



# Clinical Efficacy and Safety of Xinmailong Injection for the Treatment of Chronic Heart Failure: A Meta-Analysis

Xiaohua Lu<sup>1,2</sup>, Lu Zhang<sup>1,2</sup>, Jiabo Wang<sup>3</sup>, Honghong Liu<sup>4</sup>, Haotian Li<sup>1</sup>, Houqin Zhou<sup>1,2</sup>, Rongrong Wu<sup>1</sup>, Yuxue Yang<sup>1,2</sup>, Jianxia Wen<sup>1,2</sup>, Shizhang Wei<sup>1</sup>, Xuelin Zhou<sup>1</sup>, Yanling Zhao<sup>1\*</sup> and Xiaohe Xiao<sup>3\*</sup>

<sup>1</sup> Department of Pharmacy, 302 Military Hospital of China, Beijing, China, <sup>2</sup> Pharmacy College, Chengdu University of Traditional Chinese Medicine, Chengdu, China, <sup>3</sup> China Military Institute of Chinese Medicine, 302 Military Hospital of China, Beijing, China, <sup>4</sup> International Center for Liver Disease Treatment, 302 Military Hospital of China, Beijing, China

#### **OPEN ACCESS**

#### Edited by:

Aiping Lu, Hong Kong Baptist University, Hong Kong

#### Reviewed by:

Jianxin Chen, Beijing University of Chinese Medicine, China Dezso Csupor, University of Szeged, Hungary

#### \*Correspondence:

Yanling Zhao zhaoyl2855@126.com; Xiaohe Xiao xiaoxiaohe302@126.com

#### Specialty section:

This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

> **Received:** 04 April 2018 **Accepted:** 05 July 2018 **Published:** 27 July 2018

#### Citation:

Lu X, Zhang L, Wang J, Liu H, Li H, Zhou H, Wu R, Yang Y, Wen J, Wei S, Zhou X, Zhao Y and Xiao X (2018) Clinical Efficacy and Safety of Xinmailong Injection for the Treatment of Chronic Heart Failure: A Meta-Analysis. Front. Pharmacol. 9:810. doi: 10.3389/fphar.2018.00810 **Background:** Chronic heart failure (CHF) is one of the most stubborn cardiovascular disease. Xinmailong (XML), a bioactive fraction extracted from *Periplaneta americana* L., has been commonly used for CHF treatment in China. However, there is few comprehensive evaluation for the clinical efficacy and safety of XML for CHF.

**Objectives:** We aimed to evaluate the beneficial and adverse effects of Xinmailong Injection (XMLI) on CHF treatment with the use of meta-analysis.

**Methods:** In accordance with the Cochrane Handbook and transparent reporting of systematic reviews and meta-analysis protocol (CRD42018087091), seven English and Chinese electronic databases, including PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang database, VIP medicine information system and China Biomedical Literature Database (CBM), were searched to retrieve potential randomized controlled trials (RCTs) before November 2017. The eligible trials were evaluated for methodological quality. The main outcome measures were analyzed with RevMan 5.3 software.

**Results:** 26 RCTs involving 3447 participants were subjected to meta-analysis. The total effective rate was improved by XMLI plus conventional therapy (OR 3.10, 95% CI 2.47–3.90, P < 0.00001). When compared to the conventional treatment alone, the combination of XMLI and conventional treatment increased left ventricular ejection fraction (LVEF, MD 4.93, 95% CI 3.96–5.89, P < 0.00001) and 6-min walking distance (6-MWD, MD 46.76, 95% CI 32.51 to 61.01, P < 0.00001), and decreased left ventricular end-diastolic diameter (LVEDD, MD –4.73, 95% CI–5.64 to–3.83, P < 0.00001), serum brain natriuretic peptide (BNP, MD –149.59, 95% CI –211.31 to –87.88, P < 0.00001) and N-terminal pro-brain natriuretic peptide (NT-proBNP, MD –322.35, 95% CI –517.87 to –126.83, P = 0.001). However, the frequency and severity of adverse effects was similar between these two different medications. Poor methodological quality and the limitations also existed in this study.

1

**Conclusions:** The combinational use of XMLI on conventional treatment may exert better therapeutic effects on improving cardiac function in CHF patients, indicating that XMLI was suggested to be considered during the conventional treatment of CHF. High-quality and large scale RCTs are still required to confirm the impacts of XMLI.

Keywords: Periplaneta americana L., Xinmailong Injection, chronic heart failure, clinical efficacy and safety, meta-analysis

## INTRODUCTION

Chronic heart failure (CHF) has become one of the most prevalent cardiovascular disease, affecting about 26 million people worldwide (Ambrosy et al., 2014). It is the leading cause of death in China with a growing number of aging population (Qiu and Wang, 2017). About 0.9% of Chinese population (around 13 billion) are suffering from this disease (Fu et al., 2011). High health care utilization and poor prognosis remain challenging features of this complicated and multifaceted syndrome (Page, 2015).

Although the pathogenesis of CHF has not been fully clarified, it is widely acknowledged that CHF is caused by a structural and/or functional cardiac abnormality, leading to reduced, mid-range and preserved ejection fraction based on left ventricular ejection fraction (LVEF) (Butler, 2012; Ponikowski et al., 2016). The patients with hypertension, coronary heart disease, hyperlipemia, diabetes, and/or myocardial infarction face high risks of HF (Huang, 2015).

The treatment strategies for patients with CHF are complex due to the different pathogenesis and complications. All symptomatic patients with heart failure are recommended with different treatments as follows: (1) Angiotensinconverting enzyme inhibitors (ACEIs); (2) Beta-blockers; Mineralocorticoid/aldosterone receptor antagonists (3) (MRAs). Diuretics, angiotensin receptor neprilysin inhibitor, If-channel inhibitor, angiotensin II type I receptor blockers (ARBs), hydralazine and isosorbide dinitrate, digoxin, n-3 polyunsaturated fatty acids (n-3 PUFAs) are also used to treat patients with CHF based on individual signs and symptoms (Yancy et al., 2013; Ponikowski et al., 2016). However, the above treatments for CHF are not satisfying in terms of low clinical efficacy and safety.

Cumulative research on CHF treatments has reported the combination use of western medicine and traditional Chinese medicines (TCMs) such as Shenmai injection, Wenxin keli, Xinmailong (Fu et al., 2010; Ma et al., 2013; Shi L. et al., 2015; Wang et al., 2016), which displayed better clinical efficacy and lower incidence of side effects. Therefore, it is valuable to take TCMs into account for CHF treatment.

Xinmailong injection (XMLI) is a bioactive fraction extracted from *Periplaneta americana* L. (a species of cockroach) (2016). XMLI has polyhydric alcohols, organic acids, alkaloids and other micro constituents, with complex nucleobases and binding amino acids, including inosine, adenosine, pyroglutamic acid and saccharine, as the active constitutes (Jiao et al., 2011, 2012). XMLI combined with western medicine can treat CHF, ischemic cardiomyopathy and coronary heart failure (Wu and HH, 2015; Yang X. Q. et al., 2015). In 2006, XMLI was approved by the China State Food and Drug administration (CFDA) for CHF treatment. However, there is little comprehensive evaluation for the clinical efficacy and safety of XMLI for CHF. Therefore, this meta-analysis aimed to systematically evaluate the therapeutic effect and safety of XMLI in combination with conventional therapy for CHF treatment when compared with conventional therapy alone.

## MATERIALS AND METHODS

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines and Cochrane Handbook, and has been registered in Preferred Reporting Items for International Prospective Register of Systematic Reviews (PROSPERO, CRD42018087091).

#### **Database and Search Strategies**

Seven major electronic databases, including PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang database, VIP medicine information system and China Biomedical Literature Database (CBM), were searched to retrieve potential reports by three investigators (Xiaohua Lu, Lu Zhang and Houqin Zhou) independently, with the last search conducted on November 2017.

The initial search items were used as follows: "Xinmailong Injection" [Title/Abstract] or "Xinmailong" [Title/Abstract] and "heart failure" [Title/Abstract] or "chronic heart failure" [Title/Abstract] and "randomized controlled trial" [Title/Abstract].

#### **Inclusion Criteria**

Three investigators (Xiaohua Lu, Lu Zhang, and Houqin Zhou) worked independently and complied with the PICOS: (1) the "P" for patients diagnosed as CHF based on "2014 Guidelines for the Diagnosis and Treatment of Heart Failure in China" or "2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China" or "American College of Cardiology/American Heart Association (ACC/AHA) guidelines 2009" or "Treatment of chronic systolic heart failure 2002" or "Internal Medicine 2008" or "Diagnosis and treatment of cardiomyopathy 2007" or "2007 Guidelines for the Diagnosis and Treatment of chronic stable angina pectoris in China" or "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure"; (2) the "I" for interventions with the combination use of XMLI

and conventional therapy (Experimental Group); (3) the "C" for comparison of the conventional therapy alone (Control Group); (4) "O" for outcome measures, including the total effective rate, left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-Pro BNP), left ventricular end-diastolic dimension (LVEDD) and 6-min walking distance (6 MWD) as well as adverse effect. In addition, the type of studies was randomized controlled trials (RCTs).

Those subjects who underwent the significant relief of clinical symptoms and signs of CHF and experienced 2-level of improvement in cardiac function were defined as "remarkable effect" according to New York Heart Association (NYHA) grading. Likewise, those subjects who underwent the relief of clinical symptoms and signs of CHF and experienced 1-level of improvement in cardiac function were considered to be "valid," otherwise "invalid." The number of remarkable effect and valid cases together was the total effective rate.

#### **Exclusion Criteria**

Three investigators (Xiaohua Lu, Lu Zhang, and Houqin Zhou) worked independently using the following exclusion criteria: (1) animal studies or non-randomized controlled clinical trials; (2) publications with incomplete data or the data from an identical clinical trial; (3) unavailable or incorrect or no relevant data for meta-analysis; (4) patients with acute heart failure, ischemic cardiomyopathy, pulmonary heart disease, severe liver, and kidney diseases; (5) any other TCM or therapies in experimental or control group during the treatment.

## **Data Extraction**

Three investigators (Xiaohua Lu, Lu Zhang, and Houqin Zhou) independently conducted literature screening and data extraction according to the same inclusion and exclusion criteria. The extracted data included study title, author, year of publication, sample size, diagnosis standard, methodological information, treatment process, interventions, outcome measurements, NYHA classification, and adverse effects. Disagreements were resolved by discussion through the third party (Yuxue Yang) and a consensus was reached finally.

## **Quality Assessment**

Based on Cochrane Handbook for Systematic Review of Interventions, the methodological quality of the included trials was assessed to address the following seven criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessments (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The risk of bias was categorized as low, unclear, or high. Trials were categorized as low risk of bias when they met all the criteria, whereas those that met none were classified as high risk of bias. Others were unclear risk of bias if there was insufficient information to make a judgment. Any disagreement was settled by discussion with the third author (Yuxue Yang).

