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Meta-analysis of targeted drugs for pulmonary hypertension to improve exercise tolerance and associated factors in eisenmenger syndrome

Zhangli Yuan[1†], Yang Wang[2†], Jianling Wang[1], Yinchuan Lai[1], Xuechuan Dan[1*] and Juan Wang[1*]

Abstract

Objective The aim of this study was to systematically evaluate the effect of pulmonary arterial hypertension (PAH) targeting drugs on exercise tolerance in Eisenmenger syndrome (ES) and analyze related factors.

Methods Two researchers conducted an independent search of the Chinese database and the English database, and conducted literature screening, data extraction and quality evaluation according to the inclusion and exclusion criteria respectively. According to the heterogeneity test results, the effect model was adopted for analysis by RevMan5.4 statistical software, in which the continuity data were represented by mean difference (MD) and 95% confidence interval (CI).

Results A total of 393 patients with ES were included in 13 papers, including 8 studies of endothelin receptor antagonists (ERA), 2 studies of phosphodiesterase 5 inhibitors (PDE5i) and 3 studies of prostanoids. The results of these studies showed that the targeted drugs were effective in improving exercise tolerance in ES patients. Further analyses revealed that the differences in efficacy were related to the type of targeted drug, duration of drug treatment and the presence or absence of Down syndrome (DS). 6MWD (6 min Walk Distance) and cardiac function were significantly improved in ES patients with all three classes of drugs. Prostanoids (MD = 132.35, 95% CI: 14.82-249.89, $P < 0.0001$, $I^2 = 93\%$) improved 6MWD better than ERAs (MD = 41.60, 95% CI: 21.76–61.44, $P < 0.0001$, $I^2 = 32\%$) and PDE5i (MD = 52.33, 95% CI: 29.16–75.50, $P < 0.0001$, $I^2 = 0$). Prostanoids demonstrated a more significant improvement in cardiac function compared to ERAs and PDE5i. Specifically, prostanoids [MD= -1.26, 95% CI: (-1.66, -0.86), $P < 0.0001$] showed a greater improvement than ERAs [MD=-0.54, 95% CI: (-0.96, -0.11), $P = 0.01$] and PDE5i [MD=-0.38, 95% CI: (-0.64, -0.13), $P = 0.003$]. Short-term pharmacological therapy (less than 12 months) significantly increased 6MWD and improved clinical cardiac function in included patients. Continued targeted drug therapy further increased the level of cardiac function ($P < 0.0001$). Targeted drug therapy was effective in increasing 6MWD in patients with ES combined

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with DS, but had no significant effect on cardiac function class. Targeted drug therapy had a favorable effect on both 6MWD and cardiac function class in non-DS patients.

Conclusion Early targeted drug therapy for ES can significantly improve the exercise tolerance of patients, and a better drug regimen and treatment time should be selected according to the clinical characteristics of patients.

Keywords Pulmonary hypertension targeting drugs, Eisenmenger syndrome, Exercise tolerance, Correlation factor

Introduction

Eisenmenger syndrome (ES) is a severe form of pulmonary arterial hypertension (PAH) resulting from congenital heart disease (CHD), characterized by elevated pulmonary artery pressure and right-to-left shunting, leading to significant morbidity and mortality [1]. Clinically, ES is a multisystemic disease with a large number of complications that greatly affects the patient's ability to work, quality of life and survival [2]. It has been reported in the literature that approximately 5–10% of patients with congenital heart disease (CHD) develop PAH [3]. ES is a multisystemic disease with a poor prognosis, particularly in untreated patients, with a 10-year mortality rate of 30–40% [4]. Although the incidence of ES has declined significantly in developed countries, it remains a common complication of CHD in low- and middle-income countries [5]. The only treatment with clear efficacy is heart-lung transplantation. However, the widespread lack of organs and the survival rates of 80% and 70% at 1 month and 1 year after transplantation, respectively, have highlighted the need for alternative therapeutic options [6].

The introduction of targeted therapies for PAH in the 1990s has provided new hope for ES patients, with drugs such as endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5i), and prostacyclin analogues showing promise in improving exercise tolerance and cardiac function [7]. Currently, targeted drugs mainly work on three pathways, including endothelin receptor antagonists (ERA) (represented by bosentan, ambrisentan and macitentan), phosphodiesterase 5 inhibitors (PDE5i) (represented by sildenafil, tadenafil and vardenafil) and prostacyclin Analogues (represented by iloprost, treprostinil, epoprostenol), among which sildenafil, tadalafil and vardenafil are the most effective [8]. Among them, sitaxsentan was withdrawn from the market in October 2010 due to its ability to cause irreversible fatal liver failure [9]. Preliminary analyses of the efficacy of targeted drugs in the treatment of ES have been performed, but no further evaluation of clinical efficacy with different population characteristics has been carried out. Additionally, selexipag is a selective prostacyclin receptor (IP) agonist that has shown efficacy in treating PAH by reducing the risk of disease progression and hospitalization [8]. While selexipag has demonstrated significant benefits in PAH, its use in ES patients has not been extensively studied. The limited data available suggest that selexipag may be a promising option for ES patients, but further research is needed to establish its efficacy and safety in this specific population.

Therefore, this systematic review and meta-analysis aims to comprehensively evaluate the clinical efficacy of targeted drugs in the treatment of ES at home and abroad and to analyze the factors affecting their efficacy, so as to provide a basis for the drug treatment of this disease.

Method

Literature search

Two searchers independently searched the relevant literature in PubMed, Cochrane Library, Web of Science, ScienceDirect and Embase databases with the following search formula: #1: endothelin receptor antagonist OR ERA OR bosentan OR ambrisentan OR macitentan; #2: phosphodiesterase type 5 inhibitor OR PDE5i OR sildenafil OR tadalafil; #3: prostanoids OR prostacyclin analogs OR iloprost OR beraprost OR treprostinil OR epoprostenol; #4: eisenmenger syndrome OR ES; #5: #1 OR # 2 OR # 3; #6: # 4 AND # 5. Literature was searched from the year of construction to January 2024, supplemented by manual searching of references in relevant studies.

Inclusion and exclusion criteria

Inclusion criteria: (1) Study type: clinical studies, including randomized controlled studies (RCTs) and non-randomized controlled studies (NRCTs) (prospective studies and retrospective studies); (2) Study subjects: patients with ES caused by various types of CHDs, including atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), and other complex or compound CHDs (Com); (3) Intervention: treatment with a single targeted agent and no change in regimen during treatment; (4) Outcome: primary and/or secondary outcome for inclusion in the cohort.

