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The journal encompasses all aspects of physical medicine and rehabilitation, including basic, translational, clinical, and policy research, as well as rehabilitation education. Research areas covered by this journal include rehabilitation for brain disorders, spinal cord injuries, neuromuscular diseases, and dysphagia; cancer, cardiopulmonary, geriatric, pain & musculoskeletal, and pediatric rehabilitation; electrodiagnosis, orthosis & prosthesis, physical therapy, and sports medicine; and other emerging fields in rehabilitation medicine.

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Editorial: Outcome Measures in Rehabilitation Medicine

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Motor Function Measurement in Children: Gross Motor Function Measure (GMFM)

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The assessment and management of motor function in children, particularly those with cerebral palsy (CP) and other motor disorders, are crucial components of pediatric rehabilitation. The Gross Motor Function Measure (GMFM) and the Gross Motor Function Classification System (GMFCS) are key tools that offer structured and reliable methods to assess and classify motor abilities, guiding therapeutic decisions and tracking progress over time. The GMFM is a standardized observational measure to evaluates and monitor changes in gross motor function, especially in children with CP [1]. It is based on typical developmental stages, with items designed to be completed by typically developing children by age 5.

GMFM-88 and GMFM-66

There are two versions of GMFM: the original 88-item measure (GMFM-88) and the 66-item measure (GMFM-66) (Table 1). The GMFM-88 consists of five dimensions: (A) lying and rolling; (B) sitting; (C) crawling and kneeling; (D) standing; (E) walking, running, and jumping. Raw and percent scores are calculated for each of the five dimensions as well as a total score. The GMFM-88 uses an ordinal scale, which can reduce sensitivity at extreme score ranges. To overcome this, the GMFM-66 was developed using Rasch analysis, converting ordinal data into an interval scale, arranging items by difficulty and ensuring equal scoring intervals. This improves the accuracy and sensitivity of assessing motor function changes over time. The interrater and intrarater reliability of the GMFM-88 total score, assessed with the intraclass correlation coefficient (ICC), are both 0.99, while the interrater and intrarater reliability of the GMFM-66 are 0.98 and 0.99, respectively [1,2]. Validity was confirmed by a correlation of 0.82 between GMFM-88 scale changes and the clinical judgments of blinded assessors [1]. Both versions of the GMFM are reliable, valid, and responsive to change in children with CP.

Administration and best practice for GMFM

Children are rated on each item using a 4-point scale with specific descriptors: 0=does not initiate; 1=initiates but completes less than 10%; 2=partially completes (10% to less than 100%); and 3=fully completes the task. The GMFM-66 score can be obtained using the Gross Motor Ability Estimator (GMAE) scoring program [1]. During the assessment, all items the child can attempt must be tested. If an item is not attempted, it is scored as 0 in GMFM-88, whereas in GMFM-66, it is marked as not tested (NT) and the expected score can be estimated using the GMAE

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Table 1. Comparison between GMFM-88 and GMFM-66

Feature	GMFM-88	GMFM-66
Total items	88 items, 5 dimensions	66 items
Time to administer (min)	45–60	All 66 items: 30–45 IS, B&C: 20–30
Scoring system	Dimensional score (%) Total score (%)	Score (0–100) with 95% CI
Scale property	Ordinal scale	Interval scale
Not tested item	Scored 0 point	Marked NT; GMAE software can estimate the expected scores
Target population	Children with CP and wide range of motor disorders	Children with CP
Use of software	Scoring typically done manually or through the GMFM App+	GMAE-2 or GMAE-3 through the GMFM App+
Use of assistive devices	Allowed during the assessment	Not allowed during the assessment

GMFM, Gross Motor Function Measure; IS, GMFM-66-Item Sets; B&C, GMFM-66-Basal & Ceiling; CI, confidence interval; NT, not tested; GMAE, Gross Motor Ability Estimator; CP, cerebral palsy.

program. Each item can be tried up to three times, with the best performance recorded. Demonstrations are permitted, but physical assistance is not, as the GMFM is an observational tool. If a child becomes uncooperative, alternative methods like role play or toys can help. While no specific certification is required to use the GMFM, training has been shown to significantly improve scoring consistency and accuracy [3]. The GMFM user's manual was first published in 2002, and the most recent third edition was published in 2021 [1]. The Korean version has been translated as the K-GMFM, demonstrating construct validity and inter-rater reliability [4].

Target population

The GMFM, originally validated for children with CP aged 5 months to 16 years, has also been found valid and reliable for children with Down syndrome [5,6], acquired brain injuries [7], and osteogenesis imperfecta [8], Fukuyama congenital muscular dystrophy [9], and spinal muscular atrophy [10]. Additionally, a version adapted for children with acute lymphoblastic leukemia (GMFM-ALL) has demonstrated strong validity and reliability [11]. However, before using GMFM with other populations, it is crucial to establish its reliability and validity for those specific groups.

GMFCS and GMFM

The GMFCS is a classification system for children with CP, categorizing their functional mobility and need for assistive devices into five levels, from minimal (Level I) to severe impairment (Level V) [12]. Based on GMFM-66, five distinct motor development curves of GMFCS were created to stratify typical motor function according to age. GMFCS provides a broader, predictive measure of motor function over time, emphasizing daily performance. While GMFM is an evaluative measure, GMFCS is a classification tool not designed to measure changes, and should not be used as an outcome measure.

Which GMFM version to choose?

The choice of which GMFM version to use depends on the purpose of the assessment and the population. Since GMFM-66 excludes 22 items from GMFM-88 dimensions A, B, and C, GMFM-88 is recommended for very young children or functioning at GMFCS Level V. Additionally, GMFM-66 does not permit the use of orthoses, shoes, or mobility aids, so GMFM-88 should be used if these are required. GMFM-88 is also better suited for assessing children with motor impairments from conditions other than CP, such as Down syndrome and acquired brain injuries. The items of the GMFM-66 were weighted according to difficulty and were validated specifically for children with CP, and may not be appropriate for other conditions. Therefore, it is not recommended for use with non-CP children. For a briefer method of GMFM-66 scoring, either item set (GMFM-66-IS) or the basal & ceiling approach (GMFM-66-B&C) can be used [13]. For children with CP and cerebral visual impairment (CVI), the adapted version known as GMFM-88-CVI is recommended [14].

Applications in clinical practice and research

One of the key strengths of the GMFM is its sensitivity to changes in motor function over time. It is widely used to evaluate the impact of various interventions, such as rehabilitation

programs, medications, orthoses, and orthopedic or neurosurgical procedures, on gross motor function. The GMFM also helps set short-term goals and plan interventions aimed at improving motor function. When used alongside the GMFM-66 reference curves, it allows for a comparison of a child's development relative to peers of the same age and GMFCS level [12]. Beyond clinical applications, the GMFM plays a critical role in research, where it is used to assess the efficacy of new treatments, compare therapeutic approaches, and explore the natural history of motor development in children with CP. The minimum clinically important difference (MCID) for the GMFM has been reported vary depending on the GMFCS level and the research [1,15-17]. One study reported MCID values of 1.58 for the GMFM-66 score and 1.29 for the GMFM-88, indicating a clinically significant improvement in gross motor function [17].

In conclusion, the GMFM is an objective measure for assessing motor function, tracking progress over time, and supporting research in children with CP and other motor disorder. While GMFM effectively measure the quantitative aspects of motor function, evaluating the quality of movement remains a challenge. Selecting the appropriate tool based on the evaluation's purpose and the characteristics of the target population is crucial.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Review Article

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Effectiveness of Non-Pharmacological Interventions for Spasticity Management in Multiple Sclerosis: A Systematic Review

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This systematic review aims to determine the effectiveness of non-pharmacological interventions for the management of spasticity in people with multiple sclerosis (pwMS). A comprehensive literature search in health science databases (MEDLINE, Embase, CENTRAL, CINHAL) was performed to identify randomized controlled trials (RCTs) (up to April 2024). Manual searching in journals and screening of the reference lists of identified studies were conducted. Two authors independently selected the studies, assessed the methodological quality, and summarized the evidence. A meta-analysis was not feasible due to the methodological, clinical, and statistical diversity of the included studies. Overall, 32 RCTs (n=1,481 participants) investigated various types of non-pharmacological interventions including: physical activity, transcranial magnetic stimulation (intermittent theta burst stimulation [iTBS], repetitive transcranial magnetic stimulation [rTMS]), electromagnetic therapy, transcutaneous electrical nerve stimulation, vibration therapy, shock wave therapy, self-management educational programs, and acupuncture. All studies scored 'low' on the methodological quality assessment, implying a high risk of bias. The findings suggest 'moderate to low certainty' evidence for physical activity programs used in isolation or combination with other interventions (pharmacological or non-pharmacological), and for iTBS/rTMS with or without adjuvant exercise therapy in improving spasticity in adults with MS. There is 'very low certainty' evidence supporting the use of other modalities for treating spasticity in this population. Despite a wide range of non-pharmacological interventions used for the management of spasticity in pwMS, there is a lack of conclusive evidence for many. More robust trials with larger sample sizes and longer-term follow-ups are needed to build evidence for these interventions.

Keywords: Multiple sclerosis, Muscle spasticity, Systematic review, Rehabilitation

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disorder marked by patchy inflammation, gliosis, and demyelination within the central nervous system. The prevalence of MS is increasing, with an estimated 2.8 million people worldwide, or approximately 35.9 per 100,000 population, with an incidence rate of 2.1 per 100,000 persons per year [1]. MS manifests in various forms, with the majority (80%) classified as relapsing-remitting MS (RRMS), marked by episodes of exacerbation and remission that may transition to secondary progressive MS (SPMS), characterized by progressive disability between attacks. Other forms include primary progressive MS (PPMS, 15%), where disability progresses from onset, and progressive relapsing MS (PRMS, 5%), which involves gradual worsening followed by acute attacks. The median survival time from diagnosis of people with MS (pwMS) is estimated to be approximately 40 years, which is increasing due to advancements in medical management [2]. This longevity presents challenges such as progressive physical disability, psychosocial adjustment, and social reintegration, impacting not only the pwMS but also their caregivers, clinicians, and the healthcare system at large [3]. The clinical manifestations of MS are diverse, with patients experiencing a range of deficits affecting physical (e.g., weakness, spasticity, sensory loss, ataxia), cognitive (e.g., memory), psychosocial, behavioural, and environmental aspects, all of which limit their activity and participation.

Spasticity in MS

Spasticity is defined as "a disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" [4]. It affects nearly two-thirds of pwMS and poses significant management challenges due to the fluctuating and progressive nature of the disease [5]. The pathophysiology of spasticity is complex and not entirely understood. In the context of MS, it is believed to result from axonal degeneration or demyelination within specific descending tracts, or both, disrupting inhibitory inter-neuronal spinal network pathways [6]. MS-related spasticity can manifest as generalized, focal (affecting a localized part of a limb), or multifocal (affecting multiple parts of limbs). It causes stiffness and abnormal posturing of the limbs due to an imbalance of forces between agonist and antagonist muscles, affecting both static joint position and dynamic limb movement [7]. Truncal musculature can also be affected, leading to poor postural control. Spasticity is closely associated with disease progression, weakness, and fatigability. Additionally, adaptive features such as contractures and rheological changes in muscles, tendons, and joints may develop [8], further complicating limb positioning, movement, and overall function. Spasticity is a significant contributor to overall disability in pwMS [9]. The potential impact of spasticity-related problems in pwMS classified according to the World Health Organization (WHO) International Classification of Functioning, Disability and Health [10] at different levels is provided in Box 1.

Box 1. Potential impact of spasticity in persons with MS
- **Impairments:** Difficulties with body structures or physiological functions, such as restricted joint movement, loss of dexterity, abnormal limb postures, pain, etc.
- **Activity limitations:**
  - o Limitations in active limb use, affecting mobility , transfers, and activities of daily living, etc.
  - o Difficulties in pr oviding care to an affected limb, such as maintaining hygiene or applying a splint or orthotic.
- **Participation restrictions:** Limitations in societal roles related to family, work, and life situations.

Management of spasticity in pwMS

Managing spasticity in pwMS requires a comprehensive and individualized approach due to the multifaceted nature of MS. Patient-centred goals are collaboratively set by patients, caregivers, and the rehabilitation team, which typically focus on reducing symptoms, addressing impairments, improving activity levels (both active and passive functions), enhancing participation, and improving the quality of life (QoL) [11]. Currently, both non-pharmacological interventions and/or pharmacological agents are widely used for the management of spasticity [12-14]. Botulinum toxin A (BoNT-A) is often preferred for treating focal spasticity that does not respond well to non-pharmacological therapies [15]. Other antispasmodic medications commonly used include baclofen, diazepam, dantrolene, and tizanidine [9,16,17]. However, these medications have limited beneficial effects and are associated with high costs and systemic side effects [9,18,19].

Various non-pharmacological interventions are employed to manage spasticity in pwMS, including physical therapeutic modalities, electromagnetic therapies, whole-body vibration (WBV), acupuncture, etc. The effectiveness of these interventions varies among individuals, and often a combination of treatments is used within an interdisciplinary rehabilitation approach. Etoom et al. [20], in a systematic review, found mixed evidence for the benefits of physical therapy (PT) interventions

for spasticity in pwMS. The authors reported some evidence suggesting that exercise therapy, particularly robot-assisted gait training (RAGT) and outpatient exercise programs improved self-perceived spasticity and muscle tone, but there was no conclusive evidence for overall spasticity improvement [20]. Other non-pharmacological interventions, such as repetitive transcranial magnetic stimulation (rTMS), have shown a significant reduction in spasticity in the early post-intervention period (one week), but the evidence at follow-up (two weeks later) is insufficient [21]. Interventions like transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation (tDCS), and WBV have not demonstrated additional benefits for spasticity in pwMS [13,22-24].

There is significant ambiguity about the benefits and risks associated with many non-pharmacological interventions. Despite guidelines and consensus statements advocating various non-pharmacological approaches to spasticity management [13,25], the evidence is largely based on isolated studies, narrative reviews, or expert opinions. A comprehensive systematic review published in 2013 (n=9 randomized controlled trials, RCTs), found limited evidence to support the effectiveness of non-pharmacological interventions, indicating a need for more rigorous studies [12]. Other published reviews in the area have reported diverse and sometimes conflicting conclusions [13,14,20,26-28]. This field is dynamic and constantly evolving. A systematic evaluation of the existing evidence is needed to clarify the effectiveness and safety of these non-pharmacological interventions and to inform clinical decision-making. Therefore, this review aims to systematically evaluate the literature to determine the effectiveness and safety of non-pharmacological interventions for managing spasticity in pwMS. Specific questions addressed include: Are non-pharmacological interventions effective in improving spasticity and spasticity-related impairments in pwMS? What specific types of non-pharmacological interventions are effective, and in which settings?

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [29].

Literature search

A comprehensive search of the literature was undertaken using a multipronged approach, including search of health science databases: Cochrane Central Register of Controlled Trials (CENTRAL 2023, Issue 6), MEDLINE (PubMed), Embase (Embase.com), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host); and clinical trial registries: ClinicalTrials.gov (www.clinicaltrials.gov); WHO International Clinical Trials Registry Platform (apps.who.int/trial search). The search strategy was adapted from our published protocol and review on the same topic [12], and run in all databases from June 2012 (search date of previous review) up to 14 April 2024. A manual search of bibliographies of pertinent articles, and a grey literature search were performed using different internet search engines and websites: such as System for Information on Grey Literature in Europe; New York Academy of Medicine Grey Literature Collection and Google Scholar. Furthermore, websites of various healthcare institutions; and governmental and non-governmental organizations associated with MS were searched and experts and researchers active in this field were contacted. No search limitations in terms of study outcomes, or methods of analysis were applied. Search strategies for each database are listed in Appendix 1.

Inclusion and exclusion criteria

All RCTs trialed in adult pwMS (18 years or over) with a confirmed diagnosis of MS (all subgroups) based on validated criteria [30-32] were included. All modalities of non-pharmacological interventions aimed at reducing (generalized, focal, or multifocal) spasticity in pwMS were considered, irrespective of settings (inpatient, outpatient, community rehabilitation centers or specialist rehabilitation centers; home-based settings, patients' own homes, etc.). Reference control groups considered included: no treatment; placebo/sham; waiting list conditions, or interventions given in different settings (ambulatory, inpatient, or home) and lower-intensity or different variants of intervention (e.g., lower dosage/intensity, different mode of delivery). Concomitant pharmacological/surgical interventions were accepted if they were run along with the non-pharmacological interventions in the same way in both the control and treated groups. The review did not consider surgical and pharmacological interventions provided in isolation for spasticity management.

Study selection

All studies identified through the search process and other sources were exported to an EndNote X9 (Clarivate) database to remove duplicates. Two review authors (BA, KS) screened and short-listed all abstracts and titles of studies identified by

the search strategy, based on the predefined selection criteria. Each potential study was independently evaluated, and the full-text article was obtained for assessment to determine the likelihood of inclusion. Any disagreement regarding the possible inclusion/exclusion of any individual study was resolved by consulting with the third author (FK). The final consensus decision was made by group discussion amongst all the authors. Additional information about the method of randomization or a complete description of the interventions from the trialists was sought when required.

Data extraction

All relevant data were extracted independently by two authors (BA, KS) using a standard proforma, which included: publication details; study design, date, sample size, participants' demographic and clinical characteristics, outcome measures; and details of intervention (type, intensity, settings, delivery mode, and duration). Further details were requested from the main author of the studies to obtain additional data and clarification when the provided data were not adequate or presented in graphs or figures format only. All disagreements were resolved by group consensus with the involvement of all review authors. All data were double-checked for any errors.

Assessment of methodological quality of included studies

The Cochrane Handbook for Systematic Reviews of Interventions was followed [33]. Two review authors (BA, KS) independently assessed the methodological quality of the included studies using the Cochrane 'Risk of bias' tool [33] according to the following domains: sequence generation (generation of allocation sequence); allocation concealment (concealment of allocation of participants to different groups); blinding (procedure of blinding of participants, personnel, and outcome assessors); incomplete outcome data (assessment of outcome data); selective outcome reporting (study free of any suggestion of selective outcome reporting); and other biases (other potential threats to validity). Based on predefined criteria, each domain was categorized as 'yes' (low risk of bias), 'no' (high risk of bias), and 'unclear' (either unclear or unknown risk of bias). Based on the judgment on these individual appraisal domains, the overall methodological quality of each study was rated into 3 levels: 'high-quality' (low risk of bias for all domains); 'low-quality' (unclear or high risk of bias for one or more domains) and 'very low-quality' (high risk of bias for most domains). Any disagreements were resolved by consensus among other review authors (MG, FK).

Measures of treatment effect

All data were entered and analysed using the Review Manager Web [34]. A quantitative analysis of the impact of the interventions was not possible due to clinical heterogeneity and a high amount of variability in terms of study methods, evaluated interventions (type, quantity, intensity) and control interventions, used outcome measures and assessment time points; and insufficient data. The certainty of the body of evidence for the spasticity outcomes was independently assessed by two authors (BA, KS) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool employing parameters: risk of bias, inconsistency, imprecision, indirectness, and publication bias [35]. The quality of evidence was graded as: "high" (very confident that the true effect lies close to that of the estimate of the effect); "moderate" (moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); "low" (confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect); and "very low" (very little confidence in the effect estimates and the true effect is likely to be substantially different from the estimate of the effect) [33,35]. Any disagreements were resolved through a consensus-based discussion among all authors.

RESULTS

A PRISMA flow diagram illustrating the study screening and selection process is presented in Fig. 1. A total of 2,943 titles and abstracts were retrieved from the search criteria (MEDLINE=360; Embase=714; CENTRAL=361; CINAHL=118; clinicaltrials.gov=899; Trial Registries via WHO Portal=491). An additional 14 articles were identified from other sources. After removing duplicates, 1,764 articles were screened, with 1683 excluded based on titles and abstracts. Consequently, 81 articles passed the initial screening and were selected for closer examination. The full text of these articles was assessed for further inclusion criteria, resulting in the final inclusion of 32 studies [22,24,36-65]. A total of 49 studies were excluded, with the main reasons for exclusion including: 24 studies not being RCTs, 18 studies lacking spasticity as a specific outcome measure, and 7 published protocols only (a list of excluded studies is detailed in Supplementary Table S1).

Characteristics of the included studies

Characteristics of the included studies are detailed in Table 1. In

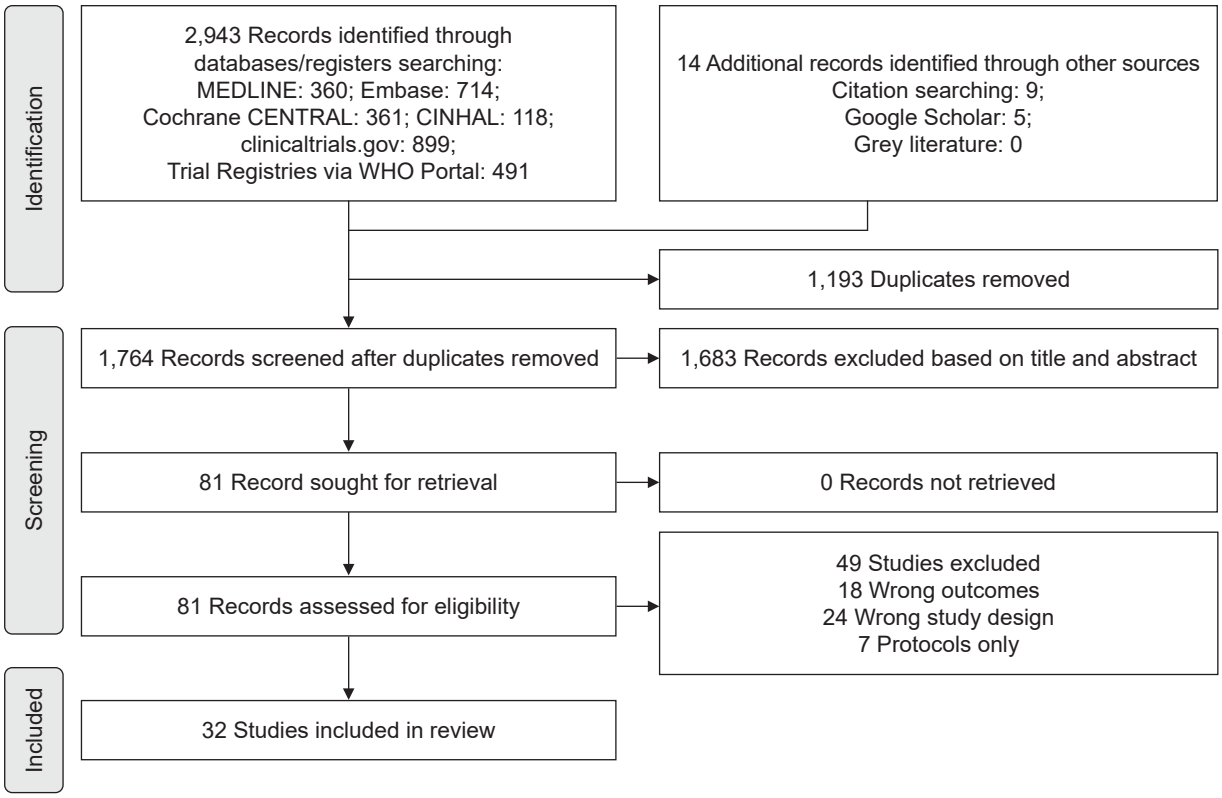

Fig. 1. PRISMA flow diagram showing a selection of article.

total, 32 RCTs involving a total of 1,481 participants were included. The studies highlighted diverse geographical distributions and a variety of non-pharmacological interventions [22,24,36-65]. Most studies were conducted in Europe (n=22), with six in Italy [40,47,50,54,55,58], three each in Turkey [38,60,62] and Austria [43,44,65], two in the United Kingdom [22,24], and one each in Slovenia [63], Denmark [57], Spain [37], France [39], Russia [52], and Germany [64]. Additionally, five studies each were conducted in Iran [36,42,46,56,61] and the United States [48,49,51,53,59], and one in Egypt [45]. Of the 32 included RCTs, four were of cross-over design [24,51,53,54], and one was conducted in two phases (open-label followed by an RCT) [44]. Only three trials were conducted in multiple centers [44,53,64].

Characteristics of the participants

All included studies recruited adult participants with a diagnosis of MS. The majority (n=19 trials) included all types of MS, while four studies exclusively included participants with RRMS [40,45,50,55], and three studies exclusively enrolled participants with SPMS [47,52,58]. The inclusion criteria varied between trials, with all including participants with definite MS, though only 18 trials specified commonly used clinical criteria. The majority (n=10) employed the McDonald criteria [38,41,45,50,52,54,55,58,62,65], four each used the Poser criteria [53,57,59,61], and Polman criteria [40,43,44,48]. The remaining 13 trials did not specify any criteria. All studies required some form of disability/impairment scale score within specified values as an entry criterion. The Expanded Disability Status Scale (EDSS) was the predominant measure used in 17 trials [36-40,45,48,50,51,54-56,58,62-65], followed by the Modified Ashworth Scale (MAS) in seven trials [22,41,46,47,52,57,60]. Four studies used both EDSS and MAS scores [38,39,54,61], two used Numeric Rating Scale (NRS) and EDSS scores [43,44], and one each used the Hauser Ambulation Index [24] and the MS Symptom Rating Form [53]. Two studies did not specify any scores in their selection criteria [42,59]. Most studies enrolled participants with lower limb spasticity.

