Systematic Review and Meta-Analysis

Medicine

OPEN

Evidence-based evaluation of adjuvant therapy with Chinese medicine for cerebral small vessel disease

A systematic review and meta-analysis

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Abstract

Background: As the population ages, the prevalence of cerebral small vessel disease (CSVD) steadily increases, resulting in a significant economic burden on society. In East Asian nations, Chinese medicine has been used extensively to teat CSVD and has been reported to improve the cognitive function of patients. The present study aimed to comprehensively assess the efficacy and safety of Chinese medicine as adjuvant therapy for CSVD.

Methods: A literature search of the CNKI, Wanfang, VIP, SinoMed, Medline, Cochrane Library, and ChiCTR databases were searched for RCTs investigating the use of TCM as an adjuvant in the treatment of CSVD, published up to July 27, 2023, was performed. Based on the Cochrane Collaboration Network bias risk assessment criteria, Review Manager version 5.3 was used to perform a meta-analysis.

Results: Meta-analysis of 27 RCTs, including 2554 subjects, revealed that the majority of the RCTs exhibited risk for ambiguous bias. The findings demonstrated that the use of Chinese medicine as an adjuvant treatment for CSVD effectively enhanced the cognitive function, as evidenced by improvements in the MMSE score (mean difference (MD) = 2.42, 95% confidence interval (CI) [1.79,3.17], $P < .00001$), MoCA score (MD = 2.39, 95% CI [1.78,2.99], $P < .00001$) and ADL score (MD = 4.13, 95% CI [1.74,6.51], $P = .0007$). Furthermore, the study also demonstrated the advantages of Chinese medicine adjuvant therapy in enhancing the Chinese medicine syndrome score (MD = –2.57, 95% CI [–3.31, –1.83], $P < .00001$), CRP (MD = –1.35, 95% CI [–2.27, –0.43], $P = .004$), Hcy (MD = –3.44,95% CI [–4.05, –2.83], $P < .00001$), and blood flow velocity (CBV) (MD = 1.37,95% CI [0.24,2.50], $P = .02$). Moreover, there was no statistical difference in the incidence of adverse reactions between the 2 groups.

Conclusion: Findings of the present study indicate that the Chinese medicine, as an adjuvant to conventional treatment, appeared to be efficacious in enhancing cognitive function, reducing Chinese medicine syndrome score, improving blood biochemical markers, and improving cerebral blood flow perfusion in patients with CSVD, without any notable adverse reactions. However, it is imperative to validate these conclusions in future high-quality investigations.

Abbreviations: ADL = activities of daily living, CBF = cerebral blood flow, CBV = blood flow velocity, CI = confidence interval, CRP = C-reactive protein, CSVD = cerebral small vessel disease, Hcy = homocysteine, MD = mean difference, MMSE = Mini Mental State Examination, MoCA = Montreal Cognitive Assessment, NIHSS = National Institute of Health Stroke Scale, PROSPERO = Prospective Register of Systematic Reviews, RCT = randomized controlled trial, RR relative risk, VCI = vascular cognitive impairment.

Keywords: cerebrovascular disease, Chinese medicine, cognitive function, meta-analysis, systematic review

1. Introduction

Cerebral small-vessel disease (CSVD) encompasses a range of clinical, imaging, and pathological syndromes involving various components of the cerebral vasculature, including arterioles, capillaries, and venules, caused by diverse factors.[1] The prevalence of CSVD is significant, with approximately 50 million individuals affected by dementia worldwide and 10 million

This work was supported by grants from the National Natural Science Foundation of China (82074251), Natural Science Foundation of Hunan Province (2022JJ30357).

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study did not involve human subjects, human tissue, or animal subjects, and thus, no ethical approval was required.

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How to cite this article: Xu Y, Chen B, Yi J, Liu B. Evidence-based evaluation of adjuvant therapy with Chinese medicine for cerebral small vessel disease: A systematic review and meta-analysis. Medicine 2023;102:52(e36221).

Received: 14 August 2023 / Received in final form: 27 October 2023 / Accepted: 30 October 2023

http://dx.doi.org/10.1097/MD.0000000000036221

new cases emerging annually. CSVD is responsible for 20% of strokes, and 45% and 70% of dementia and vascular dementia cases globally, respectively, making it the primary cause of vascular cognitive impairment (VCI).[2,3] CSVD is strongly associated with gait disorders, depression, urinary incontinence, and Parkinson disease. Moreover, it is a significant contributor to falls, diminished functional capacity, disability, and mortality among older individuals, thereby imposing a substantial burden on society.[4]

In contrast to acute VCI after stroke, VCI resulting from CSVD is regarded to be a chronic condition characterized by gradual onset and a series of progressive stages. This condition initially affects executive function and attention, and eventually leads to memory impairment. Consequently, intervention has a higher likelihood of yielding positive outcomes in patients with CSVD-induced VCI.[5] Currently, the primary recommended interventions for managing CSVD involve regulation of vascular risk factors, modification of detrimental lifestyles, administration of cholinesterase inhibitors and excitatory amino acid receptor antagonists, and cognitive training. However, it is important to note that the overall strength of evidence supporting these measures is generally limited.[6] Chinese medicine has a long history and rich practical experience in enhancing cognitive function.[7,8] Currently, an increasing number of patients with CSVD-VCI patients are being treated using Chinese medicine, and related research is increasingly extensive and in-depth. Furthermore, many randomized controlled trials (RCTs) have been performed in succession.[9]

Although some investigators have published evidence-based research schemes for the treatment of CSVD-VCI with Chinese medicine,[10] unfortunately, to date, there is no high-level evidence for the treatment of CSVD with Chinese medicine. As such, this systematic review and meta-analysis was performed to better understand the effectiveness of TCM as adjuvant therapy for CSVD and its impact on patient quality of life.

2. Materials and methods

2.1. Study design

Normative data analysis was performed in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020" guidelines.

2.2. Inclusion criteria

2.2.1. Types of study included. This meta-analysis only peer-reviewed, fully reported, RCTs, with no language restrictions.

2.2.2. Study subjects and disease diagnostic criteria. Subjects included patients clinically diagnosed with CSVD-VCI. In accordance with the Clinical Practice Guideline for Cognitive Impairment of Cerebral Small Vessel Disease in China (2019),[11] key points of diagnosis included cognitive impairment with subjective reports and objective examinations; CSVD was confirmed by magnetic resonance imaging (MRI) diagnosis; and CSVD was identified as a direct factor of cognitive impairment.

2.2.3. Intervention. Qualified experimental intervention measures included Chinese medicine combined with conventional treatment, with no restrictions on the types of Chinese medicine used (i.e., different ingredients, formulas, doses and routes of administration). Any Chinese medicine preparations, such as a decoctions, granules, oral liquids, ointments, or capsules, were considered. Specifically. The treatment group was treated using Chinese medicine combined with conventional treatment. The control group underwent conventional treatment only, which was performed according to the clinical guidelines or consensus recommendations for CSVD-VCI, such as adjusting lifestyle habits, managing the traditional risk factors for cerebrovascular disease (such as antihypertensive, hypolipidemic and antiplatelet therapy), and anti-dementia treatment such as cholinesterase inhibitors, nimodipine, memantine, citicoline, butylphthalide, cognitive training, and routine nursing, etc. In contrast, patients in the intervention group, who underwent any other non-drug treatment (such as acupuncture, massage, and Taiji exercise, etc) were excluded from the RCTs.

2.2.4. Outcomes. Primary outcomes: Primary outcomes included whether cognitive function was measured using by globally recognized assessment scales, such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), and activities of daily living (ADL).

