Meta-analysis

Meta-analysis for efficacy of modified *Zhenwu* Decoction combined with western medicine in treatment of heart failure

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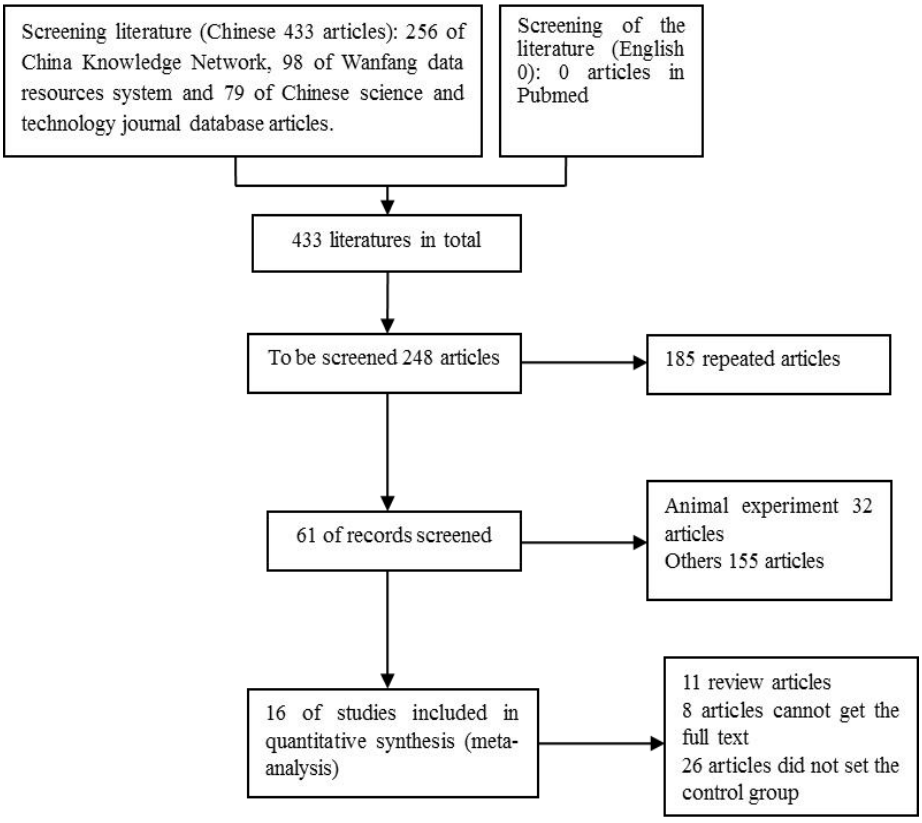
Highlights:
The meta-analysis confirmed curative effect of modified *Zhenwu* Decoction combined with western medicine in the treatment of heart failure is better than the simple western medicine treatment.



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Abstract

Objective: To carry out a systematic evaluation of the efficacy of modified *Zhenwu* Decoction combined with western medicine in the treatment of heart failure**. Methods:** Literature was retrieved in China Knowledge Resource Integrated Database (CNKI), Chinese scientific journal database (VIP), Wanfang Data Resource System (WANFANG DATA), PubMed and other traditional Chinese medicine related periodicals by retrieval methods of subject terms combined with free words and computer retrieval combined with manual retrieval. Literature was screened strictly according to the inclusion criteria.The quality of the included literature was evaluated according to the quality standard of Jadad scale and Cochrane collaboration network bias risk assessment tool. The literature data was extracted. RevMan5.3 software was used to analyze data and the curative effect of modified *Zhenwu* Decoction combined with western medicine was objectively evaluated. **Results:** The response rate of the experimental group was better than that of the control group [OR = 3.69，95% IC (2.36，5.79)]. The value of EF in the experimental group was higher than that in the control group after treatment [MD = 5.85, 95% IC (3.90, 7.79)]. The Lee, score of the experimental group was lower than that of the control group after treatment [MD = -1.37, 95% IC (-2.23, -0.52)]. The value of BNP in the experimental group was less than that in the control group after treatment [MD = -114.48, 95%IC (-186.28, -42.68)]. The life quality score in the experimental group was less than that of the control group after treatment [MD = -8.44, 95%IC (-11.73, -5.15)]. **Conclusion:** The curative effect of modified *Zhenwu* Decoction combined with western medicine in the treatment of heart failure is better than the simple western medicine treatment． So modified *Zhenwu* Decoction combined with western medicine in the treatment of heart failure is worthy of clinical promotion. However, the results of this study still need further validation by more high quality randomized double blind controlled clinical trial because the overall quality of the research included.

