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Ph.D. COURSE IN NEUROSCIENCE
XXXVI SERIES

INVESTIGATION OF CLINICAL FEATURES AND NEURAL SUBSTRATES UNDERPINNING UPPER LIMB IMPAIRMENT AND RECOVERY OF VOLUNTARY MOTOR BEHAVIOUR, AFTER STROKE

Thesis written with the contribution of IRCCS San Camillo Hospital by Industrial Ph.D.

Coordinator: Prof. Antonino Vallesi

Supervisor: Prof. Dante Mantini

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PUBLICATIONS USED IN THE THESIS

- In chapter 3, materials from **Salvalaggio, S.**, Boccuni, L. & Turolla, A. Patient's assessment and prediction of recovery after stroke: a roadmap for clinicians. Arch Physiother 13, 13 (2023). https://doi.org/10.1186/s40945-023-00167-4, under licence CC BY 4.0 © have been used.
- In chapter 6, materials from **Salvalaggio S**, Cacciante L, Maistrello L, Turolla A. Clinical Predictors for Upper Limb Recovery after Stroke Rehabilitation: Retrospective Cohort Study. Healthcare (Basel) 2023;**11**(3) doi: 10.3390/healthcare11030335, under licence CC-BY 4.0 © have been used.
- In chapter 7, materials from **Salvalaggio S**, Turolla A, Andò M, Barresi R, Burgio F, Busan P, Cortese AM, D'Imperio D, Danesin L, Ferrazzi G, Maistrello L, Mascotto E, Parrotta I, Pezzetta R, Rigon E, Vedovato A, Zago S, Zorzi M, Arcara G, Mantini D and Filippini N (2023) Prediction of rehabilitation induced motor recovery after stroke using a multi-dimensional and multi-modal approach. Front. Aging Neurosci. 15:1205063. doi: 10.3389/fnagi.2023.1205063, under licence CC-BY 4.0 © have been used.

OTHER PUBLICATIONS OVER THE ACADEMIC YEARS 2020-2023

- Cacciante L, Pregnolato G, **Salvalaggio S**, et al. Language and gesture neural correlates: A meta-analysis of functional magnetic resonance imaging studies [published online ahead of print, 2023 Nov 16]. Int J Lang Commun Disord. 2023;10.1111/1460-6984.12987. doi:10.1111/1460-6984.12987
- Bowman, T.; Mestanza Mattos, F.G.; **Salvalaggio, S**.; Marazzini, F.; Allera Longo, C.; Bocini, S.; Gennuso, M.; Materazzi, F.G.; Pelosin, E.; Putzolu, M.; et al. Classification and Quantification of Physical Therapy Interventions across Multiple Neurological Disorders: An Italian Multicenter Network. J. Clin. Med. 2023, 12, 6483. https://doi.org/10.3390/jcm12206483
- Pregnolato, G.; Rimini, D.; Baldan, F.; Maistrello, L.; **Salvalaggio, S.**; Celadon, N.; Ariano, P.; Pirri, C.F.; Turolla, A. Clinical Features to Predict the Use of a sEMG Wearable Device (REMO®) for Hand Motor Training of Stroke Patients: A Cross-Sectional Cohort Study. Int. J. Environ. Res. Public Health 2023, 20, 5082. https://doi.org/10.3390/ ijerph20065082

- **Salvalaggio, S**.; Kiper, P.; Pregnolato, G.; Baldan, F.; Agostini, M.; Maistrello, L.; Turolla, A. Virtual Feedback for Arm Motor Function Rehabilitation after Stroke: A Randomized Controlled Trial. Healthcare 2022, 10, 1175. https:// doi.org/10.3390/healthcare10071175
- Rutkowska, A.; **Salvalaggio, S**.; Rutkowski, S.; Turolla, A. Use of Virtual Reality-Based Therapy in Patients with Urinary Incontinence: A Systematic Review with Meta-Analysis. Int. J. Environ. Res. Public Health 2022, 19, 6155. https:// doi.org/10.3390/ijerph19106

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To the strength to overcome fears,

to the passion for evolution…

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ABSTRACT

Prognosis of recovery has always covered an important role in medicine, due to its relevance for monitoring and interpreting patients' achievements over time. According to Hippocrates, prognosis is a way of interpreting life as a continuum along the past, the present and the future, and not only as a sample of data points.

After stroke, clinicians, patients and caregivers always ask what is likely to be expected for their clinical conditions and life in the future, and what the best therapeutic options might be for them. Medicine has always tried to answer these questions through studies on factors able to forecast the future, considering the path of spontaneous neurological recovery. Even research in rehabilitation has always attempted to predict motor recovery by studies assessing and measuring functional aspects of movement. What is missing so far, is that we do not know how rehabilitation interventions may change the pattern of recovery after stroke, causing uncertainty on the potential of recovery of each patient, in response to specific interventions. In this perspective, being familiar with interpreting initial signs and symptoms, selecting the most appropriate assessment strategy and using prediction models is pivotal to be timely and clinically efficient.

Within this framework, we faced the important terminological issue of the concepts of *Prognosis* and *Prediction.* Prognosis, indeed, refers to the expected outcome in absence of intervention, while Prediction refers to the expected outcome in response to rehabilitation. Moreover, it is now widely accepted that patients are underdosed and do not receive enough rehabilitation.

With the aim of introducing a novel concept of prediction, focused on the expected recovery in response to rehabilitation rather than spontaneous recovery, we have conducted a series of studies (i.e. systematic review, retrospective and longitudinal studies) designed to identify potential predictive factors and investigate the impact of different doses and modalities of therapy.

In particular, we found that factors known as predictive (e.g. age, muscle strength) of spontaneous upper limb (UL) motor recovery do not predict rehabilitation-induced recovery, in subacute and chronic stroke survivors. Indeed, UL motor recovery is associated with brain lesion characteristics, genetic features and residual attentive and motor function at baseline. Moreover, higher dose of treatment leads to higher motor response, with different effect according to the type and doses of intervention. However, implementation of robust and agreed methodologies for the development of prognostic studies in rehabilitation should be implemented.

FOREGROUND OF THE PhD

The leading idea of the present PhD project started from a clinical question in my mind: *which is the motor outcome I can expect in a person survived to a stroke? Which is the chance of recoverying upper limb motor function when I provide rehabilitation to them?* I tried to find an answer from the literature and retrived some studies proposing algorithms, that collecting measurements in the first 72 hours after the event allowed to prognose the expected recovery 3 to 6 months later, but it was not enough for my practice. Indeed, in the real rehabilitation clinical practice, is common that those specific measurements collected precisely within 72 hours are not available, thus recovery prediction for these patients is inaccurate. Moreover, these algorithms do not consider what patients received as rehabilitation care during the observation period (from 72 hours, to 6 months after stroke), arguing that expected recovery can just be considered as a result of spontaneous mechanisms. Again, in real clinical practice happens that we meet a patient at different phases after stroke, always needing assessment of their impairments to decide a rehabilitation program to be delivered. Therefore, I wanted to understand how to predict an expected recovery based on rehabilitation provided. In this regard, a step back was done to understand what are current limitations of prognosis studies proposed so far. First of all, we found that the methodology for prognostic studies was not always followed, indeed, studies often confused the concept of prognosis with the concept of association, not considering appropriately the difference between prognosis and prediction. Secondly, we looked for the determinants of recovery not only based on characteristics of the patient, but also on characteristics of the treatment. Therefore, we designed and conducted three studies with different methodologies trying to answer our research questions from various perspectives.

1. STROKE

1.1 Definition and Epidemiology

Stroke is a neurological and cerebrovascular disease, characterised by clinical signs and diagnostic evidence of focal injury of the Central Nervous System (CNS)[1]. Stroke is the second leading cause of death and a major cause of disability worldwide. Its incidence increases with age, doubling after the age of 55, even though in people aged between 20 and 54 years it is increasing globally [2]. Worldwide, the highest incidence of stroke has been reported in China (331 to 378 individuals per 100,000 life years), followed by eastern Europe (181 to 218 per 100,000 life years) and the lowest in Latin America (85 to 100 per 100,000 life years)[3]. In addition, a higher number of young people are affected by stroke in low and middle-income countries. Ischemic stroke (85%) is more frequent than haemorrhagic (15%), but the latter is responsible for more deaths and disability-adjusted life-years lost [2,4]. In general, risk of stroke is higher in women at younger ages, whereas it slightly increases with older age in men[2]. Moreover, patients with haemorrhagic stroke gain greater functional motor improvements than patients with ischemic stroke, despite patients with haemorrhagic stroke suffer from worse impairment and more severe clinical conditions at baseline [5]. Both brain infarction and intracerebral haemorrhage (ICH) are common in men, but cardioembolic stroke is more prevalent among women [2]. Incidence and mortality of stroke differ among countries, geographical regions, and ethnic groups, but everywhere represents a social health issue [6].

1.2 Pathophysiology

Stroke is characterised by blockage of blood vessels in the brain, by clots interrupting blood flow, clogging arteries and causing blood vessels ruptures, with potential bleeding. Rupture of the arteries leading to brain stroke results in the sudden death of cells due to lack of oxygen [2].

The main general categorie of type of stroke are ischemic and haemorrhagic [1].

- **Ischemic stroke** can be generated by both thrombotic or embolic occlusions in the brain arteries. In thrombosis, the blood flow is interrupted by narrowing of vessels due to atherosclerosis, which may constrict the vascular chamber and form clots causing stroke [7]. Embolic stroke, instead, occurs when clots migrate from a site to distal cerebral arteries causing decreased blood flow or reduction of brain tissue perfusion, then cell death (i.e. necrosis) [2]. Cardioembolic stroke generally affects cortical regions and may affects both hemispheres [8].

- **Haemorrhagic stroke** is caused by a rupture of blood vessels due to stressors at the level of brain tissues. The main reasons for intracerebral haemorrhage (ICH) are hypertension, excessive use of anticoagulants and thrombolytic agents [2].

Overall, risk factors associated with stroke onset can be classified in non-modifiable and modifiable **[Table 1]** [2].

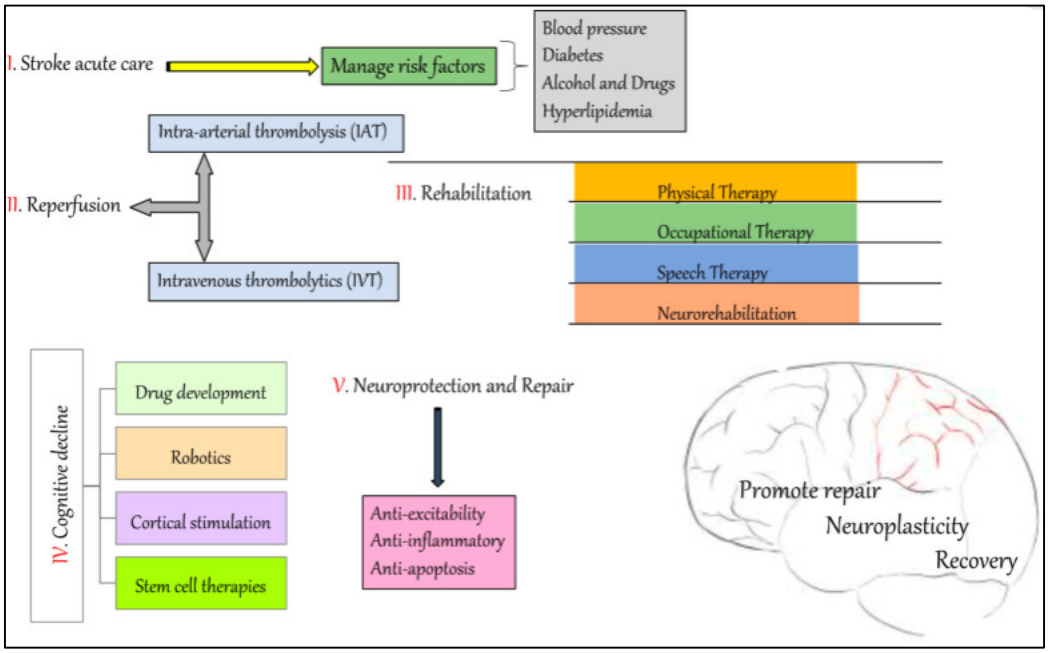
Table 1. Risk factors associated with stroke onset

Non-modifiable risk factors	Modifiable risk factors
• Age *(e.g. 69.2 years average age of stroke onset)* • Sex *(e.g. women > men)* • Race/ethnicity *(e.g. Hispanic and black population > white population)* • Previous Transient Ischemic Attack (TIA) • Genetics *(e.g. family history of stroke)*	• Hypertension • Smoking • Alcohol and Drug abuse • Physical inactivity and poor diet • Hyperlipidaemia • Diabetes mellitus • Atrial fibrillation

Anyway, a cornerstone of clinical neurology is that stroke causes many distinct neurological syndromes reflecting damage in specialized cortical and subcortical brain areas. The anatomy of stroke is predominantly subcortical (basal ganglia, central white matter, thalamus) in 80% of cases, while cortical lesions are less common (20%) and mostly occurring in the middle cerebral artery (MCA) [8].

The overall process to manage the incidence of stroke is wide and multifactorial, as proposed in **[Figure 1]** [2]. Among the potential treatments following a stroke, there are pharmacological interventions, stem cell therapies, as well as treatments targeting glycemic control and hypertension. Of primary interest for the present PhD thesis, there are the rehabilitative interventions, aimed at enhancing the functional independence of the affected individuals to the greatest extent possible. Stroke rehabilitation may encompass physical, occupational, speech, and/or cognitive therapy. Its purpose is to aid patients in regaining problem-solving skills, accessing social and psychological support, enhancing mobility, and attaining independent living. In particular for stroke rehabilitation, some indications proposed by the clinical guidelines of the various countries will be presented in chapter 2 (paragraph 2.4), as well as NICE 2023 guidelines [9].

Figure 1. Management process of stroke incidence



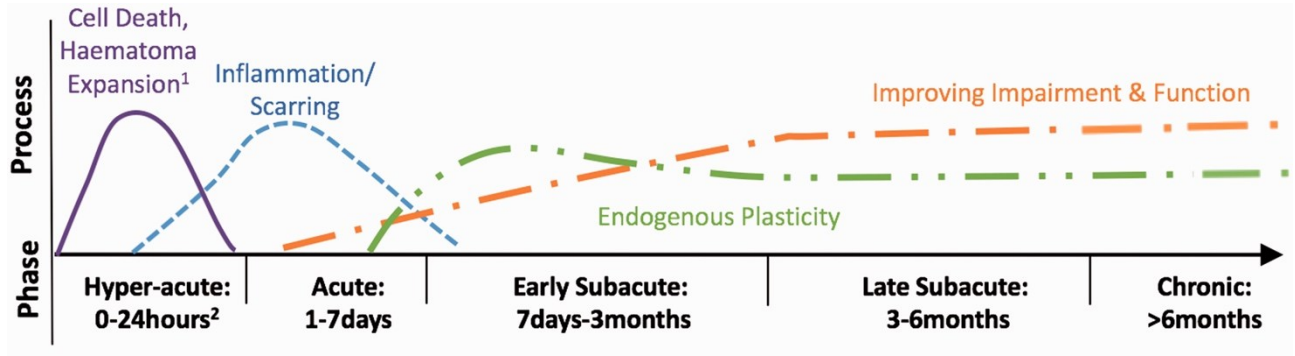
The image represents a step-procedure of stroke management, starting from the acute care to the diverse levels of rehabilitation process.

(From Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. Int J Mol Sci. 2020 Oct 15;21(20):7609. doi: 10.3390/ijms21207609. PMID: 33076218; PMCID: PMC7589849 [2] reproduced under licence CC-BY).

1.3 Principles and timeline of Recovery after stroke

After damage in the motor system, recovery may be driven by both spontaneous biological mechanisms and behavioural restitution or compensation [10] [11]. **Behavioural restitution** is defined as a return towards more normal patterns of motor control with the impaired effector (i.e. the body part that interacts with an object of the environment). **Compensation**, instead, is the patient's ability to accomplish a goal through substitution with a new approach, rather than using their normal pre-stroke behavioural patterns [10] [11]. Compensation does not require neural repair, but may require motor learning [12]. A fundamental challenge for rehabilitation field is to determine the optimal timing and modalities of interventions to be provided for recovery and repair, after stroke. However, to allow this target, it is first necessary to share common vocabulary of timeline after stroke. With this aim, the Stroke Recovery and Rehabilitation Roundtable taskforce has developed a framework, based on updated knowledge of biological mechanisms of recovery in the brain to maximise the potential of restorative interventions by targeted treatments **[Figure 2]** [12].

Figure 2. Definitions' framework of critical timepoints post stroke that link to the currently known biology of recovery

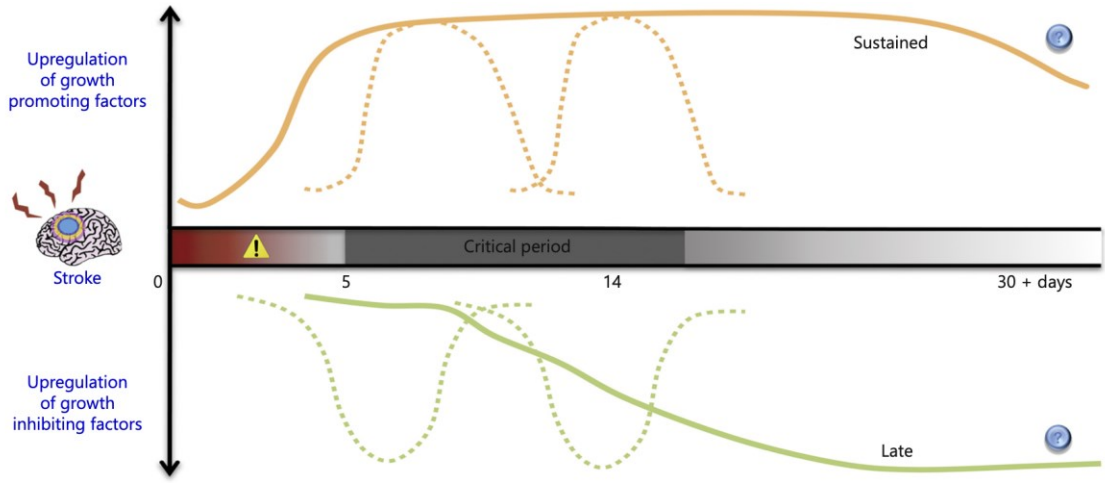


The image represents the classification phases after stroke, the respective biological processes (i.e. purple, light blue, green) and the recovery goals (i.e. orange) over the period considered.
1 Haemorrhagic stroke specific; 2 Treatment extend to 24 hours to accommodate options for anterior and posterior circulation, as well as basilar occlusion.

(From Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, Krakauer JW, Boyd LA, Carmichael ST, Corbett D, Cramer SC. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke. 2017 Jul;12(5):444-450. doi: 10.1177/1747493017711816. PMID: 28697708, [12], reproduced under license CC-BY 4.0).

In rodent models, the first days after stroke represents the *"critical period"* characterised by upregulation of growth promoting factors and inhibition of growth inhibitory proteins **[Figure 3]** [13]. This pattern of gene expression after stroke represents a *"neural niche"* where brain plasticity processes are more responsive to rehabilitation [14,15]. Therefore, rehabilitation after stroke should take into consideration this opportunity for enhancing motor learning, then starting intervention soon after lesion.

Figure 3. Critical period of post stroke rehabilitation



The figure represents the critical period of the early post-stroke recovery phase, during which a sustained upregulation of growth-promoting genes predominates (solid orange line). Most growth-inhibitory genes (i.e. solid green line) tend to be upregulated gradually, several weeks after stroke, toward the end of the critical period of stroke recovery. A few growth-promoting and growth-inhibiting genes are transiently upregulated (i.e. dashed lines) in the early and mid post-stroke recovery period. This critical period is observed in animal studies and might be different in the case of human stroke, where spontaneous recovery can extend for the first 90 days after injury.

(From Corbett D, Nguemeni C, Gomez-Smith M. How can you mend a broken brain? Neurorestorative approaches to stroke recovery. Cerebrovasc Dis. 2014;38(4):233-9, [13], under licence agreement no. 5504721356304 acknowledged by Cerebrovascular Diseases on 9th March 2023).

1.4 Upper limb motor impairment after stroke

The UL plays a pivotal role in human beings, given its versatility and functionality in performing various activities of daily living. Therefore, impairment in its functioning leads to limitations in activities of dailiy living (ADLs) and restriction in independence and participation. Consequently, one of the main aim of neurorehabilitation is minimizing sequelae and improving recovery [16].

Manual dexterity is a hallmark of human upper limb (UL) function which requires valid motor control for both reaching function (e.g. for transporting the hand to the object) and hand and fingers coordination. Moreover, functional abilities are required to control strength and precision, synergistic or individualised finger movements, flexibility and stability of all body disctricts [17]. Among stroke survivors to a first onset, the most common impairment affects UL sensorimotor functions, with 60%-80% of patients experiencing acute hemiparesis, leading to a reduction in the level of activities and participation [18,19]. These impairments typically affect one side of the body contralateral to the lesioned hemisphere. Impairments of the motor function can be related to diverse aspects of voluntary movements, such as motor planning, execution, learning and control. Clinically, they are ascribed as loss or limitation of motor function and motor control, pain and

muscle tone alterations and fluctuations [20]. In the first 4 weeks after lesion, flaccid hemiplegia may happen, that is the total abolition of voluntarily recruitment of motor units, reduction of muscle tone and absence of reflexes [21]. This condition may be followed by a progressive muscle tone and reflexes restitution, together with muscle contraction. In some cases (4%-42%), spasticity may occur, which is a condition of an abnormal hypertonia and hyperreflexia mainly on the antigravity muscles, caused by lesion of the corticobulbar or descending fascicles of the reticular midbrain formation [22]. Spasticity may also result in abnormal involuntary movements (e.g. clonus, Babinski sign, hypertonia, hyperreflexia) with impairment in executing voluntary movements (e.g. muscle weakness, loss of manual dexterity and finger individuation) [23]. However, in the long term, the chronic non-use and extintion of voluntary activation of the affected limb in execution of functional tasks, as in ADLs, could favour the development of plastic changes also in the cortical areas *("learned non-use"* phenomenon) by further reducing the capacity of the CNS to voluntarily recruit motor units [21]. Conversely, when patients are required to perform movements beyond their residual motor skills, they might use compensatory strategies potentially preventing proper motor recovery, whether established and strengthened along time *("learned bad-use"* phenomenon) [21,24]. Also impairment of sensation function may affect motor control, due to a different body representation and alteration or loss of feedback conveyed by movement execution [21]. Generally, motor deficits of the UL are greater for the distal muscles, than for the proximal muscles, although sometimes in the first few days after the event movements involving activation of the proximal (e.g. reaching) and distal (e.g. grasping) muscles may be similarly impaired, or even the former more than the latter. The longer the time from injury, the more compensation occurs with increased trunk involvement or synergistic activation of the shoulder and elbow, as a strategy implemented by the preserved descending tracts to compensate for distal impairments [25].

1.5 Role of the Corticospinal Tract in UL motor function

The corticospinal tract (CST) is the major neural tract in the human brain responsible for voluntary control of body muscles. It is part of the pyramidal tract, together with the corticobulbar tract [26,27]. It is made by a synapse between the 1st motor neuron in the cerebral cortex and the 2nd motor neuron at the level of the anterior horn of the spinal cord. The CST has three origins:

- The primary motor cortex (M1) – Betz cells, V layer, precentral gyrus
- The secondary motor area: Supplementary motor area (SMA) and Premotor cortex (PMC)
- The somatosensory cortex

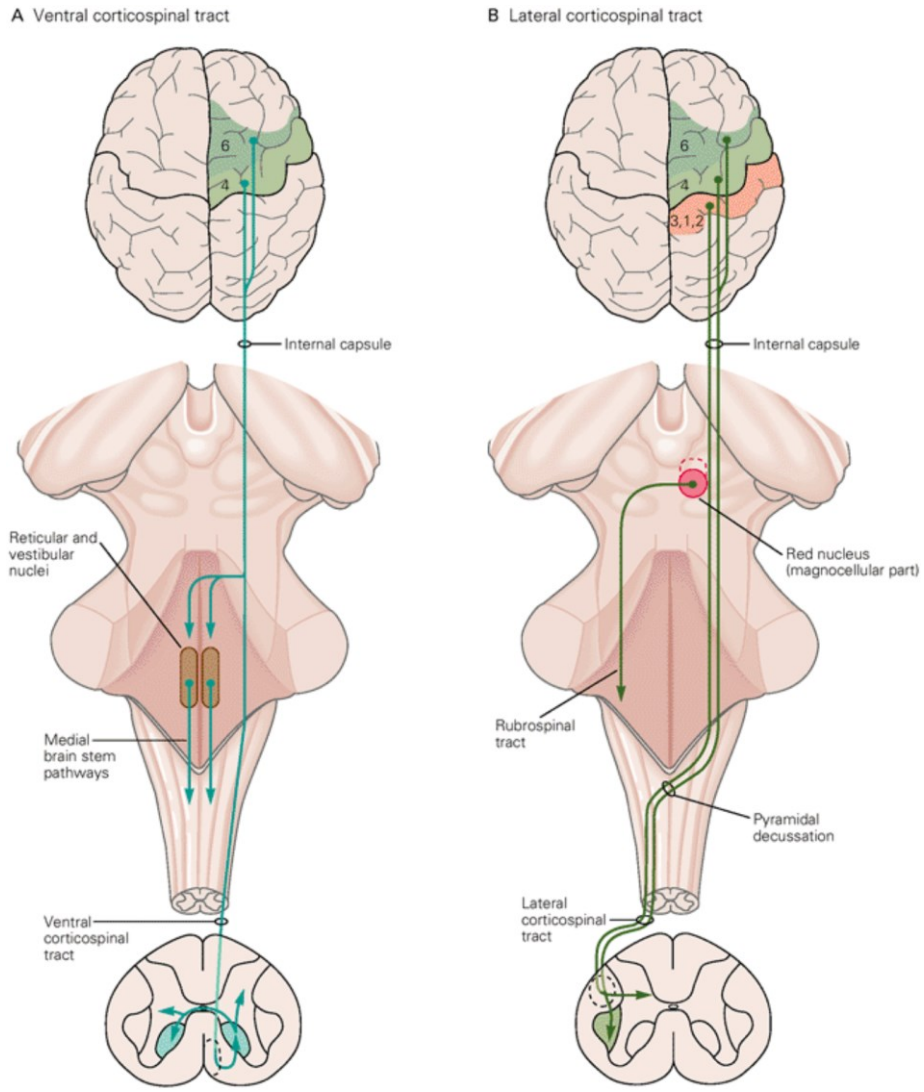
The CST is divided into lateral and anterior fascicles with different functions, as presented in **[Figure 4]** [26-28]:

- **Lateral CST:** allows movement of the distal muscles, fine hand motor movement, finger extensors and hand function, with less contribution to walking. Its axons are intermixed with axons of the rubrospinal tract and terminate directly and indirectly mainly with lower motor neurons (LMNs) associated with distal muscles, especially for skilled hand and finger movements;
- **Ventral/anterior CST**: works together with the cortico-reticulospinal tract for voluntary control of body proximal muscles. Its axons terminate directly and indirectly with LMNs that supply medial muscules of the body (e.g. trunk, shoulder).

Functions of the CST may be different also according to the region of origin.

- M1: execution of movements;
- SMA: “mental rehearsal” of a movement, planning and coordination of internally generated movement;
- PMC: planning and coordination of visually guided movements;
- Somatosensory cortex: descending control of somatosensory afferent inputs generated by movement.

Figure 4. Descending Corticospinal Tract



*A. The **ventral CST** primarily originates from premotor neurons located in Brodmann's area 6, as well as zones within area 4 responsible for controlling the neck and trunk. The descending fibers terminate bilaterally and also send collaterals to the brain stem's medial pathways.*
*B. On the other hand, the **lateral CST** originates from two motor areas (Brodmann's areas 4 and 6) and three sensory areas (3, 2, and 1). It crosses at the pyramidal decussation, descends through the dorsolateral column, and terminates in the spinal gray matter. The fibers from the sensory cortex primarily terminate in the medial portion of the dorsal horn. However, collateral fibers project to dorsal column nuclei, allowing the brain to actively modify sensory signals.*

(From the book "Principles of Neural Science", IV edition, Eric Kandel, James Schwartz & Thomas Jessell, reproduced under licence of Michael Weitz, Sr. Associate Global Publisher, McGraw Hill, Chicago (USA), obtained 18th July 2023).

The CST is responsible for muscles activation and control, with a critical role for finger extensors [26]. Given this knowledge, it appears clear the important role of the CST in UL movement. Infact, lesion of the CST may lead to the "Upper Motor Neuron Syndrome", characterised by weakness or paralysis, hyperactive reflexes, decreased motor control and abnormal muscle tone. Overtime, patients may regain the ability of rough movements, but fine movements such as writing or typing remain impaired [26]. Lesions involving the CST in critical brain structures such as the internal capsule,

the cerebral peduncle and the pons, affect also other descending motor systems intermixed, producing contralateral hemiparesis or paralysis with hypertonus, hyperreflexia and plantar extensor responses [28]. Moreover, lesions in the CST affect not only the quality of movement but also the severity of the UL impairment, as well as the ability of coordinate bimanual tasks and hand use [29,30].

Support of gross motor function is provided by other descending motor tracts (e.g. extrapyramidal tract) with projections to proximal muscles of the arm and leg, directly coding for strength of muscle activation [31].

UL motor recovery is strongly associated with residual integrity of the CST, whose prognostic value is deeper presented in chapter 3.

2. MOTOR REHABILITATION OF STROKE RECOVERY

2.1 Principles of neuroplasticity applied to motor learning and control

Neuroplasticity is the neurophysiological capacity of the CNS to change continuously in response to internal and external stimuli and allows the individual to learn new motor, cognitive and behavioural skills [32]. Specifically, motor learning is defined as the acquisition and improvement of motor behaviour through exercise and experience [33]. After a brain injury, such as after stroke, motor re-learning is possible in response to rehabilitation, whose aims are promoting positive adaptation and avoiding those maladaptive, in order to reintegrate as much as possible the impaired psychophysical abilities [32]. The mechanisms of recovery are both spontaneous and experience-dependent and can induce significant neuroplastic changes, especially in the first six months.Spontaneous recovery is due to biological processes, such as poststroke edema resolution, penumbra tissue reperfusion and reversal of diaschisis, and occurs mainly from acute phase till four weeks after brain lesion [34]. On the other side, the rehabilitative interventions able to enhance neuroplasticity and therefore motor recovery follow the ten *"Principles of Experience-Dependent Neural Plasticity"* [32]. These suggest that, in stroke rehabilitation, it is important to propose to the patient tailored activities that are: customised, varied, sufficiently intense and transferable in different contexts. In this way, it is possible to prime the neuronal substrate underpinning long-term re-learning of motor skills, by necessary formation of new synapses. Motivation is also an important element to consider: an activity that does not interest the patient does not activate cholinergic circuits and therefore limits learning and cortical reorganisation [32]. Some evidence suggests that plasticity in the motor cortex can be considered *learning-dependent* more than experience/use-dependent, since mere repetition of known movements does not induce neurophysiological and neuroanatomical changes, instead occurring when new motor skills are trained. Indeed, experiences and exercises need to be challenging and variable to induce improvement in synaptic efficiency, thus increasing the number of synapses themselves [32,35]. All these considered, it is important to highlight the fact that improvement in motor behaviour is always possible. However, in the first few weeks spontaneous recovery mechanisms may enhance and accelerate the improvements already inducible by rehabilitation, whereas in the chronic phase most of the behavioural change is due almost solely to active interventions [36].

Theoretical model proposes three main types of learning-models: unsupervised, supervised and reinforced learning [37].

- **Unsupervised learning:** is based on a high number of repetitions of a movement, which allows neuroplastic changes in the motor cortex but only in the short-term period.
- **Supervised learning**: requires internal models of the body and the environment, since they can improve performance of motor control. Such internal models consist of mental representation of the sensorimotor behaviours. The cerebellum is specialised for supervised learning, by detecting sensorimotor errors signal in the inferior olive coming from input fibres. Supervised learning is promoted by providing feedback (visual, verbal, haptic, auditory, etc.) to the patient on how a task is successfully achieved (Knowledge of Performance, KP).
- **Reinforced learning**: involves the activation of basal ganglia from the substantia nigra, by dopaminergic mediators of the reward signals. For this kind of motor learning, it is necessary to provide to the patient some feedback regarding not only the quality of the movement (KP), but also the accomplishment of the motor task (Knowledge of Results, KR) [37-39]. These augmented feedbacks can be provided to the patients as standardised scores (i.e. KR), or as information on their arm movements during the execution of motor commands (i.e. KP).

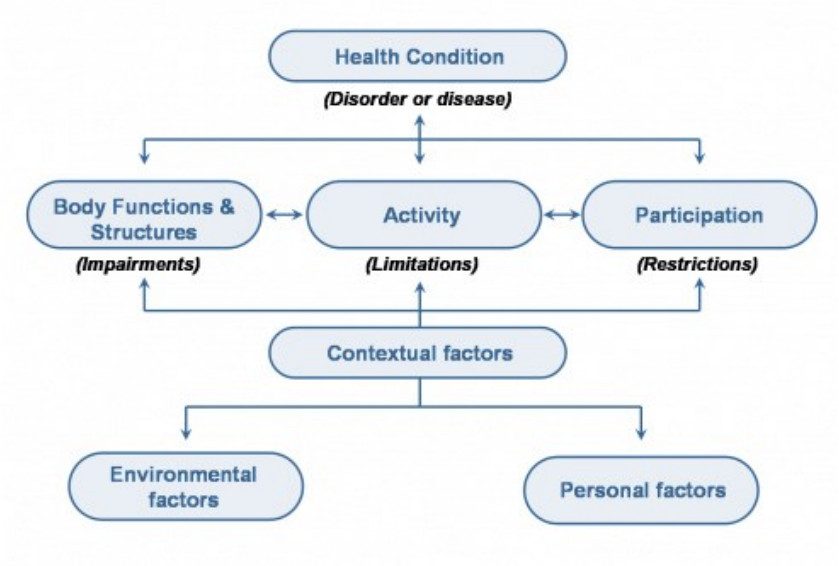
2.2 Assessment and rehabilitation of UL dysfunction after stroke

The first meeting with the patient is fundamental for imprinting the therapeutic relationship. In neurological physiotherapy, assessment is a process of collecting information about patient's movement disorders caused by a damage or disfunction of the nervous system [40]. The assessment is one of the most important aspect of taking care of a patient, since it is fundamental for the analysis of behavioral deficits in relaton to known principles of brain organization [41]. Besides, neurological rehabilitation is defined as "*an active participatory process involving a dynamic interaction between the person with neurological deficits and the health professional members of the team*" [41]. Many ways and outcomes exist to describe the motor status of a patient before and during rehabilitation, but the important thing to consider is that measurement and assessment should be performed at the beginning of the intervention and at the end, in order to monitor changing over time [41].

According to the International Classification of Functioning, Disability and Health (ICF), impairment may be described as related to body function (e.g., significant deviation or loss in neuromusculoskeletal and movement function, joint mobility, muscle power, muscle tone and/or involuntary movements), or to body structures (e.g., a significant deviation in structure of the nervous system or structures related to movement). Motor deficits due to stroke may lead to

limitations in the performance of activities of daily living, as well as to a reduction in societal participation and a lower quality of life **[Figure 5]** [42].

Figure 5. ICF framework for the description of health and health-related states



Components of health condition are divided into: ***(i) body component****, including body functions and anatomical structures. A problem in body function or structure is noted as impairments;* ***(ii) Activity*** *is defined as the execution of a task or action by an individual and* ***(iii) Participation*** *is defined by involvement in a life situation. A difficulty at the person level would be noted as an activity limitation, and at the societal level as a participation restriction.*
Component of Contextual factors is an independent and integral component of the classification and is divided into (a) 'environmental factors' and (b) 'personal factors'. 'Environmental factors' have an impact on all components of functioning and disability but 'Personal factors' are not classified in the ICF.

(From http://rssandbox.iescagilly.be/international-classification-of-functioning-disability-and-health.html, under licence CC BY NC ND 4.0)

2.2.1 Clinical outcome measure

Recently, it was developed a consensus-based core set of outcome measures recommended to be used in motor rehabilitation after stroke for profiling sensorimotor deficits [43] **[Figure 6]**.

Figure 6. Core set of outcome measures for clinical motor rehabilitation after stroke

	Body functions	Activities	Participation
Upper extremity	FMA	ARAT	SIS
Lower extremity	FMA & 10MWT*	TUG* & BBS	SIS
ADL/ stroke-specific	NIHSS	BI/ FIM	SIS

FMA: Fugl-Meyer Assessment; ARAT: Action Research Arm Test; 10MWT: 10-meter walk test; TUG: Timed up & go; BBS: Berg Balance Scale; NIHSS: National Institute of Health Stroke Scale; BI: Barthel Index; FIM: Functional Independence Measure; SIS: Stroke Impact Scale.
(From Pohl J, Held JPO, Verheyden G, et al. Consensus-Based Core Set of Outcome Measures for Clinical Motor Rehabilitation After Stroke-A Delphi Study. Front Neurol. 2020;11:875, [43], reproduced under licence CC-BY 4.0 ©)

These recommendations are linked to other studies aimed to propose a shared vision and common usage of outcome measures across countries in clinical trials and research projects, in the field of stroke rehabilitation [43-45]. These outcome measures, grouped by different domains of ICF and with respective ICF code [46], can be summarised as follows in **[Table 2]**.

Table 2. Clinical outcome measures for assessment of stroke survivors

ICF DOMAIN	CONSTRUCT	ICF code	OUTCOME MEASURE
BODY FUNCTION (IMPAIRMENT)	Control of voluntary movement functions - Upper and Lower Extremity	b760	FMA
	Coordination of voluntary movements - Walking function	b7602	10 MWT
	Consciousness functions; sensory functions; voice and speech functions; neuromusculoskeletal and movement-related functions	b110; b2; b3; b7	NIHSS
	Sensation of pain	b280	VAS NPRS
	Muscle power functions	b730	MRC MI
	Tone of isolated muscles and muscle groups	b7350	MAS
ACTIVITY	Carrying, moving and handling objects	d430-449	ARAT WMFT JHFT CAHAI NHPT BBT

	Self care	d5	RPS BI FIM MRS
	Changing and maintaining body position	d410-429	BBS
	Mobility, self care, usual activities, pain/discomfort, anxiety/depression *	d4, d5, d6, b280, /	EuroQoL EQ-5D
PARTICIPATION	Mobility, self care, domestic life, interpersonal interactions and relationships, community, social and civil life	d4, d5, d6, d7, d910, d920	SIS

*FMA-UE: Fugl-Meyer Assessment Upper Extremity; MI: Motricity Index; NHPT: Nine-Hole Pegboard Test; BBT: Box & Blocks Test; 10 Meter Walk Test; RPS: Reaching Performance Scale; NIHSS: National Institute of Health Stroke Scale; VAS: Visual Analogue Scale; NPRS: Numeric Pain Rating Scale; MRC: Medical Research Council; MAS: Modified Ashworth Scale; ARAT: Action Research Arm Test; WMFT: Wolf Motor Function Test; JHFT: Jebsen-Hand Function Test; CAHAI: Chedoke Arm and Hand Activity inventory; BI: Barthel Index; FIM: Functional Independence Measure; BBS: Berg Balance Scale; EuroQoL EQ-5D: MRS: Modified Rankin Scale; SIS: Stroke Impact Scale. *The EuroQoL EQ-5D has constructs in both body function and activity domains, while for anxiety/depression there is not a specific ICF code.*

Following is reported complete description of outcome measures administration and scoring:

- Fugl-Meyer Assessment (FMA): is the most recognised, reliable and widely used validated scale for the assessment of sensorimotor impairment in patients with post-stroke hemiparesis. The FMA, which can reach a maximum total score of 152 points, is composed of 4 sections: upper extremity (FMA-UE), which considers reflexes, simple and complex movements, grasping and coordination (0 to 66 points), pain/ROM (0 to 48 points), sensation (FMA-sens) (tactile and proprioceptive, 0 to 24 points), balance (0 to 14 points) [47];
- Motricity index (MI) is an ordinal scale for measuring limb strength. Arm score goes from 0 to 99 and the same for the leg score [48];
- Nine-Hole Pegboard Test (NHPT) measures finger dexterity. The patients has to pick the pegs from a container one by one and place them into 9 holes in a matrix 3x3 on a board as quickly as possible, using the hand being evaluated. Scoring is made by the number of seconds it takes for the patient to complete the test, with a maximum time of 50 seconds allowed to complete the task [49];
- Box & Blocks Test (BBT) is a measure for unilateral gross manual dexterity. The patient has to move, one by one, the maximum number of blocks from one compartment of a box to another of equal size, within 60 seconds [50];
- 10 Meter Walk Test (10MWT) is a performance measure to assess walking speed in meters per second over a short distance of 10 metres [51];
- National Institutes of Health Stroke Scale (NIHSS) is a 42-points scale for quantification of stroke severity [52];

- Visual Analogue Scale (VAS) is a continuous ratio pain rating scale. It is also used in clinical research and practice to measure the intensity or frequency of diverse symptoms, such as mood, appetite, asthma, pain. In case of pain, the score ranges between 0 ("no pain") to 10 ("pain as bad as you can imagine") perceived by the patient. VAS can be presented in different ways, including a graphic rating scale with descriptive terms at intervals along a line, or as a straight horizontal line of 100 mm. The patient has to mark on the line the point that they feel represents their perception of their current state [53-56];
- Numeric Pain Rating Scale (NPRS) is the segmented ordinal numeric version of the VAS, consisting of 11 points numeric scale, from 0 to 10 [57];
- Medical Research Council (MRC) is an ordinal scale to measure muscle strength or power. Scores range between 0 (no visible contraction) to 5 (full strength) [58];
- Modified Ashworth Scale (MAS) is a 6 points ordinal scale to quantify level of spastic hypertone in muscles tested one by one. It ranges from 0 (normal muscle tone) to 4 (high spasticity, affected part in rigid flexion or extension) [59];
- Action Research Arm Test (ARAT) is a 57-points ordinal scale quantifying hand and arm activities [60];
- Wolf Motor Function Test (WMFT) is a measure composed by 17 items analysing movement quality, functional ability, strength and speed of arm movement. It uses 6 points ordinal scale ranging from 0 (no attempt with UL) to 5 (normal movement), or total time needed to perform each item [61];
- Jebsen-Hand Function Test (JHFT) is a measure of fine and gross motor hand function using simulated ADLs (e.g. writing, lifting small objects, simulated page-turning). The total score is the sum of time taken for each sub-test [62];
- Chedoke Arm and Hand Activity Inventory (CAHAI) is a scale to assess arm ability to perform 13 functional tasks related to activities of daily living (ADLs) with both ULs (e.g. dial 911, open a jar of coffee, dry back with a towel). Each item is scored with an ordinal scale from 1 (total assistance needed) to 7 (total independence) [63];
- Barthel Index measures performance in ADLs [64];
- Functional Independence Measure (FIM) is a 126-points scale for measuring the level of independence in ADLs. Each item is score on a 7-points ordinal scale, similar to the scale used in CAHAI [62];

- Modified Rankin Scale (mRS) is a clinical reported measure of global disability. It is a 6 points ordinal scale with scores ranging from 0 to 5. A separate category of 6 is usually added for patients who expire. It provides a score for the level of disability following stroke [65]. mRS is a negative likert scale, where mRS = 0 corresponds to no symptoms and mRS = 6 corresponds to death;
- Timed Up & Go (TUG) is a simple test used to assess a person's mobility and requires both static and dynamic balance [66];
- Berg Balance Scale (BBS) determines a patient's level of ability to safely balance during a series of tasks [67];
- EuroQoL EQ-5D is a measure for quality of life investigating 5 dimensions of health: mobility, self-care, usual activities, pain and discomfort, anxiety and depression [68].
- Stroke Impact Scale is a self-report measure which aims to evaluate patient's perspective of how stroke has impacted health, life and perceived recovery (e.g. emotion, memory, thinking, hand function) [69].

