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Efficacy of mesenchymal stem cell transplantation on major adverse cardiovascular events and cardiac function indices in patients with chronic heart failure: a meta-analysis of randomized controlled trials

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Abstract

Background The effects of mesenchymal stem cells (MSCs) on heart failure (HF) have been controversial. This study was conducted to investigate whether the transplantation of MSCs after HF could help improve clinical outcomes and myocardial performance indices.

Methods Using a systematic approach, electronic databases were searched for randomized controlled trials (RCTs), which evaluated the transplantation of MSCs after HF. The outcomes owf interest included clinical outcomes and myocardial function indices. We also assessed the role of age, cause of heart failure, cell origin, cell number, type of donor (autologous/allogeneic), and route of cell delivery on these outcomes. Using the random-effects method, a relative risk (RR) or mean difference (MD) and their corresponding 95% confidence intervals (CI) were pooled.

Results Seventeen RCTs including 1684 patients (927 and 757 patients in the intervention and control arms, respectively) were enrolled. The RR (95% CI) of mortality was 0.78 (0.62; 0.99, p = 0.04) in the MSC group compared to the controls. HF rehospitalization decreased in the MSC group (RR = 0.85 (0.71–1.01), p = 0.06), but this was only significant in those who received autologous MSCs (RR = 0.67 (0.49; 0.90), p = 0.008). LVEF was significantly increased among those who received MSC (MD = 3.38 (1.89; 4.87), p < 0.001). LVESV (MD = −9.14 (−13.25; −5.03), p < 0.001), LVEDV (MD = −8.34 −13.41; −3.27), p < 0.001), and scar size (standardized MD = -0.32 (-0.60; -0.05), p = 0.02) were significantly decreased. NYHA class (MD = −0.19 (−0.34; −0.06), p = 0.006), BNP level (standardized MD = −0.28 (−0.50; −0.06), p = 0.01), and MLHFQ (MD = −11.55 (−16.77; −6.33), p = 0.005) significantly decreased and 6-min walk test significantly improved (MD = 36.86 (11.22; 62.50), p = 0.001) in the MSC group. Trials were not affected by the participants' etiology of heart failure, while trials with the autologous source of cells, MSC doses lower than 100 million cells, and intracoronary injection performed significantly better in some of the outcomes.

Conclusion Transplantation of MSCs for ischemic or dilated heart failure patients may reduce all-cause mortality and improve clinical condition. Moreover, this treatment would improve left ventricular function indices and reduce scar size.

Keywords Mesenchymal stem cells, Cardiomyopathy, Heart failure, Randomized controlled trials, Meta-analysis

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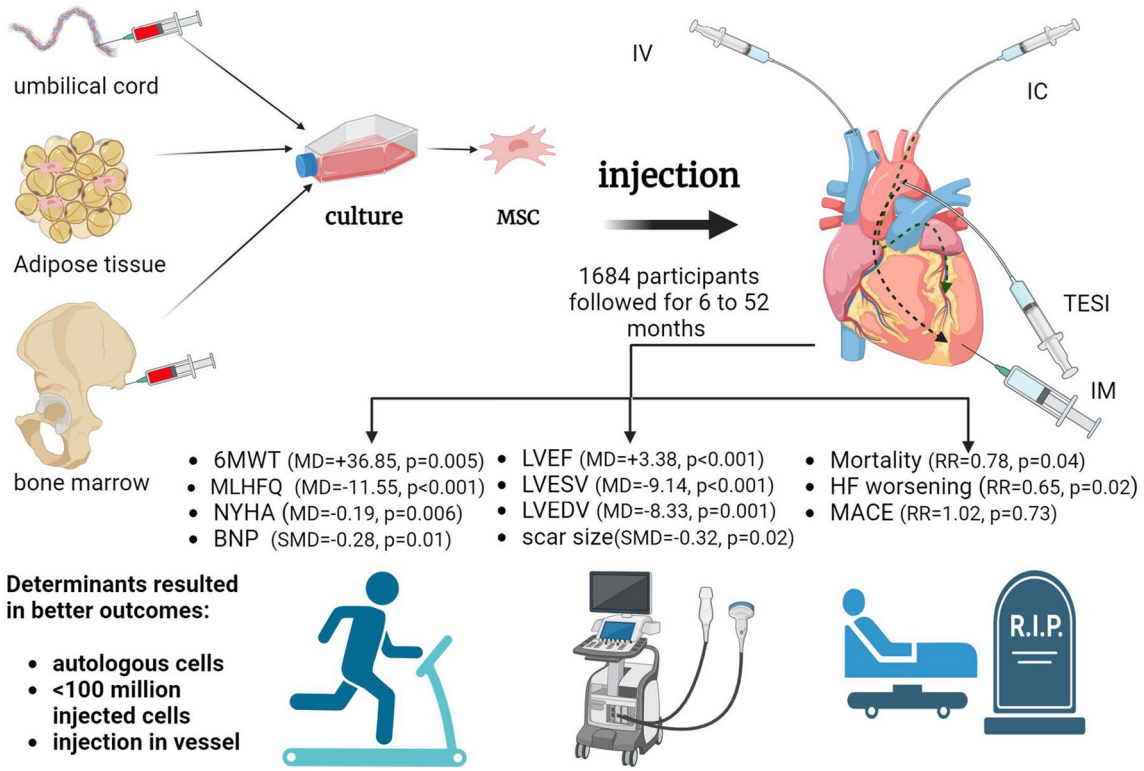
Graphical Abstract



Background

Over the past few decades due to advancements in the treatment of myocardial infarction (MI), a reduction in the mortality rate after MI was observed. However, this caused a rise in the incidence of heart failure (HF), a fatal and disabling syndrome [1]. HF affects more than 64 million people worldwide leading to significant morbidity and mortality, poor quality of life, and imposition of high costs on healthcare systems [2]. The global economic burden of HF is estimated to be $108 billion per annum; with an aging, rapidly expanding, and industrializing global population, this value will continue to rise [3]. Although the current management for HF, which imposes approximately 65 billion dollars annually [3], only increases the longevity of the patients while improving their symptoms, they do not restore the heart's normal function by inducing regeneration in the damaged myocardium [4]. Therefore, improving confirmed treatments and developing approaches to treat heart failure patients that restore the normal function of the myocardium is strongly required [4]. One of the proposed methods of treatment, which probably could lead to the reconstruction of the damaged myocardium thus restoring the normal functions of the patients, is stem cell therapy [5, 6].

As a result of promising outcomes of stem cell therapy in animal studies in MI and HF models [7], cell therapy instantly moved forward to human studies, using skeletal myoblasts in patients with HF in 2001[8]. Since then, different types of stem cells including bone marrow mononuclear cells (BM-MNCs), skeletal myoblasts, endothelial progenitor cells, mesenchymal stem/stromal cells (MSCs), cardiac stem/progenitor cells, embryonic stem cells, and induced pluripotent stem cells have been investigated to select the optimal type of cell for treating patients with heart diseases [9]. Based on a meta-analysis by Fisher and colleagues, most of the studies on cell therapy in HF are done by BM-MNCs and cell therapy showed promising results in reducing mortality and increasing left ventricular ejection fraction (LVEF) in HF by 4.66% [6]. However, investigations on MSCs yielded more promising outcomes and it was shown that MSCs are almost twice as effective as BM-MNCs in the TAC-HFT study [10] and a meta-analysis comparing the efficacy of MSCs with

BM-MNCs in patients with acute myocardial infarction showed better results in MSCs [11].

MSCs are defined as a population of cells that adhere to plastic in standard culture conditions and express CD73, CD90, and CD105 in the absence of CD34, CD45, HLA-DR, CD14, or CD11b, CD79a, or CD19 surface molecules, and can differentiate into osteoblasts, adipocytes, and chondroblasts in vitro [12]. This population of cells is discovered in organs and tissues other than its initial source, the bone marrow (BM), including Wharton's jelly, peripheral blood, menstrual blood, and adipose tissue [7, 13]. These tissues are becoming the dominant source for the isolation of MSCs due to their safety and availability [7]. Furthermore, MSCs are progressively used in cell therapy trials because of their desirable features, such as a readily obtainable source of adult stem cells, multilineage potential, ease of isolation and expansion, maintenance of stem cell niches, the potential of off-the-shelf cell therapy, and recruitment of endogenous stem cells and its anti-inflammatory effects through secretion of paracrine factors [14].

