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ORIGINAL RESEARCH ARTICLE

Association of physiotherapy dose with motor recovery in early subacute phase after stroke: results from a multicenter Italian study

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ABSTRACT

Introduction: The literature investigating the factors associated with functional recovery after stroke suggests that, in the early subacute phase, time is the factor that most significantly drives the recovery. However, it is unclear whether the dose of physiotherapy (PT) delivered is equally associated with recovery of motor function and independence.

Methods: A multivariable modeling of data from a multicenter longitudinal prospective cohort study investigating the contents of neurological PT interventions in Italy was developed, with the aim to estimate the association between the dose of PT received in the early subacute phase after stroke and recovery of walking, motor function, and independence.

Results: A total of 96 patients were included in the analyses. PT dose seems associated with recovery of manual dexterity, measured by the Box and Block test (BBT), but not with the level of independence nor walking function. The probability of achieving a score higher than 31 at the BBT is 46% (95%CI: 18-76) after 10 hours and 76% (95%CI: 42-93) after 20 hours of PT, respectively.

Conclusions: In the early subacute phase after stroke, the higher the dose of PT provided, the better the probability of significant recovery of upper limb (UL) dexterity should be.

Keywords: Dose, Expected recovery, Physiotherapy, Stroke

What is already known in this topic:

- *In the first 3 months after stroke, time is the most influential factor associated with recovery of motor functions.*

What does the study add:

- *In the first 3 months after stroke, increasing the physiotherapy (PT) dose seems associated with improvement of outcomes for manual dexterity but may require more nuanced approaches or additional interventions to show measurable impacts on broader, more complex domains of recovery.*

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Introduction

Stroke is the second cause of death and one of the leading causes of disability worldwide (1). The consequent neurological impairment dramatically impacts the daily independence and quality of life of stroke survivors (2). Functional recovery is thought to be driven by a combination of spontaneous biological processes and mechanisms involving motor re-learning and the acquisition of new skills (3). While behavioral restitution occurs mostly in the acute (1-7 days) and early subacute phase of recovery (7 days to 3 months), adaptation and compensation can continue to sustain improvement at the activity level in the chronic phase after stroke (4). Recently, an Italian multicenter study highlighted that in neurological physiotherapy (PT), walking recovery consistently emerges as the primary goal, followed by upper limb (UL) functional recovery (5). Moreover, the average hours spent on gait training were approximately twice that of those allocated to manipulation exercises in people with stroke (PwS). Interestingly, independence in activities of daily living (ADLs) was ranked only fifth in priority.

Walking recovery after a stroke typically occurs within the first 3-6 months, with most of the improvement occurring in the first 10 weeks, but with different rates based on stroke severity and individual factors (6). Analogously, the independence in ADLs, as measured by the Barthel Index (BI), achieves the highest recovery rate typically within the first month after discharge. This improvement continues for 6 months, with many PwS reaching a functional plateau.

A previous study found that initial BI scores, age, and cognitive status play a key role in modifying recovery trajectories. Those subjects with higher BI at discharge, especially more than 60 points, show a tendency to maintain or improve their ADLs independence over time (7). Other evidence showed that PwS experienced recovery in different domains, including upper limb (UL) function and gait, following a logarithmic-like trajectory, reaching a plateau around 10 weeks after the event (8).

Despite the crucial role of rehabilitation in fostering sensorimotor recovery after stroke, there is still inconclusive evidence on the interaction between rehabilitation and neurological mechanisms involved in behavioral restitution after stroke, especially in the early subacute phase (4). Moreover, studies investigating changes in UL quality of movement after rehabilitation suggested that rehabilitation is likely to induce adaptive and compensatory mechanisms rather than behavioral restitution (9). Possibly reflecting these considerations, in the subacute phase, time has been found to be the major driver of recovery (10), whereas, in later phases, rehabilitative treatments promote clinically significant effects. Indeed, there is strong evidence suggesting that a high dose of practice can induce clinically significant changes in the recovery of UL motor function, (11,12) lower limb strength (13), and walking activity (14). The dose of PT in neurological rehabilitation is defined by specific measures such as the intensity (defined as the amount of physical or mental work put forth by the patient during a particular movement or series of movements, exercise, or activity during a therapy session, and as the session's length in minutes), frequency (e.g., number of sessions per week) and duration (e.g., how many sessions in total or for how many weeks) (15,16). Recently, research on this topic has begun to explore the influence of the dose of rehabilitation, offering initial insights suggesting that the dose may indeed be associated with better functional recovery after strokes (17-20). However, these studies have predominantly focused on specific domains, like UL function and activity, and a clear statistical association or interaction between PT dose and motor recovery has not been demonstrated. Moreover, this approach has not yet been applied to more general domains, such as quality of life and levels of independence.

