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Research Article

Efficacy of Qishen Yiqi Drop Pill for Chronic Heart Failure: An Updated Meta-Analysis of 85 Studies

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Background. Despite evidence for beneficial effects of Qishen Yiqi Drop Pill (QSYQ) on congestive heart failure, the majority of studies are based on insufficient sample sizes. The aim of this study was to evaluate the therapeutic effects of QSYQ using a meta-analysis approach. *Methodology/Principal Findings*. All relevant studies published before December 31, 2019, were identified by searches of various databases with key search terms. In total, 85 studies involving 8,579 participants were included. The addition of QSYQ to routine Western medicine increased 6-minute walking distance (SMD = 2.08, 95% CI: 1.72–2.44, $p < 0.001$), left ventricular ejection fraction (SMD = 1.05, 95% CI: 0.87–1.23, $p < 0.001$), and cardiac index (SMD = 1.44, 95% CI: 0.92–1.95, $p < 0.001$) and reduced brain natriuretic peptide (SMD = −2.28, 95% CI: -2.81 to -1.76, $p < 0.001$), N-terminal prohormone of brain natriuretic peptide (SMD = −2.49, 95% CI: -3.24 to -1.73, $p < 0.001$), left ventricular end-diastolic dimensions (SMD = −0.92, 95% CI: -1.25 to -0.59, $p < 0.001$), and left ventricular end-systolic dimensions (SMD = −0.55, 95% CI: -0.89 to -0.21, $p < 0.001$). The results were stable in subgroup analyses and sensitivity analyses. *Conclusions*. Our current meta-analysis indicated that QSYQ combined with Western therapy might be effective in CHF patients. Further researches are needed to identify which subgroups of CHF patients will benefit most and what kind of combination medicines work best.

1. Introduction

Most cardiovascular diseases eventually progress to chronic heart failure (CHF) [1]. Based on Framingham data, the lifetime risk of developing CHF is 20%, and the incidence increases with age, with a steep rise from 1.4–1.9% among middle-aged individuals to 12.8–14.7% among octogenarians [2]. As the population is aging, CHF is becoming the leading public health challenge worldwide. About half of individuals who are diagnosed with heart failure die within five years [3]. However, before death, CHF patients have to encounter constantly worsening and increasingly frequent suffering of symptoms caused by CHF, such as dyspnea, fatigue, edema, and a reduced ability to exercise [4, 5]. In addition to a reduced quality of life, CHF also results in heavy economic burden to both families and society [6, 7].

Qishen Yiqi Drop Pill (QSYQ) is a traditional Chinese medicine. It is composed of extracts of four herbaceous plants, *Salvia miltiorrhiza* Bunge ("danshen" in Chinese), *Panax notoginseng* ("Sanqi" in Chinese), *Astragalus membranaceus* (Fisch.) Bunge ("huangqi" in Chinese), and *Dalbergia odorifera* T. Chen ("Jiangxiang" in Chinese) [8]. It is an effective therapeutic agent for coronary artery disease [9]. Recently, extensive studies have explored the effects of QSYQ on CHF [10–12]. However, the results of these studies are not sufficient to establish standards for evidence-based practice, as most are limited by small sample sizes and differences in treatment duration. To the best of our knowledge, only one meta-analysis has evaluated the effects of QSYQ on CHF, including only 12 studies with a Jadad score of ≥2 [13]. Quality assessment is essential for meta-analyses; however, the Jadad scale is not suitable for study exclusion, as it contains no mention of allocation concealment, which is important in the evaluation of an RCT's internal validity [14]. Furthermore, many studies have been published since August 2018, the cutoff for the previous meta-analysis. Accordingly, in this study, we conducted an updated meta-analysis to explore the effectiveness of QSYQ in patients with CHF.

2. Methods

2.1. Data Sources and Study Identification. All studies exploring the effects of QSYQ in patients with CHF published before December 31, 2019, were included. Studies were identified by searching the PubMed, Cochrane Library, Wanfang Database, China Scientific Journal Database (VIP), China National Knowledge Infrastructure (CNKI), and China Biology Medicine (CBM) databases using different combinations of terms, including "QiShenYiQi", "Qishen Yiqi", "QSYQ", "Qishen Yiqi Drop Pill", "heart failure", and "cardiac dysfunction". All studies retrieved in this search were reviewed by two experienced researchers (HW and LL) independently and in parallel to minimize subjective selection bias. Divergences were adjudicated by discussion with a third investigator (XQ). Studies were excluded if they fulfilled the following criteria: (i) animal experiments and mechanistic studies; (ii) clinical studies but using non-RCT design; (iii) the study population was not patients with CHF; and (iv) data were repetitive or unavailable. There was no limitation with respect to language and region.

2.2. Data Extraction. Data were double entered by two investigators (HW and LL) independently. For every study, the following information was extracted: name of the first author, year of publication, paper title, journal name, enrolled start and end date, region of the study population, sample size of QSYQ groups and controls, treatment course, therapy in the control group, published language, methodological information (for quality assessment), and cardiac function-related parameters (6-minute walking distance (6MWD), brain natriuretic peptide (BNP), N-terminal prohormone of BNP (NT-pro BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimensions (LVEDD), left ventricular end-systolic dimensions (LVESD), and cardiac index). If concrete data could not be obtained, the corresponding authors were contacted by e-mail or other methods.

2.3. Quality Assessment. A modified Jadad scale was used to evaluate the quality of included studies, which referred to four aspects: randomization, concealment of allocation, double blinding, and withdrawals and dropouts. The scores were 2 points, 2 points, 2 points, and 1 point, respectively. The quality of the RCT receiving 1-3 points was evaluated as low, while 4-7 points was high [15, 16].

2.4. Ethics Statement. Ethical approval is not applicable for the meta-analysis as it is a secondary study.

2.5. Data Analyses. The meta-analysis was conducted using the meta package (Schwarzer, 2007; Balduzzi et al. 2019) for R software version 4.0.2. The outcomes included 6MWD, BNP level, NT-pro BNP level, LVEDD, LVESD, LVEF, and cardiac index. The standardized mean difference (SMD) was used to enable comparisons because means differed widely among studies owing to the substantial variation in cardiac function among participants. An SMD value of 0.2, 0.5, and 0.8 presents small, medium, and large effect sizes, respectively [17]. Before combination, heterogeneity was evaluated based on the I^2 metric of inconsistency and the χ^2-based Cochran Q test. The value of I^2 reflected the proportion of the impacts caused by between-study heterogeneity rather than sampling error [18]. In the absence of notable heterogeneity ($I^2 < 50\%$), a fixed effect model was used to calculate the effect size; when heterogeneity was detected ($I^2 \geq 50\%$), a random effects model was used. Detailed differences between the two models were described in our previous studies [19]. The z-test was used to assess the combined statistical outcomes. As the value of 95% CI of effective size only reflects the average level of the current included studies, in order to expect the true effect of QSYQ used in future studies, 95% prediction interval was also calculated according to the formula introduced by IntHout [20].

The treatment dose was the same in all studies; however, the treatment duration differed. Therefore, a subgroup analysis was conducted by treatment course. Durations of 1–4 weeks, 5–8 weeks, and ≥9 weeks were defined as short, intermediate, and long treatment courses, respectively. To confirm the results of this analysis, a meta-analysis of studies classified as high quality (Jadad score ≥ 4 points) was further performed. As there is still high heterogeneity among studies in subgroups stratified by treatment course and study quality, a Galbraith plot was used to identify potential sources of heterogeneity, and data were reevaluated after excluding outlier studies [21]. Publication bias was evaluated for parameters reported in at least 10 studies based on funnel plots, Begg's rank correlation test, and Egger's linear regression test implemented in Stata version 12.0 (Stata, College Station, TX, USA). If publication bias was identified, the trim-and-fill method was used for correction by conservatively imputing hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry [22]. A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the Included Studies. A total of 2,946 potential studies were retrieved by the initial search. Among these studies, 2,815 were discarded by screening titles, abstracts, or full-length texts, as summarized in Figure 1. Ultimately, 85 studies with a total of 8,579 participants (4,333 participants treated with a combination of QSYQ and routine Western medicine; 4,246 participants treated with only routine Western medicine as a control group) were included in the final analysis. The routine Western medicine mainly contained angiotensin-converting enzyme inhibitor (ACEI), loop diuretic (LD), aldosterone receptor antagonists (MRAs), digitalis, and β-adrenergic blocker (BB).

