Aims and Scope

*Annals of Rehabilitation Medicine* (ARM) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, more than 3,500 physiatrists regularly receive this journal's table of contents via email, and the number is continually increasing. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM). International members comprise approximately half the editorial board, conducting peer-reviews of submitted manuscripts or acting as handling editors by assigning peer-review tasks to other reviewers.

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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Robot-Assisted Gait Training in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Spinal cord injury (SCI) rehabilitation emphasizes locomotion. Robotic-assisted gait training (RAGT) is widely used in clinical settings because of its benefits; however, its efficacy remains controversial. We conducted a systematic review and meta-analysis to investigate the efficacy of RAGT in patients with SCI. We searched international and domestic databases for articles published until April 18, 2024. The meta-analysis employed a random effects model to determine the effect size as either mean difference (MD) or standardized MD (SMD). Evidence quality was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Twenty-three studies with a total of 690 participants were included in the final analysis. The overall pooled effect size for improvement in activities of daily living was 0.24, with SMD (95% confidence interval [95% CI], 0.04–0.43; GRADE: high) favoring RAGT over conventional rehabilitation. Muscular strength (MD, 0.23; 95% CI, 0.02–0.44; GRADE: high), walking index for SCI (MD, 0.31; 95% CI, 0.07–0.55; GRADE: moderate) and 6 min walk test distance (MD, 0.38; 95% CI, 0.14–0.63; GRADE: moderate) showed significant improvement in the robot group. Subgroup analysis revealed that subacute patients and intervention periods >2 months were more effective. This meta-analysis revealed that RAGT significantly improved activities of daily living, muscular strength, and walking abilities. Additional studies are needed to identify the optimal treatment protocol and specific patient groups for which the protocol is most effective.

Keywords: Spinal cord injuries, Robotics, Locomotion, Gait, Recovery of function

INTRODUCTION

Spinal cord injury (SCI) can cause various impairments in sensory, motor, and autonomic functions below the level of injury. This results in muscle weakness and atrophy, gait disturbances, sensory dysfunctions, and autonomic dysfunction [1]. Rehabilitation has focused on locomotion, especially for individuals with incomplete SCI classified as C or D on the American Spinal Injury Association (ASIA) Impairment Scale, because they are more likely to regain functional gait [2]. Early gait rehabilitation programs used manually assisted overground training with manual contact by a therapist, which later evolved into body weight-supported treadmill training. Since the introduction of the Lokomat (Hocoma AG) in the late 1990s, gait training with
robots has gained traction, and is increasingly being used clinically because of its ability to perform high-intensity, repetitive movements for consistent periods of time, and is less demanding on the therapist [3].

With advancements in robotic technology, various types of robots are being utilized clinically, which can be broadly divided into three categories: exoskeleton treadmill training, wearable exoskeleton, and end-effector robots. Grounded exoskeleton robots have two programmable robotic joints in each leg, and are designed to support hip and knee movement when walking on a treadmill while supporting the body weight with a harness, with Lokomat being a prime example [3]. Wearable exoskeleton robots are ground walking systems that use a rigid external frame to support the lower limbs and torso while assisting movements at the hip and knee joints. They can be trained across a range of environments, including indoor and outdoor settings, as well as with obstacles and stairs. Examples include Eksobionics, HANK (Goga Mobility), AIDER (Buffalo Robot Technology), and ReWalk (ReWalk Robotics) [4,5]. The end effector robot has a footplate attached with a walking trajectory only for the patient’s feet, allowing the knees and hips to move freely. Examples include Morning Walk (Curexo) and G-EO systems (Reha Technology) [6,7].

In 2021, the Korea Institute of Health and Medical Research analyzed the clinical utility of robotic-assisted gait training (RAGT) compared to that of conventional rehabilitation in patients with SCI. No statistically significant differences were observed in walking ability, muscle strength, functional performance, spasticity, balance, and quality of life [8]. As the number of relevant studies has grown, subsequent meta-analyses of the international literature have shown that RAGT significantly improves spasticity, walking ability, distance, speed, function, and peak oxygen consumption [9-11]. However, no studies have analyzed the effects of the type of robot, intervention duration, or onset period. We aimed to obtain data from randomized clinical trials conducted so far and dissect them based on robot classification, intervention duration, and onset period, with the aim of offering a comprehensive overview of the efficacy of RAGT in patients with SCI. We also hope that this study will support future policy decisions in the medical technology sector and contribute to adequate health insurance coverage.

**METHODS**

This meta-analysis adhered to the guidelines outlined in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. Supplementary Material S1 includes the PRISMA checklist. Additionally, the review protocol was registered and assigned the registration number CRD42023475357 in the International Prospective Register of Systematic Reviews.

**Search strategy**

The systematic search was conducted in six international (PubMed, Embase, Cochrane library, Scopus, Web of Science, and Google Scholar) and five domestic (KoreaMed, KMBase, KISS, RISS, and NDSL) databases until October 5, 2023, and we updated our search on April 18, 2024. The search formula was as follows: (Gait OR “Gait disorder” OR walking OR “Lower Extremity” OR leg or foot or ankle or tibia or fibula or femur or thigh or lower limb) AND (paresis OR paralysis or hemiplegia or paraplegia) AND (Robotics OR automation OR “Lower Extremity” OR leg or foot or ankle or tibia or fibula or femur or thigh or lower limb) AND (paresis OR paralysis or hemiplegia or paraplegia) AND (Robotics OR automation OR computer-assisted) AND (rehabilitation OR “Physical Therapy Modalities” OR “Exercise Therapy” OR physical therapy or physiotherapy or kinesitherapy or exercise) AND (“spinal cord injury” OR SCI) (Supplementary Material S2). We selected all published randomized controlled trials (RCTs) that compare RAGT with conventional rehabilitation methods. No data or language restrictions were applied. Two reviewers (JMP and JCS) independently reviewed titles and abstracts.

**Study selection and data extraction**

The study inclusion criteria adhered to the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework. The target population comprised patients with SCI and gait impairment. The intended intervention involved RAGT. For comparison, we established a control group of patients who received standard physical therapy with a therapist or non-robotic device therapy as traditional rehabilitation treatment. Designated outcomes comprised several primary outcomes encompassing activities of daily living (functional independence measure [FIM], spinal cord independence measurement [SCIM], and modified Barthel index [MBI]), muscular strength (lower extremity motor score, LEMS), spasticity (modified Ashworth scale, MAS), and balance (Berg balance scale, BBS), and walking ability (walking index for SCI [WISCI], 10 meter walk test [10MWT] speed, 6 min walk test [6MWT] distance, and step length). Secondary outcomes included body composition (body mass, lean tissue, and fat tissue) and cardiopulmonary function (forced expiratory volume in the first second [FEV1],...
forced vital capacity [FVC], heart rate, and peak cough flow [PCF]). The study design specifically included RCTs, excluding non-human studies, cohort studies, case reports, and studies that did not conform to the PICOS framework.

Two reviewers (JMP and YWK) independently extracted relevant data, including the name of the first author, year of publication, patient demographic data, mean age, sample size, type of intervention (robot type), intervention protocol, control protocol, and outcomes. Information extraction was facilitated by ImageJ software version 1.53 (ImageJ software; National Institutes of Health, https://imagej.nih.gov) in instances where the study estimates were solely presented graphically without numerical reporting.

Quality assessment and GRADE evaluation
The quality of studies was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2), which identified potential bias risks. The RoB2 comprises five elements: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each element was appraised for low risk of bias, concerns of bias, high risk of bias, or lack of information [13]. Two reviewers (JMP and YWK) independently assessed the risk of bias, and disagreements regarding the quality assessment were resolved through discussion with a third reviewer (JCS).

The certainty of evidence in the included meta-analyses was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, which comprises five domains: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and (5) publication bias. Ratings for certainty of evidence were high, moderate, low, and very low [14].

Statistical analysis
In this meta-analysis, we conducted a statistical standardization of the effect sizes related to RAGT in patients with SCI. Initially, we calculated the mean and standard deviation (SD) of the change-from-baseline values for intervention and control groups. For studies lacking complete data, the mean and SD values of the change-from-baseline were computed, according to the guidelines outlined in Section 6 of the Cochrane Handbook (version 6.3). Effect sizes were calculated as mean difference (MD) and standardized MD (SMD), with 95% confidence interval (95% CI) within a random effects model. The included studies were from different countries and populations with different medical backgrounds; therefore, we conducted a restricted maximum likelihood random effects meta-analysis to account for an expected high level of heterogeneity [15]. Heterogeneity between studies was evaluated using the I² metric for inconsistency and Cochrane Q test p-values. As suggested in previous studies [16,17] we assessed publication bias only in meta-analyses of ≥3 studies using funnel plots and Egger’s test. All statistical analyses were performed using Stata version 18 (StataCorp LP). Two-sided statistical tests were used, and significance was set at p<0.05. Subgroup analyses were performed according to robot type (treadmill training robot [Lokomat], wearable gait robot [Ekso, HANK, AIDER], end effector gait robot [morning walk]), intervention period, and onset period.

RESULTS

Study identification and characteristics
We screened 980 studies from international databases and 5,485 studies from domestic databases, excluding 102 and 334 duplicate records, respectively. After screening the titles and abstracts, 51 studies were selected from international and domestic databases, and their full texts were screened. Of these, 35 studies were excluded for various reasons (study protocol, observational study, review article, insufficient detail in the data, inappropriate intervention, and inappropriate control), and seven articles found through citation searches were combined, resulting in 23 studies that were finally included in the meta-analysis. Fig. 1 shows a flowchart outlining the study selection process. This meta-analysis included 690 patients with SCI: 346 and 344 in the intervention and control groups, respectively. The number of participants included in a single study ranged between 7 [18] and 88 [19]. The average age of the participants was between 8.4 [20] and 59.6 years [21]. The average onset duration of the participants was between 20 [22] and 7,665 days [23]. Overall characteristics of the included studies are summarized in Table 1 [18-40].

Assessment of risk and publication biases
Of the 23 RCTs, two showed high risk [24,25], but the rest showed some risk of concern. In all but one study [25], the randomization process and allocation were well described. Because the comparison was between RAGT and conventional standard physical treatment, all participants were aware of the intervention; therefore, bias due to deviations from the intended intervention was of some concern in all the studies. Approximately
half of the studies (12 studies) showed a low risk of bias due to missing outcome data. In 11 studies (just under half of the included studies), outcome measure assessments were blinded to the intervention type, suggesting a low risk of outcome measure bias. Fourteen studies (more than half) pre-registered their study protocols and no data were duplicated, resulting in a low risk of bias in the selection of the reported results. Fig. 2 presents a traffic light diagram for each study included in the evaluation.

In Supplementary Fig. S1 illustrates the funnel plot, which displays the publication bias for each meta-analysis. We also checked for publication bias using the Eager test, as shown in Table 2. All analyses showed no significant publication bias, except for the step length and peak expiratory flow.

**Effects of RAGT on activities of daily living**

Activities of daily living, as measured using the FIM, SCIM, and MBI assessment tools, were reported in 11 studies. The overall meta-analysis showed significant improvement in the robot groups (SMD, 0.24; 95% CI, 0.04–0.43; I²=0%; p=0.02). When we analyzed the subgroups according to robot type, we found no significant difference in end-effector and wearable robots, but there was a statistically significant improvement in the Lokomat, a treadmill training robot (SMD, 0.29; 95% CI, 0.09–0.50; I²=0%; p=0.01; Fig. 3A). Activities of daily living quality of evidence was estimated to be high, according to the GRADE system (Table 2).

**Effects of RAGT on muscular strength**

Muscular strength measured using LEMS has been reported in 12 studies. The overall meta-analysis showed significant improvement in the robot groups (MD, 0.23; 95% CI, 0.02–0.44; I²=0%; p=0.03). Subgroup analysis according to robot type showed no significant difference in the end-effector and wearable robots, but a statistically significant improvement was observed in the Lokomat one (MD, 0.26; 95% CI, 0.03–0.49; I²=0%; p=0.03; Fig. 3B). The quality of evidence for muscular strength was estimated to be high using the GRADE system (Table 2).
Table 1. Characteristics of the included studies

<table>
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<tr>
<th>Study</th>
<th>No. of participants (experimental/control)</th>
<th>Age, years (experimental/control)</th>
<th>ASIA grade (experimental/control)</th>
<th>Onset duration (experimental/control) (day)</th>
<th>Tetraplegia/paraplegia (experimental/control)</th>
<th>Initial WISCI (experimental/control)</th>
<th>Intervention protocol</th>
<th>Control protocol</th>
<th>Outcome measure</th>
<th>Main findings</th>
</tr>
</thead>
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<tr>
<td>Treadmill training exoskeleton robot-Lokomat</td>
<td>37/38</td>
<td>45.2±15.5/49.5±12.8</td>
<td>C 68/71 D 32/29</td>
<td>117.4±43.3/136.3±64.9</td>
<td>Tetraplegia 39/61 Paraplegia 41/39</td>
<td>5.1±3.8/4.1±2.8</td>
<td>Standard physical treatment 40 walking training sessions of 1h duration (8 wk)</td>
<td>Standard physical treatment</td>
<td>1. Speed (m/s) 2. WISCI II 3. Walk distance (m) 4. PEM-Locomotor 5. LEMS 6. Ashworth 7. VAS</td>
<td>No significant differences were found at entry between treatment groups The WISCI II for the Lokomat group (16 [8.5–19]) was better than that for overground therapy (9 [8–16]) The 6MWT and LEMS displayed significant differences in favor of Lokomat therapy, but were not corrected for multiple comparisons</td>
</tr>
<tr>
<td>Cheung et al., 2019 [26]</td>
<td>8/8</td>
<td>55.6±4.9/53.0±12.9</td>
<td>C 7/4 D 1/4</td>
<td>510.0±210.3/312.0±189.3</td>
<td>Tetraplegia 8/8</td>
<td>16.4±4.3/17.0±2.8</td>
<td>Standard physical treatment 30-min 24 sessions (3 times per week for 8 weeks)</td>
<td>Standard physical treatment</td>
<td>1. Speed (cm/s) 2. WISCI II 3. SCIM III 4. LEMS 5. Maximal oxygen consumption (L/min) 6. PEF (L/s) 7. PEVI (L) 8. PVIC (L)</td>
<td>The Lokomat group improved walking ability and cardiopulmonary function in patients with SCI However, there were no significant differences in the control group</td>
</tr>
<tr>
<td>Duffell et al., 2015 [36]</td>
<td>27/29</td>
<td>46.6±12.6/47.8±13.1</td>
<td>C N/R D N/R</td>
<td>3304.5±3942.0/2956.5±2956.5</td>
<td>N/R</td>
<td>14.7±5.2/13.8±5.8</td>
<td>Standard physical treatment 30-min 24 sessions (3 times per week for 8 weeks)</td>
<td>Standard physical treatment</td>
<td>1. Speed (m/s) 2. Distance (m) 3. Time (s) 4. WISCI II 5. MAS</td>
<td>Walking speed and endurance improved, with no difference between interventions</td>
</tr>
<tr>
<td>Esclarín-Ruz et al., 2014 [37]</td>
<td>21/21</td>
<td>43.6±12.0/44.9±7.0</td>
<td>C 14/16 D 7/5</td>
<td>1256±65.2/140.3±45.5</td>
<td>Tetraplegia 16/16 Paraplegia 5/5</td>
<td>5.9±4.5/4.9±4.1</td>
<td>Standard physical treatment 30-min 40 sessions (8 wk)</td>
<td>Standard physical treatment</td>
<td>1. 10MWT (m/s) 2. 6MWT (m) 3. PEM-Locomotor 4. LEMS</td>
<td>RAGT yielded better results in the 6MWT and LEMS in patients</td>
</tr>
<tr>
<td>Field-Fote and Roach, 2011 [38]</td>
<td>14/17</td>
<td>45.0±8.0/42.2±15.7</td>
<td>N/R</td>
<td>&gt;365</td>
<td>N/R</td>
<td>LEMS 12.7±6.9/12.9±5.3</td>
<td>Standard physical treatment Manual assistance for stepping</td>
<td>Standard physical treatment</td>
<td>1. Speed (m/s) 2. Distance walked (m) 3. LEMS</td>
<td>In chronic motor incomplete SCI, there were no significant between-group differences</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants (experimental/control)</th>
<th>Age, years (experimental/control)</th>
<th>ASIA grade (experimental/control)</th>
<th>Onset duration (experimental/control) (day)</th>
<th>Tetraplegia/paraplegia (experimental/control)</th>
<th>Initial WISCI (experimental/control)</th>
<th>Intervention protocol</th>
<th>Control protocol</th>
<th>Outcome measure</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorman et al., 2016 [31]</td>
<td>12/6</td>
<td>51.5±12.7/52.0±15.4</td>
<td>C 2/0</td>
<td>D 10/6</td>
<td>Tetraplegia 8/6 Paraplegia 4/0</td>
<td>LEMS 34.2±11.5/36.2±8.4</td>
<td>Lokomat 25–45-min 36 sessions (12 wk)</td>
<td>Standard physical treatment</td>
<td>1. Body mass (kg) 2. Tissue fat (%) 3. Lean tissue (kg) 4. Bone mineral content (kg) 5. VO2 peak (ml/kg/min)</td>
<td>Robot group improved peak VO2 than control group</td>
</tr>
<tr>
<td>Labruyère and van Hedel, 2014 [27]</td>
<td>9/9</td>
<td>59±11</td>
<td>N/R</td>
<td>1500.0±1680.0</td>
<td>Tetraplegia 6 Paraplegia 3</td>
<td>14.0±3.0</td>
<td>Lokomat 45 min 16 sessions (4 wk)</td>
<td>Strength training 45-min 16 sessions (4 wk)</td>
<td>1. 10MWT (m/s) 2. WISCI 3. SCIM 4. BBS 5. LEMS 6. Figure eight test 7. Gait symmetry 8. PCI 9. BBS</td>
<td>Chronic incomplete SCI dependent on walking assistance; robot group was not more effective in improving walking-related outcome compared to lower extremity strength training</td>
</tr>
<tr>
<td>Ma et al., 2022 [26]</td>
<td>10/10</td>
<td>8.4±1.1/8.6±1.2</td>
<td>N/R</td>
<td>400.8±147.0/468.0±158.1</td>
<td>Tetraplegia 0/0 Paraplegia 15/15</td>
<td>16.2±1.3/15.9±2.2</td>
<td>Lokomat 30-min 40 sessions (8 wk)</td>
<td>Standard physical treatment 60-min 40 sessions (8 wk)</td>
<td>1. 10MWT (m/s) 2. 6MWT (m) 3. LEMS 4. PCI 5. WISCI 6. Centre of pressure (cm²)</td>
<td>RAGT may significantly improve the immediate motor function and walking ability of children with thoracolumbar incomplete SCI</td>
</tr>
<tr>
<td>Medkken et al., 2020 [39]</td>
<td>15/15</td>
<td>35.4±12.1/37.9±10.0</td>
<td>C 6/10</td>
<td>D 9/5</td>
<td>Tetraplegia 0/0 Paraplegia 15/15</td>
<td>9.8±1.4/11.0±1.1</td>
<td>Lokomat 30-min 15 sessions (5 wk)</td>
<td>Standard physical treatment 30-min 25 sessions (5 wk)</td>
<td>1. WISCI 2. SCIM 3. LEMS</td>
<td>Conventional rehabilitation is useful in terms of the improvement in the lower extremity motor function, walking, and functional status in men with incomplete SCI. Additional RAGT provides a better improvement in the lower extremity motor function and functional independence</td>
</tr>
<tr>
<td>Noojhen et al., 2009 [40]</td>
<td>12/13</td>
<td>44.3±18.9/38.2±14.6</td>
<td>N/R</td>
<td>3327.5±3214.8/1569.2±1545.4</td>
<td>Tetraplegia 0/11 Paraplegia 15/2</td>
<td>N/R</td>
<td>Lokomat 60-min 60 sessions (12 wk)</td>
<td>Standard physical treatment 60-min 60 sessions (12 wk)</td>
<td>1. Cadence (steps/min) 2. Symmetry index (%) 3. Step length (m) 4. Stride length (m) 5. Intralimb coordination 6. Timing of onset knee</td>
<td>No significant differences were found among training groups; however, there was an interaction effect, indicating that step and stride length improved least in the robot-assisted gait training group</td>
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</tbody>
</table>

