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Disability in Cerebrovascular Disease

Motor Deficits, Complications, and Rehabilitation Strategies in Stroke Survivors

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1. Introduction

An overview of the research studies

Stroke ranks highly as a cause of death and is the leading cause of long-term disability in many Western countries. The outcomes of a stroke can vary from minor, temporary issues to severe, long-term disabilities.

Stroke can cause significant cognitive and physical disabilities. These can include motor deficits, attention disturbances, memory issues, depression, spatial neglect (also known as hemi-inattention), apraxia (difficulty with motor planning), anosognosia (a lack of awareness about one's own condition), and dysphagia (difficulty swallowing). Aphasia (language impairment) and dysarthria (motor speech disorder) are common communication disorders that can result from stroke and may significantly affect a person's quality of life and social interactions. Moreover, the monitoring of dysphagia is crucial as it can lead to complications such as aspiration pneumonia, malnutrition, or dehydration if not properly managed.

Conditions associated with stroke can worsen the clinical situation, such as co-infections, sarcopenia, and complications due to hypomobility.

Rehabilitation is key to recovery following a stroke. It can involve a team of healthcare professionals, including physicians, specialist in physical medicine and rehabilitation, neurology, geriatric, physical therapists, occupational therapists, speech-language pathologists, and neuropsychologists. The goal is to help the patient regain as much function as possible and adapt to their new limitations.

1.1. Impact of Stroke on Motor Function and Rehabilitative approach

Stroke is a leading cause of disability worldwide, often resulting in various motor disorders that can significantly impair an individual's quality of life. Therapeutic strategies for these motor disorders are continually evolving, with research focusing on various approaches from exercise-based interventions to pharmacological treatments.

This research aims to explore diverse strategies for improving motor recovery in post-stroke survivors, highlighting promising therapeutic avenues and the need for continued research in this crucial area.

1.1.1. The effectiveness of goal-oriented dual task proprioceptive training: a systematic review

Two systematic reviews [1,2] analyses the impact of proprioceptive dual-task training on activities of daily living (ADL) and gait parameters in patients with stroke. Evidence suggests that dual-task proprioceptive training resulted in increased gait speed, cadence, stride length, and step length, and a decreased stride time compared to pre-rehabilitation measurements. Similarly, single limb support time improved after the training. Even single-task proprioceptive rehabilitation alone led to positive changes in cadence and stride length. Additionally, proprioceptive and dual-task exercises appeared crucial in promoting postural balance, gait, and quality of life, while reducing fall risk.

However, the review identified a high variability in the quality, intensity, and duration of training programs, with no specific protocols based on the severity of postural imbalance. Moreover, the heterogeneity in exercise types and timing precluded the formulation of a specific protocol for proprioceptive and dual-task exercises. Nonetheless, the review concludes that combined proprioceptive and dual-task training has demonstrated substantial effectiveness in restoring balance during ADL in chronic stroke patients.

1.1.2. The effectiveness of goal-oriented dual task proprioceptive training: an observational study

Post-stroke motor recovery often involves complex, multi-modal therapeutic approaches. One such method is goal-oriented dual task proprioceptive training, which combines cognitive and motor tasks with proprioceptive inputs to improve motor function. This section examines the effectiveness of this approach in individuals within the subacute phase post-stroke, an important period for motor recovery [3].

1.1.3. Botulinum Toxin in Post-Stroke Motor Deficits and the Potential of Experimental Antidotes for Botulinum Neurotoxin in Stroke Treatment

Pharmacological interventions, such as the use of Botulinum toxin (BoNT), play a crucial role in managing post-stroke motor deficits and conditions like dystonia. BoNT has been shown to reduce muscle tone and improve function in certain patient populations. This section delves into the role and benefits of BoNT in treating motor disorders following a stroke.

While BoNT can be a potent tool in stroke recovery, its use is not without risk. This necessitates the concurrent development and assessment of antidotes for BoNT. This section explores the potential of experimental antidotes for Botulinum neurotoxin in the context of stroke treatment, shedding light on an emerging and crucial field of research [4].

1.2. Exploring the Interplay of Stroke and Associated Complications: Insights into Infections and Sarcopenia

The research seeks to elucidate the interplay between stroke and associated complications, particularly focusing on infections and sarcopenia which pose substantial threats to stroke survivors' quality of life and overall prognosis.

Infections, including pneumonia and urinary tract infections, are common complications post-stroke, often leading to further deterioration of patients' health status. On the other hand, sarcopenia, characterized by progressive loss of muscle mass and strength, is frequently observed in elderly stroke survivors, contributing to functional decline and increasing the risk of physical disability.

1.2.1. The Impact of Infections on Stroke Complications

An observational study [5] sought to explore the impact of Clostridium difficile infection (CDI) on the rehabilitation outcomes of stroke patients. Twenty-six stroke patients, thirteen with CDI and thirteen without (control group), admitted to an intensive inpatient rehabilitation unit were retrospectively evaluated from January 2018 to May 2022. Their autonomy levels were assessed using the Barthel index and the Conley scale and the Braden scale were employed to estimate the risk of fall and predict pressure ulcer risk, respectively. The length of hospitalization, the number of lost days of rehabilitation and any requested psychological referrals did not influence the rehabilitative outcomes of CDI stroke patients. Autonomy improved at the end of the rehabilitation, as showed by Barthel index in CDI stroke group ($p=0.0005$). The Conley scale and the Braden scale did not show significant differences compared with the control group at discharge ($p = 0.2905$, $p = 0.4424$). Thus, the study concludes that stroke patients with non-severe CDI symptoms can continue their rehabilitative programs and achieve similar outcomes as patients without CDI, underscoring the importance of maintaining rehabilitation even in the presence of CDI.

1.2.2. Sarcopenia in stroke

The other research [6] utilized machine learning to identify the most accurate, speed and low-cost sarcopenia screening methods in frail patients, included those after stroke.

Sarcopenia, a significant risk factor for morbidity and preventable mortality in old age, presents a substantial cost to healthcare systems, especially given the expense of diagnostic tools such as DEXA. The study aimed to create a low-cost screening tool to mimic the performance of DEXA for detecting muscle mass loss. This new tool could enable early, large-scale diagnosis of sarcopenia, thereby reducing prevalence and associated complications.

The study analysed cross-sectional data from approximately 14,500 patients using 38 non-laboratory variables. It applied advanced machine learning methods based on decision trees to the seven years' worth of data collected from the NHANES study (1999-2006).

The findings suggest that a limited number of anthropometric parameters can predict DEXA outcomes with an area under the curve (AUC) between 0.92 and 0.94. The most complex model, which uses six variables related to body circumference and body fat evaluation, achieves an optimal sensitivity of 0.89 and specificity of 0.82. Even when the analysis is restricted to variables related to the lower limb, the accuracy remains high (AUC 0.88-0.90).

The study concludes that anthropometric data can contain all the relevant information found in a more complex set of non-laboratory variables. The new models developed are less complex and more accurate than previously published screening tools for muscle mass loss. These results suggest a potential shift in the standard diagnostic algorithm for sarcopenia, proposing a new diagnostic scheme that would require further clinical validation.

Importantly, this machine learning approach could also be applicable to screening sarcopenia in stroke patients, offering a more efficient and cost-effective method to monitor and manage this common complication.

1.3. Post-Stroke Dysarthria: A Multidisciplinary Approach to Rehabilitation

In post-stroke patients, speech difficulties such as dysarthria and aphasia are common alongside motor impairments.

Three systematic reviews allowed to explore the diagnostic and therapeutical strategies of stroke dysarthria [7,8,9].

Dysarthria is a motor speech disorder resulting from neurological injury or damage, and it often occurs in stroke patients. The condition can affect the muscles responsible for speech, making it difficult for patients to talk clearly. Depending on the area and the extent of the stroke, dysarthria can be mild or severe.

1.3.1. A Systematic Review of Measures of Dysarthria Severity in Stroke Patients

Diagnostic methods for post-stroke dysarthria included specific scales, such as the Frenchay Dysarthria Assessment second edition (FDA-2) to diagnose the severity of dysarthria post-stroke, acoustic analysis through different programs and software, the assessment of voice space area (VSA) and formants, and novel diagnostic methods, such as the Automatic Speech Recognition (ASR) system and neuroanatomical predictors through Magnetic Resonance Imaging (MRI) [7]. The psychosocial impact of speech impairment was investigated through specific tests, while numerous studies developed personalized versions of scales and scores [7]. Our findings underscore the need for standardization in diagnostic methods and highlight the potential of novel technologies in dysarthria assessment post-stroke [7].

1.3.2. Dysarthria and stroke. The effectiveness of speech rehabilitation. A systematic review and meta-analysis of the studies

The main characteristics of dysarthria include slurred or slow speech, a change in voice quality (such as hoarseness or breathiness), difficulty with the rhythm and melody of speech, or problems with the movement of the muscles that produce speech. This can make it difficult for others to understand what the person is saying, which can be frustrating for both the speaker and the listener.

Several methods assess post-stroke dysarthria severity. Very useful the acoustic parameters to follow the results of rehabilitation. Significant improvements in alternating and sequential motion rates (AMR-Pə, AMR-Tə, AMR-Kə, and SMR-PəTəKə) and maximum phonation time were recorded after speech rehabilitation [9].

1.3.3. Speech rehabilitation in dysarthria after stroke: a systematic review of the studies

There are various forms of treatment available for dysarthria [8], often led by a speech-language pathologist. The specific treatment plan is personalized to the individual's needs, but it usually involves exercises to improve the strength and coordination of the muscles involved in speech, and strategies to enhance communication. These strategies can include slowing down speech, using gestures or other non-verbal communication methods, and in some cases, using assistive communication devices. In stroke patients, dysarthria is often accompanied by other neurological symptoms and may require a multidisciplinary approach for management, including occupational therapy and physical therapy in addition to speech therapy. The treatment of dysarthria can also contribute significantly to the overall rehabilitation process after a stroke, helping to improve not only communication but also other aspects of the patient's daily life.

It's important to remember that recovery rates and the effectiveness of treatment can vary greatly depending on factors such as the severity of the stroke, the patient's overall health, and the promptness of treatment initiation. Therefore, early detection and intervention are crucial in managing dysarthria in stroke patients.

1.4. Aim of the PhD thesis

Stroke stands as one of the leading causes of long-term disability worldwide, presenting an intricate puzzle of physiological, psychological, and social challenges for the affected individuals. Within the vast realm of post-stroke complications, disability emerges as a particularly complex and multifaceted domain, influencing not only the physical realm but also the cognitive and emotional well-being of individuals. This thesis embarks on a journey through the various facets of post-stroke disability, navigating through wide topics. However, as we delve deeper into each subject, we find that they all converge, intertwined by the overarching theme of post-stroke disability. Throughout the chapters, we will explore subjects ranging from motor impairments and spasticity to language deficits and cognitive disruptions, all of which play a pivotal role in shaping the post-stroke landscape of an individual's life. By examining these topics, this thesis aims to present a holistic perspective on post-stroke disability, highlighting the critical role of comprehensive rehabilitation and the multifaceted challenges encountered by both patients and clinicians. The various topics covered have a common denominator: the post-stroke disability.

In drawing upon various research studies, and clinical insights, this work underscores the importance of viewing post-stroke disability not as an isolated condition but as a dynamic interplay of various factors. At the heart of this exploration is a singular quest: to understand the nuances of post-stroke disability better and, in doing so, pave the way for more effective and patient-centered interventions.

The aim of the PhD thesis is to delve deeply into the multifaceted realm of post-stroke rehabilitation, elucidating its pivotal role in ameliorating disabilities that arise following a stroke. Through a synthesis of current literature, research methods and clinical studies, this work aspires to bridge existing knowledge gaps, offering evidence-based recommendations to optimize therapeutic strategies and improve patient outcomes. In essence, this thesis endeavours to enhance our comprehension of rehabilitation's impact and chart the way forward for more effective and patient-centric rehabilitative care for stroke survivors.

Evidence acquisition

2.1. First topic of the PhD project

Impact of Stroke on Motor Function and therapeutical strategies

2.1.1. The effectiveness of goal-oriented dual task proprioceptive training in stroke patients: A Systematic Review of the Literature

2.1.1.1. Introduction

Balance refers to the body's ability to maintain proper positioning despite external influences. Proprioception represents the sense of the position and motion of the body parts, as well as the force exerted during movement. It plays a critical role in coordinating multiple joints and intersegmental movement. Proprioception is important for motor planning and motor response, and its role in motor learning and neuroplasticity is increasingly recognized [10,11]. Accurate sensory feedback, including proprioception, is necessary for motor control during balance and weight changes in an upright position [12]. Therefore, maintaining balance during walking or when facing external disturbances is a crucial aspect of rehabilitation, particularly in walking, where visual feedback, the vestibular system, and proprioception act as compensatory strategies when sensory impairment or balance perturbation occurs [13].

Locomotor pathways that control gait, balance, and proprioception are often compromised in stroke patients. The amount of executive resource required for walking is mirrored in prefrontal cortex activity [14]. Stroke patients exhibit increased prefrontal cortex activation during walking compared to healthy individuals, due to the increased attentional demand required for locomotion [15]. Performing an additional task while walking heightens this prefrontal cortex activity further [14]. Moreover, stroke patients show a greater activation of the bilateral superior frontal gyrus, bilateral inferior temporal gyrus, and left caudate nucleus during dual-task conditions, as compared to single-task conditions [15].

Adapting one's gait to environmental circumstances, such as avoiding obstacles and ensuring safe foot placement in cluttered environments, is essential for safe everyday walking [16]. Unfortunately, the ability of post-stroke patients to respond appropriately to various environments and activities is often compromised due to a decline in left/right weight transferability and proprioceptive dysfunction [17]. Specifically, engaging simultaneously in cognitive and motor tasks—which are crucial for most activities of daily living (ADL)—poses a significant challenge for these individuals [18].

As most activities of daily living (ADL) involve a combination of cognitive and motor task performance, stroke can significantly complicate these tasks [19]. Depending on the stage and severity of the disease and the localization of cerebral impairment, stroke can affect consciousness, sensory perception, language, sphincter control, and cognitive and motor abilities, such as postural balance and gait. Imbalances caused by stroke, often resulting from sensory deficit or motor impairment, are a major cause of functional limitations [20]. Approximately 18% of stroke patients have somatosensory impairments that influence prognosis and rehabilitation outcomes. Roughly 78% of these patients report a loss of activity [21].

Daily activities require the simultaneous combination of motor tasks and cognitive functions, such as maintaining postural control, standing, or walking [22]. After a stroke, these dual-task abilities often fail but can be restored with specific rehabilitation training [23,24]. Effective rehabilitation strategies that can improve balance, gait, autonomy, and reduce the risk of falls during dual-task activities are crucial.

The literature underscores the positive impact of dual-task exercises in stroke recovery, but few studies have combined this strategy with proprioceptive training. It is established that proprioceptive rehabilitation aids in recovering walking autonomy, and dual-task exercises reduce the risk of falls during ADL, but the literature offers little guidance on how to effectively combine the two techniques, how long to train, and which activities may influence outcomes [25].

Furthermore, there is currently a lack of consensus on what constitutes proprioceptive exercises and training. This ambiguity hinders research and necessitates a clear definition of proprioception. For instance, Aman et al. [25] defined proprioceptive training as exercises that stimulate the use of somatosensory signals like proprioceptive or tactile afferents, and recommended combined treatments for the best results.

Cognitive and motor dual-task exercises positively influence gait and balance in stroke patients, notably improving gait parameters, such as speed, stride length, cadence, Berg balance scale scores, center of pressure sway area, results of 2- and 6- minute walking tests, 10-m and 400-meter walking tests, and functional independence measure (FIM) [26].

2.1.1.2. Materials and methods

The aim of the first two projects is to demonstrate the effectiveness of dual-task proprioceptive training after stroke.

Indeed, in clinical practice, one aim of stroke rehabilitation is to improve proprioceptive skills to prevent falls during dual-task activities. Identifying the most effective strategies from the literature to restore balance, coordination, and autonomy in ADL can aid clinicians.

A systematic review aims to demonstrate the effectiveness of dual-task proprioceptive training on gait parameters in patients with chronic post-stroke conditions [2].

The other aims to define the proprioceptive strategies combined with dual-task training for treating imbalances and improving postural balance and gait after a stroke. We collected data from the literature about rehabilitation outcomes, goal achievements, duration, intensity, and types of proposed proprioceptive training combined with dual-task exercises in stroke patients. A secondary aim is to guide clinicians in designing rehabilitation protocols by adopting the most effective strategies reported in current literature [1].

2.1.1.2.1. Search Strategy

A literature review was conducted using PubMed, Cochrane Library, Scopus, and Web of Science databases. The following specific terms were used: "stroke" AND "proprioception" OR "proprioceptive" AND "rehabilitation" OR "training" OR "exercises" AND "dual-task" OR "task-performance". We added the keywords "gait analysis" OR "quantitative gait" OR "gait parameters" for the review about gait parameters.

The reference lists of included studies were checked for additional eligible studies not identified by the search. The review period was from January 2020 to February 2022. There were no publication date restrictions, thus the search included articles published between 1963 and 2021. All articles identified in the search were evaluated.

2.1.1.2.2. Selection Criteria and Data Extraction

Studies were included if they met the following criteria: (1) original English language articles on imbalance related to stroke, (2) treated with proprioceptive training, and contextual dual-task exercises, (3) subjects with confirmed stroke diagnosis. The proprioceptive exercises included in the review presented the following characteristics: (1) keeping balance in treadmill, considering the need to stimulate proprioception in maintaining the pace of walking based on the tuning of the mobile platform and adapting the gait at the proposed tasks [16,23,27,28,29,30,31,32]; (2) maintaining standing balance on an unstable balance pad [24] or during the overground walking, defined as whole-task practice involving propulsion forward, backward, or sideways, or up and down stairs [33,34,35,36,37], and changing speeds [38], also with wearable ankle weights [39] or different resistances during gait (i.e. with elastic band between legs) [40], or tilting bodies and shifting weight side to side during virtual reality games [41], aquatic game [42]; (3) proprioceptive neuromuscular facilitation techniques [43]. Both cognitive and motor dual-task exercises were included.

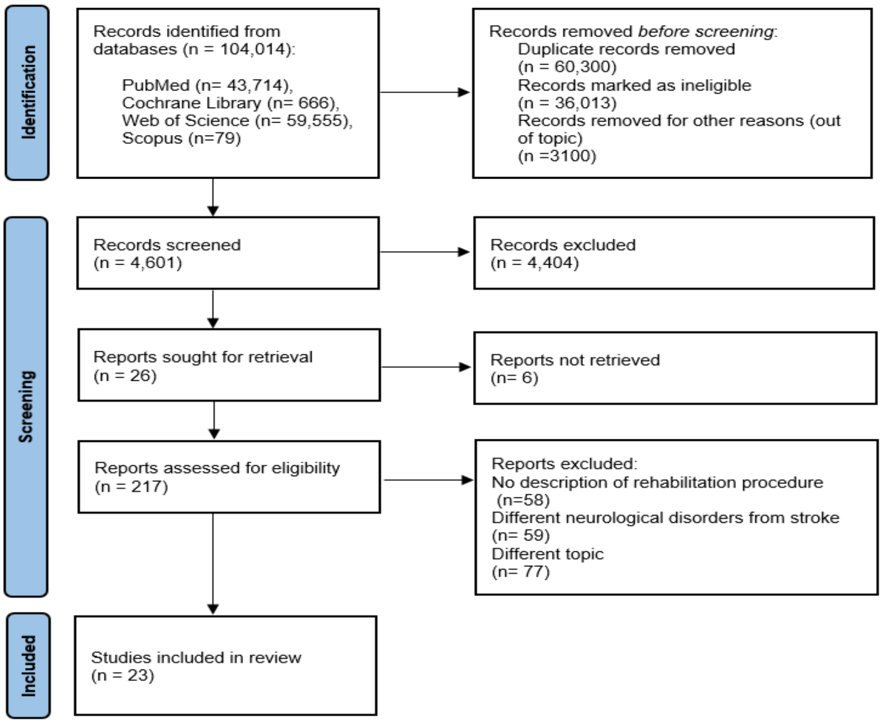
The exclusion criteria were: (1) animal studies, (2) participants with other neurological diseases apart from stroke, (3) other rehabilitation techniques, and (4) all remaining duplicates. (5) Grey literature and unpublished data were not considered.

To assess relevance based on predetermined inclusion criteria, two authors independently performed data extraction, screened titles and abstracts, and collected information. In case of disagreements, consensus was reached through discussion between the authors, with other authors consulted if necessary. Titles and abstracts were initially screened, followed by full-text assessments. A large number of papers that did not focus on proprioception or proprioceptive training were excluded. The Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines [44] and the Participants, Interventions, Comparison, Outcome, and Study Design (PICOS) [45] criteria were followed.

The systematic review was registered in the PROSPERO platform with the registration number CRD42021276239 (Proprioceptive and Dual-Task Training: The Key of Stroke Rehabilitation, A Systematic Review) [1].

The Figure 1 describes the review process of the systematic review about proprioceptive and dual-task training in stroke patients [1].

Figure 1 Review process of the systematic review about proprioceptive and dual-task training in stroke patients



The researches described their specific proprioceptive rehabilitation protocol with concomitant dual-task activity comparing it with other exercises: single-task motor exercises, such as gait training [27,34,38,43] or anaerobic exercises with elastic band [40], a combination of strengthening exercises and gait training [39], bodyweight exercises performed as self-guided rehabilitation at home [33], and balance training with single-task proprioceptive exercises [16,17,35,36,41,46]. Specific rehabilitative protocols such as neurodevelopmental treatment [46] were compared with dual-task proprioceptive training. Cognitive and motor dual-task exercises were compared each other [23,24]. Motor dual-task exercises with different rehabilitation protocols were compared with each other [42]. Only one article compared the results between motor dual-task exercises and no rehabilitation training [37].

The effectiveness of motor dual-tasks was investigated in most articles, with a high variability of dual-task activities (Table I). Cognitive dual-task training was considered in 5 articles [27,33,40,41]. Cognitive and motor dual-task training were compared in very few articles [23,24]. Cognitive and motor task exercises were conducted separately but in the context of the same rehabilitation program in the same group of patients in 4 articles [24,41,43,47].

Even if a quantitative analysis was not possible for the heterogeneity of the duration and intensity of the training, the measures most used to understand the effectiveness of proprioception and dual-task training were the spatio-temporal gait parameters, the balance scales, such as Activities-Specific Balance Confidence Scale (ABC) [48], and Berg Balance

Scale (BBS) [49] and the scales that predicts the risk of falls and the ability/autonomy in walking, such as Timed Up and Go Test (TUG) [50], 10-Minutes Walking Test (10-MWT) [51], and Functional Ambulation Category (FAC) [52].

A final analysis was carried out independently by 2 researchers to assess the methodological quality of the full texts that met the eligibility criteria. Depending on the type of research study, different tools were used. The papers included in this review are randomized controlled trials (RCTs), retrospective, prospective, and observational studies, and the scales used were as follows: PEDro (Physiotherapy Evidence Database) [53] and an adapted Sackett's level of evidence scale [54] from the strongest (rating =1) to weakest (rating =5), where ranked RCTs are considered the highest level and case series or expert opinions are considered the lowest level.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines for systematic reviews were used to evaluate the quality of the results [55,56,57,58,59].

2.1.1.2.3. Risk of bias

The authors independently assessed the risk of bias in the included studies as low, moderate, unclear, or high risk by considering the characteristics of the Cochrane risk of bias tool [60] and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I), according to Cochrane methodology [61,62]. The points of risk of bias include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Due to the heterogeneity and non-uniformity of the data in the included studies, the results were summarized descriptively.

2.1.1.3. Results

2.1.1.3.1. Variations in Experimental Conditions Across the Studies

It is worth noting that none of the study groups were homogeneous in terms of general clinical features such as clinical presentation, types of gait analysis, balance parameters, and scales examined. A wide variation also existed among the studies regarding the disease duration, timing of the initial imbalance examination, treatment duration, and the follow-up period post-rehabilitation. On the other hand, the studies showed homogeneity in the type of patients and their disease, as well as the rehabilitative strategy.

Table I. Rehabilitation programs after stroke for postural imbalance, proprioception and dual-task training. Characteristics and outcomes of studies included in the systematic review, according to PICOS criteria for inclusion of studies.

Authors, yr	**Study Design**	**Sample size, y**	**Months after stroke**	**Outcomes measure**	**Rehabilitive therapy**	**Duration therapy**	**Exercises description**	**Results after therapy**
Ada 2003 [33]	CLT	A: 13 p B: 14 p 66±11 y	>6	Walking speed, distance, step length, step width, cadence, SA-SIP30	A: cognitive task and walking program B: home exercises	3 d/w, for 4 w	Cognitive task at treadmill and overground walking program for 30 min. Proprioceptive group walked around an outdoor circuit, such as curbs, slopes, stairs and rough terrain, while performing a cognitive dual task. The cognitive task consisted of matching the word "red" with the response "yes" or the word "blue" with the response "no". For the control group: home exercise program, such as stretching and strengthening exercises of lower limbs, training of balance and coordination.	Effectiveness of treadmill and overground walking training. Gain of 18 cm/s in stroke patients
An 2014 [23]	CLT	A: 12 p B: 12 p C: 12 p -	Chronic stroke	STI, WDI with open and closed eyes, TUG, FSST, 10MWT	A: motor DT gait training B: cognitive DT gait training C: motor and cognition DT gait training	3d/w, for 8 w	15 min of walking on the treadmill, with motor or cognitive tasks or both types of tasks (30'). The motor tasks included: "tossing up and catching a ball', 'rehanging loops on different hooks', 'doing up buttons after unbuttoning', 'holding a cup of water without spilling it', and 'receiving and returning a cup of water'. Dual cognitive tasks included: 'discerning colours', 'mathematical subtraction', 'verbal analogical reasoning', 'spelling words backward' and 'counting backward'.	Motor and cognitive DT training improve motor performance and balance and gait abilities

Baek 2021 [27]	CLT	A:17 p B: 17 p -	Chronic stroke	Gait parameters (speed, stride, variability, and cadence), CRR, DTC, FES	A: gait training on a treadmill and cognitive task exercises at the same time B: separately, before gait training on a treadmill, then cognitive task exercises	2 d/w, For 6 w	60 min of treadmill training with a cognitive task: serial subtraction by three from two-digit numbers randomly selected	Dual-task gait treadmill training was more effective in improving gait ability in dual-task training and dual-task interference than single-task training involving gait and cognitive tasks separately in subjects with chronic stroke.
Cho 2015 [29]	CLT	A: 11 p 60.0 y B: 11 p 58.6 y	Chronic stroke patients A: 273.9 d B: 263.9 d	Spatio-temporal gait parameters: speed, cadence, step and stride length	A: virtual reality training with cognitive task B: virtual reality treadmill training	5d/w, for 4 w	The standard rehabilitation program consisted of physical and occupational therapies. 30 min/session of treadmill and cognitive task (memory, arithmetic, verbal task)	Effectiveness of virtual reality training with cognitive Load L on walking function under the dual task condition.
Choi 2014 [43]	CLT	A: 19 p 49.1 11.9 B: 18 p 49.2±7.05 y	18.2±5.7	TUG, sway velocity	A: cognitive-motor dual-task B: single-task training	3 d/w, for 4 w	Dual cognitive-motor task group performed rehabilitation for 15 min with a random auditory cue while walking on a treadmill. The sound of the bell was the auditory cue sign indicating that the participants should move the circle ring from side to side. The	Cognitive and motor dual-task training and auditory cues improved balance

							single-task group walked on the treadmill. Conventional physical therapy included progressive resistance exercise and postural control, neurodevelopment, and occupational training, Brunnstrom movements, proprioceptive neuromuscular facilitation techniques.	
Fishbein 2019 [28]	CLT	A: 11 p B: 11 p 65.2±9 y	>12	10 MWT, TUG, FRT LRT-L/R, ABC, BBS	A: DT training B: single-task treadmill walking	2 d/w, for 4 w	Mobilization and flexibility exercises for 8 min and walking around for 3 min, treadmill for 3 min. Subsequently, the single-task group walked for 20 min, the dual-task training group, while walking for 20 min, trained with 3 virtual games: hit the virtual ball, touch the virtual boxes, clean the virtual windows	Improvements in BBS, FRT, LRT-L/R, 10 MWT, ABC in A group; in gait variables. No changes in TUG.
Her 2011 [24]	RS	A: 12 p B: 13 p C: 13 p 64.8 ±5.2 y	>12	BBS, FIM, centre of pressure	A: MDT B: CDT C: MCDT	3 d/w, for 6 w	Group A: Exercises of motor tasks for 30 min, such as exchanging a ball, receiving of a ball with a basket, bouncing a ball on the floor, holding a glass with water and exchanging a water glass while maintaining balance on an unstable balance pad. Group B: Exercises of cognitive tasks such as counted backwards, calculated two subtractions, called the correct names of objects, and recited words in reverse order while maintaining balance. Group C: Motor and cognitive exercises with postural control task.	To obtain improvement in balance and gait both motor and cognitive DT were needed, not only motor or cognitive DT alone
Hong 2020 [40]	CLT	A: 8 p 56.6±8.7 y	>6	TUG, BBS	A: CDT B: general task group	3 d/w for 4 w	Exercises with a cognitive task for 30 min. The program consisted in maintaining a	Cognitive task training is a more

