ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2024 August 26; 16(8): 436-495

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

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World Journal of Cardiology

Monthly Volume 16 Number 8 August 26, 2024

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
August 26, 2024

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World Journal of Cardiology

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World J Cardiol 2024 August 26; 16(8): 469-483

DOI: 10.4330/wjc.v16.i8.469

ISSN 1949-8462 (online)

SYSTEMATIC REVIEWS

Tissue-source effect on mesenchymal stem cells as living biodrugs for heart failure: Systematic review and meta-analysis

Moaz Safwan, Mariam Safwan Bourgleh, Mohamed Aldoush, Khawaja Husnain Haider

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Goebel WS

Received: May 6, 2024
Revised: June 24, 2024
Accepted: July 23, 2024
Published online: August 26, 2024
Processing time: 112 Days and 3.2 Hours

Moaz Safwan, Mariam Safwan Bourgleh, Mohamed Aldoush, Khawaja Husnain Haider, Department of Basic Sciences, Sulaiman Al Rajhi University, Al Bukairiyah 51941, Saudi Arabia

Corresponding author: Khawaja Husnain Haider, PhD, Professor, Department of Basic Sciences, Sulaiman Al Rajhi University, PO Box 777, Al Bukairiyah 51941, Saudi Arabia. kh.haider@sr.edu.sa

Abstract

BACKGROUND

Mesenchymal stem cells (MSCs), as living biodrugs, have entered advanced phases of clinical assessment for cardiac function restoration in patients with myocardial infarction and heart failure. While MSCs are available from diverse tissue sources, bone-marrow-derived MSCs (BM-MSCs) remain the most well-studied cell type, besides umbilical-cord-derived MSCs (UC-MSCs). The latter offers advantages, including noninvasive availability without ethical considerations.

AIM

To compare the safety and efficacy of BM-MSCs and UC-MSCs in terms of left ventricular ejection fraction (LVEF), 6-min walking distance (6MWD), and major adverse cardiac events (MACEs).

METHODS

Five databases were systematically searched to identify randomized controlled trials (RCTs). Thirteen RCTs (693 patients) were included using predefined eligibility criteria. Weighted mean differences and odds ratio (OR) for the changes in the estimated treatment effects.

RESULTS

UC-MSCs significantly improved LVEF *vs* controls by 5.08% [95% confidence interval (CI): 2.20%-7.95%] at 6 mo and 2.78% (95%CI: 0.86%-4.70%) at 12 mo. However, no significant effect was observed for BM-MSCs *vs* controls. No significant changes were observed in the 6MWD with either of the two cell types. Also, no differences were observed for MACEs, except rehospitalization rates, which were lower only with BM-MSCs (odds ratio 0.48, 95%CI: 0.24-0.97) *vs* controls.

CONCLUSION

UC-MSCs significantly improved LVEF compared with BM-MSCs. Their advant-

ageous characteristics position them as a promising alternative to MSC-based therapy.

Key Words: Cardiovascular disease; Heart disease; Mesenchymal stem cells; Umbilical cord stem cells

Core Tip: Mesenchymal stem cells (MSCs) are fast emerging as living biodrugs to repair and replace dysfunctional myocardium. While MSCs are available from diverse adult and fetal tissues, bone-marrow-derived MSCs (BM-MSCs; adult tissue source) and umbilical-cord-derived MSCs (UC-MSCs; fetal tissue source) remain the most well-studied types during recent clinical trials. The primary aim of this systematic review and meta-analysis was to evaluate the comparative safety and effectiveness of BM-MSC- and UC-MSC-based therapy in heart failure patients, analyzing left ventricular ejection fraction and 6-min walking distance as the primary functional and clinical outcomes.

Citation: Safwan M, Bourgleh MS, Aldoush M, Haider KH. Tissue-source effect on mesenchymal stem cells as living biodrugs for heart failure: Systematic review and meta-analysis. *World J Cardiol* 2024; 16(8): 469-483
URL: https://www.wjgnet.com/1949-8462/full/v16/i8/469.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i8.469

INTRODUCTION

Cardiovascular diseases (CVDs) remain the most common cause of morbidity and mortality worldwide despite recent advances in pharmacological disease management[1]. The akinetic fibrous scar that develops as part of the inefficient intrinsic repair mechanism in the heart after recurrent myocardial infarction (MI) is one of the critical factors responsible for putting the heart into the vicious cycle of remodeling, leading to heart failure (HF). Most contemporary therapeutic options, at best, can only provide symptomatic relief. In this regard, mesenchymal stem cell (MSC)-based therapy to repair and replace dysfunctional myocardium is fast emerging as a viable option and has progressed to advanced phases of clinical assessment[2].

MSCs were identified as a unique cell group characterized by preferential plastic surface adherence, specific surface marker expression, and trilineage differentiation potential[3]. They showed high proliferation and exceptional abilities to generate proangiogenic and anti-inflammatory paracrine factors[4]. Preclinical studies have demonstrated that MSCs possess a nonimmunogenic phenotype and the capacity to evade immunosurveillance[5]. These characteristics render them a choice for a cell-based therapy approach, and they are being reckoned as prototypes of the living biodrug family with some products already approved for different clinical conditions, such as Prochymal and Lomecel.

While MSCs are available from diverse adult and fetal tissues[6], bone-marrow-derived MSCs (BM-MSCs; adult tissue source) and umbilical-cord-derived (UC-MSCs; fetal tissue source) remain the most well-studied types during recent clinical trials. As of April 20, 2024, 59 clinical trials assessing MSCs for cardiac disease are registered on ClinicalTrials.gov, with 25 focusing explicitly on BM-MSCs. Nevertheless, most of these studies have reported less-than-expected results than the preclinical, experimental data[7]. The modest outcome may be attributed to various confounding factors, encompassing treatment-related factors, such as route of administration and cell dose [8,9], to the quality of cell preparation, such as donor age and health status[10,11]. However, UC-MSCs are readily accessible from medical waste for clinical applications without moral and ethical concerns[12]. Since the first reports of UC-MSCs, they have been extensively studied in experimental animal models of myocardial injury[13,14]. UC-MSCs have recently garnered more attention in clinical settings because of their advantages, including ready-to-use "off-the-shelf" availability, noninvasive collection, lack of ethical issues, younger age origin, and embryonic-cell-like characteristics[12,15,16]. Building upon near-ideal features and promising preclinical data, UC-MSCs have recently advanced to phase II pivotal trials for heart therapy.

We have conducted a rigorous systematic review comparing the clinical performance of BM-MSCs with UC-MSCs, which may be crucial to establishing a more reliable guide for designing future MSCs-based clinical trials. The primary aim of this systematic review and meta-analysis was to evaluate the comparative safety and effectiveness of BM-MSC- and UC-MSC-based therapy in HF patients by analyzing left ventricular ejection fraction (LVEF), 6-min walking distance (6MWD) as the primary functional and clinical outcomes. We examined the safety profile of the two cell types using the major adverse cardiovascular events (MACEs), *i.e.*, cardiac death, rehospitalization for HF, recurrent MI, infract-vessel revascularization procedure, arrhythmias, and stroke as the secondary outcomes.

MATERIALS AND METHODS

Protocol registration and search strategies

A search strategy was conducted to identify relevant trials based on the Preferred Reporting Item for Systematic Reviews

and Meta-Analysis guidelines[17]. The protocol was registered at the International Prospective Register of Systematics Reviews (PROSPERO; CRD4202348206). Our search strategy encompassed PubMed, Cochrane database, ClinicalTrials.gov, Embase, and ScienceDirect databases from their inception to April 2024. The search terms included common text words and Medical Subject Headings, such as myocardial infarction, coronary artery disease, heart failure, ischemic cardiomyopathy, non-ischemic cardiomyopathy, dilated cardiomyopathy, decompensated heart failure, mesenchymal stem cells, umbilical cord mesenchymal stromal cells, and bone marrow mesenchymal stem cells. These terms were also combined using specific algorithms, such as umbilical cord mesenchymal stem cells and heart failure. Manual searches were conducted to explore potential trials among the selected articles. No language restrictions were applied to the investigation.

