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Nuanxin capsule for heart failure
A systematic review of randomized controlled trials

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Abstract

Objective To assess the efficacy and safety of Nuanxin capsule for patients with heart failure (HF).

Methods A systematic literature search was performed in 6 databases: PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wan-fang Data Information Site, Chinese BioMedical Database (CBM), VIP Chinese Science and Technique Journals Database from the date of its inception up to November 2016. Review Manager 5.2 software was used for assessment of risk of bias, data synthesis and subgroup analysis. Begg and Egger tests were used for assessing symmetries of funnel plot by software Stata 12.0. We conducted the GRADE system to assess the quality of evidence.

Results 12 trials involving 1418 participants were eligible. Compared with western medicine (WM) alone, Nuanxin capsule plus WM showed statistical significance in total effective rate (RR 1.18, 95% condidence interval [CI] 1.13–1.25). According to subgroup analysis, the 6-months group and the 12-months group have better effect than the 3-month group. As for 6-minute walking distance (6MWT), Nuanxin capsule plus WM compared with WM has significantly increased walking distance (weighted mean difference [WMD] 42.56, 95% CI 34.27–50.85). Nuanxin capsule plus WM has significantly decreased in mortality (RR 0.29, 95% CI 0.18–0.46) and re-admission rate (RR 0.48, 95% CI 0.39–0.60) compared with WM. Nuanxin capsule plus WM was beneficial for B-type natriuretic peptide (−240.47, 95% CI −332.45–148.49). gger's and Begg's test showed that there was no publication bias exist (P = .937). Influence analysis showed that no single study affected the overall result. The GRADE quality of the evidence was very low to Moderate across the different outcomes.

Conclusions Despite of the apparently positive findings, we cannot draw a sound conclusion that Nuanxin capsule has positive effect in patients with HF, because of the insufficient evidence.

Abbreviations: 6MWT = six-minute walking distance, ACEI = angiotensin converting enzyme inhibitor, BNP = B-type natriuretic peptide, HF = heart failure, PPARδ = peroxisome proliferator-activated receptor (delta), RAAS = Renin-Angiotensin-Aldosterone System, RCTs = randomized controlled trails, RRs = risk ratios, TCM = traditional Chinese Medicine, WM = western medicine, WMD = weighted mean difference.

Keywords: heart failure, Nuanxin capsule, systematic review

1. Introduction

1.1. Description of the condition

Heart Failure (HF) is the terminal stage of a series of cardiovascular diseases, resulting from dysfunction of the cardiac systole and diastole and a greater load on the heart. HF is a syndrome which may produce cardiac insufficiency, reduce exercise tolerance, ventricular arrhythmias and eventually shorten patients' life.[1] Due to its high morbidity and mortality, HF is one of the leading causes of deaths, making it a public health concern globally.[2,3] there are more than 23 million HF patients worldwide.[4] Data came from the Global Burden of Disease Study indicate that approximately 17.3 million people died from cardiovascular events in 2013, increasing by 41% from 1990.[5] The morbidity varies depending on the characteristics of population and exposure factors. As a result of the pursuit of high-quality life, the changing environment and the abuse of antibiotics, the proportion of coronary heart disease and hypertension are increasing significantly year by year. They are the leading reasons giving rise to HF.[6] The patients were hospitalized over and over again and yet not cured. What is worse, total medical costs are estimated $53.1 billion in 2030, increasing more than 2 times than those in 2012 of $20.9 billion.[7] Under this circumstance, the high medical expense not only concerns patients with HF but also poses a burden on the government.

1.2. Description of the intervention

The regular therapy for HF is angiotensin-converting enzyme inhibitor (ACEI) and β-blockers etc,[8,9] which can help improve patients' condition and lower the mortality, but yet, not quite effectively. Therefore, traditional Chinese Medicine (TCM) has

become an important recommendation in clinical application, TCM has been practised for thousands of years. It counts a lot in health care in China owing to its unique theoretical system and the treatment based on differentiation of symptoms and signs.[10] Professor DENG Tie-tao, a famous scholar of TCM in China, holds the view that HF is related to 5 Zang-organs, phlegm and blood stasis. He has developed Nuanxin capsule based on his academic ideas and years of clinical experience to improve the heart function.

Many clinical trials in China have shown the efficacy and safety of Nuanxin capsule. These foregoing clinical trials have reflected positive effects. Nevertheless, evidence is insufficient to support the widely and routine use of Nuanxin capsule due to the small sample size. Moreover, systematic review of the efficacy and safety of Nuanxin capsule are not yet to be reported. Therefore, in this study, we conduct a systematic review and meta-analysis to assess the current evidence regarding the efficacy, safety, and potential advantages of Nuanxin capsule for HF.

2. Methods

2.1. Types of studies

We merely included the randomized controlled trails (RCTs) which evaluated the efficacy and safety of Nuanxin capsule in treating HF despite of blinding, publication status or language.

2.2. Types of participants

The participants of any age or sex with HF were included. The definition of HF which we used in the studies should meet the following diagnostic criteria:

1) Diagnostic criteria for HF should be followed the HF diagnostic criteria
2) Primary disease includes coronary heart disease, rheumatic heart disease, hypertensive heart disease, pulmonary heart disease, dilated heart disease.
3) The following patients were excluded:
4) Acute myocardial infarction and unstable angina pectoris occurred 28 days prior to enrollment;
5) Acute HF, Secondary to HF and Unstable decompensated HF;
6) Pregnant or lactating women;
7) Patients with Drug allergy;
8) Combined with a tumor;
9) Severe arrhythmia and Uncontrolled high blood pressure;
10) Severe liver and kidney dysfunction.

As the present meta-analysis was performed based on previous published studies, thus no ethical approval and patient consent are required.

2.3. Types of interventions

For the controlled group, the patients were given routine care such as taking diuretics, ACEI, angiotensin II receptor blockers (ARB), β-blockers, digitalis and so on. By contrast, the patients of treatment groups were given Nuanxin capsule interventions plus western medicine (WM), and pharmacotherapy in the treatment groups should be consistent with the controlled groups. Furthermore, there were no other therapies in the treatment groups. We excluded the trials, which included any other Chinese medicine interventions (e.g. decoction of Chinese medicine, acupuncture and etc.)

2.4. Types of outcome measures

The primary outcome measures included total effective rate and 6 minutes walking distance. The secondary outcome measures included mortality rate, Re-admission rate and B-type natriuretic peptide (BNP).

2.5. Search methods for identification of studies
2.5.1. Electronic searches. We electronically identified relevant studies by searching Pub Med, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wan-fang Data Information Site, Chinese Biomedical Database (CBM) and VIP Chinese Science and Technique Journals Database. The publication time was from the start of each data-base up to November 2016. The Chinese search term and key words including ("xin li shuai jie" or "xin shuai" or "xin gong neng bu quan") and ("nuanxin capsule" or "nuan xin") for the literature were used to search the Chinese databases. The English search term and key words including ("heart failure") and ("nuanxin capsule" or "nuan xin") were used to search the English databases.