		B: 9 p 66.2±11.5 y					standing posture, while moving the lower extremity of the less-affected side toward the 3 flexion directions of the hip joint and then moving it back in place.	effective intervention method to improve balance and gait ability after stroke
Iqbal 2020 [39]	CLT	A: 32 p 58.2±7.13 y B: 32 p 58.8±6.13 y	Chronic stroke	Step length, stride length, 10MWT, TUG, cycle time, cadence	A: motor dual-task training B: conventional training	4 d/w for 4 w	Motor dual-task with exercises were conducted for 40 min. Slowly walking backward, sideways, and forward on a smooth surface while holding a 100gm sandbag	Conventional physical therapy and dual-task training effectively improved gait ability of chronic stroke patients, who showed a significant improvement in all spatial and temporal gait variables
Kannan 2019 [41]	CLT	A: 13 p B:12 p 59.2±6.3 y	>3	TUG, 6MWT, ABC, BBS	A: high-intensity, tapered motor and cognitive rehabilitation B: conventional balance rehabilitation	10 sessions, for 6 w	The cognitive tasks and proprioceptive exercise included four Wii-fit games played for 5 min. The control group performed balance training exercises for 90 min: 10 min of stretching, 15 min of functional stretching, 35 min of balance training, 10–15 min of treadmill walking. The cognitive tasks include: training for semantic memory (i.e. recite as many types of animals as they could within the time limit provided), Verbal fluency (i.e. participants recited words that began with the letter provided, such as “A”, while avoiding	Effectiveness of cognitive and motor rehabilitation in improving balance control and cognition

							saying proper nouns), abstract memory (i.e. participants completed phrases according to the relationship of the cue in the sentence), repetition of letters.	
Kim 2013 [34]	RS	A:14 p B: 15 p 56.4±12.3 y	7± 2.4 m	Cadence, speed, step time, cycle time, step length, stride length	A: conservative physical therapy B: dual-motor task training	5 d/w, for 4 w	Neurological developmental treatment for 30 min. The motor dual-task training included passive and active resistance exercise and exercises of coordination, motor sensation, and balance. The proprioceptive neuromuscular facilitation lower limb patterns consisted of: flexion-adduction-external rotation knee flexion or extension-adduction external rotation knee extension. Dual task: rising from a chair from the sitting position while picking up plastic cups that lay in front of the feet, then slowly walking forward, sideways, and backward on a flat surface while holding a 100-g sandbag against to the affected wrist and going up and down a ramp or stairs while transferring cups from tables of different heights located beside the ramp or stairs in consecutive order.	Improvement in temporal (cadence, speed, step time, cycle time) and spatial parameters (step length, stride length) in a DT group
Kim 2014 [38]	RS	A: 10 p B: 10 p 68.5±7.8 y	17,9±13	Stroop test, TUG, 10MWT, F8WT	A: traditional rehabilitation program B: traditional rehabilitation	A:5 d/w 1 w B:3d/w, 4 w	Motor dual task training was conducted for 30 min and consisted in words written using inks of various colours, and having the subjects state the colour of the ink and gait tasks that included walking on a level surface, walking while changing gait speeds, walking with vertical	Improvement of cognitive skills and gait after DT training

					program + DT training		or horizontal head turns, walking with pivot turns, stepping over or around obstacles, and walking up and downstairs.	
Kim 2016 [46]	RS	A: 10 p B: 10 p 68.5±3.1 y	10.9 ±1.1	BBS, 5 Times Sit-to Stand Test, Functional Reach Test, TUG, 10 MWT, FGA	A: neurodevelopmental treatment + aquatic dual-task training B: neurodevelopmental treatment	5 d/w, for 6 w	Aquatic motor dual-task training, for 30 min a day, included stability exercise, such as standing with eyes closed, stability exercise while playing catch with the therapist, walking 10 m at a comfortable speed, and walking 10 meters at a comfortable speed while holding a 200-mL cup of water.	Improvement in balance and gait after aquatic DT training
Kim 2018 [30]	CLT	A: 13 p 52.62 ± 9.84 y B: 13 p 56.15 ± 10.82 y	Chronic stroke	Speed, cadence single support time, stride length 10-MWT	A: progressive treadmill cognitive dual-task gait training B: conventional treadmill gait training	5d/w, for 4w	30 min. of treadmill exercises with cognitive dual task: speaking numbers task, arithmetic subtraction, memory task, verbal fluency	Progressive treadmill cognitive dual-task gait training had a positive influence on the gait and clinical gait
Lee 2015 [17]	RS	A: 18 p B: 18 p 28 p < 65 y 8 p > 65 y	<11.5±1.9	BBS, TUG, joint position sense	A: Motor imagery exercises for 5’ and proprioceptive rehabilitation for 25’ B: Proprioceptive	5d/w, for 8 w	Motor image training and proprioceptive training for 30 min included exercises in a balance pad with 5 different tasks. Thes program included: standing with the support position of two feet, standing upright by moving both heels up and down. Stretching and eyes closed exercises, balance board exercises shifting the weight left and right, forward and backward to the maximum,	Improvement in K-BBS, TUG, weight bearing ratio, and joint position sense error in group A > B

					rehabilitation for 30’		sitting standing on a balance board.	
Meester 2019 [31]	CLT	A: 26 p 60.85± 14.86 y B: 24 p 62.25± 15.53 y	>6 months	SF-36, EuroQol-5D-5L, PASE, step activity.	A: traditional traidmill B: traidmill in dual-task	2d/w, for 10 w	30 min. treadmill program at an aerobic training intensity, with dual-task: listening task or talking about planning daily activities	Walking with specific additional cognitive distraction (dual-task training) might increase activity more over 12 weeks
Pang 2018 [35]	CLT	A: 25 p B: 28 p 61.2±6.4 y	75.3±64.9	ABC, Frenchay Activities Index, Stroke-specific Quality of Life Scale	A: DT balance/mobility training B: single-task balance/mobility training	1 d/w, for 8 w	For 60 min a week, the motor dual-task program, included walking combined with verbal fluency, and with serial-3-subtractions and the timed-up-and-go with verbal fluency.	After DT rehabilitation, improvement in speed, reduction of falls, no improvement in social participation and quality of life
Plummer 2021 [47]	CLT	A: 18 p B: 18 p	< 3 years	gait speed, cognitive task performance	A: dual-task gait training B: single-task gait training on cognitive-motor dual-task	3 d/w for 4 w	Cognitive task performance during walking included spontaneous speech, arithmetic word, backward spelling, working memory, random number, calculating time, backward number, naming opposites. The exercises lasted 60 min	Both single- and dual-task gait training improved single and dual-task gait speed but did not change the amount of relative interference.
Saleh 2019 [42]	CLT	A: 25 p B: 25 p 49.7±1.8 y	9.02±1.8	Stability index, speed, step length,	A: motor DT in water B: motor DT in land	3 d/w, for 6 w	The dual motor task training included exercises performed during walking: holding a ball, holding a 200 mL cup of water and standing on a balance board,	Improvement in anteroposterior and mediolateral

				time of support on limb			walking forward, walking sideway and walking backward in to each condition, transferring coins from one pocket to another. The exercises lasted 45 min	stability index, speed, step length, time of support on the affected limb after water exercises
Subramaniam 2014 [36]	RS	8 p 51,75 y	6.1±4	BBS, TUG, IMI Reaction time, speed, maximum excursion, directional control	Virtual reality balance training in DT	110'/d, for 5 d consecutive	Cognitive motor dual task training the balance of virtual reality consisted of 110 min of balance board games: table tilt, tightrope, soccer and balance bubble, played while performing cognitive tasks, such as memory tasks, word list generation, sequencing letter-number, and question-answer and memory recall games.	Improvement in balance after DT rehabilitation
Timmermans 2016 [16]	CLT	A: 20 p B: 20 p -	>3 m	10 MWT, TUG, FAC, BBS, ABC	A: treadmill-based C-Mill therapy B: overground Falls program	2 d/w, for 5 w	A group performed cognitive motor dual task training: the C-Mill treadmill training program, that consisted of 1.5 h each session, twice a w for 5 w. It included to practice avoidance of visual obstacles, to practise accurate positioning of the foot on a step-to-step basis, walking towards to a regular or irregular sequence of visual stepping objectives, exercises to practice acceleration and deceleration while maintaining the position and a functional and interactive adaptability walking game. The FALLS program consisted in an overground therapy program to reduce the number of falls practicing a walking adaptability.	Improvement after C-Mill therapy with respect to FALLS program

							It included exercises to practicing obstacle avoidance, exercises to practicing foot placement while walking over uneven terrain, tandem walking and slalom. These exercises were performed as well as under visual constraints.	
Timmermans 2021 [32]	CLT	A: 16 p 52±13 y B: 17 p 59±10 y	>3 months	Speed, 10MWT	A: treadmill-based C-Mill therapy B: overground Falls program	2d/w, for 5 w	90 min/session. A group performed cognitive motor dual task training: the C-Mill treadmill training program. The FALLS program for the other group consisted in exercises of walking adaptability	Greater improvement in context-specific walking speed in C-Mill group
Yang 2007 [37]	CLT	A: 12 p B: 13 p 59.3 ±11.8 y	64.5±63.1	Speed, cadence, stride time, stride length, temporal symmetry index	A: Ball exercise program. B: No rehabilitation training.	3 d/w for 4 w	Motor dual task program: 30 min of gait training while manipulating 1 or 2 balls with a diameter of 45, 55, 85 and 95 cm and a basketball. The training program included walking while holding 1 or 2 balls on both hands, walking to adapt to the rhythm of bouncing 1 ball with 1 hand or both hands, walking while holding 1 ball on 1 hand and simultaneously kicking another ball from basketball into a net and walked while bouncing a ball with both hands. 3 motor tasks of simple walking included walking with buttoning task, and walking with the task of carrying a cup on a tray	Walking ability was significantly improved after training. Gain of ba29.74cm/s

Legend: Patients post stroke p, group A A, group B B, group C C, years old y, female f, male m, years y, days d, hours h, months m, minutes min, weeks w, Clinical trials CLT, Observational study OS, Dual-task DT, -task-specific motor relearning program MRP, electromyography EMG, retrospective study RT, Motor Assessment Scale MAS, the Sødring Motor Evaluation Scale SMES, Nottingham Health Profile NHP, stability test index STI, weight distribution index WDI, timed up and go test TUG, four square step test

FSST, 10 m walk test 10MWT, 6 minutes walking test 6 MWT, Berg Balance Scale BBS, Activity-specific Balance confidence ABC, Functional Ambulation Category FAC, Functional Reach Test FRT, Lateral Reach Test Left/Right LRT-L/R, One Leg Stand Test OLST, Intrinsic Motivation Inventory IMI, Functional Gait Assessment FGA, subjective index of physical and social outcome SIPSO, stroke adapted 30-item version of the Sickness Impact Profile SA-SIP30, Medical Research Council scale MRC, Fugl-Meyer Upper Extremity scale F-M UE, Functional Independence Measure scale FIM, correct response rate CRR, dual-task cost DTC, Fall Efficacy Scale FES, Rivermead Mobility Index RMI, Range of Motion ROM; Physical Activity Scale for Elderly PASE

2.1.1.3.2. Study Characteristics

The sample characteristics and design details of each included study are shown in Table I. The samples included subjects with chronic stroke, which occurred at least 6 months before the proposed rehabilitation. Only two articles included individuals who had suffered a stroke 3 months prior [16,41].

2.1.1.3.3. Summary of Findings: gait parameters

The most frequently analyzed parameters included gait speed, cadence, and stride time (temporal parameters), as well as stride length and step length (spatial parameters). The frequent study of these spatio-temporal parameters led to more accurate results, while less reported parameters, such as stride time, increased the difficulty of establishing consistent findings.

The data collected indicated that chronic stroke patients generally exhibited the following gait changes after dual-task proprioceptive training: an increased gait speed, cadence, stride length, and step length, and a decreased stride time compared to pre-rehabilitation measurements. Dual-task proprioceptive training positively influenced gait speed [27,33,34,37,42,47,63,64,65], cadence [27,33,34,37,39,63,65], stride time [37,63], stride length [27,34,37,39,63,64,65], and step length [33,34,39,42,64,65]. Single limb support time also improved after the training [37,42,65].

Cadence [27,33,34,39,63,65] and stride length [27,34,39,63,65] showed positive changes even with single-task proprioceptive rehabilitation alone. Furthermore, a regular training regimen of three days a week for four weeks positively affected speed [33,37,47,63,64] , cadence [33,37,63], stride length [37,63,64], and step length [33,64]. However, it was not possible to obtain more data regarding time variables due to the high heterogeneity of the studies.

2.1.1.3.4. Summary of findings: proprioceptive dual task training

Stroke patients exhibit an increased risk of falling due to diminished proprioception, balance, and dual-tasking ability. Various biomechanical measures have been used to determine the contribution of proprioceptive signals for balance control. These include latencies and amplitudes of electromyographic signals, joint kinematics or kinetics, and variables indicative of the body's postural sway centre of mass.

With respect to proprioceptive training, this means that an intervention may focus on one or both aspects of proprioception, namely the conscious perceptual or the unconscious sensorimotor aspect [25]. Thus, proprioceptive, and dual-task exercises play a crucial role in stimulating and promoting postural balance, gait, and quality of life, as well as reducing the risk of falls.

However, current literature describing these rehabilitation protocols is limited, with research showing excessive variability in the quality, intensity, and duration of training. Additionally, there are no specific protocols based on the severity of the imbalance. According to our research, the severity of postural imbalance and the risk of falling does not alter physicians' therapeutic approach.

The most common measures used to affirm the efficacy and usefulness of proprioceptive and dual-task training are spatiotemporal gait parameters, balance scales such as Activities-Specific Balance Confidence Scale (ABC), and Berg Balance Scale (BBS), and scales that predict the risk of falls and walking ability/autonomy, such as Timed Up and Go Test (TUG), 10-Minute Walking Test (10-MWT), and Functional Ambulation Category (FAC). However, differences in duration, intensity, fatigability, and treatment adherence made a statistical comparison of the results impossible. Moreover, fatigability levels and treatment adherence, potentially compromised by post-stroke depression, were seldom reported.

2.1.1.3.5. Proprioceptive Rehabilitation Program and Dual-Task Exercises

The selected articles are described based on the proprioceptive rehabilitation examined in each study. Table I presents the proprioceptive strategies combined with dual-task training as described in the current literature.

For proprioceptive exercises, most authors suggested maintaining standing balance on an unstable balance pad [24] or during overground walking(that is a whole-task practice involving propulsion forward, backward, or sideways, or up and down stairs) [33,34,35,36,37], changing speeds [38], with wearable ankle weights [39], or elastic bands between legs [40], tilting bodies and shifting weight side to side during virtual reality games

[41], and aquatic games [42]. Other authors described balance exercises on a treadmill, focusing on the need to stimulate proprioception in maintaining the pace of walking, based on tuning the moving platform and adapting the gait to the proposed tasks [16,23,27,28,29,30,31,32]. Proprioceptive neuromuscular facilitation techniques during dual-task training were also described [43].

Dual-task exercises performed concurrently with proprioceptive training included (1) cognitive activities, such as auditory [43] or visual cues [40] triggering actions, performing arithmetic operations [16,23,24,27,30], counting backwards [32], matching words [33], exercises of verbal fluency [35], memory tasks [29,36,41], exercise imagery [17], and discussing planned activities [31]; and (2) motor activities, such as writing [38], or moving an object (e.g., cups, coins, sandbags, balls) [23,24,28,34,36,37,42], avoiding obstacles [16], and Wii-fit games [41].

Most articles reported significant results after 3 days per week of training for 4 weeks [33,37,38,40,43]. Other articles suggested continuing exercises for more than 4 weeks, such as for 6 weeks [24,27,41,42] or 8 weeks [23]. Other studies presented their results after more sessions of training in a week: 4 days a week for 4 weeks [39], 5 days for 4 weeks [29,30,34], 5 days a week for 6 weeks [46], or 8 weeks [17]. Other authors obtained the same positive results with less exercises, only 5 days of training [36], or with less sessions in a week: 2 days a week for 4 weeks [28], or for 5 weeks [16,32], 8 weeks [31] only a day in a week for 8 weeks [35].

The duration of each session varied significantly, likely due to the resistance and the clinical conditions of the patients. Consequently, most studies suggested that each session should last 30 minutes [17,23,24,29,30,31,33,34,37,38] [40,46], while one article suggested 15 minutes per session [43]. Some authors proposed longer sessions of 35 minutes [28], 40 minutes [42], 60 minutes [27,35,47], 90 minutes [16,32,41], or even 110 minutes [36].

The heterogeneity in the types of exercises and their timing precluded the formulation of a specific protocol for proprioceptive and dual-task exercises. Nevertheless, this combined training has proven to be highly effective in restoring balance during activities of daily living.

First topic of the PhD project

Impact of Stroke on Motor Function and therapeutical strategies

2.1.2. The effectiveness of goal-oriented dual task proprioceptive training in stroke patients: an observational study

2.1.2.1. Introduction

Stroke, a leading cause of disability, often results in significant balance and proprioceptive impairments that limit function and increase the risk of falls. These complications, present in 45 to 65% of patients [66], correlate negatively with motor and functional abilities. Compounding these challenges, multiple sensory impairments also contribute to an increased fall risk. Daily activities requiring simultaneous motor and cognitive functions pose additional difficulties for stroke survivors, further contributing to frailty and disability. The severity of somatosensory impairments, mobility interference during dual task activities, and balance impairments are predictive indicators of fall risk, and can help guide therapeutic strategies. The goal of rehabilitation is to improve not only patient autonomy but also balance, task performance, and to prevent falls.

The research aimed to evaluate the effectiveness of goal-oriented proprioceptive training in improving balance, autonomy, and fall prevention in subacute stroke patients [3].

2.1.2.2. Materials and methods

The study retrospectively [3] collected data from 35 subacute stroke patients who were hospitalized in an intensive rehabilitation facility from September 2021 to March 2022. These patients, who experienced an ischemic stroke event 3-11 weeks prior, were comparable in age, severity of symptoms, cognitive functionality, visual capability, and previous health condition. The study excluded two patients due to incomplete data, unstable clinical conditions during hospitalization, and comorbidities that disrupted the intensive rehabilitation program.

The patients' pain, functional autonomy, balance, and fall risk were assessed using the Numerical Rating Scale, Barthel Index, Tinetti Test, Berg Balance Scale, and Time Up and Go Test (TUG). For the TUG, patients performed the test under both single task and dual task conditions. Dual tasks included counting backwards while walking and carrying a half-filled glass of water while walking. These assessments were performed at admission and again at discharge after an average hospitalization period of approximately 60 days (Table II).

The patients underwent a 7-day rehabilitation program, which consisted of two daily sessions of goal-oriented proprioceptive training, totalling 3 hours per day.

For data analysis, the study used the R Statistical Software and the igraph package. Quantitative data, expressed as mean and standard deviation, were compared using a paired t-test. Correlations between the scales were determined using Pearson's and Spearman's coefficients. The necessity of mobility aids was ranked from 1 to 4 (1 being unnecessary, 2 for canes, 3 for walkers, and 4 for wheelchairs). A p-value < 0.05 was considered statistically significant.

Over two months, balance, autonomy, and fall risk were assessed in 35 patients.

Table II Characteristics of study participants

Characteristics of participants	**Subacute stroke patients in *dual task proprioceptive training***			**Subacute stroke patients in *single task proprioceptive training***				
Number of participants	17			18				
Number of women/men	9/8			11/7				
Age in years ± SD	74 ± 10.69			76±6.41				
Mobility aids	**At admission**	**At discharge**		**At admission**	**At discharge**			
autonomy with wheelchair	3	0		2	0			
autonomy with walker	3	7		2	6			
(antebrachial support)	3	2		5	3			
autonomy with cane (antebrachial support)	8	8		9	9			
Autonomy without aids								
Assessment scales	**Scores at admission**	**Score at discharge**	**Paired T-test Dual**	**Scores at admission**	**Score at discharge**	**Paired T-test single**	**Impaired T-test T1**	**Impaired T-test T0**
Barthel index	22.82 ±10.0	55.82 ±	**p<0.0001**	38.88 ± 10.50	79.44 ± 16.25	**p<0.0001**	p=0.5193	p=0.4440

		18.33						
NRS	3.0±3.31	0.3 ±1.4	**p=0.0026**	2.38 ± 1.57	1.27 ± 1.52	**p=0.0092**	p=0.0759	p=0.4973
BBS	14.41 ±15.03	39.59 ± 10.45	**p<0.0001**	13.38 ± 10.24	21.27 ± 14.47	**p=0.0001**	p=0.200	p=0.8145
Tinetti balance test	5.06 ± 5.52	12.29 ±3.58	**p<0.0001**	6.66±2.00	8.94±3.01	**p=0.0029**	**P=0.0052**	p=0.2705
Tinetti gait test	5.23 ± 4.60	8.59 ± 4.06	**p=0.0023**	6.94 ±2.75	9.44±3.71	**p=0.0093**	p=0.193	p=0.1972
Total score of Tinetti test	10.29 ± 9.11	20.88 ± 7.31	**p<0.0001**	9.22±4.75	18.38±6.48	**p<0.0001**	p=0.2929	p=0.6416
TUG in single task	48.54 ± 26.60	33.12 ± 14.95	**p=0.003**	37.11 ±18.13	31.77 ±17.75	p=0.1393	p=0.9907	p=0.1450
TUG in dual task	47.14 ± 23.18	33.79 ± 14.94	**p=0.0052**	37.21 ±11.18	35.41 ±10.43	**p=0.0020**	p=0.7102	p=0.1234

Standard deviation ±; Numerical Rating Scale NRS; Berg Balance Scale BBS; Timed up and go TUG; *Single task proprioceptive training group* Single; *Dual task proprioceptive training group* Dual; At admission At discharge T1

2.1.2.3. Results

Over an average hospitalization period of 59.82±2.72 days in a rehabilitation facility, 35 subacute stroke patients participated in a traditional rehabilitation program incorporating postural and core exercises, mobility training, occupational therapy, and goal-oriented proprioceptive training. 18 patients performed the proprioceptive training as a single task, while 17 patients also incorporated dual task exercises (Table III).

At discharge, statistically significant differences were recorded in both groups for (1) Barthel index (P < 0.0001), with the recovery of the autonomy in ADL; (2) Tinetti test (total score p < 0.0001, balance assessment p < 0.0001 in dual task group, p=0.0029 in single task group, gait assessment p = 0.0023 in dual task group, p=0.0093 in single task group); (3) BBS (p < 0.0001), with an improvement of balance; (4) dual task (p = 0.0052 in dual task group, p=0.0020 in single task group), and (5) TUG with single task exercises only for dual task group (p = 0.0035) with a reduction of the risk of falling. Comparing the two groups, balance, assessed with Tinetti balance assessment, showed a significant difference in dual task proprioceptive training group than single task group. Thus, the study showed that goal-oriented both single and dual task proprioceptive rehabilitation significantly improved balance, and gait and reduced the risk of falling, also during dual task conditions.

After rehabilitation, in dual task proprioceptive training group, the values of TUG in single and in dual task were associated and changed correspondingly (r=0.9867, p<0.0001). Moreover, a significant relationship was present between the total score of Tinetti test and (1) BBS (r=0.8382, p<0.0001); (2) TUG in single task (r=-0.5343, p=0.0271), (3) TUG in dual task (r=-0.5455, p=0.0235). Likewise, Tinetti gait test was significantly related to (1) BBS (r=0,7640, p=0.0004), (2) TUG in dual task (r=-0.4885, p=0.0466). Furthermore, Tinetti balance test was significantly related to (1) Barthel index (r=-0.5033, p=0.0394), (2) BBS (r=0.8443, p<0.0001), (3) TUG in single task (r=-0.5510, p=0.0219), (4) TUG in dual task (r=-0.5594, p=0.0196). Conversely, no correlation was recorded between Barthel index and (1) Tinetti gait test (r= -0.2629, p=0.3081), (2) total score of Tinetti test (=-0.3927; p=0.1189), (3) BBS (r=-0.3631, p= 0.1520); (4) TUG in single task (r= 0.3934, p=0.1182); (5) TUG in dual task (r=0.3563, p=0.1603). Likewise, no significant relationship was showed between BBS and (1) TUG in single task (r=-0.3762, p=0.1367); (2) TUG in dual task (r=-0.4012, p=0.1105); (3) total score of Tinetti (r=-0.4758, p=0.0536). Thus, after rehabilitation, the improvement of balance was related to the reduction of the risk of falling, (showed by the positive relationship between Tinetti test and TUG in single task and in dual tasks), but only partially to the recovery of autonomy (positive relationship between Barthel index and Tinetti balance test, but no significant between Barthel and BBS) (Table III).

A significant relationship was found between the use of mobility aids and (1) BBS (r=-0.625, p=0.0074); (2) Tinetti gait test (r=-0.602, p=0.0105); (3) total score of Tinetti test (r=-0.574, p=0.0160). Conversely, no significant relationship was found between the use of aids and (1) Barthel index (r=-0.0374, p=0.8865); (2) Tinetti balance test (r=-0,453, p=0.0682); (3) TUG in single task (r=0.375, p=0.1385); (4) TUG in dual task (r=0.400, p=0.1113). Therefore, these data highlighted a positive correlation between the use of aids and the recovery of balance (positive relationship of aids with BBS and total score of Tinetti test). Nevertheless, the use of aids did not improve autonomy (no significant relationship between aids and Barthel index), nor reduce the risk of falling (no significant relationship between aids and TUG in single task and dual task) (Table IV).

No significant correlation was recorded between the assessment in goal-oriented single task proprioceptive training.

Table III Rehabilitation program of about 2 months, for 6 days a week, except Sundays, organized in two sessions of 1.5 hours a day.

Traditional exercises 45 minutes twice a day	***Goal-oriented proprioceptive training*** 45 minutes twice a day
	Single task exercises
Passive exercises for the recovery of the range of motion in the joints of the involvement segments.	Exercises for balance on irregular, soft or unstable surfaces. Star Excursion Balance exercise.
Exercises of postural control during slow standing balance movements.	Exercises for feedback and feedforward control with external perturbation, mild pushes or visual, tactile and auditive cues.
Stretching of anterior and posterior kinetic chain.	Ability to adopt and maintain different postures to keep balance.
Recovery of ADL and IADL with occupational therapy.	Postural control during fast pointing movements. Changing direction or speed during fast pointing movements.
Techniques to improve muscle force: Core exercises, isometric exercises for arms and legs, Isometric for antigravity muscles, Concentric and eccentric training of the lower limbs, Closed and open kinetic chain exercises.	Keeping balance with rotation of trunk and during semi-squat on a soft pad. Proprioceptive balance pads: In sitting position In standing with support and assistance, Changing direction of movement (lateral or antero- to posterior) or free inclination in balance pad.
	Dual task exercises
Mobility and balance training: Exercises to support the body mass by lower limbs, Body weight shift and propulsion of the body in the intended direction, Basic locomotor rhythm, Gait training, Stepping.	Cognitive dual tasks: talking about planning or organizing a trip, talking about food or weather, praying, telling a story. Motor dual tasks: carrying a glass half full, moving an object from one hand to the other. Adapt the movement to changing environmental demands and goals.

Activities of daily living ADL; Instrumental activities of daily living IADL

Table IV Statistical results of the study

Assessment Scales	**Statistical correlations** ***Dual task proprioceptive training group***	**Statistical correlations** ***Single task proprioceptive training group***
Barthel index- BBS	r=-0.3631, p=0.1520	r=0.04943, p=0.8456
Barthel index – Tinetti balance test	r=-0.5033, **p=0.0394**	r= -0.08455, p=0.7387
Barthel index – Tinetti gait test	r= -0.2629, p=0.3081	r=0.1066, p=0.6737
Barthel index – Total score of Tinetti	r=-0.3927; p=0.1189	r=0.02170, p=0.9319
Barthel index – TUG in single task	r= 0.3934, p=0.1182	r=0.1837, p=0.4657
Barthel index – TUG in dual task	r=0.3563, p=0.1603	r=0.01795, p=0.9437
TUG in single task - TUG in dual task	r=0.9867, **p<0.0001**	r= -0.2182, p=0.3844
TUG in single task – BBS	r=-0.3762, p=0.1367	r=0.1224, P=0.6284
TUG in dual task – BBS	r=-0.4012, p=0.1105	r=0.07866, p=0,7564
Tinetti balance test – BBS	r=0.8443, **p<0.0001**	r=0.04883, p=0.8474
Tinetti balance test - TUG in single task	r=-0.5510, **p=0.0219**	r=-0.09165, p=0.7176
Tinetti balance test - TUG in dual task	r=-0.5594, **p=0.0196**	r=-0.07530, p=0.7665
Tinetti gait test – BBS	r=0,7640, **p=0.0004**	r=-0.01666, p=0.9477
Tinetti gait test - TUG in single task	r=-0.4758, p=0.0536	r= -0.2010, p=0.4238
Tinetti gait test - TUG in dual task	r=-0.4885, **p=0.0466**	r=0.05122, p=0.8401
Total score of Tinetti – BBS	r=0.8382, **p<0.0001**	R=0.01320, p=0.9585
Total score of Tinetti - TUG in single task	r=-0.5343, **p=0.0271**	r=-0,1579, P=0,5316
Total score of Tinetti test - TUG in dual task	r=-0.5455, **p=0.0235**	r=-0.005729, p=0.9820
Barthel index - use of aids	r=-0.0374, p=0.8865	r=-0.261, p=0.2950
BBS - use of aids	r=-0.625, **p=0.0074**	r= 0.000, p=1.0000
Tinetti balance test - use of aids	r=-0,453, p=0.0682	r=-0.103, p=0,6846
Tinetti gait test- use of aids	r=-0.602, **p=0.0105**	r=-0.0696, p=0.7837
Total score of Tinetti test - use of aids	r=-0.574, **p=0.0160**	r=-0.0683, p=0.7877
TUG in single task - use of aids	r=0.375, p=0.1385	r=-0.102, p=0.6862
TUG in dual task - use of aids	r=0.400, p=0.1113	r=0.102, p=0.6865

Berg Balance Scale BBS; Timed Up and Go TUG

The findings from this study suggest that goal-oriented proprioceptive training, whether executed with single or dual tasks, led to improved balance, increased autonomy in activities of daily living (ADL), and a reduced fall risk among subacute stroke patients. The evaluation of various scales at discharge revealed the specific rehabilitation goals that were achieved. For instance, the observed positive relationship between the Tinetti test and the Time Up and Go test (TUG) in the dual-task group indicated a reduction in fall risk due to improved balance. However, the absence of a significant correlation between the Barthel index and both the Berg Balance Scale (BBS) and the Tinetti test might explain why balance recovery only partially translated to increased autonomy. Furthermore, while the use of mobility aids was closely associated with improved balance, it did not significantly enhance autonomy or decrease fall risk. This suggests that the use of aids alone is insufficient to ensure safe mobility and gain autonomy; it only aids in balance improvement.

First topic of the PhD project
Impact of Stroke on Motor Function and therapeutical strategies

2.1.3. Botulinum Toxin in Post-Stroke Motor Deficits and the Potential of Experimental Antidotes for Botulinum Neurotoxin in Stroke Treatment

2.1.3.1. Introduction

Botulinum toxins, produced by Clostridium botulinum, are dangerous neurotoxins that can be lethal to humans causing botulism. However, in small quantities, they are used therapeutically to treat various conditions. Adverse reactions to these treatments can potentially reveal unnoticed neuromuscular impairments. These adverse events are rare and typically transient, and the only solution is to wait for the toxin's effects to subside.

Botulinum toxins, produced by Clostridium botulinum, are powerful neurotoxins causing potentially fatal neuroparalytic disease often acquired through ingestion of contaminated food. The toxins work by inhibiting the release of acetylcholine by presynaptic nerves in neuromuscular junctions, leading to muscle paralysis or respiratory arrest. Seven distinct botulinum neurotoxins exist (serotypes A-G), with serotypes A, B, E, and F causing most human botulism cases. Despite its toxicity, serotype A is used therapeutically for a variety of neurological disorders and cosmetic applications (known commercially as Botox). However, adverse reactions can occur, including both local and systemic effects, potentially revealing subclinical neuromuscular impairments. The effects and potential adverse reactions typically last 2-3 months.

Although cases of iatrogenic botulism are infrequently reported, transient weakness may not always be documented. This transient disability can negatively impact patients, making a drug that could limit the duration of these adverse effects highly desirable. Currently, the only strategy to deal with these effects is to wait and provide supportive care if necessary.