Secondary outcome: Secondary outcomes included National Institutes of Health Stroke Scale (NIHSS) score, Chinese medicine syndrome score, blood biochemical indicators (such as C-reactive protein (CRP) and homocysteine (Hcy)), cerebral blood flow perfusion (such as cerebral blood flow (CBF) and blood flow velocity (CBV)) and safety indicators.

2.3. Exclusion criteria

RCTs that did not report "random distribution" or "random control" in the full text were excluded. For multiple studies that used the same research data, only 1 published study was included. Studies for which it was not possible to obtain the full text or those with missing data, reviews, personal clinical experience summaries, research progress, animal trials, conference papers, meta-analyses, and other nonclinical trials were also excluded. Finally, studies reporting acupuncture, massage, acupoint catgut embedding, electroacupuncture, rehabilitation therapy, acupoint application, and other non-drug, TCM treatments were not considered in this study.

2.4. Search strategy

From the database inception to July 27, 2023, a comprehensive literature search of the Chinese National Knowledge Infrastructure (CNKI), Wanfang, VIP, SinoMed, Medline, Cochrane Library, and ChiCTR databases was performed. Key words included "CSVD-VCI" and "Chinese medicine," in which "CSVD-VCI" included "cerebral small vessel disease," "cognitive impairment," "cerebral small vessel disease, cognitive impairment," "CSVD-VCI," and "dementia." "Chinese medicine" included "Chinese medicine" and "Chinese herbal medicine." These terms were then translated and applied retrieve studies housed in the Chinese databases. The selection of search fields for titles, summaries or keywords varied according to the characteristics of the database.

2.5. Study selection and data extraction

Based on predefined inclusion and exclusion criteria, the retrieved studies were selected to answer the research questions. Two researchers independently performed study screening and data extraction according to predefined screening criteria. Disagreements were resolved by consultation with a third researcher.

First, the titles and abstracts were screened for studies that did not meet the inclusion criteria. The remainder of the studies were screened again to determine their final inclusion. A spreadsheet data extraction table (Excel, Microsoft Corporation, Redmond, WA, USA) was designed in advance and used to extract information from the studies, including the following: year of publication; title; corresponding author and contact information; basic characteristics of the research population; sample size; intervention(s) and control measures; and outcome indicators.

2.6. Quality assessment

The 2 researchers independently evaluated the methodological quality of the included studies according to the Risk of Bias Assessment Tool recommended by Cochrane Review Handbook version 5.0. Any differences were fully discussed and consensus was reached. Evaluation items included random allocation method, allocation scheme concealment, blinding, completeness of outcome data, selective reporting of research results, and other sources of bias.

2.7. Statistical analysis

RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for data analysis. First, different effect estimates were used for different data types. Binary data are expressed as relative risk (RR) and corresponding 95% confidence interval (CI), continuous data with the same unit of measurement are expressed as mean difference (MD) and corresponding 95% CI, and continuous data with different units of measurement are expressed as standardized mean difference and 95% CI.

2.8. Sensitivity analysis, subgroup analysis, and assessment of publication bias

When clinical, methodological, and statistical heterogeneity was consistent and small ($I^2 < 50\%$), a fixed effect model was adopted for effect size consolidation; if I^2 was > 50%, a random effect model was adopted. Subgroup analysis was performed to explore sources of heterogeneity. By observing whether the subgroup differences are statistically significant, it can be judged whether the covariates have modifying effects on the intervention measures, and then judge whether the grouping factors are the source of heterogeneity among the results of various studies. To test the robustness of the results, when the heterogeneity was large ($I^2 > 50\%$), 1 study at a time was removed, and the remaining studies were meta-analyzed to observe whether the results were significantly changed by the influence of others.

Finally, for specific outcome indicators, funnel plots were used to explore the publication bias of the results when > 10 studies were included.

2.9. Quality of evidence based on the grading of recommendations, assessment, development and evaluation method

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to evaluate the evidence quality of evidence of the outcome indicators, which was divided into high, medium, low, and very low levels. The default evidence quality of evidence for RCTs is high; as such, which mainly evaluates the evidence quality level of the outcome indicators from 5 degradation factors: the risk of bias, inconsistency, indirectness, imprecision, and publication bias.[12]

3. Results

3.1. Screening process and results

The initial literature search retrieved 2968 studies, of which 1547 were duplicates and, thus, removed. Subsequently, 168 studies remained after screening the titles and abstracts, with 141 excluded after reading the full text. Ultimately, 27 RCTs[13–39] including 2554 patients were selected for meta-analysis. The screening process is illustrated in Figure 1.

3.2. Basic characteristics of the included RCTs

The 27 included RCTs were all published in Chinese between 2014 and 2023. Among these RCTs, subjects in 16 were treated using Chinese herbal formulas combined with conventional treatment in the treatment group and only conventional treatment in the control group. Subjects in 4 RCTs were treated using Chinese medicine granules combined with conventional treatment, while the control group was only treated with conventional treatment. Subjects in 3 RCTs were treated with Chinese medicine pills combined with conventional treatment, while the control group was only treated with conventional treatment. Finally, subjects in 4 RCTs were treated using Chinese medicine capsules combined with conventional treatment, while the control group was only treated with conventional treatment. The basic characteristics of the included RCTs are summarized in Table 1.

3.3. Risk of bias assessment

Among the included RCTs, 17 reported the use of a random allocation method, of which 13 described the use of a random number table method,[13,16–19,21–23,26,27,30–32,35,37,38] 1 RCT used a questionable allocation method,[39] 1 clearly described the use of single blinding for subjects,[26] and 1 clearly described the use of a double-blind and independent input of experimental results.[17] The completeness of the outcome data and selective reporting of all studies were judged with a low risk of bias because the specified indicators were fully reported. It is noteworthy that none of the above mentioned RCTs provided original data, and researchers could only extract summary data from the RCTs for evaluation, which may have led to other biases, as shown in Figures 2–3.

3.4. Meta-analysis results

3.4.1. MMSE score. Eighteen RCTs, including 1721 subjects, reported MMSE scores. The I^2 value was 91%; accordingly, a random-effects model was used for analysis. Results revealed that, compared with conventional treatment alone, Chinese medicine combined with conventional treatment significantly improved MMSE score, and the difference was statistically significant (MD = 2.42, 95% CI [1.79, 3.17], $P < .00001$).

A subgroup analysis was performed according to the intervention measures as the source of heterogeneity. The intervention in 12 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, demonstrated more advantages than conventional treatment alone (MD = 2.42, 95% CI [1.54, 3.30], $P < .00001$). The intervention used in 3 RCTs was Chinese medicine granules, which, when combined with conventional therapy, was more advantageous than conventional therapy alone (MD = 1.54, 95% CI [0.63, 2.44], $P = .0009$). Three RCTs used Chinese medicine capsules as the intervention, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 3.71, 95% CI [2.03, 5.38], $P < .00001$), as shown in Figure 4A.

3.4.2. MoCA score. Twenty-two RCTs, including 1944 subjects, reported MoCA scores. The I^2 value was 91%; as such, a random-effect model was used for analysis. The results showed that compared with conventional treatment alone, Chinese medicine combined with conventional treatment improved MoCA score, and the difference was statistically significant (MD = 2.39, 95% CI [1.78, 2.99], $P < .00001$).

Subgroup analyses were performed using the interventions as sources of heterogeneity. The intervention in 12 RCTs was a Chinese herbal formula, a which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 1.72, 95% CI [1.18, 2.26], $P < .00001$).

