Efficacy of manual therapy on shoulder pain and function in patients with rotator cuff injury: A systematic review and meta-analysis

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Abstract. To critically evaluate the effects of manual therapy (MT) on pain and functional improvement in patients with rotator cuff injury (RCI), a systematic review of all randomized controlled trials (RCTs) on MT for RCI was conducted in the following databases: PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, Physiotherapy Evidence Database, Chinese National Knowledge Infrastructure, Wan-fang Data, Chinese Scientific Journal Database, and Chinese Biomedical Literature database from inception to March 28, 2023. A total of 1,110 participants from 24 eligible RCTs were included in the analysis. Compared with placebo, MT could not effectively relieve pain [standardized mean difference (SMD)=-0.25; 95% CI: -0.51 to 0.01; P=0.06], although its impact on functional improvement appears limited (SMD=0.20; 95% CI: -0.09 to 0.49; P=0.18). Combining MT with exercise had significant advantages over exercise alone, as combined therapy contributed to both pain reduction (SMD=0.36; 95% CI: 0.08 to 0.64; P=0.01) and functional enhancement (SMD=0.32; 95% CI: 0.11 to 0.52; P=0.002). Furthermore, MT combined with multimodal physiotherapy showed additional benefits in pain reduction (mean difference=1.57; 95% CI: 0.18 to 2.96; P=0.03) and functional improvement (SMD=0.77; 95% CI: 0.43 to 1.12; P<0.0001) compared with multimodal physiotherapy alone. These findings highlight the superior pain alleviation and functional improvement provided by MT when combined with exercise or physiotherapy. Consequently, MT has emerged as a pivotal component of therapeutic intervention for RCI.

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Abbreviations: MT, manual therapy; RCI, rotator cuff injury; RCT, randomized controlled trial; SMD, standardized mean difference; PRISMA, Systematic Review and Meta-Analyses; CI, confidence interval; MD, mean difference

Key words: RCI, MT, exercise, physiotherapy, meta-analysis, systematic review

Introduction

Rotator cuff injury (RCI) encompasses various shoulder disorders affecting the rotator cuff, including tears, tendinitis and impingement syndrome (1). Patients with RCI commonly report shoulder pain during specific movements and experience functional limitations (2,3), leading to sleep disturbance, stress and disruptions to daily and professional activities (4-6). Therefore, effective treatment is crucial to alleviate discomfort and enhance the quality of life of patients with RCI.

Treatment options for RCI include surgery (2), exercise, manual therapy (MT), physiotherapy, nonsteroidal anti-inflammatory drugs, intra-articular glucocorticoid injections and therapy using biomaterials (7-13). Surgery can restore the anatomy of rotator cuff well, but there is still a certain rate of retear (7). Non-steroidal anti-inflammatory drugs and intra-articular glucocorticoid injection can relieve pain in a short period of time, but the improvement of function is limited (7,8). Although biomaterials have made great progress in promoting the repair of RCI (9-13), they have not been widely used in clinical practice. MT is widely used as a non-pharmacological intervention by physiotherapists, chiropractors and osteopaths. MT involves the manipulation of joints and surrounding tissues by healthcare professionals. In the clinical setting, MT is administered either alone or in conjunction with exercise therapy or multimodal physiotherapy.

While previous systematic reviews and meta-analyses have assessed the efficacy of MT for RCI (14-16), these analyses often conducted qualitative syntheses of outcomes such as functional scores without pooling results into meta-analyses. Additionally, the effectiveness of MT in isolation, as well as its supplementary benefits when combined with exercise or physiotherapy, remain unclarified.

Previous randomized controlled trials (RCTs) have suggested that MT, alone or in combination with exercise or multimodal physiotherapy, yields positive outcomes for RCI (17-25). To provide a comprehensive overview, an updated systematic review and meta-analysis was conducted to evaluate the effectiveness of MT, either alone or as part of a multimodal intervention, on pain and function in patients with RCI.

Materials and methods

Data sources/searches. The registration number of the present systematic review in PROSPERO database is CRD42021246202 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=246202). The present study followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (26). The following electronic databases were searched from their date of inception to March 28, 2023: PubMed (https://pubmed.ncbi.nlm.nih.gov), Cochrane Central Register of Controlled Trials (https://www.cochranelibrary.com), Embase (https://www.embase.com/), Web of Science (https://www.webofscience.com), Physiotherapy Evidence Database (PEDro) (https://pedro.org.au), Chinese National Knowledge Infrastructure (https://www.cnki.net), Wan-fang Data (https://www.wanfangdata.com.cn/), Chinese Scientific Journal Database (http://qikan.cqvip.com/index.html) and Chinese Biomedical Literature database (http://www.sinomed.ac.cn/index.jsp). A combination of MESH terms and text words was used to identify relevant articles. These search terms were translated into Chinese for use in searching the aforementioned Chinese databases. Additionally, the reference lists of identified studies were screened to ensure that no relevant studies were overlooked. The complete PubMed search strategy is presented in Table SI.

Study selection

Inclusion criteria. Two investigators independently screened the studies by reading the titles, abstracts and complete texts. The inclusion criteria were: i) participants aged ≥18 years diagnosed with RCI, including rotator cuff tendinopathy/tendinitis, shoulder impingement syndrome, or subacromial bursitis, regardless of sex; ii) interventions comparing MT vs. placebo, MT plus exercise vs. exercise alone, or MT plus multimodal physiotherapy vs. multimodal physiotherapy alone; iii) outcomes broadly categorized into pain and shoulder function scores, with no restrictions; iv) RCT design and v) publication in English or Chinese.

Exclusion criteria. The exclusion criteria were: i) inability to locate a summary or full text; ii) studies from which data could not be accurately extracted; and iii) inconsistent outcome indicators. For republished studies, the most comprehensive reported data with the longest follow-up were selected.

