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Review Article

Xinmailong Injection for Improvement of Cardiac Function in Patients with Heart Failure: A Systematic Review and Meta-Analysis

Yuan-long Sun,[1,2] Yi-ping Li,[1,2] Ting-ting Qiang,[1,2] Xiao-fen Ruan ,[1,2] and Xiao-long Wang [1,2]

[1]*Cardiovascular Department, Shuguang Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*
[2]*Cardiovascular Research Institute of Traditional Chinese Medicine, Shuguang Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*

Correspondence should be addressed to Xiao-fen Ruan; ruanxiaofeng@shutcm.edu.cn and Xiao-long Wang; wangxiaolong@shutcm.edu.cn

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Background. Insect drugs have great potential for treating cardiovascular diseases. Xinmailong (XML) injection, a bioactive composite extracted from *Periplaneta americana* (a species of cockroach), was wildly used in treating heart failure in China. This meta-analysis aimed to assess the efficacy and safety of XML injection for the improvement of cardiac function in HF. *Materials and Methods*. Online literature search for relevant studies was performed using databases including PubMed, EMBASE, Cochrane Library, CNKI, and Wanfang. Left ventricular ejection fraction (LVEF), six-minute walk test (6MWT), and brain natriuretic peptide (BNP) were selected as target outcomes. The analysis was performed using Stata 12.0, and sources of heterogeneity were explored by subgroup analysis and metaregression. *Results*. 32 studies were included in this meta-analysis after meeting the inclusion/exclusion criteria. The results demonstrated that additional use of XML improved LVEF (WMD = 5.82, 95% CI: 5.52–7.13, $P < 0.00001$) and 6MWT (WMD = 51.48, 95% CI: 35.83–67.13, $P < 0.00001$) and reduced BNP (WMD = −172.84, 95% CI: −205.79 to −139.89, $P < 0.00001$). The results of subgroup analyses and metaregression suggested that XML injection has more cardiac function improvement for middle-aged HF patients than youth, and greater LVEF and 6MWT improvement were associated with higher average age. *Conclusions*. XML plus conventional treatment demonstrated a significant effect in reducing cardiac dysfunction in HF patients, and age is a potential factor of higher efficacy. Given the heterogeneity and bias of the included RCTs, large, prospective, rigorous trials are still needed.

1. Introduction

Heart failure (HF) is a global healthcare issue, defined as a severe and terminal-stage symptom after heart disease, and has high patient mortality [1, 2]. HF induces structural, neurohumoral, cellular, and molecular dysfunctions and leads to several organ and system dysfunction resulting in complex clinical manifestations [3]. About 12% of individuals over 80 have HF [4]. As of 2015, 8.9% of Chinese population over 35 years of age have HF [5].

Insect drugs, a type of traditional Chinese medicine (TCM), have great potential for the treatment of several cardiovascular diseases. Insect extracts are rich sources of pharmacopeias occurring naturally and have great scientific and medical value [6]. In the TCM theory system, insect drugs have the effect of activating blood circulation and removing blood stasis, which fits the TCM pathogenesis of HF.

Xinmailong injection (XML, commercialized by the Yunnan Teng Yao Pharmaceutical Co., Ltd, China) is a kind of Chinese patent medicine made by extracting effective substances from *Periplaneta americana* (a species of cockroach) with modern technology [7]. As a kind of insect drug, fresh adult *P. americana* bodies were dried and processed into powder for the treatment of disease. The *P. americana*

powder has a history of applying for thousands of years that can be traced back to the Ming Dynasty (A.D. 1578). It was recorded in the "Compendium of Materia Medica" for its therapeutic effects of promoting blood circulation, detoxification, and urination [8].

Extracts of *P. americana* have many effects, such as promoting wound healing, antitumor activity, and treating HF and gastrointestinal ulcers. Research studies obtained the chemical compounds from *P. americana*, which were polyhydric alcohols, organic acids, alkaloids [9], divinyl sulfide, noradrenaline, ketone compounds [10, 11], adenosine, inosine, protocatechuic acid, and pyroglutamate acid [12]. These extracts play a specific role in the treatment of diseases with their function of antibacterial, antiviral, and antitumor activity and enhancement of immune function [8]. XML injection as a medicine has a positive inotropic activity, improves microcirculation, dilates pulmonary vessels, induces diuresis, has antiarrhythmia function, and inhibits free radical damage [13].

XML injection has achieved beneficial curative effects in clinical studies and can improve HF patients' cardiac function [14]. However, few studies systematically evaluate the effectiveness of XML injection and the quality of researches. Therefore, we performed this systematic review of available randomized controlled trials to evaluate the efficacy of XML on the improvement of cardiac function in HF patients. Left ventricular ejection fraction (LVEF), six-minute walk test (6MWT), and brain natriuretic peptide (BNP) were three typical indicators of measuring cardiac functions and were selected as target outcomes in this review. We performed several subgroup analyses and metaregression to find out the facts that caused the heterogeneity among articles.

2. Materials and Methods

The present meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2015 statement [15, 16] and was registered on PROSPERO (CRD42020163716).

2.1. Database and Literature Search Strategies. Online literature search for relevant studies was performed using five databases, which included PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang. Studies were reviewed and selected by two experienced investigators. Relevant data were extracted by an additional two independent investigators. Any discrepancies in data extraction or literature review were resolved by consensus or by consulting a third reviewer. All relevant data from the literature review were extracted from the aforementioned databases from inception to April 2020.

The following keywords were searched in various combinations (Xinmailong OR XML OR Xin Mai Long OR XMLI OR Xinmailong Injection) AND (heart failure OR HF OR cardiac failure OR Chronic Heart Failure OR CHF) AND (randomized controlled trial OR RCT).

2.2. Inclusion Criteria. All patients from the selected studies met the internationally accepted criteria for the diagnosis of HF. Only human studies for random clinical trials (RCTs) were considered. No etiology, ethnic group, severity, or course of disease were considered as exclusion criteria. In the experiment group, XML injection plus conventional therapy was considered as a treatment strategy. On the basis of the conventional therapy of western medicine, patients in the control group had placebo or not. Measurable outcomes were LVEF, 6MWT, and BNP.

