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SYSTEMATIC REVIEWS

Clinical experience with cryopreserved mesenchymal stem cells for cardiovascular applications: A systematic review

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Abstract

BACKGROUND

As living biodrugs, mesenchymal stem cells (MSCs) have progressed to phase 3 clinical trials for cardiovascular applications. However, their limited immediate availability hampers their routine clinical use.

AIM

To validate our hypothesis that cryopreserved MSCs (^{Cryo}MSCs) are as safe and effective as freshly cultured MSC counterparts but carry logistical advantages.

METHODS

Four databases were systematically reviewed for relevant randomized controlled trials (RCTs) evaluating the safety and efficacy of ^{Cryo}MSCs from various tissue sources in treating patients with heart disease. A subgroup analysis was performed based on MSC source and post-thaw cell viability to determine treatment effects across different ^{Cryo}MSCs sources and viability status. Weighted mean differences (WMDs) and odds ratios were calculated to measure changes in the estimated treatment effects. All statistical analyses were performed using RevMan version 5.4.1 software.

RESULTS

Seven RCTs (285 patients) met the eligibility criteria for inclusion in the meta-analysis. During short-term follow-up, ^{Cryo}MSCs demonstrated a significant 2.11% improvement in left ventricular ejection fraction (LVEF) [WMD (95%CI) = 2.11 (0.66-3.56), P = 0.004, I^2 = 1%], with umbilical cord-derived MSCs being the most effective cell type. However, the significant effect on LVEF was not sustained over the 12 months of follow-up. Subgroup analysis demonstrated a substantial 3.44% improvement in LVEF [WMD (95%CI) = 3.44 (1.46-5.43), P = 0.0007, I^2 = 0%] when using MSCs with post-thaw viability exceeding 80%. There was no statistically significant difference in the frequency of major cardiac adverse events observed in rehospitalization or mortality in patients treated with ^{Cryo}MSCs *vs* the control group.

CONCLUSION

[Cryo]MSCs are a promising option for heart failure patients, particularly considering the current treatment options for cardiovascular diseases. Our data suggest that [Cryo]MSCs could be a viable alternative or complementary treatment to the current options, potentially improving patient outcomes.

Key Words: Cardiovascular; Cryopreservation; Heart; Mesenchymal stem cells; Umbilical cord stem cells; Randomized controlled trials; Stem cells

Core Tip: Our study yields significant findings that are crucial for regenerative medicine and cardiology. Our findings revealed that cryopreserved mesenchymal stem cells ([Cryo]MSCs) treatment, compared to the control group, resulted in a 2.11% improvement in left ventricular ejection fraction during six months of follow-up, offering hope for potential future therapies. Left ventricular ejection fraction improvement was higher when using umbilical cord-derived mesenchymal stem cells or [Cryo]MSCs with more than 80% post-thaw viability. The [Cryo]MSCs treatment was safe, as there was no significant difference in the incidence of major cardiac adverse events compared to the control group. In addition, no significant effects on mortality and readmission were observed in the [Cryo]MSCs group compared to the control group.

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INTRODUCTION

Cardiovascular diseases (CVDs), such as myocardial infarction and heart failure, are a pressing global health issue, contributing to 32% of all global deaths[1,2]. The current treatment options provide only symptomatic relief, failing to repair or regenerate the damaged myocardium or preserve declining cardiac function. In this context, cell-based therapy using mesenchymal stem cells (MSCs) has emerged as a promising solution for heart failure patients[3].

