European Review for Medical and Pharmacological Sciences 2024; 28: 879-898

Effects of robot-assisted gait training on motor performance of lower limb in poststroke survivors: a systematic review with meta-analysis

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Abstract. – OBJECTIVE: This study aimed to investigate the effects of robot-assisted gait training (RAGT) on improving walking ability, and to determine the optimal dosage of task-specific training based on RAGT for stroke patients.

MATERIALS AND METHODS: Two investigators independently searched electronic databases, including PubMed, Embase, Cochrane Library, and Physiotherapy Evidence Database (PEDro) from inception to 31 January 2020. The study design was a systematic review with meta-analysis of randomized controlled trials (RCTs), comparing the intervention of RAGT plus conventional therapy to conventional therapy alone. RCTs mainly focus on lower limb motor function as the primary outcomes, while the secondary outcomes involve gait speed, walking distance, cadence, balance, and activities of daily living (ADL). Pooled effect estimates were calculated by comparing the change from baseline to the end of the study in each group.

RESULTS: Twenty-eight RCTs were included. The pooled analysis showed that RAGT had a significantly short-term effect on improving lower limb function [standardized mean difference (SMD) 0.32, 95% CI 0.10 to 0.55]. Additionally, there were significant improvements in gait speed (MD 0.10, 95% CI 0.06 to 0.14) and ADL (SMD 0.17, 95% CI 0.02 to 0.32). Subgroup analyses indicated that RAGT lasting for 30-60 minutes per day over 4 weeks yielded a moderate effect size (SMD 0.53, 95% CI 0.16 to 0.90). Additionally, RAGT significantly promoted lower limb function recovery in the early stage after a stroke (SMD 0.33, 95% CI 0.07 to 0.58) or in non-ambulatory patients (SMD 0.35, 95% CI 0.10 to 0.59).

CONCLUSIONS: RAGT demonstrated significant positive effects on lower limb function post-stroke. Our results provide additional evidence to support that RAGT is a potentially appropriate intervention to promote lower limb recovery in individuals who have had a stroke.

Key Words:
Robot-assisted gait training, Lower limb, Motor function, Stroke, Meta-analysis.

Introduction

Stroke is considered the second leading cause of death and the third leading cause of acquired disability for adults in developing nations, affecting approximately 17 million individuals worldwide every year[1,2]. Particularly, lower limb motor impairments are disabling and persistent after a stroke[3]. Although there have been some commonly used interventions in the past few decades to restore lower limb function, such as conventional gait training, electrical stimulation, and surgery[1,4], it is still challenging for patients and therapists to correct the abnormal and asymmetrical movement patterns associated with stroke *via* passive participation[5].

To our knowledge, the key factor in lower limb recovery is intensive and repetitive training. This means that repeatedly practicing the same movement allows the nervous system to develop circuits that improve communication between the motor center and sensory pathways[6]. Robot-assisted gait training (RAGT), an approach that has been adopted ever since 1980, is capable of achieving such integration and thus can function as a great aid to patients with motor dysfunction due to neurological diseases[1]. There are two types of robots: exoskeleton robots and end-effector robots[7]. The former focuses on the joint of lower limbs during the walking phase involving the hip, knee, and ankle, while the latter serves as a support for

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the footplate, merely for moving feet, which corrects the stance during the phase of swing in the gait training[8].

Lokomat, which is the most commonly used exoskeletons robot-assisted device, features a harness-supported body weight system based on the treadmill, which is distinct from the typical treadmill with body weight support[9]. However, the movement of the patient's lower limb joints is guided by a pre-programmed near-normal gait pattern. Actually, the majority of all functional exoskeletons rely on additional assisted tools in order to maintain balance. Users strategically positioned their feet to achieve optimal balance and stability, whereas individuals with disabilities may require additional assistive devices such as crutches[7]. Gait trainer (GT) is another widely used end-effector robot that consists of two footplates, two rockers, and two cranks[7,10]. It is capable of producing a symmetrical gait pattern in both lower limbs. However, a limitation of the GT is that the footplate remains in contact with the foot and causes movement of the foot during the walking phase. The G-EO system utilizes the end-effector principle in order to reduce the amount of effort required by therapists in the process of retraining patients' walking ability. Overall, one of the advantages of exoskeletons is their ability to easily control the gait pattern during gait cycles, in contrast to patients using end-effector devices who would have unrestricted knee extension[11].

A number of reviews supported the effectiveness of robot-assisted gait training (RAGT) on lower limbs compared to conventional therapies. These reviews concluded that non-ambulatory patients benefited more from RAGT than patients who were already ambulatory at the beginning of the study[12,13]. Even Mehrholz et al[12] believed that end-effector devices produced greater improvements than exoskeleton training. In spite of the aforementioned, two reviews did not prove that RAGT was superior to traditional therapies, although improvements have been found in the RAGT group[14,15]. Furthermore, Ferreira et al[16] found a mild effect of robot-assisted training on lower limbs. However, the results may have been influenced by the poor quality of research methods included in the above review and the limited number of studies. Although these reviews mentioned the repetition, duration, and intensity of robot-assisted device interventions, they failed to establish a clear relationship between these dosages and outcomes.

Therefore, the research questions addressed in this systematic review were as follows: (1) Does the use of RAGT contribute to the enhancement of walking ability and the improvement of quality of life in individuals who have experienced a stroke? (2) May stroke survivors experience greater benefits from specific task training based on RAGE when the detailed dosage threshold is determined? (3) The impact of RAGT features and patient characteristics on the outcomes of RAGT.

Materials and Methods

Our current meta-analysis was conducted and documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. However, it is important to note that the protocol was not registered.

Identification and Selection of Studies

Electronic databases, including PubMed, EMBase, Cochrane Library, and Physiotherapy Evidence Database (PEDro) were systematically searched from the inception to 31 January 2020 to identify relevant randomized control trials (RCTs) reported in the English language. The search strategy involved utilizing various combinations of the following terms: (stroke OR cerebrovascular accident OR brain ischemia OR poststroke OR post-stroke) AND (robot OR robotic OR robot-assisted training OR robotic-assisted training OR robot-assisted therapy OR robot-assisted gait training OR Lokomat OR electromechanical OR gait trainer OR RAT OR RAGT). Please refer to **Supplementary Table I** for an illustrative example of the comprehensive EMBase search strategy. The criteria for the inclusion of studies in the review are outlined in **Appendix 1**. Nevertheless, certain studies were excluded from the analysis if they involved the combination of robotics with other interventions that could potentially influence brain plasticity, such as mirror therapy, Transcranial Magnetic Stimulation, transcranial Direct Current Stimulation, or Virtual Reality. This decision was made due to the inability to isolate or detect the specific effects of robotics, as well as the lack of precise information regarding intensity and training parameters in these studies.

Assessment of Characteristics of Trials

Methodology quality

The methodology quality of the included articles was evaluated using the PEDro scale, which consisted of 11 assessment items. These included

random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, > 85% follow-up for at least one key outcome, intention-to-treat analysis, between-group statistical comparison for at least one key outcome, and point and variability measures for at least one key outcome[17]. Each item on the PEDro was assigned a score of either 1 or 0. A study[18] with a total score ranging from 6 to 8 was classified as having "good" quality, while scores ranging from 9 to 10 were considered to be of "excellent" quality. Scores below 6 were categorized as "fair" quality. Two researchers independently assessed the quality of the articles. When an agreement is not reached, it should be discussed by a third researcher.

Participants

Adult participants with a diagnosis of stroke, regardless of whether it was hemorrhagic or ischemic, and presenting with lower limb dysfunction were included in the study. Therefore, the pertinent attributes of participants were systematically extracted from each eligible study, including sample size, gender, mean age, and mean stroke duration.