#### **Data Analysis**

RevMan 5.3 software (http://tech.cochrane.org/revman/ download) from the Cochrane Collaboration was utilized to perform the meta-analysis. Dichotomous data were expressed as the Odds ratio (OR) with 95% confidence intervals (95% CI), whereas continuous variables were expressed as mean difference (MD) with 95% confidence intervals (95% CI). Pooled analyses were calculated using fixed-effect models if  $P \ge 0.10$  and  $I^2 \le 50\%$ , indicating low heterogeneity; whereas a random-effect model was applied in case of significant heterogeneity (P < 0.10and  $I^2 > 50\%$ ).

# RESULTS

## **Description of the Included Trials**

One thousand two hundred and thirty-two articles were potentially retrieved after the primary search from the seven Chinese and English databases. Eight hundred and twenty-five articles were excluded because of duplicate collections. Two hundred and ninety-one publications were further excluded because they were non-clinical studies. Ninety articles were excluded due to the following reasons: not RCTs or not real RCTs, without confirmed diagnostic criteria, control group or treatment group not meet the demand. Finally, 26 RCTs, published from 2010 to 2017, were included as shown in Figure 1 (Zhao et al., 2010; Yang et al., 2012, 2014; Huang et al., 2013; Lu et al., 2013, 2015; Peng et al., 2014; Li and Li, 2015; Shi H. R. et al., 2015; Wu, 2015; Xue et al., 2015; Yang M. et al., 2015; Yuan et al., 2015; Zhang, 2015; Guo and Ren, 2016; Han and Guo, 2016; Li et al., 2016; Xu and Xu, 2016; Fan et al., 2017; Quan and Miu, 2017; Qu et al., 2017; Shen et al., 2017; Si, 2017; Wang, 2017; Ye et al., 2017; Yu et al., 2017).

All these trials were conducted in China and published in Chinese. A total of 3,447 participants (1,781 cases in the experimental group, and 1,666 cases in the control group) were included in these 26 eligible trials. Participants were divided into experimental (XMLI in combination with conventional therapy) and control group (conventional therapy) with no significant difference between these two groups in general information (**Table 1**). All the XMLI were from Yunnan Teng yao Pharmaceutical Co., Ltd.

# **Methodological Quality**

As shown in **Figure 2**, among these 26 included articles, 6 trials reported that the methodology was used to generate the allocation sequence, as well as 5 trials for completely random number table (Guo and Ren, 2016; Quan and Miu, 2017; Si, 2017; Wang, 2017; Ye et al., 2017) and 1 trial for randomized complete block design (Xue et al., 2015); While the rest mentioned random sequence generation without specific random method. All these involved trials did not mention the allocation concealment. Two studies mentioned blinding of participants and personnel and outcome assessment (Xue et al., 2015; Shen et al., 2017). One study was published with a high risk with incomplete outcome (Xue et al., 2015). All included trials were published with low risk of selective reporting and without clear statement of other bias.



# **Effects of the Interventions**

#### The Total Effective Rate

A total number of 19 studies involving 2,649 participates assessed the clinical improvement based on the total effective rate (Yang et al., 2012; Huang et al., 2013; Li and Li, 2015; Lu et al., 2015; Wu, 2015; Xue et al., 2015; Yang M. et al., 2015; Yuan et al., 2015; Zhang, 2015; Guo and Ren, 2016; Han and Guo, 2016; Li et al., 2016; Xu and Xu, 2016; Quan and Miu, 2017; Qu et al., 2017; Shen et al., 2017; Si, 2017; Ye et al., 2017; Yu et al., 2017). The fixed-effect model was performed because of low heterogeneity (P = 0.89,  $I^2 = 0\%$ ). As shown in **Figure 3**, XMLI in combination with conventional therapy had improved the total effective rate in patients with CHF vs. conventional therapy alone (OR 3.10, 95% CI 2.47 to 3.90, P < 0.00001). This indicated that XMLI could significantly increase the clinical efficacy of conventional therapy for CHF.

# Left Ventricular Ejection Fraction (LVEF)

Twenty-two trials in total involving 3,092 patients with CHF assessed the effect of XMLI plus conventional therapy vs. conventional therapy alone in boosting LVEF (Zhao et al., 2010; Yang et al., 2012; Huang et al., 2013; Peng et al., 2014; Li and Li, 2015; Lu et al., 2015; Shi H. R. et al., 2015; Xue et al., 2015; Yang M. et al., 2015; Zhang, 2015; Guo and Ren, 2016; Han and Guo, 2016; Li et al., 2016; Xu and Xu, 2016; Fan et al., 2017; Quan and Miu, 2017; Qu et al., 2017; Shen et al., 2017; Si, 2017; Wang, 2017; Ye et al., 2017; Yu et al., 2017). Random effect model was conducted due to substantial heterogeneity among these trials ( $I^2 = 86\%$ , P < 0.00001). The result of this metaanalysis showed that LVEF value in the experimental group was significantly higher than that of control group (MD 4.93, 95% CI 3.96 to 5.89, P < 0.00001), which indicated that XMLI could improve LVEF when compared those in the conventional therapy for CHF (Figure 4).