MSCs possess unique cell biology and characteristics, *i.e.*, multilineage differentiation potential, soluble and insoluble factor release as part of their paracrine activity, low immunogenicity upon transplantation, anti-inflammatory and immunomodulatory properties, *etc*[4]. They have a robust nature that withstands the rigors of genetic modulation and can carry transgenes during cell-based gene therapy. Combined with their ease of availability from diverse tissue sources, notably bone marrow, adipose tissue, and umbilical cord, non-invasive isolation without moral and ethical strings places them near the ideal cell type for use in the cell-based therapy approach[5]. These characteristic features of MSCs are critical for their diverse clinical applications and have been extensively studied during experimental animal studies and clinical trials[6]. Currently, nearly 1500 registrations with clinicaltrials.gov to assess MSCs from different tissue sources in clinical settings for diverse pathological conditions[7]. Despite these advantages, logistic issues regarding their off-the-shelf availability in large numbers remain a significant limitation that is a critical impediment in routine clinical use[8]. Moreover, repeated tissue sampling for isolation, purification, and *in vitro* expansion adds to the cost of each procedure, besides being time-intensive, which limits their routine use in clinical practice in general and especially in the emergency rooms[9].

The low-temperature storage or cryopreservation of MSCs offers a cost-effective solution to the logistical issues and ensures their ready-made availability. This significantly reduces the time needed to isolate, purify, and expand the cells *in vitro* before use for every patient. The currently available cryopreservation protocols are believed to preserve the cells' unique stemness characteristics, such as their ability to differentiate into multiple cell types and immunomodulatory properties. These characteristics are crucial for the therapeutic potential of MSCs. Despite the beneficial effects of cryopreservation's known impact on MSC biology and viability, standardized preservation methods do not lead to significant variability across preclinical data. Various techniques have been explored to mitigate cellular damage post-cryopreservation, with dimethyl sulfoxide (DMSO) being the most common cryoprotectant despite its associated adverse effects[10,11].

The potential of cryopreserved MSCs ([Cryo]MSCs) in clinical trials treating CVDs has been reported as a significant advancement. A recent meta-analysis of six randomized controlled trials (RCTs) involving 263 heart failure patients found that bone marrow-derived MSCs (BM-MSCs) significantly increased left ventricular ejection fraction (LVEF) by 6.37% at the end of the follow-up period compared to the control group[3]. This promising potential not only instills hope and optimism for the future of cardiovascular medicine but also inspires further research and development in this area. The use of [Cryo]MSCs in clinical trials opens new doors for research and treatment, and their potential could significantly impact the field. Currently, several MSC-based products are available on the market, including Prochymal (Osiris Therapeutics, Canada), Cartistem (Medipost Co Ltd, Korea), and Stempeucel (Stempeutics Research), Cellgram-AMI (FCB Pharmicell, South Korea) (Alliance for Regenerative Medicine; https://alliancerm.org/available-products/), but their

functionality and clinical efficacy are still under scrutiny. Despite the commercial availability and recent use of MSC-based products, there is a scarcity of published data comparing ^{cryo}MSCs with freshly cultured MSCs as living biodrugs to assess their safety and efficacy for patients with CVD.

The present systematic review and meta-analysis of ^{cryo}MSCs in patients with myocardial infarction and heart failure compared to freshly cultured MSC-based therapies aim to significantly contribute to cardiovascular medicine and stem cell therapy. The evidence-based insights into the efficacy and safety of ^{cryo}MSCs could pave the way for improved treatment strategies using off-the-shelf MSCs. These findings can potentially revolutionize the field, bringing an exciting new approach to cardiovascular medicine and inspiring future research and innovation in stem cell therapy, potentially dramatically improving patient outcomes.

MATERIALS AND METHODS

Protocol registration

Before any formal literature search or data analysis, a complete protocol for this study was prospectively developed and registered on the International Prospective Register of Systematic Reviews database dated June 6, 2024. The protocol is available online under the registration ID: CRD42024555501.