2.3. Exclusion Criteria. The exclusion criteria were (1) non-RCTs; (2) animal studies, mechanistic studies, case reports, and reviews; (3) patients with acute heart failure and severe liver and kidney disease; (4) use of other TCM formulas; (5) studies with unacceptable trail designs and inappropriate statistical methods; and (6) duplicate publications.

2.4. Data Extraction and Quality Assessment. Clinical data and adverse events were collected and cross-checked by two independent investigators. Any disagreements were resolved through discussion or by consulting a third investigator. The following data were extracted from studies: patient characteristics, details, differences in intervention between the control and experimental groups, outcome measures, and results from the items listed in the inclusion criteria. Methodological quality was assessed based on the Cochrane Handbook. The included RCTs were assessed for (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessments, (5) selective outcome reporting, (6) incomplete outcome data, and (7) other potential sources of bias [17].

2.5. Data Synthesis. Effect-size calculations and meta-analytical statistics were performed using Stata 12.0 obtained from its official website (http://www.stata.com). Weighted mean differences (WMD) with 95% CI were expressed for continuous variables and were analyzed using the inverse-variance method. Heterogeneity across the trials was evaluated using the Cochran Q test and the Higgins I2 test [18]. Only fixed-effect models were used for both dichotomous and continuous variables, unless the results of pooled analyses showed significant heterogeneity ($P < 0.10$ and $I2 > 50\%$). A random-effect model was used for significant heterogeneity. Potential publication bias was assessed by Begg's and Egger's tests [19]. A 2-tailed P value of less than 0.05 was set for statistical significance. Subgroup analyses and metaregression were performed for sensitivity analysis. Metaregression sensitivity analyses were performed using the "metareg" macro available in the Stata statistical package. Gender, average age, age section, pattern identification, duration time, course of disease, publication year, and sample size were set as the covariances of metaregression analyses.

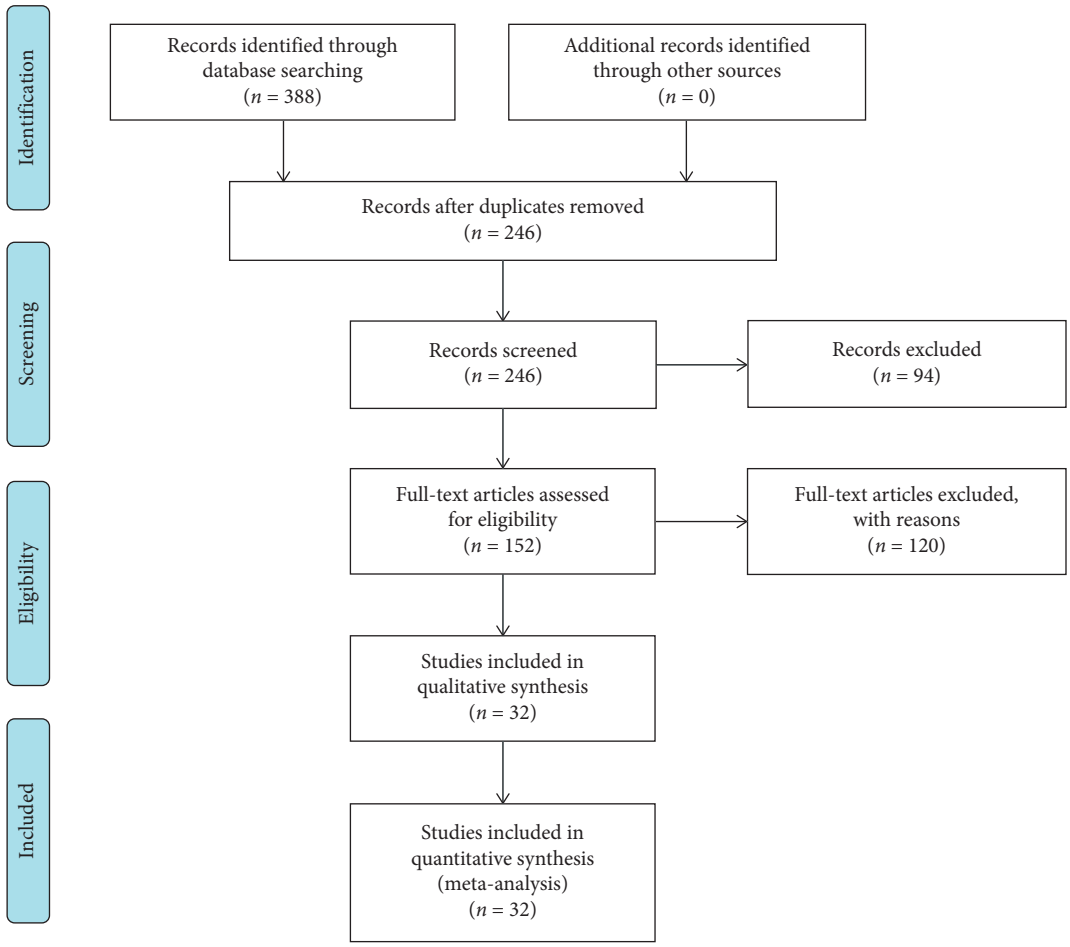

Figure 1: Flowchart depicting publication search criteria and selection.

3. Results

3.1. Description of Selected Studies. 388 potentially eligible publications were retrieved after the primary search from the eight databases. Of which 32 RCTs were included for the meta-analysis (Figure 1). Except for one selected study that was published in English, the rest studies were published in Chinese. All selected studies were conducted in China and included 3730 patients. Characteristics of the included studies are listed in Table 1.

As shown in Table 2, all 32 selected studies mentioned random sequence generation and no selective reporting bias and 9 studies mentioned allocation sequence and concealment using random number tables. Three studies cited blinding of participants and personnel, and no study mentioned blinding of outcome assessments. 4 studies reported patient attrition; among these, 2 studies reported no dropouts and 2 studies mentioned attrition rates.

