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ORIGINAL COMMUNICATION

Age is negatively associated with upper limb recovery after conventional but not robotic rehabilitation in patients with stroke: a secondary analysis of a randomized-controlled trial

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Abstract

Background There is consistent evidence that robotic rehabilitation is at least as effective as conventional physiotherapy for upper extremity (UE) recovery after stroke, suggesting to focus research on which subgroups of patients may better respond to either intervention. In this study, we evaluated which baseline variables are associated with the response after the two approaches.

Methods This is a secondary analysis of a randomized-controlled trial comparing robotic and conventional treatment for the UE. After the assigned intervention, changes of the Fugl-Meyer Assessment UE score by ≥ 5 points classified patients as responders to treatment. Variables associated with the response were identified in a univariate analysis. Then, variables independently associated with recovery were investigated, in the whole group, and the two groups separately.

Results A sample of 190 patients was evaluated after the treatment; 121 were responders. Age, baseline impairment, and neglect were significantly associated with worse response to the treatment. Age was the only independently associated variable (OR 0.967, $p = 0.023$). Considering separately the two interventions, age remained negatively associated with recovery (OR 0.948, $p = 0.013$) in the conventional group, while none of the variables previously identified were significantly associated with the response to treatment in the robotic group.

Conclusions We found that, in our sample, age is significantly associated with the outcome after conventional but not robotic UE rehabilitation. Possible explanations may include an enhanced positive attitude of the older patients towards technological training and reduced age-associated fatigue provided by robotic-assisted exercise. The possibly higher challenge proposed by robotic training, unbiased by the negative stereotypes concerning very old patients' expectations and chances to recover, may also explain our findings.

Trial registration number NCT02879279.

Keywords Stroke · Rehabilitation · Upper extremity · Robotics · Predictors

Introduction

Despite continuous progress in the treatment of acute cerebrovascular disease, and development and testing of new rehabilitation strategies, stroke remains a catastrophic event with dramatic public health impact, causing 5 million deaths per year and a much larger number of survivors living with chronic physical and cognitive disability [1]. Of those presenting a motor impairment at hospital admission (more than two-thirds) [2, 3], only about 50% of those with the initial lower limb impairment ultimately recover ambulation [4], and upper limb motor and functional recovery are even more

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difficult [5]. Indeed, of those presenting arm paresis, only 8–20% fully recover the function of the affected arm after treatment, and 50% have problems with arm function 4 years after stroke [5]. This poor outcome clearly explains why the search for new strategies to improve upper limb functional recovery after stroke has been and still is a core element of rehabilitation research [6].

Updated reviews report some evidence of effectiveness for many different interventions, such as constraint-induced movement therapy, mental practice, mirror therapy, interventions for sensory impairment, virtual reality, and a high dose of repetitive task practices in improving upper limb function after stroke [7]. Repetitive training can also be provided by electromechanical and robotic devices, which can help to maintain or improve the upper limb range of motion in patients with hemiplegic arm, and assist active movements in patients with the paretic arm. Specifically, robotic devices can provide an increase in repetitions during arm training [8], and may also increase repetitive training motivation, while allowing the possibility of exercising independently from a physiotherapist's continuous assistance [9–11]. Indeed, robotic rehabilitation has the potential to provide many advantages in terms of standardization of tasks, real-time measurements and feedback, relief of physiotherapist's physical burden, and, most important, the intensity of training, which seems to be highly correlated to the promotion of neuroplasticity and neurophysiological recovery [9–11]. In the past 2 decades, electromechanical-assisted and robotic devices to improve upper extremity impairment and functional limitations after stroke have been developed and tested in a wide variety of stroke rehabilitation trials.

Recent relevant literature [12, 13] suggests that, provided the same amount of training, robotic upper extremity (UE) rehabilitation after stroke shows consistent evidence of being at least as effective as the conventional physiotherapy, suggesting to investigate which subgroups of patients may better respond to either intervention.

