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Efficacy and safety of coenzyme Q10 in heart failure: a meta-analysis of randomized controlled trials

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Abstract

Background The effectiveness and adverse effects of coenzyme Q10 for heart failure remain unclear owing to small sample sizes and variations in the quality of existing studies in literature.

Methods The databases of EMBASE, PubMed, Web of Science, CINAHL databases, Scopus, Cochrane Central Register of Controlled Trials, VIP, Wanfang, and CNKI were searched for randomized controlled trials on the coenzyme Q10-assisted treatment of heart failure. Relevant literature was retrieved, data were extracted, and the risk of bias of the included studies was evaluated by two investigators independently using the Review Manager 5.4 software and the STATA 15 software.

Results In total, 33 studies were included in this meta-analysis, which showed that all-cause mortality [RR = 0.64, 95% *CI* (0.48, 0.85), *P* = 0.002; GRADE: moderate quality], hospitalization for heart failure [RR = 0.50, 95% *CI* (0.37, 0.67), *P* < 0.00001; GRADE: moderate quality], New York Heart Association classification [MD = −0.29, 95% *CI* (−0.39, −0.19), *P* < 0.00001; GRADE: low quality], and brain natriuretic peptide level [MD = −91.97, 95% *CI* (−103.11, −80.83), *P* < 0.00001; GRADE: low quality] were lower in the coenzyme Q10 group than in the control group. Meanwhile, left ventricular ejection fraction [MD = 0.51, 95% *CI* (0.31, 0.71), *P* < 0.00001; GRADE: low quality] and 6-min walk test result [MD = 31.70, 95% *CI* (19.96, 43.43), *P* < 0.00001; GRADE: moderate quality] were better than those in the control group.

Conclusions According to the existing evidence, coenzyme Q10 reduces all-cause mortality, hospitalization for heart failure, New York Heart Association classification, and brain natriuretic peptide level and improves left ventricular ejection fraction and 6-min walk test result in those with heart failure without major adverse effects.

Trial registration This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/prospero), with the registration number CRD42023493184.

Keywords Heart failure, Safety outcomes, Coenzyme Q10, Meta analysis, Randomized controlled trial

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Introduction

Heart failure, a complex syndrome resulting from heart abnormalities, impairs heart function and manifests in symptoms like breathlessness and fatigue, along with signs of fluid buildup [1, 2]. As a prevalent syndrome affecting millions globally, it poses substantial health and economic burdens, with costs projected to escalate [3–6]. Characterized by impaired cardiac function and recurrent exacerbations, it carries a significant mortality risk, particularly for hospitalized patients [7]. The condition involves disrupted ATP production and calcium imbalance, leading to oxidative stress and mitochondrial damage, further compounded by overactive sympathetic responses [8–12].

In the past few decades, the treatment of heart failure has mainly relied on β-blockers, ACE inhibitors, and AT1 antagonists to reduce excessive neural and fluid activation and alleviate cardiac burden [13, 14]. Despite alleviating symptoms, these interventions have limited success in improving death and readmission rates [15]. The regulation of cardiac energy constitutes a novel therapeutic approach. Therapies that prevent myocardial energy consumption may play a role in the treatment and management of heart failure. As both an electron transporter and antioxidant, coenzyme Q10 boosts mitochondrial ATP production, which increases myocardial contractility [16, 17]. At present, it is used for heart failure treatment in some studies.

According to meta-analyses of randomized controlled trials (RCTs), coenzyme Q10 improves left ventricular ejection fraction (LVEF) regardless of New York Heart Association (NYHA) class [18–19]. In addition, two systematic reviews of coenzyme Q10 in heart failure reported a reduction in mortality rates [20, 21], whereas one did not [22]. Despite not being the primary treatment method for heart failure, coenzyme Q10 has been proven safe and effective. In spite of this, its efficacy and adverse reactions remain unclear due to small sample sizes and variable quality of existing studies. Thus, the present study conducted a meta-analysis to evaluate the effectiveness and safety of using coenzyme Q10 to treat patients with heart failure and provide evidence-based guidelines.

Materials and methods

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/prospero), with the registration number CRD42023493184.

Search strategy

To identify RCTs investigating the effect of coenzyme Q10 in patients with heart failure, the databases of EMBASE, PubMed, Web of Science, CINAHL, Scopus, Cochrane Central Register of Controlled Trials, VIP, Wanfang, and CNKI were searched. Next, coenzyme Q10 and heart failure concept groups were developed using medical subject headings and keywords from PubMed. Without applying any additional filters or limits, the Cochrane RCT filter for PubMed was combined with concept groups for coenzyme Q10 and heart failure. Up to April 20, 2024, all the abovementioned databases were searched by two researchers using the search strategies listed in appendix 1, and disputed areas were referred to a third researcher for resolution. To report this systematic review and meta-analysis, the recommendations in the PRISMA statement were followed [23].

Inclusion and exclusion criteria

Study design Studies published in medical journals on the effect of coenzyme Q10 on heart failure were retrieved. In order to reduce the bias of interpretation, only Chinese and English studies were included.

Participants Patients with heart failure aged > 18 years, regardless of their race, nationality, duration of illness, or LVEF were included.

Interventions The experimental group that received coenzyme Q10 as an adjuvant therapy with conventional heart failure treatment was included. For control, patients with heart failure who received only conventional treatment with or without placebo were included. In both groups, the relevant drugs were administered at any dosage for a minimum period of 1 month.

Outcomes The primary outcomes were all-cause mortality and hospitalization for heart failure. The secondary outcomes included LVEF, NYHA classification, brain natriuretic peptide (BNP) level, 6-min walk test (6MWT), and adverse events.

Exclusion criteria Non-Chinese and non-English language studies and duplicate studies were excluded. Moreover, studies without full text and with incomplete data were not considered. Finally, non-RCTs were excluded. Studies in phase1, 2 and 3 trials, observational studies, retrospective studies, reviews, and letters were excluded.