Exclusion criteria: (1) Case reports (< 5 cases), systematic reviews or Meta-analyses, basic experiments, conference proceedings; (2) Study subjects included in non-ES patients and data could not be extracted separately; (3) Clinical studies related to the efficacy and safety of sitaxsentan; (4) Clinical studies in which data on sitaxsentan and other drugs could not be extracted separately; (5) The use of combination therapy during the treatment

period or a change to a different type of targeted drug during the course of treatment; (6) Literature with duplicate data from the same medical centre retained to contain the best data literature.

Data extraction and bias assessment

Two authors independently screened the literature and extracted relevant data according to the inclusion and exclusion criteria. The first screening was done by reading the title and abstract of the literature, and then reading the full text of the literature for the second screening and final inclusion of the literature. The extracted data included: (1) Basic information: first author, publication date, study type, study country, number of participants, target drug and type, ES etiology, whether Down's syndrome (DS) was combined, baseline cardiac function, and duration of drug treatment (short-term treatment: less than 12 months; long-term treatment: more than 12 months); (2) Effectiveness indicators: 6-minutewalk distance (6MWD), cardiac function, mortality rate, and incidence of clinical deterioration events (such as: dyspnea, syncope, and acute heart failure).

Two evaluators independently assessed the quality of the included literature. In this study, the Cochrane Risk of Bias Assessment Tool was selected to assess the quality of literature for randomized controlled trials, and the Newcastle-Ottawa Quality Assessment Criteria for cohort studies was selected to assess the quality of literature for cohort studies. If the evaluators disagreed on the quality assessment of the literature, the decision was made after discussion with a third person.

Measurement of cardiac function

Cardiac function was assessed using both functional class and specific right ventricular (RV) parameters. Functional class was evaluated based on the New York Heart Association (NYHA) classification system, which categorizes patients into four classes based on their symptoms and limitations during physical activity. Additionally, right ventricular function was assessed using echocardiographic parameters, including fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). FAC measures the change in RV area during systole, while TAPSE evaluates the longitudinal systolic function of the RV. These parameters provide a comprehensive assessment of cardiac function in patients with ES.

Statistical methods

Meta-analysis of effect indicators was performed using RevMan. Continuous data were expressed as MD and 95% CI, while frequencies and percentages were chosen to describe dichotomous data. Heterogeneity among the included literature was assessed by Q-test and I^2. $P < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity among the studies, and the source of heterogeneity was analyzed by sensitivity analysis or subgroup analysis. If the homogeneity was still poor after removing the source of heterogeneity, a random-effects model was used to combine the effect sizes; otherwise, a fixed-effects model was chosen.

Results

Results of literature search

A total of 393 patients with ES were included in 13 papers, including 8 studies of endothelin receptor antagonists (ERA), 2 studies of phosphodiesterase 5 inhibitors (PDE5i), and 3 studies of prostanoids (Fig. 1). The basic characteristics of the included studies are shown in Table 1.

Literature quality bias evaluation

Cochrane evaluation tools were used to evaluate the RCT, and the results of the specific evaluation were shown in Table 2. The evaluation of NRCT referred to the NOS cohort study quality evaluation criteria, and the evaluation results showed that none of the 9 NRCT studies had high risk bias. The specific evaluation results were shown in Table 3. No low quality was found in the included clinical studies. The results of these studies showed that the targeted drugs were effective in improving exercise tolerance in ES patients. Further analyses revealed that the differences in efficacy were related to the type of targeted drug, duration of drug treatment, and the presence or absence of Down syndrome (DS). 6MWD (6 min Walk Distance) and cardiac function were significantly improved in ES patients with all three classes of drugs.

Mortality rate and incidence of clinical deterioration events

In the included studies, data on mortality rates and incidence of clinical deterioration events were limited. Only a few studies reported these outcomes, and the overall mortality rate was low, with no significant differences observed between treatment groups. The incidence of clinical deterioration events, such as dyspnea, syncope, and acute heart failure, was also low, suggesting that targeted therapies are generally safe and well-tolerated in ES patients. However, due to the limited data, it is difficult to draw definitive conclusions about the long-term impact of these therapies on mortality and clinical deterioration.

Meta-analysis of targeted drugs improving exercise tolerance

The 13 included studies all explored the effect of targeted drugs on 6MWD in patients, with high heterogeneity ($I^2 = 74\%$, $P < 0.00001$), and adopted random effects model analysis. Our pooled results showed that targeted drugs could significantly improve exercise tolerance