Intervention

Our present study involved trials that examined the effects of RAGT in combination with conventional therapy, as compared to conventional therapy alone. We incorporated various forms of RAGT in our study, including Lokomat, GT, Hybrid Assistive Leg (HAL), G-EO, and others. Additionally, the term "conventional therapy" primarily refers to physiotherapy in the majority of the studies included in our analysis. Consequently, pertinent details regarding the intervention protocol, such as the robotic device frequency, intensity, duration of the session, and any supplementary interventions, were extracted.

Outcome Measures

The primary outcome was the assessment of lower limb function using scales, such as the Fugl-Meyer Assessment scale (FMA), Function Ambulatory Category (FAC), and others. If multiple scales were used in an individual trial, FMA was considered a priority outcome measure. This is because it provides a more precise reflection of functional improvement in the lower limbs. Otherwise, FAC, gait speed, walking distance, or the Berg Balance Scale (BBS) were taken into consideration afterward.

The secondary outcomes for this systematic review included gait speed, walking distance, cadence, balance function, and activities of daily living (ADL). Velocity was measured during gait speed in meters per second (m/s). Walking distance was calculated using the 10 Meter Walk Test or the 6-minute Walk Test. The BBS was used to assess the balance function. Furthermore, ADL was measured using the Barthel Index (Modified Barthel Index) or the Frenchay Activities Index. One author (ZQH) also solicited information from the corresponding authors *via* e-mail. The study was excluded if the authors did not respond after two emails were sent.

Statistical Analysis

The primary search was conducted by a single investigator (SL), who excluded titles and abstracts that were deemed irrelevant to the content of the review. Two additional researchers (ZQH and QC) conducted separate assessments of the remaining titles and abstracts. They obtained the full texts for all abstracts in order to ascertain whether these studies satisfied the inclusion criteria. Subsequently, the reviewers conducted independent assessments of the complete manuscripts and included studies that satisfied all the predetermined inclusion. Data from the original articles were extracted independently by two investigators (SL and YJR) utilizing a standardized data-recording method. Subsequently, the third investigator (ZQH), independently reviewed and verified the extracted data. Any disagreements were resolved by engaging in a comprehensive discussion with a third reviewer (XQH).

For the purpose of quantitative synthesis, pooled effect estimations were derived by comparing the change from baseline to the end of the study within each group. Regarding the continuous outcomes, when the unit of measurement remained consistent across trials, the findings were presented as the weighted mean difference (WMD) with 95% confidence intervals (95% CIs). Conversely, if the unit of measurement varied, the results were reported as the standard mean difference (SMD) along with 95% CI. Statistical heterogeneity of effect size across trials was assessed using a standard Chi-square test, with a significance level set at $p < 0.10$. Values above 50% and 75% were considered as indicatives of moderate and high heterogeneity, respectively. The random-effects model was employed for statistical analysis in light of the considerable clinical and methodological heterogeneity observed across the trials. Sensitivity analysis and various subgroup analyses were conducted to

identify potential heterogeneity that could impact the effectiveness measures. Publication bias was assessed through the utilization of Begg's funnel plots and Egger's test. Data were calculated using Stata version 15.0 (Stata Corp., College Station, TX, USA). A value of $p < 0.05$ was deemed to be statistically significant.

Results

Flow of Articles Through the Review

A comprehensive search was conducted to identify relevant studies that met the inclusion criteria. A total of 28 RCTs[1,6,19-45] were included in the analysis, involving 1,251 participants. These studies were selected from an initial pool of 4,215 potentially relevant documents through a systematic screening process. The comprehensive process of study selection was succinctly presented in a PRISMA study flow diagram (Figure 1).

Characteristics of Included Studies

The characteristics of the studies included in the analysis were presented in Table I. Specifically, the RAGT plus conventional therapy group consisted of 636 stroke survivors (51%), while the conventional therapy group included 615 survivors (49%). The sample size varied from 21 to 106, and the average age of the participants ranged from 44 to 70 years old. In relation to the duration of stroke from its onset, a total of 870 participants from 17 studies[6,21,22,24-26,29,31-35,37-39,42,43,45] (61%) were observed within a period of 3 months, and the rest studies[1,19,20,23,27,28,30,36,40,41,44] (39%) were > 3 months. Patients in the RAGT group received treatment involving the use of robot-assisted devices in addition to standard physiotherapy. In contrast, the control group received conventional therapy with varying dosages. Furthermore, there was variation among the studies in terms of the type of RAGT, duration of treatment, and intervention protocol. 13 studies[1,19,21,25,27-31,37,38,44,45] (46%) applied the Lokomat as the primary inter-

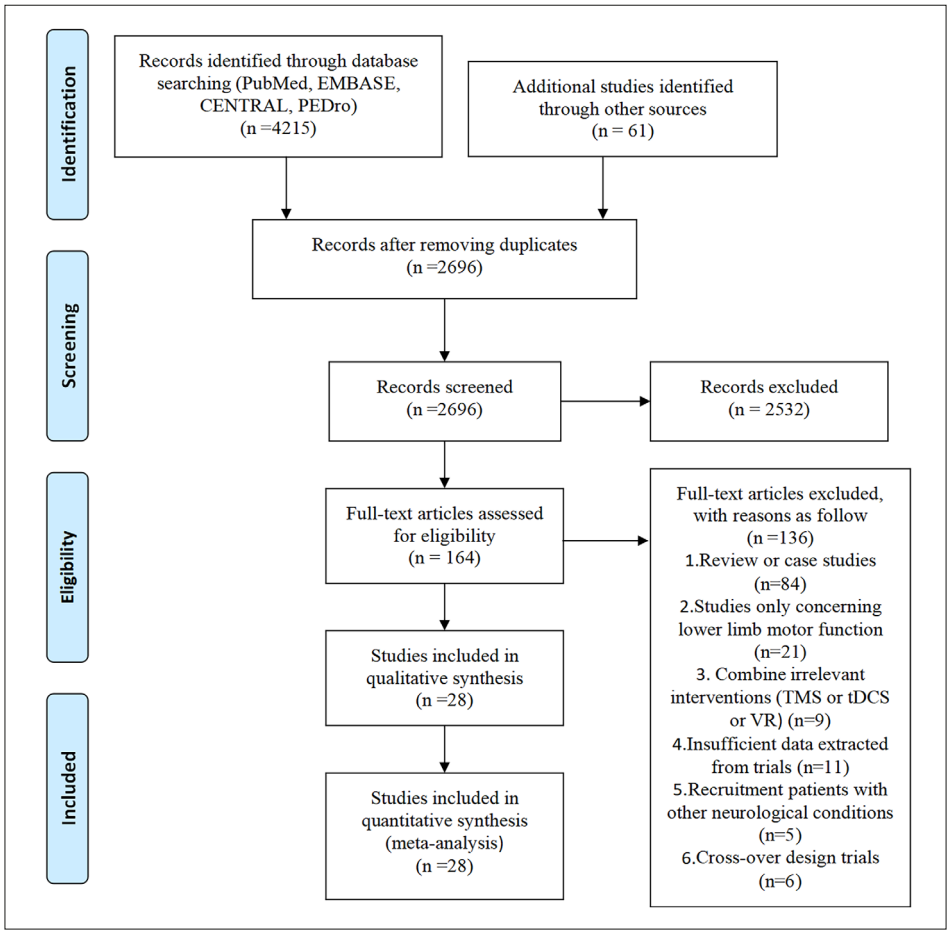

Figure 1. Flowchart of articles selection.

Table I. Summary characteristics of included studies.