Study selection

Two authors independently screened the titles and abstracts of RCTs that used coenzyme Q10 treatment for patients with heart failure. The shortlisted literature was assessed by reading the title and abstract, and after excluding irrelevant literature, the full text was read to determine final inclusion. Any differences included in the decision were discussed and resolved after reaching a consensus. The kappa agreement index was used to evaluate the level of agreement between the two authors.

Data extraction

A self-developed data extraction form was used to extract the following data: basic information about the included studies, baseline characteristics of the study participants, specific information about the interventions, duration of treatment, and outcome indicators.

Data analysis

Meta-analysis was performed using the Review Manager 5.4 software and the STATA 15 software. For count data, the relative risk (RR) was used as the effect indicator and for measurement data, the mean difference (MD) or standardized mean difference was used. Statistically significant differences were assessed using the point estimates and 95% confidence intervals (CIs). Meanwhile, heterogeneity among the included studies was analyzed using the $\chi 2$ test (test level: $\alpha = 0.1$), and I^2 quantification was used to estimate its magnitude. If there was no statistical heterogeneity among the study results, a fixed-effects model was used for meta-analysis. When statistical heterogeneity was detected between the study results, the source of heterogeneity was further analyzed, and after excluding the impact of significant clinical heterogeneity, randomization was performed. A subgroup analysis, sensitivity analysis, or descriptive analysis was performed when there was evident clinical heterogeneity. The meta-analysis test level was set at $\alpha = 0.05$. The publication bias was assessed according to the funnel plot, the Begg's test and the Egger's test. To explore the robustness of the pooled results, sensitivity analysis was carried out using the leave-one-out method.

Risk of bias assessment

Two evaluators independently assessed the risk of bias of the included RCTs using the Cochrane Handbook 5.1.0 risk of bias assessment tool [24]. A third party was consulted when necessary to ensure the accuracy of the final study results. Seven points were followed to assess quality: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting; and (7) other biases. According to the criteria of "low risk of bias," "unknown risk of bias," and "high risk of bias," the quality of the included studies was comprehensively assessed.

Certainty of evidence

GRADE (Grading Recommendations, Assessment, Development, and Evaluation) was used to rate the certainty of evidence for each outcome. The GRADE assessment was carried out using the GRADEpro Guideline Development Tool. Through this approach, bias, inconsistency, indirectness, imprecision, and other considerations (e.g. publication bias) are ranked as "high", "moderate", "low," or "very low."

Results

Search results

In total, 3961 relevant records were obtained through the electronic search. Of these, 705 duplicate records were removed using the Endnote X9 software. The remaining 3256 records were assessed based on the title or abstract, resulting in the exclusion of 2814 ineligible records. Ultimately, 32 RCTs were included after reviewing the full-text of the remaining 386 records (Fig. 1). The two authors had a high agreement in study selection and data integration (kappa value = 0.825).

Study characteristics

The 32 RCTs included 3763 patients with heart failure: 1,898 cases in the treatment group and 1,845 cases in the control group. Among the studies, the maximum sample size was 322 cases [25] and the minimum was 6 [26]. While 22 studies were conducted in Asia [27–48], 1 study recruited participants from Europe, Australia, and Asia [49]. In the intervention group, coenzyme Q10 was combined with conventional treatment. In the control group, conventional treatment was used, with placebo in addition to conventional treatment in 12 studies [25, 26, 28, 39, 44, 48–54]. Except one study [39] that involved nasal drops, coenzyme Q10 was administered orally in all others. The characteristics of the included studies are shown in Table 1.

Risk of bias of included studies

Two investigators independently assessed the risk of bias in the included studies. There was insufficient information in most studies, which made a comprehensive assessment of the risk of bias difficult. Of the 32 studies, only 6 reported randomization methods [25, 32, 40, 48, 49, 53] and only 3 reported allocation concealment [44, 48, 49]. Meanwhile, 16 studies reported participant and personnel blinding to random assignment [25, 26, 32, 33, 36, 39, 44, 48–56]. The total number of cases in one study did not correspond to the number of grouped cases [29], whereas multiple groups were analyzed in another study, of which two data sets were used in this investigation [43]. Figure 2A and B show the risk of bias of included studies.

Meta-analysis results

Primary outcomes

All-cause mortality

Eleven studies, with 2070 participants (1035 in the coenzyme Q10 group and 1035 in the control group), reported all-cause mortality [25, 28–30, 33, 34, 36, 49–51, 53]. Meta-analysis showed that all-cause mortality