Indeed, a recent update of a previous Cochrane review by Mehrholtz et al. found high-quality evidence that the use of electromechanical-assistive devices in rehabilitation settings was associated with a slight improvement in activities of daily living, arm function, and arm strength, while they were safe and acceptable to most participants to the included trials [12]. The authors though point out that this did not prove that robot-assisted arm therapy after stroke is more effective than other interventions, since the possibility that a higher dose of treatment was applied by robotic-assisted rather than by other arm training could not be ruled out. On the other hand, a recent large RCT found evidence that a robot-assisted training by the MIT Manus robotic gym improved upper limb impairment more than Enhanced Upper Limb Therapy (EULT), based on repetitive tasks of the same frequency and duration, or usual care, according to the UK national quality standard. However, in the same trial, no significantly larger functional improvement was found for either of the three considered interventions, and neither robotic therapy, delivered with a one therapist:two patients ratio, nor EULT (one therapist:one patient) was cost-effective when compared to usual care [13]. Our Italian research group has also recently published a relatively large multicenter RCT comparing a technological intervention, delivered by robotic and sensor-based devices, versus conventional, individually delivered physiotherapy for upper limb rehabilitation after stroke. Both interventions were associated to improved motor and functional recovery with no significant outcome difference between them, except for a greater improvement of motricity after the technological intervention, delivered at a one therapist:three patients ratio [14]. Though apparently contradicting the Mehrholtz's review, the results of these studies converge to some pragmatically relevant evidence: when the amount of provided training is the same, robotic upper limb rehabilitation after stroke has at least similar positive motor and functional outcomes as the conventional physiotherapy, while no generalization is possible as to cost-effectiveness, which may vary according to the type of device and to the organizational model of delivery, especially regarding the therapist/patient ratio [15].

Thus, rather than pursuing the evidence of robotic rehabilitation being more effective over the conventional physiotherapy, we choose to focus our further research on the understanding of which patients may benefit more from either type of evidence-based intervention [12]. Lum et al. [16] suggested that robotic devices may be particularly effective in severely impaired patients who are unable to perform unassisted movements, while a subgroup analysis within the latest Cochrane review [12] reported that the greatest effects might occur in the first 3 months after stroke. A recent review [17] reported the factors that seem to predict functional outcomes after stroke rehabilitation. With respect to the upper limb, in the review, two studies were identified: Nijland et al. [18] found that the upper extremity Fugl-Meyer scale score for finger extension and the Motricity Index score for shoulder abduction predict the probability of achieving at least 10 out of 57 points on the Action Research Arm Test, while Stinear et al. [19] identified upper limb impairment, age, presence or absence of upper limb motor-evoked potentials elicited with transcranial magnetic stimulation, and stroke lesion load obtained from MRI, or stroke severity assessed with the NIHSS score, as predictors of excellent, good, limited, or poor upper limb outcome, based on the ARAT score. However, these studies do not assess the effect of different approaches. Other studies have suggested that recovery is strictly dependent on the baseline impairment: according to the so-called "proportional recovery rule", most stroke survivors recover a fixed proportion of lost UE function (about 70% of the maximal recovery potential) measured by the Fugl-Meyer scale [20–24]. However, this rule has been questioned because of methodological and statistical issues [25, 26].

The current study was aimed at identifying baseline patient characteristics that may predict response to either robotic or physiotherapy-based treatment in our RCT, and at verifying whether, in our sample, specific subgroups of patients may be more responsive to either intervention.

Methods

This is a secondary analysis focused on predictors of response to treatment assessed by the motor assessment of the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) scale [27] in a cohort of patients undergoing a randomized-controlled trial comparing robotic and sensor-based device rehabilitation versus conventional physiotherapy in upper limb stroke rehabilitation. Patients were enrolled in eight centers of the Fondazione don Carlo Gnocchi, a no-profit rehabilitation and research institution operating in nine different Italian Regions.

Trial registration

This trial was approved by the Fondazione don Gnocchi Ethical Committee (FDG_6.4.2016) and registered at clinicaltrials.gov (NCT02879279).