This study presented a strategy to inhibit the effects of botulinum neurotoxin type A (BoNT/A) as a potential treatment for botulism. Over 13 million compounds were screened through several analytical models, from which the ones with the highest affinity were chosen. The top four predicted compounds underwent molecular dynamics simulations for stability testing. The resulting compounds demonstrated potential inhibitory activities ranging between 316 and 500 nM, presenting a potential method to counteract botulism.

The paper focuses on developing small-molecule inhibitors for botulinum neurotoxin type A (BoNT/A). This toxin consists of a light chain and a heavy chain linked by a disulfide bond, with the light chain (LC) acting as a zinc endopeptidase that targets SNAP-25, a protein required for acetylcholine release. The design of sub micromolar inhibitors is challenging due to the large substrate enzyme interface area and the flexible nature of the enzyme. The paper also highlights efforts to find potential natural inhibitors and the use of zinc-chelating molecules [67].

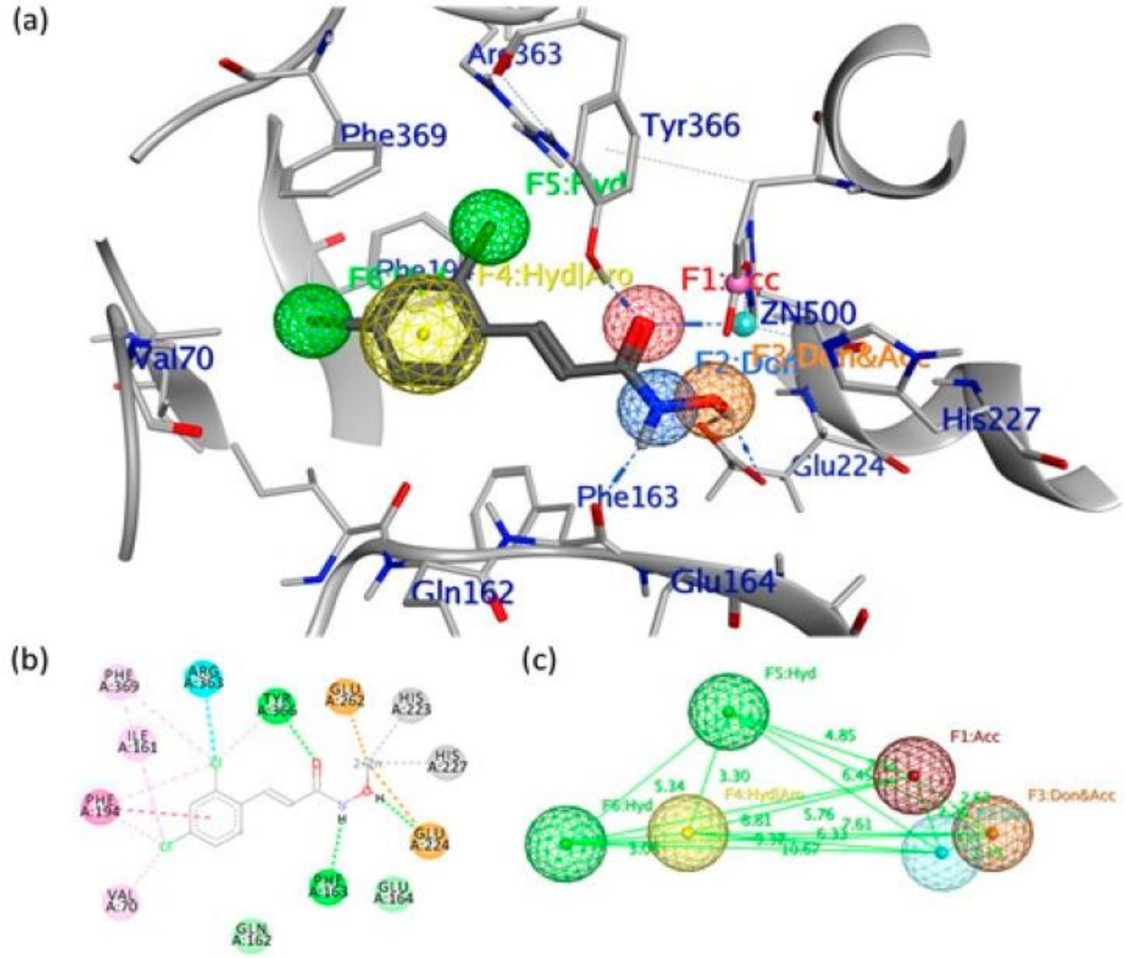
The authors utilized computer-aided molecular design (CAMD) and computational chemistry, integral aspects of modern drug design, to counteract the toxin's adverse effects. Structure-based, ligand-based, and virtual screening techniques were employed to support these efforts, both when 3D structural information on the target protein was available and when it wasn't. The paper aims to provide an alternative to merely waiting for the toxin's effects to pass and underscores the need to counteract even rare adverse drug effects.

2.1.3.2. Material and Methods

Previous efforts to identify inhibitors of the light chain of botulinum neurotoxin type A (LC/A) used a "3-zone pharmacophore" model, which led to the discovery of four inhibitors with moderate in vitro activity. However, none of these models found compounds more potent than the co-crystallized ones like (2E)-3-(2,4-dichlorophenyl)-N-hydroxyacrylamide (DCNHA) or 2-(adamantan-1-yl)-N-hydroxyacetamide [68]. As a result, the researchers decided to develop a pharmacophore model based on the characteristics of DCNHA, the most potent crystallized inhibitor.

The first step of their rational approach was to build a 3D pharmacophore model of the enzymatic cavity from the crystallized structure of the LC/A complex with DCNHA. X-ray data revealed that these inhibitors could occupy the catalytic cavity of the enzyme and coordinate the zinc atom. The model was generated using the Pharmit server [69], and it includes features like two hydrogen bond donors and acceptors, a hydrophobic/aromatic center, and two hydrophobic interactions (Figure 2).

Figure 2 (a) Pharmacophore model generated by the Pharmit server, including hydrogen bond donors (Don) (blue/orange spheres), negatively charged oxygen atom to represent a hydrogen bond acceptor (Acc) (red sphere), the hydrophobic centre (Hyd) (green sphere) and the aromatic centre (yellow sphere). (b) Binding site interactions between the light chain of botulinum neurotoxin type A (LC/A) binding pocket and the co-crystallized (2E)-3-(2,4-dichlorophenyl)-N-hydroxyacrylamide (DCNHA). (c) 3D spatial distribution of the six pharmacophore features.



This generated pharmacophore model was used to screen a large library of natural and synthetic compounds from four databases, totalling over 13.5 million compounds and 126.6 million conformers. The compounds with the lowest root mean square distance (RMSD) values, indicating the best matches with the pharmacophore model, were selected for further minimization and more accurate docking studies. The team also used a control dataset of 18 potent LC/A inhibitors to validate the entire procedure.

This process resulted in 182 structures, selected based on the pharmacophore descriptors, used for further docking studies and 3D-QSAR analysis.

The researchers applied a 3D-QSAR (Quantitative Structure-Activity Relationship) ligand-based filter to score the dataset of 182 compounds that were previously filtered through the pharmacophore model. The compounds were aligned to a 3D-QSAR model for the LC/A protein.

The QSAR model is based on the principle that molecules with similar field points (which include electrostatic, van der Waals, and hydrophobic potentials) would have similar interactions with biological targets, and thus, similar biological activity. The best-scored compounds were optimally distanced from the original model, suggesting that the original model effectively describes these molecules.

2.1.3.3. Results

The compounds selected from the pharmacophore model were also analyzed using a process called docking, using a software called Autodock4 implemented in YASARA. Docking is a method which predicts the preferred orientation of one molecule (usually a small molecule like a drug candidate) to a second (usually a larger one, like a protein) when bound to each other to form a stable complex.

Among the different series, there are three diastereoisomers, which are molecules that have the same molecular formula and sequence of bonded atoms but differ in the three-dimensional orientations of their atoms in space.

The selected compounds from the pharmacophore model were subjected to docking experiments, where they were virtually 'fit' into the LC/A protein structure using a software called Autodock4. Molecular Dynamics (MD) simulations were also performed on the first four structures to assess the stability of the compound in the active site of the protein.

The compounds showed differences in how they interacted with the active site of the LC/A protein. ZINC5008970 and ZINC5008966, for instance, formed different interactions with the site, leading to different levels of stability and binding energy. ZINC53720402 was unique in forming a bidentate (two-point) coordination with the zinc atom in the active site. ZINC5729284, like known cinnamyl hydroxamate inhibitors, also coordinated the zinc atom and showed excellent stability in the active site during the MD simulation.

MD simulations were used to measure how much the protein structure and ligand (the potential inhibitor compound) fluctuated over time, which indicates the stability of the ligand-protein complex. RMSD (Root Mean Square Deviation), a measure of the average distance between atoms of superimposed proteins, was calculated to analyze the structural stability.

An analysis of dynamic cross-correlation matrices (DCCM) and Root Mean Square Fluctuation (RMSF) further confirmed the stability of the catalytic region of the protein. Simulations were also performed on the free state (without the ligand) of the BoNT/A light chain to observe any variations.

Although the study primarily focused on LC/A inhibitors, due to the high structural similarity among different serotypes of botulinum neurotoxins, in silico studies were also conducted on BoNT LC catalytic domains of the B−G serotypes. These tests showed a high selectivity of these compounds for LC/A, confirming the effectiveness of the study's workflow.

Interestingly, compound ZINC5729284 showed decent affinity towards all serotypes, highlighting the possibility of developing broad-spectrum inhibitors against iatrogenic botulism.

To validate the entire process of identifying LC/A inhibitors, the researchers traced a set of 18 control molecules known as the CONTROL dataset. These molecules passed through the same screening process, and the predicted IC50 and Ki values were compared to experimental data. The results showed excellent correlation, confirming the accuracy of the procedure.

The ADMET studies predicted that most of the molecules would be absorbed in the gastrointestinal tract, but none would passively cross the blood-brain barrier. Some of the compounds were also predicted to be effluxes from the central nervous system by a protein called P-glycoprotein.

When assessing the potential for oral availability, all compounds were predicted to have poor to moderate bioavailability due to less-than-optimal cell permeability and human gastrointestinal absorption. However, the compounds had a decent skin permeability, indicating potential for transdermal drug delivery.

The researchers also examined the volume of distribution and unbound fraction of the compounds, which are important for drug distribution and availability. The results indicated that the compounds could be distributed sufficiently within the body and a significant portion would be available in the plasma to interact with the drug target.

The compounds also showed good renal elimination, indicating the body's ability to remove the drug, and most compounds passed all toxicity tests. These results suggest that most of these compounds could potentially be developed into drugs with further studies and manipulations.

2.2. Second topic of the PhD project

Exploring the Interplay of Stroke and Associated Complications: Insights into Infections and Sarcopenia

2.2.1. The Impact of Infections on Stroke Complications

COVID-19 and Clostridium (now known as Clostridioides) infections can both pose risks to stroke patients, potentially leading to various complications. It is associated with an increased risk of coagulopathy (abnormal blood clotting), which can lead to ischemic stroke.

COVID-19 has been associated with an increased risk of stroke, even in otherwise healthy individuals, but particularly in those with pre-existing cardiovascular conditions. Moreover, as a respiratory virus, COVID-19 can lead to pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure, which can complicate stroke recovery.

Clostridioides difficile infection (CDI) is associated with antibiotic use, which is common in hospitalized stroke patients. CDI can cause severe diarrhea, leading to dehydration and electrolyte imbalances that can complicate stroke recovery.

2.2.1.1. Introduction

In rehabilitation wards, stroke patients may become infected with CDI during their hospital stay. The primary concerns are whether to continue rehabilitation despite the presence of CDI, the need to halt the spread of infection, and the need to control costs.

A European survey was conducted in 45 rehabilitation facilities to describe strategies for controlling the infection. It also referenced the recommendations for CDI management [70]. Of these facilities, 23 reported that the infection limited rehabilitation outcomes, and 19 excluded infected patients from their rehabilitation programs [71]. These results highlight a lack of consensus on whether training should continue during infection, regardless of symptom severity. A recent study showed that patients above 65 years of age had an increased mortality rate linked to CDI [72]. Age, coupled with other comorbidities, is a common risk factor for CDI and stroke, which explains the prevalence of stroke patients who develop CDI during their hospital stay.

2.2.1.2. Material and methods

Given the lack of consensus, this research investigates the appropriateness of continuing rehabilitation in stroke patients who have developed CDI. This observational, retrospective study's results, drawing from resources about stroke patients admitted to intensive inpatient rehabilitation between January 2018 and May 2022.

The patients in the study were comparable in terms of cause of hospitalization, age, comorbidities, and symptomatic onset (spastic hemiplegia without aphasia and disturbances in alertness and understanding). They had recently been admitted to a neurologic unit for an ischemic stroke in the previous two months. During their hospital stay, they underwent a three-hour-a-day neuro-rehabilitation program split into two sessions.

Thirteen patients developed CDI within the first week of hospitalization, and another 13 patients (control group) remained uninfected. The groups were comparable regarding their level of autonomy (Barthel score at admission p = 0.3980) (Table VI).

Table VI Characteristics of the two groups and statistical examination of the considered outcomes

Groups	**CDI group** (13 p)	**Control group** (13 p)
Age	78,53±12,0	79,3±8,48
Female/males	4 m, 9 f	4 m, 9 f
Causes of hospitalization	Ischemic stroke	Ischemic stroke
Comorbidities	COPD 1 Diabetes 5 Visually impaired 2 Hypertension 11	COPD 1 Diabetes 3 Hearing loss 1 Hypertension 12
Barthel index	13.84±8.69	16.53±7.07
	p=0.398	

Limitations in patient performance, levels of autonomy, and rehabilitation program outcomes were estimated using the Barthel index [73] and length of hospitalization. Specifically, length of hospitalization, the number of lost rehabilitation days, and psychological distress were considered factors influencing rehabilitative outcomes in CDI patients. The Conley [74], and Braden scales were used to assess fall risk and predict pressure ulcer risk, respectively [75].

2.2.1.3. Results

The results showed significant statistical improvements in the Barthel index at discharge compared to admission for both groups (for the CDI group p = 0.0005, for the control group p = 0.0009). No differences were found between the groups at discharge (P = 0.2071), indicating both groups improved their daily living activities due to rehabilitation, with no differences attributable to CDI.

The need for psychological counselling, associated with isolation in CDI patients, correlated with reduced adherence to rehabilitation. However, there were no additional requests for psychological counselling in the CDI group compared to the control group (p = 1.0000).

Patients with CDI continued their rehabilitation, taking note of feelings of tiredness or discomfort. As such, treatment duration was 57.84±22.65 days for the CDI group, with an interruption of 2.07±1.41 days. The length of hospital stay, and the number of lost rehabilitation days were higher in the CDI group than in the control group, but there were no significant differences related to infection or adverse drug events (length of hospital stay between groups p = 0.378; number of lost rehabilitation days between groups p = 0.2839) (Table VII).

Both the Conley and Braden scales showed no significant changes in both groups before and after rehabilitation, nor between the groups.

Table VII Length of hospitalization, lost days of rehabilitation and psychological referrals between CDI group and control group. Barthel index, Conley scale, Braden scale at admission and at discharge in CDI group and in control group., and between the groups.

Groups	**CDI group**	**p-value paired t-test CDI group**	**Control group**	**p-value paired t-test control group**	**p-value impaired t-test between the groups**
Number of days of hospitalization	57,84±22,65		46±21,20		p = 0,3785
Number of lost days of rehabilitation	2,07±1,41		1,07±0,95		p = 0,2839
Number of days of isolation	18,23±1,96				
Number of psychological referrals	1 pt		1 pt		p = 1,0000
Barthel at admission	13,84±8,69	**p = 0,0005**	16,53±7,07	**p = 0,0009**	p = 0,3980
Barthel at discharge	27,69±16,15		38,07±28,28		p = 0,2071
Conley at admission	4,69±2,42	p = 1,0000	3,69±1,41	p = 0,6727	p = 0,3806
Conley at discharge	4,69±2,68		3,69±1,41		p = 0,2905
Braden at admission	14,53±1,76	p = 0,2536	14,38±2,12	**p = 0,0395**	p = 0,8155
Braden at discharge	15,15±1,51		14,69±2,12		p = 0,4424

Legend: Clostridium Difficile Infection CDI; COPD Chronic Obstructive Pulmonary Disease; Males m; Females f; Patient pt

Between 2018 and 2022, stroke patients affected by CDI accounted for 1.95% of the total (13 CDI patients + 2 not included because they were transferred due to the severity of infection, out of a total of 767 neurological patients). This rate does not exceed the average reported in literature [71], suggesting effective hygiene and isolation practices.

Despite the limitations of the retrospective data collection method and the small number of patients, the study presents valuable insights due to the lack of guidelines and consensus on this topic.

Second topic of the PhD project

Exploring the Interplay of Stroke and Associated Complications: Insights into Infections and Sarcopenia

2.2.2. Sarcopenia in stroke

2.2.2.1. Introduction

The decline in muscle mass is a common occurrence with aging, typically associated with various conditions such as cachexia, malnutrition, and sarcopenia. Sarcopenia is the progressive loss of skeletal muscle mass and function, which can be particularly problematic for stroke survivors.

Sarcopenia in stroke may be associated with factors like immobilization, inflammation, and altered metabolism. Stroke survivors show an elevated prevalence of sarcopenia. Its prevalence in stroke ranged between 14% and 18% [76]. The presence of sarcopenia in stroke patients may impair functional recovery [77].

Diagnosis and therapy can be challenging in stroke survivors [78]. Interventions such as physical exercise and nutritional support might alleviate sarcopenia in stroke patients. A multi-disciplinary approach involving physical therapy, dietary adjustments, and possibly pharmacological treatments is often recommended. [78].

Sarcopenia can contribute to long-term disability and an increased risk of falls and fractures.

According to the most commonly used definition in the literature by EWGSOP2, sarcopenia is suspected when grip strength falls below reference cut-offs (<27 kg for men and <16 kg for women), while it is definitively confirmed with a concurrent decrease in muscle mass, typically assessed with the Dual Energy X-ray Absorptiometer (DEXA) technique (<7 kg/m2 for men and <5.5 kg/m2 for women) [79,80]. However, DEXA is relatively expensive and not always readily available or routinely used. Therefore, understanding whether the decline in muscle strength correlates with the decline in muscle mass is crucial for confirming the diagnosis and excluding alternative diagnoses in which only muscle strength is reduced [79,80].

In this context, early and highly accurate identification of individuals with sarcopenia is key to effectively reducing the incidence of sarcopenia and associated complications in the general population. This is especially critical in clinical practice in rehabilitation centers for predicting the success of rehabilitation treatment and in internal medicine centers for prognostic patient evaluation, given that sarcopenia is a significant factor for morbidity and mortality. Early identification of individuals at risk for sarcopenia allows for prompt treatment with increased chances of recovery even with non-pharmacological treatments, leading to significant cost reduction for the national health system. Therefore, a primary goal is to identify nearly zero-cost variables that do not require specialized laboratory tests but can effectively reveal a decline in a patient's muscle mass with accuracy like DEXA radiological technique.

The study aimed to create a low-cost sarcopenia screening tool using data from the National Health and Nutrition Examination Survey (NHANES) conducted in the US from 1999-2006. NHANES is a comprehensive dataset, which provided a large sample size of about 14,500 patients with complete information required for the calculation of the Dual Energy X-ray Absorptiometer (DEXA), the gold standard for sarcopenia screening.

2.2.2.2. Materials and methods

The study used the EWGSOP2 definition of muscle mass loss for diagnosing sarcopenia. The goal was to identify nearly zero-cost variables to detect muscle mass decline with an accuracy like that of DEXA.

The study population, drawn from the National Health and Nutrition Examination Survey (NHANES), provided a robust dataset spanning seven years (1999-2006) for the researchers to build their model. The NHANES dataset represents a cross-section of the U.S. population and provides a comprehensive account of the health and nutritional status of adults and children. The inclusion criteria for the study comprised of any gender patients, aged more than 18 years, and with complete information for the calculation of the DEXA. Exclusion criteria consisted of patients with missing data in one of the 38 variables of interest. The selection of these variables was based on their known significance in sarcopenia genesis and the availability of complete data.

To analyse and model the data, the researchers employed a state-of-the-art artificial intelligence technique, the Extreme Gradient Boosting (XGBoost) algorithm. XGBoost, based on decision trees, is a powerful machine learning method for classification tasks. The analysis aimed to derive a model from a dataset of 38 variables and compare it to the outcome of the DEXA technique for identifying individuals with muscle mass loss.

The variables, that provide a broad and comprehensive understanding of the patient's physical, health, and lifestyle conditions, include 1) age, 2) gender, 3) ethnic group, 4) citizenship status, 5) marital status, 6) person education level, 7) height (cm), 8) weight (kg), 9) maximal calf circumference (cm), 10) arm circumference (cm), 11) upper leg length (cm),

12) upper arm length (cm), 13) maximal thigh circumference (cm), 14) triceps skinfold (mm), 15) subscapular skinfold (mm), 16) systolic blood pressure (mmHg), 17) differential blood pressure (mmHg), 18) self-reported greatest weight (pounds), 19) osteoporosis/brittle bones, 20) high blood pressure, 21) smoked at least 100 cigarettes in life, history of 22) cancer or malignancy, 23) asthma, 24) arthritis, 25) coronary heart disease, 26) angina/angina pectoris, 27) heart attack, 28) stroke, 29) emphysema, 30) chronic bronchitis, 31) liver pathology, 32) general health condition, 33) physical, mental, emotional limitations, 34) level of physical activity each day, 35) Vigorous activity over past 30 days, 36) Moderate activity over past 30 days, 37) Muscle strengthening activities over the past 30 days, 38) Daily hours of TV, video or computer use.

The preliminary modelling phase included a learning dataset and a validation set for feature selection, i.e., identifying which variables did not significantly improve the model's predictive capabilities and could thus be omitted from the definitive model. Once these variables were excluded, an extended dataset was formed, comprising 14.535 patients.

In the final modelling phase, this extended dataset was randomly divided into definitive learning, cross-validation, and testing subsets. The learning set was used for training the model, while the cross-validation set helped in deciding the optimal hyperparameters of the model. The accuracy of the models was tested by applying various performance metrics on the definitive testing set. These metrics included area under the curve (AUC), positive and negative predictive values, and sensitivity and specificity at various cut-offs.

2.2.2.3. Results

The study conducted on the National Health and Nutrition Examination Survey (NHANES) data aimed at predicting muscle mass loss, a significant indicator of sarcopenia. It started with the 38 different variables under consideration, but after examining the preliminary dataset, it was found that only 16 out of these 38 carried considerable significance in predicting muscle mass loss. Out of these 16, thigh circumference (BMXTHICR) held the most substantial importance.

To do this, the researchers developed three different models: a complex model and two simpler models. The complex model utilized six anthropometric variables, which were thigh circumference (BMXTHICR), calf circumference (BMXCALF), arm circumference (BMXARMC), weight (BMXWT), height (BMXHT), and triceps skinfold (BMXTRI) (Figure 5). This model demonstrated an impressive performance with an Area Under the Curve (AUC) value of 0.93. The model was able to correctly predict 89% of patients with muscle mass loss (sensitivity), while also accurately identifying 82% of patients without muscle mass loss (specificity) (Figure 6).

Figure 5 Feature importance for all variables in the preliminary validation dataset. The red line represents the accuracy of the model, in the preliminary validation set, when the model is derived (using all patients of the preliminary training dataset) excluding all the features with a smaller importance parameter than a given feature. No statistically significant degradation of the accuracy is observed until the first 8 most important features are used, as schematically indicated by the dashed line. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

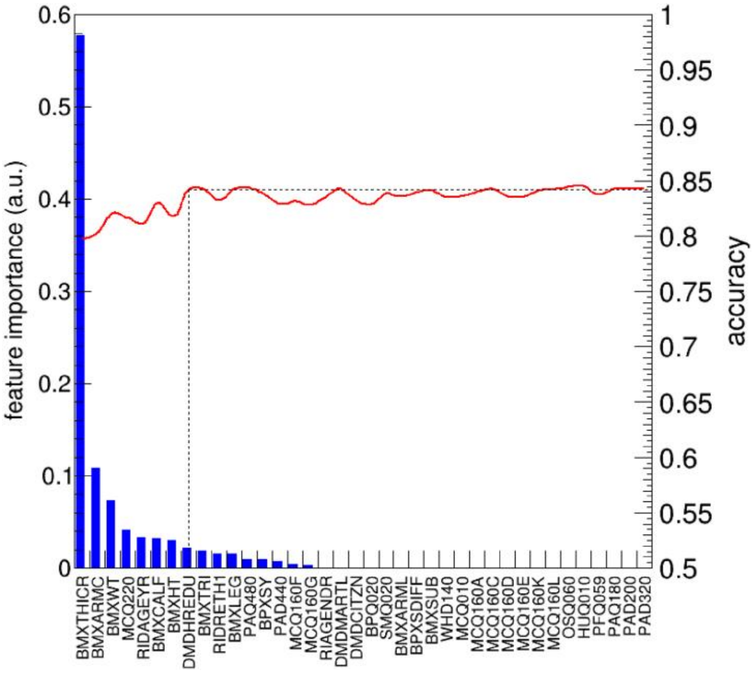
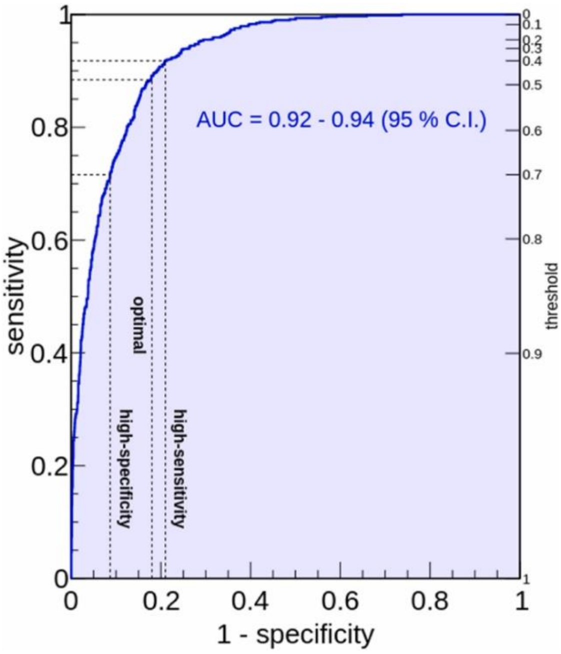


Figure 6 Receiving Operator Characteristic (ROC) curve for the most complex decision tree model proposed in this work. The range of AUC values (95% C.I.) is indicated. The model achieves an AUC of 0.93. For each trade-off between sensitivity and specificity, the corresponding threshold on the model output is shown (right vertical axis). Dashed lines indicate the position of the optimal trade-off, alongside with the high-sensitivity and high-specificity trade-offs (see text for additional details).

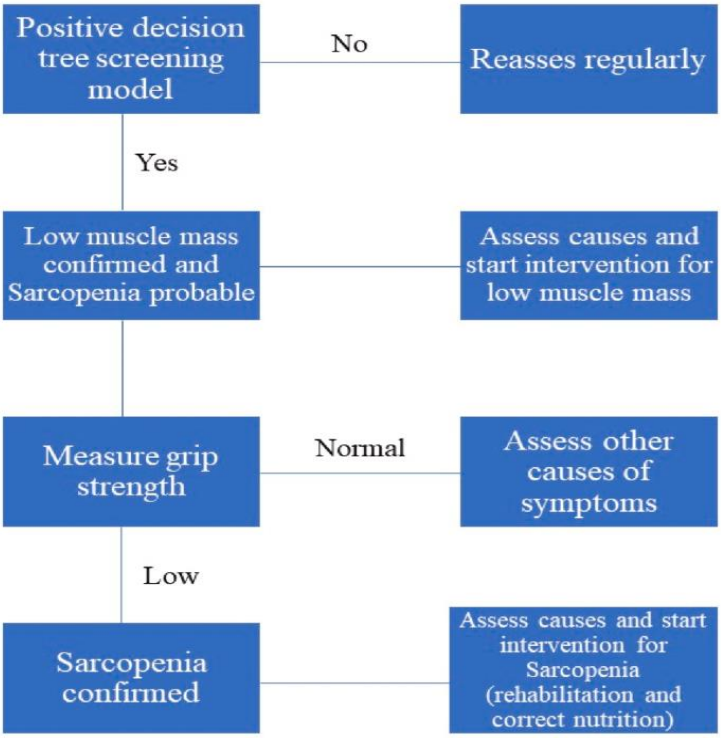


The two simpler models employed three and two variables, respectively. The three-variable model used thigh circumference, calf circumference, and arm circumference. The two-variable model included only thigh circumference and calf circumference. Both of these models achieved an AUC value of 0.89, which indicated a high level of performance. The two-variable model, despite its simplicity, displayed performance almost equivalent to the three-variable model, suggesting that the addition of arm circumference didn't significantly boost the prediction capabilities.

The results show that muscle mass loss prediction can be achieved with high accuracy, even when using a reduced number of anthropometric variables. This suggests the viability of using such simplified models for cost-effective and accessible early identification of sarcopenia, which can guide intervention and treatment.

The Figure 7 suggests the sarcopenia diagnostic algorithm for stroke patients.

Figure 7 Newly suggested sarcopenia diagnostic algorithm.


Positive decision tree screening model
No
Reasses regularly
Yes
Low muscle mass confirmed and Sarcopenia probable
Assess causes and start intervention for low muscle mass
Measure grip strength
Normal
Assess other causes of symptoms
Low
Sarcopenia confirmed
Assess causes and start intervention for Sarcopenia (rehabilitation and correct nutrition)

2.3. Third topic of the PhD project

Post-Stroke Dysarthria: A Multidisciplinary Approach to Rehabilitation

2.3.1. A Systematic Review of Measures of Dysarthria Severity in Stroke Patients.

2.3.1.1. Introduction

After a stroke, in the acute phase the prevalence of dysarthria is about 41.5%–53% [81]. According to Geddes et al. [82], the speech disorders due to stroke represent the third most common residual impairment. The prevalence of speech disorders is of 51% immediately after stroke, while after the acute phase the prevalence of the residual impairments spontaneously decrease at 27% [82].

This systematic review [7] defined the several methods to measure dysarthria due to a stroke and to better guide the physician to delineate a diagnostic protocol adopting the better strategies described in the current literature. We analysed all the approaches we found in the current literature to realize a guide to provide a common language to the multidisciplinary team such as physiatrists, otolaryngologists, neurologists, speech therapists, physiotherapists, nurses and neuropsychologists that have to treat stroke-related dysarthria. Our guide could help the multidisciplinary team to measure objectively and easily the severity of dysarthria and to assess the disorder and confirm the effect of treatment.

