



Systematic Review and Meta-analysis of Randomized Controlled Trials on Manual Therapy for the Treatment of Gastroesophageal Reflux Disease

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Abstract

Objective The objective of our study was to systematically evaluate the clinical efficacy and safety of manual therapy in the treatment of gastroesophageal reflux disease (GERD), providing a reference value for clinical decision-making.

Method Studies of randomized controlled trials (RCTs) evaluating the efficacy of manual therapy in patients with GERD were searched through Chinese National Knowledge Infrastructure, Wanfang, VIP China Science and Technology Journal Database, China Biology Medicine Database, PubMed, The Cochrane Library, OVID Medline, and Embase. Two researchers independently reviewed the literature, extracted data, and performed a risk of bias analysis using the Cochrane risk of bias assessment tool, and conducted meta-analysis analysis and publication bias evaluation, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool 26 was used to rate the caliber of the data in this meta-analysis.

Results This study included 11 RCTs. Meta-analysis showed that the manual therapy group had a higher total effective rate (odds ratio [OR] = 4.63, 95% confidence interval [CI; 3.01, 7.14], $p < 0.00001$) and better Reflux Disease Questionnaire scores {weighted mean difference (WMD) = -1.59, 95% CI [-2.85, -0.33], $p = 0.01$ } than the control group. The subgroup analysis showed significant differences in improving the total effective rate in manual therapy versus Western medicine, manual therapy versus Chinese medicine decoction, manual therapy + Western medicine versus Western medicine, and manual therapy + conventional treatment versus conventional treatment groups. Among the 11 trials, 5 reported adverse events, and all RCTs had the possibility of publication bias. Subgroup analysis shows that the differences in age could significantly influence heterogeneity; The GRADE analysis revealed that the overall quality of evidence for all outcome indicators was low and did not support our recommendation for the outcome.

Conclusion Manual therapy is more effective than medication therapy alone in relieving GERD symptoms. Furthermore, conventional therapy combined with manual therapy was

Keywords

- ▶ gastroesophageal reflux disease
- ▶ manual therapy
- ▶ tuina
- ▶ massage
- ▶ systematic review
- ▶ meta-analysis

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found to be even more effective. Hence, it is crucial to consider these findings when applying manual therapy to GERD patients to enhance treatment outcomes. Future studies must address issues such as study quality, treatment duration, and generalizability.

Introduction

Gastroesophageal reflux disease (GERD) refers to an illness in which stomach contents reflux into the esophagus, causing discomfort or complications like peptic stricture, esophageal ulceration, Barrett's esophagus (BE), or esophageal adenocarcinoma.¹ Common symptoms of GERD include heartburn and reflux. However, when the reflux spreads to adjacent tissues such as the mouth, larynx, lungs, and heart, it may cause dysphagia, dental erosion, laryngitis, chronic cough, asthma, chest pain, or occur in isolation.^{2,3} Two subgroups of GERD exist, including nonerosive gastroesophageal reflux disease (NERD) and reflux esophagitis (RE), which vary based on the degree of mucosal damage.⁴ GERD is a widespread disorder, with an average global prevalence of approximately 13 and 8.7% in China,⁵ and its incidence is increasing yearly.^{6,7} In the United States, it is the most common gastrointestinal disease with GERD becoming a risk factor for tumors such as BE and esophageal adenocarcinoma, although the mortality rate is not high.^{8,9} Furthermore, the treatment of GERD is expensive, mainly related to the long-term use of proton pump agents (PPIs).^{10–12} PPIs are the recommended first-line therapy for GERD and can heal esophagitis in 72 to 83% of patients (compared with 18–20% for placebo).¹³ However, the standard dose of PPI can only resolve the heartburn symptoms in 37–61% of patients with nonerosive esophagitis, while the treatment rate is low in patients with atypical GERD. Therefore, the efficacy of PPIs depends on the type of GERD disease present.^{14,15} Besides the cost burden, using PPIs involves difficulties in compliance and the inability to rule out associations with polyps, mucosal degeneration, and osteoporosis.^{16,17} Other medication options such as H2 receptor antagonists, potassium-competitive acid blockers, antacids and gastric stimulants, etc., and surgery may have limited suitability for certain populations, long-term efficacy, or side effects.^{15,18,19}

In the past decade, drug development has experienced a significant decline, while research on novel nonpharmaceutical therapeutic technologies has increased dramatically.²⁰ Manual therapy, such as Chinese tuina or therapeutic massage, which is mediated by the limbs, has been widely used in some gastrointestinal diseases, including GERD, under the guidance of the basic theory of traditional Chinese medicine (TCM) or the theory of Western neuromuscular anatomy. Modern medical mechanisms for the effectiveness of massage for visceral diseases often involve enhancing blood circulation in local tissues, increasing parasympathetic excitability, decreasing neuromuscular excitability, and regulating hormone levels.²¹ Clinical studies have also revealed that osteopathic visceral therapy can increase the pressure of the lower esophageal sphincter (LES), which can improve the

symptoms of GERD.^{22,23} Additionally, in preterm infants with GERD, acupuncture has been found to be more effective in increasing LES pressure and reducing reflux than conventional treatment.²⁴ Combining acupuncture with pharmacological therapy has also been shown to have a significant advantage over drug therapy alone in terms of symptom improvement and endoscopic esophageal mucosal repair.²⁵ Despite these findings, there is no consensus on the efficacy of manual therapy for the treatment of GERD. Therefore, this study aims to systematically evaluate the efficacy and safety of manual therapy for GERD by screening relevant RCTs, with the goal of providing evidence to support medical decisions.

Methods

Search Strategy

Chinese National Knowledge Infrastructure, China Biology Medicine Database, WanFang, VIP, PubMed, The Cochrane Library, OVID Medline, and Embase databases were searched by computer. The search period was from the establishment of the database to November 30, 2022. Chinese search terms included [“Tui Na” OR “An Mo (massage)” OR “Shou Fa (manipulation)” OR “Shou Dong Zhi Liao (manual technique)” OR “Xue Wei An Ya (acupressure)”] AND [(“Wei Shi Guan Fan Liu Bing (gastroesophageal reflux disease)” OR “E Ni (hiccup)” OR “Shao Xin (heartburn)” OR “Fan Suan (acid reflux)”] AND [(“Sui Ji Dui Zhao Shi Yan (randomized controlled trial)” OR “Lin Chuang Yan Jiu (Clinical study)”)], English search terms include (“massage” OR “tuina” OR “anmo” OR “manipulat*” OR “chiropractic” OR “manual technique” OR “manual therap*” OR “acupressure”) AND (“gastroesophageal reflux” OR “GERD” OR “heartburn” OR “hiccup”) AND (“randomized controlled trial” OR “controlled clinical trial”). The search method was a combination of subject terms and keywords, which would be moderately adjusted according to the database. ► **Table 1** displays the full literature retrieval technique with OVID Medline as an example.

