Systematic Review

The Effectiveness of Manual Therapy for Relieving Pain, Stiffness, and Dysfunction in Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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Background: Knee osteoarthritis (KOA) is the most common form of arthritis, leading to pain disability in seniors and increased health care utilization. Manual therapy is one widely used physical treatment for KOA.

Objective: To evaluate the effectiveness and adverse events (AEs) of manual therapy compared to other treatments for relieving pain, stiffness, and physical dysfunction in patients with KOA.

Study Design: A systematic review and meta-analysis of manual therapy for KOA.

Methods: We searched PubMed, EMBASE, the Cochrane Library, and Chinese databases for relevant randomized controlled trials (RCTs) of manual therapy for patients with KOA from the inception to October 2015 without language restrictions. RCTs compared manual therapy to the placebo or other interventional control with an appropriate description of randomization. Two reviewers independently conducted the search results identification, data extraction, and methodological quality assessment. The methodological quality was assessed by PEDro scale. Pooled data was expressed as standard mean difference (SMD), with 95% confident intervals (CIs) in a random effects model. The meta-analysis of manual therapy for KOA on pain, stiffness, and physical function were conducted.

Results: Fourteen studies involving 841 KOA participants compared to other treatments were included. The methodological quality of most included RCTs was poor. The mean PEDro scale score was 6.6. The meta-analyses results showed that manual therapy had statistically significant effects on relieving pain (standardized mean difference, SMD = -0.61, 95% CI -0.95 to -0.28, P = 76%), stiffness (SMD = -0.58, 95% CI -0.95 to -0.21, P = 81%), improving physical function (SMD = -0.49, 95% CI -0.76 to -0.22, P = 65%), and total score (SMD = -0.56, 95% CI -0.78 to -0.35, P = 50%). But in the subgroups, manual therapy did not show significant improvements on stiffness and physical function when treatment duration was less than 4 weeks. And the long-term information for manual therapy was insufficient.

Limitations: The limitations of this systematic review include the paucity of literature and inevitable heterogeneity between included studies.

Conclusion: The preliminary evidence from our study suggests that manual therapy might be effective and safe for improving pain, stiffness, and physical function in KOA patients and could be treated as complementary and alternative options. However, the evidence may be limited by potential bias and poor methodological quality of included studies. High-quality RCTs with long-term follow-up are warranted to confirm our findings.

Key words: Knee osteoarthritis, manual therapy, systematic review

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Osteoarthritis (OA) is the most common form of arthritis, and the leading cause of disability and pain affecting middle-aged and elderly people worldwide (1,2), caused by structural changes in joints resulting in pain, deterioration of function, and disability (3,4). In Western countries, most people over 65 years of age suffer from this disease (5), and it is particularly common in the knee (6,7). Current conventional treatments include non-pharmacological measures, medication, and surgical procedures. According to recommendations by the American College of Rheumatology (ACR), the pharmacological treatment of knee osteoarthritis (KOA) relies on pain relief medication, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and intraarticular injection. However gastrointestinal upset and dose dependency are frequent problems with these medications. For non-pharmacological intervention, losing weight is strongly recommended, but long-term acceptance or compliance of weight loss is generally poor. In other words, interests in developing alternative approaches for KOA are needed.Among non-pharmacologic interventions, manual therapy is widely used for musculoskeletal conditions. Manual therapy means that doctors or patients only use their hands to control deterioration of function and pain. In the United States, massage is one of the most popular complementary and alternative therapies (8). Every country's manual therapy style may be different, but as a rule it involves massage, joint mobilization, and manipulation. In recent years, several guidelines recommended manual therapy as an adjunct to core treatments (7,9,10). Three randomized controlled trials (RCTs) have demonstrated that manual therapy could reduce pain, alleviate stiffness, and improve physical function (11-13). The most recent systematic review (SR) suggests that manual therapy is effective compared to no intervention (14), but it is no better than medication or placebo for treating pain in patients with KOA. However, the evidence is insufficient, mostly due to excluding non-English publications and other kinds of manipulations such as tuina (a manual therapy of traditional Chinese medicine), for those studies mostly are published in Chinese. Apart from this, meta-analysis is not performed for heterogeneity using standardized assessment tools and adverse events (AEs) are not included.

For KOA patients, the most common symptoms are pain, stiffness, and physical dysfunction, which also affect quality of life (15). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a self-report questionnaire for OA of the hip or knee, with higher scores indicating more serious pain, poorer physical function, and increased stiffness. It has been widely used as a tool by clinical investigators to assess patients with KOA. Since it was published in 1988, it has been translated and validated in many languages (16-22). The reliability, validity, and sensitivity to the change in the physical condition of KOA patients has been proven (16). Focusing on those important aspects of clinical outcomes, we performed an updated systematic review and meta-analysis to critically evaluate the effectiveness as well as AEs of manual therapy for KOA.

Methods

Study Selection

All eligible studies were randomized controlled trials (RCTs). After duplicates were removed, abstracts of all articles were independently screened based on predefined inclusion criteria. There were no limitations on the participants' age, country, gender, and sample size. The following selection criteria were applied: 1) patients, a clear diagnosis of KOA; 2) intervention, including manual therapy, massage, tuina, manipulation, joint mobilization, and osteopathy.

Studies were excluded: 1) if the studies were not RCTs; 2) if the outcome was not assessed by WOMAC; 3) if the intervention was multimodal treatment such as manual therapy combined with pharmacologic; and 4) if participants underwent surgery.

Data Sources and Searching Strategy

Relevant studies were retrieved from the following electronic databases up to October 2015: PubMed, EMBASE, Cochrane Library, China Knowledge Resource Integrated Database (CNKI), Weipu Database for Chinese Technical Periodicals (VIP), CBM, and Wanfang Data, using all the possible Medical Subject Headings (MeSH) and keywords: (manual ther* OR musculoskeletal manipulation OR manipulat* OR joint mobili* OR tuina OR massage OR osteopath*) AND (osteoarthritis, knee OR gonarthrosis OR osteoarthrosis OR osteoarthrit* OR osteoarthropathy OR arthralgia). The search strategy consisted of 3 groups of terms. The first terms were osteoarthritis, gonarthrosis, osteoarthrosis, osteoarthropathy, or arthralgia. The second terms were musculoskeletal manipulation, manual therapy, joint mobilization, tuina, massage, or osteopathy, and the last term was random. We combined these terms for

the search. There was no limitation to study publication status or language. The three main database search strategies were presented in Appendix I.