Participants

All patients accessing either of the eight involved Centers for stroke rehabilitation were considered for eligibility. Inclusion criteria were: (1) a first-ever stroke (cerebral infarction or hemorrhage), confirmed by CT or MRI; (2) a time since stroke ranging from 14 to 180 days; (3) age between 40 and 85 years; (4) cognitive and language abilities sufficient to follow instructions. Exclusion criteria were: (1) FMA-UE score > 58; (2) behavioral and cognitive disorders and/or reduced compliance that would interfere with active therapy; (3) fixed contraction deformity in the affected limb that would interfere with active therapy (ankylosis; Modified Ashworth Scale = 4); (4) inability to distinctly discriminate the images shown on a 22 monitor placed at the eye level of each subject at a distance of about 50 cm, even with corrective glasses. Eligible patients were asked informed consent to participate in the RCT. All participants gave informed consent according to the Declaration of Helsinki.

Treatment

Patients were randomized to the Robotic Group (RG), or the Conventional Group (CG). In the RG, patients were treated with a set of robotic- and sensor-based devices (Motore, Humanware; and Amadeo, Diego, and Pablo, from Tyromotion), while in the CG, the treatment focused on sensorimotor reprogramming, hypertonus inhibition, and functional improvement, including task-oriented exercises. In both groups, the treatment was performed daily for 45 min, 5 days/week, for 30 sessions. More details on the treatments are reported elsewhere [14]. All patients also underwent individual conventional physiotherapy (6 times/week), lasting 45 min, focused on lower limbs, sitting and standing training, balance, and walking. Furthermore, according to the team evaluation, patients underwent occupational and speech and neuropsychological therapy, as needed. After the experimental upper limb sessions, patients continued usual care rehabilitation focused on paretic limbs, sitting and standing training, balance, and walking.

Motor recovery assessment

Motor recovery was measured as changes from baseline of the Motor Assessment of the FMA-UE. Patients were evaluated at baseline and at the end of a 30-session rehabilitation intervention. According to the baseline impairment, as measured by the FMA-UE, patients were categorized as follows [28]:

1. Severe ($0 \leq$ FMA-UE ≤ 28);
2. Moderate ($29 \leq$ FMA-UE ≤ 42);
3. Mild ($43 \leq$ FMA-UE ≤ 66).

We have decided to group patients in severity categories, since different patterns of recovery are observed in patients with a different impairment at baseline. A similar approach was followed by other authors [29, 30].

After treatment, patients were classified as *responders* if the change from baseline of the FMA-UE was equal to 5 points, or higher; otherwise, they were classified as non-responders [31]. This threshold was already used as a reference to categorize patients with stroke as those with favorable prognosis or outcome and those with unfavorable prognosis after a rehabilitation intervention [32].

Statistical analysis

Differences between responders and non-responders were first analyzed using Student's *t* test, for continuous variables, the Pearson chi-squared test for dichotomous variables, or the Mann–Whitney *U* test for ordinal variables (univariate analysis). Variables significantly different between responders and non-responders in the univariate analysis ($p < 0.10$ [33]) were entered into a multivariable logistic regression predicting the probability of response. To internal validate the model, bootstrap-adjusted 95% confidence intervals (CI) on 5000 bootstrap samples were also computed. A P value lower than 0.05 was deemed significant. Statistical analysis was performed using SPSS (version 25).

Results

From August 2016 to October 2017, 631 subjects were assessed for eligibility; 247 patients met the inclusion criteria and, therefore, randomized either to the RG or the CG. Because of clinical problems, 23 patients were not assessed after randomization. Two hundred and twenty-four patients were assessed and received the allocated intervention (111 in the RG and 113 in the CG). The baseline characteristics of the enrolled sample are reported in Table 1. Of the 224 patients recruited, 34 patients did not complete the rehabilitation protocol and, therefore, considered as dropouts. Data from 190 patients who completed the treatment were used in this analysis.