Eligibility criteria

To be eligible for inclusion, a study met the following criteria: (1) It should be a phase I/II randomized controlled clinical trial that investigates the efficacy and safety of UC-MSCs and BM-MSCs; (2) The study involved patients diagnosed with MI, HF, or cardiomyopathy; (3) The intervention group should be treated with UC-MSCs or BM-MSCs; (4) There should be a control group; (5) The study should report at least one of the following clinical outcomes: LVEF, 6MWD test, death, readmission for HF, and MACEs (arrhythmia, recurrent MI, and stroke); and (6) The follow-up duration should be > 6 mo. Only studies that met the inclusion criteria and were complete or had available full text were included. All other randomized controlled trials (RCTs) were excluded from the study.

Data extraction

Three coauthors independently assessed the eligibility of the studies for meta-analysis using the inclusion/exclusion criteria and a predefined data-extraction sheet. Each included study was examined, and the following variables were extracted: (1) First author; (2) year of publication; (3) trial location (country); (4) intervention type (BM-MSCs or UC-MSCs); (5) source of stem cells (autologous *vs* allogenic); (6) sample size; (7) sex; (8) mean sample age; (9) comorbidities; (10) follow-up period for key endpoint measurements; (11) dose (number of cells transferred in millions); (12) cell delivery mode (*e.g.*, intravenous, intramyocardial, or intracoronary infusion); (13) cell status (fresh or frozen); (14) New York Heart Association classification of study participants at baseline; (15) study end-point assessment method/tools (*e.g.*, electrocardiogram, echocardiogram, magnetic resonance imaging, cardiac computed tomography, and single-photon emission computed tomography); (16) LVEF (mean ± SD); (17) 6MWD (mean ± SD); and (18) MACEs.

Quality assessment

The methodological quality of the included RCTs was evaluated using the Cochrane Collaboration tool, which assessed the risk of bias based on the following criteria: sequence generation randomness, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias. Each study was categorized as having low risk, high risk, or unclear risk of bias for each criterion. The overall risk of bias was determined by considering all the criteria and presenting it as a risk of bias graph.

Statistical analysis

Two intervention groups from one of the UC-MSC trials were combined into one group[18]. One group received human UC-MSCs (hUC-MSCs) encapsulated in a collagen hydrogel, while the other received only hUC-MSCs. We calculated and presented fixed-effects Peto odds ratios (OR) with 95% confidence interval (CI) for dichotomous data of adverse events, including death, MACEs, and rehospitalization. We chose the Peto OR method due to the anticipated rarity of adverse events reported across the included studies[19]. This method adds a continuity correction factor of 0.5 for any cells containing zero events, allowing for better estimating rare events. We calculated random-effect mean difference pooled effects for continuous data, presented with 95%CI. This included the change in LVEF and 6MWD from baseline to 6 and 12 mo of follow-up. We used a random-effect model due to expected differences in the study samples and countries. We conducted a weighted mean difference (WMD) meta-analysis as LVEF and 6MWD were reported in the same units across the studies (*i.e.*, percentages and meters).

For continuous outcomes, the data reported in CIs or SE were converted to SD using the Cochrane Handbook equations[20]. When examining the mean ± SD difference from baseline to 6 and 12 mo of follow-up, we found that only one of the UC-MSCs studies[21] provided the mean ± SD change from baseline values. To ascribe the missing change in SD for LVEF, we applied a correlation coefficient of 0.65 derived from the study by Gao *et al*[21] as recommended by the Cochrane Handbook[20,21]. None of the UC-MSCs studies reported the change in mean ± SD for 6MWD; hence, we used a conservative value of 0 as the correlation coefficient to calculate the change in SD[22]. For the BM-MSCs studies that did not report the change in mean ± SD, we used a correlation coefficient value of 0.75 derived from Bolli *et al*[23] for both LVEF and 6MWD changes in SD calculations.

Subgroup analysis was conducted on studies involving BM-MSCs to explore the impact of patients' conditions on the significance of the pooled effects of our primary outcome, LVEF. The analysis focused on two subgroups: HF and MI. However, the same subgrouping could not be performed on the UC-MSCs studies due to the limited number of studies available. Only one study focused on MI patients, while the remaining focused on HF patients.

A new methodological approach was implemented to compare MSCs from the two tissue sources and mitigate any potential overestimation of the effect of the control arm in some studies compared to others. The data from the control arm across all included RCTs were consolidated to derive a unified mean (± SD). Using a similar strategy, the intervention arms (UC-MSCs and BM-MSCs) were analyzed, combining the means (± SDs) reported in the relevant RCTs for each cell type into a single combined mean (± SD). Subsequently, the combined mean (± SD) for each cell type was

compared with the unified control, providing insights into the performance of both cell types in the unified control group. This methodology facilitated a comprehensive evaluation of the effectiveness of UC-MSCs and BM-MSCs compared to the same established control. All calculations used were according to the formulas provided by the Cochrane Handbook[20].

The risk of publication bias was assessed by creating funnel plots of our primary functional outcome, LVEF, in UC-MSCs and BM-MSCs studies. We then evaluated asymmetry, indicating the publication bias.

Statistical heterogeneity was assessed using the I^2 statistic. I^2 < 25% was considered unimportant. A 25%-75% value indicated moderate heterogeneity, and 75%-100% considerable heterogeneity[20]. All statistical data analysis was performed using RevMan 5.4.1 software[24]. $P \leq 0.05$ was considered statistically significant.

RESULTS

Eligible studies

Figure 1 summarizes the process of including studies for the meta-analysis. The literature search across multiple databases yielded 807 potentially relevant studies. Title and abstract screening retained 106 studies, of which 93 were excluded for reasons given in Figure 1, leaving 13 eligible RCTs for analysis.

The risk of bias included in the studies was assessed using the Cochrane Collaboration risk-of-bias tool. The studies were evaluated for selection, performance, detection, attrition, and reporting biases. A risk of bias graph was generated to present the review authors' judgments for each domain in the included studies (Figure 2).

Characteristics of RCTs included in the meta-analysis

Details of the characteristics of included trials are presented in Tables 1, 2 and 3 for UC-MSCs-based and BM-MSCs-based trials, respectively. The 13 RCTs used for meta-analysis spanned from 2009 to 2020, including four RCTs evaluating UC-MSCs, eight RCTs assessing BM-MSCs, and one RCT utilizing both cell types[25]. Locations of the RCTs were Türkiye [25], China[18,22,26,27], Chile[28], India[29], USA[24,30], Denmark[31], Netherlands[32], and South Korea[33].

In the five UC-MSC RCTs (296 patients), 160 patients were in the intervention group, while 130 were in the control group. Male percentages ranged from 78%-100% (intervention group) to 58%-100% (control group). Similarly, in the eight BM-MSC-based RCTs (397 patients), 197 patients were in the intervention group, and 200 patients were in the control group. Males comprised 43%-100% (intervention) and 24%-100% (control). The follow-up duration in the RCTs ranged from 1 to 18 mo (Tables 1, 2 and 3).

Regarding cell characteristics, six RCTs used frozen MSCs, and seven used fresh MSCs. BM-MSCs were obtained from allogeneic[24,29,30], or autologous[25,27,31-33] tissue sources. Diverse routes of administration were used, including intravenous[29,30], intramyocardial[24,25,31,32], intracoronary[27,33] (Tables 4 and 5).