3.2. Results of Outcomes

3.2.1. Left Ventricular Ejection Fraction (LVEF). Twenty-seven studies reported the LVEF level; the results showed significant increase in LVEF in HF patients with XML injection (WMD = 5.82, 95% CI: 5.52–7.13, $P < 0.00001$) (Figure 2). Subgroup analyses showed significantly higher LVEF improvement ($P = 0.006$) in HF patients of middle age (WMD = 7.7, 95% CI: 5.6–9.79) than those of youth (WMD = 4.11, 95% CI: 2.61–5.62) (Table 3). However, there was no significant difference ($P = 0.88$) between studies performing TCM pattern identification (WMD = 5.68, 95% CI: 3.83–7.53) and those not performing TCM pattern identification (WMD = 5.87, 95% CI: 4.38–7.36). There was no publication bias according to Begg's test ($P = 0.505$) and Egger's test ($P = 0.109$) (Table 4).

3.2.2. Six-Minute Walk Test (6MWT). Fifteen studies reported the 6MWT; the results showed significant increase in 6MWT in HF patients with XML injection (WMD = 51.48, 95% CI: 35.83–67.13, $P < 0.00001$) (Figure 3). Subgroup analysis indicated that XML injection has more 6MWT improvement for HF patients of middle age (WMD = 77.39, 95% CI: 58.94–95.84) than those of youth (WMD = 34.58, 95% CI: 21.26–47.89, $P < 0.0002$ for between subgroups) (Table 3), but similar increase in pattern identification (WMD = 60.6, 95% CI: −1.01 to 122.21 for pattern identification and WMD = 48.88, 95% CI: 34.52–63.24 for non-pattern identification, $P = 0.72$ for between subgroups). No

Table 1: Characteristics of the selected studies.

Study	Indication	NYHA	Sample size (E/C)	Mean age (year)	Male/female (E/C)	Course of disease (year)	Intervention	Duration (day)	Endpoints
Chen 2012 [20]	CHF	III-IV	47/53	69.3 ± 6.9	NA	5.7 ± 1.2	5 mg/kg bid	5	LVEF, BNP
Du et al. 2016 [21]	CHF	II–IV	49/49	49–79	53/45	NA	5 mg/kg bid	10	LVEF, BNP, 6MWT
Guo and Ren 2016 [22]	CHF	II–IV	52/52	E: 69 ± 8 C: 68 ± 5	E: 26/26 C: 28/24	E: 8.3 ± 6.0 C: 8.3 ± 6.1	6 ml bid	10	6MWT, LVEF, BNP
Han et al. 2012 [23]	CHF	II–IV	25/21	E: 65 ± 7 C: 68 ± 6	E: 15/10 C: 13/8	NA	5–10 mg/kg bid	14	LVEF, 6MWT
Han and Gu 2016 [24]	CHF	NA	136/147	E: 79 ± 11 C: 77 ± 12	E: 109/27 C: 122/25	NA	4 ml bid	14	LVEF, BNP
Han and Liu 2018 [25]	CHF	II–IV	56/56	E: 72.5 ± 11.4 C: 74.3 ± 12.7	E: 38/18 C: 36/20	NA	5 mg/kg bid	10	LVEF
He 2017 [26]	CHF	II–IV	47/48	E: 70.8 ± 7.6 C: 69.6 ± 7.9	E: 23/24 C: 23/25	NA	5 mg/kg bid	15	LVEF, 6MWT
Li and Li 2015 [27]	CHF	II–IV	35/30	E: 62 ± 10 C: 58 ± 8	E: 20/15 C: 18/12	NA	8 ml bid	15	LVEF
Li 2016 [28]	CHF	I–IV	24/24	E: 63.3 ± 5.8 C: 63.7 ± 5.2	E: 16/8 C: 15/9	E: 7.6 ± 6.5 C: 7.9 ± 6.3	5 mg/kg bid	14	BNP, LVEF
Li et al. 2018 [29]	HF	II-III	100/100	E: 58.9 ± 7.2 C: 58.4 ± 7.1	E: 52/48 C: 54/46	E: 3.4 ± 1.4 C: 3.4 ± 1.5	5 mg/kg bid	**5**	**BNP**
Liu HL 2018 [30]	CHF	II–IV	80/42	E: 67 ± 8 C: 68 ± 10	E: 38/42 C: 32/48	NA	5 mg/kg bid	5	LVEF, 6MWT
Liu et al. 2018 [31]	CHF	II–IV	46/46	E: 60.3 ± 4.0 C: 61.0 ± 4.3	E: 25/21 C: 27/19	E: 7.9 ± 1.4 C: 8.0 ± 1.3	4 ml bid	14	BNP, LVEF
Liu et al. 2018 [32]	CHF	II–IV	60/60	E: 62–84 C: 63–85	E: 31/29 C: 30/30	NA	5 mg/kg bid	10	BNP
Quan and Miao 2017 [33]	CHF	II–IV	46/48	E: 67.6 ± 10.5 C: 65.8 ± 11.4	E: 35/16 C: 38/13	E: 37.8 ± 7.5 C: 39.6 ± 8.6	5 mg/kg bid	10	LVEF, 6MWT
Shen et al. 2017 [34]	CHF	II–IV	58/58	E: 62.8 ± 7.1 C: 61.6 ± 7.8	E: 34/24 C: 36/22	E: 8.3 ± 7.5 C: 8.1 ± 7.8	4 ml bid	14	6MWT, LVEF
Shi et al. 2016 [35]	HF	NA	58/58	E: 56.2 ± 8.74 C: 55.6 ± 9.18	E: 28/30 C: 29/29	NA	5 mg/kg bid	5	BNP
Teng and Wang 2017 [36]	CHF	II-III	40/40	E: 75.5 ± 3.8 C: 73.4 ± 3.7	E: 22/18 C: 23/17	E: 1.7 ± 0.5 C: 1.5 ± 0.3	5 mg/kg bid	5	LVEF
Wang et al. 2012 [37]	CHF	III-IV	24/26	NA	NA	NA	10	LVEF, 6MWT, BNP	
Wu et al. 2017 [38]	HF	NA	48/42	E: 54.05 ± 3.96 C: 56.13 ± 4.87	E: 28/20 C: 31/11	E: 6.33 ± 0.94 C: 6.01 ± 0.33	5 mg/kg bid	10	BNP
Wu and Yang 2015 [39]	HF	III-IV	50/50	E: 70 ± 7.5 C: 71 ± 7.1	E: 30/20 C: 29/21	NA	5 mg/kg bid	10	BNP
Xu and Xu 2016 [40]	CHF	NA	76/76	NA	E: 50/26 C: 48/28	NA	5 mg/kg bid	14	LVEF, 6MWT
Xue et al. 2015 [41]	CHF	II-III	120/115	E: 63.1 ± 9.80 C: 63.9 ± 9.01	E: 69/46 C: 60/60	E: 2.07 C: 2.37	5 mg/kg bid	5	LVEF, 6MWT
Xue et al. 2019 [14]	CHF	II-III	50/50	E: 63.8 ± 9.46 C: 64.3 ± 7.78	E: 29/21 C: 27/23	E: 2.48 ± 2.25 C: 1.90 ± 1.65	5 mg/kg bid	16	LVEF, 6MWT, BNP
Yang et al. 2012 [42]	CHF	III-IV	57/53	E: 79 ± 10 C: 78 ± 11	E: 46/11 C: 44/9	NA	4 ml bid	14	LVEF, BNP
Yang et al. 2017 [43]	CHF	II–IV	33/33	E: 60.2 ± 5.8 C: 61.1 ± 4.5	E: 18/15 C: 19/14	E: 3.9 ± 1.2 C: 3.9 ± 1.0	5–10 mg/kg bid	**14**	LVEF
Yuan et al. 2015 [44]	CHF	I–IV	54/34	E: 51.5 ± 5.6 C: 52.3 ± 6.0	E: 30/24 C: 19/15	E: 2.5 ± 2.3 C: 2.8 ± 3.1	5 mg/kg bid	5	6MWT

