LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Cardiologia

Upper limb robotic rehabilitation in chronic stroke

Tiago Miguel Ferreira Fernandes

Orientado por:

Drª Michele dos Santos Gomes da Rosa

Coorientado por:

Drª Maria Margarida Francisco

JULHO'2021

Resumo

Introdução: acidente vascular cerebral (AVC) é a segunda maior causa de anos de vida ajustados por incapacidade (DALYs). Mesmo após fisioterapia e terapia ocupacional, os défices motores persistem em 55-75% das pessoas, seis meses após AVC (crónico). Nas últimas décadas, com o desenvolvimento tecnológico da nossa sociedade, novos robots foram desenvolvidos para a reabilitação motora.

Objetivo: desenvolver uma revisão sistemática que compara o impacto da terapia robótica (TR) contra a terapia convencional (TC), na função motora do membro superior em pessoas com AVC crónico.

Métodos: recolhemos 17 ensaios clínicos randomizados (ECT) que aplicavam a TR com recurso a diferentes robots (Bi-Manu-Track, InMotion, ARMin III, UL-EX07, Haptic Master e Amadeo). Calculamos o impacto de cada robot na função motora do membro superior e comparamos a terapia robótica à terapia convencional, baseado no Fugl-Meyer Assessment – Upper Limb (FMA-UL).

Resultados: 17 ECT, envolvendo 620 pessoas, foram incluídos na revisão. Os robots mais utilizados foram o Bi-Manu-Track (BMT) e InMotion (IMT). Após a intervenção de TR, ocorreu uma diferença média de 2.66 e 2.42 no FMA-UL, para o BMT e IMT, respetivamente. Apesar do Amadeo ter apenas sido utilizado num estudo, foi o que apresentou melhores resultados quando comparado com TC. Comparando a TR com TC, não houve uma diferença significativa no aumento médio do FMA-UL. No entanto, o Risk Ratio foi de 1.65, mostrando uma tendência para a TR.

Conclusão: foi possível determinar que com a adição de terapia robótica ao programa de reabilitação, é possível alcançar ganhos razoáveis na função motora do membro superior de pessoas com AVC crónico, comparáveis aos obtidos com terapia convencional. Então, abre-se a possibilidade de tratar um maior número de pessoas, visto que estes robots não são dependentes do terapeuta. Para além disso, propomos várias ideias a serem implementadas em estudos futuros.

Palavras-chave: Inteligência Artificial, AVC, Robot, Reabilitação Motora.

Abstract

Introduction: stroke is the second leading cause of disability-adjusted life years, with physiotherapy and occupational therapy being the standard of care for recovery of post-stroke motor function. Despite rehabilitation programs, motor impairments persist in 55-75% of chronic patients (time-since-stroke > 6 months). In the last decades, with the technological development of our society, new robot-based therapy approaches have been created.

Objective: to develop a systematic review comparing robot-based therapy (RBT) to conventional therapy (CT), regarding its impact on upper limb motor function from chronic stroke patients.

Methods: we gathered 17 randomized clinical trials (RCT) from different RBT with the application of several robot devices (Bi-Manu-Track, InMotion, ARMin III, UL-EX07, Haptic Master and Amadeo). We calculated each robot's impact on upper limb motor function and compared overall RBT to CT, based on our main outcome, the Fugl-Meyer Assessment - Upper Limb (FMA-UL).

Results: we included in the review 17 RCT, involving 620 patients. The most used robots were Bi-Manu-Track (BMT) and InMotion (IMT). After RBT intervention, there was a mean difference of 2.66 and 2.42 in FMA-UL, for BMT and IMT, respectively. Despite Amadeo only appearing in one study, it was the one with the highest increase in FMA-UL, when compared to CT. Comparing RBT to CT, we could not find a significant difference in the increase of FMA-UL. However, the Risk Ratio was 1.65, showing a tendency towards RBT.

Conclusion: it was possible to determine that adding robot-based therapy to the rehabilitation of the upper limb in chronic stroke patients accomplishes reasonable gains in motor function, comparable to conventional therapy alone. This opens the possibility to treat a bigger number of patients, since the robots are not therapist dependent. We also propose several ideas to be implemented in future studies.

Key words: Artificial intelligence, Stroke, Robot, Motor rehabilitation.

Index

Abbreviations

WHO - World Health Organization

DALYs – Disability-adjusted life years

RBT - Robot-based therapy

CT - Conventional therapy

FMA-UL - Fugl-Meyer Assessment - Upper Limb

UL - Upper limb

LL - Lower limb

BMT - Bi-Manu-Track

IMT - InMotion (2.0 / 3.0)

IMT-LR - InMotion Linear Robot

HM - Haptic Master

DOF - Degree of freedom

TBAT - Therapist-based bilateral arm training

FES - Functional electrical stimulation

dCIT - Constraint induced therapy

ML - Motor Learning

NMES – Neuromuscular electrical stimulation

MAS – Modified Ashworth Scale

WMFT – Wolf Motor Function Test

SIS – Stroke Impact Scale 3.0

Introduction

According to the current WHO definition, stroke is defined as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death”(Aho et al., 1980), secondary to an acute compromise of the cerebral perfusion or vasculature (Khaku & Tadi, 2021).

In 2016, according to the Global Burden of Disease, this cerebrovascular event is the second leading cause of disability-adjusted life-years (DALYs), having increased since 1990 and only being surpassed by ischemic heart disease (Johnson et al., 2019).

Post-stroke motor recovery follows a nonlinear trajectory, where patients reveal more responsiveness to rehabilitation within the first 3-6 months, explained by the increased neuroplasticity (Kwakkel et al., 2004). This hypothesis justifies the tendency to diminish rehabilitation efforts at the chronic stage of disease.

However, a study has shown that rehabilitation beyond the so called “critical window”, as far as 18 months post-stroke, provides significant improvement in motor function (Ballester et al., 2019).

Despite rehabilitation programs, motor impairment of the upper limb occurs in 55–75% of chronic stroke patients. Given this poor outcome, in the last two decades, with the technological evolution of our society, new neurotechnology-aided interventions have been developed “to deliver high-intensity motor training to stroke victims with severe motor impairments” (Coscia et al., 2019).

Among them are several robot devices that assist upper limb or gait movement, coupled with virtual reality to enhance feedback to the patient and simulate task-specific therapy (Weber & Stein, 2018).

With this in mind, we propose a systematic review to compare the efficacy of robot-based therapy to conventional therapy for chronic stroke patient’s motor function recovery.

Methods

Search strategy

We searched the PubMed electronic database on studies published from 2005 until 2021. We used the English language as it is the international language accepted for scientific research. Search terms used were "Artificial intelligence, Stroke, Robot, Motor rehabilitation". A total of 710 studies were retrieved.

Table 1 Search strategy

PubMed	Keywords: Artificial Intelligence + Stroke + Robot + Motor Rehabilitation Publication date: 2005-2021 Search result: 710 articles Selected RCT + CT: 201 articles - Exclusion (185): Clinical trials (67) Protocols (3) Other language than English (2) Absence of stroke (2 spinal cord injury + 3 healthy population) (5) Lack of trials: Acute (12) Subacute + Upper limb (23) Subacute + Lower limb (15) Subacute + Chronic (9) Chronic + Lower limb (9)

	Chronic + Upper + Lower limb (1) Chronic + Upper limb, but: Absence of CT (6) RBT vs RBT (28) Absence of RBT (2) Absence of FMA-UL (1) Repeated trial (1) - Result: 17 RCT's regarding chronic stroke patients receiving RBT vs CT.

Study eligibility

We included randomized clinical trials with the following inclusion criteria: that compared upper limb robot-based therapy to conventional therapy (physiotherapy and/or occupational therapy) in improving motor function (measured by the Fugl-Meyer Assessment - Upper Limb), in patients with time-since-stroke > 6 months (chronic).

Population: Patients with upper limb motor impairment (based on our main outcome), at least 6 months after stroke (chronic)

Intervention: Upper limb Robot-based therapy

Control: Upper limb Conventional therapy

Outcome: Fugl-Meyer Assessment – Upper Limb

The exclusion criteria were:

1) no open access.
2) clinical trials, reviews, book, and documents.
3) protocols.
4) other language than English.
5) time-since-stroke < 6 months (acute/subacute).
6) lower limb robot-based therapy.
7) control receiving non-conventional therapy.
8) absence of robot-based therapy.
9) absence of stroke (spinal cord injury/healthy population).
10) absence of desired outcome (Fugl-Meyer Assessment - Upper Limb).
11) repeated trial.

Results

Included studies

From the descriptors used found 133 randomized clinical trials, and after careful evaluation 2 were excluded for being protocols, 2 for using other language than English, 59 for time-since-stroke < 6 months and 5 for absence of stroke.

There were 48 articles regarding chronic stroke, among which only 19 compared upper limb robot-based therapy to conventional therapy, the others were excluded: 30.

For the 19 selected studies, 1 did not use our desired outcome (FMA-UL) and 2 were repeated (we included the first being published), leaving us with 17 RCT's to work on.

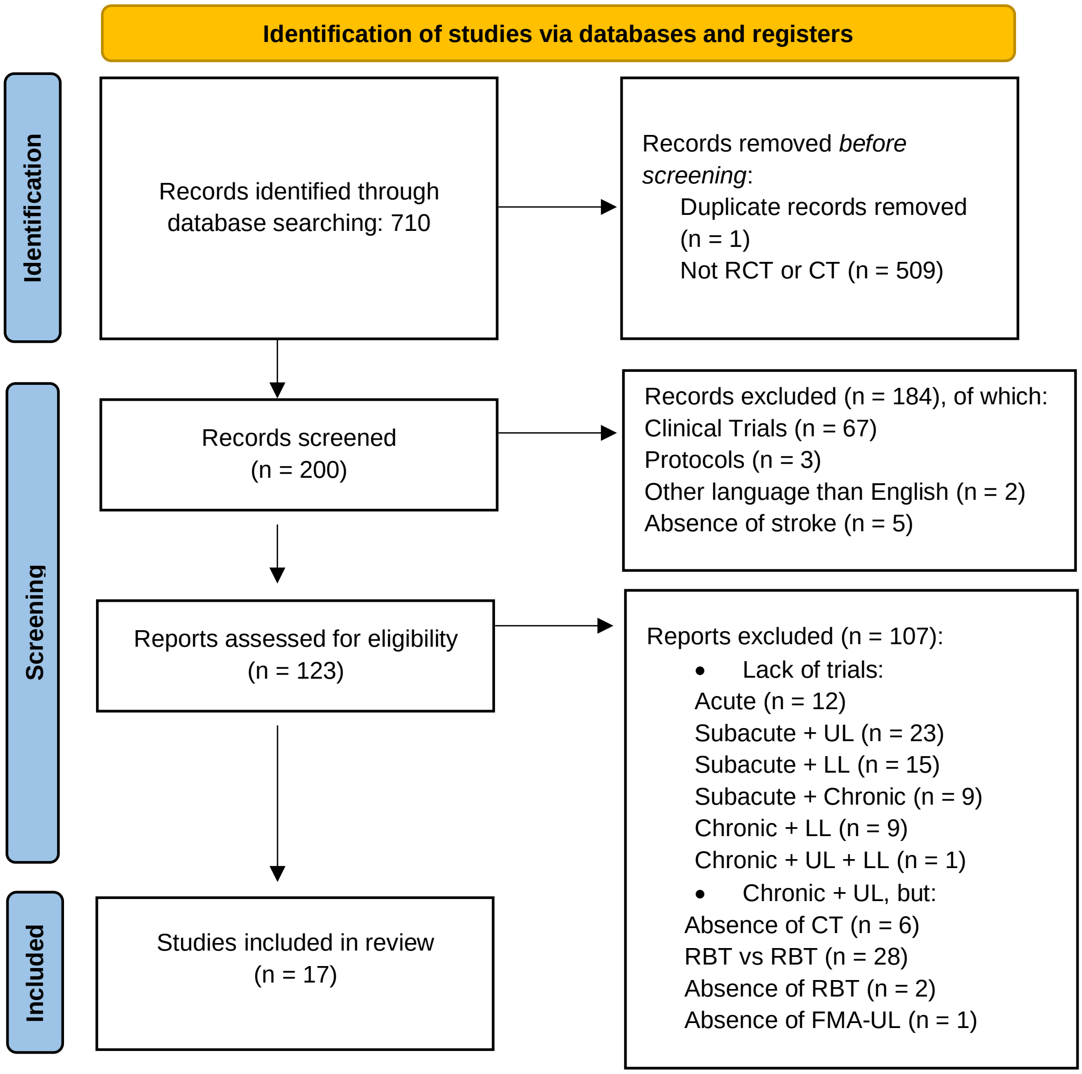


Figure 1 *Study flow diagram of systematic review.*

The 17 selected articles were evaluated for methodological quality, sample size, type of intervention and outcome (FMA-UL).

Our primary outcome was the Fugl-Meyer Assessment – Upper Limb (FMA-UL), a stroke-specific impairment index that is designed to evaluate motor functioning, balance, sensation, and joint functioning in patients with post-stroke hemiplegia. Its upper limb component is the most accepted measure for recovery of body function and structure (Kwakkel et al., 2017).

The recommended measure for stroke severity is the NIHSS (Kwakkel et al., 2017), however we could not find that scale in the reviewed articles. For that reason, we did not determine the average stroke severity in each study.

We then grouped the articles according to the robot device used in the intervention, leaving us with 6 Bi-Manu-Track (BMT), 7 InMotion (IMT), 1 ARMin III, 1 UL-EX07, 2 Haptic Master (HM) and 1 Amadeo.

For each study, we gathered information on sample size, population characteristics (age and time-since-stroke), the intervention regimen (robot characteristics, time per sessions + total, and sessions per week) (Table 2) and, finally, determined the robot-based therapy effect on upper limb motor function recovery, at post-intervention (FMA-UL), compared to conventional therapy.

To determine the impact on motor function, we gathered all the RBT groups from each robot device and calculated the mean difference between the Post-treatment and Basal FMA-UL (Total, Proximal and Distal).

Finally, we coupled several robots to compare overall robot-based therapy to conventional therapy in improving upper limb motor function.