Author, year	N	Gender	Mean age	Stroke duration		Robot type	Dosage (session/min/ frequency/wk)	Mode	Outcome measure
	EXP/CON	EXP/CON	EXP/CON						
Bang and Shin[19], 2016	9/9	9/9	53.6/53.7	Mean months EXP:11.56 CON:12.56	> 3 months	Locomat	20 sessions, 60 min, 5 times, 4 weeks	Bilateral	Step length Cadence Gait speed BBS
Buesing et al[20], 2015	25/25	23/17	60/62	Mean years EXP:5.4 CON:7.1	> 3 months	SMA	18-24 session; 45 min, 3 times, 6-8 weeks	Bilateral	Stride length Cadence Gait speed Step time
Chang et al[21], 2011	20/17	23/14	55/59.7	Mean days EXP:16.1 CON:18.2	≤ 3 months	Locomat	10 sessions; 40 min, 5 times, 2 weeks	Bilateral	FAC FMA
Chua et al[22], 2016	53/53	22/31	62.1/60.7	Mean days	≤ 3 months EXP:27.2	GT	48 sessions; 20 min, 6 times,	Bilateral	Cadence Gait speed Gait endurance BI
Dias et al[23], 2007	20/20	30/10	70.35/68	Mean months	> 3 months EXP:47.1 CON:48.5	GT	25 sessions;	Bilateral 20 min, 5 times, 5 weeks	Step length Gait speed walking distance BBS
Fisher et al[24], 2011	10/10	10/10	60	Mean days EXP:57 CON:60	≤ 3 months	Gait drive ambulator	30-40 session; 30 min, 5 times, 6-8 weeks	Bilateral	Tinetti score 8-m walk

Continued

Table I *(Continued).* Summary characteristics of included studies.

Author, year	N	Gender	Mean age	Stroke duration		Robot type	Dosage (session/min/ frequency/wk)	Mode	Outcome measure
	EXP/CON	EXP/CON	EXP/CON						
Han et al[25], 2016	30/26	32/24	67.89/63.2	Mean days EXP:21.56 CON:18.1	≤ 3 months	Locomat 30 min, 5 times, 4 weeks	20 sessions;	Bilateral	FAC FMA Gait speed BBS K-MBI
Hesse et al[26], 2012	15/15	12/18	63.7/66.4	Mean weeks EXP:5.7 CON:5.1	≤ 3 months	G-EO	20 sessions; 30 min, 5 times, 4 weeks	Bilateral	FAC
Hidler et al[27], 2008	33/30	39/24	59.9/54.6	Mean days EXP:110.9 CON:138.9	> 3 months	Locomat	24-30 sessions; 45 min, 3 times, 8-10 weeks	Bilateral	FAC Cadence BBS FAI
Hornby et al[28], 2008	24/24	30/18	57/57	Mean months EXP:50 CON:73	> 3 months	Locomat	12 sessions; 30 min	Bilateral BBS FAI	Cadence
Husemann et al[29], 2007	14/14	21/9	60/57	Mean days EXP:79 CON:89	≤ 3 months	Locomat	20 sessions; 60 min, 5 times, 4 weeks	Bilateral	FAC Cadence BI Time walking test

Continued

Table I *(Continued)*. Summary characteristics of included studies.

Author, year	N	Gender	Mean age	Stroke duration		Robot type	Dosage (session/min/ frequency/wk)	Mode	Outcome measure
	EXP/CON	EXP/CON	EXP/CON						
Kelley et al[30], 2012	11/10	13/8	66.9/64.3	Mean years EXP:3.71 CON:1.44	> 3 months	Locomat	40 sessions; 60 min, 5 times, 8 weeks	Bilateral	6 MWT
Kim et al[6], 2019	25/23	33/15	57.7/60.4	Mean months EXP:2 CON:2.6	≤ 3 months	Morning walk (GT)	15 sessions; 30 min, 5 times, 3 weeks	Bilateral	FAC 10MWT BBS
Mayr et al[31], 2018	33/28	41/33	68/68	Mean weeks EXP:5 CON:4	≤ 3 months	Locomat	40 sessions; 40 min, 5 times, 8 weeks	Bilateral	FMA
Morone et al[32,33], 2011 & 2013	24/24	NA	68.3/62.9	Mean days 20	≤ 3 months	GT	60 sessions; NA, 5 times,	Bilateral 3 months	FAC BI
Ng et al[34], 2008	17/17	24/14	66.6/73.4	Mean weeks EXP:2.7 CON:2.5	≤ 3 months	GT	20 sessions; 20 min, 5 times, 4 weeks	Bilateral	FAC FIM Gait speed BBS BI
Peurala et al[35], 2009	16/20	19/18	67/65.3	Mean days EXP:8.6 CON:7.8	≤ 3 months	GT	15 sessions; 20 min, 5 times, 3 weeks	Bilateral	FAC FMA 6 WMD

Continued

Table I *(Continued)*. Summary characteristics of included studies.

Author, year	N	Gender	Mean age	Stroke duration		Robot type	Dosage (session/min/ frequency/wk)	Mode	Outcome measure
	EXP/CON	EXP/CON	EXP/CON						
Peurala et al[36], 2005	15/15	NA	51.2/52.3	Mean years EXP:2.4 CON:4	> 3 months	GT	15 sessions; 20 min, 5 times, 3 weeks	Bilateral	FIM
Pohl et al[37], 2007	77/78	104/51	62.3/64	Mean weeks EXP:4.2 CON:4.5	≤ 3 months	Locomat	20-28 sessions; 20 min, 5-7 times, 4 weeks	Bilateral	FAC Gait speed Gait endurance BI
dos Santon et al[1], 2018	7/8	11/4	44.4/56.4	Mean years	> 3 months EXP:4.8 CON:10.5	Locomat	9 sessions;	Bilateral 60 min, 3 times, 3 weeks	FIM BBS
Schwartz et al[38], 2009	337/30	41/26	62/65	Mean days EXP:21.6 CON:23.6	≤ 3 months	Locomat	30 sessions; 30 min, 5 times, 6 weeks	Bilateral	FIM
Tong et al[39], 2006	15/20	21/14	66.1/71.4	Mean weeks EXP:2.7 CON:2.7	≤ 3 months	GT	20 sessions; 2 0 min, 5 times, 4 weeks	Bilateral	FAC FIM Gait speed BBS BI

Continued

Table I *(Continued)*. Summary characteristics of included studies.

Author, year	N	Gender	Mean age	Stroke duration		Robot type	Dosage (session/min/ frequency/wk)	Mode	Outcome measure
	EXP/CON	EXP/CON	EXP/CON						
Valles et al[40], 2016	10/10	7/13	44.1/64.1	≥ 6 months	> 3 months	MOTO med viva2LE	18-32 sessions; 90 min, 3-4 times, 6-8 weeks	Unilateral	FMA 6MWT 10MWT
Waldman et al[41], 2013	12/12	NA	51.3/53	Mean months EXP:41.3 CON:29.8	> 3 months	Protable rehabilitation robot	> 18 sessions; 60 min, 3 times, > 6 weeks	Unilateral	6MWT BBS
Watanabe et al[42], 2017	12/12	16/8	66.9/76.8	Mean days EXP:57 CON:50.6	≤ 3 months	HAL	12 sessions; 20 min, 3 times, 4 weeks	Unilateral	FAC FMA Cadence Gait speed 6MWT
Watanabe et al[43], 2014	11/11	11/11	67/75.6	Mean days EXP:58.9 CON:50.6	≤ 3 months	HAL	20-28 sessions; 20 min, 5-7 times, 4 weeks	Unilateral	FAC FMA Cadence 6 MWT
Westlake et al[44], 2009	8/8	13/3	58.6/55.1	Mean months EXP:43.8 CON:36.8	> 3 months	Locomat	> 12 sessions; 30 min, 3 times, > 4 weeks	Bilateral	FMA 6MWT BBS
Yun et al[45], 2018	18/18	19/17	63.6/64.3	Mean days EXP:31.3 CON:28.8	≤ 3 months	Locomat	20 sessions; 30 min, 5 times, 4 weeks	Bilateral	FMA BBS BI