Table 1: Continued.

Study	Indication	NYHA	Sample size (E/C)	Mean age (year)	Male/female (E/C)	Course of disease (year)	Intervention	Duration (day)	Endpoints
Zhao et al. 2014 [45]	CHF	II–IV	30/30	E: 41–78 C: 40–76	E: 13/17 C: 16/14	NA	5 mg/kg bid	14	LVEF, 6MWT
Zhao et al. 2010 [46]	CHF	IV	131/112	NA	NA	NA	5–10 mg/kg bid	14	LVEF, BNP
Jiang et al. 2019 [47]	HF	/	52/56	E: 63.1 ± 7.2 C: 62.7 ± 7.6	E: 29/23 C: 31/25	E: 7.87 ± 4.2 C: 7.57 ± 5.7	5 mg/kg bid	10	6MWT, LVEF
Li 2019 [48]	CHF	II–IV	200/60	E: 63.79 ± 8.82 C: 62.96 ± 9.34	E: 131/69 C: 40/20	E: 9.06 ± 2.42 C: 8.96 ± 2.25	8 ml qd	14	LVEF
Liu and Zhao 2019 [49]	CHF	I–IV	42/42	E: 57.43 ± 6.45 C: 56.55 ± 5.94	E: 25/17 C: 20/22	NA	5–10 mg/kg bid	5	LVEF
Zhang and Zhao 2019 [50]	CHF	II–IV	47/46	E: 68.85 ± 6.20 C: 69.03 ± 6.31	E: 27/20 C: 28/18	NA	5 mg/kg bid	14	LVEF

NYHA, New York Heart Association; E, experimental group; C, control group; CHF, chronic heart failure; HF, heart failure, NA, not applicable; BNP, brain natriuretic peptide; 6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction; IVST, interventricular septal thickness.

Table 2: Risk of bias.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Chen 2012 [20]	+	/	/	/	/	+	/
Du et al. 2016 [21]	+	/	/	/	/	+	/
Guo and Ren 2016 [22]	+	+	/	/	/	+	/
Han et al. 2012 [23]	+	/	/	/	/	+	/
Han and Gu 2016 [24]	+	/	/	/	/	+	/
Han and Liu 2018 [25]	+	/	/	/	/	+	/
He 2017 [26]	+	/	/	/	/	+	/
Li and Li 2015 [27]	+	/	/	/	/	+	/
Li 2016 [28]	+	+	/	/	/	+	/
Li et al. 2018 [29]	+	+	/	/	/	+	/
Liu et al. 2018 [30]	+	/	/	/	/	+	/
Liu 2018 [31]	+	/	/	/	/	+	/
Liu et al. 2018 [32]	+	/	/	/	/	+	/
Quan and Miao 2017 [33]	+	+	/	/	+	+	/
Shen et al. 2017 [34]	+	/	+	/	/	+	/
Shi et al. 2016 [35]	+	/	/	/	/	+	/

Table 2: Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Teng and Wang 2017 [36]	+	+	/	/	/	+	/
Wang et al. 2012 [37]	+	/	/	/	−	+	/
Wu et al. 2017 [38]	+	+	/	/	/	+	/
Wu and Yang 2015 [39]	+	/	/	/	/	+	/
Xu and Xu 2016 [40]	+	/	/	/	/	+	/
Xue et al. 2015 [41]	+	+	+	/	−	+	/
Xue et al. 2019 [14]	+	+	+	/	+	+	/
Yang et al. 2012 [42]	+	/	/	/	/	+	/
Yang et al. 2017 [43]	+	/	/	/	/	+	/
Yuan et al. 2015 [44]	+	/	/	/	/	+	/
Zhao et al. 2014 [45]	+	/	/	/	/	+	/
Zhao et al. 2010 [46]	+	/	/	/	/	+	/
Jiang et al. 2019 [47]	+	/	/	/	/	+	/
Li 2019 [48]	+	/	/	/	/	+	/
Liu and Zhao 2019 [49]	+	/	/	/	/	+	/
Zhang and Zhao 2019 [50]	+	+	/	/	/	+	/

+, low risk; −, high risk; /, unclear risk.

publication bias was observed in the 6MWT of HF patients ($P = 0.451$ for Begg's test and $P = 0.209$ for Egger's test) (Table 4).