Evaluated outcomes

Spasticity outcomes

A variety of outcome measures were employed to evaluate spasticity outcomes, and many used more than one tool. The mea-

Table 1. Characteristics and findings of included studies

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Physical therapeutic (exercise) program						
Abadi Marand et al., 2023 [36], Iran	N=64: TG=32, CG=32 TG: age=40.4±6.0 yr, M/F: 17/15, SPMS=21, RRMS=11, EDSS: 4.1±1.1, DD: 14.4±5.2 yr CG: age= 40.7±6.2 yr, M/F: 18/14, RRMS=10, SPMS=22, EDSS: 3.8±1.0, DD: 12.8±5.9 yr	TG: DNS exercises CG: CS Frequency: 15 60-min sessions 3 times per week for 5 weeks	Spasticity: MSSS-88, MAS Balance: BBS, postural stability Falls: falling rate; Fear of falling: activities-specific balance confidence, Biodex Balance System Trunk function: Trunk Impairment Scale Mobility: MSWS-12, TUG Baseline, post intervention (5 wk) & 17 wk	· Significant improvement in spasticity MSSS-88 at post-intervention & 17 weeks follow-up compared with the CS group, (group×time) (F=11.28, p>0.001) · No effect on MAS scores (p>0.05)	At post-intervention & 17 weeks significant improvement in DNS group compared with the CS group (group×time): · BBS (F=65.8, p<0.001) · Trunk Impairment Scale (F=40.6, p<0.001) · Postural stability (F=16.9, p<0.001) · Activities-specific balance confidence (F=10.1, p>0.001) · Reduced falling rate (F=9.0, p<0.001) · TUG (F=9.4, p<0.001) · MSWS-12 (F=3.8, p<0.05) · No AEs from both interventions	⊕⊕⊖⊖ Low
Andreu-Caravaca et al., 2022 [37], Spain	N=30: TG=18, CG=12 Age: 46.0±10.4 yr, M/F=15:15, RRMS=27, SPMS=3, EDSS: 3.2±1.5	TG: strength training (fast-velocity concentric) CG: usual care Frequency: 3 sessions/week on alternating days for 10 weeks	Spasticity: pendulum test Muscle activity: vastus lateralis (sEMG, peak sEMG), voluntary activation (central activation ratio), muscle contractile function Pre & post intervention (10 wk)	· Post-intervention significant improvement in spasticity, with differences between groups, in first swing excursion (right leg: p<0.01, ES=-1.4; left leg: p<0.05, ES=-1.2), number of oscillations (right leg: p=0.001, ES=-0.4; left leg: p<0.05, ES=-0.4) & duration of oscillations (left leg: p<0.01, ES=-0.6)	· Significant improvement with differences between groups in muscle activity (p<0.05, ES=-0.8) & maximal neural drive (p<0.05, ES=-0.8) · Voluntary muscle activation (central activation ratio) increased after intervention in IG (p<0.05, ES=-0.4) · Contractile properties remain unchanged in both groups · No AEs	⊕⊕⊖⊖ Low
Calabrò et al., 2017 [39], Italy	N=40 (RRMS): TG=20, CG=20 TG: age=44 (40–48) yr, M/F=7/13, EDSS: 4.4 (4–4.9), DD=11.5 (8–14) yr CG: age=41 (38–47) yr, M/F=8/12, EDSS: 4.75 (4.1–5.5), DD=11.5 (8–16) yr	TG: RAGT with VR CG: RAGT only Frequency: 5 sessions (30 min general conditioning+40 min RAGT) per week for 8 weeks	Spasticity: MAS Function & balance: TUG, BBS, FIM Cognition: COPE, HRSD Pre & post intervention (8 wk)	· No significant effect on spasticity between group (p>0.05, ES=-0.01, 95% CI=-0.5 to 0.5) or within group (p>0.05 for both groups)	· Non-significant difference between the groups for BBS (ES=-0.02, 95% CI=-2.4 to 2.4, p>0.05) & TUG (ES=-0.06, 95% CI=-0.4 to 0.5, p>0.05) · Significant moderate-to-large effect for positive attitude (ES=-0.5, 95% CI=-3.6 to 2.6) & problem-solving (ES=-0.9, 95% CI=-2.1 to 0.3, p<0.01) · No AEs	⊕⊕⊖⊖ Low

(Continued to the next page)

Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Eftekharsadat et al., 2015 [42], Iran	N=30: TG=15, CG=15 TG: age=33.4±8.1 yr, M/F=5/10, DD=5.8+3.9 yr CG: age=37.0±8.3 yr, M/F=3/12, DD=8.3+4.3 yr	TG: postural stability training program Biodex Balance System with VR CG: no intervention Frequency: 2 sessions (20 min) per week for 12 weeks	Spasticity: MAS Function & balance: MMT, TUG, Romberg test, BBS Fall risk & postural stability tests: FRI, and OSI Pre & post intervention	· No significant difference between groups on spasticity (MAS) scores of the knee & hip (p>0.05)	· Significant improvement in functioning but not in balance · No significant difference between groups on MMT scores of the wrist, hip, & knee, or BBS scores (p>0.05 for all) · Significant improvement in TUG scores in intervention group (p=0.01) · Significant improvement in FRI (p<0.001) & OSI (p<0.01) in intervention group · No report on AEs	⊕⊕⊖⊖ Low
Ergül et al., 2021 [46], Iran	N=26: TG=13, CG=13 TG: age=45.3±12.0 yr, M/F=7/5, DD=13.4±7.9 yr CG: age=43.8±7.6 yr, M/F=5/7, DD=13.4±7.9 yr	TG: SSE of hamstrings, quadriceps, hip adductors, plantar flexors muscles CG: FSE Frequency: 3 sessions (25–30 min) per week for 4 weeks	Spasticity: MAS Function: TUG, T25FWT, active ROM assessment Pain: VAS QOL: EQ-5D-5L Pre & post intervention (4 wk)	Significant reduction in spasticity in both groups (p<0.05), but no difference between groups In SSE group: · Strong correlation between decreased spasticity of quadriceps & improved function (TUG, r=0.7, p<0.01) · Strong correlation between decreased spasticity of quadriceps & improved walking (T25FWT, r=0.7, p<0.01) · Moderate correlation between decreased spasticity of hip adductors & improved strength (TUG, r=0.7, p<0.05) In the FSE group · Moderate correlations between decreased spasticity & increased ROM (r=0.7, p<0.05) & between increased ROM & functional improvement (p<0.05) · Strong correlation between decreased spasticity & increased HRQOL (p<0.01)	· Compared to baseline both groups showed significant improvement of functional tests, decrease of pain, increase of ROM & increase of HRQOL (p<0.05) · No significant differences between both groups in all variables before & after treatment (p>0.05) · No report on AEs	⊕⊕⊖⊖ Low

(Continued to the next page)

Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Giovannelli et al., 2007 [47], Italy	N=37: TG=20, CG=20 (18 at follow-up) TG: age=46.0±9.0 yr, M/F=2/18, EDSS: 5.8±1.3 CG: age=48.1±7.5 yr, M/F=2/16, EDSS: 6.0±1.1	BoNT & PT (passive or active exercise & a stretching regimen) Frequency: 40 min session daily/15 days after BoNT Control group: BoNT alone	Spasticity: MAS & VAS Function: EDSS Baseline, & weeks 2, 4, & 12	Significant decrease in MAS score in TG from baseline at (MD±SD): · Week 2: TG=-0.91±0.52, CG= -0.39±0.50, p<0.01 · Week 4: TG=-1.0±0.69, CG= -0.28±0.46, p<0.01 · Week 12: TG=-0.95±0.78, CG= -0.28±0.46, p<0.01 Mean (%) difference in MAS between baseline & 12 weeks: TG=-0.95 (26.1), CG=-0.28 (7.7) (p<0.01) Significant improvement in spasticity in VAS rating scale (MD± SD): · Week 2 to week 4: TG=1.77± (0.87), CG=0 (1.08), p<0.01 · Week 4 to week 12: TG=2.68 (1.08), CG=1.06 (1.16), p<0.01	· No adverse events post BoNT injections	⊕⊕⊖⊖ Low
Hugos et al., 2024 [49], USA	N=231: IG=115, CG=116 IG: age=53.7±12.1 yr, M/F=16/99, RRMS=64, PPMS=50, DD= 15.3 yr CG: age=55.1±11.1 yr, M/F=16/100, RRMS=54, PPMS=62, DD=17.0 yr	IG: STC: stretching exercise & education program CG: ROM exercises & education program Frequency: 2 h/wk classes; exercises: 15–30 mins/day	Spasticity: MSSS-88, NRS Function: MSWS, TUG, T25MW Fatigue: MFIS Others: PSQI, PROMIS (short form 8a), MSIS At 1 and 6 months	· No significant difference in MSSS scores between STC and ROM at 1 month (MD=0.28, 95% CI=-9.45 to 10.01, p>0.05) or 6-month (MD=-0.86, 95% CI=-12.2 to 10.5) · Significant improvements in group mean MSSS scores at 1 and 6 months in both groups	· Significant difference between groups in fatigue (MFIS, NRS) and impact of MS (MSIS) · No significant improvement in function (MSWS, TUG, T25FW)	⊕⊕⊖⊖ Low
Negahban et al., 2013 [56], Iran	N=48 (12 in each TGs & CG) TG I: age=36.3±7.6 yr, M/F: 2/10, EDSS=3.8±1.4, DD=48.7±97.1mts TG II: age=6.7±6.7 yr, M/F: 2/10, EDSS: 3.5±1.1, DD=102±81.1 mts TG III: age=36.7±7.6 yr, M/F: 2/10, EDSS: 3.6±1.4, DD=115.3±78.3 mts CG: age=36.8±8.7 yr, M/F: 2/10, EDSS=3.8±1.4, DD=86.6±34.3 mts	4 parallel groups: TG I: Swedish massage; TG II: exercises (strength, stretch, endurance & balance); TG III: combined massage & exercise CG: standard medical care Frequency: three 30 min sessions a week for 5 weeks	Spasticity: MAS (ankle plantar flexors) Pain: VAS Fatigue: FSS Function & gait/balance: BBS, TUG, 10MWT HRQOL: MSQLI-54 Pre & post intervention (5 wk)	· Significant improvement in MAS in TG I: MD±SD=0.54±0.6, p<0.01) & TG II: 0.47±0.7, p<0.05), but not in TG III: 014±0.8, p>0.05) · Significant worsening in MAS scores in CG: -0.33±0.5, p<0.05 · No significant difference between groups	· FSS scores improved in all TGs but worsened in CG · No significant difference in MSQL-54 between groups · Significant improvement in TUG in TG I (4.78±5.9, p<0.01 · TG I showed significantly larger change scores in all outcome measurements than the CG · TG II showed significant improvement in all outcomes except pain VAS scores than CG · No intolerance or the AEs of intervention	⊕⊕⊕⊖ Moderate

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Tarakci et al., 2013 [62], Turkey	N=110: TG=55, CG=55 TG: age=41.49±9.37 yr, M/F=17/34, EDSS: 4.38±1.37, DD: 9±4.71 yr CG: age=39.65±11.18, M/F=18/30, EDSS: 4.21±1.44, DD: 8.42±5.38 yr	Group exercise training including strength training, balance & coordination, core stabilisation, etc. Frequency: 3 sessions (1 h) a week for 12 weeks	Spasticity: MAS Function & balance: BBS, 10MWT, 10-steps climbing test Fatigue: FSS QOL: MSIQOL Pre & post intervention	Significant improvements in all lower limb spasticity (MAS scores) (p<0.05 for all) post-treatment: · R hip flexors: p<0.001, ES=1.01 · L hip flexors: p=0.015, ES=0.3 · R hamstring: p<0.001, ES= 0.92 · L hamstring: p<0.001, ES=0.8 · R Achilles: p<0.05, ES=0.54 · L Achilles: p<0.001, ES=0.95	Significant improvements in TG compared to CG: · Balance: BBS score increased 4.33 in the exercise group, while a decrease of 2.33 in CG (p<0.01) · Walking: 10MWT-decreased 2.72 seconds in TG, while increased by 1.44 in CG (p<0.001) · Reduction in fatigue: FSS score (<0.001) · Improve QOL: MusiQOL (p<0.05) · No AEs	⊕⊕⊕⊖ Moderate
Velikonja et al., 2010 [63], Slovenia	N=20: number of participants in each group not stated TG: (median): age=42, EDSS: 4.0 CG (median): age=41, EDSS: 4.2	TG: sports climbing (climbing wall, climbing belt and top rope system, climbing up and down wall) CG: yoga (stretching, strengthening exercises, breathing exercises, isometric muscle contraction & relaxation) Frequency: once a week for 10 weeks	Spasticity: MAS Function: EDSS Cognition: (executive function, attention span), Mazes subtest of Executive module from NAB, TOL, Brickenkamp d2 test Mood: CES-D Fatigue: MFIS Baseline & after treatment (10 wk)	· No significant improvements in spasticity after both interventions (p>0.05) · SC group had 25% reduction (p=0.046) in EDSS per year; before 4.0 (3.0–4.0) after 3.0 (2.5–4.0)	· Significant reduction in fatigue in TG (32.5%, p<0.05), while CG had no effect · Improved fatigue impact in TG before & after: MFIS 40.0 (36.5–53.0) to 27.0 (21.5–45.5), p<0.05 and MFIS cognition 17.0 (8.5–21.5) to 8.0 (6.0–19.5), p<0.05; MFIS physical 25.0 (21.5–28.5) to 19.0 (9.0–26.5), p<0.05 · No differences in executive function and mood · Increase in selective attention performance in the yoga group (17% increase; baseline: 151.0 (94.5–175.5); after: 176.5 (116.5–191.3; p<0.01) · No report on AEs	⊕⊖⊖⊖ Very low
Vermöhlen et al., 2018 [64], Germany	N=70: TG=32, CG=38 TG: age (Md, IQR)=50 (45–53), M/F=3/27; EDSS<5.0 in 33%, DD (Md, IQR): 16.5 (11–20) CG: age=51 (47–56), M/F=10/27, EDSS<5.0 in 30%, DD: 17.6 (11–27)	TG: hippotherapy & standard care CG: standard care Frequency: once a week for 12 weeks	Spasticity: NRS Balance: BBS Others: FSS, MSQOL-54, VAS pain scale Baseline, 6 weeks & 12 weeks	· Spasticity significantly improved in TG (NRS) from baseline to week 12: change from baseline=-1.7 points, no change in CG (-0.6), MD: -0.9 (95% CI: -1.9 to -0.1, p<0.05)	· Significant improvement in balance (BBS score, MD=2.33, 95% CI=0.03 to 4.63, p=0.047) · Benefit was largest for the subgroup with an EDSS≥5 (BBS score SD=5.1, p=0.001) · Significant improvement in fatigue (FSS score, MD=-6.8, p<0.05) · Significant improvement in QOL (MSQol-54, physical (MD=12, p<0.001) & mental health (MD=14.4, p<0.001) · 49 AEs (IG: 22 AEs in 13 patients, CG: 27 AEs in 15 patients); 3 serious AEs due to the necessary hospitalization (IG: 1 SAE [MS relapse], CG: 2 SAEs [MS relapse & infection])	⊕⊖⊖⊖ Very low

(Continued to the next page)

Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Zrzavy et al., 2021 [65], Austria	N=39: TG I=13, TG II=8, CG=11 TG I: age=43.9±6.2 yr, M/F=4/13, EDSS (MD, range): 4 (4–5), DD: 13±9 yr TG II: age=41.5±11.3 yr, M/F=4/7, EDSS=3.5 (2–5), DD=6±5 yr CG: age=43.9±6.1 yr, M/F=2/9, EDSS=6 (4–5), DD=14±7 yr	TG I: rehabilitation program+hypoxic endurance training TG II: rehabilitation program+normoxic endurance training CG: rehabilitation program Frequency (group 2 & 3): 45 minutes over 12 days (separated by a day without training)	Spasticity: MSSS-88 Fatigue: Erschöpfungsinventar bei Multipler Sklerose (WEIMuS), MFIS Walking: 6MWT Depressive symptoms: ADS Baseline, 7 days & 14 days	· Significant lower spasticity scores (MSSS-88) in both endurance training groups at 14 days (TG I: p=0.012; TG II: p<0.05) · Significant improvement in spasticity at 1 week in TG II (p<0.01) · No improvement in CG	· Significant improvement in walking endurance (6MWT) in TG I only at 14 days (p=0.001) · Fatigue scores improved significantly in all groups, but these improvements reached faster in TG I (p<0.01) & TG II (p=0.004) · No report on AEs	⊕⊕⊖⊖ Low
Magnetic brain stimulation						
Boutière et al., 2017 [39], France	N=17: TG= 9, CG=8 TG: age=48.2±9.4 yr, M/F=5/4, SPMS=6, RRMS=3, EDSS (Md, IQR): 6 (4–7), MAS: 7.6±4.7, DD: 12.2±8.2 yr CG: age=55.4±11.1 yr; M/F=4/4, SPMS=7, RRMS=1, EDSS=6 (6–6.5), MAS=5.6±2.7, DD=18.7±11 yr	TG: iTBS (10 bursts of 3 stimuli (50 Hz) repeated at theta frequency (5 Hz) every 10 seconds for a total of 600 stimuli (192 s) adjuncts to rehabilitation program CG=sham iTBS Frequency: once a day for 13 consecutive working days	Spasticity: MAS, VAS Brain function: resting-state fMRI Baseline, day after the last session of iTBS (week 3) & at the end of the 5-week rehabilitation program (week 5)	· Significant improvement in VAS spasticity score in iTBS group (p=0.026) · MAS score improved in both groups, but no significant difference between groups (p>0.05) · Changes in inter-hemispheric balance were correlated with improvement of spasticity (p<0.05)	· Significant effect of iTBS on the balance of the connectivity degree between the stimulated & the homologous primary motor cortex (p<0.01) · No effect of iTBS on global topology of brain network, suggesting that iTBS over the primary motor cortex does not alter global organization of brain network · No report on AEs	⊕⊕⊕⊖ Very low
Dieguez-Varela et al., 2019 [41], Spain	N=17: TG=10, CG=7 Age: 49.8±9.8 yr, M/F: 7/10, DD=12.4±6.4 yr	TG: iTBS (10 bursts with 3 pulses at 50 Hz repeated at 200 ms intervals (5 Hz) every 10 s for a total of 600 stimuli CG: sham stimulation Frequency: 10 daily sessions for 2 weeks	Spasticity: MAS, H/M amplitude ratio, PCS in the soleus muscle Assessments: immediately after 1 (S1), 5 (S5) & 10 (S10) sessions; 1 week (day 19) & 2 weeks after treatment	· No significant differences between the two groups in MAS & other clinical variables (PCS, adductor tone, joint balance, foot support & the Hauser ambulatory index) at any of the assessment time points · Significant decrease in H/M amplitude ratio from baseline (0.42±0.29) vs. S1 (0.35±0.25, p<0.05), vs. S5 (0.35±0.26, p<0.01) & vs. S10 (0.35±0 .27, p<0.01) · Effect was maintained up to 1 week after the last stimulation session: S1 (0.42±0.29) vs. day 19 (0.36±0.28), p<0.05 · No significant changes in CG	· AEs: 2 reported (subjective weakness in the right foot after the second session & a subsequent fall; & mild headache)	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Korzhova et al., 2019 [52], Russia	N=34 SPMS: TG I: 12, TG II: 12, CG: 10 TG I: age=38 (29–54) yr, M/F=4/8, EDSS=6.5 (6–6.5) TG II: age=47 (43–53) yr, M/F=5/7, EDSS=6.5 (6–6.5) CG: age=45.0 (41–47) yr, M/F=5/5, EDSS=6.5 (6–6.5)	TG I: rTMS (20 Hz) & PT 45–55 min spastic muscle strengthening sessions TG II: iTBS CG: sham rTMS Frequency: 1 stimulation per day for 5 sessions for 2 weeks	Spasticity: MAS, SESS, NAS Fatigue: MFIS Other: pain level scale Baseline (T0), post intervention (T1, 10 sessions), 2 weeks (T2) & 12 weeks (T3)	· At T1, significant reduction MAS in both TG I (MD= -1.0, 95% CI: -1.3, -0.6, p<0.001), & TG II (MD=-1.5, 95% CI: -2.1, -0.8, p<0.001), but not in CG (MD= -0.2, p<0.05) · At T1 significant reduction of spasticity level as measured by SESS in both TG I: MD (95% CI)= -1.0 (-2.0, 0.0) & TG II: MD=-1.0 (-1.5, -0.5), but not in CG: MD=-0.5 (-1.3, 0.3) · At T1 significant reduction in NAS scores TG I: MD (95% CI=-2.8 (-4.0, -1.5), TG II: MD=1.6 (-2.9, -0.2), & CG=-1.3 (-2.3, -0.3) · At T3 significant reduction in SESS score only in iTBS group	· Significant reduction in pain in TG I only: MD (95% CI) =-5.0 (-8.6, -1.4) but not in TG II or CG · Significant reduction in MFIS score in TG I only: -7.0 (-11.7, -2.3), but not in TG II or CG · No AEs	⊕⊕⊕⊖ Moderate
Mori et al., 2011 [55], Italy	N=30: TG I: 10, TG II: 10, CG: 10 TG I: age=39.1±10.7 yr, M/F=7/3, EDSS=3.6±1.2 TG II: age 38.3±11.9 yr, M/F=5/5, EDSS=3.5±1.0 CG: age=37.7±12.3 yr, M/F=6/4, EDSS=3.8±1.6	TG I: iTBS (10 bursts, with each burst of 50 Hz 3 stimuli, repeated at a theta frequency of 5 Hz every 10 seconds, for a total of 600 stimuli (200 s) & exercise therapy TG II: iTBS alone CG: sham stimulation & exercise therapy Frequency: 10 bursts, 2 weeks	Spasticity: MAS, MSSS-88 Fatigue: FSS ADLs: BI HRQOL: MSQOL-54 Baseline & after treatment (2 wk)	Significant improvement in TG I: · MAS from the stimulated leg (2.1±0.4 before treatment; 1.3±0.4 after treatment; p<0.05) · MSSS-88 (74.3±11.4 before treatment; 53.2±10.9 after treatment; p<0.001) · In TG II, significant improvement in MAS (3.3±0.8 before treatment; 1.6±0.8 after treatment; p<0.05) · No significant changes in CG	Significant improvement in TG I on: · FSS (39.5±4.2 before treatment; 31.6±4.6 after treatment; p<0.05) · BI (92.5±2.4 before treatment; 95.0±1.85 after treatment; p<0.05) · MSQOL-54 physical health composite (59.7±2.7 before treatment; 64.8±2.7 after treatment; p<0.05) scores after treatment · None of the measured scales showed significant changes in CG · No report on AEs	⊕⊕⊖⊖ Low
Nielsen et al., 1996 [57], Denmark	N=38, TG: 21, CG: 17 TG: age=44 (34–67) yr, M/F=7/14, DD=12 (2–34) yr CG: age=44 (26–66) yr, M/F=5/12, DD: 13 (2–30) yr	TG: rTMS (1 25 Hz session of 16 stimuli over the leg motor area & 1 session of 5 Hz rTMS CG: sham stimulation Frequency: twice daily for 7 days	Spasticity: AS & Achilles tendon reflex grading scores; ease of ADLs (related to spasticity) Electrophysiological & biomechanical measurement: stretch reflex threshold Baseline & after treatment (1 day, 8 days, & 16 days)	At day 1 post-treatment: · AS score improved significantly in TG (MD= -3.3± 4.7 AU vs. 0.7± 2.5 AU, p<0.01) · Threshold of the stretch reflex significantly increased in TG (4.3±7.5 deg/s vs. -3.8±9.7 deg/s, p=0.001) At day 8 post-treatment · Threshold of the stretch reflex remain improved significantly in TG (4.4±7.5 deg/s vs. -1.8±8.5 deg/s, p<0.05) · No statistically significant difference in AS or self-score of ease of ADLs between groups At day 16 post-treatment · No statistically significant difference in any of the scores between two groups	· Significant improvement in self-score of ADLs in both groups · Self-score of ease of ADLs improved significantly in both groups on day 1 post-intervention (p<0.05 for both groups), but was no difference between the two groups · No report on AEs	⊕⊕⊖⊖ Low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Şan et al., 2019 [60], Turkey	N=16, TG=10, CG=6 TG: age=48.7±14.3 yr, M/F=6/4, DD=14.7±7.7 yr CG: age=53.0±8.8 yr, M/F=2/4, DD=19.5±10.9 yr	rTMS (5 Hz, 900 pulses over 15 minutes over vertex region targeting lower extremity motor area) CG: sham rTMS Frequency: 15 minutes for 10 sessions over 2 weeks	Spasticity: MAS, PSFS, Passive ROM Others: MSQOL-54, Epworth Sleepiness Scale, patient satisfaction, voiding diary Baseline, 1 week & 1 month after post-intervention	· Significant reductions in the MAS scores for the hip adductors bilaterally over time in TG ($p<0.01$), but no significant differences in CG ($p>0.05$) · Significant improvements in spasm (PSFS) in TG at both 1 week & 1 month ($p<0.01$), but no significant differences in the CG ($p>0.05$)	· Significant improvements in the rTMS group patient satisfaction, amount of urine leakage, actual health status, perceived health status, energy & fatigue, role limitations due to physical problems, social function ($p<0.05$ for all) · Significant improvement in overall QOL in TG (MSQOL-54) ($p<0.05$) · No AEs or complications were observed	⊕⊕⊖⊖ Low
Vibration therapy						
Ayvat et al., 2021 [38], Turkey	N=33: TG I=11, TG II=11, CG=11 TG I: age=37.7±9.7 yr, EDSS: 3.0±1.1, DD: 135.6±77.2 mo TG II: age=38.4±11.1 yr, EDSS: 2.75±1.0, DD= 84.0±56.9 mo CG: age=33.9±6.7 yr, EDSS=3.0±0.8, DD=127.0±84.4 mo	TG I: local vibration 50 Hz & exercise TG II: local vibration 100 Hz & exercise CG: exercise only Frequency: 1 hour a day for 3 sessions per week for 8 weeks	Spasticity: MAS Ankle joint position sense: isokinetic dynamometer Balance: Single Leg Stance Test & post-urographic assessment Gait: GAITRite Analysis System Baseline & post-treatment (8 wk)	· Significant decrease in spasticity & increase in fascicle length in TG I (both $p<0.05$) · No change in TG II and CG · No significant difference between groups	· Significantly improvement in ankle joint position sense, single-leg stance time, limits of stability/postural sway range in the mediolateral direction in both treatment groups (all $p<0.05$) · Significant improvement in antero-posterior limits of stability & postural sway in all groups (all $p<0.05$) · TG I showed significant improvement in all walking parameters & mediolateral limits of stability · Significant improvement in velocity, step length & base of support values in the TG II (all $p<0.05$) · Between group comparisons, significant difference was found only in mediolateral limits of stability ($p<0.05$) · CG showed significant improvement only for single support & stance phase percentages of the gait cycle (both $p<0.05$) · No report on AEs	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Paoloni et al., 2013 [58], Italy	N=48: TG I=14, TG II=14, CG=14 TG I: age=54.9±8.8 yr, M/F=6/8, EDSS: 5.3 (4–5.5) TG II: age=47.4±5.6 yr, M/F=5/9, EDSS: 4.8 (3.5–5.5) CG: age=50.6±8.9 yr, M/F=7/7, EDSS: 5.5 (4–6)	TG I: segmental muscle vibration (120 Hz) TG II: vibration & BoNT-A injection CG: BoNT-A injection Frequency: 30 min 3 times per week, over 4 weeks	Spasticity: MAS Fatigue: FSS ADLs: BI Baseline, 10 weeks & 22 weeks	· MAS score at knee & ankle significantly decreased over time (p<0.001) in all groups, but no differences between groups · Participants not receiving BoNT-A injection only displayed a significant increase in knee & ankle spasticity at 10 weeks (p<0.05)	· Significant reduction in fatigue (FSS scores) in vibration group & BoNT-injection only group at both 10 weeks & 22 weeks (p<0.05 for both), while no differences were detected in BoNT+vibration group · Significant improvement in spasticity in all participants · No differences in disability (BI) over time · No adverse events	⊕⊖⊖⊖ Very low
Schyns et al., 2009 [24], UK	N=16, TG I=8, TG II=8 Cross over design TG I: age=45.8±8.4 yr, M/F=3/5, DD: 6.7 yr (10 mo–23 yr) TG II: age=49.5±6.14 yr, M/F=1/7, DD=11.8 (3.5–11.8) yr	TG I: WBV 40 Hz, low amplitude (2 mm) for 30 seconds & stretching+strengthening exercise TG II: treatment in reverse order to TG I Frequency: 3 times/week for 4 weeks, 2 weeks no intervention & then 4 weeks of exercise alone	Spasticity, MAS, MSSS-88 Function: 10MWT, TUG Muscle force: dynamometer Sensation & proprioception: Nottingham sensory Assessment HRQOL: MSIS-29 Baseline & after treatment (4 wk) twice with 2 weeks cool off period	· No change in MAS scores for either intervention · Tone tended to increase more for exercise alone compared with whole body vibration & exercise · MSSS-88 spasm: greater reduction in score in TG compared CG (p<0.05, 95% CI=2.00, 14.50)	· Significant improvement in MSSS-88 scores pain (p=0.036) · No statistically significant changes for other MSSS-88 components (ADL, social functioning, stiffness, gait, body movement & emotional health) · No effects on sensation · Walking: both interventions increased the subjects' walking speed, no difference between groups (10MWT, p>0.05), (TUG, p>0.05) · MSIS-29: overall well-being improved in both groups, no statistically significant difference between groups (p<0.05) · No report on AEs	⊕⊖⊖⊖ Very low
Educational/self-management programs						
Ehling et al., 2017 [43], Austria	N=94: TG=47, CG=47 2 phases: open label followed by RCT TG: age=46.6 (43.2–50.1) yr, M/F=5/5, SPMS: 8, RRMS: 2, EDSS=4.2 (3.1–5.3), DD: 12.6 (8.8–16.5) yr CG: age=50.5 (44.6–56.5) yr, M/F=6/4, SPMS: 9, RRMS: 1, EDSS: 5.4 (4.2–6.5), DD: 16.3 (10.6–22.0) yr	Both groups received 4 weeks of inpatient MDR TG: 'MS-spasticity APP'-based exercises program CG: paper-based exercise program for 3 months, after 3-months all received MS-spasticity-based program for another 3 months	Spasticity: NRS, MAS, Spasm Frequency Score Muscle strength: Motricity Index Function: T25FWT, Others: self-rating scale for QOL, cognition, pain, fatigue Baseline, 12 weeks & 24 weeks	· No change in MAS scores · At 12 weeks, significant reduction in TG (NRS MD=1.2, p<0.05) · At 24 weeks, "MS-spasticity APP" was associated with a decrease in spasticity (NRS scores) in all participants (MD=2.5±1.7)	· No difference in QOL, strength, pain, fatigue & cognition	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Ehling et al., 2022 [44], Austria	N=94: TG=47, CG=47 TG: age=50.8 (41.8–57.9) yr, M/F=18/29, SPMS:13, RRMS: 26, PPMS: 8, EDSS: 5.0 (4–6), DD (median, IQR): 13.3 (10.1–22.7) yr CG: age=46.4 (41.7–55.5),; M/F=14/33, SPMS: 21, RRMS: 120, PPMS: 6, EDSS: 6.0 (4.5–6.5), DD: 12.5 (9.7–20.1) yr	MDR-inpatient (phase A) followed by TG: MS-Spasticity App delivered CG: paper-based exercise self-training program over 12 weeks (phase B)	Spasticity: NRS, MAS, Spasm Frequency Score Function: Motricity Index Balance: FSST Walking: T25FWT, 2MWD Fatigue: Würzburger Erschöpfungs-Inventar bei Multipler Sklerose Cognition: HADS, SF-36 Pre & post intervention	· Significant reduction in spasticity after MDR (NRS) (p<0.000), MAS (p<0.001), Spasm Frequency Score (p=0.001) · Superior effects on spasticity in the TG (median NRSs difference=-1.0, 95% CI=-1.7 to -0.3, p<0.01)	· MDR was also associated with significant improvements strength of lower extremities (p<0.001), & all mobility outcome measures (p<0.001) MS-Spasticity App was associated with: · Some improvement in balance (FSST) & walking distance (2MWD) · Significant reduction in cognitive fatigue (p<0.05), but no differences in levels of physical fatigue · Significantly higher exercise completion rate (92% vs. 72%, p<0.001)	⊕⊖⊖⊖ Very low
Hugos et al., 2017 [48], USA	N=40: TG=20, CG=20 TG: age=52.8±12.3 yr, M/F=7/13, SPMS: 6, RRMS: 10, PPMS: 3, EDSS: 4.8±1.1, DD: 15.1±8.1 yr CG: age=53.4±12.8 yr, M/F=4/16, SPMS: 4, RRMS: 8, PPMS: 7, EDSS: 4.9±1.5, DD: 15.7±10.5 yr	TG: group self-management program CG: usual care (stretching booklet & home stretching) Frequency: 2 hourly session & daily stretch for 4 weeks	Spasticity: MAS, MSSS-88 Function: TUG, T25FWT, 2MWD, MSWS-12 Cognition: MSIS-29, BDI-II Pre & post intervention	· No significant changes in MAS between TG & CG (MD=-1.6 vs. -1.4, p=0.953) · Significant improvement in MSSS-88 total scores in TG compared to CG (MD=-27.8 vs. -3.7, p<0.05); on the pain & discomfort subscale (MD=-3.9 vs. +0.3, p<0.05) & muscle spasms subscale (MD=-5.0 vs. -0.5, p<0.05)	· Significant improvement in TG in fatigue (MFIS p=0.03), depression (BDI-II, p=0.004), physical function (MSIS-29, p<0.01), & knowledge about spasticity on a written test (p<0.05) · No significant group difference (p>0.05) · No significant changes in physical tests	⊕⊖⊖⊖ Very low
tDCS						
El Habashy et al., 2022 [45], Egypt	N=20: TG=10, CG=10 TG: age=30±6.53 yr, EDSS=4.15±1.31, DD=3.70±3.09 yr CG: age=3.0±9.8 yr, EDSS=4.15±0.91, DD=4.30±3.47 yr	TG: anodal tDCS CG: sham tDCS Frequency: 1/daily session of 20-minute stimulation, 5 consecutive days	Spasticity: MAS, H latency, H/M amplitude ratio Before & after treatment (5 days)	· No significant differences in the MAS scores in both groups (p=0.22) · H/M amplitude ratio: TG showed significant improvement (0.6±0.2 vs. 0.5±0.1), no change in CG (0.6±0.2 vs. 0.6±0.2) · H latency: no difference in TG (30.8±2.8 vs. 30.3±2.6), but significant decreased in CG (32.9±2.6 vs. 31.9±2.6)	· No report on AEs	⊕⊖⊖⊖ Very low
Iodice et al., 2015 [50], Italy	N=20: TG=10, CG=10 TG: age=43.3±7.5 yr, M/F=2/8, EDSS: 3.6±0.9, DD=7.0±3.1 yr CG: age=40.3±4.5 yrs, M/F=3/7, EDSS: 3.8±0.9, DD=7.8±1.9 yr	TG: anodal tDCS (2 mA to primary motor cortex of the more affected side) CG: sham tDCS Frequency: 20 min/day for 5 days	Spasticity: MAS, MSSS-88 Function: MSWS-12 Baseline & post-intervention (5 days)	· No significant interaction for spasticity scales: MAS (p>0.05); MSSS-88 (p>0.05) · No significant differences between the two groups post-intervention: MAS, MSSS-88 (p>0.05 for both)	· No significant changes in walking in both groups (MSWS-12, p>0.05) · No group difference (MSWS-12, p>0.05) · No AEs	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Pulsed electromagnetic device						
Lappin et al., 2003 [53], USA	N=117 multisite cross-over design, all underwent treatment device alternating with control device and vice versa Age (range)=21–64, M/F=28/89, SPMS: 27, RRMS: 52, PPMS: 12, DD (range)=1 to >13 yr	TG: PEM device CG: placebo Frequency: 4 weeks for up to 24 h/day), separated by a 2-week washout period	MSQLI: fatigue, pain, spasm/spasticity, bladder control, QOL Function: MS Performance scales; MS Rating Form and Mobility Index Baseline, after 4-week treatment & 10 weeks	· No significant reduction in spasticity · Significant improvement in spasms (MD=-0.13; p<0.05) · No further data or analysis reported for spasms/spasticity	· Significantly greater Improvement in fatigue & overall QOL · No significant differences in the treatment effects for bladder control (p>0.05) (MSQLI) & disability composite (p>0.05) (MSPS) · 3 scales (fatigue, pain & spasticity) used to create the QOL index (QLI) showed moderate inter-correlations (r=0.32 to 0.60), however, bladder control scale showed poor correlation with other MSQLI scales (r=0.00 to 0.26) · No report on AEs	⊕⊖⊖⊖ Very low
Richards et al., 1997 [59], USA	N=30: TG=15, CG=15 TG: M/F=8/11, SPMS or PPMS: 8, RRMS: 7, EDSS: 5.1 (0–9) CG: M/F=5/10, SPMS or PPMS: 10, RRMS: 5, EDSS: 4.98 (0–8.5)	TG: magnetic pulsing device (Enermed), range: 4–13 Hz (50–100 milliCauss) CG: sham device Frequency: 10–24 hours a day for 2 months	Patient-reported performance scale-symptoms: spasticity, bladder control, cognitive level, fatigue level, hand function, mobility, sensation, vision Function: EDSS brain electric activity: quantitative EEG during a language task) Baseline & after treatment (2 mo)	· Significant difference between pre-treatment & post treatment within the treatment group in spasticity: MD=-0.80±0.23; p<0.01 · No difference between group	· No significant change in EDSS scale · Significant improvement in the performance scale combined rating for: bladder control, cognition, fatigue, mobility, vision (p<0.05 for all) · Significant change between pre-treatment & post-treatment in alpha EEG magnitude during the language task · 19 AEs reported (11 in intervention group & 8 in control group)	⊕⊖⊖⊖ Very low
TENS						
Miller et al., 2007 [22], UK	N=32: TG=16, CG=16 Cross-over design Demographic not reported	TENS (100 Hz, 0.125 ms pulse width)-60 minutes vs. 8 hours Frequency: 2 weeks of 60 minutes (period A) & 8 hours daily (period B) followed by 2 weeks washout period	Baseline & after (2 wk) treatments; & follow-up (8–20 mo) for the questionnaires for patient report for symptoms	· No statistically significant differences in the Global Spasticity Score following either 60 minutes or 8 hours daily of TENS (p>0.05 for both) · 8-hour TENS compared with 60 minutes led to significant reduction in muscle spasm (p<0.05) & pain (p<0.01)	· At the end of the study (8–20 mo) patients reported reduction in symptoms: 87.5% for spasm, 73.3% for pain & 73.3% for stiffness · No report on AEs	⊕⊖⊖⊖ Very low

