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Review

Outcomes of bilateral repetitive transcranial magnetic stimulation application after stroke on upper extremity functional status: A systematic review and meta-analysis

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Abstract: Unilateral repetitive Transcranial Magnetic Stimulation (rTMS) is commonly used in the stroke rehabilitation of upper extremity motor recovery. Bilateral rTMS, which combines inhibitory stimulation of the intact hemisphere with excitatory stimulation of the affected hemisphere, may represent a more effective neuromodulation strategy than unilateral protocols. Our aim of this study was to investigate the effects of bilateral rTMS on upper extremity motor function, as assessed by the Fugl-Meyer Upper Extremity Assessment (FMA-UE), in stroke patients. Randomized controlled trials (RCTs) comparing bilateral rTMS to placebo/sham and reporting FMA-UE outcomes in stroke patients were searched in PubMed, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials databases. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool, and certainty of evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). A random-effects model with restricted maximum likelihood estimation and Hartung-Knapp correction was used to combine mean differences (MD) in FMA-UE change scores.

Heterogeneity, sensitivity analyses, and leave-one-out analysis were performed. Six RCTs (n = 207) met the inclusion criteria. Bilateral rTMS resulted in a significantly greater improvement in FMA-UE scores compared to placebo/sham (MD = 14.53, 95% CI: 1.41–27.64, p = 0.036). Heterogeneity was high (I^2 = 98.3%, p < 0.0001). Sensitivity analyses showed that the pooled estimate was minimally affected by the assumed pre-post correlation, while leave-one-out analyses preserved the direction of the effect, although statistical significance was not maintained after exclusion of some individual studies. According to GRADE, the overall certainty of evidence was very low. Bilateral rTMS may improve upper extremity motor recovery after stroke; however, the magnitude and clinical importance of this effect remain uncertain. High heterogeneity, small sample size, and very low certainty of evidence necessitate cautious interpretation. Large-scale RCTs with adequate sample size and standardized bilateral rTMS protocols are needed to confirm these findings and explore potential predictors of treatment response.

Keywords: stroke; bilateral rTMS; upper extremity; Fugl-Meyer Upper Extremity Assessment; meta-analysis; neuromodulation

1. Introduction

Stroke is one of the leading causes of disability in adults worldwide. Furthermore, motor dysfunction negatively impacts patients' daily living activities and quality of life [1,2]. Considering activities involving the upper extremities, such as dressing and eating, cooking, and socializing, upper extremity motor dysfunction is among the most common problems limiting the independence of stroke patients [3–6]. These problems are most challenging in the chronic phase, and a significant proportion of stroke patients experience permanent limitations in arm and hand function in the advanced stages [1]. Therefore, developing effective rehabilitation approaches that support upper extremity motor recovery from the acute phase onward is of great importance [7]. Stroke rehabilitation outcomes can also vary depending on individual patient characteristics, including baseline disability status, lesion characteristics, disease stage, comorbidities, and rehabilitation needs. Multidimensional approaches in populations with severe disabilities have highlighted significant demographic, clinical, socioeconomic, and healthcare-related heterogeneity, emphasizing the importance of personalized care planning and resource allocation [8]. In stroke rehabilitation, such multidimensional patient stratification may be important for identifying rehabilitation needs, optimizing treatment allocation, and interpreting variability in treatment response. This may be important for neuromodulation interventions where treatment effects may differ across patient profiles.

Upper extremity motor recovery is essential for personal care daily activities, and one of the most commonly used measurement tools for its assessment is the Fugl-Meyer Assessment Upper Extremity (FMA-UE) [9]. FMA-UE is considered a measurement tool to determine the severity of motor impairment and is used as a primary outcome measure in stroke rehabilitation studies [9].

Moreover, non-invasive neuromodulation approaches have gained increasing attention in stroke rehabilitation [10]. Among these, repetitive transcranial magnetic stimulation (rTMS) has emerged as a non-invasive neuromodulation technique capable of modulating cortical excitability [10–13]. The effects of rTMS are thought to involve enhancement of motor cortex plasticity through reorganization of interhemispheric inhibitory balance [10]. Another proposed mechanism suggests that rTMS may

modulate abnormal neurotransmitter release following stroke, thereby supporting functional recovery [10]. Researchers have reported that the unaffected hemisphere exerts increased inhibitory effects on the affected hemisphere after stroke, potentially limiting motor recovery [14,15]. Therefore, low-frequency inhibitory stimulation of the unaffected hemisphere and high-frequency excitatory stimulation of the affected hemisphere are commonly applied in rehabilitation protocols [14,16–18]. The potential role of rTMS in post-stroke rehabilitation extends beyond motor recovery. Researchers have also investigated rTMS for post-stroke cognitive impairment, with potential improvements reported, particularly in the areas of attention and executive function. However, significant heterogeneity in stimulation parameters, cortical targets, outcome measures, and study quality limits drawing definitive conclusions [19]. These findings suggest that neuromodulation may influence multiple functional domains after stroke and further support the broader clinical relevance of rTMS within multidisciplinary neurorehabilitation.

Bilateral rTMS protocols have been developed as a more comprehensive approach aiming to increase the excitability of the affected hemisphere and reduce the excessive inhibitory effects of the unaffected hemisphere [20]. It is suggested that this approach may regulate neuroplasticity more effectively compared to unilateral protocols [20,21]. Randomized controlled trials (RCTs) have reported that bilateral rTMS may have positive effects on upper extremity motor function [20–27]. However, the evidence remains inconclusive, with significant heterogeneity regarding stimulation parameters, stroke stage, number of sessions, and stimulation frequency across studies [20–27].

Although several systematic reviews and meta-analyses have examined the effects of rTMS on upper extremity function after stroke, no systematic review and meta-analysis has specifically focused on bilateral rTMS protocols to date [7,21,28]. Furthermore, uncertainties remain regarding the methodological quality of the available evidence and the reliability of the results [7]. Therefore, there is a need for a systematic evaluation of the effects of bilateral rTMS on upper extremity motor function in stroke patients based on current RCTs. Our aim in this systematic review and meta-analysis was to investigate the effects of bilateral rTMS on upper extremity motor function, as assessed by the FMA-UE, in patients with stroke.

2. Materials and methods

The protocol of this study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29] (Supplement 1) and registered in the PROSPERO database (CRD420251230168, https://www.crd.york.ac.uk/prospero/).