A meta-analysis of patients who were randomized to receive MSCs as a treatment for acute myocardial infarction [5] has shown that transplantation of MSCs after acute MI significantly increases LVEF and may have beneficial effects on some clinical outcomes. On the other hand, clinical trials using MSCs in HF showed controversial results and most of them were conducted with a low sample size. Furthermore, many questions such as the optimal number of stem cells that must be injected, feasibility of allogenic transplant and donor selection, optimal source of mesenchymal stem cells, the effectiveness of this treatment for ischemic and non-ischemic HF, the process of patient selection for this treatment based on demographic and clinical characteristics, and the optimal time course of delivery to maximize recovery of cardiac function remain to be determined. In this study, we report a meta-analysis of clinical evidence from randomized controlled trials of MSCs in patients with heart failure caused by ischemic and non-ischemic cardiomyopathy and discuss the effects of this treatment on clinical outcomes and cardiac function indices.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for reporting this study [15]. The protocol for the present systematic review and meta-analysis was registered at PROSPERO (CRD42024502831).

Search strategy

Relevant studies were identified by searching PubMed, Scopus, Embase, Cochrane Library, and clinicaltials.gov up to July 2023. The following search terms were used alone or in combination: heart failure, congestive heart failure, dilated cardiomyopathy, ischemic cardiomyopathy, mesenchymal stem cell, progenitor, stromal cell, and multipotent stromal cell. Following the removal of duplicates, two reviewers (SK, FB) independently reviewed all the titles and abstracts considering the pre-specified eligibility criteria. The full texts of the papers were obtained and looked over for any references for which the title and abstract alone could not determine eligibility. The reference lists of the related systematic reviews found through the search were also assessed. Disagreements were settled by discussions with a third reviewer (AA).

Eligibility criteria

Studies were eligible for inclusion in the meta-analysis if they met all of the following inclusion criteria: (1) randomized controlled trials (RCTs), (2) participants presented with symptoms of HF (both ischemic and non-ischemic) according to the New York Heart Association (NHYA) functional classification (class II–IV) or clear evidence of left ventricular (LV) dysfunction, (3) the intervention group receiving mesenchymal stem cell therapy by any route of administration compared with the control groups receiving either no intervention or placebo in addition to the standard care, and (4) trials assessing clinical outcomes and cardiac function indices. The intervention group was required to receive transplantation of MSCs through either the vessels (either intracoronary or intravenous) or direct injection to the myocardium (intramyocardial or transendocardial) with any cell origin (bone marrow, umbilical cord, and adipose tissue). The source of cell donor was either autologous (the cells harvested from the same individual who received the transplant) or allogenic (harvested from a donor and transplanted to a different individual) stem cells The studies were excluded if: (1) animal or lab studies, (2) conference abstracts with no published full-length articles, (3) observational studies, and (4) studies comparing outcomes other than the endpoints of interest.

Data extraction

Data extraction was carried out separately by two reviewers (SK, AH). A third reviewer (AA) verified the obtained accuracy of the extracted data. If the included studies failed to provide the necessary data, the corresponding authors were contacted. The extracted data including authors, year of publication, manuscript type, clinical trial registration ID, study design (setting, methods of treatment allocation, randomization, blinding), characteristics of the participants (age, gender, cause of cardiomyopathy, New York Heart Association (NYHA) functional class, smoking, and comorbidity),

interventions (allogeneic/autologous donor, age of the donor, cell origin, cell number, route of delivery, number of adverse events during the intervention, measurement tools, duration of heart failure, lost to follow-up, and follow-up duration were recorded. Specific data regarding the analyses including the sample size of each group, the number of events for clinical outcomes, and data regarding pre and post-intervention and also the absolute change for the continuous outcomes were extracted.

The primary outcomes of this systematic review were clinical outcomes including all-cause mortality, rehospitalization for heart failure, major adverse cardiovascular events (MACE), and HF worsening. HF worsening was defined as the number of participants experiencing a decline in the NYHA functional class. Also, MACE was defined as a composite of myocardial infarction, stroke, and cardiovascular death. Secondary outcomes were changes in echocardiographic indices (LVEF, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV)), health-related quality of life (Minnesota living with heart failure questionnaire (MLHFQ) score), NYHA functional class, 6-min walk test (6MWT), brain natriuretic peptide (BNP), NT-proBNP levels, and scar size. Where multiple times of follow-ups were reported, data were extracted from the longest possible duration of follow-up. Whenever, the mean and standard deviation (SD) of the change in desired outcomes were reported as other measures such as median, interquartile range, or range, we calculated the mean and SD using the formula proposed by Wan and colleagues [16].

Risk of bias (quality) assessment

Two authors (SK, FB) independently assessed the quality of the studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [17]; the studies were assessed in 5 domains including randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Then, each domain was labeled as low, with some concerns, or high. For each study, we assessed the overall risk of bias. If all domains were scored low, the study was judged as low risk of bias. The study was judged to raise some concerns when at least one domain scored some concern, but not at high risk of bias for any domain. When one domain was scored high risk of bias or multiple domains of a study were labeled with some concerns, the study was judged to be at high risk of bias. Any disagreement was resolved by discussion. Finally, the traffic light and summary plot were drawn using the robvis tool [18].

Statistical analysis

All the statistical procedures were performed using the Comprehensive Meta-Analysis version 3.7 (Biostat Inc. 14 North Dean Street Englewood, NJ 07631 USA). Meta-analysis was restricted to outcomes that were reported in at least three trials. The results of the dichotomous data were presented as relative risk (RR) with a 95% confidence interval (CI) and for continuous variables, the studies were pooled to present the mean difference (MD) with 95% CI. For MACE, we reported a rate ratio (RR) and for two of the other outcomes (BNP/NT-proBNP and scar mass), the results were presented using standardized mean difference (SMD) and its 95% CI. In case the mean change and SD were not reported in each study, we calculated the mean changes and estimated SD using the correlation coefficient formula. A random-effects model was used throughout the analyses due to the likely heterogeneity arising from the different study settings. Multiple modalities [magnetic resonance imaging (MRI), echocardiography, and single-photon emission computed tomography (SPECT)] were considered in the analysis of LVEF, with some studies reporting data for multiple techniques. Wherever the results of more than one modality were reported, we extracted data from echocardiographic variables. For trials with more than two treatment arms and a single control or placebo group, multiple pairwise comparisons of treatment groups were avoided by pooling treatment groups [19]. The heterogeneity between studies was assessed using Cochran's Q test and I^2.

We used meta-regression and subgroup analysis to find the possible sources of heterogeneity in variables. Type of donor (allogeneic/autologous), age of the donor (≥ 45 vs. < 45 years of age), cell origin (bone marrow/umbilical cord/ adipose tissue), number of transplanted cells ($\geq$ or < 100 million cells), route of delivery (through vessels (intracoronary or intravenous) vs direct injection into the heart muscle (intramyocardial or transendocardial), age of participants (< 60 vs. ≥ 60 years of age), cause of HF (ischemic vs. non-ischemic) were specified for conducting subgroup analyses. The non-linear potential effects for age, donors' age, follow-up duration, cell number, percentage of male participants, percentage of patients with ischemic etiology, and baseline mean values of LVEF, and NYHA functional class were examined using fractional polynomial modeling. Sensitivity analyses were used to assess the impact of risk of bias on significant results from meta-analyses, by "one study removed" test. Influence analysis was performed to test the possible effect of individual studies on results. We explored the potential small-study effects (publication bias) using Egger's test and funnel plots. $P \leq 0.05$ were considered statistically significant.

Results

Eligible studies and quality assessment

Figure 1 shows the PRISMA flow diagram of the study. During the initial search in databases, 1,872 articles were identified; 298 duplicate records were removed, of which 1574 studies were screened. 1474 studies were excluded during the screening of titles and abstracts. Among the remaining 100 studies, a total of 17 trials [10, 19–34] were included in the quantitative synthesis.

