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BMJ Open

Effect of robotic-assisted gait training on gait and motor function in spinal cord injury: a protocol of a systematic review with meta-analysis

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Keywords:	REHABILITATION MEDICINE, NEUROSURGERY, Neurological injury < NEUROLOGY

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**Effect of robotic-assisted gait training on gait and motor function in spinal cord
injury: a protocol of a systematic review with meta-analysis**

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Effect of robotic-assisted gait training on gait and motor function in spinal cord injury: a protocol of a systematic review with meta-analysis

Abstract :

Introduction: Robotic-assisted gait training (RAGT) has been reported to be effective in the rehabilitation of patients with spinal cord injury (SCI). However, studies on RAGT showed different results because they varied in terms of the number of samples. Thus, summarizing studies based on robotic-related factors is critical for the accurate estimation of the effects of RAGT on SCI. This work aims to search for strong evidence showing that using RAGT is effective in the treatment of SCI and to analyze the deficiencies of current studies.

Methods and analysis: The following publication databases were electronically searched in December 2022 without restrictions on publication year: Medline, Cochrane Library, Web of Science, Embase, PubMed, and China National Knowledge Infrastructure. All articles on randomized controlled trials using RAGT to treat SCI that were published in English and Chinese and met the following criteria will be included. Outcomes included motor function, and gait parameters included those assessed by using instrumented gait assessment, the Berg balance scale, the 10 m walking speed test, the 6 min walking endurance test, the functional ambulation category scale, the Walking index of SCI, and the ASIA assessment scale. Research selection, data extraction, and quality assessment will be conducted independently by two reviewers to ensure that all relevant studies are free from personal bias. The Cochrane Bias Risk Assessment Tool will be used to assess the risk of bias. Review Manager V.5.3 software will be utilized to produce deviation risk maps and perform paired meta-analyses.

Strengths and limitations of this study

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2
3
4 1. This study will be the first meta-analysis to systematically evaluate the efficacy and safety of
5
6 RAGT in the treatment of SCI.

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9 2. The results of this study will provide evidence for the treatment of SCI patients, and help therapists
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11 and patients to choose appropriate treatment methods.

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22
23
24 **Key words:** Spinal Cord Injuries; Motor disorders; Rehabilitation; Robotics, Gait Analysis

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27 **Ethics and dissemination:** Ethics approval is not required for systematic reviews and network
28
29 meta-analyses. The results will be submitted to a peer-reviewed journal or presented at a conference.

30
31
32 **Trial registration number:** PROSPERO (CRD42022319555).

33 34 35 **Introduction**

36
37 Spinal cord injury (SCI) is a serious disabling disease that often causes paraplegia or quadriplegia
38
39 and affects the patient's sensory, motor, and autonomic nervous functions^[1]. SCI leads to a variety
40
41 of complications, such as pressure ulcers, lung infections, and urinary tract infections^[2]. Moreover,
42
43 it affects the quality of life and living standard of patients and imposes a heavy burden on families^[3]
44
45 and society. It ultimately shortens the life expectancy of patients^[4]. National statistical data show
46
47 that the incidence rate of SCI is increasing annually and that the incidence rate of TSCI per million
48
49 residents is 9.3 persons/year^[5]. During the rehabilitation treatment of SCI, improving the walking
50
51 ability, self-care ability, and self-esteem of patients is an important aspect that helps patients return
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53 to society and reduces their costs. Therefore, the rehabilitation of the lower limbs, which mainly
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4 function in standing and walking, is crucial.
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6 Robot-assisted gait training (RAGT) can improve the walking ability^[6], lower limb strength, and
7
8 independence of patients with incomplete SCI^[7]. It can also improve balance function^[8]. RAGT has
9
10 been gradually applied in patients with SCI. Some clinical evidence shows that in patients with SCI,
11
12 robots for lower limb rehabilitation can effectively and safely improve walking ability; reduce
13
14 pressure ulcers, lung infections, urinary tract infections, and other complications; improve dignity;
15
16 and reduce costs. However, high-quality evidence-based medical studies that systematically
17
18 evaluated the efficacy of RAGT in the treatment of SCI remain scarce.
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24 Summarizing studies based on RAGT-related factors is critical for the accurate estimation of the
25
26 effects of RAGT on SCI. This meta-analysis aims to evaluate systematically the efficacy of RAGT
27
28 in alleviating motor dysfunction and restoring speech ability in patients with SCI according to
29
30 randomized clinical trials (RCTs); find strong evidence demonstrating that using RAGT is effective
31
32 in the treatment of SCI; and analyze the deficiencies of current studies.
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37 **Methods**

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39 The protocol of this systematic review was planned and conducted in accordance with the Preferred
40
41 Reporting Items for Systematic Reviews and Meta-Analyses Protocols Guideline and Cochrane
42
43 Collaboration^[9]. The review process is shown in **Figure**
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48 **Search strategy**

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50 Two reviewers (Jin-lin Peng and Lei Wang) electronically searched the following publication
51
52 databases in December 2022 without restrictions on publication year: Medline, Cochrane Library,
53
54 Web of Science, Embase, PubMed, and China National Knowledge Infrastructure. Various
55
56 combinations of keywords, including “motor disorders,” “robotics”, “robotic assisted gait training,”
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4 “noninvasive brain stimulation,” “SCI”, and “gait analysis”, were used as search terms. The key
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6 terms matched the appropriate Medical Subject Headings terms. Presearches were performed. Then,
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8 the final search was conducted follows: Relevant journals and references of review articles were
9
10 manually searched online to identify papers that may have been missed in the electronic database
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12 searches.
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16 **Eligibility criteria**

17 **Inclusion criteria**

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20 (1) Study design: Only RCTs were included. (2) Selected population: Participants diagnosed with
21
22 SCI, namely, individuals with any level of traumatic SCI, regardless of the time since injury, sex,
23
24 and age, were included. (3) Type of intervention: The experimental groups received tDCS or tDCS
25
26 combined with other physical therapies. The control group received sham tDCS or other types of
27
28 physical therapy. (4) Comparison: The treated subjects were compared at baseline then with the
29
30 control or sham-stimulated subjects. (5) Type of outcomes measured: Gait analysis indicators,
31
32 including gait speed (m/s), step length (cm), double support phase (% walking cycle), single support
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34 phase (% walking cycle), and symmetry index; Berg balance scale; ASIA assessment scale; Holden
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36 walking ability classification (functional ambulation category scale); 10 m walking speed test; 6
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38 min walking endurance test; and WISCI II score.
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48 **Exclusion criteria**

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50 Studies involving animal research, conference research, protocol studies, or computer model
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52 research and duplicate papers were excluded. Two reviewers (Jin-lin Peng and Lei Wang)
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54 independently screened titles and abstracts to identify articles reporting studies that met the
55
56 inclusion criteria. Then, the full-text versions of the identified articles were obtained and separately
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4 screened to ensure that they met the inclusion criteria. A third reviewer (Ai-lian Chen) made the
5
6 final assessment regarding whether or not full-text papers met the inclusion criteria.
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9 **Data extraction**

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11 A reviewer (Lei Wang) prepared the general information and data collection process by another
12
13 reviewer (Jin-lin Peng). The format of data collection included the following factors: research
14
15 design, participants (number, diagnosis, age, and target population numbers in each group),
16
17 eligibility criteria, intervention used on the research group and control group (i.e., site of stimulation,
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19 intensity, number of sessions, and time of each session), and outcomes of interest.
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24 **Quality assessment**

25
26 The quality evaluation of the included studies was performed independently by two reviewers (Jin-
27
28 lin Peng and Lei Wang) and was revised by the third reviewer (Ai-lian Chen). The methodological
29
30 quality of the intervention studies was assessed by using the Physiotherapy Evidence Database
31
32 (PEDro) scale. The PEDro scale is a valid and reliable measure of the methodological quality of
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34 RCTs. This 10-item scale is based on the core criteria for RCT quality assessment^[10]. The quality
35
36 of papers was classified as follows in accordance with the PEDro scale: Studies with scores of less
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38 than 6 points were considered low-quality studies, whereas those with scores equal to or greater
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40 than 6 points were considered high-quality studies (where scores of 6–7 indicate good quality and
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42 those of 8–10 indicate excellent quality)^[11].
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50 The GRADEpro GDT online tool was used to evaluate the level of evidence quality of the outcome
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52 indicators. The tool is available at its official website <http://www.guidelinedevelopment.org/>. The
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54 GRADEpro GDT online tool for evaluating the quality of outcome indicators includes five
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56 degrading factors: risk of bias, inconsistency, indirectness, imprecision, and other considerations.^[12]
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4 The quality of evidence can be divided into four levels of “high”, “moderate”, “low”, and “very
5
6 low.”^[13]
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9 **Risk-of-bias assessment of individual studies**

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11 The quality of the included studies was evaluated and their scores were compared in a consensus
12
13 meeting between two independent authors (Jin-lin Peng and Lei Wang) to minimize errors and
14
15 potential biases in the evaluation. In the event of any disagreement, a third author (Ai-lian Chen)
16
17 was included in the discussion for a final consensus. The Cochrane risk-of-bias assessment tool
18
19 outlined in Chapter 8 of the *Cochrane Hand-book for Systematic Reviews of Interventions* (Version
20
21 5.1.0) was used to assess the risk of bias of the articles. Each article was assessed for selection bias
22
23 (random sequence generation and allocation concealment), performance bias (blinding of
24
25 participants and personnel), detection bias (blinding of outcome assessment), attrition bias
26
27 (incomplete outcome data reporting), and reporting bias (selective outcome reporting). Each domain
28
29 was rated as high risk of bias, unclear of bias, or low risk of bias. The risk map of the biases of the
30
31 studies' quality was prepared with RevMan 5.2 software.
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40 **Patient and public Involvement**

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42 No patient participated in writing the system review plan. However, the results will be disseminated
43
44 to patients with SCI.
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48 **Statistical analysis**

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50 A meta-analysis will be conducted by using Review Manager 5.3. Heterogeneity between studies
51
52 will be evaluated on the basis of the I^2 statistic for the quantification of the proportion of the total
53
54 outcome attributable to variability among studies. The following ranges were defined: $I^2 = 0\%–30\%$
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56 (no heterogeneity), $I^2 = 30\%–49\%$ (moderate heterogeneity), $I^2 = 50\%–74\%$ (substantial
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4 heterogeneity), and $I^2 = 75\%–100\%$ (considerable heterogeneity)^[14]. On the basis of heterogeneity,
5
6 a random-effects model was used when $I^2 > 30\%$, and a fixed-effects model was utilized when $I^2 =$
7
8
9 $0\%–30\%$.