The characteristics of the 85 studies are summarized in Table S1 (supplementary data). In brief, all of the studies were published in Chinese. Twenty-five studies were defined as high quality by the modified Jadad scale (score ≥ 4). Both men and women were enrolled in all studies. Ischemic heart disease was the main cause of heart failure, and other causes included valvular heart disease, dilated cardiomyopathy, and hypertensive myocardiopathy, as well as pulmonary heart disease. The majority of patients were in NYHA functional classes II to IV, and half were

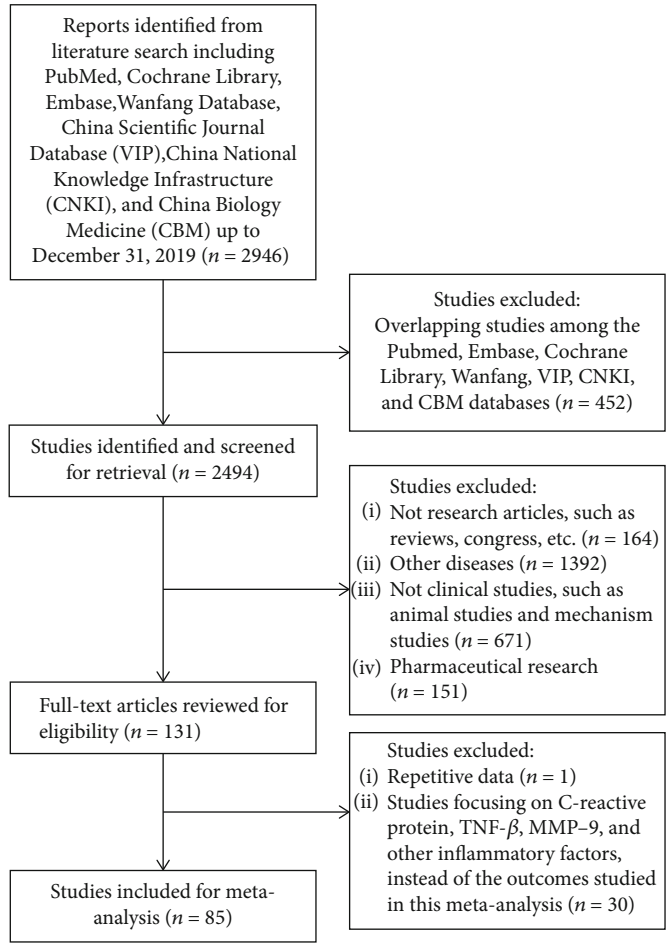


Figure 1: Flow diagram of studies included in this meta-analysis.

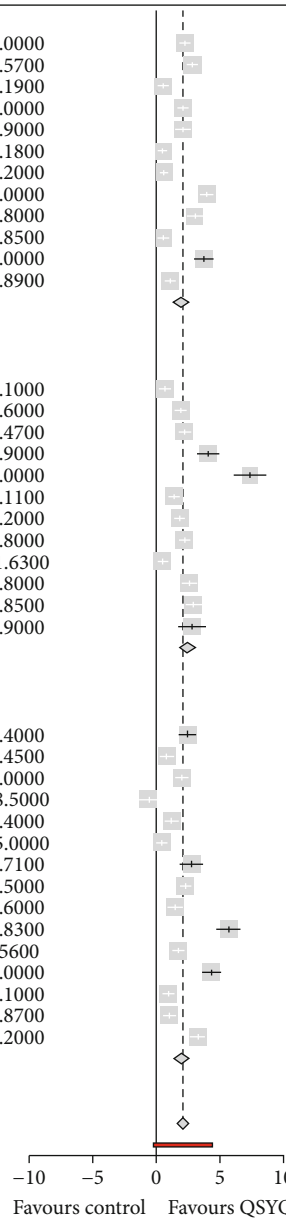
NYHA III to IV. Patients with CHF in the experimental groups were all treated with QSYQ (0.5 g once orally, 3 times daily) combined with routine Western drugs, and those in the control group were treated with routine Western drugs only. In total, 29, 24, and 32 studies reported short, intermediate, and long treatment durations, respectively.

3.2. Effects of QSYQ on Observed Outcomes. As shown in Figures 2(a)–2(g), the addition of QSYQ to conventional Western therapies in patients with CHF significantly increased 6MWD (SMD = 2.08, 95% CI: 1.72–2.44, $p < 0.001$); improved left ventricular enlargement, as evidenced by decreased LVEDD and LVESD (LVEDD: SMD = −0.92, 95% CI: -1.25 to -0.59, $p < 0.001$; LVESD: (SMD = −0.55, 95% CI: -0.89 to -0.21, $p < 0.001$); increased LVEF (SMD = 1.05, 95% CI: 0.87–1.23, $p < 0.001$); elevated cardiac index (SMD = 1.44, 95% CI: 0.92–1.95, $p < 0.001$); and decreased levels of BNP and NT-pro BNP (BNP: SMD = −2.28, 95% CI: -2.81 to -1.76, $p < 0.001$; NT-pro BNP: SMD = −2.49, 95% CI: -3.24 to -1.73, $p < 0.001$). In addition, we conducted a subgroup analysis stratified by treatment duration. Consistent results were observed among all subgroups for the parameters 6MWD, LVEF, BNP, NT-pro BNP, and cardiac index. In a sensitivity analysis of high-quality studies (JADAD score ≥ 4 (on a 7-point scale)) in both overall and subgroups, QSYQ administration in addition to conventional Western therapy significantly reduced levels of BNP and NT-pro BNP and improved cardiac function as well as exercise tolerance (Table 1).

In order to make further exploration of the true effect of QSYQ in the future practice settings, 95% prediction interval was also calculated. As shown in Figure 2(a), the effect size of 6MWD is 2.08 (95% CI 1.72-2.44), but its 95% prediction interval is -0.22 to 4.38. The prediction interval contains zero and values below zero. It indicated that QSYQ may not always be beneficial in clinical application. It might be even slightly harmful in some cases. The similar phenomena were also observed in the value of 95% prediction interval of BNP (-5.56 to 1.00), NT-pro BNP (-5.75 to 0.77), cardiac index (-0.38 to 3.25), LVEF (-0.52 to 2.62), and LVEDD (-2.97 to 1.12), as well as LVESD (-2.39 to 1.28).

3.3. Heterogeneity Analysis. Significant heterogeneity was observed in all analyses, including analyses of subgroups stratified by treatment course and study quality. Accordingly, a Galbraith plot was conducted. We identified 31 studies, 27 studies, 9 studies, 36 studies, 26 studies, 15 studies, and 5 studies, respectively, as the main sources of heterogeneity for 6MWD, BNP, NT-pro BNP, LVEF, LVEDD, LVESD,

Study	Total Mean	QSYQ SD	Total	Mean	Control SD	Standardised mean difference	SMD	95%-CI	Weight
Short-treatment course									
Zhong D 2010	74 353.00	35.0000	74	284.00	26.0000		2.23	[1.81; 2.64]	2.6%
Lin X 2010	106 456.43	30.7200	106	372.14	28.5700		2.83	[2.45; 3.21]	2.7%
An YX 2010	64 460.00	36.1100	64	442.00	31.1900		0.53	[0.18; 0.88]	2.7%
Zhang JL 2012	79 358.00	40.0000	79	280.00	34.0000		2.09	[1.70; 2.48]	2.7%
Zhao GH 2014	39 558.90	41.2000	39	482.90	30.9000		2.07	[1.51; 2.62]	2.6%
Gu MF 2014	65 459.21	35.1000	65	441.98	30.1800		0.52	[0.17; 0.87]	2.7%
Li YF 2015	90 462.10	36.1000	90	442.30	31.2000		0.58	[0.29; 0.88]	2.7%
Yuan L 2016	90 364.00	21.0000	90	279.00	22.0000		3.94	[3.43; 4.44]	2.6%
Wang QQ 2016	41 442.60	40.3000	41	321.60	38.8000		3.03	[2.39; 3.67]	2.5%
Ren LF 2017	58 426.15	68.1500	42	388.62	60.8500		0.57	[0.17; 0.98]	2.6%
Li GL 2018	40 478.00	46.0000	40	332.00	30.0000		3.72	[2.99; 4.46]	2.5%
Liu T 2019	54 538.72	71.4600	54	465.58	61.8900		1.09	[0.68; 1.49]	2.6%
95% CI random effects model 800			784				1.91	[1.24; 2.58]	31.4%
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 1.3377$, $p < 0.01$									
Mid-treatment course									
Jia HL 2012	40 412.80	66.7000	40	364.40	75.1000		0.67	[0.22; 1.13]	2.6%
Qin CH 2013	60 550.40	40.7000	54	480.80	30.6000		1.91	[1.46; 2.35]	2.6%
Jiao XQ 2013	62 466.23	31.2700	60	398.24	29.4700		2.22	[1.77; 2.68]	2.6%
Shao ZB 2015	35 467.00	17.4000	35	388.00	20.9000		4.06	[3.23; 4.90]	2.4%
Yu CY 2015	40 431.60	13.3000	40	330.50	14.0000		7.33	[6.09; 8.58]	2.1%
Wang CR 2016	50 458.32	34.8100	50	411.32	32.1100		1.39	[0.95; 1.83]	2.6%
Tang MX 2017	70 364.80	20.5000	70	329.80	17.2000		1.84	[1.44; 2.24]	2.6%
Xu J 2017	76 356.00	50.4000	70	248.00	46.8000		2.21	[1.79; 2.62]	2.6%
Yang K 2017	50 341.74	112.6600	50	287.58	101.6300		0.50	[0.10; 0.90]	2.6%
Wang QD 2018	48 562.50	41.3000	48	464.70	32.8000		2.60	[2.05; 3.15]	2.6%
Jin H 2019	45 572.52	41.5500	40	460.45	33.8500		2.91	[2.29; 3.53]	2.5%
Xu L 2019	15 356.80	47.5000	15	218.50	48.9000		2.79	[1.75; 3.83]	2.2%
95% CI random effects model 591			572				2.42	[1.78; 3.07]	30.3%
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.1765$, $p < 0.01$									
Long-treatment course									
Wu TC 2013	30 473.60	21.6500	30	353.87	65.4000		2.43	[1.75; 3.10]	2.5%
Zhang B 2013	30 437.47	51.9800	30	389.70	65.4500		0.80	[0.27; 1.32]	2.6%
Zhang JL 2013	50 424.00	18.0000	50	388.00	18.0000		1.98	[1.50; 2.47]	2.6%
Yin W 2014	20 344.50	136.5000	20	425.50	128.5000		−0.60	[−1.23, 0.04]	2.5%
Xie F 2015	36 449.10	60.3000	36	378.20	57.4000		1.19	[0.69; 1.69]	2.6%
Liu SQ 2016	52 416.00	162.0000	50	346.00	155.0000		0.44	[0.05; 0.83]	2.7%
Wang LZ 2016	20 569.61	40.6100	20	463.62	34.7100		2.75	[1.86; 3.64]	2.4%
Qiu YH 2016	80 579.80	43.6000	80	474.70	48.5000		2.27	[1.87; 2.67]	2.6%
Wu P 2017	30 368.30	65.2000	30	265.80	71.6000		1.48	[0.90; 2.05]	2.6%
Zhang XQ 2017	48 478.54	23.5600	48	359.43	17.8300		5.66	[4.75; 6.57]	2.3%
Chen M 2018	61 419.07	9.2200	61	404.36	7.5600		1.73	[1.32; 2.15]	2.6%
Wu BL 2018	50 368.00	18.0000	50	285.00	20.0000		4.33	[3.60; 5.06]	2.5%
Lv XB 2019	49 421.80	65.7000	49	356.20	72.1000		0.94	[0.53; 1.36]	2.6%
Zhang BZ 2019	40 512.29	80.1600	40	432.82	72.8700		1.03	[0.56; 1.50]	2.6%
Li XH 2020	62 360.50	45.3000	63	205.30	49.2000		3.26	[2.72; 3.80]	2.6%
95% CI random effects model 658			657				1.95	[1.32; 2.57]	38.3%
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.4381$, $p < 0.01$									
95% CI random effects model 2049			2013				2.08	[1.72; 2.44]	100.0%
95% prediction interval								[−0.22; 4.38]	
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.2566$, $p < 0.01$									
Residual heterogeneity: $I^2 = 96\%$, $p < 0.01$									