Table 2 *Characteristics of the studies included in the review.*

Robot	Identification	Sample (total)	Intervention	Hours	Time per session (Sessions x weeks)	Time-since-stroke (months)	Mean Age (years)
BMT	(Hsieh et al., 2011)	18	High-intensity RBT vs Low-intensity RBT vs CT	30-35h	90-105min x (5 x 4)	20.89	54.16
BMT	(Hsieh et al., 2012)	54	High-intensity RBT vs Low-intensity RBT vs CT	30-35h	90-105min x (5 x 4)	24.80	54.52
BMT	(C. Wu et al., 2012)	28 (42)	RBT vs CT vs (TBAT)	30-35h	90-105min x (5 x 4)	17.79	53.22
BMT	(Hsieh et al., 2014)	32 (48)	RBT vs CT vs (RBT + dCIT)	30-35h	90-105min x (5 x 4)	25.69	53.23
BMT	(Hsu et al., 2019)	43	RBT vs CT	10h	50min x (3 x 4)	14.19	52.86
BMT / IMT	(C. S. Hung, Hsieh, Wu, Lin, et al., 2019)	20 / 20	RBT (BMT / IMT*) vs CT	30-33h	90-100min x (5 x 4)	22.75 / 25.50*	53.79 / 56.52*
IMT	(Volpe et al., 2008)	21	Planar RBT vs CT	18h	60min x (3 x 6)	37.38	61.05
IMT	(Lo et al., 2010)	52 (127)	Planar + Vertical + Distal RBT vs CT vs (Intensive CT)	36h	60min x (3 x 12)	56	64.6
IMT	(Conroy et al., 2011)	57 (62**)	Planar vs Planar + Vertical RBT vs Intensive CT	18h	60min x (3 x 6)	50.4	57.8
IMT	(McCabe et al., 2015)	23 (39)	Planar RBT + ML vs ML vs (ML + FES)	300h	5h x (5 x 12)	Not found.	Not found.
IMT	(Hsieh et al., 2018)	40	Planar RBT vs Distal RBT vs CT	30-33h	90-100min (5 x 4)	20.57	54.42
IMT	(Conroy et al., 2019)	41 (45**)	Planar + Distal RBT vs CT	36h	60min x (3 x 12)	36.4	56.1
UL-EX07	(Byl et al., 2013)	15	Bilateral RBT vs Unilateral RBT vs CT	18h	90min x (2 x 6)	101.6	59.6
ARMin III	(Klamroth-Marganska et al., 2014)	73 (77)	RBT vs CT	18h	45min x (3 x 8)	43.8	53.5
HM	(Timmermans et al., 2014)	22	RBT vs CT	32h	60min x (4 x 8)	39	59.3
HM	(Fluet et al., 2015)	21	RBT vs CT	24h	3h x (4 x 2)	74.14	51.4
Amadeo	(Calabrò et al., 2019)	50	RBT vs CT	120h	3h x (5 x 8)	10	64.5

*Hung, 2019: the population submitted to RBT was equally divided into BMT and IMT. **Studies only showed mean age and time-since-stroke attributed to the () sample.

Abbreviations: Planar = IMT 2.0; Vertical = IMT Linear-Robot; Distal = IMT 3.0; ML = Motor Learning; TBAT = therapist based bilateral arm training; dCIT = constraint induced therapy.

Bi-Manu-Track

A total of 195 patients (mean age = 53.65 years; mean time-since-stroke = 21.03 months) were submitted to the upper limb therapy intervention, in a total of 160-183 hours over the course of 4 weeks.

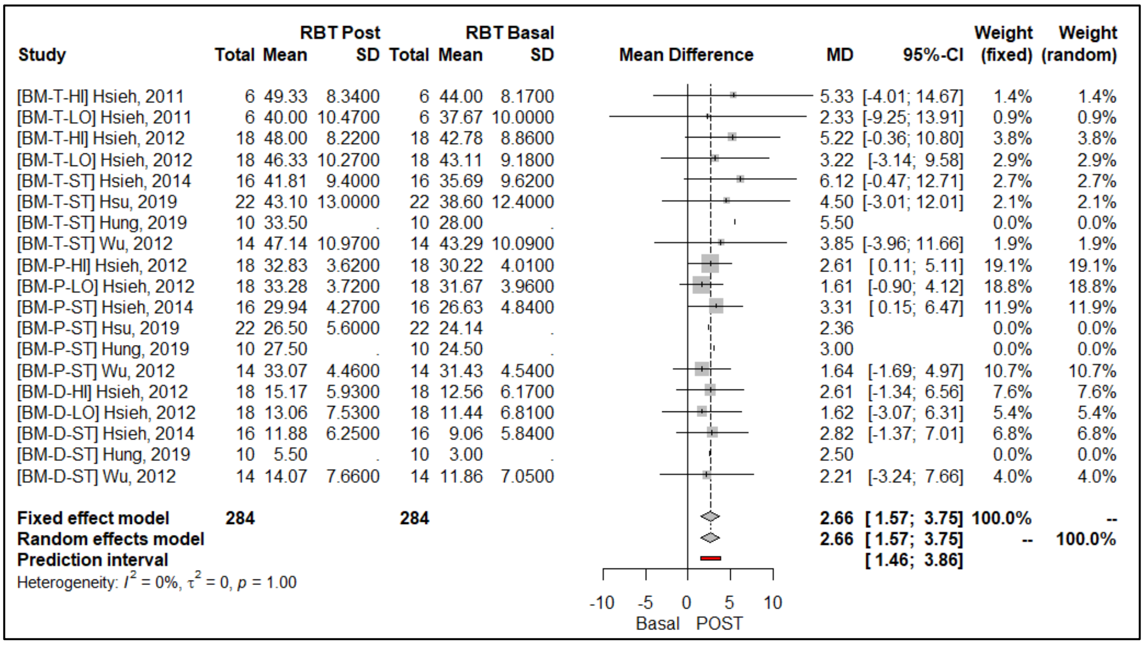


Figure 2 *Mean difference between Post-treatment and Basal FMA-UL after robot-based therapy with Bi-Manu-Track. Abbreviations: BM = Bi-Manu-Track; T = FMA-UL Total; P = FMA-UL Proximal; D = FMA-UL Distal; HI = High-intensity RBT; LO = Low-intensity RBT; ST = standard training.*

For the Bi-Manu-Track, with a fixed effect model of 284, the overall mean difference between post-treatment and basal FMA-UL was 2.66 [1.57; 3.75] (Figure 2).

InMotion

A total of 254 patients (mean age and time-since-stroke not found in two articles) were included, with a total of 468-474 hours over the course of 4 to 12 weeks.

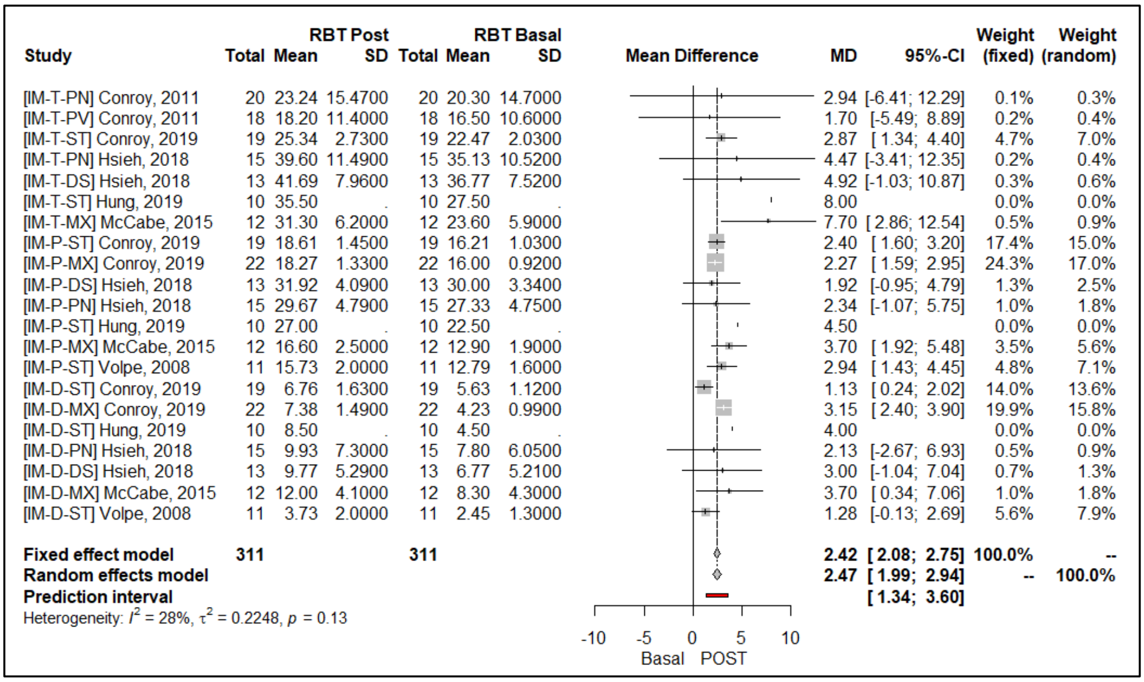


Figure 3 *Mean difference between Post-treatment and Basal FMA-UL after robot-based therapy with InMotion. Abbreviations: IM = InMotion; T = FMA-UL Total; P = FMA-UL Proximal; D = FMA-UL Distal; PN = Planar; PV = Planar + Vertical; ST = Standard Training; DS = Distal; MX = Robot and Conventional Mixed Training.*

For the InMotion, with a fixed effect model of 311, the overall mean difference between post-treatment and basal FMA-UL was 2.42 [2.08; 2.75] (Figure 3).

ARMin III

A total of 73 participants (mean age = 53.5 years; mean time-since-stroke = 43.8 months) were included, with a total of 18 hours over the course of 8 weeks.

UL-EX07

A total of 15 participants (mean age = years; mean time-since-stroke = months) were included, with a total of 18 hours over the course of 6 weeks.

Haptic Master

A total of 43 participants (mean age = 55.44 years; mean time-since-stroke = 56.16 months) were included, with a total of 56 hours over the course of 2 to 8 weeks.

Amadeo

A total of 50 participants (mean age = 64.50 years; mean time-since-stroke = 10 months) were included, with a total of 120 hours over the course of 8 weeks.

Other Robots (ARMin III + Ul-EX07 + HM + Amadeo)

Regarding ARMin III, Ul-EX07, Haptic Master and Amadeo, due to their small sample size and subsequent low statistic power, we coupled them together.

With a fixed effect model of 94, the overall mean difference between post-treatment and basal FMA-UL Total was 5.77 [4.16; 7.39] (Figure 4).

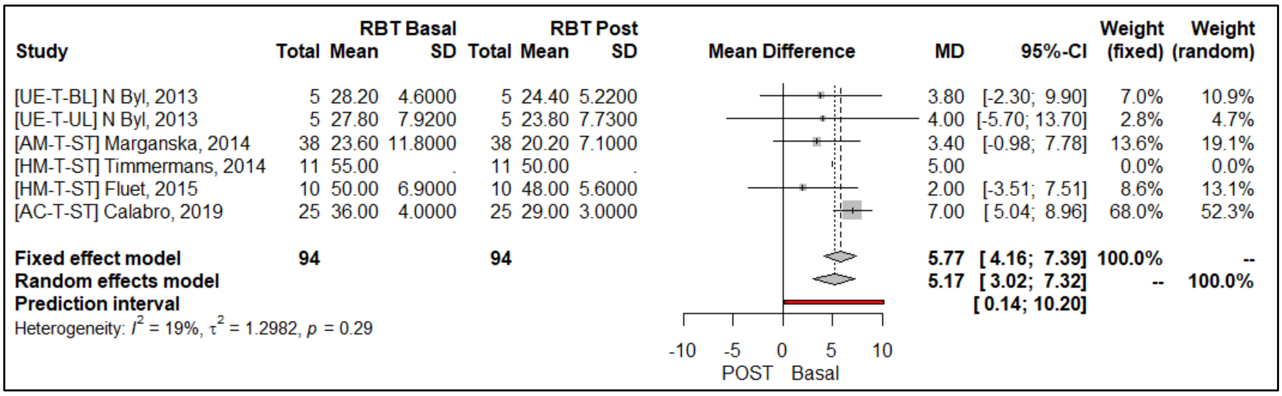


Figure 4 *ARMin III + UL-EX07 + HM + Amadeo vs Conventional therapy impact on FMA-UL Total.*
Abbreviations: T = FMA-UL Total; UE = UL-EX07; AM = ARMin III; HM = Haptic Master; AC = Amadeo; BL = Bilateral; UL = Unilateral; ST = Standard Training.

Robot-based therapy (overall)

To compare the effect on FMA-UL (Total, Proximal and Distal) between robot-based therapy and conventional therapy, we calculated the Risk Ratio for several robot devices (shown in Figure 5, 6 and 7). The selected articles for each of the outcomes was based on similar treatment regimens and the ability to achieve similar sample sizes between intervention group and control group, to allow for Forest Plot analysis.

The overall Risk Ratio was:

- FMA – UL Total = 1.65 [1.01; 2.68] (Figure 5).
- FMA – UL Proximal = 1.18 [0.58; 2.38] (Figure 6).
- FMA – UL Distal = 1.22 [0.54; 2.79] (Figure 7).