2.1. Review question

The review question was prepared using the Participants, Intervention, Comparison, Outcomes, Study Design (PICOS) framework: Does bilateral rTMS improve upper extremity motor function in stroke patients? (P: Stroke patients; I: rTMS interventions; C: Control, sham, or placebo groups; O: Upper extremity motor function assessed using the FMA-UE; S: RCTs evaluating the effects of rTMS on upper extremity motor function in stroke patients).

2.2. Search strategy

The literature search was independently conducted by two researchers (MK and DO) with doctoral degrees using PubMed, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify eligible studies, from the beginning to 21 August 2026. The search strategy is presented in Supplement 2.

2.3. Eligibility criteria

Inclusion criteria were: (1) RCTs published in peer-reviewed scientific journals investigating bilateral rTMS protocols in stroke patients, including a control or placebo group, and reporting results related to the FMA-UE; (2) full-text articles published in English; (3) studies involving only adult participants aged 18 and over; and (4) studies providing sufficient quantitative data for analysis.

Exclusion criteria were: (1) animal studies, conference abstracts, letters to the editor, case reports, case series, case-control studies, retrospective or prospective cohort studies, review articles, and expert opinions; (2) studies involving participants under 18 years of age; (3) studies investigating non-bilateral rTMS protocols in stroke patients; and (4) duplicate publications or studies with insufficient data for data extraction.

2.4. Study selection

Articles obtained from the literature search were reviewed by two independent authors using the Rayyan program (https://www.rayyan.ai/) via their titles and abstracts, employing inclusion and exclusion criteria. The full texts of the remaining articles were evaluated to determine their eligibility for inclusion in the review. In cases of disagreement, a third author was consulted to reach a consensus.

2.5. Risk of bias assessment

The risk of bias (RoB) was assessed by two independent authors (MK and DO) using the Cochrane RoB 2 tool [30]. Discrepancies were resolved through consultation with a third author (VS). Five domains were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain and the overall risk of bias were judged as low risk, some concerns, or high risk. All RoB 2 assessments targeted the effect of assignment to intervention.

2.6. Data extraction

Data extraction was performed to collect patient-intervention-assessment data and conduct quantitative analyses. This included the country of origin of the participants, sample sizes, mean age, sex, side of stroke, duration of rTMS intervention, number of sessions, intervention content, FMA-UE, and other outcome measures evaluated.

2.7. Level of evidence

The level of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system. Five items were used to determine the level of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias [31].

2.8. Data synthesis and analysis

Meta-analysis was conducted using the R Studio Program [32] (Supplement 3). Effect sizes were calculated as mean differences (MD) based on change scores (post-intervention minus pre-intervention values) for bilateral rTMS and sham groups. A random-effects model (REM) was applied using the restricted maximum likelihood (REML) estimator to account for between-study variability. To improve the robustness of statistical inference under conditions of substantial heterogeneity, the Hartung-Knapp (HK) adjustment was used for confidence interval estimation and hypothesis testing [32–34]. Between-study variance was quantified using τ^2. In addition, a 95% prediction interval was calculated to estimate the range of true treatment effects that might be expected in a new study conducted under comparable conditions.

For each intervention arm, directly reported change-score means and SDs were used when available. When change scores were not directly reported, the mean change was calculated as the post-intervention mean minus the pre-intervention mean. When the SD of the change score was not directly reported, it was reconstructed from the reported pre- and post-intervention SDs using the following formula: $SDchange = \sqrt{(SDpre^2 + SDpost^2 - 2r \times SDpre \times SDpost)}$, where r represents the within-person pre-post correlation. A correlation coefficient of r = 0.60 was assumed for the primary analysis. The study-level treatment effect was defined as the difference between the mean change in the bilateral rTMS group and the mean change in the sham group. To assess the influence of the assumed correlation, sensitivity analyses were repeated using r values ranging from 0.30 to 0.90. No median-to-mean conversion or imputation of missing pre- or post-intervention SDs was required for the six studies included in the quantitative analysis. Study-level input data and reproducible R code are provided in the Supplementary Materials. In addition, leave-one-out analyses were performed to assess the influence of individual studies on the overall effect size [35,36]. Given that potential participant overlap between the two studies by Chen et al. [25,26] could not be definitively ruled out based on the published data, additional sensitivity analyses were conducted to assess the impact of this uncertainty on the pooled estimate. These analyses were performed by including only one of the two studies by Chen et al. at a time [25,26].

Between-study heterogeneity was assessed using Cochran's Q test (χ^2 test), the I^2 statistic, and τ^2. Heterogeneity was interpreted according to conventional thresholds as low (25%), moderate (50%), and high (75%) [35,36].

Clinical and protocol heterogeneity was examined descriptively using study-level characteristics, including stroke phase/chronicity, stroke type, lesion location where reported, stimulation frequency and intensity, pulse number, number of sessions, and concomitant rehabilitation. Because only six studies were available and several characteristics were incompletely reported, formal subgroup analyses for these variables were not performed. These factors were instead considered as potential clinical sources of heterogeneity when interpreting the pooled estimate.

3. Results

3.1. Study selection and descriptive characteristics of the studies

A total of six RCTs were included in this systematic review and meta-analysis. The study selection is presented in the PRISMA flowchart diagram (Figure 1), which provides a visual representation [29]. All included studies were published in English. The total number of participants in the meta-analysis was 207.