N, Number; EXP, Experimental group; CON, Control group; NA, Not available; SMA, Stride Management assist system; GT, Gait trainer; BBS, Berg Balance Scale; FAC, Functional Ambulation Category Scale; FMA, Fugl-Meyer Assessment; BI, Bathel Index; K-MBI, Korea Modified Bathel Index; FAI, Frenchay Activities Index; 6MWT, 6 Minutes Walking Test; 10MWT, 10 Minutes Walking Test; FIM, Function Independent Measure.

vention equipment, while eight studies[6,22,23,32-36,39] (29%) used GT. Two studies[42,43] (7%) adopted HAL, and the remaining five studies[20,24,26,40,41] (18%) employed different robot-assisted devices such as the stride management assist (SMA), gait drive, G-EO, gait-assistance robot (GAR), and portable rehabilitation robot. The duration of intervention is considered to be a crucial factor that influences the extent of benefits derived from RAGT. A total of 6 studies[1,6,21,28,35,36] (21%), implemented RAGT for a duration < 4 weeks. Conversely, the remaining studies[19,20,22-27,29-34,37-45], accounting for 79% of the sample, involved patients who underwent training for a period ranging from 4 weeks to 3 months. In addition, the training frequency of RAGT ranged from 3 to 7 times per week across all studies. However, the majority of studies utilized 5 times per workday as the standard criterion for training frequency. The duration of each training session varied from a minimum of 20 minutes to 1 or 2 hours. In terms of RAGT modes, Lokomat, GT, and SMA were used to target both lower limbs, whereas HAL and other devices primarily focused on the affected limb.

Risk of Bias Assessment

The average PEDro score of the studies included in the analysis was 7.4 (SD = 1.015). PEDro scores ranging from 9 to 10 were observed in 4[19,22,26,29] (14%) out of 28 studies, indicating relatively higher scores. The remaining studies (86%) received scores between 6 and 8. However, two studies[21,23] (7%) failed to provide a comprehensive description of the sources from which patients were obtained, and one study[1] (4%) did not mention the process by which allocation was determined. Furthermore, with the exception of four studies (14%)[19,20,25,26], the therapists in the remaining studies were not blinded to allocation due to their responsibility of administering treatment to patients. All the studies included in this research incorporated statistical analysis to assess the differences between groups. Additionally, they provided point measures and measures of variability, as summarized in Table II.

Primary Outcome

The meta-analysis of pooled data revealed that RAGT had a significant and positive impact on lower limb function in stroke patients in terms of immediate benefits. The analysis showed a small to moderate mean effect size [SMD = 0.32 (0.10-0.55); $p = 0.005$; Figure 2], indicating a favorable outcome. However, moderate heterogeneity was observed (Q = 91.63, df = 27; $I^2 = 70.5\%$; $p < 0.001$), suggesting some variability in the results. Sensitivity analysis revealed that the effect size remained relatively stable, even when excluding any individual trial (**Supplementary Figure 1**). However, when considering the long-term effects of RAGT, a comprehensive analysis of data from 10 studies[19,21,22,25,26,29,32,33,36,44] revealed no significant difference between the RAGT group and the control group [SMD = 0.27 (-0.21-0.74); $p = 0.269$; Figure 2].

Secondary Outcomes

In the current investigation, the secondary outcomes encompassed gait speed, walking distance, cadence, BBS, and ADL. Eight studies[18,19,21,24,33,36,38,41] reported gait speed, indicating that RAGT resulted in a walking velocity that was 0.10 m/s faster (0.06-0.14; $p < 0.001$) than conventional therapy. There was moderate heterogeneity (Q = 12.89, df = 7; $I^2 = 45.7\%$; $p = 0.075$). Furthermore, RAGT yielded a significant and small effect on ADL [SMD = 0.17 (0.02-0.32); $p = 0.03$] with minimal heterogeneity (Q = 14.03, df = 10; $I^2 = 17.4\%$; $p = 0.278$). However, there were no significant effects of RAGT on walking distance [SMD = 0.11 (-0.10-0.32); $p = 0.30$], cadence [SMD = -0.67 (-3.28-0.49); $p = 0.678$], and balance function [MD = 1.18 (-0.16-3.77); $p = 0.071$], respectively. Detailed data is shown in **Supplementary Figures 2, 3, 4, 5, 6**.

Subgroup Analyses

Time from stroke onset

We initiated an examination to determine if the magnitude of benefits of RAGT on lower limb function varied during stroke recovery. The time from stroke to intervention, which was ≤ 3 months, ranged from 16 to 89 days across 17 studies[5,20,21,23-25,28,30-34,36-38,41,44]. Eleven studies[1,18,19,22,26,27,29,34,39,40,43] included chronic stroke survivors with an average stroke duration of more than 3 months, ranging from 6 to 42 months. The meta-analysis showed that introducing RAGT therapy ≤ 3 months post-stroke had a significant and small to moderate effect on lower limb function [SMD = 0.33 (0.09-0.58); $p = 0.008$] with moderate heterogeneity ($I^2 = 61.4\%$; $p < 0.001$). However, there was no significant effect of RAGT on lower limb function for patients in the chronic stroke phase [SMD = 0.30

Table II. Quality of studies based on PEDro scale.

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score
Bang and Shin[19], 2016	1	1	1	1	0	1	1	1	1	1	1	10
Buesing et al[20], 2015	1	1	1	1	0	1	0	1	0	1	1	8
Chang et al[21], 2011	0	1	1	1	0	0	1	1	1	1	1	8
Chua et al[22], 2016	1	1	1	1	0	0	1	1	1	1	1	9
Dias et al[23], 2007	0	1	1	1	0	0	1	1	1	1	1	8
Fisher et al[24], 2011	1	1	1	1	0	0	0	1	1	1	1	8
Han et al[25], 2016	1	0	0	1	0	1	0	1	1	1	1	7
Hesse et al[26], 2012	1	1	0	1	0	1	1	1	1	1	1	9
Hidler et al[27], 2008	1	1	0	1	0	0	0	1	0	1	1	6
Hornby et al[28], 2008	1	1	0	1	0	0	1	0	0	1	1	6
Husemann et al[29], 2007	1	1	1	1	0	0	1	1	1	1	1	9
Kelley et al[30], 2013	1	1	0	1	0	0	1	1	1	1	1	8
Kim et al[6], 2019	1	1	0	1	0	0	0	1	1	1	1	7
Mayr et al[31], 2018	1	1	1	1	0	0	0	1	0	1	1	7
Morone et al[32], 2012	1	1	1	1	0	0	0	1	1	1	1	8
Ng et al[34], 2008	1	1	0	1	0	0	0	1	1	1	1	7
Peurala et al[35], 2009	1	1	0	1	0	0	0	1	1	1	1	7
Peurala et al[36], 2005	1	1	0	1	0	0	0	1	1	1	1	7
Pohl et al[37], 2007	1	1	1	1	0	0	1	0	1	1	1	8
dos Santos et al[1], 2018	1	1	0	0	0	0	1	1	1	1	1	7
Schwartz et al[38], 2009	1	1	0	1	0	0	0	1	1	1	1	7
Tong et al[39], 2006	1	1	0	1	0	0	0	1	1	1	1	7
Valles et al[40], 2016	1	1	0	1	0	0	0	1	1	1	1	7
Waldman et al[41], 2013	1	1	0	1	0	0	0	1	0	1	1	6
Watanabe et al[42], 2017	1	1	0	1	0	0	0	0	1	1	1	6
Watanabe et al[43], 2014	1	1	0	1	0	0	0	0	1	1	1	6
Westlake et al[44], 2009	1	1	1	1	0	0	0	0	1	1	1	7
Yun et al[45], 2018	1	1	1	1	0	0	0	1	1	1	1	8

Q1: eligibility criteria were specified; Q2: subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); Q3: allocation was concealed; Q4: the groups were similar at baseline regarding the most important prognostic indicators; Q5: there was blinding of all subjects; Q6: there was blinding of all therapists who administered the therapy; Q7: there was blinding of all assessors who measured at least one key outcome; Q8: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; Q9: all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"; Q10: the results of between-group statistical comparisons are reported for at least one key outcome; Q11: the study provides both point measures and measures of variability for at least one key outcome.

