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Stem cell therapy for non-ischemic dilated cardiomyopathy: a systematic review and meta-analysis

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Abstract

Background Stem cell therapy is the transplantation of human cells to aid the healing of damaged or wounded tissues and cells. Only a few small-scale trials have been conducted to investigate stem cell therapy for non-ischemic dilated cardiomyopathy (DCM). We aimed to perform a systematic review and meta-analysis to assess the efficacy and safety of stem cell therapy for DCM.

Methods A comprehensive search of the databases of PubMed, Embase, Web of Science Core Collection, Cochrane Library, and ProQuest was conducted from their inception to June 30, 2024, to access randomized controlled trials (RCTs) that were centered on stem cell therapy for DCM. The primary outcome was left ventricular ejection fraction (LVEF), and the secondary outcomes included left ventricular end-diastolic dimension (LVEDD), left ventricular end-diastolic volume (LVEDV), 6-min walk test (6MWT), NYHA functional classification, quality of life (QoL) such as Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Kansas City Cardiomyopathy Questionnaire (KCCQ), N-terminal pro-brain natriuretic peptide (NT-proBNP), and VO_2 peak. Moreover, major adverse cardiovascular events (MACEs) were also recorded. The Cochrane risk-of-bias assessment tool was used to evaluate the quality of the included RCTs, and the certainty of the evidence was assessed using the GRADE method. Sensitivity analysis was taken into consideration to determine the stability of the results. This review was registered with PROSPERO (CRD42024568912).

Results Eleven RCTs involving 637 participants were included in the quantitative analysis. The results indicated that there was a significant increase in mean LVEF (*MD* = 4.84, 95% *CI* 3.25–6.42, *P* < 0.00001) and considerable decrease in LVEDV (*MD* = − 29.51, 95% *CI* − 58.07 to − 0.95, *P* = 0.04) and NT-proBNP (*MD* = − 737.55, 95% *CI* − 904.28 to − 570.82, *P* < 0.00001) in DCM patients treated with stem cell therapy compared with controls. Stem cell therapy was also related to the improvement in functional capacity, as evaluated by 6MWT (*MD* = 44.32, 95% *CI* 34.70 − 53.94, *P* < 0.00001) and NYHA functional classification (*MD* = − 0.63, 95% *CI* − 0.96 to − 0.30, *P* = 0.0002). It also had positive effects on improving QoL, including significantly decreasing MLHFQ score (*MD* = − 16.60, 95% *CI* − 26.57 to − 6.63, *P* = 0.001) and increasing the KCCQ score (*MD* = 14.76, 95% *CI* 7.76 − 21.76, *P* < 0.0001). No significant differences were observed in LVEDD, VO_2 peak, and MACEs between the two groups. The GRADE analysis revealed that the evidence was graded from low to moderate. Sensitivity analysis of the results suggested that the results were stable.

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Conclusion The systematic review and meta-analysis indicates that stem cell therapy may be an effective and safe approach to improve cardiac function and quality of life in DCM patients. Nevertheless, given the limitations of existing studies, larger well-designed RCTs are required to confirm and support our findings.

Keywords Stem cell therapy, Bone marrow, Dilated cardiomyopathy, Heart failure, Meta-analysis, Systematic review

Introduction

Dilated cardiomyopathy (DCM) is distinguished by the presence of left ventricular dilatation and contractile dysfunction in the absence of abnormal loading conditions and severe coronary artery disease [1]. DCM is the most common form of non-ischemic cardiomyopathy worldwide [2, 3], accounting for approximately one-third of heart failure cases and one of the leading causes for heart transplantation globally [4–7]. DCM was first described by the World Health Organization (WHO) in 1980 (WHO/ISFC 1980), and its prevalence is estimated at 1 in 2500 individuals [8, 9]. This condition makes up around 60% of pediatric cardiomyopathies, with the largest frequency occurring in infants under the age of 12 months [10–12]. Racial disparities exist, although sex differences are less stable [13, 14]. Clinical and echocardiographic screening in families of affected individuals show evidence of familial transmission in 20–35% of cases, while acquired causes of cardiomyopathy include infectious agents, drugs and toxins, and endocrine disturbances [6]. Treatment for patients with established DCM focuses on the primary clinical symptoms of heart failure and arrhythmias [15]. Despite advances in heart failure therapy, which have resulted in increased survival and symptom relief, the morbidity and mortality associated with heart failure remain a substantial healthcare issue [16]. Thus, the search for novel approaches that may enhance the prognosis of DCM patients continues.

The potential use of stem cell therapy to improve outcomes in DCM patients with congestive heart failure and left ventricular dysfunction is a topic of considerable importance [17]. Even though current trials on stem cell therapy for dilated cardiomyopathy are not well understood, past studies have found cell therapy to be a promising strategy to treating heart failure [18, 19]. A brief overview revealed that multiple cell types, including CD34 + cells, CD45 + cells, bone marrow-derived mesenchymal stromal cells, and umbilical cord-derived mesenchymal stromal cells, have produced promising results in DCM patients after minithoracotomy or intracoronary transplantation [17]. Although the majority of cell therapy research has concentrated on ischemic cardiomyopathy, there is an increasing interest in investigating the application of cell therapy for non-ischemic DCM. However, the utility of cellular therapies for non-ischemic DCM-induced heart failure remains unclear because of the small number of reported trials, their small size, and inconsistent design [20–22], which requires further systematic evaluation.

Therefore, we aimed to comprehensively evaluate the published trials, consolidating the existing evidence on stem cell therapy for non-ischemic DCM and providing an extensive overview of the current situation. This review may help advance the understanding of the clinical efficacy and safety of cell therapy for non-ischemic DCM and may provide an important perspective for future research and clinical applications.

Methods

The present review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) extension statement [23]. A PRISMA 2020 checklist was included as an additional file (Additional file 1). The protocol for the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024568912.

Search strategy

We searched PubMed, Embase, Web of Science Core Collection, Cochrane Library, and ProQuest from their inception to June 30, 2024, by two researchers (S. T. and L. Y.) independently using a search strategy developed through combining the following keywords: "dilated cardiomyopathy," "bone marrow," "mononuclear cell," "hematopoietic," "stem cell," and "cell therapy" (Additional file 2). Search strategy was tailored for each database, and related studies were further manually retrieved from the databases.