However, the outcome measures just presented are not intended as suggestions for assessment protocols to be used, but merely a description of the measures that exist to date for the UL assessment. Indeed, there are too many of them to be administered by a clinician in a single session. therefore, to suggest a basic assessment to be applied in clinical practice, the core sets represent those recommended outcomes. For instance, the core set recommends to use the outcome measures presented in **[Figure 6]** and also indications for correct time of assessment in **[Figure 7]** [43].

Figure 7. Measurement time points of the core set for clinical motor rehabilitation after stroke

	d 2±1	d 7	wk 2	wk 4	wk 12	wk 26	+26 wks
Body functions	✓ (1)	✓ (1)	✓	✓	✓	✓	✓
Activities		✓ (2)	✓	✓	✓ (2)	✓	✓ (2)
Participation					✓		✓

D: day; wk: week; (1) exceptional time points for the National Institutes of Health Stroke Scale, only indicated at these time points; (2) exceptional time points for the Barthel Index/Functional Independence Measure, only indicated at these time points.
(From Pohl J, Held JPO, Verheyden G, et al. Consensus-Based Core Set of Outcome Measures for Clinical Motor Rehabilitation After Stroke-A Delphi Study. Front Neurol. 2020;11:875, [43], reproduced under licence CC-BY 4.0 ©)

A recent systematic review found that the majority (72 %) of clinical trials uses more than one UL outcome measure, for example FMA and ARAT or WMFT, thus covering complementary domains of ICF. However, the FMA is the most frequently used outcome measure, applied in 36 % of the clinical trial in UL stroke rehabilitation, followed by WMFT (19 %), MAS and ARAT (18%) [70]. Infact, advantages of FMA include its feasibility (i.e. clinical application) and good psychometric properties (i.e. validity and reliability) [71,72].

2.2.2 Instrumental assessment: Magnetic Resonance Imaging and Transcranial Magnetic Stimulation

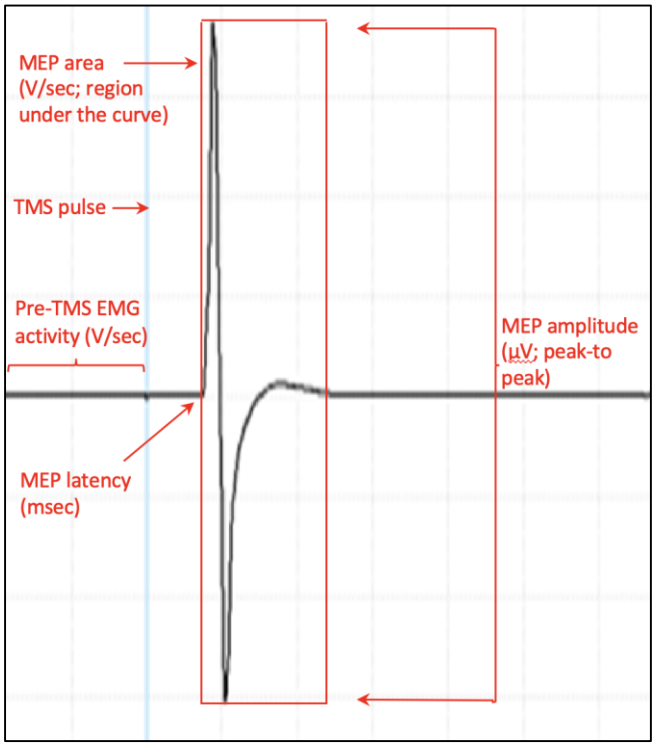
Clinical outcome measures are widely used in clinical studies, but many of them have weaknesses, such as questionable measurement properties, like *ceiling* and *floor effects* [70]. Trying to overcome these limitations which may decrease their use, investigators often prefer more quantitative UL methods of measurement, such as kinematics. Infact, kinematics allows to incorporate accelerometers and force sensors, which may provide measures with enhanced sensitivity and more fine-grained information on sensorimotor changes [73,74]. In this perspective, technologies such as robots or virtual reality (VR) systems may offer more quantitative, objective and reliable measures than classical clinical outcome measures [70]. Indeed, they may also allow measurement of aspects of sensory-motor integration difficult to be assessed clinically, such as visuospatial neglect or position sense [75].

Moreover, other instrumental methods of UL assessment in stroke patients may consider neurophysiological (e.g. Transcranial Magnetic Stimulation, TMS) and neuroimaging (e.g. magnetic resonance imaging, MRI) techniques [70]. Indeed, they can be useful in the study of the CST, which is very important for the recovery of manual dexterity, as already reported in Chapter 1. Core recommendations have been recently established for biomarkers ready to be used in research clinical trials [76]. For example, fMRI and TMS can be used to test the functionality of the CST, while neuroimaging techniques such as MRI and DTI can be used to determine its structural integrity [77,78]. Both TMS and MRI have been using widely to investigate integrity of the CST, in studies on prediction of motor recovery, aspects which will be deepen discussed in Chapter 3.

- **TMS** is a non-invasive neuromodulation technique for the assessment and treatment of neurological disorders [79,80]. By inducing eddy currents at the level of the cortex, it is possible to modulate the membrane potential of neurons in either inhibitory or excitatory fashion. When a TMS stimulus is delivered with sufficiently high intensity at the level of the motor cortex, it generates an action potential that can be recorded peripherally as electromyography (EMG) activity, also called Motor Evoked Potential (MEP). Based on the

peak-to-peak amplitude above or below a threshold (50 µV, when evaluating a muscle at rest), MEPs can be classified as present (MEP+) or absent (MEP-), respectively [79] **[Figure 8]**.

Figure 8. Raw supra-threshold Motor Evoked Potentials (MEPs)



Example of a prototypical motor evoked potential (MEP), indicating characteristics and measures of the main indexes of interest (i.e., MEPs amplitude, area, and latency).

(From Salvalaggio et al., Front. Aging Neurosci. 15:1205063. doi: 10.3389/fnagi.2023.1205063 [81], reproduced under licence CC BY 4.0 ©).

- **MRI** is an imaging technique reconstructing pictures of the anatomy and physiological processes of the body, specifically targeted to the brain for applications in neurological conditions. MRI scanners use magnetic field gradients and radio waves to generate images of the brain. In particular, MRI studies white matter (WM) and grey matter (GM) integrity of the brain, providing information about structural and functional aspects that may be called "biomarkers" [82]. Structural MRI biomarkers detect WM integrity and can be classified as macrostructural and microstructural. Macrostructural biomarkers assess the integrity of regions of interest, for instance the volume of lesion within the CST (lesion load), whereas microstructural biomarkers detect the direction of water diffusion as measure of the integrity of axons and glial cells (e.g. fractional anisotropy, radial diffusion, axial diffusion) [83-85]. Among structural MRI, the *Diffusion Tensor Imaging* (DTI) is particularly used in the stroke

field since it helps in measuring the WM microstructure integrity and reorganization during recovery, even in areas distant from injury. DTI allows in vivo noninvasive measurement of the motion translation of water, providing information about its anisotropy in different tissues [86]. Use of DTI for prediction will be further presented in Chapters 3 and 7. Functional MRI (fMRI), instead, measures the fluctuations of grey GM metabolic activity and can be related to active or passive conditions [87]; those related to active conditions measure the change in metabolism caused by the active performance of a functional task, whereas those related to passive conditions requires patient to rest without performing any task (resting state fMRI, rs-fMRI), or while receiving passive stimuli (e.g. visual, physical, body mobilization) [88,89]. Notably, while structural MRI has been classified as a tool ready to be used in clinical trials, fMRI is still at the level of developmental priority [82].

However, a disadvantage with neurophysiological and neuroimaging techniques is that they are not readily feasible in typical rehabilitation settings since they are time-consuming, expensive, requiring specific equipment and specialised skills for analysis and interpretation.

2.3 Taxonomy of Neurorehabilitation interventions

In neurorehabilitation, three main modalities of interventions are acknowledged, based on principles developed by Frey et al. and Sathian et al. [41,90,91] : Priming, Augmenting and Task-oriented. Some authors have proposed this classification of rehabilitation modalities with identification of the specific target each one is referred to **[Figure 9]** [92].

2.3.1 Priming techniques

Priming techniques act by modulating arousal of the motor system, thus increasing its excitability and promoting its plastic reorganization in response to physical activation (e.g. manual therapy, TMS, drugs). Priming interventions may prepare the sensorimotor system for subsequent motor practice, thereby enhancing its effect. The concept of priming after stroke deals with recent advances in neurophysiological techniques, providing methods to condition temporarily neural networks by administration of electrical (e.g. transcranial direct current stimulation, tDCS) or magnetic (repetitive transcranial magnetic stimulation, rTMS) fields to the brain through the scalp. This brain stimulation can influence the synaptic balance between neurons, promoting what is known as "*metaplasticity*" (i.e., the plasticity of synaptic plasticity) [93]. In a broader sense and for

rehabilitation purposes, all modalities capable of inducing a temporary modification of any structure in the musculoskeletal system (e.g., soft tissue passive mobilization, tactile stimulation) and neurological system (e.g., motor and visual imagery, action observation) are considered to promote priming of the structures involved in expressing voluntary motor behavior. Also pharmacological agents are among the oldest and most common adjuvant for inducing priming effects, enenthough there are no evidence of the efficacy of one drug over another [94].

2.3.2 Augmenting techniques

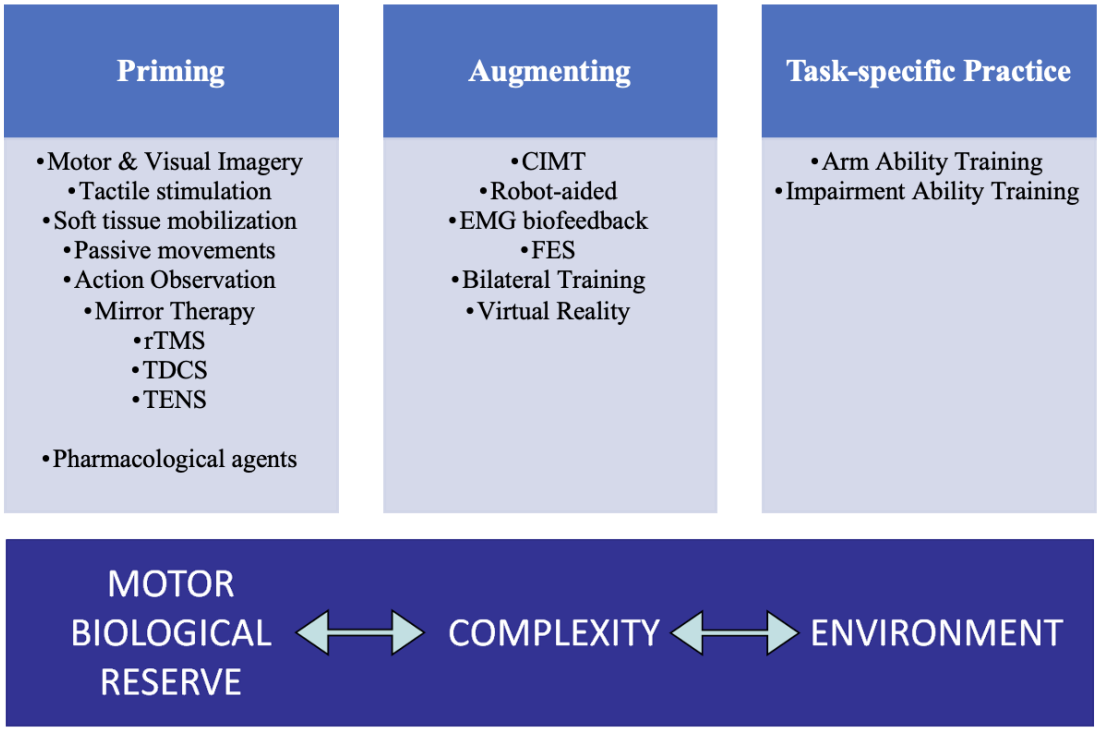
Augmenting techniques exploit enriched environment for providing augmented feedback, information and repetitions to patients. During physical practice, these techniques are supposed to enhance their effects by boosting voluntary muscle activation when interacting with a controlled setting (e.g. virtual reality, robotics). The concept of augmented modalities involves the notion that enriching the external environment in which animals or subjects interact can result in significant modifications to their own functional systems, both at a central level (e.g. CNS) and a peripheral level (e.g. muscles) [41,90,91]. This evidence has also been applied to stroke rehabilitation, where all artificial environments (e.g., robots, virtual reality, biofeedback) that enhance specific features and provide feedback information on the results and performance of accomplished tasks are considered the clinical translation of enriched environments [95]. Among them, the best studied approaches are: electromyography biofeedback (EMG), robot-assisted therapy, virtual reality (VR) based interventions, constrain induced movement therapy (CIMT) and functional electrical stimulation (FES) [96,97]. However, despite advances in the development of innovative rehabilitation methods, there is no evidence that suggests superior efficacy of one method over others [95]. In particular, robotic therapy and FES add variety to rehabilitation programs, but their benefit has not been shown to exceed that of standard care [98].

2.3.3 Task-oriented techniques

Task-oriented techniques (also called *"task-specific practice"*) are based on massive practice of specific tasks performed in real environment, with the aim to maximise transferability of skills and learned tasks in functional activities of real life [41]. The concept of task-oriented techniques originates from the movement and motor skill learning literature and has been defined by Teasell and colleagues as the training or therapy where patients engage in context-specific motor tasks and receive some form of feedback [99-101]. This broad definition can be applied to nearly all therapeutic

settings available in rehabilitation care. As a result, all modalities aimed at extensive practice of everyday tasks using real-world objects are considered task-specific practice in clinics. The goal is to achieve optimal functional performance that can be replicated in daily activities, thereby improving the quality of life in real-life environments.

Figure 9. Priming, Augmenting and Task-oriented modalities of rehabilitation intervention in neurological rehabilitation



rTMS: repetitive transcranial magnetic stimulation; TDCS: transcranial direct current stimulation; TENS: transcutaneous electrical nerve stimulation; CIMT: constraint induced movement therapy; EMG: electromyography; FES: functional electrical stimulation.

(From Turolla A. Chapter 2 - An overall framework for neurorehabilitation robotics: Implications for recovery. In: Colombo R, Sanguineti V, editors. Rehabilitation Robotics: Academic Press; 2018. p. 15-27, with permission from Elsevier © 2018 [92] Elsevier Ltd, under licence agreement no. 5504870473204 acknowledged by Rehabilitation Robotics on 9th March 2023).

No strong recommendations are still available on which modality could be better than the other, for regaining motor function after lesion of the CNS. However, some evidence suggest a significant role of augmenting techniques (e.g. VR and robotics) for improving UL motor function, with at least 15 hours of treatment delivered, thus introducing the concept of dose-effect [16,102]. However, time contingency, specificity, intensity, exercise parameters and dose of therapy are known to be critical aspects for the planning of effective rehabilitation programs more than the modality chosen [92]. In this framework, it is worth defining the concepts of *restorative* and *adaptive* interventions.

- **Restorative interventions** aim to improve impairment of function directly modifying the underlying neural mechanisms [41]. In this regard, the more is the residual excitability in the lesioned primary motor area (M1), the better the prognosis for motor recovery [92].
- **Adaptive interventions**, conversely, consist in providing a substitute way to perform the same task. In this regards, when excitability is predominant in the unaffected hemisphere, a substitution strategy may be used, aimed at inhibiting overactivation of the unaffected side potentially masking the affected one, with maladaptive mechanisms [92]. For instance, task-oriented training is a restorative intervention, while training to use an assistive device (e.g. a tool to grasp) may be considered adaptive [41].

2.4 Dose and timing of rehabilitation interventions after stroke

Dose is the amount of therapy provided to patients. Dose can be seen in terms of [41]:

- **Intensity:** number of repetitions or time per session;
- **Frequency:** the rate at which sessions occur over a particular period of time (e.g. number of sessions per week);
- **Duration:** length of time of observation over a defined period (e.g. 6 weeks).

Around the world, there is no consensus on the appropriate dosage of treatment for stroke patients. For example, in Canada, the guidelines recommend a minimum of 3 hours of task-specific training per day, 5 days a week. In England, the recommendation is 45 minutes of cognitive therapy per day. In Australia, stroke patients should receive a minimum of one hour of active practice at least 5 days a week, while in Italy patients hospitalised in rehabilitation facilities should receive 3 hours/day [103-106]. The NICE 2023 guidelines states that rehabilitation in both subacute and chronic phase should be delivered for at least 3 hours/day for at least 5 days/week [9]. A recent systematic review of clinical trials has found that time in therapy ranges from 23 to 121 min/day, time on task from 8 to 44 min/day, repetitions from 36 to 57/session, and for a total of 15 to 282 days. Moreover, results revealed that time on task was lowest in the stratum of people with severe UL impairment (8 min/day) [107].

Also the correct time to start rehabilitation after stroke is still matter for debate. As seen in **[Figure 2]**, there are different phases with different respective biological processes after stroke, therefore also rehabilitation intervention are supposed to be different. The concept of dose between acute, subacute, or chronic phase are pretty different. While in the acute phase it seems that providing

high dose of physical intervention may be detrimental, in subacute and chronic phase evidence suggests that high dose of therapy provides better outcomes.

For instance, in the **acute phase** (i.e. 1-7 days), in particular in the first 48 hours, there is no rationale for restricting people to bed rest if they can move independently. However, particular care is needed to avoid durations out of bed in people >76y and with more severe strokes (NIHSS > 7). Then, as patients tolerate more out-of-bed activity, it is better to increase frequency of sessions than duration of each session [108]. With this regard, an important randomised controlled trial (RCT) (*A Very Early Rehabilitation Trial after stroke*, AVERT) has investigated the effectiveness of frequent high dose of very early mobilisation (VEM) [109,110]. VEM refers to stimulation of the patient to actively perform out-of-bed activities, such as maintaining sitting and standing position, or walking with frequent sessions according to functional level. It should begin within 24 hours after stroke onset and should be performed at least three times per day, in addition to usual care. Results showed that for two patients of similar age and stroke severity, receiving a similar frequency and daily amount of out-of-bed activity, the patients who starts mobilisation earlier has improved odds of a favorable outcome. Moreover, from the results it seems that for favorable outcome it is preferable, in the first week after stroke, to provide frequent sessions but of short duration. Indeed, increase frequency of mobilitation helps reduce disability and increase the odds of walking by 3 months and reduces the odds of death. Conversely, incresing the minutes of out-of-bed activity is more likely to result in worse outcomes [109,110]. However, because of the heterogeneity of timing, frequency and intensity of training provided, together with inadeguate reporting of therapy interventions, it is difficult to provide recommentations for rehabilitation care, in the first week after stroke, thus the optimal time to commence out-of-bed activity remains unknown. What is clear is that physiotherapist's intervention delivered in the acute phase of care can change patient's long-term outcomes, and that more practice is not always better in the first week after stroke [110]. However, the AVERT study is not specific for the UL but in general for the good recovery according to mRS. The VECTORS study [111] (*Very Early Constraint-induced Movement during Stroke Rehabilitation*), instead, is UL-specific and allows for similar conclusions: shorter but more frequent mobilisation early after stroke (9.65 ± 4.5 days after onset) are associated with a more favourable outcome. In particular, CIMT (i.e. 2 hours/day of shaping therapy plus wore a paddle for 6 hours/day) was equally as effective but not superior to an equal dose of CT. Higher intensity CIMT (i.e. 3 hours/day of shaping therapy plus wore a paddle for 90% of waking hours) resulted in less motor improvement at 90 days, indicating an inverse dose-response relationship.

Regarding the **subacute phase** (i.e. within 2 to 3 months after stroke), according to another clinical trial, the *Critical Periods After Stroke Study* (CPASS), receiving 20-hours dose of intensive UL motor traning leads to clinically relevant improvement, higher than improvements obtained by patients starting intensive training in the acute phase (within 30 days), or in the chronic phase (6 – 9 months) [112]. However, authors suggest to consider that all the patients received also conventional therapy (CT) starting soon after lesion and that improvement of patients in the subacute group may be due to the potential cumulative effect of the large dose of motor therapy delivered continuously even during the acute phase. Indeed, this study suggest not to shift motor therapy to the subacute phase, but to preserve acute interventions [112]. An important study of Kwakkel et el. confirmed that in the first 3 months after stroke, recovery displays a nonlinear, logarithmic pattern, which means that the largest improvements are observed early after stroke onset and these changes subsequently gradually level off, especially for body function and activity [36]. In other words, a profound effect of time post stroke on UL activity is observed in the first three months, when the most of the motor improvement are driven by the 'time' factor [36].

In the **chronic phase,** some evidence from pragmatic studies suggests that 18 to 36 hours of rehabilitation, delivered in 8 to 12 weeks, did not lead to relevant improvement of patients' motor function [113] [114]. Moreover, breaks in rehabilitation treatments might extinguish UL skills gained by motor training, meaning that clinical benefits are not maintained at long term follow-up. These limitations have been overcome in other clinical trial providing high dose of training (i.e. 90 to 300 hours), with high intensity (i.e. 6 or 5 hours/day) and long duration (i.e. 3 to 12 weeks), where patients were titled to clinically relevant improvement (i.e. up to 9-11 points in the FMA-UE), also maintained at long-term follow-up [115-117]. In this framework, augmenting techniques are more likely to promote motor improvement, if can be delivered for long time and intensively to each patient [118].

3. PROGNOSIS AND PREDICTION

In the present chapter, materials from *Salvalaggio, S., Boccuni, L. & Turolla, A. Patient's assessment and prediction of recovery after stroke: a roadmap for clinicians. Arch Physiother 13, 13 (2023). https://doi.org/10.1186/s40945-023-00167-4, under licence CC BY 4.0 © have been used.* Activities for the development of this paper started on November 2020 and it was published in June 2023.

Alongside with behavioural interventions, also recovery expectation is fundamental in the rehabilitation field, with the aims to know the optimal level of functional improvement that can be expected, and time needed to achieve that level. These information may help in tailoring rehabilitation treatment, by selecting appropriate goals to share with the patient, thus monitoring advancements overtime [119,120]. As an example, some factors found to be relevant for prognosis of UL recovery are preserved MEPs, high level of strength of shoulder abduction and finger extension (SAFE), structural integrity of the CST [121,122]. However, studies on prognostic factors investigated only spontaneous recovery and did not provide information on rehabilitation exposure (i.e. rehabilitation received or not) during time of observation [121,122]. Thus, it is not yet possible to know whether and how behavioural interventions may influence prediction of UL recovery, leading to difficulties in differentiating improvements due to spontaneous recovery against ones induced by behavioural interventions [123]. This black box in the literature may be due to debates on definition of "spontaneous", since patients are always acting behaviours after a stroke [123]. In this chapter the role and state of the art in the field of prognosis in rehabilitation after stroke will be presented, together with clinical and instrumental techniques utilized for this purpose.

One of the most important aim of this chapter is to discuss the critical difference on the concepts of *Prognosis* and *Prediction* and its relevance to the rehabilitation of people with stroke. To date, the literature has been mainly focused on investigating *Prognosis*, meant as spontaneous neurological recovery, however we feel that is time to push in the direction of *Prediction*, thus considering which rehabilitation treatments patients are exposed to.

3.1 Traditional definition of prognosis and clinical value in medicine

Prognosis is defined by the Medical Subject Heading as *"A prediction of the probable outcome of a disease based on an individual's condition and the usual course of the disease as seen in similar situations"* [124].

The concept of *Prognosis* in the western medicine was born with Hippocratic oath in ancient Greek. For Hippocrates, considered the Father of Medicine, prognosis was a "noble thing that physicians may do for their patients, since it creates a link between the past, the present and the future, able to explain what patients leave untold" [119]. Considering just its ethimology the word means *"foreword-knowledge"* or *"knowledge before"*, which suggests that clinician knows the patient beyond what is immediately appearing. In Hippocrates' vision, making prognosis deals with creating a continuum between past, present and future, and not considering the patient's life only as a sample of data points. In modern medicine, it is the equivalent to try identifying risk factors, or any events from the past linked with the patient's health and/or illness [119].

Predicting events in medicine is fundamental for giving clinicians, patients and their families answers regarding what is expected from their clinical conditions, in terms of "*what is likely to happen in the future"* [125,126]. In clinical practice, prognosis links diagnosis and therapy, deepening the comprehension of the potential benefit or harm of treatment. Prediction may avoid overtreatment or undertreatment and facilitate shared decision making between clinicians and patients [125]. Historically, medicine has always been based in identifying the current disease affecting patients (i.e. diagnosis). Thus, making useful diagnosis requires also to choose which treatments or evidence is more likely to change the final outcome. In this framework, the culture of diagnosis gains one step further for patients, if also a prognosis is provided [127].

In modern medicine, the first prognostic model was developed in 1953 for patients with myocardial infarction, introducing the concept of prognosis as a quantified estimate of risk mortality and life expectancy, despite the low accuracy of the prediction which might have led to stressful and difficult situations for clinicians in communicating estimates to patients [128 129]. Over the years, a number of clinical guidelines has been developed with the aim to use prognosis for recommendations regarding screening and treatment, bringing experienced clinicians to monitor changes in their patients over time and use the trajectory of these changes, together with risk factors, to help foresee the future course of their patients [119,130].

3.2 Conceptual framework of Prognosis and Prediction: terminological aspects and research development

An essential terminological aspect to clarify is the difference between the terms *Prognosis* and *Prediction,* defined by Clark [131] as follows:

- A ***Prognostic Factor*** is defined as "*a measurement associated with clinical outcome in absence of therapy or with the application of a standard therapy that patients are likely to receive. It can be thought of as a measure of the natural history of the disease. A control group from a randomized clinical trial is an ideal setting for evaluating the prognostic significance of a biomarker";*
- A ***Predictive Factor*** is defined as "*a measurement that is associated with response or lack of response to a particular therapy. Response can be defined using any of the clinical endpoints commonly used in clinical trials. A predictive factor implies a differential benefit from the therapy that depends on the status of the predictive biomarker. In statistical terms, this constitutes an interaction between treatment benefit and biomarker status that is best evaluated in a randomized clinical trial with a control group".*

This terminological difference plays a fundamental role in this PhD project. Indeed, the largest part of the literature so far have focused on the study of spontaneous neurological recovery, thus *Prognosis*. Instead, the overreaching aim of this PhD project is to open and spread the concept of *Prediction*, thus considering the rehabilitation intervention as a proper driving factor of recovery, influencing the known prognosis. For this reason, from here on throughout the thesis, the two terms will be used with these two different meaning: the concept of prognostic research remains general, and the term prognosis continues to refer to the known knowledge concerning the prognosis of spontaneous recovery. Conversely, the term prediction will be used as a new term to introduce the concept of prediction of recovery in response to rehabilitation.

In the field of prognostic research, there are still some methodological issues that are not completely defined, indicating that the methodology regarding the design, conduct and analysis of prognostic factor studies is not yet fully shared and used robustly [132].

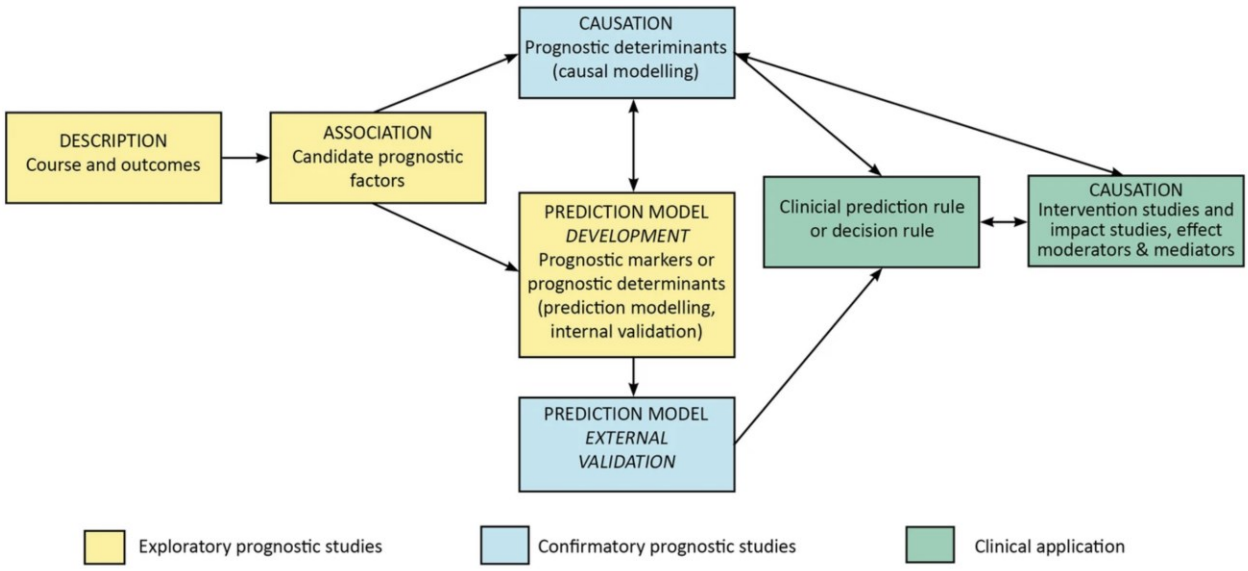
Prognostic studies are useful to [133]:

- Describe the natural history and clinical course of certain health conditions;
- Investigate variables associated with the desired health outcome;
- Estimate the probability of an individual developing specific outcomes;
- Study the clinical application of prognostic/predictive models;
- Examine the determinants of recovery with a causal relationships with the outcome, that can provide information on the development of interventions to improve patient outcomes.

In order to accomplish these aspects, there are two types of studies, also described in **[Figure 10]** [132]:

- **<u>Exploratory studies</u>:** used for description, association and prognostic/prediction model development, and represent the vast majority of developed studies. The appropriate study design for this type of investigation is the cohort study, needed to identification of candidate prognostic factors.
- **<u>Confirmatory studies</u>**: used for external validation of the prediction model and investigation of causal relationships. For the external validation of the prognostic/prediction model, a cohort study is required. For the development of these model, inception cohort would allow to study the causal relationships between factors and outcome. Finally, to develop ***clinical decision rules***, randomized controlled trials (RCT) or cost-effectiveness studies would be appropriate.

Figure 10. Framework for prognostic studies development

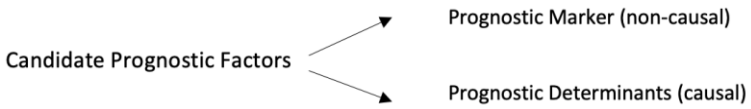


The image represents different phases and type of study design of prognostic studies development. First steps (yellow) are needed for identification of candidate prognostic factors in association studies. Then, the developed prognostic/predictive model needs to be externally validated (light blue) to study possible causal (prognostic determinants) or non-causal (prognostic markers) relationships with the outcomes. Finally, prognostic determinants can be tested in intervention studies to determine their impact on patient outcomes or cost-effectiveness of care (green).
(from Kent, P. et al. A conceptual framework for prognostic research. BMC Med Res Methodol 20, 172 (2020) [133]*. https://doi.org/10.1186/s12874-020-01050-7 © The Author(s) 2020 (CC-BY 4.0)*

In all the study designs, especially in cohort studies, to strengthen the association between prognostic factor and outcome, confounding factors should be considered thus adjusted in the statistical analyses [132,134].

In association studies (i.e. exploratory studies), the ***Candidate Prognostic Factors*** are the ones identified between the variable and the outcome of interest, and are necessary when their relationship is not clear at all and as a potential to be prognostic. Among them, those improving the accuracy of the prognosis are defined as ***Prognostic Markers*** having no causal relationship with the final outcome; conversely, those with a causal relationship with the expected outcome are the ***Prognostic Determinants*** **[Figure 11]**. These latter can be tested in intervention studies to determine their impact on patient outcomes or cost-effectiveness of care.

Figure 11. Type of candidate prognostic factors according to their relationship with the final outcome



3.3 Prognosis in physiotherapy

Rehabilitation is one of the main treatments provided after an injury to optimize recovery. It is a process of active change by which a person with disability is enabled to achieve goals and skills needed to optimize physical, psychological and social functioning of personal health condition and interactions with own environment [135].

Stroke rehabilitation aims to improve patient functioning, independence and participation using a biopsychosocial model, as defined by the International Classification of Functioning, Disability and Health (ICF) [42]. Recovery is a complex process which happen through a combination of spontaneous and learning-dependent processes, including restitution, substitution and compensation [96]. Although patient outcome is heterogeneous and vary among patients, recovery of body functions and activities is prognosticable in the first days after stroke [96].

Prognosis for physical therapist refers to the expectation of optimal level of functional improvement to be expected, and the respective time required to achieve it. Moreover, prognosis of recovery potential may be used as guidance for setting concrete goals with patient, thus referring the patient to the best tailored rehabilitation program, but also for monitoring patient's progresses over time [136]. However, prognosis is not applied systematically in rehabilitative setting, leading to unawareness of potentials of recovery for both clinicians and patients. A recent survey shown that only 9% of physiotherapists and occupational therapists use prognostic tools in clinical practice,

despite the vast majority (i.e. 89%) of them acknowledge the importance of predicting the potential for recovery after stroke [120].

A proper prognosis begins with a proper assessment, to allow a tailored rehabilitative planning. Therefore, clinicians should dedicate sufficient time and resources for developing comprehensive clinical assessment strategies. In the field of neurological rehabilitation, a patient-centered integrated framework for decision making was proposed, that consider assessment, diagnosis, prognosis and plan of care as circular pattern of patient care [137]. Like other clinicians with direct access to patients, responsibilities of physiotherapists include the possibility to conduct a thorough clinical assessment, exploiting advanced skills for diagnosing the motor behavioural disorder affecting the patient, to formulate an individual prediction that considers personal factors influencing recovery, thus referring the patients to the best tailored rehabilitation program by planning personalized treatments, in accordance with the most updated evidence available [138]. In this perspective, being familiar with interpreting initial signs and symptoms, selecting the most appropriate assessment strategy and using prediction models is pivotal to be time and clinically efficient. However, referring to evidence for each step of the process requires significant knowledge of the available literature, which is not always possible for clinicians deploying daily rehabilitation services.

3.4 Prognosis of recovery after stroke

In 1951 Twitchell described the pattern of natural recovery of a stroke patient, in seven sequential steps that may have occurred differently among patients, with those who progress quite quickly or stop at any given level depending on stroke severity [139]. The sequential steps were:

- Initial loss of voluntary movement and reflexes;
- Rapid restoration of reflexes proceeding to hyperreflexia;
- Development of increased muscle tone;
- First voluntary movements in shoulder and hip;
- Appearance of further voluntary movement with flexor pattern in UL and extensor pattern in lower limb;
- Both flexor and extensor movements appear in upper and lower limbs;
- Spasticty is reduced as isolated joint and finger movements emerge.

In 2015 Harvey reconsidered these steps by dividing factors that were *positive* (i.e. only mild spasticity or none at shoulder and rapid progression through synergy to isolated movement) and

negative (i.e. late return of reflexes, late onset of voluntary movement, increasing severity of spasticity) prognostic factors of better outcome of recovery [140].

Accurate prediction of functional outcome in stroke patients may enhance both clinical care and research and has the potential to allow accurate planning of patient-tailored treatment for those who may benefit, while avoiding unnecessary treatment for ones unlikely to respond [140]. In terms of long-term independence, the most common and non-specific factors of best recovery after stroke are: preservation of the CST, good neurologic status at stroke onset, young age, absence of urinary incontinence, good upper and lower limb motor ability, fast walking speed and good language comprehension [140].

With the aim to deliver efficient and effective services for the management of stroke sequalae, the decision-making process for prediction of recovery may influence significantly the access to rehabilitation services of stroke survivors. In clinical settings, prediction and discharge destination are typically based on clinical impression, incorporating clinical and demographic factors (e.g. stroke severity, age, social support) leading to possible improvement and inequitable access to rehabilitation services. [141-143]. Therefore, tools allowing to predict future outcomes for specific body functions or activities might be more useful, than clinical outcome measures providing binarized good or poor outcome [141]. Prediction tools that combine in a systematic way information coming from different clinical and instrumental sources could be used by clinicians to improve the accuracy of prognoses and personalization of rehabilitation plans [141].

What is still missing in literature is the role and impact of rehabilitation interventions for clinical prediction of stroke recovery.

3.5 Biomarkers for prognosis of recovery after stroke

As already discussed in Chapters 1 and 2, UL motor recovery after stroke is associated with initial impairment and CST integrity. Clinical assessment is a strong independent prognostic tool, especially for patients with mild to moderate impairment [144]. However, for severely impaired patients, prediction models may benefit by the inclusion of more objective and reliable outcomes, such as neurophysiology and neuroimaging techniques [76]. Indeed, they might have a key role in detecting changes overtime, therefore in determining potential of recovery [77,78].

According to most robust evidence, the most important biomarkers are integrity of CST indexed by DTI or by lesion overlap, and TMS measure of MEPs of the UL [76].

3.5.1 Neurophysiology for prognosis

For the prognosis of motor recovery after stroke, TMS has been used to investigate the functional integrity of the CST. Patients with MEP(+) were classified as having relatively preserved CST, whereas MEP(-) was indicative of severe disruption of the CST integrity [145]. In line with this hypothesis, when considering studies on patients with initial severe UL motor impairment, those with MEP(+) showed higher recovery potential than those with MEP(-) [122,145]. However, TMS is an expensive techniques not always available in all clinical settings, therefore in some studies it has been investigated whether it could be replaced by more sustainable tests. To date, it was found that it can be replaced by a clinically valid surrogate, that is the presence or absence of any visible muscle contraction when attempting to perform SAFE movements [146].

MEPs from TMS on the M1 have been considered as an index of the CST integrity, but other motor pathways are responsible for motor control [145]. Indeed, according to the presence or absence of MEPs, patients can be classified as recovering about 70% from initial impairment or not recovering that amount of function (severely compromised) [145]. However, patients without MEPs can still recover some function of UL, enlightening the need of adding to TMS other (clinical) outcome measures for the prediction of UL recovery [122,147].

The presence of MEP has been found to identify which patients will follow the PRR [145]. Prediction of recovery is more challenging for patients without MEPs and combining TMS with MRI biomarkers may be useful in explaining the relationship between corticomotor function and motor performance [82].