According to the characteristics of different databases, we combined with the methods of corresponding advanced search and free word retrieval to search all RCTs of Nuanxin capsule combining with WM for HF.

2.5.2. Searching other resources. We also searched International Clinical Trials Registry Platform and Chinese Clinical Trial Registry and referenced section of each study. In addition, we obtained relevant conference papers on Nuanxin capsule for HF.

2.6. Data collection and analysis
2.6.1. Selection of studies. According to the criteria which established above, 2 reviewers (CY and WS) reviewed the titles and abstracts to select potential references independently. The 2 reviewers applied a standardized data extraction form including the basic information of studies, patients, interventions and outcomes to perform the data extraction.

If 2 reviewers encountered discrepancies, the discrepancies would be discussed and resolved through consultation with a third reviewer (JW) until a consensus is reached. Study selections were shown in a PRISMA flow diagram.

2.6.2. Assessment of risk of bias in included studies. Two reviewers (CY and WS) used the Cochrane Handbook Version 5.2 to evaluate the risk of bias of all included studies that include Random sequence generation; Allocation concealment; The blinding of participants, Personnel and outcome assessor; Incomplete outcome data; Selective reporting and other sources of bias.

2.6.3. Data synthesis and statistical analysis. We used Cochrane Collaboration Review Manager Software (RevMan version 5.2, the Nordic Cochrane Centre, Copenhagen, Denmark) for meta-analysis and statistical analyses. For Dichotomous data, we used the risk ratios (RRs) as the analysis of statistics. For continuous data, we used the weighted mean difference (WMD) as the analysis of statistics. All analysis calculated 95% confidence interval (CI). We used a standard chi-square test to estimate the results of heterogeneity between trials. The random effect model was adopted if data with statistical heterogeneity ($P < .05$, $I^2 > 50\%$); Otherwise ($P \geq .05$, $I^2 \leq 50\%$), we used a fixed effect model.

2.7. Subgroup analysis

We analyzed the heterogeneity source by subgroup analysis through study design, different treatment regimens and so on.

2.8. Publication Bias

The publication bias was shown using a funnel plot in RevMan V.5.2. Begg and Egger tests was used for assessing symmetries of funnel plot by software Stata 12.0, and the statistical significance on reporting bias were existed, if $P < .05$.

2.9. Quality of evidence

We considered the quality of evidence using the GRADE System.[11]

3. Results

3.1. Description of studies

The electronic database search yielded a total of 127 records, and 70 publications were remained after de-duplication. After screening titles and abstracts, a total of 34 studies were excluded: 8 were case analysis; 15 were animal experiments; 11 were review articles. 23 full-text articles were retrieved for possible inclusion. Because 10 were not RCTs and 1 reported no useful outcomes, only 12 studies[12–23] met the inclusion criteria which had extractable data to evaluate the effects of Nuanxin capsule plus WM compared with WM or placebo in patients with HF. Figure 1 shows the study selection process summarized in the PRISMA flow diagram.

3.2. Study characteristics

A total of 12 studies reporting data on a total of 1418 participants (ranging between 40 to 400) aged 38 to 80 years with symptomatic HF have been incorporated in this review. All 12 included trials were published in China from 2005 to 2015, but not 1 was multi-center trials. There were 371 patients (31.49%) in NYHA II, 689 patients (58.49%) in NYHA III, and 118 patients (10.02%) in NYHA IV. In addition, there were approximately equal in number of men and women in all involved studies, and the primary diseases of them were mainly Coronary Heart Disease (475 patients; 42.72%) and Hypertensive Heart Disease (379 patients; 34.08%). Included studies are described in further detail in the Tables 1 and 2.

Most trials included limited samples, which were ranging from 40 to 100 participants, while 4 studies[15,18,22,23] included larger samples (116 to 400 participants). The mean disease course in these studies ranged from 1.7 to 11.15 years. Only 4 studies[15,19,22,23] compared Nuanxin capsule with placebo on the basis of WM. Most trials (66.67%) were seeking care for a short-term treatment of less than 3 months, while the remaining studies were at least 6 months (6 MWT). All studies except 1[18]
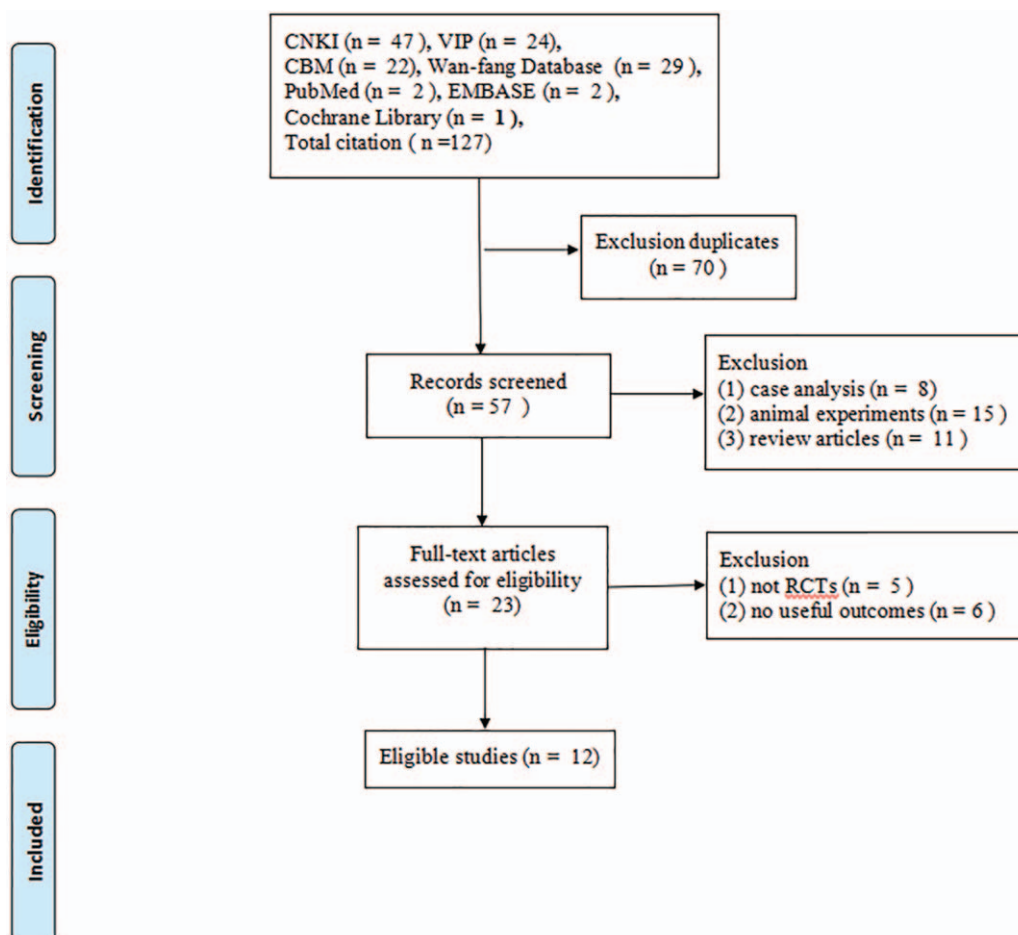

Figure 1. Study selection flow diagram.