Aims

The primary aim of this study was to investigate the association between PT dose and motor recovery in PwS. The secondary aim was to identify clinical and demographic features that might be associated with rehabilitation-induced motor recovery.

In summary, our hypothesis is that the PT dose may be an additional component of motor recovery of specific UL functions during the early subacute phase after stroke, whereas it could be more challenging to discern its impact in broader domains like gait recovery and independence in ADLs.

Methods

Study design

Data for this longitudinal study are retrieved from a multicenter longitudinal prospective cohort study investigating the contents of neurological PT interventions in Italy (5). The multicenter network comprised seven facilities including UO di Riabilitazione Specialistica, Presidio ospedaliero San Carlo Borromeo, ASST Santi Paolo e Carlo, Milan (Center 1); Azienda Ospedaliera Universitaria Ospedali Riuniti di Ancona Torrette (Center 2); Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno Infantili, University of Genova (Center 3); Presidio Sanitario San Camillo, Torino (Center 4); Università degli Studi di Trieste (Center 5); IRCCS San Camillo, Venezia (Center 6); IRCCS Santa Maria Nascente, Fondazione Don Carlo Gnocchi, Milan (Center 7).

Details on the ethics committees and recruitment methods are described elsewhere (5).

Participants

For the purpose of our work, we analyzed only PwS included in the acute and early sub-acute phase (0-12 weeks) after stroke and with rehabilitation goals of improving manipulation, gait, or independence in ADL. Individuals under 18 years of age or those unable to comprehend the study protocol were excluded.

Physiotherapy interventions

PwS completed PT sessions according to the Italian National Healthcare System (NHS). Each physiotherapist in charge of the PwS was free to choose the most appropriate intervention according to the patient's need as in daily clinical practice, then completed the PT Interventions Form (i.e., a checklist gathering information on PT goals, e.g., walking or hand dexterity) and intervention details (e.g., PT hours, type of exercises performed, etc.). This allowed us to characterize the PT dose (in hours) dedicated to each specific goal and to investigate PT effects using the appropriate outcome measure. To minimize the assessment burden, physiotherapists were requested to fill out the "PT Intervention Form" only at the conclusion of the rehabilitation program.

Clinical assessment and outcome measures

All the participants were clinically assessed at two time points: baseline and after the intervention (follow-up). An experienced clinical researcher who was not involved in the PT sessions conducted all the clinical assessments. Motor function was assessed before and after treatment using the following outcome measures: Modified Barthel Index (BI) score (21), a measure of physical disability used widely to assess behavior relating to ADL with higher scores indicating a lower level of disability; Two-Minute Walk Test (2MWT) distance (22) to evaluate walking performance, that is the distance walked in two minutes along a 30 m walkway; Box and Blocks test (BBT) score (23), which measures unilateral gross manual dexterity and consists in the number of blocks carried out from a box to a close one overtaking a barrier in one-minute. For quantification of stroke severity, the National Institutes of Health Stroke Scale (NIHSS) (24) was used (0-42 points, where 0 represents intact neurological functions and 42 very severe stroke).

The dose of PT was reported both as total dose (i.e., total hours of therapy for each goal – manual dexterity, walking, and independence) and through specific metrics, including frequency (number of sessions per week), intensity (minutes for the session) and total duration (total number of sessions), for each rehabilitation center involved in the project.