3.5.2 Neuroimaging for prognosis

Neuroimaging techniques, such as Computed Tomography (CT) and MRI, along with clinical signs and symptoms, are necessary for diagnosis of cerebral stroke[1]. In the hyperacute phase after stroke (i.e. within the first 24 hours) results from neuroimaging and laboratory tests may define the correct treatment according to the etiopathogenic characteristics of the lesion (i.e. hemorrhagic or ischemic), supporting the administration of potentially risky therapies such as thrombolysis and endovascular thrombectomy [148]. Afterwards, other features extracted from brain imaging techniques can be used for prediction of recovery. For instance, lesion volume can be used in combination with age and scores obtained at the NIHSS within 72 hours after stroke, for prognosis of outcome at 3 months [122]. Furthermore, brain's morphological data, lesion size and location data, involvement of functional networks and quality of blood supply to the brain and their combination, can be used also in improving accuracy of recovery prediction [148]. In particular, the lesion

involvement of descending pathways (e.g. CST and extrapyramidal tract) is crucial for motor function and prognosis of recovery [148]. The concept is that localizing a lesion in the CST, especially in the posterior limb of the internal capsule (PLIC), or in some subcortical areas such as the extrapyramidal tract or the centrum semiovale, is a negative prognostic factor for contralateral motor skills, in patient with chronic stroke [149-154]. For instance, lesion in the insula is associated with increased mortality, while lesion in the internal capsule is linked to a worse prognosis, than lesion in the corona radiata, or the motor cortex [148,150]. Moreover, involvement of the CST and secondary motor areas (e.g. red nucleus) limits the upper and lower limb motor recovery, but less the walking ability [154-156].

Important indexes of DTI neuroimaging used for motor prognosis are the fractional anisotropy (FA) and the related asymmetry index (FAAI). FA is a measure to estimate the WM organization and integrity in the brain (i.e. the axonal organization). Within cerebral WM, water molecules tend to diffuse more freely along the direction of axonal fascicles, rather than across them. Such directional dependence of diffusivity is called "*anisotropy*". FA then reflects the directionality of molecular displacement by diffusion and varies between 0 (isotropic diffusion) and 1 (infinite anisotropic diffusion). In the brain, water is free to move in all the directions in the cerebrospinal fluid (CSF) and FA value is estimated as 0. When water is restricted in a tract, as in a motor descending fibers or CST, FA value is estimated as 1. Injuries, neurological diseases or a tissue lesion in the brain may alter water motion, thus FA values can range from 0 (meaning that diffusion is isotropic or unrestricted, indicating a complete lesion of the white matter tract), to 1 (meaning that diffusion occurs along one axis and is fully restricted, indicating a healthy tract tissue). FA is influenced by myelination, diameter, density and orientation of axons, and after stroke its value decline because of Wallerian degeneration, then recover over a period of weeks to months, demonstrating a correlation with motor performance, especially in the chronic phase [86]. With regard to motor function impairment, index of FA in the PLIC is particularly useful, since in this brain structure occurs the maximum concentration of motor descending fibers of the CST, which are responsible of voluntary motor commands [122,141,157,158]. Therefore, FA in the PLIC is considered to be the best neuroimaging prognostic factor of motor outcome, even better than stroke volume [159]. For instance, evidence shows how a low value of FA, especially in the PLIC in the first days after stroke, is a significant prognostic factor of motor impairment at 1 to 3 months, and a low FA values in the superior longitudinal and arcuate fasciculi of the left hemisphere are correlated with lower ability to repeat spoken language and comprehension ability [148]. However, FA is becoming a promising

biomarker for motor recovery after stroke, mainly at the level of research rather than routine clinical practice [82].

The FAAI (defined as FAcontralesional − FAipsilesional / FAcontralesional + FAipsilesional) measures the ratio between the lesion in the two hemispheres for the extension of the lesion [160,161]. This yields a value between -1.0 and +1.0, where positive values indicate reduced FA in the affected PLICs, and a value of 0 indicates symmetrical FA in the PLICs. Increased use of the contralesional hemisphere may produce a descrease in contralesional internal capsule FA, which would lead to a decrease in FA asymmetry [162]. FAAI is used since it was found that changes are developed in both ipsilesional and contralesional CSTs and that physiological balance of activity between them can be disturbed after stroke [163].

Changes of functional networks and the presence of collateral flow are assessed by functional methods, such as resting state functional MRI (rs-fMRI) [148]. Together with the reduction of blood supply in a cerebral region, also collateral circulation (presence, quality, extention) is crucial for surviving of the affected area, leading to lower mortality and severe permanent deficits [148].

Structural and functional imaging techniques for prognosis can also be combined, for example mapping the site of the lesion with T1-weithed MRI, measuring structural connectivity and intactness of the CST with DTI and DWI, and assessing the functional connectivity (FC) between different area in the brain, by fMRI [164].

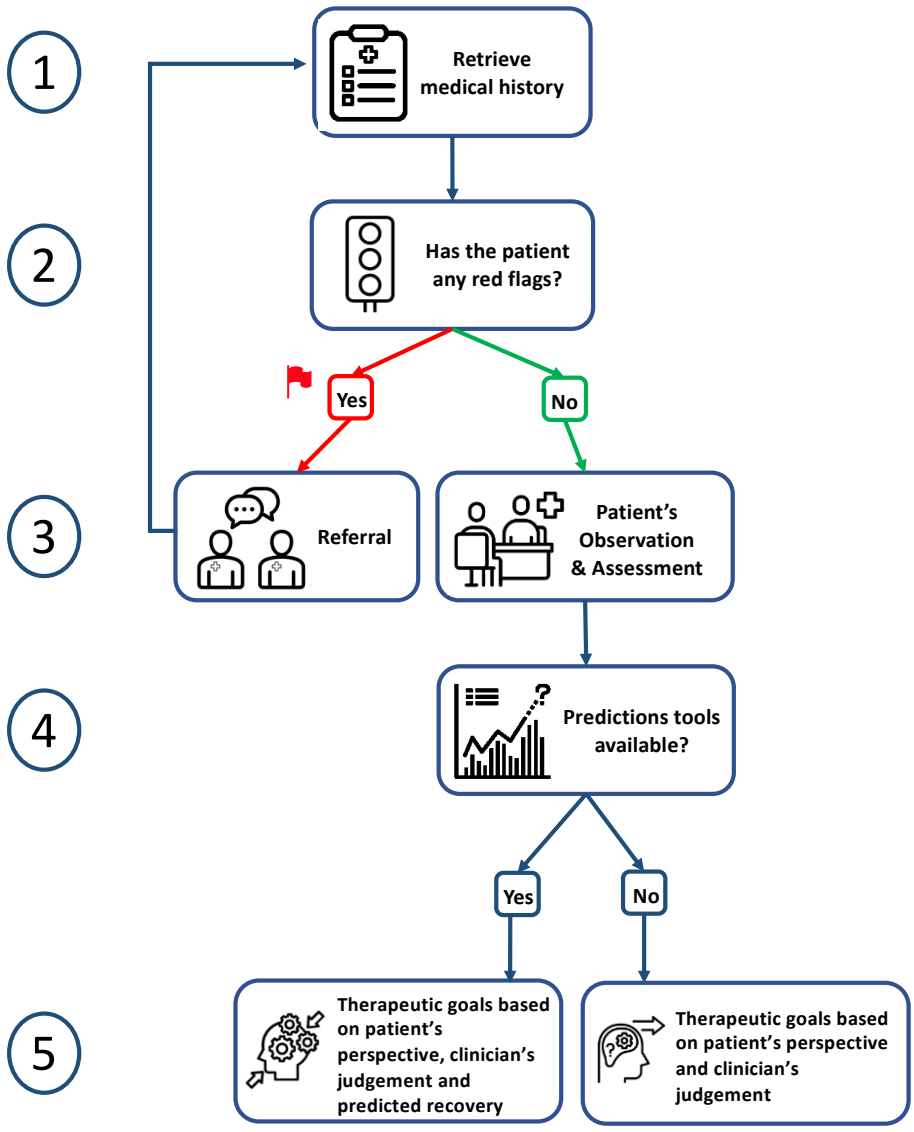
A model for prognosis of motor stroke recovery, combining both functional (i.e. fMRI) and structural connectivity (i.e. DTI-FA), was performed by Leanne et al. in 2018, demonstrating that DTI and FC have changes over time and highly correlated with motor recovery, even further 3 months after stroke, when DTI is more prognostic of motor function in the chronic phase than inter-hemispheric FC [86].

3.6 Clinical aspects for prognosis of recovery after stroke

Overall, the more investigated and developed prognostic models are those for the UL [78,122]. However, despite their high accuracy (even up to 90 %), they are valid when applied within 72 hours from stroke onset [78,122]. For this reason, available prognostic models pay the price of poor transferability to real clinical-rehabilitation setting, where patients are accepted at variable time from the event (e.g. early subacute, late subacute, chronic phase) and follow-up are usually shorter than 6 months. Moreover, the use of instrumental exams is not always available and affordable, because of costs and time needed.

For stroke rehabilitation clinical practice, a pragmatic and user-friendly clinical guide for clinical examination and decision has been developed **[Figure 12]** [165].

Figure 12. Five steps towards the definition of therapeutic goals, from medical history to the use of recovery prediction tools



(From Salvalaggio, S., Boccuni, L. & Turolla, A. Patient's assessment and prediction of recovery after stroke: a roadmap for clinicians. Arch Physiother 13, 13 (2023). https://doi.org/10.1186/s40945-023-00167-4, under licence CC BY 4.0 ©).

When first meeting a stroke survivor, after complete collection of clinical information (i.e. clinical, motor, neurological, functional), interpretation of findings can be difficult, yet fundamental. Through examination and assessment, the process of establishing a therapeutic alliance with the patient and setting of rehabilitation goals is kicked-off. In this process, clinicians must consider

patient's goals for negotiating shared therapy goals and tailoring personalized rehabilitation interventions. At this stage, prediction can be considered as the expected degree of recovery to be properly calculated by validated prediction tools. In case that prediction tools are missing, clinicians can only focus the rehabilitation intervention on improving residual motor function, according to results from the assessment process.

As a first instrument, a synoptic table summarising the available prognostic tools applicable at different time points after stroke is proposed, for estimating recovery of a variety of functions **[Table 3]**.

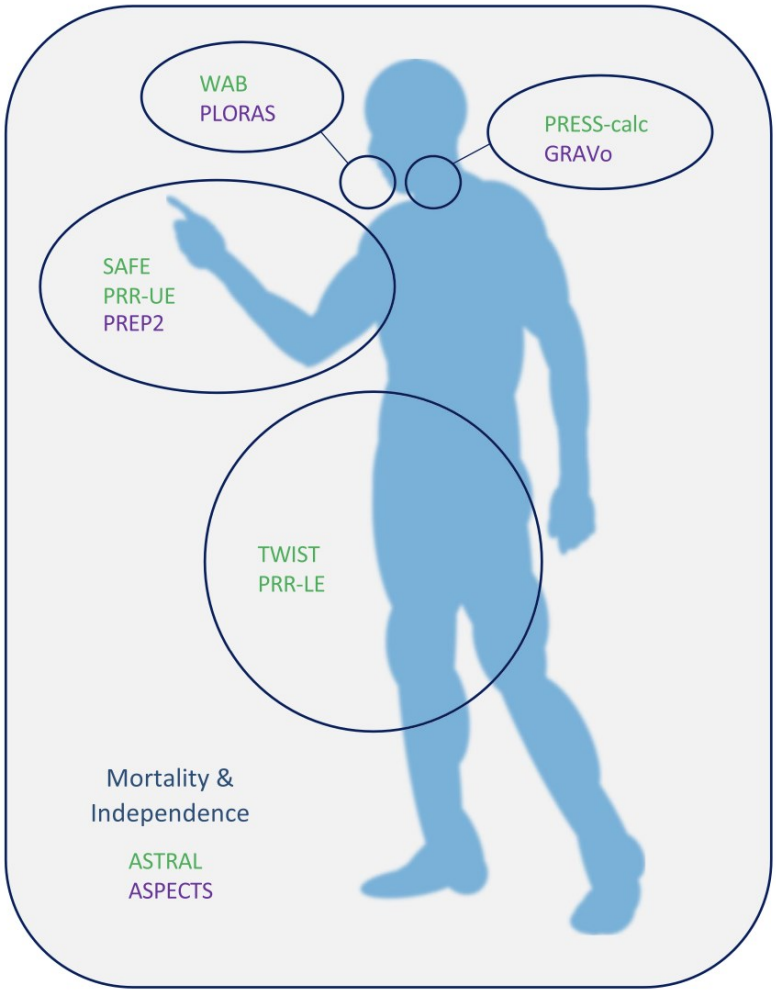
Table 3. Prognostic tools for recovery after stroke, at different time points

Assessment time (baseline, T0)	***Timing of predicted outcome (follow-up, T1)***							
	15 days	**30 days (1 month)**	**40 days**	**3 months**		**6 months**		**12 months**
24 hours (1 day)				ASPECTS; ASTRAL *(Mortality & Independence)*				
72 hours (3 days)	GRAVo *(PEG)*			PREP2 *(UE)*	WAB *(Language)*	PRR-UE; SAFE *(UE)*	PRR-LE *(LE)*	
5 days		*Language*		*Language*				*Language*
7 days (1 week)			PRESS calc *(Swallowing)*	TWIST *(LE)*		*UE*		
10 days						SAFE *(UE)*		
30 days (4 weeks)				*UE*				
2-6 weeks				*UE*				

ASPECTS: *Alberta Stroke Program Early Computed Tomography Score*; ASTRAL: Acute Stroke Registry and Analysis of Lausanne; GRAVo: Glasgow Coma Scale, Race, Age, hematoma Volume; *LE: Lower Extremity; PEG: Percutaneous Endoscopic Gastrectomy; PREP2: Predict Recovery Potential; PRESS: Predictive Swallowing Score; PRR: Proportional Recovery Rule; SAFE: Shoulder Abduction Finger Extension; TWIST: Time to Walking Independently After Stroke; UE: Upper Extremity; WAB: Western Aphasia Battery.*

Furthermore, **[Figure 13]** depicts which tools are available for each body region and function, and whether they require only clinical examination, or additional neuroimaging/neurophysiological testing.

Figure 13. Existing Prognostic tools for each body parts



The image represents schematics of the prognostic tools available, according to the body region and function examined, and whether they require only clinical testing (green) or additional neurophysiological/neuroimaging evaluations (purple).
(From Salvalaggio, S., Boccuni, L. & Turolla, A. Patient's assessment and prediction of recovery after stroke: a roadmap for clinicians. Arch Physiother 13, 13 (2023). https://doi.org/10.1186/s40945-023-00167-4, under licence CC BY 4.0 ©*).*

3.6.1 Prognosis of mortality and Independence level

The mortality rate after stroke is about 15% at 1 month, 25% at 1 year, and 50% at 5 years, while 70% of patients are either dead or disabled 5 years after the event [166].

After intracerebral haemorrhage, the case fatality rates are about 55% at 1 year and 70% at 5 years [167]. About 40% of stroke survivors are disabled (defined as a score between 3 and 5 at the modified Rankin Scale – mRS), between 1 month and 5 years after the event [166]. In 2019, stroke was the second leading cause of Disability-adjusted life year (DALYs) in patients over 50 years old, after

ischemic heart disease [4]. Prognostic factors of disability at 6 months include stroke severity, employment status, marital status, and recurrent stroke [166].

One of the first use of statistical methods for prognosis of outcome in stroke survivors was done by Counsell et al. in 2002, developing and validating two prognostic models for patients in the acute and subacute phases. In this study, the authors investigated the variables best predicting survival at 30 days and autonomy at 6 months. They found age, living alone, independence in activities of daily living (ADLs) before stroke, the verbal component of the Glasgow Coma Scale (GCS), arm power and ability to walk, as prognostic variables for survival at 30 days and survival in a nondisabled state at 6 months, with an area under the curve (AUC) of 0.88 and 0.84, respectively [168]. A few years later, other studies found that age, verbal component of the GCS, arm power, ability to walk, and pre-stroke dependency measured by Barthel Index (BI) predicted independent survival at 3 months and 12 months after stroke [169]. Also, history of atrial fibrillation, diabetes mellitus, patient age and stroke severity are significant prognostic factors of death or disability, after stroke [141,166].

The mRS is a 7-point ordinal scale ranging from a score of 0 for no symptoms, to a score of 6 for death, it assesses the level of independence [170]. Prediction of recovery can be binarized on good or poor recovery according to the mRS in the acute stage, where good means a mRS score ≤2 (independent), and poor means a mRS score ≥3 (dependent or dead). Nevertheless, no follow-up time has been established for this clinical predictor and its use in clinical settings is very poor [141]. In addition to mRS, Barthel Index (BI), Functional Independence Measure (FIM) and Frenchay Activities Index (FAI) are used to foresee patient's level of disability. Their predictive properties are related with patient's age, premorbid function, stroke lesion location, neurological impairment, incontinence, visuospatial inattention, history of diabetes mellitus, previous stroke and white matter disease [141].

After stroke, the presence of aphasia is negatively associated with autonomy, since a high residual impairment in comprehension foresees a lower probability of return home and is also associated with lower motor and cognitive scores on FIM [140,171,172]. Alongside, for predicting mortality and independence level at 3 months after stroke, ASTRAL (Acute Stroke Registry and Analysis of Lausanne) and ASPECTS (*Alberta Stroke Program Early Computed Tomography Score*) scores have been developed according to clinical information collected at 24 hours after stroke. ASTRAL score is an online calculator developed for mortality and independence level expectation from 24 hours to 3 months, or 5 years after ischemic stroke [173 174]. The clinical information required at 24 hours are age, severity of stroke (measured with NIHSS), stroke onset to admission time, range of visual fields,

acute level of glucose and level of consciousness [173]. ASPECTS is a quantitative score evaluating lesion location in the MCA territory, based on CT scan of the hyperacute phase [148,150,175]. Ten brain regions are assigned either a score of 1 (normal) or 0 (ischaemic change), and the total sum score is calculated. Starting from a score of 10, 1 point is lost for each brain region involved. ASPECTS demonstrated a sensitivity of 0.78 and specificity of 0.96 for the expectation of functional independence at three months based on the modified Rankin Scale, with a cut-off of 7 or lower clearly discriminant between functional independence and dependence or death, at three months (i.e. ASPECTS score < 7 predicts poor functional outcome). Similar results were obtained with the pc-ASPECTS scale, adapted to stroke in the posterior cerebral artery, where pons and midbrain are scored 2 points each [176].

3.6.2 Prognosis of Return to Work and Quality of life after stroke

Post-stroke depression (PSD) is a common mental and behavioural disorder after stroke, affecting more than one third of all stroke survivors [177]. The occurrence of PSD at 6-8 weeks after stroke, can be predicted by medical history of hypertension and angina pectoris, and the dressing BI item [178-180]. Employment status is one of the most important prognostic factors of quality of life, since employed-people report a better quality of life and a better health status, than non-employed people [181]. There is a lack of reporting on the proportion of people returned to work after stroke, but one year after injury, it seems that approximately 50% of patients with mild to moderate stroke returned to the same number of working hours/week as before stroke [182]. In this population, global cognitive functioning was the only prognostic variable of RTW according to the Montreal Cognitive Assessment (MoCA), which is a validated screening tool ranging from 0 to 30, and patients with MoCA < 26 are considered cognitively impaired [182,183]. RTW is a common goal for adults after stroke, but its prognostic factors are different according to patients' living country and are not much reported. Therefore, there are not prognostic models for RTW prediction and precise determinatino of factors predicting the reintegration into working life is not possible [184,185].

3.6.3 Prognosis of placement of tube feeding and percutaneous endoscopic gastrostomy (PEG)

After hemorrhagic stroke, Glasgow Coma Scale, Race, Age, hematoma Volume (GRAVo) tool **[Table 4]** is a clinical score for prognosis of PEG placement during patient's hospitalization [186]. Clinical information (i.e. Glasgow Coma Scale – GCS, race and age) is easily retrievable from first patient

contact at admission, moreover intracerebral hemorrhage (ICH) volume is needed from a computed tomography (CT) scan.

Table 4. Description of GRAVo tool for prognosis of PEG placement in haemorrhagic stroke

Assessment at 72 hours	Parameter	GRAVo Points	Prognosis at 15 days	Accuracy of prognosis
GCS	GCS > 12 GCS ≤ 12	0 2	GRAVo ≥ 4 points PEG placement	Sensitivity = 58.62% Specificity = 84.73% AUC = 0.75
Race (African American)	no yes	0 1		
Age	≤ 50 years > 50 years	0 2	GRAVo ≥ 5 points PEG placement	Sensitivity 46.55 % Specificity 93.13 % AUC: n.a.
ICH volume	ICH ≤ 30 ICH > 30 cc	0 1		

AUC: area under the curve; GCS: Glasgow Coma Scale; ICH: intracerebral haemorrhage; GRAVo: Glasgow Coma Scale, Race, Age, hematoma Volume; n.a.: not available.

3.6.4 Prognosis of language function recovery

Expecting aphasia recovery after stroke is difficult, because of the influence of lesion, clinical features and treatment-related factors [187]. A 3 months-clinical prognosis may be performed by knowing score from the Western Aphasia Battery (WAB) assessed at 72 hours **[Table 5]** [188]. However, the most robust prognostic factors of recovery seems to be lesion related factors; in particular some evidence suggest that circumscribed lesions in frontal, parietal or temporal lobes are related to good recovery at 1, 3 and 12 months, while extensive middle cerebral artery (MCA) disruption or extensive temporo-parietal lesions are linked to persistent moderate or severe deficits at 1, 3 and 12 months [187,189].

PLORAS (*predict language outcome and recovery after stroke)* is a repository of anatomical and functional imaging data of stroke patients (PLORAS Database), allowing prediction of the language function based on a single structural (anatomical, T1-weighted) brain scan. However, direct access to the data is password protected and limited to relevant members of the PLORAS Research team and local collaborators at University College London (UCL) [190].

Table 5. Description of language function recovery at 3 months after stroke.

Assessment at 72 hours	Parameter	Prognosis at 3 months	Accuracy of prognosis	Note
WAB	WAB < 29 points	$WAB_{max} - WAB_{72h}$	Patient can recover 73% of maximal potential recovery	The role of treatment and its interference with recovery is not well understood

WAB: Western Aphasia Battery.

3.6.5 Prognosis of swallowing function recovery

For prediction of swallowing function after stroke, a prediction model has never been validated. However, if dysphagia occurs after ischemic stroke, it is possible to use the online tool *Predictive Swallowing Score* (PRESS), for predicting functional oral intake at 40 days from onset, with regard to clinical information (i.e. age, stroke severity, stroke location, risk of aspiration and impairment of oral intake), retrievable at 1 week after stroke [191,192]. Online tools are better described at the end of this chapter.

3.6.6 Prognosis of UL function recovery

As already mentioned in Chapter 1, the CST is responsible for muscles activation and control, excitability of reflexes and has a critical role for finger extensors [26]. Therefore, hand motor recovery is strongly correlated with residual integrity of the CST [193]. It is widely acknowledged that presence of active finger extension and shoulder abduction (SAFE) in the lesioned side, is a reliable clinical sign predicting UL recovery at medium-long time, after stroke [194]. SAFE movements could be present either at 72 hours and within 6 weeks after stroke, allowing to foresee active motor recovery at 3 or 6 months, with regard to ARAT or FMA-UE [122,195] [193] [194]. Moreover, SAFE was reported as the strongest prognostic factor for bimanual performance [30]. Intactness of the CST is better expressed by the presence of finger extension, than shoulder abduction, thus the soon or the strongest it appears after stroke, the higher seems to be the probability for the patient to regain arm motor function [193]. Indeed, 98% of subjects able to perform both SAFE movements and 60% of those who performed only finger extension within 72 hours, showed good functional recovery after 6 months [193]. Even for the prognosis of bimanual performance after stroke, SAFE has been demonstrated to be the strongest prognostic factor of recovery, even more than imaging outcomes. This evidence, support the use of SAFE as a clinical measure strongly predicting arm recovery, underlying the role of clinical evaluation as an essential step to be administered in any clinical setting, at any time after lesion and regardless the rehabilitation plan ongoing [30].

Alongside SAFE sign, other validated outcome measures were used to predict recovery of UL function [144] [194]. The *Proportional Recovery Rule* (PRR) [144], mainly based on the FMA-UE, claimed that 70% of the patients recover approximately 70% of their maximal improvement potential (*recoverers*), while 30% of them do not (*non-recoverers*). The *non-recoverers* were defined as the patient with severe impairment at 72 hours (i.e. Fugl-Meyer Lower Extremity < 18 points, 0 < FMA-UE < 17, facial palsy and no finger extension) [144]. This rule has been criticised for its statistical and mathematical methods, because of the confounded nature of the correlation between initial scores and change overtime [196] [197]. Anyway, neither FMA-UE, nor SAFE have never been investigated in prediction models with baseline assessment performed later than 6 weeks after stroke, thus prediction of arm motor recovery can be performed with certain degrees of evidence only with clinical information collected within this limited timeframe.

Finally, the presence of some of the following features have positive predictive value on UL prognosis, after stroke [121]:

- Sex (male)
- Preserved CST
- Stroke on the left hemisphere
- High UL function
- Low
    - age (the younger the better)
    - global disability
    - UL and LL impairment
- Absence of
    - urinary incontinence
    - sensation deficit
    - visual disorder
- Presence of
    - MEPs
    - somatosensory evoked potentials (SSEPs)

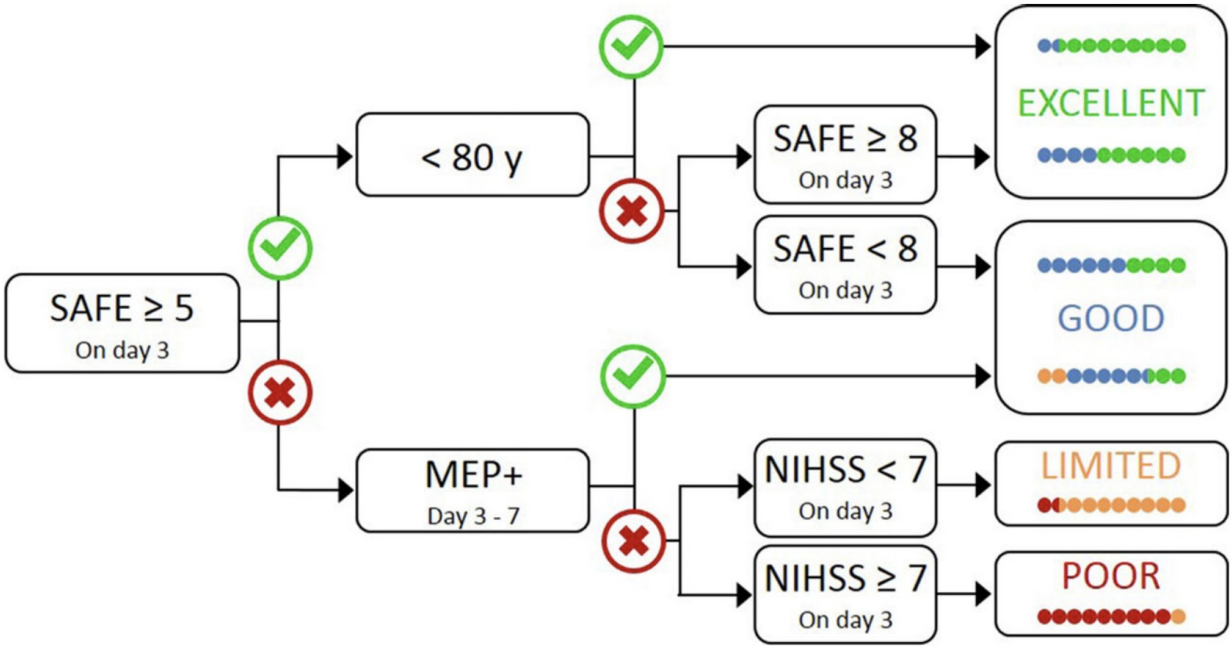
The PREP2 algorithm

To date, the *Predict Recovery Potential* (PREP2) algorithm **[Figure 14]** is the only validated prediction model for UL recovery, considering clinical and instrumental parameters to be collected within 72h

after stroke [78]. This algorithm can predict arm recovery after 3 months according to ARAT, with an overall accuracy of 75%. This algorithm allows to categorize patients according to certain combinations of information such as age, SAFE strength, presence of MEPs in the motor cortex and level of neurological status (i.e. NIHSS). TMS has to be performed only in case of SAFE < 5, then NIHSS only when MEPs are not present [122,195].

A SAFE score ≥ 8 at the Medical Research Council (MRC) allows to differentiate patients with prognosis of complete recovery from three other expected outcome categories (i.e. notable, limited and none) [58]. Only patients with a SAFE < 8 undergo neurophysiological and neuroimaging assessments. The presence of MEPs in response to TMS allows to stratify patients with expected notable recovery. After TMS, if MEPs are absent, MRI can be used to define structural integrity of the CST, thus separating patients between those with limited, from those with none potential of recovery. All these clinical parameters (i.e. MEPs, NIHSS, age, SAFE) allow since the stroke onset to link evidence of residual force at a body district with preserved functionality of the CST, in terms of recovery at 6 months. These results allow to infer the preservation of the CST system within the first days after stroke in terms of achieving dexterity at 6 months [78,122,162] **[Figure 14]**.

Figure 14. The PREP2 algorithm for prediction of UL recovery at 3 months post stroke



The image represents the PREP2 algorithm of the four color-coded possible outcomes 3 months poststroke, according to assessment performed 3-7 days after stroke.
SAFE: Shoulder Abduction Finger Extension; MEP: Motor Evoked Potentials; NIHSS; National Institutes of Health Stroke Scale.
(From Stinear, C. et al. PREP2: A biomarker-based algorithm for predicting UL function after stroke. Annals of Clinical and Translational Neurology 2017, Image reproduction under licence CCBYNCND.)

In simple terms, The PREP algorithm begins with a clinical evaluation of the SAFE impairment in the affected UL within 72 hours after symptoms onset, to establish whether adjunctive neurophysiological and neuroimaging measures are required. These measures are necessary to study how the CNS is recovering and what is underpinning the behavioral changes. Then, they have been removed, because the use of MRI was as informative as the use of a validated neurological clinical assessment (i.e. NIHSS) and the use of a clinical outcome measure allows to save money and time [122].

According to these findings, the TMS assessment is relatively simple and inexpensive compared to MRI scan, which is needed only if MEPs are absent. The PREP2 algorithm seems to be a promising tool to stratify patients by identifying those who are more or less likely to recover UL motor function, but it need to be better investigated in order to define tailored planning of UL rehabilitation since it may have strong implications for clinical decision-making [78,195].

Recently in 2017 the PREP2 algorithm has been implemented in a clinical trial demonstrating that inpatient length of stay is 1-week shortened, moreover physiotherapists referred to be more focused and confident about therapy contents. This study demonstrates for the first time that prediction algorithms can be used to guide clinical decision-making for stroke patients rehabilitation, leading to improve efficiency and economic benefits **[Table 6]** [195].

Table 6. Description of the PREP2 algorithm, for prognosis of UL recovery.

Assessment at 72 hours	Parameters cut-off	Prognosis at 3 months	Accuracy of prognosis
Age	SAFE $\geq$ 8 and age < 80 y	Excellent (ARAT 50-57)	75 %
Strength (MRC) at SAFE	5 $\leq$ SAFE < 8 and age > 89 y	Good (ARAT 34-48)	
TMS (MEPs) *	SAFE < 5, MEP + and NIHSS < 7	Limited (ARAT 13-31)	
NIHSS	SAFE < 5, MEP- and NIHSS $\geq$ 7	Poor (ARAT 0-9)	

ARAT: Action Research Arm Test; MEPs: Motor Evoked Potentials; NIHSS: National Institute for Health Stroke Scale; SAFE: Shoulder Abduction, Finger Extension; TMS: Transcranial Magnetic Stimulation.

3.6.7 Prognosis of Lower Limb & Walking function recovery

Recovery of walking activity is dependent on initial lower-limb motor impairment, stroke severity, trunk control and balance, age, lower-extremity (LE) sensory impairment, homonymous hemianopia or visuospatial inattention, presence or absence of motor-evoked potential elicited in tibialis anterior, lesion location and lesion overlap with the corticospinal tract [141]. As well as for UL, the PRR exists also for the LE, stating that patient after stroke can recover 64% of the difference between the total score of the FMA-LE (i.e. 34 points) and the initial score. From this model it seems that patients scoring FMA-LE $\geq$ 14 are 100% likely to follow the rule, while those scoring below 14 points

are 35% likely to follow the rule [198]. Moreover, similar to the PREP2 algorithm for the UL, an algorithm for expecting recovery of walking ability has been developed [199]. Is called the *Time to Walk Independently after Stroke* (TWIST) algorithm and predicts the time taken to walk independently or not after stroke, according to Functional Ambulation Category (FAC). It requires an assessment at 1 week of strength hip extension (MRC) and trunk control function (TCT) **[Table 7]**.

Table 7. Description of the TWIST algorithm, for prognosis of walking recovery

Assessment at 1 week	Parameters cut-off	Prognosis	Accuracy of prognosis
TCT	TCT > 40	FAC > 3 at 6 weeks	91 %
Hip extension (MRC)	TCT < 40 and MRC ≥ 3	FAC > 3 at 12 weeks	100 %
	TCT < 10 and MRC < 3	Dependent at 12 weeks	100 %

FAC: Functional Ambulation Category; MRC: Medical Research Council; TCT: Trunk Control Test.

3.7 Online tools for assessment and monitoring of stroke recovery

Time constraints has been reported by clinicians as a major barrier to undertake assessment and individualized treatment planning based on the available evidence [200]. To overcome this issue and to assist the decision-making process there is growing interest towards tools providing useful information in a rapid and reliable way. Following, we summarized online tool available both for prediction and also for a comprehensive assessment and treatment-decision making.

- **PRESS calc:** it is a smartphone application to foresee recovery of functional oral intake from 1 week to 40 days after dysphagic stroke [191,192].
    - Apple iOS: https://apptopia.com/ios/app/1401176212/about
    - Google Play: https://play.google.com/store/apps/details?id=ch.kssg.press
- **ASTRAL score:** to
    - disability and death over 12 months and 5 years after acute ischemic stroke [173,174].
        - Online calculator available: https://www.mdcalc.com/astral-score-ischemic-stroke
- **ViaTherapy:** it is a smartphone validated application developed by healthcare institutions and clinicians with the goal of guiding therapists from assessment to treatment selection [201]. The tool serves as indication to select evidence-based treatments specific to patient's stage of recovery and functional status.
    - Apple iOS: https://apps.apple.com/us/app/viatherapy/id1108116302?ign-mpt=uo%3D4

- Google Play: https://play.google.com/store/apps/details?id=org.viatherapy.androidapp

- **Dynamic prediction** of Vliet et al. 2020 [202] consists in a user-friendly online platform for 5 strata classification of patients recovery, based on FMA-UE assessment (https://emcbiostatistics.shinyapps.io/LongitudinalMixtureModelFMUE/). Taken together, ViaTherapy and dynamic predictions allows clinicians to access evidence-based tools for assessment, prognosis, and treatment selection.
- **Rehabilitation Measure Database**: https://www.sralab.org/rehabilitation-measures. It is a database where to find more than 500 rehabilitation outcome measures with instrumental details for each of them.
- **Outcome Measures Recommendations:** https://www.neuropt.org/practice-resources/neurology-section-outcome-measures-recommendations. It is a database of recommendations for outcome measures used in clinical practice and research of the main neurological diseases (i.e. Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson Disease, Vestibular Disorders, Spinal Cord Injury).
- **Assessment of Life Habits (LIFE-H):** https://strokengine.ca/en/assessments/assessment-of-life-habits-life-h/. It is an outcome measure to assess the quality of social participation of people with disability by estimating how the patient accomplishes ADLs and social roles. It is worth noticing because of its nature of being an outcome measure for the Participation domain of International Classification of Functioning, Disability and Health (ICF).
- **Stroke Rehabilitation Clinician Handbook**: http://www.ebrsr.com/sites/default/files/EBRSR%20Handbook%20Chapter%204_Upper%20Extremity%20Post%20Stroke_ML.pdf. It is a book for the clinical management of UL after stroke.
- **Evidence-Based Review of Stroke Rehabilitation**: www.ebrsr.com. It is a portal with the most updated evidence of the clinical management of stroke rehabilitation.

3.8 Conclusion

So far the literature has mostly developed prognostic models, not considering enough rehabilitation to which patients may be exposed. Therefore, the proper concept of prediction of stroke rehabilitation-induced recovery is now arising in the field and this doctoral thesis aims to contribute in this direction. Prediction of motor recovery requires clinicians to integrate valid and accurate

clinical and instrumental assessments of the patient, with regard to the right phase of recovery after stroke, with the aim of enhancing the use of prediction tools in their clinical practice. Accurate patients assessment requires choosing the correct outcome measures, for predicting the final expected outcome, by the most appropriate prediction tool. To date, several prognostic tools have been developed, with appropriate interpretation of clinical outcome scores, allowing to estimate the personal potential of recovery, for each individual patients. However, only for PREP2 algorithm valid accuracy of its predictions at long-term follow-up and impact on routine clinical care, have been thorougly investigated [195].

In the following chapters, three studies analysing the concept of prediction of stroke rehabilitation-induced recovery will be presented, by means of different point of views and methodologies (i.e. literature review, retrospective study, longitudinal cohort study).

4. AIMS, HYPOTHESES AND EXPECTED RESULTS OF THE PhD PROJECT

4.1 Aims

The general aim of this PhD project is to deeply investigate the role of rehabilitation interventions provided to human stroke survivors, in order to propose a prediction model of UL rehabilitation-induced motor recovery. Therefore, each study aims to investigate candidate predictive factors (e.g. neural, behavioural and physiological features), as well as different aspects of interventions (e.g. dose, contents) related to UL recovery and rehabilitation, after stroke.

Better detailed, specific aims are to investigate whether:

- (i) any factor (e.g. motor, cognitive, neurophysiological) is associated with UL motor function recovery and could therefore become a "candidate predictive factor";
- (ii) clinically important recovery of UL motor function and activities, relies on type of modalities of intervention provided, with a dose-response effect.

Thus, the overall hypothesis of this PhD project is that rehabilitation actively induce UL motor recovery driven by specific predictive factors, in stroke patients. More detailed hypotheses will be described separately in each study.

4.2 Hypotheses

The general hypothesis of this PhD project is that rehabilitation actively induce UL motor recovery, driven by specific predictive factors, in stroke patients.

More specifically, this hypothesis could be declined into the followings:

1. There are specific features (i.e. clinical, neural and physiological) associated with recovery induced by rehabilitation. This hypothesis will be tested in Study 1,2,3.
2. Structural and functional integrity of the CST may influence motor recovery. This hypothesis will be tested in Study 3.
3. Dose and modality of rehabilitation interventions are associated with UL motor recovery. This hypothesis will be tested in Study 1,2,3.

4.3 Expected results

Given all the premises, the expected results of this PhD project are:

1. To develop a neurophysiological and functional prediction model of UL recovery after stroke, by individualisation of candidate predictive factors. This model would represent the first investigating the specific role of rehabilitation for prediction of motor outcomes.
2. To individuate dose-response effect able to induce clinically relevant recovery, after stroke.

Therefore, the overall structure of next chapters will be as follows:

- Chapter 5 – Study 1: Systematic Review with Proportional Meta-analysis on predictive factors and dose-response effect of rehabilitation for UL induced-recovery.
- Chapter 6 – Study 2: Retrospective cohort study on clinical predictors for UL recovery after rehabilitation in stroke survivors.
- Chapter 7 – Study 3: Longitudinal cohort study on prediction of rehabilitation-induced motor recovery after stroke using a multi-dimensional and multi-modal approach.

5. PREDICTIVE FACTORS AND DOSE-RESPONSE EFFECT OF REHABILITATION FOR UPPER LIMB INDUCED RECOVERY, AFTER STROKE: SYSTEMATIC REVIEW WITH PROPORTIONAL META-ANALYSES

The present chapter refers to a systematic review started on December 2020 and currently under review in Physiotherapy Journal.

5.1 Introduction

Stroke is the second leading cause of death and a major cause of disability worldwide, leading also to severe UL impairment [6,18]. Stroke survivors often ask how much recovery they can expect, or whether a particular treatment approach will work for them[119,120]. To date, in relation to prognostic factors, most of the neurological literature has been focused on the study of spontaneous recovery, thus *Prognosis.* The concept of *Prediction*, however, refers to the proper effect of rehabilitation as a main driver of recovery [131]. Therefore, in this paper we referred to the *Prediction* of recovery, as the expected outcome of a rehabilitation pathway.