Table 1

Characteristics of the included studies.

Included trials	Gender (male/female)		Age (years)		Disease course (years)		NYHA classificatio
	T	C	T	C	T	C	
Chen RS 2007	25/20	23/22	65.32	67.41	1.78	2.01	II-IV
Lai RK 2015	18/12	16/14	62.2±7.8	62.6±8.2	unclear	unclear	II-IV
Lin XZ 2008	21/19	20/18	63.3±10.2	65.4±9.1	2.7±0.8	2.5±1.1	II-III
Liu ZY 2007	69/54	72/45	67.7±8.1	66.1±8.8	1.9±0.6	1.7±0.9	unclear
Mai ST2008	8/17	13/12	68.96±9.28	72.96±10.07	3.14±1.22	2.95±1.14	II-IV
Pan GM 2005	7/13	9/11	69.40±11.79	73.65±9.14	3.27±1.52	3.08±1.86	II-IV
Pan GM 2011	32/25	30/29	65.2	66.4	2.5	2.3	II-III
Yao GZ 2008	17/13	16/14	55.57±21.39	55.70±18.69	5.62±0.52	5.53±0.52	II-IV
Ye L 2011	7/13	8/12	65.00±6.34	66.90±5.80	11.15±8.40	8.37±10.20	II-IV
Zou X 2005	21/29	23/27	63±8.2	64±6.6	5.1±1.5	5.2±1.4	II-III
Zou X 2006	100/100	96/104	65.7±8.7	66.1±8.3	1.8±0.5	1.7±0.6	II-III
Zou X 2011	32/39	37/36	69.35±12.26	70.06±10.32	4.39±6.58	5.73±10.04	II-IV

Table 2

Characteristics of the included studies.

Included trials	Interventions		Outcomes	Treatment Course	Follow up (months)	Funding Support	Adverse events
	T	C					
Chen RS 2007	NXC+WM	WM	③⑤	3 months	unclear	No	No
Lai RK 2015	NXC+WM	WM	①②③	3 months	unclear	Yes	No
Lin XZ 2008	NXC+WM	WM	①②⑤	3 months	8	Yes	No
Liu ZY 2007	NXC+WM	PC+WM	①②③④	9 months	12	Yes	0/1
Mai ST 2008	NXC+WM	WM	①	2 weeks	unclear	No	No
Pan GM 2005	NXC+WM	WM	①⑤	1 month	unclear	No	No
Pan GM 2011	NXC+WM	WM	①②	3 months	unclear	Yes	Not reported
Yao GZ 2008	NXC+WM	PC+WM	①	3 months	unclear	No	No
Ye L 2011	NXC+WM	WM	①	2 weeks	unclear	No	No
Zou X 2005	NXC+WM	WM	①②③④⑤	6 months	unclear	No	0/1
Zou X 2006	NXC+WM	PC+WM	①②③④	12 months	12	Yes	0/1
Zou X 2011	NXC+WM	PC+WM	①③④	24 weeks	6	Yes	No

NXC=Nuanxin capsule, WM=western medicine, PC=placebo capsule.

①: Total effect of heart function; ②: 6-minute walking distance.

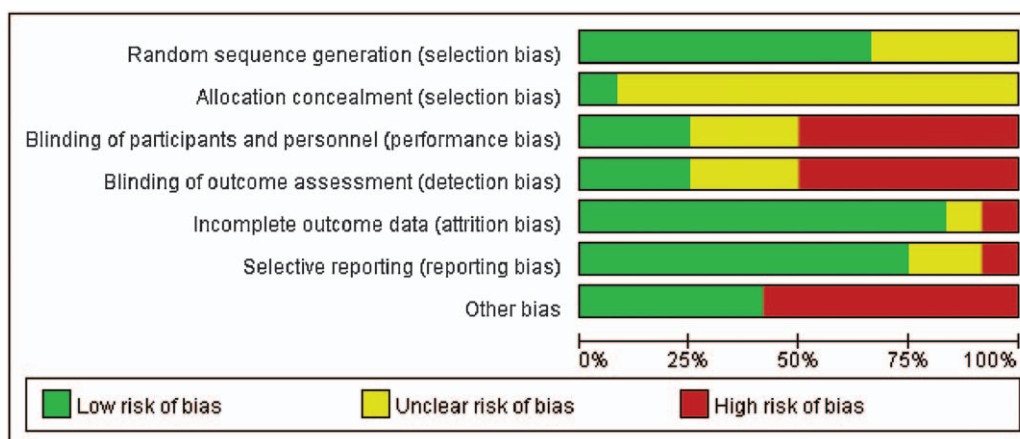③: mortality; ④: re-hospitalization; ⑤: the level of BNP.

Figure 2. The methodological quality graphs.

Figure 3. Risk of bias summary.

reported the side effects.11 studies[13–23] assessed the total effect of heart function using NYHA. 6 trials[13–15,18,21,22] reported 6-minute walking distance. Mortality and re-hospitalization rate were respectively employed in 6[12,13,15,21–23] and 4 trials.[13,21–23] Only 4 studies[12,14,17,21] measured the level of BNP.

3.3. Risk of bias

The methodological quality graph (Figs. 2 and 3) presents each item for each included study as well as each item presented as percentages across all included trails according to our established quality evaluation standard. Most trial publications (8/12) used adequate sequence generation. Only 1[23] studies were with a low risk of bias on allocation due to sealed envelope were used, while others were unclear risk bias because of insufficient information. Details about the blinding method were described in 3 (25%) trials.[15,21,22] The rest of the studies were with an unclear or high risk of bias because of insufficient information of blinding or due to the poor methodological quality. All trials were assessed with low risk of bias.

3.4. Selective reporting

All trials except 3[12,14,18] were with a low-risk bias on selective reporting. We assessed 1[13] included trial with a high-risk bias since it was not designed to evaluate the primary outcomes. And 2 trials had unclear risk bias as these trials had an unclear risk of bias regarding compliance and funding.

3.5. Other potential sources of bias

All studies were similar at baseline, while 3 trials[15,21,22] were with a high-risk bias because they did not use intention to treatment (ITT) analysis. There is potentially selective reporting bias in 3 trials[14,17,19] due to poorly described statistical methods.

