

# *A Systematic Review of the Synergy of Traditional Chinese Medicine and Western Medicine in the Treatment of Heart Failure in Dilated Cardiomyopathy*

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**Abstract:** In order to analyse the TCM treatment, TCM medication, clinical efficacy and safety of TCM synergy in the treatment of dilated cardiomyopathy heart failure, we used method of data mining was used to systematically evaluate. We searched CNKI, WanFang, VIP, Sinomad, Web of Science, Pubmed and other databases, and performed meta-analysis or descriptive analysis on clinical efficacy and LFE, LVEDD, LVESD and serum NT-ProBNP from the establishment of each database to July 2021. For the literature that meets the inclusion criteria, a database was established by selecting Chinese medicine prescriptions, and frequency statistics, association rule analysis and other methods were used to analyze Chinese medicine treatment methods, commonly used Chinese medicines and drug pairs or drug groups. Resultly, a preliminary search of 858 articles resulted in the inclusion of 20 RCTs with 1745 patients. There were 9 kinds of treatment methods involved, and the most frequently used were 29.23% for qi invigoration, 24.62% for blood revitalization, and 18.60% for water conservancy. 48 flavors of commonly used Chinese medicine, the frequency of use is 90% of astragalus, 75% of danshen and 65% of ginseng. There were 30 commonly used drug pairs or drug groups, and the high-frequency drug pairs included astragalus + danshen, laurel branch + astragalus, danshen + laurel branch, etc., and the frequency of use was 43.3%, 36.7%, 36.7%, etc. The TCM synergistic treatment group was better than the Western drug control in terms of total clinical effective rate, LFE, LVEDD, LVESD and serum NT-ProBNP. In conclusion, the main treatment methods of heart failure in dilated cardiomyopathy are qi invigoration, blood revitalization and water rejuvenation, commonly used Chinese medicines are astragalus, danshen, ginseng, etc., commonly used high-frequency drugs are astragalus + danshen, guizhi + astragalus, danshen + guizhi, etc. And the synergistic treatment of traditional Chinese and Western medicine is obviously better than that of western medicine alone.

## 1. Introduction

Dilated cardiomyopathy (DCM) is a disease that presents clinically primarily as left or bilateral ventricular dilation and systolic failure, with heart failure being the most common complication of DCM. Currently, there is a lack of specific treatment for DCM heart failure, mainly based on traditional therapy with ACE inhibitors, angiotensin receptor neprilysin inhibitors, or angiotensin II receptor antagonists and  $\beta$ -blockers [1-3] to improve symptoms, but treatment has not achieved the desired effect [4]. Studies have shown [5-8] that the synergistic treatment of this disease with traditional Chinese and Western medicines is better than conventional Western medicine, which can significantly relieve symptoms and improve heart function, and the efficacy is significantly better than conventional treatment of Western medicine. Therefore, this study intends to use meta-analysis and data mining methods to evaluate the drug use, clinical efficacy and safety of traditional Chinese and Western medicines in the synergy of traditional Chinese and Western medicines in the treatment of DCM heart failure.

## 2. Information and methodology

### 2.1. Inclusion and exclusion criteria

#### 2.1.1. Inclusion criteria

(1) Published randomized controlled clinical trials were included; (2) Literature with the subjects that met the diagnostic criteria for dilated cardiomyopathy in the "Recommendations for the Diagnosis and Treatment of Cardiomyopathy" [9] and the diagnostic criteria for central failure in the "Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018" [10] were included, regardless of age, gender and race; (3) Intervention: Literature on Western medicine group intervention drugs being only conventional Western medicine treatment drugs were included; Literature on Chinese medicine group (dosage form was not limited) were included; (4) Literature with evaluation indexes including cardiac LVEF, LVEDD, LVESD, serum BNP were included.

#### 2.1.2. Exclusion Criteria

(1) Reviews, lessons learned, case reports, conference papers and dissertations, non-RCT were excluded; (2) Literature related to other diseases that caused HF were excluded, or having severe hepatic and renal insufficiency, malignant neoplasms, hypersensitivity to study drugs; (3) Repeated published literature was excluded; (4) Literature whose data cannot be counted were excluded.

### 2.2. Search Strategy

We searched CNKI, WanFang, VIP, Sinomad, Web of Science, Pubmed and other databases from the establishment of each database to July 2021. The search terms included dilated cardiomyopathy, heart failure, cardiac failure traditional and western medicine, traditional Chinese medicine, Chinese medicine, granules, injection, Chinese patent medicine.