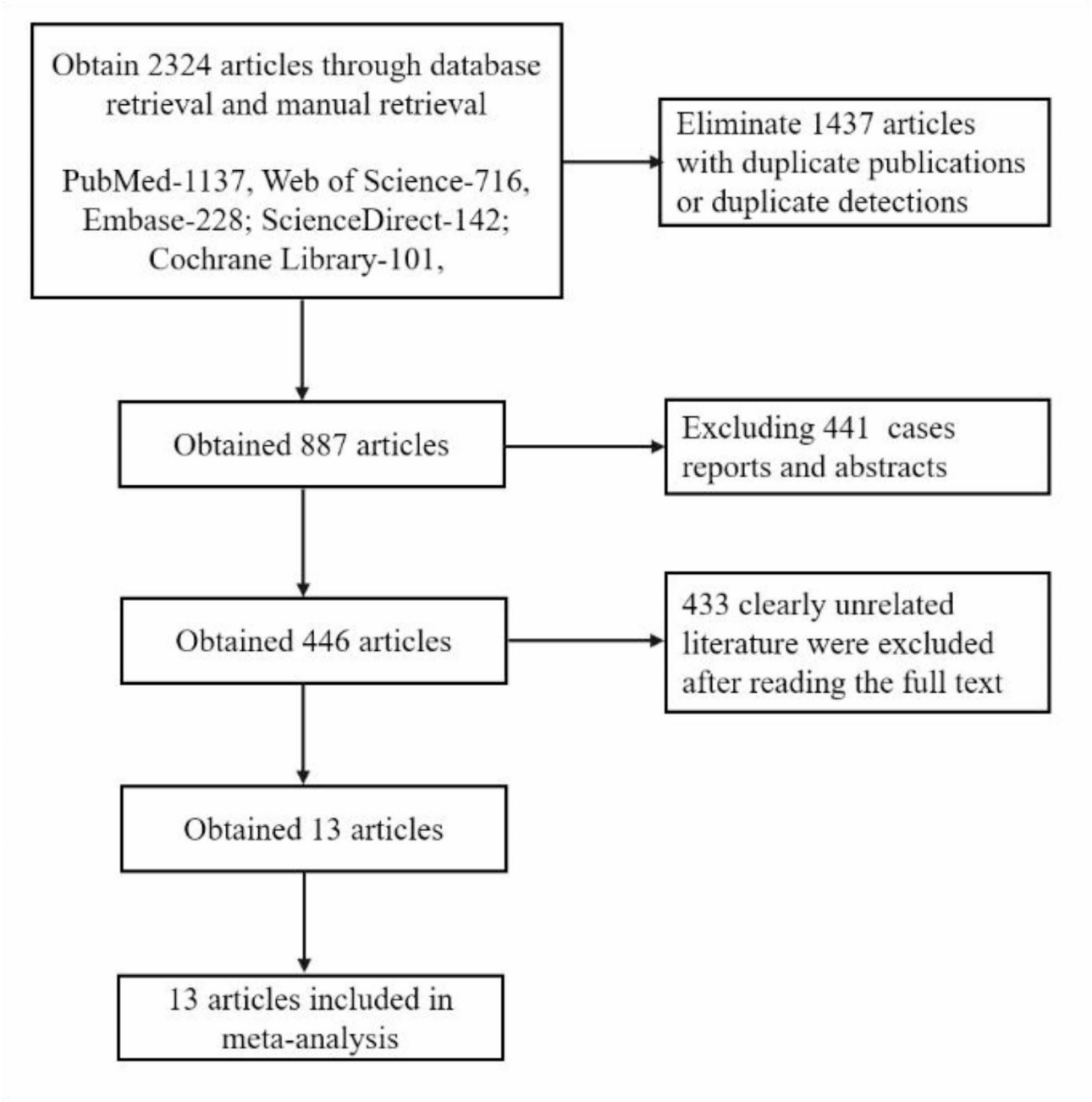

Fig. 1 Literature search results and flowchart

[(MD = 61.95, 95%CI: (38.07,85.82), $P < 0.00001$]. Sensitivity analysis found that heterogeneity was significantly reduced ($I^2 = 28\%$) after excluding Fernandes' study, indicating that the study of Fernandes may be the source of heterogeneity (Fig. 2).

Meta-analysis of targeted drugs improving cardiac functional grading

Eleven included studies exploring the effect of targeted drugs on patients' cardiac function level had high heterogeneity ($I^2 = 86\%$, $P < 0.00001$) and were analyzed using a random effects model. Our pooled results showed that targeted drugs significantly improved the level of cardiac function in patients [(MD=-0.58, 95% CI: (-0.83, -0.33), $P < 0.00001$]. Sensitivity analysis revealed a significant reduction in heterogeneity after excluding three studies ($I^2 = 10\%$), suggesting that these studies may be a possible source of heterogeneity (Fig. 3).

Table 1 Basic characteristics of enrolled studiesnote: RCT-randomized controlled studies; NRCT: Non-randomized controlled studies; ASD-atrial septal defect; VSD-ventricular septal defect; PDA-patent ductus arteriosus; Com-other complex or compound CHDs; DS-Down's syndrome; CFG-cardiac functional grading

Author	Year	Type	Country	*n*	Drugs	Age	Etiological classification	DS	Time (mo)	CFG	Primary outcome
ERAs											
Galiè [10]	2006	RCT	Italy	37	Bosentan	37.2 (12.0)	ASD (21.6%)/VSD (64.9%)/Com (13.5%)	No	4	-	6MWD
Crepaz [11]	2013	NRCT	Italy	7	Bosentan	29.6 (11.2)	VSD (100%)	Yes	24	3.0 (-)	6MWD
Serino [12]	2013	NRCT	Italy	7	Bosentan	31.7 (-)	VSD (71.4%)/Com (28.6%)	Yes	24	3.3 (0.5)	6MWD
D'alto [13]	2007	NRCT	Italy	22	Bosentan	38.0 (10.0)	ASD (4.5%)/VSD (54.5%)/Com (41.0%)	No	12	3.1 (0.7)	6MWD
Kaya [14]	2012	NRCT	Turkey	22	Bosentan	31.0 (12.0)	ASD (26.1%)/VSD (65.2%)/PDA (8.7%)	No	24	3.2 (0.4)	6MWD
Duffels [15]	2009	NRCT	Netherlands	24	Bosentan	38.0 (-)	ASD (58.3%)/VSD (29.2%)/Com (12.5%)	Yes	3	-	6MWD
Gatzoulis [16]	2018	RCT	United Kingdom	114	Macetetan	33.0 (12.8)	-	Yes	4	2.4 (0.5)	6MWD
Zuckerman [17]	2011	NRCT	America	17	Anrisentan	32.2 (11.9)	ASD (52.9%)/VSD (41.2%)/Com (5.9%)	Yes	30	-	6MWD
PDE5i											
Zhang [18]	2011	NRCT	China	84	Sildenafil	28.0 (9.0)	ASD (29.8%)/VSD (40.5%)/PAD (27.4%)/Com (2.4%)	No	12	2.6 (0.7)	6MWD
Mukhopadhyay [19]	2011	RCT	India	28	Tadalafil	29.3 (11.7)	ASD (50.0%)/VSD (46.4%)/ Com (3.6%)	No	1.5	2.2 (0.4)	6MWD
Prostanoids											
Chon [20]	2017	NRCT	Korea	11	Iloprost	44.2 (12.2)	ASD (9.1%)/VSD (54.5%)/PAD (27.3%)/Com (9.1%)	No	12	3.4 (0.5)	6MWD
Nashat [21]	2019	RCT	United Kingdom	16	Iloprost	47.3 (9.8)	VSD (68%)/Com (32%)	No	29	3 (-)	6MWD
Fernandes [22]	2003	NRCT	America	8	Epoprostenol	36.3(14.9)	ASD (37.5%)/VSD (25%)/PAD (12.5%)/ Com (12.5%)	No	3	3.8 (0.4)	6MWD

Factors affecting the clinical efficacy of targeted drugs in therapy of ES

Drug type

The included literature investigated the clinical efficacy of ERAs ($n=8$), PDE5i ($n=2$), and prostacyclin analogues ($n=3$) targeting ES, respectively. As the most important effector to assess exercise tolerance at the study endpoint in patients with PAH, the results of the Meta-analysis showed that targeted drugs were effective in increasing 6MWD in patients with ES. Among them, ERAs increased 6MWD by about 41.60 m (95% CI: 21.76–61.44, $P<0.0001$, $I^2=32\%$), PDE5i by about 52.33 m (95% CI: 29.16–75.50, $P<0.0001$, $I^2=0$), and prostacyclin significantly increased 6MWD by about 132.35 m (95% CI: 14.82-249.89, $I^2=93\%$) in these patients (Fig. 4). Cardiac function assessment revealed that all 3 targeted drugs significantly improved cardiac function in ES patients. The most significant improvement in cardiac function was observed after prostacyclin therapy [MD= -1.26, 95% CI: (-1.66, -0.86), $P<0.0001$]. ERAs and PDE5i improved cardiac function by -0.54 [95% CI: (-0.96, -0.11), $P=0.01$] and −0.38 [95% CI: (-0.64, -0.13), $P=0.003$], respectively (Fig. 5).