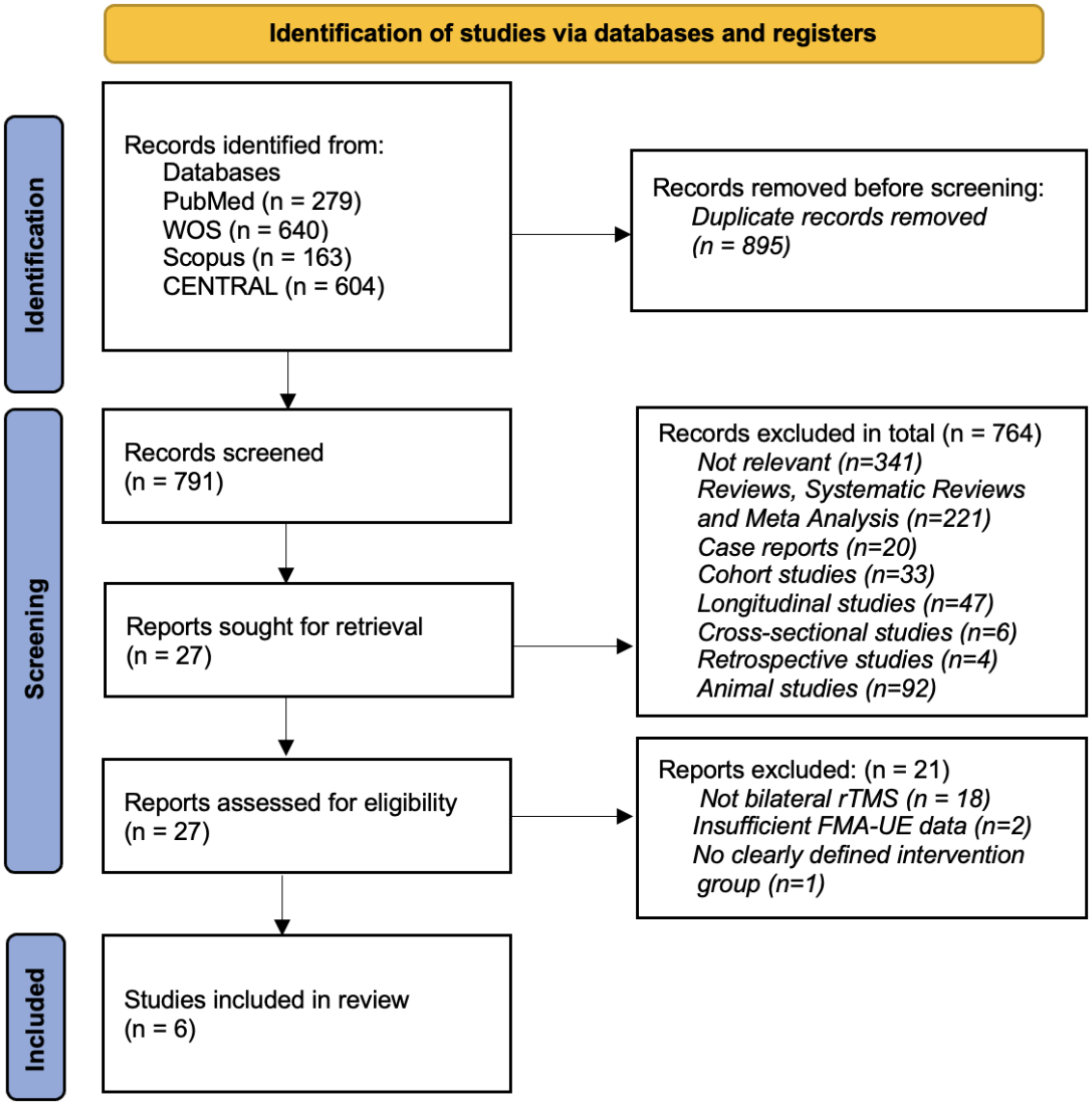


Figure 1. PRISMA flowchart diagram. WOS: Web of Science; CENTRAL: Cochrane Central Register of Controlled Trials; rTMS: repetitive Transcranial Magnetic Stimulation; FMA-UE: Fugl Meyer Assessment-Upper Extremity.

The intervention group included 24.1% (n = 26) women and 75.9% (n = 82) men; the sham control group included 30.3% (n = 30) women and 69.7% (n = 69) men. Among participants for whom stroke

laterality was reported (IG, n = 93; SG, n = 85), 50.5% (n = 47) of the intervention group had left-sided stroke and 49.5% (n = 46) had right-sided stroke. In the sham control group, 52.9% (n = 45) had left-sided stroke, and 47.1% (n = 40) had right-sided stroke.

Pre- and post-intervention FMA-UE values are presented at the individual study level for descriptive purposes. These values were not pooled as treatment effects. The meta-analysis was based on each study's between-group difference in FMA-UE change scores and the corresponding sampling variance under the random-effects model.

The included studies showed substantial clinical and protocol variation. Therefore, Table 1 presents study design, analytic sample size, baseline FMA-UE, stroke phase/type, and stimulation protocol. These differences should be considered when interpreting the pooled effect and the very high between-study heterogeneity.

3.2. rTMS treatment protocols of the included studies

Intervention durations, session frequency, stimulation parameters, and rehabilitation co-interventions varied across the included studies. Intervention protocols included bilateral rTMS and exercise-based approaches in some studies [23,25–27], whereas in other studies, the bilateral protocol combined 1 Hz rTMS to the contralesional M1 with Intermittent Theta Burst Stimulation (iTBS) to the ipsilesional M1, alongside exercise-based rehabilitation [22,24].

Long et al. applied rTMS for 15 consecutive days in addition to 30 minutes of daily physiotherapy and 60 minutes/day of occupational therapy, 6 days a week [23]. Chen et al. applied rTMS for 30 minutes a day, 5 days a week, and physiotherapy for 4 weeks [25]. Abdelkader et al. applied rTMS for 5 consecutive days in a week with physiotherapy 3 days a week, followed by physiotherapy for 4 weeks after rTMS [27]. Chen et al. applied rTMS for 5 consecutive days in a week for 4 weeks, in addition to 30 minutes of physiotherapy [26]. Sung et al. applied a total of 10 sessions of rTMS, 10 sessions of iTBS, and 1 hour of physiotherapy and occupational therapy, 5 days a week for 4 weeks [22]. Meng et al. applied a total of 10 sessions of rTMS, iTBS, and 1 hour of physiotherapy and occupational therapy, 5 days a week for 2 weeks [24] (Table 1).

Table 1. Clinical and intervention characteristics of the included RCTs of Bilateral rTMS.

Name of The Study	Country	Study design	Analytic sample size, n	Age, Mean ± SD median (range)	% Female	Stroke phase and type	Lesion location	Stimulation protocol	Outcome Measures	Baseline FMA-UE	Concomitant rehabilitation
Sung et al. 2013 [22]	Taiwan	Randomized, sham-controlled, double-blind, parallel-group trial	IG: 15 SG: 14	IG: 62.3 ± 12.2 SG:63.1 ± 12.8	IG: 20% SG: 21.4%	Chronic stroke (3–12 months after first-ever stroke); ischemic or hemorrhagic.	Cortical/subcortical	IG: Patients received 20 days of rTMS sessions, 5 days a week, for 4 weeks. The first 10 sessions consisted of real 1 Hz rTMS applied to the contralesional M1, followed by the next 10 sessions of real iTBS applied to the ipsilesional M1. SG: Same procedure was followed, but sham treatment.	• Wolf Motor Function Test (WMFT) • Fugl-Meyer Assessment Upper Extremity (FMA-UE) • Finger flexor Modified Research Council (MRC) Scale • Simple reaction time task (EMG device) • Index finger tapping task	IG: 28.0 ± 12.2 SG: 27.3 ± 11.6	Conventional physical rehabilitation and occupational therapy; 1 h/day of task-oriented training, individualized motor tasks, and activities of daily living training
Long et al. 2018 [23]	China	Prospective, randomized, double-blind, sham-controlled longitudinal trial	IG: 21 SG: 20	IG: 55.90 ± 8.89 SG: 56.85 ± 5.48	IG: 23.8% SG: 25%	Early phase/acute stroke; infarction/hemorrhagic	Subcortical lesions; cerebral subcortical infarction in MCA territory or supratentorial intracerebral hemorrhage	IG: Patients were first treated with 1,000 low-frequency rTMS pulses at 1 Hz to the contralesional M1 at 90% of the resting motor threshold. Then, 10 Hz	• FMA-UE • WMFT	IG: 34.90 ± 3.79 SG: 34.95 ± 3.25	Conventional physiotherapy 30 min/day and task-oriented occupational therapy 60