Key words: Modified *Zhenwu* Decoction, Heart Failure, Meta-analysis

摘要

目的：对加味真武汤联合西药治疗慢性心力衰竭疗效进行系统性评价。

方法：以主题词与自由词相结合、计算机检索结合手工检索相结合的检索方法，检索中国知网(CNKI)、中文科技期刊数据库(VIP)、万方数据资源系统(WANFANG DATA)、PubMed 及其他中医药相关期刊中相关的文献，严格按照纳入标准筛选文献，并根据 Jadad 量表的质量标准及 Cochrane 协作网偏倚风险评估工具对纳入文献的质量进行评价，提取文献中的原始数据，运用 RevMan 5.3 软件对数据进行分析，客观评价其疗效。

结果：试验组心功能疗效优于对照组[OR=3.69，95%IC(2.36，5.79)]；治疗后试验组 EF 值高于对照组[MD=5.85，95%IC(3.90,7.79)]；治疗后试验组 Lee 氏评分低于对照组[MD=-1.37，95%IC(-2.23,-0.52)]；治疗后试验组 BNP 小于对照组[MD=-114.48，95%IC(-186.28,-42.68)]；治疗后试验组生存质量评分低于对照组:[MD=-8.44，95% IC (-11.73,-5.15)]。

结论：真武汤加味联合西药治疗慢性心力衰竭的疗效优于单纯西药治疗，值得临床推广。但本研究纳入文献总体质量不高，且发表偏倚可能存在，所以仍需更多高质量随机双盲对照临床试验进一步验证。

关键词：真武汤；慢性心力衰竭；Meta 分析

Abbreviations: NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonists; OR, odds ratio; MD, weighted mean difference.

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Introduction

Chronic heart failure is the terminal stage of heart disease caused by various causes [1], with a high incidence of morbidity and mortality, and the five-year survival rate was comparable to that of malignancy. Patients with chronic heart failure often die from malignant arrhythmias and pump failure. How to improve patient survival and improve quality of life and prognosis has become a major research topic in recent years. In the last 50 years, the treatment of heart failure has been studied from the enhancement of myocardial systolic force to the "neuro-endocrine" system, which reduces the incidence of major cardiovascular accidents. However, its side effects are indispensable and patients with bronchial asthma or severe atrioventricular block are restricted in using β receptor blocker. In addition, Long-term use of diuretics can cause electrolyte disturbance. ACEI drugs can bring up cough, and couldn't be tolerated by patients. Hence, western treatment of heart failure needs to be improved. Modified *Zhenwu* Decoction can increase cardiac output, decrease the preload and after load of heart and then improve the systolic and diastolic function of the heart. Furthermore, modified *Zhenwu* Decoction disturbs little to internal environment, and doesn't cause electrolyte disturbance. Therefore, it's important to select a proper treatment protocol, which can reduce the mortality of chronic heart failure and improve treatment. In the present study, meta-analysis for the efficacy of modified *Zhenwu* Decoction combined with western medicine in treatment of heart failure was carried on in order to select an optimal protocol.

Materials and Methods

Retrieval Strategy

All information was collected from published data in clinical randomized controlled trials. The key terms were chosen and combined for literature search as follows: ["modified *Zhenwu* Decoction"] and ["heart failure" or "heart decompensation" or "decompensation, heart" or "myocardial failure"]. From the earliest record to May 30th 2017, CNKI, VIP, WANFANG DATA and Pubmed were retrieved, and manual retrieval of traditional Chinese medicine was supplemented to ensure the systematisms and integrity.

Inclusion Criteria

1. Randomized controlled trial enrolled with modified *Zhenwu* Decoration treating chronic heart failure. 2. Diagnosis and classification of research object accorded with diagnostic criteria for chronic heart failure and Heart function grade as Ⅱ ~ Ⅲ grade of New York Heart Association (NYHA). The diagnostic criteria for chronic heart failure refer to Diagnostic criteria for chronic heart failure (1971). The weight loss greater than 4.5 kg within 5 days after treatment, and two main conditions or one main condition with one second condition can be diagnosed with chronic heart failure (Table 1). The NYHA standards for the classification of cardiac function were below (Table 2). 3. Participants age 55-75 years old. 4. Gender, vocation and races are not restricted. The difference between experimental group and control group is not significant in baseline information.

Exclusion Criteria

1. Non-randomized controlled trial.
2. No control group was set in the study.
3. Papers published repeatedly.
4. Review.
5. Research on animal experiment
6. Be unable to get full text.