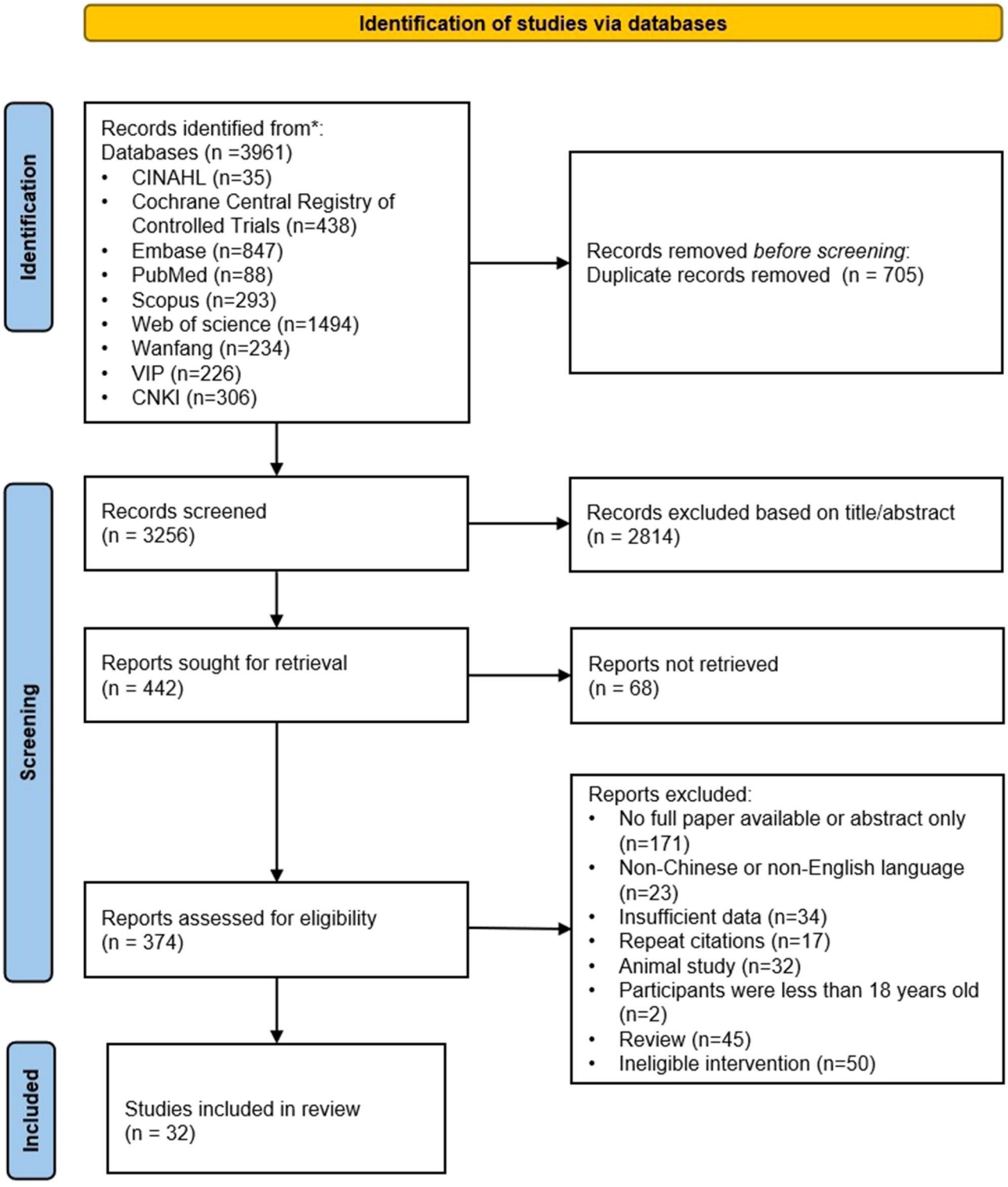

Fig. 1 Literature search flow diagram

Table 1 Characteristics of included studies

No.	study	Country	Sample size (EXP/CON)	Age(year) (EXP/CON)	Baseline LVEF (%)(EXP/CON)	Intervention	Control	Intervention duration	Outcomes	Follow-up
1	Permanetter et al. (1992)	Germany	15/10	52 ± 9	NR	CoQ10(33.3 mg, 3 times/day) + conventional therapy	conventional therapy alone	4months	④	NR
2	Morisco et al. (1993)	Denmark	319/322	26∽89/ 30∽88	NR	coenzyme Q10 50 mg twice or 3 times daily + conventional therapy	Placebo + conventional therapy	12months	①②	NR
3	Morisco et al. (1994)	Italy	6/6	49.8 ± 6.7	29 ± 11	CoQ10(50 mg, 3 times/day) + conventional therapy	Placebo + conventional therapy	1month	③⑥	12months
4	Hofman-Bang et al. (1995)	Denmark	79/79	61 ± 10	22 ± 10	CoQ10(100 mg, 1 time/day) + conventional therapy	placebo + conventional therapy	3months	①③⑥	6months
5	Li & Li (1999)	China	56/68	NR	NR	CoQ10(10∽20mg, 3 times/ day) + conventional therapy	conventional therapy alone	1month	⑦	12months
6	Munkholm et al. (1999)	Denmark	11/11	43∽73/ 39∽75	31 ± 5/ 26 ± 6	oral coenzyme Q10 100 mg twice daily + conventional therapy	placebo + conventional therapy	3months	①③	NR
7	Watson et al. (1999)	Australia	30/30	55 ± 11	26 ± 6	CoQ10(33 mg, 3 times/day) + conventional therapy	placebo + conventional therapy	3months	③	NR
8	Khatta et al. (2000)	America	28/27	67	27/30	oral coenzyme Q10 200 mg/ day + conventional therapy	placebo + conventional therapy	1months	①③	6months
9	Keogh et al. (2003)	Australia	79/79	62 ± 7/61 ± 9	NR	oral coenzyme Q10 150 mg/ day + conventional therapy	placebo + conventional therapy	3months	④⑥	3months
10	Belardinelli et al. (2006)	Italy	21/21	59 ± 9	37 ± 7	CoQ10(100 mg, 3 times/day) + conventional therapy	placebo + conventional therapy	1month	③	NR
11	Adarsh et al. (2008)	India	46/41	24.4∽77.5	NR	CoQ10(100 mg, 2 times/day) + conventional therapy	placebo + conventional therapy	14.5months	①	27.5months
12	Feng et al. (2010)	China	109/92	69 ± 7/ 68 ± 9	30.7 ± 6.3/ 31.2 ± 5.8	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	24months	①③⑥	24months
13	Pei et al. (2010)	China	62/66	62.47 ± 6.48	36 ± 4	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	12months	①③	12months
14	Bi (2012)	China	27/27	49.5 ± 12.5	25.77 ± 12.59/ 26.33 ± 10.43	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	3weeks	③④	NR

Table 1 (continued)