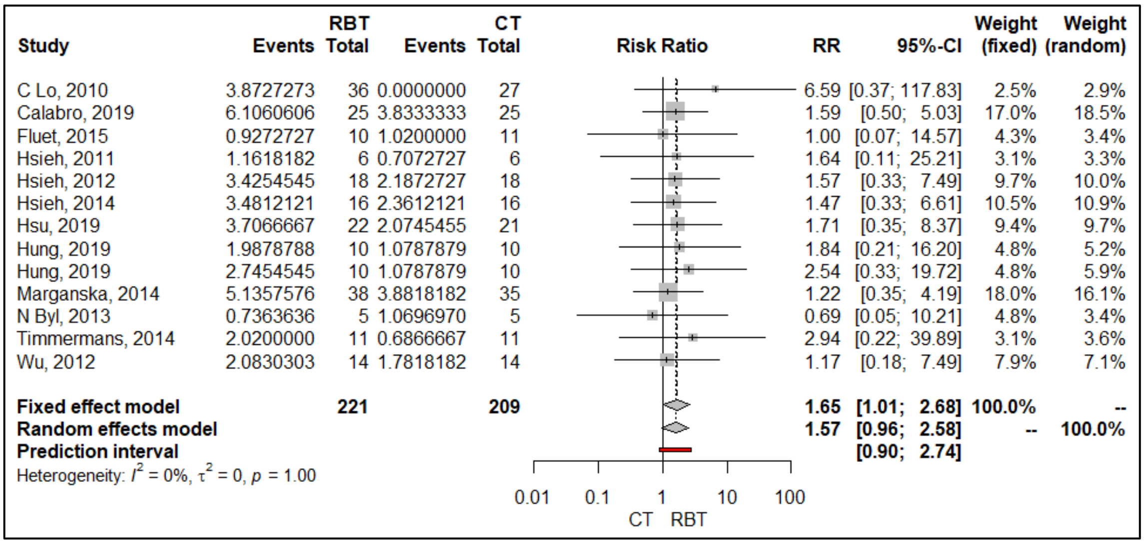


Figure 5 *Robot-based therapy vs Conventional therapy impact on FMA-UL Total.*

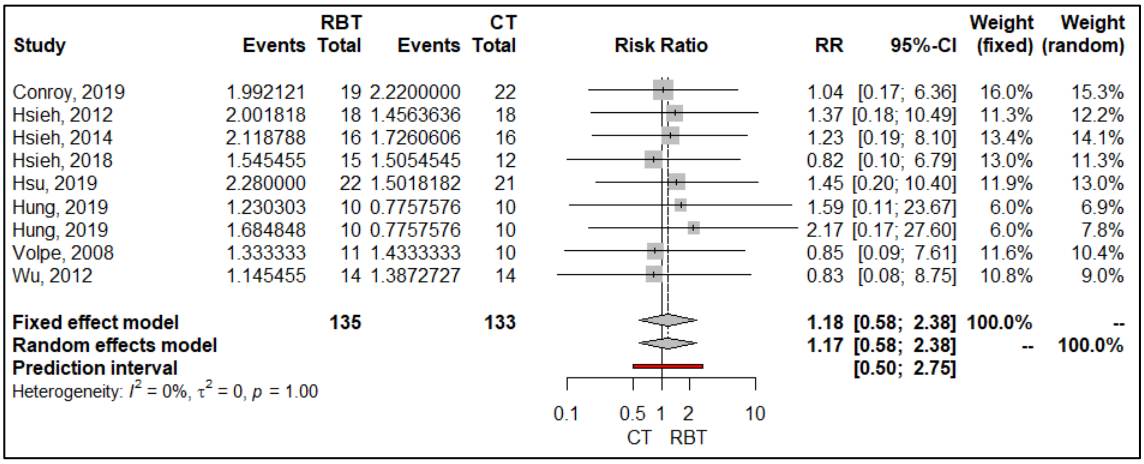


Figure 6 *Robot-based therapy vs Conventional therapy impact on FMA-UL Proximal.*

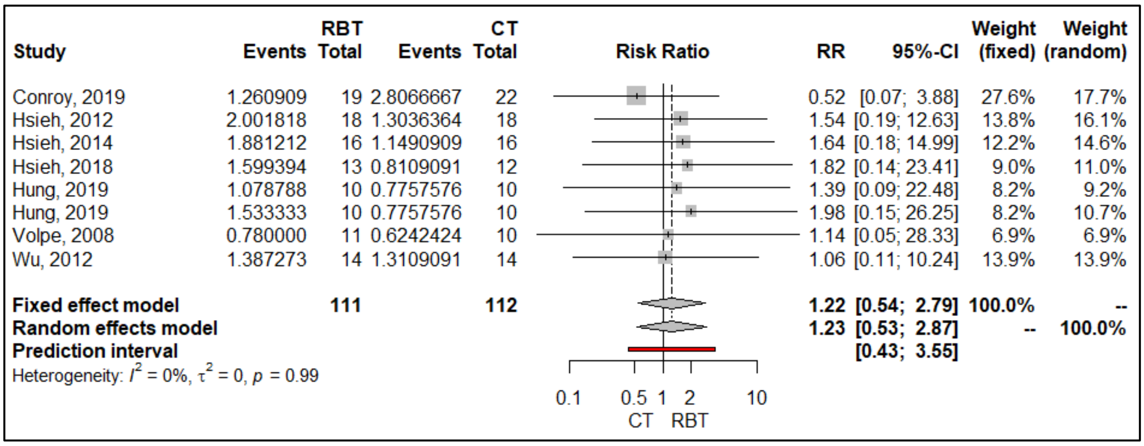


Figure 7 *Robot-based therapy vs Conventional therapy impact on FMA-UL Distal.*

To compare robot-based therapy to conventional therapy, we created Table 3 to statistically describe the mean difference between Post-intervention and Basal FMA-UL in four distinct groups: robot-based therapy (RBT), robot-based therapy coupled with alternative treatment, conventional therapy (CT) and Conventional therapy coupled with other rehabilitation strategy (CT_ALT).

The CT_ALT group comprised only 3 insertions from McCabe, 2015, regarding CT + functional electrical stimulation (FES). For that reason, and even though the mean gains were expressive, it was not incorporated into Figures 8 and 9, because a sample of 12 individuals is too statistically weak compared to the other groups.

		Change FMA-UL	N
CT	Minimum	-1,06	5
	Maximum	9,90	46
	Mean	2,66	15
	Standard Deviation	1,90	8
	Insertions	34	
CT_ALT	Minimum	3,80	12
	Maximum	8,80	12
	Mean	5,73	12
	Standard Deviation	2,69	0
	Insertions	3	
RBT	Minimum	1,11	6
	Maximum	8,00	47
	Mean	3,40	17
	Standard Deviation	1,67	8
	Insertions	36	
RBT_ALT	Minimum	1,70	5
	Maximum	8,50	22
	Mean	3,87	15
	Standard Deviation	1,80	5
	Insertions	19	

Table 3 *Mean difference between Post-treatment and Basal FMA-UL.*
Abbreviations: CT = Conventional therapy; CT_ALT = Conventional therapy + alternative therapy; RBT = Robot-based therapy; RBT_ALT = Robot-based therapy + alternative therapy.

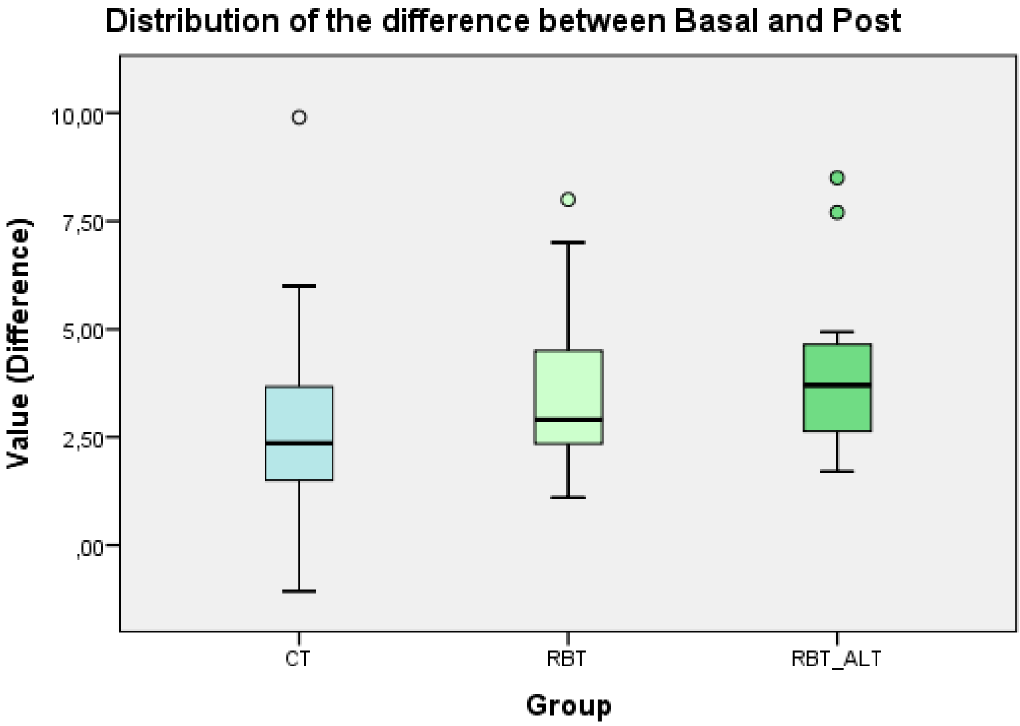


Figure 8 *Box Plot for the distribution of the difference between Basal and Post-Intervention FMA-UL.*

From the Box Plot in Figure 8, we can perceive that robot-based therapy group values are globally higher than conventional therapy group. The inferior quartile from RBT is close to the median of the CT group, the superior and inferior limits of RBT are higher than CT's and the third quartile from RBT is higher than CT group. This demonstrates that robot-based therapy presents better results than conventional therapy at improving FMA-UL.

Regarding the RBT_ALT group, when compared to RBT alone, the distribution of results between the first and the third quartile are similar. On the other hand, the median is higher in comparison to RBT group, wish opens the possibility that alternative therapies coupled with RBT can promote additional gains in motor performance.

Based on the intervention schedule shown in Table 2, we describe the total hours and number of treatment sessions from each study (Table 4 and Figure 11).

We can see wide variety across studies, ranging between 18 to 300 hours of rehabilitation, distributed into 8 to 60 sessions.

Table 4 *Hours and treatment sessions from each study.*

Author	Robot	Hours	Sessions
Hsieh, 2011	BMT	32,50	20,00
Hsieh, 2012	BMT	32,50	20,00
Wu, 2012	BMT	32,50	20,00
Hsieh, 2014	BMT	32,50	20,00
Hsu, 2019	BMT	10,00	12,00
Hung, 2019	BMT / IMT	31,60	20,00
Volpe, 2008	IMT	18,00	18,00
C Lo, 2010	IMT	36,00	36,00
Conroy, 2011	IMT	18,00	18,00
McCabe, 2015	IMT	300,00	60,00
Hsieh, 2018	IMT	32,50	36,00
Conroy, 2019	IMT	36,00	36,00
N Byl, 2013	UL-EX07	18,00	12,00
Marganska, 2014	ARMin III	18,00	24,00
Timmermans, 2014	HM	32,00	32,00
Fluet, 2015	HM	24,00	8,00
Calabro, 2019	Amadeo	120,00	40,00

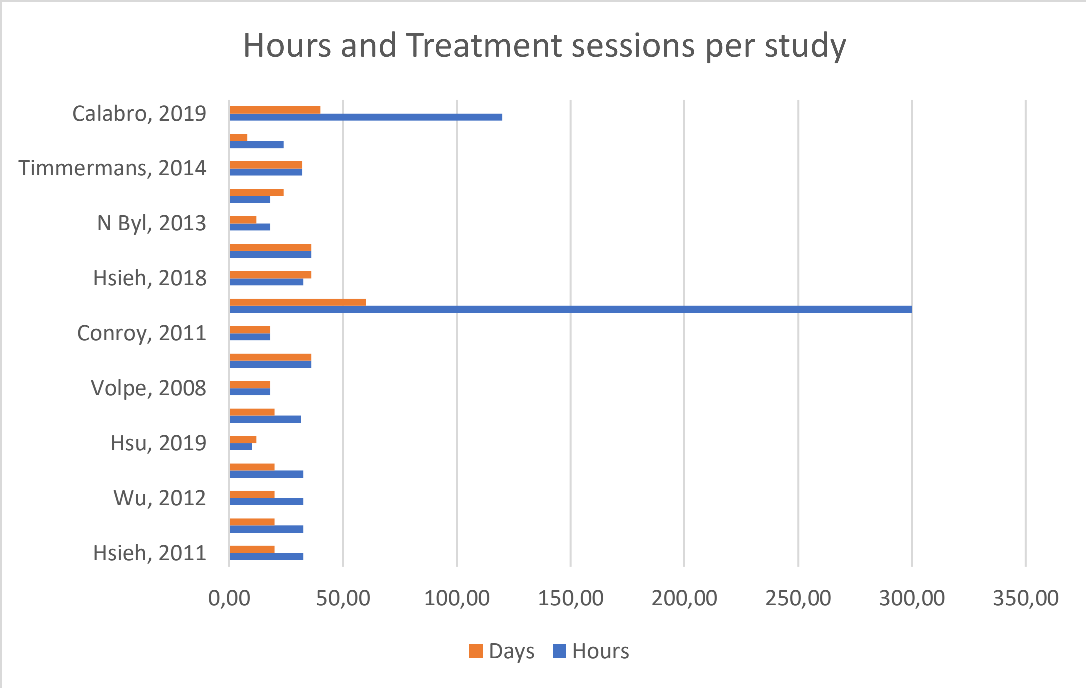
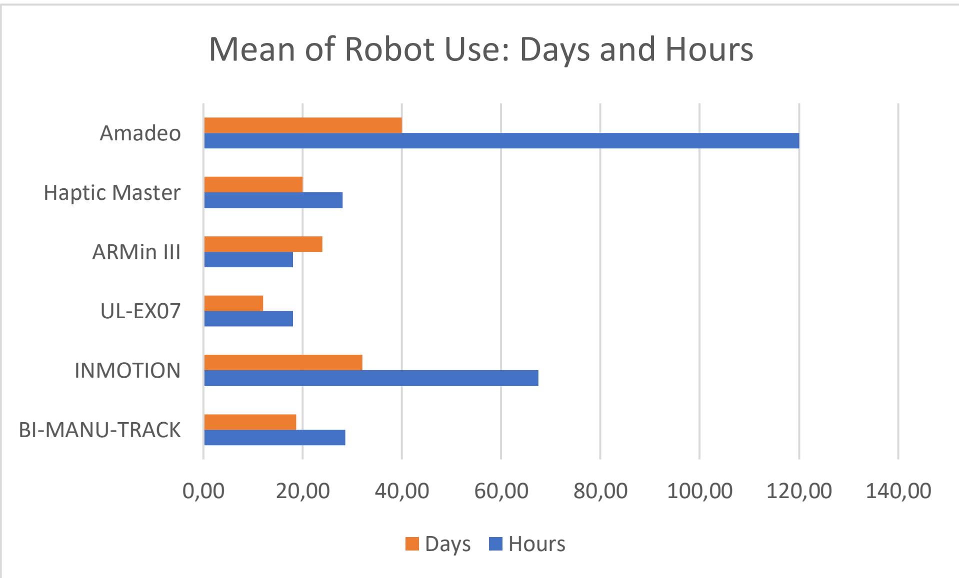


Figure 11 *Hours and treatment sessions from each study.*

Based on the 17 reviewed studies and its robot-based therapy programs, we calculated the mean time spent on each robot device (Table 5 and Figure 11).