Document quality evaluation

The quality of the included literature was evaluated by the inclusion of two reviewers according to the Jadad scale and the Cochrane Collaboration Network Bias Risk Assessment Tool. If there was any objection, the third reviewer will review the document and evaluated the literature again.

Treatment methods

Both the experimental group and the control group were treated with conventional western medicine for chronic heart failure, including diuretics, aldosterone receptor antagonists, angiotensin converting enzyme inhibitors (ACEI), beta-blockers, angiotensin receptor antagonists (ARB), nitrates, digitalis preparations and the like. The experimental group was supplemented with *Zhenwu* Decoction on the basis of the control group.

Evaluation of efficacy

1. EF value: Left ventricular ejection fraction, measured by the heart color Doppler ultrasound.
2. (N) = (total score before treatment - total score after treatment) / total score before treatment × 100%.
3. BNP: B-type natriuretic peptide.
4. Quality of life score: Minnesota Heart Failure Quality of Life Scale score was used. The lower the score represented the higher quality of life.

Table 1 Diagnosis criteria for chronic heart failure

Main Conditions	Secondary Conditions
1.paroxysmal nocturnal dyspnea or orthopnea	1. Ankle edema
2. distention of jugular vein	2. cough at night
3. lung rale	3. Difficulty breathing after activity
4. cardiac dilatation	4. Hepatomegaly
5. acute pulmonary edema	5. pleural effusion
6. gallop rhythm of third heart sound	6. The lung capacity drops to a third of the maximum lung capacity
7. venous hypertension > 1.57 kPa	7. Tachycardia (heart beat > 120 bpm)
8. cycle time > 25s	
9. Hepatic carotid venous regurgitation was positive	

Outcome

Treatment efficiency was evaluated according to heart function improvement. Significantly effective, heart function improved more than 2 ranks. Effective: heart function improved more than 1 rank. Invalid: did not meet the effective indicators. Exacerbations: heart function deterioration of 1 rank or more.

Data extraction

Data classification based on treatment efficiency. Classification information: treatment efficiency. Continuity information: EF value, Lee's score, BNP and quality of life score.

Statistical methods

The data of the literature were analyzed by RevMan 5.3 software, and meta-analysis of various evaluation indexes was carried out. The heterogeneity test was performed on each study data first. $P \leq 0.05$ indicated that the heterogeneity of the study was large, and the random effect model would be used for further analysis, while P> 0.05 indicated that the heterogeneity was small and the fixed effect model was used for further analysis. The classification data and continuous data was analyzed by odds ratio (OR) and weighted mean difference (MD) analysis, respectively. A funnel analysis of bias was performed if ≥ 10 articles had a similar efficiency index.

Results

Search results

A total of 433 articles were selected, including 433 Chinese articles and 0 articles in English. After examining and rejecting unqualified literature, 16 articles were included in the study. There were 1167 patients in total, including 587 cases in the experimental group and 580 cases in the control group (Figure 1, Table 3).

Table 2 Standards for classification of cardiac function

Classification of cardiac function	Major performance
grade I	Heart disease patients, whose daily activity quantity is not limited. Patients with general physical activity do not have the symptoms of anemic breathing difficulties and other heart failure symptoms. Patients are in cardiac functional compensatory period.
grade II	Heart disease patients are mildly limited in physical activity. The patient is all conscious when resting, but general physical activity can cause heart failure symptom. Mild or I degree heart failure.
grade III	Heart disease patients are obviously limited in physical activity. Under general physical activity can cause heart failure symptom. Media degree or II heart failure.
grade IV	Heart disease patients cannot engage in all physical activity. The patients are in heart failure state when resting, and get worse after activity. Severe degree or III heart failure.

The inclusion of literature quality evaluation

The literature scores were scored according to the Jadad scale, Of the 16 papers, there were 2 papers in the score of 3 and 8 papers in 2, and 6 papers in 1 (Table 4). The Cochrane collaborative network bias risk assessment of the literature was shown in Figure 2 and Figure 3.