(a)

Figure 2: Continued.

Study	Total	Mean	QSYQ SD	Total	Mean	Control SD	SMD	95%-CI	Weight
Short-treatment course									
Zhang JL 2012	79	90.80	6.5000	79	105.00	18.0000	−1.04	[−1.38; −0.71]	2.8%
Zhao GH 2014	39	140.90	20.6000	39	187.60	20.9000	−2.23	[−2.80; −1.66]	2.7%
Ding SG 2014	50	468.60	214.5000	48	773.30	289.5000	−1.19	[−1.62; −0.76]	2.8%
Yuan L 2016	90	106.20	6.1000	90	149.50	12.4000	−4.41	[−4.96; −3.87]	2.7%
Ren LF 2017	58	171.60	98.5000	42	351.50	239.3000	−1.04	[−1.46; −0.61]	2.8%
Hu YC 2017	43	478.12	214.1300	42	778.56	290.6300	−1.17	[−1.63; −0.71]	2.8%
Shen J 2018	40	31.27	7.0200	40	72.66	9.5500	−4.89	[−5.78; −4.00]	2.6%
Hu YJ 2018	34	469.56	225.6900	34	763.48	204.1500	−1.35	[−1.88; −0.82]	2.7%
Zou J 2019	38	254.79	46.9800	38	359.85	54.3800	−2.05	[−2.61; −1.49]	2.7%
95% CI random effects model	471			452			−2.12	[−2.90; −1.33]	24.7%
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.3661$, $p < 0.01$									
Mid-treatment course									
Teng W 2012	30	210.00	141.2000	31	321.00	163.2000	−0.72	[−1.24; −0.20]	2.8%
Qin CH 2013	60	140.60	20.5000	54	186.50	20.7000	−2.21	[−2.68; −1.74]	2.8%
Hua JY 2013	43	684.30	103.4000	43	935.20	101.7000	−2.42	[−2.99; −1.86]	2.7%
Jiao XQ 2013	62	35.03	3.0300	60	48.01	3.4700	−3.96	[−4.58; −3.35]	2.7%
Shao ZB 2015	35	130.00	17.3000	35	166.00	23.7000	−1.72	[−2.27; −1.16]	2.7%
Ma CY 2015	30	21.51	19.0800	30	35.91	32.4400	−0.53	[−1.05; −0.02]	2.8%
Wang CR 2016	50	346.74	32.9100	50	471.56	30.6200	−3.90	[−4.57; −3.22]	2.7%
Xu J 2017	76	415.30	110.7000	70	975.10	107.1000	−5.11	[−5.79; −4.43]	2.7%
LiP 2017	47	136.52	14.3500	47	217.39	19.8700	−4.63	[−5.42; −3.84]	2.7%
Tang MX 2017	70	314.60	38.9000	70	394.80	41.5000	−1.98	[−2.39; −1.58]	2.8%
Wei Y 2017	95	123.58	24.5400	96	151.64	32.9400	−0.96	[−1.26; −0.66]	2.8%
Jin H 2019	45	244.12	29.1200	40	344.12	32.4500	−3.22	[−3.88; −2.57]	2.7%
Xu L 2019	15	68.32	10.2500	15	93.53	10.2400	−2.39	[−3.36; −1.43]	2.6%
95% CI random effects model	658			641			−2.58	[−3.33; −1.82]	35.4%
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 1.8403$, $p < 0.01$									
Long-treatment course									
Chen SR 2011	43	417.20	41.5000	47	592.10	51.2000	−3.70	[−4.39; −3.01]	2.7%
Chen TG 2011	60	933.00	125.0000	59	158.70	14.2000	8.61	[7.44; 9.78]	2.5%
Zhang B 2013	30	103.09	84.4300	30	119.93	93.3200	−0.19	[−0.69; 0.32]	2.8%
Zhang JL 2013	50	342.00	48.0000	50	576.00	36.0000	−5.47	[−6.34; −4.61]	2.6%
Wu B 2013	60	985.00	136.0000	60	1796.00	133.0000	−5.99	[−6.84; −5.14]	2.6%
Wu TC 2013	30	437.10	61.6100	30	450.53	68.0400	−0.20	[−0.71; 0.30]	2.8%
Zhang ZH 2013	40	40.87	2.6300	40	71.48	2.4500	−11.93	[−13.87; −9.98]	2.0%
Yin W 2014	20	204.50	176.5000	20	294.50	196.5000	−0.47	[−1.10; 0.16]	2.7%
He SL 2015	40	768.50	150.0800	40	1230.54	286.4100	−2.00	[−2.54; −1.46]	2.7%
Wang LZ 2016	20	170.61	40.6100	20	238.62	44.7100	−1.56	[−2.28; −0.84]	2.7%
Qiu YH 2016	80	198.20	40.5000	80	240.40	41.7000	−1.02	[−1.35; −0.69]	2.8%
Zhang XQ 2017	48	245.64	28.9500	48	342.39	31.4400	−3.18	[−3.78; −2.57]	2.7%
Li RC 2018	105	128.55	36.3200	105	231.52	38.5700	−2.74	[−3.12; −2.36]	2.8%
Wu BL 2018	50	76.00	10.3000	50	110.00	13.6000	−2.80	[−3.35; −2.24]	2.7%
Zhang BZ 2019	40	200.56	56.8300	40	243.66	50.7400	−0.79	[−1.25; −0.34]	2.8%
95% CI random effects model	716			719			−2.15	[−3.26; −1.04]	39.9%
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 4.6385$, $p < 0.01$									
95% CI random effects model	1845			1812			−2.28	[−2.81; −1.76]	100.0%
95% prediction interval								[−5.56; 1.00]	
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 2.5343$, $p < 0.01$									
Residual heterogeneity: $I^2 = 97\%$, $p < 0.01$									

Standardised mean difference

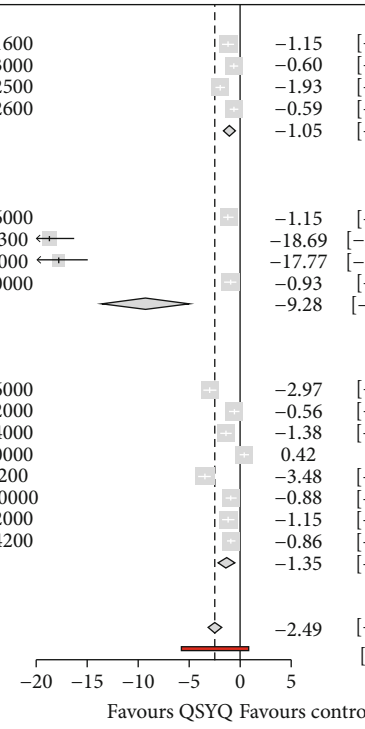
−10 −5 0 5 10

Favours QSYQ Favours control

(b)

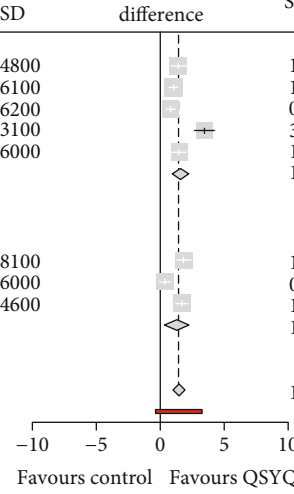
Figure 2: Continued.