3.6. Effects of interventions
3.6.1. Total effective rate. Eleven trials[13–23] with a total of 1294 patients reported total effective rate. The pooled analysis using a fixed-effect model showed that there was a borderline

statistical significance between Nuanxin capsule plus WM and WM alone (RR 1.18, 95% CI 1.13–1.25). There was a statistical significance on less than 1-month group (n = 130; RR 1.27, 95% CI 1.09–1.47; P = .0002). Nuanxin capsule plus WM are more effective than WM only for HF on both 6-month group (n = 239; RR 1.17, 95% CI 1.02–1.33; P = .02) and 12-month group (n = 611; RR 1.20, 95% CI 1.11–1.29; P < .00001). Similarly, the pooled total effect on 3-month group was also positive (n = 314; RR 1.14, 95% CI 1.05–1.25; P = .003) (Fig. 4).

3.6.2. Six-minute walking distance (6MWT). Six trials[13–15,18,21,22] (953 participants) performed 6MWT with an extractable data to assess heart function of HF patients. The pooled mean difference using fixed-effects model (I^2 = 42%) indicated the significant increase in 6MWT compared WM only (WMD 42.56, 95% CI 34.27–50.85; P < .00001). Three trials which reported walking distance on less than 3-months group showed a favorable effect with a statistical significance (n = 247; WMD 33.33, 95% CI 19.49–47.18; P < .00001), while the change on ≥6-month group was with a statistical significance too (2 trials:706 participants; WMD 47.72, 95% CI 37.37–58.07; P < .00001) (Fig. 5).

3.6.3. Mortality. Six[12,13,15,21–23] (n = 1143) of the included trials reported total mortality. In these trials, the decrease in mortality with Nuanxin capsule was of borderline statistical significance (fixed-effect RR 0.29, 95% CI 0.18–0.46; P < .00001). We found that Nuanxin capsule was more effective than WM only. However, this estimate may be opposed to bias since the reduction was with no statistical significance less than 3-month group (3 trials: 293 participants; RR 0.34, 95% CI 0.08–1.40; P = .13), whereas the pooled mortality on 6-month group (2 trials: 239 patients; RR 0.30, 95% CI 0.12–0.78; P < .05) and 12-month group (2 trials: 611 patients; RR 0.28, 95% CI 0.16–0.49; P < .0001) showed in combination with Nuanxin capsule are more effective than WM only (Fig. 6).

3.6.4. Re-hospitalizations. Four trials[15,21–23] (850 participants) of included studies reported total hospitalizations, which showed a significant difference when Nuanxin capsule plus WM was compared to WM only (fixed-effect RR 0.48, 95% CI 0.39–0.60; P < .00001). The pooled analysis of re-hospitalizations on 6-month group (2 trials:239 patients; RR 0.41, 95% CI 0.27–0.62; P < .0001) and 12-month group (2 trials: 611 patients; RR
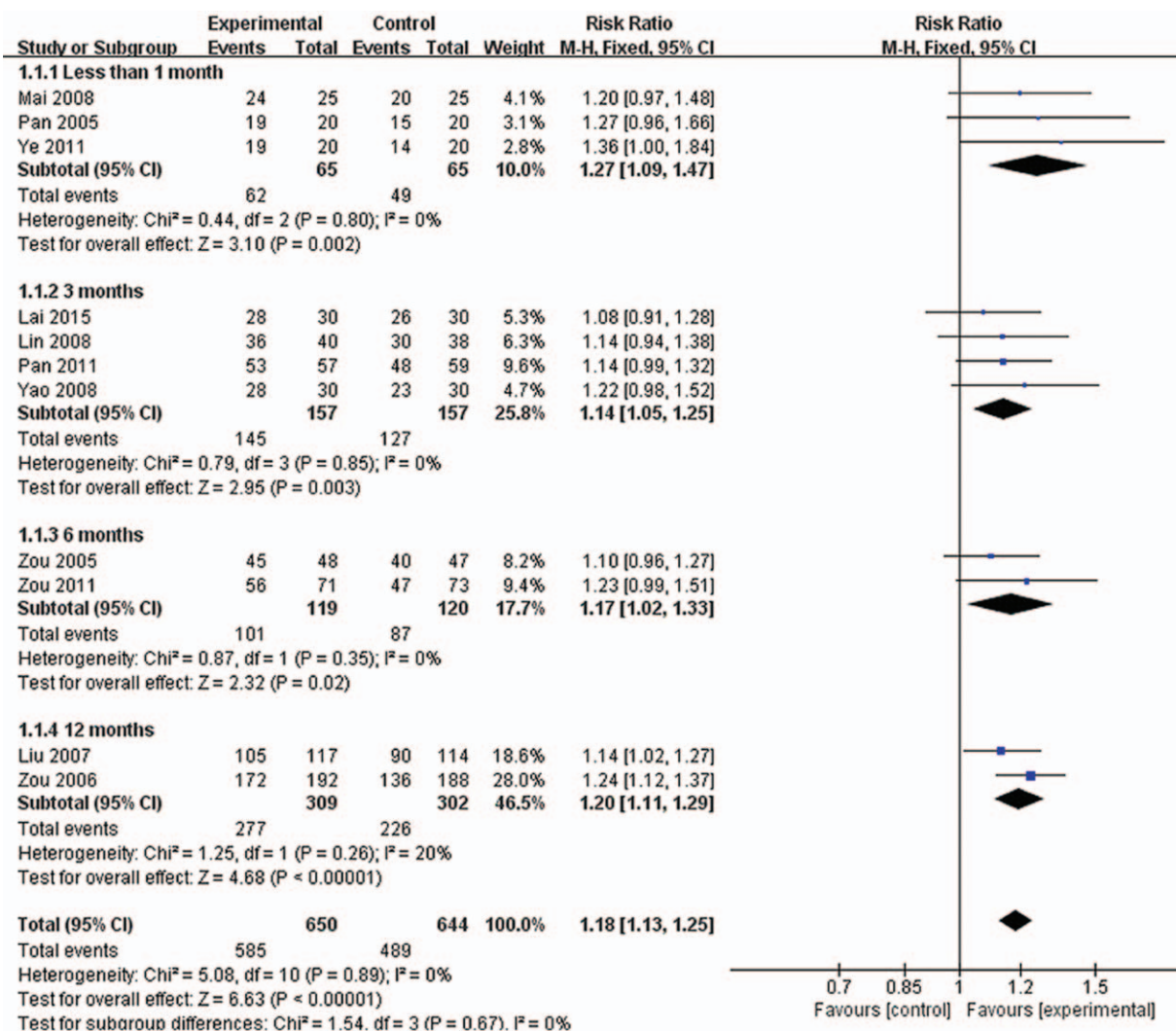
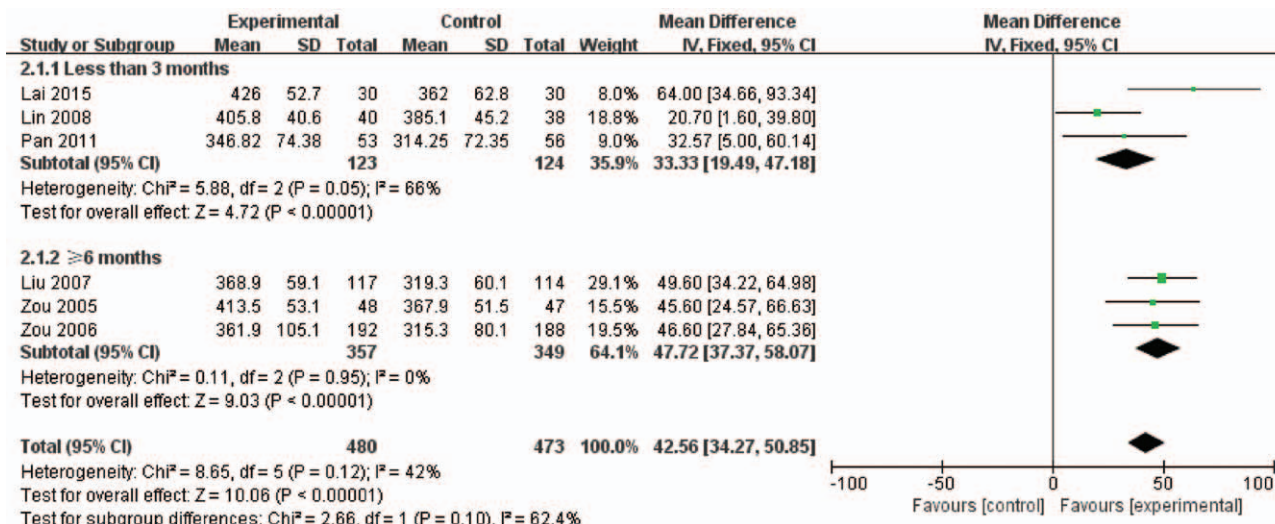Figure 4. Forest plot of Nuanxin capsule for total effect of heart function.