Robot	Hours	Days
BI-MANU-TRACK	28,60	18,67
INMOTION	67,44	32,00
UL-EX07	18,00	12,00
ARMin III	18,00	24,00
Haptic Master	28,00	20,00
Amadeo	120,00	40,00

Table 5 and Figure 12 *Average time spent on robot (hours and days).*



Discussion

The objective is to discuss the main results and complement them with other randomized clinical trials, in the attempt to better understand the importance of robot-based therapy in chronic stroke patients.

The present systematic review included a sample of 17 randomized clinical trials, counting for 620 participants in total.

Even though it is a significant population size, we found subdivisions of the intervention groups in several RCT's, impairing its statistic power.

Some reasons made it impossible to directly compare robot-based therapy and conventional therapy groups:

- Several studies distributed the population into 3 groups (Example: 2 RBT groups and 1 CT group), creating distinct sample sizes to overall RBT and CT groups.
- In the rehabilitation program, the percentage of time allocated to robot-based therapy for the intervention group was widely different across studies, generating a great heterogeneity and impairing our ability to use the time variable in the statistics analysis.

Regarding the duration of intervention, we could verify an enormous diversity in time per session, sessions per week and total weeks. Nonetheless, a minimum of 8 sessions was achieved in each study and, in six of the seventeen articles, the upper limb training sessions were applied 5 times a week, for 4 weeks and with a time per session of 90 to 105 minutes.

It's important to elucidate that several studies present low viability in the presented results, due to several limitations.

From the reviewed studies, we can confirm the benefits for implementing robot devices in the recovery of upper limb motor function, even beyond 6 months since stroke, as our results show a tendency towards the improvement of FMA-UL from basal to post robot-based therapy intervention, similar to conventional therapy.

However, we could not directly determine if robot-based therapy is better than conventional therapy at improving upper limb motor function.

In an efficiency point of view, implementation of these neurotechnology devices in post-stroke rehabilitation programs opens the possibility to increase the number of patients treated, since its use is not therapist dependent.

Robot-based therapy can also be used for home-training, with the limitation of technological literacy that can be supplanted with education by the healthcare professionals.

As we show with this review, rehabilitation with robot devices can be equally effective to a therapist in the training of the upper limb, but with the cost of losing the human component of the therapeutic act. This aspect may impair its efficacy, since depression affects one third of stroke survivors (Towfighi et al., 2017).

For future trials, we suggest the application of a similar percentual distribution of time to RBT in the intervention group, a detailed description of time exposure for each aspect of the physical rehabilitation and, if possible, more than 150 hours of intervention regimen (Daly et al., 2019). This could be achieved with the creation of a consensus in the rehabilitation program to be studied worldwide.

We also propose FMA-UL measurements at follow-up (only made in six of our reviewed articles), to determine the long-term effect of the intervention.

Bellow, we discuss each robot device (movement patterns and individual impact on FMA-UL), particular characteristics of the reviewed studies and some studies that investigate the best application of each robot and the impact of complementing them with alternative therapies.

Bi-Manu-Track

The BMT enables bilateral and symmetrical training of two movement patterns: forearm pronation/supination and wrist flexion/extension.

Each movement can be achieved in 3 different computer-controlled modes:

- Mode 1: passive-passive
- Mode 2: active (unaffected limb) - passive
- Mode 3: active-active

At (Hsieh et al., 2011, 2012), the population was distributed into two groups: high-intensity RBT and low-intensity RBT (pre-determined by the number of movement repetitions to be achieved in each session).

As for this review, we found that robot-based therapy with the Bi-Manu-Track shows a tendency towards the improvement in upper limb motor function.

- Bilateral is better than unilateral training

Regarding its optimal application, several RCT's have shown that bilateral training provokes a greater improvement in several motor function variables (including FMA – UL), when compared to unilateral training (C. S. Hung, Hsieh, Wu, Chen, et al., 2019; C. shan Hung et al., 2019; C. Y. Wu et al., 2013).

- Bi-Manu-Track coupled with neuromuscular electrical stimulation

When it comes to combining therapeutic approaches, (Lee et al., 2015) has shown that coupling BMT with neuromuscular electrical stimulation (NMES), when compared to sham-NMES, demonstrates greater improvements in wrist flexor MAS score (spasticity), WMFT (quality of movement), and the hand function domain of the

SIS. This opens the possibility to combine these two therapeutic approaches, not only with Bi-Manu-Track but also with the other robot devices reviewed in our work.

InMotion

The InMotion is a modular system consisting in three components (2.0, 3.0 and Linear Robot), which can be used individually or coupled.

The IMT 2.0 is a 2-DOF robot that enables shoulder flexion/extension with gravity-compensated horizontal reaching.

At (Lo et al., 2010) and (Conroy et al., 2011), the IMT-LR (1-DOF) was additionally used to allow vertical movements against gravity.

The IMT 3.0 (3-DOF) focuses essentially on distal movements, such as, wrist flexion/extension, radial/ulnar deviation, and forearm pronation/supination (Conroy et al., 2019).

At (Lo et al., 2010), both proximal and distal limb motor function was trained, with the regimen being sequentially changed every 3 weeks at this order: IMT 2.0, IMT-LR + grasp-hand device, IMT 3.0 and a combination of the three.

At (Conroy et al., 2019), in order to achieve both proximal and distal improvements, every month the intervention changed sequentially from: IMT 3.0 to IMT 2.0 to a combination of the two in alternating days.

Studies where IMT 2.0 and IMT 3.0 were both used measured upper limb function not only based on the total FMA-UL, but also on its proximal and distal subcomponents.

As for this review, we found that the application of the InMotion, in the rehabilitation of chronic stroke, shows a tendency towards the improvement in upper limb motor function.

- Improvements beyond 150 hours of robot-based therapy

(Daly et al., 2019) has shown that beyond 150h of robot-based therapy, the motor function keeps improving, rather than plateauing, indicating that rehabilitation should be given in a longer dose than most of our reviewed studies.

- Task-specific is better than impairment oriented

At (C. S. Hung et al., 2016), the improvements in FMA – UL with a combination of RBT and task-specific training were significantly superior to RBT and impairment-oriented training. This suggests that further studies should keep their focus on task-specific rehabilitation.

- External focus equal to internal focus

On the contrary, and despite research in healthy individuals being widely supportive to the use of external focus of attention during motor training to facilitate greater retention of motor improvements, at (Kim et al., 2017), after treatment and at 4 weeks follow-up, there was no significant difference in the improvement of FMA – UL between external focus and internal focus while training with the IMT 2.0.

ARMin III

The ARMin (7-DOF) is an adjustable exoskeleton that allows shoulder flexion/extension plus external/internal rotation, elbow flexion/extension and forearm pronation/supination. This device is coupled with a custom software that enables 3D gaming and functional training in the form of simulated activities of daily living (Brokaw et al., 2014; Weber & Stein, 2018).

- ARMin III plus muscle vibration

At (Calabrò et al., 2017), the Armeo-Power device, a commercial version of the ARMin (Weber & Stein, 2018), was combined with muscle vibration (MV) and, compared to Armeo + sham-MV, showed greater improvements in upper limb spasticity and motor function. This opens the possibility to combine these two therapeutic approaches, in further studies, not only with ARMin III but also with the other robot devices reviewed in our work.

UL-EX07

A 7-DOF robot device that matches 95% of normal movement of the human arm and allows either unilateral or bilateral upper limb motor rehabilitation (Byl et al., 2013).

Haptic Master

The HM (6-DOF) allows the patient to reach, grasp and transport objects in a three-dimensional space (Timmermans et al., 2014).

- Simultaneous proximal and distal training

At (Fluet et al., 2014), the combination of HM and CyberGlove, and therefore the simultaneous training of hand and arm, showed similar improvements in WFMT when compared to HM alone. However, the gains were better retained at the three months follow-up.

Therefore, at (Fluet et al., 2015), the Haptic Master was coupled with the CyberGlove and CyberGrasp.

Amadeo

Amadeo is a hand robot (5-DOF) used for finger flexion/extension coupled with visual feedback, allowing the movements to be task-oriented (Calabrò et al., 2019).

Other Robots (ARMin III + UL-EX07 + HM + Amadeo)

As for this review, due to the lack of studies regarding this robot devices, we cannot confidently say they have a major impact on chronic stroke patient’s motor function.

However, individually, the studies show improvement in FMA-UL with robot-based therapy. In order to take further conclusions, more studies with these four robot devices are necessary in the future.

Limitations of the study

Although our study demonstrated favorable outcomes, there were important limitations:

- Conventional therapy is highly variable across trials, because of the different types of treatment, and within trials, as it is therapist dependent. Therefore, the intervention applied to the control is not equal across studies.
- The inclusion and exclusion criteria for each study varied significantly, therefore, limiting the population homogeneity.
- In most randomized clinical trials, the inclusion criteria of chronic stroke (> 6 months post-stroke) produces a wide and variable range of time-since-stroke, wish compromises the homogeneity of the population.
- In several articles, the intervention group was stratified into 2 subgroups, with slightly different types of interventions, impairing the studies statistic power.

Conclusion

In general, it was possible to determine that robot-based therapy in the rehabilitation of the upper limb in chronic stroke patients is somewhat equal to conventional therapy.

We faced several difficulties, particularly related to inconsistencies found in the percentual time allocated to robot-based therapy in RBT groups, impairing our ability to directly compare the two rehabilitation modalities. However, the main objective that we initially proposed was accomplished.

From our systematic review, stands the idea that adding robot-based therapy to the rehabilitation of chronic stroke patients accomplishes reasonable gains in upper limb motor function, comparable to conventional therapy.

In an efficiency point of view, implementation of these neurotechnology devices in post-stroke rehabilitation programs opens the possibility to treat a bigger number of patients, since its use is not therapist dependent.

From now on, future studies, with Bi-Manu-Track, InMotion, ARMin III, UL-EX07, Haptic Master, Amadeo or any other upper limb robot device developed in the upcoming years, should try to implement an intervention program with similar characteristics, for example in terms of percentual time allocated to robot-based therapy and equal sample sizes for RBT and CT groups, to facilitate further systematic reviews. We also propose that RBT intervention group should not be divided into subgroups, in order to increase its statistics power.

Nonetheless, our systematic review stimulates the integration of new robot training modalities in the rehabilitation program, at least in patients with six months since stroke.

References

Aho, K., Harmsen, P., Hatano, S., Marquardsen, J., Smirnov, V. E., & Strasser, T. (1980). Cerebrovascular disease in the community: results of a WHO collaborative study. *Bulletin of the World Health Organization*, *58*(1), 113–130.

Khaku, A. S., & Tadi, P. (2021). *Cerebrovascular Disease*. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK430927/#_NBK430927_pubdet_

Johnson, C. O., Nguyen, M., Roth, G. A., Nichols, E., Alam, T., Abate, D., Abd-Allah, F., Abdelalim, A., Abraha, H. N., Abu-Rmeileh, N. M., Adebayo, O. M., Adeoye, A. M., Agarwal, G., Agrawal, S., Aichour, A. N., Aichour, I., Aichour, M. T. E., Alahdab, F., Ali, R., … Murray, C. J. L. (2019). Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(5), 439–458. https://doi.org/10.1016/S1474-4422(19)30034-1

Kwakkel, G., Kollen, B., & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke: facts and theories. *Restorative Neurology and Neuroscience*, *22*(3–5), 281–299.

Ballester, B. R., Maier, M., Duff, A., Cameirão, M., Bermúdez, S., Duarte, E., Cuxart, A., Rodríguez, S., Mozo, R. M. S. S., & Verschure, P. F. M. J. (2019). A critical time window for recovery extends beyond one-year post-stroke. *Journal of Neurophysiology*, *122*(1), 350–357. https://doi.org/10.1152/jn.00762.2018

Coscia, M., Wessel, M. J., Chaudary, U., Millán, J. del R., Micera, S., Guggisberg, A., Vuadens, P., Donoghue, J., Birbaumer, N., & Hummel, F. C. (2019). Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain*, *142*(8), 2182–2197. https://doi.org/10.1093/brain/awz181

Weber, L. M., & Stein, J. (2018). The use of robots in stroke rehabilitation: A narrative review. *NeuroRehabilitation*, *43*(1), 99–110. https://doi.org/10.3233/NRE-172408

Kwakkel, G., Lannin, N. A., Borschmann, K., English, C., Ali, M., Churilov, L., Saposnik, G., Winstein, C., van Wegen, E. E. H., Wolf, S. L., Krakauer, J. W., & Bernhardt, J. (2017). Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *12*(5), 451–461. https://doi.org/10.1177/1747493017711813

Hsieh, Y. W., Wu, C. Y., Liao, W. W., Lin, K. C., Wu, K. Y., & Lee, C. Y. (2011). Effects of Treatment Intensity in Upper Limb Robot-Assisted Therapy for Chronic Stroke: A Pilot Randomized Controlled Trial. *Neurorehabilitation and Neural Repair*, *25*(6), 503–511. https://doi.org/10.1177/1545968310394871

Hsieh, Y. W., Wu, C. Y., Lin, K. C., Yao, G., Wu, K. Y., & Chang, Y. J. (2012). Dose–Response Relationship of Robot-Assisted Stroke Motor Rehabilitation The Impact of Initial Motor Status. *Stroke*, *43*(10), 2729–2734. https://doi.org/10.1161/STROKEAHA.112.658807

Wu, C., Yang, C., Chuang, L., Lin, K.-C., Chen, H., & Chen, M. (2012). Effect of Therapist-Based Versus Robot-Assisted Bilateral Arm Training on Motor Control, Functional Performance, and Quality of Life After Chronic Stroke: A Clinical Trial. *Physical Therapy*, *92*(8), 1006–1016. https://doi.org/10.2522/ptj.20110282

Hsieh, Y. W., Lin, K. C., Horng, Y. S., Wu, C. Y., Wu, T. C., & Ku, F. L. (2014). Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: a randomized controlled trial. *Journal of Neurology*, *261*(5), 1037–1045. https://doi.org/10.1007/s00415-014-7345-4

Hsu, H. Y., Chiu, H. Y., Kuan, T. S., Tsai, C. L., Su, F. C., & Kuo, L. C. (2019). Robotic-assisted therapy with bilateral practice improves task and motor performance in the upper extremities of chronic stroke patients: A randomised controlled trial. *Australian Occupational Therapy Journal*, *66*(5), 637–647. https://doi.org/10.1111/1440-1630.12602