The functional outcome: LVEF

Four of five UC-MSCs studies (intervention group = 102; control group = 72) and six of nine BM-MSCs studies (intervention group = 115; control group = 115) reported the change of LVEF after 6 mo of follow-up and were included in the meta-analysis. The pooled effect of UC-MSCs on LVEF during 6 mo follow-up showed a significant improvement of 5.08% compared to its control group, with moderate heterogeneity (MD 5.08, 95%CI: 2.20%-7.95%; $P = 0.0005$; $I^2 = 61\%$) (Figure 3A). The pooled effect of BM-MSCs changed LVEF insignificantly compared to its control group (MD 2.70%, 95%CI: -1.40 to 2.83; $P = 0.11$; $I^2 = 81\%$). Although both subgroups of BM-MSCs according to the patient's condition did not reach the significance level, BM-MSC-based intervention in HF patients showed a higher improvement (MD 4.53%, 95%CI: -0.85 to 9.91; $P = 0.10$; $I^2 = 85\%$) compared to the MI patients (MD 0.72%, 95%CI: -1.40 to 2.83; $P = 0.51$; $I^2 = 0\%$) (Figure 3B). When the combined mean (± SD) of each cell type was compared with the unified control group, both cell types showed a statistically significant improvement in LVEF with UC-MSCs achieving 5.53% improvement (MD 5.53%, 95%CI: 3.45-7.61, $P < 0.0001$) and 1.54% LVEF improvement with BM-MSCs (MD 1.54%, 95%CI: 0.06-.02, $P = 0.04$) (Supplementary Figure 1).

Four of five UC-MSCs studies with a total of 130 patients in the intervention group and 101 in the control group were followed up for 12 mo[18,22,25,28]. The pooled effect of their mean LVEF showed a significant improvement of 2.78% of LVEF in the intervention group compared to its control group (MD 2.78, 95%CI: 0.86-4.70; $P = 0.004$; $I^2 = 16\%$) (Figure 4A). On the contrary, after 12 mo of follow-up, the five BM-MSC studies showed that 63 patients in the BM-MSC intervention group experienced a 4.35% improvement in LVEF within the HF subgroup. This improvement was significantly greater compared to the control group (99 patients) with moderate heterogeneity (MD 4.34, 95%CI: 0.66-8.03; $P = 0.02$; $I^2 = 44\%$). In contrast to the HF group, no significant LVEF change was observed with BM-MSCs in the MI subgroup (MD -0.16, 95%CI: -5.85 to 5.52; $P = 0.96$; $I^2 = 87\%$) (Figure 4B).

When the combined means and SDs of each cell type were compared with the unified control, UC-MSCs improved LVEF by 1.18% (MD 1.18%, 95%CI: -0.43 to 2.79, $P = 0.15$), but without reaching the level of statistical significance. Combined means and SDs of BM-MSCs showed a significant improvement in LVEF by 2.38% compared to the unified control group (MD 2.38%, 95%CI: 0.38-4.38 $P = 0.02$) (Supplementary Figure 2). A funnel plot of LVEF was plotted to assess publication bias. The distribution of the studies showed asymmetry, suggesting a potential publication bias (Supplementary Figure 3).

Table 1 Baseline characteristics of randomized clinical trials included in the meta-analysis for mortality in umbilical-cord-derived mesenchymal-stem-cell-based heart therapy, *n* (%)

		Gao *et al*[21], 2015 (China)	He *et al*[18], 2020 (China)	Zhao *et al*[26], 2015 (China)	Bartolucci *et al*[28], 2017 (Chile)	Ulus *et al*[25], 2020 (Türkiye)
Study type		RCT	RCT	RCT	RCT	Open-label RCT
Phase		I/II	I	I/II	I/II	I/II
Sample size	Total	116	50	59	30	41
	Intervention (male)	58 (94.8)	32 (78.12)	30 (80.0)	15 (80.0)	25 (100)
	Control (male)	58 (87.9)	12 (58.30)	29 (65.5)	15 (93.3)	16 (100)
Mean age (mean ± SD)	Intervention	57.3 ± 9.90	59.6 (7.9)/63.6 (8.6)	52.90 ± 16.32	57.33 ± 10.05	61.8 ± 10
	Control	56.7 ± 12.95	65.2 (7.9)	53.21 ± 11.46	57.20 ± 11.64	65.3 ± 6.8
Mean BMI (mean ± SD)	Intervention	24.9 ± 2.28	25.5 ± 3.3 /24.4 ± 3.3	N/A	29.12 ± 2.88	26.5 ± 4.5
	Control	25.4 ± 2.28	23.59 ± 2.28	N/A	29.52 ± 4.00	26.6 ± 4.8
Number of smokers	Intervention	34 (58.6)	4 (25.0)/7 (43.8)	N/A	7 (46.7)	21 (84)
	Control	32 (55.2)	3 (25.0)	N/A	4 (26.7)	15 (88.2)
HTN	Intervention	33 (56.9)	10 (62.5)/14 (87.5)	N/A	7 (46.7)	15 (60)
	Control	26 (44.8)	9 (75.0)	N/A	8 (53.3)	11 (64.7)
DM	Intervention	17 (29.3)	8 (50.0)/4 (25.0)	N/A	5 (33.3)	16 (66.7)
	Control	14 (24.1)	8 (66.7)	N/A	7 (46.7)	9 (52.9)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	N/A	III (4 / 8), IV (12 / 8)	N/A	2.03 ± 0.61	1.9 ± 0.44
	Control	N/A	III (7) IV (5)	N/A	1.67 ± 0.49	2.1 ± 0.37
Comparison		Placebo	CABG only	HF drugs only	Placebo	CABG only
Follow-up, months		1, 4, 12 and 18 mo	3, 6 and 12 mo	1 and 6 mo	3, 3, 6 and 12 mo	1, 3, 6 and 12 mo
Assessment modality (yes/no)	ECG	Yes	-	Yes	Yes	Yes
	Echo	Yes	-	Yes	Yes	Yes
	MRI	No	Yes - CMR	-	Yes - CMR	Yes
	Cardiac CT	Yes	-	-	-	No
	SPECT	Yes	-	-	-	Yes
Measured outcomes		Safety and adverse event (primary), efficacy, and LV functions LVEF (secondary)	Serious adverse events at 12 mo (primary), the efficacy of hUC-MSCs and collagen scaffold assessed according to the CV-CMR-based LVEF and infarct size at 3, 6 and 12 mo after treatment, and NYHA (secondary)	Changes in LVEDD, LVEF, BNP, 6MWD, symptoms of HF, death, and adverse events	Safety: Adverse events after IV infusion -/-. Efficacy: (primary). Change in LVEF in ECHO, changes in -(LVESV) & (LVEDV) at ECHO; LVEF, LVESV, and LVEDV in CMR; NYHA score (secondary)	LVEF, LV remodeling, myocardial mass, 6MWD, NYHA score change

HUC-MSCs: Human umbilical cord mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; BNP: Brain natriuretic peptide; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography.

Clinical outcome: 6MWD

Two of five studies on UC-MSCs, with 55 patients in the intervention group and 45 patients in the control group, were followed up[25,26]. Similarly, three of nine BM-MSCs studies with 60 patients in the intervention group and 49 patients in the control group = 49) reported 6MWD data[24,25,30]. The pooled analysis found no significant difference in 6MWD between the intervention and its respective control groups for either UC-MSCs or BM-MSCs. For BM-MSCs, the mean difference was -6.08 m (95%CI: -46.56 to 34.38; P = 0.77; I^2 = 51%) (Supplementary Figure 4A). Similarly, for UC-MSCs, the mean difference was 53.25 m (95%CI: -81.61 to 188.11, P = 0.44, I^2 = 83%) (Supplementary Figure 4B). Both results indicate

Table 2 Baseline characteristics of randomized clinical trials included in the meta-analysis of bone-marrow-derived mesenchymal-stem-cell-based cardiac therapy, *n* (%)