Figure 5. Forest plot of Nuanxin capsule for 6MWT. 6MWT=6-minute walking distance.
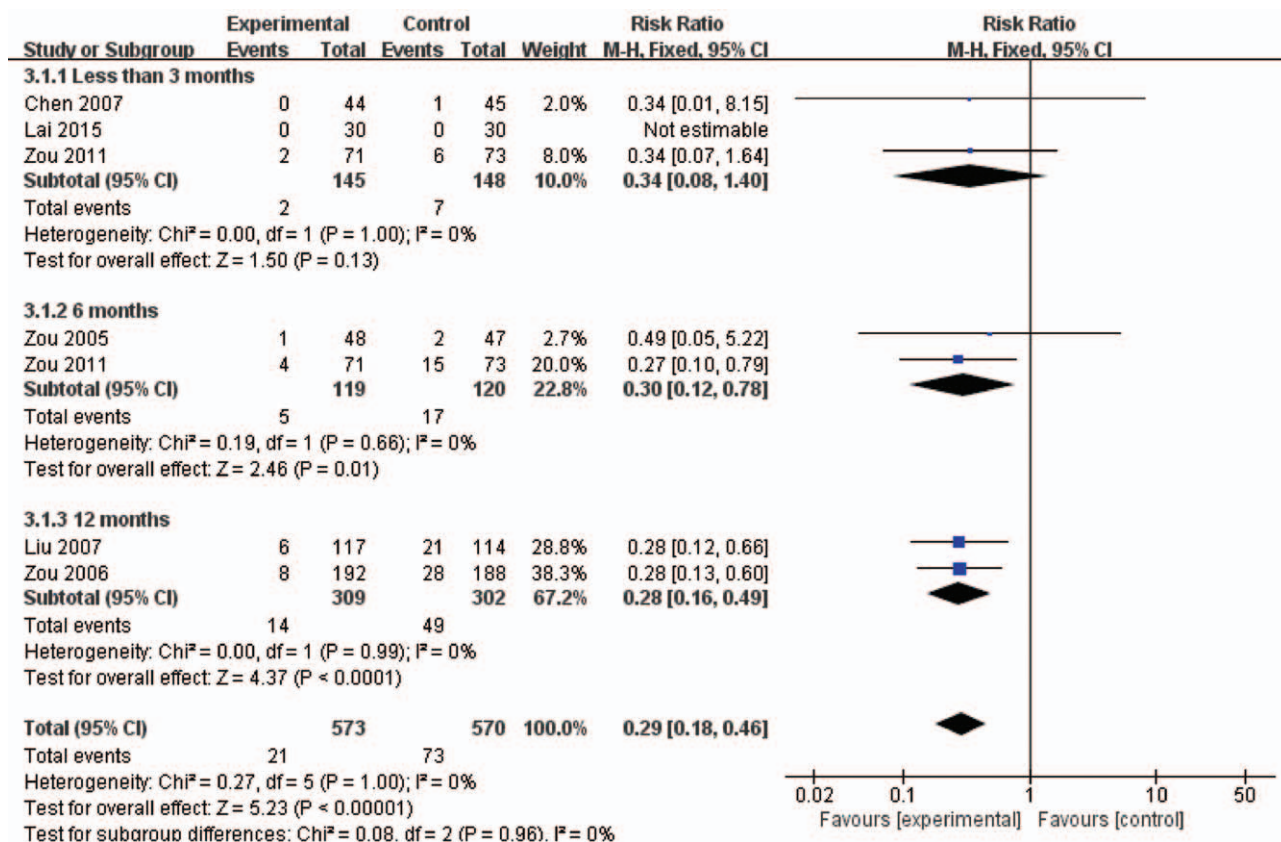
Figure 6. Forest plot of Nuanxin capsule for mortality.

0.52, 95% CI 0.40–0.67; $P < .00001$) were both with a statistical significance (Fig. 7).

3.6.5. The level of BNP. Four studies[12,14,17,21] with a total of 303 participants reported the level of BNP. All trials were small-sample trials including 40 to 100 patients. In the pooled analysis of these trials regarding BNP change showed that Nuanxin capsule plus WM showed a favorable effect on BNP

(random-effects mean difference −240.47, 95% CI −332.45 to −148.49; $P < .00001$). There was a significant amount of heterogeneity ($I^2 = 97\%$) (Fig. 8).