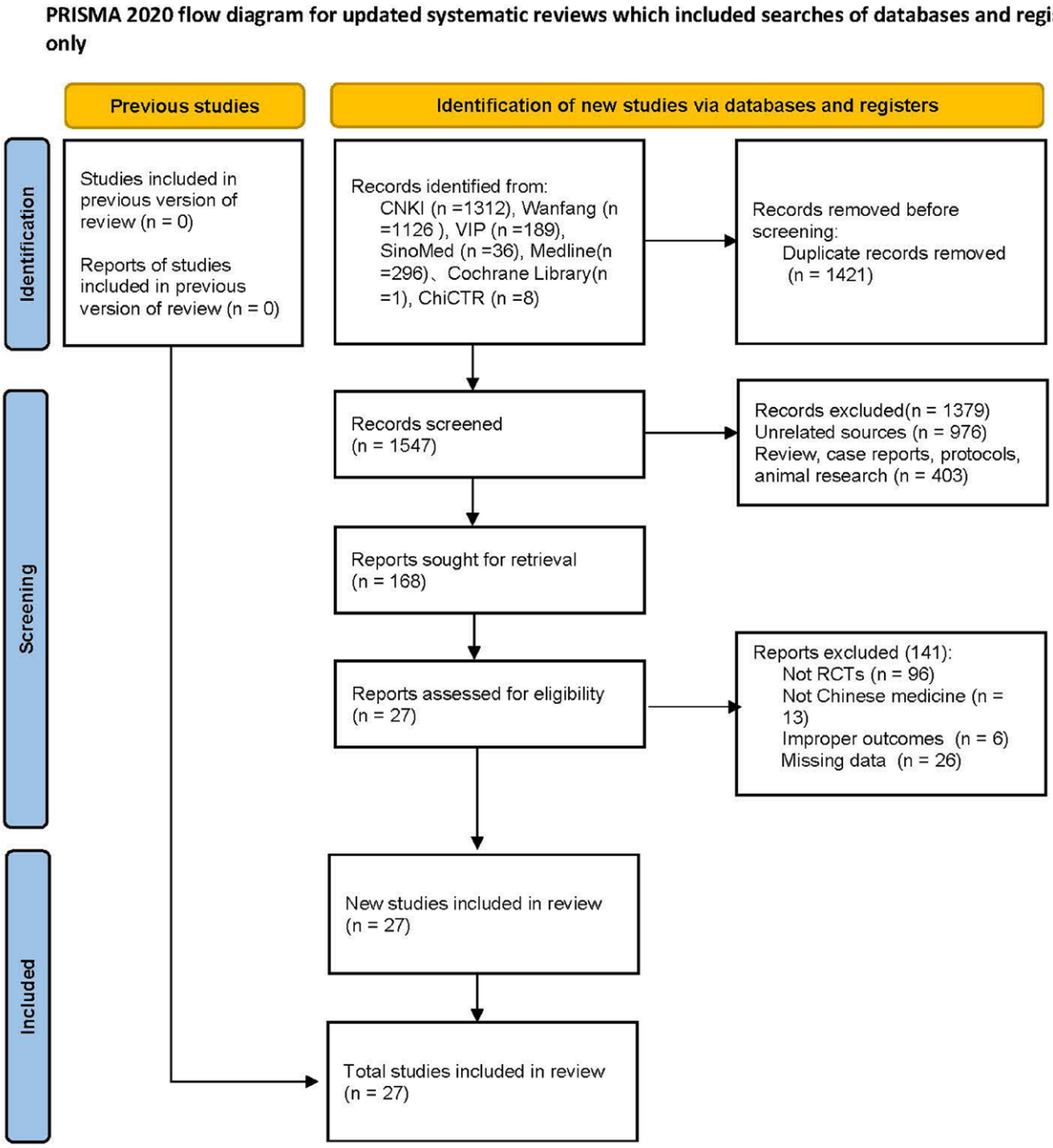


Figure 1. Study selection process for the meta-analysis.

Chinese medicine granules were used as the intervention in 2 RCTs, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 2.33, 95% CI [0.37, 4.29], $P = .02$). Chinese medicine pills were the intervention in 3 RCTs, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 3.68, 95% CI [1.55,5.81], $P = .0007$). Chinese medicine capsules were the intervention in 4 RCTs, which, when combined with conventional treatment was more advantageous than conventional treatment alone (MD = 3.08, 95% CI [1.94, 4.22], $P < .00001$), as shown in Figure 4B.

3.4.3. ADL score. Ten RCTs, including 811 subjects, reported ADL scores. The I^2 value was 94%; as such, a random effect model was used for analysis. The results showed that, compared with conventional treatment alone, Chinese medicine combined with conventional treatment improved the ADL scores, and the difference was statistically significant (MD = 4.13, 95% CI [1.74, 6.51], $P = .0007$).

Subgroup analyses were performed using the interventions as sources of heterogeneity. The intervention in 7 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 5.05, 95% CI [1.42, 8.67], $P < .00001$). The intervention in 2 RCTs was Chinese medicine granules, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = 0.88, 95% CI [0.31,1.45], $P = .02$), as shown in Figure 4C.

3.4.4. NIHSS score. Three RCTs, including 438 patients, reported NIHSS scores. The I^2 value was 98%; as such, a random effect model was used for analysis. The results showed that compared with conventional treatment alone, the addition of

Table 1

Characteristics of RCTIs included in the meta-analysis.