							without cortical involvement	rTMS was applied to the motor hotspot in the ipsilesional hemisphere at 90% of the rMT for 10 seconds, followed by a 50-second interstimulus interval. A total of 1000 pulses of 10 Hz rTMS pulses were applied. The rTMS intervention was administered for 15 consecutive days. SG: Same procedure followed but with sham stimulation.			min/day, each reported as 6 days/week[a]
Meng et al. 2020 [24]	China	Randomized, sham-controlled, participant- and assessor-blinded, three-arm controlled trial	IG: 10 SG: 8	IG: 55.3 ± 7.47 SG: 53.87 ± 10.73	IG: 30% SG: 50%	Subacute (30–60 days after first-ever stroke); ischemic/hemorrhagic	Basal ganglia/other	IG: Patients received 1 Hz rTMS treatment with 1200 pulses at 100% rMT on the motor representation of the abductor brevis pollicis in the contralesional M1, 5 days a week, for two weeks. iTBS was applied with three pulses at 50 Hz, repeated for 2 seconds	• FMA-UE • Barthel Index • Electrophysiological measures.	Baseline not numerically reported; change: IG 8.7 ± 6.2 SG 3.0 ± 1.9	Conventional physical rehabilitation + occupational therapy; 1 h/day of task-oriented training and regular daily exercise

								at 200 ms intervals, at 60%–80% rMT on the ipsilateral M1 (initial intensity was 60% rMT, and rMT was increased by 5% daily until 80% rMT was reached). A 2-second iTBS sequence was repeated every 10 seconds for a total of 1200 pulses. SG: Same procedure was followed, but sham treatment.			
Chen et al. 2021 [25]	China	Randomized, sham-controlled clinical trial	IG: 22 SG: 22	IG: 56 (39.3–64) SG: 60.5 (54.3–65.5)	IG: 18.2% SG: 31.8%	Acute ischemic stroke	Subcortical/cortical + subcortical	IG: Patients received 1 Hz, then 10 Hz rTMS for 4 weeks. The 10 Hz rTMS consisted of 600 pulses at 90% of the resting motor threshold (rMT) and was applied to the M1. The 1 Hz rTMS also consisted of 600 pulses at 90% of the rMT and was applied to the motor region of the first dorsal	• MRS for disability • FMA-UE • The Activities of Daily Living Scale • Mini-Mental State Examination (MMSE) • MRI Assessments	IG: 21.8 ± 15.5 SG: 19.5 ± 18.1	Routine medical treatment + physiotherapy; passive and active motor exercises, 30 min/day, 5 days/week for 4 weeks, following rTMS sessions

								interosseus muscle in the contralesional hand. SG: Same procedure was followed, but sham treatment.			
Chen et al. 2021 [26]	China	Randomized, sham-controlled, four-arm trial	IG: 25 SG: 25	IG: 58 (44.5–65.5) SG: 65 (52–73)	IG: 28% SG: 28%	Acute ischemic stroke	Cortical/subcortical /massive	IG: Patients received a real 1 Hz rTMS protocol in 4-week sessions, in addition to a real 10 Hz treatment course. The 10 Hz rTMS sequences consisted of 600 pulses at 90% of rMT and were applied to the M1; and the 1 Hz rTMS sequences, also consisting of 600 pulses at 90% of rMT, were applied to the motor region of the first dorsal interosseus muscle in the contralesional hand. SG: Same procedure was folloed, but sham treatment.	• National Institutes of Health Stroke Scale • Modified Rankin Scale (MRS) for disability • FMA-UE • Grasping evaluation • MMSE • Hamilton Depression Rating Scale • Electrophysiological measures.	IG: 18.60 ± 2.83 SG: 16.88 ± 2.83	Routine medical treatment + physiotherapy; passive and active motor exercises, task-oriented training, ADL training and individualized motor tasks; 30 min/day, 5 consecutive days/week for 4 weeks

Abdelkader et al. 2024 [27]	Egypt	Blinded randomized controlled study	IG: 15 SG: 10	IG: 53.5 ± 20.4 SG: 51.8 ± 15.7	IG: 26.7% SG: 40%	Subacute; first-ever ischemic or hemorrhagic stroke	Subcortical hemispheric stroke; supratentorial/infratentorial	IG: 1000 pulses per session were reported at 90% of the motor threshold. The bilateral protocol consisted of 20 excitatory 5 Hz trains (10 s, 50 stimuli each) over the lesional M1, each alternating with five inhibitory 1 Hz trains (10 s each) over the non-lesional M1, yielding 20 excitatory and 100 inhibitory trains daily.[b] SG: Same procedure was followed, with sham stimulation replacing the active rTMS component.	• FMA-UE • WMFT • The modified Ashworth Scale	IG: 45.07 ± 11.59 SG: 46.20 ± 12.67	Conventional and task-oriented physiotherapy, individualized to the patient; 3 days/week during rTMS and continued for 4 weeks afterward

Note: rTMS: Repetitive Transcranial Magnetic Stimulation; rMT: Resting Motor Threshold; iTBS: Intermittent Theta Burst Stimulation; LF: Low Frequency; HF: High Frequency; IG: Intervention Group; SG: Sham Group; SD: Standard Deviation; EMG: Electromyography; MRI: Magnetic Resonance Imaging; FMA-UE: Fugl-Meyer Assessment Upper Extremity; MMSE: Mini-Mental State Examination; WMFT: Wolf Motor Function Test; MRS: Modified Rankin Scale. [a]The original article reports both that rTMS, PT and OT were delivered daily for 15 consecutive days and that PT and OT were given 6 days per week; both are presented as reported. [b]The original article reports 50 stimuli per 10-s 1 Hz train, which is arithmetically inconsistent (1 Hz × 10 s = 10 pulses) and does not reconcile with the stated total of 1000 pulses per session. Parameters are presented as reported by the authors.