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Table 1. Continued

Reference	Participants' characteristic	Intervention	Outcome measure, assessment time point	Result		Certainty of evidence (GRADE)
				Spasticity outcome	Other outcome	
Shaygannejad et al., 2013 [61], Iran	N=58: TG=28, CG=30 TG: age=39.5±9.3 yr, M/F=9/17, SPMS: 5, RRMS: 20, PPMS: 1, EDSS: 2.1±1.4, DD: 7.2±5.0 yr CG: age=38.9±7.8 yr, M/F=6/12, SPMS: 8, RRMS: 18, PPMS: 0, EDSS: 2.6±1.3, DD: 5.3±2.8 yr	TG: TENS (100 Hz, with pulse width set at 250 ps) 20–30 minutes CG: baclofen (10 mg twice daily, increasing over 3 weeks to 25 mg) Frequency: 4-week	Spasticity: MAS Baseline & 4 weeks	· Significant reduction in MAS score at 4 weeks in both groups (TG MD=-1.04, CG: MD=-0.58, p<0.001 for both) · MAS scores significantly lower in TG at 4 weeks than CG (MD=-0.42, p<0.05)	· Four participants from the baclofen group dropped out due to AEs	⊕⊖⊖⊖ Very low
Shock wave therapy						
Marinelli et al., 2015 [54], Italy	N=68: TG=34, CG=34 TG: age=51.7± 11.3 yr, M/F=14/20, EDSS: 6.6± 0.8 CG: age=51.00±13.2 yr, M/F=16/18, EDSS: 6.2±1.2	TG: RSWT over ankle extensor muscles (4 Hz frequency, with a pressure of 1.5 Bars, 2,000 shots) CG: placebo RSWT Frequency: 4-session course, with a 1-week interval between sessions	Spasticity: MAS Spinal excitability: H-reflex Pain: VAS Ankle strength: Medical Research Council rating Walking: 10MWT Baseline; 1 week after the first session; & 4 weeks after last session	· MAS scores significantly decreased only at 1 week (MD=-0.78, p<0.0001) · No changes at 4 weeks · No significant changes in H-reflex compared to healthy controls	· Significant reduction in pain VAS scores at all follow-up assessments, with the maximal effect at 1 week (MD= 3.05, p<0.0001) · No significant changes in ankle strength & walking · Spinal excitability was unaffected · No significant changes in any of the parameters in CG · No AEs	⊕⊖⊖⊖ Very low
Complementary and alternative medicine						
Karpatkin et al., 2023 [51], USA	N=12: TG=6, CG=6 Crossover design Age=52.7±16.3 yr, M/F=6/6, SPMS: 2, RRMS: 9, PPMS: 1, EDSS: 3.4±0.76	TG: acupuncture CG: no treatment Frequency: twice weekly for 4 weeks, followed by a 1-week washout period, & then crossed over to the other condition for 4 weeks	Spasticity: MAS Gait & balance: 6MWT, T25FWT, Mini-Balance Evaluation System Test Strength: handheld dynamometer Sensory testing: Biothesio meter Baseline & post intervention	· Significant improvement in spasticity (MAS) score in right hip flexors (p<0.05) · Other lower limb muscles were unaffected (p>0.05 for all)	· No statistically significant changes were observed in the gait or balance measures · Small statistically significant changes were observed in upper extremity strength · No changes in sensation · No AEs	⊕⊖⊖⊖ Very low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; TG, treatment group; CG, control group; M/F, male/female; EDSS, Expanded Disability Status Scale; DD, disease duration; MS, multiple sclerosis; RRMS, relapsing-remitting MS; DNS, dynamic neuromuscular stabilization; CS, core stabilization exercises; MSSS-88, MS Spasticity Scale-88; MAS, Modified Ashworth Scale; BBS, Berg Balance Scale; MSWS, MS Walking Scale; TUG, Timed Up and Go; AE, adverse event; sEMG, surface electromyography; ES, effect size; IG, intervention group; RAGT, robot-assisted gait training; VR, virtual reality; FIM, Functional Independence Measure; COPE, Coping Orientation to Problem Experienced; HRSD, Hamilton Rating Scale for Depression; CI, confidence interval; MMT, Manual Muscle Test; FRI, Fall Risk Index; OSI, Overall Stability Index; SSE, static stretching exercise; FSE, functional stretching exercise; T25FWT, Timed 25-Foot Walk Test; ROM, range of motion; VAS, visual analogue scale; QOL, quality of life; HRQOL, health-related QOL; BoNT, botulinum toxin; PT, physiotherapy; MD, mean difference; SD, standard difference; PPMS, primary progressive MS; STC, Spasticity: Take Control; NRS, Numeric Rating Scale; MFIS, Modified Fatigue Impact Scale; PSQI, Pittsburgh Sleep Quality Index; PROMIS, Patient-Reported Outcomes Measurement Information System; MSIS, MS Impact Scale; 10MWT, 10-Meter Walk Test; MSQLI, MS QOL Inventory; FSS, Fatigue Severity Scale; MSQOL-54, Multiple Sclerosis QOL-54 Scale; MSIQOL, MS International QOL; NAB, neuropsychological assessment battery; TOL, Tower of London Test; CES-D, Center for Epidemiologic Studies Depression Scale; MSQOL, MS QOL Scale; 6MWT, 6-Meter Walking Test; ADS, Allgemeine Depressionsskala; SPMS, secondary progressive MS; iTBS, intermittent theta burst stimulation; fMRI, functional magnetic resonance imaging; PCS, cortical silent period; rTMS, repetitive transcranial magnetic stimulation; SESS, Subjective Evaluating Spasticity Scale; NAS, Numerical Analog Scale; AS, Ashworth Scale; ADLs, activities of daily living; BI, Barthel Index; PSFS, Penn Spasm Frequency Scale; WBV, whole body vibration; RCT, randomized controlled trial; MDR, multi-disciplinary rehabilitation; FSST, Four Square Step Test; 2MWD, 2 meter walking distance; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form-36; BDI-II, Beck Depression Inventory; tDCS, transcranial direct current stimulation; MSPS, MS Performance Scale; EEG, electroencephalogram; TENS, transcutaneous electric nerve stimulation; RSWT, radial shock wave therapy.

surement tools employed to assess the spasticity outcomes included followings: MAS-most frequently utilized (n=21 studies) [36,38-40,42,44-48,50-56,58,61-63]; Multiple Sclerosis Spasticity Scale (MSSS-88, n=7 studies) [24,36,48-50,55,65]; electrophysiological parameters (H-reflex excitability, electromyography [EMG] muscle activity) (n=3 studies) [41,45,54]; NRS (n=4 studies) [43,44,49,64]; visual analogue scale (VAS) (n=2 studies) [39,47]; pendulum test for muscle tone (n=1 study) [37]; Spasm Frequency Score (n=1 study) [44]; Patellar Tendon Reflex Scale (n=1 study) [24]; Penn Spasm Frequency Score (n=1 study) [60]; Global Spasticity Scales (n=1 study) [22]; Subjective Evaluating Spasticity Scale (SESS) (n=1 study) [52]; other assessment tools such as patient self-reported scores [57,59].

Other outcomes

Other commonly assessed outcomes included balance, fatigue, mobility, gait/walking speed, overall function, cognition, QoL, pain, and others. The recruitment period was not disclosed in any of the studies. Follow-up periods varied across trials, with most evaluations occurring immediately after treatment or within two weeks. Only two trials reported a long-term follow-up, ranging from eight to 20 months, focusing solely on patient-reported symptoms using subjective questionnaires [22,49].

Quality assessment of included studies

The authors' judgments of each item presented as percentages across all included studies are presented in Fig. 2 and the assessment of methodological quality is shown in Fig. 3. The methodological quality of the 32 included trials was generally low, with substantial flaws and a high risk of bias in at least one domain. Key issues included randomization procedures, blinding of participants, therapists, and outcome assessors, small sample sizes, and outcome analysis. Although all included studies stated they used randomization, fewer than half (15 studies) adequately reported their methods of randomization. Many studies did not provide sufficient details on the generation and concealment of the random allocation sequence. Only 10 studies described and implemented adequate concealment of allocation prior to study entry [40,46,53,56-59,61,62,65], while three did not report on this aspect [22,48,49], and the remaining studies had incomplete reporting on sequence generation methods.

Adequate blinding of participants and treating personnel was reported in only seven studies [46,48,53,54,57,59,65]. Seventeen studies did not implement blinding [22,24,36-38,40,42,47,49-51,56,58,61-64], and the blinding status was unclear in the remaining studies. Variability in attrition was observed, with the majority of studies reporting no participant withdrawals or lost follow-ups. However, eight studies had substantial dropout rates [24,38,43,44,51,53,62,65], leading to a high risk of bias due to small sample sizes and the potential impact of dropouts on results. One study [63] provided no information on attrition, while three studies only reported the total number of dropouts without specifying treatment arms [22,51,53]. Selective reporting bias was not evident, as all studies reported pre-specified primary and secondary outcomes. However, 14 studies had small sample sizes (≤30 participants) and were not adequately powered [24,37,39,41-43,45,46,50,51,55,59,60,63]. Furthermore, thirteen studies did not utilize a conventional control group but employed comparative control groups involving another non-pharmacological intervention [24,36,38,40,43,44,46,49,63,65] or pharmacological interventions [47,58,62]. Most studies had short-term follow-ups, with assessments limited to immediate post-treatment evaluations.

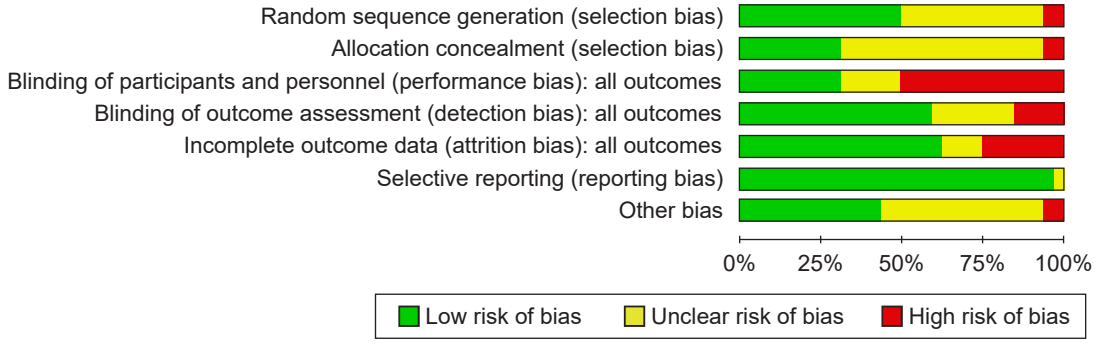

Fig. 2. Risk of bias graph.

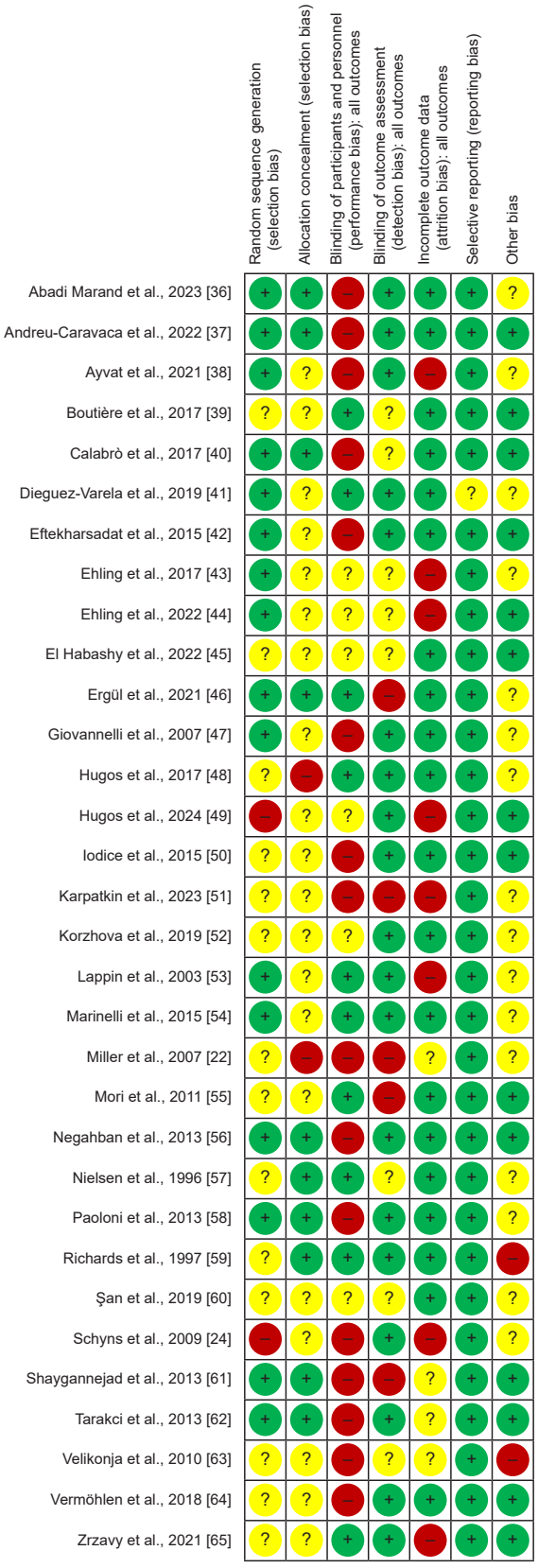

Fig. 3. Risk of bias summary.

Effects of interventions

A diverse array of non-pharmacological interventions was evaluated in the included studies, which underscores the intricate nature of non-pharmacological approaches in addressing the multifaceted effects of spasticity in this patient population. Many of these interventions are frequently employed in conjunction with other treatments, including pharmacological therapy or additional non-pharmacological interventions. The non-pharmacological interventions assessed in the included studies fall into nine primary categories, based on their mode of application (APP): physical therapeutic programs, magnetic brain stimulation (rTMS, intermittent theta burst stimulation [iTBS]), tDCS, pulsed electromagnetic field (PEMF) devices, TENS, vibration therapy, shock wave therapy, educational and self-management programs, and complementary and alternative medicine (CAM). The summary of the findings is presented below and detailed in Table 1.

Physical therapeutic programs

Twelve studies evaluated the impact of diverse physical activity programs on individuals with various forms of MS. These programs encompass structured physiotherapy, exercise regimens, stretching, balance and coordination exercises, postural stabilization, sports climbing, hippotherapy, RAGT, and others [36,37,40,42,46,47,49,56,62-65]. The effectiveness of these modalities varied, and they were often used in combination with other approaches.

Giovannelli et al. [47] evaluated (n=38 SPMS) the efficacy of combining PT with BoNT-A injections for managing focal spasticity. The intervention group received BoNT-A injections and daily PT (passive or active exercise and stretching regimens) for 15 days, while the control group received only the BoNT injections. The treatment group showed significant reductions in spasticity, as measured by the MAS, compared to the control group at weeks two (2.73 vs. 3.22), four (2.64 vs. 3.33), and twelve (2.68 vs. 3.33) ($p<0.01$ for all time points). Further, there was a significant improvement in MAS scores from baseline to the end of the 12-week follow-up in the treatment group (mean difference [MD]=-0.95 vs. -0.28, $p<0.01$). The intervention group also showed superior efficacy in reducing spasticity symptoms, as measured by the VAS, at week four (6.95 vs. 5.50, $p<0.01$) [47].

A RCT by Zrzavy et al. [65] (n=39 pwMS) allocated participants into three parallel groups: a routine clinical rehabilitation program combined with either hypoxic or normoxic endur-

ance training, and a control group with rehabilitation program only. The study found significantly lower spasticity scores, as measured by the MSSS-88, in both the hypoxic and normoxic endurance training groups at 14 days (p=0.012 and 0.048, respectively). Remarkably, a significant reduction in spasticity was observed after just one week of hypoxic endurance training (p=0.009). Additionally, all groups showed significant improvements in fatigue scores, with faster improvements in the endurance training groups (p=0.004 for normoxic and p=0.002 for hypoxic). Only the hypoxic group demonstrated a significant improvement in walking speed (p=0.001) [65].

A RCT with a wait-list control group (n=110 pwMS) evaluated the efficacy of a 12-week (36 sessions) physical therapist supervised group exercise program involving flexibility, strength training, balance and coordination exercises, core stabilization, and functional activities [62]. all by a. Post-treatment, significant improvements in lower limb spasticity were observed in the exercise group (MAS scores, p<0.05). Additionally, the exercise group showed significant improvements in balance (Berg Balance Scale [BBS] score increased by 4.33 points, compared to a decrease of 2.33 points in the control group, p=0.003) and walking ability (10-meter walk test time decreased by 2.72 seconds in the exercise group, compared to an increase of 1.44 seconds in the control group, p<0.001). The intervention group also experienced significant improvements in fatigue and QoL (p<0.001 and p=0.006, respectively) [62].

Another RCT (n=30 pwMS) examined the effects of 10 weeks of strength training on voluntary activation, muscle activity, muscle contractile properties, and spasticity [37]. There were significant improvements in spasticity in the strength training group, with notable differences between groups after the intervention. Specific parameters showing improvement included first swing excursion (right leg: p=0.006, effect size [ES]=-1.4; left leg: p=0.031, ES=-1.2), number of oscillations (right leg: p=0.001, ES=-0.4; left leg: p=0.031, ES=-0.4), and duration of oscillations (left leg: p=0.002, ES=-0.6). Additionally, significant improvements were observed in muscle activity (p=0.031, ES=-0.8) and maximal neural drive (p=0.038, ES=-0.8). Voluntary muscle activation, measured by the central activation ratio, also increased in the strength training group (p=0.010, ES=-0.4). However, there were no changes in muscle contractile properties in either group [37].

One RCT (n=30 participants with RRMS or SPMS) evaluated the efficacy of a short-term virtual reality (VR)-based balance training program on patients' balance ability, compared to a control group with no intervention [42]. The study found no significant difference between the groups in spasticity scores for the knee and hip (MAS, p>0.05). However, the intervention group showed significant improvements in mobility (Timed Up and Go [TUG] scores, p=0.01), an increased ability to maintain stability (Overall Stability Index, p=0.005), and a reduced risk of falls (Fall Risk Index, p<0.001). The authors found no significant differences between the groups in muscle power and balance (p>0.05 for all) [42].

Another RCT (n=64 pwMS) evaluated the effects of core stabilization and dynamic neuromuscular stabilization on balance, trunk function, mobility, falling, and spasticity [36]. The findings revealed a significant improvement in spasticity, at both post-intervention and 17-week follow-up in the dynamic neuromuscular stabilization group compared to the core stabilization group (group×time inter action, p>0.001). However, there was no significant difference in MAS scores between the groups (p>0.05). Further, compared to the core stabilization group, the dynamic neuromuscular stabilization group exhibited significant enhancements in balance (BBS, Trunk Impairment Scale, postural stability, activities-specific balance confidence), reduced falling rate, and improved mobility (TUG test, and MS Walking Scale-12, p<0.0001) [36].

One RCT (n=40 pwMS with walking disabilities) investigated the efficacy of RAGT with or without a VR system over 8 weeks [40]. The authors found no significant effect on spasticity (p=0.4, ES=-0.011), and there was a non-significant difference between the groups regarding balance (BBS, p=0.8) and mobility (TUG, p=0.3). However, there was a significant moderate-to-large effect observed mainly favouring RAGT with the VR group for the positive attitude (p=0.005) and problem-solving (p=0.002) sub-items of the Coping Orientation to Problem Experienced scale [40].

Ergül et al. [46] 2021 conducted an RCT (n=26 pwMS) comparing the effects of static stretching exercise (SSE) and functional stretching exercise (FSE) over 4 weeks (12 sessions) on lower limb spasticity, function, lower limb pain, active range of motion (ROM), and health-related quality of life (HRQOL). All participants underwent stretching exercises targeting the hamstrings, quadriceps, hip adductors, and plantar flexor muscles. Both groups exhibited significant improvements compared to baseline, including decreased spasticity, enhanced functional tests, reduced pain, increased ROM, and improved HRQOL (p<0.05 for all). However, there were no significant differences between the groups in any of these variables before or after

treatment (p>0.05). In the SSE group, a strong correlation was observed between decreased spasticity and functional improvement (r=0.793, p=0.002), while in the FSE group, moderate correlations were found between decreased spasticity and increased ROM (r=0.689, p=0.013) and increased ROM and functional improvement (r=0.593, p=0.042). Additionally, a strong correlation was identified between decreased spasticity and increased HRQOL in the FSE group (r=0.721, p=0.006) [46].

Negahban et al. [56] (n=48 participants) explored the comparative effects of exercise programs (strength, stretch, endurance, and balance) and Swedish massage. Participants were randomly assigned into four equal subgroups: massage therapy, exercise therapy, combined massage and exercise therapy, and control group (standard medical care). The authors found that both massage therapy and exercise therapy resulted in significant improvement in MAS scores (MD=0.05, p=0.006 and MD=0.47, p=0.031, respectively). However, there was no significant improvement in the massage and exercise combination group (MD=0.14, p=0.53) and significant worsening in the control group (MD=-0.33, p=0.031). The massage therapy also resulted in a significantly larger improvement in pain reduction (MD=2.75 points, p=0.001), dynamic balance (MD=3.69 seconds, p=0.009) and walking speed (MD=7.84 seconds, p=0.007) than exercise therapy. Further, patients in the combined massage and exercise therapy showed significantly larger improvement in pain reduction than those in the exercise therapy (MD=1.67 points, p=0.001) [56].

Velikonja et al. [63] (n=20 participants with RRMS and PPMS) explored the effects of two 10-week contemporary aerobic physical activities, sports climbing, and yoga. Both activities involved a series of stretching techniques that required body control and planning of complex movements. The study found no significant improvements in spasticity following either intervention. However, the sports climbing group experienced a notable 25% reduction in the EDSS pyramidal function score post-treatment (p=0.046). In contrast, the yoga group showed a significant 17% improvement in selective attention performance post-treatment (p=0.005). Further, the sports climbing group demonstrated a substantial 32.5% decrease in fatigue (p=0.015), whereas yoga did not have any effect on fatigue levels [63].

A multi-center RCT (n=70 pwMS) examined the impact of an additional 12 weeks of hippotherapy alongside standard care (control group) [64]. There was a significant improvement in spasticity in the intervention group at 12 weeks (NRS, MD=-0.9, 95% confidence interval [CI]: -1.9 to -0.1, p=0.031). Additionally, significant improvements were observed in the treatment group for balance (BBS score, p=0.047), with the most substantial benefit seen in patients with an EDSS score of ≥5 (BBS score, p=0.001). There was also a significant reduction in fatigue (Fatigue Severity Scale [FSS] score, p=0.02) in the intervention group. Further, improvements were noted in the QoL of participants in the intervention group, both in terms of physical (SD=12, p<0.001) and mental health (SD=14.4, p<0.001) [64].

One most recent RCT (n=231 participants) evaluated the impact of a guideline-based program of spasticity education and stretching exercises "MS Spasticity: Take Control (STC)" compared to a control program of different spasticity education and ROM exercises in ambulatory pwMS [49]. The authors found significant improvements in spasticity and fatigue, and psychological scores at 1 and 6 months in both groups. However, there was no significant difference between STC and ROM at 1 month (MSSS scores MD=0.28, 95% CI=-9.45 to 10.01, p=0.955) or 6-month (MD=-0.86, 95% CI=-12.2 to 10.5) [49].

Magnetic brain stimulation

TMS is a non-invasive neurostimulation technique that uses electromagnetic induction to generate electric currents in the brain. Six studies evaluated the effectiveness of various types of rTMS, each with its specific parameters and APPs: two studies evaluated the efficacy of iTBS [39,55], three studies assessed rTMS [41,57,60], and one study compared rTMS with iTBS [52].