Inclusion Criteria

(1) Types of studies: Clinical randomized or quasirandomized controlled trials (RCTs) on manual therapy for GERD, limited to Chinese and English, and blinded or nonblinded in article design were eligible. (2) Participants: Studies with a clinical diagnosis of GERD and stating clear diagnostic criteria were included. Disease types included but were not limited to NERD, RE (erosive esophagitis), and BE. There were no restrictions on the patient's gender, age, race, occupation, course of disease, and TCM patterns. (3) Interventions and comparators: The experimental group underwent tuina or massage techniques alone (regardless of type,

Table 1 Searching strategy

| Search | Query | Results |
|--------|--|-----------|
| 1 | exp Massage/ | 6,794 |
| 2 | tuina.mp. | 255 |
| 3 | anmo.mp. | 7 |
| 4 | massage therap*.mp. | 1,599 |
| 5 | manipulat*.mp. | 229,989 |
| 6 | Zone Therap*.mp. | 50 |
| 7 | chiropractic.mp. | 7,363 |
| 8 | manual technique.mp. | 524 |
| 9 | manual therap*.mp. | 3,365 |
| 10 | acupressure.mp. | 1,680 |
| 11 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 | 245,018 |
| 12 | Gastroesophageal Reflux/ | 27,841 |
| 13 | gastroesophageal reflux disease.mp. | 13,017 |
| 14 | GERD.mp. | 10,099 |
| 15 | heartburn.mp. | 6,247 |
| 16 | hiccup.mp. | 1,423 |
| 17 | 12 or 13 or 14 or 15 or 16 | 37,360 |
| 18 | Randomized controlled trial. pt. | 581,153 |
| 19 | controlled clinical trial. pt. | 95,105 |
| 20 | randomized.ab. | 583,079 |
| 21 | placebo.ab. | 233,428 |
| 22 | drug therapy.fs. | 2,549,487 |
| 23 | randomly.ab. | 395,949 |
| 24 | trial.ab. | 624,493 |
| 25 | groups.ab. | 2,437,379 |
| 26 | 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 | 5,516,267 |
| 27 | exp animals/ not humans.sh. | 5,066,999 |
| 28 | 26 not 27 | 4,808,227 |
| 29 | 11 and 17 and 28 | 28 |

site, duration, frequency, etc.) or in combination with other therapies such as Western medicine, Chinese medicine, or other TCM external treatments. The control group used the same Western medicine, Chinese medicine, or other TCM external treatments as the intervention group except for manual therapy, or the control group was simply a sham manual therapy group. (4) Outcomes: The primary outcome indicator was the total treatment effectivity rate, and the secondary outcome indicators were the Reflux Disease Questionnaire (RDQ) score and adverse events.

Exclusion Criteria

Exclusion criteria were as follows: (1) studies with unreasonable diagnostic methods or criteria; (2) articles with incomplete data that could not be extracted; (3) repeatedly

published literature; (4) clinical trials that were not RCTs; RCTs using before–after control in the same patients; and other kinds of literature works such as reviews, case reports, systematic reviews, animal experiments, and conference papers.

Literature Screening and Data Extraction

Two researchers conducted an independent and consecutive screening of the literature based on predetermined research criteria and cross-checked their results. Any differences of opinion were resolved through discussion. In cases where disagreements persisted, a third evaluator was consulted. The PRISMA 2020 flow diagram was used to document the literature screening process, and data were extracted independently by both researchers. Any missing data were obtained from the authors, and if complete data information could not be obtained, the literature was discarded. Extractions included general information (such as the title, authors, source, and date of publication of the literature), study characteristics (such as study site, characteristics of the study population, method of study design, and specific interventions in the experimental and control groups), study outcomes (such as outcome indicators, duration of treatment, follow-up time, adverse effects, and shedding), and other relevant and important variables. The literature information was collected and presented using a characteristic table.

Risk of Bias Assessment

In this study, two researchers utilized version 5.0 of the Cochrane Collaboration Risk of Bias Assessment Tool to evaluate the risk of bias in RCTs. The tool includes seven entries, namely: random assignment method, allocation concealment, blinding of the participants and doctors who performed the intervention, blinding of the outcome evaluators, completeness of the data counted and final conclusions, selective outcome reporting, and other bias. The potential for bias in each item was rated as either “high” “low” or “unclear” Two evaluators initially assessed the items, which were then reviewed by a third evaluator. Any disagreements were resolved through a tripartite discussion or by the third evaluator. If there was uncertainty regarding the level of risk, the authors were contacted for clarification.

Statistical Analysis

The meta-analysis used RevMan 5.4.0 software provided by the Cochrane Collaboration Network. Dichotomous variables were analyzed using odds ratio (OR) with 95% confidence intervals (CIs), while continuous variables were assessed using mean difference with 95% CI. A statistical inspection standard of $p < 0.05$ was employed. The combined effects of outcomes were demonstrated in a forest plot. Heterogeneity was examined using the χ^2 test with a test level of $p < 0.1$, and I^2 was utilized to quantify heterogeneity, with a fixed-effects model utilized for smaller heterogeneity ($p \geq 0.1$ and $I^2 \leq 50\%$) and a random-effects model used for larger heterogeneity ($p < 0.1$ and $I^2 > 50\%$). If heterogeneity was still significant after statistical heterogeneity treatment, further

analysis such as subgroup or sensitivity analysis was conducted to identify the source of heterogeneity.

Publication Bias Assessment

As more than 10 RCTs were included, we drew funnel plots as a means to assess potential publication bias.

Level of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool²⁶ was used to rate the caliber of the data in this meta-analysis. The degree of the level of evidence for each outcome indicator was rated as high, moderate, low, and extremely low. We decreased levels in accordance with the following five criteria: risk of bias, inconsistency, imprecision, indirectness, and publication bias. The degree of evidence was evaluated independently by two evaluators. Disagreements were handled by a third investigator or discussed by both sides.

Results

Study Selections

The initial search yielded 1,565 studies, and 573 were later screened out by the filter. The software NoteExpress 3.5 was then used to remove 309 duplicates. By browsing through the titles and abstracts, 40 relevant papers were finally selected. Among these, four articles were unavailable for full text and could not be read, leaving 36 articles remaining.

However, 5 articles had incomplete data, 1 study had unknown efficacy evaluation criteria, 13 studies had outcome indicators that were inconsistent, 2 studies had unclear diagnostic criteria, 1 study had noncompliant intervention, 1 study had unreasonable control group settings, and 2 studies were non-RCT. Finally, 11 studies that met the criteria were included in the meta-analysis.^{25,27–36} As shown in ►Fig. 1.

Basic Characteristics of the Included Studies

Types of Participants

A total of 1,107 patients were included in our research, with 558 in the experimental group and 549 in the control group. The number of patients in each study ranged from 30 to 200, and the age of patients varied from preterm infants to adults up to 70 years old. One of the studies included three groups, but only two groups satisfied the inclusion criteria, so we extracted data from these two groups only. ►Table 2 presents the details.