Number	Author	Sample size		Mean age (yr)		Male/female (Male%)		Intervention		Course of treatment	Outcomes
		Treat	Control	Treat	Control	Treat	Control	Treat	Control		
1	Xu Mengqiu, 2021	33	33	68.18 ± 7.038	70.09 ± 8.549	20/13	18/15	Qianyin Yuyang decoction + basic treatment	Basic treatment	24 weeks	①②④⑥⑦⑧⑨
2	Li Xing, 2020	34	35	67.00 ± 7.88	65.37 ± 8.73	16/18	18/18	Huazhuo Yisui decoction + basic treatment	Basic treatment	90 days	①②③⑤⑭
3	Wang Ying, 2014	30	27	63.01 ± 8.54	64.39 ± 6.03	22/8	19/8	Buyang Huanwu decoction + basic treatment	Basic treatment	12 weeks	①⑩⑪
4	Zhang Zhanpeng, 2020	150	150	62.19 ± 6.08	62.17 ± 6.02	87/63	89/61	Xifeng Tongyu Kaiqiao decoction + basic treatment	Basic treatment	14 days	①④⑤⑫⑬
5	Ge Yujie, 2016	33	33	61.28 ± 6.908	64.61 ± 6.189	17/16	15/18	Peiyuan Kaizhi decoction + basic treatment	Basic treatment	60 days	①②④⑦⑪
6	Chen Gang, 2019	45	44	59.0 ± 6.4	58.3 ± 6.9	27/18	25/19	Dihuang Yinzi + basic treatment	Basic treatment	14 days	①②④⑦⑭
7	Zhang Shangxin, 2019	30	30	62.2 ± 8.4	61.7 ± 8.1	16/14	20/10	Dihuang Yinzi + basic treatment	Basic treatment	3 mo	①②
8	Yuan Binwei, 2021	33	35	57.76 ± 7.95	60.2 ± 9.91	19/14	16/19	Huatan Tongluo decoction + basic treatment	Basic treatment	12 weeks	①②④⑪⑭
9	Huang Runchao, 2017	29	29	70.48 ± 8. 971	69.90 ± 9.155	12/17	15/14	Huayu Tongluo decoction + basic treatment	Basic treatment	3 mo	①②⑭
10	Chen Sina, 2019	30	30	67.53 ± 6.06	69.83 ± 4.8	14/16	16/14	Huayu Tongluo decoction + basic treatment	Basic treatment	12 weeks	②⑪
11	Chen Bin, 2023	82	83	61.2 ± 6.3	60.8 ± 6.5	49/33	48/35	Huayu Tongluo decoction + basic treatment	Basic treatment	12 weeks	①②⑪⑭
12	Li Honghai, 2016	20	20	59.1 ± 6.75	62.4 ± 6.87	10/10	9/11	Huayu Tongluo decoction + basic treatment	Basic treatment	12 weeks	②
13	Lu Yaoqiang, 2017	45	45	64.41 ± 5.17	64.14 ± 5.01	25/20	26/19	Chaiqin Wendan decoction + basic treatment	Basic treatment	1 months	①②
14	Liang Fan, 2019	106	106	67.21 ± 6. 76	66.16 ± 7.23	52/54	42/64	Bushen Huayu decoction + basic treatment	Basic treatment	24 weeks	②
15	Meng Shengxi, 2020	39	39	64.35 ± 6.86	63.74 ± 6.57	22/17	21/18	Wenxiao III decoction + basic treatment	Basic treatment	24 weeks	①⑪⑭
16	Huang Qingsong, 2020	40	40	64.3 ± 8.56	63.22 ± 8.61	26/14	27/13	Yishen Congming decoction + basic treatment	Basic treatment	8 weeks	②④⑨⑪⑭
17	Fan Xuejing, 2022	34	35	68.02 ± 6.13	66.09 ± 7.44	22/12	19/16	Huazhuo Xinxue particle + basic treatment	Basic treatment	8 weeks	①②③④⑤⑪⑭
18	Chen Yiran, 2020	46	46	57.09 ± 6.42	56.16 ± 6.82	26/20	25/21	Naokang particle + basic treatment	Basic treatment	4 weeks	①⑦⑨⑬⑭
19	Guo Dawei, 2019	48	47	62.29 ± 9.30	63.73 ± 10.81	27/21	28/19	Yangxue Qingnao particle + basic treatment	Basic treatment	8 weeks	②⑦⑨⑬
20	Ma Chunchao, 2020	40	40	47–78	45–80	25/15	21/19	Yangxue Qingnao particle + basic treatment	Basic treatment	12 weeks	①⑪
21	Jiao Yang, 2015	40	40	64.43 ± 5.23	63.62 ± 4.25	20/20	20/20	Shida Lazhi pill + basic treatment	Basic treatment	14 days	②⑭
22	Yang Tao, 2015	40	40	62.4 ± 4.6	63.2 ± 3.8	22/18	24/16	Bunao pill + basic treatment	Basic treatment	12 weeks	②⑭
23	Zhao Xueling, 2015	55	51	64.5 ± 3.8	64.1 ± 4.2	25/30	24/27	Tongshen Funao pill + basic treatment	Basic treatment	6 mo	②⑨
24	Li Wangjian, 2014	37	32	/	/	/	/	Naotong capsule + basic treatment	Basic treatment	3 mo	①②
25	Miao Hui, 2018	69	69	68.38 ± 4..57	67.90 ± 6.01	45/24	43/26	NaoXintong capsule + basic treatment	Basic treatment	6 mo	①②⑭
26	Zhou Hui, 2019	42	46	66.7 ± 10.8	68.7 ± 8.18	24/18	26/20	NaoXintong capsule + basic treatment	Basic treatment	3 mo	②⑪
27	He Xin, 2018	48	48	65.79 ± 7.91	65.27 ± 7.67	27/21	29/19	Gingko Leaf capsule + basic treatment	Basic treatment	3 mo	①②④⑨

Note: ①MMSE, ②McoA, ③Barthel, ④Chinese medicine syndrome score, ⑤NIHSS, ⑥POMA, ⑦CRP, ⑧Uric acid, ⑨Hcy, ⑩CDR, ⑪ADL, ⑫FMA, ⑬Hemodynamics, ⑭Safety indicators.

Figure 2. Risk of bias graph.

Chinese medicine to conventional treatment yielded no obvious advantage in improving the NIHSS score; the difference was not statistically significant (MD = –1.82,95% CI [–4.04, 0.40], $P = .38$).

Subgroup analyses were performed using the interventions as sources of heterogeneity. The intervention used in 2 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, had no obvious advantage in improving NIHSS scores; the difference was not statistically significant (MD = –2.64, 95% CI [–7.74, 2.47], $P = .31$), as shown in Figure 5.

3.4.5. Chinese medicine syndrome score. Eight RCTs, including 834 subjects, reported TCM syndrome scores. The I^2 value was 72%; accordingly, a random-effect model was used for analysis. The results revealed that compared with conventional treatment alone, the addition of Chinese medicine to conventional treatment improved the Chinese medicine syndrome score, and the difference was statistically significant (MD = –2.57,95% CI [–3.31, –1.83], $P < .00001$).

Subgroup analyses were performed using the interventions as sources of heterogeneity. The intervention used in 6 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = –3.11, 95% CI [–4.27, –1.94], $P < .00001$), as shown in Figure 6.

3.4.6. CRP levels. Five RCTs, including 409 subjects, reported CRP levels. The I^2 value was 96%; as such, a random-effects model was used for analysis. The results revealed that compared with conventional treatment alone, Chinese medicine combined with conventional treatment significantly reduced CRP level, and the difference was statistically significant (MD = –1.35,95% CI [–2.27, –0.43], $P = .004$).

Subgroup analyses were performed using the interventions as sources of heterogeneity. The intervention used in 3 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, demonstrated no obvious advantage in reducing CRP levels, and the difference was not statistically significant (MD = –0.97, 95% CI [–2.04, 0.11], $P = .08$). The intervention in 2 RCTs was Chinese medicine granules, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = –2.08, 95% CI [–3.35, –0.81], $P = .001$), as shown in Figure 7.

3.4.7. Hcy level. Six RCTs, including 535 subjects, reported Hcy levels. The I^2 value was 0%; accordingly, a fixed-effects model was used for analysis. The results revealed that compared with conventional treatment alone, Chinese medicine combined with conventional treatment could significantly improve the Hcy levels; and the difference was statistically significant (MD = –3.44,95% CI [–4.05, –2.83], $P < .00001$).

Subgroup analyses were performed using interventions as sources of heterogeneity. The intervention in 2 RCTs was a Chinese herbal formula, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = –3.48, 95% CI [–4.80, –2.15], $P < .00001$). The intervention in 2 RCTs was Chinese medicine granules, which, when combined with conventional treatment, was more advantageous than conventional treatment alone (MD = –3.69, 95% CI [–4.66, –2.72], $P = .001$), as shown in Figure 8.

3.4.8. Cerebral blood flow perfusion. Three RCTs, including 486 patients, reported CBV data. The I^2 value was 90%; accordingly, a random-effect model was used for analysis. Results revealed that compared with conventional treatment alone, Chinese medicine combined with conventional treatment significantly improved CBV, and the difference was statistically significant (MD = 1.37,95% CI [0.24, 2.50], $P < .0001$).

In addition, 3 RCTs, including 486 subjects, reported CBF data. The I^2 value was 88%; as such, a random effect model was used for analysis. Results revealed that, compared with conventional treatment alone, Chinese medicine combined with conventional treatment significantly improved CBF, and the difference was statistically significant (MD = 0.82,95% CI [0.22, 1.42], $P = .0003$), as shown in Figure 9.