Figure 2 depicts the risk of bias in the included trials. Among the seventeen studies, all studies were randomized however five studies [19, 20, 24, 26, 30] had some concerns in their randomization process (domain 1). In one study the randomization process was not mentioned [20] and all five of them did not provide any information regarding the allocation concealment [19, 20, 24, 26, 30]. Regarding domain 2, deviation from the intended intervention, 4 studies raised some concerns [20, 23, 26, 30]. Two studies were not blinded [23, 26];

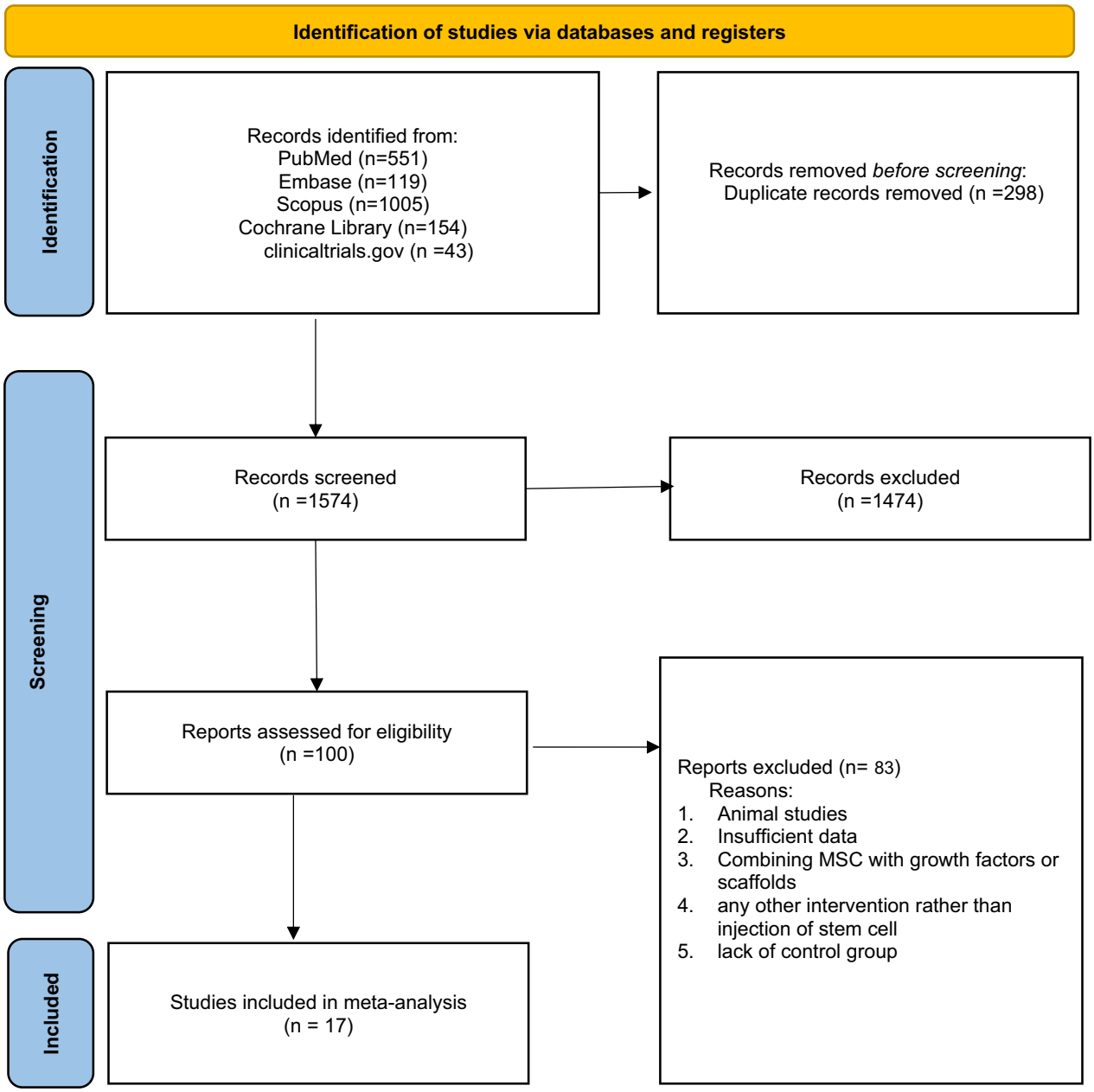


Fig. 1 PRISMA flowchart of the screening and inclusion process

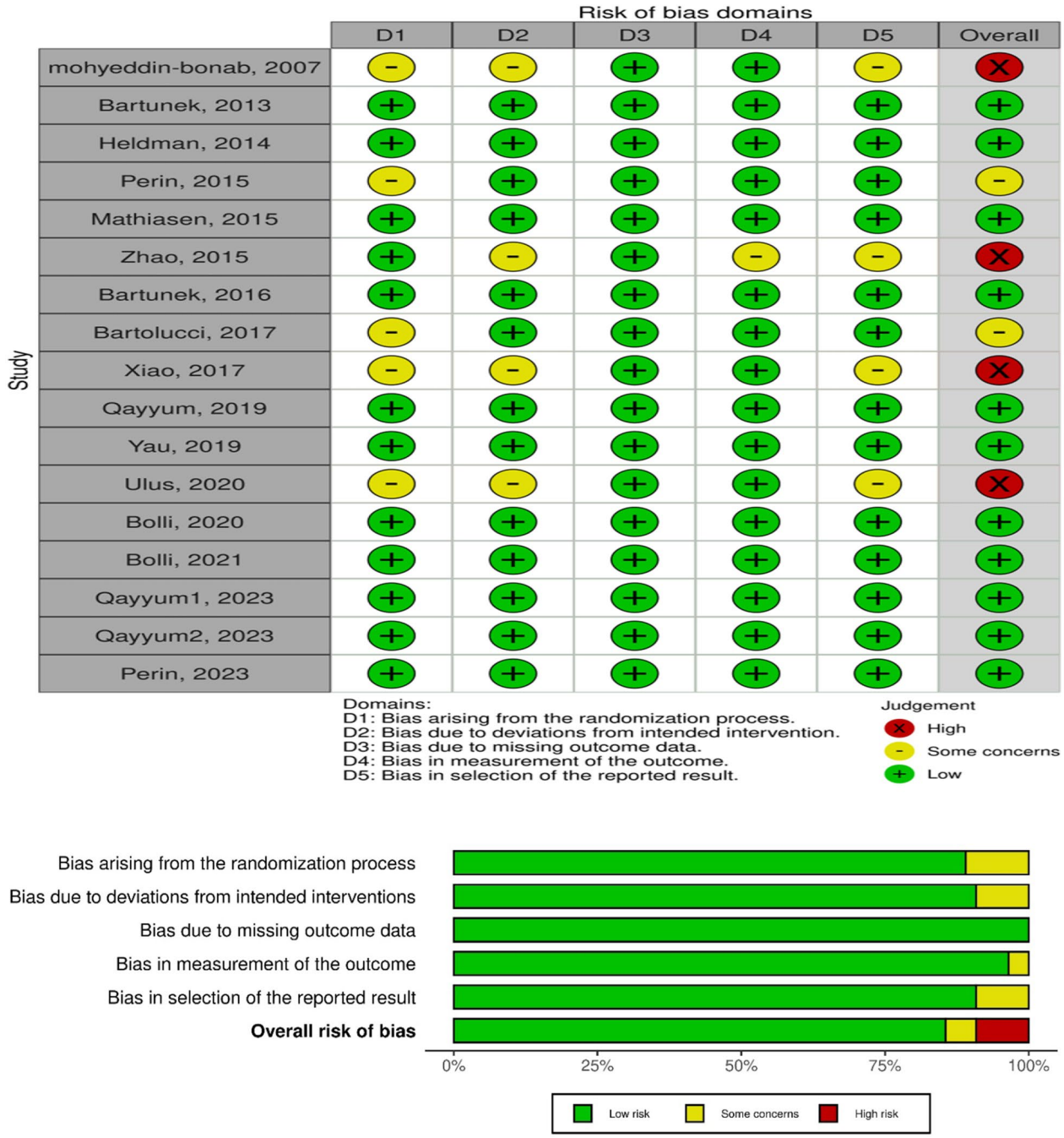


Fig. 2 risk of bias assessment using RoB 2

one was unclear [20], and three were single-blinded [19, 21, 30]. None of the trials had concerns regarding domain 3 either being without missing outcome data or there was evidence that the result was not biased due to missing outcome data. Only one study had some concerns regarding domain 4 (bias in the measurement of the outcomes) [23]. Four studies had some concerns regarding selective reporting [20, 23, 26, 30]. Overall, four studies were judged as having a high risk of bias [20, 23, 26, 30], two had some concerns [19, 24], and the remaining 11 studies had a low risk of bias.