10
11 For the comparison of data from different scales, pooled statistics will be calculated by using
12
13 standardized mean differences (SMDs). Means and standard deviations after intervention and
14
15 follow-up evaluation for the RAGT and control groups (when relevant) will be applied to compute
16
17 SMDs.
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22 **Addressing missing data**

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24 The original author will be contacted for additional information regarding missing data. In the
25
26 absence of a reply, the data will be calculated on the basis of the availability factor. The potential
27
28 effect of the missing data on meta-analysis results will be tested through sensitivity analysis.
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32 **Subgroup analysis**

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34 Grouping analysis will be performed to address potential heterogeneity and inconsistencies and will
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36 be conducted in accordance with age, gender, SCI plane, disease course, treatment prescription, and
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38 treatment duration. At the same time, meta-analysis will be conducted to explore the possible
39
40 sources of heterogeneity.
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45 **Sensitivity analysis**

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47 For the verification of the robustness of the research conclusion, sensitivity analysis will be
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49 conducted on the main results to assess the effect of method quality, research quality, sample size,
50
51 missing data, and analysis methods on the results of this review^[15].
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55 **Assessment of publication bias**

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57 Each included study will be evaluated in accordance with the PEDro scale. Funnel charts will be
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4 used to assess the publication bias of the main results included in the study. If the funnel chart is
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6 found to be asymmetrical, attempts will be made to explain its asymmetry ^[16].
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9 **Discussion**

10 RAGT can improve the walking ability of patients with incomplete SCI and can be used by patients
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12 with stable vital signs. For patients with complete SCI, RAGT acts mainly to maintain the range of
13
14 motion of joints. In recent years, studies on using RAGT to improve walking ability in SCI have
15
16 increased, and the new exoskeleton robot for lower limb rehabilitation has shown the advantage of
17
18 safe transfer. Our current query shows that our work is the first systematic review and meta-analysis
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20 on RAGT for patients with SCI. The results of this meta-analysis can help patients and therapists
21
22 select the appropriate treatment method for SCI and improve new options on the basis of the
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24 comparative evidence for effectiveness and safety. We hope that the results of this study will provide
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26 evidence for guideline recommendations.
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34 **Data Availability**

35 The datasets used and analyzed in the current study are included in this article.
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37

38 **Ethical Approval**

39 This research is a review, does not involve ethical issues, and did not apply for ethical approval.
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41

42 **Funding**

43 This study has no funding support.
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45

46 **Disclosure**

47 All authors have read and approved the final manuscript.
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52 **Contributors**

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54 WL and P-JL, as the first authors, have made equal contributions to this work. Research concept
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56 and design: WL and C-AL. Data acquisition: WL and P-JL. Draft: WL and P-JL. Supervised by: C-
57
58 AL. All the authors approved the publication of the Protocol.
59
60

Conflicts of Interest

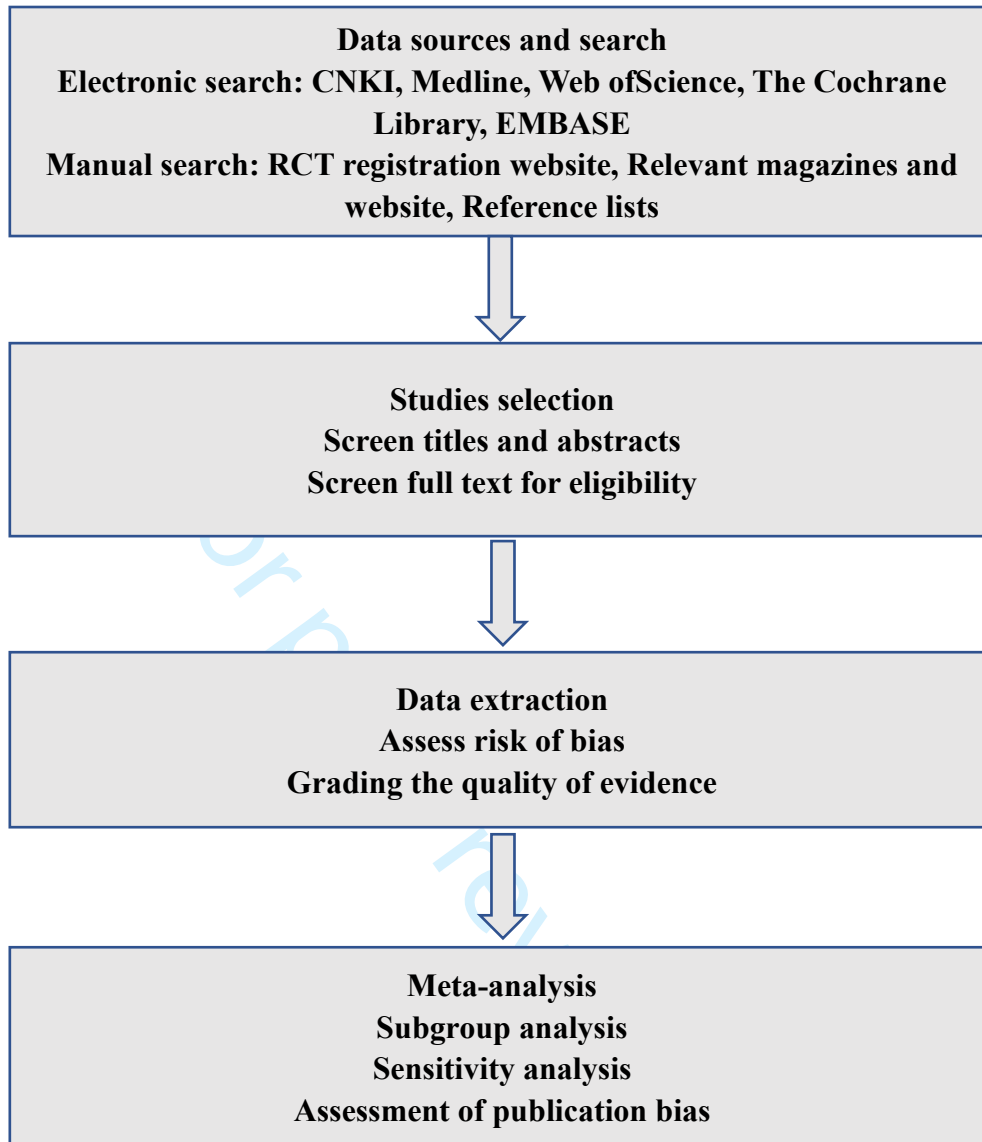
All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Reference

- [1] Eckert MJ, Martin MJ. Trauma: Spinal Cord Injury[J]. *Surg Clin North Am*, 2017,97(5):1031-1045. DOI: 10.1016/j.suc.2017.06.008.
- [2] Stricsek G, Ghobrial G, Wilson J, et al. Complications in the Management of Patients with Spine Trauma[J]. *Neurosurg Clin N Am*, 2017,28(1):147-155. DOI: 10.1016/j.nec.2016.08.007.
- [3] Zhang JM, Li N, Zhu L, et al. Effects of pelvic floor biofeedback electrical stimulation combined with lower limb rehabilitation robot training on intestinal function of patients with spinal cord injury [J]. *Journal of Brain and Nervous Diseases*,2021,29(01):53-57.
- [4] Xiang XN, Zhong HY, He HC. Research progress of lower limb exoskeleton rehabilitation robot in improving walking ability of patients with spinal cord injury [J]. *Chinese Journal of Rehabilitation Medicine*,2020,35(01):119-122. DOI: CNKI:SUN:ZGKF.0.2020-01-024
- [5] Bárbara-Bataller E, Méndez-Suárez JL, Alemán-Sánchez C, et al. Change in the profile of traumatic spinal cord injury over 15 years in Spain[J]. *Scand J Trauma Resusc Emerg Med*, 2018,26(1):27. DOI: 10.1186/s13049-018-0491-4.
- [6] Grasmücke D, Zieriacks A, Jansen O, et al. Against the odds: what to expect in rehabilitation of chronic spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis of 55 patients according to age and lesion level[J]. *Neurosurg Focus*, 2017,42(5):E15. DOI: 10.3171/2017.2.FOCUS171.
- [7] Holanda LJ, Silva P, Amorim TC, et al. Robotic assisted gait as a tool for rehabilitation of individuals with spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):126. DOI: 10.1186/s12984-017-0338-7.
- [8] Nam KY, Kim HJ, Kwon BS, et al. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):24. DOI: 10.1186/s12984-017-0232-3.
- [9] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions[J]. *Cochrane Database Syst Rev*, 2019,10:ED000142. DOI: 10.1002/14651858.ED000142.
- [10] Elbanna ST, Elshennawy S, Ayad MN. Noninvasive Brain Stimulation for Rehabilitation of Pediatric Motor Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials[J]. *Arch Phys Med Rehabil*, 2019,100(10):1945-1963. DOI: 10.1016/j.apmr.2019.04.009.
- [11] Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials[J]. *Phys Ther*, 2003,83(8):713-721.
- [12] Nasser M, Fedorowicz Z. Grading the quality of evidence and strength of recommendations: the GRADE approach to improving dental clinical guidelines[J]. *J Appl Oral Sci*, 2011,19(1):0. DOI: 10.1590/s1678-77572011000100001.
- [13] Brožek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in

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3 clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations[J]. Allergy,
4 2011,66(5):588-595. DOI: 10.1111/j.1398-9995.2010.02530.x.
5
6 [14] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis[J]. Stat Med, 2002,21(11):1539-
7 1558. DOI: 10.1002/sim.1186.
8
9 [15] Li J, Zhong D, Ye J, et al. Rehabilitation for balance impairment in patients after stroke: a protocol of a
10 systematic review and network meta-analysis[J]. BMJ Open, 2019,9(7):e026844. DOI: 10.1136/bmjopen-
11 2018-026844.
12
13 [16] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot
14 asymmetry in meta-analyses of randomised controlled trials[J]. BMJ, 2011,343:d4002. DOI:
15 10.1136/bmj.d4002.
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20 **Figure:** Flow chart of meta-analysis for robotic-assisted gait training in patients with spinal
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22 cord injury.
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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine, Neurology
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24 **injury: a protocol of a systematic review with meta-analysis**

25 **Abstract :**

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6 46 RAGT in the treatment of SCI.

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9 47 2. The results of this study will provide evidence for the treatment of SCI patients, and help therapists
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23
24 53 **Key words:** Spinal Cord Injuries; Motor disorders; Rehabilitation; Robotics, Gait Analysis

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26
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28
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30
31
32 56 **Trial registration number:** PROSPERO (CRD42022319555).

33 34 35 57 **Introduction**

36
37 58 Spinal cord injury (SCI) is a serious disabling disease that often causes paraplegia or quadriplegia
38
39 59 and affects the patient's sensory, motor, and autonomic nervous functions^[1, 2]. SCI leads to a variety
40
41 60 of complications, such as pressure ulcers, lung infections, and urinary tract infections^[3]. It affects
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43 61 the quality of life and living standard of patients and imposes a heavy burden on families^[4] and
44
45 62 society. It ultimately shortens the life expectancy of patients^[5]. In addition, the mortality rate of
46
47 63 patients with spinal cord injury is higher than that of the general population ^[6-8]. National statistical
48
49 64 data show that the incidence rate of SCI is increasing annually and that the incidence rate of SCI
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51 65 per million residents is 9.3 persons/year^[9]. During the rehabilitation treatment of SCI, improving
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53 66 the walking ability, self-care ability, and self-esteem of patients is an important aspect that helps
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4 67 patients return to society and reduces their costs. Therefore, increased exercise capacity of the lower
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6 68 limbs is crucial to daily independence and social reintegration for this population, which mainly
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9 69 function in standing and walking^[10, 11].

10
11 70 Robot-assisted gait training (RAGT) can improve the walking ability^[12], lower limb strength, and
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14 71 independence of patients with incomplete SCI^[13]. It can also improve balance function^[14]. RAGT
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17 72 has been gradually applied in patients with SCI. Some clinical evidence shows that in patients with
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20 73 SCI, robots for lower limb rehabilitation can effectively and safely improve walking ability; reduce
21
22 74 pressure ulcers^[15], lung infections^[8], urinary tract infections, and other complications^[16]; improve
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24
25 75 dignity; and reduce costs. However, high-quality evidence-based medical studies that systematically
26
27 76 evaluated the efficacy of RAGT in the treatment of SCI remain scarce.

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30 77 Summarizing studies based on RAGT-related factors is critical for the accurate estimation of the
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32 78 effects of RAGT on SCI. This meta-analysis aims to evaluate systematically the efficacy of RAGT
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35 79 in alleviating motor dysfunction and restoring speech ability in patients with SCI according to
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38 80 randomized clinical trials (RCTs); find strong evidence demonstrating that using RAGT is effective
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40 81 in the treatment of SCI; and analyze the deficiencies of current studies.

