REVIEW ARTICLE

Effectiveness of Rehabilitative Interventions Beginning within the First Month of Stroke Onset in Improving Lower Extremity-related Outcomes: A Systematic Review and Network Meta-Analysis

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Received: 21 July 2023 / Accepted: 06 November 2023

ABSTRAK

Kajian-kajian terkini mengenai intervensi awal yang memainkan peranan penting dalam meningkatkan plastisiti neural ketika sesi rehabilitasi strok secara relatif masih terhad. Objektif kajian ini adalah untuk menyiasat keberkesanan pelbagai intervensi yang dilaksanakan dalam tempoh sebulan selepas strok bagi meningkatkan pemulihan anggota bawah berbanding dengan rehabilitasi konvensional dan untuk memberikan penilaian tahap keberkesanan bagi setiap intervensi tersebut. Pangkalan data dari Cochrane, Ovid, PubMed, dan Scopus telah digunakan untuk carian artikel-artikel yang berkaitan sehingga tarikh 18 Mac 2022. Ujian terkawal secara rawak dianalisis jika penyelidik menilai keberkesanan dua atau lebih intervensi bukan ubat, tidak invasif dan bukan pembedahan terhadap pemulihan fungsi anggota bawah yang dilaksanakan dalam masa sebulan selepas strok. Analisis meta rangkaian menunjukkan bahawa stimulasi arus terus transkranial, stimulasi magnet berulang transkranial, terapi cermin, berbasikal, stimulasi saraf vagus aurikular bawah kulit, stimulasi elektrik otot saraf, kombinasi robot serta stimulasi elektrik otot saraf, dan stimulasi terma adalah sangat berkesan dalam mempertingkatkan pemulihan fungsi anggota bawah berbanding dengan rehabilitasi konvensional. Dalam konteks pemulihan mobiliti, terapi cermin, berbasikal dan stimulasi terma menunjukkan keberkesanan yang lebih ketara. Sementara itu, dalam konteks pemulihan keseimbangan, bola fisio, stimulasi elektrik saraf bawah kulit, berbasikal, stimulasi terma dan robot menunjukkan keberkesanan yang lebih ketara. Stimulasi terma mencatatkan keberkesanan tertinggi dalam mempertingkatkan fungsi motor anggota bawah dan mobiliti, manakala robot dan berjalan ke belakang masing-masing menunjukkan tahap

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keberkesanan tertinggi dalam mempertingkatkan pemulihan keseimbangan dan kelajuan berjalan.

Kata kunci: *Anggota bawah; analisis meta; rehabilitasi strok*

ABSTRACT

Reviews about early interventions, which are important in stroke rehabilitation due to significant neural plasticity, are relatively less. This study objective was to investigate the effectiveness of different interventions started within one-month post-stroke in improving lower extremity-related outcomes as compared to conventional rehabilitation and the corresponding effectiveness ranking. Cochrane Library, Ovid, PubMed, and Scopus were searched for articles dated up to 18 March 2022. Randomised controlled trials were included if they evaluated the effectiveness of two or more different non-drug, non-invasive, and non-surgical interventions which were started within one-month post-stroke on lower extremity-related outcomes. Network meta-analysis revealed that transcranial direct current stimulation, repetitive transcranial magnetic stimulation, mirror therapy, cycling, transcutaneous auricular vagus nerve stimulation, neuromuscular electrical stimulation (NMES), combination of robot and NMES, and thermal stimulation were significantly more effective in improving lower extremity motor function than conventional rehabilitation. In improving mobility, mirror therapy, cycling, and thermal stimulation were significantly more effective. In enhancing balance, physio ball, transcutaneous electrical nerve stimulation, cycling, thermal stimulation, and robot showed significantly higher effectiveness. Thermal stimulation scored the highest effectiveness ranking in improving lower extremity motor function and mobility whereas robot and backward walking achieved the highest effectiveness ranking in improving balance and gait speed respectively.

Keywords: Lower extremity; meta-analysis; stroke rehabilitation

INTRODUCTION

Stroke rehabilitation encompasses a range of interventions to improve patients' impaired abilities after the stroke onset (Dobkin 2004; Langhorne et al. 2011). There are various types of interventions (Langhorne et al. 2009) with different defined goals that target the recovery of specific abilities (Langhorne et al. 2011). The interventions must be carefully selected due to the limitation of resources. To customise a suitable set of rehabilitation programs for the patients, the effectiveness of each intervention in enhancing different outcomes must be determined.

The selection of intervention is critical throughout all the stages of stroke recovery, including acute, sub-acute, and chronic stages. The mechanisms that drive stroke recovery, such as neural plasticity, spontaneous recovery, and compensatory strategies, as well as the ability of the patient to adapt, can differ at varying points of time after stroke onset (Bernhardt et al. 2017; Murphy & Corbett 2009). As a result, the optimal interventions for different phases of stroke recovery may be different too (Stinear et al. 2013). Among the phases of stroke recovery, early stages, i.e. acute and early sub-acute phases exhibit interesting characteristics but are relatively less studied. Several reviews showed that early rehabilitation may yield certain benefits (Bernhardt et al. 2017; Coleman et al. 2017; Li et al. 2018). Notably, it is recommended to initiate the rehabilitation program earlier between the first week and the first month after stroke onset (Bernhardt et al. 2017). From the physiological perspective, it is observed that endogenous neural repair happens with protein inductions within two weeks of stroke onset (Kawamata et al. 1996; McNeill et al. 1999; Stroemer et al. 1995). The basic fibroblast (Dahlqvist et al. 1999), nerve growth factors (Speliotes et al. 1996), and other growth-promoting factors are changed during this period, possibly increasing the neural plasticity which causes the brain to be responsive to rehabilitative interventions (Biernaskie et al. 2004). On the other hand, several previous works showed that early rehabilitation exhibited favorable effects in recovery outcomes when the rehabilitation was implemented with appropriate timing and dosage (Bernhardt et al. 2016; Chippala & Sharma 2016; Momosaki et al. 2016). Besides, early commencement of rehabilitation can result in advantages such as shortened hospitalisation (Li et al. 2018), potential reductions of patients' financial burden, and diverting the resources to other patients in need as soon as possible. Therefore, to optimise the recovery rate of the stroke patient, it is vital to select the most effective intervention to be started within one-month post-stroke.

Systematic review or meta-analysis is helpful in identifying effective interventions to promote stroke recovery. The authors (Lin et al. 2019) carried out a systematic review of stroke rehabilitative interventions implemented within six months after stroke onset. However, the review included interventions implemented in the late subacute stage (Bernhardt et al. 2017), and the interventions were only compared to conventional rehabilitation. In another review, the reviewers (Stinear et al. 2013) included rehabilitation studies within the first month of stroke but did not perform any effectiveness comparison or ranking analysis. To date, no previous work has been done on the comparison and ranking of intervention effectiveness of early rehabilitation interventions performed within one month of the stroke onset. The comparison of early intervention effectiveness is important to facilitate the selection of interventions to achieve optimal stroke recovery outcomes. As there are many types of interventions, it is impractical to compare the intervention effectiveness via clinical trials. Hence, a systematic review, which is more feasible in terms of effort, cost, and time, is warranted to address the research gap.

In this study, we aimed to compare the effectiveness of different rehabilitative interventions initiated within one-month post-stroke that target lower limb recovery. A period of one month was chosen according to the recommendation of previous work (Bernhardt et al. 2017). Lower extremity recovery outcomes including motor function, mobility, balance, and gait speed were considered in this study due to the corresponding importance. Basic motor function recovery such as the ability to perform simple flexion and extension movements is the most fundamental recovery that should be achieved before other more advanced functionalities can be regained. With improved mobility, stroke patients can conduct various activities of daily living that require locomotion. In addition, the ability to maintain balance reduces the risk of falling while sufficient gait speed enables the adaptation to tasks such as crossing the road (An et al. 2015). A network meta-analysis is performed to compare the intervention's effectiveness in improving these outcomes (Balduzzi et al. 2023). The interventions were also compared with conventional rehabilitation to determine if these interventions were significantly more effective than conventional rehabilitation. Conventional rehabilitation includes exercises or tasks performed by patients according to the typical routines implemented in rehabilitation facilities, such as stretching, walking, occupational therapy, and others as specified in Table 1. The effectiveness ranking of

TABLE 1: List of intervention categories including conventional rehabilitation

Intervention category	Description
Conventional rehabilitation	Exercises or treatment such as stretching, trunk control training, walking with or without assistance from a physiotherapist or parallel bars, bed mobilization, bedside rehabilitation, standing and sitting, occupational therapy, pelvic bridging, balance training, speech therapy, neuropsychology, medical services, postural training, Bobath technique, cardiac training, neuromuscular facilitation, sensory integration exercise, body weight resistance exercise, social rehabilitation, swallowing training, cognitive training, any form of sham or placebo, and other similar methods.
Backward walking (Rose et al. 2018)	Backward walking was carried out whereby physiotherapists may provide support.
Cycling (da Rosa Pinheiro et al. 2021; Katz-Leurer et al. 2006; Katz-Leurer et al. 2003; Wu et al. 2020)	Cycling training on a cycle ergometer was conducted.
Family-mediated exercise (Galvin et al. 2011)	The intervention focus was the family member's presence and effort in aiding the patient with rehabilitation exercises.
Focal muscle vibration (Toscano et al. 2019)	An electromechanical transducer was used to provide vibration to the target muscle.
Force platform (Rao et al. 2013)	The patient tried to lean in specific directions or maintain balance while standing on a force platform. The force platform may be static or changing its orientation.

Mirror therapy (Mohan et al. 2013; Pagilla et al. 2019)	A mirror was placed between the paretic and non-paretic lower limbs, inclined to hide the paretic limb from sight and provide a reflection of the non-paretic limb. The patient tried to perform the movements of the non-paretic limb while looking at its reflection.
Neuromuscular electrical stimulation (NMES) (Pagilla et al. 2019; van Bloemendaal et al. 2021; Yen et al. 2019)	Electrical stimulation was carried out on muscles of the paretic lower limb through electrodes to produce visible muscle contraction and partial joint movement. Functional electrical stimulation was classified under this category due to a similar mechanism.
Overground walking (Brunelli et al. 2019; Lura et al. 2019)	The patient walked on the ground using assistive devices such as a weight suspension system.
Physio ball (Karthikbabu et al. 2011)	The exercise was performed on a physio ball, which provided postural perturbation to train the patient to maintain posture and balance.
Robot (Forrester et al. 2014; Tangmanee et al. 2021)	The robot was fixed on the lower limb of the patient. It aided the implementation of a certain movement in rehabilitation therapy.
Repetitive transcranial magnetic stimulation (rTMS) (Guan et al. 2017; Khedr et al. 2010)	A coil was placed on the scalp to perform magnetic stimulation on a certain part of the brain.
Self-regulated exercise (Liu et al. 2014)	The patient was guided by a physiotherapist to understand his or her performance and identify improvement strategies.
Transcutaneous auricular vagus nerve stimulation (ta-VNS) (Li et al. 2022)	Electrical stimulation was carried out on the auricular concha through the afferent auricular branch of the vagus nerve.
Transcutaneous electrical nerve stimulation (TENS) (Yen et al. 2019)	A low-voltage current was passed through electrodes attached to the skin without causing muscle contraction or joint movement.
Transcranial direct current stimulation (tDCS) (Bornheim et al. 2020; Chang et al. 2015)	Electrical stimulation was conducted on a certain part of the brain through the electrodes attached to the scalp.
Thermal stimulation (Chen et al. 2011; Liang et al. 2012)	The patient was required to perform paretic lower limb movement in response to hot or cold stimuli presented to the limb.
Treadmill (Lura et al. 2019)	The patient carried out gait training on the treadmill.
Virtual reality (VR) (Lin et al. 2020; Zakharov et al. 2020a; Zakharov et al. 2020b)	The patient performed exercises in the virtual environment with any degree of immersiveness.

various therapies was calculated using the P-score (Rücker et al. 2015).

With this work, we hoped to provide a better understanding of the following questions: (i) Which interventions started within one-month post-stroke were significantly more effective compared to conventional rehabilitation in improving lower extremity-related outcomes? and (ii) What were the effectiveness ranking of these interventions?

MATERIALS AND METHODS

This work was implemented based on the PRISMA guidelines to ensure the clarity and transparency in the reporting of systematic review and meta-analysis (Liberati et al. 2009).

Identification and Selection of Studies

On 18 March 2022, an electronic search was carried out on databases including PubMed, Cochrane Library, Scopus, and Ovid to gather the relevant trials. The search terms consisted of synonyms, medical subject headings, and related words with similar meanings to “stroke”, “rehabilitation”, “early”, and “lower extremity”. Boolean operators (e.g. “AND” and “OR”) and descriptors (e.g. “MeSH” in PubMed) were used in the search strategies. Filter was used whenever possible to include only clinical trials in the search. The full search strategies were listed in Table 2.