(Continued to the next page)
<table>
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<tr>
<th>Study</th>
<th>No. of participants (experimental/control)</th>
<th>Age, years (experimental/control)</th>
<th>ASIA grade (experimental/control)</th>
<th>Onset duration (experimental/control) (day)</th>
<th>Tetraplegia/paraplegia (experimental/control)</th>
<th>Initial WISCI (experimental/control)</th>
<th>Intervention protocol</th>
<th>Control protocol</th>
<th>Outcome measure</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Piira et al., 2019 [23]</td>
<td>7/12</td>
<td>55±18.0/46.0±15.0</td>
<td>C 1/5</td>
<td>7665±839.0/5475.0±6570.0</td>
<td>Tetraplegia 4/6 Paraplegia 3/6</td>
<td>LEMS 26.6±22.0/27.8±31.9</td>
<td>Lokomat 20–30 min 60 sessions (24 wk) &lt;40% bodyweight support</td>
<td>Standard physical treatment 60 sessions (24 wk)</td>
<td>1. 10MWT (m/s) 2. 6MWT (m) 3. LEMS 4. BBS 5. Modified functional reach test</td>
<td>In chronic SCI robot-assisted gait training did not restore independent walking function. A modest, but non-significant, effect was seen on muscle strength and balance.</td>
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<tr>
<td>Shin et al., 2014 [24]</td>
<td>27/26</td>
<td>43.2±14.4/48.2±11.5</td>
<td>N/R</td>
<td>Median 189</td>
<td>Tetraplegia 15/16 Paraplegia 12/10</td>
<td>5.9±10.9/6.9±12.6</td>
<td>Lokomat at 40-min 12 sessions (4 wk) -In addition to standard physical treatment 50% bodyweight support and a speed of 1.2 km/h</td>
<td>Standard physical treatment 30-min 40 sessions (4 wk)</td>
<td>1. WISCI 2. SCIM 3. LEMS 4. Ambulatory motor index (AMI)</td>
<td>RAGT combined with conventional physiotherapy could yield more improvement in ambulatory function than conventional therapy alone.</td>
</tr>
<tr>
<td>Tang et al., 2014 [25]</td>
<td>15/15</td>
<td>38.1±7.1/39.2±8.1</td>
<td>D 15/15</td>
<td>Median 189</td>
<td>Tetraplegia 0/0 Paraplegia 15/15</td>
<td>N/R</td>
<td>Lokomat at 50-min</td>
<td>Standard physical treatment</td>
<td>1. SCIM</td>
<td>RAGT not only decreased reaction time, but also improved the walking ability.</td>
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<td>Wirz et al., 2017 [31]</td>
<td>9/9</td>
<td>35.5±6.13/8/35.1±18.6/6.9±25.7</td>
<td>Paraplegia 2/3</td>
<td>34.3±16.0/43.2±25.7</td>
<td>Paraplegia 2/3</td>
<td>34 sessions (8 wk)</td>
<td>Speed of 1.6–3.5 km/h</td>
<td>Standard physical treatment</td>
<td>1. SCIM</td>
<td>No significant differences were found among training groups.</td>
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<tr>
<td>Yıldırım et al., 2019 [19]</td>
<td>44/44</td>
<td>32±5.2/36.5±5.5</td>
<td>A21/18</td>
<td>Tetraplegia 9/7 Paraplegia 35/37</td>
<td>5.0±6.9/5.0±5.1</td>
<td>34 sessions (8 wk)</td>
<td>-Lokomat 30-min 16 sessions (8 wk) -Standard physical treatment 30-min 40 sessions (twice a day) (8 weeks)</td>
<td>Standard physical treatment 30-min 40 sessions (twice a day) (8 wk)</td>
<td>1. WISCI 2. FIM</td>
<td>RAGT combined with conventional therapy was found to be superior to the conventional therapy in terms of gait function and level of disability.</td>
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<tr>
<td>Song et al., 2012 [22]</td>
<td>11/11</td>
<td>53.7±8.8/53.3±6.0</td>
<td>N/R</td>
<td>Tetraplegia 9/10 Paraplegia 2/1</td>
<td>N/R</td>
<td>Lokomat 20-min 20 sessions (4 wk) -Standard physical treatment 20-min 20 sessions (4 wk)</td>
<td>Standard physical treatment 20-min 20 sessions (4 wk)</td>
<td>1. 10MWT (m/s) 2. 6MWT (m) 3. LEMS 4. MBI</td>
<td>RAGT significantly improved in walking ability and lower fall risk.</td>
<td></td>
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<tr>
<td>Wearable gait robot-Ekso, HANK, AIDER</td>
<td>Chang et al., 2018 [18]</td>
<td>4/3</td>
<td>56±17.0/60±2.0</td>
<td>Tetraplegia 2/1 Paraplegia 2/2</td>
<td>N/R</td>
<td>-Ekso 60-min 15 sessions (3 wk)</td>
<td>Lokomat 20-min 15 sessions (3 wk)</td>
<td>Standard physical treatment 20-min 15 sessions (3 wk)</td>
<td>1. 10MWT (m/s) 2. 6MWT (m) 3. TUG (s) 4. Step length (m)</td>
<td>RAGT could be applied to individuals with incomplete SCI to facilitate gait recovery.</td>
</tr>
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</table>

(Continued to the next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants (experimental/control)</th>
<th>Age, years²</th>
<th>ASIA grade (experimental/control)</th>
<th>Onset duration (experimental/control) (day)</th>
<th>Tetraplegia/paraplegia (experimental/control)</th>
<th>Initial WISCI (experimental/control)</th>
<th>Intervention protocol</th>
<th>Control protocol</th>
<th>Outcome measure</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards et al., 2022 [33]</td>
<td>9/10</td>
<td>41.7±8.5/51.9±14.5</td>
<td>C 6/3 D 3/7</td>
<td>3066.0±3134.2/2568.3±1594.1</td>
<td>Tetraplegia 7/8 Paraplegia 2/2</td>
<td>12.1±4.4/13.8±4.5</td>
<td>-Ekso GT 45-min 36 sessions (12 wk)</td>
<td>Body weight support treadmill training 45-min 36 sessions (12 wk)</td>
<td>1. Gait speed (m/s)</td>
<td>RAGT not statistically significant in gait speed</td>
</tr>
<tr>
<td>Evans et al., 2021 [38]</td>
<td>8/8</td>
<td>41.0±11.0/38.0±14.0</td>
<td>C 4/5 D 4/3</td>
<td>4745.0±2920.0/2555.0±2190.0</td>
<td>Tetraplegia 8/8 Paraplegia 0/0</td>
<td>N/R</td>
<td>-Ekso GT 60-min 72 sessions (24 wk)</td>
<td>60-min 72 sessions (24 wk) Warming-up and mobility (5 min) Resistance training (20–30 min) Cardiovascular training (20–30 min)</td>
<td>1. Heart rate 2. Heart rate variability 3. Systolic blood pressure (mmHg) 4. Diastolic blood pressure (mmHg) 5. Ankle brachial pressure index (ABPI) 6. Distance (m) 7. Rating of perceived exertion (Borg)</td>
<td>Cardiovascular efficiency of exoskeleton walking improved, particularly over the first 6 weeks</td>
</tr>
<tr>
<td>Gil-Agudo et al., 2023 [34]</td>
<td>11/10</td>
<td>41.0±12.4/51.8±11.9</td>
<td>C 8/4 D 3/6</td>
<td>144.6±39/166.5±69</td>
<td>Tetraplegia 4/2 Paraplegia 7/8</td>
<td>11.9±4.3/11.7±3.8</td>
<td>-HANK 30-min 15 sessions (5 wk)</td>
<td>Standard physical treatment 30-min 15 sessions (5 wk)</td>
<td>1. LEMS 2. 10MWT (m/s) 3. TUG (s) 4. 6MWT (m) 5. WISCI 6. SCIM</td>
<td>Exoskeleton improved their walking independence as measured by the WISCI-II after the treatment</td>
</tr>
<tr>
<td>Shackleton et al., 2023 [39]</td>
<td>8/8</td>
<td>40.5±11.2/38.4±14.3</td>
<td>C 4/5 D 4/3</td>
<td>5037.0±3029.5/2664.5±2336.0</td>
<td>Tetraplegia 8/8 Paraplegia 0/0</td>
<td>N/R</td>
<td>-Ekso Bionics 60-min 72 sessions (24 wk)</td>
<td>Standard physical treatment 60-min 72 sessions (24 wk)</td>
<td>1. Bone mineral density (g/cm²) 2. Fat mass (kg) 3. Fat-free soft tissue mass (kg)</td>
<td>Twenty-four weeks of robot locomotor training is possibly a sufficient duration to prevent the progressive decline of bone mineral density</td>
</tr>
<tr>
<td>Xiang et al., 2021 [30]</td>
<td>9/9</td>
<td>39.8±12.2/36.6±11.8</td>
<td>A 8/4 B 0/3 C 1/3</td>
<td>60.0±118.5/60.0±13.1</td>
<td>Tetraplegia 5/4 Paraplegia 4/5</td>
<td>N/R</td>
<td>-AIDER 60-min 16 sessions (4 wk) -40%–60% maximal heart rate</td>
<td>Standard physical treatment 60-min 16 sessions (4 wk)</td>
<td>1. FVC (L) 2. FEV₁ (L) 3. PEF (L/s) 4. Maximal voluntary ventilation (MVV) (L) 5. Distance (m) 6. Heart rate 7. Rating of Perceived Exertion 8. SpO2 9. LEMS</td>
<td>Exoskeleton-assisted walking has potential benefits to facilitate pulmonary function parameters among individuals with lower thoracic neurological level of SCI compared with conventional therapy</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Effects of RAGT on spasticity
Spasticity measured using the MAS was reported in three studies. The overall meta-analysis showed no significant difference (MD, -0.05; 95% CI, -0.37 to 0.28; I²=0%; p=0.77; Fig. 3C). The spasticity quality of evidence was estimated as low performing using the GRADE system (based on risk of bias and imprecision) (Table 2).

Effects of RAGT on balance
Balance, measured using the BBS, was reported in three studies. The overall meta-analysis showed no significant difference (MD, 0.44; 95% CI, -0.18 to 1.06; I²=33.42%; p=0.16). Subgroup analysis by robot type showed no significant difference in the Lokomat, but a statistically significant improvement was observed for end-effector robot (MD, 0.95; 95% CI, 0.17–1.72; I²=uncheckable; p=0.02; Fig. 3D). The balance quality of evidence was estimated as low performing using the GRADE system (based on inconsistency and imprecision) (Table 2).

Effects of RAGT on walking ability
Ten studies reported the WISCI, and the overall meta-analysis showed significant improvement in the robot group (MD, 0.31; 95% CI, 0.07–0.55; I²=30.67%; p=0.01). Subgroup analysis according to robot type showed no significant difference in the Lokomat, but there was statistically significant improvement in the end-effector and wearable robots, with a larger effect size for wearable robots (MD, 1.30; 95% CI, 0.35–2.25; I²=uncheckable; p=0.01; Fig. 4A). The WISCI quality of evidence was estimated to be moderate, according to the GRADE system (based on risk of bias) (Table 2).

Thirteen studies reported 10MWT Speed, and the overall meta-analysis showed no significant difference (MD, -0.02; 95% CI, -0.46 to 0.42; I²=73.44%; p=0.91). Subgroup analysis according to robot type showed no significant differences between the end-effector, Lokomat, and wearable robots (Fig. 4B). The 10MWT Speed quality of evidence was estimated to be very low when the GRADE system was used (based on risk of bias, inconsistency, indirectness, and imprecision) (Table 2).

Ten studies reported 6MWT distance, and the overall meta-analysis showed significant improvement in the robot group (MD, 0.38; 95% CI, 0.14–0.63; I²=0%; p=0.00). Subgroup analysis according to robot type showed no significant difference in the end-effector and wearable robots, but a statistically significant improvement was observed in the Lokomat (MD, 0.40; 95% CI, 0.10–0.70; I²=0%; p=0.01; Fig. 5A). The 6MWT
distance quality of evidence was estimated to be moderate, according to the GRADE system (based on risk of bias) (Table 2).

Two studies reported step length, and the overall meta-analysis showed no significant difference (MD, -0.15; 95% CI, -0.84 to 0.55; I²=0%; p=0.68). Subgroup analysis according to robot type showed no significant differences between the Lokomat

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**Table 2.** Risk of bias domains

<table>
<thead>
<tr>
<th>Study</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
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<td>Duffell et al., 2015 [36]</td>
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<td>Esclarín-Ruz et al., 2014 [37]</td>
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<td>Goman et al., 2016 [31]</td>
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<td>Labruyère and van Hedel, 2014 [27]</td>
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<td>Gil-Agudo et al., 2023 [34]</td>
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</table>

**Fig. 2.** Traffic light diagram for the risk of bias of included studies as assessed using the Cochrane Risk of Bias 2.0 tool.
<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Summary of findings</th>
<th>Heterogeneity</th>
<th>Publication bias</th>
<th>Quality of evidence assessment (GRADE)</th>
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<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Effect size</td>
<td>Egger’s test</td>
<td>Risk of bias&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Activities of daily living</td>
<td>No. of patients</td>
<td>Effect size</td>
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<td></td>
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<tr>
<td>FIM, SCIM, MBI</td>
<td>208/203 (11)</td>
<td>SMD 0.24</td>
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<td>Muscular strength</td>
<td>184/187 (12)</td>
<td>MD 0.23</td>
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<td>0.592</td>
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<tr>
<td>Spasticity</td>
<td>73/75 (3)</td>
<td>MD -0.05</td>
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<td>Balance</td>
<td>32/34 (3)</td>
<td>MD 0.44</td>
<td>33.42</td>
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<td>Walking ability</td>
<td>WISCI</td>
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<td>10MWT speed (m/s)</td>
<td>MD -0.02</td>
<td>73.44</td>
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<td>6MWT distance (m)</td>
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<td>Body composition</td>
<td>Body mass (kg)</td>
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<td>Lean tissue (kg)</td>
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<td>Tissue fat (%)</td>
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<td>Cardiopulmonary Function</td>
<td>FEV1 (L)</td>
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<td>Forced vital capacity (L)</td>
<td>MD 0.33</td>
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<td>Heart rate (beats/min)</td>
<td>MD 0.56</td>
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<td>Peak expiratory flow (L/s)</td>
<td>MD 0.26</td>
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<td>N/A</td>
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</table>

GRADE, Grading of Recommendations Assessment, Development and Evaluation; FIM, functional independence measure; SCIM, spinal cord independence measurement; MBI, modified Barthel index; LEMS, lower extremity motor score; MAS, modified Ashworth scale; BBS, Berg balance scale; WISCI, walking index for spinal cord injury; 10MWT, 10 meter walk test; 6MWT, 6 min walk test; FEV1, forced expiratory volume in first second; SMD, standardized mean difference; MD, mean difference; N/A, not applicable.

<sup>a</sup>Risk of bias based on the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2).

<sup>b</sup>Downgraded if significant and unexplained heterogeneity (I²>50%, p<0.10) was not explained by the meta-regression or subgroup analysis results.

<sup>c</sup>Downgraded if there were any factors related to the participants, interventions, or results that limited the generalizability of the results.

<sup>d</sup>Downgraded if the 95% confidence interval crossed the benefit-or-harm boundary.

<sup>e</sup>Downgraded if there was evidence of publication bias using Egger’s test or suspecting publication bias when visualizing with funnel plots.

<sup>f</sup>Because all included studies were meta-analyses of randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded according to prespecified criteria. The quality was graded as high, medium, low, or very low.

**p<0.05.
**Activities of daily living**

<table>
<thead>
<tr>
<th>Endeffector</th>
<th>Study</th>
<th>Effect size with 95% CI</th>
<th>Weight (%)</th>
</tr>
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<tbody>
<tr>
<td>Shin et al., 2023 [21]</td>
<td>Heterogeneity: T=0.00, F=1, H²=0.00</td>
<td>-0.21 [-0.95, 0.52]</td>
<td>7.07</td>
</tr>
<tr>
<td>Test of θ=0: Q (1)=0.00, p=0.95</td>
<td>Test of θ=0: z=0.57, p=0.57</td>
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<td></td>
</tr>
<tr>
<td>Lokomat</td>
<td>Labrolyte and van Hedel, 2014 [27]</td>
<td>-0.04 [-0.97, 0.88]</td>
<td>4.46</td>
</tr>
<tr>
<td>Shin et al., 2014 [24]</td>
<td>Song et al., 2012 [22]</td>
<td>0.70 [-1.17, 1.55]</td>
<td>5.12</td>
</tr>
<tr>
<td>Miskl et al., 2020 [39]</td>
<td>Wix et al., 2017 [32]</td>
<td>0.38 [-0.35, 1.19]</td>
<td>3.84</td>
</tr>
<tr>
<td>Alcobendas-Maestro et al., 2012 [35]</td>
<td>Cheung et al., 2019 [28]</td>
<td>0.43 [-0.03, 0.99]</td>
<td>17.94</td>
</tr>
<tr>
<td>Esclarín-Ruiz et al., 2014 [37]</td>
<td>Yildirim et al., 2019 [19]</td>
<td>0.17 [0.24, 0.59]</td>
<td>21.75</td>
</tr>
<tr>
<td>Test of θ=0: Q (8)=0.00, p=0.65</td>
<td>Test of θ=0: z=2.76, p=0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wearable</td>
<td>Gil-Agudo et al., 2023 [34]</td>
<td>-0.07 [-0.93, 0.79]</td>
<td>5.19</td>
</tr>
<tr>
<td>Heterogeneity: T=0.00, F=1, H²=0.00</td>
<td>Test of θ=0: Q (1)=0.00, p=0.95</td>
<td>Test of θ=0: z=0.16, p=0.87</td>
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</tr>
<tr>
<td>Test of θ=0: Q (10)=0.00, p=0.95</td>
<td>Test of group differences: Q (2)=2.24, p=0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Wirz et al., 2017 [32]</td>
<td>0.21 [-0.32, 0.74]</td>
<td>4.72</td>
</tr>
<tr>
<td>Test of θ=0: Q (1)=0.17, p=0.68</td>
<td>Test of θ=0: z=2.24, p=0.03</td>
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<td></td>
</tr>
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</table>