### 2.3. Literature screening, data extraction and quality evaluation

(1) According to the process of screening literature, the searched literature is screened multiple times and multi-step and the literature included is preliminarily decided, and the quality evaluation and extraction of the literature should be carried out in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions in the Cochrane Library.

## 2.4. Statistical methods

Use the Review Manager 5.4 software from the Cochrane Collaboration Network to analyze the metrics that need to be analyzed. The dichotomous variables used the count data using odds ratio (OR), all expressed in 95% confidence interval (CI); Continuous variables, combined using Mean Difference (MD) or Standard Deviation (Std.MD) using metrological data. Heterogeneity was assessed using the I2 test, and a fixed-effect model was used if  $I^2 < 50\%$ ; If  $I^2 \geq 50\%$ , a random-effects model was used and the sources of heterogeneity were analysed using sensitivity analysis. If the data heterogeneity was high, sensitivity analysis was performed by removing them one by one to find the source of heterogeneity.

The data entered in Excel and quantified binary values were imported into SPSS Modeler 18.0, and the associated Apriori algorithm was selected in the modeling method for association rule analysis to mine common drug combinations. Import the data entered in Excel into SPSS Statistic 25.0 software to statistic and analyze the frequency, frequency, classification and clustering of Chinese medicines.

## 3. Results

### 3.1. Literature Screening Process

858 articles were initially searched, 159 were selected after eliminating duplicates, 31 were selected after reading the title and abstract, and the full text was further read, and 20 RCTs were finally included in strict accordance with the inclusion and exclusion criteria.

### 3.2. Inclusion of literature features

A total of 20 RCTs were included, all of which were treated with traditional Chinese and Western medicines for DCM heart failure, and a total of 1745 patients, 869 control groups and 876 treatment groups were included. (see Figure 1 and Table 1)