All the search results were imported

TABLE 2: Search strategies for Cochrane Library, Ovid, PubMed, and Scopus

Database	Search strategy
Cochrane Library	1. MeSH descriptor: [Stroke] explode all trees 2. MeSH descriptor: [Stroke Rehabilitation] explode all trees 3. MeSH descriptor: [Brain Ischemia] explode all trees 4. (stroke*):ti,ab,kw OR (cerebrovascular accident*):ti,ab,kw 5. (brain):ti,ab,kw AND (vascular accident*):ti,ab,kw 6. (brain):ti,ab,kw AND (infarct*):ti,ab,kw 7. (cerebral):ti,ab,kw AND (infarct*):ti,ab,kw 8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 9. (acute):ti,ab,kw OR (early):ti,ab,kw 10. MeSH decriptor: [Rehabilitation] explode all trees 11. (rehabilitat*):ti,ab,kw OR (recover*):ti,ab,kw OR (train*):ti,ab,kw OR (practic*):ti,ab,kw OR (exercis*):ti,ab,kw 12. (therap*):ti,ab,kw 13. #10 OR #11 OR #12 14. MeSH descriptor: [Lower Extremity] explode all trees 15. (lower limb*) OR (lower extremit*) OR (leg) OR (legs) OR (knee*) 16. (ankle*) OR (foot) OR (feet) 17. #14 OR #15 OR #16 18. (clinical trial):pt 19. #8 AND #9 AND #13 AND #17 AND #18
Ovid	((stroke or "stroke rehabilitation" or "brain ischemia").hw. or (stroke* or (cerebrovascular and accident*) or (brain and "vascular accident*") or (brain and infarct*) or (cerebral and infarct*)). ab,ti.) and ((acute).ab,ti. or (early).ab,ti.) and ((rehabilitation).hw. or (rehabilitat* or recover* or train* or practic* or exercis* or therap*).ab,ti.) and (("lower extremity").hw. or ("lower limb*" or "lower extremit*" or leg or legs or knee* or ankle* or foot or feet).mp.) and (article or miscellaneous or "miscellaneous article").pt.
PubMed	(stroke[mesh] OR "stroke rehabilitation"[mesh] OR "brain ischemia"[mesh] OR stroke*[tiab] OR "cerebrovascular accident*"[tiab] OR (brain[tiab] AND "vascular accident*"[tiab]) OR (brain[tiab] AND infarct*[tiab]) OR (cerebral[tiab] AND infarct*[tiab])) AND (acute[tiab] OR early[tiab]) AND (rehabilitation[mesh] OR rehabilitat*[tiab] OR recover*[tiab] OR train*[tiab] OR practic*[tiab] OR exercis*[tiab] OR therap*[tiab]) AND ("lower extremity"[mesh] OR "lower limb*"[tiab] OR "lower extremit*"[tiab] OR leg[tiab] OR legs[tiab] OR knee*[tiab] OR ankle*[tiab] OR foot[tiab] OR feet[tiab]) AND ("clinical trial"[Filter] OR "randomized controlled trial"[Filter])
Scopus	(KEY (stroke OR "stroke rehabilitation" OR "brain ischemia") OR TITLE-ABS (stroke* OR (cerebrovascular AND accident*) OR (brain AND "vascular accident*") OR (brain AND infarct*) OR (cerebral AND infarct*))) AND TITLE-ABS-KEY (early OR acute) AND (KEY (rehabilitation) OR TITLE-ABS (rehabilitat* OR recover* OR train* OR practic* OR exercis* OR therap*)) AND (KEY ("lower extremity") OR TITLE-ABS ("lower limb*" OR "lower extremit*" OR leg OR legs OR knee* OR ankle* OR foot OR feet)) AND DOCTYPE (ar)

into EndNote™ X8.2. Automatic duplicate removal was implemented to exclude duplicated citations. Next, title and abstract screening were done to exclude the studies that did not fulfill the inclusion criteria defined in Table 3 according to the PICOS structure (Methley et al. 2014). Following that, full texts of included articles were examined and studies that failed to satisfy the inclusion criteria were excluded. If the full text of an article was not available, the authors of the article were contacted in an attempt to obtain the full text. Only clinical trials were included in the systematic review. The article screening process was done by four reviewers. Each article was reviewed by at least two reviewers. Any disagreement or ambiguity was resolved via group discussion.

Assessment of Study Characteristics

The risk of bias in the included studies was evaluated using the PEDro scale (de Morton 2009). The quality of the studies was classified as poor (<4), fair (4-5), or high (>5) based on the PEDro scale range (Lin et al. 2019). Four categories of lower extremity-related outcomes were considered in this work, including lower extremity motor function, mobility, balance, and gait speed. The four outcome categories were measured respectively by Fugl-Meyer Scale (Gladstone et al. 2002), Functional Ambulation Categories (Mehrholz et al. 2007), Berg Balance Scale (Berg et al. 1992), Ten Meter Walk Test (Watson 2002), and other similar scores.

Data Extraction

A data collection table was used to record the characteristics of the included trials, consisting of inclusion and exclusion criteria, sample size, age, gender, type of stroke, damaged side, time from stroke onset, conventional rehabilitation description, intervention description, intervention duration, time from intervention onset to follow-up, and outcome measures included in the network meta-analysis. Standardised mean difference (SMD) (Higgins et al. 2019a) was used to quantify the effect

TABLE 3: Article inclusion criteria

Item	Inclusion criteria
Participant	Time from stroke onset was less than 31 days or summation of mean time from stroke onset and two times its standard deviation was less than 31 days, which meant that almost all (approximately 97.5%) of the participants' time from stroke onset were less than 31 days. Age span, stroke diagnosis method, and stroke severity were not limited to any particular range or category.
Intervention	Any non-drug, non-invasive, and non-surgical intervention.
Comparison	The study compared two or more different categories of interventions.
Outcome	The study measured outcomes related to lower extremities including motor function, mobility, balance, and gait speed. A study would be included if it reported at least one of the outcomes.
Study design	The study design was based on a randomized controlled trial (RCT).
Other criteria	The study was published in English.

size if different outcome scores under the same outcome categories were used in different studies (Takeshima et al. 2014). Mean difference (MD) (Julian Higgins et al. 2019a) was used if there was only one type of outcome score used to quantify an outcome category. If the data was reported in graphical form, a Web plot digitiser was used to extract the value (Tawfik et al. 2019). For studies that reported median, first quartile, third quartile, maximum, and minimum values, the distribution skewness was evaluated (Shi et al. 2020). If there was no significant evidence to show that the distribution was skewed, the mean and standard deviation were estimated (Luo et al. 2018; Shi et al. 2020; Wan et al. 2014). If only raw data was provided, the effect size was calculated from the raw data. The studies in which the effect size could not be extracted were excluded from the quantitative data analysis.

Quantitative Data Analysis

The data analysis procedures described in this section were performed independently for each outcome category. Before the data analysis, interventions that shared similar characteristics were grouped under the same intervention category such as that specified in Table 1. When a study reported the same outcome at different times after the start of the intervention, only the outcome with the time closest to the median value was considered in the data analysis.

Network graphs were drawn using Statistical Analysis System (SAS) Visual Analytics to display the types of comparison between interventions (Law et al. 2019). Forest plots that contained the effect size and 95% confidence interval (CI) of each included study were plotted. The CI that did not overlap with zero indicated that either the intervention or the conventional rehabilitation was significantly better than the other in improving the outcome. Frequentist network meta-analysis was carried out by using the "netmeta" function (Rücker 2012; Balduzzi et al. 2023) of R language. This allowed the comparison of the effectiveness of any pair of interventions through direct and indirect effects. The effect sizes under the same intervention category were pooled. Random-effect model (Hedges & Vevea 1998) was then applied to account for the heterogeneity between studies. To assess the heterogeneity across studies, Cochrane's Q value (Cochran 1954) and I^2 score (Higgins & Thompson 2002) were computed. The DerSimonian-Laird estimator was applied in the heterogeneity calculation (Higgins & Thompson 2002). I^2 scores higher than 50% indicated moderate to substantial heterogeneity (Higgins & Thompson 2002). Sensitivity analysis was carried out by removing the trial with a high Cochrane's Q value from the network meta-analysis. In this way, the network meta-analysis could be performed with reduced heterogeneity among the analysed works. The effectiveness ranking of each intervention was inferred by calculating the respective P-score (Rücker et al. 2015). The higher the P-score, the more effective the intervention was compared to the others.

Several additional criteria must be fulfilled by the studies to be eligible for the network meta-analysis. For instance, the conventional rehabilitation carried out in the studies must not include therapy classified under any intervention category in this review. This criterion was necessary to avoid potential heterogeneity due to the pooling of interventions with conventional rehabilitation. Besides, only interventions that could be compared with conventional rehabilitation through direct or indirect effects (Kiefer et al. 2015) were included in the network meta-analysis.

RESULTS

The PRISMA flow diagram of studies was shown in Figure 1. The systematic review included 32 trials and a total of 1243 participants (Bornheim et al. 2020; Brunelli et al. 2019; Chang et al. 2015; Chang et al. 2012; Chen et al. 2011; da Rosa Pinheiro et al. 2021; Forrester et al. 2014; Galvin et al. 2011; Guan et al. 2017; Karthikbabu et al. 2011; Katz-Leurer et al. 2006; Katz-Leurer et al. 2003; Khedr et al. 2010; Li et al. 2022; Liang et al. 2012; Lin

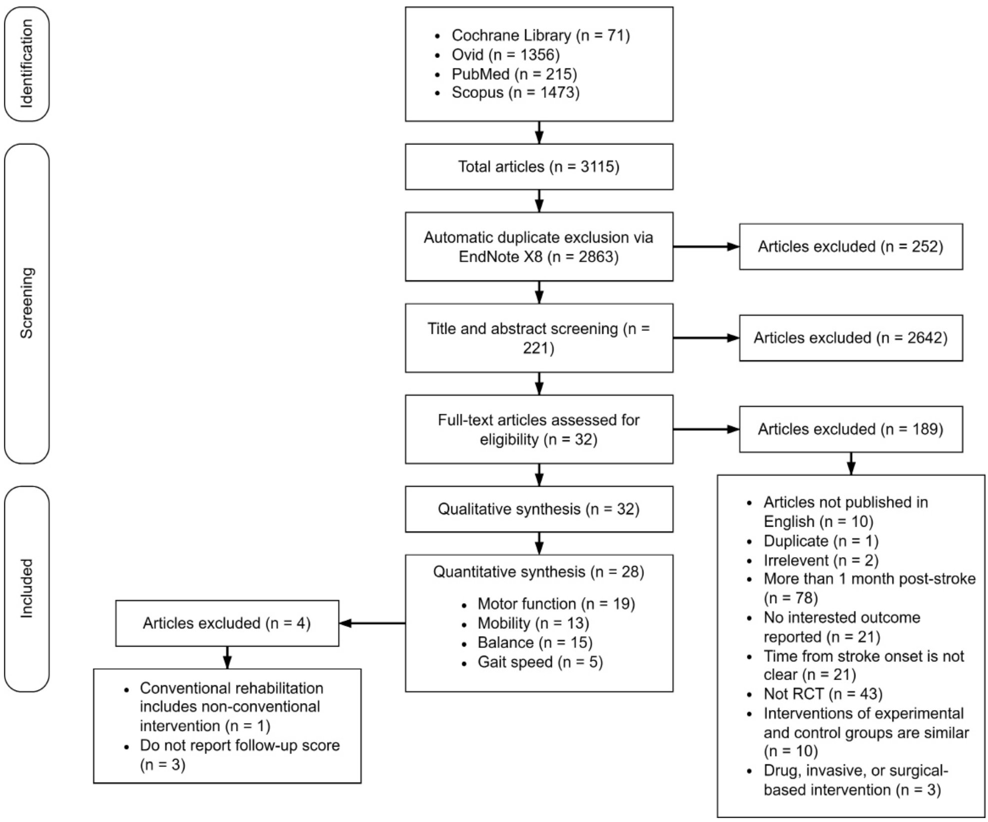

FIGURE 1: PRISMA flow diagram of studies

et al. 2020; Liu & Chan 2014; Lura et al. 2019; Mohan et al. 2013; Pagilla et al. 2019; Park et al. 2021; Rao et al. 2013; Rose et al. 2018; Sasaki et al. 2017; Solopova et al. 2011; Tangmanee et al. 2021; Toscano et al. 2019; van Bloemendaal et al. 2021; Wu et al. 2020; Yen et al. 2019; Zakharov et al. 2020a; Zakharov et al. 2020b). From the studies, conventional rehabilitation and 18 individual interventions were identified (Table 1). Table 4 outlined the outcome scores included in the network meta-analysis according to their respective categories. If a study reported two or more outcome scores from the same category, only the outcome score with the highest priority based on Table 4 would be included in the network meta-analysis.

The PEDro scale of each study was shown in Table 5. The mean ± standard deviation of the PEDro scale was recorded as 7.0 ± 1.00. There were 29 (90.63 %) high-quality and 3 (9.37 %) fair-quality trials. The characteristics of the 32 studies were summarised in Table 6. The description of the conventional rehabilitation and interventions of each study were delineated in Table 7.