3.3. Risk of bias results

According to the RoB 2 assessment, all six included studies were judged as having some concerns overall. The overall risk of bias assessment and summary percentage plot are given in Figure 2.

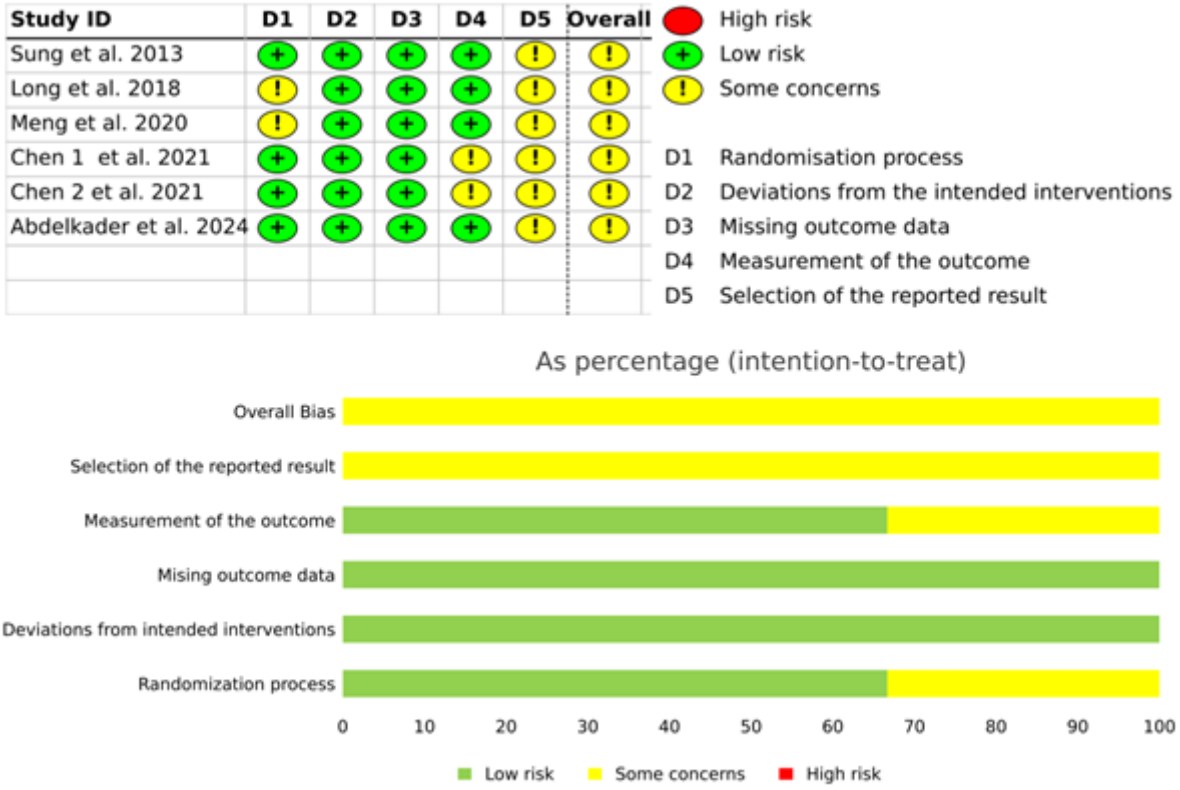


Figure 2. The risk of bias assessments of the RCTs.

3.4. Meta-analysis

3.4.1. Overall effect

The random-effects meta-analysis using REML estimation with Hartung-Knapp adjustment yielded a pooled between-group mean difference of 14.53 FMA-UE points (95% CI: 1.41 to 27.64, p = 0.036) in favor of bilateral rTMS compared with sham stimulation (Figure 3). The certainty of evidence was rated as very low according to the GRADE assessment (Table 2).

3.4.2. Heterogeneity (Inter-study differences)

Between-study heterogeneity was extreme ($\tau^2 = 148.75$; $I^2 = 98.3\%$; $Q(5) = 466.59$, $p < 0.0001$). The 95% prediction interval ranged from −19.46 to 48.51 FMA-UE points and included the null value. Therefore, although the pooled mean difference favored bilateral rTMS, the pooled estimate should be interpreted as an average effect across clinically heterogeneous studies rather than as a uniform

treatment effect expected across settings. Differences in stroke phase, stimulation protocols, and concomitant rehabilitation may have contributed to the observed heterogeneity (Figure 3).

3.4.3. Sensitivity analysis

Under different correlation assumptions, the pooled mean difference remained stable, ranging from 14.49–14.57. The confidence interval remained positive in all scenarios and did not include 0 [22–27]. The results were robust and not sensitive to the assumed pre-post correlation values (Figure 3). Because potential participant overlap between the two Chen et al. studies could not be definitively excluded, additional sensitivity analyses were performed, retaining only one of these studies at a time. When Chen et al. [25] was excluded and Chen et al. [26] was retained, the pooled MD was 12.52 FMA-UE points (95% CI: −3.18 to 28.22; p = 0.091). When Chen et al. [26] was excluded and Chen et al. [25] was retained, the pooled MD was 10.21 points (95% CI: −0.45 to 20.88; p = 0.056). Although the direction of the pooled effect remained in favor of bilateral rTMS in both analyses, the confidence intervals included the null, indicating reduced statistical precision when either Chen study was excluded [25,26].

3.4.4. Leave-One-Out analysis

When each study was individually excluded from the analysis, the combined effect size was observed to range from 10.21 to 17.02. No single study reversed the result, and the direction of the effect was preserved in all analyses. However, statistical significance was not maintained in some leave-one-out analyses [22–27] (Figure 3).