Characteristics of the enrolled studies

As shown in Table 1, a total of 1684 patients were included in our final synthesis, of which 927 patients underwent MSC therapy and 757 received either placebo or no intervention. The pooled mean age in the control and treatment groups was 60.70 (95% CI 58.79–62.80) and 59.85 (95% CI 57.38–62.32), respectively. Eight studies extracted the autologous cells [10, 20–22, 25–27, 31] while the remaining studies used allogenic cells extracted [19, 23, 24, 28–30, 32–34]. In 11 studies, the origin of cells was bone marrow [10, 19–22, 25, 26, 28, 29, 31, 34], three used the umbilical cord as their source of cells [23, 24, 30], and the remaining three studies extracted cells from adipose tissue [27, 32, 33]. The injected cell dose ranged from 5.55×10^6 [20] to 733×10^6 [21]. Twelve studies used echocardiography as the measurement tool [10, 19–21, 24–26, 28, 30, 32–34], four studies used SPECT [19, 20, 26, 30], seven studies used MRI for measuring ejection fraction [10, 22, 24, 27, 29–31], and the method of measurement in one study was not mentioned [22].

The method of delivery in the included trials could be categorized into two main groups: group A consisting of three studies that delivered cells via vessels [23, 24, 26], and group B including 13 studies in which the cells were directly injected into the heart muscle [10, 19, 21, 22, 25, 27–34]. In group A, 2 trials used the intracoronary method (IC) to deliver the cells [23, 26] and one study used the intravenous (IV) route for the delivery of the cells [24]. One study used both groups of delivery methods including intramyocardial (IM) and IC [20]. Among group B studies, eight trials delivered the cells via the IM method [21, 22, 25, 27, 28, 30, 32, 33] while the remaining 5 trials injected the cells into the heart muscle via the transendocardial (TE) method [10, 19, 29, 31, 34].

The number of participants randomized to these trials ranged from 16 [20] to 537 [34] and the duration of follow-up ranged from six months [22, 23] to over 52 months [29]. Overall, the number of adverse events during the procedure of MSC administration was few and ranged from 0 [10, 24, 29–31] to 14 [25]. The cause of heart failure in two studies was non-ischemic HF [26, 29], five studies included patients with both ischemic and non-ischemic causes of HF [19, 23, 24, 28, 34], and the remaining studies only enrolled patients with Ischemic HF [10, 20–22, 25, 27, 30–33]. All trials administered standard medical therapy to all participants. The baseline LVEF of patients ranged from 16.2 [28] to 54% [27]. Characteristics of the patients enrolled in the included trials are summarized in Table 2.

Clinical outcomes

Mortality

Mortality was reported in all but one trial including 905 participants in the treatment group and 426 participants in the control group [29]. The pooled risk ratio showed that the risk of death in the MSC group was 21% lower compared to the control group (RR = 0.79; 95% CI 0.62–0.99, p = 0.043) (Fig. 3a). Subgroup analysis (Table S1) showed no difference in the risk of mortality between any subgroups of trials. Meta-regression (Table S2) was done to assess the effect of age, donors' age, follow-up duration, cell number, percentage of male participants, percentage of patients with ischemic cause, baseline mean values of LVEF, and NYHA that yielded no significant relationship with mortality. The risk of publication bias was not significant (Figure S1).

Rehospitalization

All-cause rehospitalization was reported in twelve trials [10, 19, 22–25, 28, 29, 31–34] including 827 participants in the treatment group and 715 participants in the control group. Although the risk of re-hospitalization in the treatment group was lower in comparison with the control group, it was not statistically significant (RR = 0.85; 95% CI 0.71–1.01, p = 0.06) (Fig. 3b). In this outcome, the risk of publication bias was significant (Figure S2). Although the overall difference between groups was not significant (p = 0.06), subgroup analysis showed that the trials using less than 100 million cells had a significantly lower risk of rehospitalization (RR = 0.72; 95% CI 0.55–0.93, p = 0.01) (Figure S3). Subgroup analysis showed a significantly lower risk of rehospitalization in trials using autologous cells compared to trials using an allogeneic source of cells (p = 0.04; autologous (RR = 0.67; 95% CI 0.49–0.90; p = 0.008) vs allogeneic (RR = 0.96; 95% CI 0.80–1.15; p = 0.64)) (Fig. 4a). Moreover, meta-regression showed that trials injecting a higher number of cells to the patients had a higher risk of re-hospitalization and the risk of rehospitalization would increase by 1% with each million more cells injected (Coefficient = 0.00000001; p = 0.03; $R^2 = 0.27$) (Figure S4).

Heart failure worsening

HF worsening was reported in ten trials [19, 22, 24, 25, 27, 29, 31–34] including 700 participants in the treatment group and 635 participants in the control group. However, one trial dominated [34] the results of this outcome, and with that trial removed, the lower risk of HF worsening in the treatment group became significant (RR = 0.65; 95% CI 0.45–0.93, p = 0.019) (Fig. 3c). Similar to rehospitalization, subgroup analysis showed that the trials using less than 100 million cells had a significantly

Table 1 Characteristics of included studies

Author	Year of publication	Clinical trial registration	Sample size (control; intervention)	Weight (%)	Blinding	CHF cause	Route of delivery	Donor	cell origin	Cell number (mean)	Modality	Patients did not complete the study	Follow- up duration(month)
Mohyeddin [20]	2007	FWA00001331	8;8	0.95	_	IH	IC & IM	Auto	BM	5,550,000	Echo, Spect	0	18.5
Bartunek [21]	2013	NCT00810238	15;21	2.14	SB	IH	IM	Auto	BM	733,000,000	Echo	3	24
Heldman [10]	2014	NCT00768066	11;19	1.78	DB	IH	TE	Auto	BM	200,000,000	Echo, MRI	3	12
Perin [19]	2015	NCT00721045	5;15 5;15 5;15	3.56	SB	IH & nIH	TE	Allo	BM	25,000,000 75,000,000 100,000,000	Echo, Spect	6	36
Mathiasen [22]	2015	NCT00644410	20;40	3.56	DB	IH	IM	Auto	BM	77,500,000	MRI	5	6
Zhao [23]	2015	#122101310500	29;30	3.50	NB	IH & nIH	IC	Allo	UC	_	_	_	6
Bartunek [25]	2016	NCT01768702	151;120	16.09	DB	IH	IM	Auto	BM	> 24,000,000	Echo	28	39
Bartolucci [24]	2017	NCT01739777	15;15	1.78	DB	IH & nIH	IV	Allo	UC	1000000/kg	Echo, MRI	2	12
Xiao [26]	2017	_	20;17	2.20	NB	nIH	IC	Auto	BM	490,000,000	Echo, Spect	4	12
Qayyum [27]	2019	NCT01449032	13;28	2.43	DB	IH	IM	Auto	AT	72,000,000	MRI	1	36
Yau [28]	2019	NCT02362646	53;106	9.44	DB	IH & nIH	IM	Allo	BM	150,000,000	Echo	62	12
Ulus [30]	2020	NCT02323477	16;26	2.49	SB	IH	IM	Allo	UC	23,000,000	Echo, MRI, Spect	4	12
Bolli [29]	2020	NCT02509156	17;14	1.84	DB	nIH	TE	Allo	BM	100,000,000	MRI	3	52.1
Bolli [31]	2021	NCT02501811	32;29	3.62	DB	IH	TE	Auto	BM	108,000,000	MRI	16	12
Qayyum1 [32]	2023	NCT03092284	27;54	4.81	DB	IH	IM	Allo	AT	100,000,000	Echo	6	12
Qayyum2 [33]	2023	NCT02673164	43;90	7.90	DB	IH	IM	Allo	AT	100,000,000	Echo	8	12
Perin [34]	2023	NCT02032004	272;265	31.89	DB	IH & nIH	TE	Allo	BM	150,000,000	Echo	0	30

SD standard deviation, *auto* autologous, *allo* allogenic, *BM* bone marrow, *UC* umbilical cord, *AT* adipose tissue, *Echo* echocardiography, *SPECT* single-photon emission computerized tomography, *MRI* magnetic resonance imaging, *IM* intramyocardial, *IC* intracoronary, *TE* trans endocardial, *IV* intravenous, *IH* ischemic heart failure, *nIH* non- ischemic heart failure, _ = not mentioned, *DB* double-blind, *SB* single-blind, *NB* not blinded