Study Selection and Date Abstraction

We scanned all records by title and abstract to identify relevant studies. Then full text articles were retrieved for further analysis. Two researchers (YLC and HYH) independently conducted study selection and extracted data of studies meeting the predefined criteria. The data of every study included the first author, publication year, sample size, participants' mean age, outcome assessment, duration of treatment, and type of study. If there were disagreements, the authors reached consensus by discussing them with the third author (YXZ).

Methodological Quality Assessment

Two researchers (XZW and TL) independently assessed the methodological quality of each article using the PEDro scale. The PEDro scale is based on the Delphi list and has been reported to have sufficient reliability for RCTs of physical therapy in systematic reviews (23). The PEDro scale consists of 11 items, including (1) specified eligibility criteria of studies, (2) random allocation of studies, (3) concealed allocation, (4) similarity between groups at baseline, (5) blinding of all subjects, (6) blinding of all therapists, (7) blinding of all assessors, (8) less than 15% dropouts, (9) intention to treat analysis, (10) statistical comparisons between-group, and (11) point measures and variability data. Item 2 through 11 were used to calculate the PEDro score. Each item was scored as either 1 or 0 according to whether the item was met or not, respectively. The score was summed and a higher score represents a better methodological quality. When the PEDro score exceeds the cut-off point 6, this indicates high quality (23). Disagreement was resolved by discussion with the third review author (JP). If a study ranked as low quality it was still included, but this might reduce our confidence of recommendation.

Data Synthesis and Analysis

All data were combined and analyzed using Cochrane Collaboration software (Review Manager Version 5.2 for Windows; Copenhagen: The Nordic Cochrane Centre). The WOMAC index including 3 items was used to evaluate hip or knee OA patients, i.e. pain, stiffness, and physical function. Each item consisted of 24 parameters. Higher WOMAC scores indicated greater pain, stiffness, or physical disability. Because of different subscales of WOMAC measuring the outcomes, and property of continuous variables, we choose the standard mean difference (SMD) to calculate the mean difference (24). The mean changes in outcome measures between the end of the final intervention and the baseline was used to assess the difference between the manual therapy group and control group in the meta-analyses. SMD and 95% confidence intervals (CIs) were calculated. All the treatment effectiveness estimates summary calculations used a random effects model. For the heterogeneity, we used the P statistic, a quantitative measure to assess it (25). Results with an P of 25% to 50% indicated low heterogeneous, P of 50% to 75% indicated moderate heterogeneous, and P above 75% indicated high heterogeneous (25). If the heterogeneous rate is too high, the result of the analysis will be biased. So, when $P > 50\%$, the heterogeneity was moderate or high, we should try to seek out the potential sources of it by sensitivity analysis. In view of different treatment duration, subgroups analyses were performed. AEs were also considered.

Results

Result of Search

Seven electronic databases (3 English and 4 Chinese) were searched. Of the 2,249 originally identified publications, 1,078 were excluded for duplication. In the following title and abstract screening, 1,072 studies were excluded for not meeting the included criteria. A further 99 potentially related records were retrieved and reviewed for full text. Of which, 85 studies were excluded because they were not RCTs (n = 3), the outcome assessment was not WOMAC (n = 48), they were only abstracts (n = 4), they included multimodal treatment (n = 22), they were study protocols (n = 4), or they had unrelated outcomes (n = 4). A final library of 14 articles remained for meta-analysis. The articles selection process is summarized in Fig. 1.

Study Characteristics

Of the 14 RCTs, 9 were published in English (13,26-29) and 5 were published in Chinese (30-38). All studies were parallel designed RCTs and conducted in a single center. The sample size of the studies ranged from 36 to 120 (total 841, including 233 men and 608 women). All participants were older adults.

Maitlan joint mobilization, Swedish massage, Chinese tuina, self-massage, acupressure, manipulation, and manual stretching were the main KOA techniques