42 82 **Methods**

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44
45 83 The protocol of this systematic review was planned and conducted in accordance with the Preferred
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48 84 Reporting Items for Systematic Reviews and Meta-Analyses Protocols Guideline^[17] and PRISMA
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51 85 2020 guidelines^[18] and was performed following a protocol registered in PROSPERO
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53 86 (CRD42022319555). The plan starts on March 1, 2023 and ends on June 1. The review
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55
56 87 process is shown in **Figure**

57 58 88 **Search strategy**

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4 89 Two reviewers (Jin-lin Peng and Lei Wang) electronically searched the following publication
5
6 90 databases in December 2022 without restrictions on publication year: Medline, Cochrane Library,
7
8
9 91 Web of Science, Embase, PubMed, the Cochrane Central Register of Controlled Trials, and China
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11 92 National Knowledge Infrastructure. Various combinations of keywords, including “motor disorders,”
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14 93 “robotics”, “robotic assisted gait training,” “noninvasive brain stimulation,” “SCI”, and “gait
15
16
17 94 analysis”, were used as search terms. The key terms matched the appropriate Medical Subject
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19
20 95 Headings terms. Presearches were performed. Then, the final search was conducted follows:
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22 96 Relevant journals and references of review articles were manually searched online to identify papers
23
24
25 97 that may have been missed in the electronic database searches.

27 98 **Eligibility criteria**

29 99 **Inclusion criteria**

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31
32 100 (1) Study design: Only RCTs were included. (2) Selected population: Participants diagnosed with
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35 101 SCI, namely, individuals with any level of traumatic SCI, regardless of the time since injury, sex,
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38 102 and age, were included. (3) Type of intervention: The experimental groups received RAGT or
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41 103 RAGT combined with other physical therapies. The control group not received RAGT or received
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43
44 104 other types of physical therapy. (4) Comparison: The treated subjects were compared at baseline
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46
47 105 then with the control or sham-stimulated subjects. (5) Type of outcomes measured: Gait analysis
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50 106 indicators, including gait speed (m/s), step length (cm), double support phase (% walking cycle),
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53 107 single support phase (% walking cycle), and symmetry index; Berg balance scale; ASIA assessment
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56 108 scale; Holden walking ability classification (functional ambulation category scale); 10 m walking
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59 109 speed test; 6 min walking endurance test; and WISCI II score.

60 110 **Exclusion criteria**

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4 111 Studies involving animal research, conference research, protocol studies, or computer model
5
6 112 research and duplicate papers were excluded. Two reviewers (Jin-lin Peng and Lei Wang)
7
8
9 113 independently screened titles and abstracts to identify articles reporting studies that met the
10
11 114 inclusion criteria. Then, the full-text versions of the identified articles were obtained and separately
12
13
14 115 screened to ensure that they met the inclusion criteria. A third reviewer (Ai-lian Chen) made the
15
16
17 116 final assessment regarding whether or not full-text papers met the inclusion criteria.

117 **Data extraction**

118 A reviewer (Lei Wang) prepared the general information and data collection process by another
119 reviewer (Jin-lin Peng). The format of data collection included the following factors: research
120 design, participants (number, diagnosis, age, and target population numbers in each group),
121 eligibility criteria, intervention used on the research group and control group (i.e., site of stimulation,
122 intensity, number of sessions, and time of each session), and outcomes of interest.

123 **Quality assessment**

124 The quality evaluation of the included studies was performed independently by two reviewers (Jin-
125 lin Peng and Lei Wang) and was revised by the third reviewer (Ai-lian Chen). The methodological
126 quality of the intervention studies was assessed by using the Physiotherapy Evidence Database
127 (PEDro) scale. The PEDro scale is a valid and reliable measure of the methodological quality of
128 RCTs. This 10-item scale is based on the core criteria for RCT quality assessment^[19]. The quality
129 of papers was classified as follows in accordance with the PEDro scale: Studies with scores of less
130 than 6 points were considered low-quality studies, whereas those with scores equal to or greater
131 than 6 points were considered high-quality studies (where scores of 6–7 indicate good quality and
132 those of 8–10 indicate excellent quality)^[20].

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4 133 The GRADEpro GDT online tool was used to evaluate the level of evidence quality of the outcome
5
6 134 indicators. The tool is available at its official website <http://www.guidelinedevelopment.org/>. The
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8
9 135 GRADEpro GDT online tool for evaluating the quality of outcome indicators includes five
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11 136 degrading factors: risk of bias, inconsistency, indirectness, imprecision, and other considerations.^[21]
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13
14 137 The quality of evidence can be divided into four levels of “high”, “moderate”, “low”, and “very
15
16 138 low.”^[22]

19 139 **Risk-of-bias assessment of individual studies**

22 140 The quality of the included studies was evaluated and their scores were compared in a consensus
23
24 141 meeting between two independent authors (Jin-lin Peng and Lei Wang) to minimize errors and
25
26 142 potential biases in the evaluation. In the event of any disagreement, a third author (Ai-lian Chen)
27
28 143 was included in the discussion for a final consensus. The Cochrane Risk of Bias 2.0 tool^[23] was
29
30 144 used to assess the risk of bias of the articles. Each article was assessed for selection bias (random
31
32 145 sequence generation and allocation concealment), performance bias (blinding of participants and
33
34 146 personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data
35
36 147 reporting), and reporting bias (selective outcome reporting). Each domain was rated as high risk of
37
38 148 bias, unclear of bias, or low risk of bias. The risk map of the biases of the studies' quality was
39
40 149 prepared with RevMan 5.2 software.

48 150 **Patient and public involvement**

51 151 No patient participated in writing the system review plan. However, the results will be disseminated
52
53 152 to patients with SCI.

56 153 **Statistical analysis**

58 154 A meta-analysis will be conducted by using Review Manager 5.3. Heterogeneity between studies

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4 155 will be evaluated on the basis of the I^2 statistic for the quantification of the proportion of the total
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6 156 outcome attributable to variability among studies. The following ranges were defined: $I^2 = 0\%–30\%$
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9 157 (no heterogeneity), $I^2 = 30\%–49\%$ (moderate heterogeneity), $I^2 = 50\%–74\%$ (substantial
10
11 158 heterogeneity), and $I^2 = 75\%–100\%$ (considerable heterogeneity)^[24]. On the basis of heterogeneity,
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13
14 159 a random-effects model was used when $I^2 > 30\%$, and a fixed-effects model was utilized when $I^2 =$
15
16 160 $0\%–30\%$.

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19 161 For the comparison of data from different scales, pooled statistics will be calculated by using
20
21 162 standardized mean differences (SMDs). Means and standard deviations after intervention and
22
23 163 follow-up evaluation for the RAGT and control groups (when relevant) will be applied to compute
24
25 164 SMDs.

165 **Addressing missing data**

166 The original author will be contacted for additional information regarding missing data. In the
167 absence of a reply, the data will be calculated on the basis of the availability factor. The potential
168 effect of the missing data on meta-analysis results will be tested through sensitivity analysis.

169 **Subgroup analysis**

170 Grouping analysis will be performed to address potential heterogeneity and inconsistencies and will
171 be conducted in accordance with age, gender, SCI plane, disease course, treatment prescription, and
172 treatment duration. At the same time, meta-analysis will be conducted to explore the possible
173 sources of heterogeneity.

174 **Sensitivity analysis**

175 For the verification of the robustness of the research conclusion, sensitivity analysis will be
176 conducted on the main results to assess the effect of method quality, research quality, sample size,

177 missing data, and analysis methods on the results of this review^[25].

178 **Assessment of publication bias**

179 Each included study will be evaluated in accordance with the PEDro scale. Funnel charts will be
180 used to assess the publication bias of the main results included in the study. If the funnel chart is
181 found to be asymmetrical, attempts will be made to explain its asymmetry^[26].

182 **Discussion**

183 RAGT can improve the walking ability of patients with incomplete SCI and can be used by patients
184 with stable vital signs. For patients with complete SCI, RAGT acts mainly to maintain the range of
185 motion of joints. In recent years, studies on using RAGT to improve walking ability in SCI have
186 increased, and the new exoskeleton robot for lower limb rehabilitation has shown the advantage of
187 safe transfer. Our current query shows that our work is the first systematic review and meta-analysis
188 on RAGT for patients with SCI. The results of this meta-analysis can help patients and therapists
189 select the appropriate treatment method for SCI and improve new options on the basis of the
190 comparative evidence for effectiveness and safety. We hope that the results of this study will provide
191 evidence for guideline recommendations.

192 **Data Availability**

193 The datasets used and analyzed in the current study are included in this article.

195 **Ethical Approval**

196 This research is a review, does not involve ethical issues, and did not apply for ethical approval.

198 **Funding**

199 This study has no funding support.

201 **Disclosure**

202 All authors have read and approved the final manuscript.

203

204 Contributors

205 WL and P-JL, as the first authors, have made equal contributions to this work. Research concept
206 and design: WL and C-AL. Data acquisition: WL and P-JL. Draft: WL and P-JL. Supervised by: C-
207 AL. All the authors approved the publication of the Protocol.

209 Conflicts of Interest

210 All authors declare no potential conflicts of interest with respect to the research, authorship, and/or
211 publication of this study.

212 参考文献

- 213
- 214 [1] Eckert MJ, Martin MJ. Trauma: Spinal Cord Injury[J]. Surg Clin North Am, 2017,97(5):1031-1045. DOI:
215 10.1016/j.suc.2017.06.008.
- 216 [2] Anjum A, Yazid MD, Fauzi Daud M, et al. Spinal Cord Injury: Pathophysiology, Multimolecular Interactions,
217 and Underlying Recovery Mechanisms[J]. Int J Mol Sci, 2020,21(20)DOI: 10.3390/ijms21207533.
- 218 [3] Stricsek G, Ghobrial G, Wilson J, et al. Complications in the Management of Patients with Spine Trauma[J].
219 Neurosurg Clin N Am, 2017,28(1):147-155. DOI: 10.1016/j.nec.2016.08.007.
- 220 [4] Zhang JM, Li N, Zhu L, et al. Effects of pelvic floor biofeedback electrical stimulation combined with lower
221 limb rehabilitation robot training on intestinal function of patients with spinal cord injury [J]. Journal of Brain
222 and Nervous Diseases,2021,29(01):53-57.
- 223 [5] Xiang XN, Zhong HY, He HC. Research progress of lower limb exoskeleton rehabilitation robot in
224 improving walking ability of patients with spinal cord injury [J]. Chinese Journal of Rehabilitation
225 Medicine,2020,35(01):119-122. DOI: CNKI:SUN:ZGKF.0.2020-01-024
- 226 [6] Buzzell A, Chamberlain JD, Eriks-Hoogland I, et al. All-cause and cause-specific mortality following non-
227 traumatic spinal cord injury: evidence from a population-based cohort study in Switzerland[J]. Spinal Cord,
228 2020,58(2):157-164. DOI: 10.1038/s41393-019-0361-6.
- 229 [7] Mirzaeva L, Lobzin S, Teinzerling N, et al. Complications and mortality after acute traumatic spinal cord
230 injury in Saint Petersburg, Russia[J]. Spinal Cord, 2020,58(9):970-979. DOI: 10.1038/s41393-020-0458-y.
- 231 [8] Li R, Ding M, Wang J, et al. Effectiveness of robotic-assisted gait training on cardiopulmonary fitness and
232 exercise capacity for incomplete spinal cord injury: A systematic review and meta-analysis of randomized
233 controlled trials[J]. Clin Rehabil, 2023,37(3):312-329. DOI: 10.1177/02692155221133474.
- 234 [9] Bárbara-Bataller E, Méndez-Suárez JL, Alemán-Sánchez C, et al. Change in the profile of traumatic spinal
235 cord injury over 15 years in Spain[J]. Scand J Trauma Resusc Emerg Med, 2018,26(1):27. DOI:
236 10.1186/s13049-018-0491-4.
- 237 [10] Mahooti F, Raheb G, Alipour F, et al. Psychosocial challenges of social reintegration for people with spinal
238 cord injury: a qualitative study[J]. Spinal Cord, 2020,58(10):1119-1127. DOI: 10.1038/s41393-020-0449-z.
- 239 [11] Rahimi M, Torkaman G, Ghabaee M, et al. Advanced weight-bearing mat exercises combined with