(-0.15-0.83); $p = 0.292$] (Figure 3). However, no statistical significance between-groups difference was found ($Q_B = 1.00$; $p = 0.701$). Detailed data is shown in Table III and **Supplementary Figure 7**.

Intervention Duration

Sixteen studies[1,5,18,20,24,25,27,28,33-36,38,41,42,44] reported that stroke patients who underwent a 4-week course of RAGT therapy experienced significant and positive benefits in lower limb function [SMD = 0.53 (0.16-0.90); $p = 0.005$], with moderate heterogeneity ($I^2 = 67.6\%$; $p = 0.001$). However, longer intervention durations of more than 4 weeks were not associated with significantly greater benefits on lower limb function compared to conventional therapy [SMD = 0.32 (-0.05-0.68); $p = 0.087$]. Further analysis showed that patients receiving 30-60 minutes per day of RAGT achieved more motor performance gains [SMD = 0.35 (0.02-0.68)] than those receiving over 60 minutes [SMD = 0.17 (-0.32-0.66)] or less than 30 minutes [SMD = 0 .27 (-0.17-0.70)] per day (Figure 4). Detailed data is shown in **Supplementary Figures 8, 9**.

RAGT Characteristics

The types of robot-assisted devices applied in stroke survivors were different and were divided into Lokomat, GT, HAL, and others, based on the studies we included. There were 13 studies[1,18,20,24,26-30,36,37,43,44] that applied Lokomat

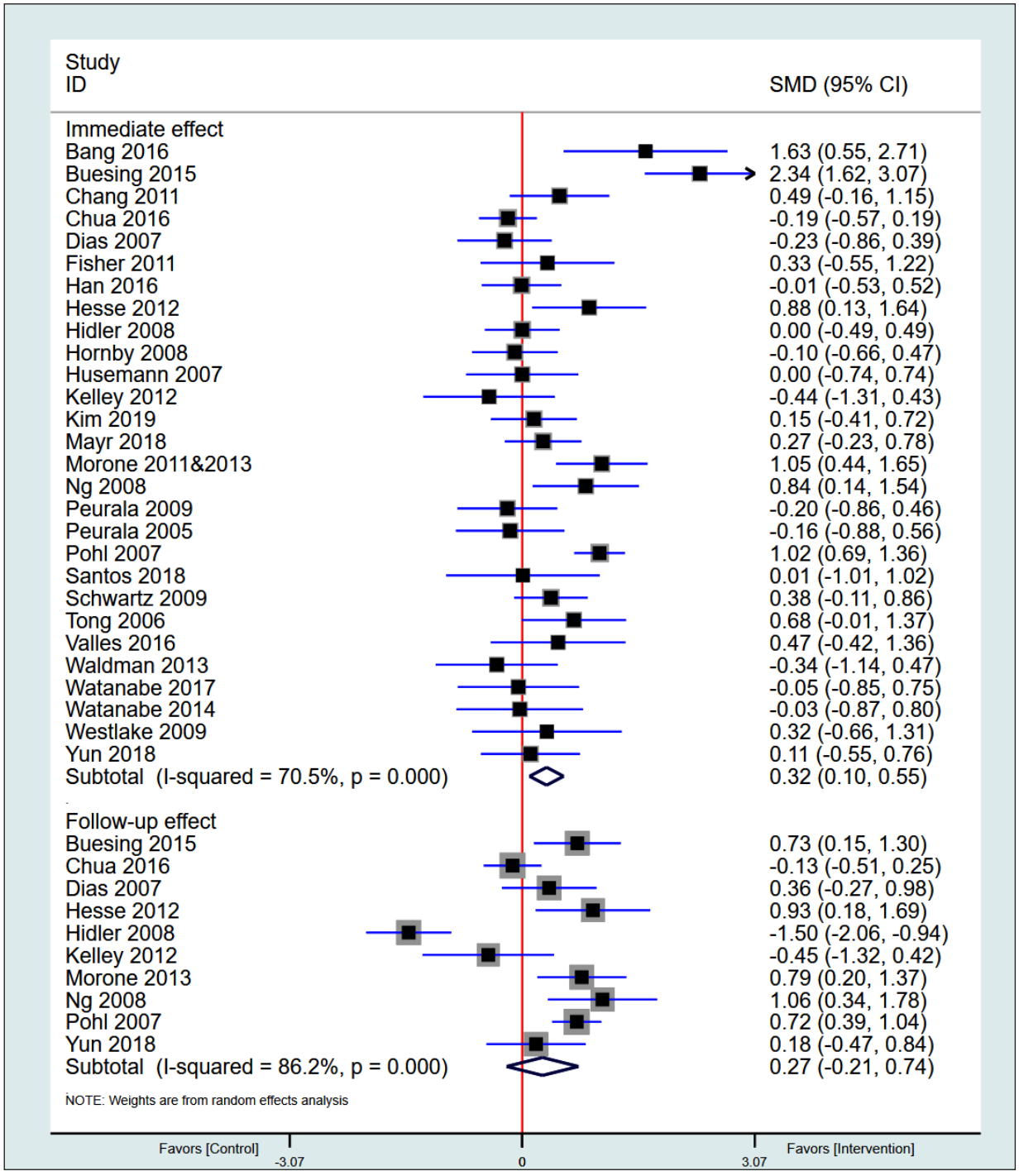

Figure 2. Pooled analysis of immediate effect and follow-up effect of RAGT on lower limb motor function by SMD (95% CI) from 28 studies and 10 comparisons, respectively.

to stroke participants, revealing that Lokomat resulted in significant, small to moderate, and positive effects on lower limb function [SMD = 0.28 (0.12-0.44); p = 0.001]. Studies with other robot-assisted devices, except for the three mentioned above showed large effects [SMD = 0.84 (0.48-1.2); $p < 0.001$]. Either GT [SMD = 0.18 (-0.03-0.38); p = 0.087] or HAL [SMD = 0.41 (-0.17-1.00); p = 0.166] did not yield significant benefits to patients, but the difference between