Of the 32 studies, 28 of them (Bornheim et al. 2020; Brunelli et al. 2019; Chang et al. 2015; Chang et al. 2012; da Rosa Pinheiro et al. 2021; Forrester et al. 2014; Galvin et al. 2011; Guan et al. 2017; Karthikbabu et al. 2011; Katz-Leurer et al. 2006; Katz-Leurer et al. 2003; Khedr et al. 2010; Li et al. 2022; Liang et al. 2012; Lin et al. 2020; Lura et al. 2019; Mohan et al. 2013; Pagilla et al. 2019; Park et al. 2021; Rao et al. 2013; Rose et al. 2018; Sasaki et al. 2017; Solopova et al. 2011; Tangmanee et al. 2021; W. X. Wu et al. 2020; Yen et al. 2019; Zakharov et al. 2020a; Zakharov et al. 2020b) were included in the network meta-

TABLE 4: List of lower extremity-related outcomes included in the network meta-analysis. Outcome scores of each outcome category are arranged in descending order of priority. The priority is determined based on the frequency of the outcome scores applied in the reviewed studies. The higher the frequency of an outcome score applied in the reviewed studies, the higher priority would be given to the outcome score to be included in the meta-analysis.

Outcome category	Outcome score
Motor function	1. Fugl-Meyer Scale for lower extremity 2. Medical Research Council Scale (Paternostro-Sluga et al. 2008) 3. Hemispheric Stroke Scale (Adams et al. 1987)
Mobility	1. Functional ambulation category 2. Functional Independence Measure (Linacre et al. 1994) for mobility 3. Rivermead Mobility Index (Chen et al. 2007) 4. ICU Mobility Scale (Hodgson et al. 2014) 5. Revised Version of the Ability for Basic Movement Scale (Tanaka et al. 2010)
Balance	1. Berg Balance Scale 2. Postural Assessment Scale for Stroke (Benaim et al. 1999) 3. Brunnel Balance Assessment (Tyson & De Souza 2004) 4. Fugl-Meyer Scale for balance
Gait speed	1. 10 Meter Walk Test 2. Any methods that measured walking speed

TABLE 5: PEDro scales of studies included in the systematic review

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15 % dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total	Quality
Bornheim et al. (2020)	/	/	/	/	/	/	/		/	/	**9**	**High**
Brunelli et al. (2019)	/	/	/			/	/		/	/	**7**	**High**
Chang et al. (2012)	/	/	/			/	/		/	/	**7**	**High**
Chang et al. (2015)	/	/	/	/	/	/	/		/	/	**9**	**High**
Chen et al. (2011)	/	/	/			/	/		/	/	7	High
da Rosa Pinheiro et al. (2021)	/	/					/		/	/	5	Fair
Forrester et al. (2014)	/		/				/		/	/	5	Fair
Galvin et al. (2011)	/	/	/			/	/	/	/	/	8	High
Guan et al. (2017)	/	/	/	/	/				/	/	7	High
Karthikbabu et al. (2011)	/	/	/			/	/		/	/	7	High
Katz-Leurer et al. (2003)	/	/	/			/	/		/	/	7	High
Katz-Leurer et al. (2006)	/	/	/			/	/		/	/	7	High
Khedr et al. (2010)	/	/	/	/		/			/	/	**7**	**High**

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15 % dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total	Quality
Li et al. (2022)	/	/	/	/	/		/		/	/	**8**	**High**
Liang et al. (2012)	/	/	/			/		/	/	/	7	High
Lin et al. (2020)	/	/	/			/	/	/	/	/	8	High
Liu et al. (2014)	/	/	/			/	/		/	/	7	High
Lura et al. (2019)	/	/	/				/		/	/	6	High
Mohan et al. (2013)	/	/	/			/	/		/	/	7	High
Pagilla et al. (2019)	/	/	/			/	/		/	/	7	High
Park et al. (2021)	/	/	/			/	/		/	/	7	High
Rao et al. (2013)	/	/	/			/	/		/	/	7	High
Rose et al. (2018)	/	/	/			/			/	/	6	High
Sasaki et al. (2017)	/	/	/	/	/	/	/		/	/	9	High
Solopova et al. (2011)	/	/	/				/		/	/	6	High
Tangmanee et al. (2021)	/	/	/						/	/	5	Fair
Toscano et al. (2019)	/	/	/	/	/		/		/	/	**8**	**High**

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15 % dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total	Quality
van Bloemendaal et al. (2021)	/	/	/			/		/	/	/	7	High
Wu et al. (2020)	/	/	/			/	/		/	/	7	High
Yen et al. (2019)	/	/	/			/	/		/	/	7	High
Zakharov et al.(2020a)	/	/	/			/	/		/	/	7	High
Zakharov et al. (2020b)	/	/	/				/		/	/	6	High

analysis. According to Figure 1, four studies were not included in network meta-analysis as either the performed conventional rehabilitation involved non-conventional interventions which were not listed in the 'conventional rehabilitation' category as shown in Table 3 (van Bloemendaal et al. 2021), or the study did not report the follow-up score related to lower limb recovery (Chen et al. 2011; Liu & Chan 2014; Toscano et al. 2019). The network meta-analysis was conducted using SMD as the studies reported different outcome scores for all outcome categories. The follow-up score was used to calculate SMD as more studies reported follow-up scores instead of the change in score from baseline. The median time from stroke onset reported for lower extremity motor function, mobility, balance, and gait speed outcome categories was 29.5, 17.5, 21 and 14 days respectively.

The network meta-analysis on the outcome category of lower extremity motor function included 19 trials and 14 interventions. Figure 2 illustrates the forest plot of individual studies, network graphs, network meta-analysis, and sensitivity analysis results. According to Figure 2C, eight interventions, namely transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), mirror therapy, cycling, transcutaneous auricular vagus nerve stimulation (ta-VNS), neuromuscular electrical stimulation (NMES), the combination of robot and NMES, as well as thermal stimulation reported significant effects in comparison with conventional rehabilitation. In contrast, six

TABLE 6: Summarized information of studies included in systematic review

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Bornheim et al. (2020) / tDCS	Inclusion criteria First stroke; diagnosis via CT or MRI Exclusion criteria One "yes" in the high and relatively high-risk sections of the Transcranial direct current stimulation Safety Screening Tool; hemineglect; unable to understand consent form	Baseline Sample size (IG / CG) 25 / 25 23 / 23 (analyzed) Age IG: 62.48 ± 11.86 CG: 63.48 ± 12.94 Male / female IG: 15 / 10 CG: 18 / 7	Baseline Ischemic / haemorrhagic IG: 25 / 0 CG: 25 / 0 Stroke hemisphere (left / right) IG: 15 / 10 CG: 13 / 12	Stroke onset 48 hours Intervention onset to follow-up 1 week 2 weeks 3 weeks 4 weeks (intervention ended) 3 months 6 months 1 year	FMS-LE
Brunelli et al. (2019) / Overground walking	Inclusion criteria Subacute hemiparesis due to first ischemic or haemorrhagic stroke; FAC < 2; maintain standing position at parallel bars for at least 30 seconds (even with physiotherapist help); cardiovascular stability; diagnosis via CT or MRI Exclusion criteria Comorbidities that affect walking; MAS > 3; sacral skin lesions; unable to understand command	Sample size (IG / CG) 15 / 19 Age 70 ± 10.74 Male / female 16 / 18	Ischemic / haemorrhagic 23 / 11 Hemisphere lesion (left / right) 17 / 17	Stroke onset < 4 weeks Intervention onset to follow-up 4 weeks (intervention ended) 5 weeks	RMI
Chang et al. (2012) / Robot + treadmill*	Inclusion criteria First unilateral ischemic or haemorrhagic stroke; supratentorial lesion; FAC < 2; can cooperate during exercise testing Exclusion criteria Contraindications to exercise established by American College of Sports Medicine; contraindications for Lokomat; lower limb musculoskeletal disease; other neurological diseases	Sample size (IG / CG) 20 / 17 Age IG: 55.5 ± 12 CG: 59.7 ± 12.1 Male / female IG: 13 / 7 CG: 10 / 7	Ischemic / haemorrhagic IG: 12 / 8 CG: 11 / 6 Side of paresis (left / right) IG: 14 / 6 CG: 11 / 6	Stroke onset < 1 month Intervention onset to follow-up 2 weeks (intervention ended)	FMS-LE FAC

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Chang et al. (2015) / tDCS	Inclusion criteria First unilateral ischemic stroke in cortical or subcortical area; hemiparesis; walking without assistance Exclusion criteria Severe somatosensory, apraxia or cognitive impairments; serious medical complications; lesions in the cerebellum or brain stem	Sample size (IG / CG) 12 / 12 Age IG: 59.9 ± 10.2 CG: 65.8 ± 10.6 Male / female 15 / 9	Ischemic / haemorrhagic IG: 12 / 0 CG: 12 / 0 Lesion side (left / right) IG: 6 / 6 CG: 5 / 7	Stroke onset 7 - 30 days Intervention onset to follow-up 2 weeks (intervention ended)	FMS-LE FAC BBS Walking speed
Chen et al. (2011) / Thermal stimulation	Inclusion criteria First stroke; no cardiac or orthopaedic problems; can follow instructions; Brunnstorm stage < 4; FAC < 2 Exclusion criteria History of diabetes or sensory impairment due to peripheral vascular disease or neuropathy; speech disorder or global aphasia which prevented cooperation	Sample size (IG / CG) 17 / 16 Age IG: 58.0 ± 11.5 CG: 62.3 ± 11.3 Male / female IG: 13 / 4 CG: 9 / 7	Ischemic / haemorrhagic IG: 5 / 12 CG: 6 / 10 Side of paresis (left / right) IG: 11 / 6 CG: 9 / 7	Stroke onset < 4 weeks Intervention onset to follow-up 4 weeks 6 weeks (intervention ended)	NA
da Rosa Pinheiro et al. (2021) / Cycling	Inclusion criteria First ischemic stroke on middle cerebral artery; hemiparesis or hemiplegia; responded to command Exclusion criteria Hemodynamic instability; GCS ≤ 8; bilateral or cerebral trunk injury; pathological alteration in ECG that could invalidate protocol performance; signs of new stroke; previous cognitive and musculoskeletal dysfunctions; joint injury which affects mobility	Sample size (IG / CG) 10 / 10 Age IG: 63.5 ± 4.5 CG: 68.9 ± 8.5 Male / female IG: 5 / 5 CG: 3 / 7	Ischemic / haemorrhagic IG: 10 / 0 / 0 CG: 10 / 0 / 0 Hemiparesis (left / right) IG: 4 / 6 CG: 7 / 3	Stroke onset 24 hours Intervention onset to follow-up 5 days (intervention ended)	MRCS ICUMS BBS 10MWT

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Forrester et al. (2014) / Robot	Inclusion criteria First ischemic or haemorrhagic stroke; 1/5 ≤ manual muscle testing ≤ 4/5; can generate trace muscle activation in plantar or dorsiflexors; adequate language and neurocognitive function to participate and give informed consent; clinical, neurological, and hemodynamic stability to sit in the chair for 30 to 60 minutes Exclusion criteria Total plegia at paretic ankle; fixed or painful contractures or other lower extremity pain syndrome; dementia; orthopaedic, arthritic, or inflammatory condition limiting ankle movement; signs of deep venous thrombosis or pulmonary thromboembolism; vision impairment; severe receptive or global aphasia	Sample size (IG / CG) 18 / 16 Age IG: 63.6 ± 2.3 CG: 60 ± 3.1	Side of lesion (left / right) IG: 9 / 9 CG: 9 / 7	Stroke onset IG: 11.9 ± 1.5 days CG: 10.8 ± 1.2 days Intervention onset to follow-up Approximately 2 weeks (intervention ended)	FIM-M BBS Walking speed
Galvin et al. (2011) / Family-mediated exercise	Inclusion criteria First unilateral stroke; diagnosis via CT and MRI; MMSE score > 23; family member willing to participate; 3.2 ≤ Orpington Prognostic Scale ≤ 5.2; family member was medically stable and physically able to assist in delivery of exercises	Sample size (IG / CG) 20 / 20 Age IG: 63.15 ± 13.3 CG: 69.95 ± 11.69 Male / female IG: 13 / 7 CG: 7 / 13	Ischemic / haemorrhagic IG: 16 / 4 CG: 18 / 2 Side of stroke (left / right) IG: 9 / 11 CG: 14 / 6	Stroke onset IG: 18.9 ± 2.9 days CG: 19.7 ± 3 days Intervention onset to follow-up 8 weeks (intervention ended) 3 months	FMS-LE BBS
Guan et al. (2017) / rTMS	Inclusion criteria Ischemic stroke; unilateral subcortical lesions in middle cerebral artery territory; diagnosis with diffusion weighted imaging Exclusion criteria History of stroke or cerebral small vessel disease; MMSE score ≤ 24; serious lung and heart diseases; liver and renal failure diseases or malignant tumors; MRI contraindications	Baseline Sample size (IG / CG) 21 / 21 13 / 14 (analyzed) Age IG: 59.7 ± 6.8 CG: 57.4 ± 14 Male / female IG: 16 / 5 CG: 14 / 7	Baseline Ischemic / haemorrhagic IG: 21 / 0 CG: 21 / 0 Lesion side (left / right) IG: 11 / 10 CG: 12 / 9	Stroke onset < 1 week Intervention onset to follow-up 2 days (intervention ended after 10 days) 1 month 3 months 6 months 1 year	FMS-LE