Duration of treatment

Subgroup analysis showed that short-term (within 12 months) targeted drug therapy significantly increased 6MWD in ES patients by about 64.33 m (MD = 64.33, 95% CI: 29.39–99.27, $P=0.0003$) and improved clinical cardiac function (MD = -0.56, 95% CI: (-0.88, -0.24), $P=0.0006$) (Figs. 6 and 7). Continuous targeted drug therapy can further improve the cardiac function of patients [MD = -0.79, 95%CI: (-1.02, -0.56), $P<0.0001$]. However, long-term therapy outcomes were more variable, likely due to differences in medication types, adherence, and patient dropout rates.

DS

Five studies included patients with ES-DS and evaluated exercise tolerance and cardiac function before and after treatment (Figs. 8 and 9). Targeted drug therapy can significantly improve 6WMD (MD = 37.33, 95% CI: 15.32–59.34, $P=0.0009$) in ES-DS patients, but has little effect

Table 2 Quality assessment of randomized controlled trials

Indicators	Galiè	Gatzoulis	Mukhopadhyay	Nashat
Random sequence generation	A	A	B	A
Allocation concealment	A	B	B	A
Blinding of participants and personnel	A	A	A	A
Blinding of outcome assessment	A	A	A	A
Incomplete outcome data	A	A	A	A
Selective reporting	A	A	A	A
Other bias	A	A	A	A
Literature quality	H	M	M	H

Note: the quality evaluation was conducted using Cochrane evaluation tools. Each evaluation item was divided into three levels: A (Yes), B (unclear) and C (no), indicating low risk, medium risk and high risk. If all evaluation items are of low risk, then the evaluation of literature quality is of high (H) quality. If there is one or more articles with moderate risk, the quality of the literature is assessed as medium (M) quality. If one or more of the articles is high risk, the quality of the document is assessed as low quality

Table 3 Evaluation of literature quality of included cohort studies

Study	Selection	Comparability	Outcome	NOS score
Crepaz	3	1	3	7
Serino	3	1	2	6
D'alto	3	2	2	7
Kaya	3	2	3	8
Duffels	3	1	2	6
Zuckerman	3	2	3	8
Zhang	3	1	2	6
Chon	3	1	2	6
Fernandes	3	1	3	7

Note: Newcastle-Ottawa (NOS) cohort study quality assessment list was used to evaluate the quality of non-randomized controlled trials. The total score was defined as 9 points, and ≥ 7 points indicated low risk. Comparability: (1) Study the control of single targeted drug therapy for PAH; (2) The study controlled for any other confounding factors (controlling for the inclusion of subjects with no other genetic metabolic disease, such as DS)

on cardiac function level [MD = -0.34, 95%CI: (-0.87, 0.19), $P = 0.21$]. Non-DS patients were treated with targeted drugs, and the levels of 6WMD (MD = 80.98, 95% CI: 46.59-115.37, $P < 0.0001$) and cardiac function [MD = -0.67, 95%CI: (-0.95, -0.39), $P < 0.00001$] were significantly improved.

Discussion

Eisenmenger syndrome (ES) is a complex clinical condition characterized by severe pulmonary arterial hypertension (PAH) secondary to congenital heart disease (CHD) [10, 11]. Although previous clinical trials have shown that PAH targeted drug therapy can improve exercise tolerance and corresponding vascular remodeling in ES patients to a certain extent, the current drug selection for such patients still mainly depends on clinical treatment. A total of 13 studies were included in this meta-analysis, covering 393 patients with Eisenmenger syndrome (ES). Among these patients, those with ventricular septal defect (VSD) accounted for more than 50%. This high prevalence may be related to the persistent high blood flow in the pulmonary circulation associated with VSD. Patients with ES who received targeted drug therapy (including ERAs (54.55%), PDE5i (18.18%) and Prostanoids (27.27%) could improve cardiac function to some extent, and the risk of death and clinical deterioration rate were relatively low, and adverse reactions were mild. It is suggested that targeted drugs are safe and effective clinical prescription for ES [12]. The study found that targeted drug therapy could improve the clinical efficacy and hemodynamics of ES patients in the early stage, but the effect gradually declined in the later stage and individual differences existed [13]. Therefore, the clinical efficacy of ES patients with different characteristics can be evaluated separately.

In the included studies, data on mortality rates and incidence of clinical deterioration events were limited. Only a few studies reported these outcomes, and the overall mortality rate was low, with no significant differences observed between treatment groups. The incidence of clinical deterioration events, such as dyspnea, syncope, and acute heart failure, was also low, suggesting that targeted therapies are generally safe and well-tolerated in ES patients. However, due to the limited data, it is difficult to draw definitive conclusions about the long-term impact of these therapies on mortality and clinical deterioration. Future studies with longer follow-up periods and larger sample sizes are needed to better assess these outcomes.

The meta-analysis and subgroup analysis of the short-term and long-term clinical outcomes of targeted drug therapy for ES showed that the three targeted drug therapies could effectively improve the clinical outcomes of ES patients, including the increase of 6MWD level and the improvement of cardiac function. Among them, prostacyclin was more effective in increasing 6MWD by 132.35 m (95% CI: 14.82-249.89, $P = 0.03$) and improving cardiac function [MD= -1.26, 95% CI: (-1.66, -0.86), $P < 0.0001$]. ERAs and PDE5i analogues showed similar improvements. ERAs improved 6MWD by approximately 41.60 m (95% CI: 21.76–61.44, $P < 0.0001$, $I^2 = 32\%$) and improved cardiac function by -0.54 [95% CI: (-0.96, -0.11), $P = 0.01$]. PDE5i improved 6MWD by approximately 52.33 m (95% CI: 29.16–75.50, $P < 0.0001$, $I^2 = 0$) and improved cardiac function [MD=-0.38, 95% CI: (-0.64, -0.13), $P = 0.003$]. Also, different treatment durations had a significant effect on the exercise tolerance effect in patients. Subgroup analyses resulted that