Types of Interventions and Controls

In terms of the experimental group, five studies implemented individual manual therapy, which included acupressure, medicated acupoint finger pressure therapy, and myofascial release techniques.^{27,29–31,35} Two combined manual therapy and Western medicine (primarily proton pump inhibitors and/or gastroprokinetic agents),^{25,34} while

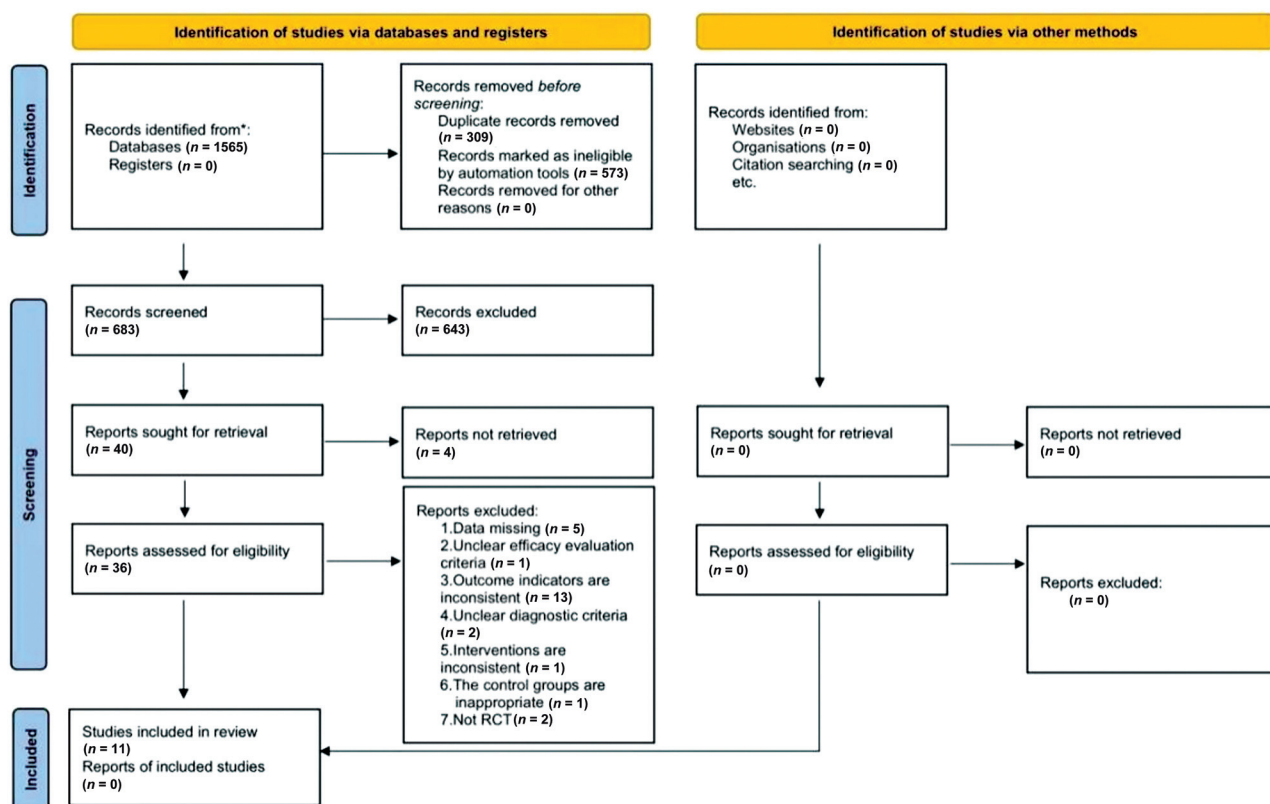


Fig. 1 Flowchart of literature screening.

Table 2 Basic characteristics of included RCTs

| Study ID | Diagnosis | Design | Sample size | | Age | | Duration of disease | | Sex (Male/Female) | | Interventions | | Intervention time | Outcome measurements | Results | Adverse events | Drop out | Follow-up |
|----------------------------------|--|--------|--------------------|--------------------|-------------------------------------|--------------------------------------|---------------------|---------------|-----------------------|------------------------|---|--------------------------|-------------------|----------------------|---|--|--------------|-----------|
| | | | E | C | E | C | E | C | E | C | E | C | | | | | | |
| Chen 2018 ³¹ | Gastroesophageal reflux disease | RCT | 30 | 30 | 50.96 ± 16.02 y | 49.00 ± 14.88 y | 6.72 ± 5.47 y | 5.88 ± 4.53 y | 13/17 | 16/14 | Acupoint finger pressure therapy | PPI | 2 wk | ① ② | The decrease in the scores of RDO scale of the experimental group was greater than that in the control group (p = 0.008). For the total effective rate, the experimental group (89.9%) was significantly higher than the control group (66.7%; p < 0.05). | NR | Non | 1 mo |
| Yan et al 2015 ³⁶ | Gastric volvulus (GV) with gastroesophageal reflux (GER)-induced pneumonia | RCT | E1 = 59 E2 = 29 | C1 = 56 C2 = 27 | E1: 21 ± 1.1 mo E2: 2.0 ± 1.0 mo | C1: 2.0 ± 1.0 mo C2: 2.0 ± 1.1 mo | NR | NR | E1: 38/22 E2: 21/9 | C1: 39/21 C2: 20/10 | Basic treatment + massage treatment | Basic treatment | 2 wk | ① | Massage treatment groups showed a significantly higher percentage of cure and total effect (p < 0.05; p < 0.01) and a lower prevalence of recurrence (but with no statistic difference, p > 0.05) than basic treatment groups. | Some cases with local redness or mild lesions | E: 2 C: 7 | NR |
| Liu 2018 ²⁷ | Gastroesophageal reflux disease | RCT | 29 | 29 | 48.00 ± 14.10 y | 46.87 ± 11.27 y | 6.83 ± 7.27 | 6.66 ± 7.04 | 9/20 | 10/19 | Acupoint finger pressure therapy | PPI and prokinetic agent | 2 wk | ① ② | The total effective rate of finger acupuncture on BackShu Point was similar to that of Western medicine (p > 0.05), but for the food/acid reflux, heartburn, diarrhea, 1 case with mouth bitter relief shows obvious advantages (p < 0.05), and long-term effect (3 mo after the end of therapy) is superior to the control group (p < 0.05). | C: 2 cases with low back pain in the early treatment E: 1 case with diarrhea, 1 case with constipation, 1 case with skin itch | E: 2 C: 1 | 3 mo |
| Liu and Liu 2016 ²⁸ | Gastroesophageal reflux disease | RCT | 40 | 40 | 12.63 ± 4.66 d | 12.63 ± 4.66 d | NR | NR | 24/16 | 22/18 | Basic treatment + Tulina | Basic treatment | 7 d | ① | The total effective rate in the observation group was 95%, which was increased significantly compared to 77.50% of the controlled group (p < 0.05). | NR | Non | NR |
| Zhang and Wei 2001 ²⁵ | Gastroesophageal reflux disease | RCT | 100 | 100 | NR | NR | NR | NR | NR | NR | Acupoint finger pressure therapy + prokinetic agent | Prokinetic agent | 4 wk | ① | The total effective rate of the treatment group was 100%, and the total effective rate of the control group was | NR | Non | NR |