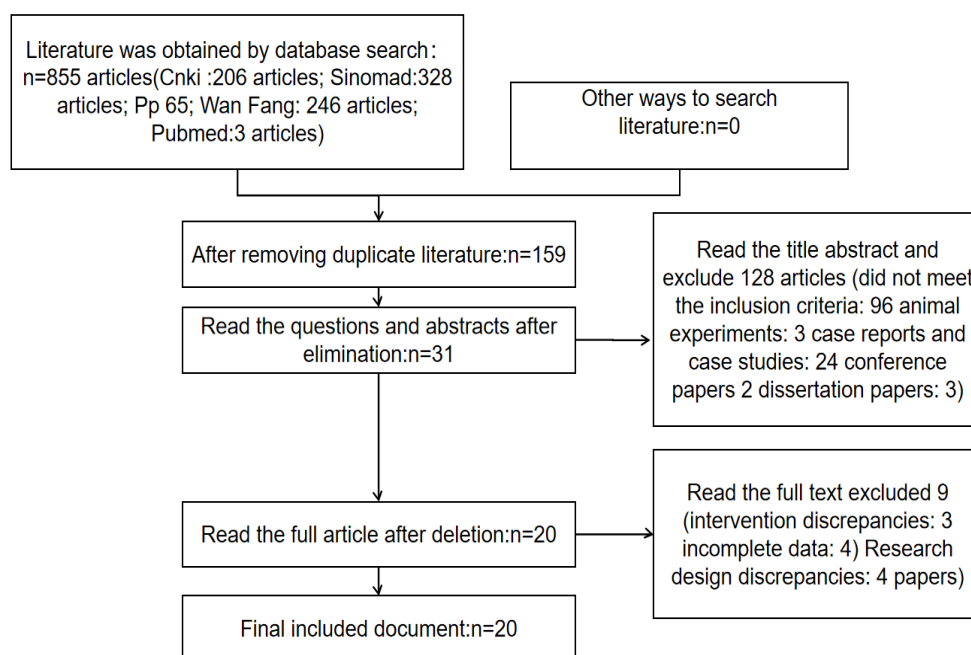


Figure 1: Flow chart of literature screening

Table 1: Basic characteristics of the included study

Inclusion study	Sample size		Treatment group	Control group	Treatment time	Clinical index
	E	C				
Wang Chaoyuan	40	40	Qili Qiangxin capsule	Western medicine	28D	①,②,④,⑥,⑦
Wang Sikun	45	41	Qili Qiangxin capsule	Western medicine	56D	①,②,③,④,⑥,⑦
Yuan Mingyi	53	52	Huoxue Tongpulse decoction	Western medicine	28D	①,②,③,④,⑤,⑥,⑨
Zheng Weiwei	52	52	Qili Qiangxin capsule	Western medicine	14D	①,②,④
Wang Zhiqian	50	50	Huoxue Tongpulse decoction	Western medicine	90D	①,②,③,⑨,⑩
Liu Yaowu	84	84	Decoction for nourishing the heart	Western medicine	90D	⑧
Zhang Yuankun	43	43	Huangqi Baoxin Decoction	Western medicine	84D	①,②,⑦,⑧,⑪
Du Yuan	32	32	Tongmai Yiqi Decoction	Western medicine	28D	⑤,⑧,⑨
Yang Yibo	54	53	Decoction for nourishing the heart	Western medicine	90D	①,③,⑨
Zhou Zhen	33	34	Huoxue Yangxue Decoction	Western medicine	84D	②,④,①
Ma Mingying	60	60	Tongmai Yiqi Decoction	Western medicine	28D	②,④,①,③,⑥,⑨
Yao Sumin	48	48	Qili Qiangxin capsule	Western medicine	28D	⑫
Tang Xiandan	40	40	Decoction for nourishing the heart	Western medicine	90D	①,③,⑨
Yi Junping	31	31	Huangqi Shenmai Wuling Tongmai Yiqi Decoction	Western medicine	90D	②,①
Zhang Chengying	30	30	Zini Decoction	Western medicine	84D	②,①,⑥
Li Zhigunag	35	35	Shenmai Ningxin Tongmai Yiqi Decoction	Western medicine	56D	②,①,⑦
Li He	30	30	Yiqi Qiangxin Decoction	Western medicine	56D	①,②,④,⑥
Jiang Zhoutian	30	30	Yixin Shu Decoction	Western medicine	90D	①,②,③,⑤
Wang Chaoliang	40	40	Fuzheng Qiangxin Decoction	Western medicine	28D	①

Note: ①LVEF ②LVEDD ③6MWT ④LVESD ⑤hs-CRP ⑥BNP ⑦NT-proBNP ⑧AngII ⑨TNF- $\alpha$  ⑩IL-6 ⑪CO ⑫Life therapy score

### 3.3. The treatment of the included study, the association of traditional Chinese medicine and high-frequency drugs

Treatment In the 20 RCT research literatures, 9 treatment methods were used, and the frequency of use was 29.23% for qi invigoration, 24.62% for blood revitalization, 18.60% for water conservancy, 7.69% for warm yang, 6.15% for spleen strengthening and 6.15% for yin nourishment. A total of 48 flavors of Chinese medicines were involved, and the Chinese medicines with high frequency of use included astragalus, danshen, ginseng, guizhi, angelica and poria, with frequency of use of 90%, 75%, 65%, 60%, 50% and 50% respectively. The high-frequency drug pairs were astragalus + danshen, laurel branch + astragalus, danshen + laurel branch, astragalus + ginseng, danshen + ginseng and angelica + astragalus according to the frequency of use, and the frequency of use was 43.3%, 36.7%, 36.7%, 33.3%, 30% and 30%.

### 3.4. Outcome measures of included studies

#### 3.4.1. Total effective rate

A total of 20 studies reported the total clinical effective rate of DCM heart failure, a total of 1745 patients were included, the heterogeneity test result  $I^2=0\%$ , using the fixed-effect model,  $OR=0.16$ , 95% CI (0.13, 0.20),  $P<0.00001$ , the synergistic treatment group of traditional Chinese and Western medicines was significantly better than that of the western medicine treatment group. (Figure 2)