3.7. Publication bias

To assess the publication bias, we created funnel plot (Fig. 9). As a result, a visual sign of funnel figure symmetry could not be
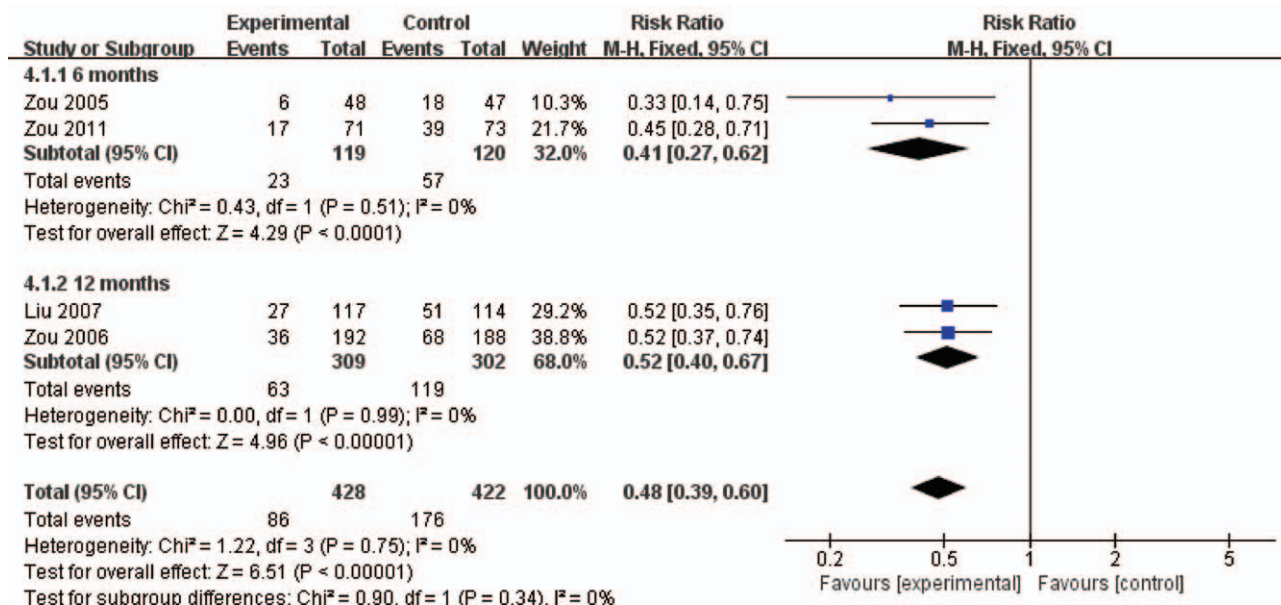

Figure 7. Forest plot of Nuanxin capsule for re-hospitalization.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV. Random, 95% CI	Mean Difference IV. Random, 95% CI
Chen 2007	295.96	194.04	45	483.73	236.69	45	25.9%	-187.77 [-277.19, -98.35]	
Lin 2008	408.7	34.6	40	714.8	27.3	38	34.1%	-306.10 [-319.90, -292.30]	
Pan 2005	402.92	303.47	20	777.17	690.19	20	6.3%	-374.25 [-704.68, -43.82]	
Zou 2005	213.9	51.5	48	403.5	53.1	47	33.7%	-189.60 [-210.64, -168.56]	
Total (95% CI)			153			150	100.0%	-240.47 [-332.45, -148.49]	

Heterogeneity: Tau² = 6417.15; Chi² = 86.02, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.12 (P < 0.00001)

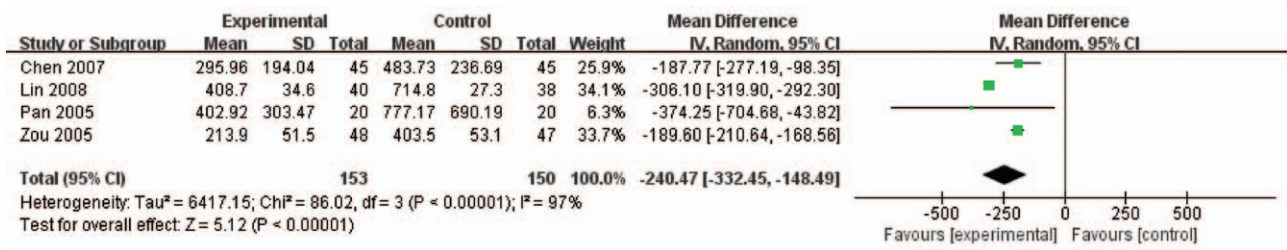Favours [experimental] Favours [control]

Figure 8. Forest polt of Nuanxin capsule for the level of BNP. BNP = B-type natriuretic peptide.
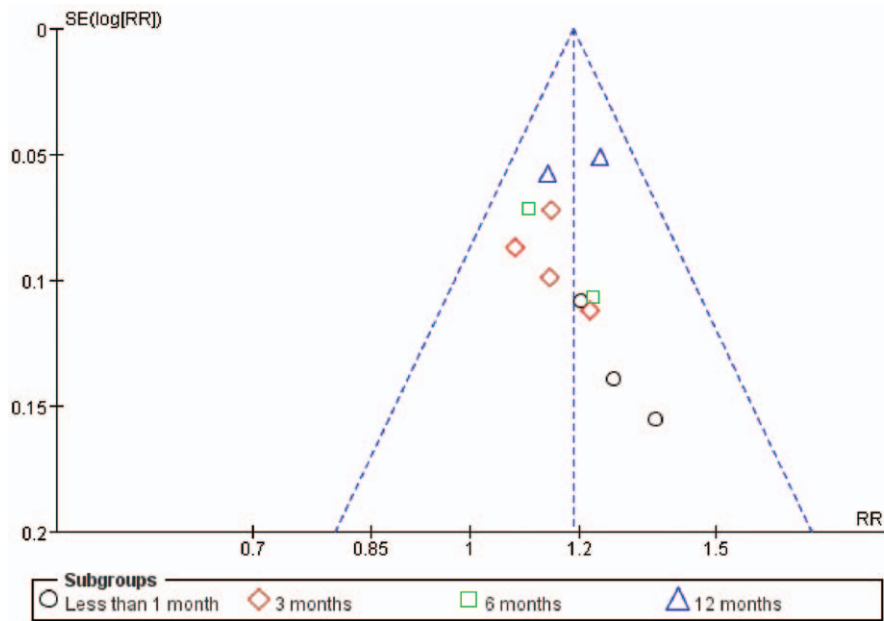