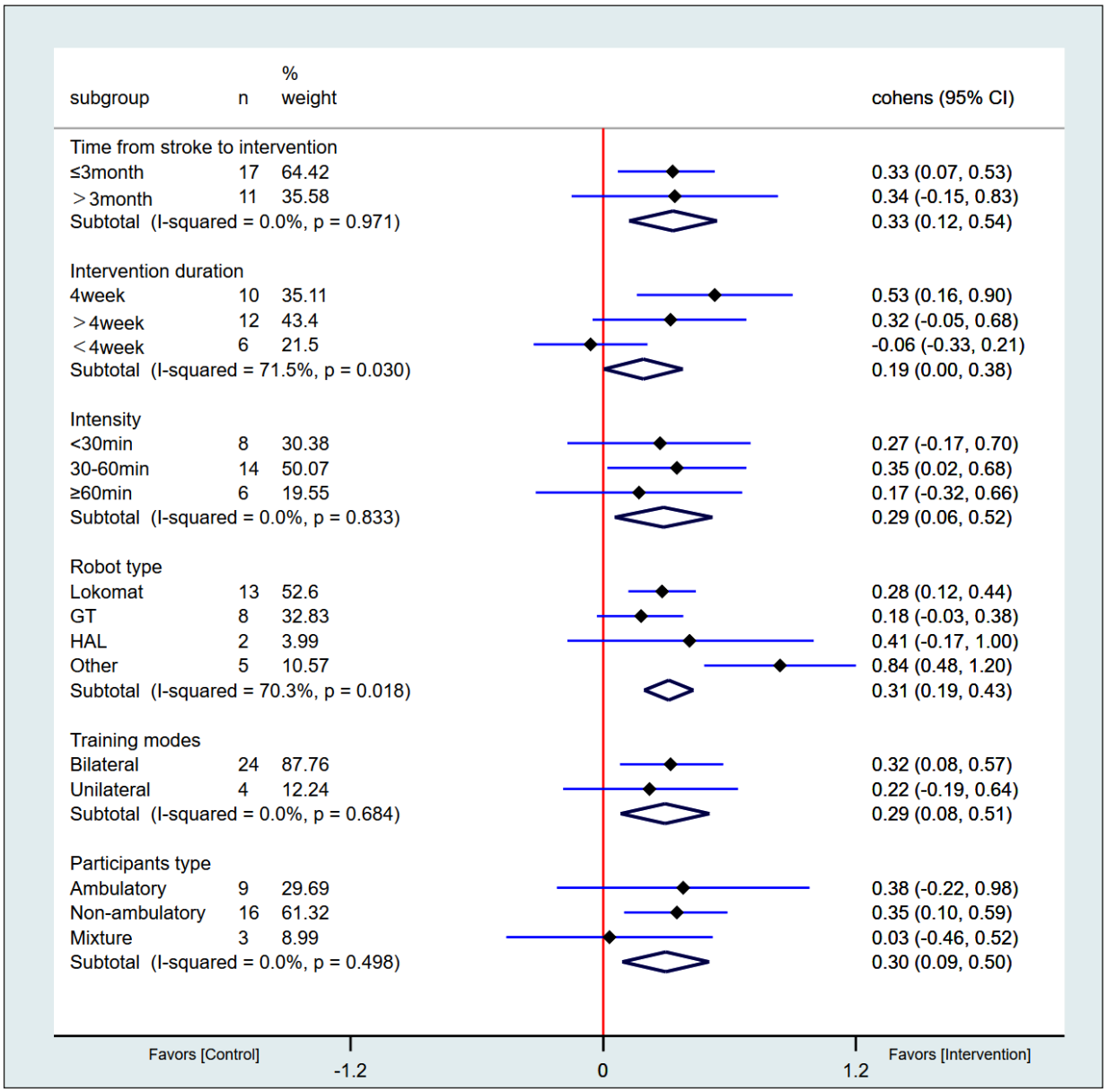

Figure 3. Sensitivity analyses the immediate effect of RAGT on lower limb motor function (95% CI) from 28 comparisons (n = 1,251).

the two groups reach statistical significance (Q_B = 10.16; p = 0.017).

In addition, the studies were stratified based on two modes of robot-assistance (unilateral assisted *vs.* bilateral assisted) to identify the influence of these two different patterns. Twenty-five studies[1,5,18-38,43,44] adopted bilateral assisted therapy, which demonstrated significant, small to moderate, and positive effects on lower limb function [SMD = 0.33 (0.07-0.58); p = 0.012]. On the other hand, 4 studies[39-42] reported no significant benefits of RAGT with unilateral assistance [SMD = 0.22 (-0.19-0.64); p = 0.291]. However, there was no statistical significance in the between-groups difference (Q_B = 0.00; p = 0.464) (Figure 3). Detailed data is shown in Table III and **Supplementary Figures 10, 11**.

Patients' Characteristics

We also investigated whether different conditions of walking ability influenced the magnitude of benefits of RAGT on lower limb function. Based on the available data, we divide it into

Table III. Meta-analytic results from included studies.

Item	N	SMD/ WMD	95% CI	p-value	Heterogeneity (Q)	I^2	Q p-value	QB	QB p-value
Primary outcome									
Immediate effect	28	0.32**	(0.10, 0.55)	0.005	91.63	70.5	< 0.001		
Follow-up effect	10	0.27	(-0.21, 0.74)	0.269	65.41	86.2	< 0.001		
Secondary outcomes									
Gait speed	8	0.10**	(0.06, 0.14)	< 0.001	12.89	45.7	0.075		
Walking distance	11	0.11	(-0.10, 0.32)	0.30	12.36	19.1	0.262		
BBS	12	1.81	(-0.16, 3.77)	0.071	34.07	67.7	< 0.001		
Daily activity	11	0.17*	(0.02, 0.32)	0.03	14.03	21.6	0.231		
Cadence	8	-0.01	(-0.49, 0.46)	0.953	26.75	73.8	< 0.001		
Modes								0.19	0.626
Bilateral	24	0.33*	(0.07, 0.58)	0.012	93.76	75.5	< 0.001		
Unilateral	4	0.22	(-0.19, 0.64)	0.292	2.57	0	0.464		
Stroke duration								1.00	0.701
≤ 3 months	17	0.33**	(0.07, 0.58)	0.012	41.43	61.4	< 0.001		
> 3 months	11	0.30	(-0.15, 0.83)	0.172	46.76	78.6	< 0.001		
Intervention time							0.694	0.229	
4 weeks	10	0.53	(0.16, 0.90)	0.005	27.74	67.6	0.001		
> 4 weeks	12	0.32	(-0.05, 0.68)	0.087	43.81	74.9	< 0.001		
< 4 weeks	6	-0.06	(-0.33, 0.21)	0.656	1.22	0.0	0.943		
Intensity								3.72	0.156
< 30 min	8	0.27	(-0.17, 0.70)	0.234	26.66	73.7	0.000		
30-60 min	14	0.35	(0.02, 0.68)	0.035	44.24	72.9	0.000		
≥ 60 min	6	0.17	(-0.32, 0.66)	0.507	86.01	56.1	0.004		
RAGT type								10.16*	0.017
Locomat	13	0.28**	(0.12, 0.44)	0.001	39.95	70.0	< 0.001		
GT	8	0.18	(-0.03, 0.38)	0.087	19.80	64.6	< 0.001		
HAL	2	0.41	(-0.17, 1.00)	0.166	0.00	0	0.956		
Other	5	0.84**	(0.48, 1.20)	< 0.001	26.61	85.0	< 0.001		
Participant type								2.16	0.339
Ambulatory	9	0.38	(-0.22, 0.98)	0.212	47.63	83.2	< 0.001		
Non-ambulatory	16	0.35**	(0.10, 0.59)	0.005	41.11	63.5	< 0.001		
Mixture	3	0.03	(-0.46, 0.52)	0.905	0.72	0	0.696		

CI, Confidence interval; RAGT, Robot-assisted gait treatment. *$p < 0.05$; **$p < 0.01$.

the following three subgroups: the ambulatory group, the non-ambulatory group, and the mixture group. Patients in the non-ambulatory group experienced significant and small to moderate benefits from RAGT therapy [SMD = 0.35 (0.10-0.59); $p = 0.005$]. However, no significant differences were observed in the ambulatory group [SMD = 0.38 (-0.22-0.98); $p = 0.212$] and the mixture group [SMD = 0.03 (-0.46-0.52); $p = 0.905$]. Additionally, the between-groups difference did not reach statistical significance ($Q_B = 2.16$; $p = 0.339$). Detailed data is shown in Table III and **Supplementary Figure 12**.