Search strategy

A comprehensive and meticulous search strategy was conducted across four databases, including PubMed, Cochrane CENTRAL, ClinicalTrials.gov, and Embase, from their inception until June 2024 to identify relevant RCTs. The search strategy incorporated common text words and medical subject headings (MeSH) such as "Mesenchymal Stem Cells", "MSCs", "Cryopreserved", "Bone marrow Mesenchymal stem cells", "umbilical cord Mesenchymal stem cells", "myocardial infarction," "ischemic heart disease", "acute coronary syndrome", "heart failure", and "cardiomyopathy". These terms were combined using specific algorithms, such as "Mesenchymal stem cells" and "Myocardial infarction". Additionally, the reference lists of included studies were manually searched to identify any relevant RCTs not captured in the initial search. Our search was not restricted by language, and the strategy adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement[12], ensuring the thoroughness and validity of the research and instilling confidence in the validity of the findings.

Eligibility criteria

For inclusion in the current systematic review and meta-analysis, a study was required to meet the following eligibility criteria: (1) It must be an RCT; (2) It assessed the efficacy of ^{Cryo}MSCs; (3) It involved patients with myocardial infarction or heart failure; (4) It must include a control group; (5) The follow-up period was at least six months; and (6) It reported one of the following outcomes: Change in LVEF, six-minute walking distance test (6-MWD), major adverse cardiac events (MACE), or readmission for exacerbation of heart failure or myocardial infarction. Any study that did not fulfill these criteria or was not available in full text was considered ineligible for inclusion.

Outcome measures

The primary outcome evaluated the efficacy of ^{Cryo}MSCs, measured by the change in LVEF and 6-MWD compared to the change observed in the control arm. The secondary outcomes focused on the safety of ^{Cryo}MSCs, assessed by the frequency of MACE across both arms during treatment. MACE encompassed various events, including mortality, arrhythmias, heart failure, recurrence of myocardial infarction, and readmission for cardiac reasons.

Data extraction

Two co-authors (Safwan M and Bourgleh MS) independently evaluated the eligibility of studies for meta-analysis based on the inclusion/exclusion criteria and utilized a standardized data extraction sheet. Each included study was examined, with the extraction of the following variables: (1) First author and publication year; (2) Trial location (country); (3) Type of stem cells; (4) Sample size; (5) Gender distribution; (6) Mean sample age; (7) Presence of co-morbidities; (8) Duration of follow-up for key endpoint measurements; (9) Dosage (number of cells transferred in millions); (10) Method of cell delivery (*e.g.*, intravenous, intramyocardial, or intracoronary infusion); (11) New York Heart Association classification of study participants at baseline; (12) Assessment method/tools for study endpoints (*e.g.*, electrocardiogram, echocardiogram, magnetic resonance imaging, cardiac computed tomography, and single-photon emission computed tomography); (13) LVEF (mean ± SD); and (14) Occurrence of MACE.

Quality assessment

The same co-authors (Safwan M and Bourgleh MS) independently followed the Cochrane collaboration tool for bias assessment to evaluate the methodological quality of the included RCTs. The overall risk of bias was visually presented in a bias risk graph. In instances of disagreement between the authors, a third independent author (Haider KH) was consulted for resolution, ensuring the objectivity and independence of the quality assessment process and reassuring the authors about the results' reliability. This rigorous quality assessment process adds further credibility to the findings, providing the audience with confidence in the reliability of the results.