Statistical analysis

Data are presented as mean and ±1 standard deviation (SD) or median and interquartile range (IQR), as appropriate. Metrics of interest are also reported as the difference between follow-up and baseline, expressed as the mean difference with 95% confidence intervals (CI) and as the count and percentage of individuals above the minimal clinically important difference (MCID). For the subacute PwS, the MCID known from the literature is 6 points for the BBT (25) and 31 meters for the 2MWT (26), while it is not known yet for the BI. The Wilcoxon signed-rank test was used to assess whether paired samples showed statistically significant differences, defined as a p-value of <0.05. We investigated the association between PT dose (hours) and the outcomes of interest (e.g., BI, 2MWT and BBT at follow-up) by fitting three semiparametric ordinal regression models: (i) the BI-model included age (years), sex (male/female), weeks post-stroke, and baseline Barthel score as adjusting covariates; (ii) the 2MWT-model included age, sex, weeks post-stroke, baseline 2MWT distance, and baseline BI score as covariates. Age and 2MWT distance were modeled using restricted cubic splines with three knots at 0.10, 0.50, and 0.90 quantiles; and (iii) the BBT model was adjusted for weeks post-stroke and baseline BBT score on top of the dose. The Huber-White method was applied to account for correlated responses across different rehabilitation centers. Models were selected based on minimizing the Akaike Information Criteria function. The choice of variables for each model was determined by the authors' expertise, which was within the limitations of the available data. In the BI model, dose refers to the total hours of PT received. In the 2MWT model, the dose specifically reflected the hours dedicated to improving gait capacity and endurance, while in the BBT model, it referred to the hours focused on enhancing hand dexterity.

Each model was validated using 200 bootstraps. Performance was reported as an optimism-corrected R^2 index and as Van Houwelingen-Le Cessie's heuristic shrinkage factor. Model estimates are accompanied by 95%CI and are expressed as predicted means and exceedance probabilities. All the analyses were performed using R Core Team 2023, version 4.4.0, with rms and Hmisc packages added (27).

Results

In total, 119 PwS were screened for inclusion and exclusion criteria, and 96 were included in the present study. Among them, 78 performed PT aiming at improving walking capacity and 31 aiming at improving manual dexterity and upper limb function. Noteworthy, some PwS underwent both UL and walking rehabilitation. In those cases, for each analysis, only the PT dose associated with the specific aim was considered. Clinical and demographic data on the included sample are reported in Table 1. A description of specific dose parameters is reported for each center involved in supplementary materials (Table S1).

TABLE 1 - Sample description at baseline

Variables at baseline	BI-model (N = 96)	2MWT-model (N = 78)	BBT-model (N = 31)
Sex (male/female)	56 (58%)/40 (42%)	44 (56 %)/34 (44%)	19 (61%)/12 (39%)
Age (years)	69.4 (12.3) 71.0 [63.5; 78.5]	70.7 (11.1) 73 [64; 79]	67.5 (12.2) 69 [61; 75]
Time from lesion (weeks)	3.4 (2.8) 2.4 [1.3; 4.4]	3.4 (2.9) 2.4 [1.3; 4.4]	3.1 (3.0) 1.9 [1.0; 3.7]
Unknown (n)	1	–	–
NIHSS score	5.4 (3.32) 5 [3; 7]	5.2 (3.27) 5 [3; 6]	5.46 (4.39) 3 [2; 9]
Unknown (n)	62	53	20
PT dose (hours)	31 (20) 25.0 [1.4, 44.0]	12.5 (9.5) 9.5 [5.6; 17.5]	9.9 (8.1) 7.5 [3.9; 14.0]
Unknown (n)	7	–	–

Values are reported as counts and percentages (%), mean(sd), and median [Q1; Q3]. NIHSS: National Institute of Health Stroke Scale; BI: Barthel Index; 2MWT: 2 minutes walking test; BBT: box & blocks test; sd: standard deviation; Q1: first quartile; Q3: third quartile; PT: physiotherapy.

Baseline and follow-up analysis for the three groups showed statistically significant improvements in the specific outcome measures (Table 2). The 59.3% (16/27) and 49.2% (37/75) of PwS showed an improvement in the BBT score and 2MWT distance equal to or above the MCID (e.g., ≥6 blocks and ≥31 m, respectively).

Results of the BI model showed that time since stroke (χ^2 = 6.6; p = 0.01) and BI at baseline (χ^2 = 41.9; p < 0.001) are the only factors associated with the BI score at follow-up (Fig. 1). With an average dose of 31 hours, the mean expected BI is 87 (95%CI: 83.5-90.4). Sex (χ^2 = 2.3; p = 0.133), dose

TABLE 2 - Performance improvement after physiotherapy

Outcome measure	Baseline	Follow-up	Mean difference [95% CI]	p-value
BI [points] (N = 96)	54.1 (23.8)	80.58 (20.1)	26.3 [21.5–31.1]	<0.001
2MWT [m] (N = 78)	39.1 (42.9)	77.4 (43.8)	38.8 [30.5–47.2]	<0.001
BBT [blocks] (N = 31)	17.4 (17.0)	27.1 (16.7)	9.7 [5.9–13.5]	<0.001

Values are reported as mean (standard deviation) for baseline and follow-up scores; BI: Barthel Index; 2MWT: 2 minutes walking test (in meters); BBT: box and blocks test; CI: confidence interval.