Publication Bias Assessment

The funnel plot was conducted to examine publication bias, which showed no evidence of publication bias for the primary outcome in the 28 included studies (**Supplementary Figure 13**). In addition, there was no potential publication bias for the primary outcome, as indicated by Egger's test ($p = 0.919$).

Discussion

Our current investigation has demonstrated that the implementation of RAGT, as compared to conventional therapy, yields greater advantages for patients who receive early robot intervention with task-oriented training. In the present study, we conducted a comprehensive review of 28 studies that specifically examined the impact of RAGT on the motor function of the lower limb. Our findings indicate that GART had immediate effects that were statistically significant, demonstrating moderate and positive effects. However, no statistical significance was observed in the

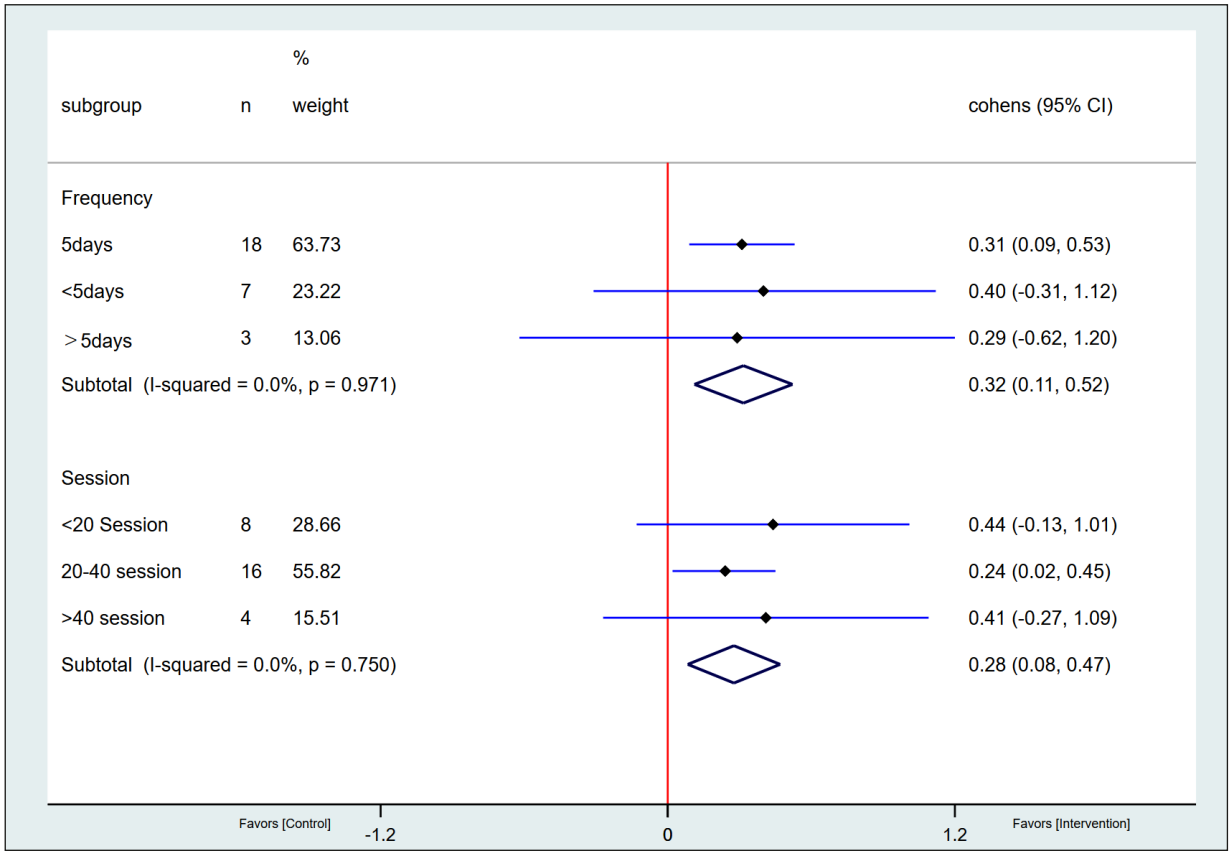

Figure 4. Subgroup analyses concerning the effect of RAGT on time from stroke to intervention, duration, intensity, robot type, training modes and participants type.

long-term effects of RAGT. The secondary outcome measures, such as gaits speed and ADL, supported the same conclusion. However, there was no significant improvement observed in walking distance, balance, and cadence. Additionally, 11 studies were identified that recruited patients within 3 months following a stroke, which further demonstrated notable improvements.

Our meta-analysis results were consistent with several previous studies[7,8,12-14], supporting the idea that RAGT facilitated functional recovery in the lower limbs. Importantly, the dosage of the training period, session, and duration for RAGT were briefly observed in the context. From the perspective of the training period, durations lasting less than 4 weeks showed a moderate effect size, while durations over 4 weeks showed no statistical significance. The training period ranges from 20 to 40 sessions, which means that the training frequency per week multiplied by the duration leads to more significant improvements. Nonetheless, as shown in Figure 4, there was no statistical significance in training sessions less than 20 or more than 40. When analyzing training duration and frequency separately, it was found in 13 included studies[5,19-21,23-27,30,39,43,44] that a training duration of 30-60 minutes delivered positive results. Additionally, a frequency of 5 times per week appeared to be more suitable for patients' functional recovery (Figure 4). However, it is clear that to achieve the most effective recovery, the optimal solution is to combine the above-mentioned parameters. This indicates that the data should only be used as a rough measure.

A recent study[7] suggested that robots should not be solely relied upon as an auxiliary therapy, despite the effectiveness of RAGT for stroke patients. In addition, 999 patients who underwent physiotherapy plus robot training experienced greater improvement, but it was not found to be superior to conventional gait training therapy[15]. As indicated above, robots cannot replace the neurorehabilitation therapy carried out by a therapist. This supports the idea that the advantage of

robots designed for walking capability is primarily related to the guarantee of a more intensive therapy that therapists cannot achieve. Especially for specific body functions such as hip flexion, plantar flexion of the ankle, and lower limb sensitivity training, the therapist's methods will be optimized and efficient.

Notably, the present study highlights the relationship between types of robots and their effects on lower limb function. Lokomat, which was adopted in 13 studies[1,18,20,24,26-30,36,37,43,44], showed more positive effects than GT. Lokomat and GT, which are commonly used robot-assisted devices with a harness-supported body weight system based on the treadmill, were used in clinics[9]. One of the major differences between the Lokomat and an ordinary treadmill with weight support lies in the movement of patients' lower limb joints. The Lokomat guides the joints of the lower limbs, including the hip, knee, and ankle, using preprogrammed near-normal gait patterns. On the other hand, the ordinary treadmill is used as a support for the footplate, only allowing for movement of the feet. Accordingly, Lokomat focuses more on promoting proprioceptive feedback and correcting posture during the swing phase of gait training[8]. At present, there have been comprehensive researches[46,47] that have investigated the true effects of these robotic devices. The aim is to comprehend the treatment and design functions of each robot device, especially when the therapist intends to treat specific patients intensively and safely in a complex environment. Both exoskeletons and end-effector robots have their own strengths and weaknesses. For example, the strength of exoskeletons lies in the fact that the gait pattern can be easily controlled during gait cycles. Additionally, patients treated by end-effector devices can freely extend their knees[11]. Based on these views, it could be considered that two types of robotic devices help patients in different ways. According to patients, these devices could be considered complementary instead of alternative. However, what can be determined right now is that the severity of the stroke determines the level of assistance and restraint the device should provide. Moreover, HAL has shown moderate functional recovery in two studies[41,42], and the effectiveness of the single-leg version of HAL has been demonstrated in several studies[41,42]. A previous study[48] reported that patients with chronic stroke achieved greater motor improvement after HAL intervention in 16 training sessions. Another study published by Mizukami et al[49] discussed the risk of falling when using HAL training. The single-leg version of HAL has electronic autonomous control and electronic voluntary control modes[50], of which the electronic voluntary control mode offers physical support by responding to the voluntary muscle activity of the wearer. However, it is still uncertain whether they freely use the autonomous control mode when it comes to severely paralyzed cases, making it essential to interpret HAL with caution.

