann-Whitney *U* test between groups at T0 and T1, respectively. BBT indicates Box and Block Test; BI, Barthel Index; CG, control group; FAT, Frenchay Arm Test; FMA, Fugl-Meyer Assessment; IQR, interquartile range; MAS, Modified Ashworth Scale; mRS, modified Rankin Scale; and RG, robotic group.

Neither as main factor ($F[1,71]=0.031$, $P=0.862$, partial eta squared=0.001) nor in the interaction with time ($F[1,71]=0.130$, $P=0.720$, partial eta squared=0.002), the cognitive impairment had a significant impact on FM score. The main effect of sex approached the statistical significance, but without achieving it ($F[1,71]=2.793$, $P=0.099$, partial eta squared=0.038), but its interaction with time and group was not statistically significant ($F[1,71]=0.077$, $P=0.782$, partial eta squared=0.001).

The number of patients who overcame the MCID of the FM score is shown in Table 3. The higher percentage recorded for RG (68.4%) was more than double that observed for CG (31.8%), and this difference was statistically significant ($P<0.001$). The relevant odds ratio was 4.64 (1.83–11.8).

At follow-up, patients did not show statistical differences in terms of BI and mRS score. Only a trend, but not statistically significant, was found in favor of RG for Disability of the Arm, Shoulder, and Hand, as shown in Table 4.

The interaction between time onset (≤ 30 and >30 days) and individuals' severity according to RG versus CG was explored with a Kruskal-Wallis analysis that did not find any statistically significant differences at T0 ($P=0.338$) among the 4 groups; conversely, significant differences were observed at T1 ($P=0.008$; Table 5).

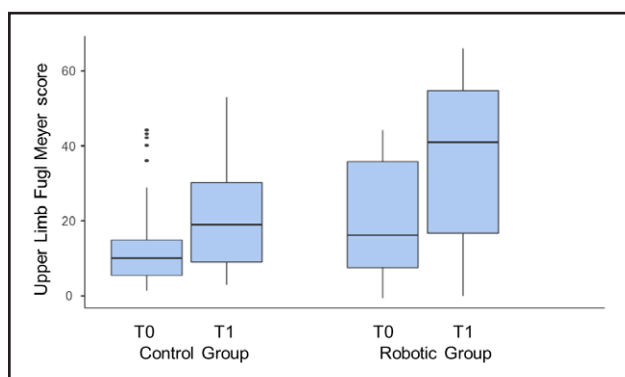


Figure 2. Box whiskers plot of Fugl-Meyer Assessment score for control and robotic groups, pretreatment (T0) and posttreatment (T1).

Post hoc *U* test showed a significant effect of R when participants had a distance since stroke onset <30 days, as shown in Table 6.

DISCUSSION

The primary hypothesis of this multicenter RCT was that UL-RAT integrated into the standard multidisciplinary rehabilitation program would result in greater motor and functional recovery than conventional therapy alone in inpatients with subacute stroke. This is supported by prior work suggesting the advantages of 3D exoskeletons in individuals with severe deficits.¹² However, robust RCTs testing 3D exoskeletons are lacking in the literature, as these devices were developed later than 2-dimensional end-effectors.^{10,12,15,16}

To our knowledge, this is the first multicenter, single-blind RCT evaluating a 3D exoskeleton during the early subacute phase, whereas most previous studies used planar end-effector devices, were monocentric, underpowered, or conducted in later stages of recovery. This study, therefore, expands the limited body of evidence by adopting a multicenter design, a standardized high-dose upper limb rehabilitation protocol integrated into clinical practice, and stratified randomization by both time since stroke onset and baseline motor impairment severity, addressing methodological gaps frequently observed in the field. The adoption of a 3D exoskeleton is additional element rarely explored in previous multicenter studies. These devices have demonstrated specific advantages in treating people with moderate-to-severe impairments.^{10,12,15} The key benefit of exoskeleton devices is their ability to deliver rehabilitation within a 3D workspace, even in severely affected individuals, thereby promoting more natural and functionally relevant movement patterns that may better engage sensorimotor brain networks and enhance neuroplastic mechanisms.^{11,13–15}