(χ^2 = 0.15; p = 0.702), and age (χ^2 = 1.2; p = 0.281) do not show evidence of association with BI at follow-up.

Figure 2 shows exceedance probabilities of follow-up BI scoring ≥50, ≥75, and ≥91 (e.g., moderate, mild, and minimal functional dependency, respectively) as a function of time. Probabilities of Barthel ≥91 at one week are 59.1% (95% CI: 37.5-77.7), 54.7% (95%CI: 34.1-73.9) at two weeks and 45.8% (95%CI: 25.4-67.7) at 4 weeks.

Results of 2MWT-model (Fig. 3) show that only 2MWT at baseline (χ^2 = 43.6; p < 0.001) is statistically associated with the 2MWT follow-up, with no evidence of association for age (χ^2 = 5.5; p = 0.064), time since stroke (χ^2 = 0.9; p = 0.334), dose (χ^2 = 0.4; p = 0.531), sex (χ^2 = 0.2; p = 0.638) and BI at baseline (χ^2 = 0.02; p = 0.878).

Results of the BBT model (Fig. 4) show that dose (χ^2 = 6.4; p = 0.011) and BBT at baseline (χ^2 = 36.9; p < 0.001) are statistically associated with BBT at follow-up. Ten and twenty hours of PT are associated with a final mean BBT of 30 (95% CI: 26-34) blocks and 36 (95%CI: 30-42) blocks. Weeks since stroke are not statistically associated with BBT score (χ^2 = 0.7; p = 0.399), with a small difference when starting one or three weeks after stroke, 29 (95%CI: 24-34) blocks, and 28 (95%CI: 24-32) blocks, respectively.

Exceedance probabilities of scoring above 50 and 90 percentiles of the predicted mean BBT are represented in Figure 5. Probabilities of BBT ≥31 blocks are 46% (95%CI: 18-76) and 76% (95%CI: 42-93) when doing 10 and 20 hours of PT, respectively.

Overall, R^2 overfitting corrected is 35%, 47%, and 74% in the BI, 2MWT, and BBT models, respectively. Overfitting (γ) is above 0.86 except in the 2MWT model, presenting with γ = 0.76, indicating some overfitting. Detailed coefficients of each model are presented in Supplementary Materials (Table S2).

Discussion

The main message of this study is that in the early subacute phase after stroke, PT dose supports manual dexterity recovery; timely intervention is key for regaining independence, but the factors influencing walking recovery remain unclear.

We did not find an association between the PT dose and the BI. However, we found that the probability of regaining a level of independence decreases over time following a stroke, suggesting that earlier initiation of rehabilitation is linked to better recovery outcomes, whereas rehabilitation dose seems less relevant.