3.2.3. Brain Natriuretic Peptide (BNP). Sixteen studies reported the BNP; the results showed that BNP level in the XML plus conventional therapy group was significantly higher compared to conventional therapy alone (WMD = −172.84, 95% CI: −205.79 to −139.89, $P = 0.00001$) (Figure 4). For the subgroup analysis based on age section, significantly higher BNP decrease was observed in middle-aged HF patients than young patients (WMD = −301.54, 95% CI: −405.38 to −197.71 for middle-aged and WMD = −156.7, 95% CI: −201.26 to −112.15 for youth, $P = 0.01$ for between subgroups) (Table 3). No significant difference was observed in subgroup analysis based on pattern identification (WMD = −243.87, 95% CI: −426.98 to −60.76 for pattern identification and WMD = −159.1, 95% CI: −193.3 to −124.89 for nonpattern identification, $P = 0.37$ for between subgroups). The results of Begg's test ($P = 0.137$) and Egger's test ($P = 0.014$) indicated potential publication bias in the BNP level (Table 4).

3.2.4. Metaregression Results. The results of metaregression (Table 5) suggested that the age section and average age could be two main sources that contributed to the heterogeneity of LVEF and 6MWT. Unfortunately, gender, pattern identification, duration time, course of the disease, publication year, and sample size showed no significant effect on LVEF and 6MWT, and none of these indicators listed had a statistically significant effect on the BNP level. The significant regression effect of age section (adj $R^2 = 26.75\%$, $P = 0.013$ for LVEF; adj $R^2 = 69.25\%$, $P = 0.003$ for 6MWT) met the results of subgroup analyses, which further indicated that middle-aged HF patients with XML administration could have higher LVEF and 6MWT improvement than the youth. The metaregression results based on average age (adj $R^2 = 16.54\%$, $P = 0.049$ for LVEF; adj $R^2 = 36.39\%$, $P = 0.048$ for 6MWT) suggested that greater LVEF and 6MWT improvements were associated with higher average age (Figure 5).

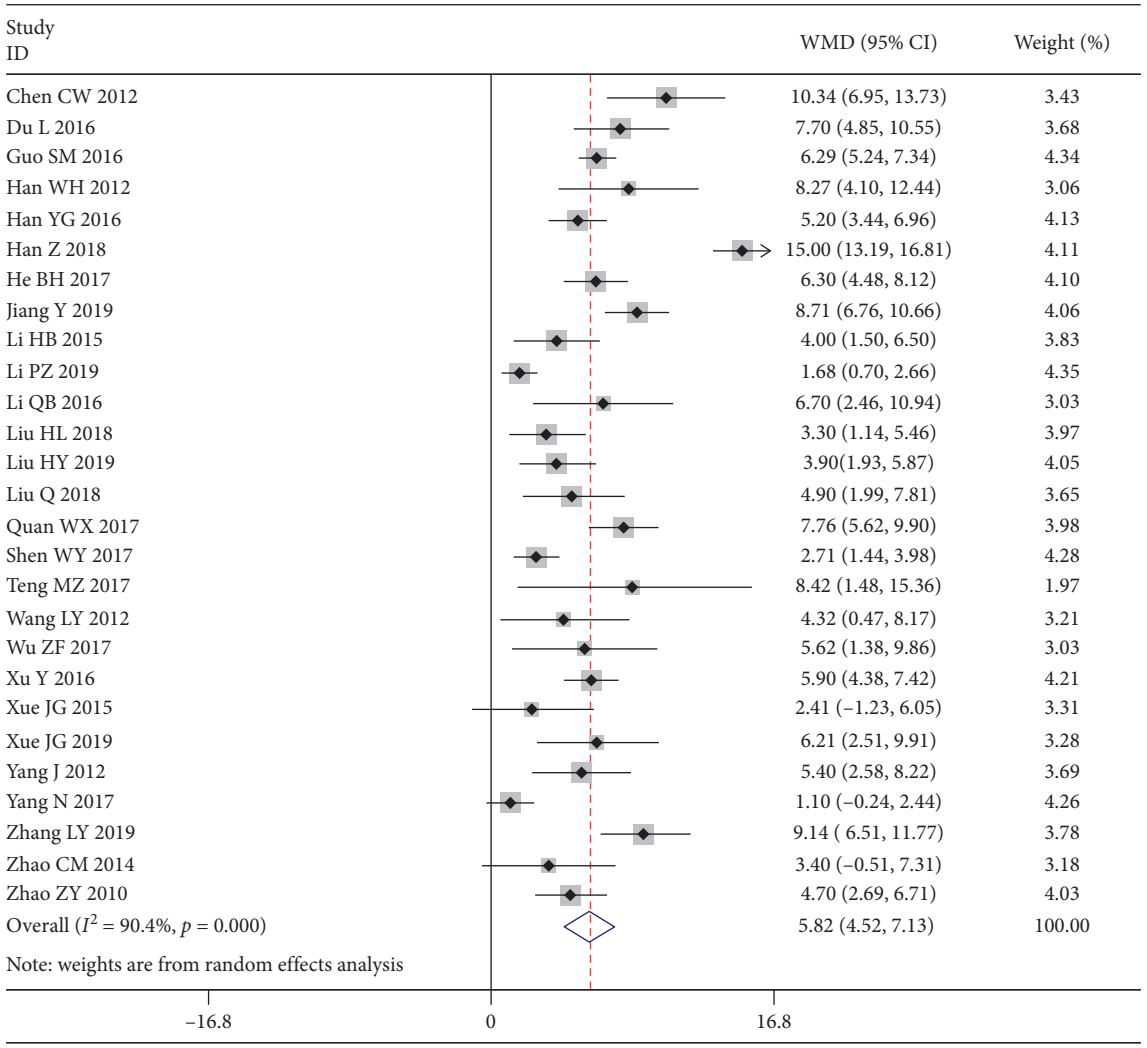

Figure 2: Forest plot of LVEF in patients administered XML plus conventional therapy versus conventional HF therapy alone.