**Muscular strength**

<table>
<thead>
<tr>
<th>Endeffector</th>
<th>Study</th>
<th>Effect size with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin et al., 2023 [21]</td>
<td>Heterogeneity: T=0.00, F=1, H²=0.00</td>
<td>-0.06 [-0.79, 0.67]</td>
<td>7.92</td>
</tr>
<tr>
<td>Test of θ=0: Q (1)=0.00, p=0.95</td>
<td>Test of θ=0: z=0.16, p=0.87</td>
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<td></td>
</tr>
<tr>
<td>Lokomat</td>
<td>Labrolyte and van Hedel, 2014 [27]</td>
<td>-0.03 [-0.65, 0.58]</td>
<td>4.97</td>
</tr>
<tr>
<td>Shin et al., 2014 [24]</td>
<td>Miskl et al., 2020 [39]</td>
<td>0.28 [-1.12, 1.77]</td>
<td>5.07</td>
</tr>
<tr>
<td>Alcobendas-Maestro et al., 2012 [35]</td>
<td>Cheung et al., 2019 [28]</td>
<td>0.48 [0.13, 0.86]</td>
<td>3.11</td>
</tr>
<tr>
<td>Esclarín-Ruiz et al., 2014 [37]</td>
<td>Ma et al., 2023 [39]</td>
<td>0.11 [0.11, 1.72]</td>
<td>2.03</td>
</tr>
<tr>
<td>Field-Fote and Roach, 2011 [38]</td>
<td>Piria et al., 2019 [23]</td>
<td>0.51 [0.43, 1.48]</td>
<td>4.72</td>
</tr>
<tr>
<td>Test of θ=0: Q (1)=0.00, F=0.00, H²=1.00</td>
<td>Test of θ=0: Q (1)=0.00, p=0.95</td>
<td>Test of θ=0: z=2.24, p=0.03</td>
<td></td>
</tr>
<tr>
<td>Wearable</td>
<td>Gil-Agudo et al., 2023 [34]</td>
<td>0.21 [-0.42, 0.84]</td>
<td>5.70</td>
</tr>
<tr>
<td>Heterogeneity: T=0.00, F=0.00, H²=1.00</td>
<td>Test of θ=0: Q (1)=0.00, p=0.95</td>
<td>Test of θ=0: z=2.24, p=0.03</td>
<td></td>
</tr>
<tr>
<td>Test of θ=0: Q (2)=0.00, H²=1.00</td>
<td>Test of θ=0: Q (2)=0.00, p=0.95</td>
<td>Test of group differences: Q (2)=0.00, p=0.71</td>
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</table>

**Spasticity**

<table>
<thead>
<tr>
<th>Endeffector</th>
<th>Study</th>
<th>Effect size with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcobendas-Maestro et al., 2012 [35]</td>
<td>Heterogeneity: T=0.00, F=0.00, H²=0.00</td>
<td>-0.20 [-0.68, 0.28]</td>
<td>50.05</td>
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<tr>
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<td>Test of θ=0: z=0.29, p=0.77</td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>Wirz et al., 2017 [32]</td>
<td>0.21 [-0.32, 0.74]</td>
<td>37.80</td>
</tr>
<tr>
<td>Test of θ=0: Q (1)=0.17, p=0.68</td>
<td>Test of θ=0: z=0.29, p=0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of θ=0: Q (2)=0.48, p=0.48</td>
<td>Test of θ=0: Q (2)=0.48, p=0.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Meta-analysis of the effects of RAGT in patients with spinal cord injury (SCI). (A) Activities of daily living. (B) Muscular strength. (C) Spasticity. (D) Balance.
Effects of RAGT on body composition

Two studies reported body mass, and the overall meta-analysis showed no significant difference (MD, 0.02; 95% CI, -0.67 to 0.71; I²=0%; p=0.96). Two studies reported lean mass, and the overall meta-analysis showed no significant difference (MD, 0.02; 95% CI, -0.67 to 0.72; I²=0%; p=0.95). Two studies reported fat tissue percentage, and the overall meta-analysis showed no significant difference (MD, 0.09; 95% CI, -0.60 to 0.79; I²=0%; p=0.79). The quality of evidence for each sub-analysis of body composition was rated as moderate (based on imprecision) using the GRADE system (Fig. 6A, Table 2).

Effects of RAGT on cardiopulmonary function

Two studies reported FEV1, and the overall meta-analysis showed no significant difference (MD, 0.49; 95% CI, -0.20 to 1.18; I²=0%; p=0.17). Two studies reported FVC, and the overall meta-analysis showed no significant difference (MD, 0.33; 95% CI, -0.35 to 1.02; I²=0%; p=0.34). Two studies reported heart rate, and the overall meta-analysis showed no significant difference (MD, 0.56; 95% CI, -0.17 to 1.30; I²=10.09%; p=0.13). Two studies reported PCF, and the overall meta-analysis showed no significant difference (MD, 0.26; 95% CI, -0.41 to 0.94; I²=0%; p=0.44). In the sub-analysis of cardiopulmonary function, the quality of evidence was assessed using the GRADE system, with only peak expiratory flow rated low (based on imprecision and publication bias) and the rest rated moderate (based on imprecision) (Fig. 6B, Table 2).

Subgroup analysis

Subgroup analyses were performed based on intervention period and onset duration (Supplementary Fig. S2, Table 3). Subgroup analysis according to intervention duration showed significant improvements in activities of daily living difference (SMD, 0.34; 95% CI, 0.09–0.60; I²=0%; p=0.01; Supplementary Fig. S2A) and WISCI (MD, 0.33; 95% CI, 0.07–0.60; I²=0%; p=0.01; Supplementary Fig. S2E) in the group that intervened for >2 months. The 6MWT distance showed significant improvement in intervention periods of <1 month (MD, 0.59; 95% CI, 0.10–1.07; I²=23.92%; p=0.02) and >2 months (MD, 0.38; 95% CI, 0.04–0.72; I²=0%; p=0.03; Supplementary Fig. S2I).

Onset duration was categorized as acute (0–3 months), sub-acute (4–12 months), and chronic (>12 months). When sub-analyzed according to onset duration, patients in the subacute phase had significant improvements in activities of daily living (MD, 0.37; 95% CI, 0.03–0.70; I²=0%; p=0.03; Supplementary Fig. S2B) and WISCI (MD, 0.51; 95% CI, 0.06–0.96; I²=35.72%; p=0.03; Supplementary Fig. S2F). The 6MWT distance showed significant improvement in acute patients (MD, 0.69; 95% CI, 0.06–1.32; I²=38.51%; p=0.03; Supplementary Fig. S2I).

Adverse events

Six [18,26-30] of the 23 studies reported no adverse events. A variety of adverse events were reported in five studies [23,31-34], of which four [23,31,33,34] reported skin abrasions at the site of the robot, which improved with the application of pads at the time of treatment. Additionally, three studies [32-34] reported musculoskeletal pain, particularly knee and neck pain; one study [33] reported possibly related numbness; and one study [34] reported fatigue. The remaining 12 studies did not
Fig. 4. Meta-analysis of the effects of RAGT on walking ability in patients with spinal cord injury (SCI). (A) Walking index for spinal cord injury (WISCI). (B) 10-min walk test (10MWT) speed (m/s).
**Fig. 5.** Meta-analysis of the effects of the RAGT on walking ability in patients with spinal cord injury (SCI). (A) 6-min walk test (6MWT) distance (m). (B) Step length (m).

**DISCUSSION**

This systematic review investigated the efficacy of RAGT in patients with SCI. A study showed a high level of evidence that RAGT significantly improves activities of daily living and muscle strength. RAGT has been shown to significantly improve walking ability, specifically WISCI and 6MWT distances. Spasticity, balance, body composition, and cardiopulmonary function did not differ significantly between RAGT and conventional rehabilitation groups. Subgroup analyses showed significant improvements in activities of daily living and WISCI in subacute patients with onset duration of 4–12 months and intervention duration of ≥2 months.

The mechanism by which RAGT improves functionality in mention safety or side effects.
patients with SCI involves reinforcing proprioceptive input to the spinal cord through walking-related rhythmic movements facilitated by robots. This process activates the central pattern generator embedded within the lumbosacral spinal cord and can induce plastic changes at the spinal cord level and within the sensorimotor cortex (S1 and S2) and cerebellar regions of the brain [41-44].

When analyzing the effects of robot type, the results were heterogeneous. For activities of daily living and muscular strength, the Lokomat had the largest effect size; for the WISCI, the wearable robot had the largest effect size; and for balance, the end effector had the largest effect size. Among existing studies, none compared the effects of the three types of robots simultaneously; however, studies comparing the Lokomat and wearable robots have shown that wearable robots show greater improvement in walking speed [10]. In previous studies, the difference has been explained between wearable robots and stationary treadmill systems, such as the Lokomat, because the former is an overground walking system that requires patients to exert greater effort on their trunk and arms while engaging in higher cognitive and cardiovascular efforts [45]. This increased effort results in elevated muscle activity in the torso and pelvic floor [46], significantly enhancing motor and sensory functions [47]. Additionally, wearable robots provide more proprioceptive stimulation and adaptability to real-world environments through overground walking programs, thereby promoting
Table 3. Subgroup analysis

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>No. of patients Experimental/control (trials)</th>
<th>Effect size (95% confidence interval)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention ≤1 month</td>
<td>89/84 (6)</td>
<td>SMD 0.10 (-0.20 to 0.40)</td>
<td>0</td>
</tr>
<tr>
<td>Intervention &gt;2 months</td>
<td>119/119 (5)</td>
<td>SMD 0.34 (0.09–0.60)**</td>
<td>0</td>
</tr>
<tr>
<td>Acute</td>
<td>107/103 (5)</td>
<td>SMD 0.19 (-0.09 to 0.46)</td>
<td>0</td>
</tr>
<tr>
<td>Subacute</td>
<td>69/68 (3)</td>
<td>SMD 0.37 (0.03–0.70)**</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>32/32 (3)</td>
<td>SMD 0.14 (-0.35 to 0.63)</td>
<td>0</td>
</tr>
<tr>
<td>Muscular strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention ≤1 month</td>
<td>87/82 (6)</td>
<td>MD 0.20 (-0.13 to 0.53)</td>
<td>12.97</td>
</tr>
<tr>
<td>Intervention &gt;2 months</td>
<td>76/76 (4)</td>
<td>MD 0.29 (-0.03 to 0.62)</td>
<td>0</td>
</tr>
<tr>
<td>Intervention &gt;3 months</td>
<td>21/29 (2)</td>
<td>MD 0.15 (-0.42 to 0.71)</td>
<td>0</td>
</tr>
<tr>
<td>Acute</td>
<td>52/48 (3)</td>
<td>MD 0.00 (-0.39 to 0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Subacute</td>
<td>69/68 (3)</td>
<td>MD 0.26 (-0.07 to 0.60)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>63/71 (3)</td>
<td>MD 0.38 (-0.02 to 0.78)</td>
<td>22.67</td>
</tr>
<tr>
<td>WISCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention ≤1 month</td>
<td>105/102 (6)</td>
<td>MD 0.37 (-0.11 to 0.84)</td>
<td>62.54</td>
</tr>
<tr>
<td>Intervention &gt;2 months</td>
<td>110/110 (4)</td>
<td>MD 0.33 (0.07–0.60)**</td>
<td>0</td>
</tr>
<tr>
<td>Acute</td>
<td>87/83 (3)</td>
<td>MD 0.35 (-0.09 to 0.78)</td>
<td>45.65</td>
</tr>
<tr>
<td>Subacute</td>
<td>69/68 (3)</td>
<td>MD 0.51 (0.06–0.96)**</td>
<td>35.72</td>
</tr>
<tr>
<td>Chronic</td>
<td>59/61 (4)</td>
<td>MD 0.10 (-0.34 to 0.54)</td>
<td>26.96</td>
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<tr>
<td>10MWT speed (m/s)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intervention ≤1 month</td>
<td>66/61 (6)</td>
<td>MD 0.12 (-0.24 to 0.48)</td>
<td>2.52</td>
</tr>
<tr>
<td>Intervention &gt;2 months</td>
<td>76/76 (4)</td>
<td>MD 0.19 (-0.13 to 0.51)</td>
<td>0</td>
</tr>
<tr>
<td>Intervention &gt;3 months</td>
<td>30/39 (3)</td>
<td>MD -0.70 (-2.60 to 1.20)</td>
<td>91.81</td>
</tr>
<tr>
<td>Acute</td>
<td>31/27 (3)</td>
<td>MD 0.10 (-0.67 to 0.87)</td>
<td>47.35</td>
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<td>Subacute</td>
<td>84/83 (4)</td>
<td>MD 0.14 (-0.16 to 0.44)</td>
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</tr>
<tr>
<td>Chronic</td>
<td>57/66 (6)</td>
<td>MD -0.23 (-1.21 to 0.75)</td>
<td>84.61</td>
</tr>
<tr>
<td>6MWT distance (m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention ≤1 month</td>
<td>51/46 (5)</td>
<td>MD 0.59 (0.10–1.07)**</td>
<td>23.92</td>
</tr>
<tr>
<td>Intervention &gt;2 months</td>
<td>68/68 (3)</td>
<td>MD 0.38 (0.04–0.72)**</td>
<td>0</td>
</tr>
<tr>
<td>Intervention &gt;3 months</td>
<td>15/20 (2)</td>
<td>MD -0.04 (-0.72 to 0.64)</td>
<td>0</td>
</tr>
<tr>
<td>Acute</td>
<td>40/36 (4)</td>
<td>MD 0.69 (0.06–1.32)**</td>
<td>38.51</td>
</tr>
<tr>
<td>Subacute</td>
<td>69/68 (3)</td>
<td>MD 0.31 (-0.02 to 0.65)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>25/30 (3)</td>
<td>MD 0.26 (-0.35 to 0.86)</td>
<td>18.50</td>
</tr>
</tbody>
</table>

Acute (0–3 months), subacute (4–12 months), and chronic (>12 months).

WISCI, walking index for spinal cord injury; 10MWT, 10 meter walk test; 6MWT, 6 min walk test; SMD, standardized mean difference; MD, mean difference.

⁎p<0.05.

greater neuroplasticity and facilitating connectivity remodulation [48]. The findings suggest that caution is needed in generalizing the efficacy of end-effector robots in improving balance, owing to limited studies. However, unlike exoskeleton-type robots, end-effector robots allow the knee and hip joints of participants to move freely, while their feet remain attached to the robot’s footplates. Previous studies have shown that this unrestricted movement of the hip and knee joints encourages destabilization training and promotes the coordination of postural control through feedback and feed-forward mechanisms, ultimately improving overall postural control [49].

Typically, approximately half of the recovery occurs within the initial 2 months following an injury, with a declining recovery rate over the subsequent 4 months. According to the 1-year mark post-injury, neurological recovery is generally close to completion [50]. Engaging in repetitive functional gait training during the acute phase aids in restoring muscle activation and relearning proper gait patterns. However, individuals with chronic SCI face challenges due to a slower rate of neuroplasticity, making motor relearning and reducing dependence on walking aids more challenging. The sub-analysis results of this study can also be said to support the above hypothesis because there was a significant improvement in the activities of daily living and WISCI in subacute patients with an onset period of 4–12 months. However, in this analysis, RAGT was more effective in the subacute phase than in the acute phase because, firstly, in the acute phase, there is a lack of medical stability and a higher complication rate [51], which may reduce the effectiveness of RAGT, which is a high-intensity repetitive exercise, and, secondly, because of the difference in treatment duration be-
tween the two groups. Previous subgroup analyses have shown that RAGT is more effective when the treatment duration is 2 months or more, but 71.4% of the trials in the acute phase had a treatment duration of less than 1 month, and only 25% of the trials in the subacute phase had a treatment duration of less than 1 month, which may explain the smaller effect analyzed in the acute phase. Future studies comparing treatment effects in groups of patients with the same treatment duration and protocol but different onset times are needed.

Strengths and limitations
The strength of this meta-analysis is that it provided the most up-to-date and comprehensive information on the efficacy of RAGT in individuals with SCI. Additionally, we sub-analyzed the effects of robot type, duration of intervention, and onset of SCI.

This meta-analysis has several limitations. First, there was a limited pool of involved articles, with the majority having small sample sizes. The included papers varied according to robot type: 16 Lokomat papers, 6 wearable robot papers, and 1 end-effector robot paper. The largest sample size of the included papers was 88, and the remaining papers all had small sample sizes of less than 100. Previous research has shown that pilot studies or studies with small sample sizes can inflate pooled effect sizes, even in meta-analyses [52], so this study should be interpreted with this in mind. Second, heterogeneity was observed among the included studies. For the primary outcome, the 10MWT speed meta-analysis was highly heterogeneous, with an $I^2$ value of 73.44%. This was because the study protocols varied according to robot type, intervention duration, treatment time, robot body weight support percentage, guidance force, and speed, and the injury level, severity, and onset time of the included patients varied. To address this heterogeneity, we performed subgroup analyses based on the duration of intervention and onset. Third, it does not take into account initial ASIA assessment results, level of injury, and patient age. Studies have shown that recovery and ambulation in SCI patients are associated with initial ASIA assessment results and age, and the applicability of RAGT varies depending on whether the patient is a paraplegia or tetraplegia [53]. However, none of the RCTs published to date compared patients according to ASIA grades and level of injury, so a meta-analysis could not be performed. Further studies are needed to address this issue.

CONCLUSION
The meta-analysis findings indicated that RAGT resulted in beneficial enhancements in the activities of daily living, muscular strength, and walking ability. Notably, these improvements were more prominent in interventions lasting >2 months and among subacute patients. Consequently, RAGT appears to be a viable option for individuals with SCI, with positive outcomes without significant adverse events.

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

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AUTHOR CONTRIBUTION
Conceptualization: Park JM, Shin JC. Methodology: Park JM. Formal analysis: Park JM. Funding acquisition: Shin JC. Project administration: Park JM. Visualization: Park JM. Writing – original draft: Park JM, Kim YW, Lee SJ, Shin JC. Writing – review and editing: Park JM, Kim YW, Lee SJ, Shin JC. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS
Supplementary materials can be found via https://doi.org/10.5535/arm.230039.

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Effects of Botulinum Toxin-A for Spasticity and Nociceptive Pain in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis

Dewan Md. Sumsuzzman, PhD, Zeeshan Ahmad Khan, PhD, Irin Sultana Nila, PhD, Vanina Myuriel Villagra Moran, BPT, Madhuvilakku Rajesh, PhD, Won Jong Yang, MD, PhD, Yonggeun Hong, PhD

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We conducted a systematic review and meta-analysis to examine the protective effects of botulinum toxin-A (Botox-A) on spasticity and nociceptive pain in individuals with spinal cord injuries (SCIs). PubMed, Embase, and Cochrane Library databases were searched from inception to July 2023. The primary outcome of interest was spasticity and nociceptive pain. We pooled the available data using the generic inverse variance method, and we used a fixed-effect/random-effects model. We then calculated standardized mean difference (SMD) and 95% confidence intervals (95% CIs) to estimate the effect size. A total of fourteen studies meeting the inclusion criteria comprised two randomized controlled trials, five pre-post studies, and seven case reports. Across the various study designs, the majority of trials were assessed to have fair to high quality. The meta-analysis shows that Botox-A significantly decreased spasticity (SMD, -1.73; 95% CI, -2.51 to -0.95; p<0.0001, I^2=48%) and nociceptive pain (SMD, -1.79; 95% CI, -2.67 to -0.91; p<0.0001, I^2=0%) in SCI patients. Furthermore, Botox-A intervention improved motor function, activities of daily living (ADL), and quality of life. Our study suggests that Botox-A may alleviate spasticity and nociceptive pain in SCI patients. Moreover, the observed improvements in motor function, ADL, and overall quality of life following Botox-A intervention underscore its pivotal role in enhancing patient outcomes.