Shirl, R, et al., 2015CHD2014 Galdelines for the Diagnosis and Theament of Heart Falure in DinaM86/58E56.20 + 87.4E2020Lue tal., 2015CHF2007 Guidelines for the Diagnosis and Theament of Heart Falure in ContraM80.56E56.1 ± 5.9E20173Lue tal., 2015CHF2007 Guidelines for the Diagnosis and Theament of Chronic Heart and Theament of Chronic Heart Peng et al., 2014M80.56E56.1 ± 5.9E2073Han and Guo, 2016CHF2007 Guidelines for the Diagnosis and Theament of Chronic Heart Falure in ChinaM80.56E61.2 ± 5.9E2073Han and Guo, 2016CHF2007 Guidelines for the Diagnosis and Theament of Chronic HeartII2025E68.4 ± 1E7024E7024Yang et al., 2014CHFZHFZHM2007 Guidelines for the DiagnosisII80.56E73 ± 12E10927Yang et al., 2014CHFZHMHeart Falure OCII80.56E73 ± 12E10275Yang et al., 2014CHFZHMSHM81.42075E68.4 ± 1E775 ± 6.2E33716Yang et al., 2014CHFZHMSHMST/55E734 ± 10E7471E4471Yang et al., 2015CHFAmerican College of Cardology/III118/1202E7324 ± 0E73275Yang et al., 2015CHFAmerican College of Cardology/III118/1202E7324 ± 0E7475Yue et al., 2015CHFAmerican College of Cardology/III118/1202E653 ± 10E7	(E/C) (Year) Fe	Female disease (E/C) (Year)		(day)
OIS         OHD         2014 Guidelines for the Diagnosis of Treatment of Theatr Failure in Onlina         NA         58/56         E-56.6.0.4.8.1/k         E-28/30           OHF         2007 Guidelines for the Diagnosis of Treatment of Chronic Heart         NA         36/36         E-61.2.4.5.9         E-23/13           I6         CHF         2007 Guidelines for the Diagnosis Failure in Chronic Heart         NA         36/36         E-61.2.4.5.9         E-23/13           I6         CHF         2007 Guidelines for the Diagnosis Failure in Chronic Systolic         NA         147/136         E-61.2.4.5.9         E-23/13           I6         CHF         2007 Guidelines for the Diagnosis Failure in Chronic Systolic         NA         147/136         E-73/14         E-109/27           I6         CHF         American Heart Association         NA         147/136         E-73/14         E-109/27           I6         CHF         Panetican Heart Association         NA         147/136         E-73/14         E-109/27           I6         CHF         Teatment of Chronic Systolic         I1         2-75/2.4         E-33/16         E-33/16           I6         Heart Failure 2002         I1         13/1/12         E-73/24         E-33/16         E-33/16           I6         Heart Failure 2002			Experimental Group	
CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Fature in Chrian         NA         6/5/36         E6/12 ± 5.5         E2/37/3           16         CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Fature in Chrian         IIV         2/5/2         E/69 ± 45         E/2/3/3         E/2/3/3           16         CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart         IIV         5/5/5         E/69 ± 45         C/2/2/3           16         CHF         American Heart Association increatment of Chronic Heart         IIV         5/5/5         E/7/1 ± 12         C/2/2/2           17         Teatment of Chronic Heart         IIV         5/5/5         C/7/3 ± 12         C/2/2/2           18         American Heart Association in CC/AHAJ guidelines 2003         III         4/4/3         C/7/3 ± 12         C/2/2/2           17         American Heart Association in CC/AHAJ guidelines 2003         III         4/4/3         C/7/2 ± 26         C/3/2/3           17         American Heart Association in CC/AHAJ guidelines 2003         III         1/1/120         E/7/3 ± 10         E/7/3           18         American Heart Association in CC/AHAJ guidelines 2003         III         1/1/120         E/7/3 ± 10         E/7/3           17         American He	E:56.20 ± 8.74 C:55.6 ± 9.18	28/30 NA 29/29	XML 5 mg/kg bid+ Control	5 BNP, LVEF, TC, TG, HDL-C, LDL-C, UA, blood glucose, hsCRP, VEGF
16       CHF       2007 Guidelines for the Dlagnosis and Treatment of Chronic Heart Failure in China       IIIV       52/52       E:69 ± 6       C:2824         16       CHF       American Tolinga       Cini (1+1)       C:09/27       C:09/27         16       CHF       American Tolinga       Cini (1+1)       C:07/2 ± 12       C:09/27         17       Treatment of chronic systolic       IIIV       56/56       E:771 ± 2.6       C:30/26         18       ColorAH3 guidelines for the Dlagnosis       IIII       49/43       E:771 ± 2.6       E:37/15         18       CHF       Z007 Guidelines for the Dlagnosis       IIII       49/43       E:771 ± 2.6       E:37/15         19       CHF       Z007 Guidelines for the Dlagnosis       IIII       49/43       E:771 ± 2.6       E:37/15         10       CHF       Z007 Guidelines 2003       IIII       49/43       E:77/5 ± 6.2       E:39/45         11       TAmerican College of Cardology/       III       118/120       C:76±4.5       C:31/12         11       American Heart Association       M       Z/5/53       E:69/46       C:31/12         11       American College of Cardology/       III       III       25/25       C:31/12       C:48/71	E:61.2 ± 5.9 C:62.3 ± 5.5	23/13 NA 24/12	XML 5 mg/kg bid+ Control	5 the total effective rate, BNP, LVEF, 6-WMD, adverse effect
16         CHF         American College of Carciology/ American Heart Association         NA         147/136         E79 ± 11         E.109/27           CHF         American Heart Association         No         56/56         E77 ± 12         C:12226           American Heart Association         II         56/56         E77 ± 12         C:12226           CHF         Treatment of chronic systolic         II         49/43         E:77 ± 62         E:3076           CHF         American College of Carciology/ American Heart Association         II         8/43         E:77 ± 62         E:31/12         C:12226           CHF         American College of Carciology/ American Heart Association         II         8/43         E:77 ± 62         E:31/12           CHF         American College of Carciology/ American Heart Association         II         8/43         E:77 ± 62         E:31/12           CHF         American College of Carciology/ American Heart Association         II         18/120         E:63/14 ± 9.80         E:69/46           CHF         American Heart Association         II         18/120         E:63/14 ± 9.80         E:69/46           CHF         American Heart Association         II         II         18/1120         E:69/46         E:69/46         E:69/46	E:69 ±8 C:68 ± 5	27/25 E:8.3±6.0 28/24 C:8.3±6.1	XMLI 6 mL bid+ Control	10 the total effective rate, BNP, LVEF, LVEDD, 6-WMD, adverse effect
CHF         Treatment of chronic systolic heart failure 2002         IIV         56/56         E:71:1±2.8         E:32/26           CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China         III         49/43         E:77:5±6.5         E:33/16           CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China         III         49/43         E:77:5±6.5         E:33/16           CHF         American College of Carciology/ American Heart Association (ACC/AHA) guidelines 2009         III         118/120         E:77:5±6.5         E:33/16           CHF         American Heart Association American Heart Association (ACC/AHA) guidelines 2009         III         118/120         E:65:1±9.80         E:69/46           CHF         American Heart Association (ACC/AHA) guidelines 2009         III         25/25         E:65:1±9.80         E:69/46           CHF         American Heart Association (ACC/AHA) guidelines 2009         III         25/25         E:65:1±9.80         E:07/61           CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China         III         36/53         E:65:4±5.5         E:16/10           CHF         2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China         III         36/53         E:65:4±5.5         E:16/12	E:79 ± 11 C:77 ± 12	109/27 NA 122/25	XMLI 4 mL bid+ Control	14 the total effective rate, BNP, LVEF
CHF       2007 Guidelines for the Diagnosis       III       49/43       E:775±6.2       E:33/16         Failure in China       Treatment of Chronic Heart       E       C:75.2 ± 6.5       C:31/12         Failure in China       American Heart Association       III       118/120       E:79±10       E:44/9         American Heart Association       American Heart Association       III       118/120       E:653.1±9.80       E:69/46         American Heart Association       American Heart Association       III       118/120       E:653.1±9.80       E:69/46         American Heart Association       American Heart Association       III       118/120       E:63.1±9.80       E:69/46         American Heart Association       American Heart Association       III       118/120       E:63.1±9.80       E:69/46         American Heart Association       III       118/120       E:65±4.5       E:15/10       E:06/60         American Heart Association       American Heart Association       III       III       E:65±4.5       E:16/10         CHF       2007 Guidelines for the Diagnosis       III       S:9/58       E:65±4.5       E:16/10         CHF       2007 Guidelines for the Diagnosis       III       S:0/58       E:65±4.5       E:66/54         CHF <td>E:71.1 ± 2.8 C:70.2 ± 2.6</td> <td>32/24 NA 30/26</td> <td>XMLI 4 mL bid+ Control</td> <td>14 LVEF, LVEDD, 6-WMD, CO, SV, LVS, LVESV, LVEDV, HR, life quality score, adverse effect</td>	E:71.1 ± 2.8 C:70.2 ± 2.6	32/24 NA 30/26	XMLI 4 mL bid+ Control	14 LVEF, LVEDD, 6-WMD, CO, SV, LVS, LVESV, LVEDV, HR, life quality score, adverse effect
CHF       American College of Cardiology/ American Heart Association (ACC/AHA) guidelines 2009       III N       57/53       E:79±10       E:46/11         CHF       American Heart Association (ACC/AHA) guidelines 2009       III N       118/120       E:63:1±9:80       E:69/46         American Heart Association (ACC/AHA) guidelines for the Diagnosis       NA       25/25       E:65:±4:5       E:15/10         American College of Cardiology/ American Heart Association (ACC/AHA) guidelines for the Diagnosis       NA       25/25       E:65:±4:5       E:15/10         CHF       2007 Guidelines for the Diagnosis       III N       59/58       E:65:±4:5       E:15/10         American College of Cardiology/ Eallure in China       III N       59/58       E:65:±4:5       E:15/10         CHF       2007 Guidelines for the Diagnosis       III N       59/58       E:65:±4:5       E:16/10         American College of Cardiology/ Eallure in China       III N       59/58       E:65:±4:5       E:16/10         CHF       2007 Guidelines for the Diagnosis       III N       59/58       E:65:±4:5       E:16/10         American College of Cardiology/ Eallure in China       CHF       American College of Cardiology/ American Heat Association       II N       35/30       E:65:±4:5       E:16/10         CHF       American College of Car	E:77.5± 6.2 C:75.2 ± 5.5	33/16 NA 31/12	XMLI 6 mL bid+ Control	7 6-WMD, NF-proBNP, CTnl
CHF       American College of Cardiology/ American Heart Association (ACC/AHA) guidelines 2009       II II       118/120       E:63:1± 9:80       E:69/46         American Heart Association (ACC/AHA) guidelines 2009       II II       25/25       E:65± 4.5       E:15/10         CHF       2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in Chrina       III V       59/58       E:65± 4.5       E:15/10         CHF       2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in Chrina       III V       59/58       E:65± 4.5       E:15/10         CHF       2007 Guidelines for the Diagnosis and Treatment of Chronic Heart       III V       59/58       E:65± 4.5       E:07/5         CHF       2007 Guidelines for the Diagnosis       III V       59/58       E:65± 4.0       E:07/5         CHF       2007 Guidelines for the Diagnosis       II V       35/30       E:62± 10       E:20/15         American College of Cardiology/ American Heart Failure in Ochia       II V       35/30       E:62± 10       E:20/15         CHF       American College of Cardiology/ American Heart Failure in Ochia       II V       35/30       E:62± 10       E:20/15         CHF       American College of Cardiology/ American Heart Failure in Ochia       II V       35/30       C:80/28       C:18/12	E:79± 10 C:78±11	46/11 NA 44/9	XMLI 4 mL bid+ Control	14 the total effective rate, BNP, LVEF
CHF       2007 Guidelines for the Diagnosis       NA       25/25       E:65±4.5       E:15/10         and Treatment of Chronic Heart       Failure in China       C:66±5.5       C:31212         CHF       2007 Guidelines for the Diagnosis       III N       59/58       E:65±4.5       E:15/10         CHF       2007 Guidelines for the Diagnosis       III N       59/58       E:65±4.5       C:13/12         CHF       2007 Guidelines for the Diagnosis       II N       59/58       E:65±4.0       C:13/12         Failure in China       2007 Guidelines for the Diagnosis       II N       35/30       E:65±4.0       E:60-83       E:0/28         CHF       2007 Guidelines for the Diagnosis       II N       35/30       E:62±10       E:20/15         CHF       American College of Cardiology/       II N       35/30       E:62±10       E:20/16         American College of Cardiology/       II N       35/30       E:62±10       E:20/16         American College of Cardiology/       II N       35/30       E:62±10       E:20/16         CHF       2007 Guidelines 2009       NA       E:60-83       E:60/26         CHF       2007 Guidelines for the Diagnosis       NA       152/01         CHF       2007 Guidelines for the D	E:63.1±9.80 C:63.9±9.01	59/46 E:754 days 60/60 C:865 days	XMLI 5 mg/kg bid+ Control	5 the total effective rate, LVEF, 6-WMD, adverse effect, the total effective rate of Chinese medical syndrome efficacy, scores for Chinese medical symptoms
CHF       2007 Guidelines for the Diagnosis       III IV       59/58       E:63-82       E:26/33         and Treatment of Chronic Heart       Ealure in China       C:60-83       C:30/28         Failure in China       American College of Carciology/       II IV       35/30       E:62±10       E:20/15         CHF       American College of Carciology/       II IV       35/30       E:62±10       E:0/15         American Heart Association       NA       76/76       NA       E:62±10       E:0/15         American Heart Association       NA       76/76       NA       E:62/15       C:18/12         CHF       2014 Guidelines for the Diagnosis       NA       76/76       NA       E:50/26         CHF       2007 Guidelines for the Diagnosis       N       131/112       NA       152/91         CHF       2007 Guidelines for the Diagnosis       N       131/112       NA       152/91         CHF       2007 Guidelines for the Diagnosis       N       131/112       NA       152/91         CHF       2007 Guidelines for the Diagnosis       N       131/112       NA       152/91         CHF       2007 Guidelines for the Diagnosis       N       131/112       NA       152/91         CHF	E:65± 4.5 C:66±5.5	15/10 NA 13/12	XML 5 mg/kg bid+ Control	5 the total effective rate, NT-proBNP, adverse effect
CHF     American College of Cardiology/ American Heart Association     II N     35/30     E:62±10     E:20/15       American Heart Association     American Heart Association     C:58±8     C:18/12       (ACC/AHA) guidelines 2009     NA     76/76     NA     E:50/26       (ACC/AHA) guidelines for the Diagnosis     NA     76/76     NA     E:50/26       CHF     2014 Guidelines for the Diagnosis     N     76/76     NA     E:50/26       China     China     N     131/112     NA     152/91       China     Coo7 Guidelines for the Diagnosis     N     131/112     NA     152/91       OHF     2007 Guidelines for the Diagnosis     N     131/112     NA     152/91       CHF     2007 Guidelines for the Diagnosis     N     131/112     NA     152/91       CHF     2007 Guidelines for the Diagnosis     N     131/112     NA     152/91       CHF     2007 Guidelines for the Diagnosis     N     131/112     NA     152/91       CHF     2007 Guidelines for the Diagnosis     N     131/112     NA     152/91       CHF     Treatment of Chronic systolic     II     N     132/128     E:34-78     E:88/40	E:63-82 C:60-83	26/33 NA 30/28	XML 5 mg/kg bid+ Control	10 the total effective rate, NT-proBNP, LVEF, metabolic equivalent of energy, adverse effect
CHF     2014 Guidelines for the Diagnosis     NA     76/76     NA     E:50/26       and Treatment of Heart Failure in China     China     C:48/28     C:48/28       CHF     2007 Guidelines for the Diagnosis     IV     131/112     NA     152/91       Image: CHF     2007 Guidelines for the Diagnosis     IV     131/112     NA     152/91       Image: CHF     2007 Guidelines for the Diagnosis     IV     131/112     NA     152/91       Image: CHF     2007 Guidelines for the Diagnosis     IV     131/112     NA     152/91       Image: CHF     2007 Guidelines for the Diagnosis     IV     132/128     E:34-78     E:88/40       Image: CHF     Treatment of chronic systolic     III IV     132/128     E:34-78     E:88/40	E:62± 10 C:58±8	20/15 NA 18/12	XML 8 mL qd+ Control	15 the total effective rate, LVEF, LVEDD
CHF 2007 Guidelines for the Diagnosis IV 131/112 NA 152/91 and Treatment of Chronic Heart Failure in China D15 CHF Treatment of chronic systolic III IV 132/128 E:34-78 E:88/40 heart failure 2002 CI C:37-84 C:34/38	NA	50/26 NA 48/28	XML 5 mg/kg bid+ Control	14 the total effective rate, LVEF, LVEDD, 6-WMD, LVESD
CHF Treatment of chronic systolic III IV 132/128 E:38/40 heart failure 2002 C:37-84 C:94/38	AN	2/91 NA	XML 5-10mg/kg bid+ Control	14 BNP, LVEF, central venous pressure, adverse effect
	E:34-78 C:37-84	88/40 NA 94/38	XMLI 6 mL bid+ Control	7-14 the total effective rate, LVEF, NT-proBNP, LVEDD, 6-WMD, adverse effect
Yuan et al., 2015         CHF         Internal Medicine 2008         I IV         54/34         E:51.5± 5.6         E:30/24           C:52.3±6.0         C:19/15	E:51.5± 5.6 C:52.3±6.0	30/24 E:2.5±2.3 19/15 C:2.8±3.1	XMLI 5 mg/kg bid+ Control	5 the total effective rate, NT-proBNP, 6-WMD, adverse effect

Frontiers in Pharmacology | www.frontiersin.org

TABLE 1 | Characteristics of the included studies.