No.	study	Country	Sample size (EXP/CON)	Age(year) (EXP/CON)	Baseline LVEF (%)(EXP/CON)	Intervention	Control	Intervention duration	Outcomes	Follow-up
15	Yao et al. (2012)	China	50/50	62 ± 8/61 ± 9	36 ± 8	CoQ10(100 mg, 1 time/day) + conventional therapy	conventional therapy alone	3months	③④⑥	NR
16	Yang(2013)	China	100/100	68.4 ± 13.85	NR	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	2months	①	12months
17	Mortensen et al. (2014)	Multicenter	202/218	62.3 ± 12/ 62.3 ± 11	31 ± 10	oral coenzyme Q10 100 mg 3 times daily + conventional therapy	placebo with standard HF therapy	26.5months	①②③⑦	NR
18	Wu (2014)	China	35/35	84.5 ± 12.2/ 86.6 ± 14.3	NR	CoQ10(10 mg, 3 times/day) + conventional therapy	Placebo + conventional therapy	2months	①⑦	NR
19	Zhao et al. (2015)	China	62/66	63 ± 7/62 ± 6	36 ± 4	oral coenzyme Q10 30 mg/ day + conventional therapy	conventional therapy alone	12months	①③	NR
20	Ping et al. (2015)	China	61/61	58.3 ± 4.7	36.82 ± 8.53/ 37.19 ± 7.96	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	3months	③⑥	NR
21	Zhang (2015)	China	28/28	65.4 ± 10.4/ 63.1 ± 10.2	NR	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	6months	⑥⑦	NR
22	Zhang (2016)	China	30/30	38∽83	29 ± 7/ 31 ± 8	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	3months	②③④⑥	NR
23	Mareev (2017)	Russia	101/47	NR	39.3	coenzyme Q10 nasal drops (90 mg/ day = equivalent 225 mg/day for liposoluble tablets) + conventional therapy	placebo + conventional therapy	6months	③⑤	NR
24	Sobirin et al. (2019)	Indonesia	15/15	62 ± 8	55/58	oral coenzyme Q10 100 mg 3 times/day + conventional therapy	conventional therapy alone	1month	③	14months
25	Gan & Hu (2019)	China	30/30	57.5 ± 6.1/ 58.4 ± 6.7	35.1 ± 4.0/ 34.5 ± 3.9	CoQ10(30 mg, 1 time/day) + conventional therapy	conventional therapy alone	12months	③	NR
26	Jiang (2019)	China	100/100	61.9 ± 5.6/ 61.3 ± 5.9	32.78 ± 3.40/ 33.58 ± 3.76	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	1month	③⑥⑦	NR
27	Wu et al. (2019)	China	34/33	55.28 ± 12.53/ 55.12 ± 12.12	31.86 ± 6.53/ 31.86 ± 6.38	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	2months	③⑥⑦	NR

Table 1 (continued)

No.	study	Country	Sample size (EXP/CON)	Age(year) (EXP/CON)	Baseline LVEF (%)(EXP/CON)	Intervention	Control	Intervention duration	Outcomes	Follow-up
28	Kawashima et al. (2020)	Japan	10/10	70 ± 9	34.5 ± 4.0	ubiquinol 200 mg twice daily (400 mg/day) + conventional therapy	placebo + conventional therapy	3months	③⑤⑦	3months
29	Liu (2020)	China	59/59	58.67 ± 7.28/58.43 ± 7.55	33.47 ± 3.82/32.67 ± 3.59	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	1month	③⑥⑦	NR
30	Wan et al. (2021)	China	30/30	63.52 ± 3.76/63.41 ± 3.70	38.25 ± 3.19	CoQ10(20 mg, 3 times/day) + conventional therapy	conventional therapy alone	1.5months	③⑥⑦	NR
31	Zheng et al. (2021)	China	44/34	62.0 ± 3.9/62.8 ± 3.5	29	CoQ10(10 mg, 3 times/day) + conventional therapy	conventional therapy alone	3months	③	NR
32	Samuel et al. (2022)	Israel	19/20	75.4 ± 9.48	59.1 ± 6.1/59.3 ± 6.1	Treatment in the CoQ10 arm consisted of 100 mg three times daily + conventional therapy	placebo + conventional therapy	4months	③	4months

Note EXP, Experimental group; CON, Control group; NR, Not report; ①All-cause mortality; ②Hospitalization for heart failure; ③LVEF (%); ④NYHA classification; ⑤BNP (pg/mL); ⑥6MWT; ⑦Adverse events

was significantly lower in the coenzyme Q10 group than in the control group [RR = 0.64, 95% *CI* (0.48, 0.85), *P* = 0.002; GRADE: moderate quality]. Figure 3A shows that there was no heterogeneity among the included studies (*P* = 0.99, I^2 = 0%).

Hospitalization for heart failure

Three studies reported hospitalization for heart failure as an outcome indicator [25, 38, 49]. A total of 1034 participants were included, 511 in the coenzyme Q10 group and 523 in the control group. As shown in Fig. 3B, there was no significant heterogeneity among the included studies (*P* = 0.93, I^2 = 0%). The result showed that the coenzyme Q10 was able to reduce the hospitalization for heart failure compared to the control group. [RR = 0.50, 95% *CI* (0.37, 0.67), *P* < 0.00001; GRADE: moderate quality].

Secondary outcomes

Left ventricular ejection fraction (LVEF, %)

With regard to LVEF, 2339 patients from 24 RCTs were included (1197 in the coenzyme Q10 group and 1142 in the control group) [26, 29–32, 35, 36, 38–54]. Notably, the LVEF of patients with heart failure included in these studies was not statistically different at baseline. There was significant heterogeneity among the included studies (*P* < 0.00001, I^2 = 80%), and a random-effects model was used for the meta-analysis. Patients with heart failure in the coenzyme Q10 group had a significantly better LVEF than those in the control group [MD = 0.51, 95% *CI* (0.31, 0.71), *P* < 0.00001; GRADE: low quality]. In the subgroup analysis by the baseline LVEF, 22 RCTs including heart failure with reduced ejection fraction (HFrEF) demonstrated that the coenzyme Q10 group had a significantly higher LVEF than the control group [MD = 0.55, 95% *CI* (0.34, 0.76), *P* < 0.00001]. (Fig. 4).

NYHA classification

Five studies were included in this outcome index, covering 269 patients with heart failure (138 in the coenzyme Q10 group and 131 in the control group) [31, 32, 38, 55, 56]. The results showed that patients in the coenzyme Q10 group had a significantly lower NYHA classification than those in the control group [MD = −0.29, 95% *CI* (−0.39, −0.19), *P* < 0.00001; GRADE: low quality; Fig. 5A]. Heterogeneity among the included studies was low (*P* = 0.10, I^2 = 49%).

BNP (peg/mL)

Two RCTs reported BNP as an outcome indicator, including 162 participants (106 in the coenzyme Q10 group and 56 in the control group) [39, 44]. There was no significant heterogeneity among the included studies (*P* = 0.94, I^2 = 0%), and BNP was significantly lower in the coenzyme Q10 group than in the control group [MD = −91.97, 95% *CI* (−103.11, −80.83), *P* < 0.00001; GRADE: low quality; Fig. 5B].