Study selection

Studies were considered eligible for inclusion if the following criteria were met:

(1) Participants: Patients enrolled in the RCTs were diagnosed with DCM based on the diagnostic criteria [24], and their cardiac function was consistent with grades II to IV of the New York Heart Association (NYHA) functional classification [25]; the patient's physical activity ranged from mild limita-

tion to inability to engage in any physical activity. We imposed no limitations on gender, nationality, or ethnic origin.

(2) Intervention and control: Patients in the experimental group received stem cell therapy along with the optimal medical treatments for DCM, while the control group received optimal medical treatments alone. There were no restrictions on the type of injected cells, number of injected cells, follow-up, and route of administration.

(3) Outcome: The primary outcome was left ventricular ejection fraction (LVEF), and the secondary outcomes included left ventricular end-diastolic dimension (LVEDD), left ventricular end-diastolic volume (LVEDV), 6-min walk test (6MWT), NYHA functional classification, quality of life (QoL) such as Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Kansas City Cardiomyopathy Questionnaire (KCCQ), N-terminal pro-brain natriuretic peptide (NT-proBNP), and VO_2 Peak. Besides, major adverse cardiovascular events (MACEs) would also be recorded and analyzed in this study.

(4) Study design: The study was an RCT with no limitations on language, publication year, publication status, or the use of blinding methods.

We excluded (1) republished studies would only be kept for larger sample numbers and more thorough data, (2) incomplete or imprecise data or studies for which the entire text was unavailable, and (3) single-arm studies.

Data extraction

The literature from multiple databases was organized using EndNote 20 software. According to the inclusion criteria, the literature was independently screened by two researchers (S. T. and L. Y.). After identifying duplicate studies, the researchers excluded irrelevant material by reviewing the titles and abstracts. Finally, the entire text was examined to identify qualifying research. Based on a specially designed form, the two researchers separately retrieved data from the qualifying RCTs. The first author, publication year, country, registration number, sample sizes, gender, age, randomization and blinding method, baseline LVEF levels, type and number of injected cells, route of administration, follow-up, outcomes, and details regarding quality assessment of RCTs were among the items included in the recorded information. Any disagreement was settled by a third researcher or through conversation (J. L.).

Quality assessment

Using the Cochrane risk-of-bias assessment tool [26], two reviewers (S. T. and L. Y.) independently assessed the quality assessment of included RCTs. The quality assessment items for Cochrane tools comprised the following: (1) Selection bias: random sequence generation and allocation concealment; (2) performance bias: blinding of the participants and personnel; (3) detection bias: blinding of the outcome assessment; (4) attrition bias: incomplete outcome data; (5) reporting bias: selective reporting; and (6) other bias. Bias in each area was classified as "low risk," "unclear," or "high risk." The third researcher was consulted, or any differences that already existed were discussed (J. L.).

Grading of the evidence

The certainty of the evidence was evaluated using the GRADE method [27]. The evidence was rated as high, moderate, low, or very low. Initially assigned a high grade by default, RCTs are subsequently downgraded according to predetermined standards: risk of bias (the included studies were biased in randomization, allocation concealment, and blinding), inconsistency (the overlapping degree of confidence intervals of different studies was poor, and the I^2 value of the combined results was > 50%), indirectness (the presence of factors that limit the generalizability of the results), imprecision (the sample size of included studies was small, and the confidence interval was wide), and other considerations.

Data synthesis

The meta-analysis was performed using Review Manager 5.4.0 and Stata 16.0. Meta-analysis was conducted if two or more studies provided the same effect concerning the outcomes. For reviews of quantitative data where statistical synthesis is not possible, narrative synthesis of quantitative data is often the alternative method of choice. Narrative synthesis involves collating study findings into a coherent textual narrative, with descriptions of differences in characteristics of the studies including context and validity, often using tables and graphs to display results. For continuous variables, the mean difference (MD) and 95% confidence interval for the two groups were determined, and change scores from baseline values are pooled. The risk ratio (RR) and 95% confidence interval were computed comparing the two groups for binary variables. Cochrane Q test and I^2 statistic were used to assess the heterogeneity between various effects. Values of $I^2 > 50\%$ were considered significant identifiers of heterogeneity according to the Cochrane Handbook [28]. The choice of meta-analysis model was pre-specified and based on anticipated clinical homogeneity or heterogeneity of studies. Homogeneous data was analyzed under a

fixed-effects model, while heterogeneous data was analyzed under the random-effects model. Sensitivity analysis was taken into consideration to investigate how each study affected the stability of the meta-analysis findings. Funnel plots were used to assess publication bias for outcomes that included 10 or more studies. Forest plots were developed using Review Manager 5.4.0 to visualize the comparison results, and funnel plots were performed using Stata 16.0 to test the publication bias.

Results

Search results

A total of 2108 records were initially retrieved from the database. After screening, 216 studies were eligible and examined, of which 206 were further excluded due to the following reasons: (1) irrelevant study design ($n=157$), (2) ineligible intervention ($n=15$), (3) irrelevant outcome ($n=26$), and (4) unusable data for which study authors could not be contacted to provide summary statistics ($n=8$). Moreover, nine studies were obtained from other sources, and eight studies were excluded due to duplications and irrelevant reports. After screening, a total of 11 studies [20–22, 29–36] were ultimately included (Fig. 1).

Study characteristics

Eleven RCTs of 637 participants were included, including 326 patients in the experimental groups and 311 patients in the control groups [20–22, 29–36]. Men accounted for about 80% of the participants, and the majority had a baseline LVEF of less than 40%. Of the 11 trials, 1 was conducted in China [36], 1 in India [33], 1 in Chile [29], 1 in the UK [20], 2 in Slovenia [34, 35], 2 in the USA [21, 31], and 3 in Brazil [22, 30, 32]. The included trials were conducted from 2010 through 2018. Participants in experimental group and control group both received optimal medical treatments, including angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonists, cardiac glycosides, nitrates, and beta-blockers. The experimental groups received stem cell therapy based on the control groups. CD34+was the most commonly used type of injected cells, and intracoronary transplantation was one of the routes of administration adopted by most studies. Follow-up in RCTs ranged from 6 months to 5 years, with 6 studies having a 1-year follow-up. The characteristics of the included studies are shown in Table 1.