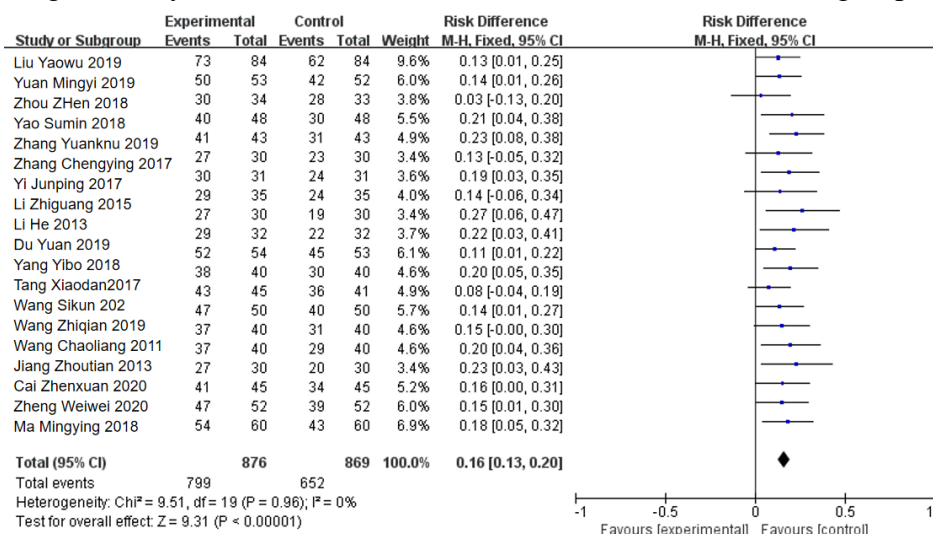


Figure 2: Meta analysis of the total effective rate

#### 3.4.2. Cardiac LVEF level

A total of 16 studies reported LVEF level, 1079 patients were included, heterogeneity test results  $I^2=12\%$ , fixed-effect model  $SMD=0.95$ , 95% CI(0.82, 1.07),  $P<0.00001$ , the synergistic treatment group of Chinese and Western medicines was significantly better than that of the Western medicine treatment group. (Figure 3)

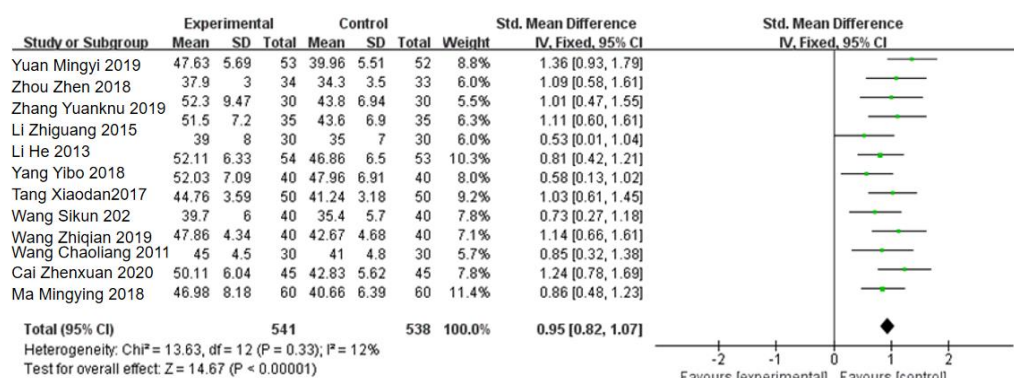


Figure 3: Meta analysis of Cardiac LVEF level

### 3.4.3. Cardiac LVEDD level

A total of 11 literature reported LVEDD level, a total of 695 patients were included, the heterogeneity test result I<sup>2</sup>=0%, using a fixed-effect model, SMD=-0.79, 95% CI (-0.95, -0.64), P<0.00001, the Chinese and Western medicine synergistic treatment group was significantly better than the Western medicine treatment group. (Figure 4)

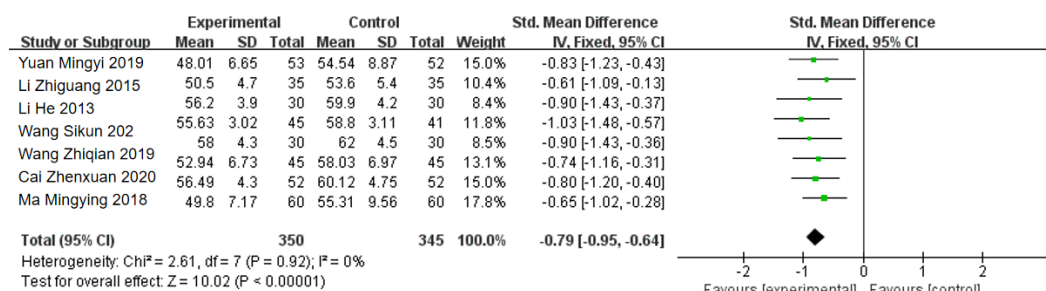


Figure 4: Meta analysis of Cardiac LVEDD level

### 3.4.4. Cardiac LVESD level

A total of 7 literature reported that 607 patients were included in LVESD, the heterogeneity test result I<sup>2</sup>=0%, using the fixed-effect model, SMD=-0.90, 95% CI (-1.07, -0.73), P<0.00001, the synergistic treatment group of traditional Chinese and Western medicines was significantly better than that of the western medicine treatment group. (Figure 5)