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Karthikbabu et al. (2011) / Physio ball	Inclusion criteria Medically stable; understand command; diagnosis by CT or MRI; first unilateral supratentorial lesion; could sit for 30 seconds on a stable surface Exclusion criteria Neurological disease affecting balance; musculoskeletal disorders or other degenerative diseases of the lower limbs which affect motor performance	Sample size (IG / CG) 15 / 15 Age IG: 59.8 ± 10.5 CG: 55 ± 6.5 Male / female IG: 8 / 7 CG: 9 / 6	Ischemic / haemorrhagic IG: 9 / 6 CG: 8 / 7 Hemiplegic side (left / right) IG: 5 / 10 CG: 6 / 9	Stroke onset IG: 11.8 ± 8.1 days CG: 12.1 ± 7.5 days Intervention onset to follow-up 3 weeks (intervention ended)	BBA
Katz-Leurer et al. (2003) / Cycling	Exclusion criteria Brainstem lesions or bilateral signs; no lower limb paralysis; unconscious or incontinent; ECG showed pathological change; significant change in blood pressure upon exertion; resting systolic blood pressure > 200 mmHg; resting diastolic blood pressure > 100 mmHg; arrhythmia; heart failure; receiving beta-blockers; inflammatory; degenerative joint diseases	Baseline Sample size (IG / CG) 46 / 46 46 / 44 (analyzed) Age IG: 62 ± 11 CG: 65 ± 11 Male / female IG: 26 / 20 CG: 23 / 23	Baseline Ischemic / haemorrhagic IG: 40 / 6 CG: 40 / 6	Stroke onset < 31 days Intervention onset to follow-up 8 weeks (intervention ended)	Walking speed
Katz-Leurer et al. (2006) / Cycling	Inclusion criteria First ischemic stroke Exclusion criteria Cannot sit for 10 s or stand without support for more than 1 min; Brainstem lesion or bilateral signs; unconscious or totally incontinent; significant change in blood pressure; a resting systolic blood pressure over 200 mmHg or a resting diastolic blood pressure more than 100 mmHg; arrhythmia, heart failure or receiving beta-blockers; lower back pain, inflammatory or degenerative joint diseases	Sample size (IG / CG) 10 / 14 Age IG: 59 ± 8 CG: 65 ± 9 Male / female IG: 8 / 2 CG: 5 / 9	Ischemic / haemorrhagic IG: 10 / 0 CG: 14 / 0 Brain lesion location (left / right) IG: 7 / 3 CG: 7 / 7	Stroke onset < 31 days Intervention onset to follow-up 3 weeks (intervention ended) 6 weeks	FMS-LE PASS

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Khedr et al. 2010) / rTMS	Inclusion criteria Acute ischemic stroke; acute hemiplegia with single thromboembolic non-haemorrhagic infarction in the distribution of one of the territories of middle cerebral artery; diagnosis via CT Exclusion criteria Extensive infarction; severe flaccid hemiplegia; head injury or neurological disease other than stroke; unstable cardiac arrhythmia; epilepsy; previous administration of tranquilizer; unable to give informed consent; intracranial metallic, magnetic pieces, with pacemakers or any other device	Baseline Sample size, IG (3 Hz) / IG (10 Hz) / CG 16 / 16 / 16 Age IG (3 Hz): 58.25 ± 15.07 IG (10 Hz): 58.37 ± 13.96 CG: 58 ± 11.64 Male / female IG (3 Hz): 8 / 8 IG (10 Hz): 7 / 9 CG: 9 / 7	Baseline Ischemic / haemorrhagic IG (3 Hz): 16 / 0 / 0 IG (10 Hz): 16 / 0 / 0 CG: 16 / 0 / 0 Side of stroke (left / right) IG (3 Hz): 12 / 4 IG (10 Hz): 6 / 10 CG: 9 / 7	Stroke onset 5 - 15 days Intervention onset to follow-up 5 days (intervention ended) 1 month 2 months 3 months 1 year	HSS
Li et al. 2022) / ta-VNS	Inclusion criteria First ischemic or haemorrhagic stroke; diagnosis via imaging Exclusion criteria Progressive decline in cardiac, pulmonary, liver, and kidney function; apraxia; heart rate < 50 beats/min; previous operation on vagus nerve; alcohol or drug abuse; participation in other trial; other diagnoses that might interfere with rehabilitation or outcome assessments	Baseline Sample size (IG / CG) 30 / 30 28 / 28 (analyzed) Age IG: 69.2 ± 12.3 CG: 68.3 ± 12.1 Male / female IG: 15 / 15 CG: 14 / 16	Baseline Ischemic / haemorrhagic IG: 27 / 3 CG: 28 / 2 Stroke hemisphere (left / right) IG: 18 / 12 CG: 20 / 10	Stroke onset < 1 month Intervention onset to follow-up 2 weeks 1 month (intervention ended) 3 months 6 months 1 year	FMS-LE
Liang et al. (2012) / Thermal stimulation	Inclusion criteria First stroke; no history of cardiac or orthopaedic disease; can follow instructions; Brunnstrom stage < 4 Exclusion criteria History of severe diabetes or sensory; impairment due to peripheral vascular disease or neuropathy; global aphasia; previous psychological disorder	Sample size (IG / CG) 15 / 15 Age IG: 56.1 ± 11.9 CG: 59.73 ± 11.6 Male / female IG: 12 / 3 CG: 7 / 8	Ischemic / haemorrhagic IG: 9 / 6 CG: 9 / 6 Side of paresis (left / right) IG: 9 / 6 CG: 8 / 7	Stroke onset < 4 weeks Intervention onset to follow-up 4 weeks 6 weeks (intervention ended) 3 months 6 months 1 year	FMS-LE FAC BBS

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Lin et al. (2020) / VR	Inclusion criteria Acute ischemic infarction; can communicate with verbal or non-verbal methods; understand Mandarin; 1 ≤ mRS ≤ 4; agreed to be randomized Exclusion criteria Global aphasia; transient ischemic attack; visual or auditory impairment; history of cancer; end-stage renal disease with dialysis; dementia; mental health disorder; transferred from other wards; unable to participate due to comorbid neurological and musculoskeletal conditions; prolonged stay in hospital for over 3 weeks; decline to treatment and transfer to other hospital	Sample size (IG / CG) 38 / 107 Age IG: 64.5 ± 13.5 CG: 66.9 ± 13.3 Male / female IG: 27 / 11 CG: 60 / 47	Ischemic / haemorrhagic IG: 38 / 0 CG: 107 / 0 Affected side (left / right) IG: 23 / 15 CG: 53 / 54	Start time of intervention post-admission IG: 1.8 ± 0.5 days CG: 3.8 ± 0.8 days Intervention onset to follow-up IG: 14.0 ± 4.1 days (intervention end) CG: 11.7 ± 4.2 days (intervention end)	MRCS PASS
Liu et al. (2014) / Self-regulated exercise	Inclusion criteria Acute unilateral stroke at middle cerebral artery system Exclusion criteria Brain stem or cerebellar lesions; medical comorbidity; cognitive problems; communication problems	Sample size (IG / CG) 24 / 20 Age IG: 69.70 ± 6.00 CG: 72.30 ± 9.90 Male / female IG: 11 / 13 CG: 11 / 9	Side of hemisphere (left / right) IG: 9 / 15 CG: 4 / 16	Stroke onset IG: 13.80 ± 8.20 days CG: 12.90 ± 6.80 days Intervention onset to follow-up 1 week (intervention end)	NA
Lura et al. (2019) / Treadmill Overground walking	Inclusion criteria Diagnosed with acute unilateral cerebrovascular accident affecting at least the lower limb; medically stable Exclusion criteria Previous cerebrovascular accident with residual lower limb deficit; other lower extremity pathology on affected side	Sample size, IG (treadmill) / IG (overground walking) 18 / 20 Age IG (treadmill): 63.8 ± 10.8 IG (overground walking): 60.4 ± 16.1 Male / female IG (treadmill): 15 / 3 IG (overground walking): 12 / 8		Stroke onset < 14 days Intervention onset to follow-up IG: 23.5 ± 8.9 days (intervention ended) CG: 18.1 ± 4.1 days (intervention ended)	FIM-M Walking speed

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Mohan et al. (2013) / Mirror therapy	Inclusion criteria First unilateral stroke with hemiparesis; understand command; Brunnstrom recovery stage > 1; MMSE score > 23; stable medical condition; ambulatory before stroke Exclusion criteria Neglect; Pusher syndrome; visual deficits; history of comorbidities that influenced lower extremity usage	Sample size (IG / CG) 11 / 11 Age IG: 62.64 ± 17.30 CG: 63.27 ± 7.63 Male / female IG: 4 / 7 CG: 8 / 3	Ischemic / haemorrhagic IG: 7 / 4 CG: 7 / 4 Paretic side (left / right) IG: 2 / 9 CG: 4 / 7	Stroke onset < 2 weeks Intervention onset to follow-up 2 weeks (intervention ended)	FMS-LE FAC BBA
Pagilla et al. (2019) / NMES Mirror therapy	Inclusion criteria First unilateral supratentorial stroke with hemiparesis; diagnosis by neurologist or physician; Brunnstrom lower extremity recovery stages > 3; MMSE score > 24 Exclusion criteria Severe visual deficits, somatosensory deficits; uncontrolled hypertension; cardiac disease; hemineglect; skin and peripheral circulation disorders	Sample size. IG (NMES) / IG (mirror) 15 / 15 Age IG (NMES): 52.75 ± 12.1 IG (mirror): 54.05 ± 11.4 Male / female IG (NMES): 9 / 6 IG (mirror): 11 / 4	Ischemic / haemorrhagic IG (NMES): 8 / 7 IG (mirror): 9 / 6 Side with paresis (left / right) IG (NMES): 6 / 9 IG (mirror): 7 / 8	Stroke onset < 3 weeks Intervention onset to follow-up 6 days (intervention ended)	FMS-LE BBS
Rao et al. (2013) / Force platform	Inclusion criteria Acute stroke; residual hemiparesis with observable stance asymmetry; cannot stand or walk unassisted; understand and follow instructions Exclusion criteria Unstable medical conditions; history of other neurological diseases; major orthopaedic or chronic pain conditions; MAS > 3/5; unable to elicit palpable muscle contraction; leg length discrepancy	Sample size (IG / CG) 14 / 14 Age IG: 57.88 ± 15.51 CG: 60.57 ± 9.60 Male / female IG: 11 / 3 CG: 12 / 2	Ischemic / haemorrhagic IG: 13 / 1 / 0 CG: 13 / 1 / 0 Hemiparetic site (left / right) IG: 10 / 4 CG: 8 / 6	Stroke onset 3 - 14 days Intervention onset to follow-up 2 weeks (intervention ended)	FMS-LE FIM-M FMS-B

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Park et al. (2021) / Robot + treadmill + VR*	Inclusion criteria First acute cortical or subcortical ischemic stroke or prior stroke with no residual deficits affecting ambulation; can follow command; FMS sensory score > 2; can ambulate at least one step with assistance; 132 < height < 200 cm; 33 < hip knee joint length < 48 cm; 33 < knee joint-to-foot length < 48 cm Exclusion criteria Cerebellar or brainstem stroke; weight < 135 kg; uncontrolled hypertension (stage 2) with blood pressure > 160/100 mmHg; cardiopulmonary impairments that can affect the ambulation test; integumentary impairment; persistent mental illness; lower-extremity fixed contracture or deformity; bone instability; other neurodegenerative disorders; MAS score > 3 in the affected leg; back or leg pain causing inability to tolerate movement; unable to perceive whether the device is properly fitted; unable to communicate discomfort	Sample size (IG / CG) 10 / 10 Age IG: 75.4 ± 11.21 CG: 70.6 ± 13.6 Male / female IG: 5 / 5 CG: 3 / 7	Ischemic / haemorrhagic IG: 10 / 0 CG: 10 / 0 Side of hemiplegia (left / right) IG: 6 / 4 CG: 6 / 4	Stroke onset IG: 7.6 ± 4.95 days CG: 13.2 ± 7.2 days Intervention onset to follow-up 2 weeks (intervention ended) FMS-LE	FMS-LE
Rose et al. (2018) / Backward walking	Inclusion criteria First stroke; maintain upright standing posture with assistance; anticipated rehabilitation length of stay 2 - 3 weeks; anticipated remaining in the geographic area for study duration; vision within functional limits Exclusion criteria BBS > 45; lower extremity joint or weight-bearing pain; other neurological diagnoses; cannot follow command; contraversive pushing syndrome; cerebellar stroke	Sample size (IG / CG) 8 / 8 Age IG: 53.8 ± 12.1 CG: 66.6 ± 7.3 Male / female IG: 4 / 4 CG: 2 / 6	Affected hemisphere (left / right) IG: 5 / 3 CG: 5 / 3	Stroke onset < 30 days Intervention onset to follow-up 10 days (intervention ended) 3 months	FIM-M BBS Walking speed