		Chullikana *et al*[29], 2015 (India)	Hare *et al*[30], 2009 (USA)	Heldman *et al*[34], 2014 (USA)	Mathiasen *et al*[31], 2015 (Denmark)	Xiao *et al*[27], 2017 (China)
Study type		RCT	RCT	Open label RCT	RCT	Open label RCT
Phase		I/II	I	I/II	I/II	I/II
Condition		MI	MI	HF	HF	HF
Sample size	Total	20	53	30	60	37
	Intervention (male)	10 (100)	34 (82.4)	19 (94.7)	40 (90)	17 (70)
	Control (male)	10 (80)	19 (78.9)	11 (90.9)	20 (70)	20 (70)
Mean age (mean ± SD)	Intervention	47.31 ± 12.10	59 ± 12.3	57.1 ± 10.6	66.1 ± 7.7	51.6 ± 12.2
	Control	47.79 ± 6.48	55 ± 10.2	60.0 ± 12.0	64.2 ± 10.6	54.4 ± 11.6
Mean BMI (mean ± SD)	Intervention	23.32 ± 3.74	29.8 ± 6.7	N/A	29.8 + 4.7	N/A
	Control	24.86 ± 1.88	30.3 ± 4.3	N/A	28.7 ± 5.3	N/A
Number of smokers	Intervention	N/A	3 (8.8)	14 (73)	7 (17)	N/A
	Control	N/A	2 (10.5)	9 (81.9)	1 (5)	N/A
HTN	Intervention	N/A	16 (17.6)	12 (63.2)	0	4 (23)
	Control	N/A	9 (47.4)	6 (54.5)	0	7 (35)
DM	Intervention	N/A	6 (17.6)	3 (15.8)	15 (37)	5 (29.4)
	Control	N/A	1 (5.3)	3 (27.3)	3 (15)	6 (30)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	N/A	N/A	I (5)/II (12)/III (2)	II (11)/III (29)	II
	Control	N/A	N/A	I (2)/II (5)/III (3)	II (5)/III (15)	II
Comparison		Placebo (multiple electrolytes injection)	Placebo	HF treatments	HF treatments	HF treatments
Follow-up		6 mo to 2 yr	6 mo	12 mo	6 mo	12 mo
Assessment modality (yes/no)	ECG	No	Yes	Yes	No	Yes
	Echo	Yes	Yes	No	No	Yes
	MRI	Yes	Yes	Yes	Yes	No
	Cardiac CT	No	Yes	Yes	Yes	No
	SPECT	Yes	No	No	No	Yes
Measured outcomes		Adverse events, LVEF (Echo and SPECT), total perfusion score, and total infarct volume	Safety, adverse events, LVEF (Echo), and 6MWD	Adverse events (primary), 6MWD, NYHA, and LV parameters (secondary)	LVESV (primary), LVEF, NYHA, 6MWD, and LV parameters (secondary)	LVEF, NYHA, LVEDV, and MAE are primary endpoints

HUC-MSCs: Human umbilical cord mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; BNP: Brain natriuretic peptide; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography.

no significant treatment effect of either stem cell type on 6MWD compared to their control group.

When compared with the unified control group, UC-MSCs showed a non significant improvement of 7.47 m (MD 7.47, 95%CI: -20.69 to 35.63, P = 0.60). However, the comparison between the combined means and SDs of BM-MSCs and the unified control group resulted in a significant improvement of 49.74 m in the BM-MSCs group (MD 49.74, 95%CI: 5.53-93.95, P = 0.03) (Supplementary Figure 4C).

Table 3 Baseline characteristics of randomized clinical trials included in the meta-analysis of bone-marrow-derived mesenchymal-stem-cell-based cardiac therapy, *n* (%)

		Ulus *et al*[25], 2020 (Türkiye)	Rodrigo *et al*[32], 2013 (Netherlands)	Kim *et al*[16], 2018 (South Korea)	Bolli *et al*[23], 2020 (USA)
Study type		Open-label RCT	RCT	RCT	RCT
Phase		I/II	I/II	I	I
Condition		CIC	MI	MI	HF
Sample size	Total	28	54	26	31
	Intervention (male)	12 (100)	9 (78)	14 (100)	14 (43)
	Control (male)	16 (100)	45 (78)	12 (100)	17 (24)
Mean age (mean ± SD)	Intervention	56.9 ± 5.20	56 ± 8	55.3 ± 8.6	54.7 ± 12.8
	Control	65.3 ± 6.8	61 ± 11	57.8 ± 8.9	58.2 ± 11.2
Mean BMI (mean ± SD)	Intervention	26.2 ± 3.12	N/A	N/A	30.2 ± 9.0
	Control	26.6 ± 4.8	N/A	N/A	30.4 ± 6.5
Number of smokers	Intervention	11 (91.6)	6 (67)	5 (35.7)	5 (36)
	Control	15 (88.2)	19 (42)	5 (41.7)	3 (18)
HTN	Intervention	6 (50)	4 (44)	5 (35.7)	6 (43)
	Control	11 (64.7)	18 (40)	5 (41.7)	10 (59)
DM	Intervention	4 (33.3)	1 (11)	3 (21.4)	3 (21)
	Control	9 (52.9)	5 (11)	2 (16.7)	5 (29)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	2.2 ± 0.6	N/A	N/A	II (13), III (1)
	Control	2.1 ± 0.37	N/A	N/A	II (13), III (4)
Comparison		CABG only	No placebo (optimal MI treatment)	No placebo (optimal MI treatment)	HF treatments
Follow-up duration		1, 3, 6, and 12 mo	3, 6, 12 mo, 4, 5 years	4 and 12 mo	6 and 12 mo
Assessment modality (Yes/no)	ECG	Yes	Yes - Holter	No	Yes
	Echo	Yes	Yes	Yes	No
	MRI	Yes	No	No	Yes - CMR
	Cardiac CT	No	No	No	No
	SPECT	Yes	Yes	Yes	No
Measured outcomes		LVEF, LV remodeling, myocardial mass, 6MWD, NYHA score	Safety and feasibility of IM delivery after PCI for MI (primary). Efficacy regarding change in infarct size, LVEF, LVEDV, and LVESV (secondary)	Absolute changes in global LVEF from baseline to 4 months after PCI using SPECT, Echo changes in global LVEF at 12 mo (primary). Changes in LVEDV, LVESV, and MACE (secondary)	Safety and feasibility of allogenic MSC in population (primary). Effects of allogenic MSC on LV function (LVEF, LVEDV, LVESV, scar), morphology, and functional status (6MWD, MLHFQ) (secondary)

MSCs: Mesenchymal stem cells; HT: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; MAE: Major adverse events; MACE: Major adverse cardiac events; CABG: Coronary artery bypass grafting; HF: Heart failure; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; MI: Myocardial infarction; 6MWD: 6-min walking distance test; N/A: Not available; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; ECG: Electrocardiogram; Echo: Echocardiogram; MRI: Magnetic resonance ımaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography; MLHFQ: Minnesota living wıth heart failure questionnaire.

Table 4 Intervention characteristics of randomized controlled trials of umbilical-cord-derived mesenchymal stem cells

Refs	Cell type	Cell condition	MSCs dose and volume	Route of delivery	Concurrent procedure (if any)
He *et al*[18]	WJUC-MSCs	Frozen	1×10^8/1.5-2.5 mL +/- 1 mL collagen scaffold	IM	CABG for all groups
Zhao *et al*[26]	UC-MSCs	N/S	N/S	IC	N/A
Bartolucci *et al*[28]	WJUC-MSCs	Frozen	1×10^6/kg in 100 mL	IV	N/A
Ulus *et al*[25]	UC-MSCs	Frozen	23×10^6	IM	CABG for all groups
Gao *et al*[21]	WJUC- MSCs	Fresh	6×10^6	IC	N/A

CABG: Coronary artery bypass grafting; N/A: Not available; N/S: Not specified; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; PCI: Percutaneous coronary intervention; WJUC-MSCs: Wharton's Jelly umbilical cord mesenchymal stem cells; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; MSCs: Mesenchymal stem cells.

Table 5 Intervention characteristics of randomized controlled trials of bone-marrow-derived mesenchymal stem cells

Refs	Cell type	Cell condition	Cell source	MSCs dose and volume	Route of delivery	Concurrent procedure (if any)
Chullikana *et al*[29]	BM-MSCs	Frozen	Allogenic	2 million cells/kg, 0.5 mL/kg	IV	N/A
Hare *et al*[30]	BM-MSCs	Frozen	Allogenic	0.5, 1.6, and 5.0×10^6	IV	N/A
Heldman *et al* [34]	BM-MSCs	Fresh	Autologous	N/A	IC	PCI
Mathiasen *et al*[31]	BM-MSCs	Fresh	Autologous	$77.5 \pm 67.9 \times 10^6$ in 10-15 injections	IM	N/A
Xiao *et al*[27]	BM-MSCs	Fresh	Autologous	4.9×10^8	IC	N/A
Ulus *et al*[25]	BM-MSCs	Fresh	Autologous	70×10^7	IM	CABG
Rodrigo *et al*[32]	BM-MSCs	Fresh	Autologous	$31 \pm 2 \times 10^6$ IN 10-12 injections	IM	N/A
Kim *et al*[16]	BM-MSCs	Fresh	Autologous	$7.2 \pm 0.90 \times 10^7$	IC	N/A
Bolli *et al*[23]	BM-MSCs	Frozen	Allogenic	1×10^8 *via* 20 TC injections	IM	N/A

BM-MSCs: Bone marrow mesenchymal stem cells; CABG: Coronary Artery Bypass Grafting; N/A: Not available; IC: Intracoronary; IM: Intramyocardial; IV: Intravenous; PCI: Percutaneous Coronary Intervention; MSCs: Mesenchymal stem cells.