Study	Indication	Diagnosis Standard	ИҮНА	Sample Size (E/C)	Age (Year)	Male/ Female (E/C)	Course of disease (Year)	Intervention	Duration (day)	n Endpoints
								Experimental Group		
Lu et al., 2013	DCM	Diagnosis and treatment of cardiomyopathy 2007	≥ =	53/51	E:63.1±7.9 C:62.9±7.6	E:31/22 C:28/23	E:2.5±0.8 C:2.6±0.9	XMLI 8 mL bid+ Control	15	the total effective rate, LVEF, adverse effect
Li et al., 2016	HO H	2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China	≥ =	100/98	E:67.34 C:68.12	E:62/38 C:58/40	NA	XML 5 mg/kg bid+ Control	10	the total effective rate, NT-proBNP, LVEF, LVEDD, adverse effect
Huang et al., 2013	HO HO	2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China	≥	71/46	E:90±4.6 C:89±5.1	E:54/17 C:34/12	E:14±6.8 C:15±5.3	XMLI 8 mL qd+ Control	44	the total effective rate, NT-proBNP, LVEF, adverse effect
Shen et al., 2017	а а а о т о но	2007 Guidelines for the Diagnosis and Treatment of chronic stable angina pectoris in China, 2014 Guidelines for the Diagnosis and Treatment of Heart Failure in China	≥ ≡	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	XMLI 4 mL bid+ Control	4	NT-proBNP, LVEF, LVEDD, 6-WMD
Fan et al., 2017	HO HO	2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China	≥	44/34	E:64.2±7.6 C:63.8±6.8	E:28/16 C:20/14	T:4.5±6.8 C:4.2±6.3	XML 5 mg/kg bid+ Control	14	NT-proBNP, LVEF, APN
Ye et al., 2017	HO HO	2014 Guidelines for the Diagnosis and Treatment of Heart Failure in China, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure	=	63/63	E:71.31±11.36 C:74.01±13.22	E:39/24 C:43/20	T:9.31±3.25 C:10.51±4.13	XMLI 5 mg/kg bid+ Control	14	NT-proBNP, LVEF, adverse effect, TNF-a, IL-6, VEGF, scores of symptoms and signs for hear failure, adverse effect
Yu et al., 2017	HO	2014 Guidelines for the Diagnosis and Treatment of Heart Failure in China	NA	02/02	E:70±9 C:68±10	E:38/22 C:43/27	NA	XML 5 mg/kg bid+ Control	Q	the total effective rate, BNP, LVEF, adverse effect
Qu et al., 2017	HO	American College of Cardiology/ American Heart Association (ACC/AHA) guidelines 2009	≥	114/106	E:69±10 C:68±11	E:92/22 C:88/18	NA	XML 5-10 mg/kg bid+ Control	14	the total effective rate, BNP, LVEF, 6-WMD, adverse effect
Si, 2017	HO	2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China	AN	51/51	E:75.63±8.18 C:74.84±9.76	E:25/26 C:23/28	NA	XML 5 mg/kg bid+ Control	14	the total effective rate, BNP, LVEF, adverse effect
Wang, 2017	HO	2007 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure in China	=	21/21	E:71.38±9.23 C:71.81±9.92	E:13/8 C:12/9	E:5.19±1.28 C:5.67±1.8	XML 5 mg/kg bid+ Control	Q	NT-proBNP, LVEF, adverse effect, NYHA classification
Quan and Miu, 2017	Ч о о о с а	2014 Guidelines for the Diagnosis and Treatment of Heart Failure in China, American College of Cardiology/American Heart Association (ACC/AHA) guidelines 2009	≥ =	51/51	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	XMLI 5 mg/kg bid+ Control	0	the total effective rate, NT-proBNP, LVEF, 6-WMD, adverse effect

Xinmailong for Chronic Heart Failure

LDL-C, low density lipoprotein cholesterin; UA, Uinmalong injection; BNP, Brain matriuretic peptide; LVEF, Left ventricular ejection fraction; TC, total cholesterol; TD, coronary atherosclerotic heart disease; CHF, chronic heart failure; LDL-C, low density lipoprotein cholesterin; UA, Unic acid; hs-CPP, High-sensitivity C-reactive protein; VEGF, vescular endothelial growth; 6-MMD: 6-min walking distance; LVEDD, Left ventricular end-diastolic dimension; LVESD, Left ventricular endothelial growth; 6-min walking distance; LVEDD, Left ventricular end-sitivity C-reactive protein; VEGF, vascular endothelial growth; 6-min walking distance; LVEDD, Left ventricular end-diastolic dimension; LVESD, Left ventricular end-diastolic volume; APN, adponectin; TNF-a, tumor necrosis factor a; IL-6: Interleukin-6.

Frontiers in Pharmacology	www.frontiersin.org
---------------------------	---------------------



	Experim		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H. Fixed. 95% Cl
Aiqun Li et al. 2016	93	100	87	98	6.9%	1.68 [0.62, 4.53]	
Bangchan Yu et al. 2017	67	70	54	70	2.6%	6.62 [1.83, 23.90]	
Chuansong Wu 2015	24	25	20	25	0.9%	6.00 [0.65, 55.66]	
Fang Huang et al. 2013	68	71	39	46	2.2%	4.07 [0.99, 16.64]	
Feng Lu et al. 2015	30	36	26	36	4.9%	1.92 [0.61, 6.01]	
Guili Yuan et al. 2015	48	54	25	34	3.8%	2.88 [0.92, 9.01]	
Haibin Li et al. 2015	32	35	21	30	2.2%	4.57 [1.11, 18.87]	
Haiyan Zhang et al. 2015	51	59	38	58	5.8%	3.36 [1.34, 8.43]	
Hongyu Qu et al. 2017	106	114	80	106	6.5%	4.31 [1.85, 10.01]	
Jing Yang et al. 2012	53	57	40	53	3.3%	4.31 [1.31, 14.20]	· · · · · ·
Jingui Xue et al. 2015	77	115	58	120	21.1%	2.17 [1.28, 3.67]	
Kefeng Ye et al. 2017	52	63	42	63	8.2%	2.36 [1.03, 5.45]	
Mei Yang et al. 2015	122	128	122	132	6.3%	1.67 [0.59, 4.73]	
Shengmin Guo et al. 2016	50	52	39	52	1.7%	8.33 [1.77, 39.12]	
Wenyu Shen et al. 2017	55	58	51	58	3.0%	2.52 [0.62, 10.26]	
Wuxia Quan et al. 2017	40	46	31	48	4.4%	3.66 [1.29, 10.37]	·
Xianjun Si et al. 2017	47	51	40	51	3.5%	3.23 [0.95, 10.94]	· · · ·
Yong Xu et al. 2016	72	76	64	76	3.8%	3.38 [1.04, 10.99]	· · · · · ·
Yunguo Han et al. 2016	126	136	110	147	8.7%	4.24 [2.01, 8.92]	
Total (95% CI)		1346		1303	100.0%	3.10 [2.47, 3.90]	•
Total events	1213		987				
Heterogeneity: Chi <sup>2</sup> = 11.16,	df = 18 (P	= 0.89);	$ ^2 = 0\%$				
Test for overall effect: Z = 9.	71 (P < 0.0	00001)					0.02 0.1 1 10 50 Favours [control] Favours [experimental
<b>URE 3</b>   Forest plot of the tota	al effective r	ate of XN	Al Lolus c	onventi	onal thera	py vs. conventional th	erapy alone for CHF treatment. $l^2$ and P are the criterion fc
							jection; CHF, chronic heart failure; CI, confidence interval.

There was substantial heterogeneity among these 26 trials. Subgroup analysis of treatment course based on LVEF was further performed to examine whether the length of treatment could contribute to the heterogeneity. Five trials with 595 patients were found to treat CHF patients for less than or equal to 7 days (Lu et al., 2015; Shi H. R. et al., 2015; Xue et al., 2015; Wang, 2017; Yu et al., 2017). Seventeen studies involving 2,497 patients for over 7 days (Zhao et al., 2010; Yang et al., 2012; Huang et al., 2013; Peng et al., 2014; Li and Li, 2015; Yang M. et al., 2015; Zhang, 2015; Guo and Ren, 2016; Han and Guo,

2016; Li et al., 2016; Xu and Xu, 2016; Fan et al., 2017; Quan and Miu, 2017; Qu et al., 2017; Shen et al., 2017; Si, 2017; Ye et al., 2017). Significant difference was observed between these two treatment courses (P = 0.01,  $I^2 = 0\%$ ). Long treatment course (over 7 days) (MD 5.53, 95% CI 4.48 to 6.57, P < 0.00001, **Figure 5**) presented higher improvement in LVEF than short one (no more than 7 days) (MD 2.00, 95% CI-0.62 to 4.61, P = 0.13).

A sensitivity analysis was performed as the LVEF of XMLI for conventional therapy alone was higher than that of XMLI