Keywords: Botulinum toxins type A, Muscle spasticity, Nociceptive pain, Spinal cord injuries, Systematic review

INTRODUCTION

Spasticity and pain frequently emerge as secondary sequelae following spinal cord injury (SCI), affecting around 60%–80% of cases [1]. Spasticity is also associated with a decline in quality of life (QoL) and increased mortality rates in SCI patients [2]. Pain...
following SCI, whether nociceptive or neuropathic [3], is equally prevalent and severe, adversely affecting physical, psychological, and social well-being, often worsening alongside other pain types. In the latest systematic review, nociceptive pain was found in 45% of cases, while neuropathic pain occurred in 58% of cases [4].

Despite significant advancements in managing spasticity and pain, addressing the fundamental barriers to QoL in individuals with SCI remains challenging. The management of spasticity often necessitates a multidisciplinary approach involving anti-spasticity medications, physical therapy, and, in some cases, surgical interventions [5]. However, oral anti-spasticity medications commonly prescribed to SCI patients are associated with various systemic adverse effects, such as sedation, confusion, hallucinations, nausea, and liver toxicity [6]. Compounding the issue, a significant portion of spasticity patients, around 40%, cannot tolerate the side effects of oral anti-spasticity agents [7], and physiotherapy frequently yields inconsistent outcomes in this population [8]. Local injections of botulinum toxin-A (Botox-A) offer a promising alternative to mitigate the side effects of oral anti-spasticity drugs and address the limitations of physiotherapies in SCI patients [9,10].

Botox-A, derived from the Clostridium botulinum bacterium, exerts its potent action by proteolytically cleaving synaptosomal associated protein-25 at nerve endings, thus impeding the release of acetylcholine neurotransmitter from axon terminals, resulting in muscle relaxation [11]. Numerous studies have demonstrated the safety and efficacy of Botox-A in managing spasticity across various neurological conditions including stroke, and traumatic brain injury [12,13]. Nearly a decade ago, a systematic review assessed the efficacy of Botox-A in managing spasticity among SCI patients [14]; however, given the dynamic nature of this field and the increasing number of published studies, the findings from this review may be outdated, reflecting the evolving landscape and highlighting the need for updated evidence to inform current clinical practice. Notably, recent randomized controlled trials (RCTs), such as the study by Yan et al. [15], have begun to evaluate the safety and efficacy of Botox-A specifically in SCI patients. Botox-A has been used to reduce spasticity in the rehabilitation setting, and its potential to manage pain is increasingly popular in the last decades [16,17]. A recent clinical review was conducted to evaluate the therapeutic efficacy of Botox-A for neuropathic pain in individuals with SCI [17]. Nonetheless, the therapeutic potential of Botox-A on nociceptive pain in SCI patients remains uncertain.

This systematic review and meta-analysis explore existing evidence on the protective role of Botox-A against spasticity and nociceptive pain in SCI patients. The evidence presented underscores the therapeutic potential of alleviating spasticity and nociceptive pain to enhance QoL in individuals with SCI.

**METHODS**

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The PRISMA checklist is provided in Supplementary Material.

**Search strategy and data sources**

We searched PubMed, Embase, and Cochrane Library electronic databases to identify all relevant trials up to July 2023. The reference lists of the included studies and of relevant reviews were examined for additional relevant trials. An electronic search of three databases was conducted, using the following search terms: “spinal cord injuries,” “botulinum toxin,” and “muscle spasticity.” No limits (e.g., on language or publication date) were used. The in-depth search strategy performed in major electronic databases is given in Supplementary Table S1.

**Inclusion criteria and outcomes of interest**

**Population**

Any SCI patients who were diagnosed with spasticity will be included.

**Interventions**

Trials that evaluated the effects of Botox-A on spasticity in patients with SCI. The combined therapy of Botox-A with other interventions will be excluded. In terms of RCT, all participants in the control group underwent any therapies for spasticity, but not any types of Botox-A. In pre-post design studies, before Botox-A injection were categorized as “pre” (control arm), and after Botox-A treatment were deemed “post” (experimental).

**Outcomes**

The primary outcome encompasses spasticity, assessed through validated scales including the modified Ashworth scale (MAS), modified Tardieu scale (MTS), Ashworth scale (AS), and spasm frequency score (SFS), as well as nociceptive pain measured by the visual analogue scale (VAS) and numerical rating scale (NRS). Nociceptive pain being defined by the diagnostic crite-
ria proposed by the international SCI pain classification [18].
The secondary outcome includes the evaluation of activities of
daily living (ADL) through tools such as the Barthel index (BI),
Functional Independence Measure (FIM), or goal attainment
scale (GAS). Additionally, motor function is assessed using the
modified Rivermead mobility index or other pertinent tools,
and QoL is measured using the disability assessment scale
(DAS).

Study design
This study includes RCTs, before and after studies (pre-post de-
sign), or case report studies that assess the efficacy of Botox-A
for the treatment of spasticity in patients with SCI. Any other
studies, such as animal studies, conference abstracts, observa-
tional studies, letters, and reviews were removed.

Selection of studies
We used reference management software (Mendeley) to orga-
nize and manage a large number of citations, as well as remove
duplicate articles. The remaining unique articles were then
imported into a Rayyan web application to allocate the refer-
ences randomly (https://www.rayyan.ai/). Based on titles and
abstracts screening, two independent reviewers identified all of
the pertinent articles, and trials that did not meet the inclusion
criteria were eliminated. The same reviewers who were respon-
sible for the primary screening had also evaluated the selected
full-text articles for final inclusion. Any disagreements in study
selection or data extraction were resolved by discussion be-
tween the reviewers, if consensus had not been reached, a third
reviewer arbitrated.

Data extraction
Two reviewers individually extracted the following information:
first author name and publication year, location, study design,
sample size, patient characteristics, interventions, and outcomes
measured. With regard to the pre-post study, the mean and
standard deviation (SD) of final scores and the total number of
participants before Botox-A treatment and after Botox-A treat-
ment were extracted. Finally, we contacted the corresponding
author via ResearchGate to retrieve any missing data. If efforts
to obtain the raw data were unsuccessful, the article was re-
moved from the meta-analysis. When the data were presented
graphically, GetData Graph Digitizer [19] was used to extract
numerical data from graphs or figures.

Quality assessment
Two reviewers individually evaluated the methodological qual-
ity of the selected trials. We applied the National Institutes of
Health quality assessment tool for all pre-post design studies
(https://www.nhlbi.nih.gov/health-topics/study-quality-asses-
sment-tools). Additionally, the methodological quality of
RCT was appraised by two authors using the Physiotherapy
Reference Database (PEDro) scale, which has been designed
to explore the reliability of data and provides a score out of 1–
10 [20]. Studies with a PEDro score of 6–8, 4–5, and scoring
below 4 are categorized as good quality, fair quality, and poor
quality respectively [20]. Finally, the methodological quality of
the selected case studies had evaluated utilizing the tool pro-
posed by Murad et al. [21] to assess case series and case reports.
This tool employs four domains for assessment: (1) selection,
(2) ascertainment, (3) causality, and (4) reporting. If a trial has
sufficient data in a domain, it was given one point. A total score
of 4 out of 4 was considered high quality, 3 out of 4 was con-
sidered moderate quality, and a score ≤2 was considered low
quality. Both the high and moderate-quality trials had consid-
ered having enough data to make inferences related to clinical
practice. Finally, the Grading of Recommended Assessment,
Development and Evaluation (GRADE) approach was used to
determine the certainty of evidence for the primary outcomes
(https://www.gradeworkinggroup.org/).

Data analysis
The variation of control groups between the included two
RCTs, a formal meta-analysis was not possible. Furthermore,
our included case reports were heterogeneous and did not in-
clude a control group. Hence, quantitatively synthesizing the
results of each case study and estimating effect size is not pos-
sible either. Therefore, only descriptive and narrative results of
qualitative analysis on the role of “Botox-A” described in each
individual study were provided. However, statistical analysis
was carried out by Review Manager software (RevMan 5.3; The
Nordic Cochrane Centre) for pre-post design studies. We enu-
merated standardized mean differences (SMDs) for continuous
data where trials used different scales for each outcome [22].
For each study and each comparison, we calculated the SMD,
the pooled SD, and the standard error of the SMD. Where the
correlation coefficient was unable to be extracted from publica-
tions or raw data, a conservative value of 0.5 was assumed [22].
This can be considered a conservative estimate when using the
change scores from the baseline. When SD was not reported we
calculated SD from the t-value or the p-value [23], otherwise we inputted the highest SD from the existing meta-analysis. We pooled the available data using the generic inverse variance method, and we used a random-effects model. In the absence of clinical or statistical heterogeneity, we also applied a fixed-effect model for pooling. To assess the statistical heterogeneity, we performed a chi-squared test and calculated the I^2 value according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. The I^2 test was utilized to assess heterogeneity among the studies (I^2=25%, low heterogeneity; I^2=50%, moderate heterogeneity; and I^2=75%, high heterogeneity) [24]. The fixed-effects model was used for the meta-analysis when I^2 was ≤50% and the random-effects model when I^2 was >50% [25,26]. Finally, we performed sensitivity analyses to evaluate the effect of the correlation coefficient; one assuming no correlation (when correlation coefficient=0.00) and one assuming a higher correlation (when correlation coefficient=0.80). And, p-value <0.05 is considered statistically significant. When conducting a meta-analysis, it’s generally recommended to assess publication bias through funnel plot asymmetry only if there are at least 10 studies included. This is because with fewer studies, the tests lack sufficient power to differentiate chance from actual asymmetry. Since our study included fewer than 10 studies, evaluating publication bias through funnel plot asymmetry and Egger regression was not possible.

RESULTS

Search strategy
Our screening process is presented in Fig. 1. Initially, 914 potentially relevant articles were searched through the electronic databases, and one additional citation was identified by manual searching. After removing duplicates (n=356), 558 studies were screened in view of the title, abstract, or full text, and 498 were discarded. The remaining 60 studies were included for full-text evaluation. Finally, 14 articles met the eligibility criteria and included our review, and 46 studies were excluded with reasons (Supplementary Table S2).

Characteristics of included studies
Fourteen studies investigated the effect of Botox-A for the management of spasticity in SCI patients. The citation search identified two RCTs [15,27], five pre-post designs [16,28-31], and seven case report studies [32-38]. An overview of assessments of outcomes measured in the intervention is shown in Table 1. The MAS and VAS were the most common outcome measures for spasticity and pain assessment respectively. Regarding activity of daily living, the BI was adopted most, followed by GAS and FIM evaluation. The gait analysis was frequently adopted for the locomotion activity. Only one RCT evaluated the quality-of-life outcome by DAS scoring. A detailed characteristic of the selected studies is shown in Tables 2-4.

Quality assessment
The methodological quality of the included studies was presented in Supplementary Table S3 (RCTs), Supplementary Table S4 (pre-post studies), and Supplementary Table S5 (case reports). According to the results of quality of evidence, all RCTs had appraised of high quality [15,27], three out of five pre-post trials had appraised of high quality [19,29,30], and two studies rated...
Table 1. Description of outcome measures

<table>
<thead>
<tr>
<th>Study design (level of evidence)</th>
<th>Outcome measure</th>
<th>Category</th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-post studies (level-4)</td>
<td>Modified Ashworth scale</td>
<td>Spasticity</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Modified Tardieu scale</td>
<td>Spasticity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Visual analogue scale</td>
<td>Pain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Numerical rating scale</td>
<td>Pain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Modified Rivermead mobility index</td>
<td>Motor function</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Functional Independence Measure</td>
<td>Activities of daily living</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Barthel index</td>
<td>Activities of daily living</td>
<td>1</td>
</tr>
<tr>
<td>Case-reports (level-5)</td>
<td>Modified Ashworth scale</td>
<td>Spasticity</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Ashworth scale</td>
<td>Spasticity</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Modified Tardieu scale</td>
<td>Spasticity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Spasm frequency score</td>
<td>Spasticity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Visual analogue scale</td>
<td>Pain</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Numerical rating scale</td>
<td>Pain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rivermead motor assessment</td>
<td>Motor function</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Barthel index</td>
<td>Activities of daily living</td>
<td>1</td>
</tr>
<tr>
<td>Randomized controlled trials (level-1)</td>
<td>Modified Ashworth scale</td>
<td>Spasticity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ashworth scale</td>
<td>Spasticity</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rivermead motor assessment</td>
<td>Motor function</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Disability assessment scale</td>
<td>Quality of life</td>
<td>1</td>
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<td></td>
<td>Goal attainment scale</td>
<td>Activities of daily living</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Barthel index</td>
<td>Activities of daily living</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of included studies in the systematic review: randomized controlled trials

<table>
<thead>
<tr>
<th>Reference (country)</th>
<th>Study design</th>
<th>Participant</th>
<th>Inclusion criteria</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yan et al., 2018 [15] (China)</td>
<td>Parallel-group</td>
<td>Total: n=224 (66 male, 158 female)</td>
<td>1. Duration since injury: more than 6 months</td>
<td>BoNT-A 500 IU</td>
<td>Control group 1: locomotor training and intensive task-specific training for 6 weeks</td>
<td>MAS, DAS, BI</td>
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<tr>
<td></td>
<td></td>
<td>Control group 1: n=112 (35.47±2.21 yr)</td>
<td>2. ≤2 MAS</td>
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<td></td>
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<td>Control group 2: n=112 (36.55±3.42 yr)</td>
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<tr>
<td></td>
<td></td>
<td>BoNT-A group: n=112 (36.95±7.12 yr)</td>
<td></td>
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<tr>
<td>Richardson et al., 2000 [27] (UK)</td>
<td>Parallel-group</td>
<td>Total: n=6</td>
<td>1. Duration since injury: more than 6 months</td>
<td>BoNT-A 100 IU</td>
<td>Placebo</td>
<td>AS, RMA, BI, GAS</td>
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<tr>
<td></td>
<td></td>
<td>Placebo group: n=2</td>
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<td></td>
<td></td>
<td>BoNT group: n=4</td>
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</tbody>
</table>

Age presented as mean±standard deviation.
Control group 1=physical therapy; control group 2=baclofen.
BoNT-A, botulinum toxin-A; MAS, modified Ashworth scale; DAS, disability assessment scale; BI, Barthel index; AS, Ashworth scale; RMA, Rivermead motor assessment; GAS, goal attainment scale.

as fair quality [28,31]; and three out of seven case report studies had appraised of high quality [32,36,37], and rest of four were moderate quality [33-35,38].

Meta-analysis

Effects of Botox-A in pre-post studies on the spasticity
Short-term (2–4 weeks) Botox-A treatment was effective as determined by the MAS and MTS scales. Taken together, four
Table 3. Characteristics of included studies in the systematic review: pre-post studies

<table>
<thead>
<tr>
<th>Reference (country)</th>
<th>Population</th>
<th>ASIA impairment scale</th>
<th>N</th>
<th>Mean age (range), yr</th>
<th>Male (%)</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opara et al., 2007</td>
<td>SCI patients with lower limb paresis and spasticity confirmed by MAS</td>
<td>NR</td>
<td>8</td>
<td>40.25 (23–62)</td>
<td>100</td>
<td>BoNT-A, 100–300 IU</td>
<td>MAS, VAS, MRMI</td>
</tr>
<tr>
<td>(Poland)</td>
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<tr>
<td>Bernstein et al., 2012</td>
<td>SCI patients with lower limb spasticity and spasticity confirmed by Ely test as well as MAS</td>
<td>D</td>
<td>15</td>
<td>43 (28–58)</td>
<td>93</td>
<td>BoNT-A, 200 IU</td>
<td>MTS</td>
</tr>
<tr>
<td>(France)</td>
<td></td>
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<tr>
<td>Béseler et al., 2012</td>
<td>SCI patients with lower limb spasticity and spasticity confirmed by MAS</td>
<td>NR</td>
<td>2</td>
<td>NR (mean) (&gt;18)</td>
<td>50</td>
<td>BoNT-A, 100–300 IU</td>
<td>MAS</td>
</tr>
<tr>
<td>(Spain)</td>
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<tr>
<td>Spiegel et al., 2014</td>
<td>SCI patients with lower limb spasticity and spasticity confirmed by MAS</td>
<td>A, C</td>
<td>9</td>
<td>40 (24–56)</td>
<td>100</td>
<td>BoNT-A, 100 IU</td>
<td>MAS</td>
</tr>
<tr>
<td>(Germany)</td>
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<tr>
<td>De Icco et al., 2019</td>
<td>SCI patients with lower limb spasticity and spasticity confirmed by MAS as well as MRC</td>
<td>NR</td>
<td>5</td>
<td>39.5 (30.3–48.7)</td>
<td>100</td>
<td>BoNT-A, 50–200 IU</td>
<td>MAS, BI, FIM, NRS</td>
</tr>
</tbody>
</table>

ASIA, American Spinal Injury Association; SCI, spinal cord injury; MAS, modified Ashworth scale; NR, not reported; BoNT-A, botulinum toxin-A; VAS, visual analogue scale; MRMI, modified Rivermead mobility index; MTS, modified Tardieu scale; BI, Barthel index; FIM, Functional Independence Measure; NRS, numerical rating scale.

studies (24 patients) that used MAS and one study (15 patients) MTS to measure spasticity showed that short-term Botox-A treatment significantly decreased spasticity (SMD, -1.73; 95% CI, -2.51 to -0.95; p<0.0001, I²=48%; Fig. 2). We imputed the 0.5 correlation coefficients to ascertain missing SDs. To reduce bias, we performed the sensitivity analysis and applied correlation coefficients of 0.8 and 0.0. Using a correlation coefficient of 0.8 (SMD, -1.86; 95% CI, -2.64 to -1.07; p<0.00001, I²=80%; Supplementary Fig. S1), as well as 0.0 (SMD, -1.45; 95% CI, -2.11 to -0.78; p<0.0001, I²=1%; Supplementary Fig. S2), the pooled difference between before Botox-A treatment and after Botox-A treatment remained statistically significant.

Effects of Botox-A in pre-post studies on the pain
Short-term (3–4 weeks) Botox-A treatment significantly reduced the pain as determined using the VAS and NRS scales. Altogether, one study (8 patients) that used VAS and one study (5 patients) NRS to measure pain showed that short-term Botox-A treatment significantly decreased pain (SMD, -1.79; 95% CI, -2.67 to -0.91; p<0.0001, I²=0%; Fig. 3). We imputed the 0.5 correlation coefficients to ascertain missing SDs. As the sensitivity analysis, we applied correlation coefficients of 0.8 and 0.0. Using a correlation coefficient of 0.8 (SMD, -1.79; 95% CI, -2.34 to -1.24; p<0.00001, I²=0%; Supplementary Fig. S3), as well as 0.0 (SMD, -1.79; 95% CI, -3.01 to -0.57; p=0.004, I²=0%; Supplementary Fig. S4), the pooled difference between before Botox-A treatment and after Botox-A treatment remained statistically significant.