Study	Total	Mean	QSYQ SD	Total	Mean	Control SD	SMD	95%-CI	Weight
Short-treatment course									
Wang X 2016	30	927.15	127.6800	30	1126.62	206.1600	−1.15	[−1.70; −0.60]	6.6%
Mao BY 2018	60	751.20	518.6000	60	1214.20	944.3000	−0.60	[−0.97; −0.24]	6.7%
Liu T 2019	54	1549.47	435.6100	54	2379.28	417.2500	−1.93	[−2.39; −1.47]	6.6%
Liu NR 2019	89	4035.59	411.6500	89	4287.15	430.2600	−0.59	[−0.90; −0.29]	6.7%
95% CI random effects model	233			233			−1.05	[−1.65; −0.45]	26.6%
Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.3301$, $p < 0.01$									
Mid-treatment course									
Jia HL 2012	40	478.60	214.7000	40	774.20	290.6000	−1.15	[−1.62; −0.67]	6.6%
Sun YL 2014	60	150.00	13.3200	60	420.06	15.3300	−18.69	[−21.12; −16.26]	4.0%
Yu CY 2015	40	685.20	14.2000	40	934.60	13.6000	−17.77	[−20.62; −14.91]	3.4%
Wang JW 2019	27	965.00	475.0000	26	1442.00	532.0000	−0.93	[−1.50; −0.36]	6.5%
95% CI random effects model	167			166			−9.28	[−13.80; −4.76]	20.6%
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 20.3503$, $p < 0.01$									
Long-treatment course									
Guan XJ 2013	50	478.60	154.7000	50	1174.20	290.6000	−2.97	[−3.54; −2.39]	6.5%
Shao B 2014	36	682.60	288.8000	37	878.00	397.2000	−0.56	[−1.02; −0.09]	6.6%
Xie F 2015	36	492.10	198.6000	36	770.10	200.4000	−1.38	[−1.90; −0.86]	6.6%
Liu SQ 2016	52	403.00	134.0000	50	351.00	110.0000	0.42	[0.03; 0.81]	6.7%
Chen M 2018	61	323.24	11.0100	61	363.46	11.9200	−3.48	[−4.05; −2.91]	6.5%
Zeng J 2018	35	2140.00	1120.0000	35	3240.00	1350.0000	−0.88	[−1.37; −0.39]	6.6%
Zhang L 2018	30	927.20	127.7000	30	1127.70	206.2000	−1.15	[−1.70; −0.60]	6.6%
Lv XB 2019	49	119.77	107.4200	49	215.99	113.4200	−0.86	[−1.28; −0.45]	6.7%
95% CI random effects model	349			348			−1.35	[−2.20; −0.49]	52.8%
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.4699$, $p < 0.01$									
95% CI random effects model	749			747			−2.49	[−3.24; −1.73]	100.0%
95% prediction interval								[−5.75; 0.77]	
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 2.1631$, $p < 0.01$									
Residual heterogeneity: $I^2 = 98\%$, $p < 0.01$									



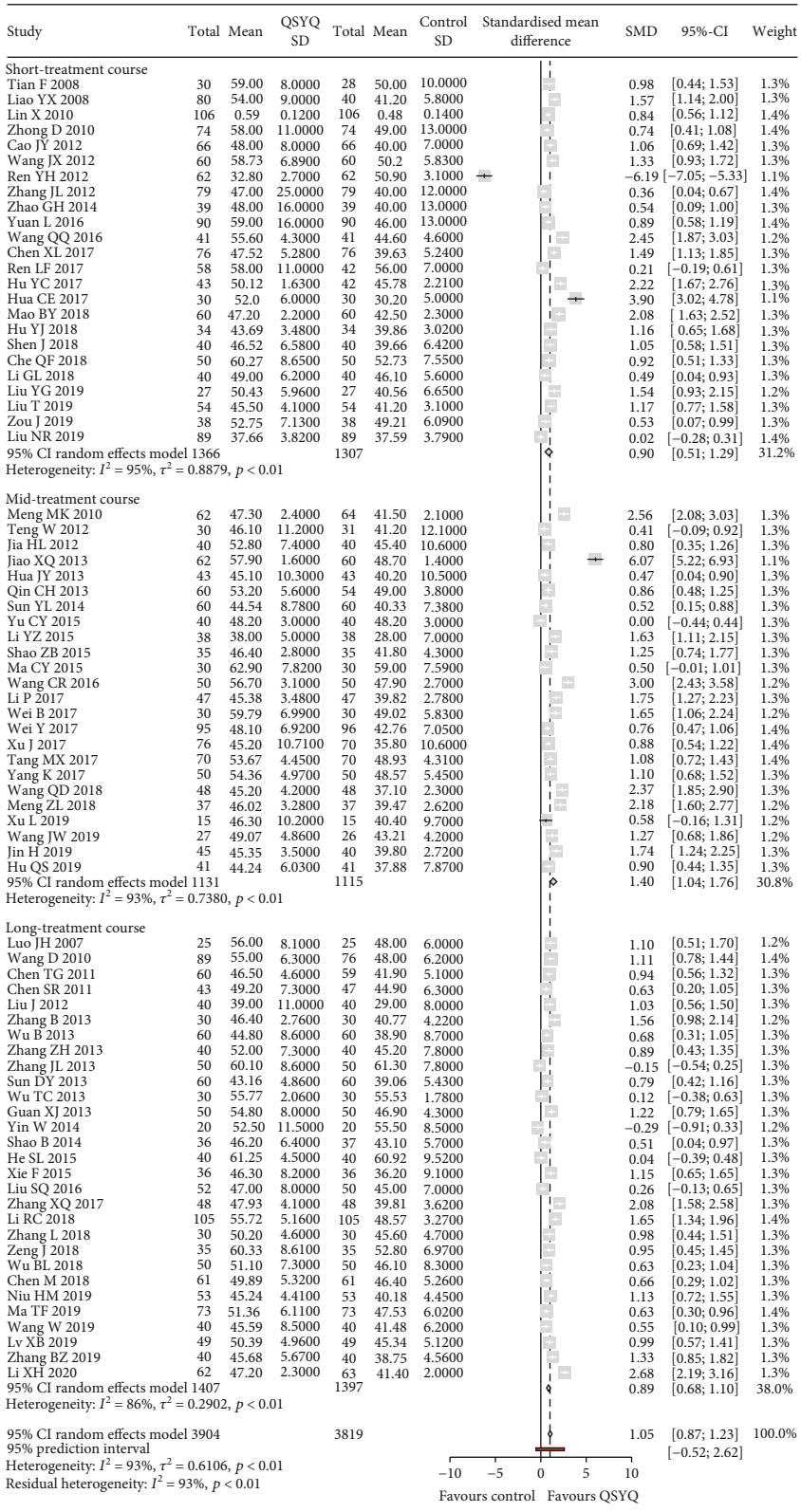
(c)

Study	Total	Mean	QSYQ SD	Total	Mean	Control SD	SMD	95%-CI	Weight
Short-treatment course									
Tian F 2008	30	3.14	0.3800	28	2.54	0.4800	1.37	[0.80; 1.95]	12.0%
Lin X 2010	106	3.15	0.7600	106	2.46	0.6100	1.00	[0.71; 1.28]	13.5%
Zhong D 2010	74	3.17	0.8500	74	2.59	0.6200	0.78	[0.44; 1.11]	13.3%
Zhao GH 2014	39	3.67	0.2500	39	2.69	0.3100	3.45	[2.74; 4.16]	11.1%
Hua CE 2017	30	3.20	0.5000	30	2.40	0.6000	1.43	[0.86; 2.00]	12.0%
95% CI random effects model	279			277			1.55	[0.86; 2.24]	61.9%
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.5480$, $p < 0.01$									
Long-treatment course									
Zhang ZH 2013	40	3.89	0.2800	40	2.78	0.8100	1.81	[1.29; 2.34]	12.3%
Guan XJ 2013	50	3.10	0.6000	50	2.90	0.6000	0.33	[−0.06; 0.73]	13.0%
Niu HM 2019	53	3.21	0.5800	53	2.33	0.4600	1.67	[1.22; 2.11]	12.8%
95% CI random effects model	143			148			1.26	[0.29; 2.24]	38.1%
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.6872$, $p < 0.01$									
95% CI random effects model	422			420			1.44	[0.92; 1.95]	100.0%
95% prediction interval								[−0.38; 3.25]	
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.4830$, $p < 0.01$									
Residual heterogeneity: $I^2 = 92\%$, $p < 0.01$									



(d)

Figure 2: Continued.



(e)