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Sasaki et al. (2017) / rTMS	Inclusion criteria Supratentorial intracerebral haemorrhage or subcortical cerebral infarction in area of the middle cerebral artery; diagnosis via CT; eye opening score of 4 and best verbal response of 5 on the GCS; no surgical management; no administration of tissue plasminogen activator; no active physical or mental illness requiring medical management; no convulsion; no contraindications for rTMS in the guidelines suggested by Wassermann; no prior experience with rTMS application	Sample size (IG / CG) 11 / 10 Age IG: 66.5 $\pm$ 16.6 CG: 62.4 $\pm$ 10.3 Male / female IG: 8 / 3 CG: 5 / 5	Ischemic / haemorrhagic IG: 4 / 7 CG: 7 / 3 Side of cerebral lesion (left / right) IG: 8 / 3 CG: 4 / 6	Stroke onset IG: 11.2 $\pm$ 7.3 days CG: 10.6 $\pm$ 6.2 days Intervention onset to follow-up 5 days (intervention ended)	ABMS2
Solopova et al. (2011) / Robot + NMES*	Inclusion criteria First acute stroke; stable haemodynamic; no significant lower limb contractures; orthopaedic or cardiovascular impairments; MAS < 2 Exclusion criteria Cardiac arrhythmia; thrombophlebitis; significant perceptual, cognitive or communication impairments; diabetes; contraindication for electrical stimulation	Sample size (IG / CG) 32 / 29 Age 64 $\pm$ 18 Male / female IG: 15 / 17 CG: 18 / 11	Ischemic / haemorrhagic IG: 27 / 5 CG: 26 / 3 Plegic side (left / right) IG: 22 / 10 CG: 20 / 9	Stroke onset IG: 8.2 $\pm$ 4.3 days CG: 9.3 $\pm$ 4.5 days Intervention onset to follow-up 2 weeks (intervention ended)	FMS-LE
Tangmanee et al. (2021) / Robot	Inclusion criteria Acute ischemic stroke without any recurrent stroke; MMSE score > 22; 5 < NIHSS < 15; Brunstrom Stage of lower extremity > 1; patient or relatives can consent to study Exclusion criteria Significant communication defect; limb weakness not caused by stroke; heart disease; lung disease; joint deformity; joint inflammation; visual scale in NIHSS = 3; sensory scale in NIHSS = 2	Sample size (IG / CG) 10 / 10 Age IG: 53.8 $\pm$ 6.14 CG: 59.2 $\pm$ 2.28 Male / female IG: 6 / 4 CG: 7 / 3	Ischemic / haemorrhagic IG: 10 / 0 CG: 10 / 0 Paretic side (left / right) IG: 8 / 2 CG: 9 / 1	Stroke onset IG: 3.9 $\pm$ 1.38 days CG: 4.1 $\pm$ 1.28 days Intervention onset to follow-up 2 weeks 4 weeks 8 weeks 12 weeks (intervention ended)	FMS-LE

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Toscano et al. (2019) / Focal muscle vibration	Inclusion criteria First stroke; diagnosis via MRI or CT; motor deficit of upper or lower limb; ability to perform minimal isometric voluntary contraction of affected limb Exclusion criteria Transient ischemic attack; rapidly improving stroke; cerebral venous thrombosis; aphasia, neglect or apraxia; drugs active at central nervous system level	Sample size (IG / CG) 10 / 12 Age IG: 64.7 $\pm$ 17.24 CG: 69.5 $\pm$ 7.3 Male / female IG: 8 / 2 CG: 6 / 6	Ischemic / haemorrhagic / both IG: 4 / 4 / 2 CG: 8 / 2 / 2 Stroke side (left / right) IG: 4 / 6 CG: 8 / 4	Stroke onset < 72 hours Intervention onset to follow-up 4 days (intervention ended)	NA
(van Bloemendaal et al. 2021) / NMES	Inclusion criteria Unilateral stroke; indication for gait training; able to walk with or without assistance from one physiotherapist; range of motion on passive ankle dorsiflexion ≥ 0° with full knee extension Exclusion criteria Subarachnoid haemorrhage or cerebellar or brainstem stroke; MAS ≥ 3; comorbidities that might interfere with gait; severe cognitive problems or aphasia that might interfere with the ability to comprehend instructions; conditions that might cause inability to comply with study protocol; demand-type cardiac pacemaker, defibrillator, or electrical implant; metallic implant at paretic leg; cancerous lesion at paretic leg	Sample size (CG / IG) 19 / 18 Age IG: 57 $\pm$ 8.7 CG: 58.7 $\pm$ 10.2 Male / female IG: 15 / 4 CG: 14 / 4	Ischemic / haemorrhagic IG: 16 / 3 CG: 15 / 3 Hemisphere lesion (left / right) IG: 5 / 14 CG: 9 / 9	Stroke onset < 31 days Intervention onset to follow-up 6 weeks 10 weeks (intervention ended) 3 months	NA
(Wu et al. 2020) / Cycling	Inclusion criteria Acute ischemic stroke; diagnosis by CT or MRI; stable vital signs; NIHSS item VI ≥ 1; no contraindication to mobilization within 48 hours post-stroke Exclusion criteria Premorbid mRS > 3; lower limb fracture that prevented mobilization; intravenous thrombolysis or arterial thrombectomy before admission; other progressive neurological or serious cardiovascular diseases; severe cognitive, visual, hearing impairment or aphasia	Sample size (CG / IG) 16 / 15 Age IG: 61.06 $\pm$ 10.31 CG: 62.67 $\pm$ 10.57 Male / female IG: 12 / 4 CG: 11 / 5	Ischemic / haemorrhagic IG: 16 / 0 CG: 15 / 0 Side (left / right IG: 9 / 7 CG: 5 / 10	Stroke onset 72 hours Intervention onset to follow-up 2 weeks (intervention ended) 4 weeks 3 months	FMS-LE BBS

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Yen et al. (2019) / NMES TENS	Inclusion criteria First stroke; 5 ≤ NIHSS ≤ 20; ADLs independent before stroke; unilateral hemiparesis lesion; diagnosis via MRI or CT; cortical, subcortical infarction or haemorrhage without operation; stable vital signs; no nervous system dysfunction; no inflammation or pathological change in joints Exclusion criteria Other medical condition affecting walking performance; insufficient comprehension or collaboration; contraindications of using electric stimulation; severe sensory deficit; allergies	Sample size, IG (TENS) / IG (NMES) / CG 13 / 13 / 14 Age IG (TENS): 58.38 ± 13.49 IG (NMES): 61.62 ± 9.31 CG: 61.42 ± 12.61 Male / female IG (TENS): 7 / 6 IG (NMES): 7 / 6 CG: 9 / 5	Ischemic / haemorrhagic IG (TENS): 7 / 6 IG (NMES): 6 / 7 CG: 6 / 8	Stroke onset IG (TENS): 1.54 ± 0.78 days IG (NMES): 1.38 ± 0.51 days CG: 1.36 ± 0.50 days Intervention onset to follow-up 2 weeks (intervention ended) 4 weeks	PASS
Zakharov et al. (2020b) / VR	Inclusion criteria Confirm the focus of ischemic stroke of supratentorial localization according to CT; motor disorders in the lower extremities in the form of a central paresis (MRCS < 3) Exclusion criteria MoCA < 24; concomitant neurological diseases that cause reduced muscle strength or increased muscle tone in the lower extremities or rigidity; late stages of arthritis or significant limitation of passive movements in joints due to other reasons; use of drugs that affect muscle tone; Snellen Eye Chart > 20 / 160	Sample size (IG / CG) 17 / 16 Age Mean (min - max) IG: 64 (41 - 77) CG: 65 (40 - 79) Male / female IG: 10 / 7 CG: 9 / 7	Ischemic / haemorrhagic IG: 17 / 0 CG: 16 / 0 Middle cerebral artery side (left / right) IG: 9 / 8 CG: 12 / 4	Stroke onset < 14 days Intervention onset to follow-up 10 days (intervention ended)	RMI

Study / Intervention	Inclusion and exclusion criteria	Demographic information	Stroke information	Temporal information	Outcome score included in network meta-analysis
Zakharov, et al. (2020a) / VR	Inclusion criteria First acute ischemic cerebral circulation disorder in the carotid pool; confirmed focus of ischemic stroke of supratentorial localization according to CT; motor disorders in the lower extremities in the form of a central paresis (MRCS < 4); can comply with the protocol of study; signed written informed consent Exclusion criteria MoCA < 11; neurological diseases that cause a decrease in muscle strength or increase in muscle tone in the lower extremities; significant limitation of passive movements in the lower extremities; amputation; medical condition that might affect interpretation of results, conduct of study or patient safety; abuse of alcohol or narcotics; treatment with botulinum toxin; recent surgery; severity which does not allow full rehabilitation intervention; Snellen Eye Chart > 20 / 30	Sample size (IG / CG) 35 / 27 Age IG: 68.1 $\pm$ 1.6 CG: 65.4 $\pm$ 1.9 Male / female IG: 18 / 17 CG: 14 / 13	Ischemic / haemorrhagic IG: 35 / 0 CG: 27 / 0 Stroke pool localization (left / right) IG: 22 / 13 CG: 20 / 7	Stroke onset < 6 days Intervention onset to follow-up 3 weeks (intervention ended)	FMS-LE RMI BBS

Abbreviations: IG=intervention group; CG=control group which carried out conventional rehabilitation; NMES=neuromuscular electrical stimulation; rTMS= repetitive transcranial magnetic stimulation; ta-VNS=transcutaneous auricular vagus nerve stimulation; TENS=transcutaneous electrical nerve stimulation; tDCS= transcranial direct current stimulation; VR=virtual reality; FMS-LE=Fugl-Meyer Scale for lower extremity; MRCS=Medical Research Council Scale; HSS=Hemispheric Stroke Scale; FAC=Functional ambulation category; FIM-M=Functional Independence Measure for mobility; RMI=Rivermead Mobility Index; ICUMS=ICU Mobility Scale; ABMS2=Revised Version of the Ability for Basic Movement Scale; BBS=Berg Balance Scale; PASS=Postural Assessment Scale for Stroke; BBA=Brunnel Balance Assessment; FMS-B=Fugl-Meyer Scale for balance, 10MWT=10 Meter Walk Test; CT=computerized tomography; MRI=magnetic resonance imaging; MAS= Modified Ashworth Scale; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; MMSE=Mini Mental State Examination; GCS=Glasgow Coma Scale; ECG=electrocardiography; MoCA=Montreal scale assessment of cognitive function.

* Two or more interventions were implemented by an IG at the same time

Notes: Information of subjects involved in previous study analyses were always shown under the demographic, stroke, and temporal information columns. The word "baseline" indicate information of subjects enrolled at baseline before dropout occur are displayed due to the incomplete or absence of analysed subject information. The phrase "stroke onset" refers to the time from stroke onset until intervention onset. The phrase "intervention onset to follow-up" refered to the time from start of intervention to follow-up. Data could be recorded in form of "mean $\pm$ standard deviation" or "median (first quartile – third quartile)".

TABLE 7: Summarised interventions conducted in studies that were included in systematic review

Study	Control group (CG)	Intervention group (IG)
Bornheim et al. (2020)	· Sham tDCS. · Intensive physiotherapy and occupational therapy for functional improvement (5 days per week, 120 mins per day).	· Anodal tDCS. · Physiotherapy and occupational therapy similar as that of CG.
Brunelli et al. (2019)	· Trunk stabilization, weight transfer to the paretic leg and conventional assisted overground walking (with or without parallel bars) with task-specific walking orientated leg exercises (5 days per week, 40 mins per day). · Standard physiotherapy focussing on facilitation of movements on the paretic side and upper-limb exercises, and exercises for improving balance, standing, sitting, and transferring tasks (5 days per week, 40 mins per day).	· Body weight supported gait training with LiteGait (5 days per week, 40 mins per day). · Standard physiotherapy similar as that of CG.
Chang et al. (2012)	· Conventional physical therapy consisting of Bobath techniques, sitting and standing balance training, active transfer, sit-to-stand training, strengthening exercise, functional gait training with device, and dynamic standing balance training (5 days per week, 100 mins per day).	· Gait training using Lokomat (5 days per week, 40 mins per day). · Conventional physical therapy similar as that of CG (5 days per week, 60 mins per day).
Chang et al. (2015)	· Sham tDCS where current was only delivered for the initial 15 s (5 days per week). · Movement therapy to improve postural control, motor function, and movement patterns in affected extremities (6 days per week, 60 - 150 mins per day).	· Anodal tDCS delivered while patient was receiving conventional physical therapy (5 days per week). · Movement therapy similar as that of CG.
Chen et al. (2011)	· Physiotherapy and occupational therapy (5 days per week, 40 mins per day). · Discussion session (at least 3 sessions per week, 20 mins per session).	· Thermal stimulation therapy where patients performed passive or active movement away from the thermal stimulus presented to the paretic leg (5 days per week, 48 mins per day). · Physical and occupational therapy similar to that of CG.
da Rosa Pinheiro et al. (2021)	· Conventional physiotherapy consisting of kinesiotherapy with stretch and strength exercise, trunk control training, walking with and without assistance, and breathing exercise (2 sessions per day, 20 mins per session).	· Aerobic cycling training with electrical cycle ergometer and visual feedback regarding strength symmetry (1 session per day, 20 mins per session). · Conventional physiotherapy similar to that carried out in CG (1 session per day, 20 mins per session).
Forrester et al. (2014)	· Stretching session where paretic ankle was manually moved in plantarflexion, dorsiflexion, invert or evert direction (5 days per week, 60 mins per day). · Usual physical therapy.	· Seated anklebot training conducted with volitional ankle movements visually guided by moving targets (5 days per week, 60 mins per day). · Usual physical therapy similar as that of CG.