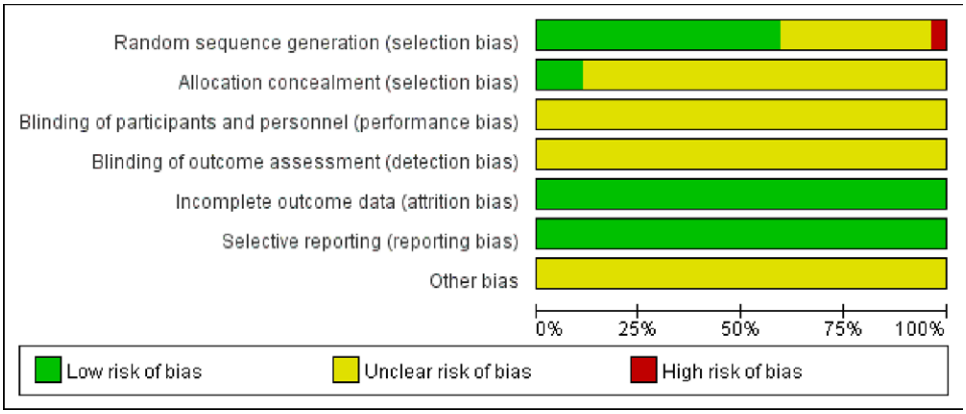


Figure 3. Risk of bias summary.

3.4.9. Adverse reactions. Twelve RCTs reported adverse reactions, of which 5 reported no adverse reactions during the study, and 7 reported detailed adverse reactions, mainly including abdominal distension, dry mouth, constipation, and rash. The I^2 value was 0%; accordingly, a fixed effects model was used for analysis. Results revealed no statistically significant difference in the incidence of adverse reactions between Chinese medicine combined with conventional treatment and conventional treatment alone (RR = 1.11, 95% CI [0.67, 1.85], P = .67), as shown in Figure 10.

3.4.10. Publication bias. In this study, the number of studies with MMSE, MoCA and ADL outcome indicators included in the analysis was more than 10, the funnel plot analysis of the above 3 indicators was biased. The funnel plot displayed asymmetry, thus indicating the potential for publication bias. A possible reason is that many low-quality small-sample studies were included, with few negative results, and all of them were in the Chinese literature, as shown in Figure 11.

3.4.11. Sensitivity analysis. Sensitivity analysis was performed using the MMSE, MoCA and ADL, with > than 10 included RCTs. After one-by one exclusion of original RCTs one by one, results of analysis revealed no significant change in each outcome index, suggesting that the results of the meta-analysis were relatively robust.

3.4.12. GRADE evidence quality rating. The GRADE evidence quality evaluation was performed on the included outcome indicators, in which the MMSE, MoCA, ADL, and TCM syndrome scores were low-quality evidence, and the other outcome indicators were very low-quality evidence, as shown in Table 2.

4. Discussion

The present study systematically and comprehensively retrieved relevant RCTs, adhered to the rules and procedures of systematic review/meta-analysis, and systematically evaluated the effectiveness and safety of adjuvant treatment of CSVD-VCI using Chinese medicine based on the results of 27 RCTs. The analysis revealed that adjuvant treatment with Chinese medicine was not only better than conventional treatment alone in improving MoCA, MMSE and ADL cognitive function scores, but also had obvious advantages in terms of CRP, Hcy, and cerebral blood flow perfusion. No significant safety risks were observed in patients in whom Chinese medicine was used.

CSVD-VCD is the most common form of VCI and vascular dementia. The potential mechanism of cognitive decline may be that lacunar infarction or deep white matter lesions damage the frontal subcortical loop, and deep white matter lesions damage the white matter fibers, which are crucial for cognitive function and emotional regulation.[40] Among the RCTs included in this study, the MoCA, MMSE, and ADL scores were included, and the reporting rate of the cognitive function score was 100%, indicating that the original investigators fully understood and devoted attention to the main symptoms of CSVD-VCI. Vascular endothelial dysfunction, inflammation, and other pathological factors are also associated with the occurrence and development of CSVD.[41] The degree of endothelial dysfunction can be evaluated by detecting the molecules that interact with endothelial cells, such as Hcy and CRP. Chronic cerebral ischemia/hypoperfusion plays a key role in the pathogenesis of CSVD. This may be related to structural changes of in cerebral microvessels and small vessels, and the damage to deep cerebral perforating arteries, resulting in decreased cerebral perfusion and selective oligodendrocyte apoptosis.[42] In this study, the above indicators were included to systematically and comprehensively evaluate the clinical efficacy of Chinese medicine in the adjuvant treatment of CSVD.

CSVD-VCI is a new disease name that has been proposed only in recent years. According to its clinical symptoms and the ancient Chinese medicine literature, it is often classified as "dementia" and "forgetfulness." Chinese medicine formulas are usually composed of a variety of herbs, which act on the body organs through multiple targets and play a therapeutic role. This multichannel and multitarget feature is consistent with the multifactorial pathological mechanisms of CSVD. Emerging studies have shown that various Chinese medicinal formulas exert therapeutic effects on CSVD.[43] In vivo animal experiments and clinical case-control studies have confirmed the effectiveness of Chinese medicine in the treatment of CSVD.[44] It is believed that Chinese medicine can be used as an effective supplement to the conventional treatment of CSVD.

The present meta-analysis, however, had some limitations. First, all the 27 included RCTs reported random distribution, but only 13 specifically described random sequence generation methods, and only 2 reported blinding methods, which lack a certain rigorous design and may have introduced bias. Only 2 RCTs had sample sizes of more than 100 subjects, and the different RCTs using different dosage forms of Chinese medicine may have introduced some bias. Unpublished negative results were not included in this study because positive results are easier to publish. The number of included RCTs was limited, and all were single-center, and small-sample studies. Some experimental designs were incomplete, which reduces the recommendation level and evidence strength of the systematic reviews. In addition, when describing the safety indicators, the RCTs included in this study did not specify the specific name, frequency, duration and degree of adverse events or reactions; the causal relationship