Systematic review
Effects of Botox-A on spasticity in RCTs
Two RCTs were included in our systematic review [15,27]. Both trials measured spasticity and found that Botox-A yielded a significant reduction of spasticity when compared with a comparator group. Yan et al. [15] compared the efficacy of Botox-A with baclofen and/or physical therapy at 2, 4, and 6 weeks of follow-up. Compared with the baseline score, at 2 weeks, physical therapies had no effect (p=0.063), baclofen (p=0.003), and Botox-A (p=0.0224) had decreased MAS scores. At 4 weeks, physical therapy (p<0.0001) baclofen (p<0.0001), and Botox-A (p<0.0001) had reduced MAS scores. Final follow-up after 6 weeks, baclofen (p=0.02) had not improved, and Botox-A (p=0.02) had decreased MAS score compared to physical therapy. In another study, Richardson et al. [27] compared the efficacy of Botox-A with placebo at 3, 6, 9, and 12 weeks follow-up. Across both groups, AS was significantly decreased at 3 weeks relative to baseline (p<0.0001) but when compared with subsequent successive time contrasts such as 6 weeks vs. 3 weeks; 9 weeks vs. 6 weeks; 12 weeks vs. 9 weeks were insignificant (p>0.2, in every case).

Effects of Botox-A on motor function, ADL, and QoL in RCTs
Richardson et al. [27] also assessed motor function and ADL by RMA and GAS scale respectively, but there was no group difference in aggregate outcome scores. Yan et al. [15] measured ADL by BI score and demonstrated that physical ther-
### Table 4. Characteristics of included studies in the systematic review: case report studies

<table>
<thead>
<tr>
<th>Reference (country)</th>
<th>Study population</th>
<th>Case definition</th>
<th>Intervention (dose)</th>
<th>Outcome</th>
<th>Author conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson et al., 1997 [37] (UK)</td>
<td>23 Male 1</td>
<td>Incomplete C5/6 SCI with flaccid paralysis of all four limbs. Mild spastic paraparesis in the right leg, and mild hyperreflexia and clumsiness in the left arm and weakness in the right arm, most noticeable in the wrist, finger and thumb extensors</td>
<td>BoNT-A (210 IU)</td>
<td>RMA, VAS, AS</td>
<td>BoNT-A produced a temporary effect on muscle strength but may have a prolonged effect on function</td>
</tr>
<tr>
<td>Al-Khodairy et al., 1998 [32] (Switzerland)</td>
<td>50 Male 1</td>
<td>Incomplete T12 paraplegia (ASIA impairment scale=C) patient. presenting spasticity in his lower limbs with frequent painful spasms predominantly at night and with cold humid weather</td>
<td>BoNT-A (100–400 IU)</td>
<td>MAS, SFS, VAS</td>
<td>BoNT-A has its place in the treatment of spasticity in SCI. Although high doses of the product are well tolerated, the quantity should be tailored to the patient’s needs</td>
</tr>
<tr>
<td>Tang et al., 2009 [38] (USA)</td>
<td>60 Male 1</td>
<td>C3-C4 SCI with right upper and lower limbs painful spasms. On the physical exam, he had right upper and lower limb hyperspasticity, hemiparesis, and poor positional and vibrational sense</td>
<td>BoNT-A (50–100 IU)</td>
<td>AS, NRS</td>
<td>BoNT-A can relieve pain to biceps, flexor digitorum superficialis, brachialis, and pronator teres muscles</td>
</tr>
<tr>
<td>Naicker et al., 2009 [36] (Malaysia)</td>
<td>56 Male 1</td>
<td>C-5 SCI with spasticity in hips and knees. Patient had generalized pain in his legs, which was movement-related, dull, aching, and increased during spastic cramps</td>
<td>BoNT-A (NR)</td>
<td>MAS, BI, VAS</td>
<td>BoNT-A reduced spasticity and improved functional outcomes</td>
</tr>
<tr>
<td>Gross et al., 2012 [34] (France)</td>
<td>54 Male 1</td>
<td>The traumatic SCI patient, AIS grade C spastic tetraplegia with right motor level C8, left motor level C5, right sensory level C6, and left sensory level C4. The initial ASIA upper limb motor score was 32 and the lower limb motor score 30</td>
<td>BoNT-A (100 IU)</td>
<td>MAS</td>
<td>The spastic activity of the rectus femoris and the abnormal knee motion totally reversed after BoNT-A injection</td>
</tr>
<tr>
<td>Htwe et al., 2016 [35] (Malaysia)</td>
<td>22 Female 1</td>
<td>T5 AIS A paraplegic patient, who presented with severe lower limb spasticity with unstable hips</td>
<td>BoNT-A (25–75 IU)</td>
<td>MAS, MTS</td>
<td>BoNT-A effective in a case of severe spasticity with unstable hips in SCI patient</td>
</tr>
<tr>
<td>Frost et al., 2021 [33] (Canada)</td>
<td>64 Female 1</td>
<td>The traumatic SCI patient, C6 AIS D with hip adductor spasticity that affecting her gait</td>
<td>BoNT-A (200 IU total)</td>
<td>MTS, pain</td>
<td>BoNT-A minimizing postoperative increase in spasticity, reduce pain, and no longer required a gait aid</td>
</tr>
</tbody>
</table>

C, cervical; SCI, spinal cord injury; ASIA, American Spinal Injury Association; AIS, ASIA impairment scale; T, thoracic; BoNT-A, botulinum toxin-A; NR, not reported; RMA, Rivermead motor assessment; VAS, visual analogue scale; AS, Ashworth scale; MAS, modified Ashworth scale; SFS, spasm frequency score; NRS, numerical rating scale; BI, Barthel index; MTS, modified Tardieu scale.

Effects of Botox-A on spasticity and pain in case studies

The anti-spasticity effect of Botox on individuals with SCI was reported in seven case studies. The authors’ conclusions and population characteristics from included case studies were presented in Tables 2-4. Among the seven case studies, five studies featured SCI patients with lower limb spasticity [32-36], while two studies included upper limb spasticity [37,38]. In addition, five case studies [32-36] also measured pain by different pain assessment scales, including VAS, and NRS. A study by Frost et
al. [33] demonstrated that preoperative Botox-A reduces postoperative spasticity and pain, and eliminated the need for gait aids in patients with SCI-spasticity. Similarly, Botox-A treatment of spasticity in SCI patients reduced lower limb spasticity and spasticity-related pain after 24–72 hours [32]. Consistent with these findings, Al-Khodairy et al. [32] also reported that the clinical effects initiate within 24–72 hours after the Botox-A injection, peak in around 4–6 weeks, and are sustained for more than 3 months. The results, as shown by Htwe et al. [35], indicated that Botox-A response was very promising with a significant reduction in lower limb MAS score. Gross et al. [34] further disclosed that Botox-A markedly decreased spasticity of the rectus femoris. Naicker et al. [36] reported that Botox-A reversed the spasticity, spasticity- associated pain in the lower limb as indicated by SCI patient decreased MAS, VAS score, and sleep quality. In the upper limb, Botox-A treatment notably reduced AS (from 3 to 1) and maintain over 12 weeks [34]. Furthermore, the VAS score was significantly decreased by Botox-A injection, and the patient was able to shake hands during the 12-week study period [34]. Similarly, Tang et al. [38] found that Botox-A reduced spasticity and pain in upper limb muscles, including biceps, flexor digitorum superficialis, brachialis, and pronator teres muscles.

### Certainty of the evidence

The certainty of evidence for the efficacy of Botox-A on spasticity and pain outcomes was assessed using the GRADE approach. Details of GRADE certainty of evidence for the spasticity outcomes are shown in Supplementary Table S6.

### DISCUSSION

This systematic review of the literature summarized the available evidence on the effects of Botox-A for the management of spasticity in SCI patients. We identified two RCTs [15,27], five pre-post studies [18,28-31] and seven case reports [32-38], from three major electronic databases. The meta-analysis from pre-post studies suggested that patients with SCI could eventually show benefits regarding decreased spasticity (p<0.0001) within 2–4 weeks of Botox-A treatment. However, as depicted in Fig. 2, one study [29] approached the threshold of no effect, suggesting that Botox-A may not significantly improve spasticity outcomes. This study included two SCI patients: one female at 4 months post-onset and one male at 3 years post-onset [29], highlighting the potential impact of elapsed time between SCI onset and treatment administration on Botox-A effectiveness for spasticity. A further study is imperative to determine the op-
timal timing of Botox-A administration relative to SCI onset for achieving maximum efficacy in improving spasticity outcomes. Furthermore, Botox-A treatment may be also effective in SCI for the reduction of nociceptive pain (p<0.0001). Our quality assessment of included studies indicates the pre-post studies are fair to good quality. We rated all RCTs are high quality, and case reports are moderate to high quality. It is important to note that due to variation of the control group between two included RCTs, we did not perform the pairwise meta-analysis. In addition, case reports based on a single patient do not permit the estimation of effect size. Thus, the findings of RCTs and case reports were narratively described.

Despite our ample efforts, we were only able to include 14 studies in this review. Of these, two (RCTs) are level 1, five (pre-post) studies are level 4, and seven (case reports) are level 5 evidence [39]. The encouraging findings of our study that we are included two RCTs and performed for the first-time meta-analysis based on pre-post design studies in the SCI population. Consistent with other studies our meta-analysis has shown that Botox-A significantly reduced lower limb spasticity in SCI patients [40]. Recently, Yan et al. [15] performed one large RCTs to evaluate the efficacy of Botox-A in SCI patients. The results of this study also corroborated our findings that Botox-A notably decreased MAS score after a 2, 4, and 6 weeks follow-up period. Richardson et al. [37] compared the efficacy of Botox-A with the placebo up to 12 weeks follow-up period. This RCT only included 6 SCI patients (placebo group=2, and Botox-A group=4) and also concluded that Botox-A significantly decreased lower limb spasticity. In our systematic review, we only retrieved two RCTs and outcome measures estimated for short follow-up periods (2 to 12 weeks). In future, long-term follow-up studies in RCT design are urgently required to establish the efficacy of Botox-A in spasticity caused by SCI. Our meta-analysis based on level 4 evidence in SCI showed very promising results for spasticity management through Botox-A, but meta-analysis based on level 1 evidence is required to confirm our findings before getting approval for this drug. In the future, a well-design, multicenter RCT on the current topic is therefore recommended. While we conducted searches across databases without restricting by language or publication date, we excluded non-English language articles and conference abstracts. This exclusion may introduce publication bias and result in an incomplete representation of the available evidence. Future studies should consider including non-English literature, grey literature like conference abstracts, and expanding search strategies to encompass country-specific databases such as CNKI and WANFANG, thus ensuring a comprehensive representation of available evidence.

Abnormal posture and soft tissue changes by spasticity can aggravate the risk of pain, in turn, pain may worsen spasticity [18]. Thus, patients with SCI-spasticity and spasticity-related pain can enter a vicious circle that can intensify both pain and spasticity. Most recently, a cross-sectional survey reported that spasticity and chronic pain commonly appears following SCI [41]. Tibbett et al. [1] also reported that spasticity and chronic pain are directly related, which significantly impact ADL in SCI patients. Our included case reports [32-38] also support the idea that spasticity and pain are interrelated. Interestingly, Botox-A treatment not only reduced the spasticity but also pain in SCI patients [27,32,33,35,36,38]. Our meta-analysis based on level 4 evidence demonstrated that Botox-A treatment markedly reduced nociceptive pain (p<0.0001) in the SCI population. Surprisingly, no RCTs yet evaluated the efficacy of Botox-A to reduce nociceptive pain in SCI subjects. However, our included RCTs reported other beneficial effects of Botox-A in SCI, including improvement of motor function, ADL, and QoL [15,27]. Further research should be undertaken to investigate the salutary effects of Botox-A for the management of spasticity and nociceptive pain in SCI are therefore recommended.

CONCLUSION

This systematic review and meta-analysis provide promising insights into the potential of Botox-A therapy in alleviating spasticity and nociceptive pain among individuals with SCI, supported by pre-post studies and case reports. Moving forward, there is a critical need for additional high-quality RCTs with extended follow-up periods to firmly establish the efficacy of Botox-A in managing SCI. Furthermore, our study underscores the complex relationship between spasticity and pain in SCI patients, suggesting the potential for Botox-A treatment to address both conditions simultaneously. Future research should explore the broader impact of Botox-A therapy on motor function, ADL, and overall QoL within this demographic, advancing our understanding of its clinical application in treating spinal cord injuries.

CONFLICTS OF INTEREST

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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INTRODUCTION

Resistance exercises at 40%–85% of maximum voluntary contraction (MVC) has been reported to be important for preventing age-related muscle weakness and physical dysfunction [1-5]. However, resistance exercises are often difficult to continue performing because they depend on individual motivation. Therefore, electrical stimulation, which has little relevance to motivation, is used to maintain and improve muscle strength. Recently, application of repetitive peripheral magnetic stimulation (rPMS), which can be stimulated over clothing, to skeletal muscles has been reported to be useful for muscle strengthening as an alternative to electrical stimulation [6,7]. Since rPMS induces skeletal muscle contraction without activating cutaneous...
nociceptors [7], it produces less pain than electrical stimulation does [8,9].

Several rPMS intervention studies have reported muscle strengthening effects in healthy participants, patients with stroke and chronic obstructive pulmonary disease, and after total hip replacement [10-14]. However, in other studies, rPMS did not produce any significant changes in muscle thickness or cross-sectional area after 4 weeks [12] or did not clearly increase muscle strength in the lower extremities [15]. Thus, rPMS intervention studies have inconsistent results and are limited in number compared with studies on electrical stimulation. We have previously examined the stimulation methods, such as the intensity and application site, and confirmed that strong muscle contraction can be obtained by selecting the optimal stimulation intensity and application site [16,17]. Differences in the shape of the stimulating coil can have a large effect on muscle contraction. Stimulation of the femoral nerve with a figure-eight coil reportedly induces greater muscle contraction than stimulation with a circular coil does [18]. Additionally, the larger the coil size, the stronger the muscle contraction force induced by femoral nerve stimulation, when the shape of the coil is the same [19].

Although the effects of equipment differences and stimulation methods on muscle contraction have been clarified gradually in our study and previous studies, reports on the measurement of rPMS-induced muscle contraction are limited. Recently, magnetic stimulators that can induce stronger muscle contractions without generating excessive heat have been developed; however, reports on the actual measurement of muscle contraction force using such stimulators are scarce. Thus, in this study, the muscle torques induced by two stimulators with different coil properties were compared, and the factors that caused strong contractions were examined. Furthermore, we conducted a comprehensive search for previous studies that measured the muscle contraction force during rPMS and compared our study results with those of the previous studies. The results of this study could aid in the clinical application of rPMS-induced muscle contractions for the prevention of disuse atrophy or strengthening of lower extremity muscle in older adults.

METHODS

Participants
Thirty healthy young adults (mean age, 21.5±4.1 years; 15 females and 15 males) without any history of orthopedic, neuromuscular, or central nervous system diseases voluntarily participated in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki. The purpose of the study was explained in detail to all participants, both orally and in writing. Written informed consent was obtained from all the participants. This study was approved by the Ethics Committee of the Kawasaki University of Medical Welfare (No: 20-108; April 2021).

Equipment
Two types of magnetic stimulators manufactured by IFG Co. Ltd. (Stim A) and REMED Co. Ltd. (Stim B) were used for rPMS. Stim A and Stim B were air-cooled and oil-cooled magnetic stimulators, respectively (Fig. 1). Stim A contained a 10.1 cm² rectangular iron core coil with rounded corners, while Stim B contained a large round coil (radius 7.8 cm, area 191 cm²). The maximum outputs of the magnetic stimulation just below the probe surface of Stim A and Stim B were 1.08 T and 1.47 T, respectively, at a frequency of 30 Hz.

Stimulation conditions
The right vastus lateralis (VL) was magnetically stimulated according to previous reports [17,20-23]. Participants were seated with their right knee and hip joints flexed at 75°. The trunk and pelvic girdle were strapped to the seat, and the distal end of the right lower extremity was strapped to a machine that measured the isometric contraction (Fig. 2).
First, we used Stim A to identify stimulation points that could induce the maximum right VL contraction. The area between the proximal and distal 1/3 of the line connecting the anterior superior iliac spine and the superolateral margin of the patella was examined to identify the stimulation points [12]. Five to ten stimulations were applied to find the optimal point that could induce a stable and strong muscle contraction force; the identified point was marked.

When measuring the rPMS-induced muscle contraction force, great care was taken to ensure that the central part of the probe with the built-in coil coincided with the optimal stimulation point and that the long axis of the coil was parallel to the long axis of the thigh. Magnetic stimulation pulse trains were gradually increased to the maximum output intensity. After habituation to the magnetic stimulation was acquired, the VL was stimulated three times at the maximum output intensity of each stimulator (A100% and B100%). Each stimulation lasted 3 seconds with a 2 seconds rest interval between stimulations. Subsequently, additional muscle contractions were induced with Stim B at 70% of the maximum output intensity (B70%), that is 1.07 T/sec, to produce a magnetic stimulation output equivalent to that of Stim A at A100%.

The participants were instructed to relax their entire body as much as possible to avoid voluntary contraction of the quadriceps femoris during rPMS. The isometric knee extensor torque (KET) was measured three times in each condition (A100%, B100%, and B70%). Immediately after each stimulation, the degree of pain during rPMS was evaluated using a visual analogue scale (VAS). The participants were instructed to place an “x” mark on a 100 mm straight line. The left end (0 mm) of the line was set as “no pain” and the right end (100 mm) as “pain too intense to be tolerated.” The VAS values were recorded to one decimal place.

Measurement of KET
The right-sided KET was measured using a dynamometer (BIODEX System 3®; Biodex Medical Systems, Inc.), at a frequency of 100 Hz. Before MVC measurement, four sets of 3 seconds isometric knee extension exercises were performed with approximately 90% MVC as a warm-up. A rest interval of 5 seconds was maintained between the sets. After a 5 minutes post-warm up break, the muscle torque during a MVC of 3 seconds was measured twice with a 5 seconds rest interval between measurements. The larger of the two measurements was used in the analysis.

After another 5 minutes break, the rPMS-induced KET was measured at A100%, B100%, and B70%. The mean torque value for 1 second from 500 to 1,500 ms before the waveform returned to baseline after contraction was used for the analysis (Fig. 3). To compare the rPMS-induced muscle torque under the three conditions, the mean of the three measurements in each condition was calculated. The relative value of MVC (%MVC) was obtained by dividing the rPMS-induced KET by the MVC.

Data analysis
The Shapiro–Wilk test was performed on all data obtained in this study to determine if they were normally distributed. To examine the effects of the stimulation conditions on the KET (%MVC) and pain level (VAS value), their mean values at A100%, B100%, and B70% were compared. The Friedman test

![Fig. 2. Muscle contraction induced by repetitive peripheral magnetic stimulation and measurement of muscle torque. (A) Contraction induced by the stimulator manufactured by IFG Co. Ltd. (Stim A). (B) Contraction induced by the stimulator manufactured by REMED Co. Ltd. (Stim B).](image)

![Fig. 3. Knee extensor torque waveform during repetitive peripheral magnetic stimulation. Torque value: mean torque for 1 second from 500 to 1,500 ms before the waveform returned to baseline after contraction.](image)
was used for multiple comparisons, followed by the Bonferroni correction for post-hoc testing. IBM SPSS version 22.0 (IBM Corp.) was used for the statistical analysis, and the significance level was set at $p<0.05$.

**Comprehensive literature search**

A comprehensive literature search was conducted to compare our study's rPMS-induced KET with those of previous studies. PubMed was searched independently by two researchers. The titles, abstracts, and texts of studies published on rPMS in humans were searched without restrictions on publication date or methodological design.