Galvin et al. (2011)	· Routine physiotherapy delivered by physiotherapy staff.	· Family-mediated exercise program at bedside with the assistance of trained family member (35 mins per day). · Routine physiotherapy similar as that of CG.
Guan et al. (2017)	· Sham rTMS with coil perpendicular to the scalp daily, where other configurations were same as that of IG. · Standardized therapies including antiplatelet drugs and motor rehabilitative training.	· rTMS with coil tangential to the scalp, involving 50 trains of 20 pulses with 2-second intertrain interval daily. · Standardized therapies similar as that of CG.
Karthikbabu et al. (2011)	· Trunk exercise on stable plinth consisting of task-specific movements of trunk in the supine and sitting positions (4 days per week, 60 mins per day). · Regular acute-phase physiotherapy treatment such as tone facilitation and a range of movement exercises for hemiplegic side.	· Trunk exercise similar as that of CG on unstable physio ball (4 days per week, 60 mins per day). · Regular physiotherapy similar as that of CG.
Katz-Leurer et al. (2003)	· Regular therapy including physical therapy, occupational therapy, and speech therapy (5 days per week).	· Trained on cycle ergometer (3 - 5 days per week, 10 - 30 mins per day). · Regular therapy similar as that of CG.
Katz-Leurer et al. (2006)	· Regular therapy including physical therapy based on Bobath approach, occupational therapy, and speech therapy (5 days per week).	· Trained on cycle ergometer (5 days per week, 10 - 30 mins per day). · Regular therapy similar as that of CG (5 days per week).
Khedr et al. (2010)	· Sham stimulation of the same site as that of IG daily. · Conventional therapy, medical treatment, and rehabilitation including passive limb movement beginning on the second day, modified to a more active one as a patient improved at the end of first week.	· rTMS over the hand area of motor cortex (3 Hz or 10 Hz) of the affected hemisphere daily. · Conventional therapy similar as that of CG.
Li et al. (2022)	· Sham ta-VNS with no current (5 days per week, 20 mins per day). · Immediately after ta-VNS, conventional rehabilitation including postural control, neuromuscular facilitation, and sensory integration exercises is carried out (5 days per week, 30 mins per day).	· ta-VNS (5 days per week, 20 mins per day). · Conventional rehabilitation similar as that of CG.
Liang et al. (2012)	· Physical and occupational therapy (5 days per week, 40 mins per day). · Discussion session (3 sessions per week, 20 mins per session).	· Thermal stimulation therapy where patients perform passive or active movement away from the thermal stimulus presented to the paretic leg (5 days per week, 40 mins per day). · Physical and occupational therapy similar to that of CG.
Lin et al. (2020)	· Conventional therapy consisting of standardized stroke care and early rehabilitation such as postural training, facilitation techniques, stretching, and strengthening exercise (5 days per week, 60 mins per day).	· Supervised virtual reality training using Kinect sensor (5 days per week, 2 sessions per day, 15 mins per session). · Conventional therapy similar to that of CG.

Liu et al. (2014)	· Conventional occupational therapy where therapist considered patient limitations and designed adapted task strategies (5 days per week, 60 mins per day). · Physical therapy with mobilization and walking exercise (60 mins per day).	· Occupational therapy where therapists guided patients to understand own difficulties, improve task performance, and reflect on performance success (5 days per week, 60 mins per day). · Physical therapy similar as that of CG.
Lura et al. (2019)	· Conventional gait training with LiteGait system consisting of overground walking with assistive device, gait belt, manual, and verbal cueing provided by therapist. · Regular physical therapy evaluation and treatment.	· Gait training with the LiteGait system (overhead suspension system with a harness) performed on a standard treadmill while therapist provided manual and verbal cueing. · Regular physical therapy similar as CG.
Mohan et al. (2013)	· Sham mirror therapy where non-reflecting surface was kept facing the non-paretic limb (6 days per week, 30 mins per day). · Conventional rehabilitation consisting of neurodevelopmental facilitation techniques, sensory motor re-education, active exercises, mobility training, balance, and gait training (6 days per week, 60 mins per day).	· Mirror therapy program focusing on performance of functional movement synergies using non-paretic hip, knee and ankle joints (6 days per week, 30 mins per day). · Conventional rehabilitation similar as that of CG.
Pagilla et al. (2019)	· NMES on gluteus maximus, gluteus medius, quadriceps, hamstring, tibialis anterior, and gastrocnemius (30 mins per day). · Eclectic poststroke rehabilitation training program including Rood, Brunnstrom, and Bobath, and motor learning approaches, which primarily aimed at modifying muscle tone, facilitating the postural control mechanism, and encouraging static and dynamic balance activities, bed mobility, and gait recovery (60 mins per day).	· Mirror therapy where a mounted wooden mirror was placed between subject lower limbs, with the reflecting side facing the unaffected side and mild inclination toward the effected extremity (30 mins per day). · Eclectic poststroke rehabilitation similar as that of CG.
Park et al. (2021)	· Additional standard physical therapy in pre-ambulatory phase for gait training (7 days per week, 30 mins per day). · Physical therapy (7 days per week, 60 mins per day).	· Additional training using ankle-knee-hip interlimb coordinated humanoid robot with virtual reality or augmented reality games (7 days per week, 30 mins per day). · Physical therapy similar as that of CG.
Rao et al. (2013)	· Physical therapy consisting of strengthening exercises, balance training (3 more sessions compared to IG), and functional mobility training (6 days per week, 60 mins on weekdays, 30 mins on Saturday). · Occupational therapy. · Speech therapy. · Neuropsychology therapy. · Medical services.	· Weight supported balance therapy using force platform and visual feedback. · Physical, occupational, speech, neuropsychology therapy, and medical services similar as that in CG.
Rose et al. (2018)	· Standing balance training consisting of quiet stance, dual-task with upper extremity manipulation, and reaching for targets both within and outside the patient's base of support (5 days per week, 30 mins per day). · Standard rehabilitation including physical, occupational, and speech therapy.	· Backward walking over ground without use of assistive devices (5 days per week, 30 mins per day). · Standard rehabilitation similar to that of CG.

Sasaki et al. (2017)	· Sham rTMS (2 sessions per day). · Conventional rehabilitation programs, such as range-of-motion exercise, muscle exercise, sitting and/or standing training, and gait training (40 - 80 mins per day).	· High frequency rTMS (2 sessions per day). · Conventional rehabilitation program similar as that of CG
Solopova et al. (2011)	· Conventional therapy consisting of stretching, active or passive mobility, and exercises (5 days per week, 30 mins per day).	· FES-therapy combined with assistive leg movement and progressive limb loading using motorized tilt table with integrated robotic stepping technology. · Conventional therapy similar as that of CG.
Tangmanee et al. (2021)	· Exercise consisting of hip flexion-extension, knee flexion-extension, ankle dorsiflexion-plantarflexion and hip bridging (5 days per week, 30 mins per day). · Standard rehabilitation (5 days per week, 30 mins per day).	· Exercise with DIY robotic device (5 days per week, 30 mins per day). · Standard rehabilitation similar as that of CG group.
Toscano et al. (2019)	· Sham repetitive focal muscle vibration with setup similar as that of IG (daily, 10 mins per limb). · Physio kinesiotherapy including passive or active movements, mobilization, and proprioceptive neuromuscular facilitation of the affected limb (daily, 60 mins per day).	· Repetitive focal muscle vibration where transducer is placed perpendicularly to muscle belly (daily, 10 mins per limb). · Physio kinesiotherapy similar as that of CG.
van Bloemendaal et al. (2021)	· Individualized conventional gait training including overground and treadmill walking (5 days per week, 30 mins per day). · Fitness training, sports, and hydrotherapy given based on needs and interest.	· Individualized conventional gait training assisted by multichannel functional electrical stimulation (5 days per week, 30 mins per day). · Fitness training, sports, and hydrotherapy similar as that of CG.
Wu et al. (2020)	· Conventional physiotherapy consisting of positioning, range of motion exercises, and bed mobilization (at least 5 days per week, 20 - 30 mins per day).	· Recumbent cycle ergometer training and early sitting and standing practicing (at least 5 days per week, 30 mins per day).
Yen et al. (2019)	· Standard early rehabilitation consisting of functional training activities, neurodevelopment facilitation techniques, active range of motion exercises, and pelvic bridging exercises (5 days per week, 30 mins per day).	· TENS or NMES at affected tibialis anterior and quadriceps muscles during standard early rehabilitation similar as that of CG (5 days per week, 30 mins per day).
Zakharov et al. (2020b)	· Rehabilitation care according to the standards of medical services.	· Rehabilitation using VR where patients were instructed to walk on a horizontal surface with proprioceptive confirmation of step (15 mins per session). · Rehabilitative care similar to that of CG.
Zakharov et al. (2020a)	· Standard rehabilitation based on functional state of the patient.	· Immersion in a life-like VR environment and walking imitation with visual and tactile biofeedback based on physical impact (10 mins per session). · Standard rehabilitation similar to that of CG.

Abbreviation: CG=control group; IG=intervention group; tDCS=transcranial direct current stimulation; NMES=neuromuscular electrical stimulation; rTMS=repetitive transcranial magnetic stimulation; ta-VNS=transcutaneous auricular vagus nerve stimulation; FES=functional electrical stimulation; DIY=do it yourself; TENS=transcutaneous electrical nerve stimulation; VR=virtual reality interventions i.e. the combination of the robot, treadmill and virtual reality (VR), VR only, force platform, family-mediated exercise, the combination of robot and treadmill, as well as robot did not show a significant effect. The P-score for each intervention was arranged in ascending order, indicating that the combination of robot, treadmill, and VR was least effective while thermal stimulation was most effective in improving lower extremity motor function. The I^2 score was high at 72.95% while large values

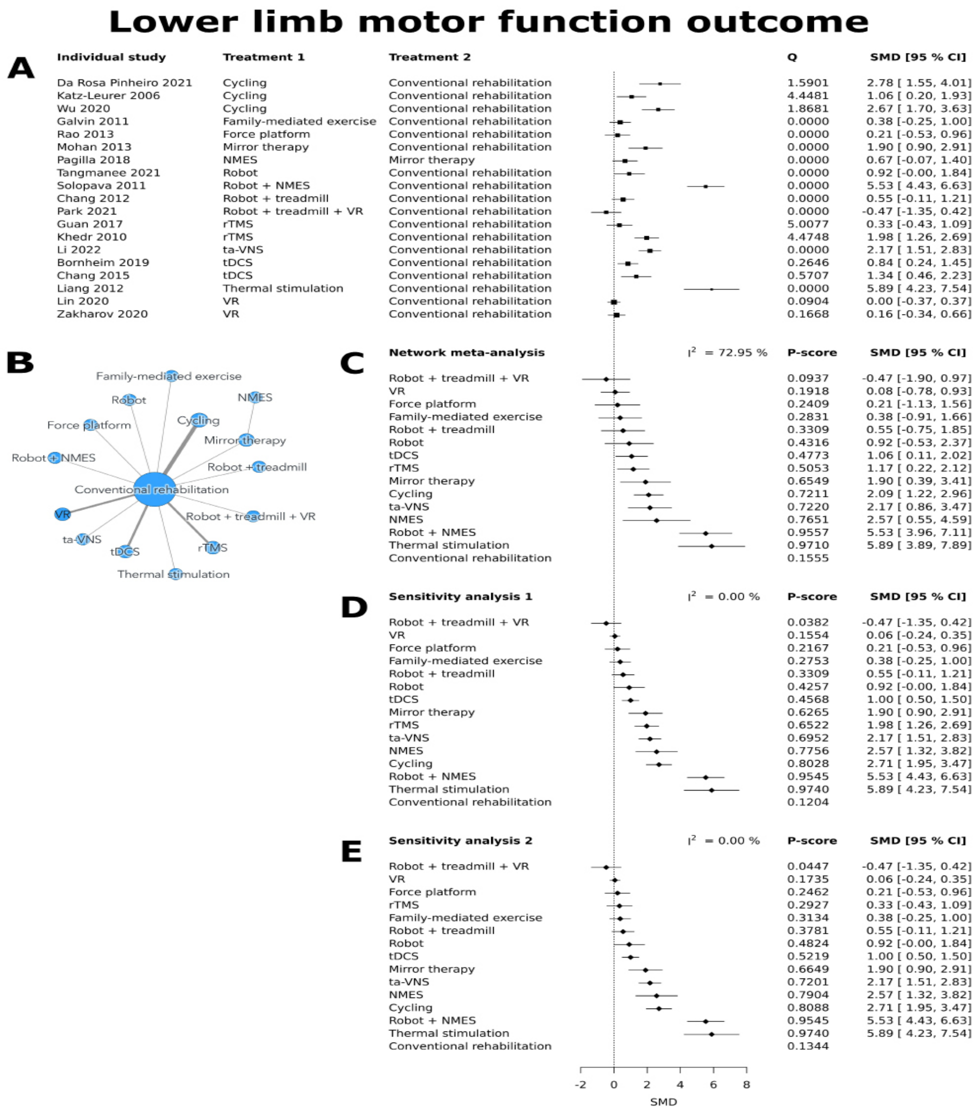

FIGURE 2: Forest plot of (A) individual studies, (B) network graph, (C) network meta-analysis of lower extremity motor function outcome category, (D) sensitivity analysis by removing the works (Guan et al. 2017; Katz-Leurer et al. 2006), and (E) sensitivity analysis by removing the studies (Katz-Leurer et al. 2006; Khedr et al. 2010). For (A), positive SMD favors Treatment 1 and vice-versa. For (C), (D), and (E), positive SMD favors intervention instead of conventional rehabilitation and vice-versa

of Cochrane Q were spotted in studies that investigated cycling (Katz-Leurer et al. 2006) and rTMS (Guan et al. 2017; Khedr et al. 2010). From the sensitivity analysis (Figures 2D & E), the ranking of cycling and rTMS had changed. However, rTMS did not appear as significantly more effective compared to conventional rehabilitation after excluding the work (Khedr et al. 2010) due to high heterogeneity.