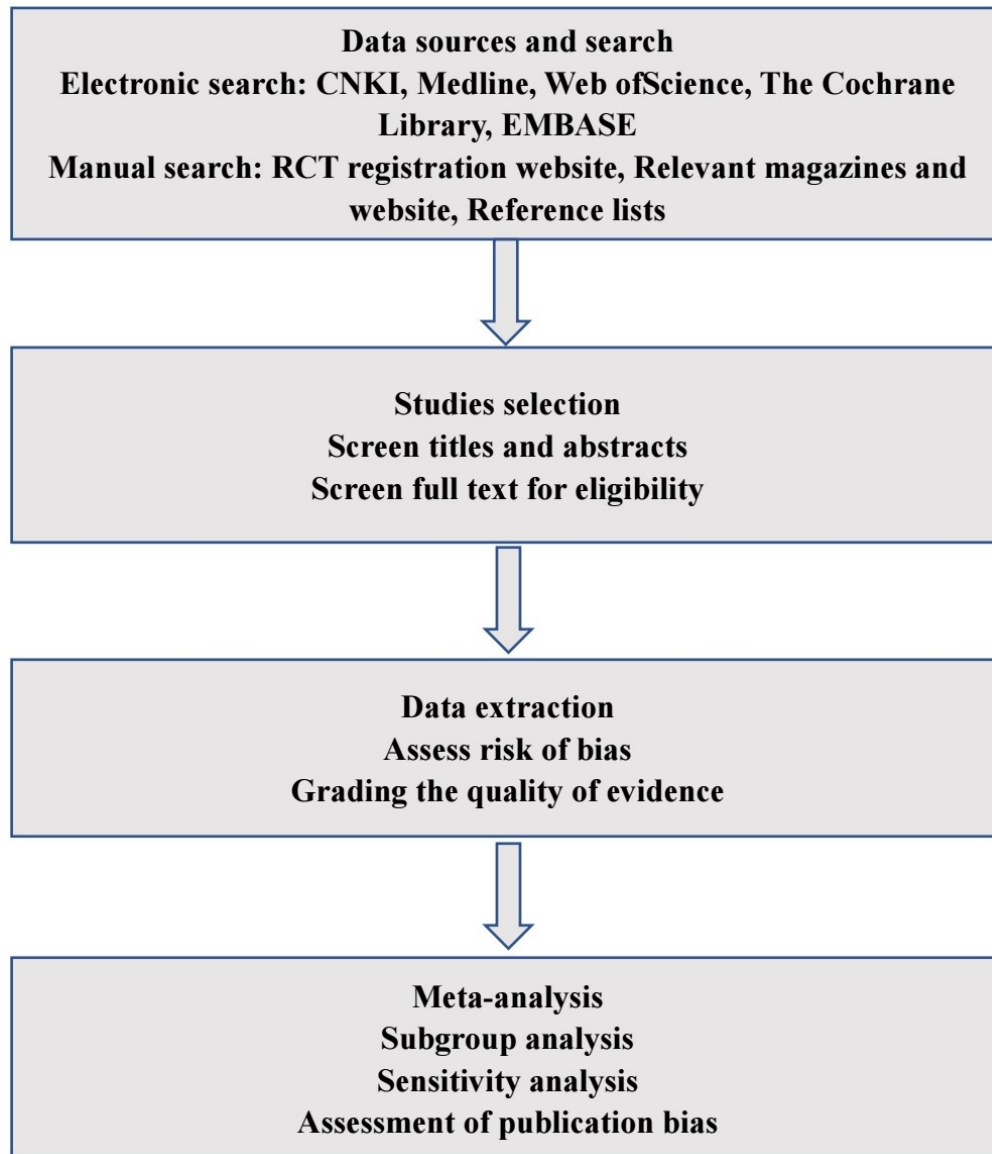
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3 240 functional electrical stimulation to improve the ability of wheelchair-dependent people with spinal cord
4 241 injury to transfer and attain independence in activities of daily living: a randomized controlled trial[J]. *Spinal*
5 242 *Cord*, 2020,58(1):78-85. DOI: 10.1038/s41393-019-0328-7.
- 7 243 [12] Grasmücke D, Zieriacs A, Jansen O, et al. Against the odds: what to expect in rehabilitation of chronic
8 244 spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis
9 245 of 55 patients according to age and lesion level[J]. *Neurosurg Focus*, 2017,42(5):E15. DOI:
11 246 10.3171/2017.2.FOCUS171.
- 13 247 [13] Holanda LJ, Silva P, Amorim TC, et al. Robotic assisted gait as a tool for rehabilitation of individuals with
14 248 spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):126. DOI: 10.1186/s12984-017-
15 249 0338-7.
- 17 250 [14] Nam KY, Kim HJ, Kwon BS, et al. Robot-assisted gait training (Lokomat) improves walking function and
18 251 activity in people with spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):24. DOI:
19 252 10.1186/s12984-017-0232-3.
- 21 253 [15] Rathore A, Wilcox M, Ramirez DZ, et al. Quantifying the human-robot interaction forces between a lower
22 254 limb exoskeleton and healthy users[J]. *Annu Int Conf IEEE Eng Med Biol Soc*, 2016,2016:586-589. DOI:
23 255 10.1109/EMBC.2016.7590770.
- 25 256 [16] Pattanakuhar S, Ahmady F, Setiono S, et al. Impacts of Bladder Managements and Urinary Complications
26 257 on Quality of Life: Cross-sectional Perspectives of Persons With Spinal Cord Injury Living in Malaysia,
27 258 Indonesia, and Thailand[J]. *Am J Phys Med Rehabil*, 2023,102(3):214-221. DOI:
28 259 10.1097/PHM.0000000000002066.
- 30 260 [17] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the
31 261 *Cochrane Handbook for Systematic Reviews of Interventions*. *Cochrane Database Syst Rev*. 2019. 10:
32 262 ED000142.
- 34 263 [18] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting
35 264 systematic reviews[J]. *BMJ*, 2021,372:n71. DOI: 10.1136/bmj.n71.
- 37 265 [19] Elbanna ST, Elshennawy S, Ayad MN. Noninvasive Brain Stimulation for Rehabilitation of Pediatric Motor
38 266 Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials. *Arch Phys Med*
39 267 *Rehabil*. 2019. 100(10): 1945-1963.
- 41 268 [20] Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating
42 269 quality of randomized controlled trials. *Phys Ther*. 2003. 83(8): 713-21.
- 44 270 [21] Nasser M, Fedorowicz Z. Grading the quality of evidence and strength of recommendations: the GRADE
45 271 approach to improving dental clinical guidelines[J]. *J Appl Oral Sci*, 2011,19(1):0. DOI: 10.1590/s1678-
46 272 77572011000100001.
- 48 273 [22] Brożek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in
49 274 clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations[J]. *Allergy*,
50 275 2011,66(5):588-595. DOI: 10.1111/j.1398-9995.2010.02530.x.
- 52 276 [23] Sterne J, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials[J].
53 277 *BMJ*, 2019,366:l4898. DOI: 10.1136/bmj.l4898.
- 55 278 [24] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis[J]. *Stat Med*, 2002,21(11):1539-
56 279 1558. DOI: 10.1002/sim.1186.
- 58 280 [25] Li J, Zhong D, Ye J, et al. Rehabilitation for balance impairment in patients after stroke: a protocol of a
59 281 systematic review and network meta-analysis[J]. *BMJ Open*, 2019,9(7):e026844. DOI: 10.1136/bmjopen-
58 282 2018-026844.
- 60 283 [26] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot

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3 284 asymmetry in meta-analyses of randomised controlled trials[J]. BMJ, 2011,343:d4002. DOI:
4 285 10.1136/bmj.d4002.
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9 287 **Figure:** Flow chart of meta-analysis for robotic-assisted gait training in patients with spinal
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11 288 cord injury.
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For peer review only



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BMJ Open

Effect of robotic-assisted gait training on gait and motor function in spinal cord injury: a protocol of a systematic review with meta-analysis

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine, Neurology
Keywords:	REHABILITATION MEDICINE, NEUROSURGERY, Neurological injury < NEUROLOGY

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Manuscripts

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4 1 **Effect of robotic-assisted gait training on gait and motor function in spinal cord**
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6 2 **injury: a protocol of a systematic review with meta-analysis**
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32 12 **Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University),**
33
34 13 **Changsha 410005, Hunan, Peoples R China.**

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37 14 **(Note: The name in the article is correct, and the name in parentheses comes from ScholarOne.**

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39 15 **As ScholarOne cannot modify the name, it is hereby stated in the article)**
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6 24 **Effect of robotic-assisted gait training on gait and motor function in spinal cord**
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9 25 **injury: a protocol of a systematic review with meta-analysis**
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12 26 **Abstract :**13
14 27 **Introduction:** Robotic-assisted gait training (RAGT) has been reported to be effective in
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17 28 rehabilitating patients with spinal cord injury (SCI). However, studies on RAGT showed different
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20 29 results due to a varied number of samples. Thus, summarising studies based on robotic-related
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23 30 factors is critical for the accurate estimation of the effects of RAGT on SCI. This work aims to
24
25 31 search for strong evidence showing that using RAGT is effective in treating SCI and analyse the
26
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28 32 deficiencies of current studies.29
30 33 **Methods and analysis:** The following publication databases were electronically searched in
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32
33 34 December 2022 without restrictions on publication year: Medline, Cochrane Library, Web of
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38 36 Knowledge Infrastructure. Various combinations of keywords, including ‘motor disorders’,
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40 37 ‘robotics’, ‘robotic-assisted gait training’, ‘Spinal Cord Injuries’, ‘SCI’ and ‘gait analysis’ were
41
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43 38 used as search terms. All articles on randomised controlled trials (excluding retrospective trials)
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45
46 39 using RAGT to treat SCI that were published in English and Chinese and met the inclusion criteria
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48 40 were included. Outcomes included motor function, and gait parameters included those assessed by
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51 41 using the instrumented gait assessment, the Berg balance scale, the 10-m walk speed test, the 6-min
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54 42 walk endurance test, the functional ambulation category scale, the Walking index of SCI and the
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56 43 ASIA assessment scale. Research selection, data extraction and quality assessment were conducted
57
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59 44 independently by two reviewers to ensure that all relevant studies were free from personal bias. In
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4 45 addition, the Cochrane Bias Risk Assessment Tool was used to assess the risk of bias. Review
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6 46 Manager V.5.3 software was utilised to produce deviation risk maps and perform paired meta-
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9 47 analyses.

11 48 **Strengths and limitations of this study**

- 14 49 1. This study was the first meta-analysis to systematically evaluate the efficacy and safety of RAGT
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17 50 in the treatment of SCI.
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19 51 2. The results of this study provided evidence for the treatment of SCI patients and helped therapists
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21
22 52 and patients to choose appropriate treatment methods.
23
24 53 3. Two reviewers independently conducted research selection, data extraction and quality
25
26
27 54 assessment to ensure that all relevant studies were free from personal bias.
28
29 55 4. The language categories of the research search were only included in English and Chinese, and
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31
32 56 the final search results would have some bias.
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35 57 **Key words:** Spinal Cord Injuries; Motor disorders; Rehabilitation; Robotics, Gait Analysis

37 58 **Ethics and dissemination:** Ethics approval is not required for systematic reviews and network
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40 59 meta-analyses. The results will be submitted to a peer-reviewed journal or presented at a conference.
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43 60 **Trial registration number:** PROSPERO (CRD42022319555).
44

45 61 **Introduction**

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48 62 Spinal cord injury (SCI) is a serious disabling disease that often causes paraplegia or quadriplegia
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51 63 and affects patient's sensory, motor and autonomic nervous functions^[1, 2]. SCI leads to various
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53 64 complications, such as pressure ulcers, lung infections and urinary tract infections^[3]. It also affects
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56 65 patients' quality of life and living standard and imposes a heavy burden on families^[4] and society.
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58 66 It ultimately shortens patients' life expectancy ^[5]. In addition, the mortality rate of patients with SCI
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4 67 is higher than that of the general population [6-8]. National statistical data show an increasing
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6 68 incidence rate of SCI annually, and that the incidence rate of SCI per million residents is 9.3
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9 69 persons/year^[9]. During the rehabilitation treatment of SCI, improving the walking ability, self-care
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11 70 ability and self-esteem of patients is an important aspect that helps them return to society and
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14 71 reduces their costs. Therefore, increased exercise capacity of the lower limbs is crucial to daily
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17 72 independence and social reintegration for this population, which mainly functions in standing and
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19 73 walking^[10, 11].