Data extraction. The following data were independently extracted by two reviewers: first author, publication year, study characteristics (sample size, age, interventions, and intervention dosage and frequency), quality assessment details (randomization, allocation concealment, blinding, and outcome reporting), and study results. Data were cross-checked by two reviewers; in cases of disagreement, a third reviewer participated in discussions until a consensus was reached.

Outcome definitions. Outcome measures included shoulder pain and functional scores. Pain was assessed using the visual analogue scale, numeric pain rating scale, and pain component of composite scales. Functional scores comprised the Disability of the Arm, Shoulder and Hand Score, Shoulder Pain and Disability Index, Constant-Murley Score and Pennsylvania Shoulder Score. Due to limited long-term follow-up after the end of treatment in most studies, only data obtained at the end of treatment were included in the meta-analysis. A descriptive analysis was performed for studies with long-term follow-up (the follow-up period was >1 year).

Quality assessments. The risk of bias in included trials was assessed using items 2-11 of the PEDro scale, which gives a total score of 10 (27) (Table I). The PEDro scale has favorable reliability and validity (28-30) and is commonly used in systematic reviews of physiotherapy efficacy (31-33). Trials scoring ≥6 out of 10 were considered to have a low risk of bias (34,35). The risk of bias was independently evaluated by two reviewers.

Statistical analysis. Meta-analysis was conducted by calculating effect sizes and 95% confidence intervals in Review Manager 5.4 (Cochrane Collaboration; https://www.cochrane.org/). Results were organized based on outcome measures and intervention types. Numerical variables were analyzed using the mean difference (MD) or standardized MD (SMD). Pre- to post-treatment changes in pain and functional scores were pooled. In studies with crossover designs, outcome measures were analyzed at the first intervention exchange. Subgroup analysis was performed based on intervention dosage or frequency discrepancies.

Statistical heterogeneity was assessed using the I^2 statistic and the chi-squared test. If $I^2 \leq 50\%$ and $P \leq 0.05$, the heterogeneity between studies was considered acceptable (36). If there was significant heterogeneity ($I^2 > 50\%$ and $P < 0.05$) (37), the source of heterogeneity was explored by one-by-one exclusion sensitivity analysis. Because the included studies were from different study populations, a random effects model was used in all meta-analyses. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

A total of 4,774 articles were retrieved from the online databases. Among these, 1,907 articles were excluded due to duplication, while another 2,788 articles were excluded after independent screening of titles and abstracts by two reviewers. A total of 24 studies (38-52) met the inclusion criteria and were included in the quantitative synthesis after full-text review. No republished studies were reviewed.

Table I. Physiotherapy evidence database scale.

Item	Criteria
1	Eligibility criteria were specified
2	Subjects were randomly allocated to groups
3	Allocation was concealed
4	Group were similar at baseline for the most important prognostic indicators
5	All participants were blinded
6	All participants who administered therapy were blinded
7	All assessors who measured at least one key outcome were blinded
8	Measures of at least one key outcome measures were obtained from more than 85% of the participants initially allocated to groups
9	All participants for whom outcome measures were available received the treatment or control condition as allocated, or, where this was not the case, data for a least one key outcome was analyzed by intention to treat
10	The results of between group statistical analysis are reported for at least one key outcome
11	The study provides both point measures and measures of variability for at least one key outcome.