Hung, C. S., Hsieh, Y. W., Wu, C. Y., Lin, K. C., Lin, J. C., Yeh, L. M., & Yin, H. P. (2019). Comparative Assessment of Two Robot-Assisted Therapies for the Upper Extremity in People With Chronic Stroke. *American Journal of Occupational Therapy*, *73*(1), 1–9. https://doi.org/10.5014/ajot.2019.022368

Volpe, B. T., Lynch, D., Rykman-Berland, A., Ferraro, M., Galgano, M., Hogan, N., & Krebs, H. I. (2008). Intensive Sensorimotor Arm Training Mediated by Therapist or Robot

Improves Hemiparesis in Patients With Chronic Stroke. *Neurorehabilitation and Neural Repair*, *22*(3), 305–310. https://doi.org/10.1177/1545968307311102

Lo, A. C., Guarino, P. D., Richards, L. G., Haselkorn, J. K., Wittenberg, G. F., Federman, D. G., Ringer, R. J., Wagner, T. H., Krebs, H. I., Volpe, B. T., Bever, C. T., Bravata, D. M., Duncan, P. W., Corn, B. H., Maffucci, A. D., Nadeau, S. E., Conroy, S. S., Powell, J. M., Huang, G. D., & Peduzzi, P. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. *New England Journal of Medicine*, *362*(19), 1772–1783. https://doi.org/10.1056/NEJMoa0911341

Conroy, S. S., Whitall, J., Dipietro, L., Jones-Lush, L. M., Zhan, M., Finley, M. A., Wittenberg, G. F., Krebs, H. I., & Bever, C. T. (2011). Effect of Gravity on Robot-Assisted Motor Training After Chronic Stroke: A Randomized Trial. *Archives of Physical Medicine and Rehabilitation*, *92*(11), 1754–1761. https://doi.org/10.1016/j.apmr.2011.06.016

McCabe, J., Monkiewicz, M., Holcomb, J., Pundik, S., & Daly, J. J. (2015). Comparison of Robotics, Functional Electrical Stimulation, and Motor Learning Methods for Treatment of Persistent Upper Extremity Dysfunction After Stroke: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, *96*(6), 981–990. https://doi.org/10.1016/j.apmr.2014.10.022

Conroy, S. S., Wittenberg, G. F., Krebs, H. I., Zhan, M., Bever, C. T., & Whitall, J. (2019). Robot-Assisted Arm Training in Chronic Stroke: Addition of Transition-to-Task Practice. *Neurorehabilitation and Neural Repair*, *33*(9), 751–761. https://doi.org/10.1177/1545968319862558

Hsieh, Y. W., Lin, K. C., Wu, C. Y., Shih, T. Y., Li, M. W., & Chen, C. L. (2018). Comparison of proximal versus distal upper-limb robotic rehabilitation on motor performance after stroke: A cluster controlled trial. *Scientific Reports*, *8*(1), 1–11. https://doi.org/10.1038/s41598-018-20330-3

Byl, N. N., Abrams, G. M., Pitsch, E., Fedulow, I., Kim, H., Simkins, M., Nagarajan, S., & Rosen, J. (2013). Chronic stroke survivors achieve comparable outcomes following virtual task specific repetitive training guided by a wearable robotic orthosis (UL-EXO7) and actual task specific repetitive training guided by a physical therapist. *Journal of Hand*

Therapy, *26*(4), 343–352. https://doi.org/10.1016/j.jht.2013.06.001

Klamroth-Marganska, V., Blanco, J., Campen, K., Curt, A., Dietz, V., Ettlin, T., Felder, M., Fellinghauer, B., Guidali, M., Kollmar, A., Luft, A., Nef, T., Schuster-Amft, C., Stahel, W., & Riener, R. (2014). Three-dimensional, task-specifi c robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. *The Lancet Neurology*, *13*(2), 159–166. https://doi.org/10.1016/S1474-4422(13)70305-3

Timmermans, A. A. A., Lemmens, R. J. M., Monfrance, M., Geers, R. P. J., Bakx, W., Smeets, R. J. E. M., & Seelen, H. A. M. (2014). Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, *11*(1). https://doi.org/10.1186/1743-0003-11-45

Fluet, G. G., Merians, A. S., Qiu, Q., Rohafaza, M., Van Wingerden, A. M., & Adamovich, S. V. (2015). Does training with traditionally presented and virtually simulated tasks elicit differing changes in object interaction kinematics in persons with upper extremity hemiparesis? *Topics in Stroke Rehabilitation*, *22*(3), 176–184. https://doi.org/10.1179/1074935714Z.0000000008

Calabrò, R. S., Accorinti, M., Porcari, B., Carioti, L., Ciatto, L., Billeri, L., Andronaco, V. A., Galletti, F., Filoni, S., & Naro, A. (2019). Does hand robotic rehabilitation improve motor function by rebalancing interhemispheric connectivity after chronic stroke? Encouraging data from a randomised-clinical-trial. *Clinical Neurophysiology*, *130*(5), 767–780. https://doi.org/10.1016/j.clinph.2019.02.013

Towfighi, A., Ovbiagele, B., El Husseini, N., Hackett, M. L., Jorge, R. E., Kissela, B. M., Mitchell, P. H., Skolarus, L. E., Whooley, M. A., & Williams, L. S. (2017). Poststroke Depression: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*, *48*(2), e30–e43. https://doi.org/10.1161/STR.0000000000000113

Hung, C. shan, Lin, K. chung, Chang, W. ying, Huang, W. chih, Chang, Y. J., Chen, C. ling, Grace Yao, K., & Lee, Y. yun. (2019). Unilateral vs Bilateral Hybrid Approaches for Upper Limb Rehabilitation in Chronic Stroke: A Randomized Controlled Trial. *Archives of*

Physical Medicine and Rehabilitation, *100*(12), 2225–2232. https://doi.org/10.1016/j.apmr.2019.06.021

Wu, C. Y., Yang, C. L., Chen, M. De, Lin, K. C., & Wu, L. L. (2013). Unilateral versus bilateral robot-assisted rehabilitation on arm-trunk control and functions post stroke: A randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, *10*(1), 1–10. https://doi.org/10.1186/1743-0003-10-35

Hung, C. S., Hsieh, Y. W., Wu, C. Y., Chen, Y. J., Lin, K. C., Chen, C. L., Yao, K. G., Liu, C. T., & Horng, Y. S. (2019). Hybrid Rehabilitation Therapies on Upper-Limb Function and Goal Attainment in Chronic Stroke. *OTJR Occupation, Participation and Health*, *39*(2), 116–123. https://doi.org/10.1177/1539449218825438

Lee, Y. Y., Lin, K. C., Cheng, H. J., Wu, C. Y., Hsieh, Y. W., & Chen, C. K. (2015). Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: A double-blinded randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, *12*(1), 1–10. https://doi.org/10.1186/s12984-015-0088-3

Daly, J. J., McCabe, J. P., Holcomb, J., Monkiewicz, M., Gansen, J., & Pundik, S. (2019). Long-Dose Intensive Therapy Is Necessary for Strong, Clinically Significant, Upper Limb Functional Gains and Retained Gains in Severe/Moderate Chronic Stroke. *Neurorehabilitation and Neural Repair*, *33*(7), 523–537. https://doi.org/10.1177/1545968319846120

Hung, C. S., Hsieh, Y. W., Wu, C. Y., Lin, Y. T., Lin, K. C., & Chen, C. L. (2016). The Effects of Combination of Robot-Assisted Therapy With Task-Specific or Impairment-Oriented Training on Motor Function and Quality of Life in Chronic Stroke. *PM and R*, *8*(8), 721–729. https://doi.org/10.1016/j.pmrj.2016.01.008

Kim, G. J., Hinojosa, J., Rao, A. K., Batavia, M., & O'Dell, M. W. (2017). Randomized Trial on the Effects of Attentional Focus on Motor Training of the Upper Extremity Using Robotics With Individuals After Chronic Stroke. *Archives of Physical Medicine and Rehabilitation*, *98*(10), 1924–1931. https://doi.org/10.1016/j.apmr.2017.06.005

Brokaw, E. B., Nichols, D., Holley, R. J., & Lum, P. S. (2014). Robotic Therapy Provides a

Stimulus for Upper Limb Motor Recovery After Stroke That Is Complementary to and Distinct From Conventional Therapy. *Neurorehabilitation and Neural Repair*, *28*(4), 367–376. https://doi.org/10.1177/1545968313510974

Calabrò, R. S., Naro, A., Russo, M., Milardi, D., Leo, A., Filoni, S., Trinchera, A., & Bramanti, P. (2017). Is two better than one? Muscle vibration plus robotic rehabilitation to improve upper limb spasticity and function: A pilot randomized controlled trial. *PLoS ONE*, *12*(10), 1–20. https://doi.org/10.1371/journal.pone.0185936

Fluet, G. G., Merians, A. S., Qiu, Q., Davidow, A., & Adamovich, S. V. (2014). Comparing integrated training of the hand and arm with isolated training of the same effectors in persons with stroke using haptically rendered virtual environments, a randomized clinical trial. *Journal of NeuroEngineering and Rehabilitation*, *11*(1), 1–11. https://doi.org/10.1186/1743-0003-11-126

Tables, Figures and Attachments

Table 2 Search strategy

PubMed	Keywords: Artificial Intelligence + Stroke + Robot + Motor Rehabilitation Publication date: 2005-2021 Search result: 710 articles Selected RCT + CT: 201 articles - Exclusion (185): Clinical trials (67) Protocols (3) Other language than English (2) Absence of stroke (2 spinal cord injury + 3 healthy population) (5) Lack of trials: Acute (12) Subacute + Upper limb (23) Subacute + Lower limb (15) Subacute + Chronic (9) Chronic + Lower limb (9) Chronic + Upper + Lower limb (1) Chronic + Upper limb, but: Absence of CT (6) RBT vs RBT (28)

	Absence of RBT (2) Absence of FMA-UL (1) Repeated trial (1) - Result: 17 RCT’s regarding chronic stroke patients receiving RBT vs CT.

Robot	Identification	Sample (total)	Intervention	Hours	Time per session (Sessions x weeks)	Time-since-stroke (months)	Mean Age (years)
BMT	(Hsieh et al., 2011)	18	High-intensity RBT vs Low-intensity RBT vs CT	30-35h	90-105min x (5 x 4)	20.89	54.16
BMT	(Hsieh et al., 2012)	54	High-intensity RBT vs Low-intensity RBT vs CT	30-35h	90-105min x (5 x 4)	24.80	54.52
BMT	(C. Wu et al., 2012)	28 (42)	RBT vs CT vs (TBAT)	30-35h	90-105min x (5 x 4)	17.79	53.22
BMT	(Hsieh et al., 2014)	32 (48)	RBT vs CT vs (RBT + dCIT)	30-35h	90-105min x (5 x 4)	25.69	53.23
BMT	(Hsu et al., 2019)	43	RBT vs CT	10h	50min x (3 x 4)	14.19	52.86
BMT / IMT	(C. S. Hung, Hsieh, Wu, Lin, et al., 2019)	20 / 20	RBT (BMT / IMT*) vs CT	30-33h	90-100min x (5 x 4)	22.75 / 25.50*	53.79 / 56.52*
IMT	(Volpe et al., 2008)	21	Planar RBT vs CT	18h	60min x (3 x 6)	37.38	61.05
IMT	(Lo et al., 2010)	52 (127)	Planar + Vertical + Distal RBT vs CT vs (Intensive CT)	36h	60min x (3 x 12)	56	64.6
IMT	(Conroy et al., 2011)	57 (62**)	Planar vs Planar + Vertical RBT vs Intensive CT	18h	60min x (3 x 6)	50.4	57.8
IMT	(McCabe et al., 2015)	23 (39)	Planar RBT + ML vs ML vs (ML + FES)	300h	5h x (5 x 12)	Not found.	Not found.
IMT	(Hsieh et al., 2018)	40	Planar RBT vs Distal RBT vs CT	30-33h	90-100min (5 x 4)	20.57	54.42
IMT	(Conroy et al., 2019)	41 (45**)	Planar + Distal RBT vs CT	36h	60min x (3 x 12)	36.4	56.1
UL-EX07	(Byl et al., 2013)	15	Bilateral RBT vs Unilateral RBT vs CT	18h	90min x (2 x 6)	101.6	59.6
ARMin III	(Klamroth-Marganska et al., 2014)	73 (77)	RBT vs CT	18h	45min x (3 x 8)	43.8	53.5
HM	(Timmermans et al., 2014)	22	RBT vs CT	32h	60min x (4 x 8)	39	59.3
HM	(Fluet et al., 2015)	21	RBT vs CT	24h	3h x (4 x 2)	74.14	51.4
Amadeo	(Calabrò et al., 2019)	50	RBT vs CT	120h	3h x (5 x 8)	10	64.5

Table 2 *Characteristics of the studies included in the review.*
**Hung, 2019: the population submitted to RBT was equally divided into BMT and IMT. **Studies only showed mean age and time-since-stroke attributed to the () sample.*
Abbreviations: Planar = IMT 2.0; Vertical = IMT Linear-Robot; Distal = IMT 3.0; ML = Motor Learning; TBAT = therapist based bilateral arm training; dCIT = constraint induced therapy.

Table 3 *Mean difference between Post-treatment and Basal FMA-UL.*
Abbreviations: CT = Conventional therapy; CT_ALT = Conventional therapy + alternative therapy; RBT = Robot-based therapy; RBT_ALT = Robot-based therapy + alternative therapy.