Coupar et al. explored potential factors predicting UL recovery, but regardless having received or specific doses and modalities of rehabilitation care [121]. For instance, maintenance of voluntary SAFE, and preserved conduction and anatomical integrity of the CST were consistently found to predict motor recovery [121,122]. However, these studies only apply to spontaneous recovery, since the effect of rehabilitation has never been considered as a factor potentially associated with motor recovery [121,122]. In the subacute phase after stroke (i.e. 0-6 months), time is the most significant factor predicting and driving motor recovery, while in the chronic phase (i.e. > 6 months), high dose of intervention (i.e. 90 to 300 hours) was found to promote clinically relevant changes [36 117 115]. However, only one study suggested that less CST injury, greater ipsilesional motor cortex activation and greater interhemispheric connectivity were the best predictors of response to robotic treatment, although the dose was still relatively low [203]. Moreover, it is not yet clear whether putative predictive factors will change depending on treatment delivered [123].

In neurorehabilitation, three main modalities of treatments are acknowledged: Priming, Augmenting and Task-oriented [41,90,91]. Priming techniques act by modulating activation of the motor system enhancing its excitability in response to physical agents (e.g.

manual therapy, transcranial magnetic stimulation (TMS), drugs); Augmenting techniques exploit enriched environment for providing augmented feedback and repetitions, boosting voluntary muscle activation when interacting with a controlled setting (e.g. virtual reality, robotics); Task-oriented techniques are aimed to maximize transferability of skills in functional activities of daily living [16,41].

Our hypothesis is that expected rehabilitation-induced recovery is driven by specific predictive factors such as modalities and dose of intervention received, at different time from stroke onset.

5.2 Aim of the study

The purpose of this review is firstly to investigate whether any factor allows to predict the amount of recovery and the likelihood of responding to UL rehabilitation interventions, after stroke. Secondly, we asked whether UL clinically important recovery relies on type and dose of rehabilitation, at different times after stroke.

5.3 Methods

This is a systematic review with proportional meta-analysis following the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guideline for reporting [204]. We considered the intervention as an exposure for assessing clinically important effects and associated predictive factors. The protocol was registered in PROSPERO database (registration number: CRD42021258188) on 30th June 2021. The systematic process of screening, selection, and data extraction was conducted by four independent couples of reviewers. In case of disagreements another reviewer was involved.

5.3.1 Search strategy

Literature search was performed by querying the following databases: PubMed, The Cochrane Library, EMBASE, Scopus, CINAHL, Web of Science. Study selection was conducted on articles published from inception until 23rd December 2022. The search strategy was developed using the Medical Subject Headings (MeSH) and text-keywords, then adapted to each database. A detailed description of the search strategy is presented in the supplementary materials (Appendix S1).

5.3.2 Eligibility criteria and study selection

We included publications (i) in English, (ii) designed as longitudinal-prospective single-cohort study and case-series study (i.e. with at least 2 patients), (iii) enrolling adult patients with stroke (i.e. > 18 years), (iv) undergoing UL rehabilitation intervention, (v) with UL assessment by validated clinical outcome measures, detected before and after intervention and (vi) with data available for reliable extraction of number of responders and non-responders. Studies were excluded in case of (i) controlled or single-case report study design, (ii) impossibility to extract number of responders and non-responders, (iii) unreported clinical outcome measures, (iv) only neuroimaging outcomes. The EndNote software was used to remove duplicates (https://endnote.com/). Grey literature was not searched. For abstracts selection, the tool Rayyan (https://rayyan.qcri.org/) was used.

5.3.3 Outcomes

Specific clinical outcome measures according to those proposed by the core-outcome-set for UL stroke rehabilitation were considered [43,45]. Moreover, we added outcome measures on strength and sensation considered significant for UL recovery prediction. Overall, the outcome considered, according to the different ICF domains were:

- UL function and structure: Chedoke-McMaster Stroke Assessment Measure (CMSA) [205]; Fugl-Meyer Assessment for Upper Extremity (FMA-UE) and sensation (FMA-s) [47], Motricity Index (MI) [48], Medical Research Council (MRC) [58], National Institute of Health Stroke Scale (NIHSS) [52], Visual Analogue Scale (VAS) for pain [53], Nottingham Sensory Assessment (NSA) [206], Modified Ashworth Scale (MAS) [207];
- UL activity: Action Research Arm Test (ARAT) [60], Chedoke Arm Hand Activity Inventory (CAHAI) [63], Nine-Hole Pegboard Test (NHPT) [49], Box & Blocks Test (BBT) [50], Wolf Motor Function Test (WMFT) [61], Functional Independence Measure (FIM) [208], Barthel Index (BI) [64], Abilhand [209]; Frenchay Arm Test (FAT) [210]; Motor Assessment Scale [211], Jebsen-Hand Function Test (JHFT) [62].
- UL participation: Stroke Impact Scale (SIS) [69].

The primary outcome was the FMA-UE.

5.3.4 Data extraction and management

We extracted general characteristics of studies (e.g. authors, population) and information on predictive factors according to Coupar et al. [121] (i.e. age, sex, time since stroke, side of lesion, severity of stroke by NIHSS, presence of MEPs, lesion of the CST, motor or sensation impairment, visual disorders, comorbid condition), together with any other variable investigated as potential predictors, if explicitly claimed or included in statistical models in the primary study. In case of missing data, authors of included studies investigating predictive factors were contacted. Moreover, we searched whether any study investigated dose or modality of treatment as factor potentially associated with the final outcome. For the primary outcome measure, we extracted the following data: sample size, number of Responders/Non-Responders, exposure (i.e., intervention details), dose of intervention (i.e., hours).

Studies were grouped according to the type of rehabilitation modality received (i.e., Priming, Augmenting, Task-oriented) and included only if the numbers of responders were retrievable or explicitly declared in the study. Responders were defined as patients whose improvement was higher than the Minimally Clinically Important Difference (MCID). In case the MCID was neither declared in the study nor available in the literature, the Minimal Detectable Change (MDC) was considered. In case neither MCID nor MDC were available, 10% of improvement was considered as cut-off. Reference values for each outcome measures are reported in [**Table 8**]. Data were synthesized in synoptic tables.

Table 8. Cut-off values of outcome measures for definitions of responders and non-responders

MCID (points)		MDC (points)		△ ≥ % 10
FMA-UE [212]	5	FAT [213]	7	JHFT, MRC, NHPT, FMA-s, NSA, NIHSS, VAS, MAS, Motor Assessment Scale [72]
MI[214]	13	BBT [215]	6	
ARAT [216]	6			
WMFT [217]	1 points or 19 seconds			
FIM [218]	22			
BI [219]	2			
Abilhand [220]	0.26 - 0.35 logits			
SIS [221]	9 (strength), 6 (ADL), 5 (mobility), 18 (hand function)			
CMSA [205]	8			
CAHAI [222]	6			

Cut-off values were established according to Minimally Clinically Important Difference (MCID), Minimal Detectable Change (MDC) or difference in percentage from baseline scores. FMA-UE: Fugl-Meyer Assessment Upper Extremity; MI: Motricity Index; ARAT: Action Research Arm Test; WMFT: Wolf Motor Function Test; FIM: Functional Independence Measure; BI: Barthel Index; SIS: Stroke Impact Scale; CMSA: Chedoke Mc-Master Stroke Assessment Measure; CAHAI: Chedoke Arm and Hand Activity Inventory; FAT[213]; BBT: Box & Blocks Test; JHFT: Jebsen Hand Function Test; MRC: Medical Research Council; NHPT: Nine-Hole Pegboard Test; FMA-s: Fugl-Meyer Assessment sensation; NSA: Nottingham Sensory Assessment; NIHSS: National Institute of Health Stroke Scale; VAS: Visual Analogue Scale; MAS: Modified Ashworth Scale.

5.3.5 Assessment of risk of bias in included studies

Risk of bias (RoB) in included studies were assessed by the Newcastle-Ottawa Scale (NOS) for cohort studies [223]. Since the control group was not present in the included studies, the item for comparability was adapted to the search of predictive factors in the study. Thus, the maximum number of stars achievable were 8 instead of 9, therefore the RoB levels were adapted accordingly: 0 to 2 stars (high risk); 3 to 5 (unclear risk); 6 to 8 (low risk). Graphs for risk of bias were done by online tools (https://mcguinlu.shinyapps.io/robvis/).

5.3.6 Data synthesis and statistical analysis

The number of included studies, demographic and clinical characteristics of the population, were reported by descriptive statistics. We reported information on available predictive variables. Then we used the proportional meta-analysis for indirect comparison of different treatments, along their Confidence Intervals (CIs). The Effect Size (ES) represented the percentage of responders to treatment among the total number of patients included in each study, grouped by treatment modality, ranging from a minimum probability of 0 to a maximum of 1. Magnitude of ES was defined as small (0 – 0.39), moderate (0.40 – 0.74) and large (≥ 0.75) [224]. The forest plot presented the study as specific proportions with 95% exact

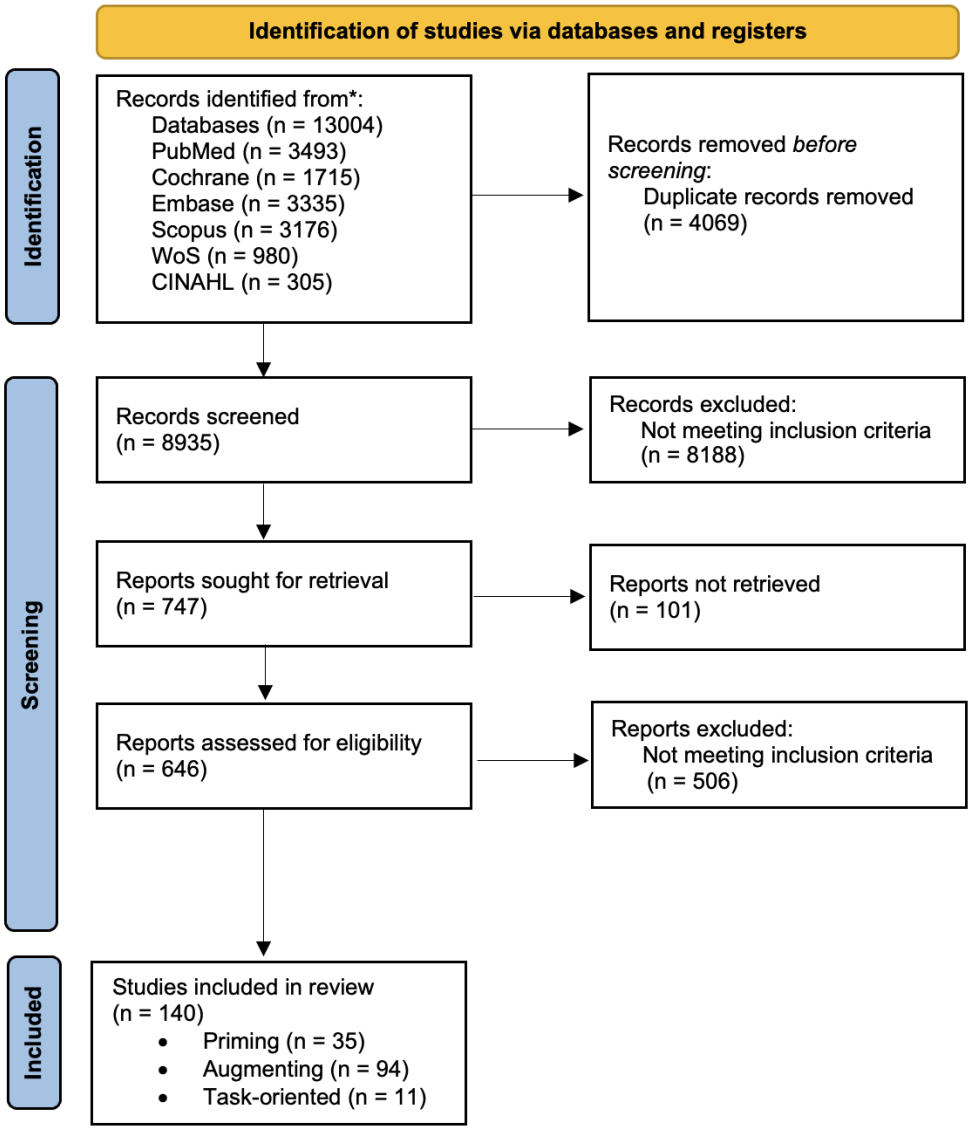
CIs for each study, the sub-group and overall pooled estimate with 95% Wald CIs and the I^2 statistic, describing the percentage of total variation due to inter-study heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic and assumed to be influent when higher than 75% [225]. Thus, we performed subgroup analysis based on phase after lesion, i.e. subacute (0-6 months) and chronic (> 6 months), and dose of treatment. The latter (in hours) was based on clinical rationale: low dose (0h - 10h), medium dose (11h - 30h) and high dose (> 30h). Studies with no data on dose were not included in the meta-analyses. For hypothesis testing, a probability value of < 0.05 was considered as statistically significant. All statistical tests were 2-sided. Descriptive analyses were performed using the free software RStudio Team[226], while proportional meta-analyses were done with STATA software version 17 using the metaprop command [227], as an adaptation of the metan programme developed by Harris et al.[228].

5.4 Results

5.4.1 Studies selection

At the beginning, 13004 studies were identified, and 140 records were finally included in the review for the quantitative analysis **[Figure 15]**.

Figure 15. PRISMA 2020 flow diagram for the study selection process



5.4.2 Demographic factors

Overall, 1661 adult stroke survivors were included, with a mean age of 59 years, in the chronic phase after lesion. The most frequent intervention was Augmenting (n = 94 studies; 67%), then Priming (n= 35; 25%) and Task-oriented techniques (n = 11; 8%). Overall, 856 patients

were classified as Responders and 805 as Non-Responders. On average, 35 hours of therapy were delivered, ranging from a minimum of 1 single session (e.g. botulinum toxin injection) to a maximum of 2.5 years of intervention and 265 hours **[Table 9]**. On average, the sample size was of 12 patients per study.

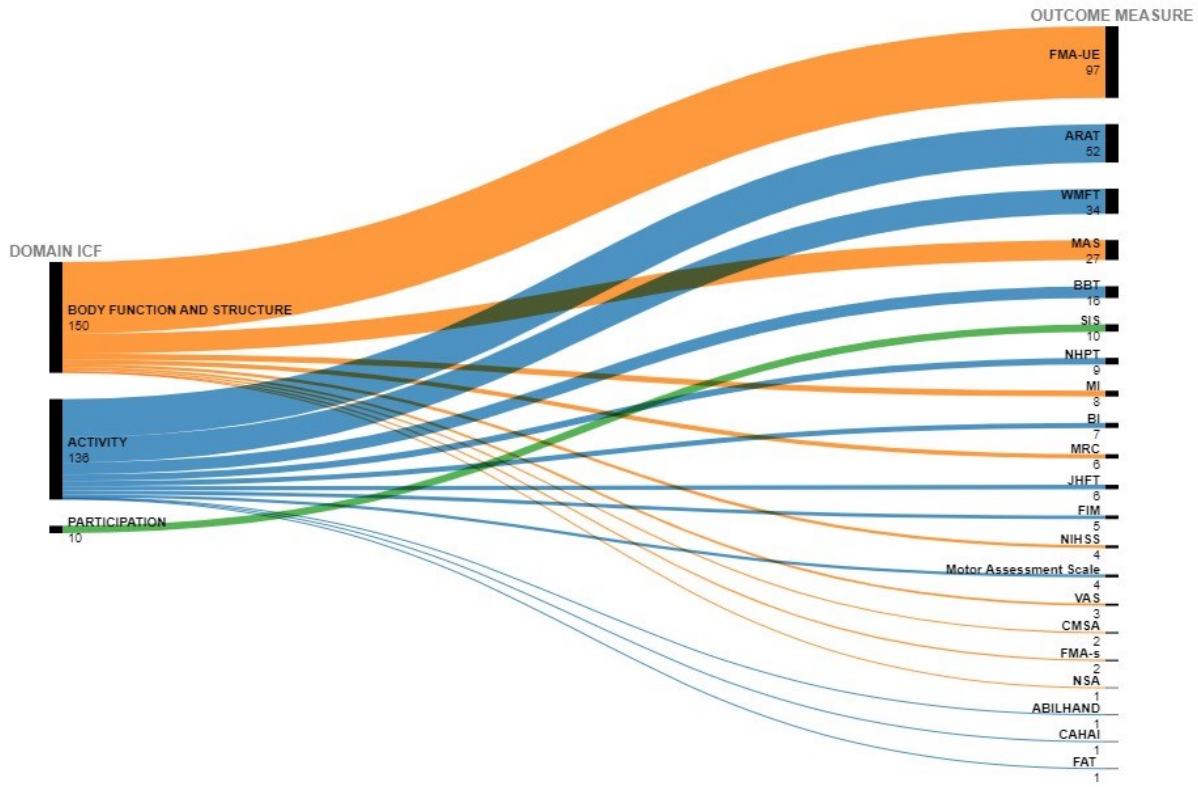
Table 9. Demographic characteristics of the population and dose of rehabilitation

Demographics	Overall (N = 140 studies)	Priming (N = 35 studies)	Augmenting (N = 94 studies)	Task-oriented (N = 11 studies)
Sex, Total, Male (%) / Female (%) / N.A. (%)	1661 1008 (61%) / 613 (37%) / 40 (2%)	398 236 (59%) / 145 (37%) / 17 (4%)	833 523 (63%) / 290 (35%) / 20 (2%)	430 249 (58%) / 178(41%) / 3 (1%)
Age, mean (SD)	59.04 (7.03)	59.52 (7.43)	58.7 (6.61)	60.45 (9.51)
Type of stroke, Isch (%) / Haem (%) / N.A.	660 (40%) / 231 (14%) / 770 (46%)	216 (54%) / 99 (25%) / 83 (21%)	350 (42%)/ 104 (12%) /379 (46%)	94 (22%) / 28 (6%) / 308 (72%)
Affected side, Right (%) / Left (%) / N.A.	766 (46%) / 783 (47%) / 112 (7%)	179 (45%) / 167 (42%) / 52 (13%)	391 (47%) / 395 (47%)/ 47 (6%)	196 (46%) / 221 (51%) / 13 (3%)
Months from injury, mean (SD)	35.47 (30.73)	33.62 (33.38)	37.65 (29.94)	23.75 (27.70)
Responders/Non-Responders, n (%)	856 (52%) / 805 (48%)	189 (47%) / 209 (53%)	370 (44%) / 463 (56%)	297 (69%) / 133 (31%)
Dose of rehabilitation (h), mean (SD)	35.21 (44.13)	33.81 (35.97)	31.95 (43.88)	84.57 (57.45)

Patients are grouped according to overall population, and priming, augmenting and task-oriented modality of intervention. Mean (Standard Deviation).

All the 21 outcome measures selected were retrieved in at least one study. The most commonly outcome measure was FMA-UE (97 times) **[Figure 16]**.

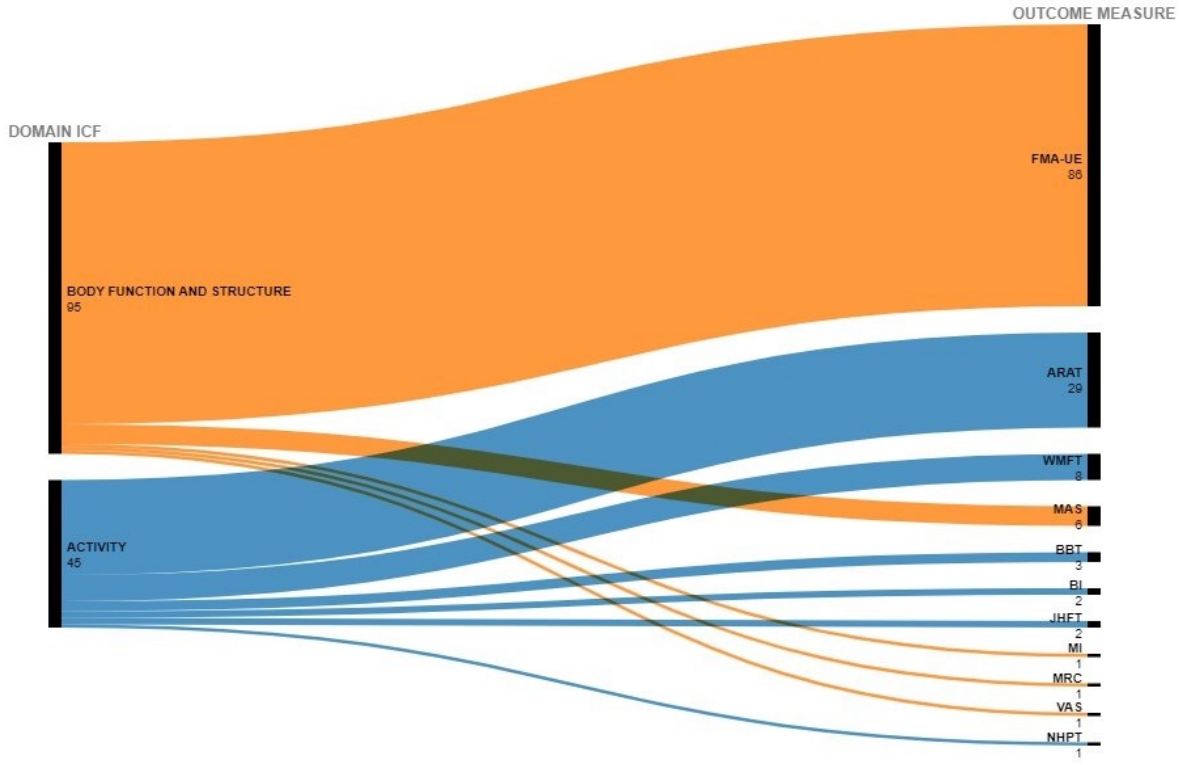
Figure 16. Alluvial diagram of the frequencies of outcome measures used across the studies



On the left, outcome measure grouped according to ICF domains (i.e orange: body function and structure, blue: activity, green: participation). On the right, outcome measures ordered according to decreasing order of frequencies of times used across the studies. FMA-UE: Fugl-Meyer Assessment Upper Extremity; ARAT: Action Research Arm Test; WMFT: Wolf Motor Function Test; MAS: Modified Ashworth Scale; BBT: Box & Blocks Test; SIS: Stroke Impact Scale; NHPT: Nine-Hole Pegboard Test; MI: Motricity Index; MRC: Medical Research Council; BI: Barthel Index; JHFT: Jebsen-Hand Function Test; FIM: Functional Independence Measure; NIHSS: National Institute of Health Stroke Scale; VAS: Visual Analogue Scale; FMA-s: Fugl-Meyer Assessment sensation; NSA: Nottingham Sensory Assessment; CMSA: Chedoke Mc-Master Stroke Assessment Measure; FAT: Franchay Arm Test.

The FMA-UE was also the most frequent primary outcome (86 times), followed by ARAT (29 times) **[Figure 17]**.

Figure 17. Frequencies of outcome measures used as primary outcome across the studies



On the left, primary outcome measures grouped according to ICF domains (i.e orange: body function and structure, blue: activity). On the right, primary outcome measures ordered according to decreasing order of frequencies of times used across the studies. FMA-UE: Fugl-Meyer Assessment Upper Extremity; ARAT: Action Research Arm Test; WMFT: Wolf Motor Function Test; MAS: Modified Ashworth Scale; BBT: Box & Blocks Test; BI: Barthel Index; JHFT: Jebsen-Hand Function Test; Motricity Index (MI); Medical Research Council (MRC); Nine-Hole Pegboard Test (NHPT); VAS: Visual Analogue Scale.

5.4.3 Predictive factors

Predictive factors were investigated in 8 out of 140 studies (6%), belonging to all the modalities (Priming = 3, Augmenting = 3, Task-oriented = 2). In **[Table 10]** baseline factors (T0) related to improvement of UL body function (e.g., FMA-UE, BBT) [115,203,229-234] and activity (e.g., ARAT) [115,203] after treatment (T1), are reported.

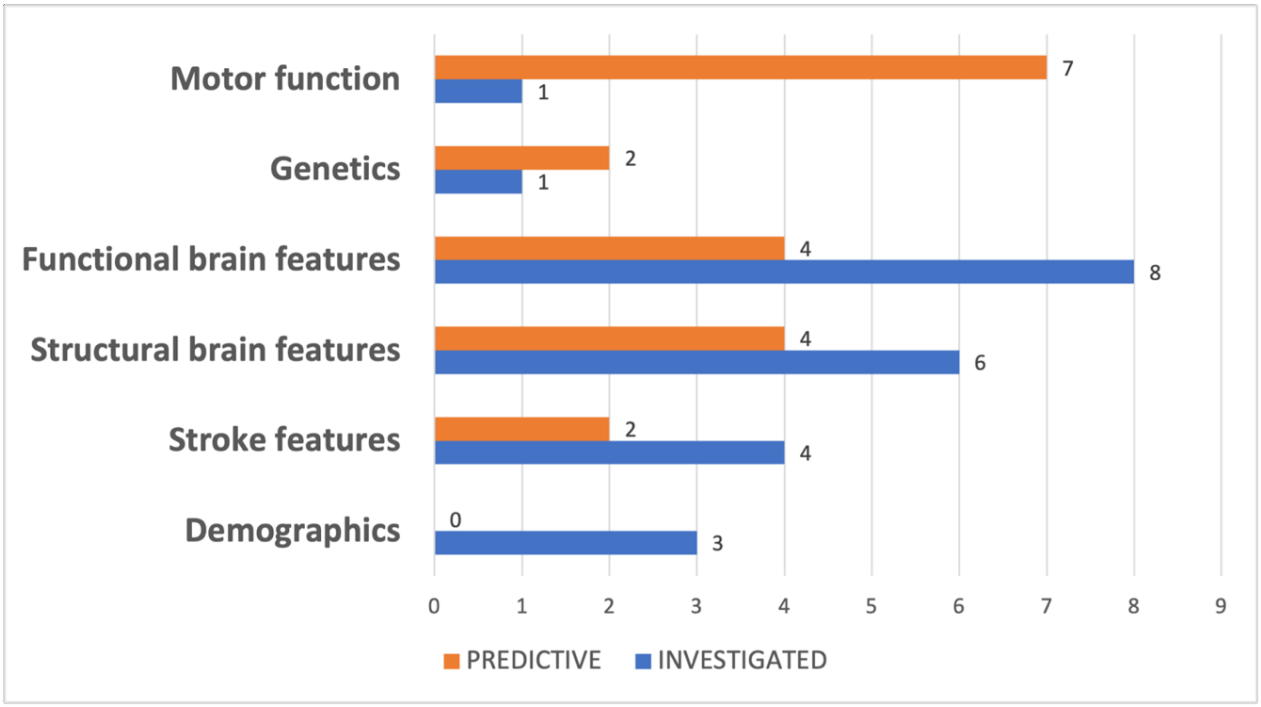
Table 10. Baseline factors (T0) individuated to be relevant for prediction of motor recovery after treatment (T1)

Investigated	Predictive	Outcome predicted
	Demographic	
Age Sex	/	FMA-UE improvement
	Stroke features	
Type of stroke (ischemic/haemorrhagic) Affected side (right/left) Type of lesion (cortical/subcortical) Time since stroke	Non-dominant affected side Long time since stroke	FMA-UE improvement
	Structural brain features	
DTI-FA (CST integrity) Lesion volume	Ipsilesional CST integrity Whole brain lesion volume Small CST injury CST symmetry (DTI) (asymmetry: CST (DTI) > 0.13)	FMA-UE improvement ARAT improvement
	Functional brain features	
MEP Cortical function Cortical connectivity Cortical coherence	MEP (MEP+: increased SMC activation, MEP-: decreased or no change SMC activation) Great ipsilesional motor cortex activation Great inter-hemispheric M1-M1 functional connectivity	FMA-UE improvement ARAT improvement BBT improvement
	Genetics	
BDNF Klotho polymorphism	BDNF Val66Met (-) polymorphism klotho SNP rs650439 heterozygosity (-)	FMA-UE improvement
	Motor function	
FMA-UE Proprioception ARAT WMFT Grip strength	FMA-UE > 15 pts Small finger proprioception error at baseline (robotic assessment) Good proprioception (high score on FMA-s) ARAT T0 Short WMFT time Lower paretic hand grip strength BBT T0 > 4 pts	FMA-UE improvement ARAT improvement BBT improvement

Variables are grouped according to different clinical domains. Outcome predicted is presented. ARAT: Action Research Arm Test; BBT: Box & Blocks Test; BDNF: brain derived neurotrophic factor; CST: Corticospinal Tract; DTI: Diffusion Tensor Imaging; FMA-UE: Fugl-Meyer Assessment for Upper Extremity; M1: primary motor cortex; MEP (+): presence of Motor Evoked Potentials; MEP (-): absence of Motor Evoked Potentials; SMC: sensorimotor cortex

Looking at frequencies of the reported variables found to be potential predictors, the most investigated were brain features with functional (n = 8) higher than structural (n = 6). Amongst variables found to be predictive, those related to motor function were reported with the highest frequency (n = 7). Demographic variables were the only ones that were not significant. However, considering motor functions and genetics factors, those found to be predictive outnumbered those investigated, highlighting a non-clear statistical methodology of reporting and conducting the analyses **[Figure 18]**.

Figure 18. Frequencies of variables investigated as predictive in the primary studies



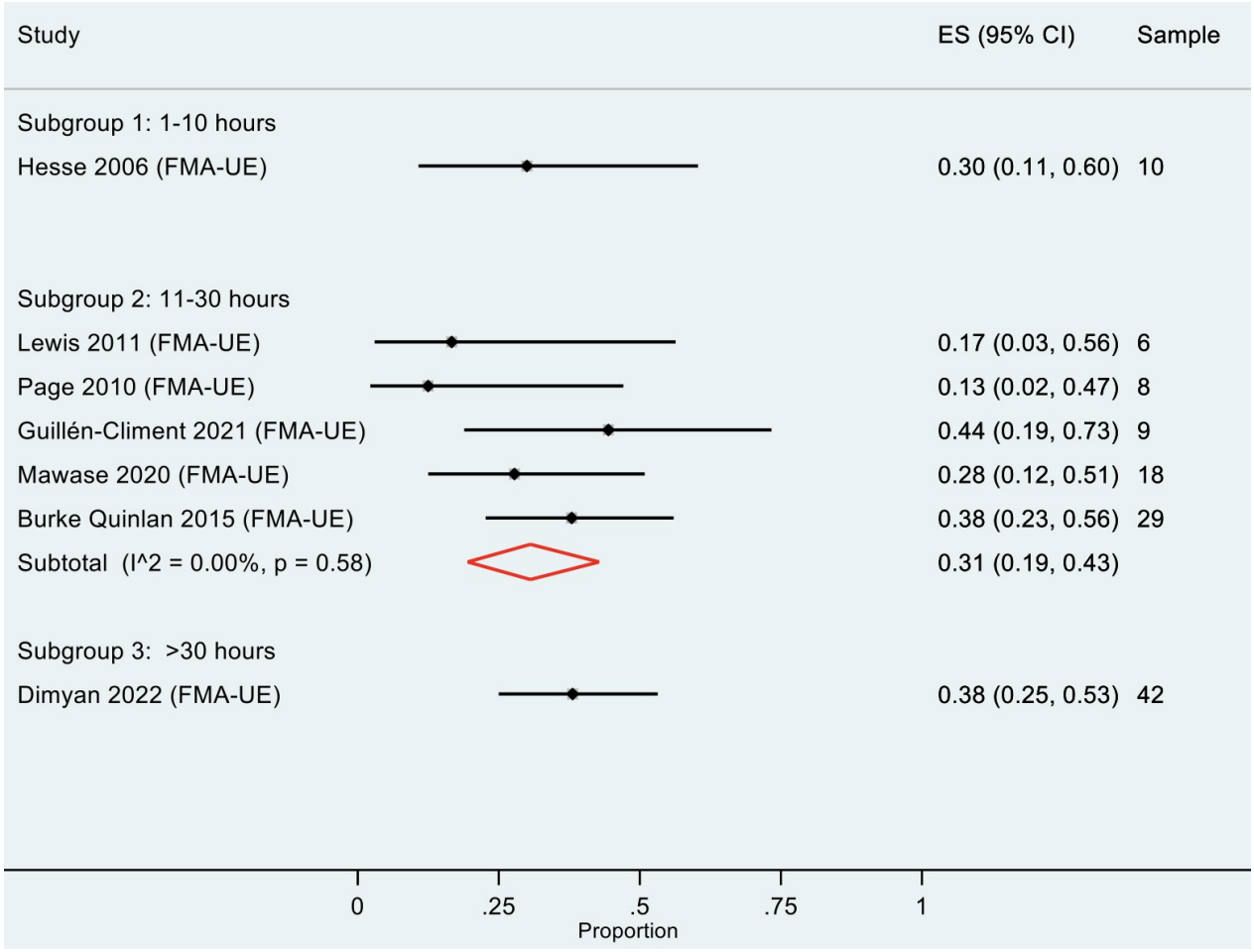
Variables are grouped according to different clinical domains. Only those explicitly declared in the primary study were considered for frequencies counting.

5.4.4 Dose response-effect on subacute patients on FMA-UE

Only one study providing high dose of Priming modalities in the subacute phase was included, therefore was not possible to run a meta-analysis.

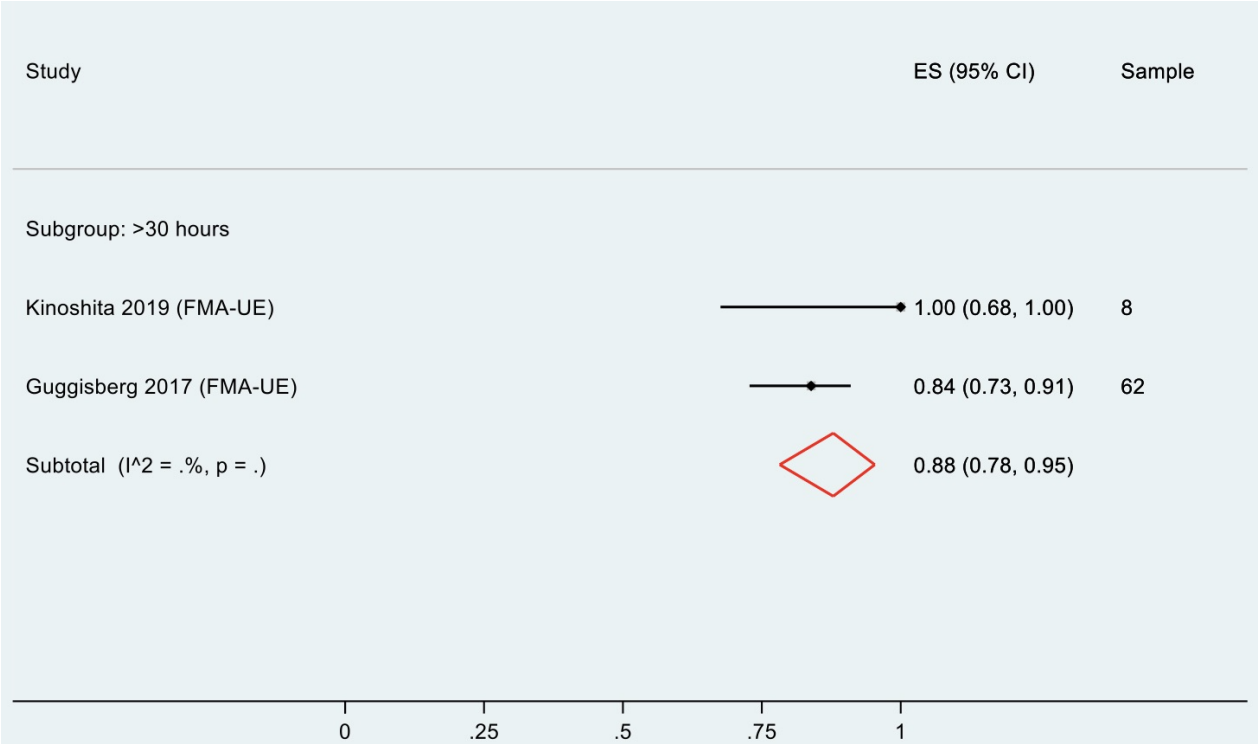
For Augmenting modalities (n = 7 studies), moderate effect size was achieved for low (ES = 0.3, $CI_{95\%}$: 0.11 – 0.6), medium (ES = 0.31, $CI_{95\%}$: 0.19 – 0.43) and high (ES = 0.38, $CI_{95\%}$: 0.25 – 0.53) doses [**Figure 19**].

Figure 19. Effect on subacute patients on FMA-UE of Augmenting modality, according to dose of treatment



For Task-oriented modalities (n = 2), there were no studies providing low or medium dose, while high dose of treatment provided a large effect (ES = 0.88, $CI_{95\%}$: 0.78 – 0.95) **[Figure 20]**.

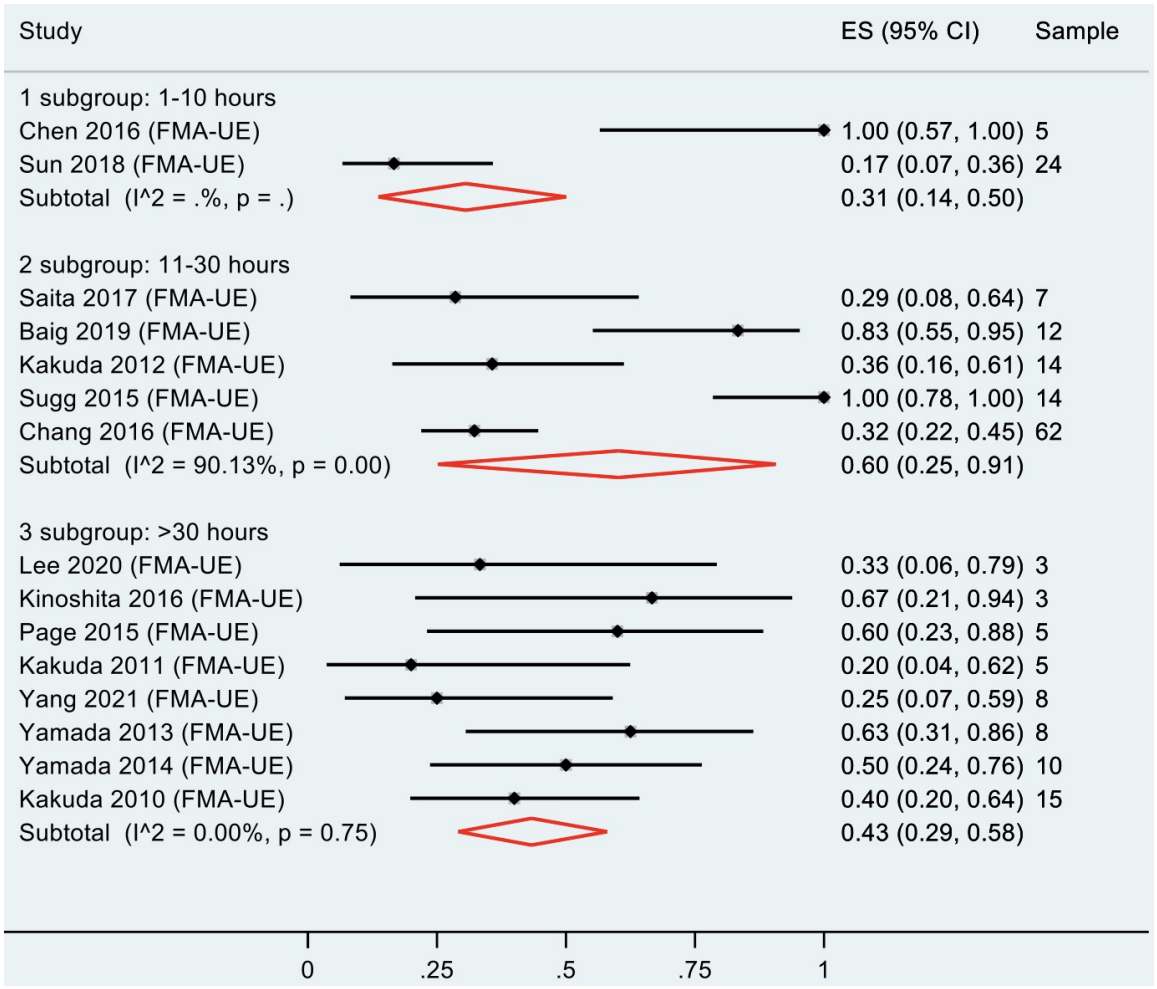
Figure 20. Effect on subacute patients on FMA-UE of Task-oriented modality, according to dose of treatment



5.4.5 Dose response-effect on chronic patients on FMA-UE

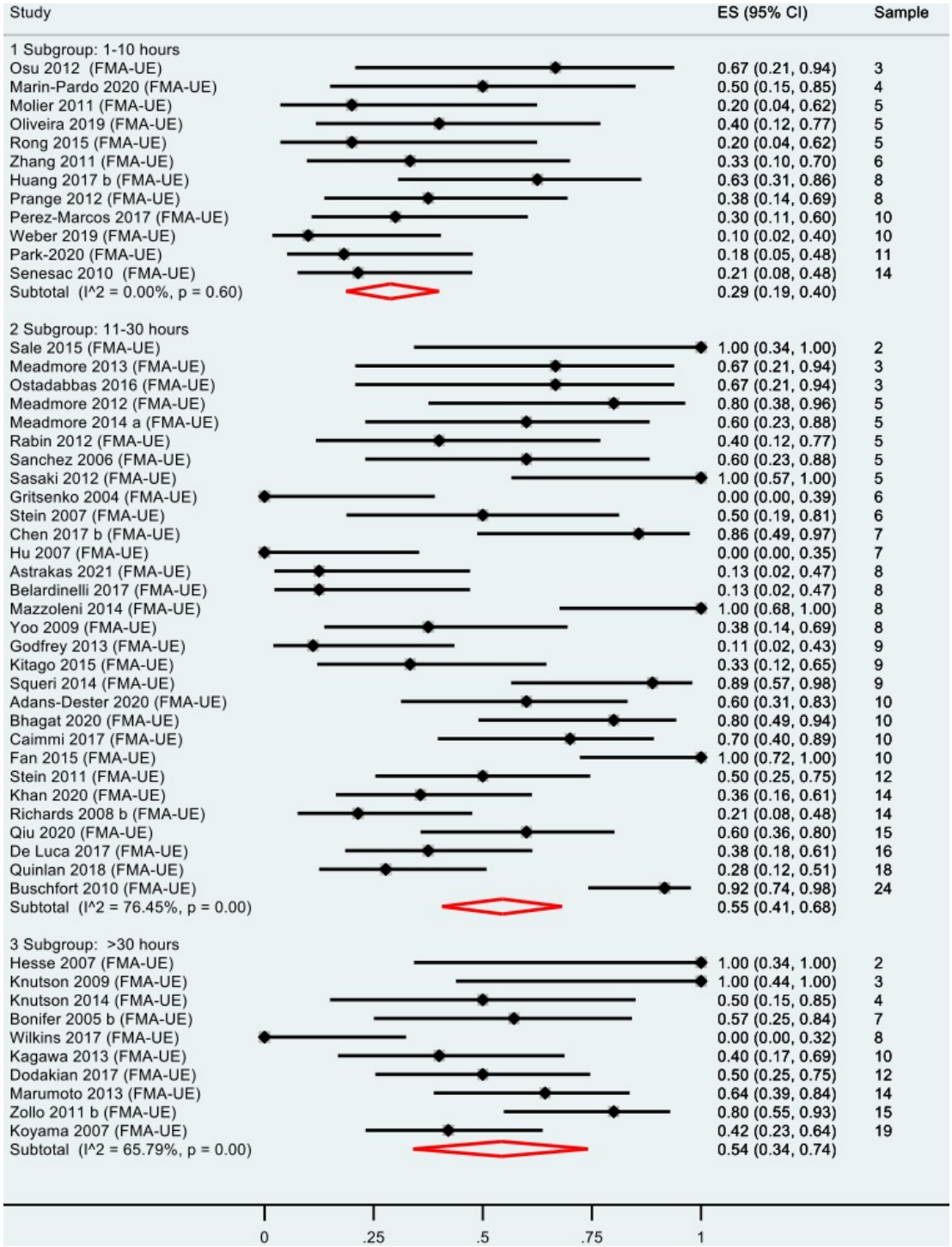
In the chronic phase, Priming interventions (n = 15) provided small effect for low dose (ES = 0.31, $CI_{95\%}$: 0.14 – 0.5), while a moderate effect for medium (ES = 0.6, $CI_{95\%}$: 0.25 – 0.91) and high (ES = 0.43, $CI_{95\%}$: 0.29 – 0.58) doses **[Figure 21]**.