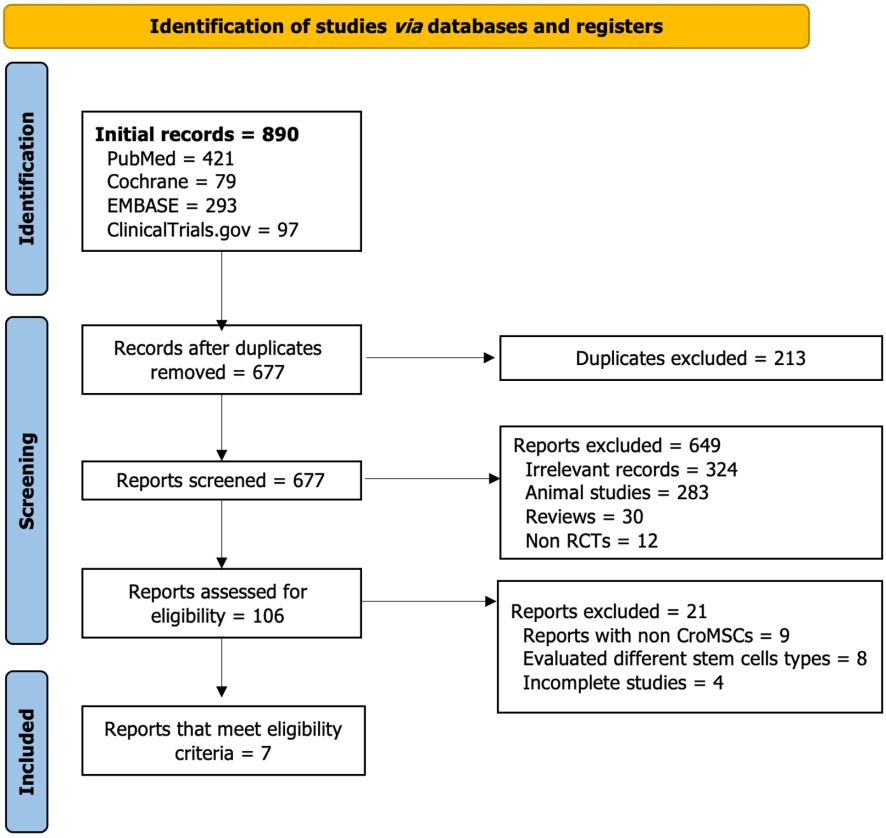

Figure 1 Study selection flow diagram (PRISMA chart). RCTs: Randomized controlled trials; Cryo-MSCs: Cryopreserved mesenchymal stem cells.

Statistical analysis

Statistical data analysis was performed using Review Manager (RevMan) 5.4.1 software. The odds ratio (OR) was calculated and presented with confidence intervals (CI) for dichotomous outcomes, mortality, MACE, and readmission. For continuous outcomes, LVEF and 6MWD, any data extracted in mean ± SE or mean and CI were converted into mean ± SD using equations of the Cochrane Handbook[13]. Weighted mean difference (WMD) analysis was performed due to the consistent measurement units across all the studies for LVEF and 6MWD. Considering the expected heterogeneity between studies due to variations in sample sizes, countries, and doses, a random effect model was employed. To explore the potential variations in efficacy and safety based on the cell source, subgroup analysis was performed using two different cell sources: Bone marrow and umbilical cord tissue. Additionally, a subgroup analysis was conducted based on the release criteria for post-thaw viability, comparing groups with viability rates above 80% to those below 80%. Between-study heterogeneity was assessed using the I^2 statistic and interpreted as follows: 25% < I^2 < 75%: Low and unimportant heterogeneity; I^2 25%-75%: Moderate heterogeneity; 75% < I^2 < 100%: High heterogeneity. The significance cutoff for statistical significance was set at a P value of less than 0.05. A sensitivity analysis was conducted in case high heterogeneity was observed between the studies.

RESULTS

Eligible studies

Figure 1 summarizes the process of systematically searching for eligible RCTs. Initially, a search was conducted across various databases, resulting in 890 records. After removing duplicates and performing title and abstract screening, 28 RCTs remained for full-text screening. Seven RCTs were included, and the remaining 21 were excluded based on the reasons outlined in Figure 1. The risk of bias for the included studies was assessed using the Cochrane collaboration tool [14]. The assessment was based on selection, performance, detection, attrition, and reporting biases. Figure 2 presents a graphical summary of the bias assessment.