Quality evaluation

Quality evaluation of included RCTs was performed using the Cochrane risk-of-bias assessment tool. Two studies [20, 32] generated randomization using a dedicated trial software system, and one study [22] generated randomization via block randomization method. One study [29]

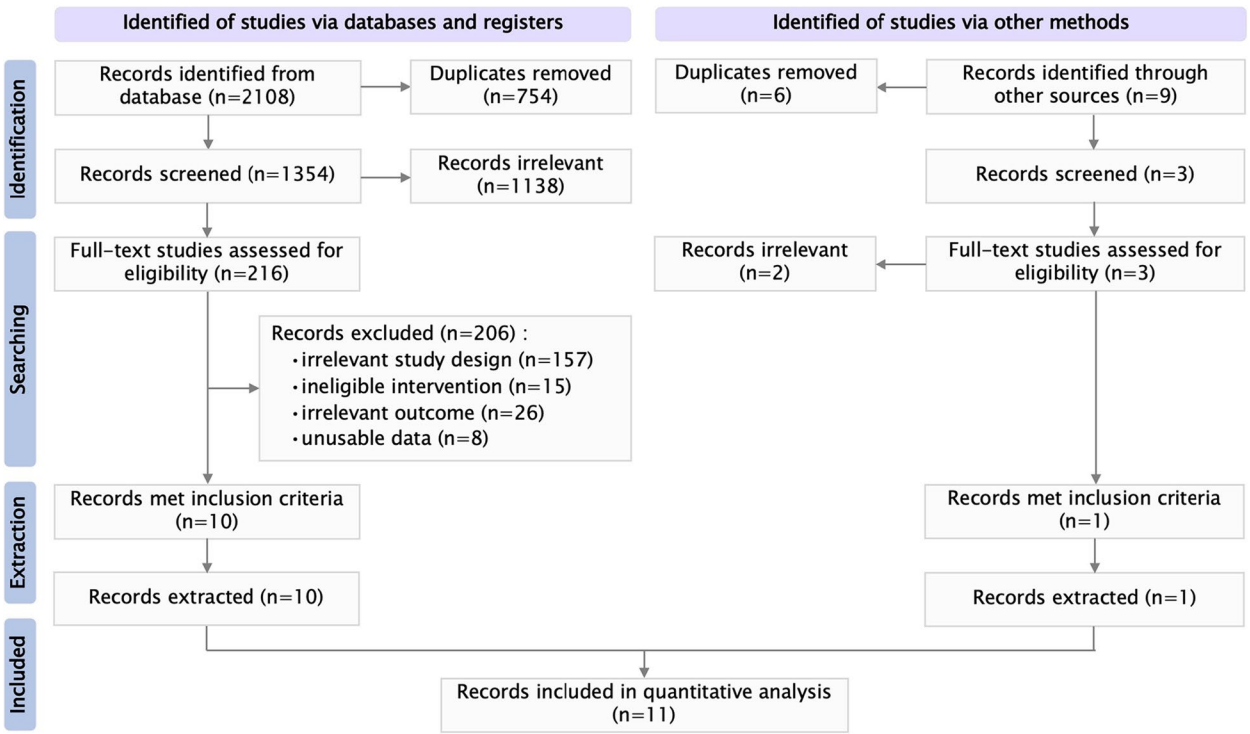

Fig. 1 Flow diagram of study selection

Table 1 Characteristics of the included studies

Study ID	Country	Registration number	N (E/C)	Male/female		Age (years)		Baseline LVEF (%)		Type of injected cells	Number of injected cells	Route of administration	Follow-up	Outcomes
				E	C	E	C	E	C					
Bartolucci (2015) [29]	Chile	NR	12/11	8/4	9/2	59 ± 9	54 ± 11	32.2 ± 9.3	31.1 ± 7.8	CD34 +	8.19 ± 4.43 × 10^6 cells	Intracoronary	37.7 ± 9.7 mo	①③⑤⑥⑦⑩
Bocchi (2010) [30]	Brazil	NR	8/15	NR	NR	57.67 ± 12.32	54.57 ± 9.76	32.93 ± 16.46	36.5 ± 13.26	CD34 +	NR	Intracoronary	468 ± 374 d	①②⑨
Frljak (2018) [31]	USA	ClinicalTrials.gov (NCT02248532)	30/30	27/3	26/4	57.9 ± 11	52.3 ± 11	25.8 ± 7	24.7 ± 6	CD90 +, CD45 +	NR	Transendocardial	6 mo	①②④⑧⑩
Hamshere (2015) [20]	UK	ClinicalTrials.gov (NCT01302171)	15/14	10/5	10/4	51 ± 11.1	49.6 ± 11.1	23.8 ± 7.2	24.7 ± 7	CD34 +, CD105 +, CD133 +	4.91 × 10^6 ± 2.75 cells	Intracoronary	1 y	①③⑦⑧⑨⑩
Henry (2014) [21]	USA	ClinicalTrials.gov (NCT00765518)	18/11	13/5	7/4	48.3 ± 8.71	51.6 ± 7.79	25.09 ± 3.98	26.10 ± 4.49	CD34 +, CD45 +, CD14 +, CD3 + CD4 +, CD3 + CD8 +, and CD34 + CD38 −	0.35 × 10^8 ~ 2.95 × 10^8 cells	Minithoracotomy or intramyocardial	1 y	①③④⑥⑩
Martino (2015) [22]	Brazil	ClinicalTrials.gov (NCT00333827)	82/78	60/22	54/24	45 ± 15	49 ± 9	NR	NR	CD34 +	2.36 × 10^8 cells	Intracoronary	1 y	⑩
Sant'Anna (2014) [32]	Brazil	ClinicalTrials.gov (NCT00743639)	20/10	13/7	5/5	52 ± 8	54 ± 7	25.6 ± 5.1	26.7 ± 3.9	CD34 +	1.06 × 10^8 cells	Intramyocardial	1 y	①②④⑤⑥⑩
Seth (2010) [33]	India	NR	41/40	33/8	35/5	53 ± 8	55 ± 7	24.3 ± 6.5	25.7 ± 4.1	CD34 +	1.68 ± 0.96 × 10^8 cells	Intracoronary	28 ± 9 mo	①③⑦⑩
Vrtovec (2011) [34]	Slovenia	ClinicalTrials.gov (NCT00629018)	28/27	26/2	23/4	51.6 ± 12.2	54.4 ± 11.6	34.1 ± 3.6	33.7 ± 4	CD29 +, CD34 +, CD44 +, CD45 +, and CD166 +	1.23 ± 0.23 × 10^8 cells	Intracoronary	1 y	⑩
Vrtovec (2013) [35]	Slovenia	ClinicalTrials.gov (NCT01350310)	55/55	45/10	44/11	59 ± 9	54 ± 11	32.2 ± 9.3	31.1 ± 7.8	CD34 +	1.13 ± 0.26 × 108 cells	Intracoronary	5 y	⑩
Xiao (2017) [36]	China	NR	17/20	12/5	14/6	57.67 ± 12.32	54.57 ± 9.76	32.93 ± 16.46	36.5 ± 13.26	CD34 +	4.9 ± 1.7 × 10^8 cells	Intracoronary	1 y	①②⑤⑩