A total of 13 studies and 12 interventions were analysed in the network meta-analysis on mobility. The forest plot and network graph were presented in Figure 3. According to Figure 3C, three of the interventions (mirror therapy, cycling, and thermal stimulation) exhibited significant effects in improving mobility compared to conventional rehabilitation, while the other nine interventions did not (treadmill, the combination of robot and treadmill, force platform, robot, VR, overground walking, tDCS, rTMS, and backward walking). Thermal stimulation recorded the highest P-score, thus indicating that it was the most effective intervention in improving mobility. In contrast, the treadmill was the least effective mobility recovery intervention with the lowest value. The I^2 score was low in this analysis and there was no high Cochrane Q value.

The network meta-analysis on the balance outcome category was carried out on 15 studies and 12 interventions (Figure 4). From the

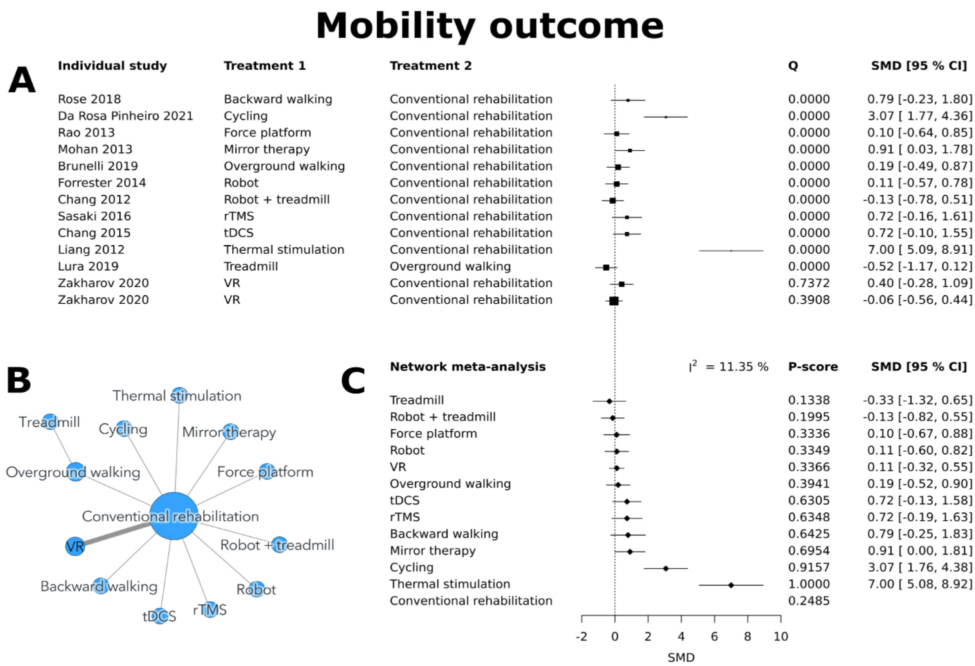

FIGURE 3: Forest plot of (A) individual studies, (B) network graph, and (C) network meta-analysis of mobility category. For (A), positive SMD favors Treatment 1 and vice-versa. For (C), positive SMD favors intervention instead of conventional rehabilitation and vice-versa.

forest plot (Figure 4C), it was observed that the physio ball, transcutaneous electrical nerve stimulation (TENS), cycling, thermal stimulation, and robot enhanced the balance recovery significantly compared to conventional rehabilitation. Seven interventions (force platform, VR, tDCS, mirror therapy, backward walking, family-mediated exercise, and NMES) did not improve balance significantly in comparison with conventional rehabilitation. The robot was the most effective intervention while the force platform was the least effective intervention. A moderate I^2 score was recorded, with a trial on cycling (da Rosa Pinheiro et al. 2021) scored large Cochrane Q values. Following the sensitivity analysis, the ranking of cycling dropped (Figure 4D).

Lastly, five trials and four

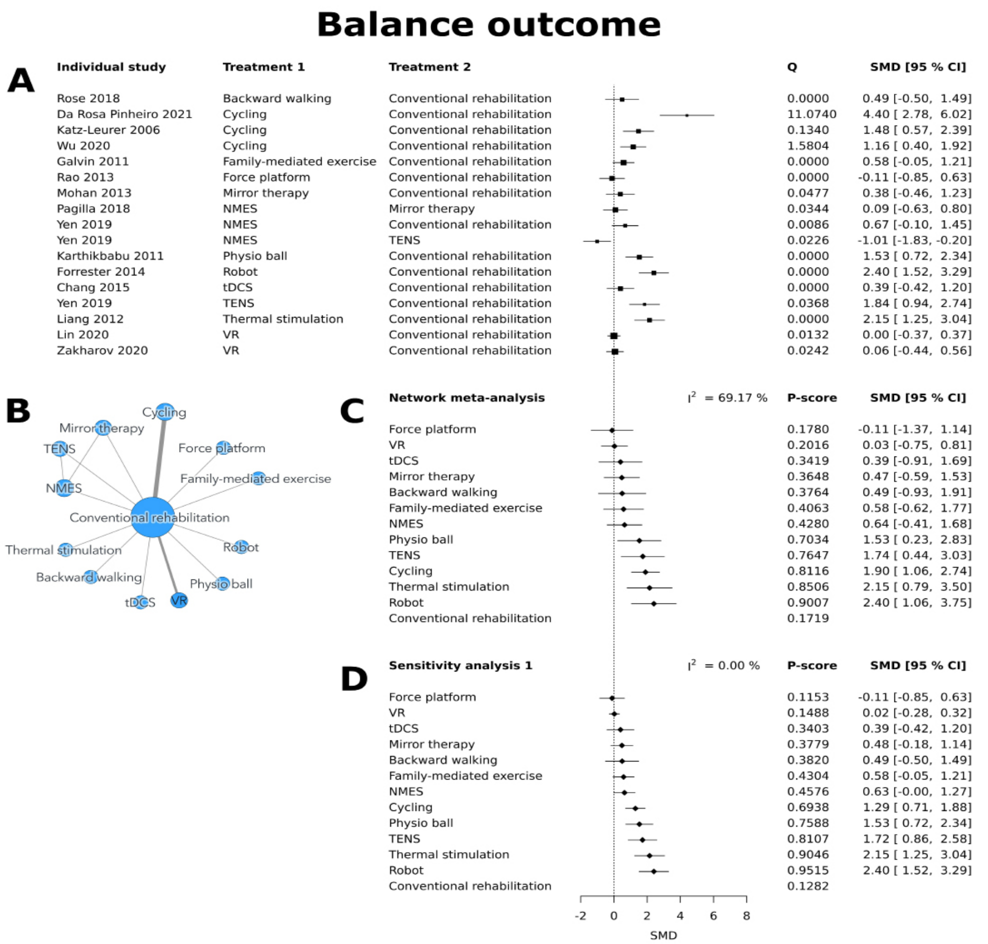

FIGURE 4: Forest plot of (A) individual studies, (B) network graph, (C) network meta-analysis of balance outcome category, and (D) sensitivity analysis by removing the work (da Rosa Pinheiro et al. 2021). For (A), positive SMD favors Treatment 1 and vice-versa. For (C) and (D), positive SMD favors intervention instead of conventional rehabilitation and vice-versa

interventions were analysed in a network meta-analysis for the gait speed outcome category. Figure 5 depicted the corresponding forest plot and network graph. According to Figure 5C, no intervention showed a significant effect in improving gait speed compared to conventional rehabilitation. P-score indicated that the robot was the least effective intervention while the most effective intervention was backward walking. The heterogeneity was moderate with a 62.12% I^2 score. Again, this was due to the trial investigating cycling (da Rosa Pinheiro et al. 2021) that had high Cochrane Q values. In the sensitivity analysis (Figure 5D), backward walking showed a significant effect compared to conventional rehabilitation.

DISCUSSION

In this work, the effectiveness of different interventions in improving lower extremity-related outcomes of stroke patients in comparison with that of conventional rehabilitation was conducted through network meta-analyses. The effectiveness of each intervention was ranked with P-scores. The discussion was conducted based on the result of the network meta-analysis before the implementation of sensitivity analysis to avoid the removal of trials that might introduce bias (Higgins et al. 2019b).

The network meta-analysis on lower extremity motor function revealed that tDCS, rTMS, mirror therapy, cycling, ta-VNS, NMES, the combination between robot and NMES, as well as thermal

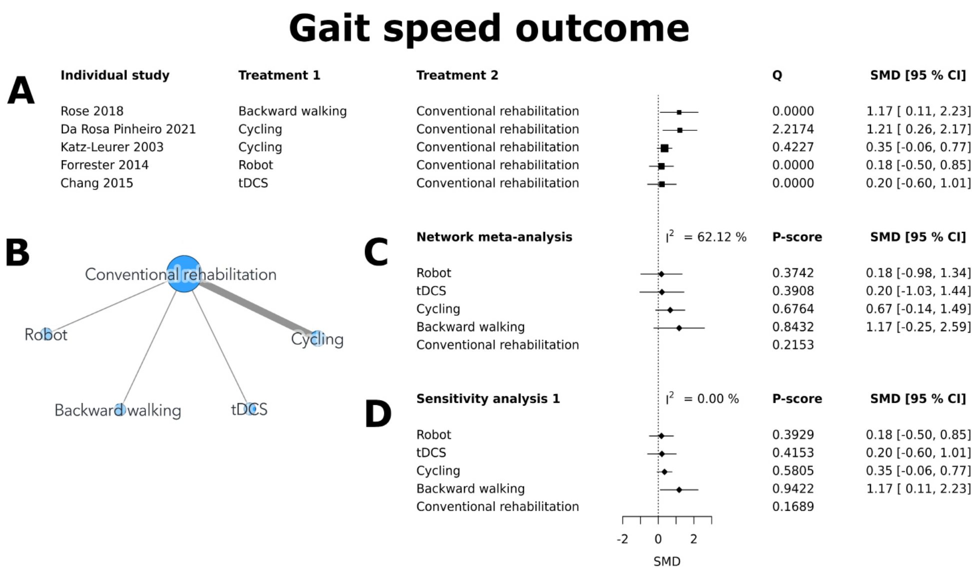

FIGURE 5: Forest plot of (A) individual studies, (B) network graph, (C) network meta-analysis of gait speed outcome category, and (D) sensitivity analysis by removing the study (da Rosa Pinheiro et al. 2021). For (A), positive SMD favors Treatment 1 and vice-versa. For (C) and (D), positive SMD favors intervention instead of conventional rehabilitation and vice-versa

stimulation were significantly more effective compared to conventional rehabilitation. The better performance of tDCS, rTMS, NMES, and mirror therapy was consistent with that reported in previous meta-analyses (Bai et al. 2019; Broderick et al. 2018; Y. Li, J. Fan, et al. 2018b; Y. Li, Q. Wei, et al. 2018; Louie et al. 2019; Sun et al. 2021; Tung et al. 2019). However, other works (Li et al. 2018a; Lin et al. 2019; Wist et al. 2016) presented some contradictory results regarding rTMS and NMES, indicating other underlying factors that might have caused the heterogeneity. It is important to mention that the significant effect of mirror therapy in the reviewed study (Mohan et al. 2013) was not confirmative as the baseline Fugl-Meyer Scale for lower extremities between the intervention and the control group differed significantly. When the change in score from baseline to follow-up was considered, no significant improvement was observed in the Fugl-Meyer Scale of the lower extremity as reported in the reviewed study.

In addition, interventions that involved a robot or treadmill did not significantly improve the lower extremity motor function, except in the case of the combination of robot and NMES. These insignificant effects were in line with the previous meta-analysis results (Hsu et al. 2020; Lin et al. 2019; Schröder et al. 2019). Other previous works (Lee et al. 2019; Zhang et al. 2021) inferred that VR significantly improved lower extremity motor function but this contradicted our finding. One of the possible reasons might be most of the previously published trials recruited patients who were more than one-month post-stroke. In other words, time from stroke onset could have affected the effectiveness of VR in improving lower extremity motor function. However, it was still inconclusive as only two studies investigating VR were included in our review. Other heterogeneity sources such as types of VR and training dosage might have also caused the discrepancy. The effectiveness of force platform, family-mediated exercise, cycling, ta-VNS, and thermal stimulation in improving lower extremity motor function was not supported by any meta-analysis.

In this review, the heterogeneity in network meta-analysis on lower limb motor function was likely caused by studies on cycling (Katz-Leurer et al. 2006) and rTMS (Guan et al. 2017; Khedr et al. 2010). The study on the cycling effect (Katz-Leurer et al. 2006) recruited patients within 31 days from stroke onset while the other similar works (da Rosa Pinheiro et al. 2021; Wu et al. 2020) enrolled patients within 72 hours after stroke occurrence. Therefore, the difference in the range of time from stroke onset may have caused the heterogeneity. However, the observation might also indicate that very early cycling intervention could lead to better improvement in lower limb motor function recovery. Apart from that, in studies related to rTMS (Guan et al. 2017; Khedr et al. 2010), gender ratio, lesion side ratio, outcome score, and the frequency of rTMS were different, thus possibly attributing to the differences.