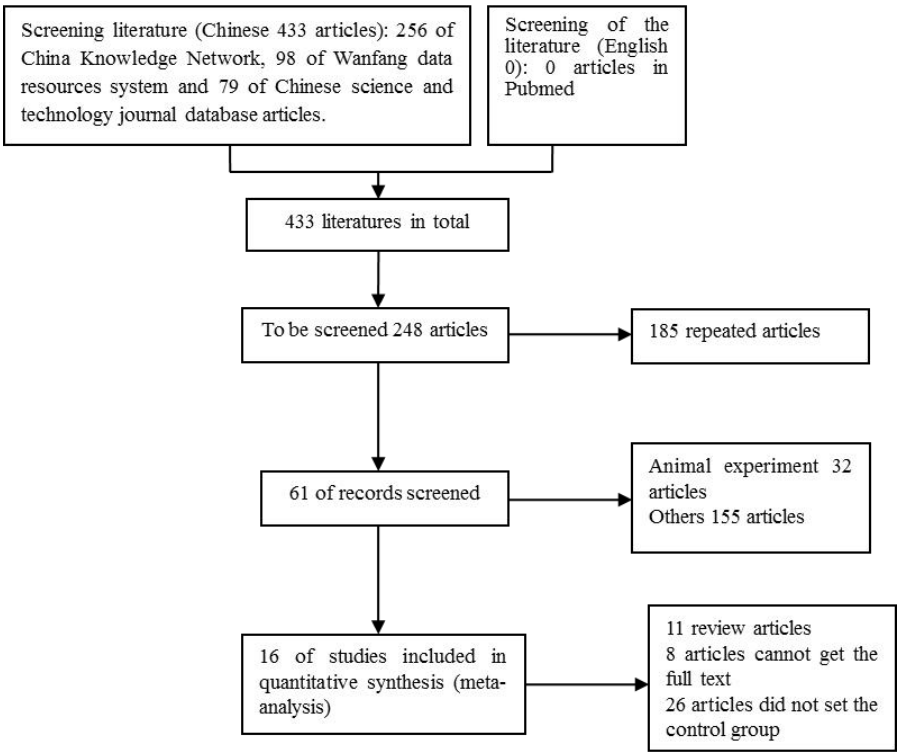

Figure 1 Literature retrieval flow chart

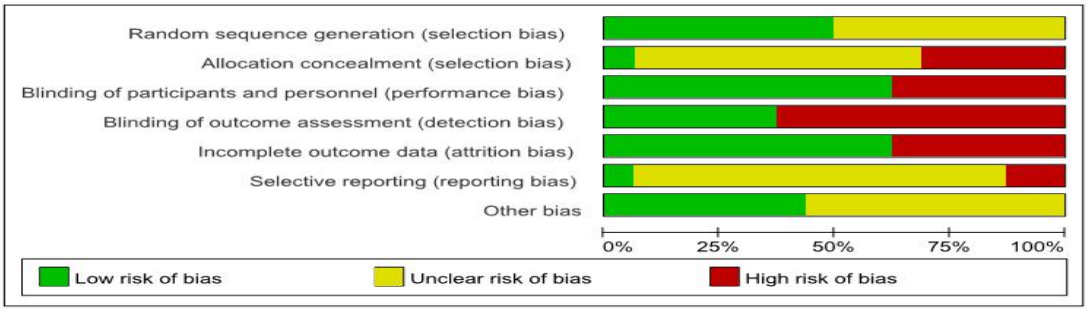

Figure 2 Cochrane Collaboration Network Bias Risk Assessment

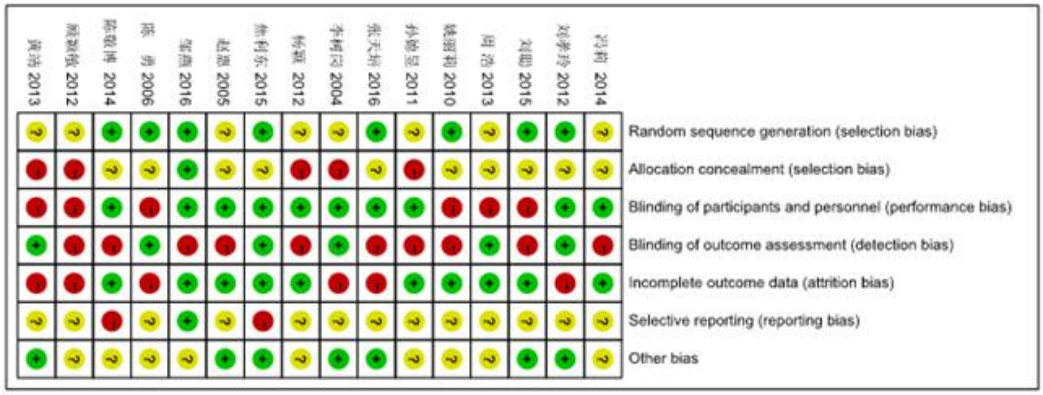

Figure 3 Cochrane Collaboration Network Bias Risk Assessment

Table 3 The basic information of the research included

Literatures	N	Treatment		Evaluation
	T/C	T	C	
Gu Yingmin 2012	30/30	MZD+WM	WM	①②④⑤
Liu Cong 2015	20/20	MZD+WM	WM	②③④
Li Shugang 2004	30/30	MZD+WM	WM	②④
Chen Yong 2006	50/48	MZD+WM	WM	①②
Zhang Tianpei 2016	39/39	MZD+WM	WM	①②⑤
Liu Xiaolingg 2012	55/55	MZD+WM	WM	②
Zhou Hao 2013	32/32	MZD+WM	WM	①
Jiao Lidong 2015	47/47	MZD+WM	WM	①②
Sun Deyu 2011	30/28	MZD+WM	WM	①
Yao Lili 2010	30/30	MZD+WM	WM	①②
Zou Yan 2016	39/39	MZD+WM	WM	②
Chen Jingbo 2014	53/53	MZD+WM	WM	①
Feng Li 2014	30/30	MZD+WM	WM	①③④
Huang Jing 2013	38/37	MZD+WM	WM	②③
Yang Ying 2012	24/24	MZD+WM	WM	②⑤
Zhao Hui 2005	40/38	MZD+WM	WM	②⑤

Note: T: experimental group C: control group; MZD, modified *Zhenwu* Detection; WM, western medicine; ① cardiac function ②EF value ③ Lee's score ④BNP ⑤ quality of life score

Combined analysis

Effective rate of treatment

The meta-analysis of 10 studies was carried out with the effect scale of treatment efficiency[2, 4, 6-7, 9, 11-12, 14-15, 17],the heterogeneity test: $Chi^2 = 3.31$, $df = 9$ ($P = 0.95$), showed that 10 studies had good homogeneity, using Meta-analysis