2.3.1.2. Evidence Acquisition

2.3.1.2.1. Search Strategy

The search was performed on the following medical electronic databases: PubMed, EMBASE, Cochrane Library and Scopus Web of Science. The review was conducted from 15 January 2020 to 22 February 2021. We searched for the following terms and keywords: "stroke" OR "ictus" OR "cerebral vascular accident" AND "dysarthria" OR "Speech and Language Disorders" AND "diagnosis" OR "assessment".

2.3.1.2.2. Information sources and database search

The systematic review and the meta-analysis are consistent with the PRISMA statement [44] and the MOOSE checklist [83]. Searches were conducted between January 2020 and February 2020 in the following databases: PubMed, Wiley Online Library Cochrane Library, EMBASE. The reference lists of related articles were also searched for eligible papers.

2.3.1.2.3. Selection criteria and data extraction

From 1981 to 2019, the database searches yielded 402 references for the search with the keywords “stroke” and “dysarthria” and “diagnosis” and 84 references for the search with the keywords stroke" and "dysarthria" and "assessment". whose titles and abstracts were screened by the reviewers. The papers remained for full text screening were 69 and the eligibility of the study inclusion was assessed independently.

Thirty-seven publications met the inclusion criteria and were included in the systematic review. Thirty-two articles were excluded for the following reasons: 12 involved individuals with aphasia or other speech problems different from dysarthria, 12 examined different topics from our aim, 8 did not included cases due to a stroke.

We included original articles about dysarthria in subjects with confirmed diagnosis of stroke. We excluded animal studies, participants with other neurological diseases or other speech impairment, such as aphasia. We also excluded all the remaining duplicates.

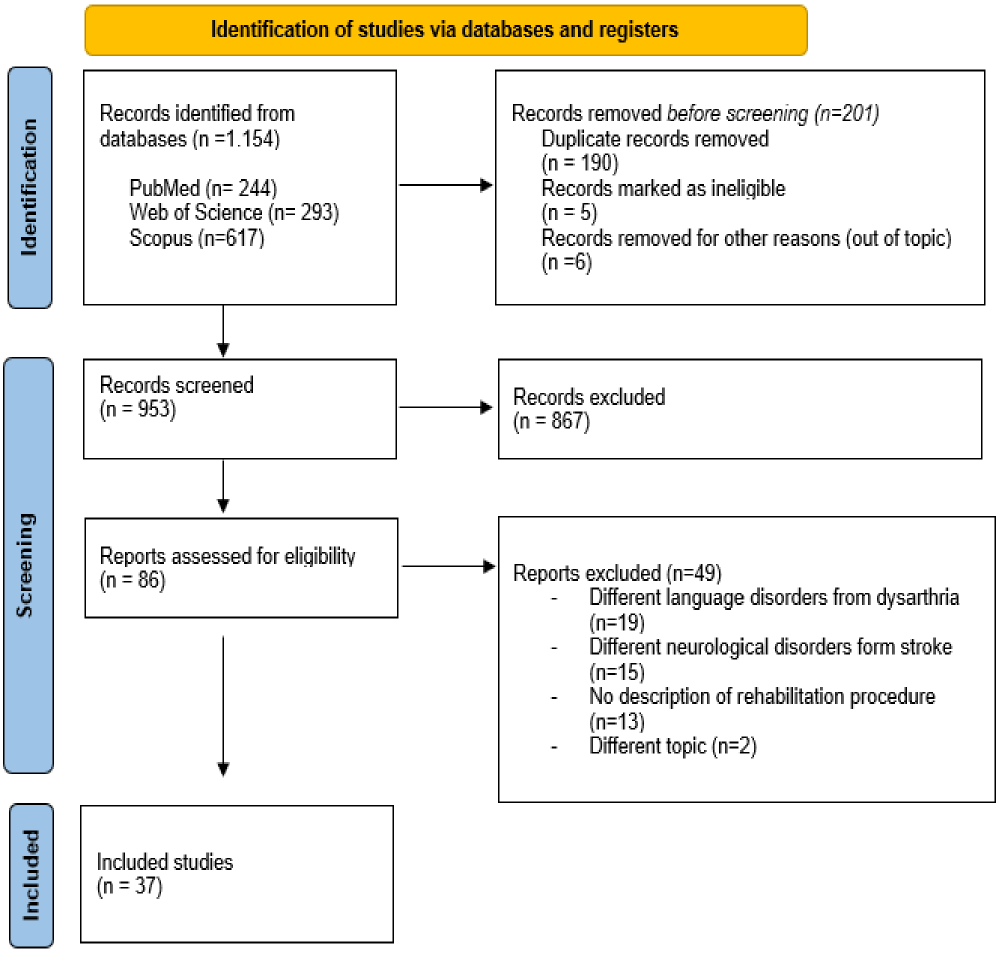
Two reviewers (C.R. and V.M.) independently screened the titles and abstracts from the initial search to identify relevant records and to identify eligible studies based on title and abstract. Selected full texts were then reviewed and included in the systematic review and in the meta-analysis, following the PRISMA protocol [44] and the MOOSE checklist [83].

2.3.1.3. Evidence Synthesis

2.3.1.3.1. Description of the studies

The number of studies yielded at each stage of the search for the meta-analysis and for the systematic review is displayed in Figure 8.

Figure 8 Flowchart of the process of initial literature search and extraction of studies meeting the inclusion criteria.



The qualitative information synthesis for each parameter was attributed to the following evidence levels according to the recommendations of the Oxford Centre for Evidence-Based Medicine: evidence from systematic review of randomised controlled trials (1a), clinical controlled studies (2a), case-control-studies (3a) and from non-systematic reviews (4).

2.3.1.3.2. Variations of experimental conditions across the studies

All study groups were not homogeneous for relevant general clinical features as clinical presentation, localization of the vascular lesion causing stroke, duration of disease, electronic device, kinds of diagnostic measures, voice parameters, severity of dysarthria, rehabilitation speech therapy, time of starting therapy, duration of treatment (Table VIII). The disease duration ranged from 6-35 months. A large variation existed between the studies regarding the duration of the disease, the time of the first examination of the dysarthria, the duration of the treatment, the period of follow up at the end of therapy. For this inhomogeneity of the sample, we could include in the meta-analysis only a few studies. For the meta-analysis' we considered the results of the dysarthria assessment at the baseline and immediately after treatment to compare homogeneous data.

Table VIII Treatment of dysarthria post-stroke: characteristics and outcomes of studies included in the systematic review.

Study Design	Sample size, years old	Localization vascular lesion	Outcomes measure	Dysarthria severity	Rehabilitation speech therapy	Start of therapy	Duration of treatment	Outcomes	Results after therapy
Retrospective study	6192 p	-	Best Dysarthria domains of NIHSS [84]	-	-	After 3 months since stroke	-	-	Dysarthria persisted in at least a quarter of people at 3 months following stroke.
Retrospective study	3 p 60.3 y	-	Scale ratings for intelligibility, pleasantness, orthographic transcription [85]. Changes in the vowel space. F0, PRAAT	Moderate	EST	1.16 m	4 w	20 w after therapy	Significant increase of speech intensity and of DIDC in the occlusion phase of voiceless plosives
RCT	A: 33 p 70 ± 11.4 y B: 36 c 75.5 y	-	COAST [86]. TOMA [87].	Severe	A: Speech therapy group B: No therapy group	Within the first 4 m post stroke	4 m 60’ 3 times/w	6 m after therapy	No evidence of enhancement with an early communication therapy

Retrospective study	24 p 63.5	-	Dysarthria interview [88]	Mild to severe	-	-	-	-	Psychosocial impact of dysarthria due to stroke
Retrospective study	24 p 34–86 y	-	Dysarthria interview [88]	Mild to severe	-	-	-	-	Psychosocial impact of dysarthria due to stroke
Case series	2 p	-	Clinical examination of velopharynx	Dysarthria and severe hypernasality	Nasal obturator with a one-way valve	-	-	After application of the device	Improvement of velopharyngeal dysfunction
Retrospective study	22 p	Hemispheric or brainstem stroke	MDVP. Word intelligibility test	-	-	-	-	-	Association between unilateral hemispheric stroke and voice disorder involving especially frequency perturbation parameters, amplitude parameters,

									and f0 variability.
Retrospective study	20 p 5 HC	-	Acoustic analysis of 6 words (coat, hail, sigh, shoot, row and wax) repeated 10 times	-	-	-	-	-	Reduced F2 slopes in p. The F2 slopes of only two words, shoot and wax, were significantly correlated with scaled speech intelligibility
Retrospective study	39 p 9 HC 23-91 y	Mild 6, moderate 2, severe 4	Repeated of 3 sentences (1) 'The blue spot is on the key', (2) 'The potato stew is in the pot', and (3) 'Combine all the ingredients in a large bowl' in 4 conditions: (1) 'high-adjusted', (2) 'high-unadjusted', (3)	-	-	-	-	-	Decrease in speech intelligibility when the stimuli were adjusted to have fixed intensity on the most intense vocalic nuclei of each word, while no significant change was found between

			‘low-adjusted’, and (4) ‘low-unadjusted’						‘high’ and ‘low’ presentation level conditions
Retrospective study	6 p 58.8 y	-	Acoustic measures with PRAAT: MPT, F0, jitter, shimmer, NHR, DDK.	-	AMSP	Within one year	30’ 12 sessions	At the end of therapy	Increase of MPT, F0, dB, SMR. Improve speech production and oral-motor function of speech
RCT	A: 10 p 69.4 ± 11.8 B: 10 p 68.8 ± 9.8 y	Unilateral middle cerebral artery infarction	Test of Articulation and Phonology. AMRs. Urimal Test of Articulation and Phonology [89]	-	A: rTMS group B: Sham stimulation group	Within the first 2 m	26.4 ± 15 d 30’, 5 d/w for 2 w	Immediately after therapy	Improvement in intelligibility in rTMS group
53.8 ± 9.5	A: 9 p Ischemic stroke	20.4 ± 28.3	APAC test [84]	-	-	-	-	-	APAC and a specific software HMM to assess

	B: 15 p Haemorrhagic stroke C: 100 p HC 44.6 ± 12.9								dysarthria severity
RCT	A: 50 p B: 50 p 40-80 y	-	FDA dysarthria assessment score, FDA speech breathing level, MPT, MCA, S/Z ratio, loudness level	-	A: traditional breathing training B: LQG	2 w–6 m after stroke	Once a day, 5 times a w, for 3 w	At baseline, 1 w, 2 w, 3 w after treatment	Effectiveness of LQG for improvement of speech breathing function and speech ability
Retrospective study	8 p 57.7 y	-	Word intelligibility test [90]. 7 points scale for effectiveness of communication [91]. DIP [92].	Moderate	Behavioural communication intervention	19.6 m	16 sessions, for 8 w	2 m after treatment	Improvement of communication effectiveness during conversation and of reading and word intelligibility after treatment
Case report	1 pt 69 y	Left hemisphere of frontal lobe	Rate, pause, intonation, single word phonetic	Severe	Behavioural communication intervention	7-9 m after stroke	16 sessions of 45’, for 8 w	8 w after therapy	Improvement of intelligibility

		and cerebellar hemisphere	transcription. FDA-2 [93]						
Retrospective study	19 p 68.8±12.9 y	- Right insula - Right and left external capsule, cerebellar / pons - Left posterior circulation - Left parietal - Right basal ganglia	QCLS, SIT, CEM. [91], CES, GHQ-12, SSKT [94].	-	A: Living with Dysarthria group	34.4± 26.7 m post stroke	8 sessions of 2h, one/w	At the end of therapy	Improvement in sentence level intelligibility
RCT	A: 16 p 62.8 ± 12.8 y B: 19 p 67.95 ± 12.1 y	-	CEM [91], SIT, FDA-II [93]	A: Mild 12 p Severe 7 p B: Mild 9 p Severe 11 p	A: behavioural, activity level practice B: the same of A +NSOMe	3 m post stroke	A: 10.8±7.09m 40’ once/w B: 9.3±5.12 m 40’ once/w Included 10’ of NSOMe	2 m post treatment	Improvement in lip and tongue movements
Retrospective study	4 p 31 y	-	MDVP dB SPL Vowel space area	Mild - Moderate	LSVT	9 m post stroke	16 sessions in 4 w	2 w after treatment	Improved voice quality

			AIDS [95]. MDVP: RAP and PPQ						
Retrospective study	30 p 62 y	-	RIPA-2 [96]	-	Mobile tablets at a mean 6.8 days from admission and used them for a mean 149.8 min/d	-	6 m	Mobile tablet technology is feasible in acute care	Individualized speech-language therapy delivered by mobile tablet technology is feasible in acute care
Retrospective study	30 p 65 y	-	Oral physical and dysarthria assessment [97]	-		25 m post stroke			Phonetic transcription of word and a taxonomy of error types in dysarthria after stroke
RCT	26 pt 69 y	-	TOMA [87]. COAST [86]. DIP [92]. FDA-II [93]	-	ReaDySpeech	-	14 m, 40’ session duration	-	Evidence for the feasibility of a RCT into the effectiveness of ReaDySpeech

RCT	n. 24 pt 69 y (37–99)	Anterior circulation: 9p Postrior circulation: 4p	FDA-II [93]. TOMA [87]. COAST [86]. DIP [92].	-	ReaDySpeech	-	14 m, 6 sessions of 40’ duration	-	Possibility of recruitment and retention in this trial of computerized therapy of acute stroke
Retrospective study	31 p 25-83 y 38 HC 21-76 y		Acoustic analysis during the pronunciation of /a, i, u, ɤ, y, o/	-	-	-	-	-	The deviations of the vowel acoustic features guide the rehabilitation.
Case report	1 p 79 y	-	9-point rating scale [98]	Moderate-severe	Palatal lift prosthesis + palatal augmentation prosthesis+ speech therapy	2 y and 5 m post stroke	3 times/w for 3 m	Immediately after treatment	Improving velopharyngeal incompetence
Case series	6 p 64.8 y	-	/pa/ and /ta/ AMRs, 5 point scale [99]	-	-	-	-	-	AMRs in individuals with spastic and ataxic dysarthria were significantly decreased, as compared to

									those in normal speakers
Retrospective study	2 p 46.5 y	-	7 points scale ranging [100]	Mild / moderate: 1 p Severe: 1 p	Be Clear	20 m post stroke	1 h, 5 times/w for 1 m	Immediately after treatment, 1-3 m after treatment	Improvement in speech intelligibility
Retrospective study	16 p -	-	FDA-2 [93]	-	VitalStim acupuncture + speech therapy	within 1 m post stroke	30’, once a d, for 28 d	Immediately after treatment	Improvement in Barthel index e FDA-2
Case series	12 p 74.7 y	Right hemisphere ischemic stroke	Alternating motion rate. 5-point intelligibility rating scale [101].	Mild and moderate	Oral motor exercises	-	45’ Twice/w for 2 m	Immediately after treatment	No improvement
Case series	8 p 70.2 y	-	Dysarthria scores [102].	-	Oro-facial and articulation exercises	3.7 w post stroke	10 w 10 session, 1/w 45’	10 w after of therapy	Improvement in speech intelligibility
Case report	n. 1 pt 33 y	Bulbar	SIT	-	CIDT	After stroke	2 m	12 m after stroke	Increased communicative participation
Case series	4 p 40.5 y	-	SIT, Waveform analysis, ROS.	Mild to severe	Vocal exercises and singing + speech therapy	< 18 m post stroke	30’, 24 sessions, 8 w	Immediately after therapy	Significant improvements in functional speech intelligibility.

									No improvements in rate of speech.
Retrospective study	16 p 16 HC 70.9 y p 70.3 y HC	-	Transducer system for lip force	Mild to severe	-	38.06 m post stroke	-	-	After stroke: deficits in maximum lip force, endurance of lip strength and rate of lip movements
Case series	1 p	-	Interviews	-	-	48 m after stroke	-	-	The impact of dysarthria in physical disability
Retrospective study	3 pt 48.3 y	- Brainstem - Left posterior circulation, middle cerebral artery	AusTOMs [103] AIDS [95] Participant self-report questionnaire [104] Communication Partner questionnaire [104]	Mild-moderate	LSVT	59.3 m post stroke	4 w	Immediately after therapy and 6 months post-therapy	Significant increase of vocal loudness, vocal frequency range, intelligibility

RCT	A: 13 p B: 13 p 48.6 ± 21.3 y	-	Acoustic measures	A: Mild / moderate 7 p, Moderate / severe 6 p B: Mild / moderate 7 p, Moderate / severe 6 p	A: TRAD B: LSVT	6 m post stroke	1 h/d, for 4 d/w for 4 w	Post-treatment and 6 m after stroke	Improvement in articulatory precision
Case control study	6 pt	Acute middle cerebral artery infarction	MDVP MPT, AMR-Pa, AMR-Ta, AMR-Ka, and SMR-PaTaKa	-	tDCS at 2 milliampere with 25 cm^2	-	30’, 5 times/w, for a total of 2 w	Immediately after treatment	Improvement of MPT, AMR-Pa, AMR-Ta, AMR-Ka, and SMR-PaTaKa
RCT	A: 10 p 73 y B: 11 -	-	COAST [86].	-	A: Early speech therapy B: no-therapy group	After 6 m post stroke	4 m	6 m after therapy	No significant benefit of early communication therapy

Constrained-Induced Dysarthria Therapy CIDT, year y, m males, w women, months m, weeks w, days d, hours h, patients p, controls c, number n, Frenchay Dysarthria Assessment second edition FDA-II, Dysarthria Therapy Outcome Measures Activity TOMA, Communication Outcomes After Stroke Scale COAST, Dysarthria Impact Profile DIP, Speech Intelligibility Test SIT, maximum phonation time MPT, rTMS repetitive transcranial magnetic stimulation treatment, Communicative Effectiveness Measure CEM, Randomised controlled trial RCT. A: group A, B: group B, healthy controls HC traditional dysarthria therapy TRAD, Lee Silverman Voice Treatment LSVT, transcranial direct stimulation tDCS, MDVP multi-dimensional voice program, fundamental frequency F0, noise to harmonics ratio NHR, diadochokinesis DDK, sequential motion rates SMR, accent-based music-speech protocol AMSP, familiars f, Quality of Communication Life Scale QCLS, Communicative Effectiveness Survey CES, Short General Health Questionnaire GHQ-12, Stroke and Speech Knowledge Test SSKT, Assessment of Intelligibility of Dysarthric Speech AIDS, Australian Therapy Outcome

Measures Scale AusTOMs, E-learning based Speech Therapy EST, intensity during closure DIDC, non-speech oro-motor exercises NSOMe, Liuzijue qigong LQG, maximal counting ability MCA, vocal sound pressure level dB SPL, relative average perturbation RAP, pitch perturbation quotient PPQ, Ross Information Processing Assessment, Second Edition RIPA-2, rate of speech ROS, National Institutes of Health Stroke Scale NIHSS, alternating motion rates AMRs, Assessment of Phonology and Articulation for Children APAC, software with hidden Markov models HMM, Dysarthria Impact Profile DIP, Alternative motion rates (AMR)-Pa, AMR-Ta, AMR-Ka, and sequential motion rates (SMR)-PaTaKa.

2.3.1.3.3. Diagnostic Speech examination

We listed all the methods used for the treatment of dysarthria due to a stroke, found in the current literature.

2.3.1.3.3.1. Conventional speech evaluation

Stroke-related dysarthria is characterized by imprecise articulation [105]. The intelligibility tests evaluate indirectly the language, the clinical examination allows the direct assessment of facial muscles, anatomic and articulator disorders, phonetic and phonologic impairments. For this reason, at the beginning of each examination, a clinical assessment of articulatory component of the patients should be essential. The intelligibility tests and the acoustic analysis improve the examination and complete the diagnostic picture.

The examination of the range of motion (ROM), strength and coordination of the muscles implicated in speech production should be conducted at the beginning of each clinical examination. The diagnostic protocol of Known et al. [106] included the examination of lips, tongue, lower jaw, velum, throat, vocal folds and diaphragm during speech production. The Authors assessed the AMR too [106]. They performed the diagnostic protocol on 20 individuals within a year from the stroke and repeated the examinations at the end of the speech treatment [106].

In the study of Thompson et al. [107] two speech-language therapists examined the speech articulation of 16 individuals with dysarthria after about 38 months since the stroke. The examined features were the precision in the pronunciation of vowels and of consonants and length of phonemes.

According to Wenke et al. [108] the evaluation of lip movement was crucial for a precise production of the vowels /i/ and /u/, whereby lip retraction and rounding were respectively required.

Several studies highlighted the importance also of the examination of respiration, phonation, prosody and resonation to obtain an accurate evaluation of dysarthria after a stroke [106,109,110,111].

Mackanzie in a study of 2007 [91] examined the conversation, the intelligibility, the ability of reading aloud in 8 individuals affected by moderate dysarthria due to a stroke. In this study [91], the participants were invited to read aloud, and the intelligibility was estimated by listeners. The examinations were performed within 2 years from stroke and 2 months after the speech treatment.

Known et al. [106] explained how the assessment of oro-facial and lingual muscles, especially orbicularis oris, could help to achieve a prognostic information on the recovery of alternate motion rates (AMR) and sequential motion rates (SMR)[1], especially in AMR-Pə and SMR-PəTəKə [106] in dysarthria after stroke. The closure of lips allows to assess the function of orbicularis oris [112]. During articulation, the orbicularis oris together with the buccinator and risorius muscles produces the /f, v/, /w/ and /p, b, m/ [113]. In addition, the orbicularis oris together with the elevator labii superioris, mentalis and elevator labii superioris protrudes the lips [113]. Thus, the coordination of these muscles is essential for an adequate pronunciation during speech. The examination of the action and of the coordination of these muscles should be always performed because lays the foundations for the study of intelligibility and loudness of the speech [91]. Hakel et al. [109] added the clinical examination of velopharynx in the assessment of dysarthria after stroke.

2.3.1.3.3.2. Lip force transducer

Thompson et al. [107] quantified the lip force with a transducer system. The system was constituted by a flexible, stainless-steel ring divided in two levers in which could be placed the lips. Lip forces were recorded in grams. The system calculated the maximum lip force, the sustained maximum lip force and the fast rate of repetitions of maximum lip for 10 seconds.

2.3.1.3.3.3. Measures of non-speech oral motor task performance

The measures of oromotor-nonverbal performance included the assessment of maximal strength, submaximal force or pressure control, speed of force or pressure increase, endurance of the oral articulators such as jaw, lip, and tongue [114]. Thompson et al. [107] measured strength and articulatory performance of lip and tongue, vowel or consonant precision.

The article of Bunton et al. [114] treated a topic different from our aim, it reviewed the studies of the relation of oromotor nonspeech activities to speech production. For this reason, it is not present in our systematic review.

2.3.1.3.3.4. Scales for the evaluation of dysarthria

2.3.1.3.3.3.4.1. The Assessment of Intelligibility of Dysarthric Speech (AIDS) [95]

The aim of AIDS [95] is to identify the phonetic patterns associated with reduced intelligibility and to estimate the severity of dysarthria. The dysarthric speaker reads 50 words of one- or two- syllable and 22 sentences. The productions are audio-recorded and presented to one or more listeners. To avoid the expectation of listener, the words are a lot and selected at random. The test is based on a multiple-choice response and the listener must select one alternative from several phonetically similar words. Wenke et al. [104] used the AIDS to examine word

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[1] Alternate motion rates (AMR) and sequential motion rates (SMR): tests of articulatory diadochokinesis.
AMR: rapid repetition of a single syllable /pa/, /ta/ or /ka/. SMR: rapid repetition of a syllable sequence /pataka/.

and sentence intelligibility in 3 patients during the reading of the middle three sentences of ‘The Rainbow Passage’ (Fairbanks G. Voice and articulation drill book) in the normal speaking voice. AIDS revealed an improvement in the intelligibility immediately after the end of therapy (LSVT) and 6 months after the end of speech therapy [104].

2.3.1.3.3.3.4.2.Assessment of Phonology and Articulation for Children (APAC) [84]

APAC test, developed by Kim et al. [84], evaluates the consonant production accuracy (CPA). The CPA is defined as the percentage of pronounced correct consonant and is the only quantitative value provided in the APAC test [84]. Lee et al. [115] compared APAC to an automatic speech recognition-based software to assess the dysarthria, the hidden Markov models (HMM). HMM takes into consideration both consonants and vowels, the APAC test uses only consonants for the examination of dysarthria [115]. Both HMM and APAC are considered accurate tools for dysarthria after a stroke [115]. With APAC, Lee et al. [115] assessed clarity, degree of response to stimulus, error pattern and comprehensibility of individuals with post-stroke. Twenty-four individuals affected by post-stroke dysarthria had to repeat 37 words of APAC. The words were displayed on a tablet PC, and the utterances were recorded in a quiet control booth (noise level $\leq$ 40 dB). The accuracy in the production of consonants was calculated as a measure of dysarthria severity [115].

2.3.1.3.3.3.4.3.Australian Therapy Outcome Measures Scale (AusTOMs) [103]

Another test used for dysarthria due to a stroke is AusTOMs. It indicates the participants’ ability to effectively communicate [104]. It was considered adequately sensitive to detect the progression and changes in dysarthria after stroke after speech treatment such as LSVT. Wenke et al. [104] quantified the impact of the therapy LSVT on 3 participants with dysarthria after 2 year since the stroke, immediately after therapy and 6 months post-therapy. Wenke et al. [104] examined the ability to perform daily activities, participation in life roles and well-being using the AusTOMs in individuals with dysarthria due to stroke.

2.3.1.3.3.3.4.4.Communication Effectiveness Measure (CEM) [91] and Communicative Effectiveness Survey (CES) [116]

CES [116] and CEM [91] examine intelligibility, speech naturalness, non-verbal aspects of communication, comprehensibility. The tests depend on the communication effectiveness perceived by the listener during a conversation of 5-10 minutes about several topics such as typical day, changes in life since stroke, recent activities, work, family, and friends. The score of CES is between 1 (not at all effective) and 4 (very effective) (maximum=32). The score of CEM is between 1 and 7 (1 = not at all effective, 7 = very effective). In two different studies Mackenzie [117,118] used CES and CEM. In a study of 2013, Mackenzie [117] examined 19 individuals with dysarthria due to a stroke (34.4 ± 26.7 months post stroke) and at the end of speech therapy. In a study of 2014, Mackenzie [118] examined 16 individuals 3 months after the stroke and 2 months after speech therapy.

2.3.1.3.3.3.4.5. Communication Outcomes After Stroke scale (COAST) [86]

The COAST [86] measures the perceived level of communication disability, the impact on daily life, the participants' perception of their communication effectiveness and the impact of speech disorders on their own quality of life [86]. A parallel version, the Carer COAST (Communication Outcomes After Stroke scale, carer version) [119], was validated to provide the carers' perspective on the communication effectiveness of the patients and its effect on the carers' quality of life [119]. Bowen et al. [120], Mitchell et al. [121,122] and Young et al. [123] used COAST. Within the first 4 months from the stroke, Bowen et al. [120] administered the COAST to 69 individuals and repeated the scale 6 months after treatment. Young et al. [123] administered the COAST 6 months from the stroke and repeated it 6 months after the end of speech therapy. Mitchell et al. [121,122] did not specify when administer the scale.

2.3.1.3.3.4.6. Dysarthria Impact Profile (DIP) [92]

DIP [92] includes four sections, the first about the effect of dysarthria on own person, the second about acceptance of the speech disorder, the third about the own perception of the impairment judged by other persons, the last about the impact of dysarthria on quality of life and the relationship. Each session contains 10-14 statements. The scores is between 5 and 1 (5 strongly agree, 4 agree, 3 not sure, 2 disagree, 1 strongly disagree) [92]. Mackenzie et al. [91] used DIP in 8 patients with dysarthria 19 months after the stroke and 2 months after therapy. Mitchell et al. [121,122] evaluated the participation level and the ability of communication in respectively 26 and 24 individuals post stroke with DIP.

2.3.1.3.3.4.7. Frenchay Dysarthria Assessment second edition (FDA-2) [93]

FDA-2 [93] is one of the formal assessment tools used to obtain a complete oral-facial examination and a method to identify the speech characteristics, which can contribute to the neurological diagnosis and treatment [93]. The FDA-2 is composed of 8 major items (including reflex, respiration, lips, tongue, jaw, palate, larynx, and speech) and 28 sub-items. The principal assessments regard the measures of articulation such as range, speed, strength, and coordination. A higher score means good recovery from dysarthria, from 1 (low) to 9 (high) (maximum = 54) [93]. Even if it is considered a tool mostly for neurologists, every physician member of the multidisciplinary team should know and apply this assessment. Mitchell et al. [121,122] and Li et al. [124] conducted three clinical trials in which they used FDA-2. Li et al. [124] used the speech breathing level of the FDA-2 to examine the effectiveness of Liuzijue Qigong and of traditional breathing training in individuals with dysarthria. The first examination was performed 2-6 weeks after stroke, the following after 1, 2 and 3 weeks after treatment. In two studies, Mitchell et al. [121,122] used this scale, without adding specific features.

2.3.1.3.3.4.8. Best Dysarthria domains of National Institutes of Health Stroke Scale (NIHSS) [84]

The Best Language item of the NIHSS derives from the Boston Diagnostic Aphasia Examination. In NIHSS [84], dysarthria is assessed by asking patients to read or repeat standard phrases to determine their articulation. The NIHSS can be administered quickly and efficiently at the bedside. Therefore, the use of NIHSS can be an indicator of aphasia and dysarthria in the acute stroke setting. Ali et al. [125] conducted epidemiologic research about the persistence of dysarthria after stroke and its spontaneous resolution. The Authors [125] used NIHSS in a very large sample of 6192 individuals after 3 months since the stroke.

2.3.1.3.3.4.9. Reading connected speech [126]

Mackenzie et al. [91] used the reading connected speech [126] described by Lowit-Leuschel [126]. Eight individuals red aloud a passage of 150 words about 19 months after the stroke and 2 months after therapy. Several tasks were presented to the subjects: language tests, contrastive stress tasks, reading and spontaneous conversation. The speech tasks were presented in alternating order to control the effects of fatigue on the performances [91].

2.3.1.3.3.4.10 Ross Information Processing Assessment 2 (RIPA-2) [96]

The RIPA-2 [96] is used to quantify cognitive-linguistic deficits. It includes 10 areas about communicative and cognitive functioning: immediate memory, recent memory, remote memory, spatial orientation, orientation to environment, recall of general information, problem solving and abstract reasoning, organization and auditory processing and retention. Mallet et al. [127] examined 30 individuals with dysarthria after the stroke using the Ross Information Processing Assessment 2 (RIPA-2), without any other specific information about the assessment they used.

2.3.1.3.3.4.11. Speech Intelligibility Test (SIT) [128]

SIT [128] assesses speech intelligibility for people with dysarthria also due to stroke. It is used to correlate the relationships between dysarthric profiles and acoustic markers of speech production [90]. SIT data were distributed as files and transcribed orthographically. The modified shortened version of this test (11 sentences instead of 15) is often used to avoid the fatigue that affects this clinical population, as recommended by three articles [117,118,129]. Eleven sentences were computer generated from pools of 100 sentences of each length. The test uses a six-response format. The sentences include 9, 10, and 12 words in length. Scores were presented as percentages of words correctly identified by listeners.