Table 2 Characteristics of participants in included studies

Study	Sample size	Male %	Ischemic cause %	Mean age (SD)	Smoking	DM	HTN	Mean BMI(SD)	Mean NYHA (SD)	Mean baseline EF (SD)	Adverse event during injection
Mohyeddin [20]	8;8	75;87.5	100;100	53.2 (6.6); 49 (9.4)	–;–	–;–	–;–	– (–);– (–)	2.7 (0.7);2.7 (0.7)	41.88 (8.42); 38.75 (13)	_
Bartunek [21]	15;21	91.6;95	100;100	59.5 (8); 5.7 (10.4)	5;6	8;4	13;10	– (–);– (–)	– (–);– (–)	27.8 (3.95); 27.5 (4.67)	2
Heldman [10]	11;19	90.9;94.7	100;100	60 (12); 57.1 (10.6)	9;14	3;3	6;12	– (–);– (–)	2.1 (0.7);1.8(0.6)	28.1 (9.8); 35.7 (9)	0
Perin [19]	5;15	73.3;100	53.3;100	62.7 (11.2); 60.1 (8.8)	9;10	2;5	9;10	31.3 (9.2);29.6 (4.5)	2.6 (0.5);2.4 (0.5)	34.6 (6.43); 29.2 (9.2)	0
	5;15	73.3;100	53.3;80	62.7 (11.2); 63.9 (11.5)	9;11	2;5	9;9	31.3 (9.2);30 (5.2)	2.6 (0.5);2.3 (0.4)	34.6 (6.43); 30.2 (6.86)	0
	5;15	73.3;93.3	53.3;73.3	62.7 (11.2); 62.7 (10.8)	9;11	2;3	9;10	31.3 (9.2);29.9 (2.4)	2.6 (0.5);2.2 (0.4)	34.6 (6.43); 34.3 (9.01)	3
Mathiasen [22]	20;40	70;90	100;100	64.2 (10.6); 66.1 (7.7)	16;33	3;15	–;–	28.7 (5.3);29.8 (4.7)	2.7 (0.4);2.7 (0.4)	25.1 (8.5); 28.2 (9.3)	1
Zhao [23]	29;30	65;80	20.68;43.3	53.2 (11.4); 52.9 (16.3)	–;–	–;–	–;–	– (–);– (–)	– (–);– (–)	28 (5.1); 30 (4.5)	1
Bartunek [25]	151;120	90.1;89.2	100;100	62.1 (8.7); 61.6 (8.6)	25;12	71;45	124;99	28.6 (4.4);28.2 (3.7)	2.7 (0.4);2.8 (0.4)	28 (6); 27.3 (6.8)	14
Bartolucci [24]	15;15	93.3;80	73.3;66.7	57.2 (11.6); 57.3 (10.0)	4;7	7;5	8;7	29.52 (4);29.12 (2.88)	1.7 (0.4);2.07 (0.6)	31.53 (4.89); 33.5 (6.09)	0
Xiao [26]	20;17	70;70.6	0;0	54.4 (11.6); 51.6 (12.2)	–;–	6;5	7;4	– (–);– (–)	2.7 (0.6);2.7 (0.7)	33.7 (4); 34.1 (3.6)	1
Qayyum, [27]	13;28	100;87.5	100;100	65.3 (8.7); 65.5(9.7)	19;31	6;16	12;33	30 (4.8);30 (4.1)	2.7 (0.6);2.4 (0.6)	54 (8); 52 (8)	_
Yau [28]	53;106	88.7;88.7	50.9;40.6	56.9 (11.7); 55.5 (12.3)	–;–	–;–	–;–	– (–);– (–)	3.7 (0.4);3.7 (0.4)	16.2 (6); 17.3 (5.8)	_
Ulus [30]	16;26	100;100	100;100	65.3 (6.8); 61.8 (10)	15;21	9;16	11;15	26.6 (4.8);26.5 (4.5)	2.1 (0.4);1.9 (0.5)	36.18 (5.59); 34.79 (4.78)	0
Bolli [29]	17;14	24;43	0;0	58.2 (11.2); 54.7 (12.8)	3;5	5;3	10;6	30.4 (6.5);30.2 (9)	2.2 (0.4);2.0 (0.2)	33.31 (6.21); 34.54 (2.86)	0
Bolli [31]	32;29	96.8;93.1	100;100	63.1 (8.8); 61 (11.1)	20;16	12;10	27;23	30 (4.4);30.4 (5.4)	2.0 (0.3);2.1 (0.4)	29.66 (6.18); 29.26 (5.91)	0
Qayyum1 [32]	27;54	88.9;81.5	100;100	66.6 (8.1); 67 (9)	4;9	8;14	15;35	26.9 (4.3);28.8 (5.1)	2.3 (0.4);2.2 (0.4)	31.4 (7.2); 34.2 (7.9)	_
Qayyum2 [33]	43;90	88.4;93.3	100;100	64 (8.8); 66.4 (8.1)	5;15	17;38	29;72	29.9 (3.8);28.5 (4.6)	2.3 (0.4);2.3 (0.4)	32 (8.9); 31.6 (7.2)	2
Perin [34]	272;265	78.4;78.4	56;56.9	62.6 (10.4); 62. 7(10.9)	169; 180	120; 124	222; 233	29.7 (6.3); 30.5(6.8)	2.63 (0.4; 2.62 (0.5)	28.6 (7); 28.6 (6.6)	_

All data are presented as (control; intervention)

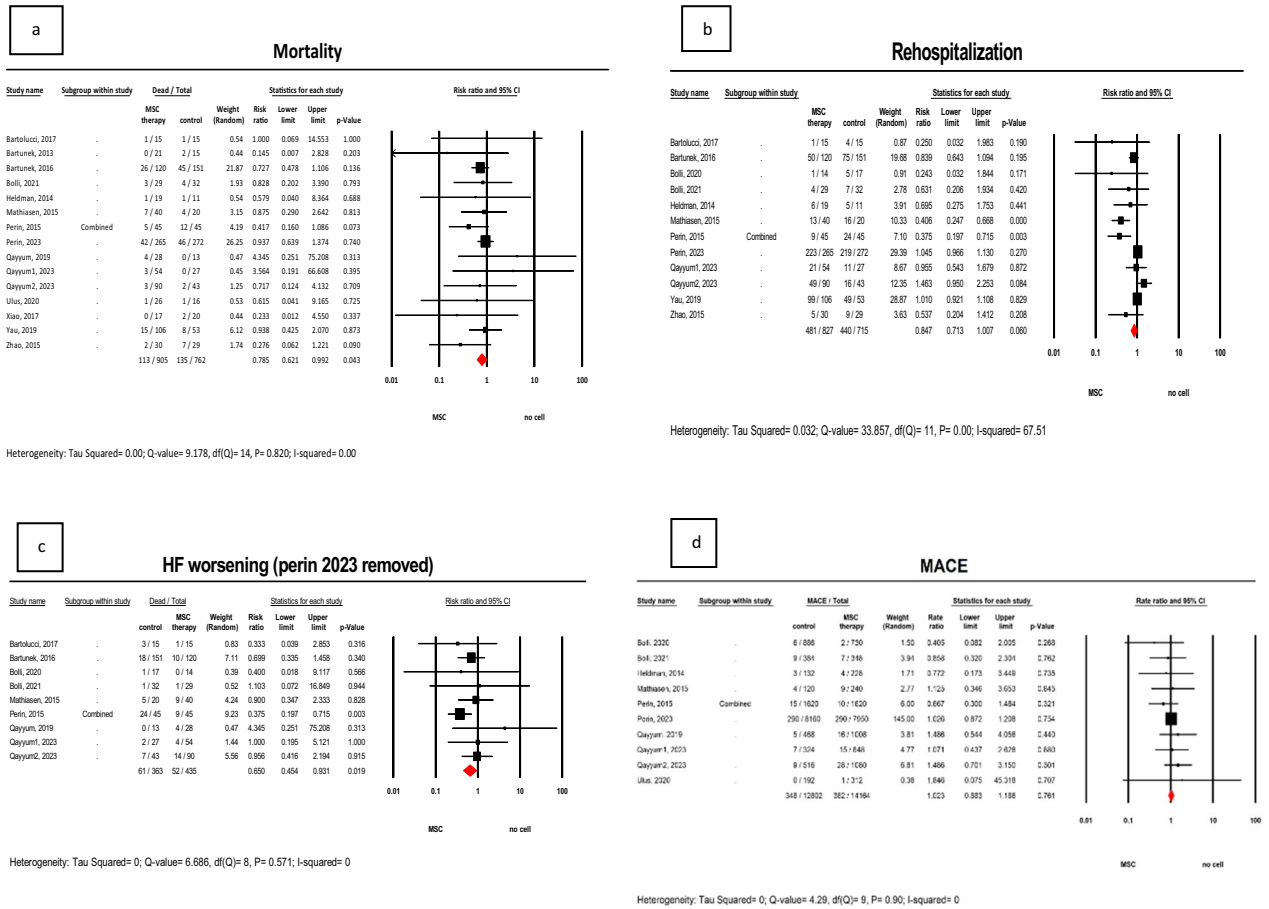


Fig. 3 Forest plot of the comparison between the changes in treatment and control groups regarding primary outcomes: **a** death, **b** rehospitalization, **c** heart failure worsening, and **d** major adverse cardiac events