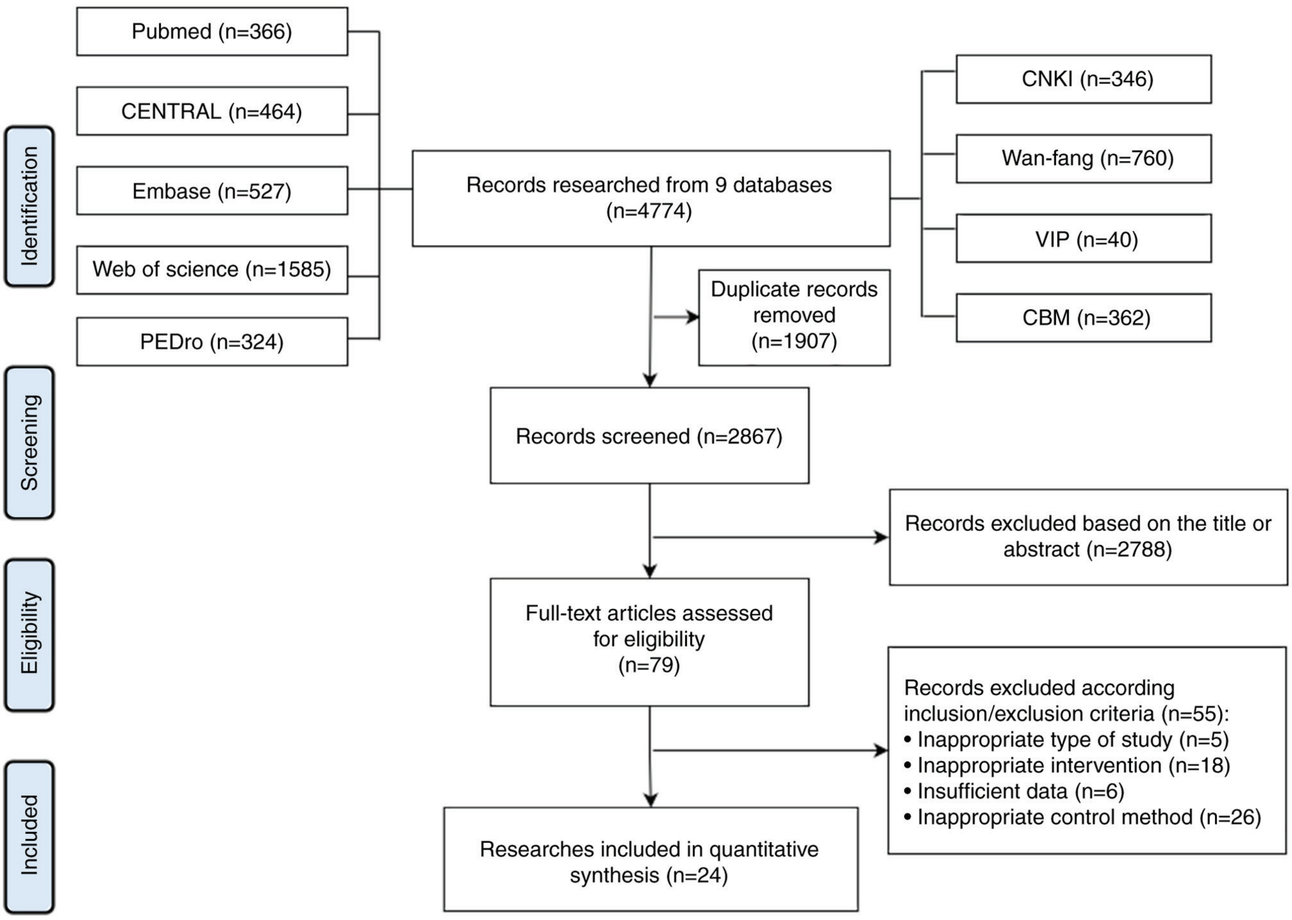

Figure 1. Literature screening flow diagram. CENTRAL, the Cochrane Central Register of Controlled Trails; PEDro, Physiotherapy Evidence Database; CNKI, the Chinese National Knowledge Infrastructure; VIP, the Chinese Scientific Journal Database; CBM, the Chinese Biomedical Literature database.

A detailed depiction of the literature screening process is provided (Fig. 1).

Basic characteristics of included studies. The characteristics of the included trials are summarized in Table II. A total of 24 eligible RCTs evaluated the efficacy of MT for RCI, involving 1,110 participants (546 in the experimental group, 564 in the control group). All studies included adults >18 years of age, and only one study (24) restricted the age range to young adults between 18-35 years of age. Among these RCTs, 10 compared MT with placebo, 11 evaluated the additional efficacy of MT added to exercise therapy vs. exercise alone, and three assessed

Table II. Characteristics of the included studies.

Author, year	Diagnosis	Sample size (Exp/Ctr)	Age (Exp/Ctr)	Intervention (Exp/Ctr)	Frequency	Treatment duration	Follow-up period	Outcome	(Refs.)
Manual therapy vs. placebo									
Atkinson *et al*, 2008	Rotator cuff tendinopathy	30/30	41.53 (18-63)/42 (20-76)	MT/Placebo	6 sessions in 2 weeks	2 weeks	2 weeks	②	(38)
Aytar *et al*, 2015	Subacromial impingement syndrome	22/22	52±3/52±4	MT/Placebo	9 sessions in 3 weeks	3 weeks	11 weeks	①④	(39)
Silva *et al*, 2019	Rotator cuff	30/30	46.06±16.11/ 44.46±12.14	MT/Placebo	Only once	/	/	①	(25)
Delgado-Gil *et al*, 2015	Shoulder impingement syndrome	21/21	55.4±7.8/ 54.3±10	MT/Placebo	2 sessions per week	2 weeks	2 weeks	①	(40)
Guimarães *et al*, 2016	Shoulder impingement syndrome	14/13	30.3±6.9/ 31.9±9.2	MT/Placebo	4 treatments (48 h apart)	8 days	8 days	②⑤	(41)
Haik *et al*, 2017	Shoulder impingement syndrome	30/31	32.5±12.0/ 31.3±11.0	MT/Placebo	twice in a period of 3-4 days apart	3-4 days	1 week	②④	(42)
Hunter *et al*, 2022	Shoulder impingement syndrome	25/25	62.0±9.6/ 61.4±11.3	MT/Placebo	once a week	4 weeks	12 months	①④	(20)
Kardouni *et al*, 2015	Subacromial impingement syndrome	24/21	31.1±12.3/ 31.2±12.1	MT/Placebo	Only once	/	/	②⑥	(43)
McClatchie *et al*, 2009	Painful arc	7/14	49.8±9.8	MT/Placebo	Only once	/	/	①	(44)
Surenkok *et al*, 2009	Rotator cuff tendinitis or tenosynovitis	13/13	55.07±13.36/ 54.30±12.70	MT/Placebo	Only once	/	/	①⑦	(45)
Manual therapy plus exercise vs. exercise alone									
Akbaba *et al*, 2019	Rotator cuff pathology	20/21	50±11.23/ 54.1±9.34	MT+Ex/Ex	MT: twice a week; Ex: twice a day	6 weeks	6 weeks	①④	(17)
Bang and Deyle, 2000	Shoulder impingement syndrome	27/23	42±10.1/ 45±8.4	MT+Ex/Ex	Twice a week	3 weeks	3 weeks	①	(46)
Camargo *et al*, 2015	Shoulder Impingement	23/23	35.96±12.08/ 32.65±10.73	MT+Ex/Ex	Unclear	4 weeks	4 weeks	①④	(47)

Table II. Continued.