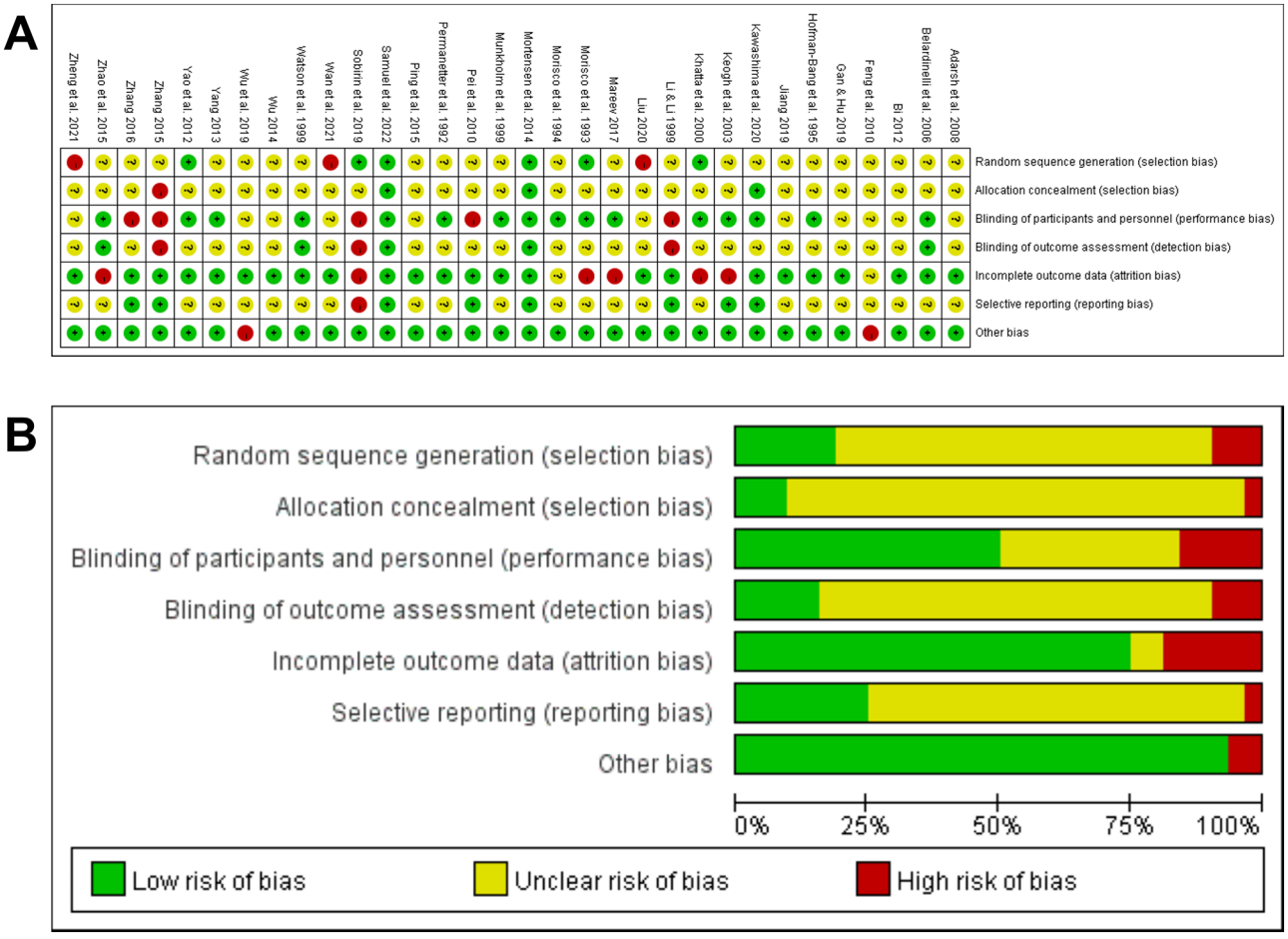

Fig. 2 Risk of bias summary and graph. *Note* **A**. Risk of bias summary; **A**. Risk of bias graph

6MWT

In total, 12 studies evaluated 6MWT in 1184 patients with heart failure, with 602 in the coenzyme Q10 group and 582 in the control group [26, 29, 32, 35, 37, 38, 42, 43, 45, 46, 50, 55]. As the included studies were highly heterogeneous ($P<0.00001$, $I^2=82\%$), a random-effects model was applied. Compared with the control group, patients with heart failure taking coenzyme Q10 had significantly longer 6MWTs [MD=31.70, 95% *CI* (19.96, 43.43), $P<0.00001$; GRADE: moderate quality]. Afterward, based on the length of the course of treatment, three groups were analyzed: ≤1-month group, 1–3-month group, and >3-month group. Figure 5C illustrates that regardless of the distances of the course of treatment, 6MWT distances were longer in patients with heart failure who received coenzyme Q10.

Adverse events

The incidence of adverse events was reported in nine studies [27, 34, 37, 42–46, 49]. A total of 1125 patients were included: 554 in the coenzyme Q10 group and 571 in the control group. Some of the adverse reactions were deep vein thrombosis, stroke, myocardial infarction, and arrhythmia. According to Fig. 5D, heterogeneity among the included studies was small ($P=0.19$, $I^2=33\%$; GRADE: moderate quality). Meanwhile, the results were inconclusive for the risk of adverse reactions between the CoQ10 and control groups [RR=0.85, 95% *CI* (0.46, 1.54), $P=0.58$].

Publication bias assessment and sensitivity analysis

Funnel plots were analyzed to detect publication bias, which indicated that the included studies were evenly distributed on the left and right sides of the combined effect value line, suggesting low publication bias. At the same time, the results of both the Begg's test and the Egger's test showed no significant publication bias (Appendix 2). A leave-one-out sensitivity analysis was performed on the outcomes of meta-analyses. Exclusion of individual studies did not lead to significant changes in the direction or magnitude of the combined estimates, indicating that the results were reliable (Appendix 3).