Figure 21. Effect on chronic patients on FMA-UE of Priming modality, according to dose of treatment



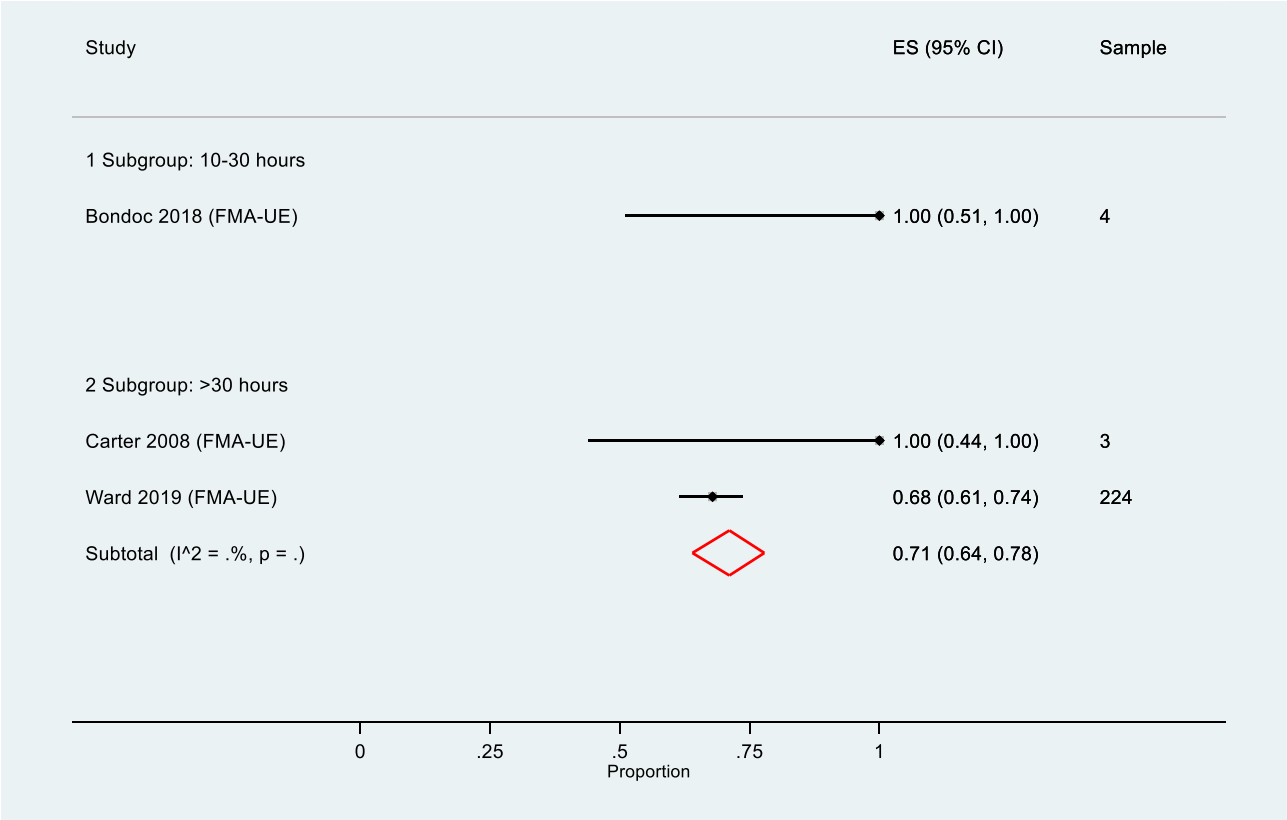
Similarly, Augmenting modalities (n = 52) provided small effect for low dose (ES = 0.29, $CI_{95\%}$: 0.19 – 0.4), and moderate effect for medium (ES = 0.55, $CI_{95\%}$: 0.41 – 0.68) and high (ES = 0.54, $CI_{95\%}$: 0.34 – 0.74) doses **[Figure 22]**.

Figure 22. Effect on chronic patients on FMA-UE of Augmenting modality, according to dose of treatment



For Task-oriented interventions (n = 3), there were no studies providing low dose, while medium and high doses promoted large (ES = 1, $CI_{95\%}$: 0.51 – 1) and moderate effects (ES = 0.86, $CI_{95\%}$: 0.57 – 1), respectively **[Figure 23]**.

Figure 23. Effect on chronic patients on FMA-UE of Task-oriented modality, according to dose of treatment



5.4.6 Summary of dose response effect

Response effects for treatment modality, dose and phase after stroke are summarised in **[Table 11]**. As reported, Task-oriented modalities led to larger effect sizes, than Priming and Augmenting modalities, both in the subacute and chronic phase.

Table 11. Summary of dose response effect for on FMA-UE for treatment modality, dose of intervention and phase after stroke

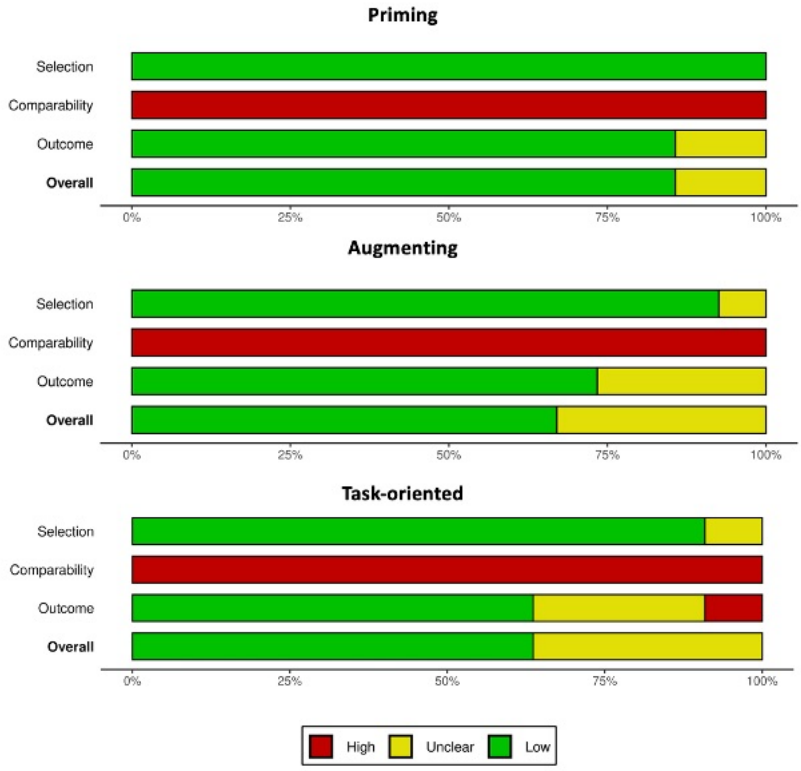
	SUBACUTE			CHRONIC		
	0-10	**11-30**	**>30**	**0-10**	**11-30**	**>30**
Priming ES (CI95%)	no study	no study	only 1 study	0.31 [0.14-0.5]	0.6 [0.25-0.91]	0.43 [0.29-0.58]
Augmenting ES (CI95%)	0.3 [0.11-0.6]	0.31 [0.19-0.43]	0.38 [0.25-0.53]	0.29 [0.19-0.4]	0.55 [0.41-0.68]	0.54 [0.34-0.74]
Task-oriented ES (CI95%)	no study	no study	0.88 [0.78-0.95]	no study	1 [0.51-1]	0.71 [0.64-0.78]

CI: Confidence Interval; ES: effect size. Studies are grouped according to low (0-10 hours), medium (11-30 hours) and high dose of treatment (>30 hours).

5.4.7 Risk of bias

The methodological quality scored between 4 and 8 points for all of the 140 studies, indicating a range from unclear to low risk of bias **[Figure 24]**.

Figure 24. Risk of bias of the included studies assessed by the NOS



5.5 Discussion

We found very few studies on the effect of rehabilitation also investigating potential predictive features of UL motor recovery, after stroke. None of them considered dose or treatment modalities as a factor potentially associated with motor outcome, therefore worth to be analysed. Investigating a possible relation between dose and motor outcomes was not possible due to insufficient data to perform a quantitative analysis. Indeed, included primary studies did not report individual patient data preventing us to perform a real insight using a systematic review approach of clinically important recovery, with a dose-response effect of intervention received. Thus, a subgroup analysis of dose was presented as an explorative assessment, and we could only report predictive factors identified by primary studies, dividing them by categories (e.g. motor function, cortical activity, genetics).

Our explorative subgroup analysis on dose of therapy open to a critical point. Results showed that providing more than 30 hours of therapy, induce small to large clinical effects depending on modality and phase after stroke. Augmenting and Task-oriented interventions led to, respectively, medium and large effect sizes (ES = 0.38, 0.88) in subacute patients. Besides, Priming, Augmenting and Task-oriented led to moderate effect (ES = 0.43, 0.54, 0.71) in chronic patients. However, Task-oriented modalities still maintain a potential large effect size (considering confidence intervals) also in the chronic phase. These findings are coherent with current evidence of existing clinical trial, where patients undergoing Task-oriented interventions, especially with high dose of therapy, reach clinically relevant motor improvement [115,117,235].

Augmenting interventions provided larger effect in chronic rather than in subacute phase, whit a potential for the biggest effect when delivered for more than 10 hours in the chronic phase. Due to lack of data, it was not possible to draw strong conclusions on the effect of Priming modalities in the subacute phase. Results for the chronic phase suggests that the optimal dose is higher than 10 hours, but no longer than 30.

Considering the clinical outcome measures recommended by the core outcome set for motor rehabilitation after stroke[43], FMA-UE and ARAT were those most used; instead, NIHSS (body function), BI/FIM (activities) and SIS (participation) were used few times. These numbers suggest that in current clinical cohort studies, body function is the main domain of assessment, rather than activities and participation. Moreover, many different outcome measures are still used among studies, leading to intrinsic variability of clinically relevant information, difficult to compare and potentially demanding in terms of resources (e.g. time, clinicians).

Qualitative analysis suggested that studies investigating predictive factors of rehabilitation-induced recovery completely lack to consider confounding factors in their modelling. Indeed, selection of independent variables was not comprehensively and homogeneously reported, underlying low quality of statistical model reporting among the primary studies.

The main limitation of our review relates to the heterogeneity of the studies also referable to eligible study designs. On one hand, we have not considered controlled studies, that would have provided (if rigorously designed) insights on different predictive factors, estimating the effects of an intervention over spontaneous biological recovery. However, controlled studies are meant to answer questions related to a larger or smaller effect of one treatment rather another one, that was not among our aims. On the other hand, the best reference design to firstly individuate the "*candidate prognostic factors"* is the longitudinal cohort study, which can then be further investigated using more complex study designs [132,236].

5.6 Conclusion

Our study highlights the actual black box on how rehabilitation may interfere with prediction of recovery after stroke. We strongly suggest that design of future clinical trials will define more comprehensively methods for investigating predictive variables, also considering rehabilitation as a factor potentially influencing motor recovery.

Besides, our findings confirm that Task-oriented modality induces the largest clinical effect, both in the subacute and the chronic phase, while Augmenting is more useful in the chronic phase. Effects of Priming intervention tend to reach their maximum expression for medium dose, slightly dropping down for high doses, in the chronic phase. In conclusion, it is worth considering incorporating analysis of candidate predictive factors to better identify patients more likely to recover.

5.7 Contribution of the study

- Patients' demographic characteristics are not associated with UL motor outcomes, in stroke survivors.
- Response to rehabilitation interventions for UL is driven by brain lesion characteristics, genetics and residual motor function at baseline.
- Task-oriented interventions lead to largest clinical effect, both in the subacute and chronic phase after stroke.

- Augmenting techniques are useful in the chronic phase after stroke.
- The maximum effect of Priming interventions in the chronic phase after stroke occurs between 10 to 30 hours of treatment.

6. CLINICAL PREDICTORS FOR UPPER LIMB RECOVERY AFTER STROKE REHABILITATION: RETROSPECTIVE COHORT STUDY

6.1 Introduction

Stroke is a cerebrovascular disease representing the second cause of death and a major cause of disability worldwide [1]. The most common sequela after stroke is the impairment of UL motor function and control, leading to restriction of activities and social participation [20]. Recovery phases after stroke are defined as acute (1–7 days), subacute (7 days–6 months) and chronic (> 6 months), with clinical improvement diminishing in accordance with distance from stroke onset, even though sustained by rehabilitation treatments [12]. Nevertheless, recovery is still possible even years after stroke, especially for cognitive domains like language [238,239]. A key factor promoting motor and functional recovery after stroke is dosage of rehabilitation therapy provided. Indeed, trials enrolling patients receiving rehabilitation for a total of 300 hours (5d/week for 5h/d), reported clinically relevant improvements of UL function at the Upper Extremity subitem of the Fugl–Meyer Assessment scale (FMA-UE) (i.e., range of score changing from 8 to 11 points) [240]. Recently, a trial aimed to assess maintenance of rehabilitation clinical effects at 6-months follow-up, found that improvements were preserved in patients receiving treatment at least 6 h per day, for three consecutive weeks, even in the chronic phase after stroke [115]. Furthermore, a combination of CT and VR for at least 40 h of rehabilitation was found to enhance clinically relevant improvement in UL motor function, in chronic stroke patients [241]. However, it is not yet known which are the clinical features (e.g., neurological profile; clinical history; level of motor, language, and cognitive functions at baseline) allowing clinicians to predict the recovery potential of a patient before rehabilitation,

also considering the treatment pathways followed within the National Health System. Despite some prognostic factors of UL recovery after stroke have been established already (e.g., presence of MEPs, preserved motor function, left lesion site [121]), a recent survey found that 89% of physical therapists (PTs) and occupational therapists (OTs) acknowledge the importance of predicting the potential for recovery after stroke, but only 9% of them actually use prognostic tools in clinical practice [120]. In addition, another under-researched aspect is how cognitive-linguistic and motor functions influence each other and mutually contribute to functional recovery, after stroke. Indeed, recent evidence showed that cognitive abilities (especially attention) support motor recovery, throughout large-scale brain networks connecting both cognitive and motor areas [242]. It is therefore reasonable consider these impairments affecting not only the recovery pattern, but also activities of everyday life [243]. Furthermore, cognitive impairments involving memory or executive functions might change responsiveness to motor rehabilitation treatments, affecting the final outcome of targeted interventions after stroke [244].

Another major concern is related to CT contents, indeed, even in studies enrolling patients with severe UL impairments after stroke, less than 30% of PTs and OTs rehabilitation sessions are specifically targeted to arm-related activities [245]. In Europe, PT interventions are generally targeted to body structures and functions with special emphasis on balance and lower limbs training, while OT interventions are more targeted to activities of daily living (ADL), domestic and leisure activities, sensory and perceptual training [245]. Recently, a systematic review on the effect of UL-targeted training dosage after stroke found that time spent on specific content of UL-targeted activities was 17% of each PT session, 49% of each OT session, in the acute phase, then ranging widely from 2% to 10% in PT session, and from 23 to 70% in OT session, in the subacute phase [246]. To face this issue, integration of technologies in clinical practice has been improved over the years, allowing to provide high dose of treatment, augmented feedback, and patients' engagement. Despite these potentials, recommendations to include technologies in current clinical practice are still limited [246].

Despite evidence for factors with positive prognostic value for UL recovery (e.g., presence of MEPs, high level of residual motor function and younger age) being available [122,196], to date, the proper prediction of a patient's recovery potential induced by rehabilitation treatments is not yet informed by patient clinical characteristics at baseline, neither eventual interactions between cognitive-linguistic and motor functions, nor rehabilitation contents.

6.2 Aim of the study

The study aims to (i) explore clinical features and (ii) potential effect of rehabilitation dose that could influence UL recovery, after stroke.

6.3 Materials and Methods

6.3.1 Study Design and Population

This study was a retrospective observational cohort analysis, from data collected on consecutive stroke subjects hospitalized between July 2019 and November 2020 at IRCCS San Camillo Hospital (Venice, Italy). Patients enrolled underwent an initial assessment of motor and cognitive-linguistic functions (T0), whereas only motor functions were reassessed after 20 h of rehabilitation (T1). The original cohort included patients according to following criteria: older than 18 years, diagnosis of a first-ever unilateral cortical-subcortical stroke (ischemic or haemorrhagic) without restriction on time from lesion and with at least 4 weeks of rehabilitation completed. Exclusion criteria were cerebellar or bilateral stroke; unstable medical conditions at time of hospitalization; diagnosis of other neurological and/or psychiatric diseases in addition to stroke (e.g., traumatic brain injury).

The retrospective study design was chosen to analyse data already collected during a standardized screening process at hospital admittance. Therefore, patients hospitalized between July 2019 and November 2020 were contacted by telephone for enrolment and informed on the study purpose, between September and December 2021. Only patients who provided written consent to use their data collected during previous hospitalization were included in the analysis.

For a better reporting of the study, the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist has been used [247]. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics committee of the IRCCS San Camillo hospital (Prot. 2021.20), which is also responsible for the integrity and conduct, the protocol was registered on ClinicalTrials.gov (NCT05478577).

6.3.2 Intervention

During hospitalization lasting 4 weeks at least, patients underwent a motor rehabilitation program consisting at minimum 1 h/day of CT for each day of hospitalization, and one or more hours of other modalities such as UL-specific OT, technology devices (i.e., robotics, VR) for UL and/or lower limb (LL). The treatment program was delivered according to the individual rehabilitation project agreed with the rehabilitation team (e.g., physiotherapist and medical doctor) and tailored on patient's

needs. Each session was adapted to individual clinical condition and ability to perform exercises, accomplishing any harm that may occur (e.g., patients referring shoulder pain, high levels of spasticity). All the technology-based modalities reported are included in the hospital clinical pathways and has been developed and validated through the institutional translational research projects funded by the Italian Ministry of Health and the European Commission.

- Conventional Therapy (CT)

The CT consisted of whole-body exercises selected autonomously by the clinician and performed in a gym or a private room, in a one-to-one setting. Among CT interventions, respiratory therapy was considered. In UL-targeted interventions, patients were asked to perform functional task exercises in each plane including shoulder and elbow flexion-extension, shoulder abduction-adduction, internal-external rotation, circumduction, forearm pronation-supination, both with and without everyday objects. Moreover, exercises were proposed for training coordination, proprioception, and effort resistance capacity in every modality to stimulate patient residual abilities, to reduce compensations and control voluntary muscle activation. If needed, the use of splints or orthosis were considered (e.g., shoulder subluxation, spastic hypertonicity). Each session lasted at least 1 hour/day, 5 days/week, for each week of the hospitalization period.

- Occupational Therapy (OT)

The OT consisted of UL-specific rehabilitation sessions based on the functional use of the limb in ADL (e.g., cooking, dressing, washing), vocational activities (e.g., using a computer, writing), or activities claimed as important by the patient (e.g., sewing). The OT intervention could be delivered in one-to-one, or group settings.

- Technology-based Rehabilitation (TBR)

Among the therapeutic modalities, technologies for both the UL and LL were available. Technologies for the UL consisted of Virtual Reality Rehabilitation System (VRRS, Khymeia Group Ltd. Noventa Padovana, Italy), with a computer-based tasks displayed in a virtual scenario. Patients were asked to emulate real arm movements, via a motion tracking system controlling a virtual object [241]. For patients who could benefit from treatments with a robotic device, AMADEO (Tyromotion GmbH, Graz, Austria) was used, an end-effector robot allowing to perform selective voluntary movements of the hand and fingers, controlled by surface electromyography (sEMG) detected from fingers flexors and extensors muscles [248]. Furthermore, among technology devices available, specific UL treatments were delivered by using DIEGO (Tyromotion GmbH, Graz, Austria), an exoskeleton

providing arm-weight support while performing virtual tasks, and REMO (Morecognition Ltd. Torino, Italy), a sEMG biofeedback armband for hand movements [249].

Regarding technologies for the LL, the VRRS were used also for LL tasks and balance activities [250]. In addition, the Gait Trainer (GT-I—Reha-Stim, Wisch GmbH & Co), an end-effector robot with body-weight support for walking training was used. Other technologies for LL rehabilitation were the Smart Balance Master (SBM—NeuroCom® Balance Manager, Natus Medical Incorporated, USA), a semi-immersive balance board providing multisensory balance training exercises with augmented visual biofeedback [251], and the OAK (Khymeia Group Ltd. Noventa Padovana, Italy), an integrated virtual reality system for the assessment and prevention of risk of fall [252]. Finally, Omego (Tyromotion GmbH, Graz, Austria) was available for LL rehabilitation, consisting of a multifunctional robot for pre-walking training (e.g., LL mobilization, muscle strength training, step, press, trunk control) [253].

Each therapy was delivered by a specialized PT for 1h/day, 5 dd/w, for 3 weeks, with a one-to-one approach. The number of repetitions and type of exercises was chosen by the PT according to clinical judgment and patient's needs, tailoring difficulties on patient's ability.

6.3.3 Clinical Data, Assessment and Outcome Measure

Clinical assessments aimed to quantify residuals motor and cognitive-linguistic functions included collection of anamnestic data from digital record of patient medical history, clinical scales measuring the level of UL functional and sensorimotor capacity, the degree of stroke severity, and communicative-linguistic rating scales.

Demographic and clinical data of each patient were retrieved from digital records of the medical history. Clinical outcomes were retrieved from clinical assessment performed by clinicians (i.e., PT, neuropsychologist, speech language therapist [SLT]). Specifically, data could be tracked back to clinical assessments performed by a PT at the beginning (T0) and end (T1) of a rehabilitation period, and linguistic-cognitive assessments performed by a SLT or neuropsychologist only at T0. The PT and SLT were blinded to rehabilitation intervention, as they were not clinically in charge of the patient. Data on dosage and therapeutic-rehabilitation modalities provided to patients were retrieved from the rehabilitation report filled out by PT.

The primary outcome measure was the FMA-UE, a reliable and validated 66-points outcome measure quantifying arm motor function after stroke [47]. Other clinical outcome measures were:

FMA for sensory function (FMA-sensation); BBT for gross manual dexterity [50]; MAS for measuring muscle tone at biceps brachii [59]; FIM for autonomy in ADLs [208].

For cognitive and linguistic functions, patients were assessed at baseline with the Oxford Cognitive Screen (OCS), a sensitive screening tool for detection of cognitive deficits after stroke. The scale consists of 10 tasks encompassing five cognitive domains: attention and executive function, language, memory, number processing, and praxis [254].

For each patient, the dose of therapy was quantified both as number of modalities and dose (i.e., total hours of rehabilitation delivered) of intervention received during hospitalization. For the analysis, classes of intervention were defined as follow: total hours of CT ("CT"); total hours of rehabilitation specific for the UL (i.e., UL technologies and OT, "TOT-UL"); total hours of rehabilitation non-specific for the UL (i.e., technologies for LL, "TOT-NUL"); total amount of rehabilitation (i.e., TOT-UL + TOT-NUL + CT = "TOT"). The CT was analysed only for the primary outcome measure (i.e., FMA-UE).

6.3.4 Sample Size

The sample size of the present study was tailored on the original cohort of stroke patients hospitalized between July 2019 and November 2020 (N = 63) and only those releasing informed consent were finally enrolled and analysed.

6.3.5 Statistical Analyses

To describe the demographic, clinical and cognitive characteristics of the sample, descriptive statistics (i.e., mean, standard deviation, and percentage) were used. Only a portion of the patients performed the cognitive assessments; therefore, it was decided to perform the descriptive analyses of these variables separately.

Missing data were found to be present for some of the variables. Where the percentage of missing data was less than 25%, the choice was made to impute data using the multivariate imputations by chain equations (MICE) method.

Depending on data distribution, tested through the Shapiro–Wilk test, a paired Student's *t*-test or Wilcoxon signed rank test was performed to study significant difference in motor outcomes before (T0) and after (T1) rehabilitation. For each outcome measure, effect sizes were calculated by Cohen's *d* to estimate the standardized effect of rehabilitation [224]. Subsequently, patients were divided in two categories (i.e., Responders, Non-Responders) according to responsiveness to

therapy, defined as an improvement greater than the MCID or MDC at clinical outcomes, only if available in the literature. For responsiveness stratification, MCID was considered for FMA-UE (i.e., 5 points), FIM (i.e., 22 points), while MDC for BBT (i.e., 6 points) [212,215,218,255]. To assess whether there was a statistically significant difference in dose of therapy between the Responder and Non-Responder patient groups, Student's *t* test for unpaired data or Mann–Whitney test for each clinical variable was performed, depending on distribution properties. Because of differences in data completeness, the variables were divided into three groups for models estimation: Clinical Group (i.e., FMA-UE, FMA-sensation, FIM, BBT, MAS-BicBrach, TOT, TOT-UL, TOT-NUL), Cognitive Group (i.e., hearts, recall, shift, assessing attention, memory and executive functions, respectively), and Demographic Group (i.e., Age, Diagnosis, Lesion Side, Time from stroke, Aphasia, Apraxia). Within each group, Generalized Linear Regression Models (GLM) were estimated using the responding variables of each clinical scale as dependent variable and results of other variables in the corresponding groups as independent variables.

Finally, to estimate the overall models of the Responders variable for the primary outcome measure (i.e., FMA-UE), GLM were estimated, using as independent variables the cognitive, demographic, and motor variables found to be significant in the models estimated within the group. For each model, the odds ratios and their 95% confidence intervals (CI) were calculated. In addition, each regression model fitting was assessed by using the following indices [256,257]: (i) McFadden's index of explained variance (pseudo-R^2) [258]; (ii) the Scaled Brier Score (sBS), which is a measure of overall accuracy and calculates the average prediction error [259]; (iii) Construction of the Receiver Operating Characteristic (ROC) curve and evaluation of the Area Under the Curve (AUC); and iv) the Hosmer–Lemeshow test for fit between expected and estimated frequencies (χ^2_{HL} ; $p - value$) [260].

The regression model fitted the original data if the indices met the following criteria: (i) the more pseudo-R^2 is close to 1, the more the model is satisfactory; (ii) Brier score for a model can range from 0 (0%) for a perfect model to 1 (100%) for a non-informative model; (iii) an AUC values >0.70 representing a moderately accurate model; (iv) a significant $\boldsymbol{\chi^2_{HL}}$ value indicating a bad model fit.

The statistical significance level was set at $p < 0.05$. All the statistical analyses were performed using the free software R Studio 4.0.5 [261].

6.4 Results

Among 63 stroke patients contacted by telephone, 35 of them gave informed consent and were included in the study. Their demographic characteristics (T0) and dose of therapy are described in **[Table 12]**.

Table 12. Demographic characteristics at baseline (T0) and dose of therapy

Patients (N = 35)	**Parameters**
Age, years, mean (SD)	65.26 (16.2)
Diagnosis, ischemic/haemorrhagic, *n* (%)	25 (71%)/10 (29%)
Lesion Side, right/left, *n* (%)	24 (69%)/11 (31%)
Time from stroke, months, mean (SD)	26.72 (67.1)
Aphasia, yes/no, *n* (%)	14 (40%)/20 (60%)
Apraxia, yes/no, *n* (%)	2 (6%)/31 (94%)
TOT, mean (SD)	80.57 (30.1)
TOT-UL, mean (SD)	13.4 (14.19)
TOT-NUL, mean (SD)	5.34 (9.5)
CT, mean (SD)	64.03 (23.46)

Values are expressed as mean ± standard deviation (SD) for quantitative measures, and frequency (n) and percentage (%) for discrete variables; N: number of patients; TOT: total amount of rehabilitation (hours); TOT-UL total amount of rehabilitation specific for the UL (hours of UL technologies and OT); TOT-NUL: total hours of rehabilitation non-specific for the UL (hours of LL technologies); CT total hours of conventional therapy of the TOT.

The UL motor function was moderately impaired before rehabilitation and significantly improved after treatment. Significant improvements were observed also for level of independence and manual dexterity, with effect sizes ranging from low to moderate (Cohen's d < 0.6), as described in **[Table 13]**.

Table 13. Motor outcome measures before (T0) and after (T1) rehabilitation

Outcome Measure (N = 35)	**T0**		**T1**			**Effect Size**
	Mean (SD)	**Median [IQR]**	**Mean (SD)**	**Median [IQR]**	***p*-Value**	**(Cohen's *d*)**
FMA-UE	31.60 (24.4)	34 [46.5]	37.20 (23.2)	45 [45]	0.005 * [1.3; 9.8]	0.45
FMA-sens	18.29 (7.3)	22 [12]	19.11 (6.1)	23 [11.5]	0.501 [-1.3; 2.6]	0.15
FIM	86.17 (29.7)	88 [58]	97.69 (26.8)	109 [40]	0.005 * [2.8; 14.7]	0.6
BBT	16.60 (17.7)	14 [32]	24.63 (20.5)	29 [43]	< 0.001* [3.7; 11.4]	0.59
MAS-BicBrach	0.91 (0.9)	1 [2]				

*Values are expressed as mean ± standard deviation (SD) and Median and Interquartile range (IQR). FMA-UE: Fugl–Meyer Assessment Upper Extremity; FMA-sens: Fugl–Meyer Assessment–sensation; FIM: Functional Independence Measure; BBT: Box and Blocks Test; MAS-BicBrach: Modified Ashworth Scale at Biceps Brachii muscle. Wilcoxon singed-rank test was used for within analyses. Significance was established at p < 0.05 *. CI95%: Confidence Interval*

The cognitive outcome measures were collected at T0 in those patients needing a cognitive screening (N = 18) and are described in **[Table 14]**. Overall, patients tested by OCS presented low-to-moderate cognitive impairments.

Table 14. Oxford Cognitive Scale (OCS) evaluated before (T0) rehabilitation

Outcome Measure (N = 18)	T0 Mean (SD)
Hearts	44.83 (6.5)
Recall	2.78 (1.2)
Shift	1.72 (4)

Values are expressed as mean ± standard deviation (SD). N: number of patients. Hearts: attentive function; Recall: memory; Shift: executive functions.

After treatment, less than half of the patients improved above the MCID or MDC at the FMA-UE, FIM and BBT, thus classified as responders to therapy **[Table 15]**.

Table 15. Patients responding to therapy in the motor domain

Outcome measure (N = 35)	Responders/Non-Responders *n* (%)
FMA-UE	12 (34%)/23 (66%)
FIM	8 (23%)/27 (77%)
BBT	17 (49%)/18 (51%)

Values are expressed as frequency (n) and percentage (%). FMA-UE: Fugl–Meyer Assessment Upper Extremity; FIM: Functional Independence Measure; BBT: Box and Blocks Test.

Among the responders to therapy for all the motor outcome measures, the difference on the amount of total dose of rehabilitation was found to be significant only in the FIM group (p = 0.031, W = 163.5). Actually, the Non-Responders received more hours of rehabilitation than Responders **[Table 16]**.

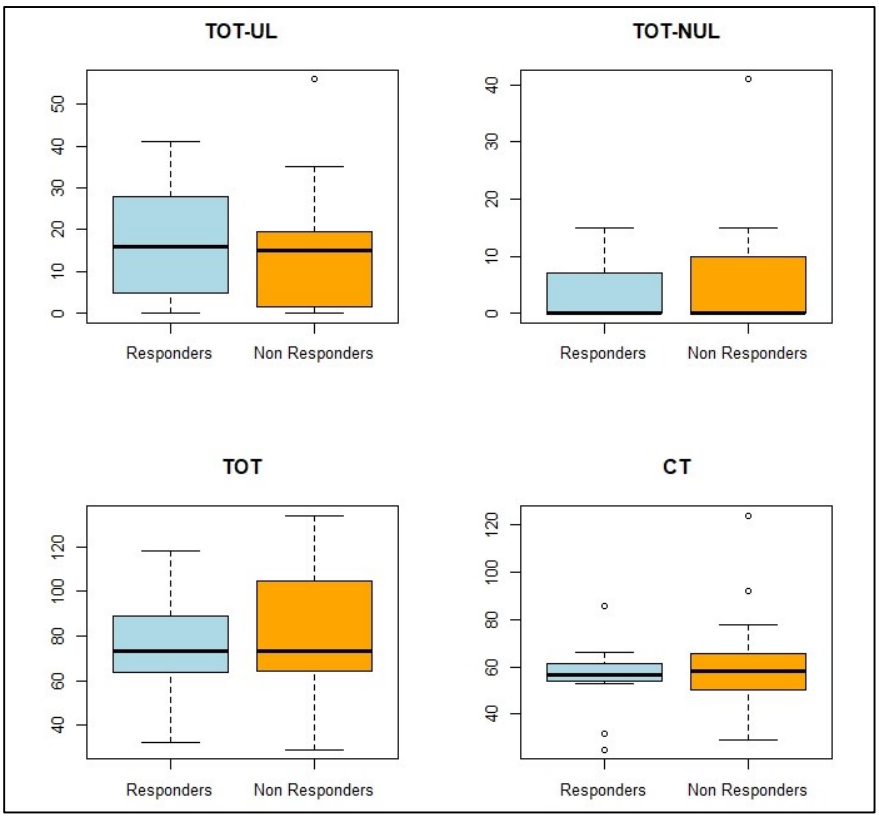
Table 16. Comparison between dose (hours) of rehabilitation between Responders and Non-Responders for UL motor function

Dose for each Outcome Measure	Responders		Non-Responders		Between Groups
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
FMA-UE	N = 12		N = 23		n = 23
TOT-UL	17.17 (14.06)	16 [18.5]	11.43 (14.16)	15 [17]	p = 0.607
TOT-NUL	3.67 (6.64)	0 [3.5]	6.22 (10.77)	0 [10]	p = 0.221
TOT	76.33 (22.71)	73.5 [21.25]	82.78 (33.55)	72 [40.5]	p = 0.524
CT	72.5 (33.7)	56.5 [26]	56.26 (12.17)	58 [13.5]	p = 0.300
FIM	N = 8		N = 27		
TOT-UL	12.00 (12.68)	10.5 [19.25]	13.82 (14.81)	14 [20]	p = 0.841
TOT-NUL	1.88 (5.30)	0 [0]	6.37 (10.32)	0 [12]	p = 0.193
TOT	61.25 (14.96)	63.5 [13]	86.29 (31.21)	75 [44]	p = 0.031*
BBT	N = 17		N = 18		
TOT-UL	12.29 (15.79)	6.0 [20]	14.44 (12.88)	15.5 [19]	p = 0.511
TOT-NUL	4.94 (8.33)	0 [8]	5.72 (10.77)	0 [11.25]	p = 0.934
TOT	82.94 (38.34)	70 [53]	78.33 (20.37)	74 [23.25]	p = 0.591

*Values are expressed as mean (± 1 standard deviation, SD) and Median and interquartile range [IQR]. * p values < 0.05; Mann–Whitney test was used for between analysis. FMA-UE: Fugl–Meyer Assessment Upper Extremity; FIM: Functional Independence Measure; BBT: Box and Blocks Test; TOT-UL: total amount of rehabilitation specific for the UL (hours of UL technologies and OT); TOT-NUL: total hours of rehabilitation non-specific for the UL (hours of LL technologies); CT: conventional therapy (hours); TOT: total amount of rehabilitation (hours).*

Consistently, the Responders and Non-Responders at the FMA-UE, did not receive different doses of rehabilitation **[Figure 25]**.

Figure 25. Box and whiskers plot of Dose of rehabilitation of the Responders and Non-Responders for FMA-UE



TOT-UL: total amount of rehabilitation specific for the UL (hours of UL technologies and OT); TOT-NUL: total hours of rehabilitation non-specific for the UL (hours of LL technologies); TOT: total amount of rehabilitation (hours); CT: conventional therapy.

Among the Responders at the FMA-UE, the total amount of rehabilitation and a high level of residual independence before rehabilitation (T0) seem to be weakly associated to higher clinically relevant motor gains. In relation to the cognitive variables assessed before rehabilitation (T0), results showed no significant evidence that attentive functions and independence in ADL influenced motor recovery, positively **[Table 17]**.

Table 17. Relationship between the FMA-UE Responders and clinical and rehabilitation features

Regression Model	β ± SE	pseudo-R2	sBS	AUC	PHL
Intercept	0.06 ± 1.66				
FIM	−0.03 ± 0.02	0.20	0.26	0.79	$p = 0.33$
TOT	0.02 ± 0.02				
Intercept	7.34 ± 4.25				
Heart* ($p = 0.06$)	−0.18 ± 0.09	0.18	0.24	0.70	$p = 0.47$
Intercept	7.06 ± 4.8				
TOT* ($p = 0.09$)	0.04 ± 0.02	0.36	0.42	0.87	$p = 0.24$
Hearts	−0.25 ± 0.12				

*The outcomes are displayed with: Estimate of regression coefficient with Standard Error (β ± SE); McFadden's index of explained variance (pseudo-R2); Scaled Brier Score (sBS); Area Under the Curve (AUC); p-value of the Hosmer–Lemeshow test (PHL). Significance was established at $p < 0.05$ *.*

6.5 Discussion

The present study explored the association between dose of rehabilitation, cognitive and motor characteristics, in a population of chronic stroke patients undergoing a period of rehabilitation. We observed that the UL motor function (FMA-UE, $p = 0.005$, V = 73), manual dexterity (BBT, $p = 0.001$, V = 9) and level of independence (FIM, $p = 0.005$, V = 88) significantly improved after 80.57 ± 30.1 h of rehabilitation, on average. The overall effect of received intervention was moderate (Cohen's *d* 0.45 to 0.60). Conversely, sensation functions did not change importantly (FMA-sensation, $p = 0.501$, V = 54.5). Less than half of the patients responded to therapy, according to FMA-UE and FIM (i.e., 34% and 23%, respectively), while almost half of the patients, regarding BBT (i.e., 49%). However, it must be reported that some patients resulted to be non-responders at FMA-UE as their baseline score, higher than 61/66, was within the ceiling effect-zone of the scale.