Manual therapy plus exercise vs. exercise alone

Author, year	Diagnosis	Sample size (Exp/Ctr)	Age (Exp/Ctr)	Intervention (Exp/Ctr)	Frequency	Treatment duration	Follow-up period	Outcome	(Refs.)
Eliason *et al*, 2021	Subacromial pain syndrome	29/52	43.2±9.8/ 45.5±8.3	MT+Ex/Ex	MT: 1-2 times a week; Ex: twice a week	6 weeks	6 months	①⑦	(18)
Haider *et al*, 2018	Subacromial pain	20/20	49.3±9.99/ 49.8±9.67	MT+Ex/Ex	3 sessions per week	2 weeks	2 weeks	②⑤	(19)
Kachingwe *et al*, 2008	Shoulder impingement	9/8	48.9±13.7/ 47.3±20.1	MT+Ex/Ex	MT: once per week; Ex: once per day	6 weeks	6 weeks	①⑤	(48)
Kromer *et al*, 2014	Shoulder impingement syndrome	46/44	50.1±12.2/ 53.7±9.9	MT+Ex/Ex	MT: 10 sessions in 5 weeks; Ex: 10 sessions in 5 weeks	5 weeks	12 weeks	①⑤	(49)
Park *et al*, 2020	Subacromial impingement syndrome	10/10	49.2±9.48/ 50.9±9.1	MT+Ex/Ex	3 sessions per week\	4 weeks	4 weeks	⑤	(23)
Sharma *et al*, 2021	Shoulder impingement syndrome	40/40	21.3±2.1/ 21.8±2.8	MT+Ex/Ex	MT:12 sessions over 8 weeks; Ex: twice per day	8 weeks	8 weeks	⑤	(24)
Senbursa *et al*, 2007	Shoulder impingement syndrome	15/15	48.1±7.5/ 49.5±7.9	MT+Ex/Ex	MT: 3 times per week; Ex: 7 times per week	4 weeks	4 weeks	①	(50)
Vinuesa-Montoya *et al*, 2017	Shoulder impingement	21/19	46.85±8.02/ 51.21±5.29	MT+Ex/Ex	MT: twice per week; Ex: twice a day	5 weeks	5 weeks	①④	(51)

Table II. Continued.

Manual therapy plus multimodal physiotherapy vs. multimodal physiotherapy

Author, year	Diagnosis	Sample size (Exp/Ctr)	Age (Exp/Ctr)	Intervention (Exp/Ctr)	Frequency	Treatment duration	Follow-up period	Outcome	(Refs.)
Barra López *et al*, 2013	Subacromial impingement syndrome	40/40	56.2±12/ 59.1±11.5	MT +MP/ MP	MT: 2 sessions per week;MP: 5 sessions per week	3 weeks	3 months	①⑦	(52)
İğrek and Çolak, 2021	Subacromial impingement syndrome	15/14	44.4±11/ 45.9±9.7	MT + MP/ MP	5 times per week	4 weeks	16 weeks	①④	(21)
Menek *et al*, 2019	Roator cuff syndrome	15/15	51.73±6.64/ 50.26±4.28	MT + MP/ MP	5 times per week	6 weeks	6 weeks	①④	(22)

(1) Exp, experiment group; Ctr, control group; MT, manual therapy; Ex, exercise; MP, multimodal physiotherapy. (2) Outcomes; ①VAS, Visual Analogue Scale; ② NPRS, Numeric Pain Rating Scale; ③ CMS, pain component of the Constant–Murley Score; ④ DASH, Disability of the Arm, Shoulder, and Hand; ⑤ SPADI, Shoulder Pain and Disability Index; ⑥ Penn, Pennsylvania Shoulder Score; ⑦ CMS, Follow-up period: the time from baseline to last follow-up visit.

the additional benefit of MT combined with multimodal physiotherapy vs. multimodal physiotherapy alone.

Risk of bias assessment. The average PEDro scale score across the 24 RCTs was 6.45 (Table III). A total of 19 trials scored ≥6 on the PEDro scale, indicating a low risk of bias. Among the five studies scoring <6, the limitations primarily involved inadequate concealment of allocation, insufficient blinding of participants and therapists, and failure to adhere to intention-to-treat principles.

MT vs. Placebo

Pain. A total of 10 studies evaluated changes in shoulder pain after MT compared with placebo. The heterogeneity analysis indicated acceptable heterogeneity (I^2=44% and P=0.07). Meta-analysis demonstrated that MT could not effectively relieve pain (SMD=-0.25; 95% CI: -0.51 to 0.01; Z=1.89; P=0.06). Subgroup analysis revealed that while a single session of MT showed no significant difference in pain reduction compared with placebo, multiple MT sessions were associated with superior pain relief (SMD=-0.43; 95% CI: -0.68 to -0.18; Z=3.38; P=0.0007) (Fig. 2). Only one study (20) conducted a 12-month long-term follow-up, indicating sustained pain relief with MT compared with placebo (P=0.01). In addition, subgroup analysis based on the MT regimen were also attempted, but there was high heterogeneity in subgroup (I^2=81% and P=0.02) and no reliable conclusions could be drawn (data not shown).

Function. A total of six studies evaluated improvements in functional scores with MT compared with placebo. Heterogeneity analysis revealed that I^2=27% and P=0.23. Comprehensive analysis showed no significant difference in functional improvement between MT and placebo (SMD=0.20; 95% CI: -0.09 to 0.49; Z=1.33; P=0.18). In subgroup analysis, there was no significant difference in functional improvement after MT alone vs. placebo, with either a single intervention or more than one session (Fig. 3).

MT plus exercise vs. exercise alone

Pain. The additional efficacy of MT in pain reduction when added to exercise therapy was examined in nine studies. There was high heterogeneity in the analysis (I^2=50%; P=0.04). Pooled results showed that the addition of MT resulted in additional pain reduction compared with exercise therapy alone (SMD=0.36; 95% CI: 0.08 to 0.64; Z=2.50; P=0.01). A sensitivity analysis was performed because of the high heterogeneity (I^2=36%; P=0.15). Removal of the study by Haider *et al* (19) provided a significant reduction in heterogeneity but did not change the overall findings (SMD=0.27; 95% CI: 0.01 to 0.53; Z=2.05; P=0.04) (Fig. 4).