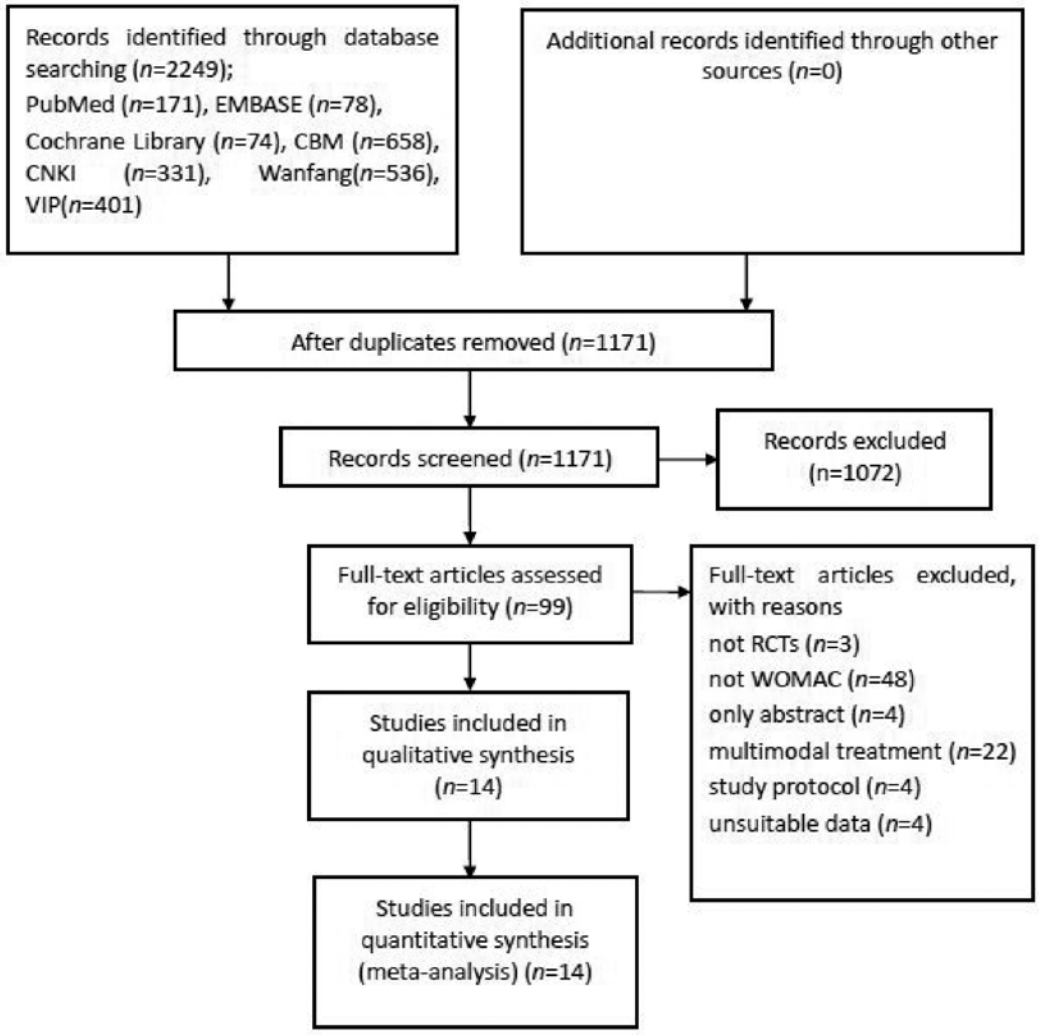

Fig. 1. *Flow diagram of studies considered for review.*

applied. Each time of treatment ranged from about 20 to 60 minutes. Treatment frequency was once a week (28), twice weekly (27,35,37), 3 times a week (26,30,34), even 7 times weekly, or ranged from twice a week to once weekly depending on the protocol (13), and treatment duration ranged from 2 to 12 weeks. All study outcomes used WOMAC, while 10 studies (13,26-29,31-33,35,36) described pain, stiffness, function, and total score, one study (37) described pain, stiffness, and function score, and the other 3 studies (30,34,38) described total score. Details of the included studies were listed in Table 1.

Methodological Quality

The quality score of the included studies was summarized in Table 2. The total score of PEDro scale ranged from 6 to 9 points, with a theoretical maximum of 10 points. Most studies exceeded the cut-off 6, but they could not be considered high quality with 6 or 7 points for most of them. Only 2 studies scored 9 points. There were serious flaws in terms of concealed allocation, subject blinding, therapist blinding, and assessor blinding. In the remaining items of the PEDro scale, the studies had higher methodological quality.

Table 1. *Characteristics of randomized controlled trials included evaluating the effectiveness of manual therapy for KOA.*

First author, year	Patients (M/F)	Age, Mean, Years(I/C)	Study Group(n)	Intervention		Outcomes (WOMAC)	Intergroup difference	Study design	Thesis
				Index group	Control group				
Ali 2014 (26)	50 (24/26)	40-60	MT (25) Control (25)	Manual therapy: Maitlan joint mobilization Dosage: 3 times weekly, 12 times in total (4 weeks) + exercise	Electrophysicalagents (Transcutaneous Electrical Nerve Stimulation with cold pack)Dosage: 3 times weekly, 12 times in total (4 weeks) + exercise	Pain Stiffness Function Total score	$P < 0.05$ $P < 0.05$ $P < 0.05$ $P < 0.05$	RCT	No
Atkins 2013 (27)	36 (18/18)	65.8/65.6	MT (18) Control (18)	Manual therapy: self-massage apply to quadriceps muscle Dosage: twice weekly, 22 times in total (11 weeks) + usual care	Usual care	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	RCT	No
Perlman 2012 (28)	50 (12/38)	62.6/63.6	MT (25) Control (25)	Manual therapy: Swedish massage Dosage: once weekly, 8 times in total (8weeks)	Usual care	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	RCT	No
Perlman 2006 (13)	68 (15/53)	70.4/66.2	MT (34) Control (34)	Manual therapy: Swedish full-body therapeutic massage technique Dosage: twice in the first 4 weeks, then once weekly for 4 weeks, 60 min a time, 12 times in total + usual care	Usual care	Pain Stiffness Function Total score	$P < 0.05$ $P = 0.05$ $P < 0.05$ $P < 0.05$	RCT	No
Zhang 2012 (29)	36 (0/36)	63.5/59.9	MT (15) Control (21)	Manual therapy: acupressure Dosage: 5 times weekly, 60 times in total (12 weeks) + usual care	Usual care	Pain Stiffness Function Total score	$P > 0.05$ $P > 0.05$ $P > 0.05$ $P > 0.05$	RCT	No
Liu 2006 (30)	42 (15/27)	65.4/67.7	MT (22) Control (20)	Manual therapy: tuina Dosage: 3 times weekly, 12 times in total (4 weeks)	Self-exercise Dosage: 4 weeks	Total score	$P > 0.05$	RCT	No
Du 2012 (31)	60 (16/44)	46.4/49.6	MT (30) Control (30)	Manual therapy: wenyang's manual therapy + functional exercise of knee Dosage: once daily, 28 times in total (4weeks)	Acupuncture Dosage: once daily, 28 times in total (4 weeks) + functional exercise of knee	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	Single-blind, RCT	Yes
Feng 2014 (32)	62 (21/41)	NR	MT (31) Control (31)	Manual therapy: tuina Dosage: once every two days, 15 times in total (1 month)	Acupuncture Dosage: once every two days, 15 times in total (1 month)	Pain Stiffness Function Total score	$P > 0.05$ $P < 0.05$ $P > 0.05$ $P > 0.05$	RCT	No

Table 1 (cont.). *Characteristics of randomized controlled trials included evaluating the effectiveness of manual therapy for KOA.*