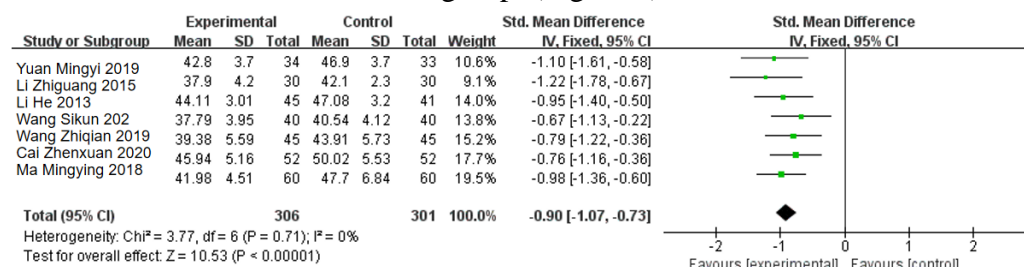


Figure 5: Meta analysis of Cardiac LVESD level

### 3.4.5. Serum BNP level

A total of 4 studies of serum BNP reported BNP levels, a total of 322 patients were included, and the heterogeneity test result I<sup>2</sup>=65%, so the random-effects model was used for analysis, SMD=-1.59,

95% CI (-2.02, -1.16),  $P < 0.00001$ , the synergistic treatment group of traditional Chinese and Western medicines was significantly better than that of the western medicine treatment group. (Figure 6)

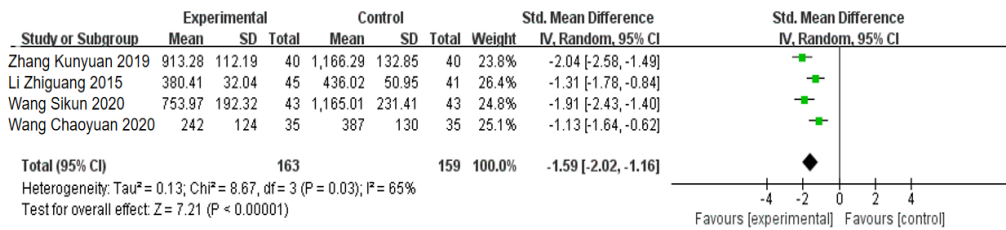


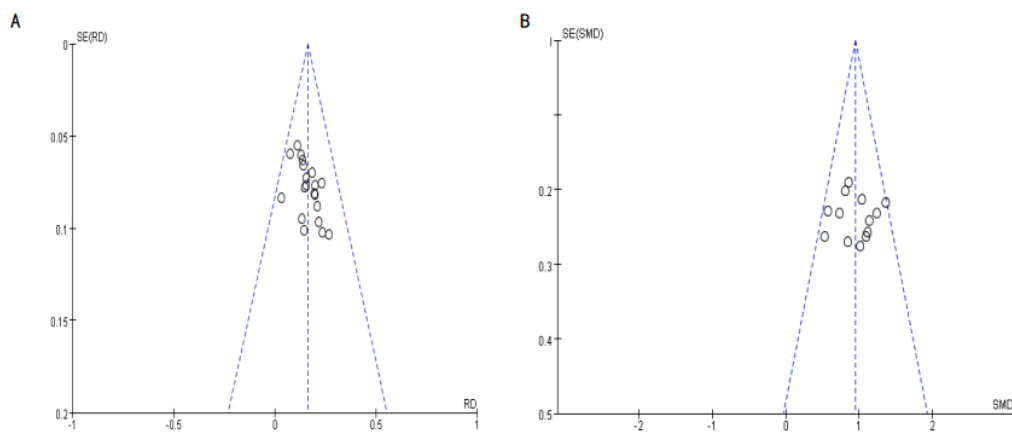
Figure 6: Meta-analysis of Serum BNP level

### 3.5. Safety Evaluation

Among the 20 studies included in this review, eight mentioned specific adverse effects, and none of the rest explicitly reported adverse effects. The existing results confirm that the synergy of traditional Chinese and Western medicines in the treatment of DCM heart failure is safe and effective, but due to the limited total number of included studies, large-scale clinical observation is still needed to make more reliable evaluation.

### 3.6. Publication bias

The number of studies was  $\geq 10$ , and the primary outcome measures were clinical total efficacy and LVEF for publication bias. It can be seen from the figure that the scatter points are not completely symmetrical, and the discretization that appears in Figure B is more obvious, which shows that the distribution of the funnel graph is not completely symmetrical. (Figure 7)



Note: A is the total clinical effective rate of Chinese and Western medicine synergy vs western medicine treatment; B is the synergy of Chinese and Western medicines versus Western medicine treatment to reduce LVEF.