Safety outcome: MACEs

Mortality: Four of five UC-MSCs studies (n = 246)[22,25,26,28] and six of nine BM-MSCs studies (n = 206)[24,25,27,29,31,34] reported on mortality during the follow-up period. No significant difference in the OR of mortality between the intervention and respective control group of UC-MSCs studies (Peto OR 0.35, 95%CI: 0.27-1.03; P = 0.06; I^2 = 0%) (Figure 5A) and BM-MSCs studies (Peto OR 0.74; 95%CI: 0.22-2.54; P = 0.64; I^2 = 0%) (Figure 5B). Similarly, both cell types did not significantly improve the mortality rate compared to the unified control.

MACEs: Four of five UC-MSCs studies (n = 246)[22,25,26,28] and eight of nine BM-MSCs studies (n = 285)[24,25,27,29-31,33,34] reported the incidence of MACEs, including angina, supraventricular tachycardia, ventricular tachycardia, and revascularization of MI. No significant effect was observed in the pooled OR of UC-MSCs studies (Peto OR 1.39; 95%CI: 0.42-4.60; P = 0.59; I^2 = 0%) (Figure 5C) and BM-MSCs studies (Peto OR 0.53; 95%CI: 0.27-1.03; P = 0.06; I^2 = 0%) between the intervention and control groups (Figure 5D).

When both cell types are compared with the unified control arm, the UC-MSCs studies demonstrated a significant reduction in the incidence of MACEs by an OR of 0.27 (0.27, 95%CI: 0.13-0.55, P = 0.0003). In contrast, the BM-MSCs studies did not significantly affect the MACE OR (1.41, 95%CI: 0.90-2.20, P = 0.13) (Supplementary Figure 5A).

Rehospitalization

Four of five UC-MSCs studies (n = 247)[18,22,26,28], and four of nine BM-MSCs studies (n = 182)[24,30,31,34], reported data on rehospitalization of the enrolled patients. UC-MSCs studies reported a nonsignificant difference between the intervention and control groups with a Peto OR of 0.62 (95%CI: 0.24-1.60; P = 0.31; I^2 = 17%) (Figure 5E). Analysis of BM-

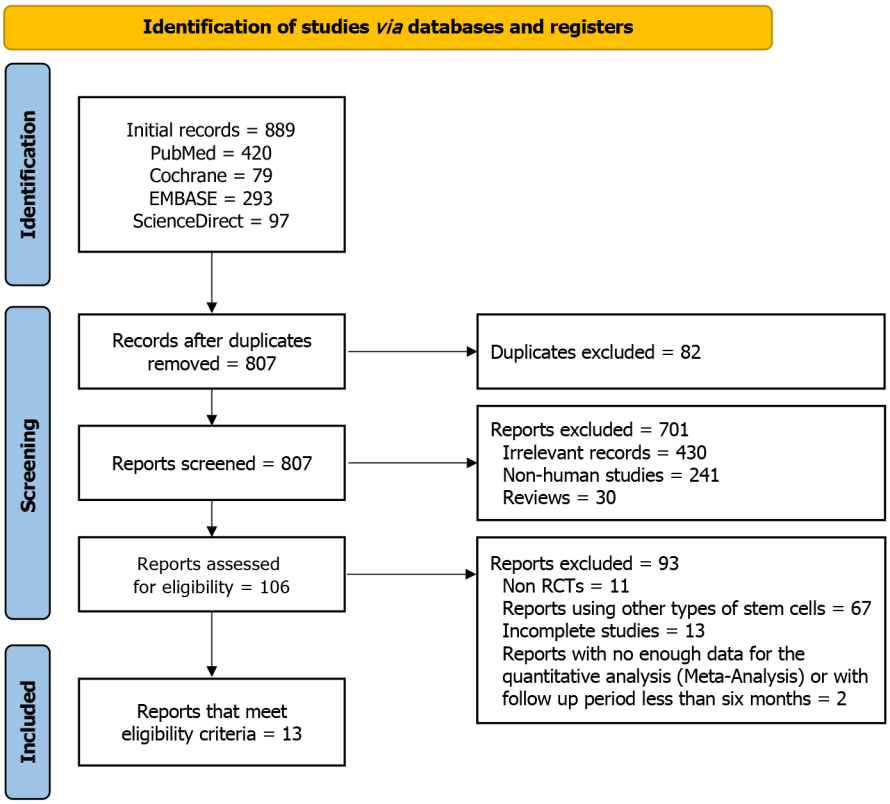


Figure 1 Study selection flow diagram of preferred reporting item for systematic reviews and meta-analysis. RCTs: Randomized controlled trials.

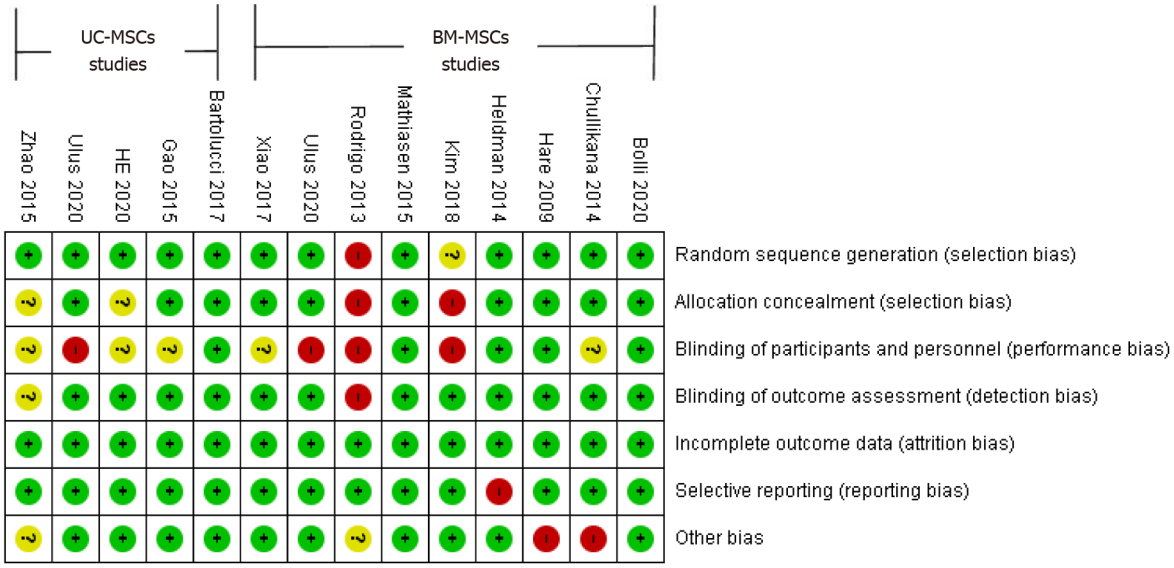


Figure 2 Risk of bias assessment graph. UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cell.

MSCs studies showed a significant reduction of rehospitalization rates by 52% and Peto OR of 0.48 (95%CI: 0.24-0.97; P = 0.04; I^2 = 39%) (Figure 5F). These findings suggest that BM-MSCs demonstrated a protective effect in the intervention group, resulting in a lower rehospitalization rate than their respective control group.