3.2.5. Adverse Events. 16 out of the 32 studies investigated adverse events. 10 of these studies reported no obvious adverse events, while the remaining 6 studies mentioned details of adverse events. As shown in Table 6, 7 adverse events were observed between the experimental and control groups. These included cutaneous pruritus (3/0), palpitation (1/4), dizziness (2/0), headaches (0/1), nausea (2/1), leukocytosis (0/2), and hypotension (1/0). All symptoms reported were resolved during study observation, and no deaths related to XML administration were reported.

4. Discussion

4.1. Summary of Main Results. XML injection is a bioactive composite extracted from *P. americana*. The injection form can avoid people's visual aversion and improve the utilization ratio of bioavailability for its advanced extraction process. XML injection has been widely used in China for decades. Studies provided evidences to support XML as an effective administration to HF patients that XML injection can mitigate epirubicin-induced cardiotoxicity via activating the PI3K/Akt signaling pathway and inhibiting the Erk1/2 and P38 MAPK signaling pathways [51]. XML can also activate *T*-type calcium channels and inhibit Na+/*K*+-ATPase to increase intracellular calcium levels when treating HF [52]. Besides, the pharmacological research on XML has being carried out continuously and many components and functions of XML are being explored [12]. Despite its treatment effects on HF, it can also repair damaged skin and treat gastric ulcers [8].

This systematic review provided evidence that additional XML injection treatment demonstrates better therapeutic effects than conventional treatment on improving cardiac function in patients with HF evidenced by the increase in LVEF and 6MWT and reduction in BNP. Subgroup analyses provided evidence that the age section is a source of causing significant differences between groups. Under XML injection administration, the cardiac function of middle-aged patients showed better improvement than young patients (average > 65 as middle aged, average < 65 as youth). Further metaregression demonstrated that age section and average age showed significant heterogeneity in LVEF and 6MWT and

Table 3: Mean difference of cardiac function of HF patients with XML injection administration in different subgroup analyses.

	LVEF				6MWT				BNP			
	N	WMD (95% CI)	I^2 (%)	P value for between-group difference	N	WMD (95% CI)	I^2 (%)	P value for between-group difference	N	WMD (95% CI)	I^2 (%)	P value for between-group difference
Overall	27	5.82 (4.52, 7.13)	90		15	51.48 (35.83, 67.13)	88		16	−172.84 (−205.79, −139.89)	94	
Subgroups												
Age section				0.006				0.0002				0.01
Youth	11	4.11 (2.61, 5.62)	83		6	34.58 (21.26, 47.89)	61		5	−156.70 (−201.26, −112.15)	88	
Middle age	11	7.70 (5.60, 9.79)	90		5	77.39 (58.94, 95.84)	77		6	−301.54 (−405.38, −197.71)	97	
Pattern identification				0.88				0.72				0.37
Yes	4	5.68 (3.83, 7.53)	33		3	60.60 (−1.01, 122.21)	87		3	−243.87 (−426.98, −60.76)	97	
No	23	5.87 (4.38, 7.36)	90		12	48.88 (34.52, 63.24)	84		13	−159.10 (−193.30, −124.89)	94	

LVEF, left ventricular ejection fraction; 6MWT, six-minute walk test; BNP, brain natriuretic peptide; WMD, weighted mean difference; CI, confidence interval.

Table 4: Publication bias.

	Number of studies	Begg's P value	Egger's P value
LVEF	27	0.505	0.109
6MWT	12	0.451	0.209
BNP	16	0.137	0.014

LVEF, left ventricular ejection fraction; 6MWT, six-minute walk test; BNP, brain natriuretic peptide.

greater improvement of LVEF and 6MWT was connected to a higher age. The above evidences lead to the conclusion that XML injection may be more suitable for middle-aged patients and its efficiency increases by age, while it has a considerable improvement in HF patients of all age ranges.

The pattern identification presented no potential heterogeneity in both subgroup analysis and metaregression, indicating XML injection, as a single-substance extract, has fixed therapeutic efficacy on HF without pattern identification, unlike other Chinese patent drugs that focus on TCM syndromes. Unfortunately, the rest covariances (gender, duration time, course of disease, publication year, and sample size) may contribute no significance to the heterogeneity.

4.2. Adverse Events. No obvious adverse reactions of Xinmailong injection were found before marketing. With the expansion of users after marketing, many adverse reactions have been reported gradually. In previous reviews, the incidence of adverse reactions was 7.6% [53]. The most common symptoms are pruritus, slight blood pressure rise, nausea, and vomiting. In this review, adverse effects of XML injection were also collected from included studies, of which 2 studies mentioned skin itching [14, 36], each study mentioned hypertension [37] and nausea [36]. Other studies also described palpitation, dizziness, headache, and leukocytosis of HF patients during XML administration. There is no case of liver and kidney function damage in the clinical study of Xinmailong. On the contrary, there is a protective effect of XML injection on the early renal function damage caused by grass carp bile [54] and extracts of *P. americana* have a protective effect on liver damage, liver fibrosis, and hepatitis [55]. Although all the adverse reactions mentioned above can be relieved by rest or slowing down the intravenous drip, no lethal events or major adverse cardiovascular events were observed. XML seemed to be generally safe for HF treatment, but the evidence is still insufficient to make a decisive conclusion on safety. Attentions are still needed in practical application, as the safety of TCM herbal injections has been increasingly concerned by both medical workers and the public.