(Continued)

Table 2 (Continued)

| Study ID | Diagnosis | Design | Sample size | | Age | | Duration of disease | | Sex (Male/Female) | | Interventions | | Intervention time | Outcome measurements | Results | Adverse events | Drop out | Follow-up |
|--------------------------------|-----------------------------------|--------|-------------|----|----------------|---------------|---------------------|---------------|-------------------|-------|--|----------------------------|-------------------|----------------------|--|--|----------|-----------|
| | | | E | C | E | C | E | C | E | C | E | C | | | | | | |
| Xie et al 2007 ²⁹ | Gastroesophageal reflux disease | RCT | 40 | 40 | 45.98 ± 13.1 y | 8.85 ± 13.1 y | 7.4 ± 4.8 mo | 27.4 ± 4.8 mo | 11/29 | 16/24 | Medicated acupoint finger pressure therapy | PPI and prokinetic agent | 3 wk | ① | 76%, and the difference between the two groups was significant ($p < 0.01$). And the degree of endoscopic esophagitis or esophageal reflux and delayed barium emptying were significantly improved before and after treatment in each group. | C: 4 cases with diarrhea, 3 cases with dizziness. E: non | Non | NR |
| Li et al 2017 ³⁰ | Gastroesophageal reflux disease | RCT | 70 | 67 | Mean 57.1 y | Mean 57.4 | Mean 4.1 y | Mean 3.8 | 31/39 | 31/36 | Medicated acupoint finger pressure therapy | Chinese medicine decoction | 4 wk | ① | Comparison of clinical efficacy of three groups was made twice: the traditional Chinese medicine group and medicine acupoint pointer therapy group ($p < 0.05$), the traditional Chinese medicine group and the combined group ($p < 0.05$), the differences were statistically significant. | NR | E:1 C:1 | NR |
| Zhong et al 2021 ³² | Reflux esophagitis and chest pain | RCT | 46 | 46 | 15 ± 5.74yr | 63 ± 5.38 y | 49 ± 2.16 y | 27 ± 2.3 y | 22/24 | 21/25 | Acupotomy therapy + tuina | Acupotomy therapy | 4 wk | ① | The clinical symptom scores in the two groups after treatment were significantly ameliorated compared with before treatment, which were lower in the treatment group ($p < 0.05$). There was no significant difference in the effective rate between the two groups ($p > 0.05$). | NR | Non | NR |

Table 2 (Continued)

| Study ID | Diagnosis | Design | Sample size | | Age | | Duration of disease | | Sex (Male/Female) | | Interventions | | Intervention time | Outcome measurements | Results | Adverse events | Drop out | Follow-up |
|-----------------------------------|---------------------------------|--------|-------------|----|-----------------|-----------------|---------------------|-------------|-------------------|-------|---|------|-------------------|--|--|----------------|----------|-----------|
| | | | E | C | E | C | E | C | E | C | E | C | | | | | | |
| Zhang 2017 ³³ | Non-erosive reflux disease | RCT | 30 | 30 | 48.33 ± 15.87 y | 45.20 ± 15.38 y | 5.73 ± 5.72 y | 4.34 ± 4.58 | 13/17 | 15/15 | E: Acupuncture + Tuina C: Acupuncture | 6 wk | ① ② | The decrease in the scores of RDQ scale of the treatment group was greater than that in the control group ($p < 0.05$). The total effective rate was 93.33% in the treatment group and 83.33% in the control group ($p = 0.228$), which was not statistically significant. | NR | Non | 1 mo | |
| Liu et al 2015 ³⁴ | Gastroesophageal reflux disease | RCT | 70 | 70 | NR | NR | NR | NR | 38/32 | 36/34 | E: Acupoint finger pressure therapy + PPI and prokinetic agent C: PPI and prokinetic agent | 8 wk | ① | The total effective rate in the observation group (90.00%) was significantly higher than that in the control group (81.43%; $p < 0.05$). | E: 1 case with dizziness and somnolence. C: 1 case with thirst and vertigo. | Non | NR | |
| Martinez et al 2019 ³⁵ | Gastroesophageal reflux disease | RCT | 15 | 15 | 49.9 ± 14.4yr | 46.9 ± 14.8 y | NR | NR | 3/12 | 4/11 | E: Myofascial release (MFR) techniques C: Sham myofascial release (MFR) techniques | 1 wk | ② | At week 4, patients receiving MFR showed significant improvements in symptomatology (mean difference -1.1; 95% CI: -1.7 to -0.5), gastrointestinal quality of life (mean difference 18.1; 95% CI: 4.8 to 31.5), and PPIs use (mean difference -97 mg; 95% CI: -162 to -32), compared to the sham group, indicating that the application of the MFR protocol used in this study decreased the symptoms and PPIs usage and increased the quality of life of patients with nonerosive GERD up to 4 wk after the end of the treatment. | No adverse events. | C:1 | 4 wk | |

Abbreviations: C, control group; CI, confidence interval; E, experimental group; GERD, gastroesophageal reflux disease; NR, not reported; PPI, proton pump inhibitor; RCT, randomized controlled trial; RDQ, reflux disease questionnaire.

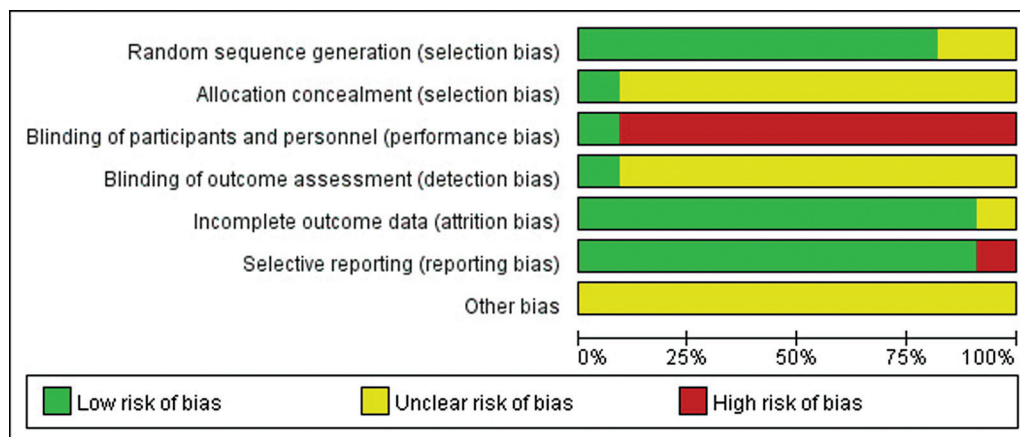


Fig. 2 Risk of bias graph.