In two studies, Mackenzie et al. [117,118] used SIT to examine respectively 19 and 16 patients with dysarthria due to a stroke. In the research of 2013 of Mackenzie [117] SIT was used 34±26.7 months after the stroke and repeated immediately at the end of speech therapy. In the research of 2014 of Mackenzie [118], SIT was administered 3 months after the stroke and 2 months after the end of treatment.

Tamplin [129] used SIT to evaluate dysarthria in 4 patients 18 months after the stroke and immediately after treatment.

Specific versions of SIT were used for individuals with dysarthria due to a stroke. Ono et al. [130] used the 9-point rating scale of the Japanese conversational SIT [98]. Three listeners with more than 5 years clinical experience and no prior contact with the patient evaluated the conversation, the reading and the intelligibility of a patient about 2 years after the stroke and immediately after therapy. Roggeman et al. [131] used the Dutch SIT [132] immediately after the stroke and one year after stroke.

2.3.1.3.3.4.12. Stroke and Speech Knowledge Test (SSKT) [94]

Mackenzie et al. [117] used SSKT in 19 individuals 34.4±26.7 months after a stroke and at the end of treatment.

2.3.1.3.3.4.13. Dysarthria Therapy Outcome Measures Activity (TOMA) [87]

TOMA [87] quantifies the level of communication activity regarding four domains: impairment, activity, participation and wellbeing. The scale ranges from 0 (severe) to 5 (normal). In two controlled trials, Mitchell et al. [121,122] used TOMA in 26 and 24 individuals with dysarthria due to a stroke without adding any details. Bowen et al. [120] evaluated with TOMA 33 patients with severe dysarthria due to a stroke on the basis of the severity of dysarthria, within the first 4 months after the stroke and 6 months after the end of speech therapy.

2.3.1.3.3.4.14. Urimal Test of Articulation and Phonology [89]

Urimal Test of Articulation and Phonology [89] is a valid and reliable assessment tool for phonological ability in repeating word and sentence. It is used mostly for children.

This test is used by Kwon et al. [106] for the clinical assessment of speech motor function [106] in 20 individuals within the first 2 months after the stroke and immediately after the therapy.

2.3.1.3.3.4.15. Word Intelligibility Test [90]

Kent et al. [90] proposed the Word Intelligibility Test for dysarthric speakers. This test [90] examines 19 acoustic-phonetic features of dysarthric impairment and of speech intelligibility also after dysarthria due to a stroke [90,91]. Kent et al. [90] suggested to use four alternatives proposed to listeners instead of three such as Mackenzie et al. [91], that is, the listeners select from four choices the word that they think was produced according the test of Kent [90], from three choices according the version of Mackenzie [91]. Seventy stimulus words were presented individually for reading aloud. Each stimulus word was presented in a horizontal line along with distracters (e.g. stimulus 'bad': bad, bed, bet, pad). Only one word was correct. Listeners circled the word they heard. The score was based on percentage of correct identifications (maximum possible score - 700). Mackenzie et al. [91] used the Word Intelligibility test in 8 patients 1-2 years after the stroke and 2 months after the end of speech therapy.

2.3.1.3.3.4.16. Oral physical and dysarthria assessment [97]

Darley [97] ideated the Oral physical and dysarthria assessment [97], useful for speech dyspraxia and dysarthria. Miller et al. [111]. used the Oral physical and dysarthria assessment in 30 individuals about 2 years after a stroke. Two speech and language therapists experienced in diagnosing neurogenic communication disorders independently examined the patients.

2.3.1.3.3.5. Questionnaire about the psychosocial impact of stroke-related dysarthria

2.3.1.3.3.5.1. Quality of communication life (QCLS) [133]

In QCLS [133] seventeen items are scored on a 1–5 scale, presented as a vertical, visual analogue method. One item was considered inappropriate by Mackenzie et al. [117] and excluded (I meet the communication needs of my job or school). Mackenzie et al. [117] subjected QCLS to 19 individuals after the stroke (34.4±26.7 months) and after speech treatment. Seventeen items are scored on a 1–5 scale, presented as a vertical, visual analogue.

2.3.1.3.3.5.2. Short General Health Questionnaire (GHQ-12) [134]

Goldberg and Williams [134] in 1988 ideated a general well-being questionnaire: the GHQ-12. Four options (e.g. better/same/less/much less than usual) are presented for each of 12 items. The questionnaire permits 4 answers (e.g. better/same/less/much less than usual). Mackenzie [117] used GHQ-12 to evaluate 9 individuals about 34.4±26.7 months after the stroke and at the end of speech therapy.

2.3.1.3.3.5.3. Interview on impact of stroke-related dysarthria on social participation [88]

Dickson [88] and Brady [135] conducted an interview about patients' perspective of living with dysarthria following stroke and in particular, the impact on social participation and identity. Stroke-related deficits such as fatigue or movement disorders and a reduced ability to participate contribute to a reduction in opportunities to participate in social activities [135]. The difficulty for people, including close family members, to understand dysarthric speakers worsens the interactions. Dickson et al. [88] investigated the experiences of 24 people with dysarthria. Brady et al. [135] used the same interview of Dickson et al. [88], to assess the association between the severity of speech disorders in 24 individuals with stroke-related dysarthria and the impact on their social participation.

2.3.1.3.3.6. Assessment of speech with own personal scales

A few Authors used personal versions of scales and scores they formulated [85,91,99,100,102,104,107,124,136] These assessments are very interesting, but not validated, not verified their reproducibility.

Beijer et al. [85] used a scale rating of 'ease of intelligibility' and a scale rating of 'perceived pleasantness' in 3 individuals about one month after a stroke and repeated 20 weeks after the end of speech treatment. The speakers read aloud two texts: ''Papa en Marloes'' (van de Weijer & Slis, 1991) and ''Finland'' (Martens et al., 2010).

In the study of Thompson et al. [107] two speech-language therapists examined the speech articulation, the precision in the pronunciation of vowels, of consonants, of length phonemes and the intelligibility of 16 individuals with dysarthria after about 38 months after stroke, using a 4-point equal interval scale where a score of 1 indicated normal function, 2 represented a just-noticeable deviance of the speech dimension, 3 indicated a moderate deviance of the speech dimension and 4 was indicative of severe dysarthria.

Walshe et al. [136] interviewed 3 patients about 4 years after the stroke on 6 themes: "dysarthria as only part of the picture", "communication has changed, 'people treat me differently', 'dysarthria resulting in negative emotions', 'barriers to communication' and 'life is different now' [136].

In the study of Ozawa et al. [99], three speech-language pathologists reviewed the speech samples about picture description and text reading to determine speech intelligibility. They [99] used a 5 point scale (1 = clear, 5 = unintelligible) and a bizarreness scores (0 = none; 4 = severe) adopting a part of the scale for motor speech disorders by the Japan Society of Logopaedics and Phoniatrics [137].

Mackenzie et al. [91], Park et al. [100] used a similar seven-point scale for intelligibility. The scale allowed to quantify the severity of dysarthria and the effectiveness of communication, on the base of intelligibility and naturalness. The score of 1 indicates not at all effective, the score of 7 indicates very effective. Mackenzie et al. [91] used the scale in 8 individuals about 2 years after the stroke and repeated it 2 months after the speech therapy. Park et al. [100] used a 7-point scale on 2 individuals 20 months after stroke, immediately after treatment, 1 and 3 months after treatment.

Dysarthria scores [102] was ideated by Robertson [102] about the efficacy of oro-facial and articulation exercises in dysarthria after stroke. The examined parameters were the strength of oro-facial muscles, the diadochokinesis (DDK) rates, the articulation, the intelligibility.

Li et al. [124] examined the loudness on the base of the perception of how intense the sounds appeared to a therapist while talking with a patient and graded as whispered, soft, conversational, loud, or shouting [124]. With the loudness scale, they [124] examined 50 subjects 2 weeks to 6 months after the stroke and 1, 2 and 3 weeks after treatment. Similarly, Kim et Kuo [138] assessed the intelligibility in 16 patients with dysarthria secondary to stroke considering two different presentation levels (‘high’ vs. ‘low’).

Wenke et al. [104] administered the participant self-report questionnaire and communication Partner questionnaire to 3 patients with mild-moderate dysarthria. These questionnaires were two multiple choice questionnaires administered after stroke and immediately after therapy and 6 months post-therapy. The participants answer to five different questions about their communication: how often they slur, how shaky or hoarse is the voice, how well do people understand conversation, how often do they participate in conversations with unfamiliar people, how often do they start a conversation with other people. In communication partner questionnaire [104], the communication partners respond to five different aspects of the participant’s everyday conversational abilities: how easy is it to understand the speaker, how often do they ask the speaker to repeat themselves, how often does the speaker initiate conversation, how often does the speaker initiate conversation with an unfamiliar person, how they rate the speaker’s speech and voice. The scale had a range of 1–7, with a rating of 7 indicating a very good ability and a rating of 1 indicating a very poor ability.

2.3.1.3.3.7.Acoustic profile of patients with dysarthria due to a stroke

The acoustic analysis permits to have a numeric and objective quantification of severity of dysarthria, of the progression, of the improvement of speech after rehabilitation treatment and of changes over time.

2.3.1.3.3.7.1. Acoustic measures

A few studies examined the objective acoustic indicators of the articulatory abnormalities in dysarthric speech due to a stroke [139,140,141]. Previous studies used auditory-perceptual ratings to examine the speech characteristics of patients with dysarthria associated with stroke with lesions at various cerebral locations [142,143,144,145,146]. These studies reported that patients with stroke-related dysarthria were characterized by reduced rate of speech and prolonged syllables [142,143,144,145,146].

The acoustic measure used by Beijer et al. [85] were intensity during closure (DIDC) in the occlusion phase of voiceless plosives, changes in the vowel space of /a/, /e/ and /o/ and fundamental frequency variation (vf0) in semantically unpredictable sentences.

Kim and Jo [140] used a computer speech software program, PRAAT (version 5.2; Boersma & Weenink, 2007) to analyse voice recording samples. Subjects repeated the phonemes /pe/, /te/, /ke/ as rapidly as possible and as long as possible at a comfortable pitch and loudness.

Mahler et al. [147] analysed the increase in the vocal sound pressure level (dB SPL), the acoustic correlate of loudness, using a customized software (Matos, 2005). SPL was measured during maximal sustained vowel phonation, reading a portion of the Farm Passage (Crystal & House, 1982).

Tamplin [129] calculated the rate of speech (ROS) in 4 patients after 1-8 months of vocal exercises of singing and speech therapy.

Kent et al. [90] used the Multi-Dimensional Voice Program (MDVP) (Kay Elemetrics, 1993) in 22 individuals affected by stroke. He found abnormal values, such as vf0 in 21 patients, Pitch Period Perturbation Quotient (sPPQ) in 18 patients, Shimmer (ShdB), and Smoothed Amplitude Perturbation Quotient (sAPQ) in 17 patients, Peak Amplitude Variation (vAm) and Amplitude Perturbation Quotient (APQ) in 16 patients with dysarthria after stroke.

Mahler et al. [147] used MDVP in 4 subjects with mild-moderate dysarthria 9 months after the stroke and 2 months after treatment with LSVT. They [147] measured the relative average perturbation (RAP) and pitch perturbation quotient (PPQ).

The study of Kent et al. [90] is not present in our meta-analysis because the values are not comparable with those of the other studies. Kent et al. [90] assessed the acoustic parameters in dysarthric patients after a stroke, without assessing the changes after a rehabilitation treatment.

2.3.1.3.3.7.2. Maximal counting ability (MCA) and S/Z ratio

Li et al. [124] examined MCA and S/Z ratio in 50 subjects 2 weeks to 6 months after the stroke and 1, 2 and 3 weeks after treatment.

2.3.1.3.3.7.3. Automatic speech recognition (ASR) [115]

Lee et al. [115] developed the ASR, a software to assess the severity of dysarthria using the hidden Markov models (HMMs), an artificial neural network. The ASR recognizes spoken language or utterances. Patients were asked to repeat the recordings for evaluating the test–

retest reliability [115]. ASR could be used for screening and follow-up of dysarthric patients after a stroke too [115].

2.3.1.3.3.8. MRI-Based Neuroanatomical Predictors of Dysarthria

Flowers et al. [148] described a neuroanatomical and clinical model to predict dysarthria after acute ischemic stroke based on MRI. According to Flowers et al. [148], the neuroanatomical predictors of dysarthria are pontine, internal capsular and insular lesions.

Third topic of the PhD project
Post-Stroke Dysarthria: A Multidisciplinary Approach to Rehabilitation

2.3.2. Dysarthria and stroke. The effectiveness of speech rehabilitation. A systematic review and meta-analysis of the studies.

2.3.2.1. Introduction

Post-stroke dysarthria is a problem that has been largely neglected in the past even if it is a very disabling condition [111]. Communication disorders are a considerable barrier to normal activity and participation in social and civic life and have a negative impact on the quality of life. A correct diagnostic and follow-up protocol could play an important role in the first examination and during the follow-up to clarify the speech impairments, variations, and improvements after treatment and could have a prognostic role. The protocol could help achieve more adequate speech therapy and ease collaboration among a multidisciplinary treatment team and clarify the assessments during each follow-up session. We assessed the effectiveness of speech therapy on stroke-related dysarthria. Our systematic review describes the measures of dysarthria severity secondary to stroke, and we performed a meta-analysis to highlight which acoustic parameters are affected in dysarthria secondary to stroke and the difference in these parameters after speech therapy to confirm treatment effects. This information could be interesting both to identify acoustic abnormalities in speech due to stroke-related dysarthria and develop specific interventions for speech rehabilitation.

2.3.2.2. EVIDENCE ACQUISITION

2.3.2.2.1. Search Strategy

The search was performed using several following medical electronic databases: (1) PubMed, (2) EMBASE, (3) Cochrane Library, and (4) Scopus Web of Science. The review was conducted from 15 January to 22 February 2020. We searched for the following terms and keywords: “stroke” and “dysarthria” and “diagnosis” and “stroke” and “dysarthria” and “assessment”.

2.3.2.2.2. Information sources and database search

The systematic review and the meta-analysis were consistent with the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) statement [44] and the Meta-analyses of Observational Studies (MOOSE) checklist [83]. Searches were conducted between January 2020 and February 2020 using the following databases: (1) PubMed, (2) Wiley Online

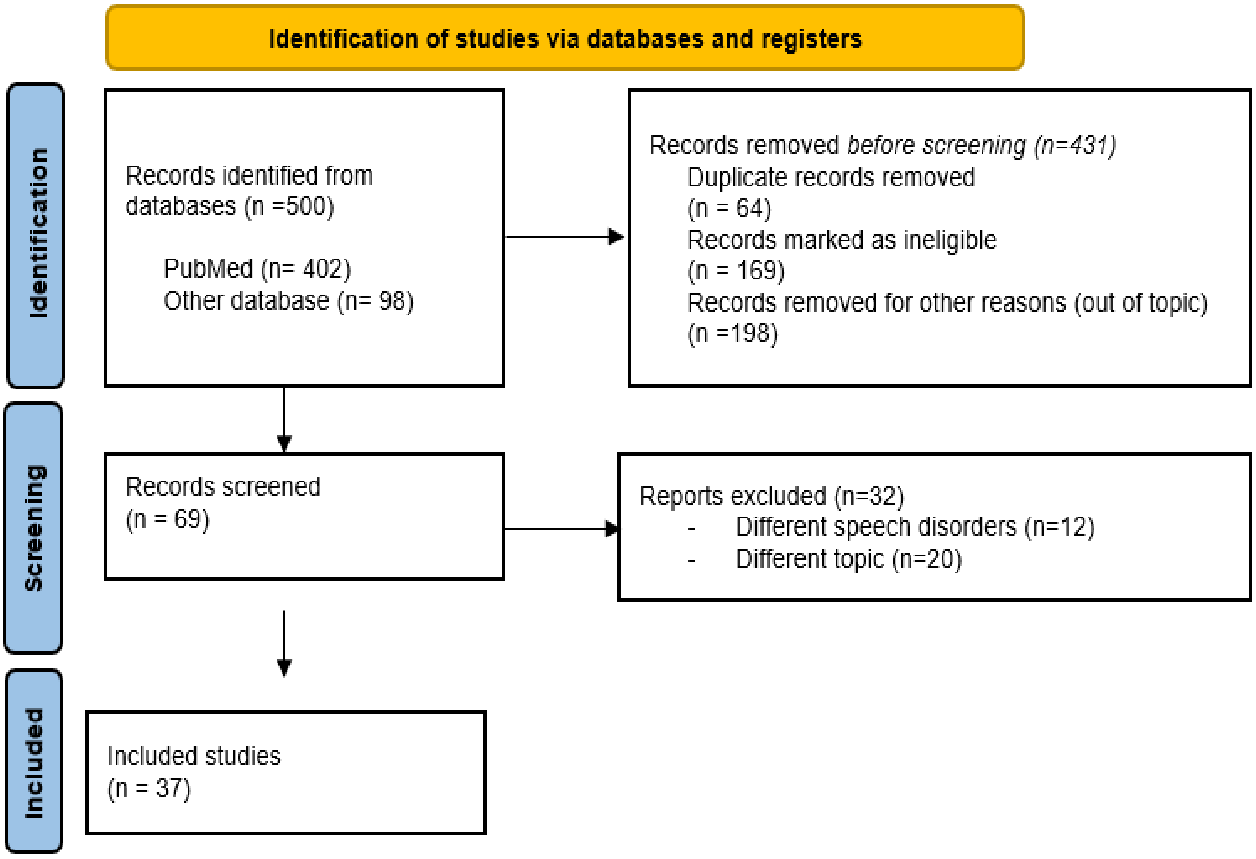
Library Cochrane Library, and (3) EMBASE. The reference lists of related articles were also examined for eligible papers.

2.3.2.2.3. Selection criteria and data extraction

Database searches from 1981 to 2019 yielded 402 references using the keywords “stroke” and “dysarthria” and “diagnosis” and 84 references for the search using the keywords stroke” and “dysarthria” and “assessment”. Titles and abstracts were screened by the reviewers. Sixty-nine papers remained for full text screening, and the eligibility for study inclusion was independently assessed.

Thirty-seven publications met the inclusion criteria and were included in the systematic review. Thirty-two articles were excluded for the reasons described in (Figure 9).

Figure 9 Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.



We included original articles about dysarthria in subjects with confirmed stroke diagnoses. We excluded animal studies and participants with other neurological diseases or other speech impairments, such as aphasia. We also excluded any remaining duplicates.

In our meta-analysis we considered the studies in which the authors compared numeric parameters useful for quantifying dysarthria severity before and after different speech rehabilitation.

2.3.2.2.4. Meta-analysis calculations

The Statistical Package for Social Sciences (SPSS, Version 18.0 for Windows; SPSS Inc., Chicago, IL) was used for data analysis. Inconsistency test (I^2) verified the impact of study heterogeneity on the results of the meta-analysis. An I^2 value <25% was indicative of low heterogeneity risk, a value between 25% and 50% of a moderate level, and >50% was considered statistically significant among included studies [149]. We used a random-effect model to estimate the combined effect sizes. The quality of identified studies followed the methods of the Cochrane Collaboration [45], and the publication bias were examined using funnel plots.

2.3.2.3. EVIDENCE SYNTHESIS

2.3.2.3.1. Description of the studies

The number of resulting studies at each stage of the search for the meta-analysis and the systematic review is displayed in Figure 9.

The studies included in our systematic review with the sample characteristics and details of the were displayed in Table VIII.

For the meta-analysis, we compared the diagnostic measures used in the articles before and after speech rehabilitation. In the meta-analysis, we considered the studies of Wenke et al. [108], Kwon et al [106]., and You et al. [150] twice because in the same articles the authors used two different speech treatments for stroke-induced dysarthria. Our meta-analysis examined the validity of the use of VSA, of formants F1 /a/,/i/,/u/ and F2 /a/,/i/,/u/, of AMR-Pə, AMR-Tə, AMR-Kə, and AMR-PəTəKə and of MPT (Table IX-XII and Figure 10-12) in the evaluation of stroke-induced dysarthria.

The qualitative information synthesis for each parameter was attributed to the following evidence levels according to the recommendations of the Oxford Centre for Evidence-Based Medicine: evidence from the systematic review of randomised controlled trials (1a), clinical controlled studies (2a), case-control-studies (3a), and from non-systematic reviews.

2.3.2.3.2. Variations of experimental conditions across the studies

The selected articles were described on the basis of the several methods used in each study for the diagnosis and post-stroke dysarthria follow-up. Study characteristics are shown in Table VIII.

All study groups were not homogeneous for relevant general clinical features, such as clinical presentation, localization of the vascular lesion causing stroke, disease duration, electronic device, types of diagnostic measures, voice parameters, severity of dysarthria, rehabilitation speech therapy, time of starting therapy, and duration of treatment. Disease duration ranged from 6 to 35 months. A large variation among studies regarding the duration of the disease, the time of the first examination of the dysarthria, the duration of the treatment, the period of follow up at the end of therapy existed. For sample inhomogeneity, we could include only a few studies in the meta-analysis. For the meta-analysis, we considered the results of the dysarthria assessment at baseline and immediately after treatment to compare homogeneous data.

2.3.2.3.3. Meta-analysis of voice and speech parameters

Our meta-analysis assessed acoustic parameters before and after speech therapy, VSA, formants, AMR, and MPT.

Data pooling within the meta-analysis revealed that several voice and speech parameters, including VSA (Table IX) (Figure 10) and formants F1 and F2 /a/, /i/, /u/ (Table X and Figures 11 a–f) did not present significant variations before and after treatment ($p > 0.05$).

On the contrary, we observed significant variations in AMR- Pə, AMR-Tə, AMR-Kə, and AMR-PəTəK (Table XI and Figures 12 a–d) and MPT (Table XII and Figure 12 e) before and after treatment.

AMR- Pə, AMR-Tə, AMR-Kə, AMR-PəTəK and MPT significantly discriminated among the severity of stroke-induced dysarthria due and its progression at the end of the speech therapy. These parameters were significantly improved ($p < 0.05$) after speech rehabilitative treatment. Thus, AMR and MPT could be used to obtain significant results to quantify the stroke-related dysarthria severity and during the follow-up examinations.

2.3.2.3.4. Heterogeneity and publication bias

The heterogeneity among studies was very low for AMR- Pə, AMR-Tə, AMR-Kə, and AMR-PəTəKə ($I^2=0$) and low ($I^2=25\%$) for VSA and MPT, and it was moderately high (I^2 between 68 and 87%) for formants as shown in Tables IX-XII. The funnel plot (Figures 10–13) showed that there was symmetry among the studies, and no significant publication bias was seen or the small study effect was insignificant. The sensitivity analysis also showed the absence of an excessive influence of individual studies.

2.3.2.3.5. Diagnostic speech examination, specific scales, acoustic parameters of voice

Several studies highlight the importance of the assessment of respiration, phonation, prosody, and resonation in order to obtain an accurate evaluation of dysarthria after a stroke [106,111,113,146] and specific scales [114,128].

The acoustic analysis permitted to a numeric and objective quantification of dysarthria severity, of dysarthria progression, speech improvement of speech after rehabilitative treatment, and speech changes over time [141].

2.3.2.3.5.1. Formant

Acoustic analysis permits to examine the formants and the vowel space area too.

Mou et al. [105] investigated the acoustic features of vowel production in 31 Mandarin-speaking patients with post-stroke dysarthria. The participants produced 6 vowels (/a, i, u, ɤ, y, o/) evaluated by 2 native Mandarin speakers. Mou et al. [105] extracted the formants (F1 and F2) to evaluate the severity of the disorder. Mou et al. [105] analysed the reduced articulatory movement in the vocal tract such as small movements of the tongue, decreased movements of jaw and lower lips, the slow pace of articulatory movement and the incoordination of articulatory gestures in dysarthric speakers compared to healthy speakers [105].

Mahler et al. [147] and Beijer et al. [85] analysed the first formant (F1) and the second formant (F2) in the vowels /a/, /e/,/i/, /o/ and /u/ in subjects with moderate dysarthria. Beijer et al. [85] examined 3 individuals about one month after the stroke and 20 weeks after therapy [85]. The noise was measured in the silent interval of the voiceless plosives /p/, /t/, /k/ [85].

Weenke et al. [108] evaluated F1 and F2 for the vowels /i/, /u/, /æ/ and /a/ and the articulatory working space for stop (/t/ and /k/) and fricative and liquid[2] (/s/ and /r/) consonants. The Authors [108] examined 13 individuals 6 months after stroke, immediately after the therapy LSVT and 6 months after therapy.

The studies of Mahler et al. [147] and Wenke et al. [108] were analysed in our meta-analysis on VSA (Table IX) and formants (Table X).

AMRs in individuals with spastic and ataxic dysarthria due to a stroke are often decreased, as compared to those in normal speakers [99]. In the study of Ozawa [99], the subjects were instructed to repeat a monosyllable as rapidly as possible for 5 seconds. The syllables /pa/ and /ta/ were used to examine alternating motions of the lips and tongue, respectively [99].

The studies of Kwon et al. [106], Kim et al. [140] and You et al. [150] were analysed in our meta-analysis on AMRs (Table XI). Kwon et al. [106] studied the AMR in 20 dysarthric

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[2] Fricative phonems: /f,v,θ,ð,s,z,ʃ,ʒ,h/. Produced squeezing air between a small gap as it leaves the body.
Liquid phonems: /l, r, m, n/, Produced by the tongue with a partial closure of the mouth.

individuals within the first 2 months since a stroke and immediately after therapy. Kim et al. [140] assessed AMR in 6 individuals within one year since the stroke and at the end of therapy. You et al. [150] assessed AMR after a stroke in 6 dysarthric subjects and immediately after treatment.

In the study of Ozawa et al., there were not present numerical values useful for meta-analysis [99].

The studies of Known et al. [106], Kim et al. [140] and You et al. [150] were analysed in our meta-analysis (Table XII). Known et al. [106] examined MPT in 10 individuals within the first 2 months from the stroke and immediately after stroke. Kim et al. [140] examined MPT in 6 individuals within one year from stroke and at the end of speech therapy. You et al. [150] examined MPT in 6 individuals after 6 months after the stroke and 6 months after stroke.

Figure 10 Graph of meta-analysis of the vowel space area (VSA)

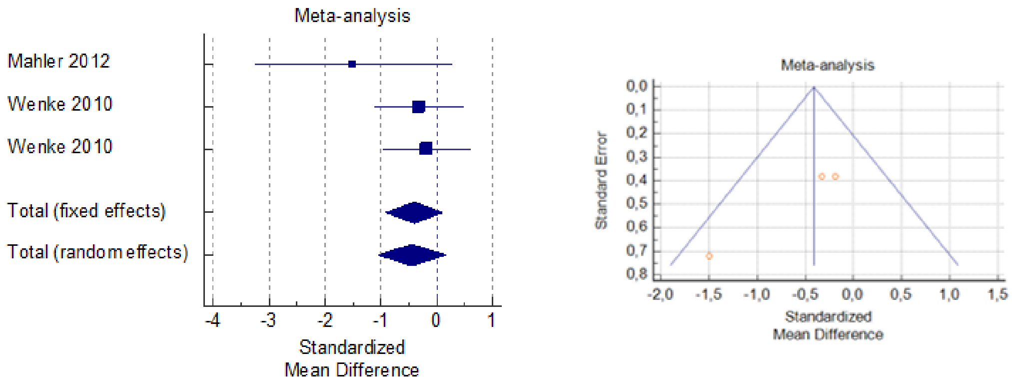


Figure 11 —A) Graph of meta-analysis of the first formant (F1) for the vowel /a/

B) graph of meta-analysis of the second formant (F2) for the vowel /a/

C) graph of meta-analysis of the first formant (F1) for the vowel /i/

D) graph of meta-analysis of the second formant (F2) for the vowel /i/

E) graph of meta-analysis of the first formant (F1) for the vowel /u/

F) graph of meta-analysis of the second formant (F2) for the vowel /u/

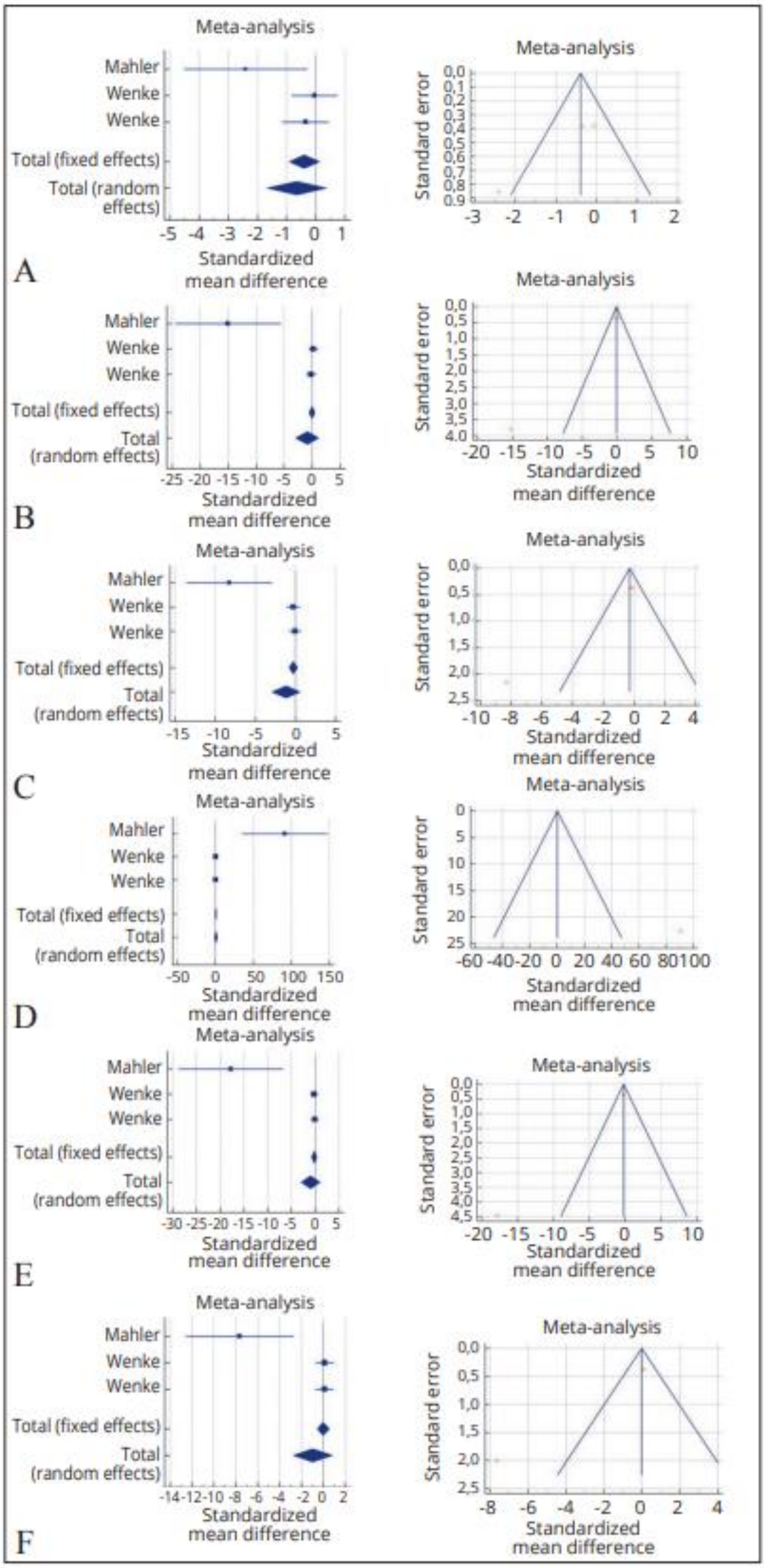


Figure 12 A) Graph of meta-analysis of the Alternate Motion Rate (AMR) for the syllable / Pə /
B) graph of meta-analysis of the Alternate Motion Rate (AMR) for the syllable / Tə /