				702					
		eriment			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean			-	IV, Random, 95% CI	IV, Random, 95% Cl
Aiqun Li et al. 2016	49.7	9.8	100	43.3	10.7	98	4.1%	6.40 [3.54, 9.26]	
Bangchan Yu et al. 2017	48.7	7.2	70	44.3	3.2	70	5.2%	4.40 [2.55, 6.25]	
Fang Huang et al. 2013	42.3	14.4	71	36.3	9.9	46	2.7%	6.00 [1.59, 10.41]	
Feng Lu et al. 2015	38.02	8.17	36	37.96	8.32	36	3.2%	0.06 [-3.75, 3.87]	
Haibin Li et al. 2015	43	5	35	40	5	30	4.5%	3.00 [0.56, 5.44]	
Haiyan Zhang et al. 2015	45.15	5.15	59	38.42	4.62	58	5.3%	6.73 [4.96, 8.50]	
Hongyu Qu et al. 2017	49.66	9.75	114	43.77	7.18	106	4.7%	5.89 [3.64, 8.14]	
Huirong Shi et al. 2015	48.1	10.47	58	47.5	9.42	58	3.4%	0.60 [-3.02, 4.22]	
Jing Yang et al. 2012	49.6	9.3	57	43.7	2.6	53	4.5%	5.90 [3.39, 8.41]	
Jingui Xue et al. 2015	51.669	13.85	112	52.566	14.211	113	3.3%	-0.90 [-4.56, 2.77]	
Kefeng Ye et al. 2017	45.12	2.84	63	38.26	3.9	63	5.8%	6.86 [5.67, 8.05]	
Mei Yang et al. 2015	46.2	2.2	128	43.6	1.6	132	6.3%	2.60 [2.13, 3.07]	+
Quan Fan et al. 2017	45.3	11.1	44	38.2	10.2	34	2.5%	7.10 [2.36, 11.84]	· · · · · · · · · · · · · · · · · · ·
Shengmin Guo et al. 2016	50.17	1.68	52	43.94	2.67	52	6.1%	6.23 [5.37, 7.09]	
Wenyu Shen et al. 2017	50.29	3.02	58	46.19	3.14	58	5.9%	4.10 [2.98, 5.22]	
Wuxia Quan et al. 2017	46.02	5.45	46	38.34	5.13	48	4.9%	7.68 [5.54, 9.82]	
Xianjun Si et al. 2017	47.68	8.02	51	43.26	7.31	51	4.0%	4.42 [1.44, 7.40]	
Xiaojing Peng et al. 2014	55.2	4.2	56	49.1	3.6	56	5.6%	6.10 [4.65, 7.55]	
Yaxue Wang et al. 2017	42.29	8.6	21	36.19	9.39	21	2.1%	6.10 [0.65, 11.55]	
Yong Xu et al. 2016	42.6	5.2	76	36.8	3.3	76	5.7%	5.80 [4.42, 7.18]	_ <u>_</u>
Yunguo Han et al. 2016	49.3	9.1	136	43.1	2.7	147	5.5%	6.20 [4.61, 7.79]	
Zhiyong Zhao et al. 2010	46.6	9.7	131	42.5	8.4	112	4.7%	4.10 [1.82, 6.38]	
Total (95% CI)			1574			1518	100.0%	4.93 [3.96, 5.89]	•
Heterogeneity: Tau <sup>2</sup> = 3.75;	Chi <sup>2</sup> = 14	6.00, df	= 21 (F	o < 0.000	01); l <sup>2</sup> =	86%			
Test for overall effect: Z = 10					<i>,.</i> .				-10 -5 0 5 10
			/						Favours [control] Favours [experimental]
IGURE 4   Forest plot of the	LVEF of X	(MLI plu	us conv	/entional	therapy	VS. CO	nventiona	al therapy alone for CH	F treatment. $I^2$ and P are the criterion for the heteroger
st, 🔶 pooled mean differend									CHF, chronic heart failure; CI, confidence interval.

plus conventional therapy (Xue et al., 2015). In parallel with the above result, LVEF in the experimental group was significantly higher than that of control group (MD 5.13, 95% CI 4.17 to 6.09, P < 0.00001).

## Brain Natriuretic Peptide (BNP) and N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP)

Nine trials measured the BNP level of patients with CHF between XMLI plus conventional therapy and conventional therapy alone. Among these 9 trials, 3 (Yang et al., 2012; Qu et al., 2017; Yu et al., 2017) and 4 (Zhao et al., 2010; Guo and Ren, 2016; Han and Guo, 2016; Si, 2017) trials accessed BNP with the unit of ng/L and pg/mL, respectively, with the rest two adopting the unit of ng/mL and pg/L (Lu et al., 2015; Shi H. R. et al., 2015). As shown in **Figure 6A**, there was substantial heterogeneity ( $I^2 = 99\%$ , P < 0.00001). Therefore, a random-effects model was used to pool this meta-analysis. In comparison with conventional therapy, XMLI plus conventional therapy could significantly decrease serum BNP in CHF patients (MD – 149.59, 95% CI – 211.31 to – 87.88, P < 0.00001, **Figure 6A**).

Twelve trials assessed the serum NT-proBNP of CHF patients, 5 (Huang et al., 2013; Zhang, 2015; Fan et al., 2017; Quan and Miu, 2017; Ye et al., 2017) and 6 (Yang et al., 2014; Yang M. et al., 2015; Yuan et al., 2015; Li et al., 2016; Shen et al., 2017; Wang, 2017) of which measured with the unit of ng/L and pg/mL, respectively, 1 of which adopted ng/mL (Wu, 2015). Random-effects models were performed because of considerable heterogeneity  $(I^2 = 100\%, P < 0.00001)$ . The treatment of XMLI plus

conventional therapy could markedly decrease this parameter in CHF patients when compared with conventional treatment (MD-322.35, 95% CI -517.87 to -126.83, P = 0.001, **Figure 6B**).

# Left Ventricular End-Diastolic Dimension (LVEDD)

Seven studies with 1007 subjects assessed the levels of LVEDD between the experimental and control group (Peng et al., 2014; Li and Li, 2015; Yang M. et al., 2015; Guo and Ren, 2016; Li et al., 2016; Xu and Xu, 2016; Shen et al., 2017). There was substantial heterogeneity among these trials ( $I^2 = 59$  %, P = 0.02). Meta-analysis was performed using a random-effect model. XMLI combined with conventional therapy could significantly reduce LVEDD when compared to conventional treatment alone (MD - 4.73, 95% CI - 5.64 to - 3.83, P < 0.00001, Figure 7).

## Six-Minutes Walking Distance (6-MWD)

There were 11 studies with 1326 subjects reporting 6-MWD between XMLI plus conventional therapy vs. conventional therapy alone. Heterogeneity between these two studies was considerable ( $I^2 = 86\%$ , P < 0.00001). Hence, a random-effect model was used to pool the meta-analysis. XMLI plus conventional therapy achieved a greater improvement when compared with conventional therapy (MD 46.76, 95% CI 32.51–61.01, P < 0.00001), which suggested that XMLI was able to increase the exercise tolerance of conventional therapy for CHF treatment (**Figure 8**).

		eriment			ontrol			Mean Difference	Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.1 less than or equal to					1.2				
angchan Yu et al. 2017	48.7	7.2	70	44.3	3.2	70	5.2%	4.40 [2.55, 6.25]	
eng Lu et al. 2015	38.02	8.17	36	37.96	8.32	36	3.2%	0.06 [-3.75, 3.87]	
uirong Shi et al. 2015	48.1		58	47.5	9.42	58	3.4%	0.60 [-3.02, 4.22]	
ngui Xue et al. 2015	51.669				14.211	113	3.3%	-0.90 [-4.56, 2.77]	
axue Wang et al. 2017	42.29	8.6	21 <b>297</b>	36.19	9.39	21	2.1%	6.10 [0.65, 11.55]	
ubtotal (95% CI)						298	17.2%	2.00 [-0.62, 4.61]	
eterogeneity: Tau <sup>2</sup> = 5.52;			= 4 (P =	0.02); l <sup>2</sup>	= 65%				
est for overall effect: Z = 1.	50 (P = 0	.13)							
.2.2 more than 7 days									
iqun Li et al. 2016	49.7	9.8	100	43.3	10.7	98	4.1%	6.40 [3.54, 9.26]	
ang Huang et al. 2013	42.3	14.4	71	36.3	9.9	46	2.7%	6.00 [1.59, 10.41]	
aibin Li et al. 2015	43	5	35	40	5	30	4.5%	3.00 [0.56, 5.44]	· · · · ·
aiyan Zhang et al. 2015	45.15	5.15	59	38.42	4.62	58	5.3%	6.73 [4.96, 8.50]	
ongyu Qu et al. 2017	49.66	9.75	114	43.77	7.18	106	4.7%	5.89 [3.64, 8.14]	
ng Yang et al. 2012	49.6	9.3	57	43.7	2.6	53	4.5%	5.90 [3.39, 8.41]	
efeng Ye et al. 2017	45.12	2.84	63	38.26	3.9	63	5.8%	6.86 [5.67, 8.05]	
lei Yang et al. 2015	46.2	2.2	128	43.6	1.6	132	6.3%	2.60 [2.13, 3.07]	-
uan Fan et al. 2017	45.3	11.1	44	38.2	10.2	34	2.5%	7.10 [2.36, 11.84]	
hengmin Guo et al. 2016	50.17	1.68	52	43.94	2.67	52	6.1%	6.23 [5.37, 7.09]	
/enyu Shen et al. 2017	50.29	3.02	58	46.19	3.14	58	5.9%	4.10 [2.98, 5.22]	
/uxia Quan et al. 2017	46.02	5.45	46	38.34	5.13	48	4.9%	7.68 [5.54, 9.82]	
ianjun Si et al. 2017	47.68	8.02	51	43.26	7.31	51	4.0%	4.42 [1.44, 7.40]	
iaojing Peng et al. 2014	55.2	4.2	56	49.1	3.6	56	5.6%	6.10 [4.65, 7.55]	
ong Xu et al. 2016	42.6	5.2	76	36.8	3.3	76	5.7%	5.80 [4.42, 7.18]	
unguo Han et al. 2016	49.3	9.1	136	43.1	2.7	147	5.5%	6.20 [4.61, 7.79]	
hiyong Zhao et al. 2010	46.6	9.7	131	42.5	8.4	112	4.7%	4.10 [1.82, 6.38]	
ubtotal (95% CI)			1277			1220	82.8%	5.53 [4.48, 6.57]	•
eterogeneity: Tau <sup>2</sup> = 3.66;	Chi² = 12	8.58, df	= 16 (F	o < 0.000	01); l² =	88%			
est for overall effect: Z = 10	0.35 (P <	0.00001	)						
otal (95% CI)			1574			1518	100.0%	4.93 [3.96, 5.89]	◆
eterogeneity: Tau <sup>2</sup> = 3.75;	Chi <sup>2</sup> = 14	6.00, df	= 21 (F	o < 0.000	01); l <sup>2</sup> =	86%			-10 -5 0 5 10
est for overall effect: Z = 10	0.04 (P <	0.00001	)						-10 -5 0 5 10 Favours [control] Favours [experimental]
est for subaroup difference	s' Chi <sup>2</sup> =	6 03 df	= 1 (P)	= 0.01).	$^{2} = 83.4^{\circ}$	%			

# **Publication Bias**

A funnel plot was used to evaluate the publication bias. A total of 19 trails were involved in the funnel plot of the total effective rate. No significant asymmetry was observed (**Figure 9**).

# **Adverse Events**

Eighteen of the included trials investigated the adverse effects (Zhao et al., 2010; Huang et al., 2013; Lu et al., 2013, 2015; Peng et al., 2014; Wu, 2015; Xue et al., 2015; Yang M. et al., 2015; Yuan et al., 2015; Zhang, 2015; Guo and Ren, 2016; Li et al., 2016; Quan and Miu, 2017; Qu et al., 2017; Si, 2017; Wang, 2017; Ye et al., 2017; Yu et al., 2017). Ten of these studies reported that there were no adverse events in terms of blood routine, urine routine, liver function or renal function in both groups (Lu et al., 2013, 2015; Peng et al., 2014; Yuan et al., 2015; Zhang, 2015; Guo and Ren, 2016; Quan and Miu, 2017; Qu et al., 2017; Si, 2017; Yu et al., 2017).

As shown in **Table 2**, the remaining 8 studies involving 1,274 participants (661 and 613 cases for experimental and control group, respectively) reported adverse effects. As found, XMLI plus conventional treatment caused cutaneous pruritus (9 cases), palpitation (6 cases), light-headed (7 cases), headache (2 cases),

hypokalemia (1 case), abnormal liver function (3 cases), major adverse cardiac event (3 cases), while conventional therapy induced leukocytosis (1 case), light-headed (1 case), palpitation (3 cases), dizziness (1 case), light-headed (2 cases), vomiting (1 case), abnormal liver function (2 cases), headache (3 cases), major adverse cardiac event (9 cases) (Zhao et al., 2010; Huang et al., 2013; Wu, 2015; Xue et al., 2015; Yang M. et al., 2015; Li et al., 2016; Wang, 2017; Ye et al., 2017). The incidence rate of adverse effect in the experimental group (4.7%) was slightly higher than that in control group (3.4%). The types of adverse effect nearly equaled between these two groups (7 and 8). The symptoms, such as palpitation, light-headed, headache, and dizziness, were relieved through rest or slowly dropping. None of these adverse events were serious and no included trials reported death during the scheduled treatment.