First author, year	Patients (M/F)	Age, Mean, Years(I/C)	Study Group(n)	Intervention		Outcomes (WOMAC)	Intergroup difference	Study design	Thesis
				Index group	Control group				
Feng 2010 (33)	62 (13/49)	63.2/65.3	MT (31) Control (31)	Manual therapy: Jingjin manual therapy Dosage: 6 times a week, 20 min a time, 12 times in total (2 weeks)	Oral diclofenac sodium sustained-release tablets Dosage: once a day, 75mg a time, 2 weeks in total	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	RCT	Yes
Qiu 2009 (34)	60 (12/48)	59.5/61.5	MT (36) Control (24)	Manual therapy: tuina and restitution therapy Dosage: 3 times a week, 24 times in total (8 weeks)	Acupuncture Dosage: three times a week, 24 times in total (8 weeks)	Total score	$P > 0.05$	RCT	Yes
Yan 2010 (35)	60 (11/49)	56.8/59.9	MT (30) Control (30)	Manual therapy: Shi'S manipulation Dosage: twice a week, 20 min a time, 8 times in total (4 weeks)	PuLi capsule (oral glucosamine hydrochloride) Dosage: 2 goals a time, 3 times a day, 4 weeks in total	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	RCT	Yes
Ye 2012 (36)	55 (14/41)	61.3/62.0	MT (27) Control (28)	Manual therapy: Jingjin manual therapy Dosage: once a day, 28 times in total (4 weeks)	Cataplasma Dosage: once a day, 28 times in total (4 weeks)	Pain Stiffness Function Total score	$P < 0.05$ $P > 0.05$ $P < 0.05$ $P < 0.05$	RCT	Yes
Zhang 2014 (37)	120 (25/95)	61.8/62.4	MT (60) Control (60)	Manual therapy: tuina Dosage: twice weekly, 30 min a time, 8 times in total (1 month)	Acupuncture Dosage: twice weekly, 30 min a time, 8 times in total (1 month)	Pain Stiffness Function	$P > 0.05$ $P > 0.05$ $P > 0.05$	RCT	No
Zhao 2012 (38)	80 (37/43)	57.3/56.1	MT (40) Control (40)	Manual therapy: dynamic drawing technique Dosage: once a day, 25 min a time, 28 times in total (4 weeks)	Oral celecoxib Dosage: once a day, 1# a time, 28 times in total + Sodium hyaluronate injection Dosage: once 7 days, 2.5ml a time, 5 times in total	Total score	$P < 0.05$	RCT	No

Note: M/F: Male/Female; I/C: Intervention/Control; MT:manual therapy; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; NR: not reported.

Table 2. *PEDro scale of quality for included studies.*

Study	Eligibility criteria	Random allocation	Concealed allocation	Similar at baseline	Subjects blinding	Therapists blinding	Assessors blinding	< 15% dropout	Intention-to-treat analysis	Between-group comparisons	Point measures and variability data	Total
Ali 2014 (26)	1	1	0	1	0	0	0	1	1	1	1	6
Atkins 2013 (27)	1	1	0	1	0	0	0	1	1	1	1	6
Perlman 2012 (28)	1	1	1	1	1	0	1	1	1	1	1	9
Perlman 2006 (13)	1	1	1	1	1	0	1	1	1	1	1	9
Zhang 2012 (29)	1	1	1	1	0	0	0	1	1	1	1	7
Liu 2006 (30)	1	1	0	1	0	0	0	1	1	1	1	6
Du 2012 (31)	1	1	0	1	0	0	0	1	1	1	1	6
Feng 2014 (32)	1	1	0	1	0	0	0	1	1	1	1	6
Feng 2010 (33)	1	1	1	1	0	0	0	1	1	1	1	7
Qiu 2009 (34)	1	1	1	1	0	0	0	1	1	1	1	7
Yan 2010 (35)	1	1	0	1	0	0	0	1	1	1	1	6
Ye 2012 (36)	1	1	0	1	0	0	0	1	1	1	1	6
Zhang 2014 (37)	1	1	0	1	0	0	0	1	1	1	1	6
Zhao 2012 (38)	1	1	0	1	0	0	0	1	1	1	1	6

0: does not meet the included criteria; 1: meets the included criteria.

Effects of Interventions

Effectiveness of Manual Therapy on Pain

There were 11 studies reporting pain for KOA (13,26-29,31-33,35-37). The meta-analysis showed favorable effects of manual therapy on pain relief (SMD = -0.61, 95% CI -0.95 – -0.28, P = 0.0003, P for heterogeneity < 0.00001, P = 76%) (Fig. 2). According to different treatment durations, we conducted subgroup analyses: < 4 weeks, 4 weeks, and > 4 weeks. For duration < 4 weeks (SMD = -0.49, 95% CI -0.85 – -0.13, P = 0.007, P for heterogeneity = 0.85, P = 0%); duration = 4 weeks (SMD = -0.39, 95% CI -0.76 – -0.02, P = 0.04, P for heterogeneity = 0.005, P = 70%); duration > 4 weeks (SMD = -0.87, 95% CI -1.55 – -0.18, P = 0.01, P for heterogeneity = 0.003, P = 79%), manual therapy significantly relieve pain (Fig. 3).

Effectiveness of Manual Therapy on Stiffness

Eleven studies assessed the effectiveness of manual therapy on stiffness for KOA versus control (13,26-29,31-33,35-37). The meta-analysis showed superior effects of manual therapy on stiffness relief (SMD = -0.58, 95% CI -0.95 – -0.21, P = 0.002, P for heterogeneity < 0.00001, P = 81%) (Fig. 2). In the subgroup analyses, manual therapy did not relieve stiffness for duration < 4 weeks (SMD = -0.09, 95% CI -0.45 – -0.26, P = 0.60, P for heterogeneity = 0.37, P = 0%), but for duration = 4 weeks (SMD = -0.32, 95% CI -0.59 – -0.06, P = 0.02, P for heterogeneity = 0.13, P = 42%) and duration > 4 weeks (SMD = -1.11, 95% CI -1.88 – -0.34, P = 0.005, P for heterogeneity < 0.00001, P = 87%) (Fig. 4).

Effectiveness of Manual Therapy on Physical Function

Eleven RCTs tested the effectiveness of manual therapy on physical function for KOA versus control (13,26-29,31-33,35-37). The aggregated results of these studies suggest that manual therapy significantly improves physical function (SMD = -0.49, 95% CI -0.76 – -0.22, P = 0.0004, P for heterogeneity = 0.002, P = 65%) (Fig. 2). In the subgroup analyses, manual therapy significantly improved physical function for duration > 4 weeks (SMD = -0.72, 95% CI -1.23 – -0.22,