Concerning the walking capabilities of the participants involved, non-ambulatory patients gained more benefits from robot training compared to patients with ambulatory levels. This is because having a relatively correct gait cycle and stable joints were more crucial for non-ambulatory patients. On the contrary, patients with a non-ambulatory level due to spasticity induced by an abnormal walking pattern would find it difficult to control and correct.

Bilateral and unilateral functional task training modes are commonly regarded as training methods in robotics. Interestingly, a positive and moderate effect of bilateral training was observed in 24 studies, whereas there was no statistical difference in unilateral training. Generally, each cerebral hemisphere controls the motor function of the contralateral side of the body, but some are also fibers that control movement on the same side (ipsilateral movement). A possible reason may be that performing bilateral tasks can lead to an expansion of the brain's network in the bilateral sensorimotor cortex (SM1), cingulate motor area, dorsal premotor cortex, posterior parietal cortex, and supplementary motor area (SMA). It is worth noting that the SMA is primarily responsible for coordinating movements between limbs (interlimb coordination)[51]. Besides, EEG studies[52] have shown that the SMA area in the brain can be specifically activated during bimanual movement, which is associated with neural coupling between the two sides of the body. However, neural decoupling between the lower limbs occurs in stroke patients. Reisman et al[53] found that treadmill training, conducted 3 times per week for 4 weeks, demonstrated greater effects in improving symmetrical gait and walking speed. Findings from other studies[54] show that this training pattern can promote training to induce horizontal reorganization of the spine and spinal column and reduce asymmetry of gait parameters. In addition, Whitall et al[55] did not find bilateral training to be superior to standard and

conventional training. However, they did observe a positive interlimb transfer from the proximal to the distal joint in the context of coupled bilateral movement.

Furthermore, 4 included studies[20,30,41,42] mentioned cardiopulmonary fitness, ataxia, and pusher syndrome. Han et al[25] and Chang et al[21] concluded that RAGT had positive effects on aerobic capacity, effectively improving walking endurance in the early phase after a stroke. Both studies utilized peak oxygen consumption (VO_2) as the outcome measure. The results indicated that after 4 weeks and 20 interventions, respectively, there was an increase in VO_2 and lower limb strength, as well as an improvement in arterial stiffness. Han et al[25] found that conventional therapies did not result in any significant changes in motor function improvement. However, aerobic exercise was found to benefit muscle activation by first altering central hemodynamics and subsequently increasing skeletal muscle capillary density. Chang et al[21] indicated that ataxia and pusher syndrome are related to trunk stability and balance ability. dos Santos et al[1] found that although there was an improvement in ataxia in the experimental group, there was no significant difference between the two groups. However, the improvement of pusher syndrome after robot intervention is more significant than that achieved through conventional therapy alone[45]. The difference may be associated with their recruitment of chronic and sub-acute patients, respectively. Due to the limited number of studies that have examined the effects of these specific characteristics, further research is needed to investigate these fields.

The safety evaluation of RAGT application in the included studies was inadequate. Only 8 trials[6,20,22,30,34,39,43,45] (29%) addressed adverse events in the manuscript. However, a trial[30] (13%) reported skin damage, such as redness or broken skin caused by pressure or rubbing of straps or cuffs, during the Lokomat intervention session. RAGT seems to be a relatively safe rehabilitation technology, but the safety of RAGT should be fully assessed and reported, especially for stroke individuals who belong to a vulnerable population.

Our present study has several limitations. First, the available heterogeneity of studies should be mentioned. The immediate effect and follow-up effect of the primary outcome were moderate to substantial levels of heterogeneity (the level of heterogeneity was 71% to 86%, respectively), which was caused by the difference in intervention duration, intervention dose, and different follow-up measurement times. Upon conducting a secondary outcome analysis using the outcome scale, it was observed that the change in I^2 heterogeneity level was more significant for balance ability (68%) and gait cadence (78%). The lack of standardized measurement methods and manual evaluation may be possible reasons for measurement bias and heterogeneity. Although the random effects model was used, which pulled the estimation towards smaller studies[14], our results were consistent with previous results[13,16]. Therefore, we believe that the results of this analysis are reliable and can be observed. Second, due to the limited scale of the included studies, the intensity, duration, and frequency of RAGT had to be analyzed separately. This suggests that future research should continue to explore the optimal dosage for robot training. Third, although the included studies showed scores ranging from 6 to 10 with moderate to good quality, these studies investigating RAGT were subject to potential methodological limitations. None of the included studies blinded all of the subjects. In fact, 25 studies[1,5,20-23,26-44] (86%) did not even blind the therapists who managed the trial. This is known as co-intervention, where the same therapist unintentionally provides conventional therapy to either the treatment or comparison group. Moreover, inadequate concealed allocation was found in 16 studies[1,5,24-27,29,33-35,37-42] (57%), which may lead to intentional allocation and then the possibility of performance bias.

At present, a large number of clinical studies have investigated the therapeutic effect of RAGT in the acute and convalescent phase of stroke patients and confirmed its positive effect. Especially in the recovery phase, it can improve abnormal gait, walking rhythm, walking endurance, and walking speed. Based on the results of this meta-analysis, we will conduct some prospective studies in the future to explore and predict whether RAGT combined with other training (such as FES, TMS, etc.) can improve the exercise training of stroke patients, and whether robot training has better effects.

Conclusions

Overall, the available evidence from meta-analysis reveals that RAGT has a positive and significant effect on improving the recovery of

lower limb function. This supports the concept that combining RAGT with conventional therapy may be more effective than conventional therapy alone, particularly for patients who are within three months from stroke onset or those who are non-ambulatory. In terms of RAGT dosage, our analysis only provides a rough estimate, suggesting that further research is needed to resolve and provide insights to determine the optimal parameters. Moreover, our findings regarding RAGT modes and types may provide significant clinical prospects. However, it is necessary to conduct a large, high-quality, multi-center randomized clinical trial to validate and confirm these findings.

Conflict of Interest
The authors declare that they have no conflict of interests.

Funding
This research was supported by grants from the National Natural Science Foundation of China (Grant No. 81871847 and 81672261), the Research and Development Projects in Key Field of Guangdong Province (Grant No. 2018B030332001), the Science and Technology Planning Key Project of Guangzhou (Grant No. 201803010119) and the Key Technologies Research and Development Program of China (Grant No. 2018YFC2001603).

Authors' Contribution
S. Liang conducted the primary search and excluded titles and abstracts that were not relevant to the content of the review. Z.-Q. Hong and Q. Cai independently evaluated the remaining titles and abstracts and obtained the full text for all abstracts to determine whether these studies met the inclusion criteria. Subsequently, they independently reviewed the full-text manuscripts and selected studies only if all inclusion criteria were met. Data from the original articles were extracted independently by S. Liang and Y.-J. Ren using a standard data recording, and then were independently rechecked by H.-Q. Zheng. Any disagreement was resolved through discussion with X.-Q. Hu.

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Availability of Data and Materials
All data generated or analyzed during this study are included in this published article and its supplementary material.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

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