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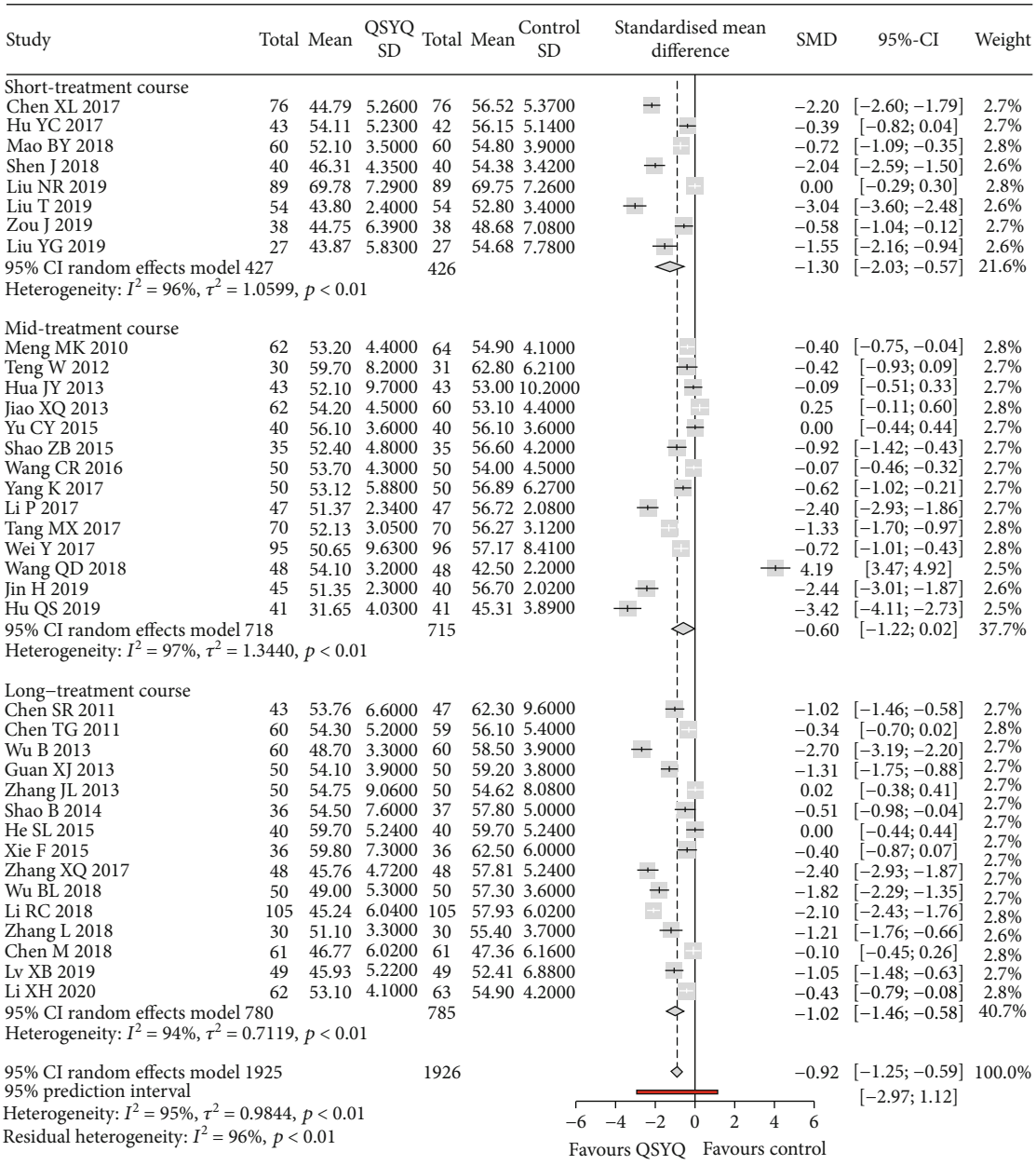

(f)

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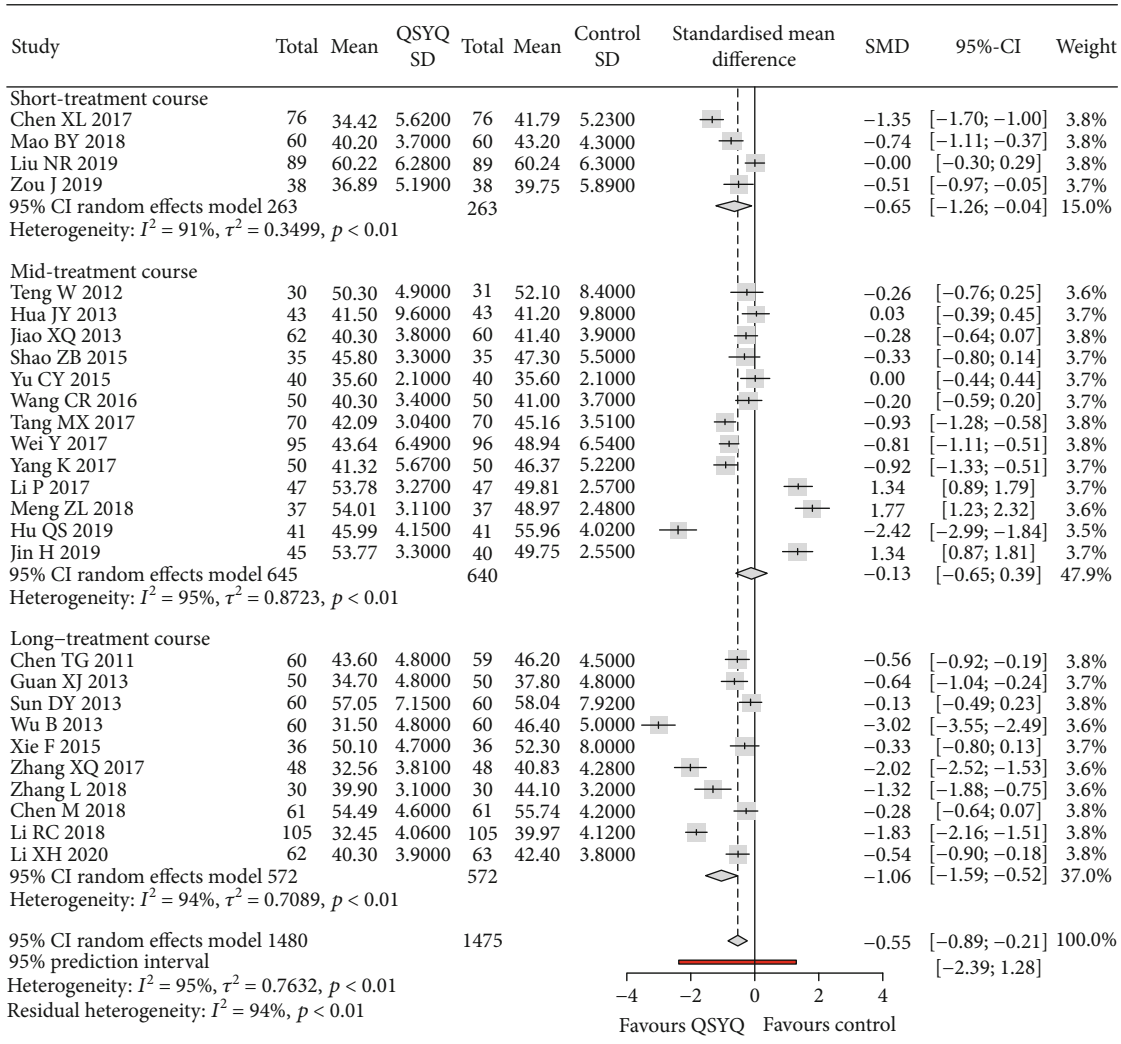

(g)

Figure 2: Forest plot of the meta-analysis of QSYQ addition on outcome parameters: (a) the forest plot for 6MWD; (b) for BNP; (c) for NT-pro BNP; (d) for cardiac index; (e) for LVEF; (f) for LVEDD; (g) for LVESD.

and cardiac index (Figure 3). The heterogeneity was effectively removed or decreased after the exclusion of these outlier studies, but the SMD values and 95% CIs did not change substantially (6WMD: SMD = 1.71, 95% CI = 1.54, 1.87, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.15; BNP: SMD = −1.93, 95% CI = −2.12, −1.75, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.28; NT-pro BNP: SMD = −1.06, 95% CI = −1.25, −0.87, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.76; LVEF: SMD = 0.93, 95% CI = 0.87, 1.00, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.10; LVEDD: SMD = −0.73, 95% CI = −0.86, −0.61, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.27; LVESD: SMD = −0.54, 95% CI = −0.66, −0.43, p_{SMD} < 0.001 , $p_{heterogeneity}$ = 0.20; and cardiac index: SMD = 1.17, 95% CI = 0.88, 1.46, p_{SMD} < 0.001, $p_{heterogeneity}$ = 0.28).

3.4. Publication Bias. A visual inspection of funnel plots for 6MWD, BNP, NT-pro BNP, and LVEF revealed asymmetry (Figure 4). Both Begg's test and Egger's test provided evidence for publication bias (6MWD: Begg's test z = 3.73, p < 0.001, and Egger's test p < 0.001; BNP: Begg's test z = 4.02, p < 0.001, and Egger's test p = 0.010; NT-pro BNP: Begg's test z = 3.47, p = 0.001, and Egger's test p < 0.001; and LVEF: Begg's test z = 3.27, p = 0.001, and Egger's test p = 0.024). We used the trim-and-fill method to recalculate the pooled effect size. A total of 10 and 19 studies, respectively, were added to the funnel plots for 6MWD and LVEF, but the pooled SMD was not affected. For BNP and NT-pro BNP, no new studies were added, but the pooled effect size changed significantly (Figure 5). See Discussion for a more detailed interpretation of these findings. There was no evidence for significant publication bias in analyses of LVEDD and LVESD.

4. Discussion

To the best of our knowledge, this is the largest systematic review and meta-analysis of the effect of QSYQ on CHF. Our results indicated that the addition of QSYQ to routine

Table 1: Summarized results of the meta-analysis in high-quality studies.