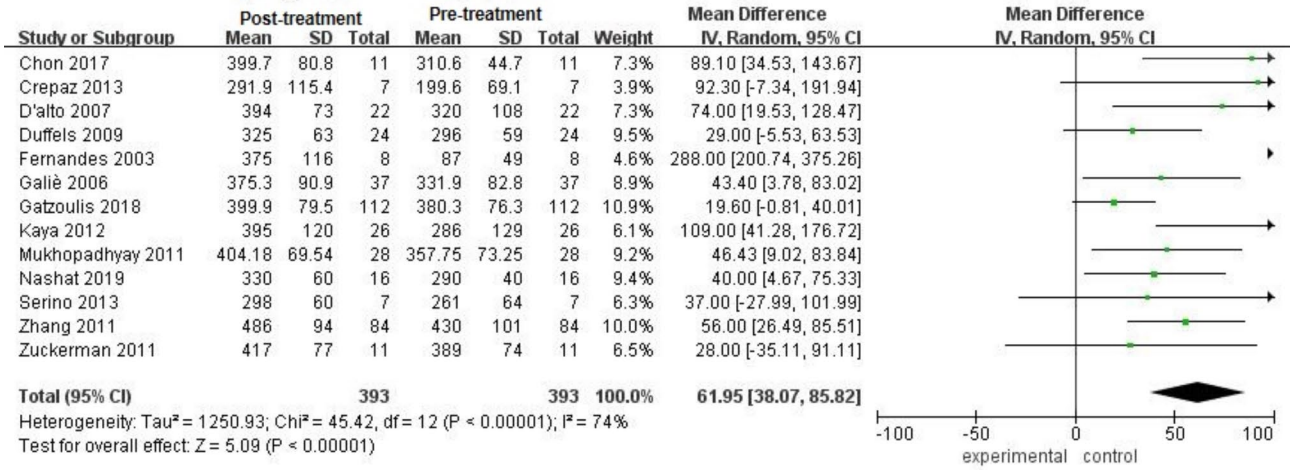

Fig. 2 Forest plot of 6MWD in specific drug therapy for ES

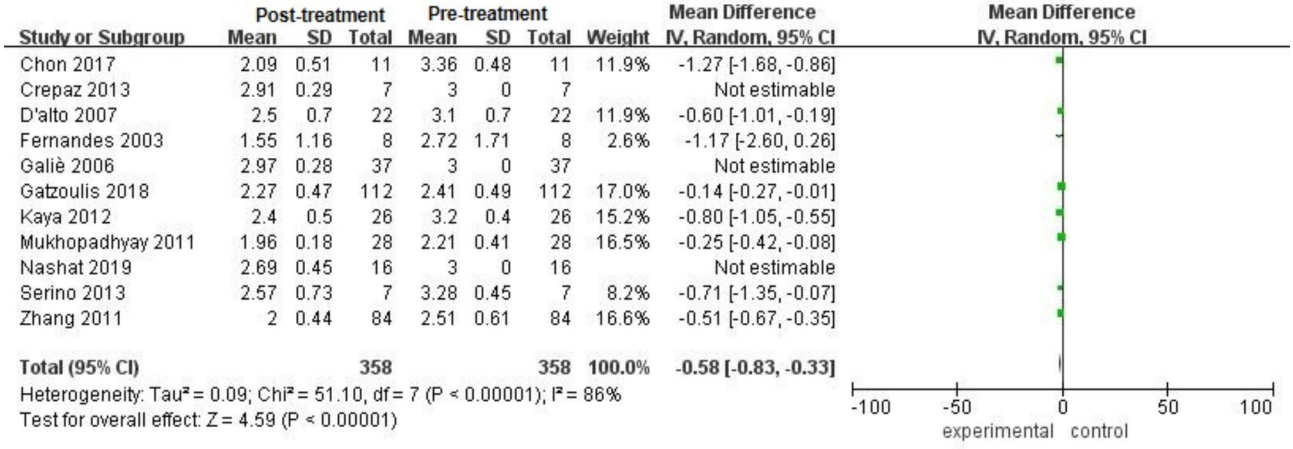

Fig. 3 Forest plot of cardiac function in specific drug therapy for ES

short-term and long-term treatments with targeted drugs increased 6MWD levels by approximately 64.33 m ($P = 0.0003$) and 51.72 m ($P = 0.0002$), respectively. The improvement effect of long-term treatment on cardiac function [MD = -0.79, 95% CI: (-1.02, -0.56), $P < 0.0001$] was better than that of short-term treatment (MD = -0.56, 95% CI: (-0.88, -0.24), $P = 0.0006$).

Patients with comorbid DS are an important subgroup of the ES population [14]. This population has a higher risk of hypoxemia and cardiac insufficiency than the non-DS population [15]. There is a lack of specific treatment for these patients [16]. Bosentan, a widely used non-selective ERA, has been shown to improve exercise tolerance and clinical symptoms in patients with ES, as well as to delay and improve pulmonary vascular remodeling to a certain extent, allowing patients to have access to heart transplantation [17]. In the present study, the proportion of ES patients with definite combined DS was about 1%. Five studies included ES-DS patients and evaluated their exercise tolerance before and after treatment, and the results showed that targeted drugs significantly increased 6MWD levels in ES-DS patients (MD = 37.33, 95% CI: 15.32–59.34, $P = 0.0009$). Three studies included ES-DS patients and evaluated their cardiac function class before and after treatment, and the results showed that the effect of targeted drugs on cardiac function class in ES-DS patients was not statistically different [MD = -0.34, 95%CI: (-0.87, 0.19), $P = 0.21$], but significantly improved cardiac function class in non-DS patients [MD = -0.67, 95%CI: (-0.95, -0.39), $P < 0.00001$]. Crepaz and Serino found that prolonged bosentan treatment further improved cardiac status, oxygen saturation, and dyspnoea index [18, 19]. Previous studies have shown that newer ERAs such as irisentan and macitentan have less hepatic damage than bosentan, and that irisentan combined with sildenafil may be slightly better than bosentan for cardiac function and cardiac remodeling in patients with congenital heart disease combined with moderate-to-severe PAH [20, 21]. However, the present study did not find that short-term treatment with irisentan and