After the assigned treatment, 121 patients (63.7%) improved their FMA-UE score of at least five points and classified as "responders", while the remaining 69 (36.3%) did not achieve the required cut-off and were consequently identified as "non-responders". Considering the severity of the impairment at baseline, as measured by the FMA-UE, about 57% of patients with severe impairment were responsive to the treatment, while a higher percentage (about 74%) was achieved when the baseline impairment was moderate-to-mild (Fig. 1). Similar percentages of baseline impairment were observed in the two rehabilitation groups (robotic and conventional, $\chi^2 = 1.549$, $p = 0.569$).

Table 1 Baseline characteristics of the enrolled sample ($N = 224$), according to the randomization groups

	Conventional group ($N = 113$)	Robotic group ($N = 111$)
Age (years)	68.5 (11.5)	69.5 (10.9)
Time since stroke (days)	45.3 (40.6)	48.0 (41.1)
Sex		
Man	64 (56.6%)	63 (56.8%)
Woman	49 (43.4%)	48 (43.2%)
Stroke type		
Ischemic	84 (74.3%)	81 (73.0%)
Hemorrhagic	29 (25.7%)	30 (27.0%)
Side		
Right	58 (51.3%)	48 (43.2%)
Left	55 (48.7%)	63 (56.8%)
Language impairment		
No	82 (72.6%)	97 (87.4%)
Yes	31 (27.4%)	14 (12.6%)
Neglect syndrome		
No	89 (78.8%)	89 (80.2%)
Yes	24 (21.2%)	22 (19.8%)
Fugl-Meyer Assessment (baseline)	21.8 (16.2)	25.0 (16.5)

Data are mean (SD) or absolute numbers (%)

The results of the univariate analysis are reported in Table 2. Age ($p = 0.020$), the severity of the impairment at baseline ($p = 0.068$), and the presence of a neglect syndrome ($p = 0.034$) were significantly different between responders and non-responders, while the sex, the type of stroke (ischemic or haemorrhagic), the affected side, the presence of a neglect syndrome, as well as the assigned treatment (conventional or robotic) did not.

Therefore, the aforementioned variables significantly different between responders and non-responders were entered in a multivariate logistic regression model (Table 3).

Considering the whole group, the model was statistically significant ($p = 0.010$, $R^2 = 0.092$), with the age as the only independent baseline variable associated with recovery (OR 0.967, $p = 0.023$, bias-corrected and accelerated bootstrap CI -0.066 to -0.001). Finally, we considered in the model patients in the CG and the RG, separately. In the CG (Table 4), the model was still significant ($p = 0.013$, $R^2 = 0.163$) and the age remained the only independent predictor of recovery (OR 0.948, $p = 0.013$, bias-corrected and accelerated bootstrap CI -0.101 to -0.005); conversely, in the RG (Table 5), the model was not statistically significant ($p = 0.603$, $R^2 = 0.041$) and none of the variables previously identified were significantly associated with the outcome.

Considering that the majority of non-responders were in the severe group, a sub-analysis was carried out in patients with an FMA-UE score lower or equal to 28 at baseline. Age was still significantly associated with recovery in the whole group ($p = 0.002$) and in the subgroup of patients undergoing conventional rehabilitation treatment ($p = 0.007$); conversely, considering only patients undergoing robotic rehabilitation treatment, age was not associated with recovery ($p = 0.145$). For the sake of clarity, Fig. 2 depicts the mean changes of the FMA-UE in different age groups, for the two rehabilitation approaches, separately. Patients' improvement decreases steadily in the conventional group starting from the 51–60 year age group, while a similar trend was not detected in the robotic group. It is worthy to note that, in the conventional group only, the mean value of the change from baseline of the FMA-UE in the oldest group of patients is below the minimal clinically important difference considered in this study.