A double-blind, sham-controlled trial (n=30 pwMS) investigated the impact of combining iTBS with exercise therapy on motor disability [55]. Participants were randomly assigned into three groups: iTBS plus exercise therapy, sham stimulation plus exercise therapy, and iTBS alone. Significant improvements in spasticity were observed in the iTBS plus exercise therapy group, with MAS scores decreasing from 2.1±0.4 before treatment to 1.3±0.4 after treatment (p<0.05) and MSSS-88 scores decreasing from 74.3±11.4 to 53.2±10.9 (p<0.001). The iTBS alone group also showed a significant reduction in MAS scores, from 3.3±0.8 before treatment to 1.6±0.8 after treatment (p<0.05), while other measures of MS-related disability remained unaffected. Furthermore, the iTBS plus exercise therapy group experienced significant improvements in fatigue (FSS scores), daily function (Barthel Index scores), and QoL (Multiple Sclerosis Quality of Life-54 Scale physical health composite scores), with all showing significant improvement compared to the sham stimulation plus exercise therapy group (p<0.05 for all) [55].

Boutière et al. [39] in a RCT (n=17 pwMS) investigated whether the modulation of spasticity induced by iTBS correlated with the functional reorganization of the primary motor cortices in patients experiencing lower limb spasticity. Participants were randomly assigned to receive either real iTBS or sham iTBS during the first half of a 5-week indoor rehabilitation program. The results indicated that improvement in spasticity was more pronounced in the iTBS group compared to the sham iTBS group at the end of the stimulation session (VAS, p=0.026). While MAS scores improved in both groups, there was no significant difference between them. Furthermore, iTBS significantly affected the balance of connectivity degree between the stimulated and homologous primary motor cortex (p=0.005), and changes in inter-hemispheric balance were correlated with spasticity improvement (p=0.015). However, there was no effect of iTBS on the global topology of the brain network, indicating that iTBS over the primary motor cortex does not alter the overall organization of the brain network [39].

Nielsen et al. [57] in a double-blind, placebo-controlled study (n=38 participants) investigated the impact of rTMS on spasticity. Participants in the intervention group received one session of 16 stimuli at 25 Hz rTMS targeting the leg motor area, followed by one session of five-minute sessions (twice daily for seven consecutive days The treatment group showed a significant improvement in MAS scores compared to the control group at day one post-treatment, (MD=-3.3±4.7 vs. 0.7±2.5, p=0.003). Additionally, the stretch reflex threshold significantly increased in the treatment group compared to the control group (4.3±7.5 deg/s vs. -3.8±9.7 deg/s, p=0.001). Both groups reported significant improvements in self-assessed ease of daily activities (p<0.05 for both groups). At day 8, there was no statistically significant difference in spasticity scores or self-assessed ease of activities of daily living (ADLs) between the groups, but the stretch reflex threshold remained significantly improved in the treatment group (p=0.028). None of the scores showed statistically significant differences between the two groups on day 16 [57].

San et al. [60] (n=16 participants) investigated the impact of rTMS on spasticity in the adductor hip muscles. All participants (including rTMS and sham rTMS) received 10 stimulation sessions along with PT and a rehabilitation program. The results indicated statistically significant improvements in bilateral MAS scores over time in the rTMS group (p=0.005), but no significant changes in the control group (p>0.05). Additionally, significant improvements in spasm frequency were observed in the rTMS group at both 1 week and 1-month post-intervention (p<0.01), with no significant differences in the control group (p>0.05). Compared to the control group, the rTMS group showed significant improvements in several other outcomes [60].

A RCT (n=34 SPMS) compared the effects of two rTMS protocols- high-frequency (20 Hz) rTMS (HF-rTMS) and iTBS on spasticity levels and associated symptoms in patients with spastic paraparesis [52]. Participants were randomized into three groups: HF-rTMS, iTBS, or sham stimulation. Both HF-rTMS and iTBS groups showed significant reductions in muscle tone (MAS scores, p<0.001) post-treatment, whereas the sham group did not exhibit significant changes (p=0.44). The reduction in spasticity levels persisted at 2 weeks post-intervention in both the HF-rTMS and iTBS groups. However, at 12 weeks post-intervention, a significant reduction in SESS score was only observed in the iTBS group. Reductions in pain and fatigue were only observed in the HF-rTMS group [52].

Another RCT (n=17 RRMS) evaluated the clinical effect and neurophysiological changes produced by iTBS on lower extremity spasticity [41]. The authors reported that 2-weeks of iTBS on the motor cortex contralateral to the most affected leg did not produce any significant clinical effect on spasticity. However, a significant decrease in the H/M amplitude ratio was observed in the treatment group from baseline after the first, fifth, and tenth sessions (p<0.05 for all), This effect was maintained up to 1 week after the last stimulation session (p=0.047). There were no significant changes in the sham control group [41].

Vibration therapy

Three studies explored various approaches to vibration therapy, including WBV, segmental muscle vibration, and local vibration [24,38,58]. Schyns et al. [24] in an RCT (n=16 participants) assessed the effectiveness of a WBV program on tone, muscle force, sensation, and functional ability in MS patients. Participants in group 1 received four weeks of WBV plus exercise (3 times/week), followed by two weeks of no intervention, and then four weeks of exercise alone (3 times/week), and participants in group 2 underwent the two treatment interventions in the reverse order. Overall, the exercise program demonstrated positive effects on muscle force and well-being, but there was insufficient evidence to suggest that the addition of WBV provided further benefit. Following the combination of WBV and exercises, there was no significant difference in MAS scores in either group, however, both groups showed a significant reduc-

tion in muscle spasms (p=0.02) and pain (p=0.036). Some improvements in functional abilities, as measured by the 10-meter walk and TUG test were observed, but these changes were not statistically significant (p>0.05 for both) [24].

A single-blind RCT (n=42 SPMS) examined the efficacy of segmental muscle vibration and BoNT-A injection, either alone or in combination, in reducing spasticity [58]. Participants were randomly assigned to three parallel groups: the vibration therapy group (receiving 30 minutes of 120 Hz segmental muscle vibration over the rectus femoris and gastrocnemius medial and lateral, three times/week for four weeks), the BoNT plus vibration therapy group (receiving BoNT-A injections in the rectus femoris, gastrocnemius medial and lateral, and soleus, in addition to segmental muscle vibration), and the BoNT group (receiving BoNT injection alone). The results showed a significant reduction in spasticity in all groups over time (MAS scores, p<0.001). Interestingly, patients in the BoNT-only group showed a significant increase in knee and ankle spasticity at the 22-week follow-up compared to 10 weeks post-intervention (p<0.05). Further, there was a significant reduction in fatigue (FSS scores) at both 10 weeks and 22 weeks compared to baseline in the vibration group and the BoNT-injection only group (p=0.03 and 0.02, respectively), while no differences were detected in the BoNT plus vibration group [58].

Another RCT (n=33 pwMS) compared the effects of 50 Hz versus 100 Hz local vibration (applied for 5 minutes to the right and left medial gastrocnemius muscles) on spasticity, functional performance, and muscle architecture [38]. Participants were randomly assigned to three groups: 50 Hz or 100 Hz local vibration, and the control group (receiving PT only). All participants received one hour of PT per day (three days a week for eight weeks). The 50 Hz vibration group demonstrated statistically significant reductions in spasticity and increases in fascicle length (p<0.05 for both). There was a significant improvement in ankle joint position sense, single-leg stance time, and limits of stability/postural sway range in the mediolateral direction in both vibration therapy groups (p<0.05 for all). Anteroposterior limits of stability and postural sway showed significant improvement across all groups (all p<0.05). The 50 Hz group exhibited significant improvement in all walking parameters (velocity, step length, and base of support values), while the 100 Hz group showed improvements only in velocity and step length (all p<0.05). The control group demonstrated significant improvements only in single support and stance phase percentages of the gait cycle (both p<0.05). Between-group comparisons revealed a significant difference only in mediolateral limits of stability (p<0.05), with better scores observed for the 50 Hz group compared to the 100 Hz and exercise groups [38].

Educational/self-management programs

Educational and self-management programs, aiming to empower individuals with knowledge and skills to understand, cope with, and manage their spasticity-related symptoms, were evaluated in three studies [43,44,48]. Hugos et al. [48] (n=40 pwMS) investigated the efficacy of a four-week group-delivered self-management program, including stretching instruction and support, in reducing spasticity. The results demonstrated a significant reduction in spasticity post-intervention in the intervention group in spasticity (MSSS-88 total scores=-27.8 vs. -3.7, p<0.03), in pain and discomfort subscale (-3.9 vs. 0.3, p<0.02) and muscle spasms subscale (-5.0 vs. 0.5, p<0.03). Additionally, participants in the intervention group experienced significant improvements in fatigue (p=0.03), depression (p=0.004), physical function (p=0.002), and knowledge about spasticity based on a written test (p<0.04). However, there were no significant group differences in any of these measures (p>0.05 for all) [48].

Ehling et al. [43] (n=20 participants) assessed the effectiveness of an individualized training program in reducing spasticity. Initially, all participants were introduced to predefined exercises targeting spasticity during their inpatient rehabilitation program, then were randomly assigned to either an APP-based home therapy program "MS-spasticity APP" (which included 85 exercises focusing on movement, strengthening and coordination of lower limbs and trunk and a video sequence showing a PT performing the exercise) or a paper-based home therapy program for three months. After three months, all received MS spasticity-based program for another three months. Compared to participants conventional paper-based program, participants in APP-based home program showed a significant reduction in spasticity (NRS scores MD=1.2, p=0.09). At 24 weeks follow-up, "MS spasticity APP" was associated with a decrease in spasticity (NRS scores MD=2.5±1.7) in all participants [43].

Another RCT (n=94 participants) conducted by the same group investigated the effects of multidisciplinary inpatient rehabilitation (MD) and an individualized self-training program delivered through a mobile APP on moderate to severe lower limb spasticity [44]. Following inpatient MD rehabilitation, those showing clinically relevant improvement in spasticity (≥20% on NRS) were randomly assigned in a 1:1 ratio to either the MS-Spasticity APP or a paper-based self-training program

for 12 weeks. Overall, the findings indicated a significant reduction in spasticity after inpatient MD rehabilitation (p<0.001), improvement in strength of lower extremities (p<0.001), and mobility outcome (p<0.001). Self-training program with the MS-Spasticity APP post-MD rehabilitation program showed sustained positive effects on spasticity, whereas paper-based self-training resulted in a worsening of spasticity (median NRS difference=1.0, 95% CI=1.7 to 0.3, p=0.009). Additionally, the MS-Spasticity APP was linked to significantly better adherence to self-training (95% vs. 72% completion rate, p<0.001) [44].

tDCS

Two studies evaluated the effectiveness of tDCS, a neuromodulation technique involving the APP of a low direct current to the scalp to modulate neuronal activity in the brain, for managing spasticity [45,50]. A single-center, randomized, double-blind, sham-controlled study (n=20 RRMS) investigated the efficacy of anodal tDCS compared to sham tDCS in modulating lower limb spasticity [50]. The intervention group received anodal tDCS stimulation to the primary motor cortex of the more affected side (20 minutes/day over 5 consecutive days). The findings showed no significant improvement in spasticity outcomes in both groups post-intervention (tDCS group: MAS and MSSS-88 scores, p>0.05). Further, there was no significant change in walking abilities in either group (MS Walking Scale, p>0.05 for both) [50].

A parallel arm RCT (n=20 RRMS) examined the effectiveness of anodal tDCS on spasticity [45]. The intervention group received active anodal tDCS targeting the ipsilesional motor cortex, with five consecutive daily sessions lasting 20 minutes each, while the control group received sham stimulation. There was no significant difference between the two groups in MAS scores post-treatment (p=0.22). However, compared to the sham group, the intervention group demonstrated significant improvement in the H/M amplitude ratio (MD=-0.16 vs. 0.07, p<0.05) and significant stability in H latency (MD=-0.54 vs. -1.03, p>0.05) [45].

PEMF devices

The effectiveness of electromagnetic therapy (pulsed electromagnetic therapy [53]; and magnetic pulsing device [Enermed] [59]) was evaluated in two studies. A multi-site, double-blind, placebo-controlled, cross-over trial (n=117 participants) assessed the effects of a pulsed electromagnetic therapy on MS-related spasticity, fatigue, bladder control, and QoL [53]. Participants received four weeks of the active and placebo treatments separated by a two-week washout period. The muscle spasm/spasticity measured at the end of each session showed statistically significant differences in favour of the active device group (p=0.04), while daily diary ratings showed no significant difference in treatment effects. The QoL index (QLI) (created using fatigue, pain, and spasticity scales) showed moderate inter-correlations (r=0.32 to 0.60). Compared to the control group, participants in the active device group showed significant improvement in fatigue (p=0.04) and QoL (p=0.03), but no significant differences in bladder control (p=0.26) or disability composite (p=0.77) [53].

Another double-blind trial (n=30 participants) evaluated the clinical and subclinical effects of a magnetic pulsing device (frequency range of 4–13 Hz) on disease activity [59]. The treatment group showed a significant improvement in the performance scale (PS) combined rating for bladder control, cognitive function, fatigue level, mobility, spasticity, and vision compared to the control group (-3.83±1.08 versus -0.17±1.07, change in PS, p<0.005). Additionally, there was a significant change in alpha electroencephalography magnitude during a language task between pre-treatment and post-treatment [59].

TENS

Two studies evaluated the impact of TENS [22,61]. A single-blind, cross-over trial (n=32 participants) randomly allocated participants into two groups: 60-minutes or 8 hours of daily TENS APPs (frequency of 100 Hz and pulse width of 0.125 ms) for 2 weeks, followed by a washout period of 2 weeks [22]. The results indicated no statistically significant differences in the Global Spasticity Score following either 60 minutes or eight hours of daily TENS (p=0.433 and 0.217, respectively). However, compared to the shorter 60-minute APP, the longer 8-hour APP duration resulted in a significant reduction in muscle spasms (p=0.038) and pain (p=0.008). At the end of the study (8–20 months), overall patients reported a reduction in symptoms: 87.5% for spasms, 73.3% for pain & 73.3% for stiffness [22].

Shaygannejad et al. [61] conducted a comparative study (n=52 participants) to assess the effectiveness of baclofen versus self-applied TENS for treating lower limb spasticity. Participants were randomly assigned to undergo a four-week treatment regimen either with baclofen (starting at 10 mg twice daily and increasing to 25 mg over three weeks) or self-applied TENS. MAS scores decreased from 1.77±0.29 at baseline to 0.73±0.70

(p<0.001) in the TENS group and from 1.73±0.38 to 1.15±0.63 in the baclofen group (p<0.001). Furthermore, the MAS score at the four-week follow-up was significantly lower in the TENS group compared to the baclofen group (MD=-0.42, 95% CI=-0.79 to -0.05, p<0.05) [61].

Shockwave therapy

A double-blind, randomized, placebo-controlled study (n=78 pwMS) evaluated the effectiveness of radial shock wave therapy (RSWT) (one session/week for 4 weeks) targeting the ankle extensor muscles for painful hypertonia [54]. Following RSWT, muscle tone significantly decreased one week after the final session (MD in MAS score: -0.78, p<0.0001). Pain levels decreased across all follow-up evaluations (one week after the initial session, and one week and four weeks after the last session, p<0.001 for all), while spinal excitability (H-reflex) and walking parameters remained unaffected. There were no significant changes in any parameters observed after the placebo treatment [54].

CAM-acupuncture

A crossover RCT (n=12 participants) evaluated the efficacy of acupuncture in alleviating symptoms related to spasticity [44]. Participants were randomly assigned to receive either acupuncture treatment (twice weekly for 4 weeks) or no treatment (control). This was followed by a 4-week washout period, after which participants switched to the alternative condition for another 4 weeks. Following the treatment period, a notable improvement in spasticity was observed in the treatment group, specifically in the right hip flexors (MAS score, p=0.030). There were no significant changes observed in any other lower limb muscles (p>0.05 for all). Further, there were no statistically significant improvements noted in gait or balance measures [44].

Quality of evidence

The GRADE approach was utilized to synthesize and interpret the quality of evidence from the included studies [33,35]. According to this method, all RCTs were initially assigned a "high (+4)" rating as the default for study design. This rating was subsequently downgraded based on the presence of factors within five domains: risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias. Majority of the studies were downgraded based on the methodological quality (risk of bias), followed by imprecision and indirectness (small sample size, indirect comparisons, lack of convenient control groups). Detailed GRADE assessments are presented in Table 2, and an overall summary of findings is summarised below.

Summary of key findings

The overall evidence supporting the beneficial effect of different non-pharmacological interventions in mitigating spasticity in pwMS is summarised below:

Physical therapeutic programs

In total, 12 studies (n=737 participants) evaluated the impact of different types of physical activity programs, either independently or in conjunction with other interventions. The findings suggest that there are:

- Moderate certainty evidence for PT programs compared to usual care or no intervention in short-term
- Low-certainty evidence for physical activity program compared to other non-pharmacological interventions for short-term
- Low certainty evidence for the addition of active physiotherapy after BoNT injection in reducing spasticity for short-term
- Very low certainty evidence for physical activity programs compared to other non-pharmacological interventions for longer-term

There is also some evidence for the beneficial impact of physical activity programs on walking, balance, fatigue and QoL.

rTMS

Six studies (n=142 participants) evaluated the different forms of rTMS. The findings suggest the following evidence supporting the beneficial effect of rTMS on the reduction of spasticity:

- Moderate certainty evidence for short-term benefits of rTMS compared to sham stimulation for improved spasticity, functional abilities and stretch reflex thresholds;
- Low certainty evidence for short-term benefits of rTMS in combination with rehabilitation program for improved spasticity and functional and abilities;
- Low certainty evidence for iTBS as a single intervention or in combination with exercise therapy reduced spasticity after two weeks of treatment

There is also some evidence for the beneficial impact of rTMS on ADLs, reduction of spasticity-related spinal hyper-excitability (H-reflex amplitude), pain, fatigue and QoL.

Table 2. Levels of quality of evidence (GRADE approach[a])

Reference	Bias risk	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Abadi Marand et al., 2023 [36]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Andreu-Caravaca et al., 2022 [37]	+ (-1)	NS	-1	NS	U	Low (+2)
Ayvat et al., 2021 [38]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
Boutière et al., 2017 [39]	++ (-2)	NS	-1	NS	U	Very low (+1)
Calabrò et al., 2017 [40]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Dieguez-Varela et al., 2019 [41]	+ (-1)	NS	-1	NS	U	Low (+2)
Eftekharsadat et al., 2015 [42]	++ (-2)	NS	NS	NS	U	Low (+2)
Ehling et al., 2017 [43]	++ (-2)	NS	-1	NS	U	Very low (+1)
Ehling et al., 2022 [44]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
El Habashy et al., 2022 [45]	++ (-2)	NS	-1	NS	U	Very low (+1)
Ergül et al., 2021 [46]	+ (-1)	NS	NS	+ (-1)	U	Low (+2)
Giovannelli et al., 2007 [47]	++ (-2)	NS	NS	NS	U	Low (+2)
Hugos et al., 2017 [48]	++ (-2)	NS	NS	+ (-1)	U	Very low (+1)
Hugos et al., 2024 [49]	++ (-2)	NS	NS	NS	U	Low (+2)
Iodice et al., 2015 [50]	++ (-2)	NS	-1	NS	U	Very low (+1)
Karpatkin et al., 2023 [51]	++ (-2)	NS	-1	NS	U	Very low (+1)
Korzhova et al., 2019 [52]	+1 (-1)	NS	NS	NS	U	Moderate (+3)
Lappin et al., 2003 [53]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Marinelli et al., 2015 [54]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Miller et al., 2007 [22]	++ (-2)	-1	NS	NS	U	Very low (+1)
Mori et al., 2011 [55]	+ (-1)	NS	-1	NS	U	Low (+2)
Negahban et al., 2013 [56]	+ (-1)	NS	NS	NS	U	Moderate (+3)
Nielsen et al., 1996 [57]	+ (-1)	-1	NS	NS	U	Low (+2)
Paoloni et al., 2013 [58]	+ (-1)	-1	NS	+ (-1)	U	Very low (+1)
Richards et al., 1997 [59]	+ (-1)	-1	-1	+ (-1)	U	Very low (0)
Şan et al., 2019 [60]	++ (-2)	NS	NS	NS	U	Low (+2)
Schyns et al., 2009 [24]	++ (-2)	NS	-1	NS	U	Very low (+1)
Shaygannejad et al., 2013 [61]	++ (-2)	-1	NS	+ (-1)	U	Very low (0)
Tarakci et al., 2013 [62]	+ (-1)	NS	NS	NS	U	Moderate (+3)
Velikonja et al., 2010 [63]	++ (-2)	-1	-1	NS	U	Very low (0)
Vermöhlen et al., 2018 [64]	++ (-2)	-1	NS	NS	U	Very low (+1)
Zrzavy et al., 2021 [65]	++ (-2)	NS	NS	NS	U	Low (+2)

+, serious; ++, very serious; NS, not serious; U, undetected.
[a]GRADE: Grading of Recommendations Assessment, Development and Evaluation. The judgment of value given for each study is specifically based on the data related to this review.

Vibration therapy

Three studies (n=97 participants) explored various approaches to vibration therapy, including WBV, segmental muscle vibration, and local vibration. The findings suggest:

- Very low certainty evidence for the beneficial effect of WBV with or without exercise program in reducing spasticity
- Very low certainty evidence for the beneficial effect of local vibration with or without exercise program in reducing spasticity
- Very low certainty evidence for the beneficial effect of segmental muscle vibration with or without BoNT injections in reducing spasticity

Self-management educational program

Three studies (n=154 participants) evaluated various forms of educational self-management programs, which included approaches such as group self-management programs and electronic app-based self-management exercise programs, the findings from these studies suggest:

- Very low certainty evidence for the beneficial effects of software-based self-management programs compared to paper-based programs for spasticity
- Very low certainty evidence for the beneficial effects of self-management programs compared to usual care for spasticity

There is also some evidence beneficial impact of educational.

tDCS

Two studies (n=40 participants) evaluated the different forms of tDCS and found:

- Very-low certainty evidence for tDCS compared to sham in reducing spasticity

TENS

Two studies (n=84 participants) evaluated the impact of TENS and found:

- Very low certainty evidence for the beneficial effect of different intensities of TENS in reducing spasticity
- Very low certainty evidence for the beneficial effect of TENS with or without Baclofen in reducing spasticity

There is also some evidence for the beneficial effect of TMS on muscle spasms and pain.

Pulsed electromagnetic therapy

Two studies (n=147 participants) investigated the effectiveness of Pulsed Electromagnetic therapy (Enermed) and found:

- Very low certainty evidence for the short-term beneficial effects of pulsing magnetic fields for spasticity, bladder control, cognitive function, fatigue level, mobility, and vision

Radial shockwave therapy

One study (n=68 participants) assessed the effectiveness of shock wave therapy over ankle extensor muscles and revealed:

- Very low certainty evidence for the short-term beneficial effects of pulsing magnetic fields for spasticity, reducing pain, or enhancing spinal excitability programs on improving ADLs, fatigue, and condition-specific knowledge and compliance.

Acupuncture

The efficacy of acupuncture was assessed in one study (n=12 participants), which suggests:

- Very low certainty evidence for the beneficial effects of acupuncture in alleviating spasticity-related symptoms

There was no effect of acupuncture on muscle strength, gait, and balance.

Non-pharmacological interventions for managing spasticity in MS are generally considered safe and well-tolerated [12,20,66]. Despite some included studies did not assess the adverse effects profile, reported adverse events and withdrawals were minor and infrequent. The overall findings suggest that physical therapeutic interventions were associated with a low risk of adverse effects, especially when tailored to the patient's individual needs and conducted under professional supervision. These interventions were well-tolerated by patients, with few reports of adverse events such as muscle soreness or fatigue [20,67]. Notably, interventions such as rTMS, tDSC, vibration therapy, or shock wave therapy interventions did not result in reported adverse effects. It is recommended that the severity of spasticity, and the patient's overall health, need to be considered with the proper execution of the techniques from trained professionals to avoid potential injuries or exacerbation of symptoms [66,67]. Further, the long-term safety of these interventions needs to be explored.

DISCUSSION

Addressing spasticity in MS remains a significant challenge due to its complex nature, the varying efficacy and safety profiles of available interventions, and the variability and reliability of spasticity assessment tools [13,68,69]. Non-pharmacological interventions play a role as primary and/or adjunctive therapies for addressing spasticity-related issues. This review rigorously assesses evidence from published RCTs to determine the efficacy of non-pharmacological interventions in managing spasticity amongst pwMS. A total of 32 RCTs investigated a range of non-pharmacological interventions (including physical therapies, electromagnetic therapy, electrical nerve stimulation, vibration therapy, shock wave therapy, educational/self-management programs, and CAM). The most frequently examined intervention was a physical therapeutic program followed by rTMS. The included trials exhibited considerable heterogeneity in terms of intervention types (contents, intensity/duration), delivery settings (institution, community, home), outcome measures used, and study quality. Further, variations were noted in comparison (control) groups employed and assessment periods across the trials. As a result, quantitative synthesis was deemed impractical, and a qualitative synthesis based on the 'best evidence' was provided. The findings indicate that the current evidence supporting the efficacy of non-pharmacological interventions for spasticity management in pwMS is still relatively weak. The quality of evidence for most outcomes is of 'low' or 'very low' quality primarily due to the risk of bias and imprecise and inconsistency of results across the small number of included studies.

The findings reflect the growing acceptance of various non-pharmacological interventions in recent years. All studies in-

cluded appropriate populations (adult participants with MS), but only 19 trials reported using commonly accepted clinical criteria (such as those by McDonald, Poser, or Pollman). Many interventions, notably exercise interventions, lacked detailed descriptions necessary for replication. Additionally, there was considerable variation in stimulation protocols (frequency, total number of stimuli, stimulation intensity) among the included studies evaluating non-invasive brain/nerve stimulations. Comparisons with conventional groups (no treatment or placebo/sham) were lacking in over two-thirds of the trials, which predominantly compared active interventions against other non-pharmacological or pharmacological interventions. There are no 'gold standard' treatments for spasticity and the efficacy of many of the evaluated interventions is still unknown [12]. An accurate judgment of their effect is superlative that the intervention is compared to a conventional group (no treatment or placebo/sham). However, descriptions of control arms, particularly those using 'usual care' or 'sham/placebo,' were often inadequate in many included studies.

The methodological quality of the included trials was generally rated as 'low' due to significant flaws in the design, including high risks of bias related to randomization procedures, blinding, allocation concealment, and outcome analysis.

Furthermore, inadequate detail was provided to assess potential biases in certain methodological quality domains (Figs. 2, 3). Patient-related factors and therapy delivery details were not adequately addressed, impacting outcomes such as patient motivation and self-efficacy. The generalizability of results was limited, as many included studies were conducted in a single center and with strict inclusion/exclusion criteria, and insufficient data on longer-term follow-up.

Most outcome measures for spasticity used across the included studies were validated, with the most common being the MAS followed by the MSSS-28. However, there were concerns regarding the indirectness of certain outcome measures as some studies did not provide details on measurement tools used, including scoring and analysis procedures. Further, patient-reported scales [57,59] and modified MSQLI [53] were not validated and it was not clear if they captured the true values. There was also marked heterogeneity in assessment timepoints with most trials assessing the outcomes immediately following the interventions. Imprecision in effect estimates was noted, with a significant number of small studies (n=12 studies with <30 participants). Further, due to the limited number of studies evaluating specific interventions, the quality of evidence was judged based on a single or two trials. Adverse events were not frequently reported, and there was no information on the cost-benefit profiles of these strategies. Subgroup analysis based on the type of MS, disease severity (EDSS scores), disease duration, and affected site (upper limb, lower limb, or both) was not feasible due to insufficient data.

This review underscores existing gaps in the literature and highlights the efficacy of certain non-pharmacological interventions for MS spasticity. There are several published systematic reviews assessing specific non-pharmacological interventions for spasticity management in individuals with MS. The overall findings and conclusions of this review align with those of these published reviews in this domain. Etoom et al. [20] in a meta-analysis (n=29 studies) examined the effectiveness of various types of physiotherapy interventions including exercise therapy, electrical stimulation, RSWT, vibration, and standing, on spasticity in pwMS. The authors did not limit their inclusion criteria solely to RCTs and included other study types such as clinical-controlled and pre-post design studies. The findings suggest that PT interventions can be a safe and beneficial option for spasticity in pwMS, however, the authors could not draw firm conclusions as the included articles were heterogeneous and lacked adequate reporting of interventions and patient characteristics [20].

Another systematic review [70] investigated the effectiveness of both pharmacological and non-pharmacological interventions targeting spasticity on functional clinical outcomes in pwMS. The authors included 8 articles examining the effect of different non-pharmacological interventions and reported limited evidence for the beneficial effects of non-pharmacological interventions targeting spasticity [70]. This was consistent with the findings of our review. The efficacy of rTMS was evaluated in several systematic reviews [21,27,71]. Consistent with our findings, these published reports also found apparent discrepancies in the results in this area and many using rTMS as an adjunct therapy with other rehabilitation programs. Another systematic review examined the effects of TENS for the management of spasticity in different neurological conditions, including MS [23]. Similar to our findings, the authors concluded that evidence for the use of TENS for the management of spasticity in MS is still limited and can be used as an adjunct therapy [23].