Parameters	Category	Studies	Participants	SMD (95% CI)	p	I^2 (%)	Heterogeneity, p
	Overall	11	1065	2.38 (1.63 to 3.13)	<0.001	96	<0.001
				Adjustment by treatment course			
6MWD	1-4 wk	1	180	3.94 (3.43 to 4.44)	<0.001	NA	NA
	5-8 wk	5	475	2.13 (1.19 to 3.07)	<0.001	94	<0.001
	<8 wk	5	410	2.31 (1.10 to 3.52)	<0.001	96	<0.001
	Overall	13	1464	-2.90 (-3.76 to -2.03)	<0.001	97	<0.001
				Adjustment by treatment course			
BNP	1-4 wk	2	278	-2.80 (-5.95 to 0.36)	0.08	99	<0.001
	5-8 wk	6	680	-2.70 (-3.77 to -1.63)	<0.001	96	<0.001
	<8 wk	5	506	-3.36 (-5.25 to -1.46)	<0.001	98	<0.001
	Overall	6	645	-3.58 (-5.15 to -2.01)	<0.001	98	<0.001
				Adjustment by treatment course			
NT-pro BNP	1-4 wk	1	178	-0.59 (-0.90 to -0.29)	<0.001	NA	NA
	5-8 wk	2	200	-9.87 (-27.06 to 7.32)	0.26	99	<0.001
	<8 wk	3	267	-1.80 (-3.46 to -0.14)	0.03	97	<0.001
	Overall	24	2611	1.08 (0.84 to 1.33)	<0.001	88	<0.001
				Adjustment by treatment course			
LVEF	1-4 wk	4	610	0.82 (0.19 to 0.45)	0.01	93	<0.001
	5-8 wk	9	962	1.29 (0.86 to 1.71)	<0.001	89	<0.001
	<8 wk	11	1039	1.02 (0.69 to 1.36)	<0.001	84	<0.001
	Overall	14	1665	-1.34 (-1.87 to -0.80)	<0.001	96	<0.001
				Adjustment by treatment course			
LVEDD	1-4 wk	2	330	-1.09 (-3.25 to 1.06)	0.32	99	<0.001
	5-8 wk	7	762	-1.58 (-2.33 to -0.83)	<0.001	95	<0.001
	<8 wk	5	573	-1.10 (-2.04 to -0.15)	0.02	96	<0.001
	Overall	13	1592	-0.60 (-1.14 to -0.05)	0.03	96	<0.001
				Adjustment by treatment course			
LVESD	1-4 wk	2	330	-0.67 (-1.99 to 0.65)	0.32	97	<0.001
	5-8 wk	7	762	-0.28 (-1.12 to 0.55)	0.51	97	<0.001
	<8 wk	4	500	-1.12 (-2.04 to-0.19)	0.02	95	<0.001

6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; NT-pro BNP: N-terminal prohormone of BNP; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimensions; LVESD: left ventricular end-systolic dimensions.

Western medicine might inhibit cardiac hypertrophy and improve cardiac function and exercise tolerance, as evidenced by decreases in LVEDD and LVESD as well as increases in 6MWD, LVEF, and cardiac index.

Qishen Yiqi is a widely used Chinese herbal medicine with a "qi invigorating and blood activating" property [23]. The dripping pill preparation (QSYQ) is a commercial herbal medicine approved by the China Food and Drug Administration (CFDA) in 2003 and is used extensively in clinical settings to treat cardiovascular diseases, such as angina pectoris, and for the secondary prevention of myocardial infarction [24, 25]. Recent studies have explored the effectiveness of OSYQ in patients with CHF [26–28]. A lack of consistency across these studies used to be explained by small sample sizes and differences in treatment courses, among other factors. Only one previous meta-analysis has been published in 2019 by Chang et al. [13]. It included 12 high-quality studies (Jadad ≥ 2) involving 942 patients with CHF and suggested that QSYQ is effective and safe for improving ventricular remodeling and heart function in patients, consistent with the results of our study. Our meta-analysis included 85 studies of 8,579 total patients with CHF, providing much greater statistical power. Besides, we made relatively more sufficient exploration on heterogeneity, such as subgroup analyses according to treatment course and study quality and analyses of heterogeneity based on Galbraith plots, as well as cut-and-fill method.

The current study showed that there were substantial heterogeneity and publication bias among all published literatures in this field. We analyzed all outlier studies identified by the Galbraith plot and found that the high heterogeneity among studies could not be explained by a single factor. It was potentially generated by a combination of factors, including population age, sex, primary diseases, courses of diseases, treatment courses, original cardiac function, and study design. For example, as to application of combined

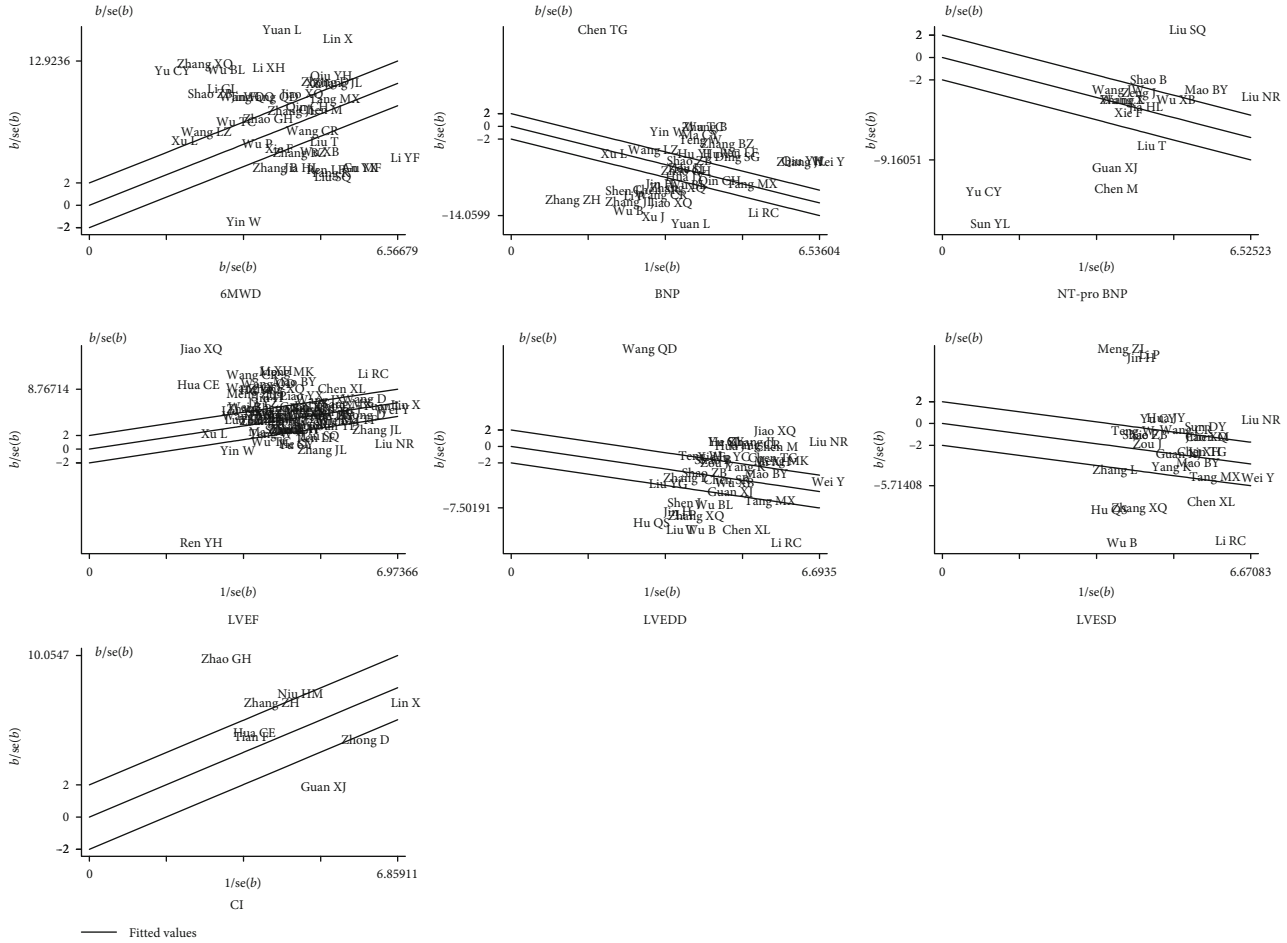

Figure 3: Galbraith plots for all the parameters.

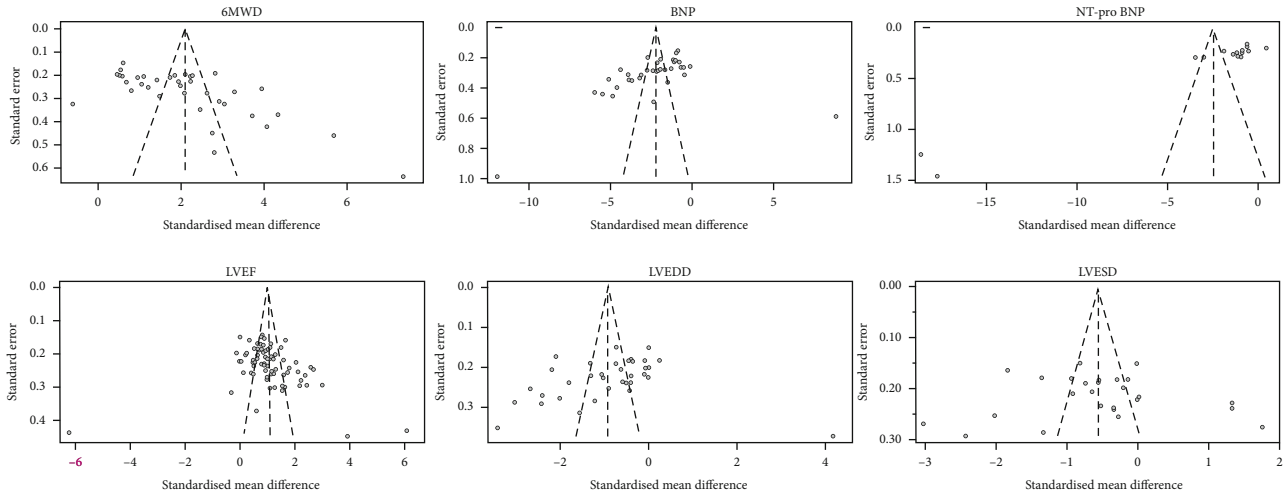

Figure 4: Funnel plots for all the parameters.