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22 74 Robot-assisted gait training (RAGT) can improve the walking ability^[12], lower limb strength and
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24 75 independence of patients with incomplete SCI^[13]. RAGT can also improve balance function^[14] and
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27 76 has been gradually applied in patients with SCI. In patients with SCI, robots for lower limb
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29 77 rehabilitation can effectively and safely improve walking ability; reduce pressure ulcers^[15], lung
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31 78 infections^[8], urinary tract infections and other complications^[16]; improve dignity; and reduce costs.
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34 79 However, high-quality evidence-based medical studies that systematically evaluated the efficacy of
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36 80 RAGT in the treatment of SCI remain scarce.

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39 81 Therefore, summarising studies based on RAGT-related factors is critical for the accurate estimation
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41 82 of the effects of RAGT on SCI. This meta-analysis aims to systematically evaluate the efficacy of
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43 83 RAGT in alleviating motor dysfunction and restoring speech ability in patients with SCI based on
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97 'robotics', 'robotic-assisted gait training', 'Spinal Cord Injuries', 'SCI' and 'gait analysis' were
98 used as search terms. The key terms matched the appropriate Medical Subject Heading terms.
99 Presearches were performed. Then, the final search was conducted, relevant journals and references
100 of review articles were manually searched online to identify papers that may have been missed in
101 the electronic database searches.

102 **Eligibility criteria**

103 **Inclusion criteria**

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105 SCI, namely, individuals with any level of traumatic SCI, regardless of the time since injury, sex
106 and age were included. (3) Type of intervention: The experimental groups received RAGT or RAGT
107 combined with other physical therapies. The control group not received RAGT or received other
108 types of physical therapy. (4) Comparison: The treated subjects were compared at baseline and then
109 with the control or sham-stimulated subjects. (5) Type of outcomes measured: Gait analysis
110 indicators, including gait speed (m/s), step length (cm), double support phase (% walking cycle),

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4 111 single support phase (% walking cycle) and symmetry index; Berg balance scale; ASIA assessment
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6 112 scale; Holden walking ability classification (functional ambulation category scale); 10-m walk
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9 113 speed test; 6-min walk endurance test; and WISCI II score.
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11 114 **Exclusion criteria**

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14 115 Studies involving animal research, conference research, protocol studies or computer model
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17 116 research and duplicate papers were excluded. Two reviewers (Jin-lin Peng and Lei Wang)
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19
20 117 independently screened titles and abstracts to identify articles reporting studies that met the
21
22 118 inclusion criteria. Then, the full-text versions of the identified articles were obtained and separately
23
24
25 119 screened to ensure that they met the inclusion criteria. Moreover, a third reviewer (Ai-lian Chen)
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27 120 made the final assessment regarding whether or not full-text papers met the inclusion criteria.
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30 121 **Data extraction**

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32 122 A reviewer (Lei Wang) prepared the general information and data collection process by another
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34
35 123 reviewer (Jin-lin Peng). The format of data collection included research design, participants
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37
38 124 (number, diagnosis, age and target population numbers in each group), eligibility criteria,
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40
41 125 intervention used on the research group and control group (i.e. site of stimulation, intensity, number
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43 126 of sessions and time of each session) and outcomes of interest.
44

45 127 **Quality assessment**

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48 128 The quality evaluation of the included studies was performed independently by two reviewers (Jin-
49
50
51 129 lin Peng and Lei Wang) and was revised by the third reviewer (Ai-lian Chen). The methodological
52
53 130 quality of the intervention studies was assessed using the Physiotherapy Evidence Database (PEDro)
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55
56 131 scale. The PEDro scale is a valid and reliable measure of the methodological quality of RCTs. This
57
58 132 10-item scale is based on the core criteria for RCT quality assessment^[19]. The quality of papers was
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4 133 classified based on the PEDro scale. Studies with scores of less than 6 points were considered low-
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6 134 quality studies, whereas those with scores equal to or greater than 6 points were considered high-
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9 135 quality studies (scores of 6–7 indicate good quality and 8–10 indicate excellent quality)^[20].

10
11 136 The GRADEpro GDT online tool was used to evaluate the level of evidence quality of the outcome
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14 137 indicators. The tool is available at its official website <http://www.guidelinedevelopment.org/>. The
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16
17 138 GRADEpro GDT online tool for evaluating the quality of outcome indicators includes five
18
19 139 degrading factors, namely, risk of bias, inconsistency, indirectness, imprecision and other
20
21
22 140 considerations^[21]. The quality of evidence can be divided into four levels, namely, ‘high’,
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25 141 ‘moderate’, ‘low’ and ‘very low’^[22].

26 27 142 **Risk-of-bias assessment of individual studies**

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29
30 143 The quality of the included studies was evaluated and their scores were compared in a consensus
31
32 144 meeting between two independent authors (Jin-lin Peng and Lei Wang) to minimise errors and
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35 145 potential biases in the evaluation. However, in the event of any disagreement, a third author (Ai-
36
37
38 146 lian Chen) was included in the discussion for a final consensus. The Cochrane Risk of Bias 2.0
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40 147 tool^[23] was used to assess the articles’ risk of bias. Each article was assessed for selection bias
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43 148 (random sequence generation and allocation concealment), performance bias (blinding of
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45
46 149 participants and personnel), detection bias (blinding of outcome assessment), attrition bias
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49 150 (incomplete outcome data reporting) and reporting bias (selective outcome reporting). Each domain
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51
52 151 was rated as high risk of bias, unclear of bias or low risk of bias. The risk map of the biases of the
53
54 152 studies’ quality was prepared with Review Manager 5.3.

55 56 153 **Patient and Public Involvement**

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58 154 No patient participated in writing the system review plan. However, the results were disseminated
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4 155 to patients with SCI.
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6 156 **Statistical analysis**

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8
9 157 A meta-analysis was conducted using Review Manager 5.3. Heterogeneity between studies was
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11 158 evaluated based on the I^2 statistic for the quantification of the proportion of the total outcome
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13 159 attributable to variability amongst studies. The following ranges were defined: $I^2 = 0\%–30\%$ (no
14
15 160 heterogeneity), $I^2 = 30\%–49\%$ (moderate heterogeneity), $I^2 = 50\%–74\%$ (substantial heterogeneity)
16
17 161 and $I^2 = 75\%–100\%$ (considerable heterogeneity)^[24]. Based on heterogeneity, a random-effects
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19 162 model was used when $I^2 > 30\%$, and a fixed-effects model was utilised when $I^2 = 0\%–30\%$.

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24 163 For the comparison of data from different scales, pooled statistics were calculated using
25
26 164 standardised mean differences (SMDs). Furthermore, means and standard deviations after
27
28 165 intervention and follow-up evaluation for the RAGT and control groups (when relevant) were
29
30 166 applied to compute SMDs.

31 167 **Addressing missing data**

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35 168 Regarding missing data, the original author was contacted for additional information. In the absence
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37 169 of a reply, the data was calculated based on the availability factor. The potential effect of the missing
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39 170 data on meta-analysis results was tested through sensitivity analysis.

40 171 **Subgroup analysis**

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43 172 Analysis results showed a situation wherein heterogeneity was high and subgroup analysis was
44
45 173 required. Grouping analysis was conducted based on age (children, adolescents, middle-aged and
46
47 174 elderly), SCI level (cervical, thoracic and lumbar), disease course (recovery and sequelae), treatment
48
49 175 prescription and treatment duration to address potential heterogeneity and inconsistency. A meta-
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51 176 analysis was also conducted to explore possible sources of heterogeneity.
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4 **177 Sensitivity analysis**

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6 178 Sensitivity analysis was conducted on the main results to assess the effect of method quality,
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9 179 research quality, sample size, missing data and analysis methods on the results of this review to
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12 180 verify the robustness of the research conclusion [25].

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14 **181 Assessment of publication bias**

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17 182 Each included study was evaluated based on the PEDro scale. Funnel charts were used to assess the
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20 183 publication bias of the main results included in the study. However, when the funnel chart was
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22
23 184 asymmetrical, attempts were made to explain its asymmetry [26].

24
25 **185 Discussion**

26
27 186 RAGT can improve the walking ability of patients with incomplete SCI and can be used by patients
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30 187 with stable vital signs. For patients with complete SCI, RAGT primarily acts to maintain the range
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33 188 of motion of joints. In recent years, there is an increasing number of studies on using RAGT to
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36 189 improve walking ability in SCI, and the new exoskeleton robot for lower limb rehabilitation has
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39 190 shown the advantage of safe transfer. Our current query shows that our work is the first systematic
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41
42 191 review and meta-analysis on RAGT for patients with SCI. The results of this meta-analysis can help
43
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45 192 patients and therapists select the appropriate treatment method for SCI and improve new options
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48 193 based on the comparative evidence for effectiveness and safety. Therefore, we hope that the results
49
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51 194 of this study will provide evidence for guideline recommendations.

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53 **195 Study limitations**

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56 196 Articles published in both Chinese and English were included. Articles in other languages were not
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59 197 included, and their exclusion may affect our research. When incorporating outcome indicators, all
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198 data were sourced from scale evaluation and gait analysis instruments. The lack of research results

199 on neural mechanisms may have had a certain effect on this study.

200 **Data Availability**

201 The datasets used and analysed in the current study are included in this article.

203 **Ethical Approval**

204 This research is a review, does not involve ethical issues and did not apply for ethical approval.

206 **Funding**

207 This study has no funding support.

209 **Disclosure**

210 All authors have read and approved the final manuscript.

212 **Contributors**

213 As the first authors, WL and P-JL have made equal contributions to this work. WL and C-AL for

214 research concept and design. WL and P-JL are responsible for data acquisition. WL and P-JL made

215 the draft, and C-AL did the supervision. All the authors approved the publication of the Protocol.

217 **Conflicts of Interest**

218 All authors declare no potential conflicts of interest with respect to the research, authorship and/or

219 publication of this study.