C) graph of meta-analysis of the Alternate Motion Rate (AMR) for the syllable / Kə /

D) graph of meta-analysis of the Sequential Motion Rates (SMR) for the syllables / PəTəKə /

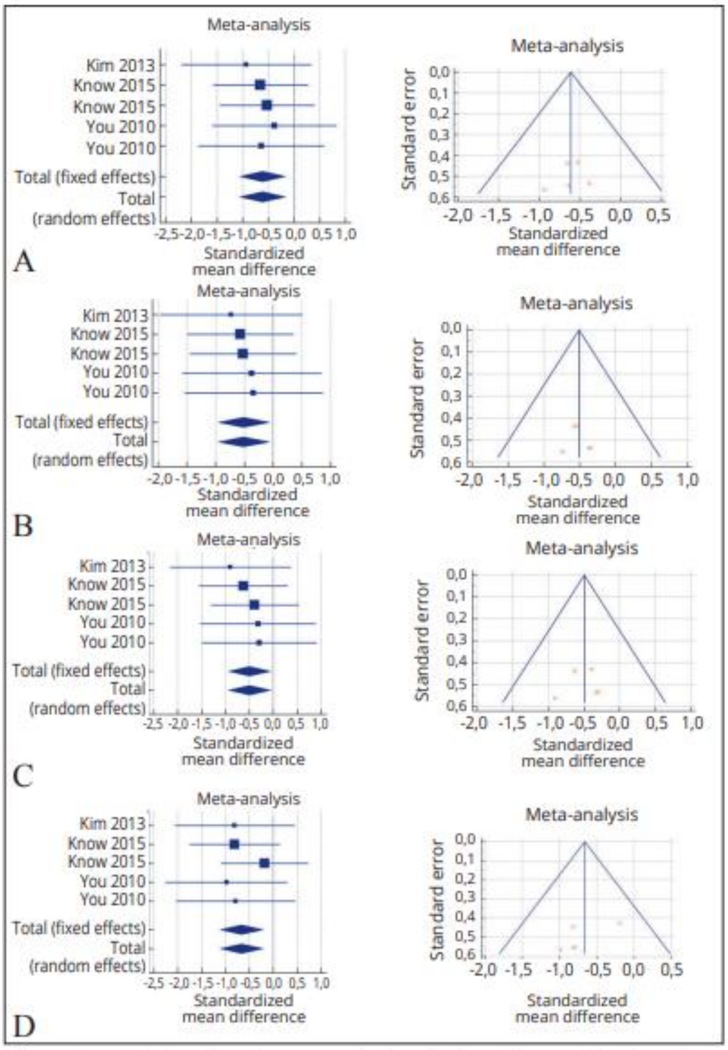


Figure 13 Graph of meta-analysis of Maximum Phonation Time (MPT)

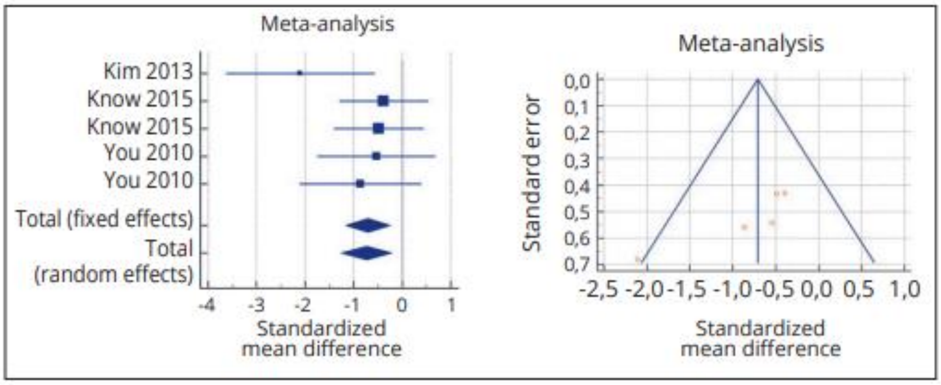


Table IX Validity of the use of vowel space area in the evaluation of results based on different speech rehabilitation. Comparison before and after treatment.

Authors	Treatment	N.	VSA pre (Hz^2)	SD pre	VSA (Hz^2) post	SD post	SMD	SE	95% CI	95 % CI	t	P	Weight (%)		Test for heterogeneity	
									Lower limit	Upper limit			Fixed	Random	Q	2,6884
Mahler 2012 [147]	LSVT	4	148.87	36.37	220.94	46.47	-1,500	0,720	-3,261	0.261			12,32	15,62	DF	2
Wenke 2008 [104]	LSVT	13	152.54	87.28	183.62	98.03	-0,324	0,382	-1,114	0.465			43,63	42,06	Significance level	P = 0,2607
Wenke 2008 [104]	Trad	13	133.40	67.92	148.81	90.13	-0,187	0,381	-0.973	0.599			44,04	42,32	I^2	25,61%
Total (fixed effects)							-0,409	0,253	-0,914	0,0970	-1,618	0,111	100,00	100,00	95% CI for I^2	0,00 to 97,50
Total (random effects)							-0,450	0,304	-1,481	0,158	-1,481	0,144	100,00	100,00		

Vowel space area VSA, standard mean differences SMD, standard error SE, confidential intervals CI, before treatment Pre, after treatment Post, N. number of patients, Lee Silverman Voice Treatment LSVT, standard deviation SD, traditional rehabilitation speech therapy Trad, inconsistency I^2

Table X Validity of the use of formants (F1 and F2 for the vowel /a/, /i/, /u/). in the evaluation of results based on different speech rehabilitation. Comparison before and after treatment.

Formant	**Treatment**	**N**	**F1 /a/ pre**	**DS pre**	**F1/a/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		
Mahler 2012 [147]	LSVT	4	704	82.6	1476.5	71.40	-2.403	0.859	-4.505 to - 0.301			8.97	20.66	Q	6.3486
Wenke 2008 [104]	LSVT	13	877	98	881	94	-0.0403	0.380	-0.824 to 0.744			45.88	39.74	DF	2
Wenke 2008 [104]	Trad	13	812	151	862	125	-0.349	0.383	-1.140 to 0.441			45.15	39.60	Significance level	P = 0.0418
Total (fixed effects)							-0.392	0.257	-0.907 to 0.123	-1.52	0.133	100.00	100.00	I^2	68.50%
Total (random effects)							-0.51	0.505	-1.662 to 0.361	-1.28	0.203	100.00	100.00	95% CI for I^2	0.00 to 90.85
Formant	**Treatment**	**N**	**F2 /a/ pre**	**DS pre**	**F2/a/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		

Mahler 2012 [147]	LS VT	4	1231.7	70.5	1255.7	91.95	-15.087	3.821	-24.437 to -5.736			0.49	6.07	Q	16.0009
Wenke 2008 [104]	LS VT	13	1499	208	1461	158	0.199	0.381	-0.587 to 0.985			49.71	46.96	DF	2
Wenke 2008 [104]	Trad	13	1473	239	1514	245	-0.164	0.381	-0.949 to 0.621			49.80	46.97	Significance level	P = 0.0003
Total (fixed effects)							-0.0571	0.269	-0.595 to 0.480	-0.21	0.832	100.00	100.00	I^2	87.50%
Total (random effects)							-0.899	1.004	-2.907 to 1.110	-0.89	0.374	100.00	100.00	95% CI for I^2	64.69 to 95.58
Formant	**Treatment**	**N**	**F1 /i/ pre**	**DS pre**	**F1/i/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		
Mahler 2012 [147]	LS VT	4	312	28.3	288.5	25.8	-8.254	2.153	-13.521 to -2,986			1.54	12.61	Q	14.1019
Wenke 2008 [104]	LS VT	13	423	60	438	47	-0.270	0.382	-1.057 to 0,518			49.00	43.68	DF	2

Wenke 2008 [104]	Trad	13	424	67	427	63	-0.0447	0.380	-0.829 to 0,739			49.46	43.71	Significance level	P = 0.0009
Total (fixed effects)							-0.281	0.267	-0.816 to 0.254	-1.05	0.297	100.00	100.00	I^2	85.82%
Total (random effects)							-1.178	0.892	-2.964 to 0.608	-1.32	0.192	100.00	100.00	95% CI for I^2	58.66 to 95.13
Formant	**Treatment**	**N**	**F2 /i/pre**	**DS pre**	**F2 /i/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		
Mahler 2012 [147]	LSVT	4	2198	184.3	2245.7	192.34	91.027	22.765	35.323 to 146.73			0.014	0.21	Q	15.8906
Wenke 2008 [104]	LSVT	13	2537	845	2259	584	0.371	0.383	-0.420 to 1.162			49.82	49.88	DF	2
Wenke 2008 [104]	Trad	13	2162	190	2081	328	0.293	0.382	-0.496 to 1.081			50.16	49.91	Significance level	P = 0.0004
Total (fixed effects)							0.344	0.271	-0.197 to 0.886	1.27	0.208	100.00	100.00	I^2	87.41%

Total (random effects)							0.521	1.043	-1.566 to 2.609	0.50	0.619	100.00	100.00	95% CI for I^2	64.39 to 95.55
Formant	**Treatment**	**N**	**F1 /u/ pre**	**DS pre**	**F1/u/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		
Mahler 2012 [147]	LSVT	4	323	25.40	333.75	22.91	-17.721	4.473	-28.666 to -6.777			0.36	4.50	Q	15.4454
Wenke 2008 [104]	LSVT	13	451	54	459	39	-0.164	0.381	-0.950 to 0.621			49.75	47.74	DF	2
Wenke 2008 [104]	Trad	13	435	59	440	56	-0.0842	0.380	-0.868 to 0.700			49.89	47.75	Significance level	P = 0.004
Total (fixed effects)							-0.188	0.268	-0.725 to 0.350	-0.699	0.487	100.00	100.00	I^2	87.05%
Total (random effects)							-0.917	0.994	-2.906 to 1.072	-0.923	0.360	100.00	100.00	95% CI for I^2	63.10 to 95.46
Formants	**Treatment**	**N**	**F2 /u/ pre**	**DS pre**	**F2/u/ post**	**DS post**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		

Mahler [147]	LSVT	4	1167	212.6	1171.75	186.87	-7.626	2.003	-12.526 to -2.725			1.77	14.11	Q	14.7254
Wenke [104]	LSVT	13	1650	220	1618	251	0.131	0.380	-0.654 to 0.916			49.11	42.95	DF	2
Wenke [104]	Trad	13	1703	222	1676	188	0.127	0.380	-0.658 to 0.912			49.12	42.95	Significance level	P = 0.0006
Total (fixed effects)							-0.0080	0.266	-0.542 to 0.525	-0.03	0.976	100.00	100.00	I^2	86.42%
Total (random effects)							-0.965	0.901	-2.769 to 0.839	-1.07	0.289	100.00	100.00	95% CI for I^2	60.83 to 95.29

Formant F, standard mean differences SMD, standard error SE, standard deviation SD, confidential intervals CI, before treatment Pre, after treatment Post, N. number of patients, Lee Silverman Voice Treatment LSVT, traditional rehabilitation speech therapy Trad, inconsistency I^2

Table XI Validity of the use of alternating motion rate (AMR- Pə, AMR-Tə, AMR-Kə, AMR-PəTəKə) in the evaluation of results based on different speech rehabilitation. Comparison before and after treatment.

DDK	**N.**	**Treatment**	**AMR-Pə pre**	**SD pre**	**AMR-Pə post**	**SD post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		Test for heterogeneity	
												Fixed	Random		
Kim 2013 [140]	6	AMSP	10.00	2.73	16.50	8.66	-0.934	0.566	-2.195 to 0.327			15.38	15.38	Q	0.5608
Kwon 2015 [106]	10	rTMS	19.9	4.7	23.0	4.4	-0,.52	0.441	-1.578 to 0.273			25.38	25.38	DF	4
Kwon 2015 [106]	10	Sham	20.8	3.2	22.5	3.0	-0.525	0.436	-1.441 to 0.892			25.88	25.88	Significance level	P = 0.9673
You 2010 [150]	6	Sham	20.3	5.4	22.5	5.3	-0.379	0.538	-1.579 to 0.820			16.99	16.99	I^2	0.00%
You 2010 [150]	6	tDCS	19.0	3.4	23.6	8.8	-0.636	0.548	-1.858 to 0.586			16.38	16.38	95% CI for I^2	0.00 to 0.00
Total fixed effects							-0.614	0.222	-1.056 to -0.171	-2.765	**0.007**	100.00	100.00		
Total random effects							-0.614	0.222	-1.056 to -0.171	-2.765	**0.007**	100.00	100.00		

DDK	**N.**	**Treatment**	**AMR-Tə pre**	**SD pre**	**AMR-Tə post**	**SD post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		Test for heterogeneity	
												Fixed	Random		
Kim 2013 [140]	6	AMSP	10.50	3.28	15.16	7.62	-0.733	0.553	-1.966 to 0.500			15.81	15.81	**Q**	0.3468
Kwon 2015 [106]	10	rTMS	20.2	4.6	22.9	4.5	-0.568	0.438	-1.488 to 0.351			25.27	25.27	**DF**	4
Kwon 2015 [106]	10	Sham	22.1	3.3	23.7	2.5	-0.523	0.436	-1.440 to 0.393			25.44	25.44	**Significance level**	P = 0.9866
You 2010 [150]	6	Sham	19.6	6.0	21.8	4.9	-0.371	0.538	-1.570 to 0.828			16.72	16.72	**I^2**	0.00%
You 2010 [150]	6	tDCS	20.6	3.8	23.3	9.6	-0.341	0.537	-1.538 to 0.856			16.77	16.77	**95% CI for I^2**	0.00 to 0.00
Total fixed effects							-0.512	0.220	-0.950 to -0.0734	-2.326	**0.023**	100.00	100.00		
Total random effects							-0.512	0.220	-0.950 to -0.0734	-2.326	**0.023**	100.00	100.00		
DDK	**N.**	**Treatment**	**AMR-Kə pre**	**SD pre**	**AMR-Kə post**	**SD post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		

Kim 2013 [140]	6	AMSP	8.16	4.35	14.16	7.52	-0.901	0,.564	-2.157 to 0.355			15.27	15.27	Q	0.9278
Kwon 2015 [106]	10	rTMS	18.7	5.2	22.2	5.5	-0.626	0.440	-1.550 to 0.297			25.10	25.10	DF	4
Kwon 2015 [106]	10	Sham	20.7	3.3	22.2	4.1	-0.386	0.433	-1.295 to 0.523			25.92	25.92	Significance level	P = 0.9205
You 2010 [150]	6	Sham	18.3	6.4	20.3	5.2	-0.316	0.537	-1.512 to 0.879			16.84	16.84	I^2	0.00%
You 2010 [150]	6	tDCS	18.1	9.2	21.0	9.2	-0.291	0.536	-1.485 to 0.904			16.88	16.88	95% CI for I^2	0.00 to 15.60
Total fixed effects							-0.497	0.220	-0.936 to -0.0584	-2.258	**0.027**	100.00	100.00		
Total random effects							-0.497	0.220	-0.936 to -0.0584	-2.258	**0.027**	100.00	100.00		
DDK	**N**	**Treatment**	**AMR-PəTəKə pre**	**SD pre**	**AMR-PəTəKə post**	**SD post**	**SMD**	**SE**	**95% CI**	**T**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		

Kim 2013 [140]	6	AMSP	3.93	1.60	5.48	1.92	-0.809	0.558	-2.052 to 0.433			16.10	16.10	Q	1.7963
Kwon 2015 [106]	10	rTMS	7.1	2.7	9.9	3.8	-0.813	0.447	-1.753 to 0.126			25.05	25.05	DF	4
Kwon 2015 [106]	10	Sham	8.1	2.1	8.5	2.1	-0.182	0.429	-1.084 to 0.719			27.19	27.19	Significance level	P = 0.7732
You 2010 [150]	6	Sham	8.5	2.4	10.8	1.9	-0.981	0.569	-2.249 to 0.288			15.47	15.47	I^2	0.00%
You 2010 [150]	6	tDCS	7.1	3.3	10.0	3.5	-0.787	0.556	-2.026 to 0.453			16.18	16.18	95% CI for I^2	0.00 to 56.41
Total fixed effects							-0.663	0.224	-1.109 to -0.217	-2.961	**0.004**	100.00	100.00		
Total random effects							-0.663	0.224	-1.109 to -0.217	-2.961	**0.004**	100.00	100.00		

DDK diadochokinesis, standard mean differences SMD, standard error SE, standard deviation SD, confidential intervals CI, before treatment Pre, after treatment Post, N. number of patients, Lee Silverman Voice Treatment LSVT, transcranial direct stimulation tDCS, transcranial magnetic stimulation treatment (rTMS), traditional rehabilitation speech therapy Trad, inconsistency I^2, accent-based music-speech protocol AMS

Table XII Validity of the use of maximum phonation time in the evaluation of results based on different speech rehabilitation. Comparison before and after treatment.

Authors	**Treatment**	**N**	**MPT pre**	**SD pre**	**MPT post**	**SD post**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%)**		**Test for heterogeneity**	
												Fixed	Random		
Kim 2013 [140]	AMSP	6	7.4	3.41	14.46	7.80	-2,103	0,684	-3,628 to -0,579			11,05	12,56		
Known 2015 [106]	rTMS	10	10.2	6.3	12.4	4.5	-0,385	0,433	-1,294 to 0,524			27,65	25,90	Q	2,6884
Known 2015 [106]	Sham	10	11.1	4.7	13.2	3.6	-0,480	0,435	-1,394 to 0,433			27,35	25,70	DF	2
You 2010 [150]	tDCS	6	8.3	4.7	11.4	5.9	-0,536	0,544	-1,748 to 0,676			17,49	18,36	Significance level	P = 0,2607
You 2010 [150]	Sham	6	6.6	3.1	9.4	2.9	-0,861	0,561	-2,111 to 0,389			16,44	17,47	I^2	25,61%
Total (fixed effects)							-0,706	0,227	-1,159 to -0,252	-3,102	**0,003**	100,00	100,00	95% CI for I^2	0,00 to 97,50
Total (random effects)							-0,736	0,262	-1,258 to -0,215	-2,813	**0,006**	100,00	100,00		

Maximum phonation time MPT, standard mean differences SMD, standard error SE, confidential intervals CI, standard deviation SD, before treatment Pre, after treatment Post, N. number of patients, Lee Silverman Voice Treatment LSVT, transcranial direct stimulation tDCS, Behavioural communication intervention BCI, traditional rehabilitation speech therapy Trad, inconsistency I^2

Third topic of the PhD project
Post-Stroke Dysarthria: A Multidisciplinary Approach to Rehabilitation

2.3.3. Speech rehabilitation in dysarthria after stroke: a systematic review of the studies.

2.3.3.1. Introduction

Speech and language difficulties such as dysarthria or aphasia are very common after a neurological damage, such as stroke, in addition to motor impairments in stroke patients [129]. Dysarthria affects 30-40% of the stroke population [151]. The presence of dysarthria is frequently documented in both acute and 3-month post-stroke clinical trial data [125].

According to research of the Mayo Clinic, the distribution of flaccid dysarthria with vascular aetiology is of 9%, of spastic dysarthria 17%, of ataxic dysarthria 11%, of hypokinetic dysarthria 4 %, of hyperkinetic dysarthria 1% [151].

At 6 months post-stroke, Wade et al. [152] found only 12% of survivors had significant aphasia, but 57% referred speech disorders. Geddes et al. [82] found that speech changes represented the third most common residual impairment, present in 51% immediately after stoke and 27% in the chronic phase.

There is a higher probability the dysarthria could resolve after 3 months after stroke [125].

On the basis of the predominant symptomatology after stroke and of the neuromuscular involvement, several type of dysarthria can be distinguished. If weakness follows the stroke, it typically indicates involvement of the lower or upper motor neurons and, if the speech disorder coexist is the flaccid or spastic dysarthria. Incoordination and arrhythmic performance, without weakness, is most often associated with cerebellar lesions and eventual ataxic dysarthria. The presence of involuntary movements and hyperkinesia is most often associated with basal ganglia involvement and. Hypokinesia and movements that are "scaled down," but can often be performed adequately in isolation, are commonly associated with basal ganglia disruption. In these cases of hypo- or hyper-kinetic dysarthria could be present [153]. The perceptual characteristics of dysarthria vary depending on the site and extent of the lesion and have been reported to include: articulatory–resonatory incompetence, imprecise consonants, distorted vowels, hypernasality, low pitch, harshness, strained strangled voice and prosodic disturbances including slow rate, to name a few [147]. It is important to differentiate the type of dysarthria to better localize the neurologic disease [153] and to better plane the impairment-based management. Flaccid dysarthria is secondary to a lesion of cranial or spinal nerves lesion. The speech features of flaccid dysarthria are hypernasality, breathiness, less distinguishing characteristics of monopitch, monoloudness, imprecise articulation, reduced range of motion (ROM) and maximum phonation time (MPT). The basic treatment is strengthening exercises. Spastic dysarthria in due to lesion of upper motor neurons. Speech features are Alternating motion rate/sequential motion rate performance, slow and regular rate, a strained-strangled voice quality, less distinguishing characteristics of monopitch, monoloudness, imprecise articulation. The exercises of relaxation are indicated. Ataxic dysarthria is characterized by arrhythmic from lack of coordination, irregular rhythm, slow rate, distorted vowels, loudness variations, incoordination of speaking and breathing. The treatment is based on coordination exercises. A lesion of the basal ganglia circuits can cause hypokinetic and hyperkinetic ataxia, characterized by arrhythmic performance from involuntary movements, fast rate of speech, monopitch, monoloudness, irregular prosody. The therapy is based on increasing loudness. Mixed ataxia needed of an integrating treatment.

The aim of this study was to perform a systematic review to list the different strategies of speech therapy for dysarthric patients after stroke. We analyzed the traditional treatment and the new therapeutic options [8]

2.3.3.2. MATERIALS AND METHODS

2.3.3.2.1. Search Strategy

The search was performed on the following medical electronic databases: PubMed, EMBASE, Cochrane Library and Scopus Web of Science. The review [8] was conducted from 15 December 2019 till 15 January 2020. We searched for the following terms and keywords: “stroke” and “dysarthria” and “speech therapy”.

2.3.3.2.2. Information sources and database search

Due to the different typology of the studies, the lack of meta-analysis and statistical analysis cannot be done. Thus, a descriptive synthesis was made.

2.3.3.2.3. Selection criteria and data extraction

From 1990 to 2019, the database searches yielded 94 references, whose titles and abstracts were screened by the reviewers. Sixty selected papers remained for full text screening, and the eligibility of the study inclusion was assessed independently. Twenty-five publications met the inclusion criteria and were included in the systematic review. Thirty-three articles were excluded for the following reasons: 12 involved patients with aphasia or other speech problems different from dysarthria, 10 examined only the clinical features of dysarthria, 3 treated on the impact of dysarthria on social participation following stroke, 8 were only descriptive or did not include clinical cases after stroke (no statistical results about the topic).

We included original articles about dysarthric patients with confirmed diagnosis of stroke. We excluded animal studies, participants with other neurological diseases. We also excluded all of the remaining duplicates.

Two reviewers (C.R. and V.M.) independently screened the titles and abstracts from the initial search to identify relevant records and to identify eligible studies based on title and abstract. In case of conflicting opinions, consensus was reached after discussion between the Authors. Selected full texts were then reviewed and included in the systematic review following the PRISMA protocol [44].

2.3.3.3. RESULTS

2.3.3.3.1. Description of the studies

The number of studies yielded at each stage of the search for the systematic review is displayed in Figure 14. A total of 25 studies were included in our review with the sample characteristics and details of the design of each included study displayed in Table XIII.

Table XIII Treatment of dysarthria post-stroke: characteristics and outcomes of studies included in the systematic review, according to PICOS (population, intervention, comparison, outcome, and study design) criteria for inclusion of studies.

Authors, yr	Study Design	Sample size, years old	Localisation of vascular lesion	Outcomes measure	Dysarthria severity	Rehabilitation speech therapy	Start of therapy	Duration of treatment	Outcomes	Results after therapy
Beijer 2014 [85]	Retrospective study	3 p 60.3 y	-	Scale ratings for intelligibility, pleasantness, orthographic transcription[12]. Changes in the vowel space. F0	Moderate	EST	1.16 m	4 w	20 w after therapy	Significant increase of speech intensity and of DIDC in the occlusion phase of voiceless plosives
Bowen 2012 [120]	RCT	A: 33 p 70 ± 11.4 y B: 36 c 75.5 y	-	COAST[48]. TOMA[49].	Severe	A: Speech therapy group B: No therapy group	Within the first 4 m post stroke	4 m 60’ 3 times/w	6 m after therapy	No evidence of enhancement with an early communication therapy

Hakel 2004 [109]	Case series	2 p	-	Clinical examination of velopharinx	Dysarthria and severe hypernasality	Nasal obturator with a one-way valve	-	-	After application of the device	Improvement of velopharyngeal dysfunction
Horton 2011 [154]	Case report	1 p 55 y	-	7 -point scaling for sentence intelligibility and transcription for words[17]	Moderate	Speech therapy	4 m post onset	Sessions of about 20’	Immediately after treatment	Engagement and learning improve the results of therapy
Kim 2013 [140]	Retrospective study	6 p 58.8 y	-	Acoustic measures: MPT, F0, jitter, shimmer, NHR, DDK	-	AMSP	Within one year	30’ 12 sessions	At the end of therapy	Increase of MPT, F0, dB, SMR. Improve speech production and oral-motor function of speech
Kwon 2015 [106]	RCT	A: 10 p 69.4 ± 11.8 B: 10 p	Unilateral middle cerebral artery infarction	Test of Articulation and Phonology.	-	A: rTMS group B: Sham stimulation group	Within the first 2 m	26.4 ± 15 d 30’, 5 d/w for 2 w	Immediately after therapy	Improvement in intelligibility in rTMS group

		68.8 ± 9.8 y		Alternative motion rates. SMR. MPT						
Li 2018 [124]	RCT	A: 50 p B: 50 p 40-80 y	-	FDA dysarthria assessment score, FDA speech breathing level, MPT, MCA, S/Z ratio, loudness level	-	A: traditional breathing training B: LQG	2 w–6 m after stroke	Once a day, 5 times a w, for 3 w	At baseline, 1 w, 2 w, 3 w after treatment	Effectiveness of LQG for improvement of speech breathing function and speech ability
Mackenzie 2007 [91]	Retrospective study	8 p 57.7 y	-	Word intelligibility test[50] 7 points scale for effectiveness of communication[26].	Moderate	Behavioural communication intervention	19.6 m	16 sessions, for 8 w	2 m after treatment	Improvement of communication effectiveness during conversation and of reading and word intelligibility after treatment

				Dysarthria Impact Profile[51].						
Mackenzie 2012 [110]	Case report	1 pt 69 y	Left hemisphere of frontal lobe and cerebellar hemisphere	Rate, pause, intonation, single word phonetic transcription. Frenchay Dysarthria Assesssment[52]	Severe	Behavioural communication intervention	7-9 m after stroke	16 sessions of 45’, for 8 w	8 w after therapy	Improvement of intelligibility
Mackenzie 2013 [117]	Retrospective study	12 p and 7 f 68.8±12.9 y	- Right insula - Right and left external capsule, cerebellar / pons - Left posterior circulation - Left parietal - Right basal ganglia	QCLS[53]. SIT[53]. CEM[26]. CES[53]. GHQ-12[54]. SKT[55].	-	A: Living with Dysarthria group	34.4± 26.7 m post stroke	8 sessions of 2h, one/w	At the end of therapy	Improvement in sentence level intelligibility

Mackenzie 2014 [118]	RCT	A: 16 p 62.8 ± 12.8 y B: 19 p 67.95 ± 12.1 y	-	CEM[26]. SIT[53]. FDA-II[56].	A: Mild 12 p Severe 7 p B: Mild 9 p Severe 11 p	A: behavioural, activity level practice B: the same of A +NSOMe	3 m post stroke	A: 10.8±7.09 m 40’ once/w B: 9.3±5.12 m 40’ once/w Included 10’ of NSOMe	2 m post treatment	Improvement in lip and tongue movements
Mahler 2012 [147]	Retrospective study	4 p 31 y	-	Sustained vowel phonation. AIDS[57].	Mild - Moderate	LSVT	9 m post stroke	16 session in 4 w	2 w after treatment	Improved voice quality
Mitchell 2017 [121]	RCT	26 pt 69 y	-	TOMA[49]. COAST[48]. DIP[51]. FDA-II[56]. EQ-5D-5L[58].	-	ReaDySpeech	-	14 m, 40’ session duration	-	Evidence for the feasibility of a RCT into the effectiveness of ReaDySpeech
Mitchell 2018 [122]	RCT	n. 24 pt 69 y (37–99 y)	Anterior circulation: 9p Postrior circulation: 4p	FDA-II[56]. TOMA[49]. COAST[48]. DIP[51]. EQ-5D-5L[58].	-	ReaDySpeech	-	14 m, 6 sessions of 40’ duration	-	Possibility of recruitment and retention in this trial of computerized

										therapy of acute stroke
Park 2015 [100]	Retrospective study	2 p 46.5 y	-	7 points scale ranging[33]	Mild / moderate: 1 p Severe: 1 p	Be Clear	20 m post stroke	1 h, 5 times/w for 1 m	Immediately after treatment, 1-3 m after treatment	Improvement in speech intelligibility
Peng 2015 [155]	Retrospective study	16 p -	-	FDA[56].	-	VitalStim acupuncture + speech therapy	within 1 m post stroke	30', once a d, for 28 d	Immediately after treatment	Improvement in Barthel index e FDA
Ray 2002 [101]	Case series	12 p 74.7 y	Right hemisphere ischemic stroke	Alternating motion rate. 5-point intelligibility rating scale[28].	Mild and moderate	Oral motor exercises	-	45' Twice/w for 2 m	Immediately after treatment	No improvement
Robertson 2001 [102]	Case series	8 p 70.2 y	-	Dysarthria scores[18].	-	Oro-facial and articulation exercises	3.7 w post stroke	10 w 10 session, 1/w 45'	10 w after of therapy	Improvement in speech intelligibility
Roggeman 2019 [131]	Case report	n. 1 pt 33 y	Bulbar	Examination of intelligibility, fluency, intensity	-	CIDT	After stroke	2 m	12 m after stroke	Increased communicative participation