of fixed effects model, merge effect quantity estimation: the OR = 3.69, 95% IC (2.36, 2.36), the significance test: Z = 5.69 ($P < 0.001$), the difference was statistically significant, the effect of treatment group is better than the control group. As shown in Figure 4.

EF value

Effective rate of treatment the meta-analysis of 12 studies was carried out with the effect scale of EF value[2-5, 7-10, 12-13, 15-16], the heterogeneity test:$Tau^2 = 9.70$, $Chi^2 = 174.14$, $df = 11$($P < 0.001$), indicated that the 12 studies were poor homogeneity, the random effect model was used for Meta-analysis, merge effect quantity estimation: MD = 5.85, 95%IC (3.90, 7.79), the significance test: Z = 5.90 ($P < 0.001$),,the difference was statistically significant,

and the EF value of the treatment group was higher than the control group. As shown in Figure 5.

Table 4 The inclusion of Jada scores in the literature

Literature	Random Method	Random Concrete method	Double-blind method	Double-blind Concrete method	Exit and loss	Grede
Gu Yingming2012	✓					1
Liu Cong 2015	✓	✓			✓	3
Li Shugang 2004	✓					1
Chen Yong 2006	✓	✓				2
Zhang Tianpei 2016	✓	✓				2
Liu Xiaoling 2012	✓	✓				2
Zhou Hao 2013	✓					1
Jiao Lidong 2015	✓	✓				2
Sun Deli 2011	✓					1
Yao Lili 2010	✓	✓				2
Zhou Yan 2016	✓	✓				2
Chen Jingbo 2014	✓	✓			✓	3
Feng Li 2014	✓				✓	2
Huang Li 2013	✓				✓	2
Yang Ying 2012	✓					1
Zhao Hui 2005	✓					1