First, an OR search was performed using "repetitive peripheral magnetic stimul*, "rPMS, "spinal magnetic stimul*, "magnetic nerve stimul*, "magnetic stimulation, and "electromagnetic stimulation." In the next OR search, the keywords used were "torque, "force, and "Nm." In the third OR search, the keywords used were "quadriceps, "vastus lateralis," and "rectus femoris." An AND search was then performed on the results of the three OR searches. The papers identified in the search were reviewed, and studies that actually measured the KET were selected. In addition, we manually searched for relevant studies among the references of the selected articles.

**RESULTS**

**Comparison of the KETs in each stimulation condition**

The Friedman test showed a statistically significant difference in %MVC between the different intensities ($p<0.001$). The mean MVC was 161.0±51.4 Nm (Table 1). The mean KETs induced by A100%, B100%, and B70% were 29.6±18.1 Nm (%MVC, 17.7%±8.3%), 66.1±24.5 Nm (%MVC, 41.1%±9.0%), and 54.9±23.4 Nm (%MVC, 33.8%±9.8%), respectively (Table 1). The mean %MVC at B100% was significantly greater than that at A70% and A100% ($p<0.001$). The mean %MVC at B70% was also significantly greater than that at A100% ($p<0.001$) (Fig. 4).

**Comparison of the pain scores in each stimulation condition**

The degree of pain evaluated using the VAS is shown in Fig. 5. The Friedman test showed a statistically significant difference in the VAS scores between the different intensities ($p<0.001$). The mean VAS score caused by A100% was lower than that caused by B70% ($p<0.05$) and B100% ($p<0.001$). The mean VAS score caused by B70% was also significantly lower than that caused by B100% ($p<0.01$). However, the pain caused by A100% was not uncomfortable.

**Comprehensive literature search**

The AND and OR searches identified 115 papers published prior to October 2022. However, a review of the selected papers revealed that only four studies actually measured the rPMS-induced KET in the quadriceps femoris muscle. The magnetic

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**Table 1.** MVC of the knee extensors and rPMS-induced KET induced under each stimulation condition

<table>
<thead>
<tr>
<th>Coil area (cm$^2$)</th>
<th>KET (Nm)</th>
<th>Output intensity (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC</td>
<td>161.0±51.4</td>
<td>-</td>
</tr>
<tr>
<td>A100%</td>
<td>10.1</td>
<td>29.6±18.1</td>
</tr>
<tr>
<td>B70%</td>
<td>191</td>
<td>54.9±23.4</td>
</tr>
<tr>
<td>B100%</td>
<td>191</td>
<td>66.1±24.5</td>
</tr>
</tbody>
</table>

Values are presented as number only or mean±standard deviation. The output intensity of the magnetic stimulation immediately below the probe surface was equivalent between B70% and A100%. MVC, maximum voluntary contraction; rPMS, repetitive peripheral magnetic stimulation; KET, knee extensor torque; A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B.

![Fig. 4. Comparison of relative value of maximum voluntary contraction (%MVC) during repetitive peripheral magnetic stimulation between each stimulation condition. %MVC was calculated by dividing the knee extensor torque during stimulation by the MVC. A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B. **$p<0.01$.](image-url)
stimulator used for transcranial magnetic stimulation (TMS), with stimulation intensities ranging from 1.8 to 2.0 T, was utilized in all four papers.

In a previous study in which the rectus femoris was stimulated, the maximum rPMS-induced KET did not exceed 20 Nm. In three other studies, in which the main trunk of the femoral nerve was directly stimulated with a stimulator equipped with booster units, the KET exceeded 20 Nm (Table 2). Among these three studies, in one study, the mean KET which was measured as the sum of four muscles, was greater than that of one muscle in our study. The other two studies using booster units reported a %MVC greater than 70%; however, the actual MVC values were not included in these papers.

None of the three studies that directly stimulated the main trunk of the femoral nerve reported on pain assessments. The study in which the rectus femoris was stimulated reported VAS scores of zero in all participants.

**DISCUSSION**

The results of this study revealed that the rPMS-induced KET with Stim B was greater than that induced by Stim A, even when the output intensity of the magnetic stimulation just below the probe surface was adjusted to be equivalent. The output intensity was previously measured, and B70% was found to be equivalent to A100%. The muscle contraction force induced by A100% was weaker than that induced by B70%, so we did not measure the muscle contraction force induced by A70%.

Although the rPMS-induced contraction force is related to the magnetic stimulation intensity [15, 16, 18, 19], coil size [19], and coil shape [18], no studies have compared the contraction forces induced by different coils at the same stimulation intensity. In the present study, the KET was compared by equalizing the stimulation intensities of the two different stimulators. Our

![Fig. 5. Comparison of pain during repetitive peripheral magnetic stimulation in each stimulation condition. A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B; VAS, visual analogue scale. *p<0.05, **p<0.01.]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equipment</th>
<th>Coil properties</th>
<th>Stimulation frequency (Hz)</th>
<th>Output intensity (T)</th>
<th>Stimulation site</th>
<th>Duration of stimulation (s)</th>
<th>Pain assessment</th>
<th>Measured value of KET</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han et al., 2006 [27]</td>
<td>Biocon-1000</td>
<td>Circumferential</td>
<td>25</td>
<td>1.8</td>
<td>Rectus femoris</td>
<td>2</td>
<td>VAS</td>
<td>9.5±4.8 Nm</td>
<td>Healthy adults</td>
</tr>
<tr>
<td>Kremenic et al., 2004 [29]</td>
<td>Magstim Rapid with four booster units</td>
<td>110-mm double-circular</td>
<td>20, 30, 40</td>
<td>2</td>
<td>Main trunk of femoral nerve</td>
<td>3</td>
<td>None</td>
<td>Approximately 70% of MVC “estimated”</td>
<td>Healthy adults</td>
</tr>
<tr>
<td>Kremenic et al., 2009 [30]</td>
<td>Magstim Rapid with eight booster units</td>
<td>110-mm double-circular</td>
<td>25</td>
<td>2</td>
<td>Main trunk of femoral nerve</td>
<td>3</td>
<td>None</td>
<td>89.6%±9.6% of MVC</td>
<td>Healthy adults</td>
</tr>
<tr>
<td>Fukunaga et al., 2019 [31]</td>
<td>Magstim Rapid with eight booster units</td>
<td>110-mm double-circular</td>
<td>35</td>
<td>2</td>
<td>Main trunk of femoral nerve</td>
<td>3</td>
<td>None</td>
<td>168.0±79.8 Nm</td>
<td>Post-reconstruction of the anterior cruciate ligament</td>
</tr>
</tbody>
</table>

“Estimated” refers to the values determined from the figures in the papers.

KET, knee extensor torque; VAS, visual analogue scale; MVC, maximum voluntary contraction.
study results indicate that not only the stimulation intensity, but also the size and shape of the coil affect the larger KET induced by Stim B than that induced by Stim A. The coil size of Stim B (191 cm²) was larger than that of Stim A (10.1 cm²). Although the stimulation was applied at the center of the optimal point, a fairly wide area of VL could have been stimulated by Stim B because it has a larger coil. The optimal point for magnetic stimulation in this study was just above the superficial proximal sub-branch of the VL branch arising from the femoral nerve trunk [17]. The central and distal sub-branches of the VL branch may also have been stimulated by Stim B. In addition, a part of the large coil was also placed on the rectus femoris; therefore, it may have cause partial contraction of the rectus femoris.

The coil shape in Stim A was rectangular with rounded corners, while that in Stim B was round. The round coil reportedly provides deeper stimulation than the rectangular coil [18]. Various factors influence muscle contraction force, and the cross-sectional area and volume of the muscle are known predictors of KET [24]. A thicker muscle reportedly produces a stronger KET [25]. Furthermore, thick subcutaneous fat decreases rPMS-induced KET because of the increase in electrical resistance and increase in the distance from the skin to muscles and nerves [20]. The present study results suggest that the deep proximal sub-branch of the VL branch was stimulated by the rounded coil of the Stim B by penetration of the magnetic waves through the subcutaneous fat. We hypothesize that Stim B was able to induce a stronger KET than Stim A, owing to the several factors mentioned above.

The intensity of resistance exercise commonly used to strengthen the quadriceps femoris muscle in older adults is reportedly 40%–85% of the MVC when performed 1–3 times a week for 6–52 weeks [1]. The present study revealed that stimulating the VL at B70% could induce more than 30% of the MVC in the knee extensors. The cross-sectional area of the VL is approximately 36.3% of the entire quadriceps femoris and that of the rectus femoris was approximately 11.4%; therefore, the contractile force of the VL or rectus femoris alone is approximately 1/3 or 1/9 [26]. Thus, when stimulated at B70%, >40% of the MVC of the VL alone can be induced, even if both the VL and rectus femoris contract. This value corresponds to the intensity of resistance exercises generally used for muscle strengthening. However, it was assumed that less than 40% of the MVC of the VL alone was induced when stimulated with Stim A. This contraction force may not have reached the intensity of resistance exercises required for muscle strengthening. Therefore, differences in the size and shape of the coils were found to be clinically important.

In the present study, the VAS value for Stim A was less than that for Stim B, and the higher stimulation intensity of Stim B produced a stronger pain. The relationship between intensity and pain in our study was consistent with those of several previous reports, validating the results of previous studies [7,8,21,27]. The VAS score for Stim A, with a smaller area, was less than that for Stim B. A large coil area expands the area being stimulated; thus, we hypothesized that Stim B was more likely to stimulate the Aδ fibers that conduct pain sensation than Stim A [28]. Therefore, stimulations with VAS values of less than 70/100 are clinically acceptable.

In this study, we compared the contraction force of a single muscle, namely the VL, between two stimulators when induced with rPMS. However, if rPMS were to be used for the purpose of strengthening muscles in a clinical setting, it would be necessary to stimulate various muscles. Additionally, even if the contractile force of stimulated muscles increases, it is unclear whether this contributes to physical activity. In the near future, intervention studies should be conducted to confirm that rPMS can be used on several muscles of the lower extremities in older persons to strengthen the muscles and to improve motor function.

The comprehensive literature search revealed that KET was measured in only four studies. In the study in which rPMS was applied to the rectus femoris using a stimulator without booster units, a strong contractile force was not induced. In the three other studies, although it was determined that >70% of MVC can be induced by direct stimulation of the main trunk of the femoral nerve, pain assessment was not reported. Because the femoral nerve contains sensory fibers, the participants must have experienced severe pain. Additionally, the stimulator was equipped with booster units to increase the stimulation frequency. However, considering the weight of the booster units, the clinical utility would be reduced [29-31]. The mean KET in the present study exceeded that of a previous report that stimulated muscle branches when induced at B100% (66.1 Nm) and B70% (54.9 Nm). Additionally, pain assessment indicated that Stim B was suitable for clinical use.

Bustamante et al. [10,11] reported on the effect of rPMS in patients with chronic obstructive pulmonary disease. Although KET induced by rPMS to the femoral nerve with a stimulator used for TMS was as low as 10 Nm, the MVC and walking endurance increased after 8 weeks of intervention [11]. How-
ever, stimulators used for TMS generate excessive heat with prolonged use. Therefore, to conduct intervention studies confirming the effect of muscle strengthening by inducing a strong KET, it is necessary to use a stimulator that does not generate excessive heat. These dedicated stimulators are expected to strengthen the muscles and improve walking endurance in older adults, but is problematic to conclude that they are a compensatory method for resistance exercise. Future studies are needed to examine whether rPMS improves physical function, whether there is pain or fatigue after continuous application of rPMS, and whether there is an overall feeling of satisfaction with rPMS.

Another limitation of this study is that the relationship between the participant characteristics and the rPMS-induced KET was not evaluated in detail. Various variables such as body size, BMI, thigh circumference, femoral length, and gender should be considered as factors of the muscle contraction force induced by rPMS. In the future, it will be necessary to investigate how the patient characteristics affect rPMS-induced KET. Based on these findings, the effectiveness of rPMS for muscle strengthening should be verified.

CONFLICTS OF INTEREST

Our university has signed a joint research agreement with OG Wellness Technologies Co., Ltd. The funders did not have any role in the study design, collection and analysis of data, preparation of the manuscript or the decision to submit the manuscript for publication.

FUNDING INFORMATION

We have borrowed equipment and received research funds from OG Wellness Technologies Co., Ltd.

AUTHOR CONTRIBUTION


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REFERENCES


Changes in Health-Related Quality of Life by Patient Education and Rehabilitation Based on a Behavior Change Program in Knee Osteoarthritis

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Objective: The purpose of this study was to examine how rehabilitation and patient education for knee osteoarthritis improves health-related quality of life (HRQOL) and to identify factors influencing HRQOL.

Methods: Between May 2020 and March 2022, 30 patients with osteoarthritis of the knee were treated conservatively and rehabilitated with a patient education program. The patient education program was based on the health belief model by Sedlak et al., and patient education using pamphlets was provided during the rehabilitation intervention. The survey items were patient basic information, instrumental activities of daily living (ADL) (FAI), fear of falling (FES), degree of depression (GDS), HRQOL (SF-8), knee function assessment (JOA score), and X-ray classification (K-L classification), and the survey method was a self-administered questionnaire at the start of rehabilitation, 1 month after the intervention, and at the end of the rehabilitation intervention. We examined factors affecting the physical component summary (PCS) and mental component summary (MCS) of HRQOL scores.

Results: JOA score, FES, FAI, GDS, and SF-8 improved significantly (p<0.01). MCS was also negatively correlated with FES and age (r=-0.486, -0.368). Sex was extracted as a factor for PCS as a factor affecting HRQOL (p<0.01). MCS was extracted with FES as a factor (p=0.046).

Conclusion: A rehabilitation intervention incorporating patient education in osteoarthritis of the knee showed improvement in HRQOL and may be useful for improving depression, fear of falling, and instrumental ADL.

Keywords: Knee osteoarthritis, Patient education, Rehabilitation, Health-related quality of life
of life. Park et al. [4] suggest that knee osteoarthritis is significantly associated with decreased mental health and health-related quality of life (HRQOL). We verified and informed the time-dependent change of HRQOL by the rehabilitation intervention on 62 cases of old osteoarthritis patients treated conservatively [5]. As a result, knee function, fear of falling, and instrumental activities of daily living (ADL) was significantly improved from the start of rehabilitation to 3 months after the intervention. However, there was no improvement in depression and HRQOL scores, physical component score and mental component score. It is necessary to establish treatment measures based on psychological factors such as depression caused by chronic pain in knee osteoarthritis. Meeus et al. [6] reported on the effects of patient education, which improved psychological factors related to pain. Snyder and Engström [7] reported on the effectiveness of oral and pamphlet teaching as a method of patient education and described its effectiveness.

Therefore, for patients with knee osteoarthritis, the introduction of patient education aimed at improving chronic pain and psychological factors as part of rehabilitation may be effective for the reduction of pain and psychological factors such as depression and anxiety, and may prevent the decrease of activity and the decrease of HRQOL. However, there have been no reports that have examined the effects and trends of rehabilitation incorporating patient education for knee osteoarthritis on psychological factors such as pain, depression, and fear of falling, as well as HRQOL. Furthermore, there have been no reports examining the time course of HRQOL in patients with knee osteoarthritis using patient education and rehabilitation intervention based on behavior change.

The purpose of this study was to examine the effect of combined patient education and conservative rehabilitation on pain, psychological factors, and change of HRQOL in patients with knee osteoarthritis.

METHODS

Subjects
The object patients were 30 patients over 65 years old who were diagnosed as osteoarthritis of the knee and underwent conservative treatment and rehabilitation from May 2020 to March 2022. Conservative treatment refers to the use of external preparations, oral medications, braces, or intra-articular injections according to symptoms. Surgical treatments were excluded. Patients were also included if they had other motor disorders and were diagnosed with knee pain and osteoarthritis on radiography.

This study was a pilot study with 30 subjects. We prospectively investigated the change over time in patient education effect in the osteoarthritis conservative treatment example.

In consideration of ethical issues, after sufficient informed consent to participate in the study, the subject’s voluntary consent form was obtained. This study was approved by the Institutional Review Board of the Nihon University Hospital (IRB No. 20200403), and informed consent was obtained from each patient.

Method

Method of patient education
The behavior change program using the pamphlet as educational tool was carried out.

The contents of patient guidance included questionnaires, individual guidance using educational tools, and goal setting. Present a questionnaire to help you discover what you want to ask. In addition, information on items related to health status and HRQOL was extracted. In the individual guidance using the education tool, the pamphlet which described the gist of the content in the patient education was used. The pamphlet in which the description on the gonarthrosis which Japanese Orthopaedic Association (JOA) announced was described was used for the method of the patient education [8]. The pamphlets describe the causes of knee osteoarthritis, the characteristics of the symptoms, the classification of the degree of progression on X-ray, and the treatment. The symptoms described include pain in the knees and difficulty walking up and down stairs, difficulty squatting or sitting upright, and stiff knees when standing up. Causes and characteristics: The causes of knee osteoarthritis can be either primary, for which the cause cannot be clearly determined, or secondary, for which an injury or disease around the knee joint affects.

Previous injuries, such as meniscus and ligament injuries, sprains and fractures, and diseases such as rheumatoid arthritis and pseudogout are classified as secondary, but most cases are primary knee osteoarthritis for which the cause cannot be determined. It is explained that the grade in the X-ray is classified from 1 to 4 according to the size of the gap of the joint. For treatment, conservative treatment such as injection and internal use, rehabilitation, and operative treatment are explained.

On the basis of this pamphlet, the knowledge on purpose, on the disease state, the guidance was carried out on prevention
method, range of motion training and muscle strengthening practice, walking practice, activity of daily living practice and home exercise program according to the individual condition. The home program included a stepwise walking program, range of motion training for bathing, and locomotion training was performed at home three times a day. Locomotion training consists of standing on each leg for 1 minute and squatting 5 to 6 times [9]. Patient education was provided at the start of rehabilitation, 1 month after the start of rehabilitation, and at the end of rehabilitation intervention.

**Practice of behavior change programs**

The behavior change program was based on the health belief model by Sedlak et al. [10]. It consists of the following; I. motivate, II. persuade verbally, and III. elicit physiologically and emotionally.

I. Motivate

The risk caused by osteoarthritis of the knee is explained. The risks of pain, restricted walking, and decreased ability to live were discussed in the pamphlet published by the JOA.

II. Persuade verbally

Goal level decisions were verbal persuasion based on achievement. Exercise therapy consisted of one-to-one gait correction, muscular strength and endurance training, and range of motion training, depending on the individual’s level.

III. Elicit physiologically and emotionally

Attention should be paid to improvements in knee function and pain as a result of exercise therapy.

As a method to confirm whether the patient understood the contents of the instruction, the degree of understanding was confirmed by interviewing the patient to confirm whether the patient understood the contents of the instruction and having the patient explain it verbally at the time of patient follow-up. The period of instruction was 5 months.

**Rehabilitation methods**

The physical therapist intervened in the rehabilitation. The rehabilitation menu included range-of-motion exercises, muscle strengthening exercises mainly for the quadriceps femoris, gait training, and balance training [11]. For patients with knee pain, we administered drugs and intra-articular injection of hyaluronic acid to control pain and implemented an education program. The rehabilitation period was 5 months.

**Evaluation of measurement index**

Evaluations were performed at three time points: before exercise therapy intervention, 1 month into intervention, at the end of the intervention. The items investigated were as follows: (1) knee osteoarthritis severity, (2) knee osteoarthritis staging, (3) fear of falling, (4) instrumental ADL, (5) degree of depression, and (6) HRQOL. Fear of falling, instrumental ADL, degree of depression, and HRQOL were determined using a self-administered questionnaire directly to subjects, which they returned completed following their medical examination.