Characteristics of included studies

The baseline characteristics of the included RCTs are detailed in Tables 1 and 2. The 7 RCTs included 285 heart disease patients, with 178 patients in the intervention and 107 in the control arms[15-21]. Four of the included RCTs used [Cryo]BM-MSCs for the intervention[15-18], involving 164 patients, 103 in the intervention arm and 61 in the control arm. The percentage of male participants in the BM-MSCs studies ranged from 43% to 100% in the intervention group and 24% to 80% in the control group. The remaining three RCTs used cryopreserved umbilical cord-derived MSCs ([Cryo]UC-MSCs)[19-

Table 1 Baseline characteristics of randomized clinical trials with cryopreserved human umbilical cord-derived mesenchymal stem cells for heart disease, *n* (%)

Ref.		He *et al*[20], 2020, China	Bartolucci *et al*[21], 2017, Chile	Ulus *et al*[19], 2020, Turkey
Study type		RCT	RCT	Open-label RCT
Phase		I	I/II	I/II
Condition		MI	HF	MI
Sample size	Total	50	30	41
	Intervention (% male)	35 (71.42)	15 (80.0)	25 (100)
	Control (% male)	15 (46.67)	15 (93.3)	16 (100)
Age (mean ± SD)	Intervention	61 ± 8.2	57.33 ± 10.05	61.8 ± 10
	Control	65.2 ± 7.9	57.20 ± 11.64	65.3 ± 6.8
BMI (mean ± SD)	Intervention	25 ± 3.35	29.12 ± 2.88	26.5 ± 4.5
	Control	23.59 ± 2.28	29.52 ± 4.00	26.6 ± 4.8
Number of smokers	Intervention	11 (31.43)	7 (46.7)	21 (84)
	Control	3 (25.0)	4 (26.7)	15 (88.2)
HTN	Intervention	24 (68.57)	7 (46.7)	15 (60)
	Control	9 (75.0)	8 (53.3)	11 (64.7)
DM	Intervention	12 (34.29)	5 (33.3)	16 (66.7)
	Control	8 (66.7)	7 (46.7)	9 (52.9)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	III (4/8), IV (12/8)	N/S: 2.03 ± 0.61	N/S: 1.9 ± 0.44
	Control	III (7) IV (5)	N/S: 1.67 ± 0.49	N/S: 2.1 ± 0.37
Comparison		CABG only	Placebo	CABG only
Follow-up		3, 6, and 12 months	3, 6, and 12 months	1, 3, 6, and 12 months
Assessment modality (yes/no)	ECG	No	Yes	Yes
	Echo	No	Yes	Yes
	MRI	Yes (CMR)	Yes (CMR)	Yes
	Cardiac CT	No	No	No
	SPECT	No	No	Yes
Measured outcomes		Serious adverse events at 12 months (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 months after treatment, and NYHA (secondary)	Safety: Adverse events after IV infusion -/-. Efficacy: Primary, changes in LVEF, LVESV & LVEDV by Echo; LVEF, LVESV, and LVEDV by CMR; NYHA score (secondary)	LVEF, LV remodeling, myocardial mass, 6MWD, NYHA score change

RCT: Randomized controlled trial; MI: Myocardial infarction; HF: Heart failure; BMI: Body mass index; HTN: Hypertension; DM: Diabetes mellitus; NYHA: New York Heart Association; N/S: Not specified; CABG: Coronary artery bypass graft; ECG: Electrocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography; CMR: Cardiac magnetic resonance; hUC-MSCs: Human umbilical cord-derived mesenchymal stem cells; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVESV: Left Ventricular end-systolic volume; LVEDV: Left ventricular end-diastolic volume; 6MWD: Six-minute walk distance.

21] with 121 patients, 75 in the intervention group and 46 in the control group. The percentage of male participants in the UC-MSCs studies ranged from 71% to 100% in the intervention group and 46% to 100% in the control groups. The included studies were published between 2009 and 2020 and were conducted across several countries: One each in India [16], Turkey[19], China[20], and Chile[21], while three RCTs were conducted in the United States[15,17,18]. The route of cell delivery varied among the included studies. Four studies employed the intramyocardial route[15,18-20], while the remaining three used the intravenous route[16,17,21].