Compared to the unified control group, the UC-MSCs studies showed a significant reduction in the rehospitalization rate with an OR of 0.31 (95%CI: 0.14-0.66, P = 0.003). However, the BM-MSCs significant reduction in rehospitalization rate compared to its respective control was not maintained with the unified control (Peto OR 1.30, 95%CI: 0.73-2.31, P = 0.38) (Supplementary Figure 5B).

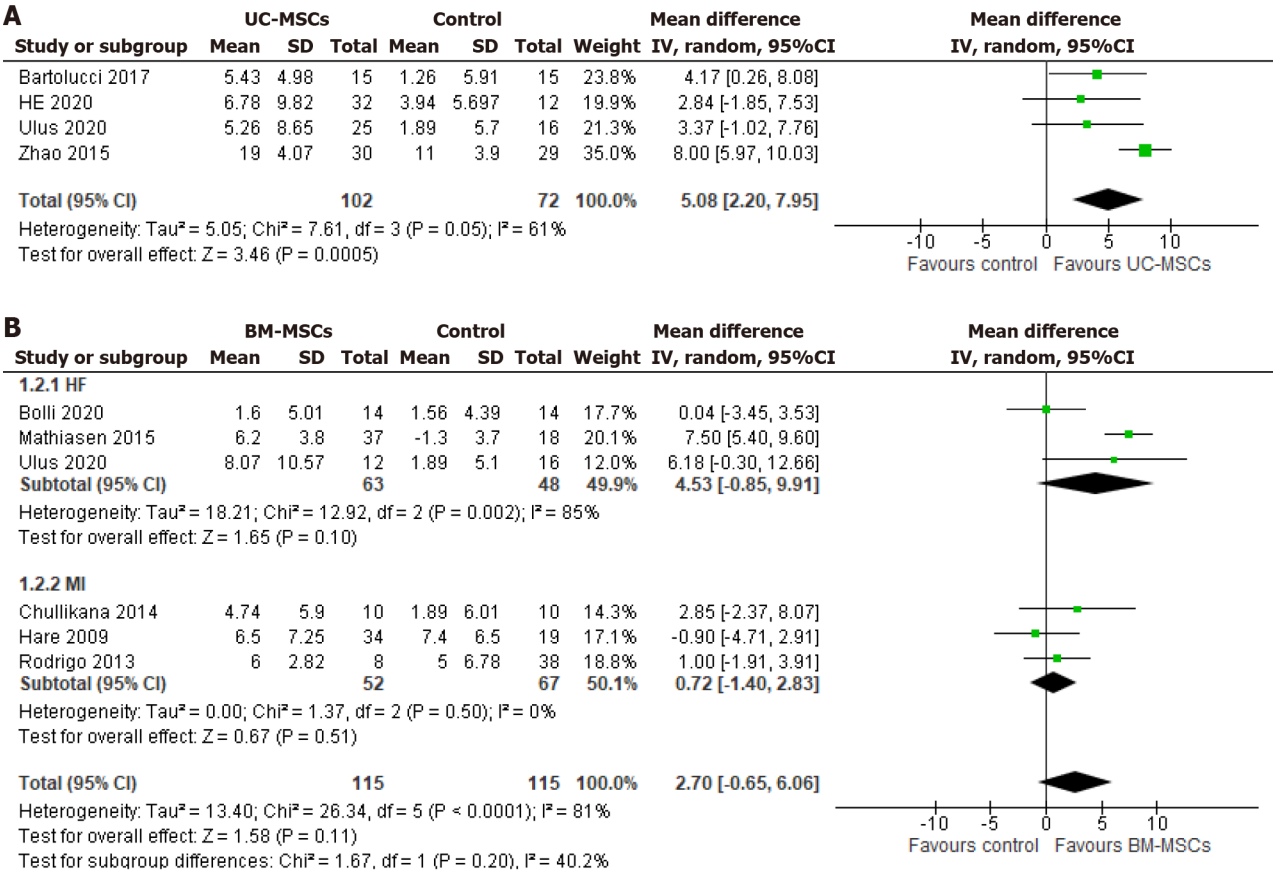


Figure 3 Forest plot of left ventricular ejection fraction change from baseline to 6 mo of follow-up. A: Umbilical-cord-derived mesenchymal stem cells; B: Bone-marrow-derived mesenchymal stem cells. UC-MSCs: Umbilical cord-derived mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cell; MI: Myocardial infarction; HF: Heart failure.

DISCUSSION

This systematic review and meta-analysis of MSC-based therapy evaluated the efficacy and safety of MSCs sourced from two different tissues as living biodrugs for treating CVD patients. Besides safety endpoints, the performance of the two cell types used was assessed for functional and clinical indicators, *i.e.*, LVEF and 6MWD. Our significant findings include: (1) UC-MSCs RCTs reported significant improvement in LVEF during 6 and 12 mo follow-up compared to controls and their BM-MSCs counterparts; (2) both cell types did not show a significant improvement in 6MWD compared to the baseline; and (3) both cell types exhibited no disparity in adverse events including MACEs, except for rate of rehospitalization, which showed significant reduction with BM-MSCs group compared to the UC-MSCs and control groups.

Comparing both cell types in MI and HF patients based on the above parameters, UC-MSC-treated patients had a significant pooled increase of 5.08% and 2.78% in LVEF during 6 and 12 mo follow-up, respectively, compared to the nonsignificant 2.70% and 2.14% improvement in BM-MSC-treated patients during 6 wk and 12 mo follow-up, respectively. The clinical efficacy of this intervention was evaluated through the measurement of 6MWD, an affordable, effective, and reproducible approach for assessing the physical endurance, functional capacity, and overall cardiopulmonary status of individuals with HF who do not require advanced technological equipment. After 6 mo of follow-up, only two UC-MSCs RCTs and three BM-MSCs RCTs have provided 6MWD data eligible for inclusion in the analysis. Further analysis showed no significant difference in 6MWD between intervention and control groups for either BM-MSCs or UC-MSCs.

The adverse events reported and analyzed in this review included patient mortality, rehospitalization rate, and MACEs. There was no notable disparity between the intervention and their respective control groups in the UC-MSCs and BM-MSCs RCTs, indicating the clinical safety of MSCs-based therapy. Similarly, no significant impact was observed in the UC-MSCs and BM-MSCs RCTs between the intervention and respective control groups for MACEs, which included angina, supraventricular tachycardia, ventricular tachycardia, and revascularization. Although the point estimate of the Peto OR suggested a higher incidence of MACEs in the UC-MSC group than in its control group, this difference was insignificant. The 95%CI for the Peto OR included the null value of 1.0, indicating no significant difference between the UC-MSC group and its control (95%CI: 0.42-4.60).

When analyzing the rehospitalization rates for cardiac causes following the treatment with both BM-MSCs and UC-MSCs compared to the control group, a significant 52% reduction was reported only in the BM-MSCs group. In contrast, the UC-MSCs group did not experience a significant reduction compared to the control group.