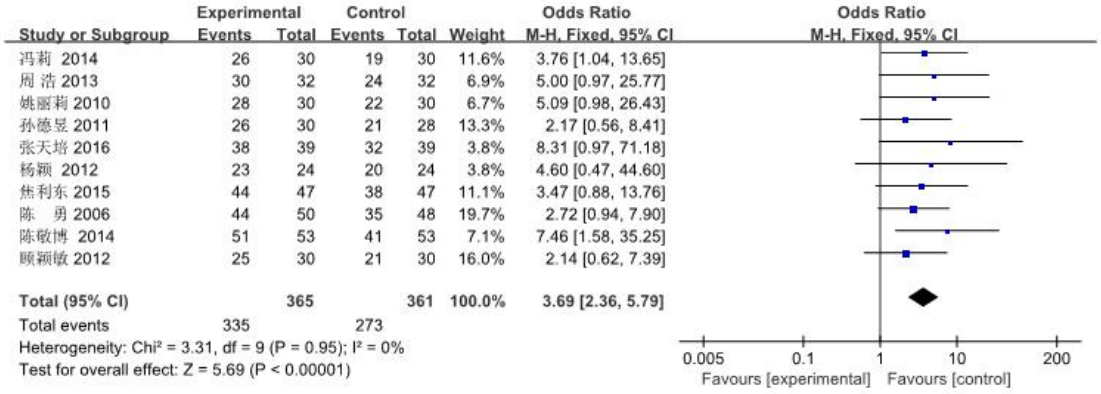

Figure 4 The analysis of forest map of effective Meta-analysis

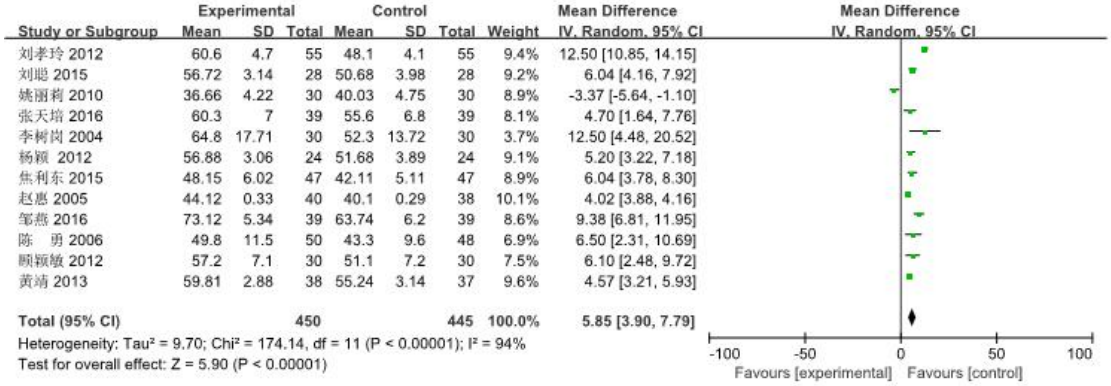

Figure 5 The analysis of forest map of EF value Meta-analysis

Lee's score

Effective rate of treatment the meta-analysis of 3 studies was carried out with the effect scale of Lee's score[2,4, 6-7, 9 ,11- 12,14-15,17], the heterogeneity test: $Tau^2 = 0.36$, $Chi^2 = 5.88$, df = 2 ($P = 0.05$), manifested that the 3 studies were poor homogeneity, the random effect model was used for Meta-analysis,merge effect quantity estimation: MD = -1.37, 95% IC (-2.23, -0.52), the significance test: Z = 3.14 ($P = 0.002$). The difference was statistically significant, and Lee's score was lower in the treatment group than in the control group. As shown in Figure 6.

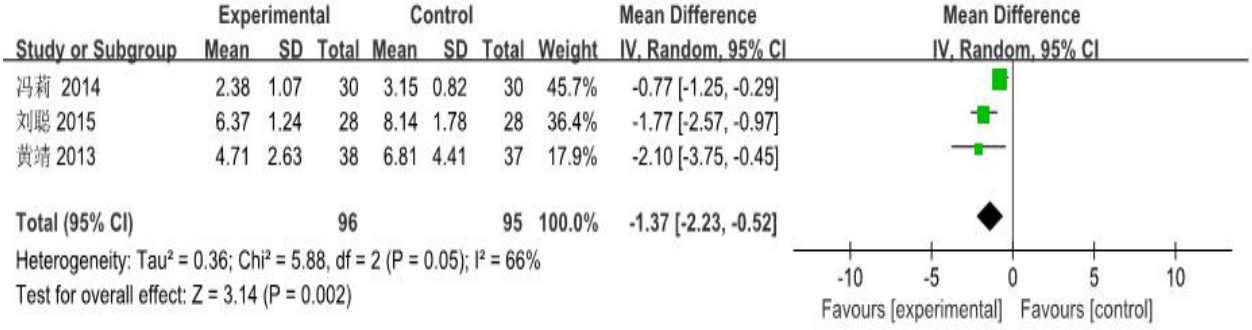

Figure 6 the analysis of forest map of Lee's score Meta-analysis

BNP

Effective rate of treatment the meta-analysis of 4 studies was carried out with the effect scale of BNP[2-3,5-6], the heterogeneity test: Tau^2 = 4747. 92, Chi^2 = 54.83, df = 3 (P < 0.001), showed t hat the 4 studies were poor homogeneity, the ran dom effect model was used for Meta-analysis, m erge effect quantity estimation: MD = -114.48, 9 5% IC (-186.28, -42.68), the significance test: Z = 3.13 (P = 0.002). The difference was statistic ally significant, and BNP was lower in the treat ment group than in the control group. As shown in Figure7.