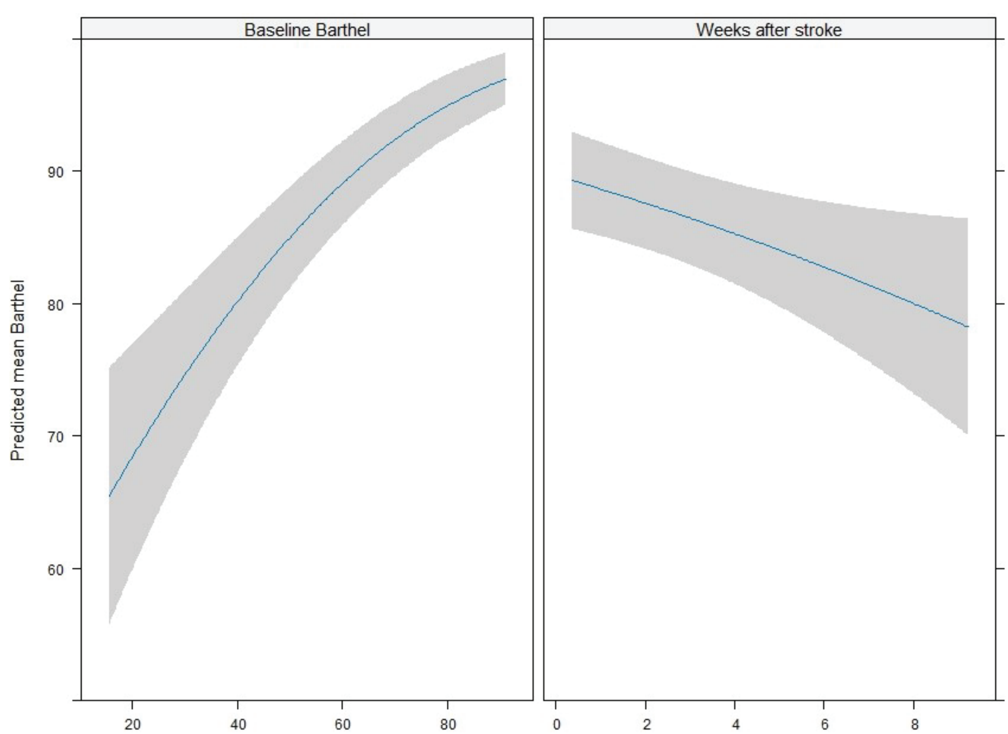

FIGURE 1 - Partial effect plot of BI-model. Partial effect plots show how baseline Barthel and weeks after stroke are associated with the predicted mean BI score. Grey bands denote 95%CI.

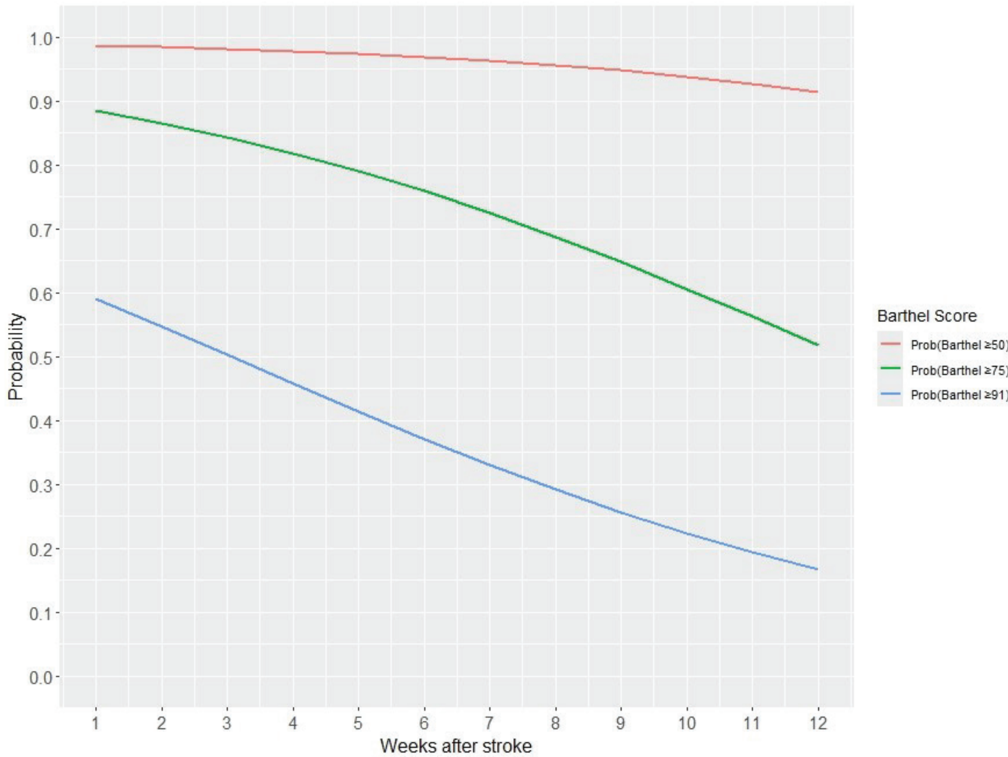

FIGURE 2 - Exceedance probabilities of Barthel Index as a function of time since stroke. Exceedance probabilities (i.e., Prob) of scoring equal or above clinically relevant BI thresholds, according to the fitted model.