Discussion

In a commentary to the updated 2018 Cochrane Review [34], Jan Mehrholtz points out that the first research remaining issue in studying upper limb robotic

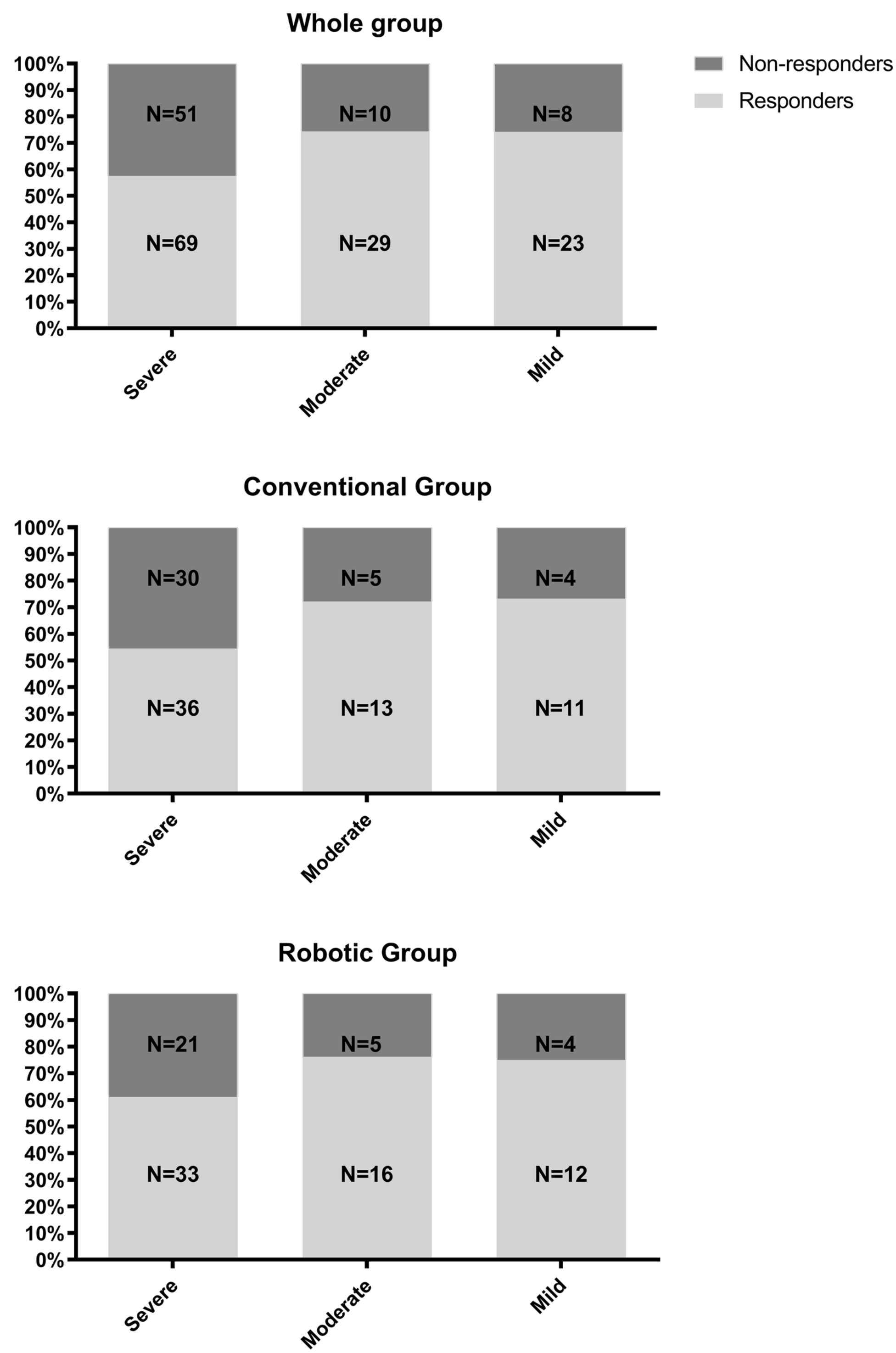

Fig. 1 Percentage of responders (according to a change in the upper extremity motor portion of the Fugl-Meyer Assessment ≥ 5) and non-responders in each severity group in the whole group of patients (top), and for patients treated with a conventional (middle) or a robotic (bottom) approach

rehabilitation for stroke patients is "to understand whether robotic devices may be particularly suitable or effective for specific subgroups of patients". Within the review, one subgroup analysis found that the greatest effects of robotic upper limb treatment may occur within the first 3 months after stroke, but this is true for most rehabilitation interventions [7].