E, experimental group; *C*, control group; *NR*, not reported. ①, left ventricular ejection fraction (LVEF); ②, left ventricular end-diastolic dimension (LVEDD); ③, left ventricular end-diastolic volume (LVEDV); ④, 6-min walk test (6MWT); ⑤, New York Heart Association (NYHA) functional classification; ⑥, Minnesota Living with Heart Failure Questionnaire (MLHFQ); ⑦, Kansas City Cardiomyopathy Questionnaire (KCCQ); ⑧, N-terminal pro-brain natriuretic peptide (NT-proBNP); ⑨, VO_2 peak; ⑩, major adverse cardiovascular events (MACEs). Higher values of LVEF, 6MWT, KCCQ, and VO_2 peak indicate a better outcome, and lower values of LVEDD, LVEDV, NYHA functional classification, MLHFQ, NT-proBNP, and MACEs indicate a better outcome

used a randomization method grouped by time of admission, which was prone to a high risk of bias. The remaining RCTs referred to only random grouping. Four studies [29, 33–35] were described as open-label designs, and participants or investigators enrolling participants may possibly foresee assignments. Two studies [20, 22] were designed as a double-blind study, and one study [31] was reported as a single-blind study. The rest of RCTs did not provide more information on allocation concealment and blinding. The detection bias of seven studies [20–22, 31, 34–36] was evaluated as "low risk" because the measurements were performed by blinded outcome assessors, or data analyzers were entirely masked to group assignment. All of the research outcome reports were comprehensive; therefore, there was no possibility of incomplete outcome data. Given the inability to obtain the entire implementation plan, the bias in reporting was assessed as "unclear risk." Since no other clear bias was found in any of the included trials, our review presumed that there were no further bias risks. The risk-of-bias graph of the included RCTs is presented in Fig. 2.

Outcomes

LVEF

A total of 8 RCTs [20, 21, 29–33, 36] including 312 participants reported LVEF, 161 participants were in the experimental group, and 151 participants were controls (Fig. 3). The fixed-effects model was performed, and the results indicated that there was a significant increase in mean LVEF ($MD = 4.84$, 95% CI 3.25–6.42, $P < 0.00001$). The heterogeneity test indicated that there was no statistical heterogeneity ($I^2 = 0\%$, $P = 0.45$).

LVED conditions

Eight RCTs provided information on LVED conditions. Of these, 4 RCTs [30–32, 36] of 150 participants recorded LVEDD (Fig. 4A). Combined results from the random-effects model indicated that difference between the two groups was not statistically significant ($MD = -3.94$, 95% CI −8.95 to 1.08, $P = 0.12$). The heterogeneity test indicated that there was significant statistical heterogeneity ($I^2 = 76\%$, $P = 0.005$).

In addition, 4 RCTs [20, 21, 29, 33] of 162 participants examined the effect of stem cell therapy on LVEDV

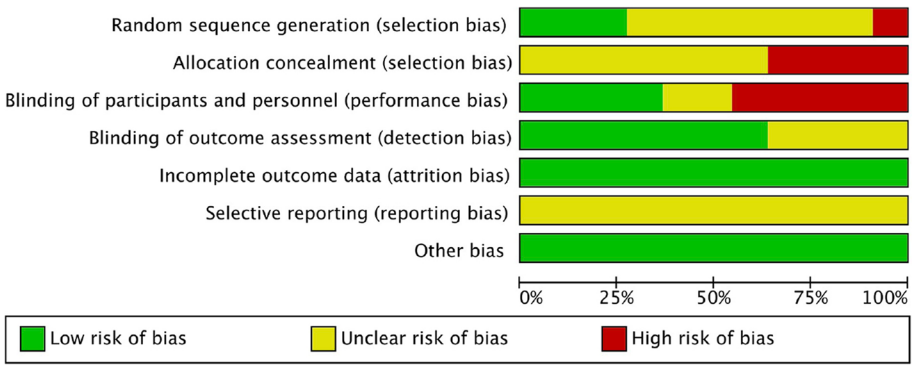

Fig. 2 Risk-of-bias graph

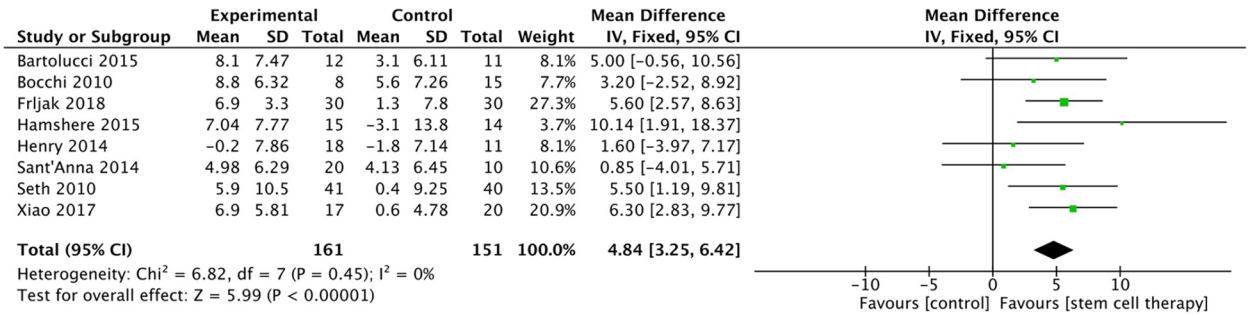

Fig. 3 Forest plot of LVEF. Each study corresponds to a line segment parallel to the *X*-axis: squares represent the weight accounted for by each study, and the larger the weight, the larger the area of the squares; width of line represents the 95%CI, the diamond represents the estimated overall effect of all studies pooled together in the meta-analysis, and the vertical line of no effect signifies "no difference" between groups if the 95% CI crosses the line (same as Figs. 4, 5, 6, 7, 8, 9, 10)