4.3. Limitations. Study limitations in this review were mostly due to the risk of bias [56] of included studies. Many studies have no description of the necessary process of clinical trials, and therefore the evaluation of these studies

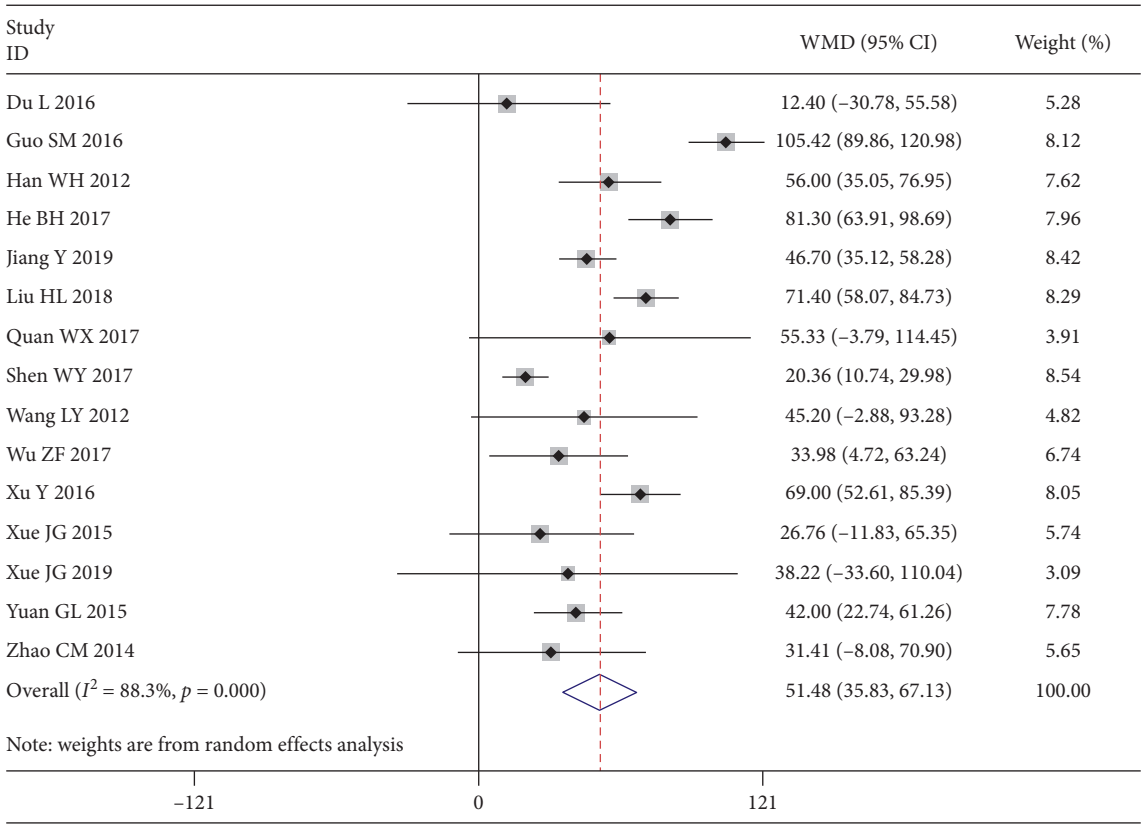

Figure 3: Forest plot of 6MWT in patients administered XML plus conventional therapy versus conventional HF therapy alone.

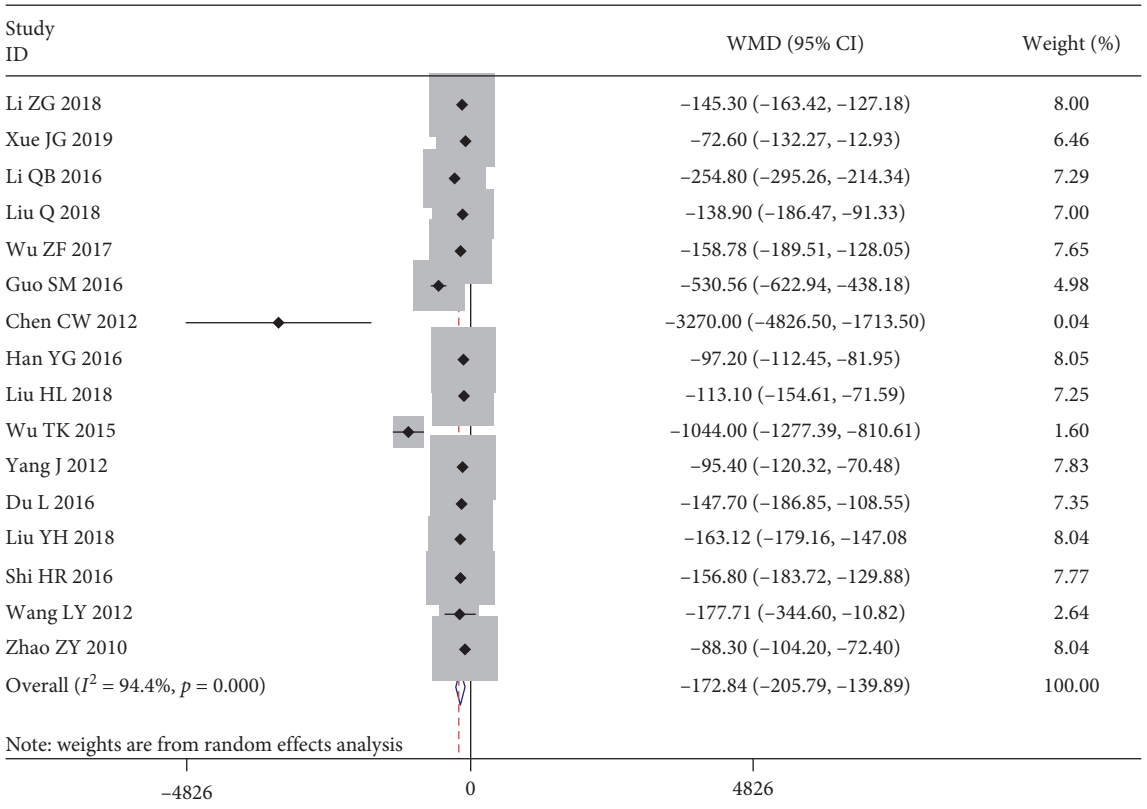

Figure 4: Forest plot of BNP level in patients administered XML plus conventional therapy versus conventional HF therapy alone.

Table 5: Metaregression analysis of association between covariates and cardiac function of HF patients with XML injection administration.