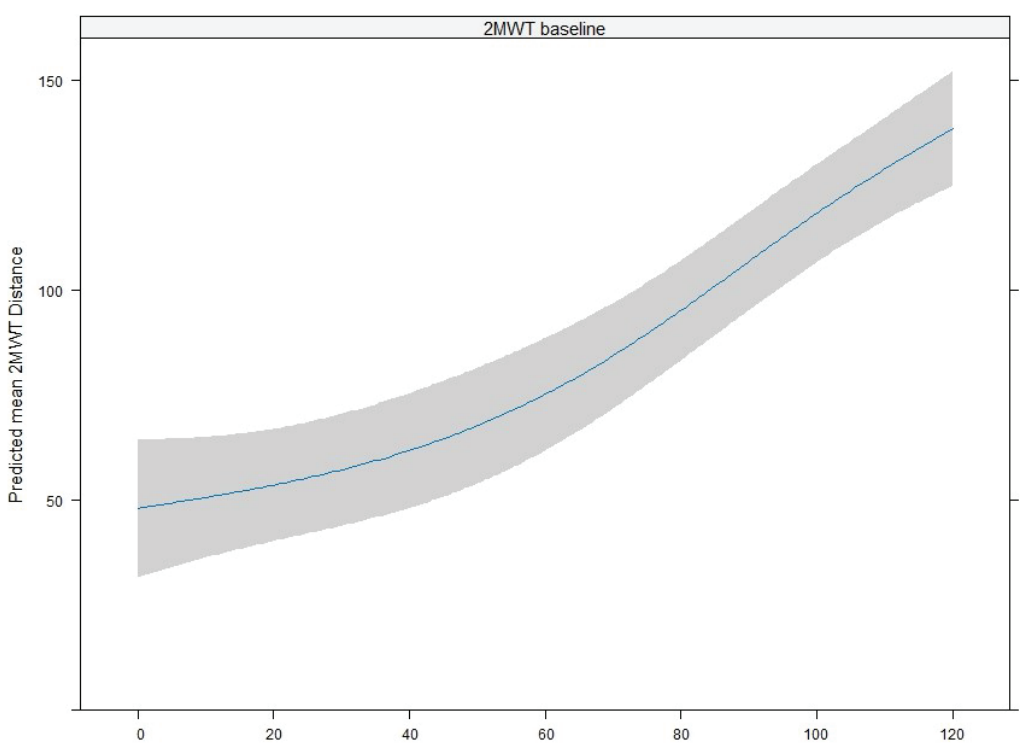

FIGURE 3 - Partial effect plot of 2MWT-model. Partial effect plot of baseline 2MWT [m] distance against 2MWT model prediction, with evidence of non-linearity (χ^2 = 6.9; p = 0.009). Grey bands denote 95%CI.

Given the results of the 2MWT model, it is worth considering that the 2MWT primarily assesses endurance rather than speed. Therefore, it is possible that the training provided was not endurance-specific, which would clarify the absence of association with PT dose. Moreover, the domain of walking is quite broad and likely influenced by factors