# DISCUSSION

# Summary of Evidence

In this review, XMLI in all the included studies were from Yunnan Teng yao Pharmaceutical Co., Ltd. The dosages of XMLI were 4/6 mL twice a day or 8 mL per day or 5–10 mg/kg twice

	Exp	erimenta	al		Control			Mean Difference		Mean	Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95%	6 CI	
Bangchan Yu et al. 2017	327.6	71.1	70	431.4	60.7	70	14.3%	-103.80 [-125.70, -81.90]		-			
Hongyu Qu et al. 2017	285.3	53.6	114	351.5	64.8	106	14.4%	-66.20 [-81.98, -50.42]		-			
ling Yang et al. 2012	337.7	73.6	57	428.3	64.8	53	14.2%	-90.60 [-116.47, -64.73]					
Shengmin Guo et al. 2016	161.44			654.1	139.15	52		-492.66 [-531.27, -454.05]					
(ianjun Si et al. 2017	335.14			494.2	34.71	51		-159.06 [-171.59, -146.53]					
/unguo Han et al. 2016	336.5			419.4	63.7	147	14.4%	-82.90 [-98.74, -67.06]		-			
Zhiyong Zhao et al. 2010	285.3			351.5	57.5	112	14.5%	-66.20 [-79.49, -52.91]					
inyong znao et al. zo ro	200.0	40.4	101	001.0	07.0	112	14.070	-00.20 [-70.40, -02.01]					
otal (95% CI)			611			591	100.0%	-149.59 [-211.31, -87.88]		•			
Heterogeneity: Tau <sup>2</sup> = 6813	3 06. Chi2	= 521 30		(P<0	00001)			-		-+			
	J.00, Off			11 -0.	.00001),	- 557			-500	-250	0	250	500
Fact for avarall offact: 7 - /	175 /D - 0	100001)							-000	200			
Test for overall effect: Z = 4	1.75 (P < 0	).00001)								s [experimenta	] Favou	rs [control]	
Test for overall effect: Z = 4	4.75 (P < (	).00001)									] Favou	rs [control]	
Fest for overall effect: Z = 4	<b>X</b>	,								s [experimenta			
	Experi	imental			ontrol	Tatal	W-1-64	Mean Difference	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup	Experi Mean	imental SD To	otal	Mean	SD		Weight	Mean Difference IV. Random, 95% Cl	Favour	s [experimenta Mear		ce	
itudy or Subgroup	Experi Mean 2.87	imental <u>SD To</u> 1.98 1	<u>otal  </u> 100	<u>Mean</u> 3.99	<b>SD</b> 2.55	98	12.1%	Mean Difference <u>IV. Random. 95% CI</u> -1.12 [-1.76, -0.48]	Favour	s [experimenta Mear	Differen	ce	
itudy or Subgroup Niqun Li et al. 2016 ang Huang et al. 2013	Experi <u>Mean</u> 2.87 1,594	imental <u>SD Tc</u> 1.98 1 842	<u>otal</u> 100 44	Mean 3.99 2,470	SD 2.55 837	98 34	12.1% 8.4%	Mean Difference IV. Random. 95% Cl -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Niqun Li et al. 2016 Fang Huang et al. 2013 Guili Yuan et al. 2015	Experi <u>Mean</u> 2.87 1,594 3,328	imental <u>SD To</u> 1.98 1 842 547	otal   100 44 : 54 3,	Mean 3.99 2,470 824.1	2.55 837 667.5	98 34 34	12.1% 8.4% 9.9%	Mean Difference IV. Random. 95% Cl -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47]	Favour	s [experimenta Mear	Differen	ce	
<mark>Study or Subgroup</mark> Xiqun Li et al. 2016 Fang Huang et al. 2013 Julii Yuan et al. 2015 Haiyan Zhang et al. 2015	Experi Mean 2.87 1,594 3,328 2,937	imental <u>SD To</u> 1.98 1 842 547 892	otal 100 44 54 3, 58 2,	Mean 3.99 2,470 824.1 331.4	SD 2.55 837 667.5 1,095.4	98 34 34 59	12.1% 8.4% 9.9% 8.6%	Mean Difference IV. Random. 95% CI -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Niqun Li et al. 2016 Fang Huang et al. 2013 Guili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2014	Experi Mean 2.87 1,594 3,328 2,937 411	imental <u>SD Tc</u> 1.98 1 842 547 892 74.6	otal 100 44 54 3, 58 2, 49 4	Mean 3.99 2,470 824.1 331.4 76.75	SD 2.55 837 667.5 1,095.4 80.21	98 34 34 59 43	12.1% 8.4% 9.9% 8.6% 12.1%	Mean Difference -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Aiqun Li et al. 2016 Gang Huang et al. 2013 Guili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2014 Kefeng Ye et al. 2017	Experi Mean 2.87 1,594 3,328 2,937 411 1,563	imental SD Tc 1.98 1 842 547 892 74.6 401	otal         1           100         44         3           54         3,         3           58         2,         49         4           63         1,         3         1	Mean           3.99           2,470           824.1           331.4           76.75           775.2	SD 2.55 837 667.5 1,095.4 80.21 449.27	98 34 34 59 43 63	12.1% 8.4% 9.9% 8.6% 12.1% 11.3%	Mean Difference <u>IV. Random, 95% Cl</u> -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Aiqun Li et al. 2016 ang Huang et al. 2013 Guili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2017 Alei Yang et al. 2015	Experi Mean 2.87 1,594 3,328 2,937 411 1,563 1,962	imental SD Tc 1.98 1 842 547 892 74.6 401 78.4 1	otal 100 44 54 3, 58 2, 49 4 63 1, 128 2,	Mean 3.99 2,470 824.1 331.4 76.75 775.2 426.8	SD 2.55 837 667.5 1,095.4 80.21	98 34 34 59 43 63 132	12.1% 8.4% 9.9% 8.6% 12.1% 11.3% 12.1%	Mean Difference IV. Random. 95% Cl -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.3] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50] -464.80 [-482.49, -447.11]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Niqun Li et al. 2016 Fang Huang et al. 2013 Juili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2014 Kefeng Ye et al. 2017 Quan Fan et al. 2017	Experi Mean 2.87 1,594 3,328 2,937 411 1,563 1,962 1,594	imental SD Tc 1.98 1 842 547 892 74.6 401 78.4 1	otal         1           100         44           54         3,           58         2,           49         4           63         1,           128         2,           44         3	Mean 3.99 2,470 824.1 331.4 76.75 775.2 426.8 2,470	SD 2.55 837 667.5 1,095.4 80.21 449.27 66.42	98 34 34 59 43 63	12.1% 8.4% 9.9% 8.6% 12.1% 11.3%	Mean Difference IV. Random. 95% CI -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50] -464.80 [-482.49, -447.11] -876.00 [-1251.57, -500.43]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Aiqun Li et al. 2016 ang Huang et al. 2013 Guili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2017 Alei Yang et al. 2015	Experi Mean 2.87 1,594 3,328 2,937 411 1,563 1,962 1,594 635.2	imental <u>SD</u> To 1.98 1 842 547 892 74.6 401 78.4 1 842 221	otal 100 44 54 3, 58 2, 49 4 63 1, 128 2, 44 58 9	Mean 3.99 2,470 824.1 331.4 76.75 775.2 426.8 2,470 49.14	SD 2.55 837 667.5 1,095.4 80.21 449.27 66.42 837 254.14	98 34 59 43 63 132 34	12.1% 8.4% 9.9% 8.6% 12.1% 11.3% 12.1% 8.4%	Mean Difference IV. Random. 95% CI -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50] -464.80 [-482.49, -447.11] -876.00 [-1251.57, -500.43] -313.94 [-400.62, -227.26]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Niqun Li et al. 2016 Fang Huang et al. 2013 Juili Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2015 Juan Fan et al. 2017 Venyu Shen et al. 2017	Experi Mean 2.87 1,594 3,328 2,937 411 1,563 1,962 1,594 635.2	imental <u>SD</u> Tc 1.98 1 842 547 892 74.6 401 78.4 1 842 221 ,885	otal         1           100         44           54         3,           58         2,           49         4           63         1,           128         2,           44         58           58         9           46         3,	Mean 3.99 2,470 824.1 331.4 76.75 775.2 426.8 2,470 49.14 650.3	SD 2.55 837 667.5 1,095.4 80.21 449.27 66.42 837	98 34 59 43 63 132 34 58	12.1% 8.4% 9.9% 8.6% 12.1% 11.3% 12.1% 8.4% 11.8% 4.7%	Mean Difference IV. Random. 95% CI -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50] -464.80 [-482.49, -447.11] -876.00 [-1251.57, -500.43]	Favour	s [experimenta Mear	Differen	ce	
Study or Subgroup Niqun Li et al. 2016 Fang Huang et al. 2013 Julii Yuan et al. 2015 Haiyan Zhang et al. 2015 Haiyang Yang et al. 2015 Haiyang Yang et al. 2017 Mei Yang et al. 2017 Vany Shen et al. 2017 Vuxia Quan et al. 2017	Experi Mean 2.87 1,594 3,328 2,937 411 1,562 1,594 635.2 2,931 1	imental <u>SD Tc</u> 1.98 1 842 547 892 74.6 401 78.4 1 842 221 ,885 ,329	otal         1           100         44           54         3,           58         2,           49         4           63         1,           128         2,           44         58           58         9           46         3,	Mean 3.99 2,470 824.1 331.4 76.75 775.2 426.8 2,470 49.14 650.3	<b>SD</b> 2.55 837 667.5 1,095.4 80.21 449.27 66.42 837 254.14 1,589.2	98 34 59 43 63 132 34 58 48 21	12.1% 8.4% 9.9% 8.6% 12.1% 11.3% 12.1% 8.4% 11.8% 4.7%	Mean Difference IV. Random. 95% CI -1.12 [-1.76, -0.48] -876.00 [-1251.57, -500.43] -496.10 [-763.73, -228.47] 605.60 [243.90, 967.30] -65.75 [-97.55, -33.95] -212.20 [-360.90, -63.50] -464.80 [-482.49, -447.11] -876.00 [-1251.57, -500.41] -313.94 [-400.62, -227.26] -719.30 [-1425.59, -13.01]	Favour	s [experimenta Mear	Differen	ce	

Study or Subgroup	Mean	erimen SD		Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
and the second s		Arrest March	1222002004	Photosof, Newson 1	100000 (Date: 10		and the second	The second second second	
Aiqun Li et al. 2016	54.09	7.28	100	59.12		98	8.9%	-5.03 [-7.51, -2.55]	
Haibin Li et al. 2015	41	2.9	35	47.4	4.1	30	13.3%	-6.40 [-8.15, -4.65]	
Mei Yang et al. 2015	53.64	4.78	128	58.56	5.62	132	17.4%	-4.92 [-6.19, -3.65]	
Shengmin Guo et al. 2016	41.42	5	52	46.06	8.37	52	8.1%	-4.64 [-7.29, -1.99]	
Wenyu Shen et al. 2017	51.08	3.75	58	53.89	4.65	58	15.0%	-2.81 [-4.35, -1.27]	
Xiaojing Peng et al. 2014	46.8	1.9	56	52.3	2.2	56	22.3%	-5.50 [-6.26, -4.74]	+
Yong Xu et al. 2016	51.7	4.7	76	55.4	4.9	76	15.1%	-3.70 [-5.23, -2.17]	
Total (95% CI)			505			502	100.0%	-4.73 [-5.64, -3.83]	•
Heterogeneity: Tau <sup>2</sup> = 0.80;	Chi <sup>2</sup> = 14	4.70, d	f = 6 (F	= 0.02	); l <sup>2</sup> = 59	9%		-	
Test for overall effect: Z = 1	0.26 (P <	0.000	01)						-10 -5 0 5 10
			/						Favours [experimental] Favours [control]
									treatment. $I^2$ and P are the criterion for the heteroge

chronic heart failure, CI: confidence interval.

a day via intravenous drip. The treatment course varied from 5 to 15 days. The combination of XMLI and conventional therapy displayed better therapeutic effects than conventional treatment alone based on the total effective rate, suggesting that XMLI could improve the clinical efficacy of conventional therapy for the treatment of CHF. The mechanism could contribute to the inhibition of the phosphorylation of ERK1/2, AKT, GSK3 $\beta$ , and protein expression of GATA4 (Qi et al., 2017).