One of the main issues in managing spasticity is the variability and reliability of assessment tools. Despite the availability of various assessment tools, none have proven to be consistently

reliable in clinical and research settings [68,69]. The MAS is the most widely used clinical measure, assesses resistance during passive muscle stretching and scores it on a 6-point ordinal scale. It has been criticized for its subjective nature and poor inter-rater reliability resulting in substantial variability in MAS scores [72]. Studies have shown that the MAS may not accurately reflect the severity of spasticity due to its simplistic ordinal scale, which does not capture the dynamic aspects of muscle resistance and can affect the accuracy and consistency of spasticity measurement [4,68,72]. Similarly, the MSSS-88, designed to assess the impact of spasticity on daily activities, has faced challenges related to its sensitivity and specificity. While it provides a more comprehensive view by including patient-reported outcomes, it is still subject to variability in patient perception and reporting, which can lead to inconsistencies in the assessment of spasticity severity and its impact on daily life [69]. Further, other neurophysiological approaches, such as H-reflex and EMG, by assessing the electrical activity of muscles and the excitability of spinal reflex pathways, offer more objective and quantifiable measurements of spasticity [73]. However, these techniques necessitate specialized equipment, advanced technology and skilled personnel to administer and interpret the results accurately, limiting their widespread adoption in clinical practice [73,74]. The variability in how these tools are administered and interpreted further complicates their reliability [69]. These limitations underscore the need for developing more reliable, valid, and standardized tools to evaluate spasticity, ensuring improved accuracy of diagnosis and severity, the effectiveness of interventions, and better clinical outcomes.

Study limitations

This review has several limitations. First, selection bias in the literature search cannot be entirely ruled out, as the search strategy primarily focused on cited literature despite using a broad range of terms to capture the widest possible selection of relevant literature. Additionally, studies where spasticity was incidentally measured (i.e., primary goal of the study was not to evaluate the reduction of spasticity), may have been overlooked or underreported. However, the literature search employed was comprehensive, utilizing a multi-pronged approach that included health science databases, trial registries, and grey literature. Study selection, data extraction, and quality assessment were conducted by two or more authors to ensure reliability. It is also important to note that this review did not evaluate pharmacological or surgical approaches, as these were beyond its scope. Publication bias remains a concern, as negative trials may remain unpublished [75]. Reference bias [76] is another potential confounder, as the search strategy included examining reference lists within relevant papers for additional articles that might have been missed in electronic searches. Given these limitations, the quality of evidence and the external validity of findings should be interpreted with caution. This is consistent with published guidelines and reviews on spasticity management [13,25,70,77]. Readers are encouraged to contact the authors regarding any high-quality studies meeting the review criteria that have not yet been included.

CONCLUSION

Recent advancements in spasticity management show evidence of the effectiveness of exercise programs in reducing spasticity and enhancing functional outcomes. However, while non-invasive brain stimulation techniques like rTMS or iTBS show potential as interventions in managing spasticity in pwMS, however, current evidence is insufficient to recommend their routine use. Currently, there is no supporting evidence for other non-pharmacological interventions in managing MS-related spasticity.

The review highlights the need for a multimodal approach involving an interdisciplinary team with regular follow-up, individualized care based on 'needs', and factors such as disease duration, spasticity characteristics, functional impairment, cost, patient/caregiver preferences. Accurate assessment, measurement, and clinician involvement in building evidence through practice is essential. This review emphasizes the variability in the effectiveness of non-pharmacological interventions due to therapist and operator dependency and potential multiple combined mechanisms (known and unknown) or 'bundled effects' [78]. The findings and clinical relevance of this review should be validated with future well-designed trials with larger sample sizes and longer-term follow-ups to improve the effective management of spasticity in MS.

CONFLICTS OF INTEREST

The review authors are professionals in the field of Physical and Rehabilitation Medicine who wish to provide the best possible service to their patients. No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

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SUPPLEMENTARY MATERIALS

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Appendix 1. Search strategies

MEDLINE

1. exp Muscle Spasticity/
2. exp Muscle Weakness
3. exp Muscle Hypertonia/
4. ("spasm*" or "muscle spasticity" or "spasticity" or "muscular spasm*" or "spastic" or "spastic paretic syndrome" or "spasticism" or "hypertonia").mp
5. 1 or 2 or 3 or 4
6. exp Multiple Sclerosis/
7. (demyelinating disease or demyelinating diseases or demyelinating disorder or demyelinating disorders).mp
8. exp Optic Neuritis/
9. (Multiple Sclerosis or Encephalomyelitis, Autoimmune, Experimental or Neuromyelitis Optica or Demyelinating Diseases).mp
10. *Myelitis, Transverse/
11. "clinically isolated syndrome".mp
12. (devic disease or Devic Syndrome or Devic's syndrome).mp.
13. transverse myelopathy.mp
14. disseminated sclerosis.mp
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 5 and 15
17. randomized controlled trial.pt
18. controlled clinical trial.pt
19. randomized.ab
20. placebo.ab
21. randomly.ab
22. trial.ab
23. groups.ab
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 16 and 24
26. exp animals/ not humans.sh
27. 25 not 26
28. exp Rehabilitation/
29. exp Neurological Rehabilitation/
30. exp Rehabilitation Centers/
31. exp Rehabilitation, Vocational/
32. exp Hospitals, Rehabilitation/
33. exp Physical Therapy Modalities/
34. exp Exercise/ or exp Exercise Therapy/
35. exp Occupational Therapy/
36. exp Transcutaneous Electric Nerve Stimulation/
37. exp Extracorporeal Shockwave Therapy/
38. (repetitive transcranial magnetic stimulation or rTMS).mp
39. exp Vibration/
40. (vibration or whole body vibration or WBV).mp
41. exp Transcranial Magnetic Stimulation/
42. (Intermittent Theta Burst Stimulation or iTBS).mp
43. exp Transcutaneous Electric Nerve Stimulation/
44. exp Self Care/
45. (Patient Education Handout or Education or Health Education).mp
46. (physical and rehabilitation).mp
47. exp "Physical and Rehabilitation Medicine"/
48. (pulsed electromagnetic therapy or magnetic pulsing device).mp
49. Self-Help Devices.mp
50. (assistive device* or assistive technolog*).mp
51. (orthotic * or orthotic devices).mp
52. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 25 and 52

Cochrane CENTRAL

#1. MeSH descriptor: [Multiple Sclerosis, Chronic Progressive] explode all trees
#2. MeSH descriptor: [Multiple Sclerosis, Relapsing-Remitting] explode all trees
#3. (multiple sclerosis):ti,ab,kw
#4. MeSH descriptor: [Optic Neuritis] explode all trees
#5. MeSH descriptor: [Demyelinating Diseases] this term only
#6. MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only
#7. MeSH descriptor: [Myelitis, Transverse] explode all trees
#8. ("Transverse Myelopathy"):ti,ab,kw
#9. MeSH descriptor: [Encephalomyelitis, Acute Disseminated] explode all trees
#10. (neuromyelitis optica):ti,ab,kw OR (NMO spectrum disorder):ti,ab,kw
#11. (optic neuritis):ti,ab,kw
#12. (demyelinating disease):ti,ab,kw OR (Demyelinating Autoimmune):ti,ab,kw
#13. (clinically isolated syndrome):ti,ab,kw
#14. (transverse myelitis):ti,ab,kw
#15. (encephalomyelitis):ti,ab,kw
#16. ("encephalomyelitis"):ti,ab,kw OR ("encephalo-myelitis"):ti,ab,kw
#17. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR#15 OR #16
#18. MeSH descriptor: [Occupational Therapy] explode all trees
#19. MeSH descriptor: [Rehabilitation] explode all trees
#20. (Rehabilitat*):ti,ab,kw
#21. MeSH descriptor: [Exercise] explode all trees
#22. (Exercise):ti,ab,kw
#23. MeSH descriptor: [Physical Therapy Modalities] explode all trees
#24. MeSH descriptor: [Exercise Movement Techniques] explode all trees
#25. MeSH descriptor: [Exercise Therapy] explode all trees
#26. (Exercise Therap*):ti,ab,kw
#27. MeSH descriptor: [Physical Fitness] explode all trees
#28. MeSH descriptor: [Physical and Rehabilitation Medicine] explode all trees
#29. MeSH descriptor: [Endurance Training] explode all trees
#30. MeSH descriptor: [Resistance Training] explode all trees
#31. MeSH descriptor: [Muscle Stretching Exercises] explode all trees
#32. (strengthening exercises):ti,ab,kw OR (stretching):ti,ab,kw
#33. (physical fitness):ti,ab,kw OR (physical rehabilitation):ti,ab,kw OR (physical endurance):ti,ab,kw OR (physical stimulation):ti,ab,kw OR (physical education):ti,ab,kw
#34. (resistance training):ti,ab,kw OR (strength training):ti,ab,kw OR (endurance program*):ti,ab,kw OR(resistance program*):ti,ab,kw AND (strength program*):ti,ab,kw
#35. (fitness program*):ti,ab,kw OR (aerobic training):ti,ab,kw OR (balance training):ti,ab,kw OR (gait training):ti,ab,kw
#36. (occupational therap*):ti,ab,kw
#37. MeSH descriptor: [Activities of Daily Living] explode all trees
#38. (Daily Living Activit*):ti,ab,kw OR (ADL):ti,ab,kw
#39. MeSH descriptor: [Self-Help Devices] explode all trees
#40. MeSH descriptor: [Splints] explode all trees
#41. MeSH descriptor: [Patient Education as Topic] explode all trees
#42. (patient education):ti,ab,kw
#43. MeSH descriptor: [Health Literacy] explode all trees
#44. (Health Literacy):ti,ab,kw
#45. MeSH descriptor: [Counseling] explode all trees
#46. (Counseling):ti,ab,kw OR (Counselling):ti,ab,kw
#47. MeSH descriptor: [Self Care] explode all trees
#48. (self-care):ti,ab,kw OR (self-efficacy):ti,ab,kw
#49. (assistive device*):ti,ab,kw OR (assistive technolog*):ti,ab,kw
#50. (energy conservation):ti,ab,kw OR (energy management):ti,ab,kw
#51. MeSH descriptor: [Electromyography] explode all trees
#52. (electromyography):ti,ab,kw OR (EMG):ti,ab,kw
#53. (transcutaneous electric nerve stimulation):ti,ab,kw OR (TENS):ti,ab,kw

#54. MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#55. MeSH descriptor: [Ultrasonic Therapy] explode all trees
#56. (shock wave*):ti,ab,kw OR (therapeutic ultrasound):ti,ab,kw
#57. MeSH descriptor: [Ultrasonic Waves] explode all trees
#58. (Orthotic*):ti,ab,kw
#59. MeSH descriptor: [Orthotic Devices] explode all trees
#60. (repetitive transcranial magnetic stimulation):ti,ab,kw OR (rTMS):ti,ab,kw
#61. MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees
#62. (thermotherap*):ti,ab,kw
#63. MeSH descriptor: [Hyperthermia, Induced] explode all trees
#64. MeSH descriptor: [Acupuncture] explode all trees
#65. MeSH descriptor: [Acupuncture Therapy] explode all trees
#66. (hydrotherap*):ti,ab,kw
#67. MeSH descriptor: [Hydrotherapy] explode all trees
#68. (Biofeedback):ti,ab,kw
#69. MeSH descriptor: [Biofeedback, Psychology] explode all trees
#70. (vibratory stimulation):ti,ab,kw OR (wholebody vibration):ti,ab,kw
#71. MeSH descriptor: [Vibration] explode all trees
#72. (uni-disciplinary therap*):ti,ab,kw OR (unidisciplinary therap*):ti,ab,kw OR (physiotherap*):ti,ab,kw OR(neurodevelopmental treatment):ti,ab,kw OR (static positioning):ti,ab,kw
#73. (continuous passive motion robotics):ti,ab,kw
#74. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR#63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73
#75. MeSH descriptor: [Muscle Weakness] explode all trees
#76. MeSH descriptor: [Spasm] explode all trees
#77. MeSH descriptor: [Muscle Spasticity] explode all trees
#78. MeSH descriptor: [Muscle Hypertonia] explode all trees
#79. (spastic paretic syndrome):ti,ab,kw OR (spasticism):ti,ab,kw OR (hypertonia):ti,ab,kw
#80. (spasm*):ti,ab,kw OR (muscle spasticity):ti,ab,kw OR (spasticity):ti,ab,kw OR (muscular spasm):ti,ab,kwAND (spastic):ti,ab,kw
#81. #75 OR #76OR #77 OR #78 OR #79 OR #80
#82. #17 AND #74 AND #81

Embase

#1. 'multiple sclerosis'/exp
#2. 'multiple sclerosis':ab,ti
#3. 'demyelinating disease'/de
#4. 'optic neuritis'/exp
#5. 'acute disseminated encephalomyelitis'/exp
#6. 'transverse myelitis'/exp
#7. 'transverse myelitis':ab,ti OR 'transverse myelopathy':ab,ti
#8. 'neuromyelitis optica':ab,ti
#9. 'optic neuritis':ab,ti
#10. 'demyelinating disease':ab,ti OR 'demyelinating autoimmune':ab,ti
#11. 'demyelinating disorder':ab,ti
#12. 'clinically isolated syndrome':ab,ti
#13. encephalomyelitis:ab,ti OR 'encephalo-myelitis':ab,ti
#14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15. 'rehabilitation'/exp
#16. rehabilitat*:ab,ti
#17. 'exercise'/exp
#18. exercise:ab,ti
#19. 'exercise therap*':ab,ti
#20. 'physiotherapy'/exp
#21. 'fitness'/exp

#22. 'rehabilitation medicine'/exp
#23. 'endurance'/exp
#24. 'physical stimulation'/exp
#25. 'convalescence'/exp
#26. 'endurance training'/exp
#27. 'resistance training'/exp
#28. 'stretching exercise'/exp
#29. 'physical fi tness':ab,ti OR 'occupational therapy':ab,ti OR 'physical rehabilitation':ab,ti OR 'physicalendurance':ab,ti OR 'physical stimulation':ab,ti OR 'physical education':ab,ti OR 'physical training':ab,ti OR'physical medicine':ab,ti OR 'physical therap*':ab,ti OR 'recovery of function':ab,ti OR 'endurance training':ab,ti OR'resistance training':ab,ti OR 'strength training':ab,ti OR 'endurance program*':ab,ti OR 'resistance program*':ab,ti OR 'strength program*':ab,ti OR 'fitness program*':ab,ti OR 'aerobic training':ab,ti OR 'balance training':ab,ti OR'gait traning':ab,ti
#30. 'transcutaneous electric nerve stimulation':ab,ti OR 'tens':ab,ti
#31. 'transcutaneous electric nerve stimulation'/exp
#32. 'ultrasound therapy'/exp
#33. 'shock waves':ab,ti OR 'therapeutic ultrasound':ab,ti
#34. 'ultrasonic waves'/exp
#35. 'orthosis':ab,ti
#36. 'orthotic devices'/exp
#37. 'repetitive transcranial magnetic stimulation':ab,ti OR 'rtms':ab,ti
#38. 'transcranial magnetic stimulation'/exp
#39. 'thermotherap*':ab,ti
#40. 'hyperthermia, induced'/exp
#41. 'occupational therapy'/exp
#42. 'occupational therap*':ab,ti
#43. 'daily life activity'/exp
#44. 'daily living activit*':ab,ti OR 'daily life activit*':ab,ti OR adl:ab,ti
#45. 'self help device'/exp
#46. 'self help device*':ab,ti OR 'self-help device*':ab,ti
#47. 'splint'/exp
#48. splint*:ab,ti
#49. 'patient education'/exp
#50. 'health literacy'/exp
#51. 'patient education':ab,ti OR 'health literacy':ab,ti
#52. 'counseling'/exp
#53. 'ergonomics'/exp
#54. ergonomic*:ab,ti OR 'ergo therap*':ab,ti
#55. 'kinesiotherapy'/exp
#56. 'self care'/exp
#57. 'self care':ab,ti OR 'self-effi cacy*':ab,ti OR 'self-care':ab,ti OR 'self effi cacy':ab,ti
#58. 'assistive technology'/exp
#59. 'assistive device*':ab,ti OR 'assistive technol*':ab,ti
#60. 'energy conservation'/exp
#61. 'energy conservation':ab,ti OR 'energy management':ab,ti
#62. 'acupuncture':ab,ti
#63. 'acupuncture therapy'/exp
#64. 'hydrotherap*':ab,ti
#65. 'hydrotherapy'/exp
#66. 'biofeedback':ab,ti
#67. 'biofeedback, psychology'/exp
#68. 'vibration'/exp
#69. 'vibratory stimulation':ab,ti OR 'wholebody vibration':ab,ti OR ‘WBV’
#70. 'uni-disciplinary therap*':ab,ti OR 'unidisciplinary therap*':ab,ti OR 'physiotherap*':ab,ti OR'neurodevelopmental treatment':ab,ti OR 'static positioning':ab,ti OR 'continuous passive motion robotics':ab,ti

#71. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR#57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
#72. 'muscle weakness'/exp
#73. 'spasm'/exp
#74. 'muscle spasticity'/exp
#75. 'muscle hypertonia'/exp
#76. 'spasm*':ab,ti OR 'muscle spasticity':ab,ti OR 'spasticity':ab,ti OR 'muscular spasm*':ab,ti OR 'spastic':ab,tiOR 'spastic paretic syndrome':ab,ti OR 'spasticism':ab,ti OR 'hypertonia':ab,ti
#77. #72 OR #73 OR #74 OR #75 OR #76
#78. #14 OR #71 OR #77
#79. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blindprocedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#80. #78 AND #79
#81. 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)
#82. #80 OR #81
#83. #80 NOT #81

CINHAL

S1. (MH "Multiple Sclerosis")
S2. TI "multiple sclerosis" OR AB "multiple sclerosis"
S3. (MH "Demyelinating Diseases")
S4. (MH "Optic Neuritis")
S5. TI "optic neuritis" OR AB "optic neuritis"
S6. (MH "Demyelinating Autoimmune Diseases, CNS")
S7. (MH "Encephalomyelitis, Acute Disseminated")
S8. (MH "Myelitis, Transverse")
S9. TI "neuromyelitis optica" OR AB "neuromyelitis optica"
S10. TI "demyelinating disease" OR AB "demyelinating disease" OR TI “Demyelinating Autoimmune” OR AB“Demyelinating Autoimmune”
S11. TI "demyelinating disorder" OR AB "demyelinating disorder"
S12. TI "clinically isolated syndrome" OR AB "clinically isolated syndrome"
S13. TI "transverse myelitis" OR AB "transverse myelitis" OR TI “Transverse Myelopathy” OR AB “Transverse Myelopathy”
S14. TI encephalomyelitis OR AB encephalomyelitis OR TI “encephalo-myelitis” OR AB “encephalo-myelitis”
S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16. (MH "Rehabilitation+")
S17. TI rehabilitat* OR AB rehabilitat*
S18. (MH "Exercise")
S19. TI Exercise OR AB Exercise
S20. (MH "Therapeutic Exercise+")
S21. TI exercise therap* OR AB exercise therap*
S22. (MH "Physical Therapy")
S23. (MH "Therapeutic Exercise")
S24. (MH "Physical Fitness")
S25. (MH "Physical Endurance")
S26. (MH "Physical Stimulation")
S27. (MH "Physical Education and Training")
S28. (MH "Endurance Training")
S29. (MH "Resistance Training")
S30. TI (“strengthening exercises” OR “stretching”) OR AB (“strengthening exercises” OR “stretching”)
S31. (MH “Stretching”)

S32. TI ((physical fitness OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR "recovery of function" OR endurance training OR resistance training OR strength training OR endurance program* ORresistance program* OR strength program* OR fitness program* OR aerobic training OR balance training OR gait training)) OR AB ((physical fitness OR occupational therapy OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR"recovery of function" OR endurance training OR resistance training OR strength training OR endurance program*OR resistance program* OR strength program* OR fitness program* OR aerobic training OR balance training OR gait training))
S33. TI Occupational Therap* OR AB Occupational Therap*
S34. TI ergotherap* OR AB ergotherap*
S35. (MH "Activities of Daily Living+")
S36. TI Daily Living activit* OR AB Daily Living activit*
S37. TI ADL OR AB ADL
S38. (MH "Assistive Technology Devices+")
S39. TI ("assistive device*" OR "assistive technolog*") OR AB ("assistive device*" OR "assistive technolog*")
S40. (MH "Splints+")
S41. TI splint* OR AB splint*
S42. (MH "Patient Education+")
S43. TI patient education OR AB patient education
S44. (MH "Health Literacy+")
S45. TI "Health Literacy" OR AB "Health Literacy"
S46. (MH "Counseling+")
S47. TI (counseling OR counselling) OR AB (counseling OR counselling)
S48. (MH "Ergonomics+")
S49. TI ergonomic* OR AB ergonomic* OR TI “ergo therap*” OR AB “ergo therap*”
S50. (MH "Self Care+")
S51. TI ("Self Care" OR "Self-Care") OR AB ("Self Care" OR "Self-Care") OR TI “self-efficacy*” OR AB “self-efficacy*”
S52. (MH "Energy Conservation")
S53. "Energy Conservation" OR AB "Energy Conservation" OR TI "Energy management" OR AB "Energy management"
S54. MH “Electromyography”)
S55. TI (“electromyography” OR “EMG”) OR AB (“electromyography” OR “EMG”)
S56. TI (“transcutaneous electric nerve stimulation” OR “TENS”) OR AB (“transcutaneous electric nerve stimulation” OR “TENS”)
S57. (MH “Transcutaneous Electric Nerve Stimulation”)
S58. (MH “Ultrasonic Therapy”)
S59. TI (“shock waves” OR “therapeutic ultrasound”) OR AB (“shock waves” OR “therapeutic ultrasound”)
S60. (MH “Ultrasonics”)
S61. TI “Orthotic*” OR AB “Orthotic*”
S62. (MH “Orthoses”)
S63. TI (“repetitive transcranial magnetic stimulation” OR “rTMS”) OR AB (“repetitive transcranial magneticstimulation” OR “rTMS”)
S64. (MH “Transcranial Magnetic Stimulation”)
S65. TI “thermotherap*” OR AB “thermotherap*”
S66. (MH “Hyperthermia, Induced”)
S67. TI “acupuncture” OR AB “acupuncture”
S68. (MH “Acupuncture”)
S69. TI “hydrotherap*” OR AB “hydrotherap*”
S70. (MH “Hydrotherapy”)
S71. TI “Biofeedback” OR AB “Biofeedback”
S72. (MH “Biofeedback, Psychology”)
S73. TI (“vibratory stimulation” OR “whole body vibration”) OR AB (“vibratory stimulation” OR “whole body vibration”)
S74. (MH “Vibration”)
S75. TI (“uni-disciplinary therap*” OR “unidisciplinary therap*” OR “physiotherap*” OR “neurodevelopmentaltreatment” OR “static positioning” OR “continuous passive motion robotics”) OR AB (“uni-disciplinary therap*” OR“unidisciplinary therap*” OR “physiotherap*” OR “neuro-developmental treatment” OR “static positioning” OR“continuous passive motion robotics”)
S76. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69OR S70 OR S71 OR S72 OR S73 OR S74 OR S75
S77. (MH “Muscle Weakness”)
S78. (MH “Spasm”)

S79. (MH "Muscle Spasticity")
S80. (MH "Muscle Hypertonia")
S81. TI ("spasm*" OR "muscle spasticity" OR "spasticity" OR "muscular spasm*" OR "spastic" OR "spasticparetic syndrome" OR "spasticism" OR "hypertonia") OR AB ("spasm*" OR "muscle spasticity" OR "spasticity"OR "muscular spasm*" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia")
S82. S77 OR S78 OR S79 OR S80 OR S81
S83. S15 AND S76 AND S81
S84. S99. (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pre-test-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB(random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos)OR PT (randomized controlled trial) OR AB (CONTROL W5 GROUP) OR MH (CROSSOVER DESIGN) OR MH(COMPARATIVE STUDIES) OR AB (CLUSTER W3 RCT)) NOT ((MH ANIMALS+ NOT MH HUMAN) OR (MH(ANIMAL STUDIES) NOT MH (HUMAN)) OR (TI (ANIMAL MODEL) NOT MH (HUMAN)))
S85. S83 AND S84

Trial registry: 'clinicaltrials.gov'

Condition or disease:

"multiple sclerosis" OR "demyelinating diseases" OR "optic neuritis" OR "demyelinating autoimmune Diseases"

Impairment

"spasm*" OR "spasticity" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia"

Intervention/treatment:

"uni-disciplinary therap*" OR "unidisciplinary therap*" OR "physiotherap*" OR "physical therap*" OR "recovery of function" OR "resistance training" OR "strengthtraining" OR "endurance program* OR "resistance program*" OR "strength program*" OR "fi tness program*" OR"aerobic training" OR "balance training" OR "physical training"OR "gait training" OR "movement" OR "rehabilitat*" OR "strengthening exercises" OR "stretching" OR "physical fitness" OR "neurodevelopmental treatment" OR "static positioning" OR "vibratory stimulation" OR "wholebody vibration" OR biofeedback OR hydrotherap* OR acupuncture OR thermotherap* OR "transcranial magneticstimulation" OR orthos* OR "shock waves" OR "therapeuticultrasound" OR "transcutaneous electric nerve stimulation" OR "electromyograph*" OR"occupational therap*" OR "physical stimulation" OR "physical education" OR "energy management" OR "energy conservation" OR "joint protection" OR "assistive device*" OR "assistive technolog*" OR "self care" OR "self-care" OR "self efficacy" OR "self-efficacy" OR ergonomic* OR "ergo therap*" OR counseling OR counselling OR "health literacy" OR "patient education" OR "splint*" OR "daily life activit*"

Trial registry: 'WHO-ICTRP' search strategy

("multiple sclerosis" OR "demyelinating diseases" OR "optic neuritis" OR "demyelinating autoimmune Diseases"OR "devic disease") AND ("spasm*" OR "muscle spasticity" OR "spasticity" OR"muscular spasm*" OR "spastic" OR "spastic paretic syndrome" OR "spasticism" OR "hypertonia") AND ("uni-disciplinary therap*" OR "unidisciplinary therap*" OR "physiotherap*" OR physical fitness OR physical rehabilitation OR physical endurance OR physical stimulation OR physical education OR physical training OR physical medicine OR physical therap* OR "recovery of function" OR endurance training OR resistance training OR strength training OR endurance program* OR resistance program* OR "strength program*" OR "fitness program*" OR "aerobic training" OR "neurodevelopmental treatment" OR "static positioning" OR occupational therapy OR "vibratory stimulation" OR "wholebody vibration"OR biofeedback OR hydrotherap* OR acupuncture OR thermotherap* OR "repetitive transcranialmagnetic stimulation" OR "rTMS" OR orthoses OR Orthotic* "strengthening exercises" OR "stretching" OR "shockwaves" OR "therapeutic ultrasound" OR "transcutaneous electric nerve stimulation" OR "TENS" OR"electromyography" OR "EMG")

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Coexistence of Non-Lower Body Mass Index and Exercise Habits Reduce Readmission in Older Patients With Heart Failure

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Objective: To investigate the impact of body mass index (BMI) and exercise habits on readmission rates among older patients with heart failure.

Methods: Ninety-seven older patients admitted for heart failure (median age: 81 years; 57.7% male) were included in the study. Patients were categorized into four groups based on the presence or absence of lower BMI and/or the absence of exercise habits. Lower BMI was defined as BMI<20.3 kg/m^2 at discharge and exercise habits were defined as engaging in 30 or more minutes of moderate or vigorous exercise at least once a week. The primary outcome was all-cause readmission during the 1-year follow-up period.

Results: The patients were distributed across four groups: lower BMI/non-exerciser (n=24, 24.7%), lower BMI/exerciser (n=22, 22.7%), non-lower BMI/non-exerciser (n=21, 21.6%), and non-lower BMI/exerciser (n=30, 30.9%). Forty-six patients (47.4%) experienced readmission during the 1-year follow-up period. In a cox proportional hazard analysis, non-lower BMI/exerciser remained an independent prognostic factor even after adjusting for confounding factors (non-lower BMI/exerciser vs. lower BMI/non-exerciser: hazard ratio, 0.26; 95% confidence interval, 0.08–0.83; p=0.022).

Conclusion: The coexistence of non-lower BMI and regular exercise habits may reduce readmission during the 1-year in older patients with heart failure. Therefore, it is imperative to conduct appropriate nutritional assessments for patients with lower BMI at discharge. Additionally, promoting and monitoring sustained physical activity after discharge is crucial for older patients with heart failure.

Keywords: Cardiovascular diseases, Body weights and measures, Physical activity, Hospitalization

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INTRODUCTION

The pandemic of heart failure has emerged as a serious global concern. The number of older people in Japan is increasing, and consequently, the number of heart failure patients is on the rise. Specifically, the count of Japanese outpatients with heart failure was 979,000 in 2005, and it is anticipated to steadily escalate as the population ages, reaching 1.3 million by 2030 [1]. The demographic of heart failure patients is also aging. There has been an absolute increase in the mean age of Japanese heart failure patients, from 71.6 years in 2007 to 77.0 years in 2015 [2]. We are being urged to implement measures in response to the aging of heart failure patients.

The readmission rates for worsening heart failure within one year for Japanese patients with heart failure is 35% [3]. Moreover, it has been reported that readmissions accelerated the escalation of healthcare expenditures [4]. Therefore, preventing readmission in heart failure patients is of paramount importance.