220 **References**

- 221 [1] Eckert MJ, Martin MJ. Trauma: Spinal Cord Injury[J]. Surg Clin North Am, 2017,97(5):1031-1045. DOI:
222 10.1016/j.suc.2017.06.008.
- 223 [2] Anjum A, Yazid MD, Fauzi Daud M, et al. Spinal Cord Injury: Pathophysiology, Multimolecular Interactions,
224 and Underlying Recovery Mechanisms[J]. Int J Mol Sci, 2020,21(20)DOI: 10.3390/ijms21207533.
- 225 [3] Stricsek G, Ghobrial G, Wilson J, et al. Complications in the Management of Patients with Spine Trauma[J].
226 Neurosurg Clin N Am, 2017,28(1):147-155. DOI: 10.1016/j.nec.2016.08.007.
- 227 [4] Zhang JM, Li N, Zhu L, et al. Effects of pelvic floor biofeedback electrical stimulation combined with lower
228 limb rehabilitation robot training on intestinal function of patients with spinal cord injury [J]. Journal of Brain
229 and Nervous Diseases,2021,29(01):53-57.
- 230 [5] Xiang XN, Zhong HY, He HC. Research progress of lower limb exoskeleton rehabilitation robot in
231 improving walking ability of patients with spinal cord injury [J]. Chinese Journal of Rehabilitation
232 Medicine,2020,35(01):119-122. DOI: CNKI:SUN:ZGKF.0.2020-01-024

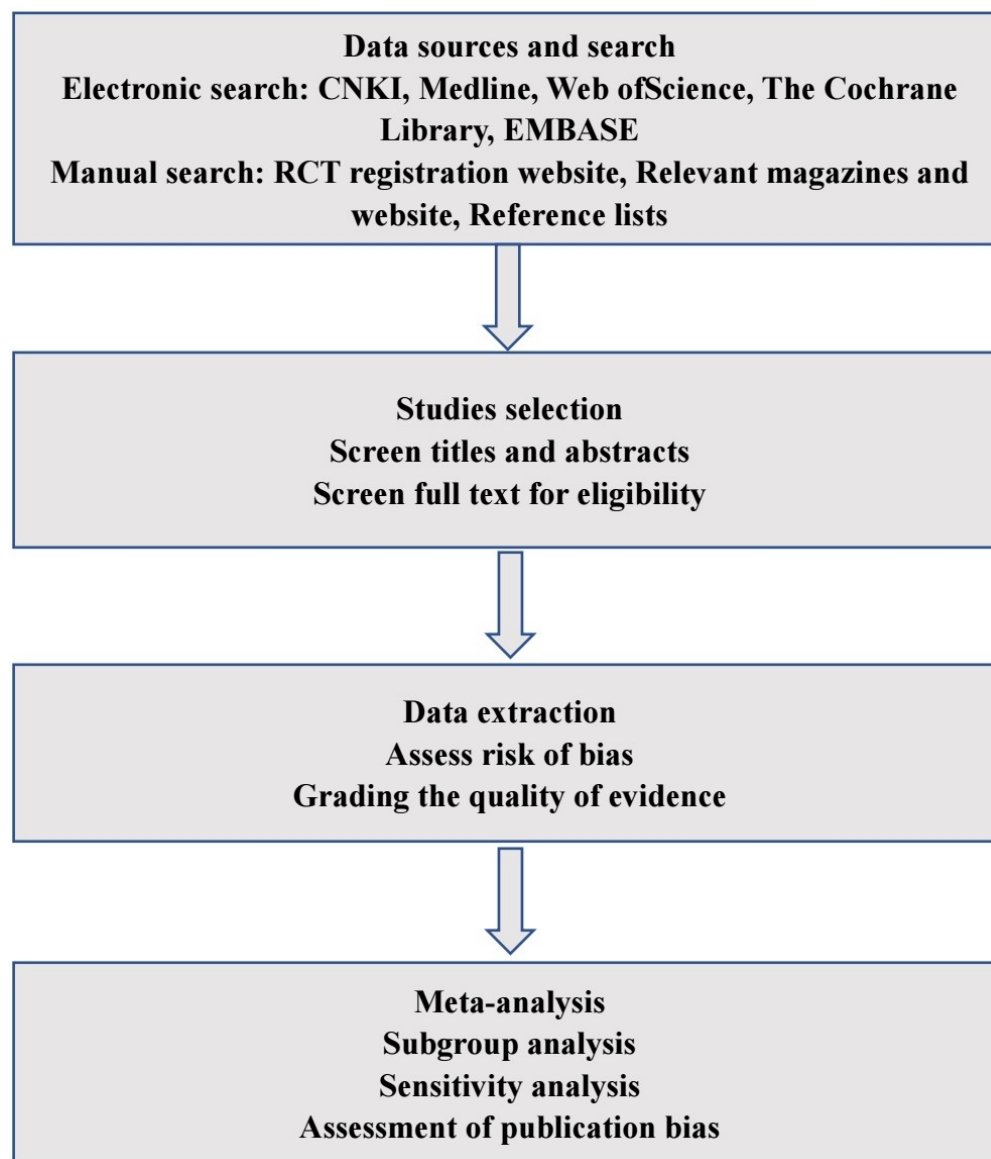
- 1
2
3 233 [6] Buzzell A, Chamberlain JD, Eriks-Hoogland I, et al. All-cause and cause-specific mortality following non-
4 234 non-traumatic spinal cord injury: evidence from a population-based cohort study in Switzerland[J]. *Spinal Cord*,
5 235 2020,58(2):157-164. DOI: 10.1038/s41393-019-0361-6.
6
7 236 [7] Mirzaeva L, Lobzin S, Teinzerling N, et al. Complications and mortality after acute traumatic spinal cord
8 237 injury in Saint Petersburg, Russia[J]. *Spinal Cord*, 2020,58(9):970-979. DOI: 10.1038/s41393-020-0458-y.
9
10 238 [8] Li R, Ding M, Wang J, et al. Effectiveness of robotic-assisted gait training on cardiopulmonary fitness and
11 239 exercise capacity for incomplete spinal cord injury: A systematic review and meta-analysis of randomized
12 240 controlled trials[J]. *Clin Rehabil*, 2023,37(3):312-329. DOI: 10.1177/02692155221133474.
13
14 241 [9] Bárbara-Bataller E, Méndez-Suárez JL, Alemán-Sánchez C, et al. Change in the profile of traumatic spinal
15 242 cord injury over 15 years in Spain[J]. *Scand J Trauma Resusc Emerg Med*, 2018,26(1):27. DOI:
16 243 10.1186/s13049-018-0491-4.
17
18 244 [10] Mahooti F, Raheb G, Alipour F, et al. Psychosocial challenges of social reintegration for people with spinal
19 245 cord injury: a qualitative study[J]. *Spinal Cord*, 2020,58(10):1119-1127. DOI: 10.1038/s41393-020-0449-z.
20
21 246 [11] Rahimi M, Torkaman G, Ghabaee M, et al. Advanced weight-bearing mat exercises combined with
22 247 functional electrical stimulation to improve the ability of wheelchair-dependent people with spinal cord
23 248 injury to transfer and attain independence in activities of daily living: a randomized controlled trial[J]. *Spinal*
24 249 *Cord*, 2020,58(1):78-85. DOI: 10.1038/s41393-019-0328-7.
25
26 250 [12] Grasmücke D, Zierjacks A, Jansen O, et al. Against the odds: what to expect in rehabilitation of chronic
27 251 spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis
28 252 of 55 patients according to age and lesion level[J]. *Neurosurg Focus*, 2017,42(5):E15. DOI:
29 253 10.3171/2017.2.FOCUS171.
30
31 254 [13] Holanda LJ, Silva P, Amorim TC, et al. Robotic assisted gait as a tool for rehabilitation of individuals with
32 255 spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):126. DOI: 10.1186/s12984-017-
33 256 0338-7.
34
35 257 [14] Nam KY, Kim HJ, Kwon BS, et al. Robot-assisted gait training (Lokomat) improves walking function and
36 258 activity in people with spinal cord injury: a systematic review[J]. *J Neuroeng Rehabil*, 2017,14(1):24. DOI:
37 259 10.1186/s12984-017-0232-3.
38
39 260 [15] Rathore A, Wilcox M, Ramirez DZ, et al. Quantifying the human-robot interaction forces between a lower
40 261 limb exoskeleton and healthy users[J]. *Annu Int Conf IEEE Eng Med Biol Soc*, 2016,2016:586-589. DOI:
41 262 10.1109/EMBC.2016.7590770.
42
43 263 [16] Pattanakuhar S, Ahmady F, Setiono S, et al. Impacts of Bladder Managements and Urinary Complications
44 264 on Quality of Life: Cross-sectional Perspectives of Persons With Spinal Cord Injury Living in Malaysia,
45 265 Indonesia, and Thailand[J]. *Am J Phys Med Rehabil*, 2023,102(3):214-221. DOI:
46 266 10.1097/PHM.0000000000002066.
47
48 267 [17] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the
49 268 Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019. 10:
50 269 ED000142.
51
52 270 [18] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting
53 271 systematic reviews[J]. *BMJ*, 2021,372:n71. DOI: 10.1136/bmj.n71.
54
55 272 [19] Elbanna ST, Elshennawy S, Ayad MN. Noninvasive Brain Stimulation for Rehabilitation of Pediatric Motor
56 273 Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials. *Arch Phys Med*
57 274 *Rehabil*. 2019. 100(10): 1945-1963.
58
59 275 [20] Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating
276 quality of randomized controlled trials. *Phys Ther*. 2003. 83(8): 713-21.

- 1
2
3 277 [21] Nasser M, Fedorowicz Z. Grading the quality of evidence and strength of recommendations: the GRADE
4 278 approach to improving dental clinical guidelines[J]. J Appl Oral Sci, 2011,19(1):0. DOI: 10.1590/s1678-
5 279 77572011000100001.
6
7 280 [22] Brożek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in
8 281 clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations[J]. Allergy,
9 282 2011,66(5):588-595. DOI: 10.1111/j.1398-9995.2010.02530.x.
10
11 283 [23] Sterne J, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials[J].
12 284 BMJ, 2019,366:l4898. DOI: 10.1136/bmj.l4898.
13
14 285 [24] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis[J]. Stat Med, 2002,21(11):1539-
15 286 1558. DOI: 10.1002/sim.1186.
16
17 287 [25] Li J, Zhong D, Ye J, et al. Rehabilitation for balance impairment in patients after stroke: a protocol of a
18 288 systematic review and network meta-analysis[J]. BMJ Open, 2019,9(7):e026844. DOI: 10.1136/bmjopen-
19 289 2018-026844.
20
21 290 [26] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot
22 291 asymmetry in meta-analyses of randomised controlled trials[J]. BMJ, 2011,343:d4002. DOI:
23 292 10.1136/bmj.d4002.
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27 294 **Figure:** Flow chart of meta-analysis for robotic-assisted gait training in patients with spinal
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29 cord injury.
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported (line numbers)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	60
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	4-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	212-215
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	206-207
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			61-85
Rationale	6	Describe the rationale for the review in the context of what is already known	81-85
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	104-113
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	104-113

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	92-101
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	92-101
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	114-120
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	114-120
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	121-126
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	121-126
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	121-126
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	142-152
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	121-126
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	156-166
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	171-180
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	167-170
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	181-184
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	181-184

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only

BMJ Open

Effect of robotic-assisted gait training on gait and motor function in spinal cord injury: a protocol of a systematic review with meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-070675.R3
Article Type:	Protocol
Date Submitted by the Author:	07-Aug-2023
Complete List of Authors:	wang, lei; Hunan Provincial People's Hospital, peng, lin; Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology chen, lian; Hunan Provincial People's Hospital
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rehabilitation medicine, Neurology
Keywords:	REHABILITATION MEDICINE, NEUROSURGERY, Neurological injury < NEUROLOGY

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Manuscripts

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4 1 **Effect of robotic-assisted gait training on gait and motor function in spinal cord**
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6 2 **injury: a protocol of a systematic review with meta-analysis**
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33
34 13 **Changsha 410005, Hunan, Peoples R China.**

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37 14 **(Note: The name in the article is correct, and the name in parentheses comes from ScholarOne.**

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39 15 **As ScholarOne cannot modify the name, it is hereby stated in the article)**
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6 24 **Effect of robotic-assisted gait training on gait and motor function in spinal cord**
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9 25 **injury: a protocol of a systematic review with meta-analysis**
1011
12 26 **Abstract :**

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14 27 **Introduction:** Robotic-assisted gait training (RAGT) has been reported to be effective in
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17 28 rehabilitating patients with spinal cord injury (SCI). However, studies on RAGT showed different
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20 29 results due to a varied number of samples. Thus, summarising studies based on robotic-related
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23 30 factors is critical for the accurate estimation of the effects of RAGT on SCI. This work aims to
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25 31 search for strong evidence showing that using RAGT is effective in treating SCI and analyse the
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27 32 deficiencies of current studies.