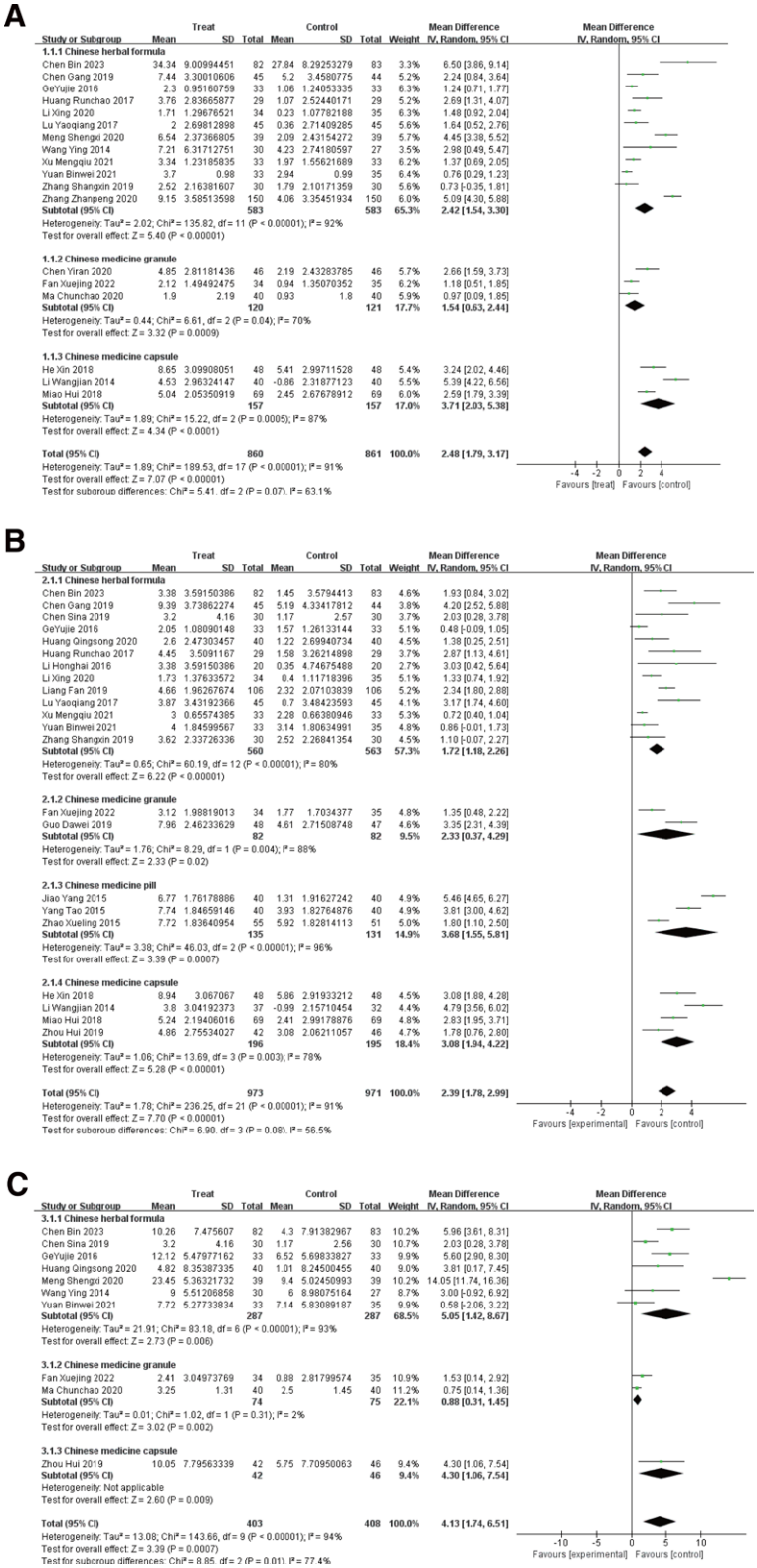


Figure 4. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in cognitive function. (A) MMSE score. (B) MoCA score. (C) ADL score. ADL = activities of daily living. MMSE = Mini Mental State Examination, MoCA = Montreal Cognitive Assessment.

between the adverse events or reactions and the intervention measures; or whether the patients stopped taking drugs, withdrew or accepted the corresponding treatment measures due to their appearance; as such, the safety evidence provided by them was not referential.

5. Conclusion

In summary, the present study extracted data from currently available RCTs for systematic evaluation, which indicated that Chinese medicine combined with conventional treatment of CSVD can not only improve the cognitive function score but

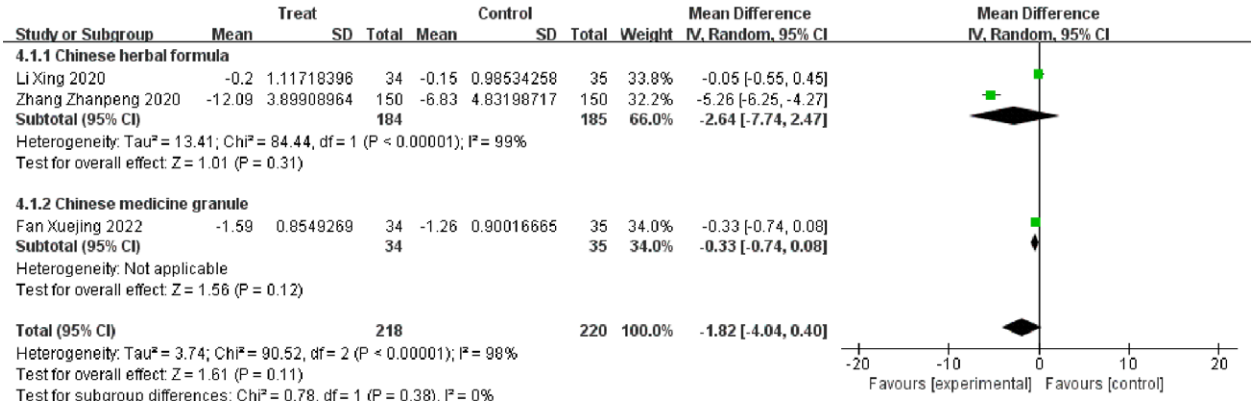


Figure 5. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in NIHSS score. NIHSS = National Institute of Health Stroke Scale.

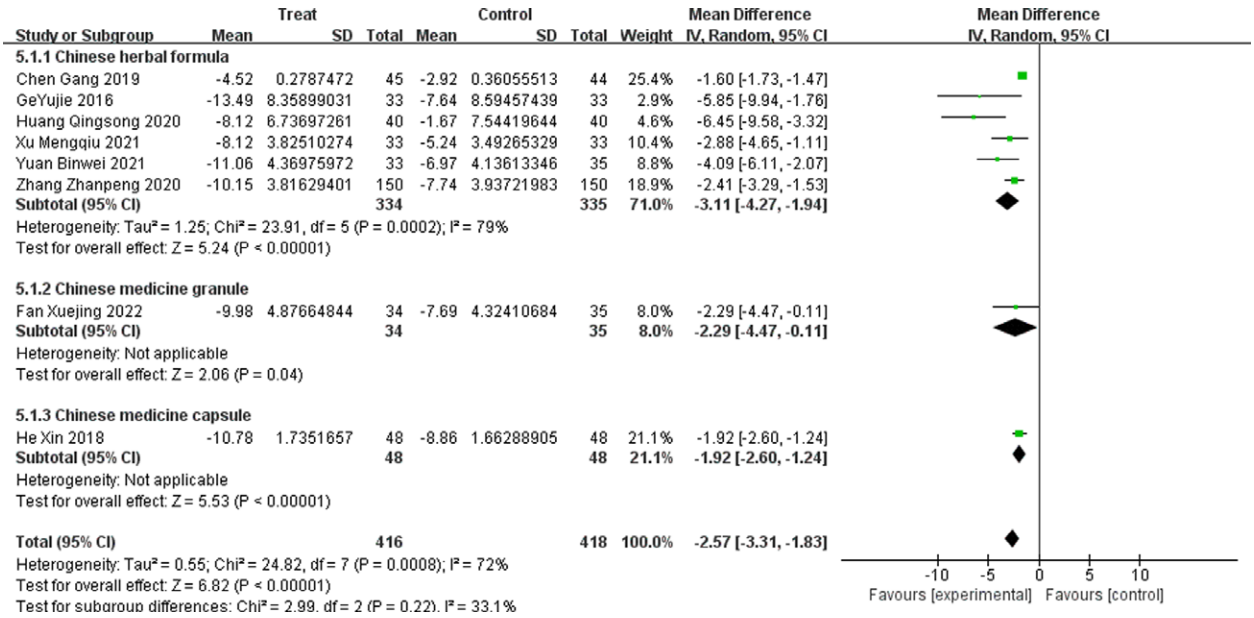


Figure 6. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in Chinese medicine syndrome score.

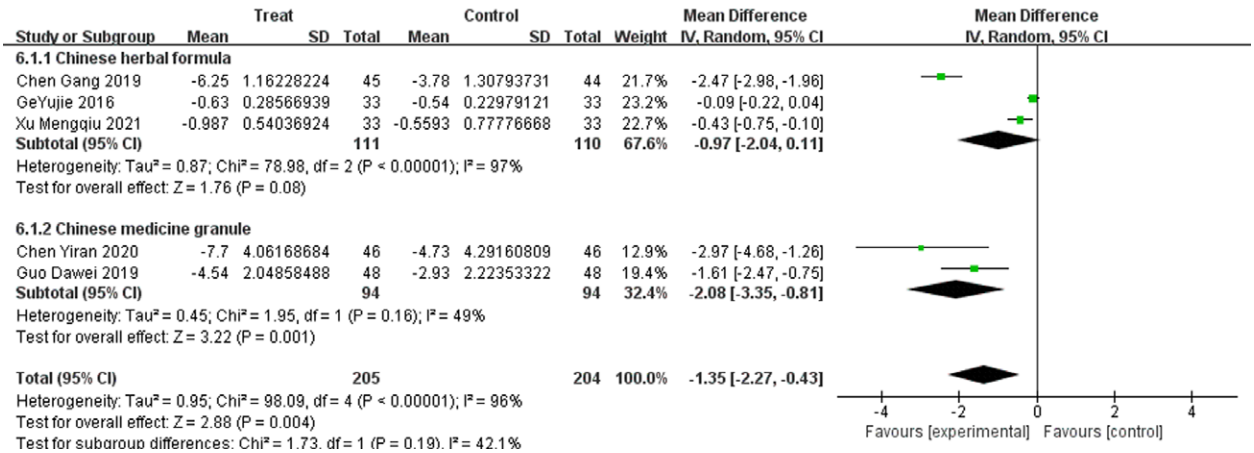


Figure 7. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in CRP level. CRP = C-reactive protein.