Figure 9. Funnel plot of Nuanxin capsule plus WM versus WM for the total effect of heart function. WM = western medicine.
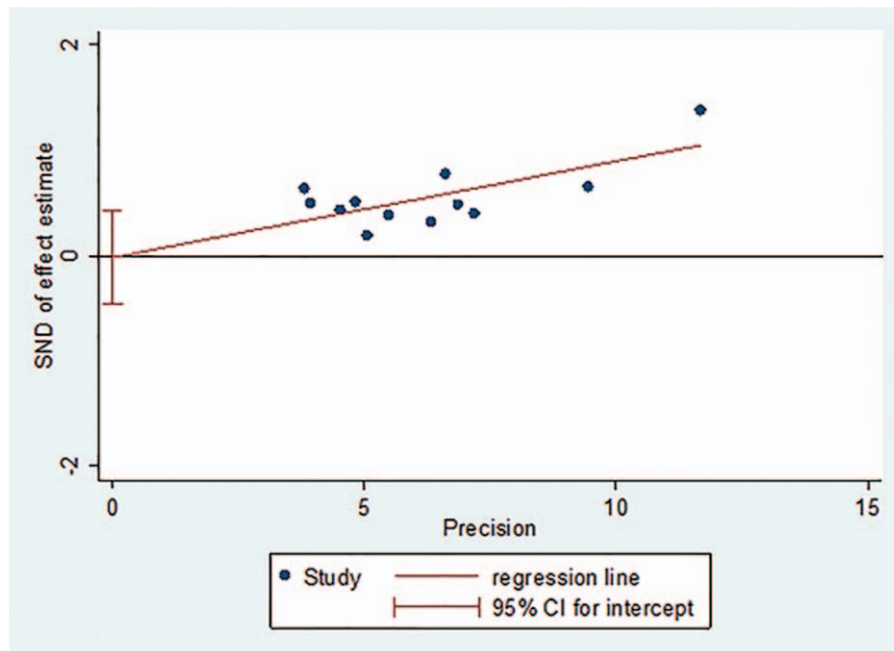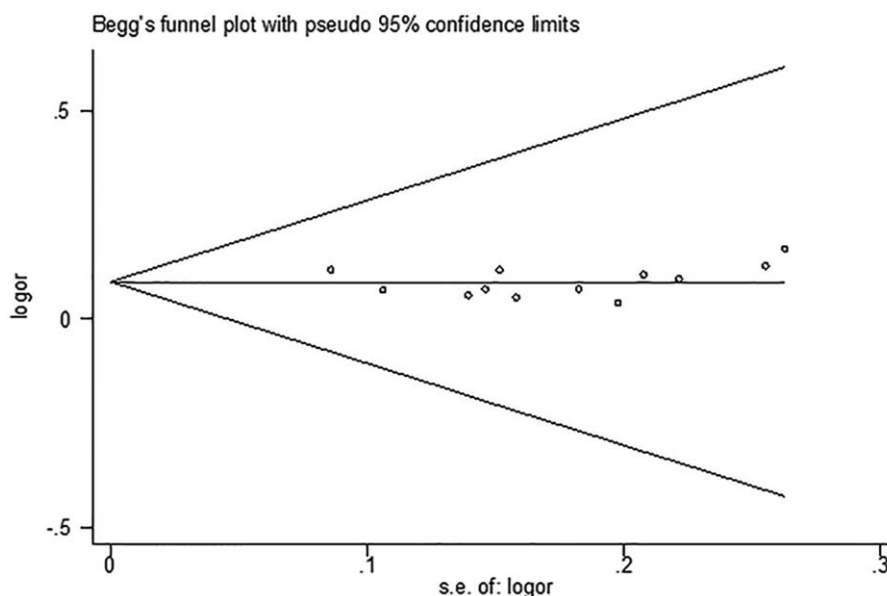

Figure 10. Eegg's funnel plot.

Figure 11. Begg's funnel plot.

observed, which showed the existence of publication bias of this research. Due to the included studies were all published in Chinese, the publication bias could not be excluded. Egger and Begg test showed that there was no publication bias exist (P = .937) (Figs. 9 and 10).

3.8. Influence analysis

The influence analysis of the included studies was conducted to assess whether the single study would affect the overall result. The result showed that no single study affected the overall result by influence analysis (Fig. 11).

3.9. Quality of evidence

We further evaluated the assessment of results by using the GRADE system. The quality of evidence of this review was assessed by the guidelines of the GRADE Working Group (Table 3).

4. Discussion

4.1. Summary of main results

This meta-analysis included 1418 patients aged from 38 to 80 years with symptomatic HF who participated in 12 RCTs. The present study mainly finds out that Nuanxin capsule could increase walking distance of HF patients, reduce mortality and re-hospitalizations, and was beneficial for on BNP. In addition, there was a borderline statistical significance in total effect of heart function between Nuanxin capsule plus WM and WM alone (RR 1.18, 95% CI 1.13–1.25). Though the findings reported was apparent positive, there was still inadequate evidence to market the routine use of Nuanxin capsule for HF due to the poor methodological quality and the relatively limited samples most trials included. Another finding indicated that Nuanxin capsule seems generally safe, because of most studies except 1 reported the adverse effects.

4.2. Mechanism of Nuanxin capsule for HF

In TCM theory, Nuanxin capsule takes effects by improving the circulation of qi, balancing the yin and yang in the body and dissolving blood stasis. Nuanxin capsule is a combination of 5 herbal medicines, mainly including *Radix Ginseng Rubra, Radix Aconiti Lateralis Preparata, Radix Notoginseng, Exocarpium citri rubrum* and *Semen Coici.* Due to its special function to heart, more and more researchers devote to doing experiments to find out how it works and providing lots of valuable thoughts (Fig. 12).

Pan holds a view that Nuanxin capsule can make abnormal heart, lung, vascular baroreceptor function normalization by inhibiting hyperactivity of the Renin-Angiotensin-Aldosterone System (RAAS), or enhance its function to reduce the activity of the sympathetic nervous system and RAAS. As a result, it can reduce the left ventricular filling pressure and volume load and inhibit endothelin, Angiotensin II (Ang II), Norepinephrine (NE) and other factors that stimulate the release of BNP secretion.[16] Mai's study suggests that Nuanxin capsule can increase cardiac output and enhance cardiac pump function. Its mechanism may be strengthened myocardial contractility through early changes in hemodynamics, which can obviously decrease the peripheral and pulmonary vascular resistance and preload and postload of heart, increase cardiac output and improve cardiac function. What is more, by using Nuanxin capsule, the decrease of peripheral vascular resistance and the postload of heart were the main reasons for the increase of cardiac output. The exact mechanism of the capsule maybe relate to multi-target and multi-link, which needs further study to clarify.[16] Besides that, *Radix Ginseng Rubra* and *Radix Aconiti Lateralis Preparata* deserve our special attention, resulting from they play the most important part in Nuanxin capsule based on the TCM theory.[24] We summarized the pharmacologic actions of them below. Nakajima et al. concluded that *Radix Ginseng Rubra* can promote the proliferation of vascular endothelial cells, inhibit the production of endothelin and increase the production of IL-1β that suppresses the formation of thrombin in blood coagulation.[25]

Table 3

Summary of findings for the main comparison.