two other studies combined tuina and conventional therapy (mostly feeding style modifications, such as posture and diet).^{28,36} Finally, two studies utilized chiropractic manipulation and acupotomy therapy.^{32,33} Regarding the control group, five were treated with Western medicine,^{25,27,29,31,34} one used herbal medicine,³⁰ two used conventional treatment,^{28,36} and two used acupuncture therapy.^{32,33} Only one study involved sham technique therapy.³⁵

Types of Outcome Measures

Ten RCTs assessed total treatment effectiveness,^{25,27-34,36} and four RCTs scored the RDQ.^{27,31,33,35} Five RCTs mentioned adverse effects.^{27,29,34-36}

Risk of Bias Assessment

(1) Randomization: Of the included literature, five studies were randomized by random number table,^{28,30-32,36} one study utilized the dynamic random Taves minimization method,²⁷ one study was randomized by calculator random numbers,²⁹ and two used random assignment software.^{33,35} So they were judged as “low risk.” The other two studies only mentioned the word “random” without specifying the grouping method and were assessed “high risk”.^{25,34} (2) Allocation hiding: Allocation concealment was only applied in one study which was judged “low risk”.³⁵ (3) Blind method: Most of the studies could not be blinded due to the specificity of manual therapy, but one study had a sham technique group, so it was judged as low risk.³⁵ (4) Completeness of outcome data: one study lacked a description of data processing for dislodged cases and was judged to be “unclear risk”.³⁶ (5) Selective reporting: one study was deemed “high risk” because it lacked the protocol-required planned outcome markers.³⁴ (6) All other biases were not described in detail and were considered as unknown risk. As shown in ►Figs. 2 and 3.

Meta-analysis

Total Effective Rate

Ten RCTs reported this outcome measure, and the forest plot demonstrated that the total effective rate of the manual

therapy group was superior to that of the control group.^{25,27-34,36} Heterogeneity among studies was low ($I^2 = 40\%$, $p = 0.09$), and the combined effect sizes showed statistically significant differences (OR = 4.63, 95% CI [3.01, 7.14], $p < 0.00001$) using a fixed effects model. The subgroup analysis based on intervention modality revealed that the total effective rate was significantly higher in the manual therapy group versus the Western medicine group (OR = 3.32, 95% CI [1.34, 8.26], $p = 0.01$), the manual therapy group versus the Chinese medicine group (OR = 3.06, 95% CI [1.18, 7.95], $p = 0.02$), manual therapy + the Western medicine group versus the Western medicine group (OR = 5.94, 95% CI [2.63, 13.41], $p < 0.0001$), and manual therapy + the conventional treatment group versus the conventional treatment group (OR = 11.13, 95% CI [3.26, 38.02], $p = 0.0001$). However, there was no statistically significance in the manual therapy + acupuncture treatment versus the acupuncture treatment group (OR = 2.43, 95% CI [0.71, 8.29], $p = 0.16$). The results showed that manual therapy was more effective than Western medicine or TCM decoction alone, and the combined effect of manual therapy + Western medicine/conventional treatment was superior to that of Western medicine or conventional treatment alone. However, there was no significant difference in the efficacy of the combination of manual therapy + acupuncture compared to acupuncture alone. As shown in ►Fig. 4.

Reflux Disease Questionnaire Scores

Four studies reported this outcome indicator.^{27,31,33,35} Heterogeneity among studies was large ($p = 0.02$, $I^2 = 70\%$), so a random effects model was employed and the final combined effect size revealed a significant difference in RDQ scores {weighted mean difference (WMD) = -1.59, 95% CI [-2.85, -0.33], $p = 0.01$ }. These findings suggested that the manual therapy group demonstrated a greater improvement in RDQ scores compared to the control group. As shown in ►Fig. 5.

Adverse Events

Out of eleven trials, five of them reported on adverse events.^{27,29,34-36} According to Martínez's report,³⁵ there were no significant adverse reactions in the subjects during

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|---|---|---|---|--|--------------------------------------|------------|
| Chen 2018 | + | ? | - | ? | + | + | ? |
| Li 2017 | + | ? | - | ? | + | + | ? |
| Liu 2015 | ? | ? | - | ? | + | - | ? |
| Liu 2016 | + | ? | - | ? | + | + | ? |
| Liu 2018 | + | ? | - | ? | + | + | ? |
| Martínez 2019 | + | + | + | + | + | + | ? |
| Xie 2007 | + | ? | - | ? | + | + | ? |
| Yan 2015 | + | ? | - | ? | ? | + | ? |
| Zhang 2001 | ? | ? | - | ? | + | + | ? |
| Zhang 2017 | + | ? | - | ? | + | + | ? |
| Zhong 2021 | + | ? | - | ? | + | + | ? |

Fig. 3 Risk of bias summary. Notes: ●: low risk of bias; ●: unclear risk of bias; ●: high risk of bias.

the trial. Yan’s report mentioned that some patients experienced skin redness or minor injuries during treatment, but there was no comment on how they were managed.³⁶ In the Liu’s report, two patients in the trial group experienced low back muscle pain during treatment with acupoint finger pressure, while one patient in the control group developed diarrhea, one developed constipation, and one developed pruritus during the administration of lansoprazole enteric tablets, but all were able to continue to participate in the study after the symptoms resolved on their own.²⁷ Xie’s report showed that during the administration of omeprazole enteric tablets and mosapride tablets, four patients in the

control group developed diarrhea (10.0%) and three patients developed dizziness (7.5%), but the symptoms were not significant and did not affect the continuation of treatment.²⁹ Liu’s report³⁴ recorded drowsiness and dizziness in one patient in the treatment group during acupuncture therapy combined with oral esomeprazole and mosapride tablets and dry mouth and vertigo in one patient in the control group after oral Western medicine. However, adverse events in both groups were not treated specifically and resolved after rest, without affecting the completion of the course of treatment.

Subgroup Analysis

In the earlier parts of the article, a subgroup analysis of intervention modalities was conducted. Although the heterogeneity for the entire group was only 40%, the within-group heterogeneity was still high in some groups, indicating that the interventions were not the source of heterogeneity. Now, subgroup analyses were conducted again, based on age (young children vs. adults), as displayed in **Fig. 6**. The findings demonstrated that the differences in age could significantly influence heterogeneity.

Publication Bias

Fig. 7 presents a funnel plot analysis of studies that utilized the total effective rate for outcome measurements. The asymmetrical shape of the graph from left to right suggested the possibility of publication bias in the included RCTs, as indicated by the results.

Level of Evidence

The GRADE analysis revealed that the overall quality of evidence for all outcome indicators was low and did not support our recommendation for the outcome. We lowered the standards mostly due to the possibility of bias, inconsistency, and imprecision. As shown in **Table 3**.