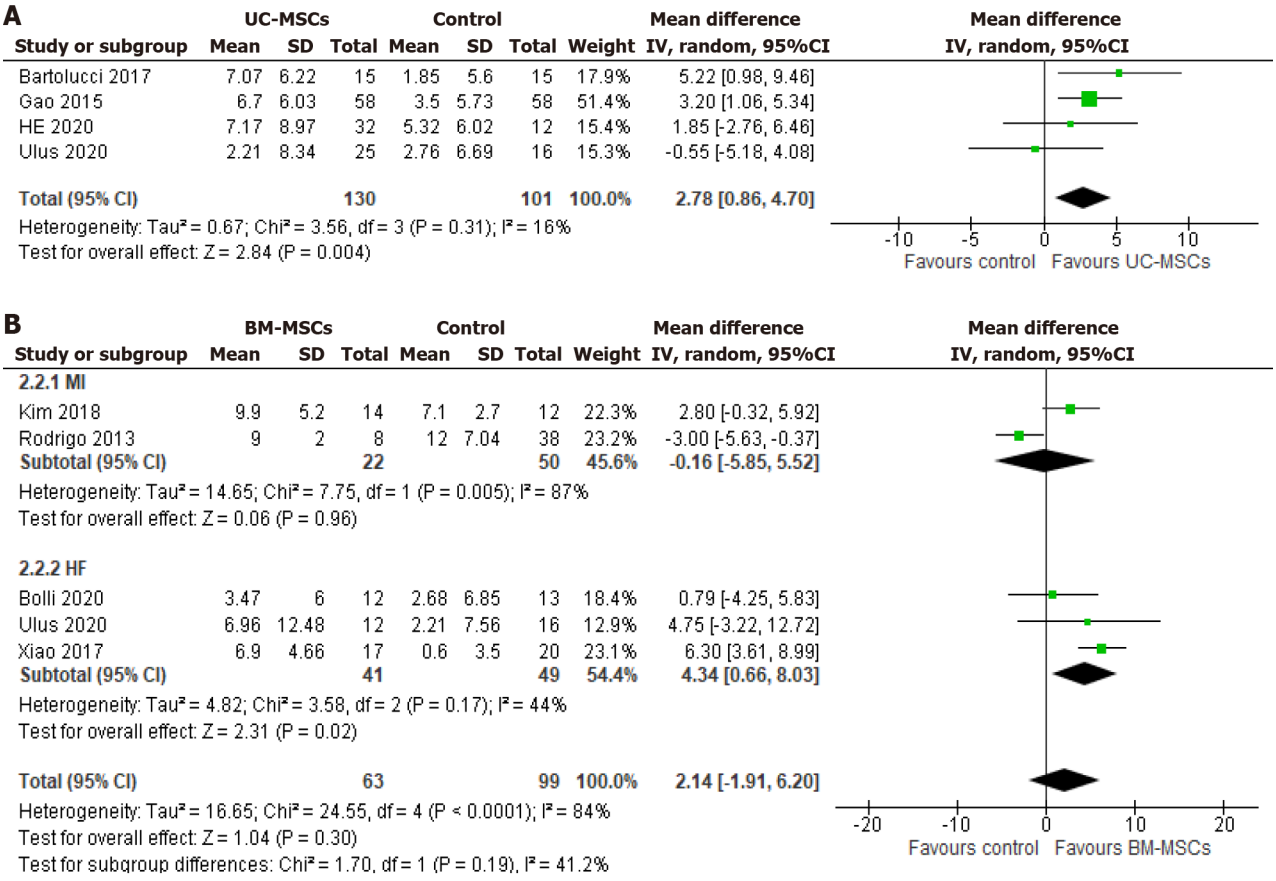


Figure 4 Forest plot of left ventricular ejection fraction change from baseline to 12 mo follow-up. A: Umbilical cord-derived mesenchymal stem cells; B: Bone marrow-derived MSCs. UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cell; MI: Myocardial infarction; HF: Heart failure.

A comprehensive comparison method between the two cell types was used while mitigating the impact of control group variations across studies. The means (± SDs) of the control group from the included studies of UC-MSCs and BM-MSCs were combined using Cochrane formulas, resulting in a unified control group. A similar approach was applied to the means (± SDs) of UC-MSCs and BM-MSCs derived from the included RCTs. Subsequently, each cell type's combined means (± SDs) were compared to the unified control group. This method thoroughly evaluated the effectiveness of UC-MSCs and BM-MSCs *vs* the unified control group. After applying this method, noteworthy findings emerged. Both cell types demonstrated the ability to improve LVEF at the 6-mo follow-up. However, only BM-MSCs exhibited a significant improvement at the 12-mo follow-up. While no cell type significantly affected 6MWT compared to their respective control groups, BM-MSCs demonstrated a considerable improvement compared to the unified control group. Additionally, UC-MSCs showed reduced MACE and readmission rates *vs* the unified control group. These findings highlight the significant effects of both cell types on the functional parameters of the infracted heart and patient prognosis when variations within control groups across studies were excluded.

This review focuses on phase I and II RCTs that have evaluated the safety and efficacy of MSCs derived from bone marrow and umbilical cord in patients with cardiac pathologies. The primary rationale for only including phase I and II RCTs was that all published UC-MSCs studies are limited to these early clinical trial phases. Therefore, only phase I/II RCTs utilizing BM-MSCs were incorporated to ensure a precise cell comparison.

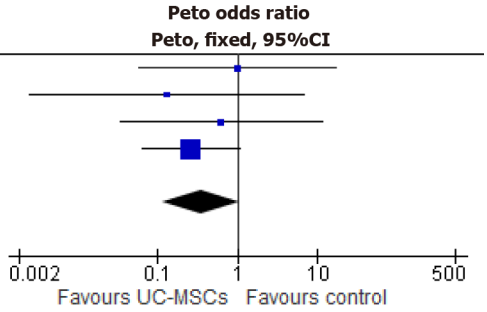
According to the data obtained from ClinicalTrials.gov, eleven ongoing RCTs investigating the use of UC-MSCs and seven RCTs studying BM-MSCs in patients with HF and MI are currently underway. These clinical trials encompass phase I to phase III.

Irrespective of the tissue source, MSCs possess low immunogenicity due to reduced expression of MHC-II molecule, lack of MHC-I expression, and the absence of co-stimulatory signals[35,36]. UC-MSCs are gaining popularity in clinical settings due to their advantages, which include noninvasive collection methods, minimal bioethical concerns, possible widespread "off-the-shelf" availability, and being rich in primitive cell populations. Additionally, like other MSC types, UC-MSCs have the added benefit of being cryopreserved for extended periods. Bárcia *et al*[36] reported successful cryopreservation of UC-MSCs using the conventional cryopreservation protocol, *i.e.*, 10% DMSO and 90% fetal bovine serum) for 3 years with a high viability rate upon thawing. Their availability without infection risk and the lack of influence from donor morbidities and aging factors put them in a position of advantage over their counterparts[37]. On the contrary, the less-than-expected results from BM-MSC-based RCTs compared to their respective control may be because most of these trials used autologous cells (Table 5). Autologous MSCs from cardiac patients are significantly affected by a plethora of comorbidities, including hypertension, diabetes mellitus, and age-related cellular changes, that

A

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	1	15	1	15	15.4%	1.00 [0.06, 16.79]
Gao 2015	0	58	1	58	8.0%	0.14 [0.00, 6.82]
Ulus 2020	1	25	1	16	14.8%	0.62 [0.04, 11.07]
Zhao 2015	2	30	7	29	61.8%	0.26 [0.06, 1.08]
Total (95% CI)		**128**		**118**	**100.0%**	**0.35 [0.12, 1.06]**
Total events	4		10			

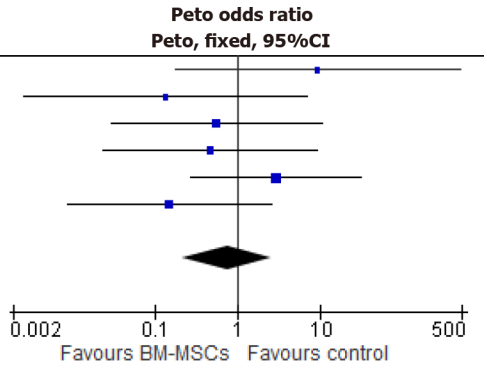
Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)



B

Study or subgroup	BM-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bolli 2020	1	14	0	17	9.7%	9.15 [0.18, 469.98]
Chullikana 2014	0	10	1	10	9.8%	0.14 [0.00, 6.82]
Heldman 2014	1	19	1	11	17.6%	0.55 [0.03, 10.30]
Mathiasen 2015	1	40	1	20	17.2%	0.47 [0.02, 9.05]
Ulus 2020	2	12	1	16	26.7%	2.86 [0.27, 30.76]
Xiao 2017	0	17	2	20	19.0%	0.15 [0.01, 2.50]
Total (95% CI)		**112**		**94**	**100.0%**	**0.74 [0.22, 2.54]**
Total events	5		6			

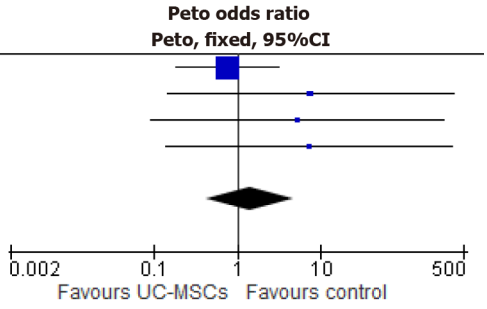
Heterogeneity: Chi² = 4.90, df = 5 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)