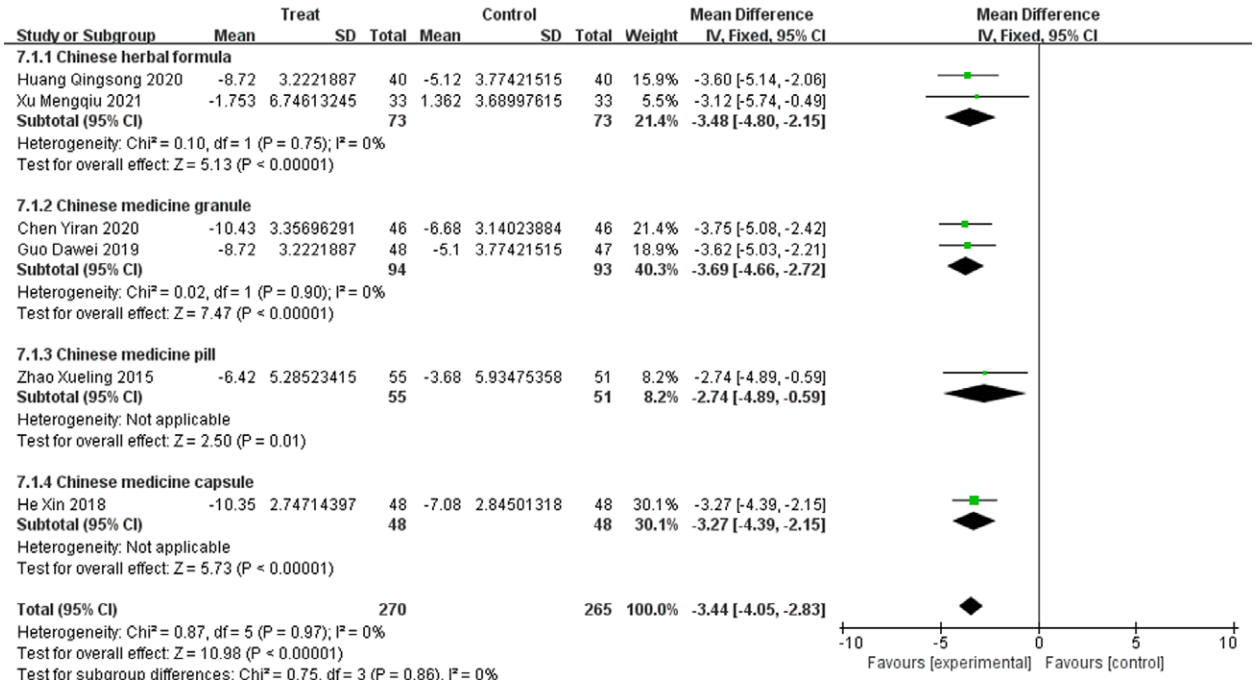
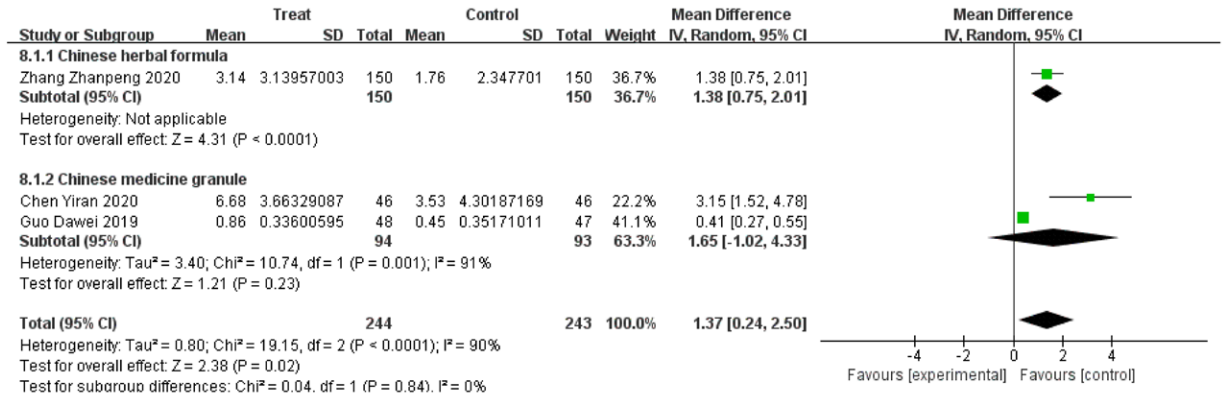


Figure 8. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in Hcy level. Hcy = homocysteine.

A



B

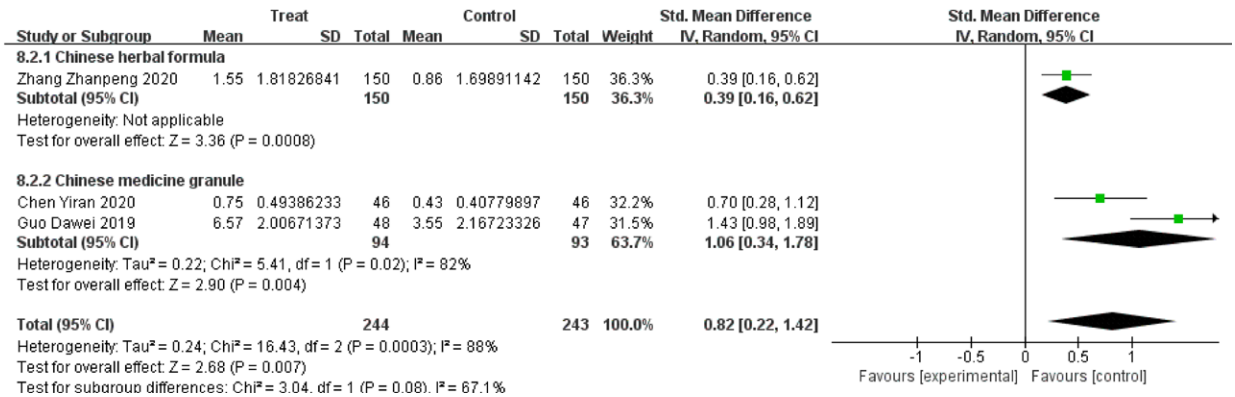


Figure 9. Comparison of the clinical efficiency between Chinese medicine combined with conventional treatment conventional treatment alone in Cerebral blood flow perfusion.