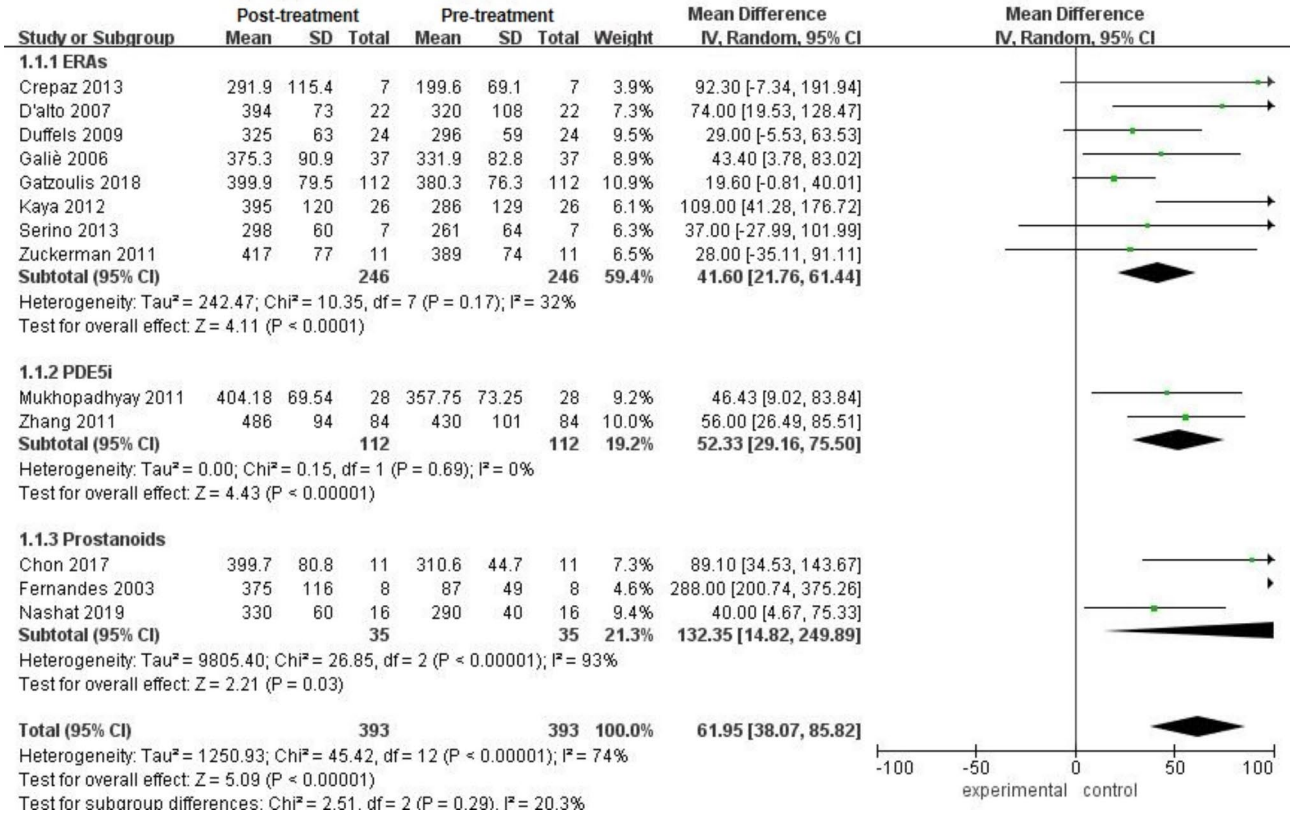

Fig. 4 Forest plot of drug type on 6MWD

macitentan was effective in improving the 6-follow-up measurements in ES patients. Therefore, the clinical efficacy and safety of these drugs in ES patients need to be further evaluated in large clinical samples.

Selexipag, a selective prostacyclin receptor (IP) agonist, has shown significant benefits in treating PAH by reducing the risk of disease progression and hospitalization [8]. While selexipag has demonstrated efficacy in PAH, its use in ES patients has not been extensively studied. The limited data available suggest that selexipag may be a promising option for ES patients, but further research is needed to establish its efficacy and safety in this specific population. Therefore, we did not include selexipag in our meta-analysis due to the lack of sufficient data on its use in ES patients. Future studies should aim to evaluate the potential benefits of selexipag in ES patients, particularly in those with severe disease or intolerance to other targeted therapies.

This study provides strong evidence supporting the use of targeted therapies to improve exercise tolerance and cardiac function in patients with Eisenmenger syndrome (ES), particularly when administered over the long term. Our comprehensive meta-analysis of 13 studies involving 393 ES patients demonstrates that all three major classes of targeted drugs—endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5i), and prostacyclin analogues—significantly enhance 6-minute walk distance (6MWD) and cardiac function. Among these, prostacyclin analogues appear to have the most pronounced effect on improving exercise tolerance and cardiac function.

However, several limitations must be addressed to refine therapeutic strategies and enhance patient outcomes. The sample sizes in some studies, especially those involving patients with Down syndrome (DS), were relatively small, which may limit the generalizability of the findings. Additionally, the lack of placebo-controlled comparisons in the included studies precludes a definitive assessment of the absolute efficacy of these targeted therapies. Future research should focus on larger, placebo-controlled trials to validate these findings and explore the differential efficacy of targeted therapies based on the type of congenital heart disease (e.g., ASD vs. VSD vs. PDA).

Conclusion

In conclusion, early targeted drug therapy may effectively improve the clinical outcomes of ES patients, including those with DS. A tailored drug regimen and treatment duration should be selected based on the clinical characteristics of individual patients to optimize therapeutic efficacy and safety.