Our findings partially confirmed this hypothesis, as significant improvements were observed in motor impairment (FM-UL), while no significant changes emerged in activity or participation domains immediately after

Table 3. Contingency Table of Participants Who Overcame the MCID (10) With the FM

Contingency table	RG	CG	Total
FM _{T1} ≥ FM _{T0} + MCID	26 (68.4%)	14 (31.8%)	40
FM _{T1} < FM _{T0} + MCID	12 (31.6%)	30 (68.2%)	42
Total	38	44	82

CG indicates control group; FM, Fugl-Meyer; MCID, minimal clinically important difference; and RG, robotic group.

treatment. Thus, although RAT effectively reduces motor impairment, its translation into higher-level functional outcomes remains debated. A possible explanation for the superior results of robotic training may be related to baseline severity. More severe patients, as in our sample, have limited ability to participate effectively in conventional sensorimotor training, and RAT may offer the structure and intensity needed for effective motor engagement.¹²

In line with this, 68% of participants in the robotic therapy group achieved a clinically meaningful improvement of ≥10 points in the FM-UL motor score, compared with 31% in the conventional group (odds ratio, 4.64). This 22-point median between-group difference at T1 clearly exceeded the MCID, indicating a substantial clinical benefit and reinforcing the potential of early 3D exoskeleton-based therapy.

We acknowledge a baseline imbalance in FM-UL scores, which may have influenced between-group differences. Although randomization was used to ensure comparability, this imbalance likely reflects the intrinsic heterogeneity of subacute stroke recovery. To account for potential confounding factors, a covariate-adjusted analysis (ANCOVA) was conducted for sensory impairment and cognitive status, addressing aspects that are underrepresented in previous robotic rehabilitation trials. Although these variables showed slight baseline differences, they were not statistically significant and did not influence the main results; sensory scores were even lower in the RG than in controls at the end of treatment. Sex was tested as an additional potential confounder and showed a small, nonsignificant main effect, with no interaction. No significant interactions with treatment efficacy emerged.

Despite these covariates being considered, the high proportion of participants achieving clinically

Table 4. Median (Interquartile Range) for the Variables Assessed at Follow-Up (T2)

Follow-up	No. of participants (RG, CG)	RG	CG	P value
BI	23, 25	82 (40)	80 (20)	0.462
mRS score	24, 25	2 (2)	3 (1)	0.813
DASH	22, 19	112 (41)	91 (36)	0.082

Mann-Whitney *U* test between groups. BI indicates Barthel Index; CG, control group; DASH, Disability of the Arm, Shoulder and Hand; mRS, modified Rankin Scale; and RG, robotic group.

Table 5. Medians (Interquartile Ranges) of Fugl-Meyer Upper Limb Motor Part at T0 (Pre) and T1 (Post)

Group	DSO	T0 (pre), median (interquartile range)	T1 (post), median (interquartile range)	P value (Wilcoxon)
CG	≤30 d	8 (9)	20 (18)	<0.001
	>30 d	12 (9)	13 (24)	<0.001
RG	≤30 d	21 (29)	43 (30)	<0.001
	>30 d	12 (19)	37 (41)	<0.001

CG indicates control group; DSO, distance since stroke onset; and RG, robotic group.

meaningful improvement in the RG strengthens the robustness and clinical relevance of our results. Moreover, although FM-UL scores varied widely at T1 (Table 2; Figure 2), the observed between-group differences are unlikely to be solely explained by baseline imbalance, given that spontaneous poststroke recovery is nonlinear and influenced by multiple factors (eg, lesion location, extent), which are not fully captured by FM-UL alone.