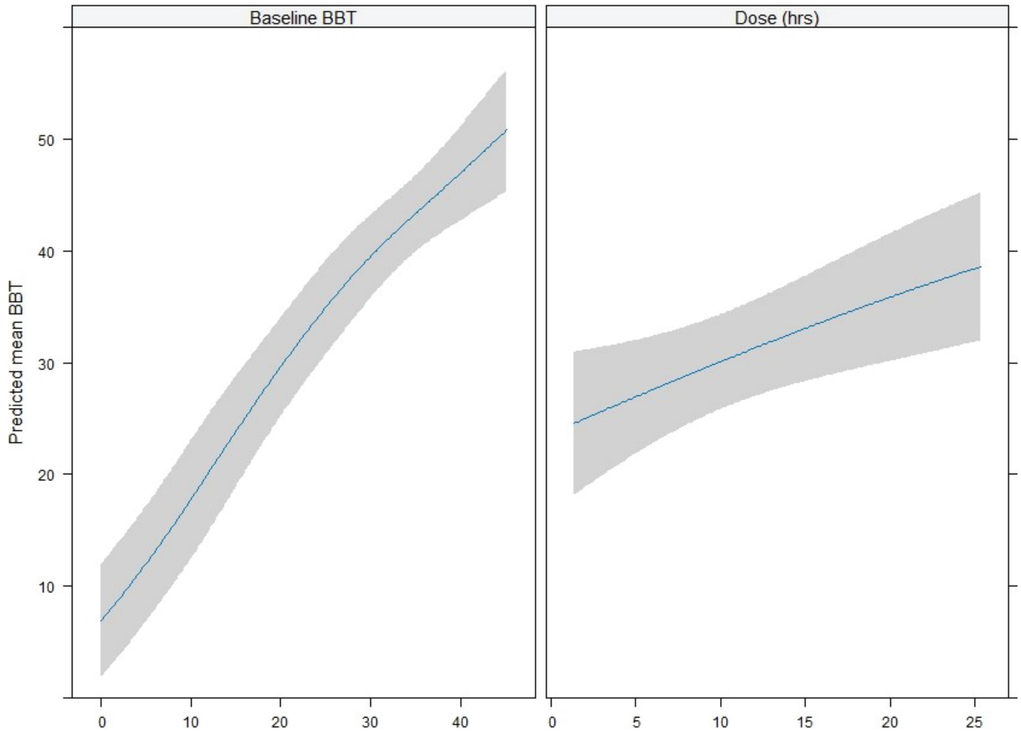

FIGURE 4 - Partial effect plot of BBT-model. Partial effect plot of mean Baseline BBT and Dose. Grey bands denote 95%CI.

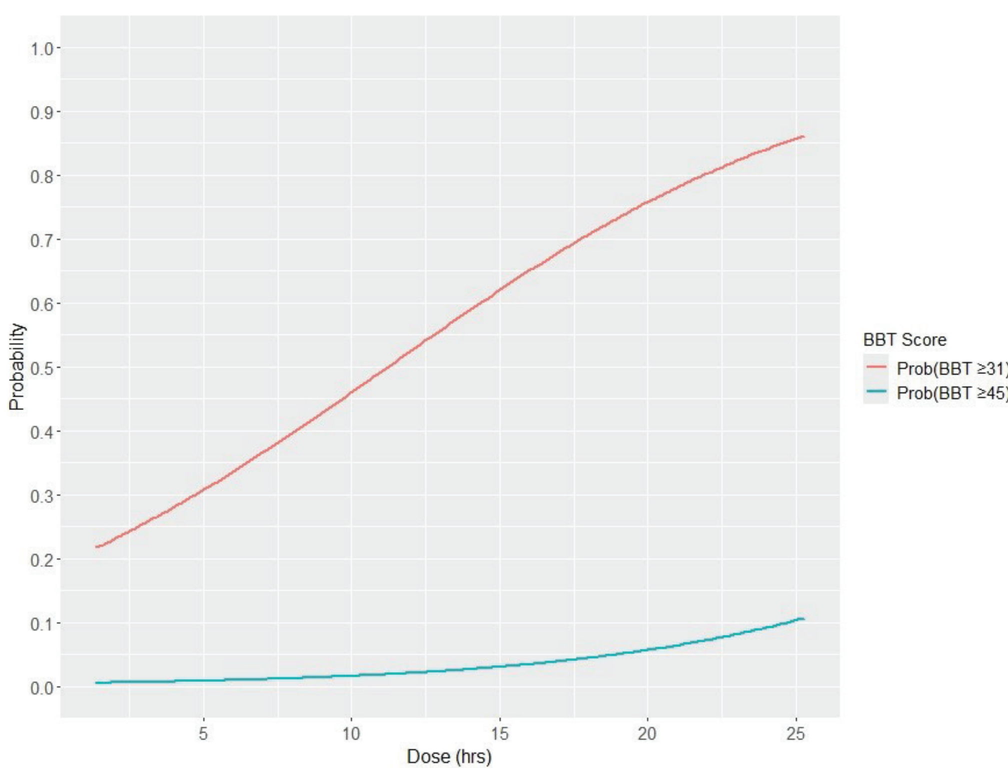

FIGURE 5 - Probabilities of BBT improvement according to increasing PT dose. Exceedance probabilities (i.e., Prob) of scoring equal or above 50 (BBT > 31) and 90 (BBT > 45) percentiles of mean BBT, according to the fitted model.

beyond specific training interventions, as well as other elements not directly related to training, suggesting a more complex interplay of variables contributing to overall performance. Indeed, walking is a motor activity that requires both sensorimotor and cognitive functions, such as muscle strength, balance, proprioception, cardiovascular fitness, and visual abilities (28-32).