An utmost finding was that patients classified as non-responders to FIM after treatment, instead received a significant higher dose of rehabilitation, than responders ($p = 0.031$). Conversely, specific interventions for the UL and total dose of rehabilitation specific for the UL did not emerge as significant factors inducing differences between responders and non-responders, confirming that total dose of rehabilitation is more impacting, than dedicated strategies targeted to specific body districts, as previously demonstrated by McCabe et al. [240]. In other words, a high dose of rehabilitation was delivered to less independent patients (i.e., low FIM score) at hospital acceptance ($p = 0.031$, W = 163.5), therefore to subjects with more severe impairments, thus with larger ranges of improvement expected. It is worth noticed that mild-moderate impairment of muscle tone, sensation, and executive functions at baseline, make patients fully suitable for any potential rehabilitation intervention targeted to the UL, as well as general cognitive functions. Indeed, 12 patients out of the 18 who performed a cognitive screening, presented good levels of attentive, linguistics and mnemonic functions, whereas 13 patients showed good performance of executive functions and no severe cognitive impairment at baseline. Therefore, because of the presence of good cognitive functions in 72% of patients, it was hard to identify the level of cognitive function relevant for empowering improvement of motor function.

Among the responders at FMA-UE, level of independence in ADLs at the beginning of rehabilitation and total dose of intervention accurately predict clinical improvement of UL motor function, as confirmed by the regression model (pseudo-$R^2 = 0.20$, AUC = 0.79).

Regarding cognitive variables, the results showed no significant evidence that cognitive-linguistic and attentive functions positively influenced motor recovery, which is not consistent with the

present literature [244]. However, it must be reported that according to FMA-UE, the contribution of attentive functions for responding to rehabilitation is close to the significance threshold, even though they seem linked negatively (β = −0.18; p = 0.06).

Some limitations of our study need to be acknowledged; the low number of enrolled patients (small sample size) may have underpowered results from the regression models and affected estimation precision, thus confounding potential significant inference. Moreover, the retrospective nature of the study design and the absence of a control group did not allow to explore strong cause-and-effect relationships [262]. Therefore, there is the need to test our findings on larger sample, to improve the model's statistical fitting and estimation precision for having an accurate view on the potential influence of the cognitive and linguistic functions on motor recovery, more consistent with current literature [242].

6.6 Conclusion

This retrospective cohort study found that total dose is more influential than dose specificity when delivering rehabilitation treatments, for the recovery of motor function, in the chronic phase after stroke. Indeed, higher dose of rehabilitation leads to higher probability of becoming a responder to rehabilitation treatment, for the recovery of the UL motor function. Conversely, the results show that a lower level of independence gain was associated with a higher probability of receiving a larger amount of rehabilitation treatment. Regarding cognitive capability, attentive functions did not seem to be associated with motor recovery, even though their contribution is close to the significance threshold.

In conclusion, the total amount of rehabilitation is confirmed to be the strongest factor contributing to a clinically important improvement in the recovery of UL motor function, after stroke.

To reach firm and strong insights on the predictive factors for motor recovery, improvement of the model's statistical fitting and estimation precision is required. Therefore, further research should be conducted with longitudinal cohort studies on a larger sample, considering also the enrolment of control cohorts and adjustments for confounding factors.

7. CLINICAL PREDICTORS OF REHABILITATION-INDUCED UPPER LIMB RECOVERY AFTER STROKE: LONGITUDINAL COHORT STUDY (NeuroPro)

The present chapter presents a longitudinal cohort study, with background, aims, methods and preliminary results. The full protocol paper was published this year and its reference is reported here, *Salvalaggio S, Turolla A, Andò M, Barresi R, Burgio F, Busan P, Cortese AM, D'Imperio D, Danesin L, Ferrazzi G, Maistrello L, Mascotto E, Parrotta I, Pezzetta R, Rigon E, Vedovato A, Zago S, Zorzi M, Arcara G, Mantini D and Filippini N (2023) Prediction of rehabilitation induced motor recovery after stroke using a multi-dimensional and multi-modal approach. Front. Aging Neurosci. 15:1205063. doi: 10.3389/fnagi.2023.1205063*, under licence CC-BY 4.0 © [81].

7.1 Introduction

Stroke survivors are likely to suffer from severe UL impairment [6,18]. Moreover, they are at great risk of experiencing motor and cognitive impairments, leading to reduction in their quality of life [6,18]. Stroke survivors frequently inquire about the extent of their potential recovery, or the effectiveness of specific treatment approaches. Nevertheless, accurately predicting the outcome or response to treatment is not commonly incorporated into the standard clinical care for stroke survivors [119,120]. After stroke, the execution of goal-directed actions requires planning and computational processes that involve connections between various areas of the brain, drawing upon motor models acquired through previous experiences [263,264]. Voluntary motor behaviour engages a broad neural network that extends beyond motor and attentional functions [242,265]. While performing movements, the motor system increases attentional demands according with complexity of controlling sensorimotor actions. Consequently, cognitive abilities such as attention may play a significant role, particularly in individuals with brain damage [266] [116]. Indeed, stroke survivors are more likely to require greater attentional resources to perform specific tasks compared to healthy subjects [244]. Indeed, some studies suggest that attention may be the most critical cognitive domain influencing motor recovery after stroke, as commonalities of the underlying mechanisms of motor and cognitive recovery have been unveiled [116,266-268]. Taking all these factors into account, preserved attentional skills can have a positive influence on motor rehabilitation outcome, as motor and attention processes synergistically contribute to performing voluntary actions [242,269].

Up to date, research studies have emphasized the role played by specific factors in predicting UL recovery following stroke [237]. These factors include maintenance of shoulder abduction and

finger extension (SAFE), as well as preserved conduction and CST anatomical integrity, which can be confirmed through motor evoked potentials (MEPs) and Fractional Anisotropy (FA) derived measures [121,122]. CST plays a fundamental role in controlling fine hand motor movement and finger extensors, and it has been widely investigated as a factor implied in prediction of UL motor outcomes [28,85,121,122]. However, it is important to note that these predictive factors are applicable only to spontaneous recovery, since rehabilitation has never been considered as a factor associated to motor improvement. Moreover, the currently accepted levels of treatment are low, and it is widely recognized that stroke survivors receive insufficient UL rehabilitation [121,122]. Indeed, only studies providing high dose of therapy (i.e. 90 to 300 hours) were able to show consistent and clinically relevant motor improvement. However, these studies did not investigate thoroughly the specific factors predicting motor recovery [115,117]. A study suggested that a low degree of CST injury, increased activation of the motor cortex on the same side as the lesion, and enhanced interhemispheric connectivity were the most effective factors associated with motor response to robotic treatment. However, it should be noted that the therapy dosage in this study was still relatively low [203]. Moreover, it is not yet clear whether putative predictive factors will change depending on treatment delivered [123].

7.2 Objective

The overreaching objective of this study is to develop a prediction model of UL motor recovery after stroke rehabilitation, therefore, to identify define the clinical features (e.g. motor, cognitive, neurophysiological and neural) associated with UL motor recovery that may become candidate predictive factors.

7.3 Hypotheses

The leading hypothesis of our study is that rehabilitation-induced recovery is driven by putative predictive factors, allowing a priori patients stratification. More specifically, this hypothesis could be declined into the followings:

- Rehabilitation, especially at high doses, is associated with UL motor recovery;
- There are some features (i.e. clinical, neural and physiological) associated with recovery induced by rehabilitation;
- Structural and functional integrity of the CST may be associated with motor recovery.

7.4 Methods

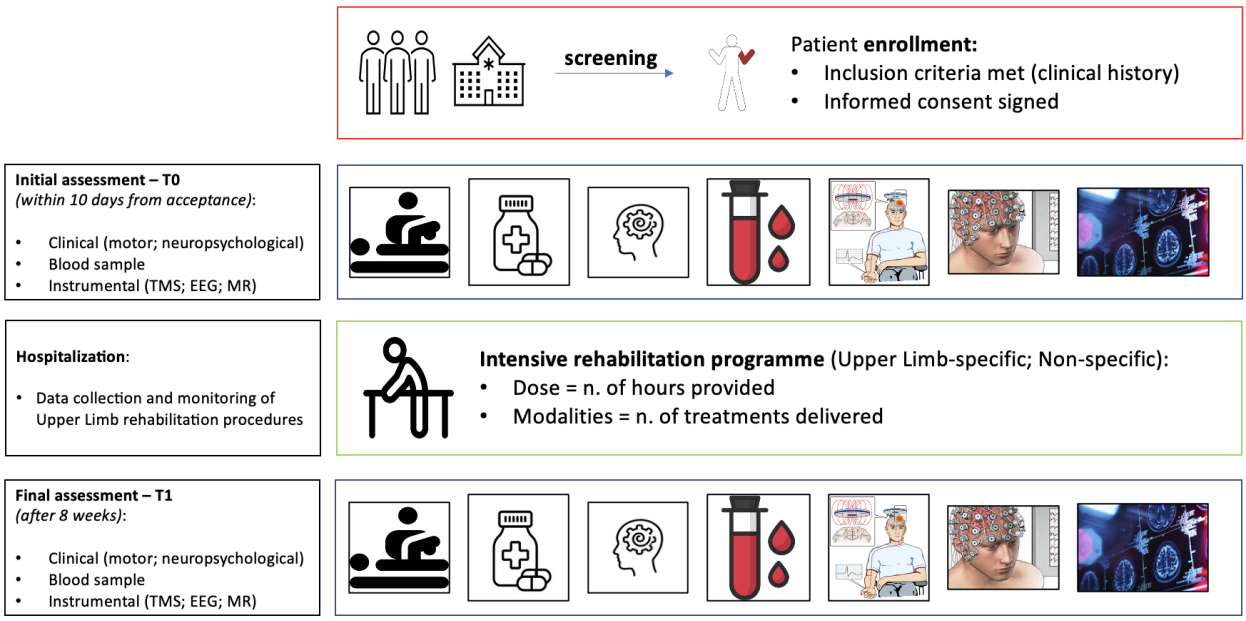
For a full and comprehensive reporting of the present study, the *Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis* (TRIPOD) has been used [270]. The full and detailed protocol is reported in the paper published in June 2023 under licence CC-BY 4.0 © [81].

7.4.1 Study design

The current design is a longitudinal observational cohort study on stroke survivors undergoing in-patient rehabilitation during a period of hospitalisation. Data analysed for this project were collected between August 2021 and March 2023 at the IRCCS San Camillo Hospital in Venice (Italy). Participation in the study did not result in the exclusion or reduction of ordinary treatment for the study-subjects. Full assessment was carried out before and after rehabilitation, according to the following scheme, **[Figure 26]**:

1. Initial assessment (T0): the participant underwent clinical (i.e. motor and cognitive) assessments, blood sampling and instrumental investigations (i.e. imaging, neurophysiology, electrophysiology), within 10 days from admission.
2. Exposure: treatment rehabilitation during a predefined period of 8 weeks hospitalisation.
3. Final assessment (T1): the participant underwent the same clinical, biological and instrumental investigations, as at T0, 8 weeks after admission (or before discharge if before 8 weeks).

Figure 26. Schematic representation summarizing the different stages and the acquired measures of each participant involved in the NeuroPro study



(From Salvalaggio et al., Front. Aging Neurosci. 15:1205063. doi: 10.3389/fnagi.2023.1205063 [81], reproduced under licence CC-BY).

It is important to declare that for this doctoral thesis and these preliminary results, only clinical, TMS and MRI data has been considered, while EEG and biological data were not included in the interim analyses. Indeed, in the framework of prognostic factors of UL motor recovery after stroke, EEG and biological data are still emerging techniques, while there is substantial evidence on the role of clinical, TMS and MRI outcomes. Therefore, we preferred to analyse how this evidence, already established in the prognostic framework, also worked in the predictive one, thus in the context of rehabilitation-induced recovery.

7.4.2 Participants

Study participants were recruited among stroke survivors admitted to a period of intensive neurorehabilitation treatment at the IRCCS San Camillo Hospital in Venice, Italy.

Inclusion criteria were: 1) age $\geq$ 18 years old; 2) first ever supratentorial ischemic or haemorrhagic, unilateral stroke, based on medical records.

Exclusion criteria were: 1) bilateral or pure cerebellar lesion; 2) presence of non-stabilized fractures; 3) diagnosis of other neurological and/or psychiatric disorder; 4) unstable medical condition (e.g. heart failure, untreated seizures, psychiatric comorbidities); 5) any other relevant musculoskeletal impairment of the UL both before and after stroke onset, hampering assessment; 6) inability to provide informed consent.

Specific exclusion criteria related to the instrumental technology (i.e. EEG, MRI, TMS) employed in this project will be detailed in each specific section.

7.4.3 Exposure

Motor rehabilitation training was tailored to the patient's motor residual capacity and needs, as planned with the rehabilitation team and medical doctors. Each session was adapted to the patient's clinical condition and with progressive exercises' targets, accomplishing any harm that may occur (e.g. patients referring shoulder pain, high spasticity).

- Conventional Therapy (CT)

The CT sessions involved a variety of whole-body exercises selected by the clinician. These exercises were conducted on a one-to-one basis either in a gym or a private room. For the UL, patients were instructed to perform functional task exercises encompassing various movements such as shoulder and elbow flexion-extension, shoulder abduction-adduction, internal-external rotation, circumduction, and forearm pronation-supination. Additionally, exercises focusing on coordination and proprioception were introduced to encourage patients to enhance their remaining abilities, minimize compensations, and control voluntary muscle activation. If necessary, the use of splints or orthosis was considered, for instance, in cases involving shoulder subluxation or spasticity of hand flexors. Each session lasted one hour per day, five days per week, throughout the entire duration of the hospitalization period, as a minimum requirement.

- Technology-based rehabilitation (TBR)

Various modalities and technologies were available for both UL and lower limb (LL). For the UL, these technologies included the Virtual Reality Rehabilitation System (VRRS®, Khymeia Group Ltd., Noventa Padovana, Italy), which requires the use of a computer to display kinematic tasks in a virtual scenario that patients emulate with their real arm movements while controlling a virtual object through a motion tracking system [241]. Another technology was the AMADEO® (Tyromotion GmbH, Graz, Austria), an end-effector robot for the hand that allows selective hand opening and closing based on electromyographic activities of the wrist flexors and extensors [248]. The DIEGO® (Tyromotion GmbH, Graz, Austria) is a wired exoskeleton that provides arm-weight support during virtual tasks, and the REMO® (Morecognition Ltd., Turin, Italy) is a biofeedback armband used for training complex hand movements [271]. For the LL, the VRRS® was also used for LL and balance tasks [272], while the Gait Trainer (GT1®, Reha-Stim Medtec Inc., NY-US) is an end-effector robot that provides body-weight support for walking training. The Smart Balance Master® (SBM, NeuroCom

International Inc., Clackamas, OR-US) is an interactive balance platform that offers visual biofeedback for training exercises. The OAK® (Khymeia Group Ltd., Noventa Padovana, Italy) is an integrated virtual reality system used for assessing and preventing the risk of falls, and the Omego® (Tyromotion GmbH, Graz, Austria) is a multimodal robot used for LL mobilization, muscle strength training, step initiation, and trunk control. Also Functional Electrical Stimulation (FES) was used, combined with cycling activity and electrical stimulation in the LL. The utilization of all these devices has been previously described in other studies conducted at IRCCS San Camillo Hospital [241,248,249,271,272].

- Occupational therapy (OT)

While hospitalized, patients may have received occupational therapy (OT), which involves specialized rehabilitation sessions UL-focused and aimed at improving activities of daily living (e.g. cooking, dressing, washing), vocational skills (e.g. use of desktop/laptop computer, writing), and recreational activities (e.g. sewing) meaningful to them. OT could be provided on an individual basis or in group sessions.

7.4.4 Clinical data for motor and cognitive profiles

Each patient recruited for the study underwent a detailed clinical assessment including: 1) collection of patient medical history and records (e.g. risk factor, demographic data); 2) validated outcome measures quantifying stroke severity, functional and sensorimotor impairments.

To quantify the severity of stroke sequelae, the following outcome measures were used:

- National Institutes of Health Stroke Scale (NIHSS) is a 42-points Likert scale for quantification of stroke severity [212]. The lower the score, the better the function (negative direction).
- Functional Independence Measure (FIM) is a 126-points scale for measuring the level of independence in activities of daily living (ADLs) [273]. The higher the score, the better the independence (positive direction).

For the motor abilities and impairments, the following outcome measures were used:

- Fugl-Meyer Assessment (FMA) [47]. We used the domain of Upper Extremity (FMA-UE) which is a 66-points scale for profiling impairment of the UL by quantifying performance of complex and segmental voluntary movements, grasping and coordination. We used also the sensation and pain/rom domains for quantifying sensory function (i.e. proprioception and light touch) and pain/range of motion, respectively with 0-24 and 0-48 points. The higher the score, the better the UE function (positive direction).

- Action Research Arm Test (ARAT) is a 57-points ordinal scale quantifying performance of hand and arm activities [60]. The higher the score, the better the UE activity (positive direction).
- Medical Research Council (MRC) muscle strength scale is a 5-points ordinal scale for assessment of voluntary force, applied to shoulder abduction (SA) and fingers extension (FE) [58]. The higher the score, the stronger the muscles (positive direction).
- Reaching Performance Scale (RPS) is a 36-points scale for assessment of voluntary UL reaching task [274]. The higher the score, the better the UE function in reaching an object in different distances from the trunk (positive direction).
- Box & Blocks Test (BBT) is a 1-minute test for assessment of gross manual dexterity [50]. The higher the score, the better the manual dexterity (positive direction).
- Trunk Control Test (TCT) is a 100-points outcome measure for assessment of trunk control [275]. The higher the score, the better the trunk control (positive direction).
- Modified Ashworth Scale (MAS) is an ordinal scale for assessment of muscle spasticity, with a range between 0 (no spasticity) to 4 (very high spasticity) [207]. In this project, we evaluated spasticity at flexor carpi and biceps brachii muscles.

All patients underwent a neuropsychological assessment. These tests explored general cognitive abilities (Mini Mental Scale Examination, MMSE) and cognitive functions (Oxford Cognitive Scale, OCS) [254]. For the purpose of exploring the role of attentional resources on motor rehabilitation responsiveness, in the present preliminary analyses we considered only “attention” function retrieved by OCS, dichotomized as impaired and non-impaired according to cut-offs adjusted for age and scholarity.

7.4.5 Quantification of rehabilitation intervention

The therapy dose was quantified in total hours, including both CT and OT, as well as TBR. To align the total hours received during the hospitalization with the timeline of assessments (i.e., after 8 weeks), the total hours were adjusted based on the actual working days. Working days were calculated on the basis of 5 days/week excluding holidays. As the patients received therapy for 5 days out of 7, we decided to make the information more understandable and practical by transforming the total therapy dose into hours per day of activity, assuming that 8 weeks of treatment corresponded to 40 working days.

In these preliminary analyses, we extracted the following outcome from clinical records filled out by each physiotherapist:

- Tot Rehab: hours of total amount of rehabilitation received, adjusted based on the actual working days, including: CT, OT, TBR.
- Tot UL: hours of total amount of rehabilitation specific for the UL, from each modality (CT, OT, TBR).

7.4.6 Neurophysiological data: TMS protocol and outcome measures

In this project, TMS (MagPro X100. MagVenture Inc., Alpharetta, GA-US) with a figure-of-eight coil (MC-B70. MagVenture Inc., Alpharetta, GA-US) was used. In order to evaluate patients' eligibility to TMS procedures, the most updated guidelines were followed [276]. The study participants wore a tissue cap with a grid of 1 cm-spaced points drawn on it. Two self-adhesive disposable electrodes (Ag/AgCl) were placed on the extensor digitorum communis (EDC) muscle of the forearm, bilaterally, for the tendon belly montage (in addition to a ground electrode). EMG was recorded with a band pass filter of 20-2000 Hz and a sampling rate of 5000 Hz. The TMS coil was always held on the scalp by the experimenter, positioned at 45° with respect to the inter-hemispheric fissure, and with the handle pointing backward.

Firstly, the researchers identified the position on the scalp (hot-spot) that allowed for the highest and most reproducible MEPs from the contralateral EDC muscle in the M1, both in the left and right hemispheres. This was done with participants at rest and with their eyes open. Resting motor threshold (RMT) was then determined bilaterally as the stimulation intensity that elicited a MEP of at least 50 μV in half of 8-10 consecutive trials when stimulating the hot-spot. Resting state was confirmed through online visual inspection of the EMG.

Subsequently, 8-10 MEPs were recorded by stimulating the contralateral EDC motor representation at 120% of RMT, with participants at rest and with their eyes open, in each hemisphere. If RMT identification was not possible (e.g., absence of MEPs in the stimulated cortico-spinal pathway), participants were asked to increase the level of EDC muscular contraction to verify the presence or absence of MEPs, thus determining the possibility of recording successive supra-threshold MEPs. For this reason, 60 msec of pre-TMS EMG recordings were always obtained to assess muscular relaxation or refer MEPs to the pre-TMS EMG baseline activity.

The TMS measure used for these preliminary analysis was the patients classification as MEP(+) or MEP(-). Indeed, patients were classified as MEP(+) when MEPs were elicitable in at least 4 out of 8

consecutive trials, otherwise they were classified as MEP(-) (i.e. no possibility to individuate thresholds; no MEPs in less than 4 out of 8 consecutive trials).

7.4.7 Neuroimaging data: MRI protocol

Brain scanning was carried out at the IRCCS San Camillo Hospital, Venice, using a 3T Ingenia Scanner (Philips Inc., Amsterdam, Netherlands) with a 32-channel receive head coil. The neuroimaging protocol comprised both structural and functional sequences and lasted approximately 40 minutes **[Figure 27]**. MRI sequences included: A) high-resolution T1-weighted, B) Diffusion Tensor Imaging (DTI), C) Fluid Attenuated Inversion Recovery (FLAIR), D) T2 and E) Susceptibility Weighted Imaging (SWI), F) resting-state functional MRI (rs-fMRI).

Data analysis was performed using FSL (FMRIB Software Library), Statistical Parametric Mapping (SPM), Free-Surfer and other available packages and in-house developed tools.

Participants with contraindications to MRI scanning (including but not limited to a history of claustrophobia, certain metallic implants and metallic injury to the eye) were excluded from the neuroimaging protocol acquisitions and analysis. An exception are patients with available computed tomography (CT) scans, which were included for partial analysis (explained in paragraph 7.4.8).

***A) T1-weighted*:** this sequence is primarily used to study grey matter (GM) structural macroscopic tissue in both cortical and subcortical brain regions. GM changes have been widely reported in brain with stroke [277] and associated with motor recovery [278]. Brain tissues can be segmented into total GM, White Matter (WM) and cerebrospinal fluid (CSF), and cortical and subcortical regions. Brain tissues and (sub)-cortical regions were visually inspected to ensure an accurate segmentation. T1-weighted images were also used to carry out the lesion segmentation procedure (i.e. the reconstruction of individual patient's lesion following the stroke event). The identification of 3D lesion maps for all the recruited patients is a necessary step for processing and analysis of both MRI and neurophysiological data.

B) Diffusion Tensor Imaging (DTI): diffusion MRI exploits the principles of traditional MRI to measure the random motion of water molecules to infer information on WM microstructural properties and to delineate the gross axonal organisation of the brain [279]. As DTI is particularly sensitive to susceptibility-induced distortions, thus we have adopted a correction strategy based on the complementary information from pairs of diffusion images acquired with reversed phase-encoding (PE) directions to correct for distortions. Moreover, a multi-shell acquisition was specifically implemented for this project, which allowed to account for crossing fibres issues and

provided a high resolution for the intravoxel structure. These aspects are crucial when attempting to accurately reconstruct WM bundles in the presence of lesions and assess how micro-structural connectivity can be affected by stroke and modulated by rehabilitation [280]. FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps, known to be sensitive to brain lesions, can be generated [281].

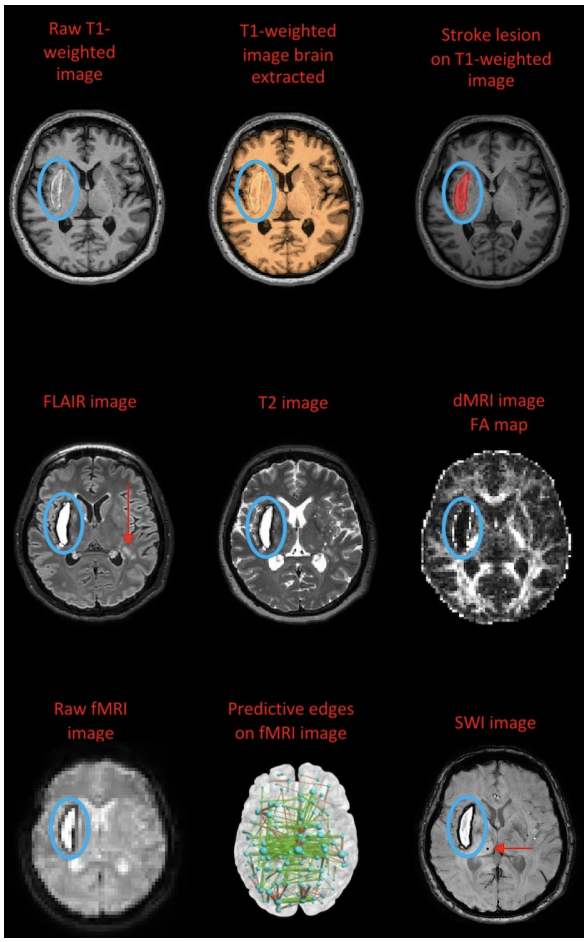
***C-D) Fluid Attenuated Inversion Recovery (FLAIR) and T2*:** both these sequences are commonly used in clinical practice to characterise stroke-induced lesions, periventricular lesions adjacent to the sulci, WM hyperintensities and WM lesions [282].

E) Susceptibility Weighted Imaging (SWI): these are particularly sensitive to compounds which distort the local magnetic field and as such they are useful in detecting blood products, iron and calcium, which are a common result of brain insults, such as stroke [283].

F) Resting state functional MRI (rs-fMRI): rs-fMRI is used to investigate resting state networks (RSNs), which encompass brain regions with a common time-course of spontaneous fluctuations and reflecting properties of functional brain organisation [284]. All study-participants were instructed to lie in dimmed light with their eyes open, blink normally, but not to fall asleep. In order to reduce images artefacts, the same correction method described for the DTI data will also be applied to rs-fMRI images.

SWI and rs-fMRI data were not used for these interim analyses [81].

Figure 27. MRI sequences for the imaging protocols



Images reported here on axial view include: raw T1-weighted image, T1-weighted image brain extracted, stroke lesion identified on T1-weighted image, FLAIR image, T2 image, fractional anisotropy (FA) map derived from diffusion MRI (dMRI) image, raw resting fMRI image, predictive functional connections from multivariate resting fMRI-behaviour mapping (adapted from Calesella et al., 2021[285]), susceptibility weighted image (SWI) in a representative participant. Red arrows on FLAIR and SWI image indicate the presence of deep white matter lesions and a black hole respectively. In all images the lesion area has been circled in blue.

7.4.8 Neuroimaging data: MRI analysis

For neuroimaging analysis, among patients with valid MRI acquisition, were included images with 1) distinguishable lesion in FLAIR sequence and 2) unilateral hemispheric lesion, while were excluded images with 1) bilateral lesion.

Specifically, for these preliminary analyses, we used only data from T1-weighted and DTI images. In case some enrolled patients did not have any available MRI sequences, we employed data from CT scans to carry out the tract disconnection analysis.

***Lesion segmentation on T1-weighted images and CT scans**:* The anatomical scans were acquired using a 3D T1-weighted (T1w) Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence

with the following parameters: Repetition Time (TR) = 6800 ms; Echo Time (TE) = 3 ms; flip angle = 8°; field of view (FOV) = 240mm x 240mm x 181mm; voxel size = 1mm isotropic; acquisition time of 3 minutes and 14 seconds.

Automated brain lesions segmentation was obtained using the Lesion Identification with Neighbourhood Data Analysis (LINDA) software [286]. The resulting lesion mask (in native MRI space) was visually inspected and manually corrected with ITK-SNAP software by two independent researchers (SS and DD) [287]. Finally, to allow direct comparisons across patients, the lesion was normalized into a standard template in MNI152 space using the pipeline of the Brain Connectivity and Behaviour toolkit (BCBtoolkit) software [288]. For CT scans the lesion segmentation was manually performed and double checked (SS and DD) and then normalized into MNI152 space using Matlab by means of the RegLSM software. In particular for these interim analyses, after normalization the disconnection maps could be estimated by means of BCBToolkit software. For instance, each MNI-registered lesion segmentation map was used as a seed to track probable passing tracks using 176 healthy controls from the Human Connectome project diffusion-weighted dataset. For the estimated tracks, information showed the probability of disconnection (above 50% is a convention threshold for disconnection) and the proportion of disconnection of each tract.

DTI pre-processing*:* The DTI scans had the following parameters: TR = 3700 ms; TE = 104 ms; voxel size = 2 mm isotropic; FOV =156 mm × 224 mm x 224mm; acquisition time of 7 minutes and 18 seconds for the AP (anterior-posterior) image and 45 seconds for the PA (posterior-anterior) image. 8, 32 and 64 diffusion gradient directions for the three b-values (300, 1000, 2000) + 12 B0s volumes, were acquired for the AP image. For the PA image 10 B0s volumes were acquired. 1 B0 DTI image with opposite phase-encoding direction [AP and PA] were fed into Topup http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP [Andersson et al., 2003] in order to estimate DTI EPI distortions. Data was corrected for eddy currents, head motion and had outlier-slices (individual slices in the 4D data) corrected, using the Eddy tool http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/EDDY [Andersson and Sotiropoulos, 2015, Andersson and Sotiropoulos, 2016]. FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps were generated using DTIFit, part of FMRIB's Diffusion Toolbox, that fits a diffusion tensor model at each voxel [289]. The FA output images were used as input for TBSS, a voxel-wise approach for analysis of FA data [290]. All subjects' FA data were aligned into a common space using FMRIB's Non-linear Image Registration Tool (FNIRT). The mean FA image was generated and thinned to create a mean FA skeleton, which represents the centres

of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton. A region of interest (ROI) approach was used to extract FA values.

As region of interest (ROI) we selected the Posterior Limb of the Internal Capsule (PLIC), which is part of the internal capsule and therefore CST. This ROI was chosen since it specifically carries fibres that transmit sensory and motor information between the cerebral cortex, the thalamus, and the brain stem to the muscles for voluntary movement. Moreover, it controls fine movement of UL and hand and has been widely studied as a predictor of UL motor recovery, as already fully depicted in the introduction of this chapter and in Ch. 1 and Ch. 3 of the present PhD thesis [28,85,121,122].

7.4.9 MRI outcome measures

From the derived data presented in the previous paragraph (7.4.7, 7.4.8), the following outcome measures were analysed:

- Fractional Anisotropy (FA): it is a measure extracted by DTI images to characterize the directionality of water diffusion within the white matter of the brain. Its values range between 0 (reduced anisotropy) and 1 (high anisotropy), with lower values suggesting reduction or integrity of the WM.
- Fractional Anisotropy Asymmetry Index (FAAI): it is a metric used to quantify and compare the difference in FA between left and right hemispheres. Values may range between -1 and + 1 where positive values indicate lateralization towards the unaffected side, while FAAI = 0 suggest symmetric FA between the hemispheres. Its value for prognosis has been already investigated in previous studies[78,122]. The formula of FAAI was:

$$\text{PLIC FAAI} = (FA_{\text{unaffected}} - FA_{\text{affected}}) / (FA_{\text{unaffected}} + FA_{\text{affected}}).$$

- CST disconnection proportion: it is a measure that expresses the percentage of lesioned voxels out of the total voxels in the CST, extracted by the BCBtoolkit (i.e. from structural images, T1w and Computed Tomography, CT, the latter used in case of unavailable T1w structural images of the enrolled patients).

More protocol details are reported in the respective published paper [81].

7.4.10 Sample size

The sample size was calculated with regards to the primary motor outcome assessing UL function (FMA-UE). From published data on the same cohort study design of stroke survivors admitted at the IRCCS San Camillo Hospital [291], and undergoing the same rehabilitative treatments described in this

protocol, is expected that UL function improves with moderate standardised effect (Cohen's d = 0.45), according to FMA-UE. Assuming an equivalent effect size f = 0.225, for repeated measures, within factors multivariable analysis of variance (MANOVA) design [292], in one group with two measurements correlating 0.5, given ⍺ = 0.05 and 1-β = 0.90, a total recruitment of 54 consecutive subjects would be needed. Considering a drop-out rate of 40%, a final number of 75 patients will be considered sufficient to conclude the study.

7.4.11 Statistical analysis and predictors

Statistical analyses were conducted on dataset frozen on March 31st, 2023. Statistical methods were based on the intention-to-treat principle [293].

Data are summarized as mean and standard deviation (SD) or median and interquartile range (IQR) values as appropriate. Metrics of interest are reported as mean difference between follow-up (T1) and admission (T0) measures, with 95% confidence intervals. Standardized difference was also reported as Cohen's d. Wilcoxon signed-rank test or Student t-test, according to normal distribution assessed with Shapiro-Wilk test, were used to test if paired means were statistically different. Further comparisons were explored within and between groups, by the means of scatter plots or other graphical presentations. Patients' motor improvement was explored stratifying baseline values of FMA-UE as <17 points (severe impaired patients) and ≥17 points (mild-to-moderate impaired patients) [294].

The inspection of motor rehabilitation responsiveness was run on the FMA-UE. In order to detect motor changes weighted by the baseline residual performance, we computed the "FMA-UE recovery index", defined as "[(FMA-UE T1 – FMA-UE T0)/FMA-UE T0]*100", as already proposed in a previous study [242]. Changes of this index were investigated according to different baseline levels of FE and SAFE, because of their importance as clinical predictor signs, using Kruskal-Wallis test.

To study the association between baseline features and predicted outcome, multivariable linear models were performed. The dependent variable was defined as the UL motor improvement (i.e. Δ FMA-UE = FMA-UE T1 – FMA-UE T0) and adjusted for FMA-UE T0. The independent variables were chosen among those collected at T0 and according to literature recommendations, such as residual motor function (e.g. strength in SAFE, ARAT), CST structural and functional integrity (e.g. lesion load, presence of MEPs) and demographic features (e.g. age, time from lesion, type of stroke).

In order to obtain an unbiased estimate of the association of total rehabilitation with the final outcome (i.e. FMA-UE) and all the other outcome measures, we used a Directed Acyclic Graph (DAG)

to identify the sets of variables necessary to adjust for [295]. A DAG is a visual representation of a directed acyclic graph, which consists of nodes connected by directed edges and does not contain any directed cycles. Nodes represent variables or events, and directed edges indicate causal relationships or dependences between them. DAG identifies confounding and modifiers variables that require conditioning when estimating causal effects. Assumed relationships between the variables of this working set is summarized in **[Figure 28]**. Considering an event-per-variable < 10, no further variable selection was performed and estimates were reported also applying a shrinkage factor, as recommended [296].

Using ordinary least squares (OLS) regression as primary analysis, we investigated the association between total rehabilitation and the score variation of Δ FMA-UE used as dependent continuous variable. Models where then adjusted for confounding covariates.

Under the assumption of missingness at random, 10 to 40 multiple imputations using a non-parametric approach in conjunction with bootstrap to incorporate all uncertainties was used to reduce bias in regression estimates and substantial loss in sample size, due to the extent of missing data in the selected covariates (attention 5%, TMS 27% and MRI 35%).

Inference on considered parameters was obtained by combining estimates over imputed data sets using Rubin's rules. Plausibility of the estimates over complete case analysis was then assessed.

As sensitivity analyses, patients were divided in two categories (i.e. *Responders*, *Non-Responders*) according to responsiveness to therapy, defined as an improvement of 5 points relative to the minimally clinically important difference (MCID) of the primary outcome measure (i.e FMA-UE) [212]. We used MCID $\geq$ 5 as dichotomous dependent variable for the logistic regression model, in order to interpret the association of selected covariates with the outcome as a likelihood of being a responder, using the same set of adjusting covariates. Two OLS regression were also fitted using CST and MEP as further adjusting covariates.

All models were validated and calibrated using 500 bootstraps; overall performance and predictive ability were reported as c or Dxy indices, maximum absolute error or square error, and as van Houwelingen-Le Cessie heuristic shrinkage estimate. Model estimates are accompanied with 95% confidence interval (CI).

The statistical significance level was set at $p < 0.05$, and all analyses were performed using R Core Team [R Core Team (2023) version 4.3.0., with rms and Hmisc packages added [297].

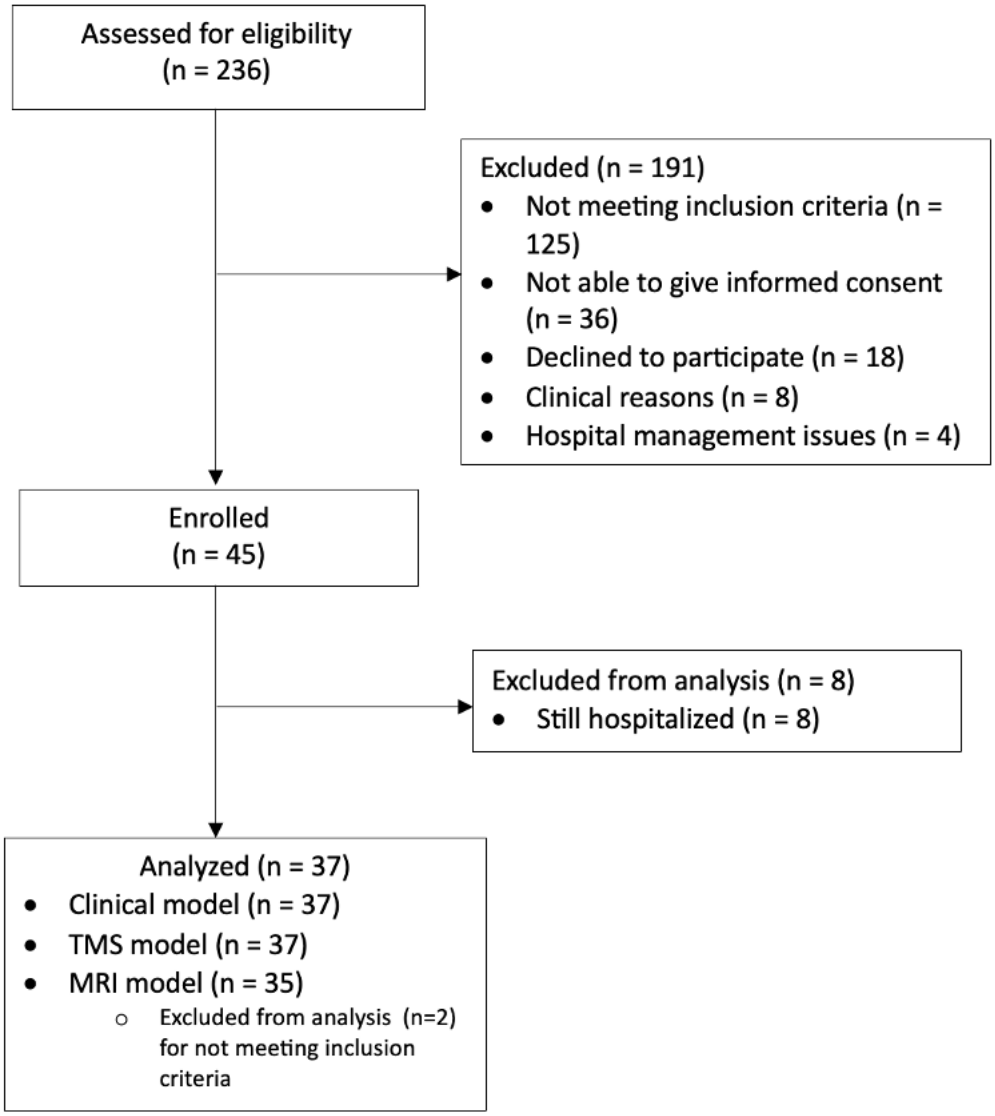
7.4.12 Funding, ethics and data access

The current research project NeuroPro receives partial funding from the Italian Ministry of Health through grants RF-2018-12366899 and GR-2018-12366092. The study obtained ethical approval from the "Comitato etico per la Sperimentazione Clinica (CESC) della Provincia di Venezia e IRCSS San Camillo" (Prot. 1375/IRCCS San Camillo). The protocol has been registered on ClinicalTrials.gov (NCT05423119). Data collection began in August 2021 and is scheduled to conclude by February 2024. The study adheres to the principles outlined in the Declaration of Helsinki. All patients provide written informed consent, and their data is anonymised, securely stored, and processed within the infrastructure of the IRCCS San Camillo Hospital. Personal information such as names and addresses is stored separately in locked filing cabinets. Access to patients' data is restricted to authorized personnel. Requests for data access can be made to the IRCCS San Camillo Hospital in accordance with GDPR and Italian regulations governing the privacy of biomedical data. Local ethical committee submission and participant consent may be necessary.

7.5 Results

In these preliminary analyses, 37 patients were included in clinical and neurophysiological analysis and 35 for analysis with neuroimaging data. Comprehensive flow-chart of the study is presented in **[Figure 29]**.

Figure 29. Flow-chart of the study population



MRI: Magnetic Resonance Imaging; TMS: Transcranial Magnetic Stimulation.