C

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	7	15	8	15	72.4%	0.77 [0.19, 3.16]
Gao 2015	1	58	0	58	9.3%	7.39 [0.15, 372.38]
Ulus 2020	1	25	0	16	8.9%	5.16 [0.09, 286.55]
Zhao 2015	1	30	0	29	9.3%	7.15 [0.14, 360.38]
Total (95% CI)		**128**		**118**	**100.0%**	**1.39 [0.42, 4.60]**
Total events	10		8			

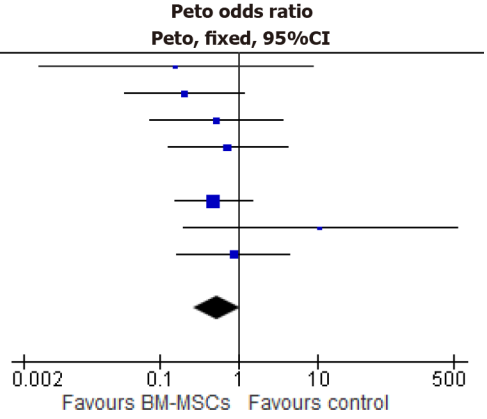
Heterogeneity: Chi² = 2.45, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



D

Study or subgroup	BM-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bolli 2020	0	14	1	17	2.8%	0.16 [0.00, 8.29]
Chullikana 2014	4	10	8	10	14.4%	0.21 [0.04, 1.17]
Hare 2009	2	14	3	12	11.9%	0.52 [0.08, 3.51]
Heldman 2014	4	19	3	11	14.7%	0.71 [0.13, 4.02]
Kim 2018	22	34	21	19		Not estimable
Mathiasen 2015	13	40	10	20	36.7%	0.48 [0.16, 1.44]
Ulus 2020	1	12	0	16	2.8%	10.31 [0.20, 541.25]
Xiao 2017	3	17	4	20	16.6%	0.86 [0.17, 4.39]
Total (95% CI)		**160**		**125**	**100.0%**	**0.53 [0.27, 1.03]**
Total events	49		50			

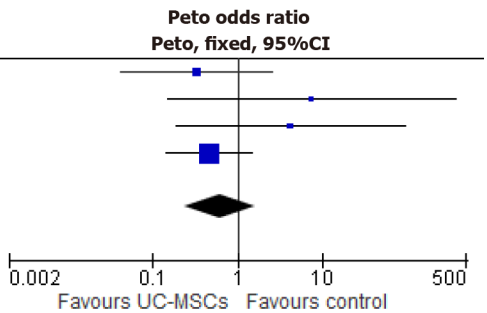
Heterogeneity: Chi² = 4.13, df = 6 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)



E

Study or subgroup	UC-MSCs Events	Total	Control Events	Total	Weight	Peto odds ratio Peto, fixed, 95%CI
Bartolucci 2017	1	15	3	15	21.0%	0.33 [0.04, 2.60]
Gao 2015	1	58	0	58	5.9%	7.39 [0.15, 372.38]
HE 2020	2	30	0	12	9.3%	4.20 [0.19, 93.78]
Zhao 2015	5	30	9	29	63.7%	0.46 [0.14, 1.51]
Total (95% CI)		**133**		**114**	**100.0%**	**0.62 [0.24, 1.60]**
Total events	9		12			

Heterogeneity: Chi² = 3.60, df = 3 (P = 0.31); I² = 17%
Test for overall effect: Z = 0.99 (P = 0.32)



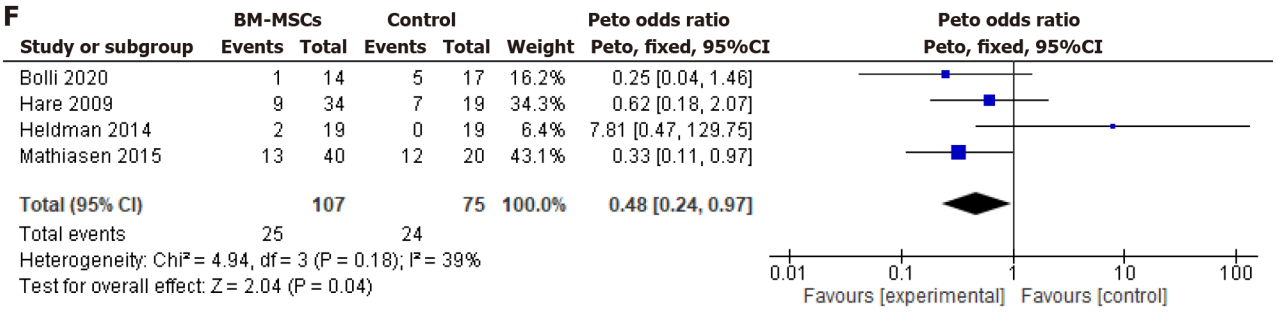


Figure 5 Forest Plot of major adverse events. A and B: Mortality in umbilical-cord-derived mesenchymal stem cells (A) and bone-marrow-derived mesenchymal stem cells (B); C and D: Major cardiac adverse events in UC-MSCs (C) and BM-MSCs (D); E and F: Rehospitalization in UC-MSCs (E) and BM-MSCs (F). UC-MSCs: Umbilical-cord-derived mesenchymal stem cells; BM-MSCs: Bone-marrow-derived mesenchymal stem cells.

compromise their therapeutic potential[10,11]. Additionally, our data showed that BM-MSCs obtained from HF patients led to a statistically significant 4.35% improvement in LVEF at the 12-mo follow-up compared to the control group. In contrast, no significant effect was observed with BM-MSCs derived from MI patients. These findings highlight the importance of the patient's clinical status in determining the therapeutic efficacy of MSC treatments.

While MSCs for cell-based therapy hold potential and have significantly affected clinical and functional study endpoints, the reported moderate improvement is also attributed to the inhospitable microenvironment in the ischemic myocardium that causes poor survival of the transplanted cells besides significantly affecting the stemness characteristics of MSCs. Various strategies are being explored, encompassing quality preconditioning of donor cells to protect them against apoptosis and ferroptosis to develop super stem cells with improved stemness and cell biology[38,39]. Based on the translational data, Xu *et al*[40] designed a multicenter phase II RCT using atorvastatin-preconditioned MSCs for patients with acute MI. This trial aimed to investigate the potential benefits of the preconditioning approach in enhancing the therapeutic effects of MSCs[40]. Additionally, optimizing cell dose and administering multiple doses of MSCs at different times may improve the outcomes[8,41].

CONCLUSION

Although RCT data from UC-MSCs in the present systematic review are encouraging, it is crucial to acknowledge that the sample size in the included studies is relatively small. Therefore, there is a need for more extensive RCTs to validate these findings. Additionally, standardization of optimal isolation and biobanking methods, time and route of administration, and cell dose are necessary for better clinical outcomes. In conclusion, our study indicated that UC-MSCs significantly improve LVEF and patient prognosis compared to their counterpart BM-MSCs. UC-MSCs may be considered a promising alternative source of MSCs for use, suggesting that they are a promising alternative for MSC-based heart therapy.

FOOTNOTES

Author contributions: Haider KH designed and produced the study and its methodology; Safwan M and Bourgleh MS performed database research and screened the extracted records against eligibility criteria; Bourgleh MS, Aldoush M, and Safwan M performed the data extraction and plotting; Safwan M and Aldoush M reviewed and validated the extracted data; Safwan M and Bourgleh MS performed the quality assessment of the included trials; Bourgleh MS and Safwan M conducted the statistical analysis; Safwan M and Haider KH drafted the first manuscript; All the authors contributed to the final manuscript, reviewed the final manuscript and have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: Saudi Arabia

ORCID number: Khawaja Husnain Haider 0000-0002-7907-4808.

S-Editor: Li L

L-Editor: Kerr C
P-Editor: Yuan YY

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