Discussion

The pathophysiology of GERD is multifactorial, often associated with an imbalance of aggressive and defensive factors, where the impaired function of anatomical structures is of much concern. The antireflux barriers comprise the LES complex, including the LES, the esophagogastric junction (EGJ), and the crura of the diaphragm (CD). These structures play a crucial role in swallowing and compress the esophagus to prevent reflux.^{37,38} GERD can be caused by a variety of factors that lead to functional or structural impairment of the digestive system. These factors can include conditions like esophageal hiatal hernia, increased intra-abdominal pressure due to obesity or pregnancy, prolonged hypergastric pressure due to delayed gastric emptying, certain hormones like cholecystokinin and glucagon, as well as high-fat, high-sugar foods or medications such as calcium channel blockers and diazepam that can cause temporary relaxation of the LES.³⁹ Moreover, cognitive and emotional changes can also play a role in GERD by increasing an individual’s sensitivity to esophageal sensation known as visceral

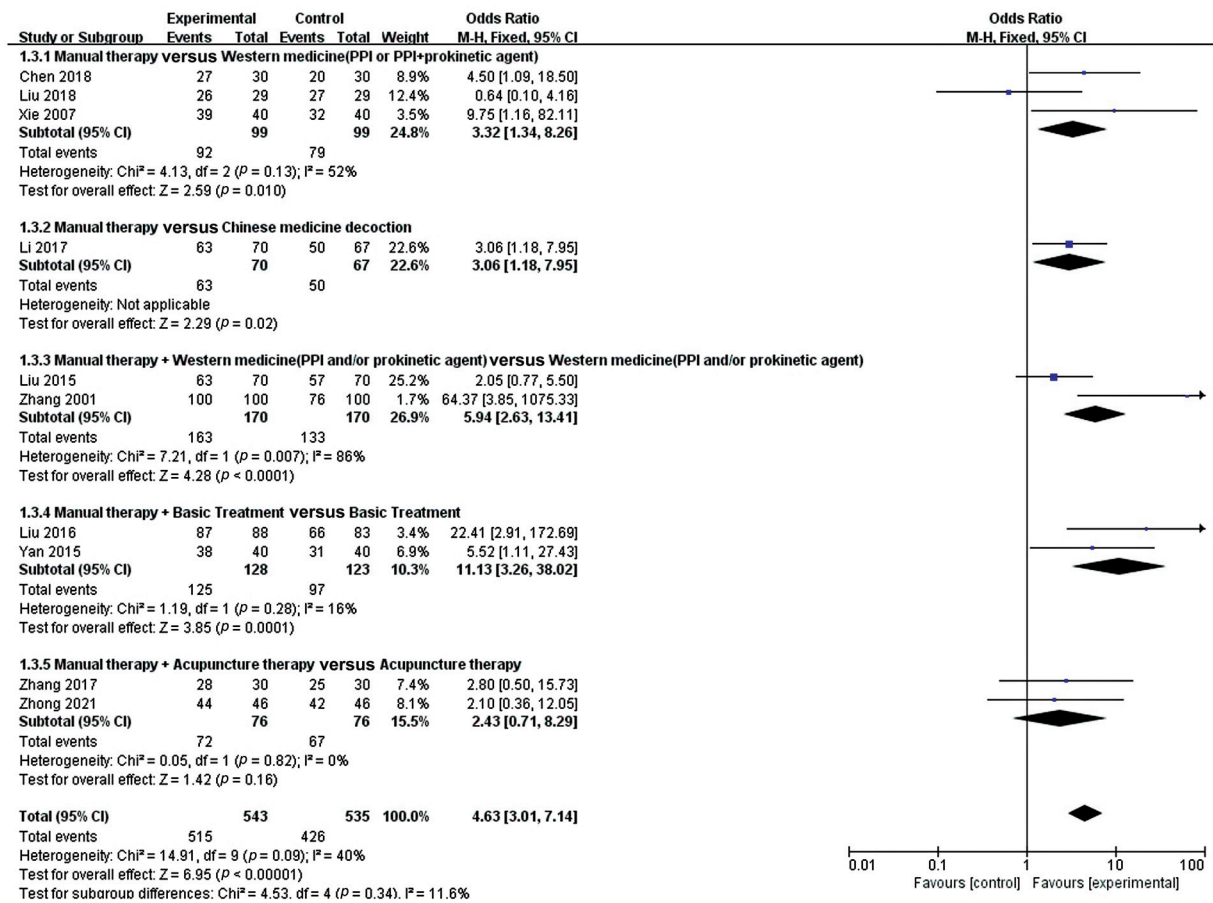


Fig. 4 Forest plots of total effective rate.

hypersensitivity, or affecting CD motor and pain modulation via neurohumoral-endocrine pathways.⁴⁰⁻⁴²

The direct damage caused by reflux to the esophagus is attributed to gastric acid and pepsin. Therefore, PPIs have become the preferred choice of medication to relieve GERD symptoms. However, studies have shown that these drugs do not significantly reduce the incidence of reflux events, with 10 to 40% of patients not responding to PPI treatment. Moreover, some symptoms of refractory GERD, including heartburn, improve by less than 50% even after 12 weeks of double-dose PPI treatment.⁴³ Consequently, the most important aspect of treating GERD is repairing the damaged antireflux barrier. Antireflux surgery, such as fundoplication, can restore LES and EGJ function and halt reflux. However,

the stringent requirements of the procedure, as well as potential adverse events such as postoperative bloating, diarrhea, or gastrointestinal dysfunction, coupled with the uncertainty of the procedure's long-term efficacy, have led physicians and patients to seek better alternatives.^{43,44}

The manipulative treatments utilized in this study possess the capability to impact the visceral state from numerous angles. The advantages conferred by manipulative treatments, including acupuncture, Chinese tuina, fascial release, and osteopathy, concerning the pathophysiology of internal organs have been established in various illnesses.^{14,45-49} According to the theory of TCM, as outlined in the ancient Chinese medicine book *Yellow Emperor's Inner Classic (Huang Di Nei Jing)*, the internal organs are linked to the body surface

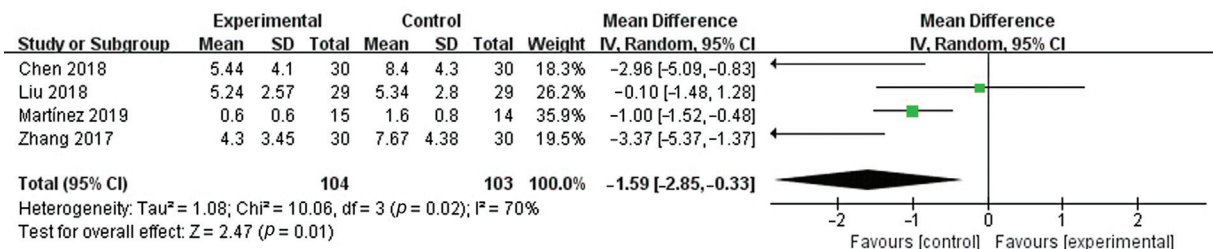


Fig. 5 Forest plots of RDQ score.