Body mass index (BMI) and exercise habits are important factors associated with readmission in heart failure patients. Lower BMI is associated with worse prognosis, and this phenomenon has also been reported in Japanese heart failure patients [5]. Additionally, maintaining exercise habits has been found to decrease readmission rates [6].

Patients with non-lower BMI and regular exercise habits are expected to have a better prognosis. However, even with a non-lower BMI, the absence of exercise habits may lead to a poorer prognosis. The potential synergistic effect between non-lower BMI and exercise habits, which could further improve readmission rates, has not been fully explored. Therefore, the purpose of this study was to examine the impact of BMI and exercise habits on readmission in older patients with heart failure.

METHODS

Study design and patient population

This study employed a single-center, prospective observational design. The patients consisted of individuals admitted to the Department of Cardiovascular Medicine at the hospital for treatment of acute decompensated heart failure. Inclusion criteria were: (1) age 65 years or older and (2) meeting Framingham criteria. Exclusion criteria were: (1) death during hospitalization; (2) death within 1 year after hospital discharge; and (3) non-response to the questionnaire.

This study was conducted in compliance with the "Declaration of Helsinki" and "Ethical Guidelines for Medical Research Involving Human Subjects." The study protocol underwent review and approval by the Ethical Review Board of Odawara Municipal Hospital (approval no. 2020-18). Informed consent was obtained from each patient, and they were given the option to decline participation in the study through an opt-out method.

Nutritional status

We assessed BMI as an indicator of nutritional status at hospital discharge. Nurses conducted weight assessments before breakfast at discharge, and height measurements were taken during admission. BMI was calculated as body weight (kg) divided by the square of height (m). In a previous study of heart failure patients in Japan, it was reported that patients with a BMI of less than 20.3 kg/m^2 had a higher mortality rate [7]. Therefore, we defined the BMI cut-off value as less than 20.3 kg/m^2.

Exercise habits

We surveyed exercise habits one year after hospital discharge. Questionnaires were mailed to the patients' homes along with return envelopes addressed to our hospital. The definition of exercise habits used in prognostic studies of patients with atrial fibrillation was adopted and modified [8]. Specifically, we inquired: (1) the frequency of engaging in moderate exercise in an average week and (2) the total duration of exercise typically performed per day. We defined exercise habits as engaging in at least 30 minutes of moderate exercise once a week.

Readmission

We recorded all-cause readmissions from the medical records. Additionally, along with questionnaires regarding the investigation of exercise habits, we also collected information: (1) the current vital status of the patient and (2) any admissions or non-scheduled hospitalizations within one year of discharge, including the reasons for these admissions. To ensure accurate information, we made phone calls to the patients' homes if confirmation could not be obtained through the questionnaires. Finally, we classified readmissions into the following categories: (1) heart failure, (2) cardiovascular, and (3) others.

Other variables

We extracted several variables from the medical records at hospital discharge, including age, sex, cognitive impairment,

medical history, smoking history, New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), geriatric nutritional risk index (GNRI) [9], blood biochemical data, activities of daily living (ADL), and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score [10]. Cognitive impairment was assessed using the Kihon Checklist-Cognitive Function (KCL-CF), a measure that predicts a Mini-Mental State Examination score of less than 23 [11]. The KCL-CF comprises three yes/no questions: (1) "Do your family or friends point out your memory loss (e.g., 'You ask the same question over and over again')?"; (2) "Do you make a call by looking up phone numbers?"; and (3) "Do you find yourself not knowing today's date?" Based on responses to these questions, each respondent received a KCL-CF score ranging from 0 to 3. Cognitive impairment was defined as a KCL-CF score of 1 or higher, according to a previous study [12]. ADL was assessed using the Barthel Index (BI) at hospital discharge. The MAGGIC risk score comprises the patients' age, sex, LVEF, BMI, creatinine level, NYHA class, smoking status, complications (diabetes and chronic obstructive pulmonary disease), history of heart failure, and medication use (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers). Moreover, we investigated physiotherapy interventions during the year following hospital discharge in the following modalities: (1) outpatient, (2) home visit, and (3) day care service.

Sample size calculation

It has been reported that BMI affects prognosis [5,7]. Therefore, the effect size for BMI was set at a moderate level of 0.30. The alpha level and power were set at 0.05 and 0.80, respectively, resulting in a total sample size of 88 cases. These parameters were used for sample size calculation in G*Power ver. 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf).

Statistical analysis

Patients were classified into the following four groups according to BMI cut-off value and exercise habits at the time of discharge: Lower BMI/non-exerciser, lower BMI/exerciser, non-lower BMI/non-exerciser, and non-lower BMI/exerciser. Data are expressed as the mean and standard deviation for normally distributed variables and as the median with quartiles for non-normally distributed data. Categorical data are presented as numbers and percentages. Baseline patient characteristics according to BMI and exercise habits were compared using a one-way analysis of variance or the Kruskal– Wallis test for continuous variables and chi-square tests for categorical variables, as appropriate.

To the all-cause readmission rates, we calculated the 100 person-years for each patient from hospital discharge to the event occurrence or the follow-up date. We described Kaplan-Meier survival curves, and event rates were compared using log-

rank tests to assess the significance of all-cause readmission among the four groups. Cox regression analysis was performed to determine the impact of BMI and exercise habits on all-cause readmission. We first examined the impact of BMI<20.3 kg/m^2 and exercise habits alone on all-cause readmission. Subsequently, we analyzed the impact of the four groups classified by BMI<20.3 kg/m^2 and exercise habits on all-cause readmission. Confounding factors included age>80, male sex, cognitive impairment, log N-terminal pro-brain natriuretic peptide (NT-pro BNP), NYHA class, LVEF, and BI score<100. Statistical analyses were conducted using SPSS software version 28.0, with a significance level set at <5%.

RESULTS

Fig. 1 shows the flowchart of the study patients. A total of 174 patients were admitted to our hospital between August 2020 and February 2022. We excluded 7 patients due to death during hospitalization, 6 patients due to missing data, 31 patients due to death within 1 year from discharge, and 33 patients due to questionnaire non-response. The causes of death for the 31 patients who died within 1 year from discharge were as follows: 17 patients died of heart failure, 10 patients died of other causes, and 4 patients died of unknown causes. Of these 31 patients, a total of 9 were readmitted to the hospital. Finally, we analyzed 97 patients in this study.

The median age of the patients was 81 years (75–87 years), with 57.7% being male. The median BMI was 20.8 kg/m^2 (18.0–22.7 kg/m^2). Fifty-two patients (53.6%) reported having exercise habits during the year following hospital discharge. Patients were categorized as lower BMI/non-exerciser (n=24, 24.7%), lower BMI/exerciser (n=22, 22.7%), non-lower BMI/non-exerciser (n=21, 21.6%), and non-lower BMI/exerciser (n=30, 30.9%).

Table 1 presents the characteristics of the patients. The lower BMI/non-exerciser group had significantly higher age and MAGGIC risk scores, as well as significantly lower BMI, GNRI, and BI at discharge compared to the non-lower BMI/exerciser

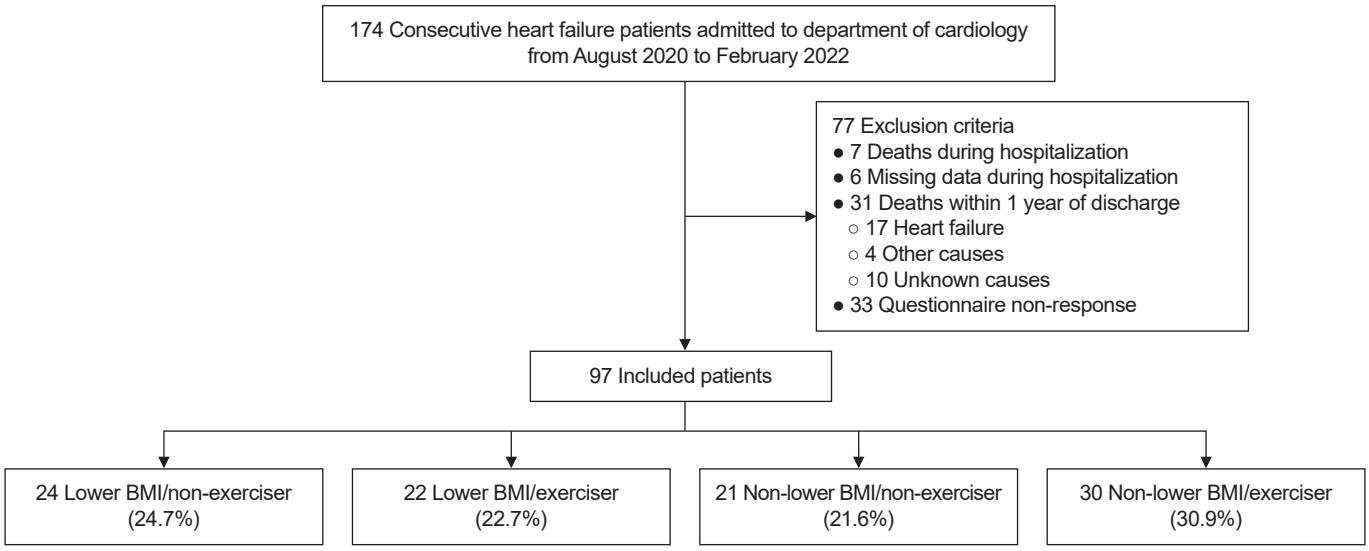

Fig. 1. Flowchart of the study. BMI, body mass index.

group. Additionally, a higher proportion of patients in the lower BMI/exerciser group were classified as NYHA class III and IV compared to the non-lower BMI/exerciser group. However, cognitive impairment, physiotherapy interventions during the year following hospital discharge, and living alone did not differ significantly among the four groups.

During the 1-year follow-up after hospital discharge, 46 patients (47.4%) experienced readmission (22 for heart failure, 9 for cardiovascular reasons, and 21 for other causes). All-cause readmissions occurred in 17 patients (70.8%) in the lower BMI/non-exerciser group, 12 patients (57.1%) in the non-lower BMI/non-exerciser group, 10 patients (33.3%) in the non-lower BMI/exerciser group, and 7 patients (31.8%) in the lower BMI/exerciser group. There were no significant differences in readmissions due to heart failure and cardiovascular reasons among the four groups.

Kaplan-Meier curves for all-cause readmission showed significant differences among the four groups (log-rank p=0.027; Fig. 2). The results of the cox proportional hazards analysis are presented in Table 2. In the multivariable model, being an exerciser or having a BMI<20.3 kg/m^2 alone did not independently impact prognosis after adjusting for age, sex, log NT-pro BNP, LVEF, NYHA class, and BI at discharge. However, the non-lower BMI/exerciser group had significantly lower readmission rates even after adjusting for confounding factors (non-lower BMI/exerciser vs. lower BMI/non-exerciser: hazard ratio, 0.26; 95% confidence interval, 0.08–0.83; p=0.022). Conversely, the non-lower BMI/non-exerciser group had no independent prognostic impact.

DISCUSSION

We examined the impact of the coexistence of BMI and exercise habits on readmission in older patients with heart failure. The main result of this study is that patients with both a non-lower BMI and regular exercise habits exhibited significantly lower readmission rates. This study represents the first to find that the coexistence of BMI and exercise habits leads to lower readmission rates in older patients with heart failure.

Patients with both a non-lower BMI and regular exercise habits exhibited significantly lower readmission rates. In Japanese patients, it has also been reported that a higher BMI is associated with lower 30-day readmission rates in patients with Japanese heart failure [13]. Additionally, non-lower BMI has been associated with significantly lower all-cause mortality and heart failure readmission rates in Japanese patients [5,7]. The indicators related to the exercise habits of heart failure patients have been shown to influence readmission rates. Reduced daily step count is associated with decreased exercise capacity [14], and exercise capacity itself is a prognostic factor in patients with heart failure [15]. Patients with no exercise habits likely had lower exercise capacity, which may have resulted in a higher rate of readmission. However, it is reasonable to conclude that the combination of a non-lower BMI and exercise habits

Table 1. Baseline characteristics at discharge

Variable	Lower BMI/non-exerciser N=24 (24.7%)	Lower BMI/exerciser N=22 (22.7%)	Non-lower BMI/non-exerciser N=21 (21.6%)	Non-lower BMI/exerciser N=30 (30.9%)	p-value
Age (yr)	84.5±5.7[b)]	79.8±7.1	82.0±7.7	77.1±8.4	0.004
Male (%)	10 (41.7)	17 (77.3)	13 (61.9)	16 (53.3)	0.095
Living alone (%)	9 (37.5)	8 (36.4)	1 (4.8)	8 (26.7)	0.054
BMI (kg/m^2)	18.2 (15.9–19.1)[b),d)]	17.8 (16.6–19.4)[b),d)]	22.6 (22.3–25.9)	22.5 (21.9–24.7)	<0.001
Cognitive impairment (%)	13 (54.2)	12 (54.5)	16 (76.2)	17 (56.7)	0.386
GNRI	80.1 (62.0–90.7)[a),c)]	84.0 (75.8–92.0)[a),c)]	98.8 (85.9–102.8)	95.1 (80.0–102.2)	<0.001
Etiology (%)					
Ischemic	3 (12.5)	2 (9.1)	8 (38.1)	10 (33.3)	0.042
Cardiomyopathy	0 (0)	5 (22.7)	2 (9.5)	2 (6.7)	0.059
Valvular heart disease	15 (62.5)	12 (54.5)	6 (28.6)	15 (50.0)	0.137
Comorbidities (%)					
Prior history of heart failure	9 (37.5)	13 (59.1)	7 (33.3)	11 (36.7)	0.280
Diabetes mellitus	6 (25.0)	5 (22.7)	10 (47.6)	11 (36.7)	0.266
Hypertension	17 (70.8)	10 (45.5)	15 (71.4)	25 (83.3)	0.034
Dyslipidaemia	3 (12.5)	2 (9.1)	6 (28.6)	7 (23.3)	0.292
Chronic kidney disease	5 (20.8)	6 (27.3)	5 (23.8)	7 (23.3)	0.966
COPD	3 (12.5)	1 (4.5)	2 (9.5)	1 (3.3)	0.556
History of cancer	7 (29.2)	7 (31.8)	4 (19.0)	6 (20.0)	0.666
Peripheral vascular disease	0 (0)	0 (0)	1 (4.8)	1 (3.3)	0.579
Smoking	4 (16.7)	6 (27.3)	9 (42.9)	7 (23.3)	0.240
NYHA class (%)					0.042
I	1 (4.2)	3 (13.6)	3 (14.3)	1 (3.3)	
II	4 (16.7)	8 (36.4)	3 (14.3)	16 (53.3)	
III	18 (75.0)	11 (50.0)	15 (71.4)	13 (43.3)	
IV	1 (4.2)	0 (0)	0 (0)	0 (0)	
NYHA class>III (%)	19 (79.2)	11 (50.0)	15 (71.4)	13 (43.3)	0.027
LVEF (%)	63.0 (50.6–67.8)[e)]	46.0 (32.8–60.2)	58.0 (35.9–63.5)	51.1 (39.8–61.5)	0.015
Laboratory data					
Creatinine (mg/dL)	1.09 (0.79–1.53)	1.00 (0.87–1.35)	1.17 (0.91–1.55)	1.11 (0.79–1.45)	0.748
BUN (mg/dL)	27.5 (22.1–40.3)	28.4 (22.8–42.1)	22.6 (17.9–29.0)	22.7 (15.0–37.4)	0.266
Albumin (g/dL)	3.4 (2.9–4.0)	3.6 (3.1–4.0)	3.6 (3.3–3.9)	3.6 (3.0–3.8)	0.628
Hemoglobin (g/dL)	11.5±1.8	11.6±1.9	11.8±2.0	11.8±3.1	0.944
NT-pro BNP (pg/mL)	4,482 (2,516–12,961)	3,728 (1,722–5,486)	3,635 (1,568–6,150)	5,170 (1,840–11,000)	0.771
Medication (%)					
ACE-I/ARB	13 (54.2)	13 (59.1)	15 (71.4)	22 (73.3)	0.412
ARNI	2 (8.3)	2 (9.1)	4 (19.0)	3 (10.0)	0.655
SGLT2	5 (20.8)	2 (9.1)	7 (33.3)	12 (40.0)	0.070
Beta blocker	12 (50.0)	17 (77.3)	19 (90.5)	21 (70.0)	0.024
Loop diuretic	19 (79.2)	20 (90.9)	17 (81.0)	27 (90.0)	0.543
MAGGIC risk score	33 (30–35)[b)]	28 (26–32)	29 (27–32)	26 (22–29)	<0.001
Barthel Index score	90 (80–100)[a)]	100 (90–100)	100 (90–100)	100 (90–100)	0.024
Barthel Index score<100	16 (66.7)	7 (31.8)	8 (38.1)	8 (26.7)	0.026
Exercise habits (exerciser)	0 (0)	22 (100)	0 (0)	30 (100)	<0.001
Readmission (%)					
All-cause	17 (70.8)	7 (31.8)	12 (57.1)	10 (33.3)	0.014
Heart failure	6 (25.0)	5 (22.7)	5 (23.8)	6 (20.0)	0.969
Cardiovascular	5 (20.8)	0 (0)	2 (9.5)	2 (6.7)	0.098
Others	7 (29.2)	3 (13.6)	5 (23.8)	6 (20.0)	0.639

BMI, body mass index; GNRI, geriatric nutritional index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; NT-pro BNP, N-terminal pro-brain natriuretic peptide; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitors; SGLT2, sodium-glucose co-transporter-2; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

[a)]p<0.05 vs. non-lower BMI/exerciser; [b)]p<0.01 vs. non-lower BMI/exerciser; [c)]p<0.05 vs. non-lower BMI/non-exerciser; [d)]p<0.01 vs. non-lower BMI/non-exerciser; [e)]p<0.05 vs. lower BMI/exerciser.

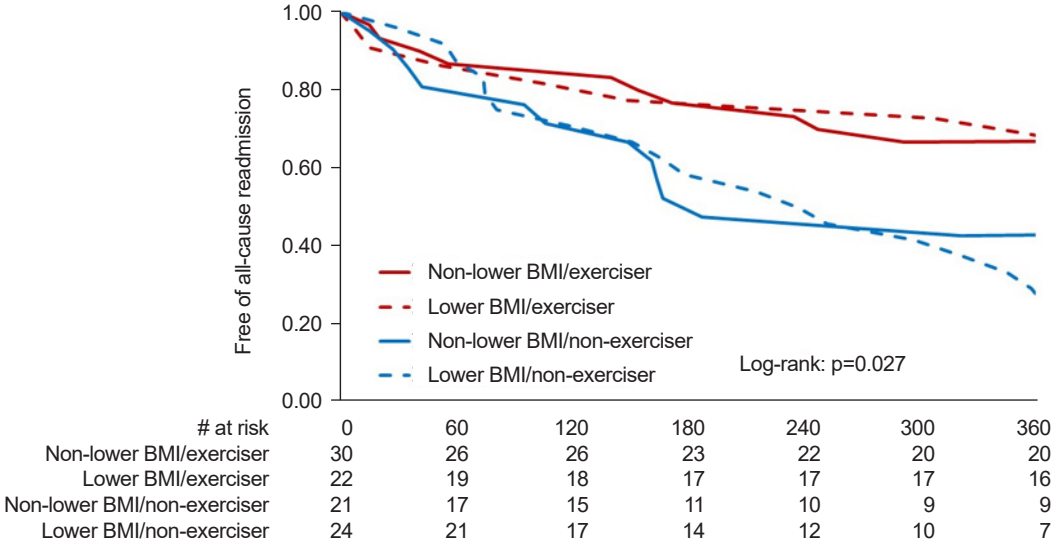

Fig. 2. Kaplan-Meier graph describing 1-year readmission for the 4 groups of patients based on body mass index (BMI) and exercise habits.

Table 2. Unadjusted and adjusted cox regression analysis for 1-year readmission

	Univariable model			Multivariable model			Multivariable model		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age>80 yr	1.32	0.72–2.43	0.368	0.65	0.23–1.82	0.410	0.65	0.23–1.86	0.424
Male sex	0.57	0.32–1.01	0.056	0.52	0.25–1.09	0.084	0.52	0.24–1.16	0.110
BMI<20.3 kg/m^2	1.21	0.68–2.17	0.512	1.76	0.81–3.81	0.155	-	-	-
Cognitive impairment	0.99	0.55–1.79	0.980	1.26	0.53–3.01	0.605	1.26	0.53–3.01	0.602
Log NT-pro BNP	1.02	0.78–1.34	0.897	1.09	0.75–1.58	0.670	1.08	0.75–1.58	0.673
NYHA class (per +1 class)	1.24	0.78–1.95	0.366	0.63	0.31–1.27	0.194	0.63	0.31–1.27	0.197
LVEF (per +1%)	1.00	0.98–1.02	0.822	1.01	0.98–1.04	0.571	1.01	0.98–1.04	0.599
Barthel Index score<100	0.92	0.49–1.75	0.803	0.80	0.32–1.99	0.634	0.81	0.32–2.04	0.652
Exerciser	0.41	0.23–0.75	0.004	0.46	0.19–1.07	0.071	-	-	-
Lower BMI/non-exerciser		1 (reference)		-	-	-		1 (reference)	
Lower BMI/exerciser	0.37	0.15–0.89	0.027	-	-	-	0.44	0.14–1.37	0.438
Non-lower BMI/non-exerciser	0.83	0.40–1.75	0.628	-	-	-	0.55	0.19–1.61	0.274
Non-lower BMI/exerciser	0.39	0.18–0.86	0.019	-	-	-	0.26	0.08–0.83	0.022

HR, hazard ratio; CI, confidence interval; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BMI, body mass index.

significantly reduced readmission rates in elderly heart failure patients.

Although the pathophysiological explanation for the poor prognosis of heart failure patients with lower BMI remains speculative, several mechanisms have been proposed to explain this outcome. First, heart failure is a well-known catabolic condition [16], and patients with lower BMI may have reduced metabolic reserves to withstand the increased catabolic stress associated with heart failure. Second, inflammatory cytokines may be involved. Elevated levels of tumor necrosis factor-α (TNF-α), a marker of inflammation, are associated with poor prognosis [17]. TNF-α has also been reported to act directly on the brain to decrease appetite [18]. Thus, increased inflammatory cytokines may contribute to BMI reduction and poor prognosis.

Despite having a non-lower BMI, a lack of exercise habits does not lead to a decrease in readmission rates. Studies have indicated that establishing regular exercise routines and increasing physical activity can effectively reduce cardiovascular mortality and readmission among individuals with heart failure [6].

Additionally, limited life space and decreased physical activity have been identified as risk factors for readmission in patients with congestive heart failure or chronic obstructive pulmonary disease [19]. The cultivation of exercise habits may also correlate with adherence to disease management protocols. Previous research has shown that greater disease knowledge is linked to higher levels of physical activity in patients with heart failure [20]. Conversely, insufficient disease knowledge has been associated with poor compliance with fluid restriction and weighing guidelines [21]. Noncompliance with prescribed medications has also been recognized as a risk factor for readmission in patients with heart failure [22]. Consequently, the absence of exercise habits may be intricately linked to factors such as disease management adherence, and these multifaceted considerations may contribute to the challenge of mitigating readmission rates, even in individuals with a non-lower BMI.

Study limitations

We found that both a non-lower BMI and regular exercise habits were associated with a significantly lower readmission rate. However, our study had several limitations. First, this was a single-center study, and future multicenter studies are needed to generalize our results. Second, we did not investigate the specific causes of the identified readmission rates. In the future, it is essential to identify readmission rates specifically attributable to heart failure. Third, because exercise habits were assessed by questionnaire, we did not obtain detailed information on physical activity behaviors, such as daily step counts, sedentary behavior, and other physical activity levels. Furthermore, the questionnaire has limitations in accurately measuring exercise. In future studies, physical activity should be objectively assessed using a three-dimensional accelerometer. Fourth, 31 patients who died within a year of discharge were excluded because their exercise habits could not be evaluated. However, 9 of these patients were readmitted within that year, which may have influenced the results. Therefore, regular post-discharge assessment of exercise habits may be necessary in future studies. Finally, our sample size was small, which may have resulted in limited statistical power. Therefore, the study should be reanalyzed with a larger number of patients.

Conclusions

We found that the coexistence of non-lower BMI and exercise habits during the 1-year may reduce readmission in older patients with heart failure. Both evaluating BMI and encouraging and monitoring continued physical activity after discharge are needed in older patients with heart failure.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Ozawa T, Sato R. Methodology: Ozawa T, Yuge M. Formal analysis: Ozawa T. Investigation: Ozawa T, Sato K, Izuoka Y. Project administration: Ozawa T, Yuge M. Visualization: Ozawa T, Inoue T, Naruke T. Supervision: Naruke T, Sato R, Shimoda N, Yuge M. Writing – original draft: Ozawa T. Writing – review and editing: Inoue T, Naruke T, Shimoda N, Yuge M. Approval of final manuscript: all authors.

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Change in Plantar Pressure and Plain Radiography in Pediatric Flexible Flatfoot: A Retrospective Cohort Study

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Objective: To investigate longitudinal changes in plantar pressure examinations and plain radiographs and to assess the correlations between these two modalities in pediatric patients with flexible flatfoot (FFF).

Methods: Pediatric patients diagnosed with FFF were analyzed in this retrospective cohort study. Medical records were reviewed to collect data on plain radiographs and plantar pressure examinations. Changes in radiographic angles and plantar pressure parameters were analyzed over a follow-up period exceeding 1 year. Statistical analyses included paired t-test, Wilcoxon signed rank test, and Spearman's correlation analysis.

Results: A total of 52 subjects was included in the plantar pressure analysis, with a mean age of 9.9 years at the first visit and a median follow-up duration of 52 months. The lateral talo-first metatarsal angle decreased by 1.3° ($p<0.001$) and calcaneal inclination angle increased by 2.5° ($p<0.001$) in these patients. The percentage value of midfoot width (W_{MF}) divided by forefoot width (W_{FF}) decreased by an average of 9.8% p ($p<0.001$), and the maximal pressure on the medial midfoot (MMF) decreased by 1.6 N/cm^2 ($p<0.001$). However, no correlations were found between plantar pressure and radiographic changes.

Conclusion: During follow-up of patients with FFF, the maximal pressure on the MMF and the ratio of W_{MF} to W_{FF} decreased in successive plantar pressure examinations. Changes observed in plantar pressure and plain radiographs were not consistent, indicating that these two testing modalities can complement each other.

Keywords: Flatfoot, Pressure, Radiography, Diagnostic imaging, Diagnosis

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INTRODUCTION

Flatfoot is a prevalent condition among pediatric populations and is not inherently pathological [1,2]. In previous studies, flatfoot was more common in boys than girls, occurring in 18.5% of 11-year-old children in South Korea [1,3]. Flatfoot can be classified into two types: rigid and flexible. The flexible type predominates among children. Although the flexible type predominates among children, its pathophysiological mechanism remains uncertain, with proposed hypotheses including subtalar joint hypermobility and muscle weakness [4]. Flexible flatfoot (FFF) typically resolves during normal growth. However, instances with persistent uncomfortable symptoms such as pain or in which normal arch development fails to manifest during maturation warrant consideration for therapeutic intervention [5]. The efficacy of insoles in FFF has been a subject of debate. In several studies, pediatric patients with FFF were followed using plain radiographs to assess the effectiveness of corrective

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shoes. In those studies, no significant differences were observed compared with control groups [6,7]. However, corrective foot orthoses are widely used in clinical practice due to their low risk of side effects, provision of pain reduction, and biomechanical benefits, including correcting bone alignment and relieving strain on ankle muscles [8-13].

Plain radiographs are commonly used in clinical practice to assess FFF in pediatric patients. There are several studies documenting the natural trajectory of FFF in pediatric populations, and significant improvements were observed in talonavicular coverage angle, anteroposterior tarso-first metatarsal angle, and lateral tarso-first metatarsal angle (LTMA) during follow-up [14,15]. Plantar pressure examination technology is increasingly widespread, but the understanding of longitudinal changes in plantar pressure remains limited. Although several studies [16-18] have investigated the use of plantar pressure in evaluating FFF patients, most have been experimental, and large-scale, long-term data on pressure changes remain limited. The cross-sectional relationship between these two diagnostic modalities has been investigated in some studies [16,17]. However, knowledge regarding their longitudinal correlation over extended follow-up periods is lacking. Elucidating the correlation between changes observed in these two diagnostic assessments could provide valuable insights for guiding clinical strategies, particularly when selecting diagnostic tests during patient monitoring.

We investigated pediatric patients diagnosed with FFF in the present retrospective cohort study. Changes in plantar pressure examination and lateral plain radiography over the follow-up duration were examined to identify correlations between changes detected by these two diagnostic modalities.

METHODS

This retrospective cohort study was approved by the Institutional Review Board (IRB) of Hanyang University Seoul Hospital (IRB confirmation No. 2022-06-030), with a waiver of informed consent granted. We reviewed past medical records for visit dates, plain lateral radiographs, and plantar pressure examination results.