Function. A total of nine RCTs evaluated the additional improvement in function with MT added to exercise therapy. The heterogeneity was acceptable (I^2=11%; P=0.34). Combined results indicated that MT plus exercise therapy led to greater functional improvement compared with exercise alone (SMD=0.32; 95% CI: 0.11 to 0.52; Z=3.07; P=0.002) (Fig. 5).

Table III. Risk of bias assessment using the physiotherapy evidence database scale.

	PEDro scale											
Trial	1	2	3	4	5	6	7	8	9	10	11	Total
Atkinson *et al* (38), 2008	√	√	√	√	-	-	-	√	-	√	√	6
Aytar *et al* (39), 2015	√	√	-	√	√	-	√	√	-	√	√	7
Silva *et al* (25), 2019	√	√	√	√	-	-	-	√	√	√	√	7
Delgado-Gil *et al* (40), 2015	√	√	√	√	√	-	√	-	√	√	√	8
Guimarães *et al* (41), 2016	√	√	-	√	-	-	√	√	√	√	√	7
Haik *et al* (42), 2017	√	√	-	√	√	-	√	√	√	√	√	8
Hunter *et al* (20), 2022	√	√	√	√	-	-	√	-	√	√	√	7
Kardouni *et al* (43), 2015	√	√	√	√	-	-	√	√	-	√	√	7
McClatchie *et al* (44), 2009	√	√	-	√	-	-	√	√	-	√	√	6
Surenkok *et al* (45), 2009	√	√	-	-	-	-	√	√	-	√	√	5
Akbaba *et al* (17), 2019	√	√	√	√	-	-	√	√	√	√	√	8
Bang and Deyle (46), 2000	√	√	-	√	-	-	√	√	-	√	√	6
Camargo *et al* (47), 2015	√	√	√	√	-	-	√	√	√	√	√	8
Eliason *et al* (18), 2021	√	√	√	√	√	-	-	√	√	√	√	8
Haider *et al* (19), 2018	√	√	-	√	-	-	-	√	-	√	√	5
Kachingwe *et al* (48), 2008	√	√	-	-	-	-	√	√	-	√	√	5
Kromer *et al* (49), 2014	√	√	√	√	-	-	-	√	√	√	√	7
Park *et al* (23), 2020	√	√	√	√	-	-	√	-	-	√	√	6
Sharma *et al* (24), 2021	√	√	√	√	√	-	-	√	-	√	√	7
Senbursa *et al* (50), 2007	√	√	-	√	-	-	-	-	-	√	√	4
Vinuesa-Montoya *et al* (51), 2017	√	√	√	√	-	-	√	√	-	√	√	7
Barra López *et al* (52), 2013	√	√	-	√	-	-	√	-	√	√	√	6
İğrek and Çolak (21), 2021	√	√	√	√	-	-	-	√	√	√	√	7
Menek *et al* (22), 2019	√	√	-	√	-	-	-	√	-	√	√	5

The search terms of #1-6, #8-14, #16-22 were connected with 'OR' respectively, and then the three combinations were connected with 'AND' to search the target study.

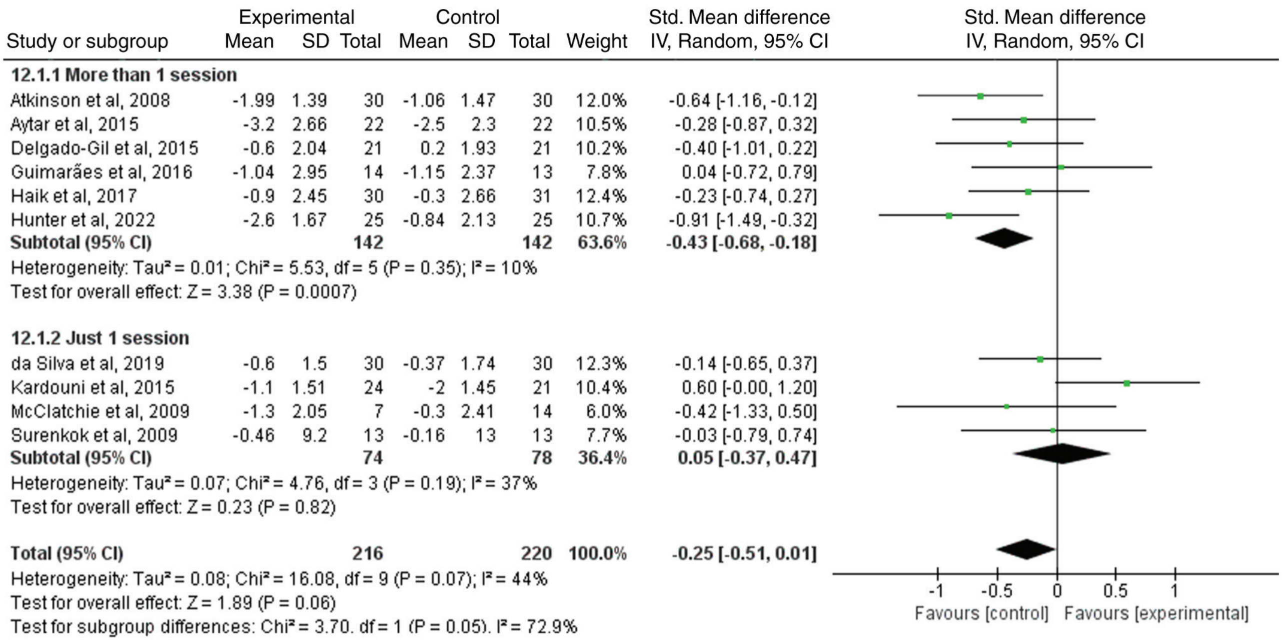

Figure 2. Forest plot of changes in pain in the manual therapy vs. placebo groups. CI, confidence interval; SD, standard deviation.