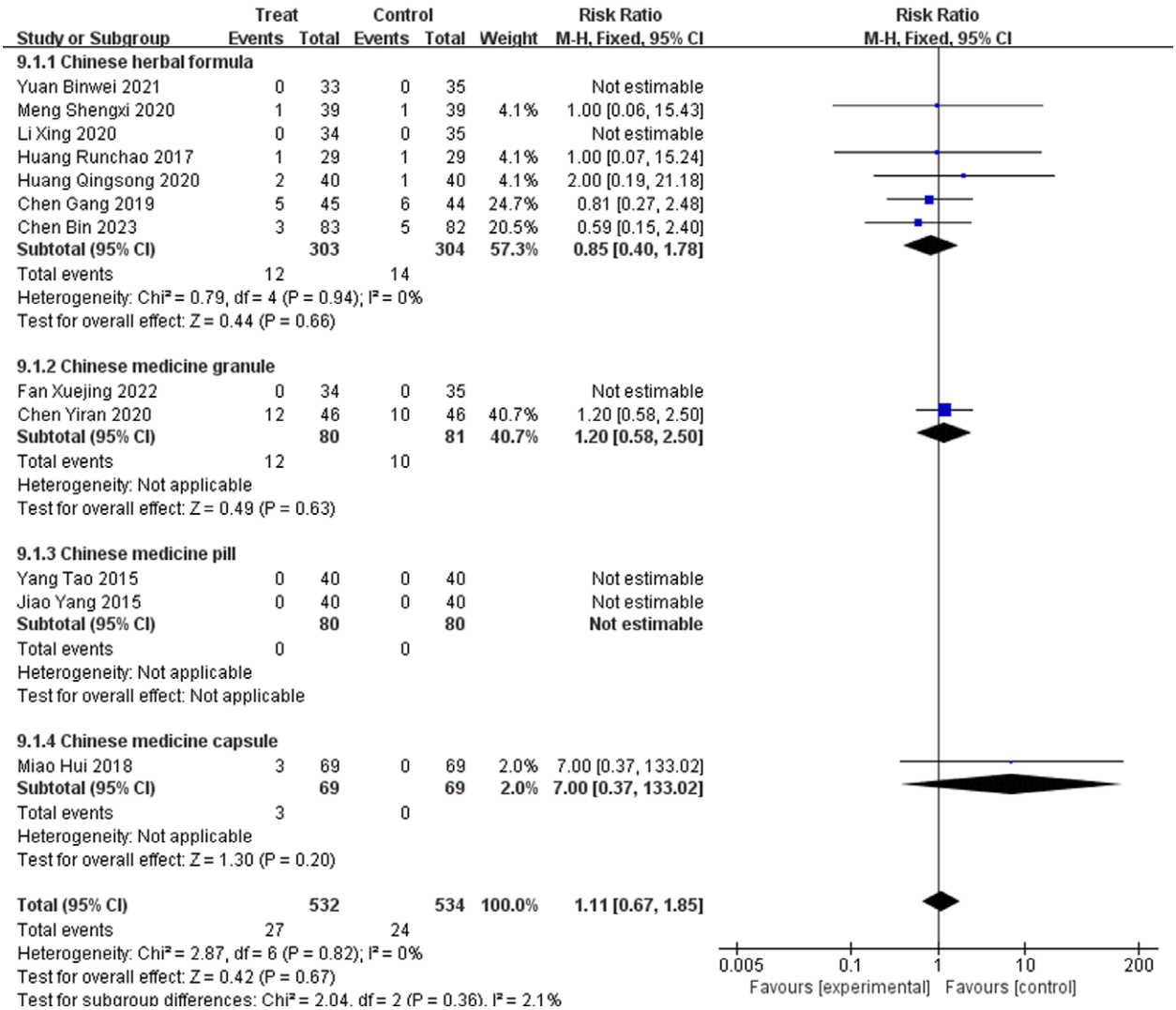


Figure 10. Meta-analysis of incidence of adverse reactions.

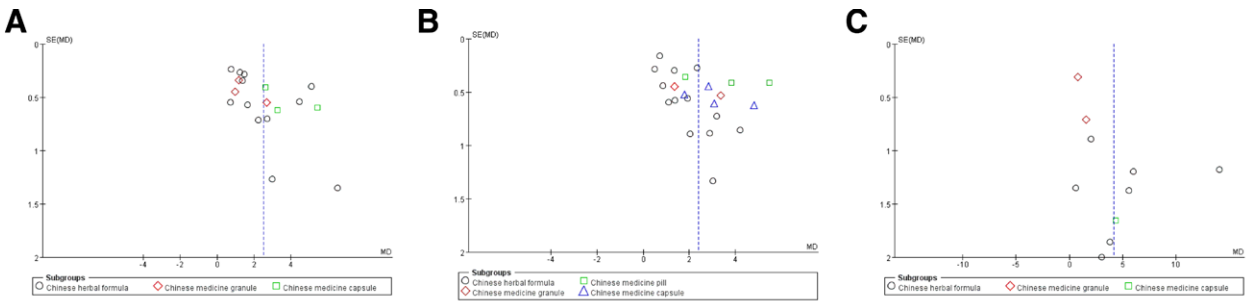


Figure 11. Funnel plot of the comparison of publication bias. (A) MMSE. (B) MoCA. (C) ADL. ADL = activities of daily living, MMSE = Mini Mental State Examination, MoCA = Montreal Cognitive Assessment.

also clear advantages in various objective laboratory indicators, and with no overt adverse reactions. In addition, for the development of future RCTs to investigate the treatment of CSVD with Chinese medicine, we offer the following suggestions. First, investigators should fully review the international high-quality clinical practice guidelines, systematic evaluations, and related RCTs. They should deeply understand the clinical characteristics and prognosis targets of the disease and scientifically select the outcome indicators in the top-level design stage of the research scheme, and reasonably avoid the risk of high bias. Second, it will be necessary to perform more high-quality RCTs with scientific methods, standardized design and rigor, such as estimating sample size before the start of the trial, clarifying the randomization method, using a blinding method, and registering with the international clinical trial registry, and truthfully recording the adverse reactions and case

Table 2

GRADE evidence quality rating.

	Certainty assessment							Number of patients			
Outcomes	**Number of studies**	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Treat**	**Control**	**Effect size**	**Certainty**
MMSE	18	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	860	861	MD = 2.42, 95% CI [1.79, 3.17]	⨁⨁◯◯ Low
McoA	22	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	973	971	MD = 2.39, 95% CI [1.78, 2.99]	⨁⨁◯◯ Low
ADL	10	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	403	408	MD = 4.13, 95% CI [1.74, 6.51]	⨁⨁◯◯ Low
NIHSS	3	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	218	220	MD = −1.82, 95% CI [−4.04, 0.40]	⨁◯◯◯ Very low
Chinese medicine syndrome score	8	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	416	418	MD = −2.57, 95% CI [−3.31, −1.83]	⨁⨁◯◯ Low
CRP	5	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	205	204	MD = −1.35, 95% CI [−2.27, −0.43]	⨁◯◯◯ Very low
Hcy	6	Randomized trials	Serious	No	Not serious	Not serious	No publication bias	270	265	MD = −3.44, 95% CI [−4.05, −2.83]	⨁◯◯◯ Very low
CBV	3	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	244	243	MD = 1.37, 95% CI [0.24, 2.50]	⨁◯◯◯ Very low
CBF	3	Randomized trials	Serious	Very serious	Not serious	Not serious	No publication bias	244	243	MD = 0.82, 95% CI [0.22, 1.42]	⨁◯◯◯ Very low

ADL = activities of daily living, CBF = cerebral blood flow, CBV = blood flow velocity, CRP = C-reactive protein, Hcy = homocysteine, MMSE = Mini Mental State Examination, NIHSS = National Institute of Health Stroke Scale.

shedding during the trial. Finally, the publication of negative results should be encouraged to provide a more comprehensive and objective basis for clinical treatment.

Acknowledgments

Thank all authors for their contributions to this manuscript.

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