	LVEF					6MWT					BNP				
	N	P value	Tau^2	I^2 (%)	Adj R^2 (%)	N	P value	Tau^2	I^2 (%)	Adj R^2 (%)	N	P value	Tau^2	I^2 (%)	Adj R^2 (%)
Gender	22	0.727	9.304	92.03	−4.89	12	0.447	656.7	88.15	−0.47	12	0.573	61293	93.91	−8.69
Age section	22	0.013	7.121	87.36	26.75	11	0.003	192.5	70.52	69.25	11	0.340	98464	95.34	−3.05
Average age	22	0.049	8.114	89.25	16.54	11	0.048	398.2	86.05	36.39	11	0.737	117450	95.15	−22.93
Pattern identification	27	0.890	8.442	90.55	−3.97	15	0.300	508	84.71	8.82	16	0.924	53996	94.60	−12.45
Duration time	27	0.436	8.202	89.67	−1.02	16	0.836	558.2	87.91	−8.62	16	0.549	54559	93.98	−13.62
Course of disease	13	0.421	7.450	89.28	−1.03	8	0.686	812	92.87	−7.69	7	0.456	20608	93.53	27.79
Publication year	27	0.884	8.464	90.61	−4.24	15	0.805	603.6	89.07	−8.36	16	0.683	55437	93.69	−15.45
Sample size	27	0.255	8.014	89.78	1.31	15	0.865	600.2	89.11	−7.75	16	0.484	49753	92.83	−3.62

LVEF, left ventricular ejection fraction; 6MWT, six-minute walk test; BNP, brain natriuretic peptide.

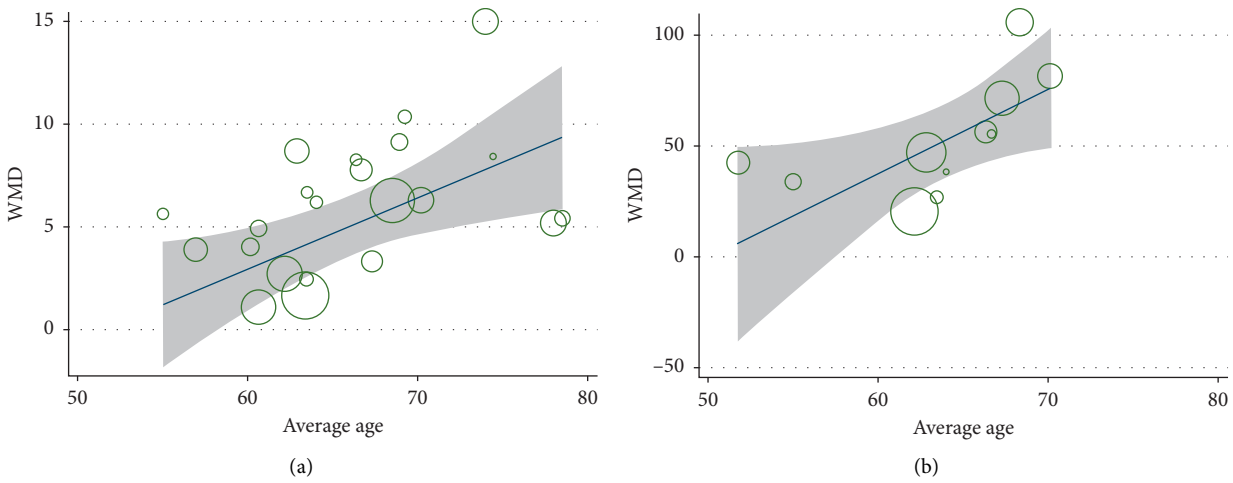

Figure 5: Metaregression bubble plot of correlation between WMD of (a) LVEF and (b) 6MWT and average age.

Table 6: Incidence rates for adverse events.

Items	No. of studies	No. of adverse events		References
		XML	Control	
Cutaneous pruritus	2	3	0	Xue et al. 2019 [14], Teng and Wang 2017 [36]
Palpitation	2	1	4	Han and Liu 2018 [25], Du et al. 2016 [21]
Dizziness	2	2	0	Du et al. 2016 [21], Zhao et al. 2010 [46]
Headache	1	0	1	Zhao et al. 2010 [46]
Nausea	1	2	1	Teng and Wang 2017 [36]
Leukocytosis	1	0	2	Xue et al. 2019 [14]
Hypotension	1	1	0	Wang et al. 2012 [37]

related to unclear risk of bias. Besides, current research studies focus on the total effect of XML injection, while paying less attention to comprehensive assessment based on basic data collection of different types of patients, which brought difficulty to follow up subgroup analyses and metaregression analysis. Studies in the future could be designed with an emphasis on confirmation and further exploration of age grouping, as average age had been explored to be a source of heterogeneity.

Concerning data extraction, the included trials used different diagnostic and measurement criteria for HF patients. These different measurement criteria and the use of different instruments affect study comparisons and hence the meta-analysis. Treatment based on pattern identification is a key characteristic of TCM [57]. Application of Chinese patent medicines without the implementation of TCM pattern identification could be a matter of heterogeneity and subsequently reduce the reliability of meta-analysis results. Subgroup analyses in this review, unfortunately, found no heterogeneity based on pattern identification. Further studies are needed for conducting patient selection in which pattern identification is classified.

The results of Begg's and Egger's tests demonstrated no significant asymmetry and suggested no potential

publication bias in this review [58]. Future clinical studies investigating XML treatment for HF should be designed with appropriate controls and better study designs using large patient cohorts, multicenter and prospective. Heterogeneity within the study should be addressed and include appropriate subgroup classification.

5. Conclusion

This review demonstrated that combinational use of XML and conventional treatment may demonstrate better therapeutic effects on improving cardiac function in patients with HF, and age is a potential factor of higher efficacy. Study limitations included the low quality of the selected trials. Additional large, multicenter, prospective clinical trials are warranted to validate our findings.

Data Availability

The data used to support this systematic review are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Wang XL, Ruan XF, and Sun YL proposed the meta-analysis and designed the study. Qiang TT, Li YP, and Ruan XF performed publication review. Li YP, Sun YL, and Wang XL performed data extraction and analysis. Sun YL wrote the manuscript.

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