(Fig. 4B). The changes in LVEDV levels were statistically significant under stem cell therapy ($MD = -29.51$, 95% CI −58.07 to −0.95, $P = 0.04$). Pooled analysis was homogeneous ($I^2 = 0\%$, $P = 0.54$).

6MWT

Three RCTs [21, 31, 32] involving 119 participants reported 6MWT as an outcome (Fig. 5). Collectively, results from the fixed-effects model indicated that 6MWT appeared substantially different in the stem cell therapy group compared with the control group ($MD = 44.32$, 95% CI 34.70–53.94, $P < 0.00001$). The heterogeneity test indicated that there was no statistical heterogeneity ($I^2 = 0\%$, $P = 0.71$).

NYHA functional classification

Three RCTs [29, 32, 36] of 90 participants examined the effect of stem cell therapy on NYHA functional classification (Fig. 6). The fixed-effects model suggested that the combined mean differences of the studies favored the experimental group ($MD = -0.63$, 95% CI −0.96 to −0.30, $P = 0.0002$). Pooled analysis was homogeneous ($I^2 = 0\%$, $P = 0.48$).

QoL

In five different RCTs, MLHFQ and KCCQ were applied to assess QoL in DCM patients. Of these, 3 RCTs [21, 29, 32] of 82 participants and 3 RCTs [20, 29, 33] including 133 participants reported MLHFQ and KCCQ as an outcome, respectively (Fig. 7). Pooled analysis was homogeneous ($I^2 = 0\%$, $P = 0.39$). Combining findings based

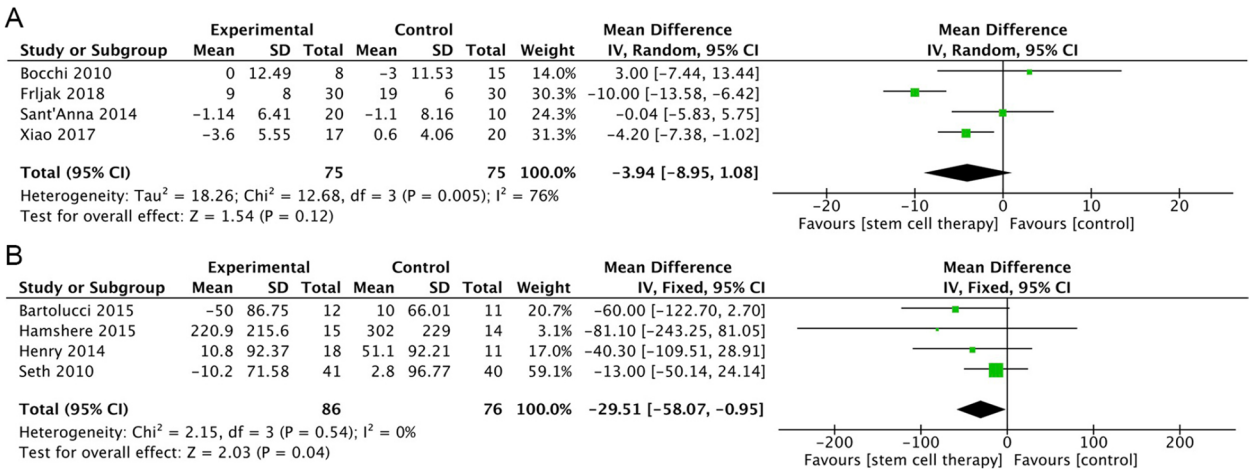

Fig. 4 Forest plot of LVED conditions. **A** LVEDD. **B** LVEDV

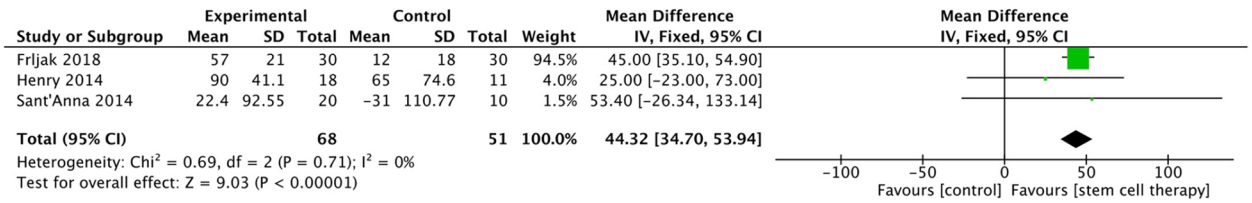

Fig. 5 Forest plot of 6MWT

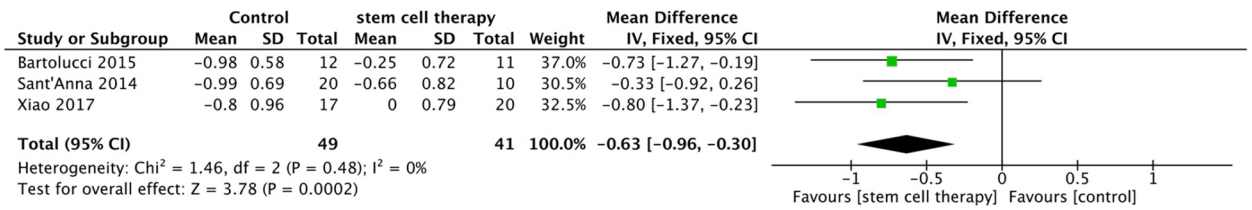

Fig. 6 Forest plot of NYHA functional classification

on the fixed-effects model, we found that both MLHFQ ($MD = -16.60$, 95% CI −26.57 to −6.63, $P = 0.001$) and KCCQ ($MD = 14.76$, 95% CI 7.76–21.76, $P < 0.0001$) levels appeared substantially different in the stem cell therapy group compared with the control group.