7.5.1 Clinical variables

The sample of this interim analysis is of 37 chronic stroke survivors, aged 65.18 (11.87) years old, in the chronic phase after stroke, on average. In more than half of the patient, attention function is impaired **[Table 18]**.

Table 18. Overview of the sample characteristics

Variable (N = 37)	Parameters
Sex, male/female	23 (62%) / 14 (38%)
Age, years	65.18 (11.87) / 65.36 [20.12]
Type of stroke, Ischemic/Haemorrhagic	21 (57%) / 16 (43%)
Hemisphere affected, Right/ Left	21 (57%) / 16 (43%)
Dominant side affected, yes/no/missing	11 (30%) / 25 (68%) /1 (2%)
Months from injury	16.01 (24.24) / 3.45 [16.61]
Attention, impaired/normal/missing	22 (60%) /13 (35%) /2 (5%)

Values are reported as number and percentages, Mean (± 1 standard deviation, sd), Median and interquartile range [IQR].

With regards to the rehabilitation dose, hours and minutes of each modality are presented in **[Table 19]**. Patients underwent an average of 48.84 days of rehabilitation, with 87.49 minutes of total activity per day, almost half of the time with UL specific activities. Sixteen of them (43%) also used some UL technological devices.

Table 19. Rehabilitation Dose

Variable (N = 37 patients)	Parameters
Days of work, mean (sd)	48.84 (24.56) / 42 [13]
Techno-UL used, yes/no	16 (43%) / 21(57)
Tot-UL (hours)	28.49 (21.16) / 21.33 [12.73]
Tot-Rehab (hours)	58.29 (23.21) / 53.64 [25.18]
Tot-Rehab/day (minutes)	87.49 (34.82) / 80.45 [37.77]

Values are reported as Mean (± 1 standard deviation, sd), Median and interquartile range [IQR]. UL: Upper Limb.

FMA-UE, ARAT, SAFE, BBT, RPS, TCT and FIM showed a significant improvement after treatment. Overall, FMA-UE, BBT and TCT identified a moderate effect, while it was high only for FIM and low for all the others outcome measures **[Table 20]**.

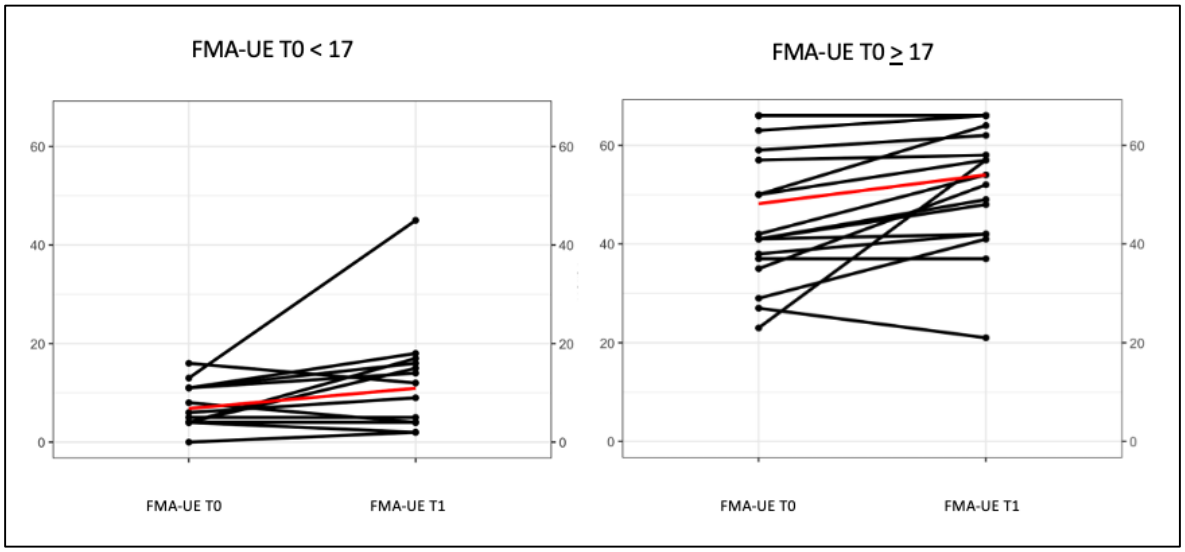
Table 20. Behavioural outcome measures modifications following rehabilitation

Variable	T0		T1		MD ($CI_{95\%}$)	P	Cohen's *d*
FMA-UE	29.78 (23.29)	29 [44]	34.86 (24.6)	46.5 [46]	5.1 (2.1; 8.0)	**0.001***	0.58
FMA-sens	17.74 (6.92)	20 [9]	17.69 (7.21)	20 [11]	0.2 (-1.5; 1.9)	0.69	0.05
FMA-pain/rom	40.47 (6.64)	40 [10.25]	41.97 (5.67)	43.5 [8.75]	1.4 (-0.3; 3.1)	0.09	0.28
ARAT	23.73 (24.07)	17 [50]	23.59 (25.02)	34.5 [57]	4.2 (0.6; 7.8)	**0.009***	0.4
SAFE	4.92 (3.4)	4 [6]	5.61 (3.38)	6.5 [7]	0.6 (0.2; 0.9)	**0.013***	0.48
NIHSS	7 (4.41)	6 [6]	6.19 (3.4)	6.5 [6]	-0.6 (-1.4; 0.3)	0.22	-0.23
BBT	11.14 (17.12)	0.5 [12.25]	17.63 (21.51)	4 [30]	5.5 (2.1; 9.0)	**0.001***	0.6
RPS	15.41 (15.17)	12 [34]	17.92 (17.74)	20 [36]	2.4 (0.4; 4.3)	**0.009***	0.41
TCT	72.19 (26.93)	75 [51]	84.26 (22.01)	100 [27]	11.5 (4.4; 18.5)	**0.006***	0.53
FIM	87 (22.76)	87 [32]	98.55 (19.84)	97 [32]	10.7 (6.4; 15.0)	**0.001***	0.88
MAS							
biceps brachii	0.86 (0.79)	1 [1]	0.83 (0.76)	1 [1]	0.0 (-0.2; 0.2)	0.83	-0.04
flexor carpi	0.86 (0.95)	1 [1]	0.89 (1.09)	1 [1]	0.0 (-0.2; 0.2)	0.83	0.04

*Values are reported as number and percentages, Mean (± 1 standard deviation, sd), Median [IQR]. MD: Mean Difference. FMA-UE: Fugl-Meyer Assessment Upper Extremity; FMA-sens: Fugl-Meyer Assessment sensation; FMA-pain/rom: Fugl-Meyer Assessment pain/rom; ARAT: Action Research Arm Test; SAFE: Shoulder Abduction Finger Extension measured by MRC: Medical Research Council; NIHSS: National Institute of Health Stroke Scale; BBT: Box & Blocks Test; RPS: Reaching Performance Scale; TCT: Trunk Control Test; FIM: Functional Independence Measure; MAS: Modified Ashworth Scale. *Statistical significance: $p < 0.05$.*

For patients (N = 16) with severe impairment at baseline (T0), we found that they generally remained in a severe condition and showed an average improvement of 4.13 points on the FMA-UE scale, except for one patient changing from 11 to 45 points, at 2 weeks post-stroke. On the other hand, patients (N = 21) with mild-to-moderate impairment improved by an average of 5.85 points. The difference between them was not statistically significant (p = 0.44) **[Figure 30]**.

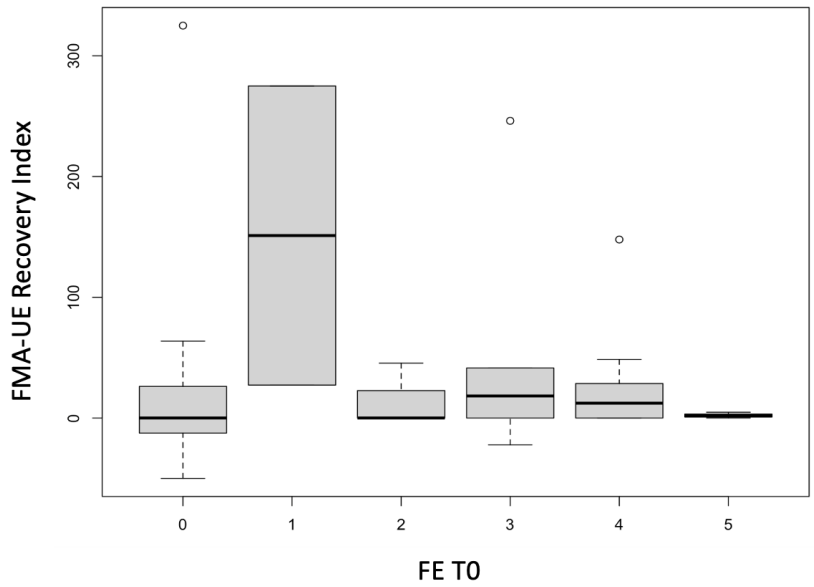
Figure 30. Change from baseline (T0) to follow-up (T1) of UL motor function



Patients are grouped according to severe (FMA-UE < 17, N = 16) and mild-to-moderate (FMA-UE ≥ 17, N = 21) level of impairment at baseline (T0). Black lines are individual trajectory, red line represents mean change. FMA-UE: Fugl-Meyer Assessment Upper Extremity.

Taking into consideration FE as a surrogate marker for integrity of the CST, we observed that different level of strength and voluntary fingers movement did not lead to different amount of improvement **[Figure 31]**. Indeed, for different baseline level of FE, patients had different level of FMA-UE Recovery Index, especially for FE = 1 which showed high dispersion.

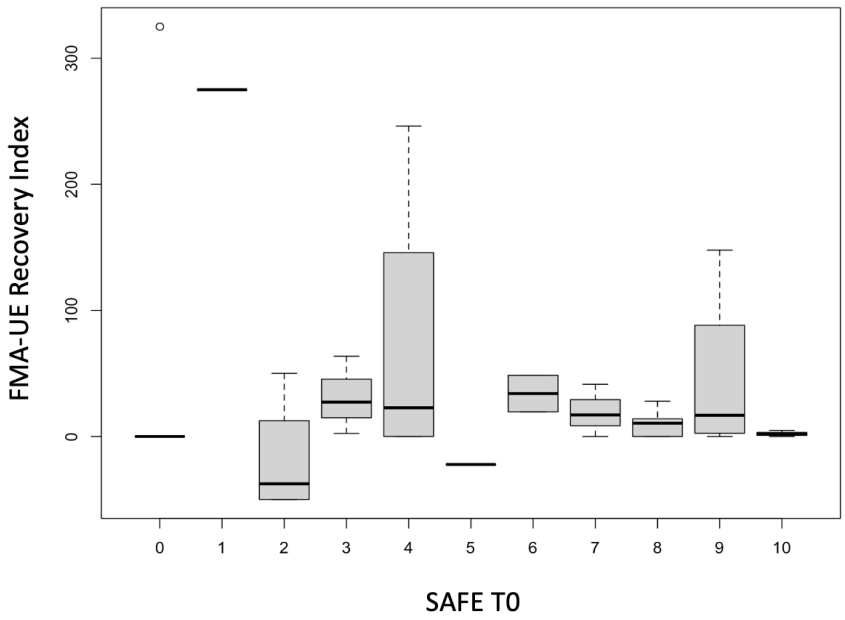
Figure 31. Box and whiskers plot of FMA-UE Recovery Index according to baseline levels of FE



Horizontal bars represent median. FE: Finger Extension strength measured by Medical Research Council (MRC). FE values range from 0 to 5. FMA-UE: Fugl-Meyer Assessment Upper Extremity.

Considering number of patients for each level of strength at SAFE **[Figure 32]** it is possible to observe that patients had different level of FMA-UE Recovery Index, especially for SAFE = 2-4, which showed high dispersion.

Figure 32. Box and whiskers plot of FMA-UE Recovery Index according to baseline levels of SAFE



Horizontal bars represent median. SAFE: Shoulder Abduction Finger Extension strength measured by Medical Research Council (MRC). SAFE values range from 0 to 10. FMA-UE: Fugl-Meyer Assessment Upper Extremity.

Considering Responders and Non-Responders to treatment, both of them had mild-to-moderate impairment at baseline, on average, but Responders improved significantly more than Non-Responders **[Table 21]**.

Overall, dose of rehabilitation was similar between the two groups, with an average of 96 minutes/day and 83 minutes/day for Responders and Non-Responders, respectively **[Table 22]**.

Table 21. Clinical variables of Responders and Non-Responders

	Responders (N = 13)							Non-Responders (N = 23)								
	T0		T1		MD ($CI_{95\%}$)	p	*d*	T0		T1		MD ($CI_{95\%}$)	p	*d*	MD ($CI_{95\%}$)	p
FMA-UE	27.2 (17.1)	29 [30]	41 (17.9)	48 [36]	13.8 (8.2; 19.3)	**0.002***	1.5	31.22 (27)	27 [56.5]	31.39 (27.43)	21 [60]	0.2 (-0.9; 1.2)	1	0.07	13.6 (8.0; 19.2)	**0.001***

*Values are reported as number and percentages, Mean (± 1 standard deviation, sd), Median [IQR]. MD: Mean Difference. d: Cohen's d (effect size). FMA-UE: Fugl-Meyer Assessment Upper Extremity. *Statistical significance set at p < 0.05.*

Table 22. Dose of treatment in hours

Outcome measure	Responders (N = 13)		Non-Responders (N = 23)		*p*-Value
Days of work	54.69 (21.82)	44 [20]	45.87 (21.82)	41 [5.5]	p = 0.181
Techno-UL used, yes/no	8 (62 %)/ 5 (38 %)	/	8 (35%) /15 (65%)	/	p = 0.229
Tot-UL	35.41 (25.94)	23.24 [21.94]	24.81 (17.91)	20.93 [13.83]	p = 0.93
Tot-Rehab	64.44 (29.92)	56.87 [21.73]	55.54 (18.8)	50.59 [28.84]	p = 0.392
Tot-Rehab/day (minutes)	96.49 (44.88)	85.3 [32.59]	83.31 (28.2)	75.88 [43.26]	p = 0.392

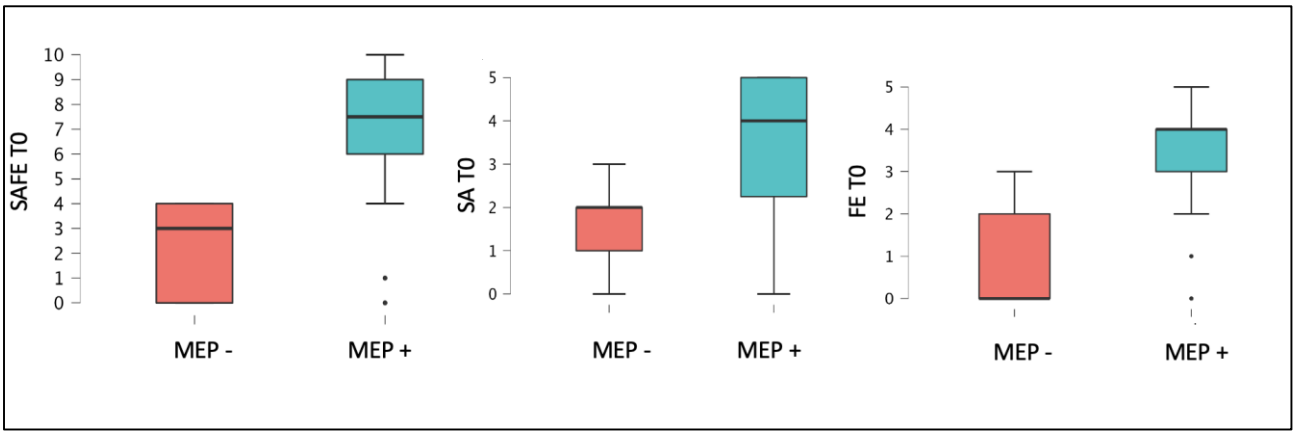
Values are reported as Mean (± 1 standard deviation, sd), Median and interquartile range (IQR). UL: Upper Limb.

7.5.2 Neurophysiological variables

Among the overall sample of 37 subjects, 27 (73%) of them performed the TMS. In particular, 18 patients (66.6%) had MEP (+) and 9 (33.3%) had MEP (-) at baseline evaluation.

We observed that patients with MEP (-) had lower values of SAFE ($p < 0.001$), SA ($p = 0.004$) and FE ($p < 0.001$) at baseline compared to patients with MEP (+) **[Figure 33]**.

Figure 33. Box and whiskers plot of UL Strength levels according to presence or absence of MEPs, at baseline (T0). Horizontal bars denote median



MEP: Motor Evoked Potentials; SA: Shoulder Abduction; FE: Finger Extension.

Relating to severe (FMA-UE T0 < 17) and mild-moderate (FMA-UE T0 ≥ 17) impaired patients, 82% of severe patients were MEP(-) and 18% were MEP(+) at baseline, while 100% of mild-moderate patients were MEP(+).

7.5.3 Neuroimaging variables

In the analyses of MRI data, 2 patients were excluded in accordance with inclusion criteria, therefore 35 included. Among them, 13 had DTI data and from 24 of them it was possible to extract features from BCBToolKit (using 17 MRI-T1w and 7 CT). According to our hypothesis, we extracted data only on PLIC and CST disconnection **[Table 23]**.

Table 23. MRI data baseline (T0)

Variable (T0)	Parameters
FA PLIC	0.6 (0.06) / 0.61 [0.06], 22 missing
FAAI PLIC	0.07 (0.06) / 0.06 [0.05], 22 missing
CST disconnection proportion	0.14 (0.15) / 0.08 [0.2], 11 missing

FA: Fractional Anisotropy; FAAI: Fractional Anisotropy Asymmetry Index; PLIC: Posterior Limb internal Capsule; CST: Cortico-Spinal Tract. Values are reported as Mean (± standard deviation, sd), Median and interquartile range [IQR].

Patients with severe (N = 16) impairment at baseline showed statistically significant higher lesion load on CST disconnection than patients with mild-to-moderate (N = 21) impairment **[Table 24]**.

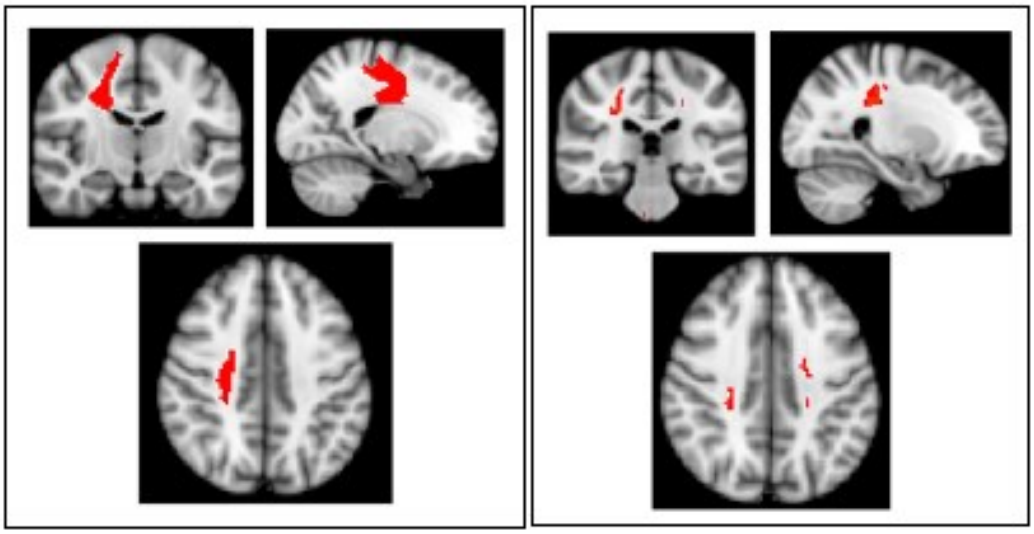
Table 24. Proportion of CST disconnection

	FMA-UE T0 < 17	FMA-UE T0 ≥ 17	MD ($CI_{95\%}$)	*p*
CST disconnection proportion	0.21 (0.14) / 0.25 [0.21]	0.07 (9.07) / 0.05 [0.09]	0.214 [0; 0.3]	0.015*

*Values are reported as Mean (± 1 standard deviation, sd), Median and interquartile range [IQR]. FMA-UE: Fugl-Meyer Assessment Upper Extremity. *Statistical significance p = 0.05*

Moreover, lesion disconnection overlay was shared from 7 out of 8 (i.e., 87.5%) of severe patients, and from 10 out of 16 (i.e., 62.5%) of mild-moderate patients, as represented in **[Figure 34]**.

Figure 34. Overlap of tracts disconnection across severe (left) and mild-moderate (right) patients



7.5.4 Multivariable models for investigating known factors associated with motor recovery

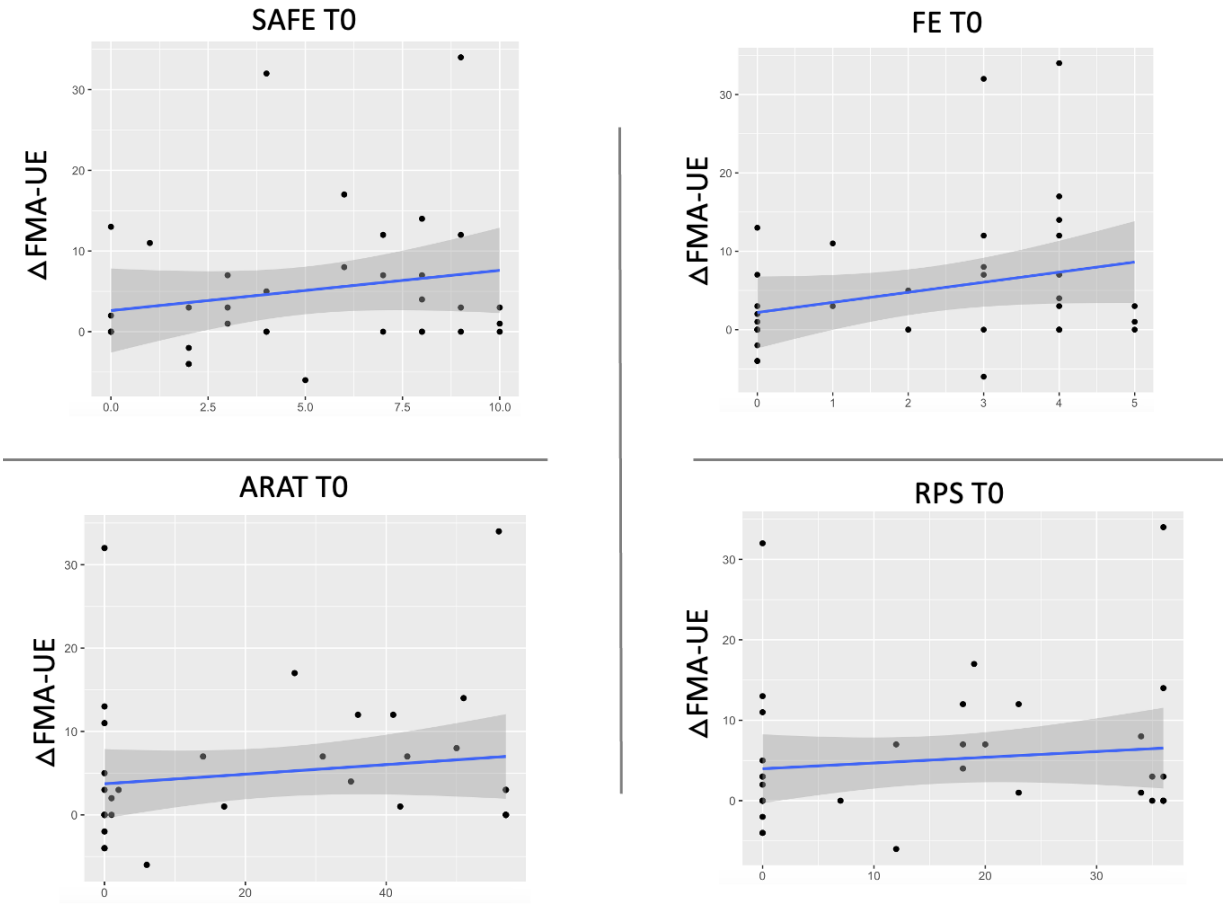
The following variables did not show statistically significant associations with improvement at UL motor function: time from lesion ($CI_{95\%}$: -2.22; 0.03), MAS at biceps brachii ($CI_{95\%}$: -5.91; 2.83), MAS at flexor carpi ($CI_{95\%}$: -9.66; -2.93), BBT ($CI_{95\%}$: -0.37; 0.29), NIHSS ($CI_{95\%}$: -1.22; 0.56), MEP(+) ($CI_{95\%}$: -1.86; 13.89), age ($CI_{95\%}$: -0.2; 0.35), sex ($CI_{95\%}$: -1.74; 11.13), lesioned hemisphere ($CI_{95\%}$: -4.81; 7.42), type of stroke ($CI_{95\%}$: -5.22; 22.97).

Conversely, SAFE, RPS, FE and ARAT scores and CST disconnection proportion at baseline showed statistically significant association with UL motor improvement. In particular, for each point increase of SAFE, patients can improve of 2.83 ($CI_{95\%}$: 1.25; 4.39) points at FMA-UE, whereas for each point

of RPS patients can improve of 0.68 ($CI_{95\%}$: 0.24; 1.26) points at FMA-UE. With regards to FE, expected unit-increase is 4.9 ($CI_{95\%}$: 2.5; 7.3), whereas for ARAT, FMA-UE increases by 0.42 ($CI_{95\%}$: 0.17; 0.67) points for one point increase of ARAT **[Figure 35]**.

The more the CST is disconnected, the lower the improvement at FMA-UE could be, but no statistical evidence is provided by the results ($CI_{95\%}$: -4.66; 17.77). Even when adjusting for time for lesion the results did not change. ($CI_{95\%}$: -3.19; 17.77).

Figure 35. Multivariable linear models between baseline (T0) clinical features and FMA-UE



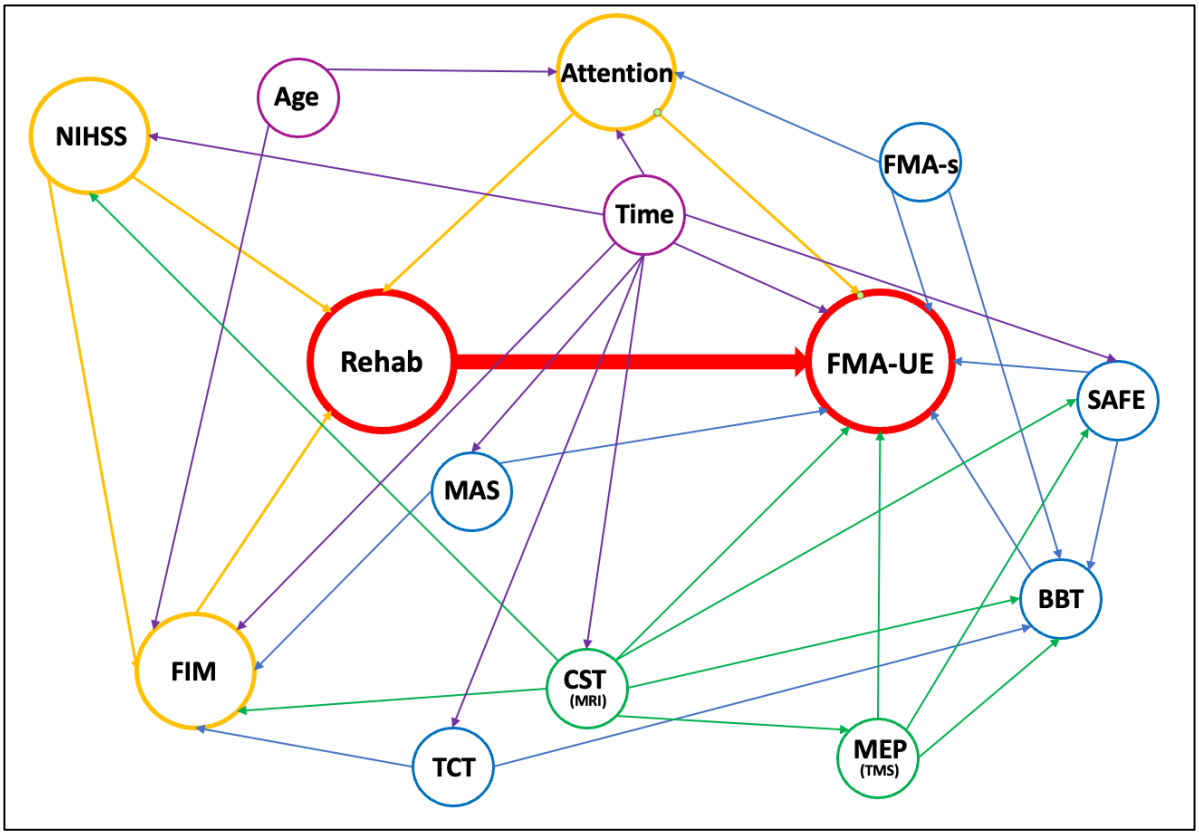
ARAT: Action Research Arm Test; FE: Finger Extension; RPS: Reaching Performance Scale; Fugl-Meyer Assessment Upper Extremity; SAFE: Shoulder Abduction Finger Extension.

7.5.5 Multivariable models for investigating association between rehabilitation and UL motor recovery.

We developed a DAG where, according to our hypothesis, rehabilitation (Tot Rehab) influences motor improvement (FMA-UE).

Assumed relationships between the variables of this working set is summarized in **[Figure 28]**.

Figure 28. DAG representing variables and their relationships



BBT: Box & Blocks Test; FIM: Functional Independence Measure; Fugl-Meyer Assessment Upper Extremity; MAS: Modified Ashworth Scale; MEP: Motor Evoked Potentials; NIHSS: National Institute of Health Stroke Scale; SAFE: Shoulder Abduction Finger Extension; TCT: Trunk Control Test; CST: Cortico-Spinal Tract. Arrows denote the direction of assumed relationship among selected variables. Colours denote type of variables (red: starting hypothesis; yellow: confounding factors; blue: motor; green: neurophysiology/neuroimaging; purple: demographics).

First of all, we assumed that the effects of rehabilitation (the exposure) could be reliably captured by FMA-UE (the outcome). Then we hypothesised that dose of rehabilitation is influenced by the level of stroke severity (NIHSS), attention (OCS) and independence (FIM). Moreover, we hypothesised that motor recovery (FMA-UE) could be influenced by the time from lesion, CST integrity, motor function at baseline (SAFE, BBT, MAS), sensation function (FMA-sens) and level of attention. Time from lesion could influence also level of stroke severity (NIHSS), motor function (SAFE, FIM, FMA-UE, MAS, TCT), neural features (CST-MTI) and attention, as well as age could influence the level of attention and independence. Besides, the integrity of the CST (assessed by TMS and MRI) could influence motor function (SAFE, BBT, FMA-UE). Provided all these relationships, FIM, NIHSS and attention (OCS) at baseline were therefore considered the minimum adjusting covariates for our analyses.

Clinical model

From the main model, we observed that total rehabilitation, impaired attention, FIM and NIHSS did not influence significantly motor improvement in FMA-UE (P=0.153) **[Table 25]**. However, it resulted that in people with normal attention, the FMA-UE variation is 6.1 ($CI_{95\%}$: -0.1 to 12.3) points greater compared to people with impaired attention (P=0.054), becoming 4.45 after shrinkage [**Figure 36**]. Attention itself explained the 63.5% of the variance whereas rehabilitation 28.5%. This model will validate on new data about 59.7% worse than on this dataset.

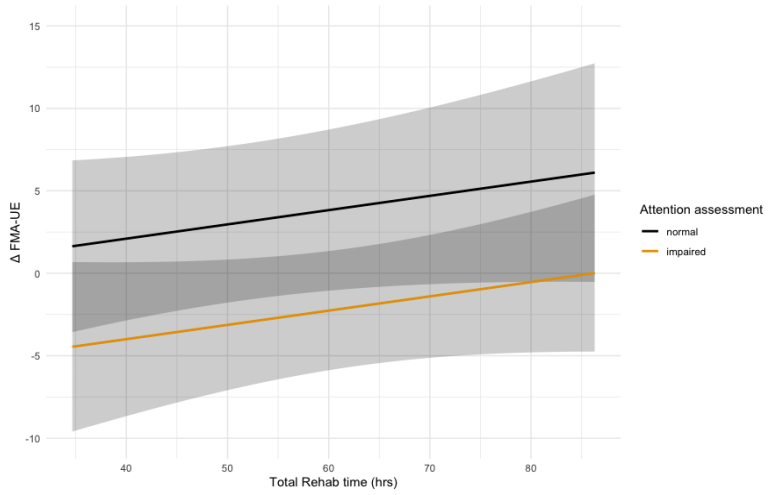
Table 25. Model estimates

	Coefficients	Shrunken Coefficients	Standard Error	P-value
Intercept	12.26	8.96	9.71	0.216
Rehabilitation	0.09	0.06	0.06	0.189
FIM	-0.13	-0.09	0.08	0.110
NIHSS	-0.36	-0.27	0.40	0.365
Attention (impaired vs normal)	-6.10	-4.45	3.04	0.054

Model significance is P=0.153. R^2=-0.070; Mean Squared Error (MSE)=82.9.

With regard to dose of rehabilitation, the effect of increasing tot rehab hours result in an estimated improvement at the FMA-UE of 1.7 ($CI_{95\%}$: -0.9 to 4.4, p = 0.189) points passing from 40 to 60 hours, 3.5 ($CI_{95\%}$: -1.8 to 8.7, p = 0.189) points passing from 40 to 80 hours and 6.9 ($CI_{95\%}$: -3.6 to 17.4, p = 0.189) points passing from 40 to 120 hours. Effect estimates correspond to 1.5, 2 and 3 hrs/day of rehabilitation, respectively.

Figure 36. UL motor improvement based on attention, with FIM set at 87 and NIHSS 7



FMA-UE: Fugl-Meyer Assessment Upper Extremity

7.5.6 Sensitivity analyses

Neurophysiological model

Once adjusting for the presence or absence of MEPs, the effect of increasing rehabilitation from 40 to 60 hours is to improve the FMA-UE of 1.7 ($CI_{95\%}$: -1 to 4.4, p = 0.217) points. Likewise, increasing rehabilitation from 40 to 80 hours and from 40 to 120 hours improve FMA-UE of 3.3 ($CI_{95\%}$: -2.1 to 8.7, p = 0.217) points and of 6.7 ($CI_{95\%}$: -4.1 to 17.5, p = 0.217) points, respectively. Model variance was mainly explained by attention (63.6%) and rehabilitation (27.1%). Accounting for MEP did not increase overall model validity, which is 75.3% worse than on this dataset.

Neuroimaging model

Once adjusting for CST disconnection, the effect of increasing rehabilitation from 40 to 60 hours is to increase the FMA-UE variation of 1.7 ($CI_{95\%}$: -1.0 to 4.4, p = 0.217) points. Likewise, in patients with normal attention, the FMA-UE variation is 6.2 ($CI_{95\%}$: -0.4 to 12.7, p = 0.063) points greater than people with impaired attention, and 3.7 after shrinkage. Moreover, improving from 40 to 80 hours and from 40 to 120 hours the improvement in FMA-UE is of 3.4 ($CI_{95\%}$: -2.1 to 8.8, p = 0.217) points and 6.7 ($CI_{95\%}$: -4.2 to 17.6, p = 0.217) points, respectively. Model variance was mainly explained by attention (65.2%) and rehabilitation (27.7%). This model will validate on new data about 70.5% worse than on this dataset.

Responders versus Non-Responders

One patient did not have the final score at FMA-UE (T1) and therefore overall sample was made by 13 (36%) Responders and 23 (64%) Non-Responders.

The logistic model was not statistically significant (P=0.426) and will validate on new data about 103.1% worse than on this dataset. Particularly, the fitted model showed that an increase of 80 hours (i.e., from 40 to 120) increase the odds by a factor of 6.6 ($CI_{95\%}$: 0.5 – 95), that is that the odds of MCID $\geq$ 5 increases by 560%, which corresponds to 86.8% probability of being a responder.

7.5.7 Summary of dose-response effect

Despite the absence of evidence of any association between FMA-UE and selected adjusting covariates, the overall clinical effect of providing 60, 80 or 120 hours of neuromotor rehabilitation yields an improvement at FMA-UE ranging from 1.7 to 6.9 points, as predicted by the fitted models **[Table 26]**, not considering shrunk estimates.

Table 26. Estimation of Dose-response effect on the FMA-UE

Model	Dose	Hours/day	Estimate ($CI_{95\%}$))
Clinical			1.7 (-0.9; 4.4)
MEP	40 – 60	1.5	1.7 (-1; 4.4)
CST			1.7 (-1;4.4)
Clinical			3.5 (-1.8;8.7)
MEP	40 - 80	2	3.3 (-2.1;8.7)
CST			3.4 (-2.1;8.8)
Clinical			6.9 (-3.6;17.4)
MEP	40 - 120	3	6.7 (-4.1; 17.5)
CST			6.7 (-4.2; 17.6)

CST: Cortico-Spinal Tract; MEP: Motor Evoked Potentials.

Similarly, the overall clinical effect of providing 60, 80 or 120 hours of neuromotor rehabilitation as predicted by the logistic model leads to a probability to become a responder of 61.5%, 72.2% or 86.8 %, respectively **[Table 27]**.

Table 27. Estimation of dose-response effect on Responders / Non-Responders

Model	Dose	Hours/day	Estimate ($CI_{95\%}$)
Responder (odds ratio)	40-60	1.5	1.6 (0.8; 3.1)
	40-80	2	2.6 (0.7; 9.7)
	40-120	3	6.6 (0.5; 95)

7.6 Discussion

Based on our results, no statistical evidence in favour of our hypotheses has emerged. However, the magnitude of coefficients and confidence intervals suggest an association between increased recovery of UL motor function and increased dose of rehabilitation, which need to be further explored.

Indeed, moving from 40 (1 hour/day, 5 days/week) to 120 hours (3 hour/day, 5 days/week) over a period of two-months, could lead to an approximate 7 points increase in FMA-UE.

From our results we found that most severely impaired patients (FMA-UE T0 < 17) have a higher overlap of CST disconnection compared to mild-to-moderate patients (FMA-UE T0 $\geq$ 17), in line with the hypothesis that there is an association between white-matter disconnections and motor improvement, even though it was not statistically significant [288]. Mild-to-moderate patients scoring between 62 and 66 points did not show any significant change before and after treatment, probably due to the ceiling effect of the scale. However, difference between groups was not statistically significant, highlighting that everyone can change, regardless of the starting level.

According to our TMS data, it is shown that disconnection of the functional integrity of the CST (MEP-) is mainly represented by no active movement of finger extension nor recruitments (median FE = 0) while some active movements at SA can still be possible (median SA = 2). This result is coherent with other studies, where finger individualisation movement was found to be impaired in patients with lesion in the CST [298].

According to our neuroimaging data, the results suggest that PLIC fibres are not entirely intact and there is an asymmetry between the lesioned and the healthy side, indicating a diminished structural integrity in the ipsilesional side after stroke, as already suggested in other studies [299].

Some known predictive factors (i.e. SAFE, FE, spasticity at flexor carpi and ARAT at baseline) were confirmed to be associated with UL motor improvement, as found in previous studies [121,122]. However, we did not find any evidence that having or not neurophysiological (i.e. MEPs) and neural (i.e. MRI) data makes a difference in exploring the association between rehabilitation and FMA-UE. Data from MEPs and CST-MRI are two pieces of information that, to date, do not seem to modify the information already provided by clinical measures.

We examined also the influence of selective attention and motor skills on motor improvement, as well as the association of white-matter disconnections with motor improvement, as already shown in other studies [288]. We found that the majority of the variance in the models is explained by attention, even when adjusting for MEP and CST, coherently with previous evidence [242].

The fact that baseline motor behavioural features (i.e. SAFE, RPS, FE and ARAT) were associated with motor outcome, but not dose of rehabilitation, could suggest that dose has not enough effect, which is then completely overshadowed and surpassed by more robust clinical predictors. This result is divergent from what found in a previous study conducted in a similar population, investigating for the first time the association between dosage and motor recovery [237].

We need to understand what other factors may come into the court: perhaps the hours of rehabilitation included too many techniques, each with different effects on the final outcome. However, even considering the evidence from literature, the most probable hypothesis could be that the dosage was too low to induce a change, thus leading to overestimated effects on deconditioned patients.

Some limitations need to be acknowledged in our study. Indeed, the use of numerous outcome measures and evaluation methods included require a careful statistical planning and modelling, also considering the potential of missing data. Moreover, the lack of a control cohort may limit the generalizability of “candidate” predictive factors in terms of causal relationship between predictors

and final outcomes [133]. For this reason, we envisage, as a possible extension of the present study, the external validation of the identified model(s) using a randomized controlled trial (RCT) or a cost-effectiveness study, which will eventually provide the possibility to guide the process of clinical decision-making regarding the time of intervention, promoting the greatest chance of recovery of the compromised functions. Then, limitations of the FMA scale could have represented the main reason for obtaining reliable prediction model. Indeed, this scale is considered to have excellent reliability and sensitivity psychometric properties, but has also important limitations, the main is the ceiling effect [71]. The latter makes the scale to be most responsive to changes in those patients with severe and moderate deficits who will not achieve the maximum possible scores, while its use as a measurement of recovery for patients with mild motor impairment is limited by a ceiling effect. Finally, it is crucial to emphasize that these analyses are interim analyses and therefore may lack the necessary statistical power to establish conclusive evidence. Consequently, we expect that our findings will be confirmed upon completion of the present cohort study.