Figure 7: Funnel chart of literature screening

## 4. Discussion

Therefore, early diagnosis, early treatment, and effective improvement of ventricular remodeling are of great significance for controlling adverse events, improving the quality of life of patients and improving survival rate.

The research on the treatment of DCM heart failure by traditional Chinese medicine is increasing,

but there are few analysis and summary of the information such as the medication rules of traditional Chinese medicines and the sexual taste, attribution and association rules of traditional Chinese medicines, and there are no reports at present, so based on data mining, the treatment and medication rules of traditional Chinese medicines for the treatment of DCM heart failure are analyzed, which provides a reliable basis for subsequent research on the therapeutic effect and mechanism of traditional Chinese medicines on this disease. The literature included in this study shows that in the synergistic treatment of Chinese and Western medicines, the most commonly used treatment is to invigorate qi and activate blood, and the rest are warm yang, water reliance, nourishing yin, expectorant and so on. Astragalus is used most frequently in the synergistic treatment of Chinese and Western medicines. The high-frequency drug pairs were astragalus + danshen, laurel + astragalus, danshen + laurel branch, astragalus + ginseng and so on in descending order. Astragalus invigorating qi solid table, danshen blood activation and stasis, is the most frequently used drug pair, which proves the conclusion that the qi and blood activation method is the most common treatment.

Studies have found that astragalus intervention in HF model mice can reduce calcium transient peaks and prolong fallback time, indicating that astragalus can improve cardiac systolic and diastolic function [11]. Among them, ASIV can inhibit oxidative stress through the Nrf2/HO-1 pathway to prevent HF [12], and the degree of myocardial fibrosis in DCM model mice can be improved by down-regulating the TGF- $\beta$ 1-SMAD signaling pathway [13]. Danshen extract has a certain inhibitory effect on ventricular remodeling in HF model rats, which can improve cardiomyocyte fibrosis and reduce cardiomyocyte damage in rats with heart failure. Danshen also improves HF inflammatory damage, and its mechanism may be related to the regulation of MD2/TLR4-MyD88 complex formation and the intervention of TLR4-TRAF6-NF- $\kappa$ B signaling pathway [14]. Xuefeng Zhang et al. found that tanshinone II.A can significantly improve cardiac function in HF-model rats by inhibiting apoptosis and activating autophagy in in vivo experiments. In cell experiments in vitro, tanshinone II.A has been found to increase autophagy levels through the AMPK-mTOR signaling pathway to improve cell viability[15]. In another study [16], tanshinone II.A was found to inhibit the expression of genes such as p67phox and reduce the production of ROS. Tang Yong [17] et al. found that the effect of Astragalus and Danshen together to improve LVEF, left ventricular short axis shortening rate and ATP in rats with Qi deficiency and blood stasis HF model was significantly better than that of the Western medicine treatment group. In the observation of Zhang Yuanli [18] et al., it was found that the total effective rate of treatment with compound danshen injection combined with astragalus injection and the improvement of LVEF were better than those of the western medicine treatment group.

In conclusion, by analyzing the frequency, sexual taste, efficacy and combination of commonly used drugs for the treatment of DCM combined with HF, this study concluded that the main symptom of DCM heart failure is qi deficiency and blood stasis, and the treatment is mainly to invigorate qi and blood, often combined with astragalus + danshen. The results of the 20 articles included in this study show that compared with the treatment effect of conventional Western medicine, the effective rate of LFE, LVESD, BNP and other indicators in patients treated with Chinese and Western medicines is better than that of conventional Western medicine treatment group, and the recovery of cardiac ejection function and cardiac function in DCM heart failure patients are significantly improved. Among them, 8 articles reported adverse reactions in the process of clinical measurement, including circulatory system symptoms, digestive system symptoms, blood routine, urine routine and liver and kidney function, etc., and the results showed that there was no significant difference between the TCM synergistic treatment group and the conventional Western medicine treatment group, suggesting that the safety of TCM synergistic treatment is high, but attention should still be paid to combining dialectical therapy and rational drug use.

In summary, the synergistic treatment of DCM heart failure by traditional Chinese and Western



medicines can significantly improve the clinical response rate, improve the level of LVEF and the level of cardiac function, and the incidence of adverse reactions does not change significantly.

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