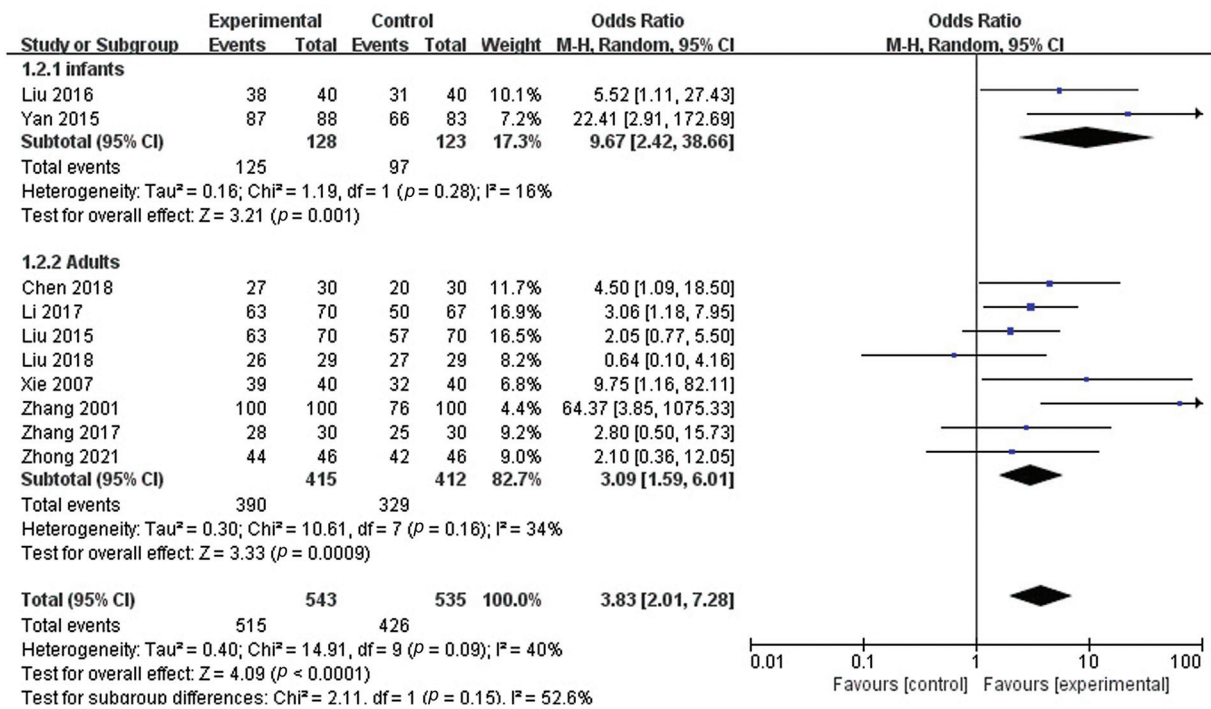


Fig. 6 Subgroup analyses of the total effective rate.

through meridians. The acupoints on the body surface denote the points where the meridians pass through, which can be utilized for palpation, visualization, and treatment purposes. Acupuncture, moxibustion, massage techniques, and other

stimuli on the acupoints can be implemented to rectify and cure internal ailments through meridians.⁵⁰ The governor vessel has the ability to govern the spinal column and spinal cord, which is also known as the middle line of the back. The

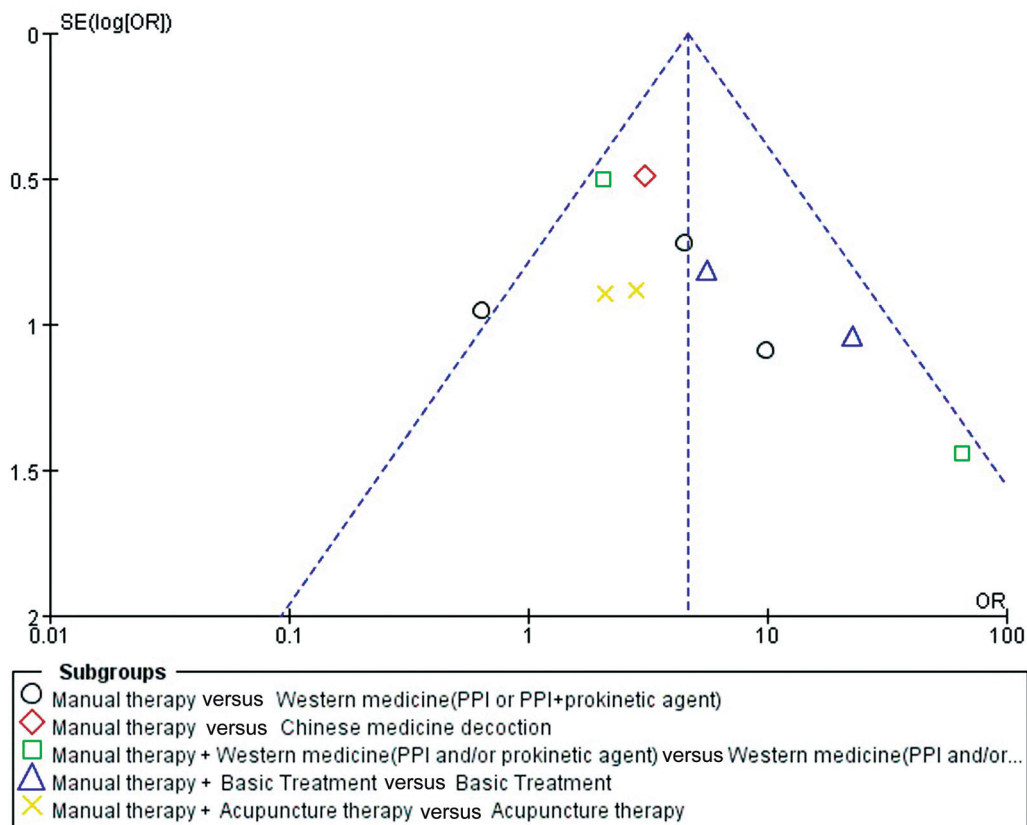


Fig. 7 Funnel plot of the total effective rate.