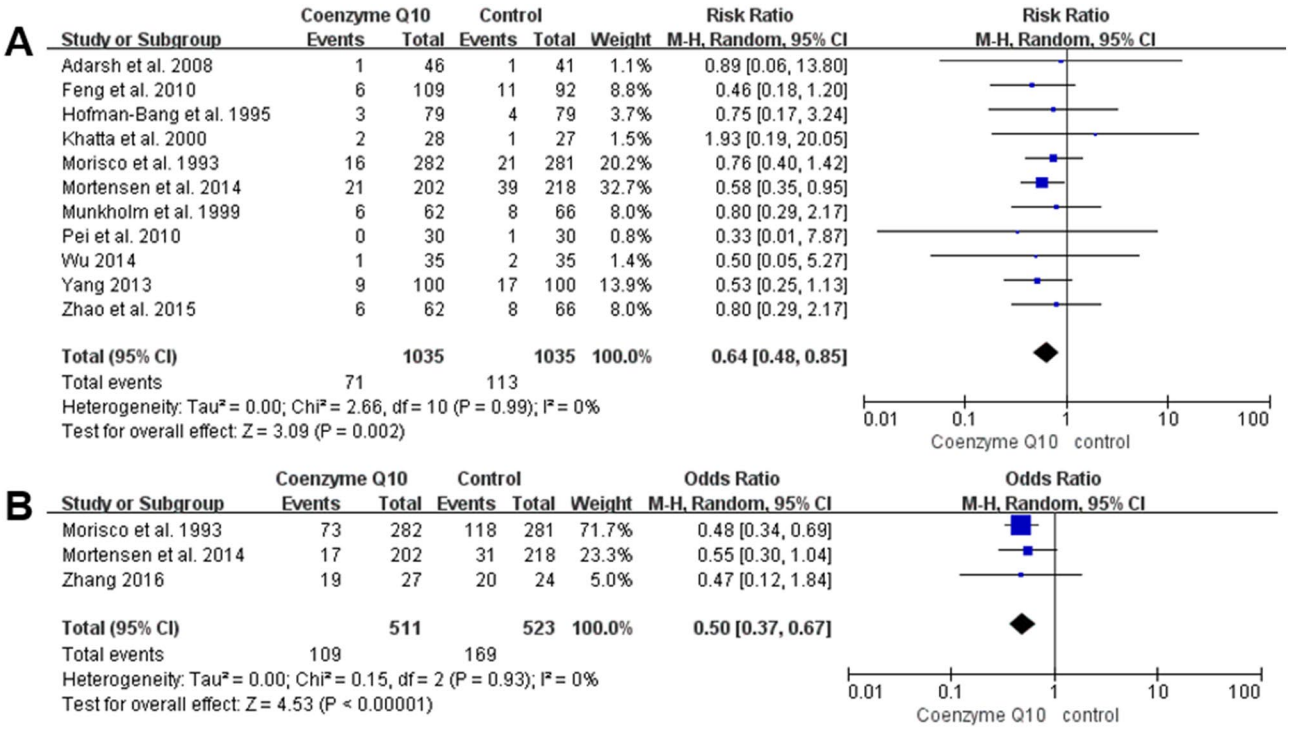

Fig. 3 Forest plot of the effect of coenzyme Q10 on primary outcomes change. *Note* **A**. Forest Plot of the Effect of Coenzyme Q10 on All-cause Mortality Change; **B**. Forest Plot of the Effect of Coenzyme Q10 on Hospitalization for Heart Failure Change

Discussion

This meta-analysis, incorporating 32 randomized controlled trials and 3,763 heart failure patients, reveals promising outcomes for coenzyme Q10 supplementation in conjunction with conventional therapy.

This study has shown that coenzyme Q10 reduced all-cause mortality and hospitalization for heart failure as well as increased LVEF in patients with heart failure [17–19], crucial for improving patient outcomes and reducing healthcare utilization. Moreover, a previous meta-analysis showed that coenzyme Q10 improved the NYHA classification of patients with heart failure, in line with a similar improvement found in the current study [21]. Coenzyme Q10 is a cofactor in the mitochondrial enzyme complex and participates in oxidative phosphorylation in the respiratory chain [57, 58]. In the absence of coenzyme Q10, ATP production is reduced and heart failure may be aggravated because of increased myocardial wall pressure. This, in turn, increases energy demand, resulting in imbalanced supply and demand [59]. Previous research has shown that there is a negative correlation between coenzyme Q10 level and the exacerbation of heart failure symptoms in patients with heart failure [20]. Therefore, the supplementation of coenzyme Q10 may reduce major adverse cardiovascular events and improve heart failure symptoms.

In addition to being a biomarker of cardiac disease, BNP is used as a surrogate marker for heart failure, acute coronary syndrome, and myocardial infarction. Research has shown that it plays a significant role in stratifying heart failure severity. To some extent, the decrease of BNP level reflects the improvement of heart function [60]. The present study showed that coenzyme Q10 significantly decreased BNP levels in patients with heart failure, similar to previous research [44]. 6MWT, which examines exercise tolerance, was chosen in this study, as it is a simple and inexpensive test that is well tolerated by patients with heart failure and is considered useful in their management [61]. The results of this meta-analysis suggested that no matter how long patients with heart failure were treated with coenzyme Q10, 6MWT distances were longer and points to its utility in promoting functional independence and daily activity among heart failure patients. Despite the moderate quality of the evidence supporting this conclusion, it deserves clinical attention. Safety data, showing no increase in adverse events, reinforces coenzyme Q10's tolerability as an adjunct therapy, important in the primary care setting where patient safety is paramount, especially for those with complex health conditions.