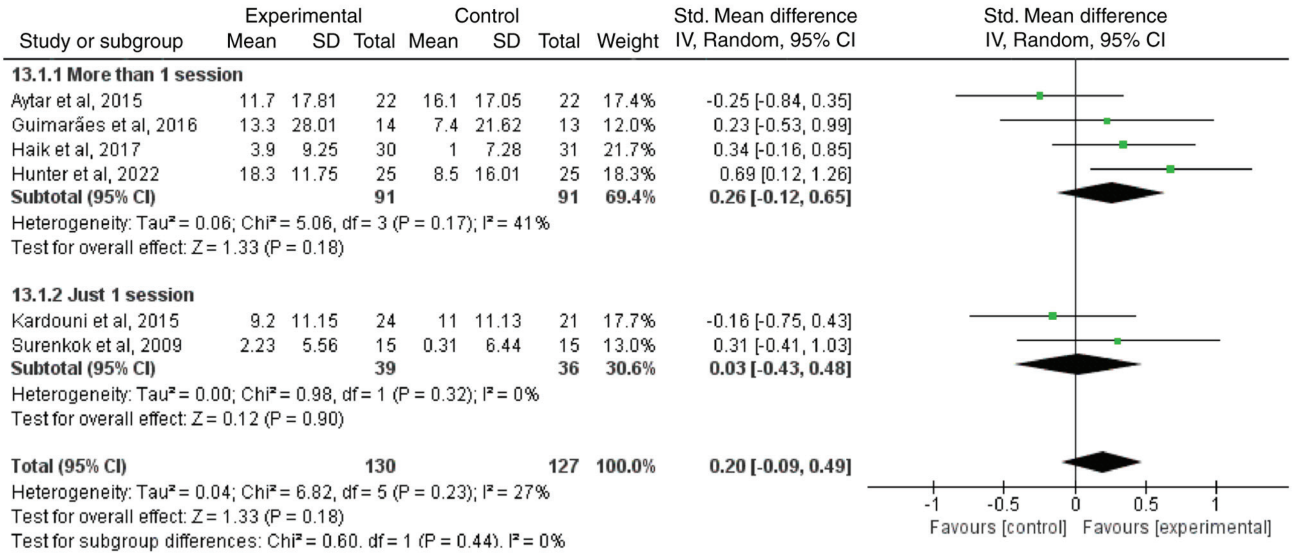

Figure 3. Forest plot of changes in functional scores in the manual therapy vs. placebo groups. CI, confidence interval; SD, standard deviation.

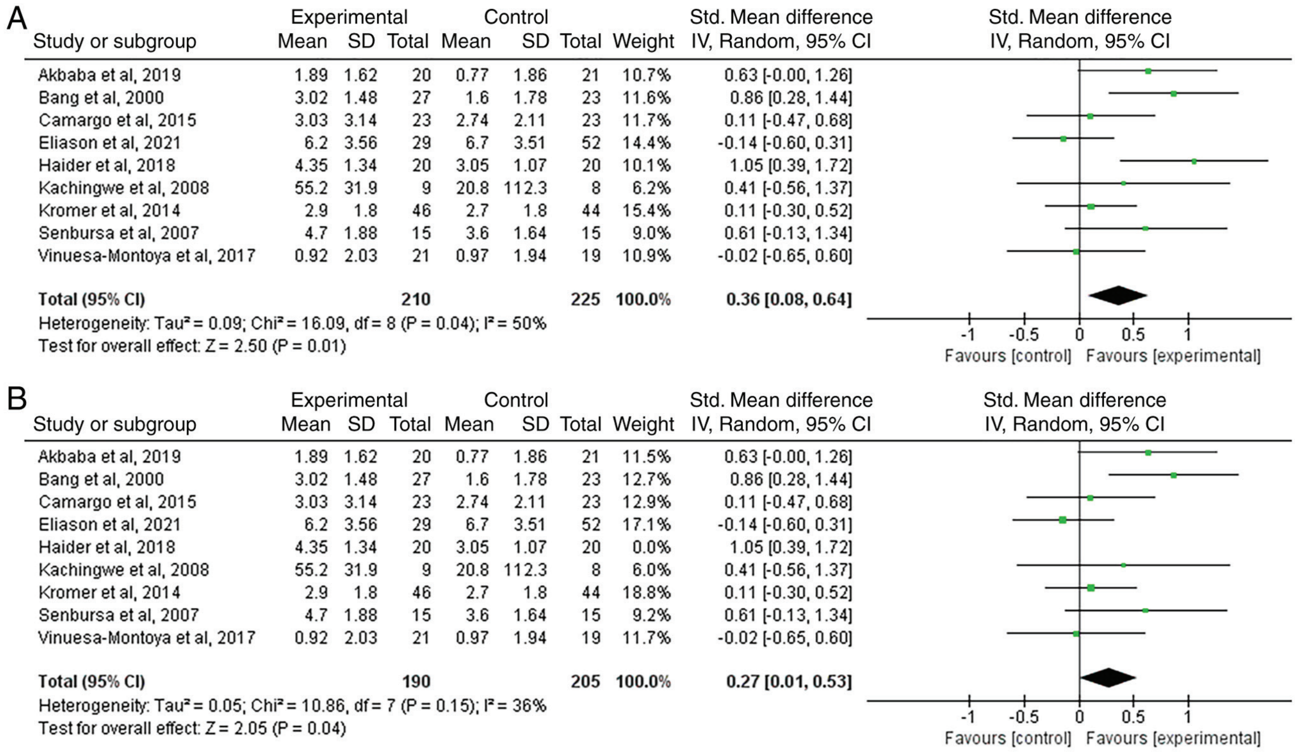

Figure 4. (A) Forest plot of changes of pain in the MT plus exercise vs. exercise alone groups. (B) Forest plot of sensitivity analysis of changes of pain in the MT plus exercise vs. exercise alone groups. MT, manual therapy; CI, confidence interval; SD, standard deviation.