Table 3 Level of evidence

| Outcomes | Sample size (studies) | Effects (95% CI) | Quality of evidence | Comments |
|--|-----------------------|-------------------------|------------------------------|---|
| Total effective rate—manual therapy vs. Western medicine ^a | 198 (3) | OR 3.32 (1.34, 8.26) | ⊕ ⁰⁰⁰ Very low | Serious risk of bias ^b , inconsistency ^c , imprecision ^d |
| Total effective rate—manual therapy vs. Chinese medicine decoction | 137 (1) | OR 3.06 (1.18, 7.95) | ⊕⊕ ⁰⁰ Low | Serious risk of bias ^b , imprecision ^d |
| Total effective rate—manual therapy + Western medicine vs. Western medicine | 340 (2) | OR 5.94 (2.63, 13.41) | ⊕ ⁰⁰⁰ Very low | Serious risk of bias ^b , Inconsistency ^e , imprecision ^d |
| Total effective rate—manual therapy + basic treatment ^f vs. basic treatment | 251 (2) | OR 11.13 (3.26, 38.02) | ⊕⊕ ⁰⁰ Low | Serious risk of bias ^b , imprecision ^d |
| Total effective rate—manual therapy + acupuncture therapy vs. acupuncture therapy | 152 (2) | OR 2.43 (0.71, 8.29) | ⊕⊕ ⁰⁰ Low | Serious risk of bias ^b , imprecision ^d |
| RDQ score | 207 (4) | MD -1.59 (-2.85, -0.33) | ⊕ ⁰⁰⁰ Very low | Serious risk of bias ^b , inconsistency ^g , imprecision ^d |

Abbreviations: CI, confidence interval; OR, odds ratio; ⊕, evidence quality level, +1 score; ◊, evidence quality level, +0 score; PPI, proton pump inhibitor.

GRADE Working Group grades of evidence:

Note: High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Note: Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Note: Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Note: Very low quality: We are very uncertain about the estimate.

^aWestern medicine: PPI or prokinetic agent or PPI + prokinetic agent.

^bAllocation concealment report is insufficient, or blinding of participants and personnel is missing, or blinding of outcome assessment is unclear.

^cThe test for heterogeneity is significant ($I^2 = 52\%$).

^dThe OIS (optimal information size) is not satisfied.

^eThe test for heterogeneity is significant ($I^2 = 86\%$).

^fBasic treatment: posture, dietary.

^gThe test for heterogeneity is significant ($I^2 = 70\%$).

first lateral line of the bladder meridian of foot-taiyang (located 1.5 cun lateral to the governor vessel) is associated with the path of the sympathetic nerve. The “Back-Shu acupoints” on the bladder meridian of foot-taiyang correspond to the locations of the sympathetic ganglia as well.⁵¹ Therefore, manipulation or stimulation of the spine-related acupoints can indirectly influence the somatic or visceral nerve fibers that travel through the intervertebral foramina of the spine via the skin, muscles, or bones, thus improving the functional status of the gastrointestinal tract. Additionally, myofascial release can directly act on the anatomical structures associated with the antireflux barrier to alleviate the underlying cause of reflux.³⁵ Warm or mechanical stimulation by abdominal manipulation can accelerate peristalsis to reduce gastric hypertension or modulate gastrointestinal hypersensitivity through vegetative reflexes.⁵² Thus, multi-path manipulations are more effective in eliminating the root cause of reflux and achieving long-term relief.

To the best of our knowledge, this is the first systematic review and meta-analysis aimed at evaluating the effective-

ness and safety of manual therapy in treating GERD. Our findings suggested that, when considering the total effective rate, manual therapy was more significant compared to Western medicine or Chinese medicine decoction used alone. Furthermore, manual therapy combined with either Western medicine or conventional treatment was more effective than either of these treatments alone. However, when compared to acupuncture treatment alone, our results showed no significant change in efficacy after manual therapy was added. Subgroup analysis of the total effective rate according to age of the participants revealed reduced heterogeneity among groups, indicating a significant difference in the response of infants and adults with GERD to manual therapy. We also observed heterogeneity among studies in terms of sample size, intervention site and modality, and duration of treatment, which may serve as sources of heterogeneity for future studies. Although we found a significant difference in RDQ scores (WMD = -1.59, 95% CI [-2.85, -0.33], $p = 0.01$), the intervention modality and symptom indicators and scoring criteria of the questionnaire varied

among studies. Therefore, it is still premature to confirm this result. Regarding adverse events, only a few instances of small skin rashes and back pain have been reported, making it difficult to determine whether other unpleasant effects are caused by the massage. In summary, the meta-analysis revealed that manual therapy treatment for GERD has positive effects and minimal adverse effects for various age groups, indicating that it could be used as an alternative or complementary therapy to traditional pharmacological treatments to alleviate negative effects. Despite methodological variations, these findings are consistent.

This study has several limitations. First, the number of literature sources included in the study was not sufficient. Although we searched for eight reputable databases, the scope needs to be expanded to gather more data. Moreover, there were not many high-quality RCTs of manual therapy for GERD, and some clinical studies were excluded because they failed to meet the inclusion criteria due to reasons such as the absence of valid randomization and incomplete results data. Second, the intervention modalities in the included literature were too diverse and not entirely independent, causing limitations. While the heterogeneity of the combined effect size only amounted to 40%, the tuina or massage methods varied between studies, and the number of literature sources accompanied by equivalent manipulations were inadequate. Furthermore, manipulation is mostly used with Western medicine, Chinese medicine decoction, or acupuncture for cotreatment purposes, which makes it hard to control variables, resulting in a final conclusion lacking relevance and caution. Third, there is a lack of sufficient outcome indicators. Outcome measurements commonly utilized in GERD-related studies, such as LES pressure measurement, 24-hour esophageal pH monitoring, gastroscopy grading, and GERD scale (Gerd Q), were excluded from this study due to differences in intervention modality, study type, and study quality. On the contrary, the total effective rate and RDQ score were commonly used, but their high subjectivity may have affected the credibility and generalizability of the meta-analysis results. Fourth, the quality of the included studies is low. To date, clinical studies investigating manual therapy for GERD have been inadequate in terms of randomization methods, blinding, and allocation concealment. Some sites may provide subjects with information about the entire trial process and other related information before conducting clinical trials to protect both doctors and patients, which might affect blinding and allocation concealment implementation. Therefore, it is essential to explore how to standardize clinical trial procedures in the current health care environment.

Conclusion

This meta-analysis suggested that manual therapy has a positive impact on the relief of symptoms such as reflux and heartburn. Manual therapy, as a standalone treatment, is more beneficial than Chinese medicine decoction or Western medicine in the management of GERD, and combination therapy is often superior to single therapy. However, the

conclusions should be viewed with caution due to the lack of methodological quality, limited literature, and low sample size. For manual therapy practitioners in clinical settings, there is evidence to support the adjunctive use of manual therapy in GERD treatment. In the future, well-designed RCTs with larger samples and multiple centers are necessary, utilizing tuina or massage as the primary and independent interventions, and employing more objective and varied evaluation indicators to establish more clearly the effectiveness, in both the short and long-term, of manual therapy in treating GERD and which techniques are more advantageous.

CRedit Authorship Contribution Statement

M.Y. was responsible for conceptualization, data curation and formal analysis, and writing original draft. Y.S. was responsible for conceptualization, methodology, and writing review and editing. Y.L. was responsible for methodology, methodology. Y.S. and M.Z. were responsible for data curation and formal analysis. S.Y., D.C., and S.L. were responsible for literature searching and funding acquisition. Y.F. was responsible for funding acquisition and writing review and editing.

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Conflict of Interest

The authors declare no conflict of interest.

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