While recognizing the variable study quality and need for more rigorous research, our findings offer primary care physicians a basis for discussing coenzyme Q10 supplementation with suitable heart failure patients. Incorporating shared decision-making, physicians can weigh the potential benefits against the current evidence,

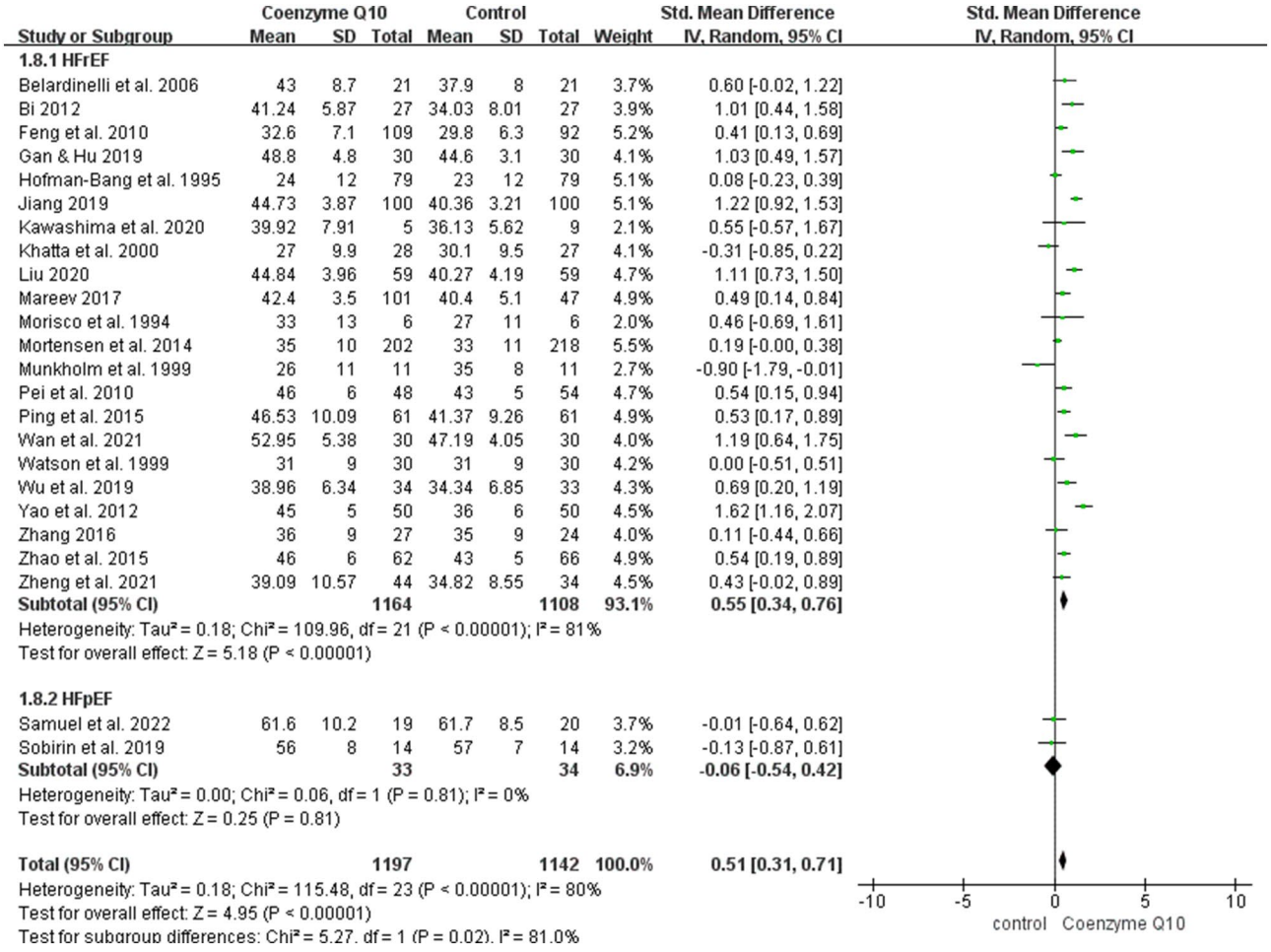

Fig. 4 Forest plot of the effect of coenzyme Q10 on left ventricular ejection fraction (LVEF) change

tailoring recommendations to each patient's circumstances. Ultimately, coenzyme Q10 emerges as a supplementary option, warranting cautious optimism and further exploration within the context of comprehensive heart failure management strategies.

Considering the importance of nonpharmacologic therapy for patients with heart failure, this study sought to explore how more data on nonpharmacologic therapy might affect outcomes. Unfortunately, few articles described non-pharmacologic treatments during the intervention, and even fewer reported whether surgically treated patients with heart failure were included. For example, one study advised patients to follow a low-fat diet during the trial, but no exercise program was provided [55]. Some studies did not make baseline comparisons related to non-pharmacological treatment for heart failure patients, such as comparing only their exercise capacity, while ignoring their exercise habits, such as their duration and frequency [49, 50]. In light of the important role exercise-based cardiac rehabilitation programs play in treating heart failure patients, further refinement is needed. Patients with heart failure were given coenzyme Q10 at doses ranging from 30 mg to 400 mg per day in the studies included. There was no determination of the minimum and optimal doses for coenzyme Q10 use, and further dose-response analyses will be required in the future.

This study significantly enhances knowledge on coenzyme Q10 (CoQ10) use in heart failure patients. By integrating recent trials with a large combined participant pool, we provide a robust update on CoQ10's effectiveness and safety, with broadened applicability of the results. A key novelty lies in the inclusion of Chinese RCTs, addressing a demographic gap in prior reviews and deepening the global comprehension of CoQ10 benefits across diverse populations. We meticulously examined CoQ10 impact on vital clinical measures, presenting a comprehensive view of its therapeutic prowess. These outcomes reinforce CoQ10 potential as a safe and efficacious supplement, accentuating its role in bolstering cardiac function and mitigating the disease's debilitating effects.