NT-proBNP

Two RCTs [20, 31] of 89 participants reported NT-proBNP (Fig. 8). The overall mean difference favored the experimental group significantly ($MD = -737.55$, 95% CI −904.28 to −570.82, $P < 0.00001$). The heterogeneity test indicated that there was no statistical heterogeneity ($I^2 = 0\%$, $P = 0.58$).

VO2 peak

Two RCTs [20, 29] of 52 participants reported VO_2 peak (Fig. 9). Combined results from the fixed-effects model indicated that difference between the two groups was not statistically significant ($MD = 0.73$, 95% CI −1.27 to 2.74, $P = 0.47$). Pooled analysis was homogeneous ($I^2 = 22\%$, $P = 0.26$).

MACEs

Regarding MACEs, 10 RCTs [20–22, 29, 31–36] involving 614 participants provided detailed information on the conditions (Additional file 3). A total of 146 MACEs were reported, 66 cases in the experimental group and 80 cases in the control group. The fixed-effects model suggested that the overall mean difference of MACEs between the two groups was not statistically significant ($RR = 0.77$, 95% CI 0.58 − 1.02, $P = 0.07$) (Fig. 10).

Sensitivity analysis

Sensitivity analyses were performed separately for all results, which indicated that each result was stable (Additional file 4).