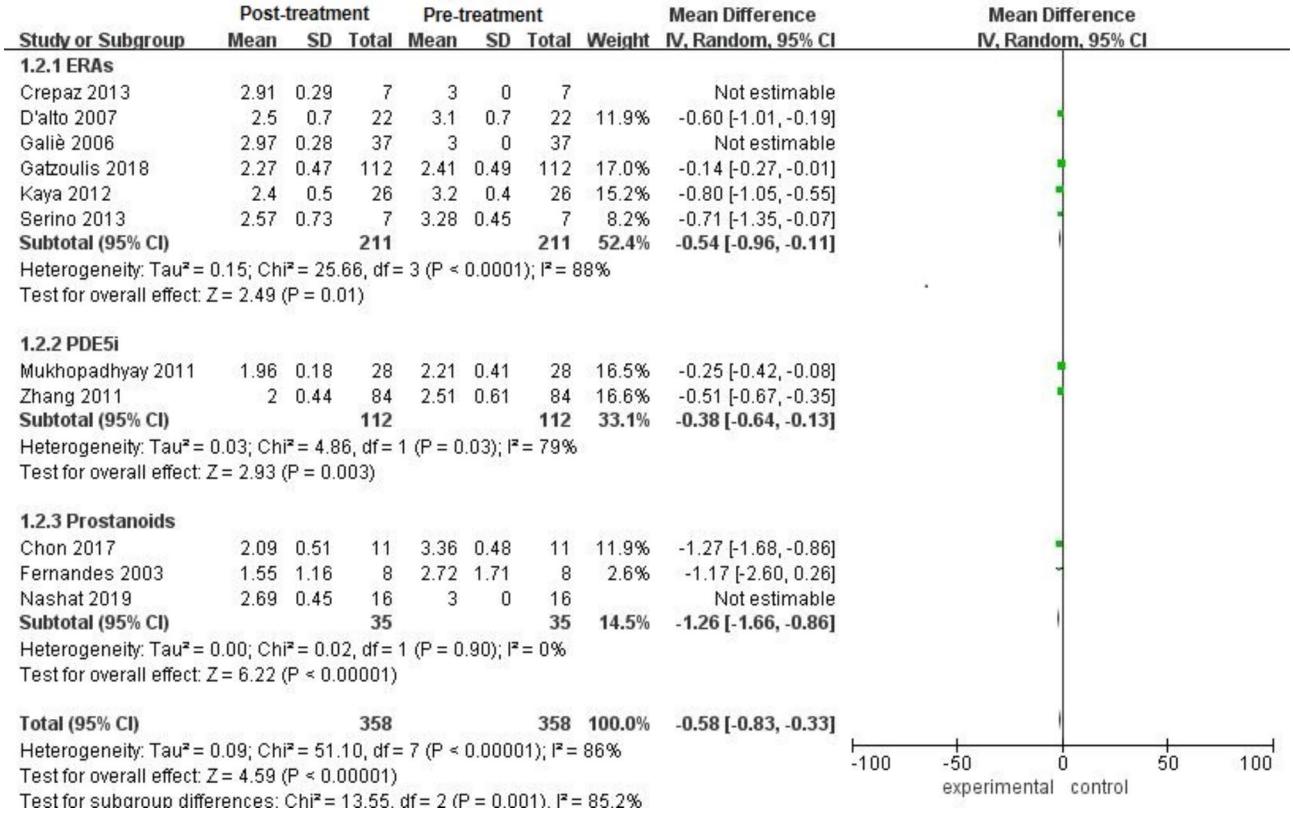

Fig. 5 Forest plot of drug type on cardiac function

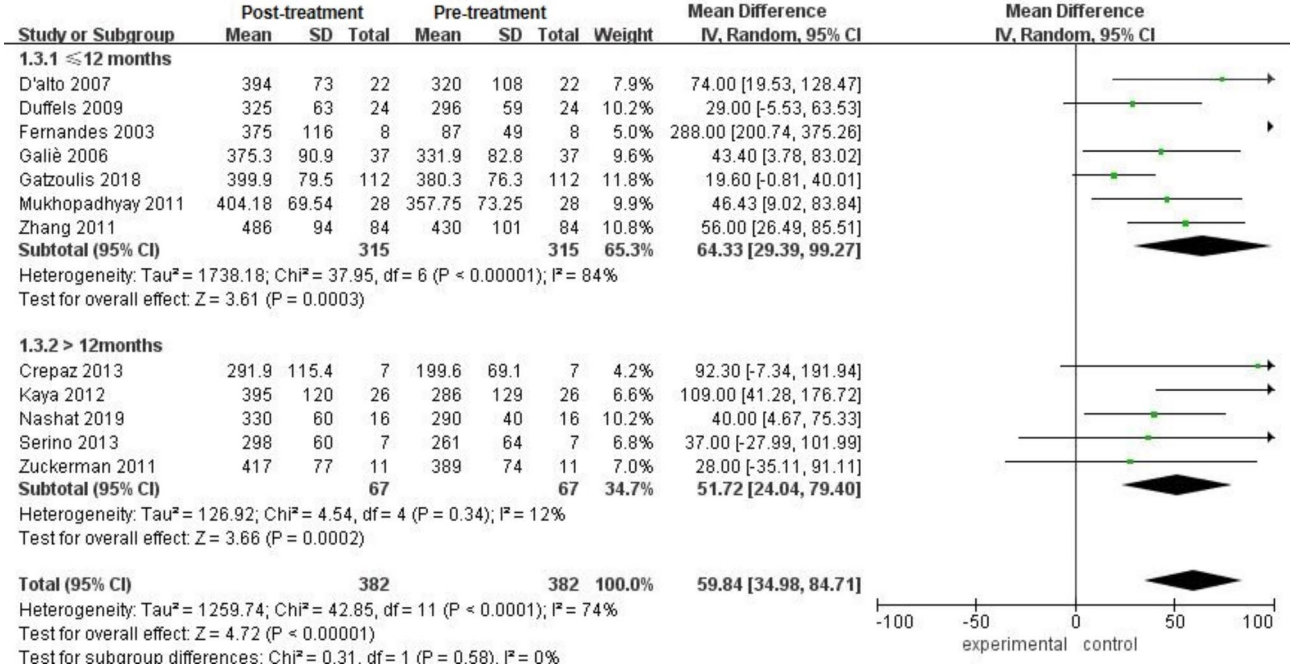

Fig. 6 Forest plot of treatment duration on 6MWD

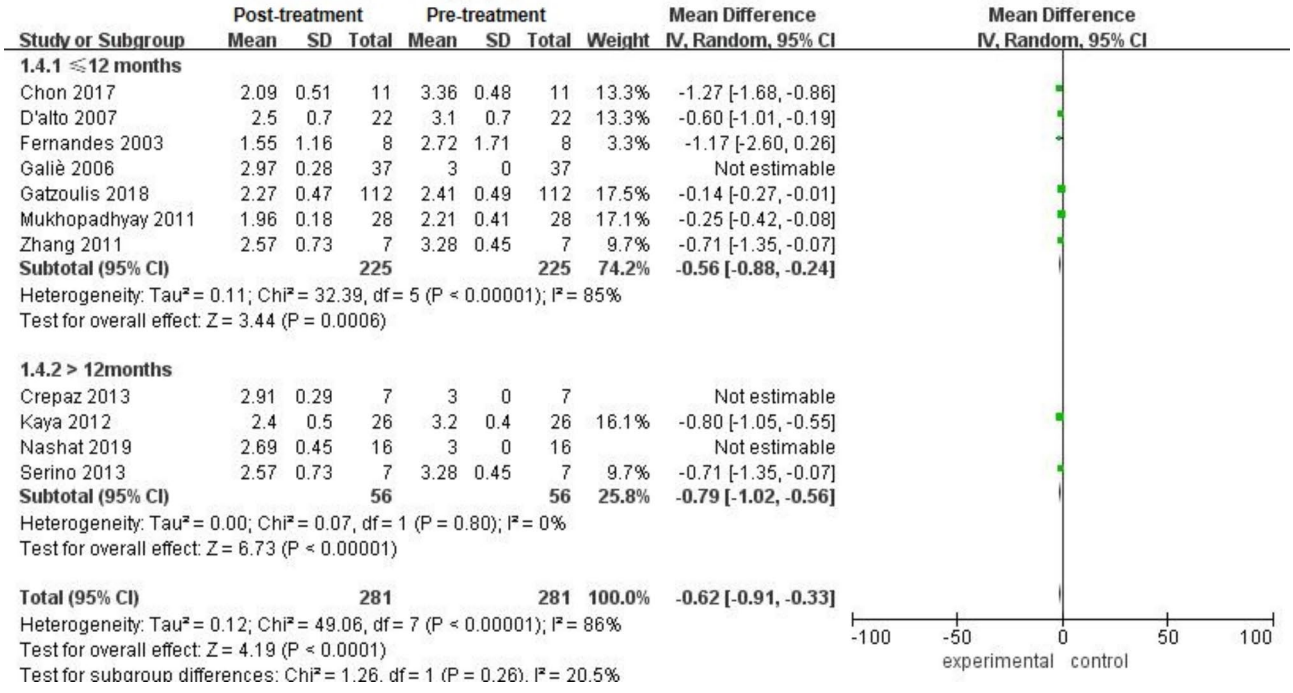

Fig. 7 Forest plot of treatment duration on cardiac function

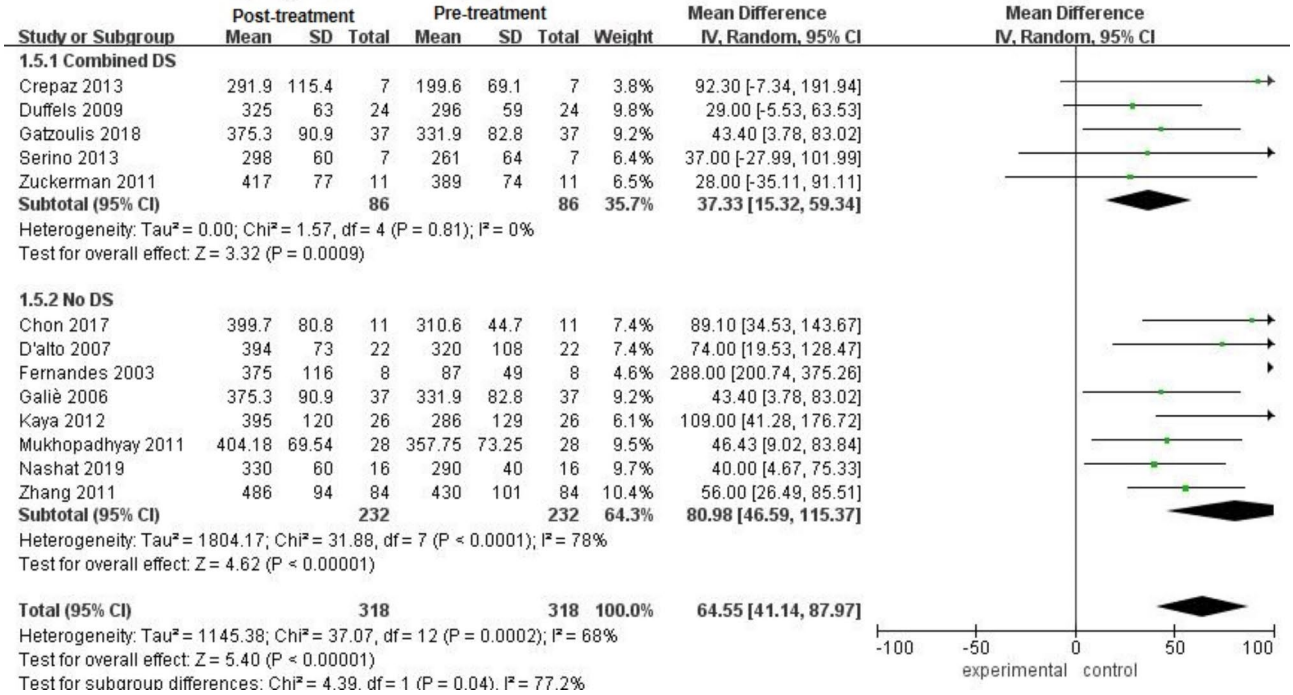

Fig. 8 Forest plot of combined DS on 6MWD

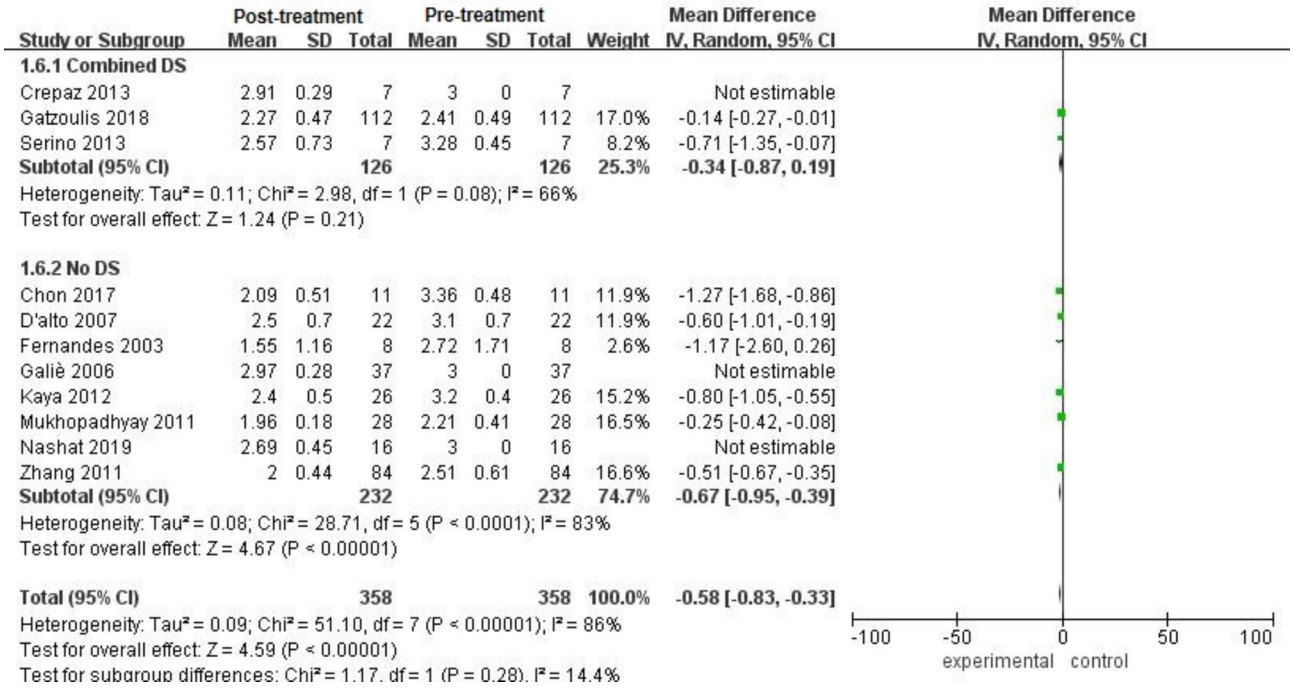

Fig. 9 Forest plot of combined DS on cardiac function

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Author contributions
ZLY and YW wrote the main manuscript. JLW and YCL prepared the data collection. XCD and JW prepared figures and tables. ZLY, YW and JLW and interpret of results. All authors reviewed the results and approved the final version of the manuscript. All authors would be informed each step of manuscript processing including submission, revision, revision reminder, etc.

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Data availability
The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study did not involve any special intervention or handling of sensitive information, and therefore did not require ethical review. The Second People's Hospital of Yibin has agreed to exemption from review.

Consent for publication
Not applicable.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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