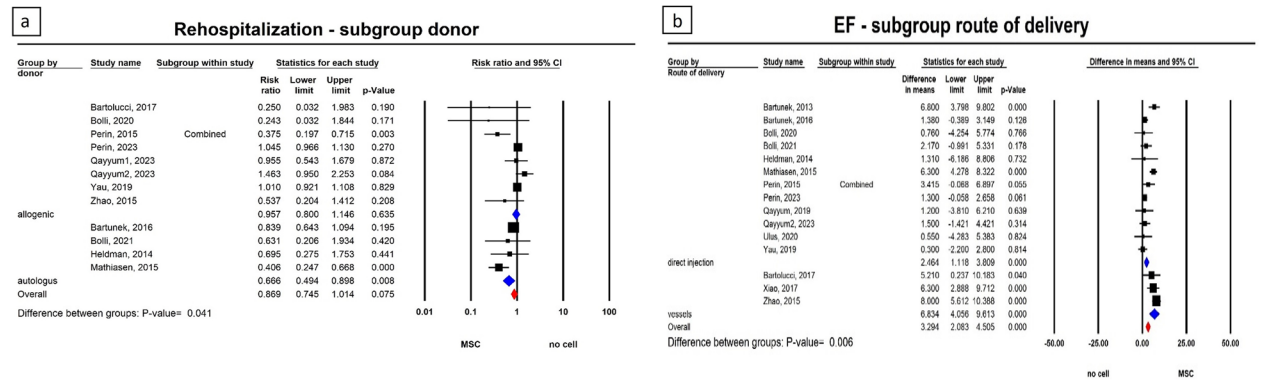


Fig. 4 Forest plot of the comparison between the changes in the treatment and control groups regarding **a** rehospitalization compared between allogenic and autologous subgroups and **b** ejection fraction compared between routes of delivery

lower risk of HF worsening compared to trials injecting more than 100 million cells (p = 0.012; < 100 million cells (RR = 0.63; 95% CI 0.43–0.91; p = 0.01) vs ≥ 100 million cells (RR = 1.01; 95% CI 0.96–1.08; p = 0.58)) (Figure S5). However, Meta regressions showed no significant result.

Major adverse cardiovascular events

Major adverse cardiovascular events were reported in ten trials [10, 19, 22, 27, 29–34] including 14,164 person-time at risk in the treatment group and 12,802 person-time at risk in the control group. The rate ratio of the

MACE compared between the MSC and control group was not statistically significant (RR = 1.02; 95% CI 0.89–1.19, p = 0.73) (Fig. 3d). Neither sub-group analysis nor meta-regression yielded any significant results.

Paraclinical parameters

LVEF

LVEF was reported in all except one trial [32] (Fig. 5a). Meta-analysis revealed a significant difference in mean change from baseline values in favor of cell therapy (MD = 3.38; 95% CI 1.89–4.87, p < 0.001). The risk of publication bias was not significant in this outcome (Figure S6). As mentioned earlier, to perform subgroup analysis for the route of delivery, all methods of cell delivery were grouped based on direct injection into the myocardium or injection into vessels [22, 24, 26] except for one study using both methods[20]. There was a statistically significant difference (p-value = 0.006) between the LVEF mean difference of these groups (Fig. 4b). Moreover, trials delivering MSC through vessels (MD = 6.83; 95% CI 4.06–9.61, p < 0.001) were superior to trials directly injecting MSC into the myocardium (MD = 2.46; 95% CI 1.12–2.80, p < 0.001). Although no meta-regression resulted in significant correlations, meta-regression to assess the effect of the mean age of patients revealed that a year increase in patients' age would decrease the mean change of LVEF by 0.29 (Coefficient = −0.29, p = 0.07) (Figure S7). Additionally, meta-regression to assess the effect of cell counts showed that with each 100 million increases in cell number, the mean change of LVEF will slightly increase by 0.6 (Coefficient = 0.000000006, p = 0.07) (Figure S8).

LVESV

The mean change of LVESV could be obtained from twelve trials that were included in the meta-analysis [10, 19, 22, 24, 25, 27, 29–34]. Pooled estimates (Fig. 5b) showed that LVESV decreased significantly after cell therapy in treatment groups compared to controls by 9.14 ml in the last follow-up (MD = -9.14; 95% CI −13.25 to −5.03, p < 0.001). Subgroup analysis indicated a significantly higher decrease of LVESV in trials using the autologous source of cells compared to trials with an allogeneic source (MD = −12.01 vs MD = −3.01; P = 0.045) (Figure S9). Similarly, subgroup analysis based on donor

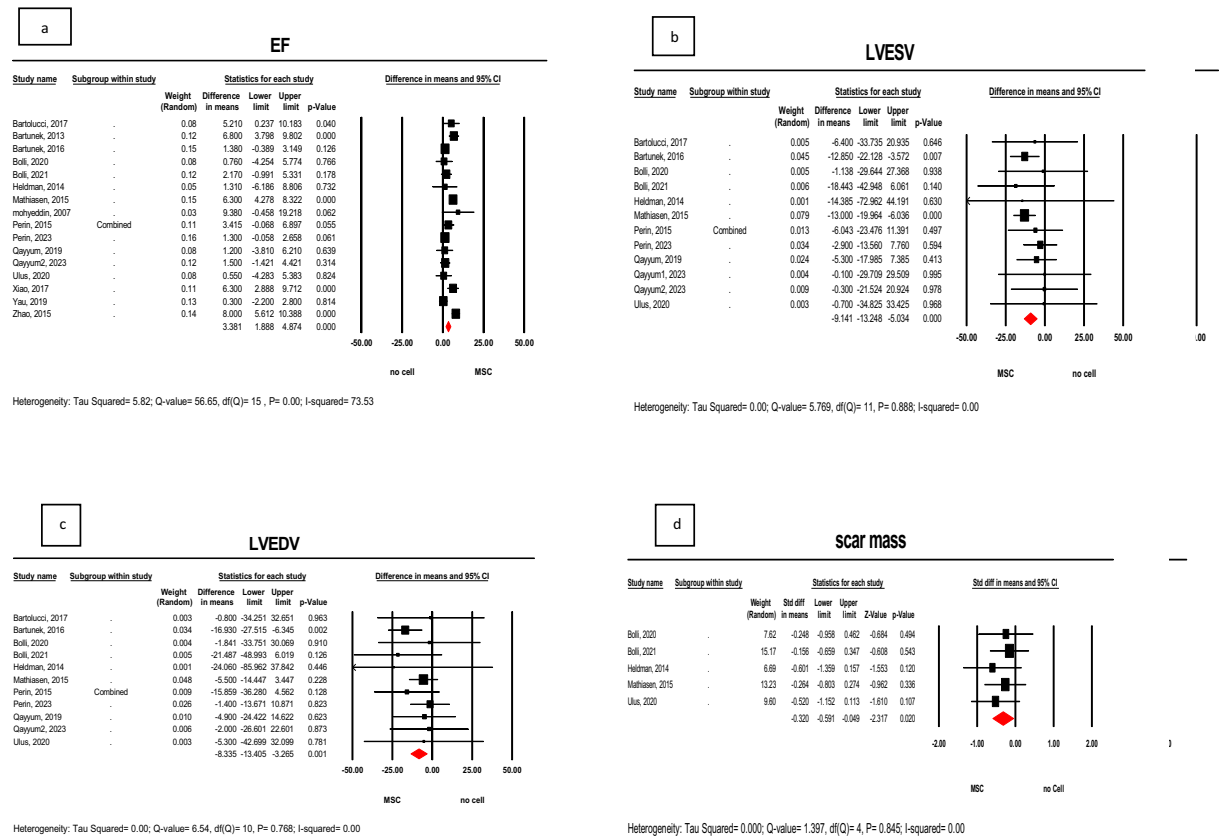


Fig. 5 Forest plot of the comparison between the changes in treatment and control groups regarding echocardiographic measurements: **a** LVEF **b** LVESV **c** LVEDV **d** scar size as a percentage of LV mass

age resulted in the same results due to including the same trials (Figure S10). However, meta-regressions showed no significant result.