7.7 Conclusion

According to our hypotheses and results, current dosage of therapy delivered to stroke patients did not seem to be associated with UL motor improvement. Attention seems to be the most important clinical factor largely explaining the variability of our patients' cohort. Future RCTs should be designed to answer questions related to the effectiveness of rehabilitation at different dosages, and larger samples are needed to understand the relationship between clinical covariates and rehabilitative outcomes.

8. GENERAL DISCUSSION

Throughout this PhD thesis we have widely investigated the existing association between rehabilitation and UL motor recovery in stroke survivors, by means of different methods and point of views. Starting from literature, evidence on UL motor recovery after stroke proposed prognostic models related exclusively to spontaneous recovery. Besides, clinical trials demonstrated beneficial effects of providing high doses of therapy to patients undergoing rehabilitation. However, the relationship between rehabilitation and prognosis had never been investigated, leaving answered the question of how rehabilitation may interfere with recovery prediction. In this PhD thesis, I have attempted to develop three projects that aimed to explore new knowledge on possible relationships between rehabilitation and prediction, by both primary and secondary research projects. Additionally, I have also tried to understand whether prognostic factors already known for spontaneous recovery were applicable also when patients undergo some form of rehabilitation. In attempting to do this, I initially faced the methodological issues raising from available prognostic studies.

First of all, as already mentioned in Chapter 3, a terminological issue on the use of the terms '*Prognosis*' and *'Prediction'* exists in the literature since those terms are used sometime interchangeably, other times erroneously. Indeed, the first term refers to the study of factors that can predict spontaneous recovery, and it is the area in which almost all the prognostic studies are concentrated. On the other hand, the term *'Prediction'* refers to the potential for recovery following a rehabilitation intervention, which is instead the area where all the literature should start to move in order to shed light on how rehabilitation can influence the expected recovery [131]. Therefore, in the present PhD project, we decided to make a clear distinction between the two terms and the respective concepts. Indeed, the term Prognosis is related to the expected recovery in the absence of rehabilitation, while with the term Prediction we want to stress the concept of expected recovery in response to rehabilitation and also trying to shape incisively this new perspective and associated methodologies in the field of stroke rehabilitation literature.

Another aspect to be emphasized is that, to truly make predictions, there are also methodological aspects related to study designs and analyses, that need to be considered. From a statistical and epidemiological perspective, experimental studies may allow a correct classification of simple association interactions and cause-effect interactions. According to the outline presented by the PROGRESS series (Prognosis Research Strategy 1, 2 and 3) [132,300,301], the path towards the

development of prognostic models must start from single cohort observational studies aiming to develop a prediction model and to define the *'Candidate Predictive Factors'*, i.e. the factors that are associated with the outcome, but that do not yet have the power to be considered true predictive factors. To reach the target of modelling the future clinical profile, following steps are necessary, such as the external validation of the model and implementation of candidate predictive factors in RCTs, with the aim to define a clear cause-effect relationship. To date, criticisms in the literature come from missing identification of candidate prognostic factors in cohort studies, thus going straight to validation studies of predictive factors whose association with the outcome had never actually been investigated. Thus, the possibility that chance might drive the causal/association relationship is not negligible and, in any case, strongly biased by researchers' beliefs. In other common scenarios, factors just "associated" with the outcome, from observational studies, were wrongly identified and called "prognostic factors" [121,141]. In this regard, the qualitative analysis of our SR (Study1), found that studies investigating association between baseline factors and final outcome, completely lack to consider confounding factors in their modelling, moreover selection of independent variable was not comprehensively reported, underlying low quality of statistical model reporting among primary studies. Based on that, we followed the recommendations for comprehensive reporting and outlining statistical methods properly [132,133,270,300,301], for designing our primary studies (Study 2 and 3).

Hence, in this PhD' projects, we properly ordered and distinguished these steps, starting with replacing the term *'Prognosis'* with *'Prediction'*, and the concept of prognosis with association, depending on the methodology used. To do so, we outlined a conceptual framework of rehabilitation interventions (also considering doses and modalities) and prediction (considered both individually and in interaction with rehabilitation).

As already seen in the introduction (paragraph 2.4), the theme of dose is a sensitive issue. Around the world, there is no consensus on how much doses should be delivered to stroke patients. For instance, Canadian guidelines [104] recommend a minimum of 3 hours of task-specific training, 5 days/week, UK guidelines [103]a minimum of 45 minutes/day of CT and Australian guidelines [105] recommend to deliver a minimum of 1 hour of active practice at least 5 days/week. In Italy, 3 hours/day are recommended in patients hospitalized in rehabilitation facilities, and UL-rehabilitation should start within the first 30 days or, at least, not later than 3 months after stroke onset [106]. A recent SR of Clark et al. found that there are very different ways of providing therapy

doses, from 90 to 1288 minutes/week, 3-7 days/week, and the total length of time is from 2 weeks to 6 months [302]. Clinically relevant difference can be found easily for motor impairment rather than activity since, according to authors, stroke patients need a large amount of extra rehabilitation for clinically relevant improvement of abilities in everyday life activities, along their recovery path [302]. As seen in paragraph 2.4, dose effect might be much different according to phase after lesion. Indeed, in the acute phase, short but frequent sessions are suggested [109,110], while in the subacute phase most of the improvement are driven by time rather than rehabilitation [36]. Finally, in the chronic phase, high dose of treatment (up to 90 to 300 hours) are needed to achieve clinically relevant improvement of motor function, defined as 9 to 11 points at the FMA-UE, also achievable in the chronic phase and maintained in the long-term follow-up [115,117,240]. These results are coherent with findings from our longitudinal study (Study 3) where, although statistical significance was not reached, providing 3 hours/day, 5 days/week of rehabilitation for two months (60 hours on average) would be expected to provide an approximate 6-points increase at FMA-UE. However, from our SR (Study 1), we found that current research clinical trials provide on average 31 or 33 hours of Priming or Augmenting treatment. This is different for trials providing Task-oriented interventions, whose average dose of treatment is around 84 hours. Indeed, other evidence suggests that the amount of practice needed to significantly improve the likelihood that extra rehabilitation would have a positive impact on activities should be 240% higher, than usually provided [303]. From our retrospective study (Study 2) we found that the total amount of rehabilitation has a higher impact than specific activities for the UL. This is coherent with previous study, highlighting that total amount of dose is more influent than specific contents when high dose of treatment are delivered [240]. Therefore, for our longitudinal observational study (Project 3) we chose to analyse total amount of dose as potentially associated with motor outcome, therefore not considering UL-specific activities in the models. Similarly, in our SR with proportional meta-analysis (Project 1) we observed that higher dose corresponds to higher effect size, and higher dose led to higher probability of becoming responder (Study 2 and 3). However, Task-oriented interventions were those able to provide higher response-effect, than Priming and Augmenting interventions.

In conclusion, there is not yet final evidence to recommend a minimum beneficial daily amount of rehabilitation treatment in clinical practice, but it seems worth considering that larger doses may lead to greater improvements in the chronic phase [302].

Regarding predictive features, in all the studies of this PhD, demographic features have never been found as associated with UL motor outcomes. We hypothesize that, when adding investigation of potential role of dose-response effect, demographic features do not impact on rehabilitation delivery, but only interferes with spontaneous neurological recovery. Stroke features, such as non-dominant side affected and longer time since lesion (Study 1), were found to be associated with UL motor improvement. For the latter, the hypothesis is that acute patients are able to achieve greater results in the first weeks after stroke, while chronic patients need more time to start improving, but once they continue rehabilitation they are more capable for skills-retentions and learning, as well as a finer motor control of limbs' movements [233]. However, from the SR (Study 1) we found that few studies investigated the effect of rehabilitation intervention, also exploring its association with motor outcomes.

One of the main findings of our longitudinal study (Study 3) is that all the patients may have a chance of improvement, regardless the baseline level of FMA-UE (i.e., severe, mild and moderate). In contrast with the Prediction Recovery Rule (PRR), we did not find a specific proportion of recovery expected to be achieved [144]. Other clinical motor features, such as preserved proprioception, manual dexterity (Study 1), and independence level (Study 2) resulted as associated with UL motor improvement.

Although our starting hypothesis was that rehabilitation is associated with motor outcomes, we found results in favour only in the retrospective study (Study 2), since current clinical trials included in our SR rarely investigated potential association between dose/modality and outcomes (Study 1) and our longitudinal study was not able to provide conclusive evidence because statistical evidence was not reached (Study 3).

Attention did not result significantly associated with UL motor outcome, both in the retrospective (Study 2) and in the longitudinal (Study 3) study. However, in the latter, attention explained most of the variance. Our results are not coherent with other evidence, where preservation of attentive functions is found to be related to higher motor response [242].

Integrity of the CST, both functional and structural, has always covered a key role in UL recovery prediction. Indeed, lesions in the CST affect not only the quality of movement but also the severity of the UL impairment [29]. In previous evidence, high level of FA-DTI and MEPs(+) were found to have positive predictive value for UL recovery 3 months after stroke [78,122]. From our results (Study 3), we found that severe impaired patients have a significant greater disconnection of the CST fibres and absence of MEPs. However, neither CST disconnection nor presence or absence of MEPs

resulted as associated with better motor recovery. The information about CST disconnection and MEPs did not add any further information to the clinical model (Study 3).

Throughout this PhD thesis we observed how outcome measures are used among studies and which could be current limitations in primary research. For example, from the SR (Study 1), it resulted that outcome measures of the body function and structures ICF domain are those most used, with FMA-UE as first, followed by activity measures. However, measures of participations are never used as primary outcome measures, but only as adjuvating the assessment's protocols. However, using the FMA-UE results in some difficulties due to its measurement properties. Indeed, FMA-UE has strong ceiling and floor effects (i.e. 5 points), therefore patients too severe or too mild are not accurately assessed since their motor performance are not intercepted by the scale [212]. Moreover, we noticed that many studies used many more outcome measures than those recommended (i.e., ARAT, FIM, NIHSS, FMA-UE)[43]. Furthermore, also kinematic and kinetic movement quantification should be implemented in clinical trials [304].

Research studies included in the present PhD thesis have several limitations. First of all, in the retrospective study, recall, attrition and selection bias may have had occurred, as well as measurement error [305]. Indeed, not all the patients had all the measures, since data on cognitive profile were retrieved only in 18 out of 35 patients with motor assessments. Furthermore, both the retrospective (Study 2) and the longitudinal (Study 3) study, as well as studies included in our SR (Study 1), had a small sample size of only 12 patients, on average. This sample size dimension could have relevantly limited the power of results and underestimated potential effects obtained from the regression models, impacting precision of estimations, thus confounding potential significant findings. Moreover, in all our studies we had only assessments before and after rehabilitation, therefore without serial measurements every few days/weeks it was not possible to control which part of the recovery curve the patient was. This limitation influence further potential analyses on predictions from cross-sectional data of the recovery curve, since patients might not be comparable if they are on a 'plateau' at 3 months, rather than on an upward curve [36]. Additionally, the retrospective nature of the Study 1 and the absence of a control group in all of the studies (i.e. Study 1, 2, 3) prevented the exploration of strong cause-and-effect relationships between the interventions and the observed outcomes [262]. Finally, in the longitudinal study (Study 3) a significant number of patients lacked to undergo the full set of instrumental assessment, resulting in less robust and less reliable results.

9. KEY POINTS OF THE PhD WORK

All the results of this doctoral thesis can be summarised in the following key findings for stroke rehabilitation and recovery:

- Patients' demographic characteristics are not associated with UL motor outcomes, in stroke survivors.
- Response to rehabilitation interventions for UL is driven by brain lesion characteristics, genetics and residual motor function at baseline.
- Higher doses of rehabilitation provide higher effect on UL motor function in the chronic phase.
- Attentive function and integrity of the CST are key factors in predicting UL motor rehabilitation-driven recovery.
- Association between doses of rehabilitation and prediction of UL motor recovery needs to be deeper investigated.
- Priming interventions:
    - Provide small effect for low dose of treatment (0-10 hours), moderate effect when at least 10 hours are delivered, in the chronic phase.
    - Provide the main effect between 10 to 30 hours, higher doses do not provide adjunctive effects, in the chronic phase.
- Augmenting interventions:
    - provide more beneficial effect in the chronic rather than subacute phase, when at least 10 hours are delivered (moderate effect).
    - independently by the dose, in the subacute phase, can provide small effects.
- Task-oriented interventions
    - provide the most beneficial effect (large effect) compared to other techniques, independently by the phase.

10. CONCLUSIONS

To summarize, this doctoral thesis investigated the association between rehabilitation and motor recovery, with a specific emphasis on the methodology required to identify predictive factors.

Based on my findings, I argue it is time to start implementing robust and agreed methodologies for the development of prognostic studies in rehabilitation, moving beyond the concept of *Prognosis*, which binds us to observational studies of spontaneous recovery, to the concept of *Prediction*, thus the estimation of the expected outcome in response to the rehabilitation intervention. In particular, an attempt should be made to carry out an awareness-raising process on the use of the correct methodology for developing knowledge in the field of prediction, to avoid creation of incorrect and therefore potentially dangerous cause-effect relationships.

An ongoing activity is data collection for Project 3, with the aim to complete a more comprehensive predictive model. Future developments will be oriented to validate the model in an external population. Moreover, to reach firm and strong insights on the predictive factors for motor recovery, improvement of the model's statistical fitting and estimation precision is required. Therefore, further research should be conducted with longitudinal cohort studies on a larger sample, considering also the enrolment of control cohorts and adjustments for confounding factors.

Finally, I am aware that the results may not provide conclusive evidence to suggest strong clinical recommendations. Nevertheless, they clearly indicate that we need to provide greater doses of rehabilitation than we are providing actually. Thus, to improve the relevance of rehabilitation intervention for motor recovery after stroke, more RCTs to reinforce evidence on the effect of doses considering predictive factors are necessary.

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APPENDIX S1

PubMed

#1 ("cohort studies"[MeSH Terms] OR "incidence"[MeSH Terms] OR "prognosis"[MeSH Terms] OR "follow up studies"[MeSH Terms] OR "predictive value of tests"[MeSH Terms] OR ("exp"[TIAB] AND "prognosis"[MeSH Terms]) OR ("prognos*"[TIAB] OR "predict*"[TIAB]) OR ("followup"[Title/Abstract] OR "follow-up"[TIAB] OR ("study"[Title/Abstract] OR ("studies"[TIAB] OR "study"[TIAB] OR "studying"[TIAB]))) OR "models, statistical"[MeSH Terms])

AND

#2 ("Stroke"[Mesh]) OR ("Stroke, Lacunar"[Mesh] OR "Hemorrhagic Stroke"[Mesh] OR "Embolic Stroke"[Mesh] OR "Thrombotic Stroke"[Mesh] OR "Ischemic Stroke"[Mesh] OR "Infarction, Posterior Cerebral Artery"[Mesh] OR "Brain Stem Infarctions"[Mesh] OR "Infarction, Middle Cerebral Artery"[Mesh] OR "Infarction, Anterior Cerebral Artery"[Mesh] OR "stroke"[tiab] OR "poststroke"[tiab] OR "post-stroke"[tiab] OR "cerebrovasc*"[tiab] OR (("brain"[MeSH Terms] OR "brain"[tiab] OR "brains"[tiab]) AND "next"[tiab] AND "vasc*"[tiab]) OR (("cerebrally"[tiab] OR "cerebrum"[MeSH Terms] OR "cerebrum"[tiab] OR "cerebral"[tiab] OR "brain"[MeSH Terms] OR "brain"[tiab]) AND "next”[tiab] AND "vasc*"[tiab]) OR "cva"[tiab] OR "apoplex*"[tiab] OR "SAH"[tiab])

AND

#3 Adult[Mesh] OR Adult[TIAB]

AND

#4 ((((((((((((((((upper extremit*[Title/Abstract]) OR (upper extremity[MeSH Terms])) OR (arm[MeSH Terms])) OR (arm[Title/Abstract])) OR (shoulder[MeSH Terms])) OR (elbow[MeSH Terms])) OR (elbow joint[MeSH Terms])) OR (forearm[MeSH Terms])) OR (hand[MeSH Terms])) OR (wrist[MeSH Terms])) OR (wrist joint[MeSH Terms])) OR (fingers[MeSH Terms]))) OR (forearm*[Title/Abstract])) OR (hand*[Title/Abstract])) OR (hand[MeSH Terms]))) OR (wrist*[Title/Abstract]))

AND

#5 ((((rehabilitation[MeSH Terms]) OR (physical and rehabilitation medicine[MeSH Terms])) OR (rehabilitation[Title/Abstract])) OR (“physical rehabilitation medicine”[Title/Abstract]))

AND

#6 ("muscle spasticity"[MeSH Terms] OR "muscle spasticity"[TIAB] OR "spastic*"[TIAB] OR "motor skills"[MeSH Terms] OR "Motor skills"[TIAB] OR "Motor"[TIAB] OR "functional*"[TIAB] OR "functioning"[TIAB] OR "functionings"[TIAB] OR "functions"[TIAB] OR "physiology"[MeSH Terms] OR "physiology"[TIAB] OR "function"[TIAB] OR "recoveries"[TIAB] OR "recovery"[TIAB] OR "recovery of function"[MeSH Terms] OR "recovery of function"[TIAB] OR "sensation"[MeSH Terms] OR "sensate"[TIAB] OR "sensation"[TIAB] OR "sensations"[TIAB] OR "muscle strength"[MeSH Terms] OR

"muscles"[MeSH Terms] OR "muscles"[TIAB] OR "muscle"[TIAB] OR "strength"[TIAB] OR "muscle strength"[TIAB] OR "shoulder pain"[MeSH Terms] OR "evoked potentials, motor"[MeSH Terms] OR "Evoked Potentials"[TIAB] OR "motor evoked potentials"[TIAB] OR "evoked potentials motor"[TIAB] OR "evoked potentials, somatosensory"[MeSH Terms] OR "somatosensory evoked potentials"[TIAB] OR "evoked potentials somatosensory"[TIAB] OR "Neuroimaging"[MeSH Terms] OR "Functional Neuroimaging"[MeSH Terms] OR "Diffusion Tensor Imaging"[MeSH Terms] OR "Diffusion Magnetic Resonance Imaging"[MeSH Terms] OR "Magnetic Resonance Imaging"[MeSH Terms] OR "Brain Mapping"[MeSH Terms] OR "Neuroimaging"[TIAB] OR "Functional Neuroimaging"[TIAB] OR "Diffusion Tensor Imaging"[TIAB] OR "Diffusion Magnetic Resonance Imaging"[TIAB] OR "Magnetic Resonance Imaging"[TIAB] OR "Brain Mapping"[TIAB] OR "Brain Mapping"[Title/Abstract] OR "imaging*"[TIAB])

#7 #1 AND #2 AND #3 AND #4 AND #5 AND #6

Cochrane

#1 MeSH descriptor: [Cohort Studies] explode all trees
#2 MeSH descriptor: [Incidence] explode all trees
#3 MeSH descriptor: [Prognosis] this term only
#4 MeSH descriptor: [Follow-Up Studies] this term only
#5 MeSH descriptor: [Predictive Value of Tests] this term only
#6 ("prognos*" OR "predict*" OR "follow-up" OR "follow up")
#7 ("follow-up" OR "study" OR "studies"):ti,ab,kw
#8 MeSH descriptor: [Models, Statistical] this term only
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 MeSH descriptor: [Stroke] explode all trees
#11 MeSH descriptor: [Stroke, Lacunar] this term only
#12 MeSH descriptor: [Hemorrhagic Stroke] this term only
#13 MeSH descriptor: [Embolic Stroke] this term only
#14 MeSH descriptor: [Thrombotic Stroke] this term only
#15 MeSH descriptor: [Infarction, Posterior Cerebral Artery] this term only
#16 MeSH descriptor: [Infarction, Middle Cerebral Artery] this term only
#17 MeSH descriptor: [Infarction, Anterior Cerebral Artery] this term only
#18 MeSH descriptor: [Brain Stem Infarctions] explode all trees
#19 MeSH descriptor: [Brain Infarction] this term only
#20 MeSH descriptor: [Brain] explode all trees
#21 MeSH descriptor: [Cerebrum] explode all trees
#22 ("stroke" OR "poststroke" OR "post-stroke" OR "cerebrovasc*" OR "brain" OR "brains" OR "next" OR "vasc*" OR "cerebrally" OR "cerebrum" OR "cerebral" OR "cva" OR "apoplex*" OR "SAH"):ti,ab,kw
#23 #10 OR #11 OR #12 OR #13 OR #14 OR #15 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24 MeSH descriptor: [Adult] this term only
#25 ("adult")
#26 #24 OR #25
#27 MeSH descriptor: [Upper Extremity] explode all trees
#28 MeSH descriptor: [Arm] this term only

#29 MeSH descriptor: [Shoulder] this term only
#30 MeSH descriptor: [Elbow] this term only
#31 MeSH descriptor: [Elbow Joint] this term only
#32 MeSH descriptor: [Forearm] this term only
#33 MeSH descriptor: [Hand] this term only
#34 MeSH descriptor: [Wrist] this term only
#35 MeSH descriptor: [Wrist Joint] this term only
#36 MeSH descriptor: [Fingers] this term only
#37 ("upper-extremity" OR "upper extremity" OR "arm" OR "shoulder" OR "elbow" OR "elbow joint" OR "forearm" OR "hand" OR "hands" OR "wrist" OR "wrist joint" OR "fingers" OR "axilla*" OR "forearm*" OR "wrist*"):ti,ab,kw
#38 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 146869
#39 MeSH descriptor: [Rehabilitation] explode all trees
#40 MeSH descriptor: [Physical and Rehabilitation Medicine] explode all trees
#41 ("rehabilitation" OR "physical rehabilitation medicine"):ti,ab,kw
#42 #39 OR #40 OR #41
#43 MeSH descriptor: [Muscle Spasticity] this term only
#44 MeSH descriptor: [Motor Skills] this term only
#45 ("muscle spasticity" OR "spastic*" OR "motor skills" OR "motor" OR "functional*" OR "functioning" OR "functionings" OR "functions")
#46 MeSH descriptor: [Physiology] explode all trees
#47 MeSH descriptor: [Recovery of Function] this term only
#48 ("physiology" OR "function" OR "recoveries" OR "recovery" OR "recovery of function")
#49 MeSH descriptor: [Sensation] explode all trees
#50 ("sensation" OR "sensate" OR "sensations")
#51 MeSH descriptor: [Muscle Strength] explode all trees
#52 MeSH descriptor: [Muscles] explode all trees
#53 ("muscles" OR "muscle" OR "strength" OR "muscle strength")
#54 MeSH descriptor: [Shoulder Pain] this term only
#55 MeSH descriptor: [Evoked Potentials, Motor] explode all trees
#56 MeSH descriptor: [Evoked Potentials, Somatosensory] explode all trees
#57 ("evoked potentials" OR "motor evoked potentials" OR "evoked potentials motor" OR "somatosensory evoked potentials" OR "evoked potentials somatosensory")
#58 MeSH descriptor: [Neuroimaging] explode all trees
#59 MeSH descriptor: [Functional Neuroimaging] explode all trees
#60 MeSH descriptor: [Diffusion Tensor Imaging] this term only
#61 MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
#62 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#63 MeSH descriptor: [Brain Mapping] explode all trees
#64 ("neuroimaging" OR "functional neuroimaging" OR "diffusion tensor imaging" OR "diffusion magnetic resonance imaging" OR "magnetic resonance imaging" OR "brain mapping" OR "imaging*")
#65 ("brain mapping"):ti,ab,kw
#66 #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65
#67 #9 AND #23 AND #26 AND #38 AND #42 AND #66

Embase

#1 'cohort studies'/exp OR 'cohort studies' OR 'incidence'/exp OR 'incidence' OR 'prognosis'/exp OR 'prognosis' OR 'follow up studies'/exp OR 'follow up studies' OR 'predictive value of tests'/exp OR 'predictive value of tests' OR ('exp':ti,ab AND ('prognosis'/exp OR 'prognosis')) OR 'prognos*':ti,ab OR 'predict*':ti,ab OR 'followup':ti,ab OR 'follow-up':ti,ab OR 'studies':ti,ab OR 'study':ti,ab OR 'studying':ti,ab OR 'models, statistical'/exp OR 'models, statistical'

AND

#2 ("Stroke"/de) OR ("Stroke, Lacunar"/de OR "Hemorrhagic Stroke"/de OR "Embolic Stroke"/de OR "Thrombotic Stroke"/de OR "Ischemic Stroke"/de OR "Infarction, Posterior Cerebral Artery"/de OR "Brain Stem Infarctions"/de OR "Infarction, Middle Cerebral Artery"/de OR "Infarction, Anterior Cerebral Artery"/de OR "stroke":ti,ab OR "poststroke":ti,ab OR "post-stroke":ti,ab OR "cerebrovasc*":ti,ab OR (("brain"/de OR "brain":ti,ab OR "brains":ti,ab) AND "next":ti,ab AND "vasc*":ti,ab) OR (("cerebrally":ti,ab OR "cerebrum"/de OR "cerebrum":ti,ab OR "cerebral":ti,ab OR "brain"/de OR "brain":ti,ab) AND "next”:ti,ab AND "vasc*":ti,ab) OR "cva":ti,ab OR "apoplex*":ti,ab OR "SAH":ti,ab)

AND

#3 Adult/de OR Adult:ti,ab

AND

#4 ((((((((((((((((upper extremit*:ti,ab) OR (upper extremity/de)) OR (arm/de)) OR (arm:ti,ab)) OR (shoulder/de)) OR (elbow/de)) OR (elbow joint/de)) OR (forearm/de)) OR (hand/de)) OR (wrist/de)) OR (wrist joint/de)) OR (fingers/de))) OR (forearm*:ti,ab)) OR (hand*:ti,ab)) OR (hand/de))) OR (wrist*:ti,ab))

AND

#5 ((((rehabilitation/de) OR (physical and rehabilitation medicine/de)) OR (rehabilitation:ti,ab)) OR (“physical rehabilitation medicine”:ti,ab))

AND

#6 ("muscle spasticity"/de OR "muscle spasticity":ti,ab OR "spastic*":ti,ab OR "motor skills"/de OR "Motor skills":ti,ab OR "Motor":ti,ab OR "functional*":ti,ab OR "functioning":ti,ab OR "functionings":ti,ab OR "functions":ti,ab OR "physiology"/de OR "physiology":ti,ab OR "function":ti,ab OR "recoveries":ti,ab OR "recovery":ti,ab OR "recovery of function"/de OR "recovery of function":ti,ab OR "sensation"/de OR "sensate":ti,ab OR "sensation":ti,ab OR "sensations":ti,ab OR "muscle strength"/de OR "muscles"/de OR "muscles":ti,ab OR "muscle":ti,ab OR "strength":ti,ab OR "muscle strength":ti,ab OR "shoulder pain"/de OR "evoked potentials, motor"/de OR "Evoked Potentials":ti,ab OR "motor evoked potentials":ti,ab OR "evoked potentials motor":ti,ab OR "evoked potentials, somatosensory"/de OR "somatosensory evoked potentials":ti,ab OR "evoked potentials somatosensory":ti,ab OR "Neuroimaging"/de OR "Functional Neuroimaging"/de OR "Diffusion Tensor Imaging"/de OR "Diffusion Magnetic

Resonance Imaging"/de OR "Magnetic Resonance Imaging"/de OR "Brain Mapping"/de OR "Neuroimaging":ti,ab OR "Functional Neuroimaging":ti,ab OR "Diffusion Tensor Imaging":ti,ab OR "Diffusion Magnetic Resonance Imaging":ti,ab OR "Magnetic Resonance Imaging":ti,ab OR "Brain Mapping":ti,ab OR "Brain Mapping":ti,ab OR "imaging*":ti,ab)

#7 = #1 AND #2 AND #3 AND #4 AND #5 AND #6

Scopus

TITLE-ABS-KEY("cohort studies" OR "incidence" OR "prognosis" OR "follow up studies" OR "predictive value of tests" OR "prognosis") OR TITLE-ABS-KEY("prognos*") OR TITLE-ABS-KEY("predict*") OR TITLE-ABS-KEY("followup" OR "follow-up") OR "study" OR TITLE-ABS-KEY ("studies" OR "study" OR "studying") OR "models, statistical"

AND

TITLE-ABS-KEY ("Stroke" OR "stroke, lacunar" OR "Hemorrhagic Stroke" OR "Embolic Stroke" OR "Thrombotic Stroke" OR "Ischemic Stroke" OR "infarction, posterior cerebral artery" OR "Brain Stem Infarctions" OR "infarction, middle cerebral artery" OR "infarction, anterior cerebral artery" OR "Stroke" OR "poststroke" OR "post-stroke" OR "cerebrovasc*") OR TITLE-ABS-KEY ("brain" OR "brain" OR "brains" OR "brains") OR TITLE-ABS-KEY ("cerebrally" OR "cerebrum" OR "cerebrum" OR "cerebral" OR "brain" OR "brain" OR "apoplex*" OR "SAH")

AND

TITLE-ABS-KEY ("adult" OR "adults")

AND

TITLE-ABS-KEY ("upper extremit*" OR "upper extremity" OR "arm" OR "shoulder") OR TITLE-ABS-KEY ("elbow" OR "elbow joint") OR TITLE-ABS-KEY ("forearm" OR "hand" OR "wrist" OR "wrist joint" OR "fingers" OR "forearm*" OR "hand*" OR "hand" OR "wrist*")

AND

TITLE-ABS-KEY ("rehabilitation" OR "physical and rehabilitation medicine" OR "rehabilitation" OR "physical rehabilitation medicine")

AND

TITLE-ABS-KEY ("muscle spasticity" OR "muscle spasticity" OR "spastic*") OR TITLE-ABS-KEY ("Motor skills" OR "Motor skills" OR "Motor") OR TITLE-ABS-KEY ("functional*" OR "functioning" OR "functionings" OR "functions") OR TITLE-ABS-KEY ("physiology" OR "function" OR "recoveries" OR "recovery" OR "recovery of function") TITLE-ABS-KEY ("sensation" OR "sensate" OR "sensations" OR "muscle strength" OR "muscles" OR "muscle" OR "strength" OR "muscle strength" OR "shoulder pain") OR TITLE-ABS-KEY ("evoked potentials, motor" OR "Evoked Potentials" OR "motor evoked potentials" OR "evoked potentials motor" OR "evoked potentials, somatosensory" OR "somatosensory evoked potentials" OR "evoked potentials somatosensory")

OR TITLE-ABS-KEY ("Neuroimaging" OR "Functional Neuroimaging" OR "Diffusion Tensor Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Magnetic Resonance Imaging" OR "Brain Mapping" OR "Neuroimaging" OR "Functional Neuroimaging" OR "Diffusion Tensor Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Magnetic Resonance Imaging" OR "Brain Mapping" OR "imaging*")

Web of Science

#1 TS=("cohort studies" OR "incidence" OR "prognosis" OR "follow up studies" OR "predictive value of tests" OR "prognos*" OR "predict*" OR "followup" OR "follow-up" OR "study" OR "studies" OR "studying" OR "models, statistical")

AND

#2
TS=("cerebrovascular disorders" OR "basal ganglia cerebrovascular disease" OR "brain ischemia" OR "carotid artery diseases" OR "intracranial arterial diseases" OR "intracranial arteriovenous malformations" OR "intracranial embolism and thrombosis" OR "intracranial hemorrhages" OR stroke OR "brain infarction" OR "brain injuries" OR "brain injury, chronic" OR stroke* OR cva OR poststroke OR poststroke OR cerebrovasc* or "cerebral vascular" OR cerebral OR cerebellar OR brain* OR vertebrobasilar near/5 infarct* OR isch?emi* OR thrombo* OR emboli* OR apoplexy OR cerebral OR brain OR subarachnoid near/5 haemorrhage OR hemorrhage OR haematoma OR hematoma OR bleed*)

AND

#3 TS=("adult" OR "adults")

AND

#4
TS=("upper extremit*" OR "arm" OR "arms" OR "shoulder" OR "shoulders" "elbow" OR "elbow joint" OR "forearm" OR "hand" OR "wrist" OR "wrist joint" OR "fingers" OR "forearm*" OR "hand*" OR "wrist*" OR "elbows")

AND

#5 TS=("rehabilitation" OR "physical and rehabilitation medicine" OR "rehabilitation" OR "physical rehabilitation medicine")

AND

#6
TS=("muscle spasticity" OR "spastic*" OR "Motor skills" OR "Motor" OR "functional*" OR "functioning" OR "functionings" OR "functions" OR "physiology" OR "function" OR "recoveries" OR "recovery" OR "recovery of function" OR "sensation" OR "sensate" OR "sensations" OR "muscle strength" OR "muscles" OR "muscle" OR "strength" OR "shoulder pain" OR "evoked potentials, motor" OR "Ev

oked Potentials" OR "motor evoked potentials" OR "evoked potentials motor" OR "evoked potentials, somatosensory" OR "somatosensory evoked potentials" OR "evoked potentials somatosensory" OR "Neuroimaging" OR "Functional Neuroimaging" OR "Diffusion Tensor Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Magnetic Resonance Imaging" OR "Brain Mapping" OR "Neuroimaging" OR "Functional Neuroimaging" OR "Diffusion Tensor Imaging" OR "Magnetic Resonance Imaging" OR "Brain Mapping" OR "imaging*")

#7 = (#1 AND #2 AND #3 AND #4 AND #5 AND #6)

Cinahl

MH cohort studies OR MH incidence OR MH prognosis OR MH follow up studies OR MH predictive value of tests OR MH prognosis OR TI prognos* OR AB prognos* OR TI predict* OR AB predict* OR TI followup OR AB followup OR TI follow-up OR AB follow-up OR TI study OR AB study OR TI studies OR AB studies OR MH models, statistical

AND

MH Stroke OR MH Stroke, Lacunar OR MH Hemorrhagic Stroke OR MH Embolic Stroke OR MH Thrombotic Stroke OR MH Ischemic Stroke OR MH Infarction, Posterior Cerebral Artery OR MH Brain Stem Infarctions OR MH Infarction, Middle Cerebral Artery OR MH Infarction, Anterior Cerebral Artery OR TI stroke OR AB stroke OR TI poststroke OR AB poststroke OR OR TI cerebrovasc* OR AB cerebrovasc* OR MH brain OR TI brain OR AB brain OR TI brains OR AB brains OR TI cerebrally OR AB cerebrally OR MH cerebrum OR TI cerebrum OR AB cerebrum OR TI cerebral OR AB cerebral OR TI cva OR AB cva OR TI apoplex* OR AB apoplex* OR TI SAH OR AB SAH

AND

MH Adult OR TI Adult OR AB Adult

AND

TI upper extremit* OR AB upper extremit* OR MH upper extremity OR MH arm OR TI arm OR AB arm OR MH shoulder OR MH elbow OR MH elbow joint OR MH forearm OR MH hand OR MH wrist OR MH wrist joint OR MH fingers OR TI forearm OR AB forearm OR TI hand* OR AB hand* OR MH hand OR TI wrist* OR AB wrist*

AND

MH rehabilitation OR TI rehabilitation OR AB rehabilitation

AND

MH muscle spasticity OR TImuscle spasticity OR muscle spasticity OR AB muscle spasticity OR TI spastic OR AB spastic OR MH motor skills OR TI Motor skills OR AB motor skills OR TI Motor OR AB motor OR TI functional* OR AB functional OR TI functioning OR AB functioning OR TI functionings OR AB functionings OR TI functions OR AB functions OR MH physiology OR TI physiology OR AB

physiology OR TI function OR AB function OR recoveries OR TI recovery OR AB recovery OR MH recovery of function OR TI recovery of function OR AB recovery of function OR MH sensation OR TI sensation OR AB sensation OR TI sensations OR AB sensations OR MH muscle strength OR MH muscles OR TI muscles OR AB muscles OR TI muscle OR AB muscle TI strength OR AB strength OR TI muscle strength OR AB muscle strength OR MH shoulder pain OR MH evoked potentials, motor OR TI Evoked Potentials OR AB Evoked Potentials OR TI motor evoked potentials OR AB motor evoked potentials OR TI evoked potentials motor OR AB evoked potentials motor OR MH evoked potentials, somatosensory OR TI somatosensory evoked potentials OR AB somatosensory evoked potentials OR TI evoked potentials somatosensory OR AB evoked potentials somatosensory OR MH Neuroimaging OR MH Functional Neuroimaging OR MH Diffusion Tensor Imaging OR MH Diffusion Magnetic Resonance Imaging OR MH Magnetic Resonance Imaging OR MH Brain Mapping OR TI Neuroimaging OR AB Neuroimaging OR TI Functional Neuroimaging OR AB Functional Neuroimaging OR TI Diffusion Tensor Imaging OR AB Diffusion Tensor Imaging OR TI Diffusion Magnetic Resonance Imaging OR AB Diffusion Magnetic Resonance Imaging OR TI Magnetic Resonance Imaging OR AB Magnetic Resonance Imaging OR TI Brain Mapping OR AB Brain Mapping OR TI Brain Mapping OR AB Brain Mapping OR TI imaging* OR AB imaging*

#7 = (MH cohort studies OR MH incidence OR MH prognosis OR MH follow up studies OR MH predictive value of tests OR MH prognosis OR TI prognos* OR AB prognos* OR TI predict* OR AB predict* OR TI followup OR AB followup OR TI follow-up OR AB follow-up OR TI study OR AB study OR TI studies OR AB studies OR MH models, statistical) AND (MH Stroke OR MH Stroke, Lacunar OR MH Hemorrhagic Stroke OR MH Embolic Stroke OR MH Thrombotic Stroke OR MH Ischemic Stroke OR MH Infarction, Posterior Cerebral Artery OR MH Brain Stem Infarctions OR MH Infarction, Middle Cerebral Artery OR MH Infarction, Anterior Cerebral Artery OR TI stroke OR AB stroke OR TI poststroke OR AB poststroke OR OR TI cerebrovasc* OR AB cerebrovasc* OR MH brain OR TI brain OR AB brain OR TI brains OR AB brains OR TI cerebrally OR AB cerebrally OR MH cerebrum OR TI cerebrum OR AB cerebrum OR TI cerebral OR AB cerebral OR TI cva OR AB cva OR TI apoplex* OR AB apoplex* OR TI SAH OR AB SAH) AND (MH Adult OR TI Adult OR AB Adult) AND (TI upper extremit* OR AB upper extremit* OR MH upper extremity OR MH arm OR TI arm OR AB arm OR MH shoulder OR MH elbow OR MH elbow joint OR MH forearm OR MH hand OR MH wrist OR MH wrist joint OR MH fingers OR TI forearm OR AB forearm OR TI hand* OR AB hand* OR MH hand OR TI wrist* OR AB wrist*) AND (MH rehabilitation OR TI rehabilitation OR AB rehabilitation) AND (MH muscle spasticity OR TImuscle spasticity OR muscle spasticity OR AB muscle spasticity OR TI spastic OR AB spastic OR MH motor skills OR TI Motor skills OR AB motor skills OR TI Motor OR AB motor OR TI functional* OR AB functional OR TI functioning OR AB functioning OR TI functionings OR AB functionings OR TI functions OR AB functions OR MH physiology OR TI physiology OR AB physiology OR TI function OR AB function OR recoveries OR TI recovery OR AB recovery OR MH recovery of function OR TI recovery of function OR AB recovery of function OR MH sensation OR TI sensation OR AB sensation OR TI sensations OR AB sensations OR MH muscle strength OR MH muscles OR TI muscles OR AB muscles OR TI muscle OR AB muscle TI strength OR AB strength OR TI muscle strength OR AB muscle strength OR MH shoulder pain OR MH evoked potentials, motor OR TI Evoked Potentials OR AB Evoked Potentials OR TI motor evoked potentials OR AB motor evoked potentials OR TI evoked potentials motor OR AB evoked potentials motor OR MH evoked potentials, somatosensory OR TI somatosensory evoked potentials OR AB somatosensory evoked potentials OR TI evoked potentials somatosensory OR AB evoked potentials somatosensory OR MH Neuroimaging OR MH Functional Neuroimaging OR MH Diffusion Tensor Imaging OR MH Diffusion Magnetic Resonance Imaging OR MH Magnetic Resonance Imaging OR MH Brain Mapping OR TI Neuroimaging OR AB Neuroimaging OR TI Functional Neuroimaging OR AB Functional Neuroimaging OR TI

Diffusion Tensor Imaging OR AB Diffusion Tensor Imaging OR TI Diffusion Magnetic Resonance Imaging OR AB Diffusion Magnetic Resonance Imaging OR TI Magnetic Resonance Imaging OR AB Magnetic Resonance Imaging OR TI Brain Mapping OR AB Brain Mapping OR TI Brain Mapping OR AB Brain Mapping OR TI imaging* OR AB imaging*)