Upper limb function after stroke has been shown to be predicted by stroke characteristics, such as stroke extension, cause, the severity of early neurological impairment, and by general patients' characteristics, such as age, comorbidities, and any-cause pre-stroke impairment or disability [35]. Upper limb initial motor impairment is known to be also strongly correlated to final functional outcome [22]. A

Table 2 Differences between the responders and the non-responders, according to the univariate analysis (*N* = 190)

	Non-responders (*N* = 69)	Responders (*N* = 121)	*P**
Age (years)	71.0 (11.2)	67.0 (11.2)	0.020
Time since stroke (days)	48.0 (41.3)	48.6 (43.4)	0.927
Baseline impairment			
Mild	8 (25.8%)	23 (74.2%)	0.068
Moderate	10 (25.6%)	29 (74.4%)	
Severe	51 (42.5%)	69 (57.5%)	
Sex			
Man	38 (35.5%)	69 (64.5%)	0.794
Woman	31 (37.3%)	52 (62.7%)	
Stroke type			
Ischemic	53 (37.9%)	87 (62.1%)	0.460
Hemorrhagic	16 (32.0%)	34 (68.0%)	
Side			
Right	32 (34.4%)	61 (65.6%)	0.592
Left	37 (38.1%)	60 (61.9%)	
Language impairment			
No	53 (35.3%)	97 (64.7%)	0.297
Yes	16 (40.0%)	24 (60.0%)	
Neglect syndrome			
No	50 (35.3%)	103 (64.7%)	0.034
Yes	19 (51.4%)	18 (48.6%)	
Group			
Conventional	39 (39.4%)	60 (60.6%)	0.357
Robotic	30 (33.0%)	61 (67.0%)	

Data are mean (SD) or absolute numbers (%)

*According to Student's t test, the Pearson chi-square test, or the Mann–Whitney *U* test, as appropriate

preliminary analysis conducted in our previous paper had shown that age and baseline impairment, as measured by the FMA-UE score, were the only baseline characteristics associated with improved rehabilitation outcomes, measured as an improvement of the FMA-UE score by at least five points from baseline to the end of treatment [31] in the whole study population, while no significant association was found for time from stroke, affected side, type of stroke, and assigned treatment [14].

In the present study, using the same cut-off of the FMA-UE score to identify responders and non-responders, we first performed a univariate analysis, but, to define the degree of upper limb impairment severity, in agreement with the literature [28], we classified patients according to FMA-UE score as having a severe, moderate or mild impairment, As expected, responders were significantly younger and presented less baseline motor impairment than non-responders; furthermore, they were also less likely to present unilateral spatial neglect [35–37]. When these factors were introduced into a multivariate regression analysis on the whole study population, age remained the only independent predictor of response to treatment. It is noticeable that, to the purpose of this pragmatic clinical RCT, we had included patients of a wide age range, to reflect what is really encountered in clinical practice, and older patients were overall more impaired than their younger counterparts. However, when we performed a separate analysis comparing predictors of response to treatment in RG vs CG, older age remained significantly associated with worse response to conventional treatment, while no baseline considered factor predicted response to robotic treatment.

The different effects of age between CG and RG response to treatment are a promising finding. Indeed, in our sample, we seem to have found a peculiarity of robotic/technological rehabilitation to escape the rule of older age predicting worse rehabilitation outcomes, which definitely deserves attention and further investigation. In support of our evidence, when searching on predictors of response to robotic treatment, we remarkably failed to find studies that identified age as influencing response to robotic treatment. In a Taiwanese study on 55 hemiparetic stroke patients undergoing robotic rehabilitation, only greater baseline manual dexterity had a higher probability of achieving clinically significant motor and functional outcomes after robotic therapy [38]. A 2018 Italian retrospective analysis was conducted on 60 stroke patients who attended robotic upper arm rehabilitation with the InMotion 2.0 robot, showing that manual