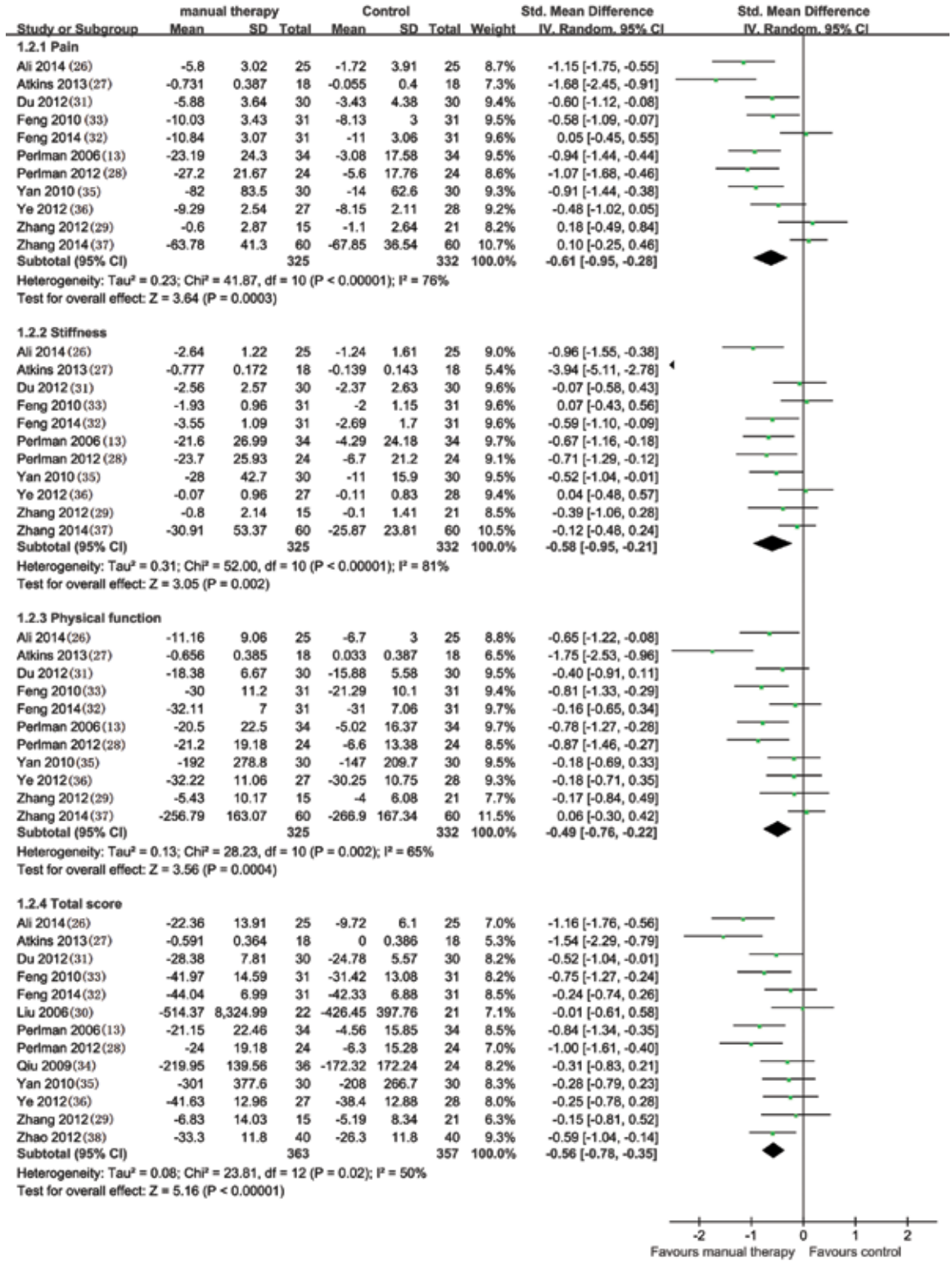

Fig. 2. *A forest plot of meta-analysis of the included studies comparing manual therapy group with control group in change of pain, stiffness, physical function and total score.*

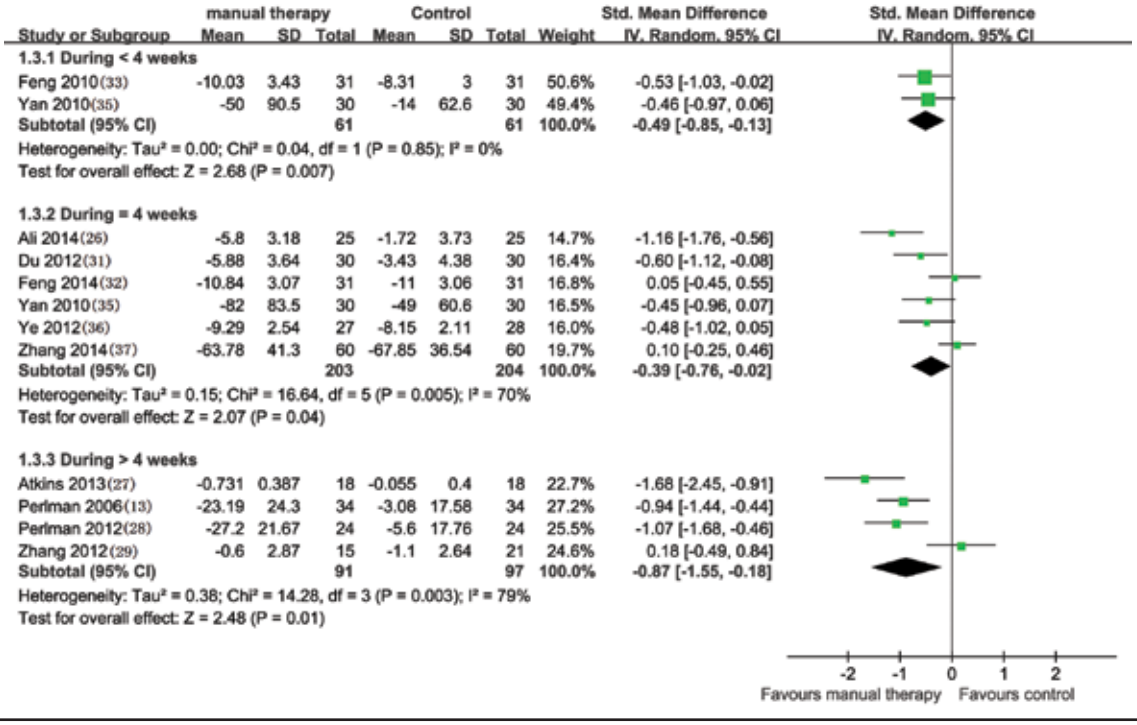

Fig. 3. *A forest plot of the subgroup analyses of the included studies comparing manual therapy group with control group in change of pain.*