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30 33 **Methods and analysis:** The following publication databases were electronically searched in
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32 34 December 2022 without restrictions on publication year: Medline, Cochrane Library, Web of
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34 35 Science, Embase, PubMed, the Cochrane Central Register of Controlled Trials and China National
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37 36 Knowledge Infrastructure. Various combinations of keywords, including ‘motor disorders’,
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39 37 ‘robotics’, ‘robotic-assisted gait training’, ‘Spinal Cord Injuries’, ‘SCI’ and ‘gait analysis’ were
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41 38 used as search terms. All articles on randomised controlled trials (excluding retrospective trials)
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43 39 using RAGT to treat SCI that were published in English and Chinese and met the inclusion criteria
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45 40 were included. Outcomes included motor function, and gait parameters included those assessed by
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47 41 using the instrumented gait assessment, the Berg balance scale, the 10-m walk speed test, the 6-min
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49 42 walk endurance test, the functional ambulation category scale, the Walking index of SCI and the
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51 43 ASIA assessment scale. Research selection, data extraction and quality assessment were conducted
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53 44 independently by two reviewers to ensure that all relevant studies were free from personal bias. In
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4 45 addition, the Cochrane Bias Risk Assessment Tool was used to assess the risk of bias. Review
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6 46 Manager V.5.3 software was utilised to produce deviation risk maps and perform paired meta-
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9 47 analyses.

11 48 **Strengths and limitations of this study**

- 14 49 1. This study was the first meta-analysis to systematically evaluate the efficacy and safety of RAGT
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17 50 in the treatment of SCI.
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19 51 2. The results of this study provided evidence for the treatment of SCI patients and helped therapists
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22 52 and patients to choose appropriate treatment methods.
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24 53 3. Two reviewers independently conducted research selection, data extraction and quality
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27 54 assessment to ensure that all relevant studies were free from personal bias.
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29 55 4. The language categories of the research search were only included in English and Chinese, and
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32 56 the final search results would have some bias.
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35 57 **Key words:** Spinal Cord Injuries; Motor disorders; Rehabilitation; Robotics, Gait Analysis

37 58 **Ethics and dissemination:** Ethics approval is not required for systematic reviews and network
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40 59 meta-analyses. The results will be submitted to a peer-reviewed journal or presented at a conference.
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43 60 **Trial registration number:** PROSPERO (CRD42022319555).
44

45 61 **Introduction**

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48 62 Spinal cord injury (SCI) is a serious disabling disease that often causes paraplegia or quadriplegia
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51 63 and affects patient's sensory, motor and autonomic nervous functions.[1 2] SCI leads to various
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53 64 complications, such as pressure ulcers, lung infections and urinary tract infections.[3] It also affects
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56 65 patients' quality of life and living standard and imposes a heavy burden on families and society.[4]
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59 66 It ultimately shortens patients' life expectancy.[5] In addition, the mortality rate of patients with
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4 67 SCI is higher than that of the general population.[6-8] National statistical data show an increasing
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6 68 incidence rate of SCI annually, and that the incidence rate of SCI per million residents is 9.3
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9 69 persons/year.[9] During the rehabilitation treatment of SCI, improving the walking ability, self-care
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11 70 ability and self-esteem of patients is an important aspect that helps them return to society and
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14 71 reduces their costs. Therefore, increased exercise capacity of the lower limbs is crucial to daily
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17 72 independence and social reintegration for this population, which mainly functions in standing and
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19 73 walking.[10 11]

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22 74 Robot-assisted gait training (RAGT) can improve the walking ability,[12] lower limb strength and
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24 75 independence of patients with incomplete SCI.[13] RAGT can also improve balance function and
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27 76 has been gradually applied in patients with SCI.[14] In patients with SCI, robots for lower limb
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30 77 rehabilitation can effectively and safely improve walking ability; reduce pressure ulcers,[15] lung
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32 78 infections,[8] urinary tract infections and other complications;[16] improve dignity; and reduce
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35 79 costs. However, high-quality evidence-based medical studies that systematically evaluated the
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38 80 efficacy of RAGT in the treatment of SCI remain scarce.

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40 81 Therefore, summarising studies based on RAGT-related factors is critical for the accurate estimation
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43 82 of the effects of RAGT on SCI. This meta-analysis aims to systematically evaluate the efficacy of
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46 83 RAGT in alleviating motor dysfunction and restoring speech ability in patients with SCI based on
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49 84 randomised clinical trials (RCTs), find strong evidence demonstrating that using RAGT is effective
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52 85 in the treatment of SCI and analyse the deficiencies of current studies.

53 86 **Methods**

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56 87 The protocol of this systematic review was planned and conducted following the Preferred
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59 88 Reporting Items for Systematic Reviews and Meta-Analyses Protocols Guideline and PRISMA
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4 89 2020 guidelines and was performed following a protocol registered in PROSPERO
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6 90 (CRD42022319555).[17 18] The plan starts on March 1, 2023 and ends on June 1. The review
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9 91 process is shown in **Figure 1**.

12 **Search strategy**

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14 93 Two reviewers (Jin-lin Peng and Lei Wang) electronically searched the following publication
15
16 94 databases in December 2022 without restrictions on publication year: Medline, Cochrane Library,
17
18 95 Web of Science, Embase, PubMed and China National Knowledge Infrastructure. Various
19
20 96 combinations of keywords, including ‘motor disorders’, ‘robotics’, ‘robotic-assisted gait training’,
21
22 97 ‘Spinal Cord Injuries’, ‘SCI’ and ‘gait analysis’ were used as search terms. The key terms matched
23
24 98 the appropriate Medical Subject Heading terms. Presearches were performed. Then, the final search
25
26 99 was conducted, relevant journals and references of review articles were manually searched online
27
28 100 to identify papers that may have been missed in the electronic database searches.

35 **Eligibility criteria**

38 **Inclusion criteria**

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40 103 (1) Study design: Only RCTs were included. (2) Selected population: Participants diagnosed with
41
42 104 SCI, namely, individuals with any level of traumatic SCI, regardless of the time since injury, sex
43
44 105 and age were included. (3) Type of intervention: The experimental groups received RAGT or RAGT
45
46 106 combined with other physical therapies. The control group not received RAGT or received other
47
48 107 types of physical therapy. (4) Comparison: The treated subjects were compared at baseline and then
49
50 108 with the control or sham-stimulated subjects. (5) Type of outcomes measured: Gait analysis
51
52 109 indicators, including gait speed (m/s), step length (cm), double support phase (% walking cycle),
53
54 110 single support phase (% walking cycle) and symmetry index; Berg balance scale; ASIA assessment
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4 111 scale; Holden walking ability classification (functional ambulation category scale); 10-m walk
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6 112 speed test; 6-min walk endurance test; and WISCI II score.
7
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9 113 **Exclusion criteria**

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11 114 Studies involving animal research, conference research, protocol studies or computer model
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13 115 research and duplicate papers were excluded. Two reviewers (Jin-lin Peng and Lei Wang)
14
15 116 independently screened titles and abstracts to identify articles reporting studies that met the
16
17 117 inclusion criteria. Then, the full-text versions of the identified articles were obtained and separately
18
19 118 screened to ensure that they met the inclusion criteria. Moreover, a third reviewer (Ai-lian Chen)
20
21 119 made the final assessment regarding whether or not full-text papers met the inclusion criteria.
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27 120 **Data extraction**

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29 121 A reviewer (Lei Wang) prepared the general information and data collection process by another
30
31 122 reviewer (Jin-lin Peng). The format of data collection included research design, participants
32
33 123 (number, diagnosis, age and target population numbers in each group), eligibility criteria,
34
35 124 intervention used on the research group and control group (i.e. site of stimulation, intensity, number
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37 125 of sessions and time of each session) and outcomes of interest.
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43 126 **Quality assessment**

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45 127 The quality evaluation of the included studies was performed independently by two reviewers (Jin-
46
47 128 lin Peng and Lei Wang) and was revised by the third reviewer (Ai-lian Chen). The methodological
48
49 129 quality of the intervention studies was assessed using the Physiotherapy Evidence Database (PEDro)
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51 130 scale. The PEDro scale is a valid and reliable measure of the methodological quality of RCTs. This
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53 131 10-item scale is based on the core criteria for RCT quality assessment.^[19] The quality of papers
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55 132 was classified based on the PEDro scale. Studies with scores of less than 6 points were considered
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4 133 low-quality studies, whereas those with scores equal to or greater than 6 points were considered
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6 134 high-quality studies (scores of 6–7 indicate good quality and 8–10 indicate excellent quality). [20]
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9 135 The GRADEpro GDT online tool was used to evaluate the level of evidence quality of the outcome
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11 136 indicators. The tool is available at its official website <http://www.guidelinedevelopment.org/>. The
12
13 137 GRADEpro GDT online tool for evaluating the quality of outcome indicators includes five
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15 138 degrading factors, namely, risk of bias, inconsistency, indirectness, imprecision and other
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17 139 considerations.[21] The quality of evidence can be divided into four levels, namely, ‘high’,
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19 140 ‘moderate’, ‘low’ and ‘very low’.[22]
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25 141 **Risk-of-bias assessment of individual studies**

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27 142 The quality of the included studies was evaluated and their scores were compared in a consensus
28
29 143 meeting between two independent authors (Jin-lin Peng and Lei Wang) to minimise errors and
30
31 144 potential biases in the evaluation. However, in the event of any disagreement, a third author (Ai-
32
33 145 lian Chen) was included in the discussion for a final consensus. The Cochrane Risk of Bias 2.0 tool
34
35 146 was used to assess the articles’ risk of bias.[23] Each article was assessed for selection bias (random
36
37 147 sequence generation and allocation concealment), performance bias (blinding of participants and
38
39 148 personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data
40
41 149 reporting) and reporting bias (selective outcome reporting). Each domain was rated as high risk of
42
43 150 bias, unclear of bias or low risk of bias. The risk map of the biases of the studies’ quality was
44
45 151 prepared with Review Manager 5.3.
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51 152 **Patient and Public Involvement**

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53 153 No patient participated in writing the system review plan. However, the results were disseminated
54
55 154 to patients with SCI.
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155 **Statistical analysis**

156 A meta-analysis was conducted using Review Manager 5.3. Heterogeneity between studies was
157 evaluated based on the I^2 statistic for the quantification of the proportion of the total outcome
158 attributable to variability amongst studies. The following ranges were defined: $I^2 = 0\%–30\%$ (no
159 heterogeneity), $I^2 = 30\%–49\%$ (moderate heterogeneity), $I^2 = 50\%–74\%$ (substantial heterogeneity)
160 and $I^2 = 75\%–100\%$ (considerable heterogeneity).[24] Based on heterogeneity, a random-effects
161 model was used when $I^2 > 30\%$, and a fixed-effects model was utilised when $I^2 = 0\%–30\%$.

162 For the comparison of data from different scales, pooled statistics were calculated using
163 standardised mean differences (SMDs). Furthermore, means and standard deviations after
164 intervention and follow-up evaluation for the RAGT and control groups (when relevant) were
165 applied to compute SMDs.

166 **Addressing missing data**

167 Regarding missing data, the original author was contacted for additional information. In the absence
168 of a reply, the data was calculated based on the availability factor. The potential effect of the missing
169 data on meta-analysis results was tested through sensitivity analysis.

170 **Subgroup analysis**

171 Analysis results showed a situation wherein heterogeneity was high and subgroup analysis was
172 required. Grouping analysis was conducted based on age (children, adolescents, middle-aged and
173 elderly), SCI level (cervical, thoracic and lumbar), disease course (recovery and sequelae), treatment
174 prescription and treatment duration to address potential heterogeneity and inconsistency. A meta-
175 analysis was also conducted to explore possible sources of heterogeneity.