The degree of progression of knee osteoarthritis was classified using the Kellgren-Lawrence (K-L) grading system [12]. The K-L system consists of five grades from 0–4: 0 is no osteoarthritis; 1 is doubtful narrowing of the joint space and/or possible osteophytes; 2 is definite osteophytes and possible narrowing of the joint space; 3 is multiple osteophytes, definite narrowing of the joint space, and some sclerosis and deformity of the bone ends; and 4 is large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of bone ends. Also, knee osteoarthritis severity, Fear of falling, Instrumental ADL, Degree of depression, and HRQOL were assessed at the beginning and end of rehabilitation.

(1) Knee osteoarthritis severity

Knee osteoarthritis severity was measured using the patient’s JOA score [13]. It is a measure to evaluate the degree of functional impairment. Rate pain, walking ability, stair climbing, flexion angle, and swelling on a scale of 1 to 100. The higher the score, the higher the knee joint function.

(2) Fear of falling

Fear of falling was evaluated using the Fall Efficacy Scale (FES) was advocated for Tinetti et al. [14]. The FES is a tool that measures the degree of confidence of a person to perform 10 different ADL without falling on a four-point scale. Scores are expressed from 10 to 40 points, and a lower score indicates less fear of falling.

(3) Instrumental ADL

Instrumental ADL was evaluated using the Frenchay Activities Index (FAI) developed by Holbrook and Skilbeck [15]. It was evaluated 15 applied ADL and social life items on a four-point
scale from 0–3 points. The maximum score is 45 points, and a higher score indicates greater instrumental ADL ability and independent applied ADL.

(4) Degree of depression
Degree of depression was evaluated using the Geriatric Depression Scale (GDS). The GDS was developed to measure depression, and a higher score means a higher degree of depression [16–18].

(5) HRQOL
The evaluation of HRQOL used Short Form-8 (SF-8) which was short version of Short-Form Health Survey (SF-36) [19]. SF-8 can be evaluated efficiently with a minimum number of items, and consists of the following eight items (subscales): general health (GH), physical functioning (PF), role physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). A higher score indicates higher QOL. Physical component summary (PCS) and mental component summary (MCS) scores are also calculated using regression equations based on the weighting of each item. Use of the SF-8 in this study was registered with the Institute for Health Outcomes & Process Evaluation Research to obtain a license. For fear of falling, instrumental ADL, depression, and HRQOL, questionnaires were given to the patients at the beginning and one month after the rehabilitation intervention and at the end of the intervention, and the questionnaires were collected after the patients answered the questionnaire contents. Correlations and associations were statistically verified for each score.

**Statistical analysis**
The controlled analysis included outcomes of PCS and MCS, HRQOL scores, and tested for influencing factors. For the validation method, the dependent variables were PCS and MCS, and the independent variables were age, sex, FES, FAI, and GDS, with a significance probability of 0.05%. In addition, factors correlated with PCS and MCS scores were verified by correlation coefficients. The statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp.). Normally distributed variables were expressed as the mean±standard deviation and variables with a skewed distribution as the median and interquartile range. The chi-square test, unpaired t-test, Mann–Whitney U-test, χ² test, and the Fisher exact test were used, as appropriate, to compare variables between the groups.

### RESULTS

The baseline characteristics of the subjects are presented in Table 1. Changes in JOA score are shown in Fig. 1. The JOA score was significantly improved 1 month after the patient education intervention compared to before the intervention (p<0.01). There was no significant difference in the presence or absence of painkillers or intra-articular injections in each period. Results of PCS and MCS scores for SF-8 items are shown (Fig. 2). MCS score ranged from 47.9 before the intervention to 48.6 at the end

### Table 1. Clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>73.0±6.6</td>
</tr>
<tr>
<td>Sex, female</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9±3.9</td>
</tr>
<tr>
<td>K-L classification</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>2</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>3</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>4</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>1</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>2</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>≥3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Follow up period (day)</td>
<td>90.4±43.7</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). BMI, body mass index; K-L, Kellgren-Lawrence; CCI, Charlson Comorbidity Index.

![Fig. 1. Change in average Japanese Orthopaedic Association (JOA) score. JOA scores at 1 month after the intervention and at the end of the intervention were significantly improved from those at the beginning of the intervention (**p<0.01). Knee joint function was significantly improved.](image-url)
of the intervention. The PCS score ranged from 40.8 before the intervention to 48.4 at the end of the intervention. PCS score was significantly improved 1 month after the patient education intervention compared to the start (p<0.01). There were no significant differences in MCS scores between the time periods.

Changes in FES and FAI are shown in Figs. 3, 4. At the end of the patient education intervention, it was significantly lower than at the start (p<0.01). GDS score is shown in Fig. 5. GDS score was significantly improved 1 month after the patient education intervention compared to the start (p<0.01). Table 2 shows the correlation between PCS score, MCS score, and measurement items at each time period. PCS score was negatively correlated with FES before and 1 month after the patient education intervention (p<0.01, p<0.05). MCS score was negatively correlated with Age and FES (p<0.05, p<0.01).

Results of multiple regression analysis with PCS and MCS scores at final follow-up as dependent variables and age, sex, FES, FAI and GDS as independent variables are shown in Table 3. Sex was extracted as an influencing factor for PCS scores (p<0.01). FES was also extracted as an influencing factor of MCS score (p=0.046).

![Fig. 2. Change in average health-related quality of life (HRQOL) score. The physical component summary improved significantly with rehabilitation and patient education (**p<0.01), but the mental component summary showed no apparent improvement. PCS, physical component summary; MCS, mental component summary.](image1)

![Fig. 3. Change in average Fall Efficacy Scale (FES). The FES was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).](image2)

![Fig. 4. Change in average Frenchay Activities Index (FAI). The FAI was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).](image3)

![Fig. 5. Change in average Geriatric Depression Scale (GDS). The GDS was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).](image4)
DISCUSSION

A prospective cohort study of patient education interventions for osteoarthritis of the knee shows two major finds. First, the patient education intervention improved PCS score but not MCS score. Second, age was found to be an influencing factor for PCS score, and fear of falling was found to be an influencing factor for MCS score.

Muraki et al. [20] describes HRQOL in knee osteoarthritis, revealed that in severe cases, the PCS score decreases and correlated with pain. The PCS score also correlated with pain and grip strength. On the other hand, the MCS is not related to the severity of knee osteoarthritis, and a variety of factors were involved. In our previous studies have examined changes in HRQOL when knee osteoarthritis is treated with rehabilitation without patient education. As a result, JOA scores, fear of falling, and instrumental ADL improved significantly from the start of rehabilitation to three months after the intervention. However, depression and mental and PCS score did not significantly improve. In the current study with patient education, depression and physical HRQOL. To improve MCS, it is necessary to review the contents of the current education program and verify the education program for cases with severe psychosomatic elements.

The association between MCS and PCS scores tended to correlate with fear of falling, indicating that taking a fall prevention approach may improve HRQOL.

Second, age was found to be an influencing factor for PCS score, and fear of falling was extracted as a factor influencing MCS score at the end of patient education. FES showed a negative correlation with MCS score. The results suggest that fear of falling affects MCS more than PCS score. Therefore, educa-

Table 2. Health-related quality of life scale correlations

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>JOA</th>
<th>K-L</th>
<th>GDS</th>
<th>FAI</th>
<th>FES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preintervention</td>
<td>-0.140</td>
<td>-0.274</td>
<td>-0.077</td>
<td>-0.266</td>
<td>0.008</td>
<td>-0.472**</td>
</tr>
<tr>
<td>1 mo</td>
<td>-0.215</td>
<td>-0.147</td>
<td>0.047</td>
<td>-0.236</td>
<td>-0.053</td>
<td>-0.431*</td>
</tr>
<tr>
<td>End of intervention</td>
<td>-0.028</td>
<td>-0.148</td>
<td>0.234</td>
<td>-0.108</td>
<td>-0.242</td>
<td>-0.192</td>
</tr>
<tr>
<td>MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preintervention</td>
<td>-0.397*</td>
<td>-0.186</td>
<td>-0.132</td>
<td>-0.264</td>
<td>0.279</td>
<td>-0.469**</td>
</tr>
<tr>
<td>1 mo</td>
<td>-0.366*</td>
<td>-0.212</td>
<td>-0.083</td>
<td>-0.296</td>
<td>0.347</td>
<td>-0.474**</td>
</tr>
<tr>
<td>End of intervention</td>
<td>-0.368*</td>
<td>-0.179</td>
<td>-0.049</td>
<td>-0.273</td>
<td>0.314</td>
<td>-0.486**</td>
</tr>
</tbody>
</table>

JOA, Japanese Orthopaedic Association; K-L, Kellgren-Lawrence grading system; GDS, Geriatric Depression Scale; FAI, Frenchay Activities Index; FES, Fall Efficacy Scale; PCS, physical component summary; MCS: mental component summary.

Spearman rank correlation coefficient, *p<0.05 and **p<0.01.

Table 3. Multiple linear regression analysis of the time from PCS and MCS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized B</th>
<th>SE</th>
<th>Standardized β</th>
<th>p-value</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.122</td>
<td>0.149</td>
<td>0.170</td>
<td>0.422</td>
<td>-0.187</td>
<td>0.431</td>
</tr>
<tr>
<td>Sex</td>
<td>-5.761</td>
<td>2.003</td>
<td>-0.531</td>
<td>0.009</td>
<td>-9.915</td>
<td>-1.608</td>
</tr>
<tr>
<td>FES</td>
<td>-0.882</td>
<td>0.873</td>
<td>-0.184</td>
<td>0.323</td>
<td>-2.692</td>
<td>0.928</td>
</tr>
<tr>
<td>FAI</td>
<td>-0.200</td>
<td>0.139</td>
<td>-0.259</td>
<td>0.165</td>
<td>-0.489</td>
<td>0.089</td>
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<tr>
<td>GDS</td>
<td>-0.182</td>
<td>0.345</td>
<td>-0.104</td>
<td>0.602</td>
<td>-0.197</td>
<td>0.532</td>
</tr>
<tr>
<td>MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.156</td>
<td>0.188</td>
<td>-0.175</td>
<td>0.418</td>
<td>-0.546</td>
<td>0.235</td>
</tr>
<tr>
<td>Sex</td>
<td>-2.226</td>
<td>2.529</td>
<td>-0.166</td>
<td>0.388</td>
<td>-7.471</td>
<td>3.019</td>
</tr>
<tr>
<td>FES</td>
<td>-2.303</td>
<td>1.995</td>
<td>-0.389</td>
<td>0.046</td>
<td>-4.563</td>
<td>-0.043</td>
</tr>
<tr>
<td>FAI</td>
<td>0.168</td>
<td>0.172</td>
<td>0.176</td>
<td>0.340</td>
<td>-0.188</td>
<td>0.524</td>
</tr>
<tr>
<td>GDS</td>
<td>-0.287</td>
<td>0.401</td>
<td>-0.132</td>
<td>0.482</td>
<td>-1.114</td>
<td>0.541</td>
</tr>
</tbody>
</table>

SE, standard error; 95% CI, 95% confidence interval; PCS, physical component summary; MCS: mental component summary; FES, Fall Efficacy Scale; FAI, Frenchay Activities Index; GDS, Geriatric Depression Scale.
tional guidance and functional training to reduce fear of falling were considered necessary to improve MCS score.

For fear of falling and HRQOL, Stanghelle et al. [21] examined whether balance training in vertebral fractures affects fear of falling and HRQOL. Balance training reduced the fear of falling and showed improvements in muscle strength and balance ability. However, they noted that balance training did not improve HRQOL. We have verified and reported the transition of HRQOL in osteoarthritis of the knee by rehabilitation intervention [5]. As with the results of Stanghelle et al. [21] there was no improvement in HRQOL with the exercise intervention, but there was a significant improvement in fear of falling.

In this study, we investigated the effects of a rehabilitation intervention incorporating patient education on HRQOL, psychological factors and motor function in patients with knee osteoarthritis. As a result, improvements in PCS score were observed in osteoarthritis of the knee by the patient education program. The patient program we implemented introduced the behavior change program proposed by Sedlak et al. [10]. As to reasons for the lack of improvement in MCS score, it is possible that the behavior change program proposed by Sedlak et al. [10] consisted of I. motivate, II. persuade verbally, and III. elicit physiologically and emotionally, which had an improving effect on the physical approach but not enough intervention on the psychological approach. It is necessary to strengthen the approach to mental health, role emotional and social functioning which are the items of MCS score.

Fear of falling was also identified as an influencing factor of HRQOL in the multivariate analysis. The reason for this was thought to be that when the fear of falling is high, the mental health may be affected by the decreased opportunity to go out and the decreased social function caused by the fear of falling. It is possible that rehabilitation approaches that reduce the fear of falling, such as strengthening gait stability, trunk balance, and lower limb muscle strength, may be effective in improving HRQOL. Regarding the relationship between fear of falling and HRQOL, Taglietti et al. [22] also reported on the association between knee osteoarthritis and fear of falling, stating that sensory instability is related to fear of falling in knee osteoarthritis. In order to improve the fear of falling in knee osteoarthritis, it is necessary to enhance trunk stability. Simsek et al. [23] also reported that fear of falling is higher among older females over 80, especially if they live alone. In order to reduce the fear of falling in the elderly, not only an exercise therapy approach, but also the enhancement of social support and support for the elderly living alone would lead to a decrease in the fear of falling and further improve HRQOL.

In our study, we introduced risk guidance for knee pain and an approach to anxiety, self-directed training guidance, and a patient education program for osteoarthritis of the knee, and examined the effects of improving HRQOL. They found improvement in PCS score, but not in MCS score. No research has examined the transition of HRQOL due to the introduction of a patient education program in patients with knee osteoarthritis, and it is necessary to improve and verify the education program considering the MCS score items of mental health, role emotional and social functioning. In addition, considering the social background, it is expected that in elderly people living alone, not only the approach of an exercise therapy but also the support for the enhancement of social support will reduce the fear of falling and lead to the improvement of HRQOL.

Furthermore, multivariate analysis extracted sex as an influential factor in PCS score. This may be because osteoarthritis of the knee is reported to be more likely to be severe in postmenopausal females [24], and as a result, sex may have been extracted as an influential factor in PCS score.

One of the limitations of this study is that, first, because of the exploratory study, we were able to verify changes and transitions over time in the same subjects through the intervention of the patient education program, but the validation of the effectiveness of the validation patient education program was insufficient. Since this study is a single arm design study, it is considered to be a limitation that it cannot be compared with a control group. It is considered that the verification g compared with the control group is necessary in future. Second, there was insufficient verification of the relationship between the patients' backgrounds, such as the presence or absence of mental illness,
the presence or absence of a history of psychiatric visits, and the use of psychotropic drugs. It is necessary to examine the influence of psychiatric disorders on knee osteoarthritis in the future.

As a result of patient education that included motivate, persuade verbally, elicit physiologically and emotionally as a behavior change program, PCS score of HRQOL items improved, but MCS score did not. In the following, it is necessary to verify patient education programs focusing on mental health, role emotional and social functioning as a treatment approach to improve HRQOL of knee osteoarthritis. The results also indicate that an educational approach to fear of falling may improve anxiety and that functional training may be effective in improving HRQOL in knee osteoarthritis.

CONFLICTS OF INTEREST

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

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None.

AUTHOR CONTRIBUTION


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Predictors for Failed Removal of Nasogastric Tube in Patients With Brain Insult

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Objective: To construct a prognostic model for unsuccessful removal of nasogastric tube (NGT) was the aim of our study.

Methods: This study examined patients with swallowing disorders receiving NGT feeding due to stroke or traumatic brain injury in a regional hospital. Clinical data was collected, such as age, sex, body mass index (BMI), level of activities of daily living (ADLs) dependence. Additionally, gather information regarding the enhancement in Functional Oral Intake Scale (FOIS) levels and the increase in food types according to the International Dysphagia Diet Standardization Initiative (IDDSI) after one month of swallowing training. A stepwise logistic regression analysis model was employed to predict NGT removal failure using these parameters.

Results: Out of 203 patients, 53 patients (26.1%) had experienced a failed removal of NGT after six months of follow-up. The strongest predictors for failed removal were age over 60 years, underweight BMI, total dependence in ADLs, and ischemic stroke. The admission prediction model categorized patients into high, moderate, and low-risk groups for removal failure. The failure rate of NGT removal was high not only in the high-risk group but also in the moderate-risk groups when there was no improvement in FOIS levels and IDDSI food types.

Conclusion: Our predictive model categorizes patients with brain insults into risk groups for swallowing disorders, enabling advanced interventions such as percutaneous endoscopic gastrostomy for high-risk patients struggling with NGT removal, while follow-up assessments using FOIS and IDDSI aid in guiding rehabilitation decisions for those at moderate risk.

Keywords: Deglutition disorders, Gastrointestinal intubation, Stroke, Traumatic brain injury

INTRODUCTION

Dysphagia is a common complication following stroke and traumatic brain injury (TBI), with reported incidence rates ranging from 27% to 80% [1,2]. Patients with these conditions often require nasogastric tube (NGT) feeding to maintain nutritional supply in acute stage and are frequently encountered in rehabilitation settings. Dysphagia can lead to malnutrition, aspiration pneumonia, prolong hospitalization, and increase the risk of morbidity and mortality [3,4]. NGT feeding may suffice for patients requiring nutritional support for up to 4 weeks [5]. Extended utilization of an NGT can lead to various adverse events,
such as nasal wing lesions, chronic sinusitis, gastroesophageal reflux, gastrointestinal bleeding, and aspiration pneumonia [6-8]. Therefore, for extended periods, the placement of a gastrostomy tube should be taken into consideration to avoid the side effects of long-term usage of NGT for nutrition supply [5].

Bedside swallowing assessments can quickly detect dysphagia, but predicting its recovery is challenging. Early identification of dysphagia recovery prognosis would enable prompt administration of appropriate therapies and consideration of suitable feeding methods such as NGT or gastrostomy tube. Preexisting studies have found that patients with high National Institutes of Health Stroke Scale (NIHSS) scores, aspiration during swallowing assessments, advanced age, dysarthria, and intubation are at a higher risk of experiencing prolonged dysphagia lasting for more than 6 weeks [9-11]. However, no work has mentioned the exact percentage of failure of complete oral feeding through the above mentioned parameters. As a result, our work attempts to develop a model capable of predicting the unsuccessful removal of NGT in dysphagia patients who have experienced a stroke or TBI. Additionally, the model may provide the information for the early intervention of gastrostomy tube.

METHODS

From January 2020 to December 2022, we retrospectively analyzed clinical data of patients admitted to the rehabilitation department in a regional hospital, who experienced stroke or TBI with dysphagia and requiring NGT feeding. A total of 203 patients, comprising 133 males and 70 females, were enrolled in the study, and their NGT removal failure rates were tracked over a six-month period. Baseline demographic characteristic of age, sex, admission diagnosis (ischemic stroke, hemorrhagic stroke, or TBI), initial Glasgow Coma Scale (GCS), body mass index (BMI), Functional Independence Measure (FIM) score, level of activities of daily living (ADLs) dependence were recorded. We define a patient as ADLs total dependent when they are completely unable to perform four aspects: personal hygiene, heavy hygiene (toilet and bathing), eating, and dressing. If the criteria mentioned above are not met, the patient is referred to as ADLs partial dependent. Clinical variables were correlated after one month of swallowing training, including the improvement in Functional Oral Intake Scale (FOIS) levels and variation in the numbers of food type according to International Dysphagia Diet Standardization Initiative (IDDSI). The swallowing training consists of direct method such as modifying food texture, utilizing chin tuck and head turn/tilt compensatory techniques, and indirect method such as applying thermal tactile stimulation, practicing pharyngeal wall contraction exercises (Masako maneuver) and practicing effortful swallowing, according to the evaluation of swallowing condition of the patients. We utilized both videofluoroscopic swallowing study, fiberoptic endoscopic evaluation of swallowing, or bedside clinical swallow assessment by physicians to evaluate patients’ swallowing function. Simultaneously, we integrate the assessment conducted by the speech-language therapist to determine the optimal timing for NGT removal.