		Change FMA-UL	N
CT	Minimum	-1,06	5
	Maximum	9,90	46
	Mean	2,66	15
	Standard Deviation	1,90	8
	Insertions	34	
CT_ALT	Minimum	3,80	12
	Maximum	8,80	12
	Mean	5,73	12
	Standard Deviation	2,69	0
	Insertions	3	
RBT	Minimum	1,11	6
	Maximum	8,00	47
	Mean	3,40	17
	Standard Deviation	1,67	8
	Insertions	36	
RBT_ALT	Minimum	1,70	5
	Maximum	8,50	22
	Mean	3,87	15
	Standard Deviation	1,80	5
	Insertions	19	

Table 4 *Hours and treatment sessions from each study.*

Author	Robot	Hours	Sessions
Hsieh, 2011	BMT	32,50	20,00
Hsieh, 2012	BMT	32,50	20,00
Wu, 2012	BMT	32,50	20,00
Hsieh, 2014	BMT	32,50	20,00
Hsu, 2019	BMT	10,00	12,00
Hung, 2019	BMT / IMT	31,60	20,00
Volpe, 2008	IMT	18,00	18,00
C Lo, 2010	IMT	36,00	36,00
Conroy, 2011	IMT	18,00	18,00
McCabe, 2015	IMT	300,00	60,00
Hsieh, 2018	IMT	32,50	36,00
Conroy, 2019	IMT	36,00	36,00
N Byl, 2013	UL-EX07	18,00	12,00
Marganska, 2014	ARMin III	18,00	24,00
Timmermans, 2014	HM	32,00	32,00
Fluet, 2015	HM	24,00	8,00
Calabro, 2019	Amadeo	120,00	40,00

Table 5 *Average time spent on robot (hours and days).*

Robot	Hours	Days
BI-MANU-TRACK	28,60	18,67
INMOTION	67,44	32,00
UL-EX07	18,00	12,00
ARMin III	18,00	24,00
Haptic Master	28,00	20,00
Amadeo	120,00	40,00

	N	Interval	Minimum	Maximum	Mean	Standard Deviation	Variance
fma_ul_total_CT_N	15	30,00	5,00	35,00	16,00	8,30	68,86
fma_ul_total_CT_B	14	34,80	18,20	53,00	35,43	11,40	129,87
fma_ul_total_CT_B_DP	11	11,90	3,00	14,90	9,25	3,16	9,99
fma_ul_total_CT_P	14	34,61	19,39	54,00	37,89	10,83	117,21
fma_ul_total_CT_P_DP	11	11,90	4,00	15,90	10,00	3,38	11,40
fma_ul_total_CT_DIF	15	7,06	-1,06	6,00	2,66	1,62	2,61
fma_ul_total_CT_DIF_DP	12	2,54	,78	3,32	2,26	,80	,64
fma_ul_total_RBT_HI_N	2	12,00	6,00	18,00	12,00	8,49	72,00
fma_ul_total_RBT_HI_B	2	1,22	42,78	44,00	43,39	,86	,74
fma_ul_total_RBT_HI_B_DP	2	,69	8,17	8,86	8,52	,49	,24
fma_ul_total_RBT_HI_P	2	1,33	48,00	49,33	48,67	,94	,88
fma_ul_total_RBT_HI_P_DP	2	,12	8,22	8,34	8,28	,08	,01
fma_ul_total_RBT_HI_DIF	2	,11	5,22	5,33	5,28	,08	,01
fma_ul_total_RBT_HI_DIF_DP	2	,41	2,10	2,51	2,31	,29	,08
fma_ul_total_RBT_LO_N	2	,00	18,00	18,00	18,00	,00	,00
fma_ul_total_RBT_LO_B	2	5,44	37,67	43,11	40,39	3,85	14,80
fma_ul_total_RBT_LO_B_DP	2	,82	9,18	10,00	9,59	,58	,34
fma_ul_total_RBT_LO_P	2	6,33	40,00	46,33	43,17	4,48	20,03
fma_ul_total_RBT_LO_P_DP	2	,20	10,27	10,47	10,37	,14	,02
fma_ul_total_RBT_LO_DIF	2	,89	2,33	3,22	2,78	,63	,40
fma_ul_total_RBT_LO_DIF_DP	2	,23	2,59	2,82	2,71	,17	,03
fma_ul_total_RBT_N	12	37,00	10,00	47,00	20,58	11,82	139,72
fma_ul_total_RBT_B	10	29,80	20,20	50,00	34,28	10,48	109,80
fma_ul_total_RBT_B_DP	7	10,37	2,03	12,40	7,12	3,83	14,69
fma_ul_total_RBT_P	10	31,40	23,60	55,00	39,10	10,24	104,79
fma_ul_total_RBT_P_DP	7	10,27	2,73	13,00	8,40	3,96	15,68
fma_ul_total_RBT_DIF	12	6,89	1,11	8,00	4,43	2,02	4,07
fma_ul_total_RBT_DIF_DP	9	4,00	,70	4,70	2,20	1,24	1,53

Table 5 Descriptive values from FMA-UL Total.
Abbreviations: N = number of participants; B = basal; P = post-intervention; DIF = difference between basal and post-intervention; RBT = robot-based therapy; CT = conventional therapy.

	N	Interval	Minimum	Maximum	Mean	Standard Deviation	Variance
fma_ul_proximal_RBT_N	7	12,00	10,00	22,00	14,57	4,69	21,95
fma_ul_proximal_RBT_B	7	18,64	12,79	31,43	22,60	6,29	39,54
fma_ul_proximal_RBT_B_DP	4	3,81	1,03	4,84	3,00	1,97	3,87
fma_ul_proximal_RBT_P	7	17,34	15,73	33,07	25,48	6,15	37,87
fma_ul_proximal_RBT_P_DP	5	4,15	1,45	5,60	3,56	1,76	3,09
fma_ul_proximal_RBT_DIF	7	2,86	1,64	4,50	2,88	,90	,81
fma_ul_proximal_RBT_DIF_DP	5	1,95	,42	2,37	1,52	,73	,54
fma_ul_proximal_CT_N	8	11,00	10,00	21,00	13,88	4,16	17,27
fma_ul_proximal_CT_B	8	19,79	11,43	31,22	24,08	6,37	40,64
fma_ul_proximal_CT_B_DP	6	6,10	1,00	7,10	4,47	2,16	4,67
fma_ul_proximal_CT_P	8	18,04	15,10	33,14	26,26	6,03	36,37
fma_ul_proximal_CT_P_DP	6	5,60	1,70	7,30	4,27	1,80	3,23
fma_ul_proximal_CT_DIF	8	2,37	1,30	3,67	2,17	,86	,74
fma_ul_proximal_CT_DIF_DP	6	1,17	1,28	2,45	1,82	,40	,16

Table 6 Descriptive values from FMA-UL Proximal.
Abbreviations: N = number of participants; B = basal; P = post-intervention; DIF = difference between basal and post-intervention; RBT = robot-based therapy; CT = conventional therapy.

	N	Interval	Minimum	Maximum	Mean	Standard Deviation	Variance
fma_ul_distal_RBT_N	6	9,00	10,00	19,00	13,33	3,67	13,47
fma_ul_distal_RBT_B	6	9,41	2,45	11,86	6,08	3,68	13,53
fma_ul_distal_RBT_B_DP	4	5,93	1,12	7,05	3,83	3,06	9,38
fma_ul_distal_RBT_P	6	10,34	3,73	14,07	8,41	3,93	15,44
fma_ul_distal_RBT_P_DP	4	6,03	1,63	7,66	4,39	3,03	9,16
fma_ul_distal_RBT_DIF	6	2,87	1,13	4,00	2,32	1,06	1,12
fma_ul_distal_RBT_DIF_DP	4	1,88	,51	2,39	1,66	,90	,81
fma_ul_distal_CT_N	7	8,00	10,00	18,00	12,86	3,24	10,48
fma_ul_distal_CT_B	7	11,80	1,60	13,40	7,82	4,32	18,67
fma_ul_distal_CT_B_DP	5	6,85	,80	7,65	5,03	2,92	8,55
fma_ul_distal_CT_P	7	12,83	2,60	15,43	9,22	4,56	20,76
fma_ul_distal_CT_P_DP	5	8,20	,90	9,10	5,50	3,19	10,16
fma_ul_distal_CT_DIF	7	1,03	1,00	2,03	1,41	,33	,11
fma_ul_distal_CT_DIF_DP	5	1,96	,84	2,80	1,97	,73	,54

Table 7 Descriptive values from FMA-UL Proximal
Abbreviations: N = number of participants; B = basal; P = post-intervention; DIF = difference between basal and post-intervention; RBT = robot-based therapy; CT = conventional therapy.

Table 8 FMA-UL Total from studies used in Forest Plot analysis (Figure 5) comparing robot-based therapy to conventional therapy.
Abbreviations: RBT = robot-based therapy; CT = conventional therapy; N = sample; B = basal; P = post-intervention; DIF = difference between basal and post-intervention.

Robot	Article	CT N	CT B	CT B_SD	CT P	CT P_SD	CT DIF	CT DIF_SD	RBT N	RBT B	RBT B_SD	RBT P	RBT P_SD	RBT DIF	RBT DIF_SD
Amadeo	Calabro, 2019	25	30	3	34	4	4	1,91	25	29	3	36	4	7	1,91
ARMin III	Marganska, 2014	35	20,7	8,2	23,3	11,3	2,6	3,1	38	20,2	7,1	23,6	11,8	3,4	4,7
BI-MANU-TRACK	Hsieh, 2011	6	44	8,17	40,33	11,86	2,83	2,44							
	Hsieh, 2012	18	44,61	11,06	47,56	10,5	2,95	2,7							
	Hsieh, 2014	16	35,94	7,9	39,75	7,97	3,81	1,85	16	35,69	9,62	41,81	9,4	6,12	2,29
	Hsu, 2019	21	41,9	14,9	44,1	15,9	2,2	3,32	22	38,6	12,4	43,1	13	4,5	2,89
	Hung, 2019	10	28		30,5		2,5		10	28		33,5		5,5	
	Wu, 2012	14	45,43	11,42	48,57	12,32	3,14	2,97	14	43,29	10,09	47,14	10,97	3,85	2,83
Haptic Master	Fluet, 2015	11	52	8,7	54	8	2	2,52	10	48	5,6	50	6,9	2	2,45
	Timmermans, 2014	11	53		54		1		11	50		55		5	
INMOTION	C Lo, 2010	27					-1,06	1	36					2,49	1,03
	Conroy, 2011	19	18,2	12,5	19,39	13,28	1,19	0,78							
	Conroy, 2019								19	22,47	2,03	25,34	2,73	2,87	0,7
	Hsieh, 2018	12	29,58	9,13	33,83	7,98	4,25	2,71							
	Hung, 2019	10	28		30,5		2,5		10	27,5		35,5		8	
UL-EX07	N Byl, 2013	5	24,6	6,8	30,6	6,92	6	1,88							

Robot + Article		RBT_HI N	RBT_HI B	RBT_HI B_DP	RBT_HI P	RBT_HI P_DP	RBT_HI DIF	RBT_HI DIF_DP	RBT_LO N	RBT_LO B	RBT_LO B_DP	RBT_LO P	RBT_LO P_DP	RBT_LO DIF	RBT_LO DIF_DP
BI-MANU-TRACK	Hsieh, 2011	6	44	8,17	49,33	8,34	5,33	2,1	18	37,67	10	40	10,47	2,33	2,59
	Hsieh, 2012	18	42,78	8,86	48	8,22	5,22	2,51	18	43,11	9,18	46,33	10,27	3,22	2,82

Table 9 FMA-UL Proximal from studies used in Forest Plot analysis (Figure 5) comparing robot-based therapy to conventional therapy.
Abbreviations: RBT = robot-based therapy; CT = conventional therapy; N = sample; B = basal; P = post-intervention; DIF = difference between basal and post-intervention.

Robot + Article		RBT N	RBT B	RBT B_SD	RBT P	RBT P_SD	RBT DIF	RBT DIF_SD	CT N	CT B	CT B_SD	CT P	CT P_SD	CT DIF	CT DIF_SD
BI-MANU-TRACK	Hsieh, 2012	.	.	.	.	.	.	.	18	31,22	4,6	32,83	4,25	1,61	1,82
	Hsieh, 2014	16	26,63	4,84	29,94	4,27	3,31	1,96	16	27,69	3,81	30,19	3,67	2,5	1,53
	Hsu, 2019	22	24,14	.	26,5	5,6	2,36	2,37	21	23,9	7,1	25,2	7,3	1,3	2,04
	Hung, 2019	10	24,5	.	27,5	.	3	.	10	21,5	.	23	.	1,5	.
	Wu, 2012	14	31,43	4,54	33,07	4,46	1,64	1,52	14	30,93	3,93	33,14	4,31	2,21	1,79
INMOTION	Conroy, 2019	19	16,21	1,03	18,61	1,45	2,4	0,42	.	.	.	.	.	.	.
	Hsieh, 2018	.	.	.	.	.	.	.	12	24,5	6,38	27,58	4,36	3,08	2,45
	Hung, 2019	10	22,5	.	27	.	4,5	.	10	21,5	.	23	.	1,5	.
	Volpe, 2008	11	12,79	1,6	15,73	2	2,94	1,32	10	11,43	1	15,1	1,7	3,67	1,28

Table 10 *FMA-UL Distal from studies used in Forest Plot analysis (Figure 5) comparing robot-based therapy to conventional therapy.*
Abbreviations: RBT = robot-based therapy; CT = conventional therapy; N = sample; B = basal; P = post-intervention; DIF = difference between basal and post-intervention.