Participants

Data were obtained from patients aged 6–15 years [18,19] who visited our clinic and were diagnosed with idiopathic FFF between January 2003 and February 2022. We included patients with records of at least two plantar pressure exams over a follow-up period exceeding one year. The follow-up period was defined based on the timing of examinations rather than timing of visits. Diagnosis of FFF was based on comprehensive evaluations including physical examinations for medial longitudinal arch collapse and hindfoot valgus, plain radiographs, and plantar pressure assessments. Patients with secondary flatfoot or who were already using corrective shoes or insoles at their first visit were excluded from the study. All patients included in this study were prescribed customized therapeutic insoles with medial longitudinal arch support and a medial heel wedge at our clinic for reasons such as pain, lack of improvement, or parental request.

Measurements

Plantar pressure examinations were conducted using the emed® (novel GmbH) to measure both the shape of the footprint on the ground and the pressure applied to each grid. To assess dynamic plantar pressure during midgait, subjects took at least three steps before and after stepping onto the platform. They were instructed to walk at a natural, comfortable pace without specific speed constraints. To ensure consistent results, a minimum of three trials was conducted per subject. Any trials in which the subject altered their speed or stride unnaturally were excluded [20]. We measured the ratio of maximal width of the midfoot (W_{MF}) to width of the forefoot (W_{FF}) and the peak pressure of the medial midfoot (MMF) using a pedobarograph. First, the long axis was drawn as the line passing through the origin of the second toe and the peak pressure point of the heel. The distance between the origin of the second toe and the tip of the heel was divided into three equal parts, with the middle section defined as the midfoot. The W_{MF} was defined as the longest line drawn perpendicular to the long axis, and W_{FF} was the distance between the two lines connecting the first and fifth metatarsal heads at the intersection of the foot contour. The peak pressure of the MMF was identified as the point of highest pressure medial to the long axis within the midfoot region (Fig. 1).

Plain radiographs were obtained in a weight-bearing state with both lower extremities extended in a neutral position. The LTMA and calcaneal inclination angle (CIA) were measured using the PACS (Picture Archiving and Communication System) program (INFINITT Healthcare; Fig. 2). The LTMA was defined as the angle between the long axis of the talus and that of the first metatarsus. The CIA was measured as the angle between a line drawn along the plantar surface of the calcaneus

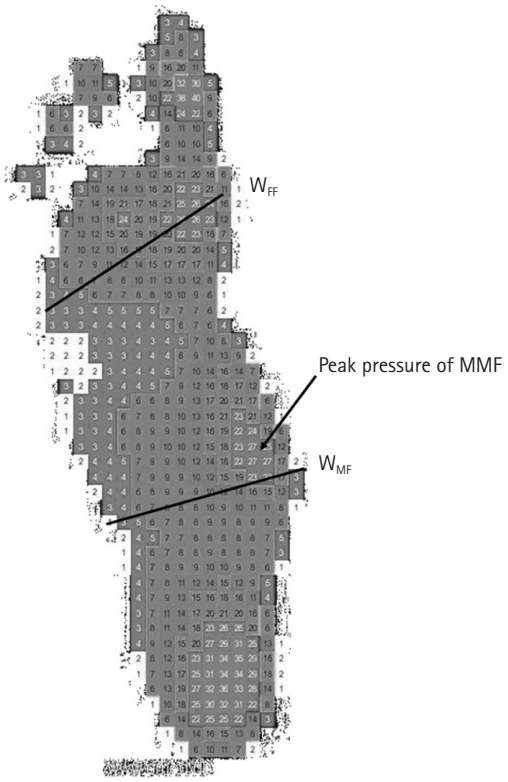

Fig. 1. Indices measured in plantar pressure examination. W_{FF}, width of the forefoot; MMF, medial midfoot; W_{MF}, width of the midfoot.

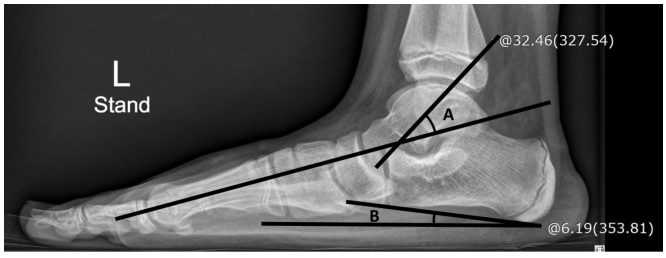

Fig. 2. Radiographic measurements in plain lateral radiographs. A, lateral tarso-first metatarsal angle; B, calcaneal inclination angle.

and the transverse plane [21,22]. The LTMA was negative when the first metatarsal bone was flexed dorsally relative to the talus axis, a finding consistent with FFF. To ensure consistency, a single rehabilitation resident performed all measurements. Previous studies have shown that LTMA and CIA exhibit strong inter-rater and intra-rater measurement reliability [21-23]. Reliability tests were performed by calculating intra-rater correlation coefficients (ICCs) using 20 randomly selected samples, with measurements performed at least two weeks apart to avoid any bias.

Outcomes

The primary outcome was the changes in both the plantar pressure test and the plain radiograph. In the plantar pressure examination, we measured the maximal W_{MF}-to-W_{FF} ratio (W_{MF}:W_{FF}) and peak pressure in the MMF. In plain radiographs, changes in LTMA and the CIA were evaluated. All indicator values were measured at both the initial and final examinations for comparison. Changes were calculated by subtracting the initial values from the final values. As a secondary outcome, we assessed the correlations between changes in plantar pressure and radiographic findings in patients who had undergone at least two lateral plantar radiographs. Radiographs were considered valid only if obtained within one year of the corresponding plantar pressure test date.

Statistical analysis

Data from the first and the last examinations were compared for each patient. The normality of each variable was assessed using the Kolmogorov-Smirnov test. The peak pressures of MMF and W_{MF}:W_{FF} measured from plantar pressure had non-parametric distributions, whereas the LTMA and CIA from plain radiographs followed parametric distributions. Based on our results, pre-post comparisons were conducted using either the paired t-test for parametric data or the Wilcoxon signed ranks test for non-parametric data. Correlation analysis was performed using Pearson's correlation for parametric variables and Spearman's correlation for non-parametric variables. Unless stated otherwise, statistical results are expressed as mean±standard deviation with statistical significance set at p-value<0.05. Statistical analysis was performed using IBM SPSS statistics ver. 22 (IBM Corp.)

RESULTS

We obtained plantar pressure examination data in 104 feet of 52 individuals, of whom 25 had corresponding radiographic data available for analysis. The demographic characteristics of the 52 subjects in the plantar pressure analysis included a mean age of 9.9±2.6 years at the first visit, a follow-up duration of 73.9±53.2 months (median of 52 months), and 42 males (80.8%). For the subset of 25 subjects involved in the correlation analysis between plantar pressure and radiographic findings, the mean age

at the first visit was 10.7±2.7 years. And there was a follow-up duration of 102.2±54.8 months (median of 111 months) between the first and last plantar pressure exams (Table 1).

The peak pressure on the MMF and W_{MF}:W_{FF} decreased and LTMA and CIA increased, indicating improvement of flatfoot (Table 2). Peak pressure of the MMF decreased in 59 feet (56.7%), remained unchanged in 15 (14.4%), and increased in 30 (28.8%). Identical measurements at the initial and last follow-up examinations were classified as unchanged. The measurement equipment used in the study has single-digit pressure measurement accuracy. The W_{MF}:W_{FF} significantly decreased in 70 feet (67.3%), was maintained in 4 (3.8%), and increased in 30 (28.8%).

The correlations among the four measured parameters were evaluated as secondary outcomes. Simple correlation analysis showed no significant relationship between changes in plantar pressure and plain radiographic findings. However, a significant correlation was observed for the two plantar pressure indices with the peak pressure of the MMF and the W_{MF}:W_{FF} ratio (Table 3). Given the influence of age on the progression of flatfoot [1,15,24], a partial correlation analysis was conducted, adjusting for age and follow-up duration. This analysis revealed no significant correlations between any of the parameter pairs (Table 4). Both LTMA and CIA had ICC values exceeding 0.9, reflecting excellent reliability.

Table 1. Demographics of participants

Characteristic	Value
Data for pre- and post-comparison of plantar pressure (n=52)	
Age at first examination (yr)	9.9±2.6
Sex, male	42 (80.8)
Follow-up duration of plantar pressure (mo)	73.9±53.2
Data for comparison of change in plantar pressure and plain radiograph (n=25)	
Age at first examination (yr)	10.7±2.7
Sex, male	21 (84.0)
Follow-up duration of plantar pressure (mo)	102.2±54.8
Follow-up duration of plain radiograph (mo)	101.8±55.7
Difference between follow-up duration of plantar pressure and plain radiograph (mo)	2.8±4.6

Values are presented as mean±standard deviation or number (%).

Table 2. Changes in plantar pressure and lateral plain radiography indices

	Initial visit	Last visit	Delta	p-value
Peak pressure of MMF (N/cm^2)	8.7±4.1	7.1±3.3	-1.6±4.3	p<0.001[a]
W_{MF}:W_{FF} (%)	71.6±13.2	61.8±17.5	-9.8±15.4	p<0.001[a]
LTMA (°)	-18.4±9.1	-17.1±7.7	1.3±7.1	p<0.001[b]
CIA (°)	13.4±5.9	15.9±4.7	2.5±4.0	p<0.001[b]

Values are presented as mean±standard deviation.
MMF, medial midfoot; W_{MF}, width of the midfoot; W_{FF}, width of the forefoot; LTMA, lateral tarso-first metatarsal angle; CIA, calcaneal inclination angle.
[a]Wilcoxon signed rank test.
[b]Paired t-test.

Table 3. Correlations between plantar pressure and plain radiographs

	ΔLTMA	ΔCIA	ΔPeak pressure of the MMF	ΔW_{MF}:W_{FF}
ΔLTMA				
ΔCIA	-0.150 (0.299)			
ΔPeak pressure of the MMF	0.198 (0.168)	0.104 (0.471)		
ΔW_{MF}:W_{FF}	-0.067 (0.644)	-0.49 (0.734)	0.317 (0.025)*	

Values are presented as correlation coefficient (p-value).
Statistical analysis: Spearman's correlation test was used for pairs including non-parametric variables (peak pressure of the MMF, W_{MF}, and W_{FF}). Pearson's correlation test was used to compare LTMA and CIA.
LTMA, lateral tarso-first metatarsal angle; CIA, calcaneal inclination angle; MMF, medial midfoot; W_{MF}, width of the midfoot; W_{FF}, width of the forefoot.
*p<0.05.

Table 4. Partial correlation analysis between change in plantar pressure and plain radiographs controlling for age and follow-up duration

	ΔLTMA	ΔCIA	ΔPeak pressure of the MMF	$\Delta W_{MF}:W_{FF}$
ΔLTMA				
ΔCIA	-0.125 (0.397)			
ΔPeak pressure of the MMF	0.179 (0.222)	0.08 (0.558)		
$\Delta W_{MF}:W_{FF}$	-0.031 (0.832)	-0.021 (0.885)	0.235 (0.107)	

LTMA, lateral tarso-first metatarsal angle; CIA, calcaneal inclination angle; MMF, medial midfoot; W_{MF}, width of the midfoot; W_{FF}, width of the forefoot.

DISCUSSION

Throughout the follow-up period, reductions were observed in the maximal pressure on the MMF and the $W_{MF}:W_{FF}$, along with increases in the LTMA and CIA. However, significant correlations were not found between indicators of plantar pressure and variables on simple radiography.

Plantar pressure

The medial concentration of plantar pressure in flatfoot patients was described in a previous study [25]. The decrease in maximum pressure on the MMF was significant in the subject demographics in the present study. With an average age of 10 years at the initial visit and a median follow-up period of 51 months, an anticipated increase in body weight over time underscores the importance of this finding. The observed decrease in pressure at the maximum point despite the expected increase in overall body weight indicates potential structural or functional improvements in foot biomechanics. In a previous study [26], notable changes were not observed in the average midfoot pressure or the ratio of midfoot pressure to total foot pressure over a mean follow-up period of 15 months. However, in the present study, we prioritized the identification of the region with the highest pressure in the MMF rather than assessing average pressure. This distinction is crucial because, even if the average midfoot pressure remains modest, other regions with focused pressure may experience discomfort or symptomatic manifestations. However, further empirical studies are needed to determine pressure thresholds that correlate with symptomatic presentation or prognostic outcomes in flatfoot patients. Furthermore, the Chippaux–Smirak index has low sensitivity for flatfoot [27]. In the present study, we focused on the maximum length of the midfoot instead of the minimum length to enhance sensitivity in identifying changes of test results during follow-up examinations. However, our results showed a degree of change comparable with previous studies utilizing the Chippaux– Smirak index [9]. The use of length ratios offers the advantage of broad clinical applicability because it circumvents the necessity for specialized pressure testing equipment.

Simple radiograph

In a previous study [15] examining the radiological progression of flatfoot, decrease in the LTMA was noted and the CIA remained unchanged. In another study [6] that included 31 individuals 10–11 years of age and an average follow-up period of 4 years with demographics similar to those in the present study, significant reductions in both the LTMA and the CIA were observed. The amount of change observed was also comparable to that in the present investigation. However, critical evaluation of the clinical significance of a 1°–3° alteration in angle is imperative. The LTMA and CIA are known to have good interobserver and intraobserver reliability [21-23]. However, the minimal clinically important difference (MCID) for these measurements has not yet been established. Additionally, studies remain inconclusive regarding LTMA and CIA cut-off values that reliably differentiate between symptomatic and asymptomatic flatfoot. A study of 28 young male soldiers [28] found mean LTMA values of 13.0 in symptomatic feet and 8.0 in asymptomatic feet, a significant difference. The mean CIA values were 10.8 and 12.5, respectively, also a significant difference. In contrast, another study of 135 flatfoot patients with an average age of 11 years [29], found no significant differences in LTMA and CIA between asymptomatic feet and symptomatic feet when treated conservatively. However, in patients who eventually required surgery, LTMA and CIA showed significant differences compared to those who did not need surgery. When the angle is extreme, symptoms are likely to be severe. However, due to the lack of consensus on a standard cutoff value or an MCID to predict symptom changes, clinicians should approach the subject with caution. In a study of 300 normal young adult Korean men [30], the reference value of LTMA was 0°±6.9°, and that of CIA was 23.9°±5°.

Correlations between plantar pressure and simple radiographs

There is limited knowledge about the longitudinal follow-up of flatfoot patients, particularly regarding the correlations between plantar pressure patterns and radiographic changes. In a cross-sectional study [17], associations were reported among MMF pressure, the LTMA, and the CIA, which is intuitively reasonable. However, the correlations between plantar pressure dynamics and radiographic changes over long-term follow-up were not significant in the present study. This indicates that dynamic biomechanical characteristics elucidated through plantar pressure analysis, specifically the distribution of pressure between the foot and the ground, cannot be inferred only from the osseous alignment shown in simple radiographs. The changes in angles measured on plain radiographs, typically 1°–3°, prompt questions regarding clinical significance, contrasting with more significant changes observed in plantar pressure examinations. Consequently, integrating plantar pressure examinations with traditional radiographic assessment offers a more comprehensive understanding of patient condition, providing objective insights into the dynamic functional aspects of flatfoot pathology.

Limitations

There are several limitations in this study. First, despite leveraging a longitudinal database spanning two decades, data were obtainable for only 50 individuals. However, relative to analogous investigations in the literature, this sample size is comparatively robust. Second, the generalizability of the study findings to the broader population of flatfoot patients may be limited. We included pediatric patients with FFF who had a follow-up duration longer than 12 months and including plantar pressure examination. All patients in this study received therapeutic insoles as part of their treatment, though the specific reasons for these prescriptions were not documented. The extended follow-up period and consistent use of insoles suggest that the study population may represent a more severe cohort of FFF patients compared to the general FFF population. Nonetheless, given the high prevalence of flatfoot among children and the spontaneous resolution observed in many cases without intervention, the findings of this study remain clinically significant. Third, total pressure and body weight were not accounted for when analyzing the pressure of the MMF. Since MMF pressure is influenced by body weight [1,14], it would have been ideal to normalize this value by dividing it by total pressure or body weight. However, due to incomplete data, particularly from older records with poor data storage conditions, these parameters were often unavailable. As an alternative, we focused on the change in pressure over time. A reduction in absolute pressure was observed during follow-up, which is a significant finding considering the age range of the participants, where body weight typically remains stable or increases over time. Last, not all patients underwent plantar pressure examination and radiographic evaluation on the same day. Discrepancies in the timing of these examinations and follow-up durations occurred due to various clinical circumstances including laboratory or patient scheduling conflicts. In some cases, both examinations were completed at early visits, but only plain radiographs were used for long-term follow-up as FFF gradually improved. To minimize these discrepancies, we only considered radiographs obtained within one year of the plantar pressure test. Consequently, the average difference in test dates between the two exams was 2.8 months. For reference, one study [15] reported that LTMA improved by 0.7 degrees per year in patients younger than 15 years with FFF.

Conclusions

Pediatric patients with FFF who used therapeutic insoles showed improvements in both plantar pressure analysis and plain radiographs. However, distinct patterns of change in plantar pressure were found compared with plain radiographs in FFF patients, underscoring the complementary nature of the two diagnostic modalities. To achieve a comprehensive understanding of flatfoot pathology, we advocate for the integration of static assessments of bone alignment through simple radiograph and dynamic evaluations of the forces interacting between the foot and the ground using plantar pressure examination.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Lee KH, Kim S. Data curation: Kim YG,

Kim S. Formal analysis: Kim S, Kim JY. Funding acquisition: Lee KH. Investigation: Kim S. Methodology: Lee KH, Kim S. Project administration: Lee KH. Supervision: Lee KH, Park SB. Validation: Lee KH, Park SB. Visualization: Kim JY. Writing – original draft: Kim S. Writing – review and editing: Lee KH, Park SB. Approval of final manuscript: all authors.

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Cross-Cultural Translation and Validation of the Thai Version of the Scale for the Assessment and Rating of Ataxia (SARA-TH)

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Objective: To culturally adapt the original English Scale for the Assessment and Rating of Ataxia to Thai (SARA-TH) and to evaluate the reliability and validity of the SARA-TH in assessing ataxia in acute ischemic stroke or transient ischemic attack (TIA) patients, as assessed by three healthcare professionals.

Methods: The SARA underwent translation and cross-cultural adaptation to Thai according to established guidelines. Reliability (e.g., internal consistency, intrarater reliability, interrater reliability) and validity (e.g., content validity, convergent validity) were assessed in a sample of 50 participants with ataxia after acute ischemic stroke or TIA. Spearman correlation analysis was used to examine the relationships between the SARA-TH and the Barthel Index (BI-TH), the National Institutes of Health Stroke Scale (NIHSS-TH), and the International Cooperative Ataxia Rating Scale (ICARS) to assess convergent validity. Interrater and intrarater reliability among experienced and novice neurologists, physiotherapists, and occupational therapists were assessed using weighted kappa.

Results: The SARA-TH demonstrated good comprehension and exhibited no significant floor or ceiling effects. It showed excellent internal consistency (Cronbach's $\alpha \geq 0.776$). Significant correlations were found between the SARA-TH score and the BI-TH score (r_s=-0.743 to -0.665), NIHSS-TH score (r_s=0.404–0.513), and ICARS score (r_s=0.859–0.917). The intrarater reliability for each rater ranged from 0.724 to 1.000 ($p<0.01$), and the interrater reliability varied from 0.281 to 0.927 ($p<0.01$).

Conclusion: The SARA-TH has excellent internal consistency, validity, and intrarater reliability, as well as acceptable interrater reliability among health professionals with varying levels of experience. It is recommended for assessing ataxia severity in individuals following acute ischemic stroke or TIA.

Keywords: Ataxia, Outcome assessment, Stroke, Translations, Reliability and validity

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INTRODUCTION

Ataxia is a neurological disorder characterized by deficits in the regulation and synchronization of voluntary muscle movements [1]. Ataxia commonly results from damage to the cerebellum or its connections, vestibular system, posterior column in the spinal cord or peripheral nervous system, which encompasses the neural pathways responsible for proprioception (joint positioning and movement information) transmission to the cerebellum. Symptoms and signs of ataxia correlate with the specific localization of lesions within the cerebellum or cerebellar connections, manifesting as disturbances in stance, gait, eye movements, muscle tone, skilled movements, and speech [2]. Cerebellar ataxia can be caused by multiple factors, such as cerebrovascular disease, infection, and genetic disorders [3]. A previous study in Hong Kong revealed that cerebellar ataxia significantly affects mobility, particularly gait ataxia, which is prevalent in up to 90% of cases and leads to falls and subsequent injuries. This impairment hampers patients' occupational engagement, resulting in pronounced economic and social ramifications. The direct and indirect financial burdens associated with patient care and treatment over a span of six months amounted to HKD 146,832 [4]. To evaluate cerebellar ataxia accurately, employing a standardized measurement tool is essential to enhance the efficacy of rehabilitation interventions for patients with this condition.

The International Cooperative Ataxia Rating Scale (ICARS), a standardized assessment tool recognized for its high validity and reliability, has been employed extensively for evaluating patients with ataxia [5]. However, the assessment involves 19 items and typically requires 20–30 minutes to complete, rendering it impractical for daily evaluations. Consequently, the Scale for the Assessment and Rating of Ataxia (SARA), a semi-quantitative evaluation tool, was developed to assess the level of impairment in individuals with cerebellar ataxia [6]. The SARA has demonstrated excellent reliability and validity for assessing ataxia [7], comprising eight items encompassing assessments of gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide test. Scoring on the SARA ranges from 0 to 40, with higher scores indicating greater severity of ataxia. The SARA has been translated or adapted into multiple languages, including Brazilian Portuguese [8], Japanese [9] Chinese [10], Korean [11], and French [12]. These versions have demonstrated strong internal consistency, along with a commendable level of accuracy and reliability [8-12]. Unfortunately, the Thai version of the SARA is unavailable.

Neurologists, physiotherapists (PTs), and occupational therapists (OTs) play crucial roles in utilizing the SARA assessment during patient rehabilitation. Neurologists conduct initial assessments for patients with ataxia, while PTs and OTs collaborate to design and implement rehabilitation programs aimed at restoring mobility and functional abilities. Therefore, this study aimed to culturally adapt the original English SARA to Thai. Additionally, we sought to evaluate the internal consistency, intrarater reliability, interrater reliability, content validity, and convergent validity of the Thai version (SARA-TH) for assessing ataxia in patients with acute ischemic stroke or transient ischemic attack (TIA), as assessed by three healthcare professionals. We hypothesized that the SARA-TH would demonstrate validity and reliability in assessing ataxia severity following a stroke by neurologists, PTs, or OTs.

METHODS

Permission was granted by Tanja Schmitz-Hübsch, the original author of the SARA. This study was divided into two stages: (1) linguistic translation of the original English version of the SARA into the Thai language and (2) tests of the reliability and validity of the SARA-TH.

Stage I: Linguistic translation of the SARA into the Thai language

The SARA-TH was translated and cross-culturally adapted according to the standard guidelines suggested by Beaton et al. [13]. An English lecturer with a PhD in linguistics and a neuro-PT with a PhD in physiotherapy and 15 years of experience, proficient in both English and Thai (with Thai as their first language), independently translated the original English version of the SARA into Thai, resulting in versions 1-A and 1-B. Subsequently, the translators, together with two researchers, a neuro-PT and a musculoskeletal PT, engaged in comprehensive discussions and prepared written reports before proceeding with back translation. Version 2 resulted from consensus and underwent back-translation into English by two proficient translators with proficiency in both English and Thai, independently yielding versions 3-A and 3-B. In the next step, an expert committee (consisting of four translators, one expert linguistic chair and 2 researchers) discussed the original questionnaire, all translated versions and written reports until they reached an agreement

regarding the semantic, idiomatic, experiential and conceptual equivalences between the original and targeted versions. The prefinal version was tested on five patients who were not included in the data analysis via video by one neurologist and one neuro-PT (15 years of experience). No modifications to the questionnaire were needed.

Stage II: Reliability and validity of the SARA-TH

The study protocol was approved by the Institutional Review Board of Naresuan University (NU-IRB P1-0084/2564) and Thai Clinical Trials Registry (TCTR) number TCTR20240423001. All processes were performed in accordance with the declaration of Helsinki. All participants provided written informed consent prior to their participation.

Participants

From April 2022 to March 2024, consecutive ischemic stroke or TIA patients admitted to the Stroke Unit of Naresuan University Hospital were included in this study. A total of 50 individuals were enrolled, adhering to guidelines recommending a sample size of ≥50 participants for evaluating reliability and validity [14]. Inclusion criteria were patients aged 20 to 80 years who had been diagnosed with ataxia due to acute ischemic stroke or TIA. The diagnosis was confirmed by brain imaging (computed tomography or magnetic resonance imaging) [15] and assessed by a neurologist with over 10 years of experience. Ataxia was determined based on clinical manifestations, including gait, truncal, and limb ataxia [2], evaluated through tandem walking, finger-to-nose, and heel-to-shin tests. Additionally, participants needed to be able to follow at least a 2-stage verbal command [16] and provide written informed consent. The exclusion criteria included patients with other neurological conditions affecting movement (e.g., Parkinson's disease or multiple sclerosis) and those with severe orthopaedic issues such as fractures.

Instruments

Participants were evaluated on all the following assessments.

(1) Barthel Index-Thai version

The Barthel Index (BI) is a reliable tool for assessing activities of daily living (ADL) poststroke [17] and consists of 10 items: feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing. Each item is scored at 0, 5, or 10, yielding a maximum total score ranging from 0 to 100. Higher scores indicate a greater degree of functional independence. Notably, it has been proposed as a suitable outcome measure for stroke trials and clinical practice [18]. Moreover, the BI has been translated into Thai and has demonstrated favourable validity and reliability [19].

(2) National Institutes of Health Stroke Scale-Thai version

The National Institutes of Health Stroke Scale (NIHSS) serves as a comprehensive assessment tool that quantifies neurological deficits following a stroke. It includes 11 items assessing the level of consciousness, horizontal eye movement, visual fields, facial palsy, motor arm, motor leg, sensory function, limb ataxia, language (aphasia), speech (dysarthria), and extinction and attention (neglect). Ratings for each item are assessed on a scale of 0 to 4 points, where 0 denotes normal function, and provisions are made for untestable items. The total score ranges from 0 to 42, with higher scores reflecting increased severity [20]. This scale holds validity in predicting mortality following acute stroke and has been proposed for supporting decisions regarding stroke rehabilitation [21]. The NIHSS was adapted and validated as a Thai version (NIHSS-TH) and has been reported to be a reliable tool [22].

(3) ICARS

The ICARS consists of 19 items categorized into four subscales: posture and gait disturbance, kinetic function, speech disorders, and oculomotor disorders. Scores on the ICARS range from 0 to 100, with higher scores indicating more significant impairments [6]. The ICARS has demonstrated strong criterion validity, excellent reliability and adequate internal consistency [5].

(4) SARA

The SARA includes 8 items: gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements and heel-shin slide. The total score ranges from 0 to 40, with higher scores indicating greater severity of ataxia [6]. The SARA showed strong concurrent validity with the BI [23] and robust construct validity by correlating significantly with the ICARS [24]. It also demonstrated excellent reliability [6] and adequate internal consistency for the original version [6] and the Chinese version [10].

Assessment procedures

Initially, the participants were assessed by the BI-TH and NIHSS-TH administered by a registered nurse who was trained to use those assessments and had more than 10 years of experience

working in the stroke unit. Subsequently, a neurologist assessed participants' ataxia using the ICARS on the same day as the BI and NIHSS-T assessments. Then, the participants underwent SARA-TH assessments in the afternoon of the same day, which were recorded via videotape. Six health professionals, comprising neurologists, PTs, and OTs, were stratified based on their professional experience: three raters had more than 3 years of experience in their respective fields (experienced), while the other three had less than 3 years of experience (novice). The three-year experience threshold was established based on the time required for a general practitioner to achieve Diplomate status with the Thai Board of Neurology. In the absence of specialized certifications for PTs and OTs in Thailand, we applied the same criteria used for neurologists to these professionals. Accordingly, the experienced neurologist, PT, and OT each have 12, 12, and 13 years of experience, respectively, since obtaining their qualifications. In contrast, the novice neurologist, PT, and OT have 2 months, 2 years, and 1 year of experience, respectively. These raters independently rated the SARA scores of each participant via video twice, with a two-week interval.

Statistical analysis

Statistical calculations were performed for 50 participants using the SPSS statistical package (version 17). Descriptive statistics (percentages, means and standard deviations) were used to describe the participants' demographic characteristics. The validity and reliability of the test were then investigated as follows.

(1) Content validity

Content validity was evaluated by an expert committee panel in the translational stage. The established threshold for identifying floor or ceiling effects is 15% [25].

(2) Convergent validity

The correlations between the SARA-TH and BI-TH, NIHSS-TH, and ICARS were examined using the Spearman rank correlation coefficient (rho). The correlations were defined as strong (rho≥0.5), moderate (0.3≤rho<0.5) or weak (rho<0.3) [26,27].

(3) Internal consistency

The internal consistency of the SARA-TH was evaluated using Cronbach's α coefficient. A Cronbach's α value higher than 0.7 was acceptable [28].

(4) Intra- and interrater reliability

The intra- and interrater reliability of the SARA-TH were assessed using kappa statistics for 50 participants. The following criteria were utilized to interpret the kappa values: ≤0 indicated no agreement, 0.01–0.20 indicated no to slight agreement, 0.21–0.40 indicated fair agreement, 0.41–0.60 indicated moderate agreement, 0.61–0.80 indicated substantial agreement, and 0.81–1.00 indicated almost perfect agreement [29].