On the other hand, the overall dose and intensity of UL-targeted rehabilitation, delivered through an intensive and specifically designed upper limb program, may have contributed to the favorable outcomes observed in both groups, consistent with evidence supporting a dose-response relationship in poststroke motor recovery.^{29,30} Importantly, all participants received upper limb-focused sessions, either exoskeleton-based or conventional, ensuring comparable and intensive UL-specific therapeutic exposure, while additional rehabilitation time was dedicated to other domains (eg, gait, balance, functional activities, cognitive or neuropsychological training). Despite these dose-matched conditions and the improvements achieved by both groups, the RG exhibited significantly greater gains, suggesting a specific therapeutic advantage of 3D exoskeleton-based training beyond the effect of overall rehabilitation intensity.

Our results align with previous pilot RCTs investigating exoskeleton use in subacute stroke patients.^{31–33} The benefits of a 3D exoskeleton are particularly evident in the stability it provides to the glenohumeral joint under

Table 6. Pairwise Comparisons—FM-UL Motor Part T1

		W	P value
CG<	CG>	−0.882	0.925
CG<	RG<	3.773*	0.038*
CG<	RG>	2.639	0.243
CG>	RG<	3.783*	0.038*
CG>	RG>	3.349	0.083
RG<	RG>	−0.682	0.963

Post hoc Mann-Whitney *U* test. CG indicates control group; FM-UL, Fugl-Meyer assessment for upper limb; RG, robotic group; and W, test statistic (standardized).

*Statistically significant values.

full gravity compensation, allowing more precise and controlled movement patterns during intensive arm training. This is especially beneficial for individuals with moderate-to-severe impairment, in whom abnormal movement patterns are more likely to emerge, particularly during the early stages of recovery.^{34,35} By contrast, our findings differ from those of the RATULS trial (Robot-Assisted Training for the Upper Limb After Stroke), a large multicenter RCT, which reported no superiority of UL-RAT over intensive training in stroke survivors.³⁶ However, RATULS used a planar end-effector device and enrolled patients at a median of 240 days poststroke, well beyond the subacute window. As highlighted in Cochrane reviews, subacute phase early intervention within the first 3 months is associated with greater responsiveness to RAT, underscoring the importance of our study's time window.^{10,37}

Moreover, whereas RATULS primarily assessed capacity-level outcomes with a biplanar device, our study focused on impairment-level motor recovery measured by the FMA and using a 3D exoskeleton. This approach aligns with the International Classification of Functioning, Disability and Health framework by addressing the domain of body structure and function, which is particularly relevant in the subacute phase, when neuroplasticity is more responsive to structured and intensive training.

Robotic therapy appears especially effective in stroke survivors with moderate-to-severe upper limb impairment, as shown both in our study and in prior work.³⁸

The controlled training environment and movement precision of 3D exoskeletons may explain these benefits. In individuals with mild motor impairment, kinematic assessments could detect subtle changes beyond conventional scales, which are prone to ceiling effects.^{38,39} Future studies should further investigate their potential to better define the role of RAT in this subgroup.

Although cost analysis was beyond the scope of this trial, it is acknowledged that robotic therapy entails higher initial investment and maintenance costs than conventional therapy. Nevertheless, when applied intensively across multiple patients and embedded in multidisciplinary programs, these costs may be amortized. Real-world evidence supports the short-term cost-effectiveness of mixed rehabilitation approaches integrating robotics.⁴⁰ Future multicenter cost-effectiveness studies, including centers with similar organizational models to ours, are warranted.

Our findings are consistent with multicenter studies such as the ROBOTAS trial, which identified key determinants of efficacy in robot-assisted upper limb rehabilitation.¹² By focusing on the subacute phase and applying a 3D exoskeleton, our study adds to this body of evidence, suggesting that early, intensive, and sensorimotor-enriched interventions may yield substantial improvements. Although we primarily assessed short-term outcomes, previous research has shown the potential for sustained functional improvement,⁴¹ underscoring the

importance of early integration of robotic therapy into rehabilitation pathways to optimize long-term recovery. Wu et al³⁴ also highlighted the value of 3D exoskeletons in stroke rehabilitation, noting that upper limb weight compensation enhances joint stability and prevents compensatory movements—an aspect particularly relevant for severely affected individuals in the subacute phase.