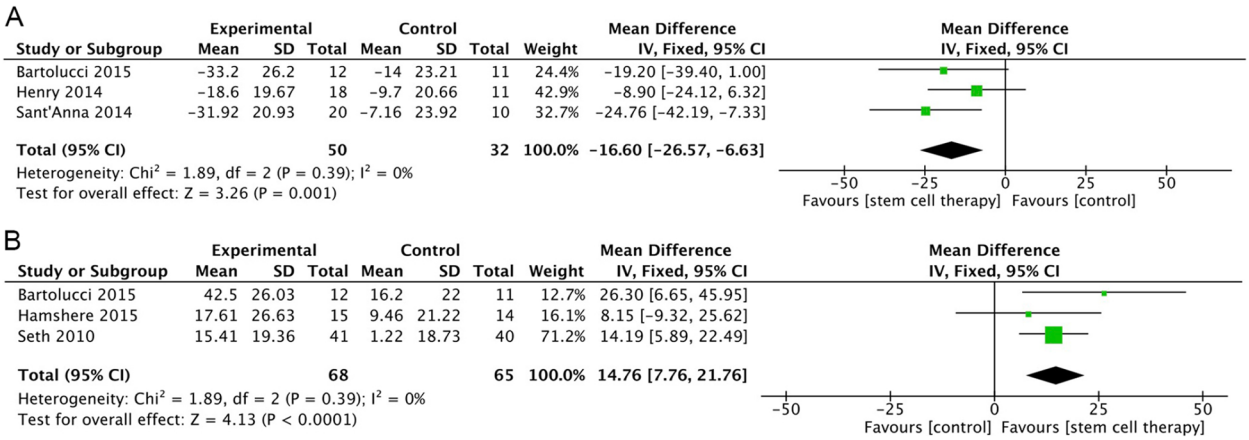

Fig. 7 Forest plot of QoL. **A** MLHFQ. **B** KCCQ

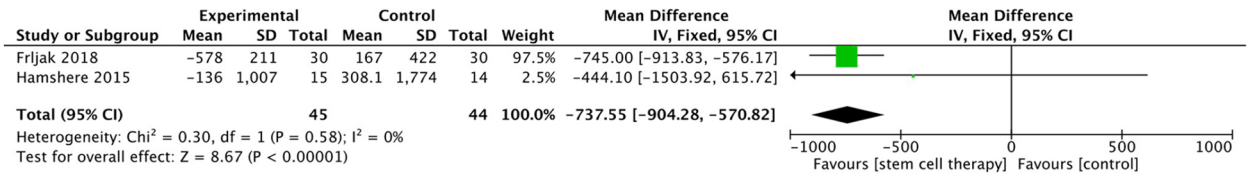

Fig. 8 Forest plot of NT-proBNP

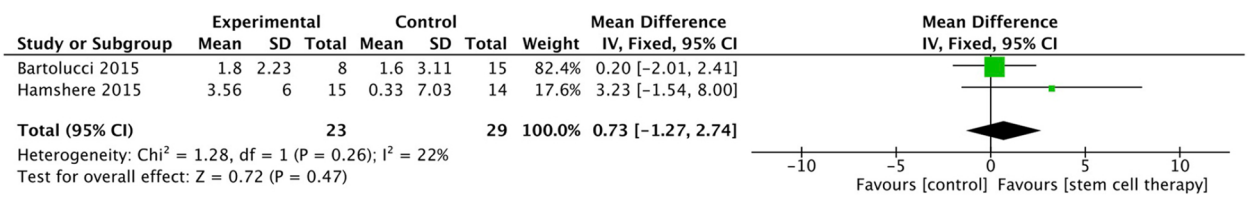

Fig. 9 Forest plot of VO_2 peak

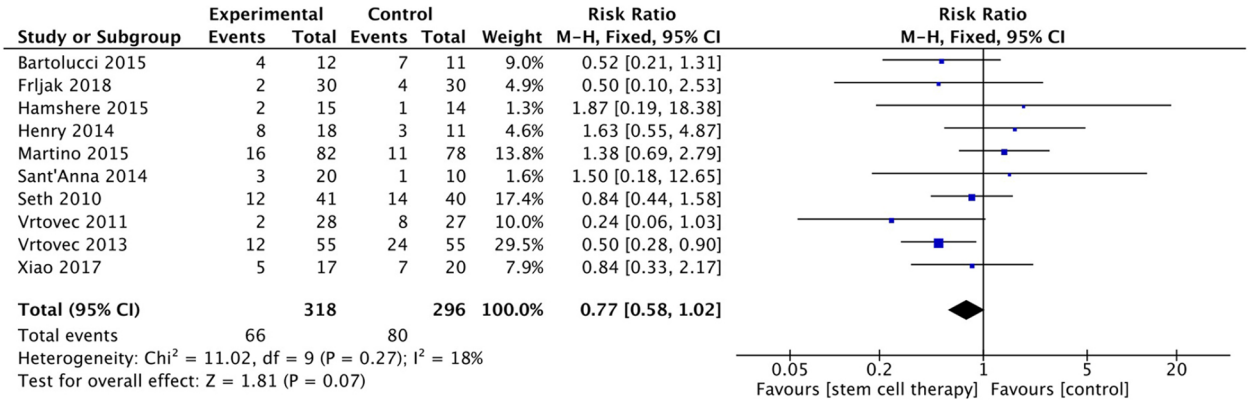

Fig. 10 Forest plot of MACEs

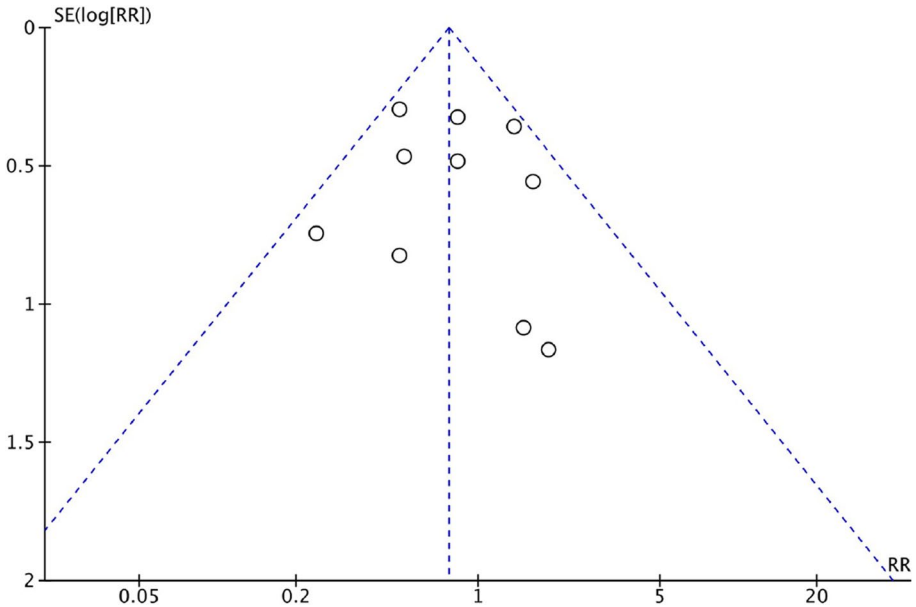

Fig. 11 Funnel plot of MACEs. Dots represent included studies, the vertical line represents pooled effect, and dashed lines on either side represent 95% CI

Publication bias

Given that the number of RCTs reporting only mace was MACEs, publication bias for MACEs was examined using a funnel plot (Fig. 11). Each point represents a study, and the size of the points is positively proportional to the sample size. The funnel plot of the 10 RCTs was found to be visually asymmetrical, which could be a sign of publication bias or a small sample effect.

GRADE assessment

Table 2 shows a summary of the evidence grade evaluation of the included outcomes using the GRADE method. The findings confirmed that the evidence was classified as low to moderate. The greatest contributing factor to evidence degradation was the possibility of bias, which was followed by imprecision and inconsistency. Randomization, allocation concealment, and blinding were common biases in the included trials, indicating that future study designs of stem cell therapy for DCM should be more focused and optimized.

Discussion

The systematic review and meta-analysis included 11 RCTs of 637 participants revealed that stem cell therapy had a potentially beneficial effect on the prognosis of patients with non-ischemic DCM. The findings showed that as compared to controls, DCM patients receiving stem cell therapy had a significantly higher mean LVEF

Table 2 GRADE quality of evidence for outcomes

Outcomes	*N*	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
LVEF	312	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯Moderate
LVEDD	150	RCT	Serious	Serious	Not serious	Not serious	None	⊕⊕◯◯Low
LVEDV	162	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯Moderate
6MWT	119	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯Moderate
NYHA functional classification	90	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯Low
MLHFQ	82	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯Low
KCCQ	133	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯Moderate
NT-proBNP	89	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯Low
VO_2 peak	52	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯Low
MACEs	614	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯Moderate

and considerably reduced LVEDV and NT-proBNP. According to the 6MWT and NYHA functional classification, stem cell therapy was also associated with a persistent increase in functional capacity. Furthermore, it also improved QoL, as seen by the considerable decline in the MLHFQ score and rise in the KCCQ score. There were no noticeable differences in MACEs, VO_2 peak, or LVEDD between the two groups. The GRADE assessment, however, found moderate certainty evidence for LVEF, LVEDV, 6MWT, KCCQ, and MACEs only and low for all other outcomes, emphasizing the importance of addressing these findings with caution. Sensitivity analyses suggested that all results were stable.

Our study found that stem cell therapy increased LVEF by 4.84% on average, which is in line with earlier systematic reviews and meta-analyses that reported improvements in LVEF of 4.87% [37]. A study [36] conducted in China reached similar conclusions. Regarding earlier clinical trials conducted on patients with non-ischemic DCM, the studies have produced contradictory findings. Two trials [20, 30] showing an improvement in LVEF in individuals with non-ischemic DCM that was sustained for a year combined stem cell treatment and granulocyte colony-stimulating factor (G-CSF). In 2010, the ABCD trial [33] reported the results of autologous bone marrow transplantation in patients with cardiomyopathy and found clinical improvements in terms of LVEF. The study population was followed up for 3 years, and no side effects were noted. Another RCT [34] of 55 patients revealed that intracoronary administration of stem cells leads to improved ventricular remodeling, increased exercise tolerance, and increased overall survival rates among DCM patients. After a couple of years, a second study [35] was conducted by the same group and found similar results. However, five RCTs [21, 22, 29, 31, 32] indicated that stem cell therapy did not significantly improve left ventricular function in patients with non-ischemic DCM.