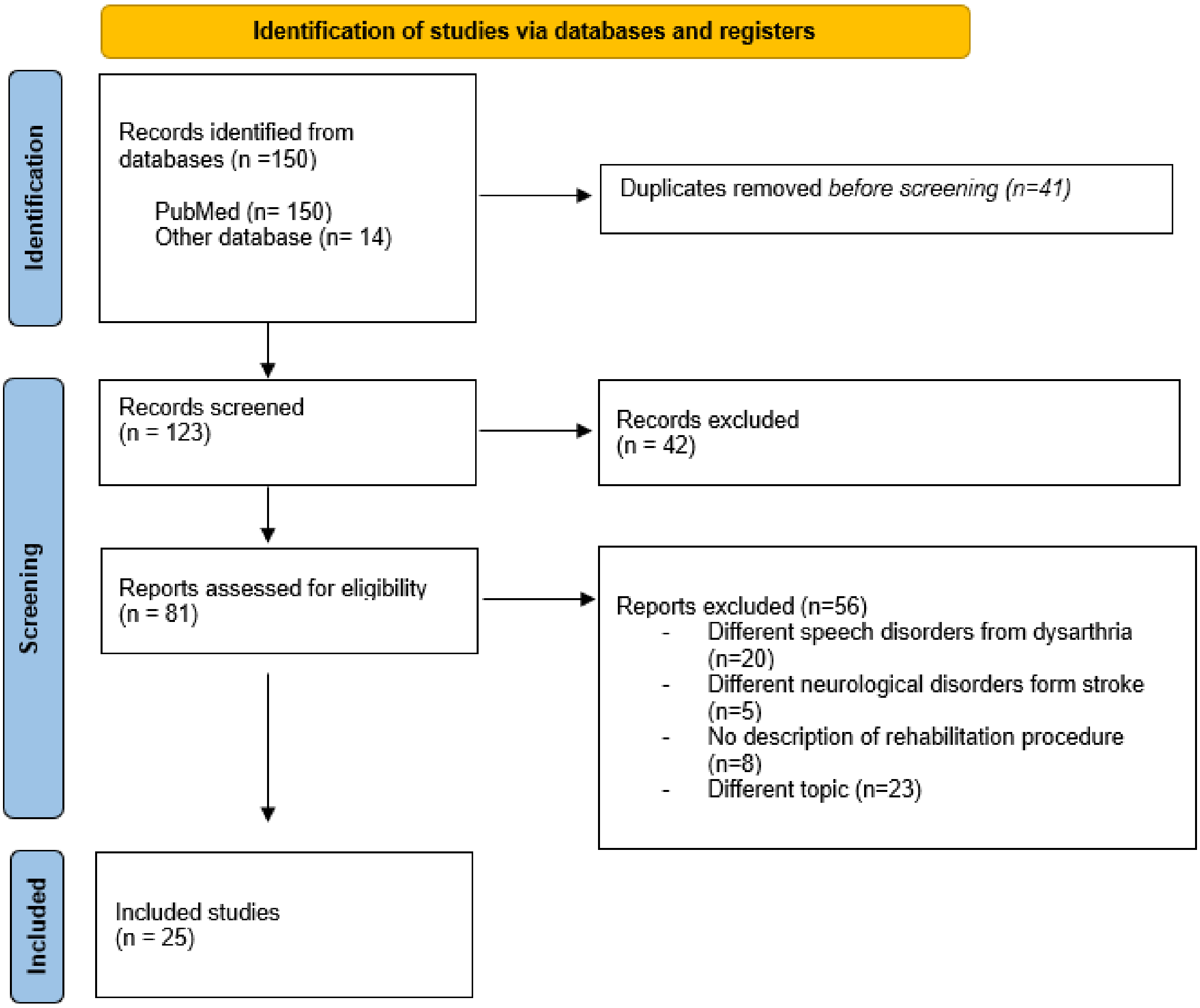
Tamplin 2008 [129]	Case series	4 p 40.5 y	-	SIT[53]. Waveform analysis. Ratings of speech naturalness.	Mild to severe	Vocal exercises and singing + speech therapy	< 18 m post stroke	30’, 24 sessions, 8 w	Immediately after therapy	Significant improvements in functional speech intelligibility. No improvements in rate of speech.
Wenke 2008 [104]	Retrospective study	3 pt 48.3 y	- Brainstem - Left posterior circulation, middle cerebral artery	AusTOMs[60]	Mild-moderate	LSVT	59.3 m post stroke	4 w	Immediately after therapy and 6 months post-therapy	Significant increase of vocal loudness, vocal frequency range, intelligibility
Wenke 2010 [108]	RCT	A: 13 p B: 13 p 48.6 ± 21.3 y	-	Acoustic and perceptual measures	A: Mild / moderate 7 p, Moderate / severe 6 p B: Mild / moderate 7 p,	A: TRAD B: LSVT	6 m post stroke	1 h/d, for 4 d/w for 4 w	Post-treatment and 6 m after stroke	Improvement in articulatory precision

					Moderate / severe 6 p					
Xu 2010 [156]	RCT	A: n. 30 B: n. 30 52.6 ± 12.7 y	-	Speech and acoustics indices	Mild and moderate	A: Acupuncture + Speech therapy B: Speech therapy	2.8 ± 2.13 y post stroke	Acupunture9 w with 1 w of no therapy at w 5. Speech therapy: 30’, 5 times/w and speech therapy for 30’ sessions, 5 times per w for 9 w	Immediately post treatment	Improvement in word articulation, correct rate of text and MPT
You 2010 [150]	Case control study	6 pt	Acute middle cerebral artery infarction	MDVP[61]	-	tDCS at 2 milliampere with 25 cm^2	-	30’, 5 times/w, for a total of 2 w	Immediately after treatment	Improvement of MPT, AMR-Pa, AMR-Ta, AMR-Ka, and SMR-PaTaKa
Young 2013 [123]	RCT	A: 10 p 73 y B: 11	-	COAST[48]	-	A: Early speech therapy B: no-therapy group	After 6 m post stroke	4 m	6 m after therapy	No significant benefit of early communication therapy

		-								

Constrained-Induced Dysarthria Therapy CIDT, year y, m males, w women, months m, weeks w, days d, hours h, patients p, controls c, number n, Frenchay Dysarthria Assessment second edition FDA-II, Dysarthria Therapy Outcome Measures Activity TOMA, Communication Outcomes After Stroke Scale COAST, Dysarthria Impact Profile DIP, EQ-5D-5L and visual analogue scale VAS, Speech Intelligibility Test SIT, maximum phonation time MPT, rTMS repetitive transcranial magnetic stimulation treatment, Communicative Effectiveness Measure CEM, Randomised controlled trial RCT. A: group A, B: group B, traditional dysarthria therapy TRAD, Lee Silverman Voice Treatment LSVT, transcranial direct stimulation tDCS, MDVP multi-dimensional voice program, fundamental frequency F0, noise to harmonics ratio NHR, diadochokinesis DDK, sequential motion rates SMR, accent-based music-speech protocol AMSP, familiars f, Quality of Communication Life Scale QCLS, Communicative Effectiveness Survey CES, Short General Health Questionnaire GHQ-12, Stroke Knowledge Test SKT, Assessment of Intelligibility of Dysarthric Speech AIDS, Australian Therapy Outcome Measures Scale AusTOMs, E-learning based Speech Therapy EST, intensity during closure DIDC, non-speech oro-motor exercises NSOMe; Alternative motion rates (AMR)-Pa, AMR-Ta, AMR-Ka, and sequential motion rates (SMR)-PaTaKa.

Figure 14 Flowchart of the process of initial literature search and extraction of studies meeting the inclusion criteria.



2.3.3.3.2. Variations of experimental conditions across the studies

All study groups were not homogeneous for the relevant general clinical features as clinical presentation, duration of disease, kinds of voice parameters examined. The disease duration ranged from 6-35 months. A large variation existed in other features, such as mean age which ranged from 41 to 69 years old, and the features of speech examined. The selected twelve articles will be described according to the speech therapies examined in each study.

2.3.3.3.3. **Speech therapy**

2.3.3.3.3.1.Traditional interventions

Wenke et al. [108] compared a traditional protocol of speech therapy with Silverman Voice Treatment (LSVT). Their protocol included behavioural techniques and consisted of different activities in each session, such as sustained phonation, oro-motor exercises of the tongue and lips, with six - seven repetitions for each task. Wenke et al. [108] found that LSVT demonstrated more significant improvements to several acoustic and perceptual parameters than traditional treatment.

Tamplin [129] added to his protocol, based on vocal exercises, and singing, traditional exercises without specific details. Beijer et al. [85] compared E-learning based Speech Therapy (EST) therapy with traditional face-to-face speech training without explaining the exercises. Horton et al. [154] described the exercises for speech training: breath control, tongue and lip movement accuracy routines, phrase repetition. Also Bowen [120], Mackenzie [118], Xu [156] and Peng [155] adopted the traditional speech therapy comparing respectively with a group control without therapy, with non-speech oro-motor exercises and acupuncture in the last two studies without details about traditional speech therapy.

2.3.3.3.3.2. Education, external supports, psychological support

Bowen et al. [120] and Young et al. [123] described the importance of visitors support on communication of dysarthric patients after stroke. The interesting research of Young et al. [123] studied the possibility of higher beneficial effects of the persons and visitors on dysarthric patients after stroke, respect to the interventions and attention control. According to Young et al. [123], people with dysarthria who receive an early speech therapy demonstrated similar levels of functional communication ability at 6 months to those who received visits from a non-therapist employed without a specific communication training. Both a visitor and a speech and language therapist contributed in the same way to improve the speech of dysarthric patients. People with dysarthria who receive an early, well-resourced and individual speech intervention demonstrated similar levels of functional communication ability at six months to those who receive visiting from a non-therapist to provide an informal conversation without a specific communication training [123].

Psychological support includes explanation and education about dysarthria, working with communication partners or communication support groups, motivational interviewing [122].

2.3.3.3.3.3. Behavioural intervention

Behavioural intervention was described in three studies of Mackenzie et al. [91,110,118]. Mackenzie et al. [110] described an individualised behavioural therapy program of 16 sessions of 45 minutes, over an 8 weeks period. Sessions included the practice of set stimuli and several activities to generate spontaneous utterances. Patients were invited to speak more slowly, make pauses for breath between sense groups, articulate sounds deliberately with wide mouth opening, avoid long sentences [91,110]. In another article of Mackenzie [118], 8 once weekly sessions of around 40 min were performed in two group. The results indicate positive outcomes in A group associated with a short period of behavioural intervention in the post-stroke dysarthria population. The inclusion of non-speech oro-motor exercises in B group did not appear to influence outcomes.

2.3.3.3.3.4. Oral motor exercises

Robertson et al. [102] planned the treatment with oral motor exercises (OME) in main areas: oro-facial muscle exercises including diadochokinetic (DDK) rates (for rapid alternating movements and sound sequences), articulation exercises ranging from single words to complex longer utterances. According to the article of Robertson et al. [102], a well-defined, traditional programme of therapy with OME improved significantly intelligibility.

Mackenzie et al [118] added 10 minutes of oro-motor exercises as part of the 40-minute session that included also non-speech oro-motor exercises in intervention B group. Also, Wenke et al. [108] added to his traditional protocol oro-motor exercises to improve articulation. Oro-motor exercises, such as training to improve range of movement, strength and speed were also used in Ready Speech protocol [121,122]. Ray et al. [101] found no significant changes in intelligibility of sentences or conversations after specified OME.

2.3.3.3.3.5. Strategies of communication

In our research, we found 3 articles that examined the way of communication to make easy the listener understands [153,157,158]. The proposed strategies of communication are writing [153], using electronic communication devices or gesture [157], alphabet board [158], dealing with a specific topic without pindaric flights [158], paying attention at the speaker interacting and using an appropriate prosody [153], encouraging the exact use of grammatic, select an adequate environment without noise and distraction avoid communication over long distances [153].

The articles of Spencer et al. [153], of Fager et al. [157] and of Hanson et al. [158] are only descriptive, for this reason we did not add their works in Table XIII. No other papers considered this type of communication strategy.

2.3.3.3.3.6. Speech supplementation and augmentative communication (AAC)

Speech supplementation techniques includes communication aids and supportive communication tools, such as alphabet charts for example indicating the first letter of the word spoken, text-to-speech aids, topic supplementation indicating the topic of the message and the gesture illustrating speech [158]. There are also compensatory technological instruments, such as alphabet boards, pacing boards, finger tapping, letter chart, smartphone, tablet [159].

The article of Hanson et al. [158] is only descriptive, without statistical results about speech treatment. For this reason, we did not add this study in the Table XIII.

2.3.3.3.3.7. Activity-level strategies

Several articles described the activity level practice to improve communication in dysarthric patients after stroke. These strategies included speech sounds in words, sentences and conversation, slowing rate, over-articulating words deliberate articulation, spelling out letters, emphasis of key syllables or words may improve the intelligibility and the success of communication [110,118,122,153].

The articles of Spencer et al. [153] is only descriptive, for this reason we did not add their works in Table XIII.

There are no articles that examined statistically the eventual benefits of the strategies of communication, the ACC and the activity-level strategies.

2.3.3.3.3.8. E-learning based Speech Therapy

Beijer et al. [85] described the rule of E-learning based Speech Therapy (EST) in neurorehabilitation. The speech training, based on the protocol of Beijer et al. [85], was conducted in web and once a week for 4 weeks a physician evaluated the web-based speech training. The speech training focused on the phonetic realization of explosives /p, t, k, b, d/, voiceless fricatives /f/and /s/ and on the realization of the vowels /e, a, o/. In addition, the suprasegmental speech dimension ‘‘intonation’’ was addressed. For patients with stroke, this speech-training program aimed at improving articulation and treating the imprecise articulation of consonants.

2.3.3.3.3.9. Constraint-induced dysarthria therapy

Roggeman et al. [131] proposed a new form of constraint-induced therapy, namely constraint-induced dysarthria therapy (CIDT). The patients received the individual speech therapy focused on breathing, articulation, phonation and resonance to improve intelligibility. The rehabilitation followed an intensive project of 10 workdays, for several hours a day (3–6 hours). The protocol was based on a progressive increased of difficulty [131]. According to the result of Roggeman [131], after a 2-month intervention, the improvement was noted for speech intelligibility, fluency and intensity. This led to increased communicative participation, including during conversation situations, which has been maintained over a 12-month follow-up after discharge.

2.3.3.3.3.10. Be Clear

Park et al. used a new intensive dysarthria treatment program: Be Clear [100] The subjects with dysarthria adopted a rate reduction and purposeful enunciation (overarticulation) of all sounds. The results of the treatment with Be Clear was an increased fundamental frequency and frequency range, increased pause frequency and duration, increased sound pressure level, vowel space expansion, increased consonant to vowel intensity ratios, decreased burst elimination and decreased alveolar flapping. Word and sentence intelligibility was clinically significantly improved after this treatment.

2.3.3.3.3.11. Non-speech oro-motor exercises in rehabilitation

Several studies highlighted the importance of non-speech oro-motor exercises for dysarthria after stroke [114,118,160,161,162]. In the study of Mackenzie et al. [118], the patients of B group were subjected to10 minutes of non-speech oro-motor exercises (tongue and lip movements) replaced 10 minutes word and sentence practice, as part of the 40-minute session. Mackenzie et al. [118] included non-speech oro-motor exercises in their speech rehabilitative protocol, despite a lack of evidence of an influence on communication outcomes. After this treatment the results indicate positive outcomes associated with a short period of behavioural speech and language therapy intervention in the post-stroke dysarthria population, maintained for 2 months after intervention. The inclusion of non-speech oro-motor exercises did not influence outcomes [118].

In another article of Mackenzie [160], showed that non-speech oro-motor exercises are a frequent component of dysarthria management in the UK countries and the most common regimes were 4 to 6 repetitions of each exercise, during three practice periods daily, each of 6–10 minutes.

In 2009 Mackenzie et al. [160] performed research to collect data about the use of non-speech oro-motor exercise in the UK, this study is not present on Table XIII. The study of McCauley et al. [161], is not present in the Table XIII because it is a review about the nonspeech oral motor exercises. The study of Clark [162] and Bunton [114] are not in the Table XIII because they did not treat the topic.

2.3.3.3.3.12. Vocal exercises and singing

Tamplin et al. [129] used vocal exercises and singing for dysarthria after stroke. This protocol included oral physical preparation, motor respiratory exercises, rhythmic and melodic articulation exercises, rhythmic speech cuing, vocal intonation therapy, and therapeutic singing using familiar songs. This program improved vocal range, rate of speech, verbal intelligibility, vocal intensity and reduces in pause time. The study of Tamplin [129] suggested that a program of vocal exercises and singing could facilitate more normative speech production for people with acquired dysarthria.

2.3.3.3.3.13. ReaDySpeech

Two randomise clinical trials about an online therapy programme, ReaDySpeech, were conducted by Mitchell et al. [121,122]. In these two studies, ReaDySpeech and usual care were administered to dysarthric subjects more than 1 week after stroke [121,122]. These studies involve a multi-centre, randomised controlled feasibility trial of a complex intervention in order to show that recruitment and retention of computerized therapy for dysarthria is feasible for acute stroke [121,122]

2.3.3.3.3.14. Acupuncture

Xu et al. [156] inserted acupuncture needles at the acupoints in different ways. The needles were pulled out when the skin sites of the major acupoints Jinjin and Yuye began to bleed. The needles inserted into the other major acupoints and additional points except these two points were left for 30 minutes at a time, 5 times/week. They submitted the subjects also to speech therapy for 30 minutes, 5 times per week for 9 weeks.

Peng et al. [155] performed VitalStim electroacupuncture on 32 patients with spastic dysarthria after stroke within one month. Subjects were randomly divided into VitalStim group and control group. Basic medical therapy, physical therapy, occupational therapy and speech therapy were used in both groups. Additionally, modified VitalStim electroacupuncture was performed in Vitalstim group. Patients in VitalStim group received extra 30-minute VitalStim therapy once a day, for a total of 28 days. The electroacupuncture was performed at acupoints of Yiming (EXHN14), Fengchi (GB20), Dazhui (BU14), Lianquan (RN23), Baihui (DU20) and lateral Jinjinyuye. Xu et al. [156] performed Acupuncture at Lianquan (CV 23), Jinjin (EX-HN 12), Yuye (EX-HN 13), Fengchi (GB 20), Yifeng (TE 17) and Wangu (GB 12). Participants in the VitalStim group received extra 30-minute VitalStim therapy once a day, for a total of 28 days. The VitalStim group presented a higher improvement of their speech function than the other group.

According to Xu et al. [156] and Peng et al. [155] acupuncture combined with speech therapy improved the effect on language and acoustics level in dysarthric patients after stroke.

2.3.3.3.3.15. Transcranial magnetic stimulation treatment

Repetitive transcranial magnetic stimulation treatment (rTMS) for dysarthric patients after stroke was described by Kwon et al. [106]. This study [106] investigated rTMS versus sham repetitive transcranial magnetic stimulation; both groups received the same speech therapy intervention.

The participant was treated with 10 consecutive sessions (5 times per week for 2 weeks) at a low frequency (1 Hz), at 90% amplitude of evoked motor threshold, 1.500 stimulations/day, 5 days a week for 2 weeks on the hotspots. According to the study of Kwon et al. [106], patients in the rTMS group showed greater improvement in articulation than did patients in the sham rTMS group.

You et al. [150] described the effects of transcranial direct stimulation (tDCS) on dysarthria in stroke patients. tDCS was delivered for 30 minutes at 2 milliampere (mA) with 25 cm², five times/week, for a total of 2 weeks. You et al. [150] demonstrated the beneficial effects of anodal tDCS on dysarthria after stroke.

2.3.3.3.3.16. Lee Silverman Voice Treatment

According to the speech rehabilitative protocol of Mahler et Ramig [147], the patient faced up the following tasks: maximal sustained vowel phonation, pitch range exercises and reading 10 functional phrases, at individual target loudness levels. Then, they faced up functional speech tasks as the repetitions of words, phrases, until to sustain a conversation. The therapy was performed 4 times a week for 4 weeks for a total of 16 individual one-hour sessions. Mahler et Ramig [147] showed that the subjects responded positively to this intensive speech treatment.

According to the study of Wenke [108], the LSVT increased articulatory precision and vowel space area that was associated with an improvement of intelligibility. In addition, LSVT increased loudness, that was associated with changes to lingual function. Wenke et al. [108] found that LSVT presented more significant improvements than traditional treatment, such as an increased vocal loudness in sustained phonation and connected speech. Another research of Wenke et al. [104] showed a statistical increasement of vocal frequency range and an improvement of word and sentence intelligibility.

2.3.3.3.3.17. Accent-based music speech protocol

The study of Kim et al. [140] presented an accent-based music speech protocol (AM). The protocol described by Kim [140] begins with warm-up for 4 minutes, moving arms, trunk and hands. The second stage was respiratory training (4 minutes). Subjects were asked to breath in and out with their hands on their abdomens. The third stage includes phonation exercises for 10 minutes, opening the throat and relaxing the muscles involved in vocalization. Lastly, melodic chant with accent was performed for 12 minutes. According the study of Kim et al. [140], the accent-based music speech protocol could improve speech motor coordination including respiration, phonation, articulation, resonance and prosody of patients with dysarthria.

2.3.3.3.3.18. Living with Dysarthria group intervention programme

The Living with Dysarthria group intervention programme described by Mackenzie [117] has a positive effect on participating people with dysarthria and family members. Programme activities included a phase of presentation and group discussion with orientation to individual experience and needs. Then, the phase of discussion and the speech practice targets the effectiveness of communication. In addition, participants see video of speech patterns of well-known people. they learned to talk against background noise.

2.3.3.3.3.19. Velopharynx and the respiratory-phonatory exercises

In the cases of velopharyngeal incompetence in dysarthric post-stroke patients a prothesis can be necessary. The protheses, designed for rehabilitation use, were describe also for dysarthric people after stroke, such as the palatal lift prosthesis (PLP) and the palatal augmentation prosthesis (PAP) [130]. After the surgery with the application of these devices, Ono et al. administered speech behavioural management. The speech rehabilitation after surgery comprised: training for self-monitoring to improve intelligibility when reading text or conversation; and bio-feedback traininùg to improve the speed and accuracy of velopharyngeal closure [130]. According to the article of Ono et al. [130] speech behavioural management was useful for promoting improvement in speech intelligibility after the application of prosthesis, due to velopharyngeal incompetence.

There are individuals for whom the palatal lift is not an option due to motor, sensory, cognitive, or dental factors. For this reason, Hakel et al. [109] developed a nasal obturator with a one-way valve to allow inhalation through the nose and closes during exhalation or nasal emission during speech. the nasal obturator reduced the velopharyngeal incompetence.

According to the systematic review of Yorkston et al. [159], the effectiveness of devices is limited by the small number of subjects studied; however, the devices could improve the speech loudness and intelligibility of subjects with hypokinetic dysarthria without success with behavioural intervention alone.

The systematic review of Yorkston et al. [159] and the descriptive study of Spencer et al. [153] were not included in the Table XIII.

2.3.3.3.3.20. Homework

About the homework between the logopaedic sessions, Bowen et al. [120] highlighted that several individuals found them useful or contributed to a feeling of overload. This article encouraged the practise of homework by the participants, but there is no further description of whether homework was carried out or completed. The homework described by the article of Mackenzie et al. [118] lasted 10 to 15 minutes, 5 days/week. The participants in both intervention A and B were encouraged to carry out their home practice. This was documented by participants in a diary and the results reported and analysed [118]. According to Wenke et al. [108], homework lasted 5 to 10. The homework was suggested between sessions for the B group that executed the traditional exercises only, but whether the exercises were carried out and recorded was not described [108]. In addition, the participants were asked to continue to practice at home activities that were taught during therapy for 5–10 minutes a day, 3–5 days a week, for 6 months [108]. LSVT programme includes homework and maintenance exercises are provided in Mahler et Ramig [147]. Mahler and Ramig [147] advised daily homework using normal loudness. The assigned daily homework included exercises using normal loudness [147]. Kwon et al. [106] describes the duration of the homework: 30 minutes, 5 days per week for the two weeks of rTMS treatment. But the content of the speech therapy intervention was not described. Horton et al. [154] mentioned the homework for one of their patients, without other description. The Be Clear program included a power point presentation with the description of homework [100].

In another study, Mackenzie et al. [110] advised home practice, 15 minutes daily to making conscious effort and to apply the maximisation strategies in all speaking situations. According to Robertson [102], throughout the 10 weeks of therapy, the subjects were encouraged to follow a home practice programme 3 times per day. An analysis conducted by Robertson [102], the subjects who made the greatest improvement practised exercises at home on average 2.5 times per day in comparison with the subjects practiced homework less than once per day (mean = 0.9), whose performances remained almost the same or who deteriorated.

3. Evidence Synthesis

The series of multi-faceted projects aim to delve deep into the myriad impacts of stroke on patients and the potential treatments that can mitigate these effects.

The first project delves into how strokes affect motor functions and the therapeutic strategies that can be employed to mitigate these effects. Recent research has underscored the effectiveness of goal-oriented dual-task proprioceptive training for improving motor function and mobility in neurological disorders, especially in stroke [1,163]. The importance of this approach forms the crux of the first part of this project, with a comprehensive systematic review of the literature to collate and analyze the current evidence [1,2]. Building upon the findings from the systematic review, the project then conducts an observational study involving data collection and analysis to gain practical insights into the effectiveness of the training [3].

Furthermore, the project explores the potential antidotes for botulinum neurotoxin, used for spasticity in stroke treatment [4].

The second project delves into the interplay of stroke and associated complications, such as infections [5], and sarcopenia [6]. It is known that post-stroke infections, especially pneumonia and urinary tract infections, worsen the prognosis of stroke patients.

The project explores the impact of these infections on stroke complications with the aim of identifying preventative strategies [5]. Furthermore, the project investigates the development and impact of sarcopenia, or loss of muscle mass and function, a common occurrence following a stroke that can contribute to disability and poor quality of life [6].

Finally, the third project explores post-stroke dysarthria, a motor speech disorder, using a multidisciplinary approach. Stroke often impacts speech capabilities, making dysarthria a common post-stroke complication. Management of dysarthria is multidisciplinary, involving a collaboration of speech-language pathologists, neurologists, physical therapists, and occupational therapists. This project seeks to emphasize the importance of this collaborative approach in diagnosis and managing post-stroke dysarthria, thereby improving patient outcomes [7,8,9].

3.1. First topic of the PhD project: Impact of Stroke on Motor Function and Rehabilitative approach

3.1.1. The effectiveness of goal-oriented dual task proprioceptive training in stroke patients: A Systematic Review of the Literature

Daily rehabilitation over approximately a month enables about 11% of stroke patients to walk with assistance, while 50% can walk independently [164]. However, the rate of falls post-discharge from rehabilitation programs among stroke survivors is high, at 70% [165], and approximately 18% of these patients do not regain their walking ability [164]. Therefore, a need exists for specialized rehabilitation programs that integrate multiple tasks while maintaining balance and promoting walking, as well as effectively distributing attention through dual-task training to ensure safe walking and prevent falls.

During the execution of dual tasks, observational and instrumented gait analyses prove to be beneficial tools for assessing walking abnormalities and fall risks. These analyses guide the creation of targeted interventions, assist in preventing further functional decline, and monitor rehabilitation results [166].

3.1.1.1. Summary of collected data about gait parameters

Gait speed is one of the most widely studied parameters, as indicated by numerous papers included in the systematic review [27,33,34,37,42,63,64,65]. Significant changes in gait parameters, especially gait speed, have been documented in individuals with Parkinson’s disease [167], dementia [163], and multiple sclerosis [168].

Perry et al. [32] provided compelling evidence that walking speed is predictive of community walking ability [169]. The normal range of gait speed falls between 1.2-1.4 meters/second. However, this can vary depending on age, gender and anthropometrics. A walking speed less than 0.8 m/sec is often associated with limited mobility in community settings [170].

In 1995, Perry et al. [171] demonstrated a statistical correlation between gait velocity and the severity of clinical conditions, establishing that walking speed was an accurate predictor of community walking status. They found that a speed of less than 0.4 m/s predicts household walking; 0.4–0.8 m/s predicts limited community walking; and more than 0.8 m/s predicts unlimited community walking [169]. Furthermore, transitioning from one speed-based category to another is associated with improvements in self-reported measures of function and quality of life [172]. Therefore, walking speed has been used to stratify patients with neurologic injury [173].

Moreover, comfortable gait speed is also linked to regular executive functioning. A higher walking speed is associated with better cognitive ability than a slower speed, reflecting optimal function of the locomotor system [163]. Conversely, poor physical function and slow walking speed are correlated with deteriorating cognitive function in older people [170]. Individuals with chronic stroke often prioritize task accuracy and completion over maintaining walking speed. This behaviour is more pronounced during cognitive tasks than motor tasks, especially at maximum walking speed [174].

Concerning dual-task activities, gait speed decreases during dual tasks, particularly in the earlier stages following a stroke [175]. Specifically, cognitive-related gait speed interference is highly prevalent early after stroke and often persists even when single-task gait gait speed improves [175].

Considering these factors, speed can be regarded as a holistic parameter that integrates all gait parameters [163]. Specifically, an adequate walking speed of 0.8 ms^{-1} or greater is necessary to enhance dual-task walking post-stroke. Therefore, only individuals with sufficient walking capacity have the potential to improve dual-task walking [176]. As a negative feedback loop, patients who fail to regain good speed may struggle with dual-task activities. This inability places them at a higher risk of falls and subsequent disability.

3.1.1.2. Summary of collected data about proprioceptive dual task training

There are limited studies in the existing literature that address dual-task exercises in the context of proprioceptive rehabilitation strategies for stroke patients.

Proprioception and multitasking capabilities are critical to maintaining autonomy in activities of daily living (ADLs). A stroke can result in impairment of these abilities, leading to significant disability, which can be mitigated with specialized rehabilitation. While traditional training methods support balance control, a dual-task regimen incorporating both motor and cognitive exercises alongside proprioceptive training could enhance recovery and decrease fall risk. Our study, backed by international literature, underlines the necessity of promoting specific protocols and formulating guidelines on proprioceptive rehabilitation in tandem with contextual dual-task strategies.

The samples examined predominantly comprised subjects who had experienced a chronic stroke. Once their clinical conditions stabilized, the primary objective of the rehabilitation project was to restore their autonomy in ADLs and facilitate their social reintegration. Task-oriented proprioceptive training was identified as an effective rehabilitation method to achieve this goal.