Considering the relevance of time since stroke, available literature suggested that starting PT early during the acute to subacute stroke phase with a higher dose may enhance walking capacity, but the evidence remains limited (14,33). For example, a previous study found that PwS can improve their walking recovery with higher doses (2 hours, 5 days/week) of aerobic and stepping activity within a critical time period for neurological recovery (14).

Another relevant aspect related to walking recovery is the specificity of the intervention. For instance, gait-oriented training (30 minutes, three to five times per week) showed promising results, but the factors associated with gait recovery are still unclear (32). Although the results are not statistically significant, it is interesting to note that PwS who were able to walk >60 meters in 2 minutes before treatment seem to recover more rapidly than those walking shorter distances. Clinically, this finding suggests that PwS should be encouraged to walk more to support recovery, while those unable to do so require careful monitoring and guidance toward alternative movement strategies. Training should be tailored to baseline performance, recognizing that progress may vary. In particular, PwS walking less than 60 meters in the first weeks after stroke should receive closer supervision and targeted support for alternative mobility approaches.

The PT dose was found to be associated with the BBT score in the early subacute phase after stroke in PwS undergoing PT.

For expected recovery of manual dexterity, its probability of recovery increases with increasing PT dose. The relationship between manual dexterity and dose suggests that part of the observed recovery may not solely be attributed to spontaneous recovery but rather to the effects of rehabilitation. This contrasts with results found for walking function and level of independence, where such association was not established. Moreover, for manual dexterity, the timing of initiation of rehabilitation treatment, whether starting a week earlier or later, has little effect on the overall outcome. Our results suggest that maintaining consistent and targeted work overtime should be encouraged throughout the subacute phase of recovery after the stroke. Worth mentioning is the fact that our findings fit into a broader scientific context where it is still unclear what works and why with PwS. We may not be able to conclude that rehabilitation dose does not impact some recovery domains. Perhaps simply not enough was provided. Additionally, it remains uncertain whether the interventions used were based on principles of motor control, motor learning, or neuroplasticity, as recently suggested in the field (34,35). Our results reflect the current reality of rehabilitation in Italian settings but should serve as a warning to adopt a broader perspective, both on recovery mechanisms and on the decision-making processes behind the interventions proposed.

Limitations of our study should be mentioned. First, there could be a recruitment bias since participants were selected according to the availability of centers. Furthermore, we examined the PT dose in terms of the total amount of hours, not frequency, number of repetitions, or specific time on task, which would be more accurate parameters. Finally, since the recruited PwS were following the rehabilitation program provided by the Italian NHS, it is possible that, in addition to PT, they were also undergoing concurrent therapies for which it was not possible to track the dosage (e.g., occupational therapy). This is due to a standardized data collection method across all centers that prioritized the acquisition of simple but consistent data over complex information storage, which would have led to a high risk of data loss. Moreover, the dose used in our models refers specifically to the goal-specific dose, not the total dose or the dose provided by individual centers. The latter was included only descriptively, as making inferences about the effects of different doses would have required a different study design with a priori hypotheses (e.g., randomized controlled trial). Instead, this work reflects conventional practices within the Italian NHS.

Conclusion

In the early subacute phase after stroke, PT dose seems associated with recovery of manual dexterity, not with level of independence or walking function recovery. Our findings suggest the idea that in the early subacute phase of recovery of the UL dexterity, *the more rehabilitation, the better the outcome*. Future research on this topic should use a prospective study design to validate our findings, including treatment frequency and intensity as crucial components of the overall treatment dose.

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Conflict of interest: The authors declare they have no conflict of interest.

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Data availability statement: The data presented in this study are available on request from the corresponding author.

Authors contribution: Conceptualization: T.B. and D.C.; methodology: T.B., F.G.M.M., F.M., A.T., S.M. and D.C.; data collection: T.B., F.G.M.M., S.S., F.M., C.A., S.B., V.B., M.G., F.G.M., E.P., M.P. and A.T.; data analysis: N.V., S.G., S.S.; writing – original draft preparation: S.S., N.V., S.G.; writing – review and editing: S.S., F.M., C.A., S.B., V.B., M.G., F.G.M., E.P., M.P., A.T.; supervision: S.M., F.G.M.M. and D.C.; project administration: T.B, F.G.M.M. and D.C.

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