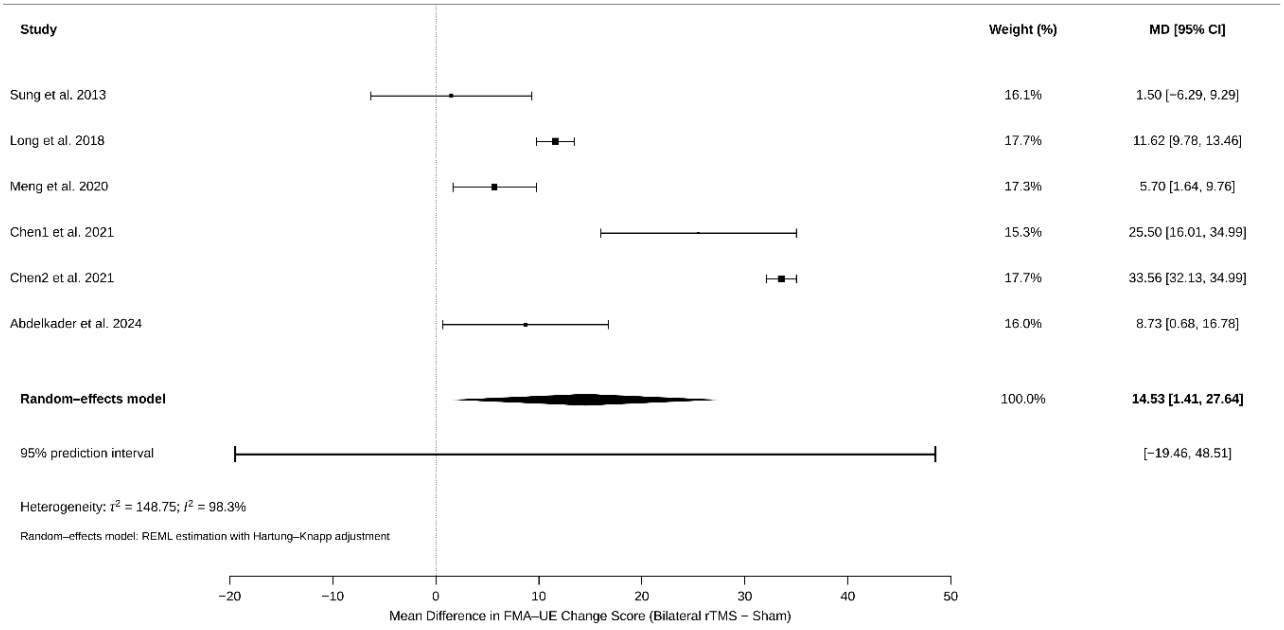


Figure 3. Meta-analysis of the Effect of Bilateral rTMS on FMA-UE Motor Function.

Forest plot of the between-group mean difference in FMA-UE change scores for bilateral rTMS versus sham. Squares represent study-specific mean differences and are scaled according to random-effects weights; horizontal lines represent 95% confidence intervals. The diamond represents the pooled random-effects estimate (MD 14.53, 95% CI 1.41 to 27.64). Between-study heterogeneity was $\tau^2 = 148.75$ and $I^2 = 98.3\%$. The 95% prediction interval was −19.46 to 48.51. The model used REML estimation with Hartung-Knapp adjustment.

Table 2. GRADE level of evidence for included studies.

Outcome	Number of studies and Participants	Risk of Bias[a]	Inconsistency[b]	Indirectness	Imprecision[c]	Publication Bias[d]	Overall Certainty of Evidence	Effect
FMA-UE improvement	6 RCTs 207	Serious	Serious	Not Serious	Serious	Not assessed	Very Low ⊕◯◯◯	Mean Difference: 14.53 (95% CI 1.41–27.64)

Note: High certainty: Confidence in the actual effect is very close to the effect estimate; Medium certainty: The actual effect is close to the effect estimate, but there is a possibility of it differing significantly; Low certainty: Confidence in the effect estimate is limited. The actual effect may differ significantly from the estimate; Very low certainty: There is little confidence in the effect estimate. It is likely that the actual effect will differ significantly from the estimate. [a]Downgraded for risk of bias because more than 75% of the included studies were not rated as low risk, [b]Downgraded for inconsistency because substantial heterogeneity was observed ($I^2 = 98.3\%$), [c]Downgraded for imprecision because the 95% confidence interval was wide indicating substantial uncertainty regarding the magnitude and clinical treatment effect, [d]Publication bias was not formally assessed because fewer than 10 studies were included; therefore, no downgrade was applied. MD: Mean difference; CI: Confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluations.

4. Discussion

In this systematic review and meta-analysis, we examined the effects of bilateral rTMS on upper extremity motor function, as measured by FMA-UE, in stroke patients. A combined analysis of six RCTs demonstrated that bilateral rTMS resulted in a significant improvement in FMA-UE scores compared to placebo/sham stimulation. However, high heterogeneity and very low certainty of evidence according to the GRADE assessment necessitate cautious interpretation of these findings.

4.1. Key findings and clinical significance

The pooled between-group effect was 14.53 FMA-UE points (95% CI 1.41 to 27.64). Although the point estimate exceeded the published minimal clinically important difference (MCID) range of approximately 4.25–13 points cited in this review, the lower confidence limit fell below the lower end of that range [37–41]. Therefore, the findings are compatible with effects ranging from below commonly cited clinically important thresholds to substantially larger benefits, and clinical importance cannot be concluded with certainty from the pooled estimate alone. This uncertainty is further reinforced by the 95% prediction interval of −19.46 to 48.51, which crossed the null value. Therefore, a clinically meaningful benefit cannot be assumed to occur consistently across individual clinical

settings or patient populations. Rather, the pooled estimate represents an average across studies with substantial clinical and methodological heterogeneity.

Researchers have also examined bilateral rTMS within broader comparisons of stimulation strategies. However, these researchers used different effect measures and analytical frameworks, including standardized mean differences and network meta-analysis. Because our meta-analysis reports the treatment effect as a mean difference in FMA-UE change scores, the magnitude of our pooled MD cannot be directly compared with SMDs reported in other reviews. Accordingly, these external findings are presented for contextual purposes and should not be interpreted as demonstrating a larger effect or superiority of bilateral stimulation based on our analysis.

A network meta-analysis revealed that bilateral rTMS showed the best performance in improving upper extremity motor function at the end of the intervention (surface under the cumulative ranking curve (SUCRA): 92.8%) and at 3 months of follow-up (SUCRA: 95.4%), as well as in activities of daily living and neurological function [42]. Another meta-analysis conducted in 2025 by Alhalabi et al. reported that 15–20 session protocols yielded significantly better results than shorter protocols, and the most consistent gains were observed in the subacute and subacute-chronic phases [43]. The studies included in our meta-analysis covered acute, subacute, and chronic stroke phases, and the session protocols varied between 5–20 sessions. Accordingly, these external findings support the potential therapeutic value of bilateral rTMS, but differences in stroke phase, stimulation parameters, and treatment duration preclude drawing firm conclusions regarding the optimal protocol or the patient population most likely to benefit.

4.2. Comparison with unilateral and bilateral stimulation approaches

Researchers comparing unilateral and bilateral stimulation approaches have reported differences in treatment effects according to stroke stage and number of sessions [28]. However, our meta-analysis included comparisons of bilateral rTMS with sham stimulation and therefore does not provide a direct test of bilateral versus unilateral stimulation.