3.1.1.3. Task-Oriented Rehabilitation Therapy in the Context of Proprioceptive Rehabilitation

ADL require a blend of cognitive and motor-task performance, particularly during postural balance and ambulation [37]. As such, balance and gait in stroke patients mirror the changes in motor and cognitive abilities required in the dual activities of daily life. Moreover, there is a significant correlation between proprioception impairment, difficulties in dual-task activities, and an increased risk of falls post-stroke [177]. In fact, the decline in balance control leads to falls in individuals post-stroke, especially during dual-tasking. This suggests that enhancing task performance is the aim of rehabilitation in the face of proprioception impairment [36]. Two studies [33,43] underscored that the risk of falls while walking increases during daily dual-task cognitive performance, such as decision-making, visuospatial memory, and working memory. Therefore, specific training enhances daily dual-task activities and, as a result, autonomy in ADL.

Various rehabilitative strategies have been explored to prevent falls and enhance balance, gait performance, and community participation. Current literature is showing increased interest in the impact of dual activity training in older adults [178], dementia [163], Parkinson's disease [179], and multiple sclerosis [180], as well as in stroke, as evidenced by the articles in this systematic review. Motor and cognitive multi-tasks that are grounded in the principles of motor learning and neuroplasticity, and aim to transfer clinic-based gains to daily life, hold a significant place in stroke rehabilitation [181]. Task-oriented exercises that offer the opportunity to engage in real-world activities and include tasks demanding both cognitive and motor abilities, promote adaptation and participation in life situations for chronic stroke patients compared to exclusively motor-problem-focused trainings [181]. Therefore, dual-task training enhances autonomy in ADL by improving the ability to process information. Despite this, only a few reports have examined which dual-task exercises could be most effective in the context of proprioceptive rehabilitation for improving balance and daily skills after stroke. According to our research, the high variability of the proposed exercises did not influence the outcomes. All the proposed cognitive and motor task exercises, when combined with proprioceptive exercises like maintaining balance on a mobile platform [16,23,27,28,29,30,31,32], an unstable balance pad [24], or during overground walking [33,34,35,36,37], changing speeds [38], wearing ankle weights [39] or using an elastic band between legs [40], proved effective. The variability in the structure of the rehabilitation session, particularly regarding timing, highlighted the positive response of patients to the treatment, on average 3 days a week for 4 weeks [33,37,38,40,43]. This held true even if the duration was shorter or longer.

3.1.1.4. Implication in rehabilitation

The primary goals of rehabilitation include reducing the risk of falls, maintaining functionality in Activities of Daily Living (ADL), preserving postural balance, and mitigating the severity of stroke-related symptoms. Dual-task exercises that require cognitive engagement can enhance motor learning for posture and gait control, thereby improving balance, motor control ability, and proprioception [182].

To decrease disability, falls, and loss of autonomy in ADL, a rehabilitation program incorporating proprioceptive training and dual-task activities may be essential for therapeutic success. Future research is expected to refine proprioceptive rehabilitation programs, developing new exercise sets, incorporating smart technologies for self-guided rehabilitation, and devising new methods for more specific diagnoses of proprioceptive impairments. Additionally, it is vital to ensure patient safety throughout the treatment, by creating safe rehabilitation environments.

3.1.1.5. Embracing Technology

Several studies [28,29,36,41] have proposed combining proprioceptive and dual-task training within a virtual reality environment.

Apart from traditional methods like the proprioceptive neuromuscular facilitation technique [43], new technologies such as virtual reality games used in rehabilitation projects are stimulating fresh interest. Subramaniam et al. [36] and Kannan et al. [41] utilized a virtual reality-based project as a form of dual-task training. This training incorporated additional cognitive tasks like semantic memory or divided attention activities. It has been shown that virtual reality enhances motivation levels, improves physical function, volitional control of stability, and boosts semantic and working memory [36].

Although virtual reality and robot-assisted gait systems are popular technology-supported rehabilitation methods post-stroke, no studies incorporating these new technologies have been found yet. Daily life requires multitasking while walking, a challenge that becomes difficult for stroke patients. Similar to virtual reality games, adding an additional task to gait exemplifies the multitasking nature of everyday walking activities and leads to patient distraction [181]. Virtual reality training in stroke patients improved the quality of movement and functional capacity [183], while robot-assisted gait training enhanced balance and gait [184]. This combined therapy motivates patients and increases active participation in the rehabilitation of stroke patients [185].

In conclusion, the rehabilitation of proprioception combined with simultaneous dual-task training, including in virtual reality settings, improves balance, postural control, walking and gait speed, and helps prevent falls.

3.1.1.6. Enhancing Enjoyment in Dual-task and Proprioceptive Training

The enjoyment derived from a rehabilitation program could potentially improve outcomes. Two studies where rehabilitation incorporated a significant motivational element were those that involved aquatic games [42] and tango lessons [186]. These studies allowed patients to find pleasure in their rehabilitation programs, which in turn improved adherence to treatment and eventual outcomes. The tango training proposed by Hackney et al. [186] wasn't included in the systematic review as it is a case report, but it is described in the text. Notably, dancing, specifically tango, when adapted to a dual-task proprioceptive program for a stroke patient, could motivate the individual to persevere with the program and ultimately achieve their set goals [186].

3.1.2. The effectiveness of goal-oriented dual task proprioceptive training in stroke patients: an observational study

The findings from this study suggest that goal-oriented proprioceptive training, whether executed with single or dual tasks, led to improved balance, increased autonomy in activities of daily living (ADL), and a reduced fall risk among subacute stroke patients. The evaluation of various scales at discharge revealed the specific rehabilitation goals that were achieved. For instance, the observed positive relationship between the Tinetti test and the Time Up and Go test (TUG) in the dual-task group indicated a reduction in fall risk due to improved balance. However, the absence of a significant correlation between the Barthel index and both the Berg Balance Scale (BBS) and the Tinetti test might explain why balance recovery only partially translated to increased autonomy. Furthermore, while the use of mobility aids was closely associated with improved balance, it did not significantly enhance autonomy or decrease fall risk. This suggests that the use of aids alone is insufficient to ensure safe mobility and gain autonomy; it only aids in balance improvement.

The rehabilitation program, comprising goal-oriented therapy, proprioceptive exercises, and dual-task training, was designed based on the goals of regaining autonomy, improving balance, and reducing fall risk. Previous research supports the positive effects of proprioceptive training on balance performance, gait speed, trunk control, and basic functional mobility in stroke patients. Similarly, dual-task training has been associated with improved step length, cadence, balance, and reduced fall risk. Task-specific training with a functionally-oriented dual task exercise has also shown positive effects on proprioception, balance, gait speed, and spasticity in stroke survivors.

According to the study's results, integrating these rehabilitation techniques with traditional treatments allowed patients to regain independence and balance, and reduce the risk of falls, proving beneficial not only for the patients but also for their families and caregivers.

3.1.3. Botulinum Toxin in Post-Stroke Motor Deficits and the Potential of Experimental Antidotes for Botulinum Neurotoxin in Stroke Treatment

The researchers used a variety of methods and tools to identify potential inhibitors of the LC/A protein from databases of natural compounds. The methods included pharmacophore-based virtual screening, molecular docking, and molecular dynamics simulations.

First, they retrieved chemical structures of compounds from the Marine Natural Product (MNP) and Super Natural Product (SNP) databases, as well as the ZINC and Molport Natural (MPN) databases. They also created a control dataset of known LC/A binders.

Next, they created a 3D pharmacophore model using the Pharmit server. This model was used to screen the databases, resulting in a list of 182 potentially interesting compounds.

The selected compounds were then prepared for molecular docking and dynamics simulations, which were performed using the AutoDock software and YASARA Structure package, respectively. These techniques allowed the researchers to predict how the compounds would bind to the LC/A protein and evaluate the stability of the resulting complexes.

Next, the researchers used a 3D-QSAR model to assess the biological activity of the compounds. The compounds were aligned to a previous QSAR model and their predicted activities were calculated.

The researchers validated their scoring functions by generating receiver operating characteristic (ROC) curves and calculating enrichment factors. These metrics help to assess the accuracy of the model and its ability to correctly identify active compounds.

Finally, in silico ADMET studies were performed using the SwissADME and pkCSM web platforms. These studies predict the absorption, distribution, metabolism, excretion, and toxicity properties of the compounds, which are important for assessing their potential as drug candidates.

3.2. **Second topic of the PhD project:** Exploring the Interplay of Stroke and Associated Complications: Insights into Infections and Sarcopenia

3.2.1. The Impact of Infections on Stroke Complications

The crucial issues of the study concern: 1) the proposal to continue rehabilitation despite CDI, 2) the role of a multidisciplinary team, 3) the possibility to stop the spread of infection, 4) the need to limit costs, and 5) an unnecessary longer hospitalization.

Despite the condition of isolation, CDI patients did not have a reduction of rehabilitation effectiveness. The results of our research confirmed a statistical improvement of the Barthel index in CDI patients and the control group, without statistically significant differences between the groups. Thus, despite the infection and on the basis of clinical conditions, our advice is to avoid any interruption of rehabilitation [187].

Moreover, the choice of rehabilitation program, pharmacologic therapy, support supplements, and the reorganization of the setting should be a shared choice, to optimize the staff, avoid inefficiency, and maintain high standards. According to the National Health System (NHS) [188] (last checked in December 2022), rehabilitation and infection control measures should not compromise the patient’s care and should not affect the patient’s rehabilitative program. A multi-disciplinary approach can quickly identify appropriate activities, educational material for staff and families, addressing cleaning practices, and standardizing the criteria for follow-up investigations is the key to interrupt the diffusion of the infection [189].

Even if specific protocols for control and infection management are known [190], a broad consensus on the individualized management of rehabilitation programs and preventive strategies to avoid multi-drug resistance organism in rehabilitation setting are lacking [191]. Though adequate measurement systems are available and followed in every department, infection containment systems must be adapted to rehabilitation units, with its sharing of spaces and equipment and the necessity to progressively reduce assistance, as autonomy increases [190]. For this reason, an inadvertent transfer of bacteria within the rehabilitation setting may occur because asymptomatic colonization is often not recognized.

Thus, managing highly complex patients includes the necessity of infection surveillance and prevention strategies [71]. These strategies could require additional personnel and equipment to avoid equipment sharing and consequence costs [192]. Despite this, there were no need for many extra support staff.

Fast track training is now standard in many intensive rehabilitation units, but concomitant CDI makes it impossible. However, according to our experience, considering the length of hospitalization, patients with CDI were hospitalized for an average of 54.84 days, which fell within the admitted hospitalization days, that is, CDI patients did not extend the hospital stay beyond the stable days (in Italy 60 days of hospitalization for neurologic disorders).

3.2.2. Sarcopenia in stroke

The study discusses a complex model for assessing muscle mass loss (sarcopenia) that leverages six anthropometric variables: thigh circumference, calf circumference, arm circumference, triceps skinfold, height, and weight. These parameters allow a very precise assessment of a patient's sarcopenic condition, achieving an AUC of 0.93. Among these, the model incorporates variables that signify muscle mass in the upper limbs (arm circumference) and three features connected to body fat assessment: triceps skinfold, height, and weight. The latter two contribute to the calculation of Body Mass Index (BMI) and thus are tied to the overall body fat assessment, particularly visceral fat.

Interestingly, a simplified model requiring only two parameters, calf and thigh circumferences, performs almost as well as the complex model. This suggests that lower limb measurements could be more effective than upper limb measures and body fat metrics for identifying muscle mass loss.

While various risk factors are linked to muscle mass loss in adults, including medical history and morbidity, the study underscores that simple anthropometric measurements can objectively predict muscle mass loss. The research suggests that variables like overall health condition and physical activity levels, although important, do not significantly improve the prediction accuracy when added to the model.

The study also suggests that sarcopenia, a preventable and treatable condition, is closely linked to physical activity levels. Regular physical activity, specifically endurance exercises, can enhance muscle mass and strength, making it a primary treatment for sarcopenia. The combination of physical activity and improved nutritional status represents an excellent intervention strategy.

The newly developed models are unique, adopting an artificial intelligence approach based on decision trees, leading to a flowchart-like structure that is easy to adopt in clinical practice. These models allow rapid, nearly costless assessment of muscle mass, potentially reducing the number of patients requiring further testing like the grip test. This could effectively invert the standard diagnostic algorithm, providing significant time and cost savings. However, the study notes that this proposed approach would require dedicated clinical validation before real-world application.

3.3. Third topic of the PhD project: Post-Stroke Dysarthria: A Multidisciplinary Approach to Rehabilitation

3.3.1. A Systematic Review of Measures of Dysarthria Severity in Stroke Patients.

Our systematic review focused on useful measures for the examination of dysarthria severity and follow-up. We listed the clinical examinations, intelligibility and neuropsychological scales, and acoustic parameters from the current literature that physicians could use. We also compiled a comprehensive overview to provide a guide to ease collaboration among multidisciplinary teams.

Assessing the degree of disability in dysarthric speakers after a stroke is indispensable for speech analysis and rehabilitation. Dysarthria has a negative psychosocial impact on the lives of stroke patients and their families. We performed a systematic review of current methods for accurate examination of dysarthria after stroke. We presented diagnostic methods for following subjects with stroke-related dysarthria, which could help to guide physicians and provide a common protocol for multidisciplinary treatment teams. Accurate and repeatable assessments of dysarthria due to stroke could also improve the outcomes of rehabilitation. Our guide could help multidisciplinary teams to collaborate, compare assessments and have more complete examinations. Nevertheless, despite the range of tools available, robust trials are lacking, and the diagnostic approaches are always different. More research is needed to find the best diagnostic methodologies and to delineate a definitive diagnostic protocol.

3.3.2. Dysarthria and stroke. The effectiveness of speech rehabilitation. A systematic review and meta-analysis of the studies.

Our systematic review focused on the several measures useful for the examination of dysarthria severity and for the follow up. Ear/nose/throat (ENT) specialists, physiatrists, and neurologists use often different types of evaluations. We used a complete overview to quantify poststroke dysarthria severity and provide a guide to ease the collaboration in a multidisciplinary team. Assessments of the dysarthria before and after speech rehabilitation were conducted with the meta-analysis to direct and suggest other studies on post-stroke acoustic analyses. Dysarthria has not been well-studied to date because the symptoms of this condition are difficult to measure. Indeed, physicians often concentrate mainly on limb weakness in stroke cases, neglecting dysarthria as a minor problem. Nevertheless, the severity of dysarthria has implications for treatment outcomes, prognoses, and psychosocial impact on people's lives. The current literature did not report any guidelines for clinical assessment of subjects with post-stroke dysarthria.

Dysarthria secondary to stroke is characterized by dysfunction in controlling articulation, respiration, phonation, prosody, and resonation. The assessment of the degree of disability in dysarthric speakers post-stroke is indispensable for speech analysis and development of a speech rehabilitation program. Indeed, dysarthria has a negative psychosocial impact on the lives of the post-stroke patients and their families. We performed a systematic review of the methods present in the current literature for an accurate examination of post-stroke dysarthria. On the basis of the described diagnostic methods, the physicians could obtain a guide and a common protocol for a multidisciplinary team. With our meta-analysis, we analyzed the differences in voice acoustic parameters after speech rehabilitation. The alternating and sequential motion rate (AMR- Pə, AMR-Tə, AMRKə, and SMR-PəTəKə) and maximum phonation time significantly improved after speech rehabilitative treatment. These diagnostic methods should help collaboration among a multidisciplinary team in order to compare their own assessments with those of other members of the team and undertake more complete examinations. For this aim, we analyzed all procedures, such as physical examination, intelligibility scales, neuropsychological and cognitive tests, MDVP and PRAAT, and neuroimaging, found in the current literature that are used to diagnose, measure, and follow up post-stroke dysarthria.

3.3.3. Speech rehabilitation in dysarthria after stroke: a systematic review of the studies.

Our systematic review collected data related to dysarthria in stroke patients. We listed all the several strategies and the possibility of rehabilitation therapy for dysarthria. To our knowledge, in the current literature, there was not a study that analyzed all types of speech rehabilitation. Furthermore, our analysis could promote the development of speech rehabilitation protocols and guidelines. This review considered any type of intervention for acquired dysarthria after stroke including speech rehabilitation exercises, behavioral and psychological approaches, use of devices and assistive technology. There is little information available describing specific therapies or supporting the efficacy of one treatment over another for a specific dysarthria type. This systematic review tries to provide to the reader a complete overview of the literature of all possible different speech treatments for dysarthria after stroke. A correct strategy could permit to improve the communication, especially immediately after stroke, and the quality of life of subjects with dysarthria after stroke. We would like to have created a guide for choosing a rehabilitation protocol combining more treatments and personalizing the rehabilitation intervention. For subjects with dysarthria, maintaining a clear speech is hard and it has consequences such as slowed speech and altered prosody and rhythm during the conversation. The presence of dysarthria may constitute a negative factor in health-related quality of life. The current literature refers to the importance of speech rehabilitation in individuals with dysarthria to avoid work impairment, activity limitations, participation restriction or psychosocial impact. Further researches in this area are required, such as large-scale, controlled trials to compare the different rehabilitation strategies and find a better protocol for this disorder.

4. General discussion

Stroke, a major global health concern, brings with it not only the immediate cerebral damage but also a cascade of subsequent functional impairments. The intricacies of stroke recovery demand a diverse approach in rehabilitation. In this PhD thesis, we delved into multiple aspects of post-stroke rehabilitation, with each topic offering distinct insights.

The cornerstone of post-stroke rehabilitation has long been centred around motor function recovery. However, the incorporation of goal-oriented dual task proprioceptive training presents a fresh paradigm. The thesis begins by delineating the significance of rehabilitation in restoring motor performance. Through a systematic review [1], we thoroughly detail the proprioceptive exercises described in the existing scientific literature for balance recovery. Moreover, the review elaborates on dual-task exercises, encompassing both motor and cognitive domains, which facilitate independence in ADLs and concurrently reduce the risk of falls. Indeed, in everyday life, motor tasks often coincide with other activities, such as walking while conversing or walking while carrying an object [1]. The other systematic review has shown that proprioceptive exercises enhance various aspects of the gait cycle. Specifically, single-task proprioceptive exercises lead to improvements in stride length, while dual-task exercises enhance speed, cadence, stride time, step and stride length. These advancements indicate a more refined and automated gait cycle pattern, ultimately reducing the risk of falls [2].

Therefore, the thesis highlights the outcomes of motor recovery in stroke patients following specific single and dual-task proprioceptive exercises, as showed in a observational study [3]. All participants underwent traditional rehabilitation, focusing on antigravity muscle strengthening, core stability, and proprioceptive exercises. However, only one group incorporated dual-task exercises into their training. After two months of therapy, both groups exhibited significant improvements in autonomy, enhanced balance, and reduced fall risk. However, when comparing the two groups, no discernible statistical differences were noted. This suggests that proprioceptive exercises primarily cause motor improvements, and adding dual-task exercises doesn't necessarily enhance the final outcomes.

Beyond the conventional realm of therapy, the thesis explored the role of the physiatrist in therapeutic interventions. Botulinum toxin presents therapeutic opportunities in motor recovery post-stroke. But no antidots are known, except for equine toxin. Thus, the importance of knowing the antidotes for iatrogenic botulism is highlighted in the face of cases of occasional side effects and excessive use during the treatment of spasticity. Although the most active substances are synthetically obtained compounds (commercially available), other potential antidotes identified in another our study are of natural origin, representing a potential low-cost drug treatment [4]. The compounds selected from the pharmacophore model were also analysed using a process called docking, using a software called Autodock implemented in YASARA. Docking is a method which predicts the preferred orientation of one molecule (usually a small molecule like a drug candidate) to a second (usually a larger one, like a protein) when bound to each other to form a stable complex. Thus, the research utilized a systematic approach that combined pharmacophore filtering, 3D-QSAR modelling, and molecular docking to identify potential botulism antidotes. This approach initially reduced the number of candidate molecules from over 13 million to 172. We used sub-linear algorithms from the Pharmit server, a powerful tool for virtual screening of compound databases, to achieve this reduction. Then, we evaluated the remaining compounds for their predicted activity and affinity for the the light chain of botulinum neurotoxin type A (LC/A) binding pocket, a target site in the botulinum toxin. The top-scoring compounds were not only synthetically derived but also of natural origin, suggesting that plant-based compounds could offer a low-cost treatment alternative. To further validate these predictions, we performed molecular dynamics (MD) simulations. These showed that all selected compounds were able to bind the zinc ion in the LC/A binding pocket in a stable manner, which is crucial for their potential effectiveness as antidotes. We also performed docking studies across all BoNT LC serotypes, revealing that the top 10 LC/A inhibitors have high selectivity, which can be useful for treating different forms of botulism. Notably, smaller inhibitors like ZINC5729284 showed potential for broad-spectrum activity, making them valuable for future development.

Rehabilitation is not merely limited to motor recovery. Patients in long-term acute-care rehabilitation facilities are often frail, susceptible to skeletal fractures, infections, delirium, and neuropsychiatric conditions, and often need several drugs, with the risk of contracting multidrug resistant bacterial infections. The complications following stroke, like infections, notably due to Clostridium difficile, bring forth additional challenges in the recovery timeline. Thus, the aim of research was also to show the impact of clostridium difficile on the outcomes of rehabilitation in stroke patients [5]. In the period between 2018 and 2022, stroke patients affected by CDI were just 1.95 % (13 CDI patients + 2 excluded CDI patients from a total of 767 neurological patients), a percentage that does not exceed the average described in the literature. Thus, the isolated CDI patients continued rehabilitation, respecting the rules of hygiene and the feelings of tiredness or malaise. At discharge, after two month of rehabilitation, no statistical differences was showed in the levels of autonomy (Barthel index and days of hospitalization), risk of fall and bedsores risk (using the Conley scale and the

Braden scale), number of lost days of rehabilitation and any requested psychological counselling as factors modifying the rehabilitative outcomes [5]. The costs in terms of personnel and disposable material were increased by 5%. In conclusion, there was no need to stop rehabilitation and prolong hospitalization, except with severe symptomatology [5].

Furthermore, the exploration of sarcopenia post-stroke underscores the broader implications of muscle mass and functional recovery. Thus, another study derives a simple zero-cost screening tool, capable to emulate the outcome of the DEXA in identifying patients with muscle mass loss, using data from the National Health and Nutrition Examination Survey (NHANES) [6]. Indeed, DEXA is relatively expensive and not always readily available or routinely used. This machine learning approach could also be applicable to screening sarcopenia in stroke patients, offering a more efficient and cost-effective method to monitor this common complication. NHANES provided a sample size of 14,500 patients with complete information required for the calculation of DEXA, the gold standard for sarcopenia screening. Initially, the study considered 38 variables, identified in the literature as good sarcopenia predictors. However, the study found that only 6 anthropometric parameters related to key corporal segment circumferences and body fat composition were needed to accurately identify muscle mass loss. Even more striking, a simpler model using just 2 variables (thigh and calf circumference) yielded only slightly lower performance. It proposes an almost zero-cost and straightforward method to predict muscle mass loss, which could streamline patient screening and guide subsequent testing. The complex developed model utilized six anthropometric variables, which were thigh, calf and arm circumference, weight, height, and triceps skinfold. The findings suggest that a limited number of anthropometric parameters can predict DEXA. The most complex model, which uses six variables related to body circumference and body fat evaluation, achieves an optimal sensitivity of 0.89 and specificity of 0.82. The two simpler models employed three and two variables, respectively. The three-variable model used thigh, calf, and arm circumference. The two-variable model included only thigh and calf circumference. Both of these models achieved an AUC value of 0.89, which indicated a high level of performance. Even when the analysis is restricted to variables related to the lower limb, the accuracy remains high (AUC 0.88-0.90), suggesting that the addition of arm circumference didn't significantly boost the prediction capabilities. The results show that muscle mass loss prediction can be achieved with high accuracy, even when using a reduced number of anthropometric variables, with cost-effective and accessible early identification of sarcopenia [6]. These results suggest a potential shift in the standard diagnostic algorithm for sarcopenia, proposing a new clinical diagnostic scheme [6]. The study suggests an early treatment approach for patients with muscle mass loss, considering it as a risk factor for sarcopenia and other morbidity, even without grip test results or more complex diagnostic methods. The study emphasizes the importance of lower limb musculature in overall muscle mass loss, indicating that physical activities like walking or running might be most effective for preventing muscle mass loss and related complications. The study also underscores the significance of evaluating anthropometric parameters, especially those related to the lower limb, not just for diagnosing sarcopenia but also for assessing treatment effectiveness. Future work could validate a specific protocol to identify patients with sarcopenia using the models derived in this study. Such validation would require further analyses involving a more extensive population, including grip test data to fully diagnose the state of sarcopenia [6].

Neurological damage often manifests in speech and communication deficits, making dysarthria a critical concern post-stroke, and patients inclined to social isolation. The series of studies in this thesis emphasize not only the assessment of dysarthria severity but also the holistic approaches required for rehabilitation, from tailored speech therapy to cognitive interventions. The most used scales for the assessment of dysarthria in stroke, described in the current literature, were the Frenchay Dysarthria Assessment (FDA), Dysarthria Impact Profile (DIP), Communicative Effectiveness Measure (CEM) [7]. Moreover, specified software allowed to have more information. Formant patterns (F1 and F2) of vowels reflect the resonance of different shapes of the vocal tract and indicate the articulatory movements and speech motor patterns. Dysarthria in stroke is characterized by lower F1 and F2 variability for vowels, and low RAP and PPQ percentage that reflects major phonatory stability. After specific speech therapies, such as LSVT, increased F1 and decreased F2 values are associated with improved articulatory movements, jaw opening, loudness of speech, and vowel space area [7]. This thesis, through a systematic review analysed the best speech therapy, described in the current literature for strke patients [8], and with a meta-analysis analysed what kind of speech rehabilitation can obtain more results. AMTS, TMS and DCS improved alternating and sequential motion rates [9].

To conclude, this thesis offers a comprehensive view of post-stroke rehabilitation, ranging from traditional methods to innovative therapeutic strategies. It emphasizes the multi-pronged nature of stroke recovery, and how interdisciplinary approaches can potentially redefine the trajectory of rehabilitation. The findings can pave the way for more integrated rehabilitation practices in clinical settings.

5. Concluding remarks

In this PhD thesis, a thorough examination of the contemporary understanding of rehabilitation's role in addressing disabilities associated with stroke was presented.

This work highlights the importance of considering post-stroke disability not as an isolated condition but as a dynamic interaction of various factors. Within the vast realm of post-stroke complications, disability emerges as a particularly complex and multifaceted area, influencing not only the functional recovery, but also the cognitive and emotional well-being of individuals. This study undertakes a journey through the various facets of post-stroke disability, exploring wide-ranging topics. Over the course of this dissertation, we will explore topics ranging from motor disorders and spasticity to language deficits and complications from hypomobility and hospitalization. By examining these topics, my PhD work aims to present a holistic perspective on post-stroke disability, highlighting the critical role of comprehensive rehabilitation and the multiple challenges faced by both patients and clinicians.

The main aim of the study is to delve into the multifaceted field of post-stroke rehabilitation, clarifying its key role in improving disabilities that arise following a stroke.

Impairment of proprioception following a stroke is well known to be strongly correlated with increased risk of falls. Moreover, dual-task activities further escalate the fall risk among stroke patients. The thesis shows a detailed examination of the literature concerning various dual-task trainings and proprioceptive interventions in post-stroke individuals. According to the research, despite the diversity in treatments - including variations in duration, types of exercises, and scales and scores used for analysing the results - all articles included in the systematic review, we performed, reported significant improvements in balance and reductions in falls during the activities of daily living related to proprioceptive and dual-task exercises. The implementation of personalized dual-task training in combination with proprioceptive interventions is crucial for enhancing motor control and learning by automating gait.

Furthermore, the effects of goal-oriented proprioceptive training - both with single and dual task exercises – was studied through an observational study. This training contributed to improved balance, enhanced activities of daily living, and reduced the risk of falls. Comparatively, dual task training demonstrated a significantly greater improvement in balance, as assessed by the Tinetti balance evaluation, over single task exercises. Undoubtedly, the corresponding improvement in balance contributed to a reduced fall risk, though it only partially boosted autonomy. Furthermore, following goal-oriented dual task proprioceptive training, the use of mobility aids was closely linked to balance recovery but did not significantly mitigate fall risk.

Moreover, the PhD researcher aimed to find an antidote for iatrogenic botulism, a potential adverse effect of treating spasticity with botulinum toxin. Compounds like ZINC5729284 could be extremely valuable for their inhibitory activity for the treatment of botulism. In conclusion, this study demonstrates a successful approach to identify potential antidotes for iatrogenic botulism, with several promising compounds highlighted for further investigation.

Furthermore, the thesis shares the multidisciplinary team's experience in organizing the training setting, limiting costs and infection spread. It also suggests adapting rehabilitation planning to clinical conditions and recommends avoiding interruptions to the rehabilitation program. Factors such as temperature, fatigue, and diarrhoea were considered when deciding whether to interrupt rehabilitation. The length of hospitalization, the number of lost rehabilitation days, and the need for psychological counselling did not significantly influence rehabilitative outcomes in CDI patients. Therefore, despite the need for isolation and support staff, there was no statistically significant difference in rehabilitation outcomes between the two groups.

Moreover, the thesis presents a comprehensive analysis of NHANES cross-sectional data to devise a highly accurate, data-driven model for predicting muscle mass loss in adults. Using artificial intelligence techniques based on decision trees, the study offers a novel way to visualize the screening process using flowchart-like structures, which is ideal for clinical applications. The result of this research offers a more objective screening method for muscle mass loss, using anthropometric and constitutional variables rather than subjective questionnaires.

The third main topic described the assessment scales and the speech rehabilitation used in stroke dysarthria. A systematic review about dysarthria delves into the examination and rehabilitation of dysarthria following a stroke, a condition characterized by challenges in articulation, respiration, phonation, prosody, and resonation. Current literature often overlooks dysarthria in favour of more visible post-stroke symptoms, despite its profound psychosocial impact on patients and their families. This review sought to address this gap by listing and analyzing various measures, including clinical examinations, intelligibility scales, neuropsychological assessments, and acoustic parameters. Furthermore, while diverse diagnostic methods are prevalent in the current literature, consistent guidelines for clinical assessments post-stroke are lacking. Our analysis hopes to unify these methodologies, providing a reference point for multidisciplinary teams and promoting more comprehensive examinations. With a focus on diagnostic procedures ranging from physical examination to neuroimaging, we highlight the importance of cohesive, multi-faceted diagnostic and rehabilitative approaches. By enhancing communication capabilities, especially immediately post-stroke, we can significantly improve patients' quality of life.

In conclusion, this thesis provides an in-depth exploration of post-stroke rehabilitation, bridging the gap between traditional modalities and cutting-edge therapeutic interventions. It underscores the multifaceted dimensions of stroke recovery, illustrating the transformative potential of interdisciplinary approaches. Such insights set the stage for holistic and integrated rehabilitation methodologies in clinical environments.

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