Robot + Article		**RBT N**	**RBT B**	**RBT B_SD**	**RBT P**	**RBT P_SD**	**RBT DIF**	**RBT DIF_SD**	**CT N**	**CT B**	**CT B_SD**	**CT P**	**CT P_SD**	**CT DIF**	**CT DIF_SD**
BI-MANU-TRACK	Hsieh, 2012								18	13,39	7,65	14,72	7,51	1,33	1,99
	Hsieh, 2014	16	9,06	5,84	11,88	6,25	2,82	2,39	16	8,25	5,92	9,56	5,98	1,31	2,39
	Hsu, 2019														
	Hung, 2019	10	3,00		5,50		2,50		10	6,50		8,00		1,50	
	Wu, 2012	14	11,86	7,05	14,07	7,66	2,21	2,36	14	13,40	7,44	15,43	9,10	2,03	2,80
INMOTION	Conroy, 2019	19	5,63	1,12	6,76	1,63	1,13	,51							
	Hsieh, 2018								12	5,08	3,34	6,25	4,00	1,17	1,84
	Hung, 2019	10	4,50		8,50		4,00		10	6,50		8,00		1,50	
	Volpe, 2008	11	2,45	1,30	3,73	2,00	1,28	1,38	10	1,60	,80	2,60	,90	1,00	,84

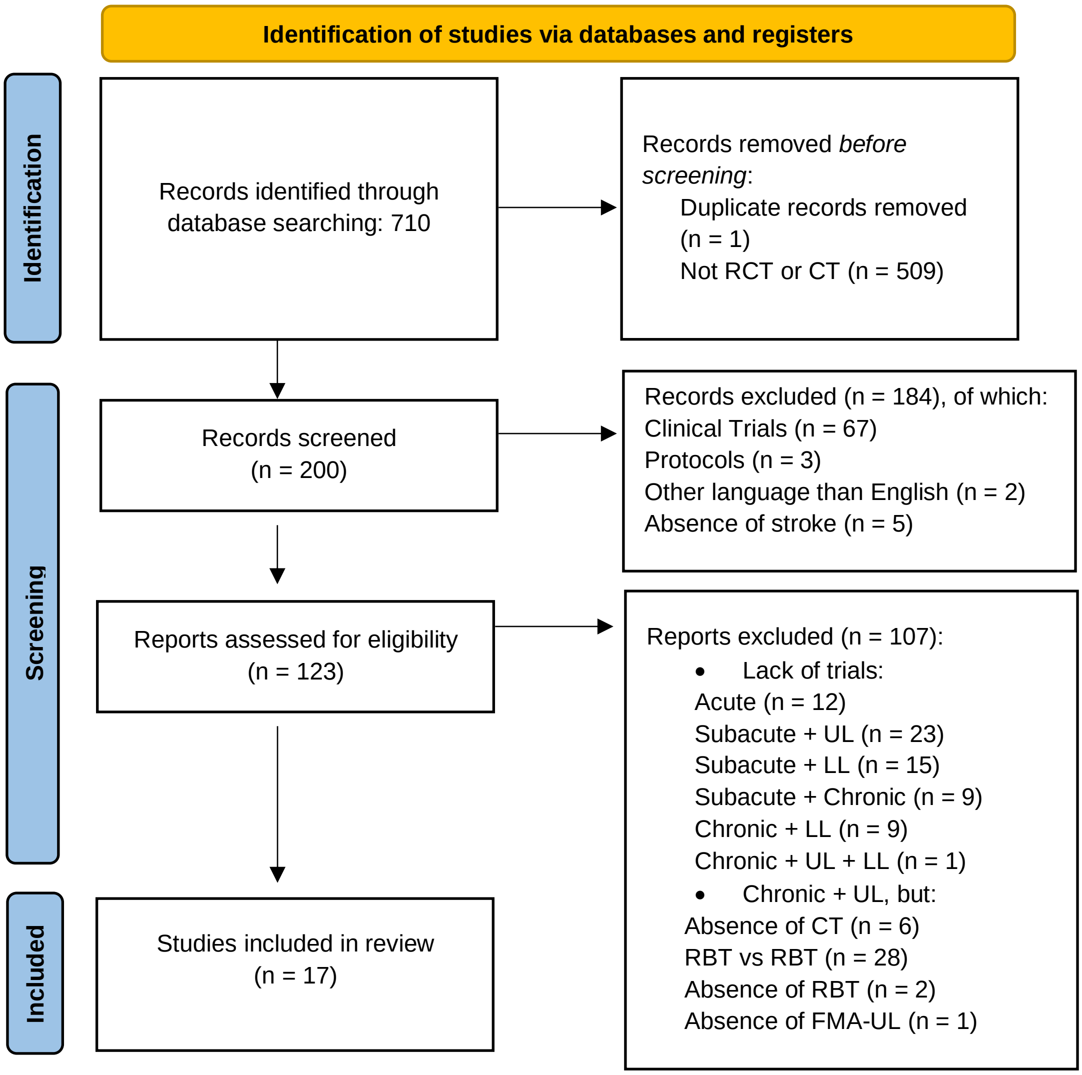


Figure 2 *Study flow diagram of systematic review.*

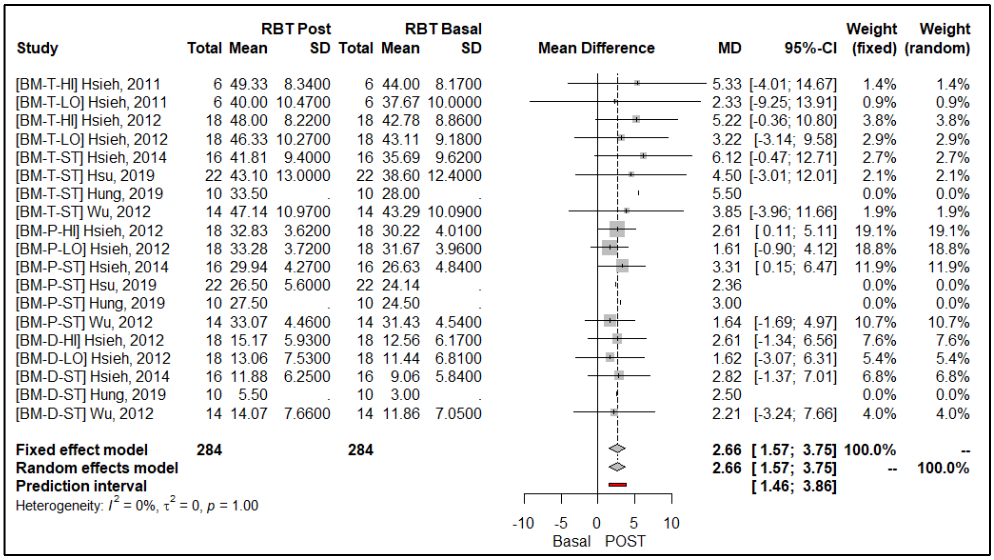


Figure 2 *Mean difference between Post-treatment and Basal FMA-UL after robot-based therapy with Bi-Manu-Track. Abbreviations: BM = Bi-Manu-Track; T = FMA-UL Total; P = FMA-UL Proximal; D = FMA-UL Distal; HI = High-intensity RBT; LO = Low-intensity RBT; ST = standard training.*

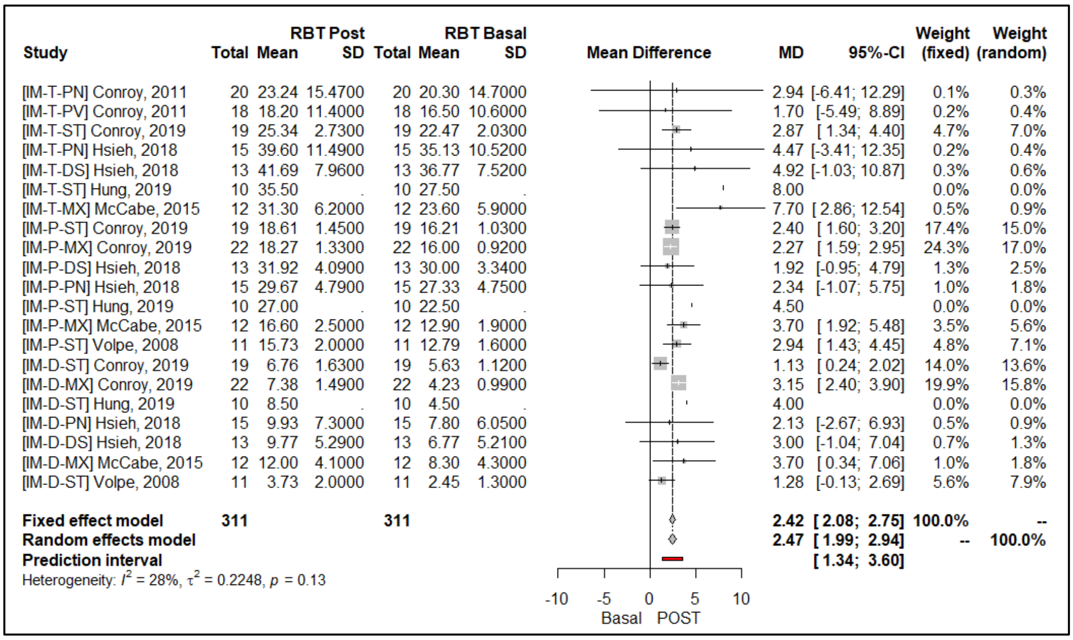


Figure 3 *Mean difference between Post-treatment and Basal FMA-UL after robot-based therapy with InMotion. Abbreviations: IM = InMotion; T = FMA-UL Total; P = FMA-UL Proximal; D = FMA-UL Distal; PN = Planar; PV = Planar + Vertical; ST = Standard Training; DS = Distal; MX = Robot and Conventional Mixed Training.*

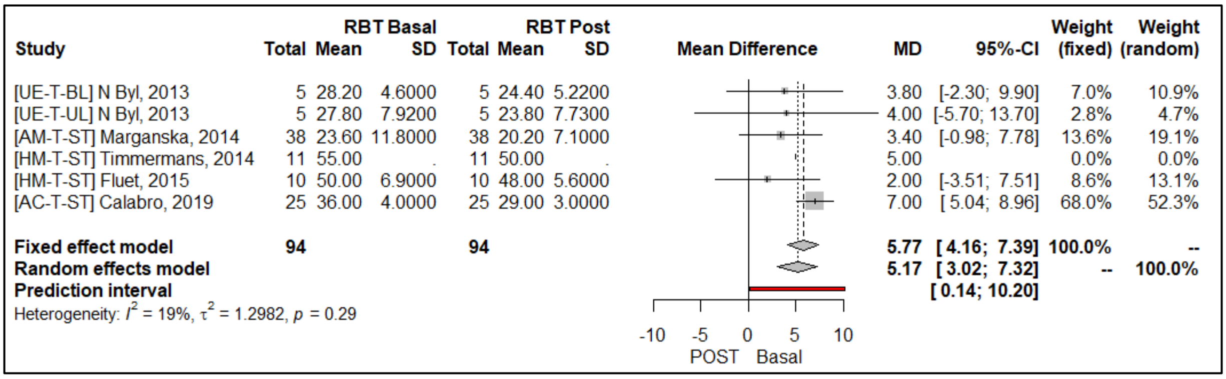


Figure 4 *ARMin III + UL-EX07 + HM + Amadeo vs Conventional therapy impact on FMA-UL Total. Abbreviations: T = FMA-UL Total; UE = UL-EX07; AM = ARMin III; HM = Haptic Master; AC = Amadeo; BL = Bilateral; UL = Unilateral; ST = Standard Training.*

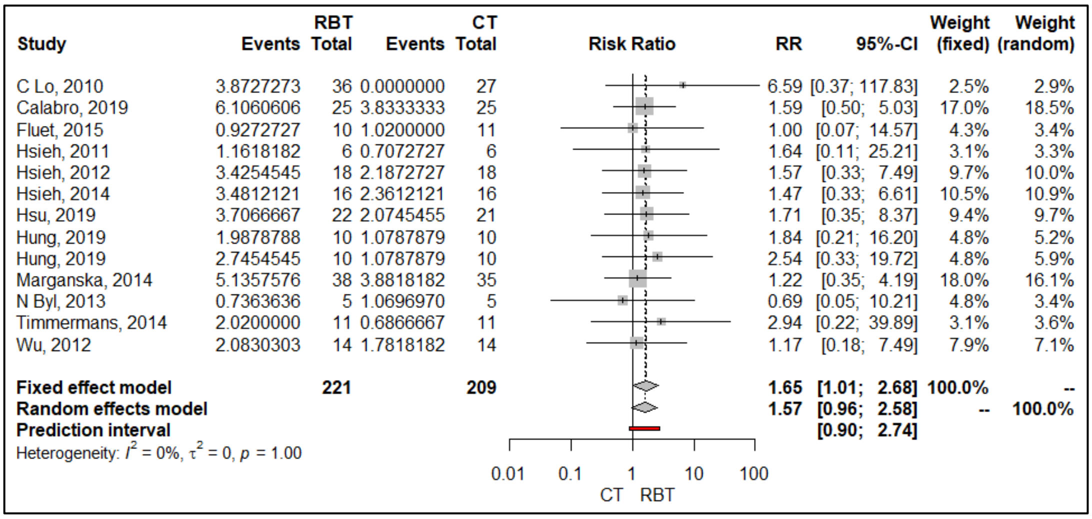


Figure 5 *Robot-based therapy vs Conventional therapy impact on FMA-UL Total.*

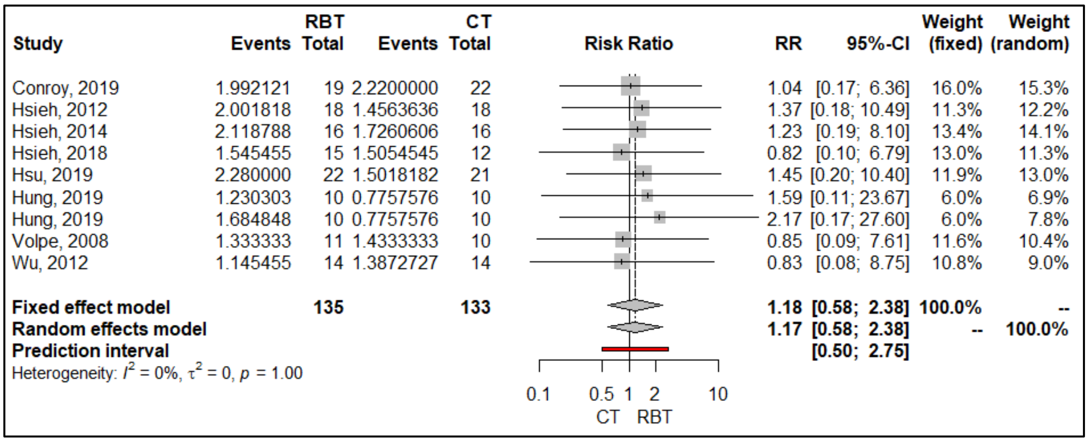


Figure 6 *Robot-based therapy vs Conventional therapy impact on FMA-UL Proximal.*