MT plus multimodal physiotherapy vs. multimodal physiotherapy

Pain. A total of three studies compared the effect of MT plus multimodal physiotherapy vs. multimodal physiotherapy alone on pain reduction. There was a high level of heterogeneity (I^2=89%; P=0.0001). Meta-analysis indicated that MT combined with multimodal physiotherapy achieved superior pain relief compared with multimodal physiotherapy alone (MD=1.57; 95% CI: 0.18 to 2.96; Z=2.22; P=0.03). A sensitivity analysis was performed because of the high heterogeneity. Removal of the study by Menek *et al* (22) provided a significant reduction in heterogeneity (I^2=0%; P=0.78) but did not change the overall findings (MD=0.86; 95% CI: 0.40 to 1.33; Z=3.65; P=0.0003) (Fig. 6).

Function. A total of three studies compared the effect of MT plus multimodal physiotherapy with multimodal physiotherapy alone on functional improvement. The heterogeneity was acceptable (I^2=0%; P=0.82). Meta-analysis revealed that MT combined with multimodal physiotherapy achieved superior

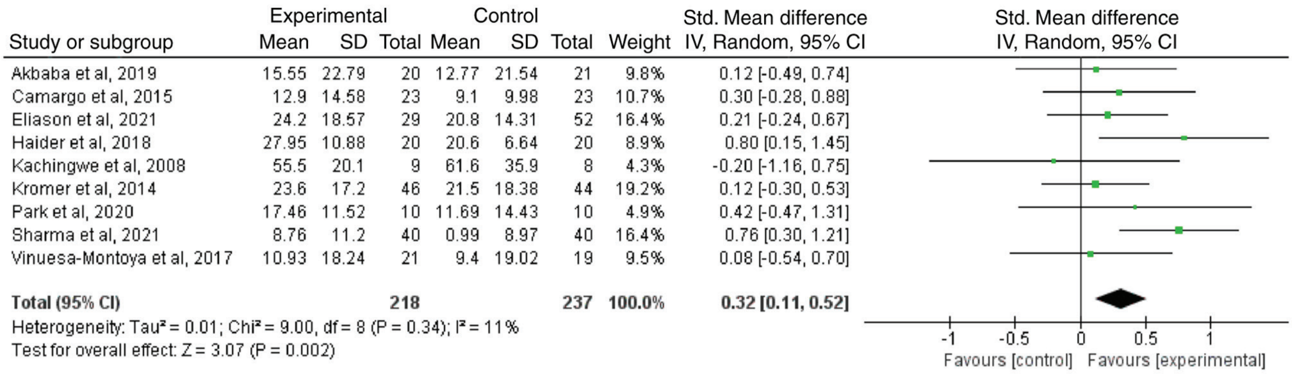

Figure 5. Forest plot of changes in functional scores in the manual therapy plus exercise vs. exercise alone groups. CI, confidence interval; SD, standard deviation.

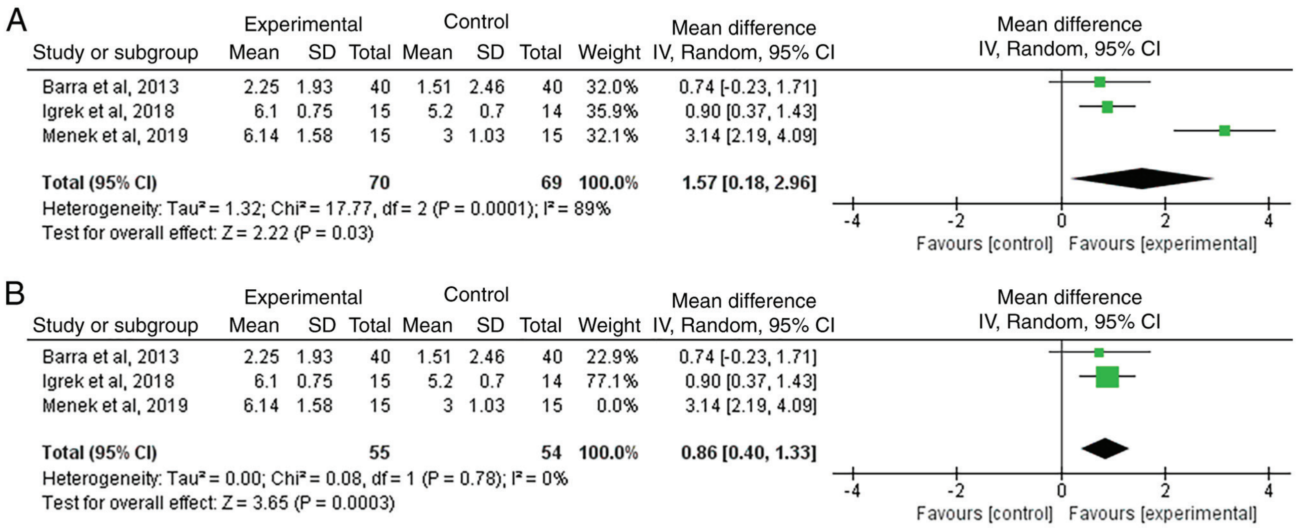

Figure 6. (A) Forest plot of changes in pain in the MT plus multimodal physiotherapy vs. multimodal physiotherapy alone groups. (B) Forest plot of sensitivity analysis of changes in pain in the MT plus multimodal physiotherapy vs. multimodal physiotherapy alone groups. MT, manual therapy; CI, confidence interval; SD, standard deviation.

functional improvement compared with multimodal physiotherapy alone (SMD=0.77; 95% CI: 0.43 to 1.12; Z=4.38; P<0.0001) (Fig. 7).