LVEDV

The mean change of LVEDV could be obtained from eleven trials [10, 19, 22, 24, 25, 27, 29–31, 33, 34]. Meta-analysis of this outcome showed a significant decrease in LVEDV in patients treated with MSC (MD = −8.33; 95% CI −13.41 to −3.26, p = 0.001) (Fig. 5c). Neither subgroup analysis nor meta-regression showed any significant results.

Scar size as a percentage of LV mass

Scar size was reported as an outcome in five trials [10, 22, 29–31]. Since scale and units of measurement were not the same, this outcome was estimated and converted to the percentage of LV mass. Therefore, in this analysis we used SMD. Accordingly, there was a statistically significant decrease in scar size in the treatment group compared to the control (SMD = −0.32; 95% CI −0.59 to −0.05, p = 0.02) (Fig. 5d). Due to the small number of studies, subgroup analysis and meta-regression were not performed.

NYHA functional class

Eight studies were included for this outcome [19, 20, 22, 24, 26, 27, 32, 33]. There was a significant improvement in NYHA functional class after MSC therapy in comparison with the control group (MD = −0.20; 95% CI −0.34 to −0.06, p = 0.006) (Fig. 6a; Figure S11). The NYHA score decreased more in trials delivering cells via intracoronary path compared to trials injecting cells directly to the heart (p = 0.016; vessels (MD = −0.54; 95% CI −0.88 to −0.19; p = 0.002) vs direct intramyocardial transplantations (MD = −0.10; 95% CI −0.203 to −0.003; p = 0.058)) (Figure S12). Moreover, subgroup analysis showed bigger improvement in trials with younger patients compared to trials with higher mean age (p = 0.002; middle age (MD = −0.59; 95% CI −0.88 to −0.29; p < 0.001) vs old (MD = −0.10; 95% CI −0.203 to −0.003; p = 0.058)) (Figure S13). In addition, meta-regression showed that the NYHA score would improve more in trials with lower mean age of patients (Coefficient = 0.036, p = 0.005)

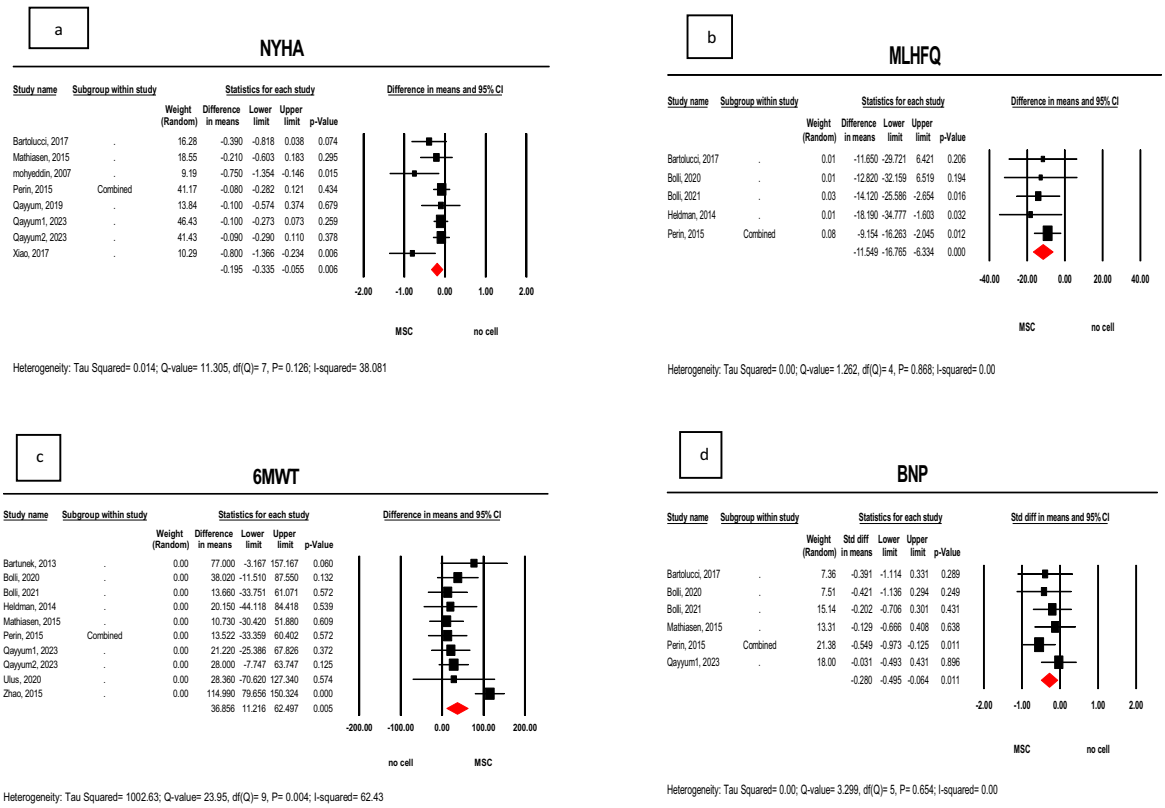


Fig. 6 Forest plot of the comparison between the changes in treatment and control groups regarding **a** NYHA **b** Quality of Life **c** 6MWT **d** BNP

(Figure S14) and more female participants (Coefficient = 0.23, p = 0.04) (Figure S15).

Quality of life assessed with MLHFQ

To assess the impact of MSC therapy on MLHFQ score, five studies were eligible [10, 19, 24, 29, 31]. Meta-analysis showed a significant decrease in the treatment group in comparison with controls regarding the MLHFQ score (MD = −11.55; 95% CI −16.76 to −6.33, p < 0.001) (Fig. 6b). Due to the small number of studies, subgroup analysis and meta-regression were not performed.

Six-minute walk test

The mean change of the 6-min walk test from baseline was available from ten trials [10, 19, 21–23, 29–33]. The meta-analysis of the included trials showed that treatment group patients performed significantly better than the control group in this exercise capacity test (MD = 36.85; 95% CI 11.21–62.49, p = 0.005) (Fig. 6c). Assessing the trials based on the mean age of participants, subgroup analysis showed that trials with middle-aged participants performed better than trials in the old age group and 6MWT was significantly more increased in middle-aged patients (p = 0.004; middle age (MD = 73.01; 95% CI: 43.82 to 102.21; p < 0.001) vs old patients (MD = 18.53; 95% CI −3.60 to 40.67; p = 0.101)) (Figure S16). Subgrouping trials based on the origin of stem cells showed that trials using umbilical cord cells (MD = 105.20; 95% CI 71.92–138.47; p < 0.001) significantly performed better than two other sources although this result must be interpreted with caution due to only two studies in umbilical cord and adipose tissue groups (p < 0.001; adipose tissue (MD = 25.49; 95% CI −2.88 to 53.85; p = 0.078) vs bone marrow (MD = 28.18; 95% CI 1.31 to 43.05; p = 0.037) (Figure S17). Meta-regression to assess the effect of the mean age of patients showed that trials with overall younger participants had better improvement in this test (Coefficient = −6.20, p < 0.001) (Figure S18). Moreover, meta-regression also showed better improvement when the donor of cells was younger (Coefficient = −1.11, p = 0.01) (Figure S19). Although not significant, meta-regression showed that studies with more patients with non-ischemic causes of heart failure showed better improvement in this outcome (Coefficient = −0.55, p = 0.052) (Figure S20).

BNP/ NT-proBNP

Four trials reported NT-proBNP [22, 29, 31, 32] while 2 trials reported BNP [19, 24]. As mentioned in a similar study [6], since no meaningful difference except for measurement scales exists between them, the standardized MD (SMD) was used to allow analysis of both BNP/ NT-proBNP. Pooled estimation of SMDs from six trials [19, 22, 24, 29, 31, 32], showed a statistically significant decrease of BNP/NT-proBNP in the treatment group (SMD = −0.28; 95% CI −0.50 to −0.06, p = 0.011) (Fig. 13). Due to the small number of studies subgroup analysis and meta-regression were not performed.

Sensitivity analysis

Except for one trial [34] dominating HF worsening outcome, sensitivity analysis showed no critical study (specifically those with a high risk of bias) that made remarkable changes in the results (Figure S21, S22).