Additionally, our analysis showed improved LVEDV in patients receiving stem cell therapy; however, this correlation was constrained by variations in imaging techniques and measurement units among studies. Sophisticated quantitative evaluation of left ventricular volumes using MRI should be incorporated into future research designs, since it offers superior spatial and contrast resolution, operator independence, and repeatability. Moreover, stem cell therapy was also associated with the sustained improvement in functional capacity, as evaluated by 6MWT and NYHA functional classification, as well as significant long-term benefits on quality of life. Moreover, 10 of the included trials reported MACEs, and quantitative analysis suggested that no obvious adverse events occurred during stem cell therapy. Given the small number of clinical studies of stem cell therapy in dilated cardiomyopathy, adverse effects remain a focus of concern.

Our study included trials using various types of cells, including autologous or allogenic bone marrow-derived cells, as well as autologous peripheral blood-derived CD34+cells acquired following G-CSF stimulation. While our research validates the effectiveness of stem cell therapy in individuals with non-ischemic DCM, there is currently not enough data to identify which particular cell type holds the most potential. Early research on non-ischemic DCM produced several kinds of findings using bone marrow-derived mononuclear cells [22, 32]. Subsequently, more consistent improvements in LVEF were observed in later using specific populations of CD34+cells [20, 34, 35]. Recently, bone marrow-derived mesenchymal stromal cells have shown promise as a

cell type for the therapy of cardiomyopathy due to their potent immune system modulation and anti-inflammatory activities [18, 38–40]. Given their potential to evade immune identification and allosensitization, allogeneic mesenchymal stem cells have tremendous promise as an off-the-shelf therapeutic agent [41–43]. Additionally, they might be administered intravenously in a safe manner [39, 44]. Numerous approaches have been put forth to improve the survival and functionality of donor cells following transplantation, including the use of combinatorial cell therapies, in vitro preconditioning through the administration of growth factors or small molecules, or through physical stimulation such as heat shock or hypoxia, genetic modification through the overexpression of pro-survival molecules, or the knockdown of proapoptotic factors, which increases paracrine factor secretion and cell survival [45, 46].

Non-ischemic DCM has received far less attention in the developing field of cell therapy trials for heart failure than ischemic cardiomyopathy, for a variety of reasons. First, the prevalence of ischemic cardiomyopathy is much higher than that of non-ischemic dilated cardiomyopathy. Second, the concept of myocardial regeneration is more easily applied to ischemic cardiomyopathy because ischemic cardiomyopathy typically has a well-defined region of myocyte death and scar, whereas non-ischemic dilated cardiomyopathy frequently has diffuse fibrosis rather than a confluent scar. Ultimately, it is challenging to model NICM in simulations since it is not a single disease but rather the culmination of numerous distinct pathophysiological processes, some of which are still poorly understood [17]. Indeed, virtually, all preclinical studies supporting cell therapy in heart failure have been performed in post-myocardial infarction models of heart failure. Although a limited number of preclinical studies of cell therapy have been conducted in NICM models with defined etiology, such as anthracycline-induced cardiomyopathy and Chagasic cardiomyopathy [47, 48], there is a dearth of models of idiopathic DCM, which is more prevalent than the first two. Non-ischemic cardiomyopathy can be caused by a variety of factors, resulting in variations in natural history, prognosis, and therapy response [49]. Thus, identification of the underlying pathophysiologic and structural substrate may aid in the selection of an optimal cell therapy [50]. For instance, an increase in cardiac oxidative stress and the buildup of reactive oxygen species, which cause endothelial dysfunction and cardiotoxicity, are closely associated with anthracycline-induced cardiomyopathy [51]. Administration of MSCs alleviates anthracycline-induced oxidative stress, thereby improving endothelial dysfunction [52, 53]. Furthermore, the POSEIDON-DCM trial [54] emphasized the need for further genetic studies because of important implications for the management of non-ischemic DCM syndromes. Overall, the current study may help to promote understanding of non-ischemic DCM and personalized stem cell therapy in individuals with non-ischemic DCM, hence improving prognosis.

Several limitations of this review need to be acknowledged. Firstly, some of the studies were conducted following an open-label design, stemming from the extremely small possibility of blinding all groups due to invasive interventions. Moreover, there was no detailed report on randomization and allocation concealment in most studies, which may lead to reduced robustness of results. Secondly, obvious inconsistencies were observed in the included studies in terms of number of participants, comorbidities, type and number of cells, route of administration, methods for assessing cardiac function, QoL measurement indices, and definition of MACEs; thus, the generalizability of our findings requires further confirmation. Although there were inconsistencies across studies, heterogeneity was modest, most likely due to small sample sizes. Thirdly, the number of studies we included was limited by the lack of published RCTs of stem cell therapy for non-ischemic DCM. The strength of this review is that it provides a systematic analysis of the efficacy and safety of stem cell therapy for non-ischemic DCM, revises the studies included in previous systematic reviews and meta-analyses, and assesses the quality of evidence for each outcome, thereby improving the robustness of the evidence.

Conclusion

In summary, stem cell therapy for DCM patients appears to be both safe and linked to improvements in cardiac function and functional ability and may lower the incidence of MACEs in individuals with non-ischemic DCM. These findings support the idea that stem cell treatment is still a promising approach to improve quality of life and reduce the morbidity associated with non-ischemic DCM. However, published randomized controlled trials of stem cell therapy for dilated cardiomyopathy are still limited. The results we obtained may support more extensive, rigorous research to definitively establish the effectiveness of stem cell therapy in non-ischemic DCM patients and to determine the optimal cell type, dosage, and route of administration.

Abbreviations

DCM	Dilated cardiomyopathy
RCT	Randomized controlled trial
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic dimension
LVEDV	Left ventricular end-diastolic volume
6MWT	6-min walk test
QoL	Quality of life
MLHFQ	Minnesota Living with Heart Failure Questionnaire
KCCQ	Kansas City Cardiomyopathy Questionnaire

MACEs	Major adverse cardiovascular events
NYHA	New York Heart Association
MD	Mean difference
RR	Risk ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Authors' contributions

JL and ST contributed to the study concept and design. ST and LY searched databases, collected data, conducted meta-analysis, and drafted the manuscript. JW, DY, and TX were responsible for the data collection and quality assessment. LZ, ZX, and XH contributed to the data checking. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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Data availability

The data used in this review were extracted from published studies, and the original data could be obtained by searching databases. Other data supporting the results of this review are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have consent for publication.

Competing interests

The authors declare that they have no competing interests.

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