Discussion

The present systematic review and meta-analysis assessed the efficacy of MT for RCI in terms of pain and function. The results of the present study indicated that the improvement of shoulder pain and function in RCI patients with MT alone is limited. However, when combined with exercise or multimodal physiotherapy, MT not only significantly reduced pain but also enhanced shoulder function.

The present study revealed that MT alone is not effective in reducing pain compared with placebo, which is inconsistent with the findings of previous meta-analyses (14,15). However, these previous studies had limitations in the number of included RCTs and lacked pooled outcomes regarding functional improvements. No significant difference in functional improvement between MT alone and placebo were discovered. Additionally, a variation in the number of interventions across trials was observed, highlighting that the optimal number of MT sessions for RCI remains unknown (53-55). Subgroup analysis revealed that multiple intervention sessions led to improved pain relief than single sessions, suggesting the need to use multiple MT sessions in clinical practice.

In the clinical setting, MT and exercises are commonly preferred as primary physiotherapy treatments for shoulder syndromes (56). Consistent with previous studies, the findings of the present study revealed that combining MT with exercise yielded superior outcomes compared with exercise alone. This may be attributed to the analgesic effect and correction of muscle-bone imbalance by early MT, providing optimal conditions for exercise implementation (23,24). Exercises should be tailored to the patient's condition and combined with appropriate restraint to regulate and repair muscle metabolism (57).

The present study is the first systematic review to examine the efficacy of MT added to multimodal physiotherapy for the treatment of RCI, and it was revealed that the addition of MT improved the effectiveness of treatment.

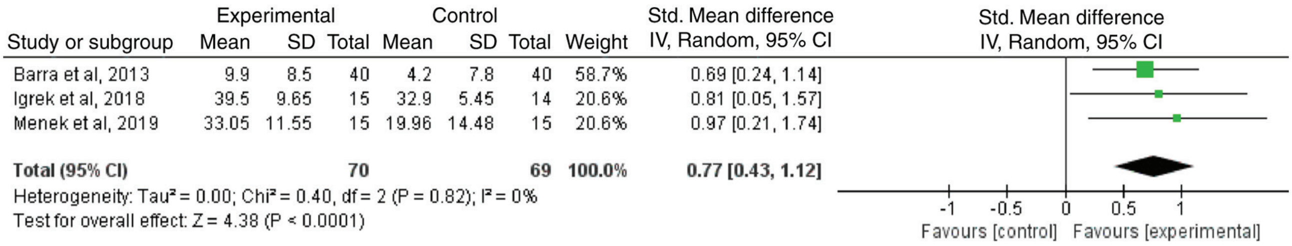

Figure 7. Forest plot of changes in functional scores in the manual therapy plus multimodal physiotherapy vs. multimodal physiotherapy alone groups. CI, confidence interval; SD, standard deviation.

Although multimodal physiotherapy was not strictly defined, the included trials commonly used exercise and electrotherapy interventions. Electrotherapy, including infrared, therapeutic ultrasound, and transcutaneous electrical nerve stimulation (58), is a common treatment modality for rotator cuff disease that achieves pain relief and muscle relaxation. The results indicated a synergistic effect of MT with multimodal physiotherapy, especially exercise and electrotherapy.

Several pooled results exhibited high heterogeneity when MT was combined with exercise or multimodal physiotherapy. In comparing the efficacy of pain reduction between the combination of MT and exercise vs. exercise alone, a significant reduction in heterogeneity was obtained after the study by Haider *et al* (19) was excluded from the sensitivity analysis. The study characteristics by Haider *et al* were reviewed and compared with other studies and the duration of intervention was revealed to be shorter in the present study (2 weeks) than in other studies (at least 3 weeks). When comparing pain improvement between MT combined with multimodal physiotherapy and multimodal physiotherapy alone, the study by Menek *et al* (22) used a longer duration of intervention (6 weeks) than the other studies (<4 weeks). These results suggested that duration of intervention may be a potential source of heterogeneity.

The present study has certain limitations. Of the 24 included studies, only one (20) had a long-term follow-up of 1 year and showed that MT improved pain more efficiently than placebo, but the study did not report whether there was disease progression. As a meta-analysis could not be performed, the long-term efficacy of MT for RCI and whether it will lead to disease progression are uncertain. Moreover, therapeutic time window, comorbidities and degree of injury are the confounding factors. Because of the lack of description of these conditions in the included studies, subgroup analysis could not be performed. Due to the limited number of studies on MT for RCI, further network meta-analysis could not be performed.

In conclusion, the results of the present meta-analysis demonstrated that combining MT with exercise therapy or multimodal physiotherapy not only enhances pain relief compared with exercise therapy or multimodal physiotherapy alone, but also effectively improves shoulder joint function. Therefore, MT is considered a pivotal component of conservative treatments, and its integration with other therapeutic approaches is recommended for optimal RCI therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SL and XL conceptualized and designed the present study. QS and XL provided administrative support. SL, LC, YF, WD and CX carried out data collection. LS and LXF confirm the authenticity of all the raw data. All authors participated in data analysis and interpretation, the writing process, and read and approved the final manuscript. All the authors confirm that the study followed PRISMA guidelines.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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