As to left ventricular structure and function, the meta-analysis demonstrated that additional XMLI therapy was superior to conventional treatment, evidenced by increase of LVEF and decrease of LVEDD. In parallel, the combined use of XMLI and conventional therapy was found to increase 6-MWD, the indicator of functional capacity. Both BNP and NT-proBNP levels are good serum markers for evaluating the improvement of heart failure because there is a good correlation between their

	Exp	erimenta	I	Co	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feng Lu et al. 2015	461.71	105.44	36	441.21	90.05	36	5.7%	20.50 [-24.79, 65.79]	
Guili Yuan et al. 2015	273	43.12	54	224	55.56	34	10.0%	49.00 [27.07, 70.93]	
Haiyang Yang et al. 2014	431.78	42.58	49	406.25	46.31	43	10.8%	25.53 [7.26, 43.80]	
Hongyu Qu et al. 2017	320.74	26.14	114	273.05	21.77	106	12.8%	47.69 [41.35, 54.03]	-
Jingui Xue et al. 2015	461.7	160.29	114	412.767	151.1	120	6.5%	48.93 [8.97, 88.89]	
Shengmin Guo et al. 2016	442.88	22.4	52	350.69	56.33	52	11.2%	92.19 [75.71, 108.67]	
Wenyu Shen et al. 2017	292.12	27.69	58	269.67	22.35	58	12.5%	22.45 [13.29, 31.61]	-
Wuxia Quan et al. 2017	476.68	164.27	46	413.87	138.4	48	3.8%	62.81 [1.28, 124.34]	
Xiaojing Peng et al. 2014	306.4	52.3	56	263.5	43.5	56	10.9%	42.90 [25.08, 60.72]	
Yaxue Wang et al. 2017	386.62	95.79	21	272.67	82.82	21	4.5%	113.95 [59.79, 168.11]	
Yong Xu et al. 2016	264	46.44	76	235	56.79	76	11.2%	29.00 [12.51, 45.49]	
Total (95% CI)			676			650	100.0%	46.76 [32.51, 61.01]	•
Heterogeneity: Tau <sup>2</sup> = 401.2	4; Chi² =	70.26, df	= 10 (F	<pre>&gt; &lt; 0.0000</pre>	1); l <sup>2</sup> =	86%		_	-100 -50 0 50 100
Test for overall effect: Z = 6	.43 (P < 0	.00001)							-100 -50 0 50 100 Favours [control] Favours [experimental]



levels and the severity of heart failure (Jourdain et al., 2007; Oremus et al., 2014). Benefits of XMLI treatment were shown on the decline of serum BNP and NT-proBNP.

Eighteen out of twenty-six studies (69.2%) reported adverse events. Our systematic review observed that the incidence rate of adverse events in the experimental group was a bit higher than that of control group. XMLI plus conventional treatment mainly contributed to cutaneous pruritus, palpitation, lightheaded, abnormal liver function and major adverse cardiac event. Similarly, conventional therapy caused palpitation, abnormal liver function, headache and major adverse cardiac event. Rest or slowly dropping was able to relive the symptoms of palpitation, light-headed, headache and dizziness. No serious adverse event was observed in these two groups. XMLI seemed generally safe, but the evidence was too limited to make a decisive conclusion on safety.

Although there was no significant difference on the adverse events between XMLI plus conventional treatment and conventional treatment, additional use of XMLI ameliorated the

**TABLE 2** | The incidence rate of adverse effect.

Туре	The number o	f adverse effect	References
	Experimental group	Control group	
Cutaneous pruritus	9	0	Huang et al., 2013; Xue et al. 2015; Yang M. et al., 2015
Palpitation	6	3	Yang M. et al., 2015; Li et al., 2016; Ye et al., 2017
Light-headed	7	1	Zhao et al., 2010; Huang et al., 2013; Wu 2015
Headache	2	3	Ye et al., 2017
Dizziness	0	1	Yang M. et al., 2015
Hypokalemia	1	0	Ye et al., 2017
Abnormal liver function	3	2	Ye et al., 2017
Major adverse cardiac event	3	9	Wang, 2017
Leukocytosis	0	1	Xue et al., 2015
Vomiting	0	1	Ye et al., 2017
Total event	31/661	21/613	-
Incidence rate	4.7%	3.4%	_

clinical efficacy and improvement of left ventricular structure and function as well as functional capacity. Therapeutic effects and safety of XMLI remains to be investigated due to a limited number of trials and poor methodological quality of the included trials.

#### **Strengths and Limitations**

CHF is a global health problem with 26 million people suffering. Even if diuretics, ACEI,  $\beta$ -blockers, and digitalis are commonly

recommended for CHF patients by ESC and ACC/AHA guidelines (Ponikowski et al., 2016; Writing Committee et al., 2016). It is unsatisfying for the western medicine alone on the treatment of CHF due to adverse reactions such as arrhythmia, nausea and impairment of vision caused by digitalis, and dry cough by ACEI (Vegter and de Jong-van den Berg, 2010; Agarwal and Amsterdam, 2015). XMLI has been proven to effectively treat various kinds of failing heart. However, a large number of trials concerning XMLI were conducted independently. This meta-analysis was the first study to systematically evaluate the effects of combined use of XMLI and conventional therapy for CHF treatment and provided preliminary evidence.

However, there still existed limitations in this meta-analysis as followed. Firstly, randomization is necessary to avoid selection bias. Only 6 studies (23.1%) provided specific information on how the random allocation was generated and 2 trials (7.7%) mentioned blinding of participants and personnel and outcome assessment. One article even reported with a high risk in incomplete outcome. For allocation concealment and other bias, no trial mentioned, which could induce exaggerated estimation of therapeutic effect of XMLI plus conventional therapy vs. conventional therapy alone. Thus, the included trials were thought to be generally low quality.

Secondly, we comprehensively searched English and Chinese databases to obtain the eligible articles. All the included studies (26) were published in Chinese. One trial in English was searched but excluded due to its data could not combine with other selected studies (Ma et al., 2013). Thus, the information about RCTs of XMLI was unclear in other countries or populations.

Thirdly, the included trials used different diagnostic criteria separately or combinatively for patients with CHF (Table 1). Participants with CHF also had different indications. Twelve of twenty-six studies mentioned the different indications, such as coronary heart disease, dilated cardiomyopathy, hypertensive heart disease, and rheumatic heart disease (Yang et al., 2012, 2014; Huang et al., 2013; Li and Li, 2015; Lu et al., 2015; Yang M. et al., 2015; Yuan et al., 2015; Guo and Ren, 2016; Han and Guo, 2016; Fan et al., 2017; Quan and Miu, 2017; Wang, 2017). But these CHF patients were not divided into subgroup of CHF before or after the treatment of XMLI plus conventional therapy or conventional therapy alone. Only three trials reported the single indication for CHF patients: coronary atherosclerotic heart disease (Shi H. R. et al., 2015), dilated cardiomyopathy (Lu et al., 2013) and coronary heart disease (Shen et al., 2017). It was unclear for the rest 11 trials in terms of the precision indication except for CHF.

Fourthly, meta-analysis results may be influenced by the treatment course. In this review, the courses were 5 (7 studies), 7 (1 studies), 10 (4 studies), 14 (11 studies), and 15 (2 studies) days. One article reported 7–14 days based on disease severity (Yang M. et al., 2015). Continued follow-up after the treatment period was necessary to investigate the long-term treatment effect. However, only three studies performed this: one evaluated the clinical effect after 2 weeks (Lu et al., 2015), one after 6 weeks (Peng et al., 2014) and one after 1 and 3 months (Wang, 2017). While the

rest assessed immediately after the termination of the treatment period.

Fifthly, seven outcome measurements, including the total effective rate, LVEF, BNP, NT-proBNP, LVEDD, 6 MWD, and adverse effect, were used to evaluate the effect of additional XMLI on CHF treatment. In fact, other outcome measures, such as high sensitivity C reactive protein (hsCRP), heart rate (HR), cardiac troponin I (CTnI), all-cause mortality, hospitalization, left ventricular end-systolic/diastolic volume, NYHA functional class, and blood pressure, are good indexes for the assessment of cardiac function on CHF patients. However, these indexes were only reported in a limited number of trials, making it nearly impossible to pool these data.

Sixthly, in the included trials, there was no precise description of medication in the control group. These trials just mentioned "conventional treat RCT ment" or "standard therapy," which indicated that ACEIs, beta-blockers, MRAs, diuretics and ARBs could be used in the control group varied from person to person according to CHF patients' signs and symptoms. Precisely, the impacts of which type of western medicine in combination with XMLI are suggested to investigate in RCTs.

Lastly, drug safety is essential in the development of alternative medicines for health care. Eighteen of the included 26 studies investigated adverse events. High-quality and large scale RCTs, with comprehensive adverse events recorded, are still needed to evaluate the impact of XMLI treatment on CHF patients.

#### CONCLUSION

The treatment of CHF has been a worldwide challenge. The traditional Chinese medicine XMLI plus conventional treatment may exert beneficial effects to improve cardiac function of patients with CHF. XMLI was therefore suggested to be taken into account during the conventional treatment of CHF. It is worth noticing the limitations in this review. The efficacy and safety of XMLI as an adjuvant treatment for CHF still need methodologically rigorous trials to verify.

## **AUTHOR CONTRIBUTIONS**

YZ, XX, and XL put forward this topic and designed this review. XL, LZ, HZ, and YY performed article screening, data collection and extraction, and manuscript writing. JW, HoL, HaL, and RW conducted the data analysis. JW, SW, and XZ polished the written English.