medication, there are 77 studies (77/85) that reported about the routine Western medicine used in their studies, which contains angiotensin-converting enzyme inhibitor (ACEI), loop diuretic (LD), aldosterone receptor antagonists (MRAs), digitalis, and β-adrenergic blocker (BB). The remaining eight (8/85) studies did not mention about the detailed definition of routine Western medicine. But as the etiology of heart failure (i.e., ischemic heart disease, valvular heart disease, dilated cardiomyopathy, and hypertensive myocardiopathy, as well as pulmonary heart disease) and complications of patients

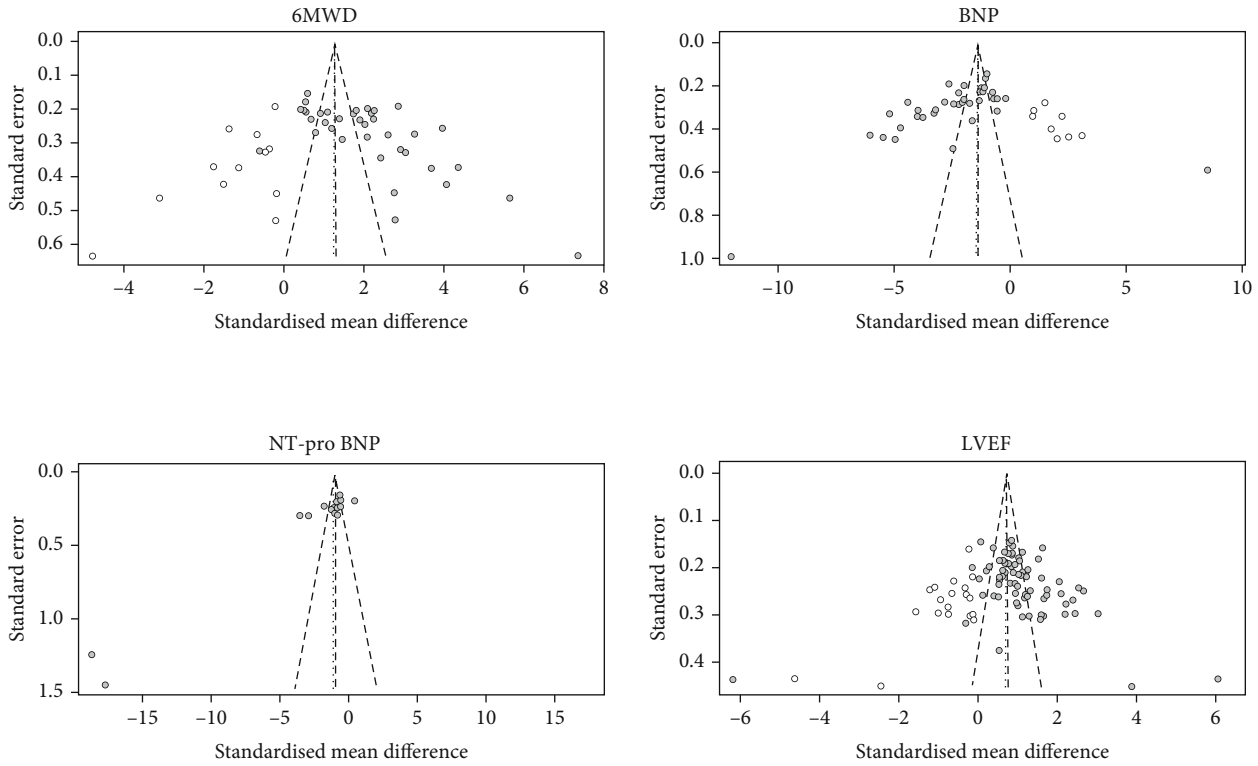

Figure 5: Filled funnel plots for all the parameters.

(i.e., blood pressure disorder and renal dysfunction) enrolled in these studies are different, the actual medicines used in every patient and also across each collected study are not consistent. Moreover, as stated by the included studies, some medicines for specific primary diseases were also used in part of these patients. For instance, patients with ischemic cardiomyopathy also take antiplatelet drugs, statin, and nitrates. This clinical diversity (or clinical heterogeneity) in clinical meta-analysis is inevitable and always unable be explored furtherly, unless more detailed individual information of every patient could be provided by the original studies. In addition, potential publication bias existing in this field and heterogeneity would impact each other when both present, which is not uncommon in many published meta-analysis [29]. Similarly, as indicated, it is unrealistic to reliably distinguish the impact of publication bias and heterogeneity in meta-analysis unless detailed and individualized data are available [30]. For the current study, a total of 85 studies were included, making it impossible to obtain detailed raw data from all these studies. Therefore, we could not make further quantified analysis on the impact of this clinical diversity on the overall heterogeneity. The existence of publication bias and the substantial heterogeneity in the published literatures may temporarily limit the clinical evidence levels and recommendation grades of QSYQ in heart failure at the moment. Besides, the results of 95% prediction interval showed that QSYQ might not always be effective in all clinical cases. Given all the abovementioned, it is suggested that, in future researches, we should focus on the efficacy of QSYQ in a certain type of patients to ensure homogeneity and, at the same time, encourage the reporting of negative results in medication researches. In practical settings, when referring to existing evidences, clinicians should make individualized dialectical therapeutic medication plan according to the specific conditions of patients.

Findings at the cellular and organismal levels tended to support the protective effect of QSYQ in CHF. Wang et al. studied an HF rat model induced by left anterior descending coronary artery ligation and found that QSYQ can exert an antifibrotic effect by downregulating the renin-angiotensin-aldosterone system pathway and subsequently inhibiting the expression of proteins in the arachidonic acid metabolic pathway [31]. Li et al. found that posttreatment with QSYQ obviously suppresses the expression of CD68 and transforming growth factor beta 1, thereby attenuating pressure overload-induced cardiac hypertrophy and myocardial fibrosis [32]. Wang et al. found that QSYQ reduces myocardial fibrosis induced by doxorubicin by promoting cardiac angiogenesis [33]. Zhang et al. showed that 24 combinatorial bioactive ingredients in QSYQ identified through UPLC-Q-TOF/MS significantly prevented myocardial injury; improved the ejection fraction and fractional shortening; decreased the release of cardiac enzymes, including CK, CK-MB, and LDH; alleviated mitochondrial dysfunction; and protected cell nuclei and mitochondrial mass [34]. Potential targets of QSYQ include extracellular signal-regulated kinase-1/2, peroxisome proliferator-activated receptor-gamma and heme oxygenase-1, β2-adrenergic receptor, and hypoxia-inducible factor 1α (HIF-1α) [35–37]. Cui et al. confirmed that QSYQ significantly suppresses myocardial hypertrophy and ventricular remodeling in aortic stenosis-induced HF rats; it is also remarkably better when

compared with single herbs [38]. Our previous study of QSYQ also indicated that it has protective effects against apoptosis and inhibits mitochondrial dysfunction [8].

Limitations of this study should be mentioned. First, we did not evaluate the prognostic value of QSYQ in CHF, including effects on mortality and rehospitalization, owing to the lack of available data from primary studies. However, since the parameters included in our study, such as LVEF and cardiac index, are strong predictors of prognosis, our results provide a reference for the prediction of prognosis in CHF [39, 40]. Second, there was high heterogeneity and potential publication bias because the sample sizes of the included studies were generally small. Our results for 6MWD, LVEF, cardiac index, LVEDD, and LVESD were stable in all sensitivity analyses. However, large-scale, multicenter, randomized, double-blind high-quality studies are still needed. Third, all studies included in the meta-analysis were conducted and published in Chinese. This is not surprising, as QSYQ is a traditional Chinese medicine. However, it is necessary to confirm its value in other populations, particularly as traditional Chinese medicines are gradually gaining popularity in Western countries.

5. Conclusion

Our current meta-analysis indicated that QSYQ combined with Western therapy might be effective in CHF patients. Further researches are needed to identify which subgroups of CHF patients will benefit most and what kind of combination medicine that works best.

Data Availability

All data used in this study have been listed in Supplementary Table S1.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

HW, LL, and XQ completed study searches, data collection, and quality assessment data. HW and LL performed statistical analyses and drafted the manuscript. SZ and SL contributed to study conception, study design, manuscript revision, and fund acquisition. All authors read and approved the final manuscript. Hao Wang and Lixia Li contributed equally to this work.

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Supplementary Materials

The detailed information of studies included in the current meta-analysis. *(Supplementary Materials)*

References

[1] A. Mosterd, B. Cost, A. W. Hoes et al., "The prognosis of heart failure in the general population. The Rotterdam Study," *European Heart Journal*, vol. 22, no. 15, pp. 1318–1327, 2001.

[2] D. M. Lloyd-Jones, M. G. Larson, E. P. Leip et al., "Lifetime risk for developing congestive heart failure," *Circulation*, vol. 106, no. 24, pp. 3068–3072, 2002.

[3] C. S. Hu, Q. H. Wu, D. Y. Hu, and T. Tkebuchava, "Treatment of chronic heart failure in the 21st century: a new era of biomedical engineering has come," *Chronic Diseases and Translational Medicine*, vol. 5, no. 2, pp. 75–88, 2019.