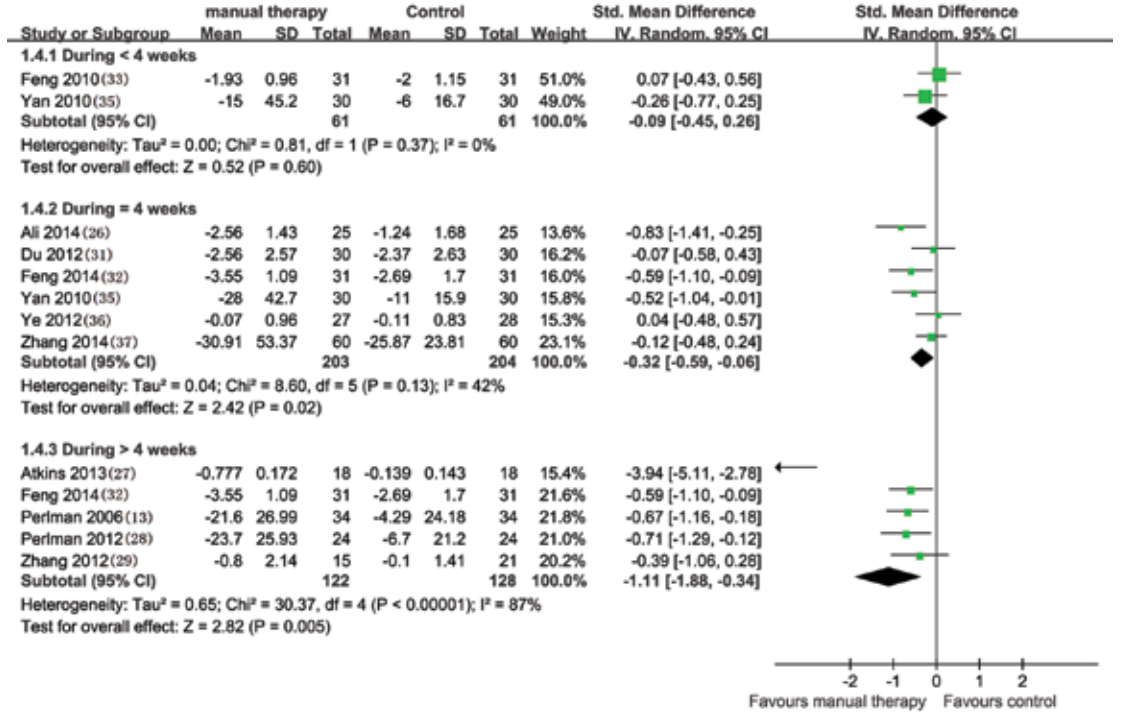

Fig. 4. *A forest plot of the subgroup analyses of the included studies comparing manual therapy group with control group in change of stiffness.*

P = 0.005, *P* for heterogeneity = 0.006, *P* = 72%). But there was no significant improvement for duration < 4 weeks (SMD = -0.50, 95% CI -1.09 – -0.08, *P* = 0.09, *P* for heterogeneity = 0.11, *P* = 62%), nor for duration = 4 weeks (SMD = -0.18, 95% CI -0.38 – 0.01, *P* = 0.07, *P* for heterogeneity = 0.51) (Fig. 5).

Effectiveness of Manual Therapy on Total Score

Thirteen studies assessed the effect of manual therapy on total score for KOA versus control (13,26-36,38). The results showed manual therapy significantly improved KOA (SMD = -0.56, 95% CI -0.78 – -0.35, *P* < 0.00001, *P* for heterogeneity = 0.02, *P* = 50%) (Fig. 2). In the subgroup analyses, manual therapy was beneficial for the management of KOA for duration < 4 weeks (SMD = -0.52, 95% CI -0.97 – -0.08, *P* = 0.02, *P* for heterogeneity = 0.22, *P* = 33%), duration = 4 weeks (SMD = -0.47, 95% CI -0.72 – -0.23, *P* = 0.0002, *P* for heterogeneity = 0.09, *P* = 43%), and > 4 weeks (SMD = -0.65, 95% CI -1.04 – -0.26, *P* = 0.001, *P* for heterogeneity = 0.02, *P* = 63%) (Fig. 6).

Finally, a funnel plot was performed for pain (n = 11 RCTs), stiffness (n = 11 RCTs), physical function (n = 11 RCTs), and total score (n = 13 RCTs), respectively. However it was difficult to interpret the result of publication bias because of the limitation of RCTs (Fig. 7).

Adverse Events

Of 14 studies with AEs of manual therapy, only one study reported that one participant felt increased discomfort and refused to complete the assessment. Seven studies (53.8%) did not report whether they had AEs or not. The remaining 6 studies (46.2%) stated that no AEs occurred.

Discussion

In our review, manual therapy was defined as contact with the soft tissues, bones, and joints with the hands, arms, or elbows of the practitioners to enhance the therapeutic effect. It is one of the oldest forms of treatment, and has been used all over the word since ancient times. It involved mobilization, manipulation, massage, and Chinese tuina techniques.