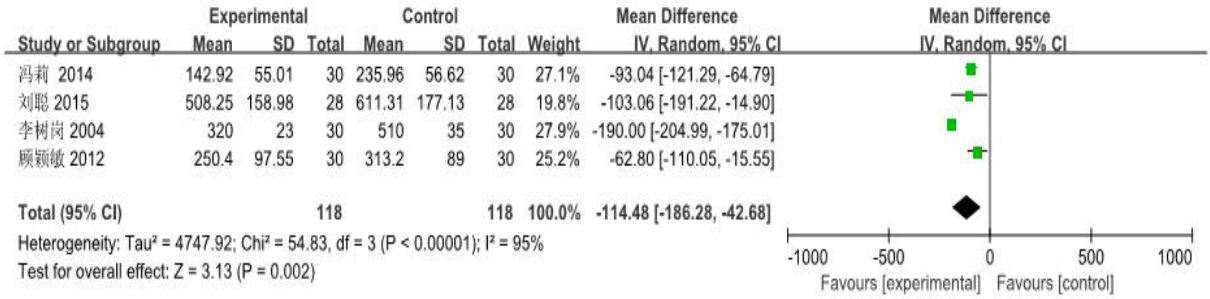

Figure 7 The analysis of forest map of BNP Meta-analysis

Survival quality score

Effective rate of treatment the meta-analysis of 4 studies was carried out with the effect scale of survival quality score, the heterogeneity test: Tau^2 = 9.05，Chi^2 = 21.36，df = 3 (P < 0.001), showed that the 4 studies were poor homogeneity, the random effect model was used for Meta-analysis, merge effect quantity estimation: MD = -8.44, 95% IC (-11.73, -5.15), the significance test: Z = 5.03 (P < 0.001). The difference was statistically significant, and was survival quality score lower in the treatment group than in the control group. As shown in Figure 8.

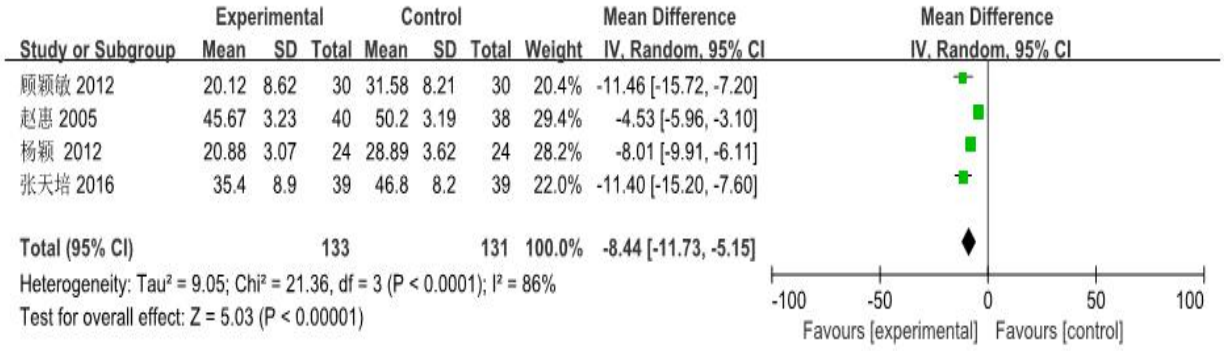

Figure 8 The analysis of forest map of survival quality score Meta-analysis

Publication bias analysis

Publication bias was analyzed by making a funnel chart for inclusion studies and /or greater than 10. In this study, an effective funnel plot for effective rate of treatment and EF value was made, and most of the study of effective funnel plot was deviated from the invalid line and concentrated on the effective side [2, 4, 6-7, 9, 11-12, 14-15, 17], due to basis, as shown in Figure 9. The funnel plot of EF is not funneled [2-5, 7-10, 12-13, 15-16]. It is estimated that a negative result has not been published, indicated that the publication bias was relatively large. As shown in Figure 10.