176 **Sensitivity analysis**

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4 177 Sensitivity analysis was conducted on the main results to assess the effect of method quality,
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6 178 research quality, sample size, missing data and analysis methods on the results of this review to
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9 179 verify the robustness of the research conclusion.[25]
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11 180 **Assessment of publication bias**

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14 181 Each included study was evaluated based on the PEDro scale. Funnel charts were used to assess the
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17 182 publication bias of the main results included in the study. However, when the funnel chart was
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20 183 asymmetrical, attempts were made to explain its asymmetry.[26]
21

22 184 **Discussion**

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25 185 RAGT can improve the walking ability of patients with incomplete SCI and can be used by patients
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27 186 with stable vital signs. For patients with complete SCI, RAGT primarily acts to maintain the range
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30 187 of motion of joints. In recent years, there is an increasing number of studies on using RAGT to
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33 188 improve walking ability in SCI, and the new exoskeleton robot for lower limb rehabilitation has
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35 189 shown the advantage of safe transfer. Our current query shows that our work is the first systematic
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38 190 review and meta-analysis on RAGT for patients with SCI. The results of this meta-analysis could
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41 191 help patients and therapists select the appropriate treatment method for SCI and improve new
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43 192 options based on the comparative evidence for effectiveness and safety. Therefore, we hope that the
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46 193 results of this study will provide evidence for guideline recommendations.
47

48 194 **Study limitations**

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51 195 Articles published in both Chinese and English were included. Articles in other languages were not
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53 196 included, and their exclusion may affect our research. When incorporating outcome indicators, all
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56 197 data were sourced from scale evaluation and gait analysis instruments. The lack of research results
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59 198 on neural mechanisms may have had a certain effect on this study.
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3 199 **Data Availability**

4 200 The datasets used and analysed in the current study are included in this article.
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6 201

7 202 **Ethical Approval**

8 203 This research is a review, does not involve ethical issues and did not apply for ethical approval.
9
10 204

11 205 **Funding**

12 206 This study has no funding support.
13
14 207

15 208 **Disclosure**

16 209 All authors have read and approved the final manuscript.
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21 211 **Contributors**

22
23 212 As the first authors, WL and P-JL have made equal contributions to this work. WL and C-AL for
24
25 213 research concept and design. WL and P-JL are responsible for data acquisition. WL and P-JL made

26
27 214 the draft, and C-AL did the supervision. All the authors approved the publication of the Protocol.
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32 216 **Conflicts of Interest**

33
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35 217 All authors declare no potential conflicts of interest with respect to the research, authorship and/or

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37 218 publication of this study.
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40 219 **REFERENCES**
41
42 220

- 43 221 1. Eckert MJ, Martin MJ. Trauma: Spinal Cord Injury. *Surg Clin North Am* 2017;97:1031-45.
44 222 2. Anjum A, Yazid MD, Fauzi Daud M, *et al.* Spinal Cord Injury: Pathophysiology, Multimolecular Interactions,
45 223 and Underlying Recovery Mechanisms. *Int J Mol Sci* 2020;21.
46 224 3. Stricsek G, Ghobrial G, Wilson J, *et al.* Complications in the Management of Patients with Spine Trauma.
47 225 *Neurosurg Clin N Am* 2017;28:147-55.
48 226 4. Zhang JM, Li N, Zhu L, *et al.* Effects of pelvic floor biofeedback electrical stimulation combined with lower
49 227 limb rehabilitation robot training on intestinal function of patients with spinal cord injury. *Journal of Brain*
50 228 *and Nervous Diseases* 2021;29:53-7.
51 229 5. Xiang XN, Zhong HY, He HC. Research progress of lower limb exoskeleton rehabilitation robot in
52 230 improving walking ability of patients with spinal cord injury. *Chinese Journal of Rehabilitation Medicine*
53 231 2020;35:119-22.
54 232 6. Buzzell A, Chamberlain JD, Eriks-Hoogland I, *et al.* All-cause and cause-specific mortality following non-
55 233 traumatic spinal cord injury: evidence from a population-based cohort study in Switzerland. *Spinal Cord*
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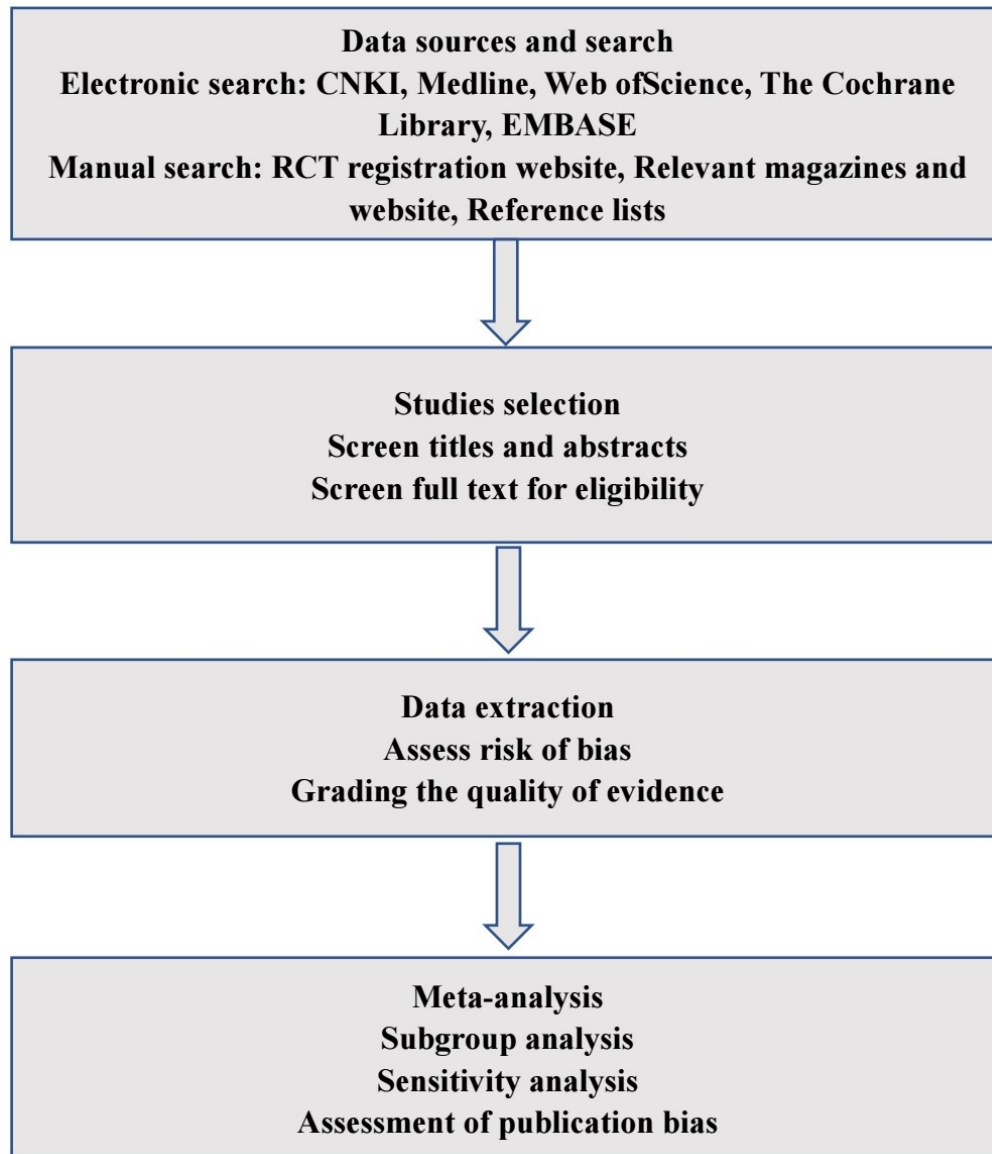
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- 234 2020;58:157-64.
- 235 7. Mirzaeva L, Lobzin S, Teinzerling N, *et al.* Complications and mortality after acute traumatic spinal cord
236 injury in Saint Petersburg, Russia. *Spinal Cord* 2020;58:970-9.
- 237 8. Li R, Ding M, Wang J, *et al.* Effectiveness of robotic-assisted gait training on cardiopulmonary fitness and
238 exercise capacity for incomplete spinal cord injury: A systematic review and meta-analysis of randomized
239 controlled trials. *Clin Rehabil* 2023;37:312-29.
- 240 9. Bárbara-Bataller E, Méndez-Suárez JL, Alemán-Sánchez C, *et al.* Change in the profile of traumatic spinal
241 cord injury over 15 years in Spain. *Scand J Trauma Resusc Emerg Med* 2018;26:27.
- 242 10. Mahooti F, Raheb G, Alipour F, *et al.* Psychosocial challenges of social reintegration for people with spinal
243 cord injury: a qualitative study. *Spinal Cord* 2020;58:1119-27.
- 244 11. Rahimi M, Torkaman G, Ghabaee M, *et al.* Advanced weight-bearing mat exercises combined with
245 functional electrical stimulation to improve the ability of wheelchair-dependent people with spinal cord
246 injury to transfer and attain independence in activities of daily living: a randomized controlled trial. *Spinal
247 Cord* 2020;58:78-85.
- 248 12. Grasmücke D, Zierjacks A, Jansen O, *et al.* Against the odds: what to expect in rehabilitation of chronic
249 spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis
250 of 55 patients according to age and lesion level. *Neurosurg Focus* 2017;42:E15.
- 251 13. Holanda LJ, Silva P, Amorim TC, *et al.* Robotic assisted gait as a tool for rehabilitation of individuals with
252 spinal cord injury: a systematic review. *J Neuroeng Rehabil* 2017;14:126.
- 253 14. Nam KY, Kim HJ, Kwon BS, *et al.* Robot-assisted gait training (Lokomat) improves walking function and
254 activity in people with spinal cord injury: a systematic review. *J Neuroeng Rehabil* 2017;14:24.
- 255 15. Rathore A, Wilcox M, Ramirez DZ, *et al.* Quantifying the human-robot interaction forces between a lower
256 limb exoskeleton and healthy users. *Annu Int Conf IEEE Eng Med Biol Soc* 2016;2016:586-9.
- 257 16. Pattanakuhar S, Ahmedy F, Setiono S, *et al.* Impacts of Bladder Managements and Urinary Complications
258 on Quality of Life: Cross-sectional Perspectives of Persons With Spinal Cord Injury Living in Malaysia,
259 Indonesia, and Thailand. *Am J Phys Med Rehabil* 2023;102:214-21.
- 260 17. Cumpston M, Li T, Page MJ, *et al.* Updated guidance for trusted systematic reviews: a new edition of the
261 Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*
262 2019;10:ED000142.
- 263 18. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting
264 systematic reviews. *BMJ* 2021;372:n71.
- 265 19. Elbanna ST, Elshennawy S, Ayad MN. Noninvasive Brain Stimulation for Rehabilitation of Pediatric Motor
266 Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials. *Arch Phys Med
267 Rehabil* 2019;100:1945-63.
- 268 20. Maher CG, Sherrington C, Herbert RD, *et al.* Reliability of the PEDro scale for rating quality of randomized
269 controlled trials. *Phys Ther* 2003;83:713-21.
- 270 21. Nasser M, Fedorowicz Z. Grading the quality of evidence and strength of recommendations: the GRADE
271 approach to improving dental clinical guidelines. *J Appl Oral Sci* 2011;19:0.
- 272 22. Brožek JL, Akl EA, Compalati E, *et al.* Grading quality of evidence and strength of recommendations in
273 clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy*
274 2011;66:588-95.
- 275 23. Sterne J, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*
276 2019;366:14898.
- 277 24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.

- 1
2
3 278 25. Li J, Zhong D, Ye J, *et al.* Rehabilitation for balance impairment in patients after stroke: a protocol of a
4 279 systematic review and network meta-analysis. *BMJ Open* 2019;9:e026844.
5
6 280 26. Sterne JA, Sutton AJ, Ioannidis JP, *et al.* Recommendations for examining and interpreting funnel plot
7 281 asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
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10 283 **Figure:** Flow chart of meta-analysis for robotic-assisted gait training in patients with spinal cord
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For peer review only



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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported (line numbers)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	60
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	4-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	212-215
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	206-207
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			61-85
Rationale	6	Describe the rationale for the review in the context of what is already known	81-85
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	104-113
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	104-113

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	92-101
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	92-101
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	114-120
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	114-120
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	121-126
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	121-126
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	121-126
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	142-152
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	121-126
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	156-166
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	171-180
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	167-170
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	181-184
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	181-184

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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3 *From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and*
4 *meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*
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