Recently, there have been an increasing number

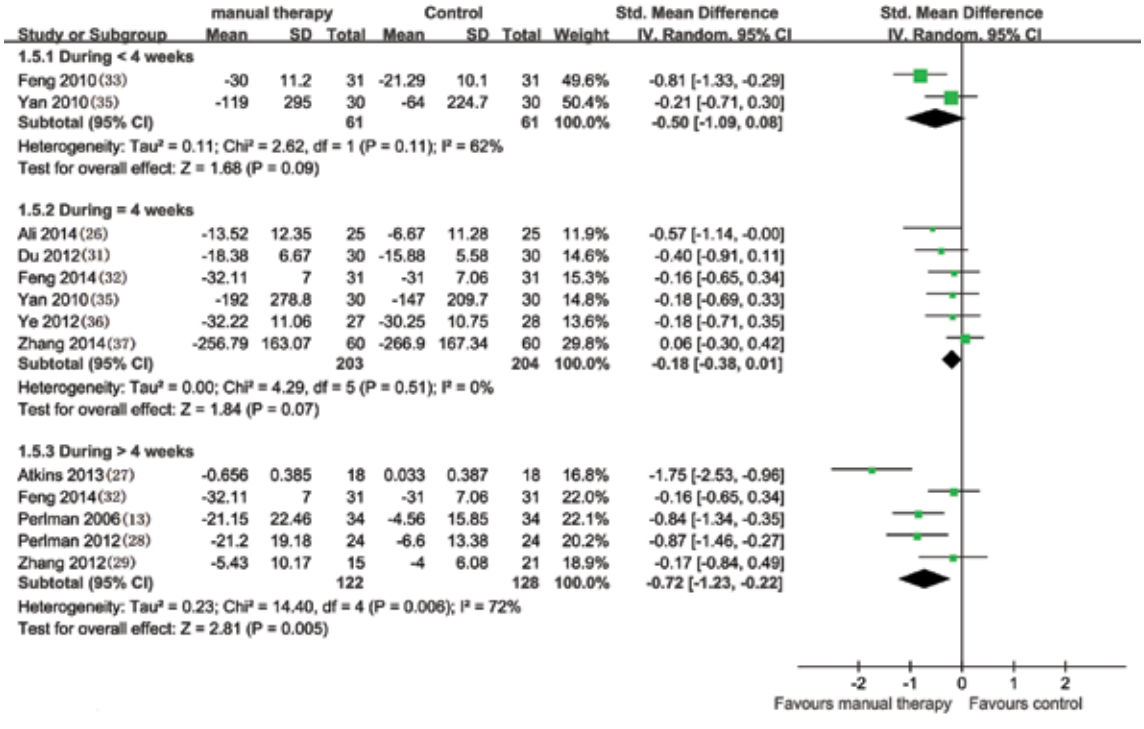

Fig. 5. *A forest plot of the subgroup analyses of the included studies comparing manual therapy group with control group in change of physical function.*

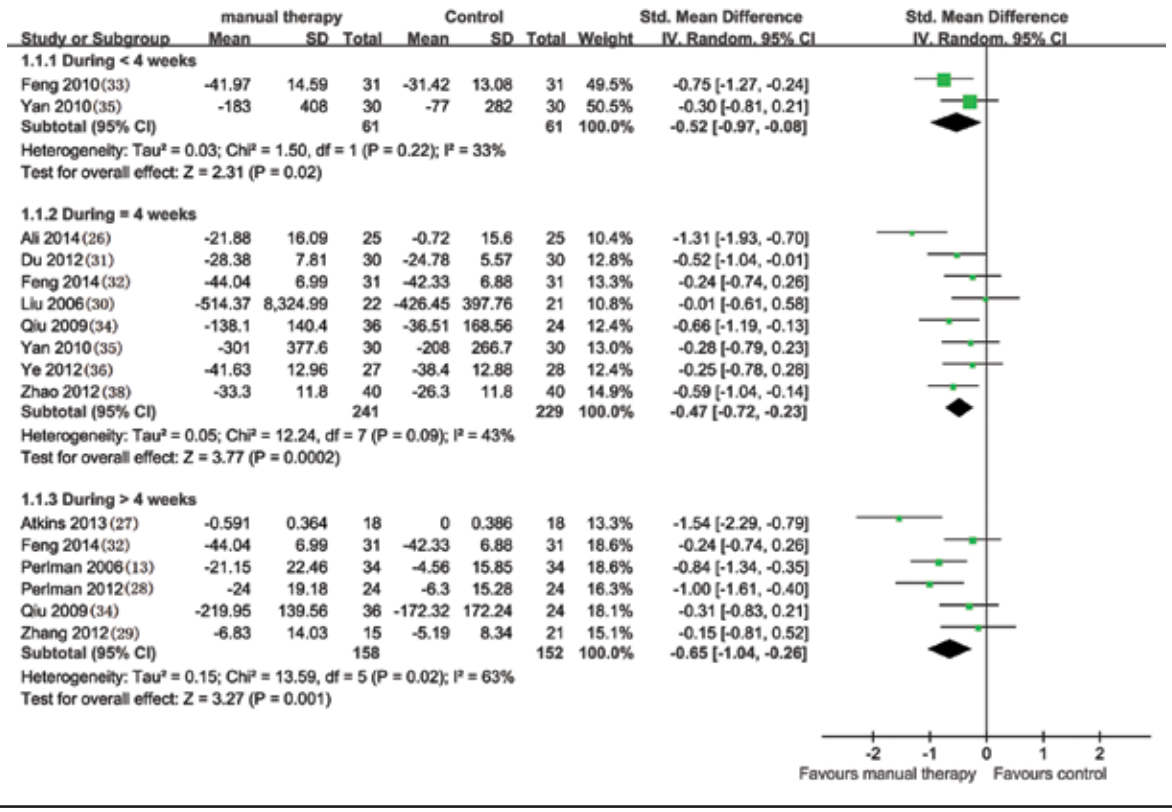

Fig. 6. *A forest plot of the subgroup analyses of the included studies comparing Manual Therapy group with control group in changes of WOMAC total score.*