Chen et al. conducted a comprehensive meta-analysis of 45 RCTs (n = 2064) and found that bilateral hemisphere stimulation was more effective than unilateral stimulation in upper extremity recovery in the acute phase of stroke, with a 20-session regimen resulting in greater recovery than fewer sessions [28]. However, in the subacute phase, 40 sessions of affected hemisphere stimulation were superior to fewer sessions of bilateral stimulation, while in the chronic phase, 10 sessions of unaffected area stimulation resulted in significantly greater recovery compared to more sessions of bilateral stimulation [28].

A real-world study by Jacques et al. provides additional evidence supporting bilateral stimulation, reporting that patients receiving bilateral stimulation in addition to physiotherapy treatment were 2.8 times more likely to recover compared to those receiving unilateral stimulation [44]. Importantly, this study also revealed that the time between stroke and treatment was inversely proportional to the rTMS response (mean 13.1 months in the recovering group, 33.3 months in the non-recovering group, $p = 0.027$), indicating that bilateral rTMS application yielded more effective recovery outcomes than unilateral application [44].

4.3. Neurophysiological mechanisms

The therapeutic effects of bilateral rTMS are thought to involve restoration of interhemispheric balance through dual mechanisms: inhibition of the contralesional hemisphere (typically 1 Hz low-frequency rTMS) to reduce excessive interhemispheric inhibition, and facilitation of the ipsilesional hemisphere (typically 5–10 Hz high-frequency rTMS) to enhance cortical excitability [45]. Functional neuroimaging studies have demonstrated that coupled inhibitory-facilitatory rTMS modulates functional connectivity within and between hemispheric motor networks, with these changes correlating significantly with motor function recovery [45].

Chen et al. used resting-state functional MRI to evaluate 63 patients with acute stroke randomized to different rTMS protocols. The coupled bilateral rTMS group (1 Hz contralesional + 10 Hz ipsilesional) showed more pronounced changes in functional connectivity between the contralesional postcentral gyrus and superior parietal gyrus, between the contralesional precentral and postcentral gyri, and between the ipsilesional postcentral gyrus and contralesional superior parietal gyrus compared to unilateral stimulation groups [45]. These functional connectivity changes were significantly correlated with motor function improvement, suggesting potential neurophysiological mechanisms through which bilateral stimulation may influence motor recovery [45]. While our meta-analysis focuses on upper extremity motor recovery, rTMS is increasingly being investigated in other areas of post-stroke rehabilitation. Evidence demonstrates the potential benefits of rTMS for post-stroke cognitive impairment while revealing significant variability in stimulation parameters, cortical targets, and rehabilitation combinations [19]. These findings broaden the clinical perspective of post-stroke neuromodulation and suggest that its effects may extend to multiple functional domains. On the other hand, since cognitive rehabilitation studies often utilize different stimulation targets and protocols, these findings should not be directly generalized to the bilateral motor cortex protocols evaluated in this meta-analysis.

4.4. Heterogeneity and its implications

The considerable heterogeneity observed in this meta-analysis (I^2 = 98.3%; τ^2 = 148.75) substantially limits the interpretation of the pooled effect. This concern is further supported by the wide 95% prediction interval (−19.46 to 48.51), which crossed the null value. Although pooling was considered appropriate for estimating an average effect of bilateral rTMS across the available randomized evidence, the included studies differed considerably in stroke phase, stimulation frequency and sequence, number of sessions, pulse parameters, and concomitant rehabilitation. Consequently, the pooled estimate should not be interpreted as a uniform treatment effect applicable to all bilateral rTMS protocols or stroke populations. Potential sources of this clinical and methodological heterogeneity are discussed below.

4.4.1. Protocol variability

The included studies used different stimulation parameters, including intervention duration, number of sessions, stimulation frequencies, pulse numbers per session, and intensity [22–27]. External studies have suggested that treatment response may vary according to protocol characteristics such as the number of sessions, stimulation frequency, and pulse dose [46]. However, these parameters

were not formally compared in the meta-analysis, and the small number of included studies precluded reliable subgroup or meta-regression analyses. Therefore, our findings do not establish an optimal stimulation protocol, and the potential influence of these parameters should be considered hypothesis-generating and evaluated in adequately powered comparative studies.

4.4.2. Population

The included studies enrolled patients at different stroke stages (acute, subacute, chronic) and with varying baseline FMA-UE severity. Other meta-analyses have shown that baseline severity significantly affects treatment response, with more severe impairment associated with greater absolute improvements [47]. In addition to motor impairment and stroke phase, variability in lesion characteristics, comorbidity burden, and patient selection criteria can also contribute to differences in treatment response. Therefore, multifaceted patient stratification may be important to interpret this variability and identify patients with different rehabilitation needs [8].

External evidence suggests that treatment response may vary according to factors such as stroke phase and baseline motor impairment. However, for our meta-analysis, we did not formally evaluate treatment-effect modification according to these patient characteristics. Therefore, no conclusions regarding optimal patient selection can be drawn from the analysis. Potential clinical predictors of response should be regarded as hypotheses requiring confirmation in appropriately designed studies.

4.4.3. Adjunctive therapies

The included studies applied bilateral rTMS alongside different rehabilitation approaches, including traditional physiotherapy, occupational therapy, and task-specific training [22–27]. In two studies, iTBS was incorporated as the ipsilesional excitatory component of the bilateral stimulation protocol [22,24]. This variability in co-interventions makes it difficult to isolate the specific contribution of bilateral rTMS to the observed improvements. Differences in the intensity, frequency, duration, and therapeutic content of rehabilitation may also alter treatment response and contribute to significant heterogeneity in the studies included in the meta-analysis.

4.4.4. Geographic concentration

Four of six studies (67%) were conducted in China, which may limit generalizability. Other meta-analyses have indicated that studies from Asian countries tend to report larger effect sizes, possibly due to differences in study design, patient selection, outcome assessment, or publication practices [48].

Despite this considerable heterogeneity, the direction of the pooled effect remained in favor of bilateral rTMS across the sensitivity analyses. The leave-one-out analysis showed that no single study reversed the overall direction of the effect (effect size range: 10.21–17.02), and the assumed pre-post correlation coefficient ($r = 0.3–0.9$) did not substantially alter the pooled estimate (14.49–14.57). These sensitivity analyses do not eliminate the substantial between-study heterogeneity or the uncertainty demonstrated by the wide prediction interval.