[4] G. Bleumink, A. Knetsch, M. Sturkenboom et al., "Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure - the Rotterdam Study," *European Heart Journal*, vol. 25, no. 18, pp. 1614–1619, 2004.

[5] E. E. van Riet, A. W. Hoes, K. P. Wagenaar, A. Limburg, M. A. Landman, and F. H. Rutten, "Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review," *European Journal of Heart Failure*, vol. 18, no. 3, pp. 242–252, 2016.

[6] N. R. Jones, A. K. Roalfe, I. Adoki, F. R. Hobbs, and C. J. Taylor, "Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis," *European Journal of Heart Failure*, vol. 21, no. 11, pp. 1306–1325, 2019.

[7] V. Askoxylakis, C. Thieke, S. T. Pleger et al., "Long-term survival of cancer patients compared to heart failure and stroke: a systematic review," *BMC Cancer*, vol. 10, no. 1, 2010.

[8] S. Zhang, H. Wang, L. Li et al., "Qishen Yiqi Drop Pill, a novel compound Chinese traditional medicine protects against high glucose-induced injury in cardiomyocytes," *Journal of Cellular and Molecular Medicine*, vol. 23, no. 9, pp. 6393–6402, 2019.

[9] C. Jianxin, X. Xue, L. Zhongfeng et al., "Qishen Yiqi Drop Pill improves cardiac function after myocardial ischemia," *Scientific Reports*, vol. 6, no. 1, 2016.

[10] X. L. Chen and Z. Li, "Observation on the efficacy of Qishen Yiqi Pills combined with conventional western medicine on chronic heart failure," *Nei Meng Gu Zhong Yi Yao*, vol. 3, no. 6, pp. 81-82, 2017.

[11] Z. Shao, X. Dai, J. Mao et al., "Effect of Qishen Yiqi Pills on heart function and hypertensitive C-reactive protein in patients with chronic heart failure," *Chinese Journal of Experimental Traditional Medical Formulae*, vol. 21, no. 15, pp. 152–155, 2015.

[12] M. Chen, X. L. Sun, and W. H. Xu, "Improvement of serum neuroendocrine and inflammatory factors in patients with chronic heart failure treated with Qishen Yiqi pills combined with traditional western medicine," *China Pharmaceuticals*, vol. 27, no. 6, pp. 48–50, 2018.

[13] M. Chang, L. Cheng, Y. Shen, Y. Zhang, Z. Zhang, and P. Hao, "Qishenyiqi dripping pill improves ventricular remodeling and function in patients with chronic heart failure: a pooled analysis," *Medicine*, vol. 98, no. 2, pp. e13906–e13906, 2019.

[14] C. M. Faggion, "Critical appraisal of AMSTAR: challenges, limitations, and potential solutions from the perspective of an assessor," *BMC Medical Research Methodology*, vol. 15, no. 1, 2015.

[15] X. Huang, X. Duan, Y. Zhu, K. Wang, J. Wu, and X. Tian, "Comparative efficacy of Chinese herbal injections for the treatment of community-acquired pneumonia: a Bayesian network meta-analysis of randomized controlled trials," *Phytomedicine*, vol. 63, p. 153009, 2019.

[16] D. Moher, B.'. Pham, A. Jones et al., "Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?," *Lancet*, vol. 352, no. 9128, pp. 609–613, 1998.

[17] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences*, Lawrence Erlbaum Associates: Routledge, Hillsdale, New Jersey, 1988.

[18] J. P. Higgins and S. G. Thompson, "Quantifying heterogeneity in a meta-analysis," *Statistics in Medicine*, vol. 21, no. 11, pp. 1539–1558, 2002.

[19] H. Wang, J. Liu, K. Liu et al., "β1-Adrenoceptor gene Arg389-Gly polymorphism and essential hypertension risk in general population: a meta-analysis," *Molecular Biology Reports*, vol. 40, no. 6, pp. 4055–4063, 2013.

[20] J. IntHout, J. P. Ioannidis, M. M. Rovers, and J. J. Goeman, "Plea for routinely presenting prediction intervals in meta-analysis," *BMJ Open*, vol. 6, no. 7, article e010247, 2016.

[21] D. Wang, Z. Y. Mou, J. X. Zhai, H. X. Zong, and X. D. Zhao, "Application of Stata software to test heterogeneity in meta-analysis method," *Chinese Journal of Epidemiology*, vol. 29, no. 7, pp. 726–729, 2008.

[22] L. Shi and L. Lin, "The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses," *Medicine*, vol. 98, no. 23, pp. e15987–e15987, 2019.

[23] W. Zhang, "Effect of Qishen Yiqi Pill on chronic heart failure of qi deficiency and blood stasis type," *Chinese Journal of Integrative Medicine on Cardio-/cerebro Vascular Disease*, vol. 7, no. 6, pp. 143-144, 2019.

[24] Z. C. Ji, H. Y. Hu, F. W. Yang et al., "Network meta-analysis of Yiqi Huoxue Chinese patent medicine for coronary heart disease with angina pectoris," *China Journal of Chinese Materia Medica*, vol. 44, no. 9, pp. 1927–1937, 2019.

[25] H. Cao, J. Zhai, W. Mu et al., "Use of comparative effectiveness research for similar Chinese patent medicine for angina pectoris of coronary heart disease: a new approach based on patient-important outcomes," *Trials*, vol. 15, no. 1, 2014.

[26] C. R. Wang, "Clinical analysis of the effect of Qishen Yiqi Pill on chronic heart failure," *China Medicine and Pharmacy*, vol. 6, no. 15, pp. 62–64, 2016.

[27] H. L. Jia and K. Q. Zhang, "Effect of Qishen Yiqi pills on cardiac function and NT-pro BNP in patients with ischemic heart failure," *Chinese Journal of Experimental Traditional Medical Formulae*, vol. 18, no. 2, pp. 228–230, 2012.

[28] M. X. Tang, S. L. Yan, and Y. L. Zhou, "Effect of Qishen Yiqi pill on capacity load and curative effect of chronic heart failure," *Zhong Yao Yao Li Yu Lin Chuang*, vol. 33, no. 5, pp. 172–175, 2017.

[29] D. Jackson, "The implications of publication bias for meta-analysis' other parameter," *Statistics in Medicine*, vol. 25, no. 17, pp. 2911–2921, 2006.

[30] J. L. Peters, A. J. Sutton, D. R. Jones, K. R. Abrams, L. Rushton, and S. G. Moreno, "Assessing publication bias in meta-analyses in the presence of between-study heterogeneity," *Journal of the Royal Statal Society: Series A (Stats in Society)*, vol. 173, no. 3, pp. 575–591, 2010.

[31] L. Lu, J. Wang, Y. Wu et al., "Qishenyiqi attenuates myocardial fibrosis in rats by inhibiting RAAS-mediated arachidonic acid inflammation," *Journal of Ethnopharmacology*, vol. 66, no. 16, pp. C103–C104, 2015.

[32] Y. C. Li, Y. Y. Liu, B. H. Hu et al., "Attenuating effect of post-treatment with QiShen YiQi Pills on myocardial fibrosis in rat cardiac hypertrophy," *Clinical Hemorheology and Microcirculation*, vol. 51, no. 3, pp. 177–191, 2012.

[33] L. J. Wang, L. Y. Wang, X. X. Zhou, G. Ruan, and G. Yang, "Qishen Yiqi Dropping Pills ameliorates doxorubicin-induced cardiotoxicity in mice via enhancement of cardiac angiogenesis," *Medical Science Monitor*, vol. 25, pp. 2435–2444, 2019.

[34] Y. Q. Zhang, J. H. Yu, W. Zhang et al., "An integrated evidence-based targeting strategy for determining combinatorial bioactive ingredients of a compound herbal medicine Qishen Yiqi dripping pills," *Journal of Ethnopharmacology*, vol. 219, pp. 288–298, 2018.

[35] X. Li, L. Wu, W. Liu et al., "A network pharmacology study of Chinese medicine QiShenYiQi to reveal its underlying multi-compound, Multi-Target, Multi-Pathway Mode of Action," *PLoS ONE*, vol. 9, no. 5, article e95004, 2014.

[36] J. Sun, H. Qian, X. Li, and X. Tang, "QishenYiqi Dripping Pill improves heart failure by up-regulation of β2-adrenergic receptor expression," *Journal of Heart Valve Disease*, vol. 26, no. 2, pp. 193–199, 2017.

[37] Y. U. Fu-Chao, X. U. Yan-Juan, T. O. Jia-Yi, L. U. Zhou-Zhou, and X. H. Zhang, "Therapeutic effects of Qishen Yiqi Dropping Pill on myocardial injury induced by chronic hypoxia in rats," *Chinese Journal of Natural Medicines*, vol. 10, pp. 776–780, 2015.

[38] Y. C. Cui, L. Yan, C. S. Pan et al., "The contribution of different components in QiShenYiQi pills® to its potential to modulate energy metabolism in protection of ischemic myocardial injury," *Frontiers in Physiology*, vol. 9, pp. 389–389, 2018.

[39] S. Kitada, S. Kikuchi, T. Tsujino, T. Masuyama, N. Ohte, and J-MELODIC study investigators, "The prognostic value of brain natriuretic peptide in patients with heart failure and left ventricular ejection fraction higher than 60%: a sub-analysis of the J-MELODIC study," *Esc Heart Failure*, vol. 5, no. 1, pp. 36–45, 2018.

[40] P. A. Grayburn, C. P. Appleton, A. N. DeMaria et al., "Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST)," *Journal of the American College of Cardiology*, vol. 45, no. 7, pp. 1064–1071, 2005.