Table 3 Multivariate analysis: independent predictors of response in the whole group of patients (*N* = 190)

	B	SE	Wald	*P* value	OR	95% BCa CI
Age	− 0.034	0.015	5.194	0.023	0.967	− 0.066 to − 0.001
Neglect = yes*	− 0.505	0.398	1.605	0.205	0.604	− 1.292 to 0.311
Severity = moderate**	0.748	0.438	2.926	0.087	2.114	− 0.220 to 1.596
Severity = mild**	0.539	0.466	1.340	0.247	1.714	− 0.469 to 1.655
Intercept	2.955	1.073	7.589	0.006	19.199	0.411 to 4.947

BCa CI bias-corrected and accelerated bootstrap confidence interval

*Ref: no

**Ref: severe

Table 4 Multivariate analysis: independent predictors of response in the conventional group ($N=99$)

	B	SE	Wald	P value	OR	95% BCa CI
Age	−0.053	0.021	6.137	0.013	0.948	−0.101 to −0.005
Neglect = yes*	−0.796	0.566	1.979	0.159	0.451	−1.988 to 0.410
Severity = moderate**	0.746	0.628	1.408	0.235	2.108	−0.568 to 1.991
Severity = mild**	0.384	0.676	0.322	0.570	1.468	−1.692 to 2.120
Intercept	4.037	1.532	6.945	0.008	56.640	0.619 to 7.576

BCa CI bias-corrected and accelerated bootstrap confidence interval

*Ref: no

**Ref: severe

Table 5 Multivariate analysis: independent predictors of response in the robotic group ($N=91$)

	B	SE	Wald	P value	OR	95% BCa CI
Age	−0.014	0.021	0.420	0.517	0.986	−0.068 to 0.036
Neglect = yes*	−0.199	0.583	0.116	0.733	0.819	−1.462 to 1.042
Severity = moderate**	0.709	0.616	1.326	0.250	2.033	−0.642 to 2.071
Severity = mild**	0.584	0.650	0.806	0.369	1.793	−1.101 to 2.066
Intercept	1.792	1.542	1.350	0.245	6.000	−1.971 to 5.296

BCa CI bias-corrected and accelerated bootstrap confidence interval

*Ref: no

**Ref: severe

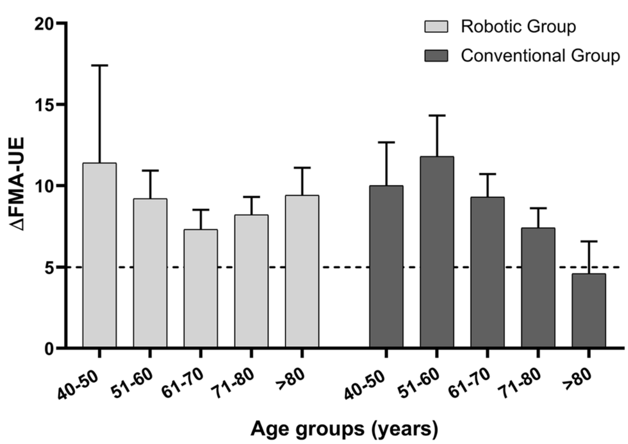

Fig. 2 Mean changes from baseline with standard errors of the Upper Extremity Fugl-Meyer Assessment (ΔFMA-UE) in different age groups, for the two rehabilitation approaches, separately. The dotted line represents the minimal clinically important difference of the FMA considered in this study

dexterity and higher baseline upper limb motor scores were independent predictors of a favorable functional outcome, while demographics, spasticity, and passive mobility were not [39]. Finally, a 2019 Korean study on 48 hemiplegic patients who performed upper limb rehabilitation using RAPAEL Smart Glove found that only baseline Mini-Mental State Examination and manual function test scores were significant predictors of functional recovery [40]. Age was included as a possible predictor of response to treatment in all three studies, but regression analyses always failed to find an independent predictive effect of age on response to any of the considered robotic intervention, in contrast to what universally reported for physiotherapy-based interventions [37, 41]. This was also true for another Italian study on robotic lower limb stroke rehabilitation, where, again, age was not a significant predictor of improved functional ambulation after robotic training [42].