4.5. Methodological strengths and limitations

4.5.1. Strengths

This study has several important strengths. First, we addressed a relatively understudied area in stroke rehabilitation research, focusing specifically on bilateral rTMS protocols for upper extremity motor recovery after stroke. The review was conducted in accordance with PRISMA guidelines and registered in PROSPERO, which increased methodological transparency and reduced the risk of selective reporting. In addition, rigorous methodological approaches, including random effects modeling with the Cochrane RoB 2 tool, the GRADE framework, and Hartung-Knapp correction, enhanced the reliability of the findings despite significant heterogeneity between studies. Another strength is that the pooled effect estimate was interpreted in relation to published MCID thresholds for the FMA-UE while considering the uncertainty reflected by the wide confidence and prediction intervals. Finally, comprehensive sensitivity analyses reinforced confidence in the consistency of the findings by showing that the overall direction of the effect remained stable across analytical assumptions, although statistical significance was not maintained in all leave-one-out analyses.

4.5.2. Limitations

The very low GRADE certainty showed serious concerns across three domains: risk of bias, inconsistency, and imprecision [31]. Risk of bias was considered serious because more than 75% of the included studies were not rated as low risk, while inconsistency was considered serious because of the substantial between-study heterogeneity (I^2 = 98.3%). Imprecision was also considered serious because the 95% confidence interval around the pooled effect was wide, indicating substantial uncertainty regarding the magnitude and clinical importance of the effect. These limitations significantly reduce confidence that the actual effect is close to the estimated effect.

The small sample size (six RCTs and 207 participants) limited the ability to conduct adequately powered subgroup analyses or meta-regressions to investigate potential sources of heterogeneity. Therefore, formal subgroup analyses and meta-regression were not performed, as such analyses would have been underpowered and potentially misleading.

Moreover, possible participant overlap between the two Chen et al. studies [25,26] could not be definitively excluded based on the published information, and separate trial registrations alone do not establish cohort independence. To address this uncertainty, additional sensitivity analyses were conducted, retaining only one Chen study at a time. The direction of the pooled effect remained unchanged, but the confidence intervals included the null in both analyses, indicating that the statistical precision of the pooled estimate was sensitive to the inclusion of these studies.

Publication bias could not be formally assessed because only six studies were included. Therefore, no downgrade was applied for this domain in the GRADE assessment. Nevertheless, the possibility of publication bias or small-study effects cannot be excluded.

Finally, the lack of long-term follow-up data in most included studies prevents the assessment of whether the observed benefits persist beyond the immediate post-intervention period.

4.6. Clinical implications and recommendations

Based on the evidence, bilateral rTMS appears to be a promising, though not yet definitively proven, intervention for upper extremity motor recovery after stroke. The intervention demonstrates a favorable safety profile, with most studies reporting only mild, transient side effects such as headache or nausea [27,42]. For clinicians considering bilateral rTMS, the evidence suggests the following.

4.6.1. Timing of application

External studies have suggested that the treatment response may vary depending on the timing of bilateral rTMS administered after a stroke, and that there may be potential differences between the acute/subacute phases and the later stages of the stroke [44,47]. These observations are derived from external studies rather than from direct comparisons within our meta-analysis. Although they provide potentially relevant hypotheses regarding treatment timing and dose, our analysis was not designed to determine the optimal post-stroke treatment window or number of sessions. These questions require confirmation in adequately powered comparative trials.

4.6.2. Patient selection

Limited evidence suggests that the response to treatment may vary depending on factors such as the stage of the stroke and the initial level of motor impairment [47]. However, for our meta-analysis, we did not formally evaluate how the treatment effect varies according to these patient characteristics. Therefore, no conclusions regarding optimal patient selection can be drawn from the analysis. Thus, these potential clinical predictors of response should be treated as hypotheses requiring validation in appropriately designed studies.

4.6.3. Protocol parameters

Evidence from meta-analyses indicates that the response to treatment may vary depending on protocol characteristics such as the number of sessions, stimulation frequency, and pulse dose [46]. However, these parameters were not formally compared in the meta-analysis, and the limited number of included studies precluded reliable subgroup or meta-regression analyses. Therefore, our findings do not establish an optimal treatment session protocol. The potential impact of these protocol characteristics should be considered hypothesis-generating and requires verification through comparative studies with sufficient statistical power.

4.6.4. Integration with rehabilitation

Bilateral rTMS has been investigated in combination with task-specific motor training to potentially enhance neuroplasticity, and the timing and nature of adjunctive rehabilitation may influence treatment outcomes [45,48].

In this context, given the very low certainty of the evidence, bilateral rTMS should be considered an adjunctive experimental treatment rather than a standard treatment. Patients and clinicians should be informed about the uncertainty regarding treatment effects and the need for additional high-quality research.

4.7. Future directions

To advance the field and improve evidence certainty, researchers should address the following priorities:

- Multi-center trials with sample sizes sufficient to detect clinically meaningful differences and enable adequately powered subgroup analyses.
- Development of standardized bilateral rTMS protocols to reduce heterogeneity and provide clearer interpretation of results and clinical effects.
- Combining neurophysiological measurements and biomechanical assessments to identify biomarkers of treatment response and elucidate mechanisms of action.
- Evaluation of long-term treatment effect to determine whether benefits persist and whether additional sessions are needed.
- Investigation of optimal stimulation parameters in terms of intensity, frequency, session duration, and total number of sessions [49].
- Conducting high-quality multicenter trials across geographic and healthcare settings to improve the external validity and generalizability of treatment effects [48].
- Head-to-head comparisons of bilateral rTMS with other neuromodulation approaches and intensive conventional therapy to establish relative efficacy and cost-effectiveness [50].

5. Conclusions

This study provides preliminary evidence that bilateral rTMS may improve upper extremity motor function after stroke, although the magnitude and clinical importance of the effect remain uncertain. However, the very low certainty of the evidence, high heterogeneity, and small sample size limit confidence in these results. The analysis does not determine the optimal timing, patient selection criteria, or stimulation parameters for bilateral rTMS. To better define the role of bilateral rTMS in stroke rehabilitation, well-designed, adequately powered RCTs with standardized protocols, populations representing different stroke phases, and long-term follow-up are needed. In future studies, researchers may also incorporate multidimensional patient stratification based on relevant clinical and lesion-related characteristics to explore potential predictors of treatment response and facilitate more personalized rehabilitation strategies.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

MK and DO drafted the manuscript; MK prepared the figures and tables; DHS performed the statistical analysis; DDM, RO, SS, ED, SV performed critical revision. All authors approved the final manuscript.

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