This study received approval from the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approval number: IRB112-206-B). Due to its retrospective nature, the requirement for informed consent was waived.

SAS Software version 9.4 (SAS Institute) was used for statistical analysis. Exclude patients with missing data and conduct individual subgroup analyses on the available data, resulting in variations in the total number of patients for different variables. The categorical variables were demonstrated as counts and percentages. The continuous variables were presented. Comparisons of these clinical data between each group were made by using the chi-square test for categorical variables and the two sample t-test for continuous variables. A stepwise logistic regression analysis was used to develop a model for predicting failure of NGT removal. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 203 patients were included in the study, of which 150 (73.9%) had their NGT successfully removed, while 53 (26.1%) experienced removal failure after six months of follow-up. Table 1 provides an overview of the subjects’ demographic and clinical variables. Univariate analysis demonstrates a significant correlation between age, admission diagnosis, BMI, FIM score, and ADLs dependence and the failure of NGT removal. The age stratification involves incorporating patients’ age groups into the logistic regression analysis to obtain odds ratios (ORs), and both the age groups of 60–70 and over 70 were found to be significant variables. Using a stepwise regression analysis, we examined the effect of these significant variables. Age between 60–70 years (OR, 3.44; p<0.05), age over 70 years (OR, 6.16; p<0.05), underweight BMI (OR, 5.09; p<0.05), total depen-

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dence in ADLs (OR, 9.90; p<0.05), and ischemic stroke (OR, 4.10; p<0.05) were found to be the strongest predictors for failed removal (Table 2). According to the OR values of significant variables, directly rounding to the nearest integer to convert to weight scores, for example: the OR for low BMI was 5.09, then its weight score would be 5. Using the weight scores derived from the predictive model for tube removal failure, the total weight score for tube removal failure in patients is calculated. Analysis of the OR distribution derived from spline regression reveals three distinct risk trends within the graphic representation (Fig. 1). Further categorization stratifies risk into groups scoring 0–6, 7–16, and 17 points or more. Following these groupings, logistic regression is utilized to estimate the ORs prior to the adjustment of other variables (Table 3). The failure rates of NGT removal were 5.1% in the low-risk group, 21.5% in the moderate-risk group, and 73.0% in the high-risk group (Table 3).

After swallowing training in high-risk and low-risk populations, the degree of improvement in FOIS and IDDSI does not impact the risk of failure in NGT removal as much as it does in the moderate-risk population. Therefore, we primarily focused on the moderate-risk population for further analysis. As shown in Table 4, for patients who did not show improvement in FOIS levels after training, the failure rate of NGT removal was 81.2% six months later. For those who improved by one FOIS level, the failure rate was 50.0%, while for those who improved by two FOIS levels, the failure rate was 37.5%. For patients whose IDDSI food types did not change after training, the failure rate

Table 1. Baseline clinical variables of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Nasogastric tube weaning</th>
<th>p-value</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% or mean±SD</td>
<td>n</td>
<td>% or mean±SD</td>
<td>n</td>
<td>% or mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>203</td>
<td>64.7±15.5</td>
<td>150</td>
<td>61.8±15.4</td>
<td>53</td>
<td>73.2±12.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>70</td>
<td>34.5</td>
<td>50</td>
<td>33.3</td>
<td>20</td>
<td>37.7</td>
<td>0.5622</td>
</tr>
<tr>
<td>Male</td>
<td>133</td>
<td>65.5</td>
<td>100</td>
<td>66.7</td>
<td>33</td>
<td>62.3</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>198</td>
<td>23.9±8.0</td>
<td>148</td>
<td>24.4±8.7</td>
<td>50</td>
<td>22.4±5.4</td>
<td>0.1344</td>
</tr>
<tr>
<td>BMI level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (18.5≤BMI≤24.0 kg/m²)</td>
<td>92</td>
<td>45.3</td>
<td>67</td>
<td>44.7</td>
<td>25</td>
<td>47.2</td>
<td>0.0124*</td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>25</td>
<td>12.3</td>
<td>13</td>
<td>8.7</td>
<td>12</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Overweight (&gt;24.0 kg/m²)</td>
<td>86</td>
<td>42.4</td>
<td>70</td>
<td>46.7</td>
<td>16</td>
<td>30.2</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>76</td>
<td>37.4</td>
<td>63</td>
<td>42.0</td>
<td>13</td>
<td>24.5</td>
<td>0.0016*</td>
</tr>
<tr>
<td>TBI</td>
<td>43</td>
<td>21.2</td>
<td>36</td>
<td>24.0</td>
<td>7</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>84</td>
<td>41.4</td>
<td>51</td>
<td>34.0</td>
<td>33</td>
<td>62.3</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>191</td>
<td>10.4±3.9</td>
<td>139</td>
<td>10.6±3.8</td>
<td>52</td>
<td>9.7±4.0</td>
<td>0.1665</td>
</tr>
<tr>
<td>ADLs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial dependent</td>
<td>100</td>
<td>49.3</td>
<td>89</td>
<td>59.3</td>
<td>11</td>
<td>20.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Totally dependent</td>
<td>103</td>
<td>50.7</td>
<td>61</td>
<td>40.7</td>
<td>42</td>
<td>79.2</td>
<td></td>
</tr>
</tbody>
</table>

| BMI, body mass index; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ADLs, activities of daily living. |
| Significant difference among groups (p<0.05). |

Table 2. Stepwise logistic regression analysis for predicting nasogastric tube removal failure model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Wald CI</th>
<th>p-value</th>
<th>Assigned weight points</th>
</tr>
</thead>
<tbody>
<tr>
<td>60≤Age&lt;70 yr</td>
<td>3.44</td>
<td>1.09–10.86</td>
<td>0.0352*</td>
<td>3</td>
</tr>
<tr>
<td>70 yr≤Age</td>
<td>6.16</td>
<td>2.10–18.08</td>
<td>0.0009*</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.10</td>
<td>1.69–9.95</td>
<td>0.0018*</td>
<td>4</td>
</tr>
<tr>
<td>BMI underweighted (&lt;18.5 kg/m²)</td>
<td>5.09</td>
<td>1.57–16.46</td>
<td>0.0066*</td>
<td>5</td>
</tr>
<tr>
<td>ADLs totally dependent</td>
<td>9.90</td>
<td>4.04–24.27</td>
<td>&lt;0.0001*</td>
<td>10</td>
</tr>
</tbody>
</table>

CI, confidence interval; BMI, body mass index; ADLs, activities of daily living. |
Significant difference among groups (p<0.05). |
of tube removal was 85.7%. However, for those who improved by one type of food, the failure rate was 10.0%, and for those who improved by two types of food, the failure rate was 21.4%.

In the moderate-risk group, improvements in FOIS levels and an increase in IDDSI food types after one month of swallowing training may be used to predict the likelihood of NGT removal failure after six months of follow-up observation. We amplified our model sample using bootstrapping by 1,000 times for internal validation and obtained the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve is 0.829. The sensitivity and specificity were 75.5% and 23.3%, respectively. In the Fig. 2, the blue line represents our model, while the dashed line represents the results obtained through bootstrapping. The Fig. 2 shows that the two lines almost overlap (DeLong test p-value=0.9831).

**DISCUSSION**

In this work, we identified several strong predictors for failed remove of NGT after six months of follow-up, including age between 60–70 years, age over 70 years, underweight BMI, total dependence in ADLs, and ischemic stroke. We also utilized the weighted scores of the ORs to create a formula to forecast the risk of NGT removal failure and found the risk score greater than 17 have 73.0% of failure of removing NGT.

For patients requiring nutritional support for up to 30 days, NGT feeding alone may be sufficient, but for longer durations, consideration should be given to percutaneous endoscopic gastrostomy (PEG) tube placement [5]. Compared to NGT, PEG offers several advantages, including a lower risk of intervention failure, fewer incidences of pneumonia among PEG recipients, improved quality of life, and higher levels of albumin [8]. Currently, PEG has become a recognized treatment option for temporary or permanent dysphagia resulting from neurological
disorders and oncological conditions [12]. Implementing continuous enteral nutrition at an earlier stage holds the potential to significantly enhance prognosis [12].

Additionally, with early gastrostomy placement, the prevalence of low albumin levels and higher comorbidity, both of which are risk factors for worse outcomes, would be reduced in patients chosen for this intervention [12]. Nevertheless, the benefits of PEG feeding remain uncertain in patient with advanced dementia, and elderly patients over 80 years old [5].

With this result, we propose the following recommendations for dysphagia patients with brain insult who require tube feeding for nutrition support: those identified as high risk based on the research results could early decide whether to undergo or not. Patients with moderate risk should evaluate improvements in FOIS and IDDSI scores after the first month of swallowing training. If there is no improvement observed, these patients may benefit from early decision of further management, considering the high failure rates of 81.2% and 85.7% for the FOIS and IDDSI non-improvement groups, respectively, as indicated in Table 4. Additionally, when suggesting PEG placement, it is advisable to take into account factors such as the presence of advanced dementia and whether the patient is over the age of 80, as per our model’s recommendations.

In our study, we observed that 26.1% of the patients failure of removing the NGT after six months follow up. This finding aligns with previous research, which reported failure rates ranging from 26% to 69% [13-15]. In spite of antecedent studies investigating the correlation between various risk factors and NGT removal in stroke patients [16,17], our study provides processional data for predicting the risk of failure of removing. Moreover, preceding research has highlighted that swallowing difficulties resulting from TBI are comparable to those observed in stroke patients [1]. Therefore, we can do early decision of alternative management of NGT feeding for the patients with dysphagia such as insertion of gastrostomy, specifically focused on patients with stroke or TBI.

The parameters in our study consistent with preexisting research findings are age, sex, initial GCS and ADLs dependence. Former research has shown that older patients and those with lower FIM scores have a reduced likelihood of NGT removal [14,15]. A lower FIM score indicates that subject has a higher degree of dependency in their daily activities. In our investigation, we also noticed significant differences in age and ADLs dependence between the nonweaned group and the weaned group. The non-weaned group comprised individuals who are older and a larger number of individuals who are completely dependent on ADLs.

Previous studies demonstrated methodological variations and reported inconsistent associations between sex and oral intake recovery [3,16,18]. Certain studies [16,18] excluded sex as a variable in their multivariable analyses due to the absence of significant differences in bivariate analysis. One study indicated that female sex was associated with better outcomes [19]. In our study, there was no significant difference in sex between the NGT-weaned group and the NGT non-weaned group. Further research is needed to explore its impact on the recovery of swallowing disorders.

In individuals with TBI, a low initial GCS consistently indicated compromised oral intake [20]. Additionally, Morgan et al. [21] noted that low GCS scores were predictive of dysphagia in pediatric TBI patients. Another study found that among stroke patients, the deterioration in verbal response, assessed using the GCS, demonstrated a notably stronger association with swallowing recovery failure [22]. However, the statistical significance of the GCS variable in the present study may be influenced by the sample size. Numerous studies [9,10,11,23] in this domain have demonstrated a link between NIHSS scores and unfavorable recovery outcomes. One study found that higher NIHSS scores were associated with delayed removal times of NGT [14]. Nonetheless, while the NIHSS is mainly employed for prognostic assessment in post-stroke patients, the GCS has broader applications, encompassing prognostic evaluation in brain injury patients and even the assessment of recovery in swallowing disorders, in addition to its use with stroke patients.

A study proposed in 2021 that there is no correlation between body weight and NGT removal [17], which differs from our research findings. Our study highlighted the significant impact of being underweight on the failure of NGT removal. A BMI below 20 is widely acknowledged as an indicator of malnutrition, and a low BMI is correlated with a higher probability of probable sarcopenia [24,25]. Previous studies have also indicated a link between malnutrition and dysphagia [26], and there is evidence of a relationship between sarcopenia and decreased swallowing function, particularly among older adults in Japan [27]. This finding may infered that malnutrition and sarcopenia may be risk factors for the poor recovery of swallowing function in individuals who have experienced a stroke or brain injury. The decline in overall muscle mass and strength that accompanies being underweight may contribute to the weakening of the muscles involved in the swallowing process [28].
weakened musculature could explain the increased likelihood of NGT removal failure observed in underweight individuals in our study. Furthermore, a separate study demonstrated that stroke survivors with lower BMI values, particularly those in the lowest quartiles, exhibited more severe stroke symptoms and experienced poorer functional recovery compared to individuals with higher BMI values [29]. These studies further support the association between underweight and greater severity of stroke, poorer functional recovery, and even swallowing function.

There are limited study mentioning the correlation between stroke types and the failure rate of NGT removal [17,30], and only one study identified intracerebral hemorrhage as a predictive factor for NGT removal [31]. Our study revealed a significant association between ischemic stroke and the failure rate of tube removal. Furthermore, another study published in Stroke provided additional insights by demonstrating that patients with cerebral infarction had poorer functional and neurological recovery compared to those with hemorrhagic stroke [32]. The relationship between stroke type and removal of NGT needs further study.

A retrospective study revealed that for each increase of one FOIS level, there was a 3.7-fold higher likelihood of tube removal [33]. Consistently, our study yielded similar results, indicating that the extent of FOIS level improvement after one month of swallowing training could predict the likelihood of NGT removal failure six months later. Patients who exhibited no change in FOIS levels following the initial month of swallowing training after experiencing a brain insult had the highest rate of tube removal failure, whereas those who demonstrated greater improvements had lower failure rates. Additionally, another study found that higher FOIS levels were correlated with a higher probability of returning to complete oral intake post-stroke [34]. Furthermore, our study identified that the greater improvement in the ability to consume various food items (according to IDDSI) after one month of swallowing training, the lower the likelihood of NGT removal failure six months after the brain insult. Although one study mentioned that FOIS at admission could predict the time to return to unrestricted oral intake [35], no previous study has evaluated the probability of NGT removal failure six months after brain insult using changes in FOIS and IDDSI following one month of swallowing training, which is a relatively unique feature of our predictive model.

Using our predictive model, patients with brain insults can be initially categorized into risk groups for swallowing disorders. Subsequently, advanced swallowing interventions can be implemented for high-risk patients who encounter difficulties in NGT removal. These interventions may include the combined use of repetitive transcranial magnetic stimulation or Vitalstim, long-term education on NGT care, or alternative options for enteral feeding. For individuals at moderate risk, a progress assessment of NGT removal rate using FOIS and IDDSI can be conducted one month later. If there is no improvement, rehabilitation training similar to that for high-risk cases should be followed, while others can undergo regular swallowing rehabilitation training.

One study utilized FIM-motor, FIM-cognition, days after onset, and age to construct the equation [15]; the other utilized the Barthel index at admission, lip-closing status, ability to answer simple questions, and functional independence before stroke to construct the equation [17]. In contrast, ours utilizes patient age, stroke history, BMI, and total dependence in ADLs to form a risk prediction model, and provides early intervention recommendations. Our risk factors are relatively simple and applicable for predicting NGT removal in both stroke and TBI patients.

There are certain limitations in our study that need to be taken into account when interpreting these findings. Firstly, it is important to note that this study is retrospective in nature, which means we are unable to control for participant consistency. Secondly, due to the retrospective nature of this research, there may be instances of missing and incomplete clinical data. Thirdly, we faced the challenge of not being able to control the intervention methods applied to participants. Not all individuals in the study received the same swallowing training, leading to variations in the methods used. Fourthly, we did not actually have the patients undergo nutritional assessments or tests for sarcopenia. These constraints highlight the need for future research with more controlled settings and comprehensive data collection to further validate and refine our findings.

In conclusion, our study identified factors predicting NGT removal failure, including older age, underweight, complete ADLs dependence, and ischemic stroke. We also created a predictive model to assess this risk, aiding healthcare professionals in identifying high-risk patients and providing suitable interventions and training.

CONFLICTS OF INTEREST

Fuk Tan Tang is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript.
Otherwise, no potential conflict of interest relevant to this article was reported.

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**AUTHOR CONTRIBUTION**

Conceptualization: Huang ST, Yeh SM, Wang TG, Tang FT, Hsieh YT, Ho CS. Methodology: Huang ST. Formal analysis: Huang ST, Yeh SM, Chen WM, Jao AT. Funding acquisition: Yeh SM. Project administration: Peng MC. Visualization: Huang ST, Yeh SM. Writing – original draft: Huang ST, Yeh SM. Writing – review and editing: Wang TG, Yeh SM. Approval of final manuscript: all authors.

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**REFERENCES**

Instructions for authors

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Revised on March 11, 2019

1. AIMS & SCOPE

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The journal encompasses all aspects of physical medicine and rehabilitation, including clinical practice, experimental and applied research, and education. Research areas covered by this journal include rehabilitation of brain disorders and spinal cord injury; electrodiagnosis; musculoskeletal disorders and pain; pediatric, geriatric, cardiopulmonary, sports, cancer, cognitive, and robotic rehabilitation; neuromodulation; neuroimaging; orthotics and prosthetics; physical modalities; clinical trials; quality of life issues; and basic research, as well as other emerging fields in rehabilitation medicine.

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This form of publication represents original research articles reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers.

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The Editorial Board welcomes state-of-the-art review articles. The *ARM* strongly prefers systematic reviews of the literature. Invited review articles provide a comprehensive review of a subject of importance to clinicians and researchers and are commissioned by the editorial board to an invited expert in the field.

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All manuscripts must be written in clearly understandable English. Authors whose first language is not English are requested to have their manuscripts checked for grammatical and linguistic correctness before submission. Correct medical terminology should be used, and jargon should be avoided. Use of abbreviations should be minimized and restricted to those that are generally recognized. When using an abbreviated word, it should be spelled out in full on first usage in the manuscript followed by the abbreviation in parentheses. Numbers should be written in Arabic numerals, but must be spelled out when placed in the beginning of a sentence. Measurements should be reported using the metric system, and hematologic and biochemical markers should be reported in International System (SI) of Units. All units must be preceded by one space except percentage (%), temperature (°C), and degree (°).

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All manuscripts should be written with strict adherence to the research and publication ethics guidelines recommended by Council of Science Editors (http://www.councilscienceeditors.org/), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/), World Association of Medical Editors (WAME, http://www.wame.org/), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). For all studies involving human subjects, the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) should be upheld, informed consent must be obtained from all participants, and must be approved by a recognized Institutional Review Board (IRB) or research ethics committee. The editor may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. Experiments involving animals should comply with the NIH guidelines for the use of laboratory animals (https://www.nlm.nih.gov/services/research_report_guide.html) and/or be reviewed by an appropriate committee (e.g., Institutional Animal Care and Use Committee, IACUC) to ensure the ethical treatment of animals in research. Also, studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (e.g., Institutional Biosafety Committee, IBC). ARM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org/) for settlement of any misconduct.

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(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).

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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.

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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.

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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).

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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.
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☐ 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.
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