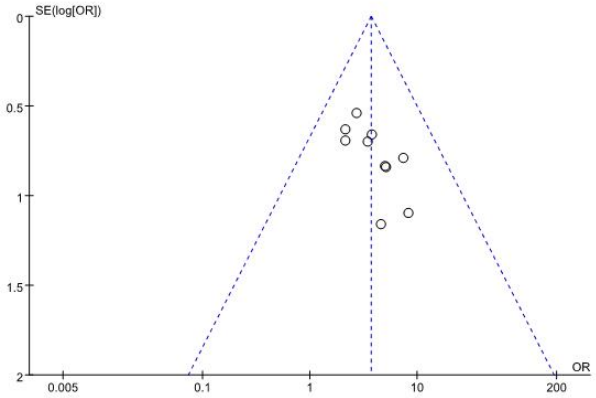

Figure 9 Treatment of efficient Meta-analysis funnel plot

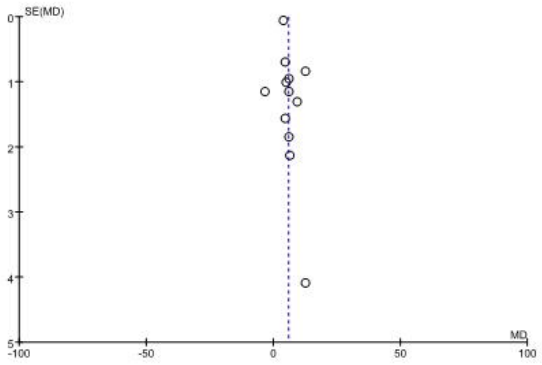

Figure 10 EF value Meta-analysis funnel plot

Discussion

Chronic heart failure is due to any cause of initial myocardial injury such as myocardial infarction, cardiomyopathy, hemodynamic overload, inflammation, etc., causing changes in myocardial structure and function, and finally leads to ventricular pump blood or filling a low function complex clinical syndrome [18]. More and more people realize that the development of chronic heart failure depends on the severity of myocardial pathological remodeling, and myocardial injury, nervous-endocrine system over-excited and related cytokine activation is closely related to myocardial pathological remodeling. So the treatment of ACEI successfully reduced the mortality rate of 27% of patients with chronic heart failure [19], and the mortality rate was further reduced by by 34% -35% when combined ACEI and β-blockers [20], but the side effects cannot be ignored. Interventional therapy can only solve the coronary stenosis but not the cardiac function, meanwhile for the risk and cost of the surgery, it cannot be accepted by the majority of patients. In recent years, with the deepen researches in the Chinese medicine treatment for chronic heart failure, we summed up the experience in long-term clinical practice, that the use of *Zhenwu* Decoction Jiawei combined with Western medicine treatment not only improve patients with cardiac function, and can improve the quality of life of patients, improve the prognosis, through *Wenshen Tongyang*, beneficial *Qi* and blood circulation.

Heart failure belongs to the TCM "palpitations", "asthma card", "edema" and other areas. Zhang [21] through the research of the 2002-2008 TCM clinical literature study on the heart failure, it can be inferred that heart and kidney deficiency is the most common chronic heart failure TCM syndromes by means of prescriptions to speculate the symptoms. Similar results as *Yan* Shiyun *et al* [22], heart kidney *Yang* deficiency and edema due to yang insufficiency are the most common chronic heart failure TCM syndromes. So the treatment of warming *Yang* for diuresis, promoting circulation and removing stasis is the main treatment of chronic heart failure. *Zhenwu* Decoction is from *Shang-han-lun* and is composed of the *Aconite*, *Atractylodes*, *Poria*, *Ginger*, *Peony*. *Aconite* is hot, and can warm the *Yang* of kidney;

Poria could remove the water; *Atractylodes* could absorb moisture; *Peony* could improve the *Yin*; *Ginger* help warm *Yang* cold. Modern studies have shown that *Zhenwu* Decoction can improve the cardiac function of chronic heart failure rats by reducing the expression of Bax in cardiomyocytes and regulating the balance of Bcl-2 and Bax [23]. And it can reduce the expression of TGF-β to improve ventricular remodeling, relieve cardiac hypertrophy, inhibit the occurrence of heart failure [24]. The results showed that the highest effective rate in the experimental group was 97.4% [9] and the lowest effective rate was 83.3% [2]. The total effective rate was 91.8% in all the studies. In the control group, the highest effective rate was 83.3% [4] and the lowest 63.3% in all the studies [6]. The total effective rate was 75.6% in all the studies. The effective rate, the lowest effective rate and the total effective rate in the experimental group were higher than those of the control group, which indicated that the effective rate of *Zhenwu* Decoction combined with western medicine was better than that of western medicine alone, and the left ventricular ejection fraction, BNP and Lee Score, quality of life were significantly improved, and better than simple Western medicine. However, the overall quality of the literatures included in this study are not high, and publication bias may exist, so reliable clinical efficacy evaluation still need more high-quality multi-center randomized double-blind controlled clinical trial evidence.

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