By examining the network meta-analysis results, the characteristics of the interventions which achieved high effectiveness rankings could be identified. The interventions which stimulated the effector muscles such as thermal stimulation and NMES recorded the highest effect size in improving lower limb motor function as compared to counterparts which stimulated brain regions or nerves not located on muscles such as rTMS, tDCS, and ta-VNS. This may indicate the higher effectiveness of recovery mechanisms which targeted spinal, cortical plasticity, and corticomotor pathway excitation via effector muscle stimulation (Bao et al. 2020) in comparison with that addressing interhemispheric inhibition (Guan et al. 2017), cerebral blood flow (Bornheim et al. 2020), neural regeneration (Li et al. 2022), cortical plasticity (Chang et al. 2015), and excitability (Khedr et al. 2010) through brain region stimulation during early rehabilitation. Cycling and robotic interventions both encouraged the patients to perform repetitive movements with the applications of machines. However, cycling exhibited significant effects as compared to conventional rehabilitation but not robotic interventions. Particularly, the robotic interventions involved in the network meta-analysis (Chang et al. 2012; Park et al. 2021) mostly constrained the gait movements to idealised patterns. The reduced volitional elements in robotic interventions as compared to cycling may have resulted in a smaller effect (Forrester et al. 2014). On the other hand, even though mirror therapy and immersive VR applied phantom or virtual limb as visual feedback to enhance the neural plasticity (Dohle et al. 2009; Zakharov et al. 2020a) and cortical excitation (Michielsen et al. 2011; Yavuzer et al. 2008), mirror therapy was more effective than VR. The effectiveness might be due to the realisticness, immersiveness, and the way the visual feedback was presented. The phantom limb was moved in mirror therapy although the affected limb was not, while in immersive VR, the virtual limb was moved according to the motion of affected counterpart.

Next, mirror therapy, cycling and thermal stimulation were significantly more effective than conventional rehabilitation in improving mobility. The significant effect of mirror therapy was similar to the finding reported in a previous meta-analysis (Louie et al. 2019). However, other published works contradicted the significant effect of mirror therapy in mobility recovery (Broderick et al. 2018; Li et al. 2018). Most of the reviewed studies in the conflicting works recruited stroke patients who were more than one-month post-stroke onset. Therefore, mirror therapy might be more effective during the early phase of stroke rehabilitation. Nevertheless, other unrecognised factors could have also contributed to the heterogeneity apart from the onset of stroke. Treadmill, the combination of robot and treadmill, robot, tDCS, as well as rTMS did not exhibit significant effects in comparison with conventional rehabilitation. These results were consistent with some of the previous meta-analyses (Hsu et al. 2020; Schröder et al. 2019; Tung et al. 2019; Vaz et al. 2019), while inconsistent with others (Li et al. 2018b; Moucheboeuf et al. 2020). Furthermore, the insignificant effect of VR in enhancing mobility was not in line with a previous meta-analysis (Zhang et al. 2021). Currently, no meta-analysis reported the effectiveness of force platforms, overground walking, backward walking, cycling, and thermal stimulation in improving mobility.

By comparing Figure 2C and 3C, it could be noticed that the effectiveness rankings of thermal stimulation, cycling, mirror therapy, rTMS, and tDCS were in same order, while VR, force plateform, robotic, and treadmill-based interventions achieved similarily low rankings. The results were in accordance with the intuition that good lower extremity motor function was the key to mobility recovery. Backward walking appeared to score a higher effectiveness ranking as compared to other forward walking-based interventions such as overground walking and treadmill-based interventions. There have been studies which reported superior effect of backward walking in comparison with that of forward walking due to the greater postural demands (Katsavelis et al. 2010), higher cerebral activations (Godde & Voelcker-Rehage 2010), reweighting of sensory feedback (Kurz et al. 2012), and increased muscle activations (Thorstensson 1986; Winter et al. 1989). In this network meta-analysis, the higher effect size of backward walking was again observed in the early rehabilitation even though machines like hoists (Brunelli et al. 2019) and treadmills (Chang et al. 2012; Lura et al. 2019) had been used to facilitate the forward walking-based interventions.

In the third outcome category of balance recovery, the network meta-analysis indicated that physio ball, TENS, cycling, thermal stimulation, and robot achieved significant effects compared to conventional rehabilitation. The results of cycling and robot were consistent with that of the previous meta-analyses (Moucheboeuf et al. 2020; Postol et al. 2019; Shariat et al. 2019; Zheng et al. 2019). However, another two meta-analyses on cycling (Da Campo et al. 2021) and robot (Hsu et al. 2020) reported insignificant effects of the interventions. The meta-analysis on cycling recruited stroke patients with times from stroke onset of more than one month. Nonetheless, the heterogeneity could also be due to other factors. Apart from that, force platform, tDCS, mirror therapy, and NMES did not show a significant effect in enhancing the balance outcome. Some previous meta-analyses (Barclay-Goddard et al. 2004; Broderick et al. 2018; Busk et al. 2020; Li et al. 2018b; Louie et al. 2019; Wist et al. 2016) results were consistent with our findings, while one (Li et al. 2018) was not. Again, five previous meta-analyses (Gibbons et al. 2016; Iruthayarajah et al. 2017; Lee et al. 2019; Wu et al. 2021; Zhang et al. 2021) reported that VR was significantly better than conventional rehabilitation in improving balance, in contrast to our results. The discrepancy could be partly due to the reviewed study on VR (Zakharov et al. 2020a) in which the SMD (± standard error) between the pre-intervention Berg Balance Scale of experimental and control groups was large (3.0756 ± 0.3767). When the change in Berg Balance Scale from baseline to follow-up was considered, a significant effect was observed in the reviewed study. As for backward walking, the insignificant effect reported in our work was the opposite of a previous meta-analysis (Chen et al. 2020). Lastly, there was a lack of evidence to support the results of family-mediated exercise, physio ball, TENS, and thermal stimulation as no previous meta-analysis was available for comparison.

In the network meta-analysis on balance, heterogeneity was observed between studies that investigated the effect of cycling (da Rosa Pinheiro et al. 2021; Katz-Leurer et al. 2006; Wu et al. 2020). The possible source of heterogeneity could be the short period between the start of intervention and outcome assessment in the work (da Rosa Pinheiro et al. 2021) (five days) as compared to that of Katz-Leurer et al. (2006) (three weeks) and Wu et al. (2020) (two weeks). The results showed that the balance recovery could be sped up in the first few days after stroke onset via cycling intervention. However, it is possible that the facilitation effect contributed by cycling intervention on balance recovery may diminish over time.

The effectiveness rankings of certain interventions in network meta-analysis of balance were different from that of lower extremity motor function. The discrepancy indicated that balance recovery was not only affected by lower limb strength, but also occurred through other mechanisms. The high effectiveness ranking of the particular robotic intervention (Forrester et al. 2014) may be due to the strategy to improve ankle range of motion, which played an important role in balance control strategies (Ha et al. 2020). It could be seen that interventions which targeted somatosensory system such as thermal stimulation and TENS achieved a better effect than other types of stimulating interventions including NMES and tDCS. Taking TENS as example, the proprioceptive system-stimulating electricity caused depolarisation in receptors, making neurons to be more likely to fire (Gravelle et al. 2002). With improved proprioceptive system, the balancing ability could be ameliorated (Yen et al. 2019). It was rather unexpected to observe that from the interventions which demanded good balancing ability such as physio ball, backward walking, and force platform, only physio ball exhibited significant effect in comparison with conventional rehabilitation. The results potentially demonstrated the counterintuitive idea that the balance demanding tasks may not be that vital in enhancing balance outcome. Instead, considering physio ball and cycling, it turned out that both interventions involved the trunk muscles (Karthikbabu et al. 2011; Segerström et al. 2011). As the movement control originated from trunk to the distal part of body (Karthikbabu et al. 2011), the recovery of trunk could possibly be correlated to the balance restoration (Verheyden et al. 2006), thereby explaining the effectiveness of the two interventions.

Last but not least, all interventions on gait speed that were included in the network meta-analysis did not exhibit a significant effect in comparison with conventional rehabilitation. For the intervention of robot, tDCS, and cycling, several published meta-analyses (Carpino et al. 2018; Da Campo et al. 2021; Hsu et al. 2020; Li et al. 2018b; Mehrholz et al. 2018; Schröder et al. 2019; Tedla et al. 2019; Vaz et al. 2019) reported similar results while others did not (Busk et al. 2020; Moucheboeuf et al. 2020; Nascimento et al. 2021; Polese et al. 2013; Postol et al. 2019; Robbins et al. 2006; Shariat et al. 2019). For backward walking, a previous meta-analysis (Chen et al. 2020) showed a contradicting result compared to our work. The heterogeneity was also due to the studies that employed cycling as a rehabilitation method (da Rosa Pinheiro et al. 2021; Katz-Leurer et al. 2003). The range of time from stroke onset and the period between the start of intervention and outcome assessment in the study (da Rosa Pinheiro et al. 2021) (within 24 hours, five days) differed greatly from the other (Katz-Leurer et al. 2003) (within 31 days, eight weeks). Therefore, it showed that the effect of cycling in enhancing gait speed may decrease with a longer time from stroke onset.

From the network meta-analysis on gait speed, it could be seen that the only walking-based interventions, backward walking achieved the highest effectiveness ranking. The observation suggested that tasks which involved walking on the ground may be necessary to improve gait speed. Despite the difference between backward and forward walking, previous work pointed out that neural control of both tasks possibly originated from the same neural circuitry (Duysens et al. 1996; Lamb & Yang 2000), which explained the improvement in gait speed via backward walking. The effectiveness ranking of cycling was slightly higher than robotic intervention even though both methods involved repetitive movements. This may be because cycling exhibited locomotor and muscle activation patterns which were more similar to gait as compared to that during the particular robotic intervention (Forrester et al. 2014) that only promoted ankle motions. In fact, gait speed effectiveness ranking of robotic intervention was not confirmatory as other types of robots which could assist the patients to perform normal gait were not involved in this network meta-analysis. Similarly, many other interventions which may improve gait speed were not involved in the analysis because gait speed was not evaluated. The future studies on early rehabilitation effectiveness should take gait speed into consideration.

In short, our review served as a preliminary study to rank the early stroke rehabilitative interventions. We generated a list of interventions that exhibited significant effects compared to conventional rehabilitation. This provided a modest direction on which early intervention to be studied by like-minded researchers in the future. More comprehensive studies are needed to produce confirmative findings of intervention effectiveness and accurate treatment ranking to facilitate a systematic selection of rehabilitative interventions for stroke patients. Apart from that, any results from our review that were not in line with previous meta-analyses are highly indicative of the effect of the time of stroke onset on the intervention's effectiveness. Further studies can be pursued in this direction to clarify the effectiveness of interventions under different recovery phases, especially via subgroup analysis or meta-regression. Notably, we would like to emphasise that the aim of intervention ranking was not to eliminate the interventions with lower rankings. Apart from treatment effectiveness, other factors such as cost, labor, duration, the dosage of intervention to achieve the observable effect, degree of acceptance, safety, contraindication, and effects on mental health should also be investigated in future studies. By taking into consideration all the relevant factors, the intervention with the highest treatment ranking may not be the best option while the intervention with a lower ranking may be preferred.

Our work had several limitations. Firstly, there was a lack of trials that investigated interventions starting within one-month post-stroke. As a result, only one to four studies were included under each intervention category. The heterogeneity ranged from moderate to high in the network meta-analysis of lower extremity motor function, balance, and gait speed. The sensitivity analysis indicated the important effect of heterogeneity that could lead to the change in effectiveness ranking and the presence of a significant effect. A cursory examination of the studies indicated that several parameters were different from other studies under the same intervention category, for example, the time from stroke onset, intervention duration, and rTMS frequency. These parameters may potentially be the sources of heterogeneity. Apart from the heterogeneity within our review, heterogeneity across our work and the previous meta-analyses also manifested due to unknown sources. Subgroup analysis or meta-regression could be conducted to identify sources of heterogeneity. However, the analysis was not feasible in our review as the number of trials was insufficient (Schwarzer et al. 2015). In addition, heterogeneity also existed within the control groups that underwent conventional rehabilitation. The standard rehabilitation procedures established in different rehabilitation centers varied to a certain extent. Besides, the conventional rehabilitation that involved a placebo or sham might have resulted in the placebo effect in the control group. In short, the effectiveness of the different interventions compared to conventional rehabilitation and the effectiveness ranking established in this review were not affirmative due to these limitations.

CONCLUSION

Our network meta-analysis compared the interventions starting within one-month post-stroke for lower extremity recovery in four categories. The three most effective interventions for lower extremity motor function recovery were thermal stimulation, the combination of robot and NMES, as well as NMES. For the recovery of mobility, thermal stimulation, cycling, and mirror therapy were the most effective interventions whereas robot, thermal stimulation, and cycling exhibited the highest effectiveness in improving the balance of stroke patients. For the outcome of gait speed, backward walking, cycling, and tDCS were the most effective interventions.

ACKNOWLEDGEMENT

The authors would like to thank Collaborative Research in Engineering, Science & Technology Center (CREST), School of Mechanical Engineering Universiti Sains Malaysia, and SAS Institute Sdn. Bhd. for their continuous support in this research (304. PMEKANIK.6050419.C121).

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