Considering the broader landscape of RAT, including both end-effector and exoskeleton devices, our findings are consistent with the conclusions of Cochrane reviews¹⁰ and recent overviews, such as the Italian Consensus Conference CICERONE, which confirmed the effectiveness of RAT, supporting its integration into neurorehabilitation programs.⁴¹ Other systematic reviews further support these results, reporting short- and medium-term functional gains and their persistence at follow-up.^{37,42}

Regarding secondary outcomes, dexterity improved in both groups, without additional gains from exoskeleton-based RAT, possibly due to the limited sample size of this subgroup. Similarly, spasticity did not significantly change, consistent with prior evidence that robotic therapy primarily enhances voluntary motor control rather than reducing reflex hyperexcitability.^{36,37} The modified Barthel Index, referred to global functional activity (International Classification of Functioning, Disability and Health activity level), showed a transient improvement not sustained at follow-up, likely reflecting its limited sensitivity to upper limb-specific changes, as lower limb or trunk function may dominate overall Activities of Daily Living (ADL) scores. A positive trend was observed in the arm activity scale, suggesting that intensive training during the subacute phase could have long-term benefits for upper limb function.

Some limitations in our study should be noted. The dropout rate was relatively high, particularly at the 6-month follow-up (52%), which limits the strength of long-term conclusions and may partly reflect challenges posed by the COVID-19 pandemic. Baseline imbalances between groups may also have influenced the results; however, the high proportion of participants who responded to robotic therapy supports the robustness of our primary findings. By applying an intention-to-treat approach and analyzing participants in their originally assigned groups whenever follow-up data were available, we aimed to minimize potential bias due to attrition and preserve comparability between treatment groups. Finally, we acknowledge that, although RAT consistently reduces motor impairment, its translation to higher-level functional outcomes remains debated.

In conclusion, UL-RAT with a 3D exoskeleton significantly enhances upper limb motor recovery when delivered within the first month poststroke, with 2 out of 3 participants in the intervention group achieving the MCID on the FM-UL scale compared with one in the conventional group. These findings underscore the importance of early intensive intervention in the subacute phase and

support the integration of exoskeleton-assisted therapy into rehabilitation programs, particularly for individuals with moderate-to-severe impairments. Further large-scale multicenter studies are needed to confirm these results, investigate underlying neuroplastic mechanisms, and assess both cost-effectiveness and long-term sustainability to promote broader clinical adoption.

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Author Contributions

Dr Morone, S. Pournajaf, and M. Franceschini conceptualized the study, designed the methodology, and supervised the research protocol. Dr Morone and S. Pournajaf provided guidance on clinical evaluations, contributed expert input on rehabilitation strategies, drafted the initial manuscript, and collaborated with Dr Iosa on data analysis and interpretation. Dr Iosa supported the study design, performed statistical analyses, and offered substantial input on the interpretation of results. Drs Straudi and Calabrò contributed to drafting the clinical sections and critically revised the manuscript. Drs Goffredo, Leo, Straudi, Calabrò, Paolucci, Gatta, and Santamato were responsible for participant enrollment, implementation of the rehabilitation protocols, and coordination of data collection at their respective sites. S. Pournajaf and Dr Franceschini, as Principal Investigators and study coordinators of the multicenter randomized controlled trial, supervised the research group, oversaw data collection, and approved the final manuscript. All authors reviewed and approved the final version of the manuscript for submission.

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figure S1
CONSORT Checklist

APPENDIX

The Italian PowerUPS-REHAB Study Group

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