Quality assessment					No of patients		Relative	Effect	Quality
								Effect	
Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nuanxin Capsule plus WCM**	**WCM**	**Relative (95% CI)**	**Absolute**	**Quality**
Total effect of heart function (follow-up 6–12 months)									
serious*	No serious	no serious	no serious	reporting bias†	585/650 (90%)	489/644 (75.9%)	RR 1.18 (1.13 to 1.25)	137 more per 1000 (from 99 more to 190 more)	⬜⬜⬜ LOW
						79%		142 more per 1000 (from 103 more to 198 more)	
6MWT (follow-up 8–12 months; Better indicated by lower values)									
serious*	no serious	no serious	serious‡	reporting bias†	480	473	—	WMD 42.56 higher (34.27 to 50.85 higher)	⬜⬜⬜⬜ VERY LOW
Mortality (follow-up 6–12 months)									
serious§	no serious	no serious	no serious	reporting bias† reduced effect for RR >> 1 or RR << 1‖	21/573 (3.7%)	73/570 (12.8%)	RR 0.29 (0.18 to 0.46)	91 fewer per 1000 (from 69 fewer to 105 fewer)	⬜⬜⬜ MODERATE
						8.2%		58 fewer per 1000 (from 44 fewer to 67 fewer)	
Re-hospitalization (follow-up 6–12 months)									
serious§	no serious	no serious	no serious	reporting bias†	86/428 (20.1%)	176/422 (41.7%)	RR 0.48 (0.39 to 0.6)	217 fewer per 1000 (from 167 fewer to 254 fewer)	⬜⬜⬜ LOW
						41.5%		216 fewer per 1000 (from 166 fewer to 253 fewer)	
the level of BNP (Better indicated by lower values)									
serious¶	no serious	no serious	serious#	reporting bias†	153	150	—	WMD 240.47 lower (332.45 to 148.49 lower)	⬜⬜⬜⬜ VERY LOW

* We assessed 3 of the included trials with a high risk of bias (with greater than 4 biases estimated as high or unclear risk) (Lin XZ 2008; Pan GM 2011; Zou X 2006). These 3 trials had an unclear risk of bias regarding compliance, unclear risk of bias regarding funding, and unclear risk of selection bias. In addition, Zou X 2006 had an unclear risk of repetitive bias. Lin XZ 2008 and Pan GM 2011 had a high risk of selection bias.

† Funnel plot finds asymmetry.

‡ The heterogeneity of the included trials was high (I^2=62%).

§ Zou X 2006 had an unclear or a high risk of bias for more than 4 biases investigated.

‖ RR=0.30 << 1.

¶ Lin XZ 2008 had an unclear or a high risk of bias for more than 4 biases investigated.

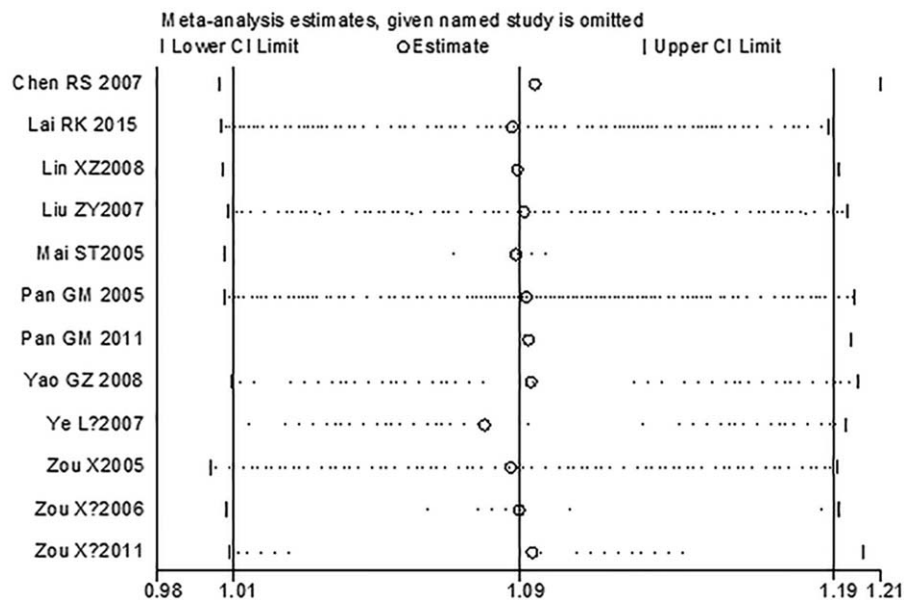# The heterogeneity of the included trials was high (I^2=97%).

Figure 12. Influence analysis of included studies.

Cheng-Chia Tsai 's study shows that *Radix Ginseng Rubra* could restore HF through an activation of peroxisome proliferator-activated receptor (delta) (PPARδ) in type 1-like diabetic rats.[17] Lin JW suggested that *Radix Ginseng Rubra* could enhance cardiac contractility through increasing PPARδ expression in cardiac cells.[26] KYU'S and Xiaomei Fan demonstrated RG can modulate antioxidant enzymes, which has biochemical and functional effects for the heart.[27,28] Studies have shown that *Radix Aconiti Lateralis Preparata* and its active component can improve left ventricular systolic and diastolic function, which is of great importance to improve chronic HF.[29]

4.3. Limitations for research

Our study has inherent limitations, which mainly stem from the poor methodological quality and the quality of reported data. First, most of these trials were small and short-term. As a result of small sizes, the 95% CIs were relatively wide, which may place the validity of our statistical analysis in doubt. The results were likely to be much underpowered. Second, nearly none of the relevant articles about TCM for HF have been published in English medical journals, and the finite evaluation of TCM out of China reduces its external validity. Third, treatment was applied by using NYHA and testing 6-minute walking distance, without further pattern differentiation according to traditional Chinese methodology. Fourth, considerable qualitative heterogeneity was present between patients in these clinical trials. Different criteria and different disease severity might limit the generalizability of our findings. Fifth, there were no trials reported death, thus, our analysis was lack of mortality data from all studies. In order to properly assess the safety of TCM, adequate concealment of allocation, blinding of outcome assessors, and functional outcome as the primary outcome and a long-term follow-up are required. Reports of the trials should conform to the CONSORT statement's recommendations.

5. Conclusion

Nuanxin capsule plus WM seems to make a favorable effect than WM alone, and it appears to be well tolerated in patients with HF compared with WCM. However, the present evidence is insufficient to support the efficacy and security of Nuanxin capsule for HF resulting from the poor methodological quality, the limited samples of the included studies. Despite certain limitations, our present findings still have potential implications. Large-size, proper design, randomized trials of TCM for HF will be required to justify the results reported here. Future trials are going to overcome the limitations of this review.

Author contributions

Jun-mao Wen, Wei Wu designed the study. Chen-guang Jiang, Tong Lin drafted the paper. Nan Jiang revised it. Chuanjin Luo, Chi Zhou developed the search strategies. Yin-he Cai, Wei-peng Sun, conducted data collection and analyzed independently. All authors have approved the final manuscript.

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