To overcome potential limitations, rigorous actions were undertaken. These included conducting a

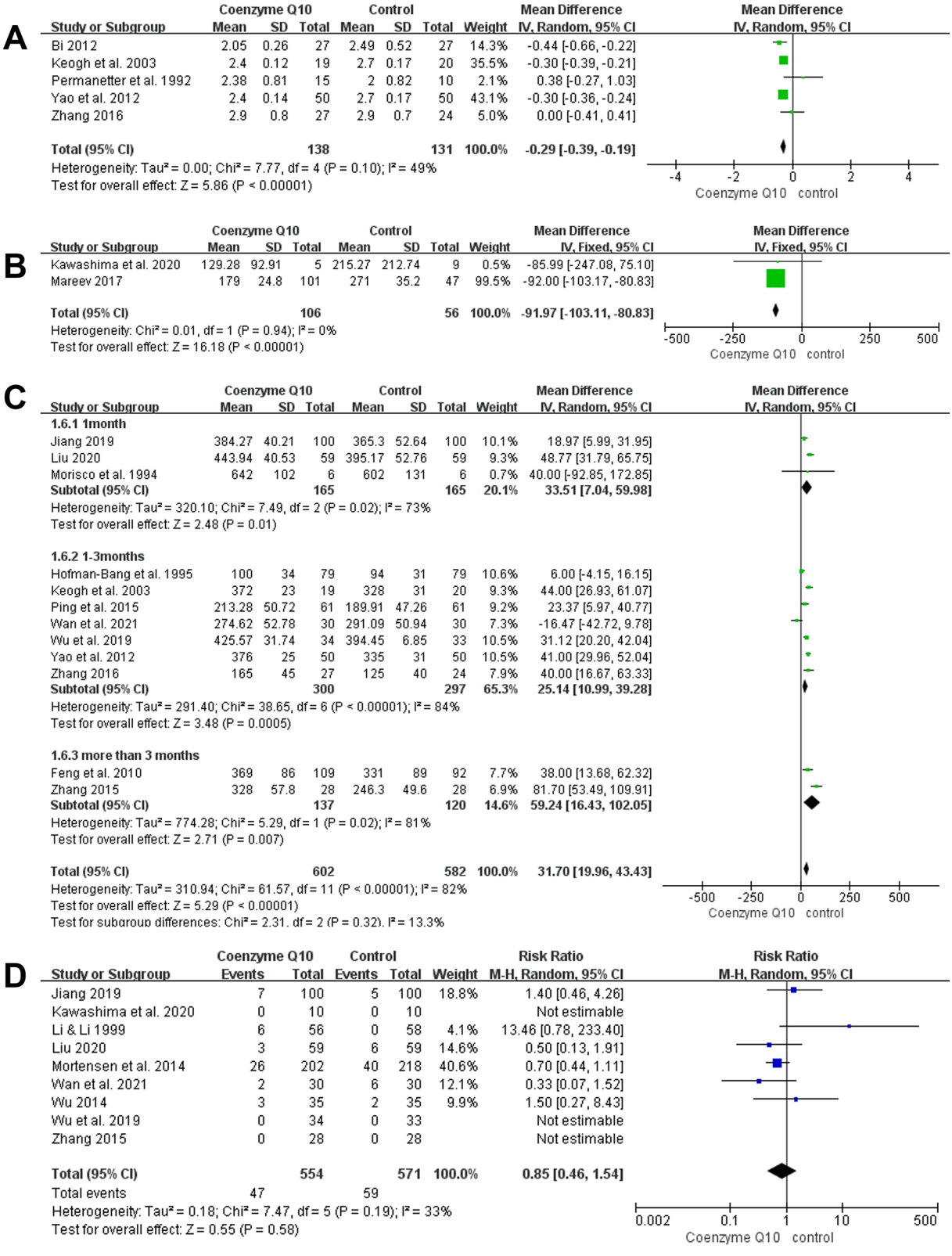

Fig. 5 Forest plots of the effect of coenzyme Q10 on NYHA classification, BNP, 6MWT, adverse events change. *Note* **A**. Forest Plots of the Effect of Coenzyme Q10 on NYHA Classification; **B**. Forest Plots of the Effect of Coenzyme Q10 on BNP Change; **C**. Forest Plots of the Effect of Coenzyme Q10 on 6MWT Change; **D**. Forest Plots of the Effect of Coenzyme Q10 on adverse events Change

comprehensive literature search focusing on high-quality randomized controlled trials, implementing strict inclusion and exclusion criteria, assessing risk of bias systematically, performing subgroup and sensitivity analyses to address heterogeneity, and other measures. However, there are still some unresolved limitations. First, heterogeneity among studies related to LVEF and 6MWT was high among the outcomes included. Although subgroup analysis based on the baseline LVEF and the length of the course of treatment had been performed, the sources of heterogeneity could not be identified. It was possible, however, that heterogeneity arose from differences in drug tolerance, different environments, and differences in how the indices were measured in different patients in addition to differences in the severity of their disease. Unfortunately, additional subgroups could not be analyzed owing to the lack of relevant data. Moreover, the dosage or duration of coenzyme Q10 administration was not uniform across studies, which may have affected the reliability of the results. In addition, accessibility issues hindered the search for grey literature, which is one of the limitations of this study. Finally, the risk of bias assessment of the included studies revealed that most were of low quality and methodologically flawed. To validate the results of the present study, additional high-quality RCTs are needed in the future.

Conclusions

In summary, current evidence suggested that adjuvant coenzyme Q10 therapy in patients with heart failure not only reduced all-cause mortality, hospitalization for heart failure, NYHA classification, and BNP levels but also improved LVEF and 6MWT. However, owing to the different severities of heart failure, long gap between studies, heterogeneity among the study populations, errors in the test results of each unit, and differences in the treatment dosages and courses, additional high-quality, large-sample, long-term follow-up clinical studies are needed to validate these conclusions.

Abbreviations

ATP	Adenosine triphosphate
ROS	Reactive oxygen species
RCTs	Randomized controlled trials
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
BNP	Brain natriuretic peptide
6MWT	6-minute walk test
RR	Relative risk
MD	Mean difference
SMD	Standardized mean difference
HFrEF	Heart failure with reduced ejection fraction

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

Designing this study: Z. G.; H. Y.; J. X.; L. X. Performed this study: J. X.; L. X.; X.Y.; H. S. Analyzing the data: J. X.; L. X.; C. C.; B. Y. Drafted the article: J. X.; L. X.; X.Y.; H. S.; C. C.; B. Y. Revised the article critically for important intellectual content: Z.G.; H. Y. All authors reviewed the manuscript.

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Data availability

The original data used during the current study can be obtained by contacting the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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