The dynamic crossing of aging with the two-way human/machine interaction in robotic therapy may explain these consistent findings [43]. One clinical observation, common to physiotherapists of all the eight Centers involved in our RCT, was that, as opposed to what they expected, older persons seemed the most enthusiastic participants to robotic rehabilitation. Possibly, the improvement in motivation, due to the feedback provided by the device or to the novelty of technology-based rehabilitation [34], would be enhanced on older persons, since they are generally less used to technology in their previous life experience; furthermore, their appreciation of the technology, for instance of the serious games proposed by our devices, would be less critical than that of persons already familiar with commercial videogames [44]. However, this is only speculation as, unfortunately, we did not investigate on patient's perception and appreciation of the received treatment, nor did we assess the psychological effects associated with either intervention.

Old and very old persons interact every day with different kinds of technologies, with increasing competence and interest [45], yet little work investigates how aging may change meaning, access, and use of technologies [46, 47]. As to conventional physiotherapy, there is long-standing evidence that the healthcare providers' attitude towards the old/very old patients is influenced by their views on aging and older persons, often reflecting deeply rooted negative stereotypes. Kvitek et al. have shown that therapists were significantly less aggressive in their goal setting with the elderly patient, and those reporting a more negative attitude towards aging [9–11] were also significantly less aggressive in goal setting [48]. More recent studies confirm that this negative attitude in healthcare still exists, and influences the perception of geriatric rehabilitation of medical, nurse, and physical therapy students [49, 50].

In analogy to what has been reported for job selection, where the technology may help overcome the human bias against older persons, by selecting on skills and aptitude, rather than on the face, age, and visual presentation of the person [51], it is then possible that technology may provide rehabilitation tools less biased than humans, offering a more diverse approach to recovery. Actually, the robot is, by definition, unbiased to patients' age or other personal characteristics. Even if the robot is set and supervised by a physiotherapist, robotic training is associated with higher progressive challenge and goal setting, with specific and gradual task progression, based on the objective measure of patients' progressive achievements [8], and, thus, possibly, less dependent on what they are "expected" to desire or achieve.

Theoretically, many other aspects of robotic rehabilitation may be particularly advantageous when training older, often comorbid, and frail patients [52]. Robots can provide a measure and simultaneous feedback of the rehabilitation progress, which may increase attention and motivation [53, 54]. Furthermore, using robots, repetitive exercises can turn into games, by far a more engaging task [55]. Finally, robotic training may allow prolonged repetitive movements by a reduced patients' physical and mental workload, compared to physiotherapy [56, 57], thus lessening patients' as well as therapists' fatigue [58]. All these aspects deserve specific further investigation as, again, to our knowledge, no study was conducted on age as possibly modulating these positive effects.

This study acknowledges many limitations. First, our results must be taken with caution, as the power of analysis was reduced by dividing our sample into two groups. Furthermore, due to the retrospective nature of this analysis, we could not consider many other factors that may have predicted outcome in these patients undergoing intensive rehabilitation after a catastrophic disabling event, such as integrity of the corticospinal tract [18], finger extension and shoulder abduction early after stroke [21], and markers of complexity [59]; quite possibly, this failure may explain why we did not find any baseline variable associated with response to treatment in the robotic group; a previous analysis on a subgroup of our sample suggested that also previous cognitive ability and professional role may specifically influence response to robotic or physiotherapy-based treatment [60], but this should be verified after considering the possible confounding influence of post-stroke cognitive impairment [61]. Thus, further research is needed to validate these findings and identify other potential baseline factors that associate with robotic rehabilitation outcomes. Were indeed our results confirmed, their translational impact would be remarkable, as, whatever the underlying mechanism, older persons, who are traditionally doomed to a worse rehabilitation outcome after stroke, may possibly be less disadvantaged when allowed to attend also robotic rehabilitation.

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Compliance with ethical standards

Conflicts of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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