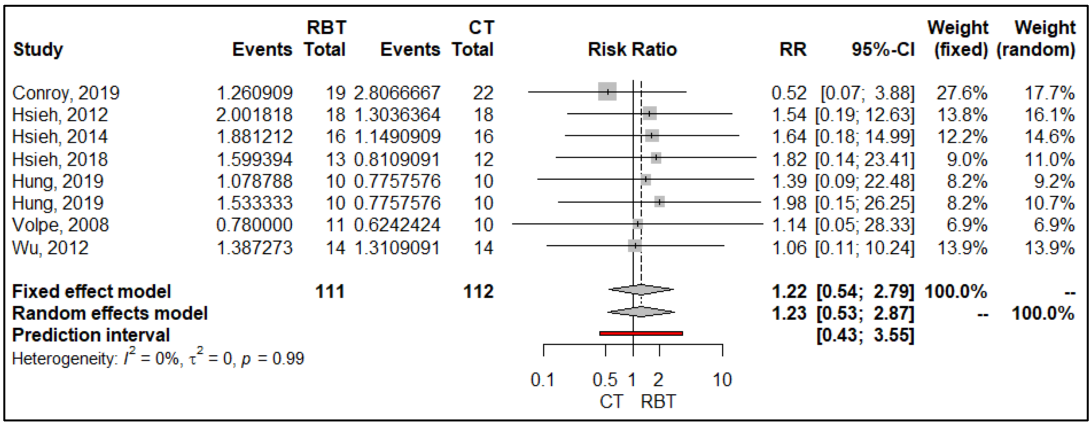


Figure 7 *Robot-based therapy vs Conventional therapy impact on FMA-UL Distal.*

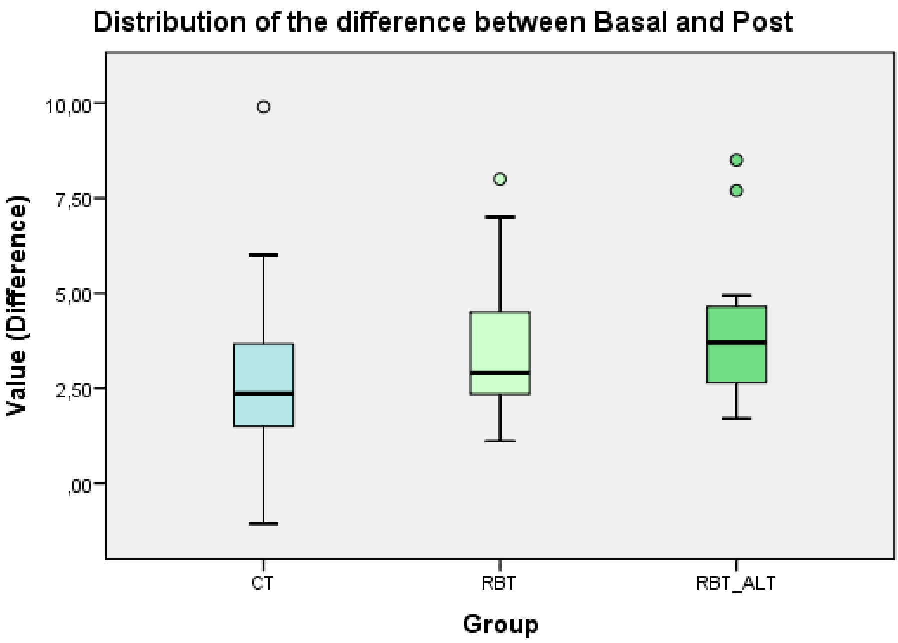


Figure 8 *Box Plot for the distribution of the difference between Basal and Post-Intervention FMA-UL.*

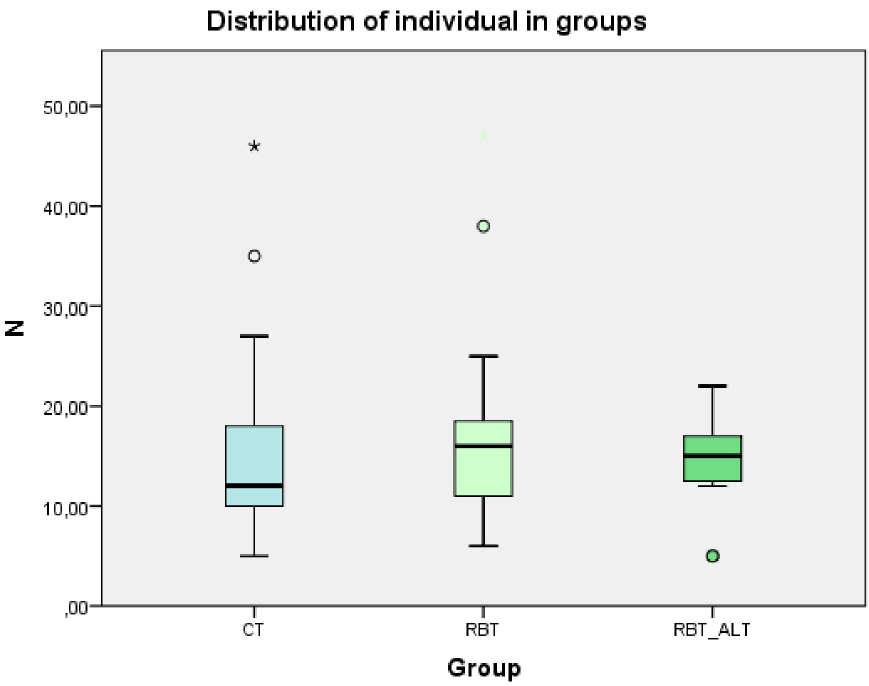


Figure 9 *Box Plot for the distribution of individuals for each group.*
Abbreviations: CT = conventional therapy; RBT = robot-based therapy; RBT_ALT = robot-based therapy + alternative therapy.

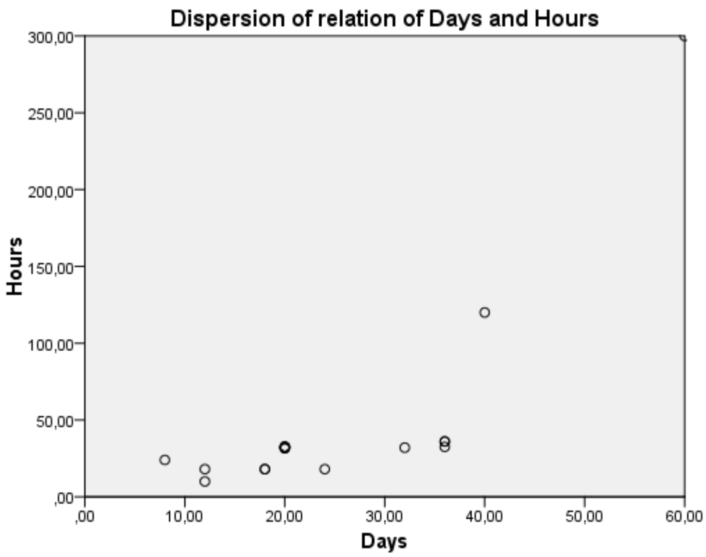


Figure 10 *Dispersion of relation of hours and treatment sessions.*

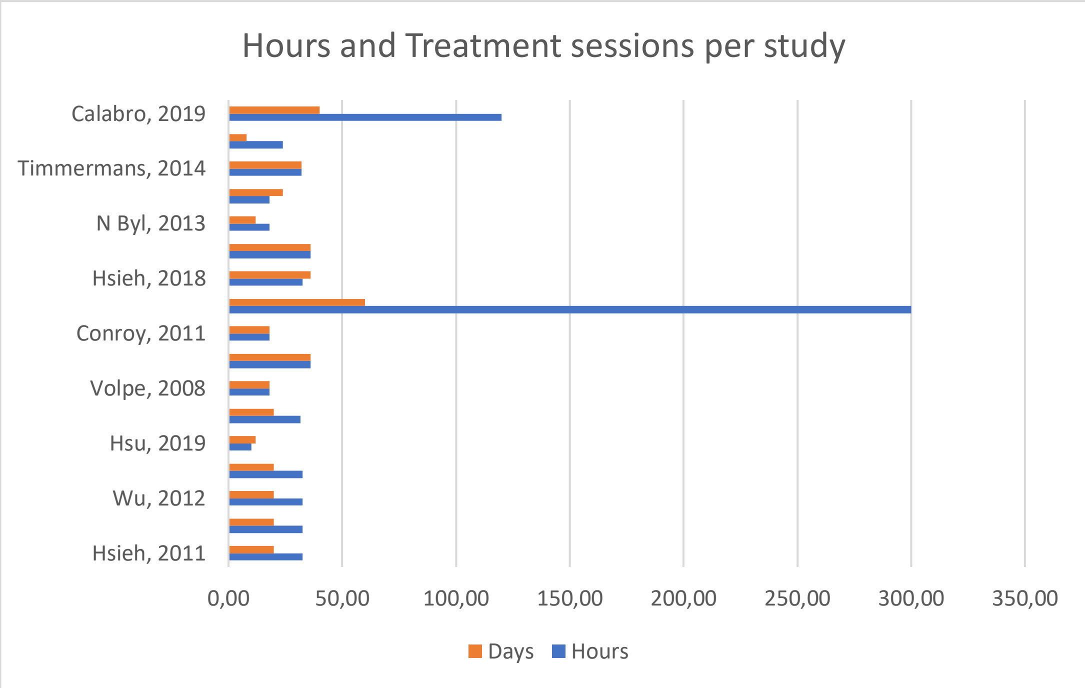


Figure 11 *Hours and treatment sessions from each study.*

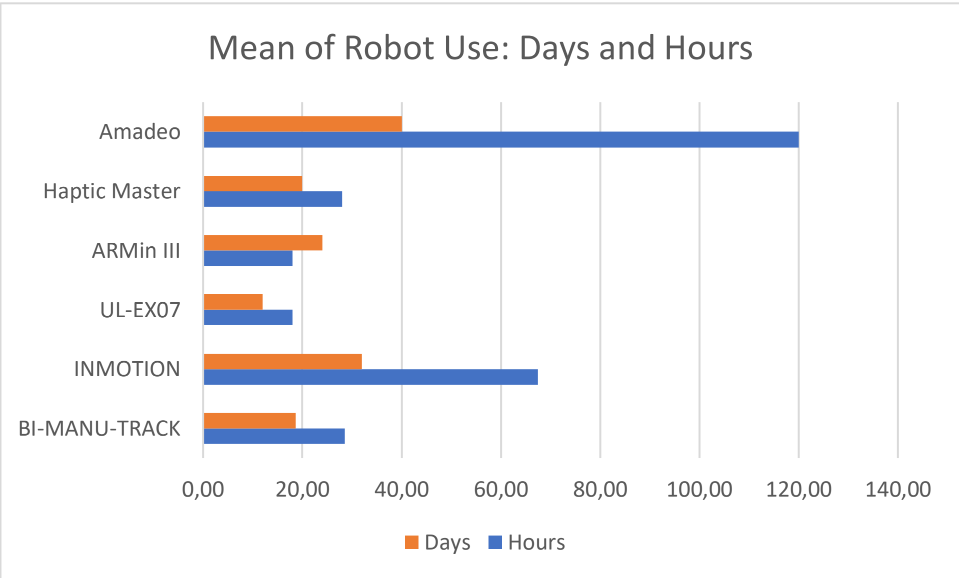


Figure 12 *Average time spent on robot (hours and days).*

Attachment 1 List of Included Studies

ID	Title	Authors	Year	Robot	DOI
1	Effects of Treatment Intensity in Upper Limb Robot-Assisted Therapy for Chronic Stroke: A Pilot Randomized Clinical Trial	Hsieh Y, Wu C, Liao W	2011	Bi-Manu-Track	10.1177/1545968310394871
2	Dose-Response Relationship of Robot-Assisted Stroke Motor Rehabilitation	Hsieh Y, Wu C, Lin K	2012	Bi-Manu-Track	10.1161/STROKEAHA.112.658807
3	Effect of Therapist-Based Versus Robot-Assisted Bilateral Arm Training on Motor Control, Functional Performance, and Quality of Life After Chronic Stroke: A Clinical Trial	Wu C, Yang C, Chuang L	2012	Bi-Manu-Track	10.2522/ptj.20110282
4	Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke	Hsieh Y, Lin K, Horng Y	2014	Bi-Manu-Track	10.1007/s00415-014-7345-4

	rehabilitation: a randomized clinical trial				
5	Robot-assisted therapy with bilateral practice improves task and motor performance in the upper extremities of chronic stroke patients: A randomized controlled trial	Hsu H, Chiu H, Kuan T	2019	Bi-Manu-Track	10.1111/1440-1630.12602
6	Comparative Assessment of Two Robot-Assisted Therapies for the Upper Extremity in People with Chronic Stroke	Hung C, Hsieh Y, Wu C	2019	Bi-Manu-Track InMotion	10.5014/ajot.2019.022368
7	Intensive Sensorimotor Arm Training Mediated by Therapist or Robot Improves Hemiparesis in Patients with Chronic Stroke	Volpe B, Lynch D, Rykman-Berland A	2008	InMotion	10.1177/1545968307311102

8	Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke	Lo A, Guarino P, Richards L	2010	InMotion	10.1056/NEJMoa0911341
9	Effect of Gravity on Robot-Assisted Motor Training After Chronic Stroke: A Randomized Trial	Conroy S, Whitall J, Dipietro L	2011	InMotion	10.1016/j.apmr.2011.06.016
10	Comparison of Robotics, Functional Electrical Stimulation, and Motor Learning Methods for Treatment of Persistent Upper Extremity Dysfunction After Stroke: A Randomized Controlled Trial	McCabe J, Monkiewicz M, Holcomb J	2015	InMotion	10.1016/j.apmr.2014.10.022
11	Comparison of proximal versus distal upper-limb robotic rehabilitation on motor performance after stroke: a cluster controlled trial	Hsieh Y, Lin K, Wu C	2018	InMotion	10.1038/s41598-018-20330-3

12	Robot-Assisted Arm Training in Chronic Stroke: Addition of Transition-to-Task Practice	Conroy S, Wittenberg G, Krebs H	2019	InMotion	10.1177/1545968319862558
13	Chronic stroke survivors achieve comparable outcomes following virtual task specific training guided by a wearable robotic orthosis (UL-EX07) and actual task specific repetitive training guided by a physical therapist	Byl N, Abrams G, Pitsch E	2013	UL-EX07	10.1016/j.jht.2013.06.001
14	Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial	Klamroth-Marganska V, Blanco J, Campen K	2014	ARMin III	10.1016/S1474-4422(13)70305-3
15	Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial	Timmermans A, Lemmens R, Monfrance M	2014	Haptic Master	10.1186/1743-0003-11-45

16	Does training with traditionally presented and virtually simulated tasks elicit differing changes in object interaction kinematics in persons with upper extremity hemiparesis?	Fluet G, Merians A, Qiu Q	2015	Haptic Master	10.1179/1074935714Z.0000000008
17	Does hand robotic rehabilitation improve motor function in rebalancing interhemispheric connectivity after chronic stroke? Encouraging data from a randomised-clinical-trial	Calabrò R, Accorinti M, Porcari B	2019	Amadeo	10.1016/j.clinph.2019.02.013