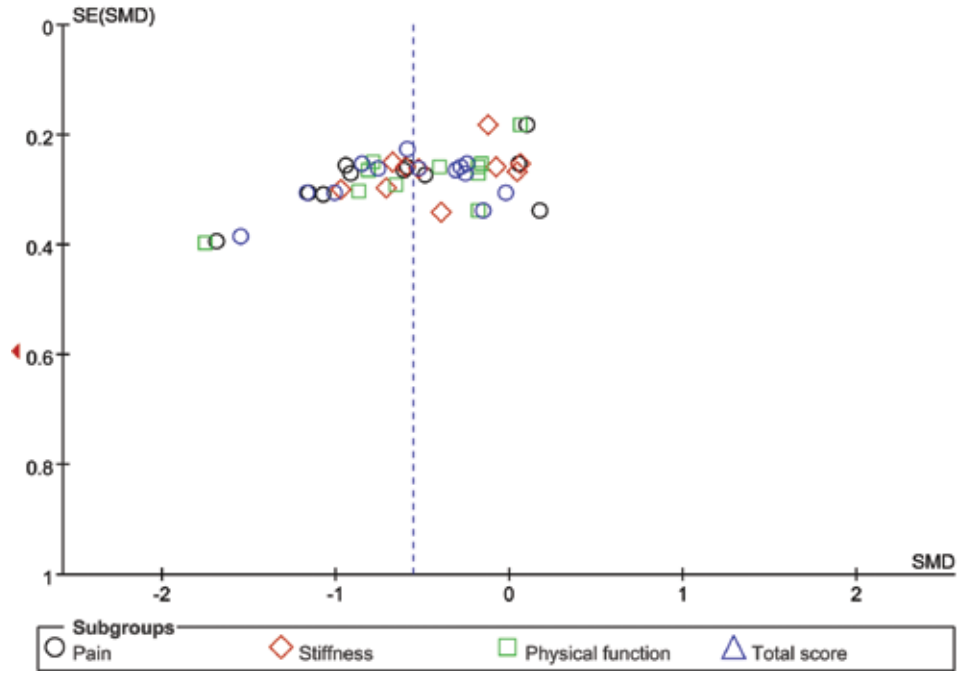

Fig. 7. *A Funnel plot for pain, stiffness, physical function, and total score*

of studies aimed at the therapeutic effect of manual therapy for KOA. However, the contribution of manual therapy to manage KOA still remains unclear. There was a systematic review on manual therapy compared to other treatments for KOA in 2011, and the authors did not find any significant evidence regarding the efficacy of manual therapy compared to placebo or meloxicam due to the limited number of studies included and the high risk of bias (14). However, the studies it included were not enough, because they only included studies published in English. We carefully researched relevant clinical outcomes, including pain, stiffness, function, and total score.

The major purpose of this meta-analysis was to update and complete the evidence by adding recent RCTs assessing the effects of manual therapy for patients with KOA. We found that manual therapy significantly reduces pain, alleviates stiffness, and improves physical function in patients with KOA. Our results indicated that manual therapy was beneficial in management of KOA and could be available in rehabilitation programs as a complementary and alternative medicine for patients. But the quality of the included studies was generally poor.

In KOA management, the most important goals are to relieve pain and stiffness, improve physical function and quality of life, and stop the development (39,40). Manual therapy includes many techniques, and is regarded as an effective non-pharmaceutical therapy in the management of OA (41,42). In western countries, the most common treatments are joint mobilization, manipulation, and massage. These treatments are commonly used in clinical practice. The surveys showed that 96% of Irish physical therapists (43) and 64% of British therapists (44) use manual therapy in the management of patients with hip and knee OA. In China, the symptoms of KOA belong to "Bi-arthralgia" and "flaccidity," a conception of Traditional Chinese Medicine (TCM) (45). Tuina, a form of manual therapy, is widely used for the treatment of KOA in Chinese hospitals. The specific mechanism of the manual therapy is not clear. One early study reviewed physiological benefits to include increasing blood flow.

Our study showed that manual therapy is effective in lessening pain, relieving stiffness, and improving physical function in patients with KOA. Subgroup analyses suggested that a dose duration of < 4 weeks manual therapy can reduce pain, = 4 weeks can reduce pain and stiffness, and > 4 weeks reduce pain and stiffness, and improve physical function. The positive results of our systematic review were consistent with relevant clinical guidelines. The clinical guidelines from the National Institute for Health and Care Excellence (NICE) in 2008 recommended manipulation and stretching as an adjunct to core treatment in the management of KOA (9). The recommendations for the non-surgical management of hip and knee OA from the Royal Australian College of General Practitioners (RACP) also found evidence for massage therapy, although the evidence grade was D (10). This indicated that manual therapy had a proven effect on KOA. The results of 2 studies supported that finding, and demonstrated the potential for pain-relief through manual therapy in KOA (46,47). Our results were not exactly similar to the latest SR (14). It suggested that manual therapy was no better than a placebo or Meloxicam medication, but massage was effective compared to no intervention. The number of RCTs and included patients was small, so this result based on 3 studies with a high risk of bias was inconclusive. The authors did not perform a quantitative analysis due to the use of different assessment measures evaluating outcomes. Therefore, we pooled the outcome measures evaluated by WOMAC for the meta-analysis. The outcomes of interest consisted of pain, stiffness, and physical function. We included more studies, and performed meta-analysis to assess the effect of manual therapy on KOA according to different durations. Our systematic review provided stronger evidence of reduced pain and stiffness and improved physical function.

In non-pharmacological studies, experience of the therapist was an important factor affecting the outcome. In our review, information about the therapists was not disclosed in most studies. Three studies reported the treatment was delivered by several practitioners (13,27,28), but all the therapists were licensed and experienced. One study used the same therapist for all participants (35). Therapist training was provided in 3 studies (27,29,31). The difference in experience and skills among studies may contribute to discordant results.

We found no significant side effects or AEs associated with manual therapy except that one patient felt uncomfortable. Participants had relatively high adherence in most studies, indicating that the use of manual therapy was safe. According to a recent SR about AEs, massage therapy was not completely safe for all conditions (48). For example, certain spinal manipulation has been reported with serious AEs. However, for KOA, AEs were not encountered and therefore we consider the

treatment to be safe in this context.

Regarding the long-term effect of manual therapy on OA, so far only 3 studies were reported. The first trial showed that the effective rate of manual therapy was higher than the control group (37). In the second study, although the 3-months recurrence rate of the treatment group was less than the control group, the statistical analysis is of no difference (31). In the third study, there were also no significant difference between manual therapy and control group at 24-weeks follow up (28). Therefore, long-term outcomes of manual therapy on OA need to be further explored.

There were a number of limitations in our review. Firstly, the distorting effects of publication and location bias on systematic reviews and meta-analyses may remain as documented by other studies (49-51). Although we were confident that our search strategy located all relevant data and had performed a funnel plot for the outcomes, it was difficult to explain the publication bias. Another possible source of bias was that some negative studies of manual therapy for KOA may be unpublished. Some of the studies were published in China, where journals are prone to report only positive studies (52), so our review may be affected by potential poor data. Secondly, most eligible studies had poor quality. Because of inadequate reporting of methodology in these studies, inappropriate allocation, concealment, and shortage of blinding may exaggerate the results of the outcome measures (53,54). Thirdly, our analysis was based on 14 RCTs with a relatively small sample size. Compared with larger sample studies, the treatment effect may be overestimated in smaller studies. Finally, our review may be affected by the high heterogeneity of manual therapy, and AEs were not sufficiently reported.

Conclusions

In summary, 14 RCTs were analyzed in our systematic review, evaluating the efficacy of manual therapy on pain, stiffness, and physical function in patients with KOA. The positive findings suggested that manual therapy was an effective complementary and alternative treatment for KOA pain, stiffness, and physical function. However, high–quality RCTs with long follow-up are warranted to confirm our findings.

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