## ACKNOWLEDGMENTS

The authors thank all authors of references to perform RCTs of XMLI for CHF treatment. This work was financially supported by the National Natural Science Foundation of China (NO. 81573631).

#### REFERENCES

- Liu, H. Y., Zhu, M. J., Mao, J. Y., and Lin, Q. (2016). Consensus on standardized using Xinmailong injection for treating chronic heart failure. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 36, 280–284.
- Agarwal, A., and Amsterdam, E. A. (2015). Too much of a good thing: digitalis toxicity. Am. J. Med. 128, 257–259. doi: 10.1016/j.amjmed.2014.11.009
- Ambrosy, A. P., Fonarow, G. C., Butler, J., Chioncel, O., Greene, S. J., Vaduganathan, M., et al. (2014). The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J. Am. Coll. Cardiol. 63, 1123–1133. doi: 10.1016/j.jacc.2013.11.053
- Butler, J. (2012). An overview of chronic heart failure management. *Nurs. Times* 108, 16–20.
- Fan, Q., Wang, Y. L., Cai L. L., Li, Z. F., Zhao, C. Q., Liu, L. J., et al. (2017). The influence of Xinmailong injection on cardiac function and Plasma adiponectin level in patients with chronic heart failure. *Chin. J. Int. Med. Cardio Cerebrovasc. Dis.* 13, 1598–1600.
- Fu, S., Zhang, J., Gao, X., Xia, Y., Ferrelli, R., Fauci, A., et al. (2010). Clinical practice of Traditional Chinese Medicines for chronic heart failure. *Heart Asia* 2, 24–27. doi: 10.1136/ha.2009.001123
- Fu, S., Zhang, J., Menniti-Ippolito, F., Gao, X., Galeotti, F., Massari, M., et al. (2011). Huangqi injection (a traditional Chinese patent medicine) for chronic heart failure: a systematic review. *PLoS ONE* 6:e19604. doi: 10.1371/journal.pone.0019604
- Guo, S. M., and Ren, J. M. (2016). Effects of Xinmailong injection at different dosages on the cardiac function and BNP level in elderly patients with chronic heart failure. *Herald Med.* 35, 54–57.
- Han, Y. G., and Guo, H. Y. (2016). Effects of Xinmailong injection in combination with conventional treatment against chronic heart failure. *Guide China Med.* 14, 10–12.
- Huang, F., Zhang, A., Fang, F., and X. M. Q. (2013). Clinical effect of Xinmailong injection in the treatment of chronic heart failure in elderly patients. *Chin. General Pract.* 16, 329–331.
- Huang, J. (2015). Epidemiological characteristics and prevention and treatment strategies of heart failure in China. *Chin. J. Heart Heart Rhythm* 2, 2–3.
- Jiao, C. X., Zhang, C. G., and Liu, G. M. (2012). Gas chromatography-mass spectrometry of the volatile components in the *Periplaneta american* A alcohol extraction of water-soluble ingredients. *Lishizhen Med. Mater. Res.* 23, 2797–2798.
- Jiao, C. X., Zhang, C. G., Liu, G. M., and Li, S. N. (2011). Establishment of HPLC fingerprint of Xinmailong Injection. *Chin. Trad. Patent Med.* 33, 1648–1652.
- Jourdain, P., Jondeau, G., Funck, F., Gueffet, P., Le Helloco, A., Donal, E., et al. (2007). Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J. Am. Coll. Cardiol. 49, 1733–1739. doi: 10.1016/j.jacc.2006.10.081
- Li, A. Q., Guan, Z. Y., and X. W. L. (2016). Clinical observation of Xinmailong injection in the treatment of chronic heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 14, 527–528.
- Li, H. B., and Li, D. D. (2015). Clinical observation on treatment of chronic heart failure with Xinmailong injection. *Hebei Med. J.* 37, 713–714.
- Lu, F., Zhu, G. G., Liu, T., and Li, X. F. (2015). Clinical study of Xinmailong injection in treating chronic congestive heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 13, 83–84.
- Lu, T. Q., Zhao, Y., Li, Y., Guo, J. F., Wang, Y. Y., and Li, X. F. (2013). Clinical study of Xinmai Long injection in improving left ventricular ejection fraction of dilated cardiomyopathy. *Chin. J. Pharm. Econ.* 4, 217–218.
- Ma, Q., Luo, Y., Guo, P., Gao, G., Yang, M., Sablok, G., et al. (2013). Clinical effects of Xinmailong therapy in patients with chronic heart failure. *Int. J. Med. Sci.* 10, 624–633. doi: 10.7150/ijms.5779
- Oremus, M., Don-Wauchope, A., McKelvie, R., Santaguida, P. L., Hill, S., Balion, C., et al. (2014). BNP and NT-proBNP as prognostic markers in persons with chronic stable heart failure. *Heart Fail. Rev.* 19, 471–505. doi: 10.1007/s10741-014-9439-6
- Page, K. (2015). A systematic approach to chronic heart failure care: a consensus statement. *Med. J. Aust.* 202:361. doi: 10.5694/mja14.01383
- Peng, X. J., M. H. L., and Zhang, Y. E. (2014). Effect of Xinmailong injection on elderly patients with chronic heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 12, 1401–1402.

- Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., et al. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* 37, 2129–2200. doi: 10.1093/eurheartj/ehw128
- Qi, J., Yu, J., Tan, Y., Chen, R., Xu, W., Chen, Y., et al. (2017). Mechanisms of Chinese Medicine Xinmailong's protection against heart failure in pressure-overloaded mice and cultured cardiomyocytes. *Sci. Rep.* 7:42843. doi: 10.1038/srep42843
- Qiu, B. Y., and Wang, Y. X. (2017). Current epidemiologic and prevention and therapy of chronic heart failure. J. Chin. Pract. Diagn. Ther. 6, 619–621.
- Qu, H. Y., Zhao, G. Y., and Yu, S. X. (2017). Observation of curative effect of Xinmailong injection on patients with chronic heart failure. *Stud. Trace Elements Health* 4, 28–29.
- Quan, W. X., and Miu, Y. D. (2017). Observation of curative effect of Xinmailong injection on patients with chronic heart failure. *Chin. J New Clin. Med.* 4, 353–356.
- Shen, W. Y., Li, Y. D., and Yang., S. Z. (2017). The influence of Xinmailong injection on cardiac function and Plasma NT-proBNP level in patients with coronary heart disease with chronic heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 7, 833–835.
- Shi, H. R., Feng, Y. P., Yang, X. Q., Song, J. W., and Lu, X. (2015). Effect of Xinmailong injection on serum BNP, hsCRP and VEGF in patients with coronary heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.*14, 168–170.
- Shi, L., Xie, Y., Liao, X., Chai, Y., and Luo, Y. (2015). Shenmai injection as an adjuvant treatment for chronic cor pulmonale heart failure: a systematic review and meta-analysis of randomized controlled trials. *BMC Compl. Altern. Med.* 15:418. doi: 10.1186/s12906-015-0939-2
- Si, X. J. (2017). Observation of curative effect of Xinmailong injection on patients with chronic heart failure. *Stud. Trace Elements Health* 14, 1736–1738.
- Vegter, S., and de Jong-van den Berg, L. T. (2010). Misdiagnosis and mistreatment of a common side-effect—angiotensin-converting enzyme inhibitor-induced cough. Br. J. Clin. Pharmacol. 69, 200–203. doi: 10.1111/j.1365-2125.2009.03571.x
- Wang, X., Wang, Y., Feng, X., Lu, Y., Zhang, Y., Wang, W., et al. (2016). Systematic review and meta-analysis of randomized controlled trials on Wenxin keli. Drug Des. Dev. Ther. 10, 3725–3736. doi: 10.2147/DDDT.S112333
- Wang, Y. X. (2017). Clinical Research of Curative Effect and Short-Term Prognosis of Xinmailong Injection in the Treatment of the Patients with Chronic Heart Failure. Kunning Medical University.
- Writing Committee, M., Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E. Jr., et al. (2016). 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 134, e282–e293. doi: 10.1161/CIR.000000000000435
- Wu, C. S. (2015). Clinical observation on Xinmailong injection in treatment of 50 patients with chronic heart failure. *Strait Pharm. J.* 27, 123–124.
- Wu, T. K., and HH, Y. (2015). Clinical effect of Xinmailong injection on patients with heart failure of ischemic cardiomyopathy. *Med. J. Chin. People Health* 27, 74–108.
- Xu, Y., and Xu, F. Z. (2016). Clinical observation of Xinmailong injection in treating chronic heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 14, 2413–2414.
- Xue, J. G., Wang, X. L., Xu, Y., Li, F. C., Liu, L., Wang, X., et al. (2015). Treatment of chronic heart failure patients with Qi-Yang deficiency and blood stasis resistance syndrome by Xinmailong Injection: a multi-center randomized control study. *Chin. J. Int. Traditional West. Med.* 35, 796–800.
- Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., et al. (2013). 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013:16. doi: 10.1161/CIR.0b013e31829e8807
- Yang, H. Y., Cao, M. J., and Fu, Z. H. (2014). Effects of Xinmailong injection on pro-brain natriuretic peptide and troponin I in elderly patients with chronic heart failure. *China Pharm.* 23, 30–32.

- Yang, J., Chen, G. H., Jiang, B., and Yang, X. Q. (2012). Observation of curative effect on Xinmailong injection in the treatment of 110 patients with chronic heart failure. *China Med. Herald* 9, 93–94.
- Yang, M., Zhang, G., and Cao, X. B. (2015). Retrospective Study of Xinmailong injection in the treatment of chronic heart failure. *Cardiovasc. Dis. J. Int. Traditional Chin. West. Med.* 3, 21–23.
- Yang, X. Q., Xue, G. M., Chang, Y., Zhang, J. L., and Lu, X. (2015). Effect of Xinmailong injection on BNP and Uric Acid in patients with coronary heart failure. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 13, 829–830.
- Ye, K. F., Sun, P., Zhang, W., Fan, P., Hua, C. E., and Xia, Q. (2017). Observation of curative effect of Xinmailong injection on senior patients with chronic cardiac insufficiency. *Chin. J. Integ. Med. Cardio Cerebrovasc. Dis.* 19, 2428–2430.
- Yu, B. C., Wang, S., Xiong, Y. L., and Zhu, B. F. (2017). Observation of curative effect of Xinmailong injection on 70 patients with chronic heart failure. J. Mod. Med. Health 08, 1195–1196.
- Yuan, G. L., Zhao, Y. Q., Li, X. T., and Yang, M. (2015). Observation of Xinmailong injection on the treatment of chronic heart failure. *Hebei J. Trad. Chin. Med.* 37, 1545–1548.

- Zhang, H. Y. (2015). Clinical observation on Xinmailong injection in treatment of 59 patients with chronic heart failure. *Chin. J. Int. Med. Cardio Cerebrovasc. Dis.* 13, 218–220.
- Zhao, Z. Y., Qi, Z., Cui, X. E., An, F., and Wang, J. (2010). Effects of Xinmailong injection in the treatment of chronic heart failure. *J. Logistics* 19, 120–122.

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Lu, Zhang, Wang, Liu, Li, Zhou, Wu, Yang, Wen, Wei, Zhou, Zhao and Xiao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.