RESULTS

Participants

A total of 50 participants were enrolled. The descriptive characteristics of the participants and scores for all measurements are provided in Table 1. There were no missing data.

Content validity

The SARA-TH was translated both forward and backwards, followed by a thorough review by a committee of investigators to address and resolve any discrepancies. The administration of SARA-TH proceeded without any issues. There were no significant floor or ceiling effects noted for the SARA-TH. Two percent of participants assessed by PT2 and four percent assessed by OT2 achieved the lowest possible SARA-TH score.

Convergent validity

The SARA-TH scores, evaluated by six raters, exhibited significant negative correlations with the BI-TH, ranging from -0.743 to -0.665 ($p<0.01$). Additionally, positive correlations were observed between the SARA-TH scores and the NIHSS-TH scores, ranging from 0.404 to 0.513 ($p<0.01$). Moreover, a strong positive correlation emerged between the SARA-TH and ICARS, ranging from 0.859 to 0.917 ($p<0.01$). Detailed correlations between the SARA-TH and BI-TH, NIHSS-TH, and ICARS scores are provided in Table 2.

Internal consistency

The Cronbach's α coefficients for the SARA-TH, which assess gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide across six raters, ranged from 0.776 to 0.823, as documented in Table 3. These measures represent satisfactory internal consistency.

Table 1. Demographic and clinical characteristics of the participants (n=50)

Measure (unit)	n (%)	Minimum score	Maximum score	Mean±SD
Age (yr)	-	46	77	61.86±7.32
Sex				
Female	13 (26.0)	-	-	-
Male	37 (74.0)			
Stroke side				
Right	12 (24.0)			
Left	15 (30.0)			
Bilateral	23 (46.0)			
Site of lesion				
MCA territory	6 (12.0)	-	-	-
Posterior circulation	20 (40.0)	-	-	-
Perforator artery	20 (40.0)	-	-	-
Unknown	4 (8.0)	-	-	-
Time since stroke (day)	-	1[a)]	18	2.56±2.91
BI-TH (0–100 points)	-	25	100	68.90±20.78
NIHSS-TH (0–42 points)	-	0	8	4.06±2.00
NIHSS-TH subscales (motor arm, motor leg, limb ataxia, sensory, and dysarthria) (0–14 points)	-	0	6	3.38±1.71
ICARS (0–100 points)	-	6	64	24.50±14.48
SARA (Neuro1) (0–40 points)	-	1	30	9.02±7.17
SARA (PT1) (0–40 points)	-	2	29	9.07±6.99
SARA (OT1) (0–40 points)	-	0.5	30	9.06±7.18
SARA (Neuro2) (0–40 points)	-	1.5	31.5	8.7±6.95
SARA (PT2) (0–40 points)	-	0	32	8.38±7.30
SARA (OT2) (0–40 points)	-	0	32	8.07±7.78

SD, standard deviation; MCA, middle cerebral artery; BI-TH, Thai version of the Barthel index; NIHSS-TH, National Institutes of Health Stroke Scale-Thai version; ICARS, International Cooperative Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia; Neuro1, experienced neurologist; PT1, experienced physiotherapist; OT1, experienced occupational therapist; Neuro2, novice neurologist; PT2, novice physiotherapist; OT2, novice occupational therapist.
[a)]Participants who presented with symptoms lasting 24 hours or less.

Table 2. Correlations between the SARA-TH scores of the 6 raters and the BI-TH, NIHSS-TH, and ICARS scores (n=50)

Item	Spearman's rho with the SARA-TH (p<0.01)					
	Neuro1	PT1	OT1	Neuro2	PT2	OT2
BI-TH	-0.667	-0.722	-0.708	-0.703	-0.743	-0.665
NIHSS-TH	0.474	0.488	0.488	0.513	0.464	0.404
ICARS	0.917	0.877	0.885	0.902	0.859	0.873

SARA-TH, Thai version of the Scale for the Assessment and Rating of Ataxia; BI-TH, Thai version of the Barthel index; NIHSS-TH, National Institutes of Health Stroke Scale-Thai version; ICARS, International Cooperative Ataxia Rating Scale; Neuro1, experienced neurologist; PT1, experienced physiotherapist; OT1, experienced occupational therapist; Neuro2, novice neurologist; PT2, novice physiotherapist; OT2, novice occupational therapist.

Table 3. Cronbach's α coefficients for the SARA-TH of 6 raters (n=50)

Item	Rater					
	Neuro1	PT1	OT1	Neuro2	PT2	OT2
Cronbach's α coefficients	0.780	0.786	0.786	0.823	0.776	0.804

SARA-TH, Thai version of the Scale for the Assessment and Rating of Ataxia; Neuro1, experienced neurologist; PT1, experienced physiotherapist; OT1, experienced occupational therapist; Neuro2, novice neurologist; PT2, novice physiotherapist; OT2, novice occupational therapist.

Intrarater reliability

The reliability of individual assessments was examined using weighted kappa scores to measure intrarater consistency, as outlined in Table 4. Among experienced neurologists, PTs, and OTs (Neuro1, PT1, and OT1), there was an exceptionally high level of agreement, ranging from 0.804 to 1.000, indicating almost

Table 4. Intrarater reliability of all items assessed by 6 raters (n=50)

Item	Weighted kappa (p<0.01)					
	Neuro1	PT1	OT1	Neuro2	PT2	OT2
Gait	0.949	0.901	0.804	0.848	0.854	0.807
Stance	0.974	0.947	0.847	0.948	0.897	0.813
Sitting	0.921	1.000	0.916	0.909	0.818	0.882
Speech	0.820	0.924	0.891	0.874	0.882	0.901
Finger chase	0.942	0.883	0.828	0.765	0.798	0.724
Nose-finger test	0.913	0.851	0.855	0.854	0.873	0.849
Fast alternative movement	0.937	0.804	0.830	0.881	0.841	0.846
Heel shin slide	0.895	0.896	0.894	0.766	0.764	0.766

Neuro1, experienced neurologist; PT1, experienced physiotherapist; OT1, experienced occupational therapist; Neuro2, novice neurologist; PT2, novice physiotherapist; OT2, novice occupational therapist.

Table 5. Interrater reliability of the SARA-TH comparison among health professionals and between experienced and novice raters (n=50)

Item	Weighted kappa (p<0.01)					
	Neuro1 & PT1	Neuro1 & OT1	PT1 & OT1	Neuro1 & Neuro2	OT1 & OT2	PT1 & PT2
Gait	0.726	0.875	0.655	0.646	0.563	0.383
Stance	0.740	0.898	0.741	0.717	0.692	0.653
Sitting	0.747	0.832	0.730	0.747	0.707	0.662
Speech	0.738	0.927	0.664	0.626	0.288	0.482
Finger chase	0.511	0.798	0.431	0.679	0.281	0.422
Nose-finger test	0.564	0.772	0.478	0.475	0.299	0.309
Fast alternating hand movements	0.816	0.593	0.652	0.726	0.434	0.543
Heel shin slide	0.612	0.736	0.453	0.662	0.438	0.415

SARA-TH, Thai version of the Scale for the Assessment and Rating of Ataxia; Neuro1, experienced neurologist; PT1, experienced physiotherapist; OT1, experienced occupational therapist; Neuro2, novice neurologist; PT2, novice physiotherapist; OT2, novice occupational therapist.

perfect agreement. Similarly, novice Neuro, PT, and OT raters (Neuro2, PT2, and OT2) displayed substantial to almost perfect agreement in their two ratings, with weighted kappa scores ranging from 0.724 to 0.948.

Interrater reliability

Interrater reliability was assessed for individual SARA-TH items by both experienced and novice neurologists, PTs, and OTs. Among experienced raters, agreement levels ranged from 0.431 to 0.927 (p<0.01), indicating moderate to almost perfect agreement. Between experienced and novice raters, substantial to almost perfect agreement was observed, with weighted kappa scores ranging from 0.281 to 0.747 (p<0.01), signifying fair to substantial agreement. Table 5 presents the weighted kappa scores for these comparisons.

DISCUSSION

This study aims to translate and cross-culturally adapt the original English version of the SARA into Thai and test its validity. Furthermore, it investigated the interrater reliability among interdisciplinary professionals engaged in ataxic stroke rehabilitation. Patients with TIA and ischemic stroke were enrolled to confirm the feasibility of using the SARA-TH for early rehabilitation in cases of hyperacute stroke. The findings suggest that the SARA-TH had satisfactory reliability and validity in ataxic stroke patients.

The findings found no significant floor or ceiling effects for the SARA-TH, suggesting good content validity. Moreover, the content validity was also verified by the expert committee during the translation process. The SARA-TH score exhibits a strong correlation with the BI-TH similar to the original version [6]. Consequently, the SARA-TH may offer utility in forecasting ADL functionality among ataxic stroke patients. Furthermore, similar to the original [30] and the Chinese [10] versions, the SARA-TH demonstrates a substantial correlation with the ICARS, a scale encompassing 19 items that necessitate a lengthier completion time [10]. These results affirm the use of the SARA-TH as a routine assessment tool for patients with ataxic stroke, potentially supplanting the need for the ICARS. However, the SARA-TH only demonstrates a moderate correla-

tion with the NIHSS. This could be because the NIHSS evaluates a wider range of neurological deficits, including facial palsy, sensory function, and language difficulties, in addition to ataxia [20]. Therefore, although the SARA-TH is effective for assessing ataxia, it may not completely replace the NIHSS-TH for predicting the severity of overall neurological deficits. It is noteworthy that the SARA-TH showed only a moderate correlation with the NIHSS but a strong correlation with the BI. This differing trend can be explained by the International Classification of Functioning, Disability, and Health conceptual framework. Eight out of ten items on the BI (i.e., feeding, bathing, grooming, dressing, toileting, chair transfer, ambulation, and stair climbing) can be categorized into the activity-disability level, similar to four out of eight items on the SARA (i.e., gait, stance, sitting, and speech disturbance). In contrast, all items on the NIHSS can be categorized into the impairment level [31]. Therefore, it can be concluded that the SARA score represents not only patients' impairments but also the activity-disability level of stroke patients. The Cronbach's alpha coefficient of the SARA-TH was greater than 0.7, indicating that all items within the test measure a unified concept or construct [32] similar to the original [6], Korean [11], Brazilian [8], Chinese [10], and French [12] versions.

The intrarater reliability of SARA-TH was almost perfect agreement (ICC 0.724–1.000) similar to the original [6] and Korean [11] versions. This robust agreement may be attributed to the standardized patient assessment facilitated by a consistent original video. Each rater had the chance to observe the subject's movements from a constant perspective during the initial assessment, reducing ambiguity in interpreting subsequent results. These findings align with a prior study [33] investigating intrarater reliability of movement performance in children based on video assessments.

The over all interrater reliability among three experienced health professionals showed substantial to nearly perfect agreement [28]. This suggests that ataxia in stroke patients can be effectively assessed using the SARA-TH among health professionals with different backgrounds. However, four specific items (finger chase, nose-finger test, fast alternating hand movements, and heel shin slide) exhibited moderate to substantial agreement among experienced neurologists, PTs, and OTs, and fair to moderate agreement among both experienced and novice health professionals in each field. These outcomes align with findings from the Japanese version study, which reported the lowest interrater reliability for the finger chase and fast alternating hand movements [9]. This suggests that accurately scoring the distance of abnormal movements of fingers or heels between raters can be challenging. The operational definition for the finger chase and nose-finger test items requires raters to distinguish between different distances, such as between 5 and 2 centimetres for the nose-finger test and more than 15 and less than 15 centimeters for the finger chase which can be tough to judge through observation alone. To boost reliability among raters, tools aiding in objectively measuring finger distance may prove essential. Similarly, accurately distinguishing the number of times the heel goes off the shin can also pose challenges in reliability between raters. Scoring the fast alternating hand movements item requires raters to pay attention to both the time taken and the performance of each participant. Without consensus on how to assess these two aspects, reliability between raters may be compromised.

The reliability of individual raters within themselves appears to be more consistent compared to the reliability between different raters. This suggests that it could be preferable to have one rater to assess SARA-TH in clinical or research settings. However, if multiple raters are involved, additional training in test administration and an exploration of interrater reliability are recommended to ensure consistent ratings. A Training Tool and Certification Program developed by the German Center for Neurodegenerative Diseases aims to enhance the quality of SARA assessments [34]. However, language proficiency, particularly in English, may limit accessibility to this program for some Thai raters.

While the SARA-TH demonstrates validity and reliability among health professionals, it does have certain limitations. First, our study participants may only represent stroke individuals who do not exhibit varying severity in sitting or speech items. Future research should investigate the psychometric properties of the SARA-TH in participants with different conditions. Second, this current study investigates the reliability between health professionals while assessing participants via video. Although we filmed all participants' movements following the SARA-TH instructions from the same viewpoint to control assessors' scoring, assessors had no chance to directly interact with participants. It would be interesting to investigate the reliability of the SARA-TH scoring participants in real-time. Last, this study solely examines the psychometric properties at a time point, emphasizing the necessity for further investigation into other properties such as predictive validity, discriminative validity, construct validity, or responsiveness in the future.

In conclusion, the SARA-TH was successfully translated

into Thai, showing excellent internal consistency, validity, and intrarater reliability, as well as acceptable interrater reliability among health professionals with varying levels of experience. It is recommended for evaluating ataxia severity in individuals following acute ischemic stroke or TIA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

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Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" is recommended to be registered to the primary registry to be prior publication. *ARM* recommend, as a condition of consideration for publication, registration in a public trials registry. *ARM* accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/), ISRCTN Resister (www.isrctn.org), ANZCTR (https://www.anzctr.org.au/), EudraCT Database (https://eudract.ema.europa.eu/), Clinical Trials Information System (https://euclinicaltrials.eu/), University Hospital Medical Information Network (www.umin.ac.jp/ctr/index/htm), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/) or The Clinical Research Information Service (http://cris.nih.go.kr/). The clinical trial registration number will be published at the end of the abstract.

5) PROCESS FOR MANAGING RESEARCH AND PUBLICATION MISCONDUCT

When the journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/guidance/Flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

6) PROCESS FOR HANDLING CASES REQUIRING CORRECTIONS, RETRACTIONS, AND EDITORIAL EXPRESSIONS OF CONCERN

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts available from: https://publicationethics.org/guidance/Flowcharts. If correction needs, it will follow the ICMJE Recommendation for Corrections, Retractions, Republications and Version Control available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html.

7) ETHICS AND AUTHORSHIP IN THE USE OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

Authorship assignment to AI is prohibited. *ARM* discourages the use of generative AI tools for the purpose of creating any types of content (including text, tables, and figures) for scientific manuscripts. If such tools are used, the authors must report their use transparently. In addition, authors who employ generative AI tools are solely responsible for all content produced and submitted. However, the use of AI tools to enhance the linguistic quality of a submission is considered acceptable and does not require specific disclosure.

5. MANUSCRIPT SUBMISSION

All submissions are made online at the journal's online manuscript submission site (http://www.e-arm.org/submission) by the corresponding author. Submitted manuscripts are initially examined for format, and then appointed a submission number. For nonbiased peer review, authors' names and institutional affiliations should not be mentioned in the text. The revised manuscript should be submitted through the same web system under the same identification numbers. The date of final review for the manuscript will be the date of acceptance for publication. If you

have any questions about the online submission process, contact the Editorial Office by e-mail at edit@e-arm.org.

1) ARTICLE PROCESSING CHARGES

Annals of Rehabilitation Medicine is an open access journal. To publish in *Annals of Rehabilitation Medicine*, authors are asked to pay an article processing charge (APC) on acceptance of their research paper. The APC for all published papers is as follows, plus VAT or local taxes where applicable. The currency KRW will be applied to the submissions from South Korea.

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†Note: As categorized by the World Bank, low-income countries will be eligible for a 20% discount on the updated APCs for original articles/brief reports/review articles/case reports. To find out if your country qualifies, please refer to the World Bank's classification available at https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.

(This updated article processing charge is applied to all submissions as of Oct 1, 2023.)

6. PEER REVIEW PROCESS

1) EDITORIAL REJECT POLICY

Conformity of the submitted manuscript to the submission instructions is examined upon submission. The Editorial Board may reject the manuscript or request the author to resubmit in the following cases: 1) Topic clearly out of scope / insufficient perceptual content 2) Work clearly does not meet sufficient standards of novelty or quality 3) Manuscript incomplete or incorrectly formatted 4) Suspected plagiarism in the manuscript.

2) PEER REVIEW PROCESS

Submitted manuscripts will be reviewed by two or more peer reviewers selected from the board's database of expert reviewers. In addition, if deemed necessary, a review of statistics may be requested. Following review, the editorial board will decide whether the manuscript will be 1) accepted for publication, 2) subject to minor revision, 3) subject to major revision, or 4) rejected for publication. For manuscripts which are either subject to minor revision or subject to major revision, the corresponding author must resubmit the revised manuscript online. The revised manuscript should clearly indicate all changes by highlighting the modified text or by using a different color for the altered sections. In addition, the corresponding author must reply to both reviewers' comments point by point, and explain in detail what changes were made in the manuscript. When considered necessary, the editorial board may make changes to the structure and phrases of the manuscript without compromising the integrity of the original paper. After completion of the peer review process, the editorial board will determine acceptance for publication and notify the corresponding author by e-mail. Manuscripts which do not comply with the present guidelines will be notified for correction or withheld from publication.

When a manuscript is not resubmitted within 2 months of notification, it will be considered that the authors have withdrawn the manuscript from submission. Manuscripts accepted for publication are generally published in order of submission, depending on the category of the manuscript and the date of acceptance for publication.

7. PREPARATION OF THE MANUSCRIPT

Use Microsoft Office Word (versions after 2003) and ensure correct spelling and grammar. Setup the MS Word document for 1-inch margins on letter or A4-sized paper. The manuscript must be written in 12-point font and the sentences must be double-spaced, including tables and figure legends. Each page should be numbered in the middle of the lower margin, and all sentences must be numbered sequentially throughout the entirety of the manuscript, starting with the title page. All papers must be accompanied by a title page. The title page should contain the title of the manuscript, a short running title, the authors' names, academic degrees, respective affiliations, and ORCID. The corresponding author must be identified, and his or her contact information (postal address, e-mail, telephone and fax numbers) should be listed. The title should clearly describe the objective of the study and contain less than 20 words. The first letter of each word of the title should be in capital letters except for prepositions, articles, and conjunctions. Provide a short running title containing less than 10 words. In cases in which the authors belong to multiple affiliations, the affiliations during the study being reported should be matched to the authors' names using a superscript of Arabic numerals. Conflicts of interest, funding information, author contribution and acknowledgements (when applicable) should also be located in the title page.

1) ORIGINAL ARTICLES

Original papers should be structured in the following order: Abstract, Introduction, Methods, Results, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. Maximum word count is limited to 5,000 words.

(1) Abstract

A structured abstract with the headings of Objective, Methods, Results, and Conclusion must succinctly describe the paper in 250 words or less. Use complete sentences and do not number the results. At the end of the abstract, list up to 5 relevant keywords which are in accordance to the Medical Subject Headings (MeSH) in the Index Medicus (http://www.nlm.nih.gov/mesh).

(2) Introduction

Clearly present the objective of the study and its relationship to earlier work in the field. A brief background to inform the readers of the relevance of the study may be necessary. However, avoid extensive review of the literature.

(3) Methods

Describe the participants or research materials of the study, and explain in detail the inclusion and exclusion criteria for both the experimental and control groups. Describe the experimental methods in a logical and systematic manner so that they can be reproducible by another investigator. Experimental drugs should be stated in the generic name. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name. When using experimental devices or other products, state the brand name then follow with the name of the manufacturer, in parentheses, e.g., Flow Cytometer (Coulter Electronic Inc.). To ensure anonymity during the peer review process, the authors' affiliations or institutional setting of the study should not be revealed. Statistical analysis and criteria for determining significance should be described in enough detail to allow the knowledgeable reader with access to the original data to verify the reported results. An ethics statement should be placed here when the studies are performed using clinical samples or data, and animals.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

(4) Results

Summarize and describe logically the significant findings and trends observed in the results using text, figures and tables. Avoid extensive repetition of contents of the tables and figures in the text.

In statistical expression, mean and standard deviation should be described as mean ± SD, and mean and standard error as mean ± SE. In general, p-values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; p-values smaller than 0.001 should be reported as $p < 0.001$.

(5) Discussion

Interpret the results in respect to the objective of the study, and describe differences with previous studies and significant findings which lead to the deduction of the conclusion. Refrain from excessive review of historic studies, textbook facts, or irrelevant references. Accentuate newly obtained observations from the study, and include significant limitations of the study.

(6) Conflicts of interest

Any potential conflicts of interest relevant to the manuscript should be described. If there are no conflicts of interest, authors should state that none exists.

(7) Funding information

All sources of funding applicable to the study should be stated here explicitly. All original articles, editorials, reviews, and new technology articles must state funding sources for the study.

(8) Author contribution

The individual contributions of the authors to the manuscript should be specified in this section.

(9) Acknowledgments

Persons who have made contributions to the study, but who are not eligible for authorship can be named in this section. Their contribution must be specified, such as data collection, financial support, statistical analysis, or experimentation. The corresponding author must inform the named contributor of the acknowledgment, and acquire consent before manuscript submission.

(10) References

- Cite only references which are quoted in the text. Limit the number of references 40.

- When quoting a reference in the text, refrain from stating the author's name, and identify references with Arabic numerals in brackets such as [1], [2-4], and [5,7,9].
- The references should be listed in order of citation in the text.
- List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."
- Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).
- For more on references, refer to the NLM Style Guide for Authors, Editors, and Publishers (http://www.nlm.nih.gov/citingmedicine).

Journals

1. Jeon JH, Jung YJ, Lee JY, Choi JS, Mun JH, Park WY, et al. The effect of extracorporeal shock wave therapy on myofascial pain syndrome. Ann Rehabil Med 2012;36:665-74.
2. Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatripan. Headache 2002;42 Suppl:S93-9.

Book & Chapter of book

3. Frontera W, Silver JK, Rizzo TD. Essentials of physical medicine and rehabilitation. 2nd ed. Saunders; 2008. p. 579-82.
4. Esquenazi A. Upper limb amputee rehabilitation and prosthetic restoration. In: Braddon RL, editor. Physical medicine and rehabilitation. 2nd ed. Saunders; 2000. p. 263-78.

Proceedings of academic conference

5. Harnden P, Joffe JK, Jones WG. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Thesis (Dissertation)

6. Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant, MI: Central Michigan University; 2002.

(11) Tables

Tables should be submitted separately from the text, and each table should be created in MS Word on separate pages, using double space throughout. They should be simple, self-explanatory, and not redundant with the text or the figures. Limit 5 tables per manuscript. The title of the tables should be written in phrases, and capitalized the first letter of the first word. The title should be placed above the table, and abbreviations and footnotes should be placed under the table. Number the tables in order of appearance in the text (e.g., Table 1, Table 2). All abbreviations used in the table must be spelled-out in full under the table in the following order: abbreviation, comma, full word (e.g., RM, rehabilitation medicine;). Table footnotes should be indicated in superscripts in the following order: [a], [b], [c]… but p-values should be indicated by asterisk (e.g., *$p<0.05$, **$p<0.01$. ***$p<0.001$).

(12) Figure legends

Legends should be submitted separately from the text, and each legend should be typed on separate pages. They should be written in full sentences to describe the content of the figure, and only the first letter of the legend should be capitalized. For lengthy legends continuing beyond one line, the left margin of the following lines should start at the same point as the first line. Any symbols, marks or abbreviations made in the figure must be explained in the legend. Figures containing histologic slides should be accompanied by legends explaining tissue origin, stain method, and microscopic amplification.

(13) Figures

Figures should be uploaded online as separate files and numbered in order of appearance in the text (e.g., Fig. 1). When a single numbered figure contains 2 or more figures, the figure should be numbered with an alphabet letter following the number (e.g., Fig. 1A, Fig. 1B). Indicate focus points in the figures with markers such as arrows and arrowheads, etc. Image files must be of resolutions higher than 300 dpi, and less than 3 MB, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. A single numbered figure containing more 2 or more figures such as Fig. 1A and Fig. 1B should be uploaded as a single file.

2) REVIEW ARTICLES

The abstract should contain no more than 250 words and 5 keywords. The text is structured in the order of Introduction, Main text, Conclusion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures.

3) BRIEF REPORTS

General guidelines are the same as for the original article. The manuscript is structured in the order of Abstract, Main text, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. A structured abstract is required and limited to 150 words, with no more than 3 keywords attached. Manuscripts

should be limited to 1,500 words of text including references and figure legends (not including abstract, tables, and figures), and no more than 10 references. The total number of figures and/or tables is limited to 3.

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General guidelines and order of manuscript preparation are the same as for the original article. Case reports are considered for publication only if they report rare conditions, atypical symptoms and signs, novel diagnostic or therapeutic approaches, or describe atypical findings for populations residing in Asia and the Pacific Rim. The editorial board will determine whether the case report fulfills the above criteria for acceptance of publication. The manuscript is structured in the order of Abstract, Introduction, Case report, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. The abstract should be nonstructured and limited to 150 words, with no more than 3 keywords attached. The introduction should briefly state the background and significance of the case. The actual case report should describe the clinical presentation and the diagnostic and therapeutic measures taken. The discussion should focus on the uniqueness of the case and should not contain extensive review of the disease or disorder. The combined number of tables and figures is limited to 5, and the number of references is limited to 10. Maximum word count is limited to 1,500 words including references and figure legends.

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All images should be accompanied by a short description of the image and a brief and concise clinical review of the specific patient or clinical issue of no more than 500 words (excluding references) with references limited to 5. Image files must be of resolutions higher than 300 dpi for photographs, and 900 dpi for line art, waveforms, and graphs, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. Images should make up a single figure, although they may contain more than one frame. The manuscript does not have an abstract.

6) LETTERS TO THE EDITOR

Letters should not have an abstract, tables, figures, and data supplements. Letters must be limited to roughly 500 words of text and no more than 5 references, 1 of which should be to the recent *ARM* article. Letters may have no more than 3 authors.

7) REPORTING GUIDELINES FOR SPECIFIC STUDY DESIGNS

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and metaanalyses	http://www.prisma-statement.org
STROBE	Observational studies	http://www.strobe-statement.org
MOOSE	Meta-analyses of observationa studies in epidemiology	http://www.consort-Statement.org/resources/downloads/other-instruments/moose-statement-2000pdf

8. SUBMISSION APPLICATION & COPYRIGHT TRANSFER

All submitted manuscripts must be accompanied by the official Submission Application & Copyright Transfer Form of the Korean Academy of Rehabilitation Medicine. The Submission Application & Copyright Transfer Form must contain the title of the manuscript, date of submission, names of all authors, authors' affiliations, and written signatures. Note the corresponding author and provide his/her affiliation, e-mail, telephone and fax numbers, and mailing address.

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1) FINAL VERSION UPLOAD

When accepted for publication, the authors' institutional affiliations should be inserted into the text of the final revised manuscript and uploaded to the online submission system. Files containing figures should be of the highest resolution (at least 300 dpi for color figures, and 900 dpi for line art and graphs) should be also be uploaded in JPEG, GIF, or TIFF format, and must be named according to the figure number (e.g., Fig. 1.jpg).

2) GALLEY PROOF

Galley proofs will be sent to the corresponding author for final corrections. Corrections should be kept to a minimum, must be returned within 2 days, otherwise publication may be delayed. Any fault found after the publication is the responsibility of the authors. We urge our contributors to proofread their accepted manuscripts very carefully. After the publication, if there are critical errors, they should be corrected as Corrigendum or Erratum.

3) PUBLICATION

The editorial board retains the right to request minor stylistic and major alterations that might influence the scientific content of the paper. The final manuscript will be published following final approval by the editor-in-chief.

Checklist for Authors

Annals of Rehabilitation Medicine

General

☐ All elements of the manuscript are printed in English and double-spaced with 1-inch margins at top, bottom, and sides. Right margins are unjustified.

☐ All pages are numbered in the following order: title page, structured or standard abstract, body of the text, conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), references, legends, and tables.

☐ The text is consecutively line numbered.

☐ The Submission Application & Copyright Transfer Form is signed by the guarantor at original submission.

Abstract (applied to original articles, review articles, brief reports, and case reports)

☐ A structured abstract with the headings of Objective, Methods, Results, and Conclusion (A nonstructured abstract for case reports) must succinctly describe the paper.

☐ At the end of the abstract, relevant keywords are listed.

References

☐ All references have been checked for accuracy and completeness.

☐ Cite only references which are quoted in the text. Limit the number of references 40 for original articles, 10 for brief reports and case reports, and 5 for images in this issue and letters to the editor.

☐ Are numbered consecutively in the order they are cited in the text; all listed references have been cited in the text.

☐ Do NOT parenthesize the superscript numerals, and hyphenate (-) when citing 3 or more references in consecutive order.

☐ The format prescribed by the "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" has been followed. Examples provided under Instructions for Authors have been uploaded.

☐ List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."

☐ Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).

Figure Legends

☐ Figure legends are provided for each figure.

☐ Figure legends are numbered and presented together in numeric order following reference page(s).

Tables

☐ Each table is headed by a title and numbered in Arabic numerals on a separate page.

☐ The title of the tables should be written in phrases, and capitalized the first letter of the first word.

☐ There are less than 5 tables in the text of original articles.

☐ Tables are cited in numeric sequence in the text.

Figures

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