Risk of publication bias

The Egger's test and funnel plot were performed to investigate the risk of bias. Except for two outcomes including NYHA and rehospitalization (Table S2), none of the p-values were significant (ranging from 0.01 to 0.94). The funnel plot of NYHA did not show any significant deviation while this was not the case for rehospitalization hence, the results drawn from this outcome should be cautiously interpreted.

Discussion

In the present study, using a meta-analysis of randomized clinical trials we have shown that transplantation of MSCs in HF patients would improve both clinical and paraclinical outcomes. To the extent of our knowledge, this is the largest available piece of evidence and the first demonstrating that such treatment would reduce mortality in these patients. Also, other outcomes including myocardial function indices such as LVEF, and HF condition including NYHA class, 6-min walk test, BNP level, quality of life, and in some subgroups even HF rehospitalization rates were improved.

Here, we noticed that transplantation of MSCs would improve LVEF (3.38%) and reduce LVEDV (8.33 ml) and LVESV (9.14 ml). Most previous studies and meta-analyses reached similar findings. In a meta-analysis conducted on 6 trials that only used Bone marrow-derived MSCs, LVEF was shown to be improved by 6.37%. [35] In another larger study including 14 trials with a sample volume of 1445 patients, LVEF improvement was 3.35% [36] which was closer to our results. It is noteworthy that in our study we also found a significant reduction in scar mass which may be translated to a more normal physiology of the heart in HF patients treated with mesenchymal stem; however, more studies evaluating this outcome in their patients with CMR are required to draw more conclusive results [5].

In the present study, we demonstrated a survival benefit for transplantation of MSCs in HF patients (RR = 0.78, P = 0.043). Although all previous meta-analyses were in

favor of MSC transplantation, none reached such significance in this outcome. This can be explained by the fact that all previous studies did not reach a sample volume large enough to demonstrate this effect, while we enrolled 17 trials with 1684 participants which to the best of our knowledge is the largest available piece of evidence. Regarding the rehospitalization for HF rate, we saw a trend toward reduction with a borderline p-value (RR:0.85, p = 0.06) and this outcome reached significance when only trials using an autologous source of cells were included (RR = 0.67, P = 0.04). The results of this outcome in most other studies were in favor of MSC transplantation. Shen et al. (N = 823; RR = 0.53; p = 0.0004) [37], Fan et al. (n = 612; RR = 0.66; P = 0.001) [38], and Fu et al. (N = 625, RR = 0.41; p = 0.003) [39]found significant reduction in rehospitalization rate among these patients. However, Krishna Mohan and collogues [36] did not find a significant benefit although there was a trend toward reduction (N = 1445; RR = 0.55; p = 0.07).

In this meta-analysis, we assessed several factors that would affect the efficacy of MSC transplantation in HF patients. To the best of our knowledge, this is the first meta-analysis that has assessed these factors extensively. In general, subgroup analysis and meta-regression explained the heterogeneity among different trial outcomes. As shown in supplementary Tables S1 and 2, trials were not affected by the participant's ischemic or non-ischemic etiology of heart failure, baseline EF, baseline NYHA score, and follow-up duration of trials. Conversely, trials using an autologous source of cells, less than 100 million cells, delivering cells intracoronary or intravenous, and younger participants (< 60 years old) showed better results in different outcomes compared to other trials. Here, we found that the route of delivery through vessels is much more effective than that of direct injection to the myocardium. This issue can be related to the fact that the healing properties of these cells are mainly through Mesenchymal stem cell-derived extracellular vesicles [40, 41]. Moreover, the number of adverse events during injection of cells was higher in routes of direct injection to the myocardium. As a result, the safer and more effective route of delivery which is through vessels, especially intracoronary injection can be the choice method of delivery for MSC deliveries. A similar finding was noticed in the meta-analysis by Fan and co-workers [38]. In addition, we assessed the efficacy of MSC transplantation in ischemic vs non-ischemic patients. Although trials investigating the effect of MSCs in DCM patients are rare and most trials investigating the effect of this intervention on this population used a mixed sample of ischemic and DCM patients; overall, our subgroup analyses showed similar effects for both groups in most outcomes.

An interesting finding in the present meta-analysis was the outperformance of autologous MSCs in decreasing the relative risk of HF rehospitalization compared with allogenic stem cells. This finding has not been mentioned in the previous studies. A meta-analysis of animal studies showed similar improvement of LVEF in both allogenic and autologous cell types. Both of these cell lines showed better results compared to placebo [42]. The immunophenotype and potent immunosuppressive activity of MSCs enable them to be transplanted from an allogeneic donor. Furthermore, MSCs exhibit moderate expression of major histocompatibility complex class I, while they do not express major histocompatibility complex class II molecules. Additionally, these cells lack the expression of costimulatory molecules such as B7 and CD40 ligands and interact with both innate and adaptive immune cells, resulting in an immunomodulatory impact which is accomplished through direct contact with targeted immune cells and the release of factors, such as nitric oxide, indoleamine 2,3-dioxygenase, and heme oxygenase-1 [7]. Furthermore, there was no observed difference between allogenic vs. autologous transendocardial injection of MSCs in terms of LVEF which was shown in the results of the POSEIDON trial [43]. Although the previous studies have shown no difference between autologous and allogenic stem cells, we found that autologous injection of MSCs may be superior to allogenic stem cells regarding hospitalization. The results of future randomized trials are warranted to further address the potential differences between these two types of MSCs.

To obtain autologous cells, all of the trials included in this study used bone marrow-derived MSCs, while MSCs obtained from BM showed no superiority to other sources of cells in this study, including adipose tissue and umbilical cord. Furthermore, the associated morbidity from the acquisition of MSCs from the bone marrow and the different properties of MSCs isolated from different tissues led to the investigation of alternative stem cell sources to determine the optimal source for therapeutic transplantation [44]. However, so far, only three sources of MSCs have been investigated in Randomized controlled trials -mostly using bone marrow- while other sources of MSCs are easier to obtain and have shown promising results such as Dental pulp [45, 46], menstrual blood [13], and peripheral blood cells [47].

Limitations

Our study faces some limitations. First of all, the studies included in this meta-analysis used various protocols for cell transplantation, patient follow-up, and study outcomes. However, we tried to address this issue by performing several subgroup analyses. In addition, there may be some factors that may affect the efficacy of MSC

transplantation that were not reported in many studies and we could not analyze them such as the level of CRP at the baseline. Furthermore, most of the studies included have a small sample volume and our finding may be influenced by the two large included trials.

Lastly, although the quality of life in heart failure patients is an important factor to be considered, the meta-analysis of the Quality of life included only 6 studies due to different questionnaires being used. Therefore, we suggest the use of the same questionnaire in future trials on cell therapies in heart failure patients besides whatever questionnaire that investigators find suitable for the study population. In the end, since some of the previous studies have assessed baseline and final quality of life with these tools, we recommend the use and report of MLHFQ [10, 19, 24, 25, 29, 31] and NYHA [20, 22, 24, 26, 27, 32, 33] in future cell therapy trials on heart failure patients.

Conclusions

It can be concluded that transplantation of MSCs for ischemic and dilated heart failure patients may reduce all-cause mortality, improve HF symptoms and quality of life, improve ejection fraction, and reduce scar size. These results should be interpreted with caution as the included studies used various routes of transplantation, number of cells, and duration of follow-up. Performance of large clinical trials with long duration of follow-up would better clarify this situation. Furthermore, there are some unsolved issues including the cost-effectiveness that should be further investigated.

Abbreviations

6MWT	Six-minute walk test
CI	Confidence interval
DCM	Dilated cardiomyopathy
HF	Heart failure
ICM	Ischemic cardiomyopathy
LVEF	Left ventricular ejection fraction
MD	Mean difference
MSCs	Mesenchymal stem cells
NYHA	New York Heart Association
RCTs	Randomized controlled trials
RR	Relative risk
TESI	Trans endocardial stem cell injection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05352-y.

Supplementary material 1.

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Author contributions

SK searched databases. SK and FB screened manuscripts based on eligibility criteria and AA checked the screened manuscripts. SK and AH extracted the data from manuscripts and AA checked the accuracy of the gathered data. SK performed the meta-analysis. SK and AA wrote the manuscript and all the authors read and approved the final manuscript.

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Availability of data and materials

Available data in this study exist in randomized controlled trials cited in this study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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