In the included studies, the control group received a placebo treatment besides standard pharmacological or adjunct surgical intervention. For example, in three studies[15,18,21], the control group also received standard heart failure therapy, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or

Table 2 Baseline characteristics of randomized clinical trials with cryopreserved human bone marrow mesenchymal stem cells for heart disease, *n* (%)

Ref.		Chullikana *et al*[16], 2015, India	Hare *et al*[17], 2009, United States	Bolli *et al*[15], 2020, United States	Perin *et al*[18], 2015, United States
Study type		RCT	RCT	RCT	RCT
Phase		I/II	I	I	II
Condition		MI	MI	HF	HF
Sample size	Total	20	53	31	60
	Intervention (% male)	10 (100)	34 (82.4)	14 (43)	45 (97.8)
	Control (% male)	10 (80)	19 (78.9)	17 (24)	15 (73.3)
Age (mean ± SD)	Intervention	47.31 ± 12.10	59 ± 12.3	54.7 ± 12.8	62.2 ± 10.3
	Control	47.79 ± 6.48	55 ± 10.2	58.2 ± 11.2	62.7 ± 11.2
BMI (mean ± SD)	Intervention	23.32 ± 3.74	29.8 ± 6.7	30.2 ± 9.0	29.8 ± 4.1
	Control	24.86 ± 1.88	30.3 ± 4.3	30.4 ± 6.5	31.3 ± 9.2
Number of smokers	Intervention	N/A	3 (8.8)	5 (36)	7 (15.6)
	Control	N/A	2 (10.5)	3 (18)	2 (13.3)
HTN	Intervention	N/A	16 (17.6)	6 (43)	29 (64.4)
	Control	N/A	9 (47.4)	10 (59)	9 (60)
DM	Intervention	N/A	6 (17.6)	3 (21)	13 (28.9)
	Control	N/A	1 (5.3)	5 (29)	2 (13.3)
NYHA; I (*n*), II (*n*), III (*n*), IV (*n*)	Intervention	N/A	N/A	II (13), III (1)	II (31), III (14)
	Control	N/A	N/A	II (13), III (4)	II (6), III (9)
Comparison		Placebo (multiple electrolytes injection)	Placebo	Placebo	Placebo
Follow-up, months		Six months till two years	Six months	6 and 12 months	3, 6, 12 months
Assessment modality (yes/no)	ECG	No	Yes	Yes	No
	Echo	Yes	Yes	No	Yes
	MRI	Yes	Yes	Yes (CMR)	No
	Cardiac CT	No	Yes	No	No
	SPECT	Yes	No	No	Yes
Measured outcomes		Adverse events, LVEF (Echo & SPECT), total perfusion score, and total volume of infarct	Safety, adverse events, LVEF (Echo), and 6MWD	Safety and feasibility of allogenic MSC administration in this population (primary). Effects of allogenic MSC administration on LV function (LVEF, LVEDV, LVESV, scar morphology) and functional status (6MWD, MLHFQ) (secondary)	Safety (primary), LV volume, LVEF, 6MWD (secondary)

RCT: Randomized controlled trial; MI: Myocardial infarction; HF: Heart failure; BMI: Body mass index; N/A: Not applicable; HTN: Hypertension; DM: Diabetes mellitus; NYHA: New York Heart Association; ECG: Electrocardiogram; MRI: Magnetic resonance imaging; CT: Computed tomography; SPECT: Single-photon emission computed tomography; CMR: Cardiac magnetic resonance; MSCs: Mesenchymal stem cells; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVESV: Left Ventricular end-systolic volume; LVEDV: Left ventricular end-diastolic volume; 6MWD: Six-minute walk distance; MLHFQ: Minnesota Living with Heart Failure Questionnaire.

aldosterone antagonists. In two studies[19,20], the control group underwent coronary artery bypass graft surgery, while in one study[16], the control group received percutaneous coronary intervention. The remaining study[17] did not provide specific information on the medications or procedures administered to the control group.

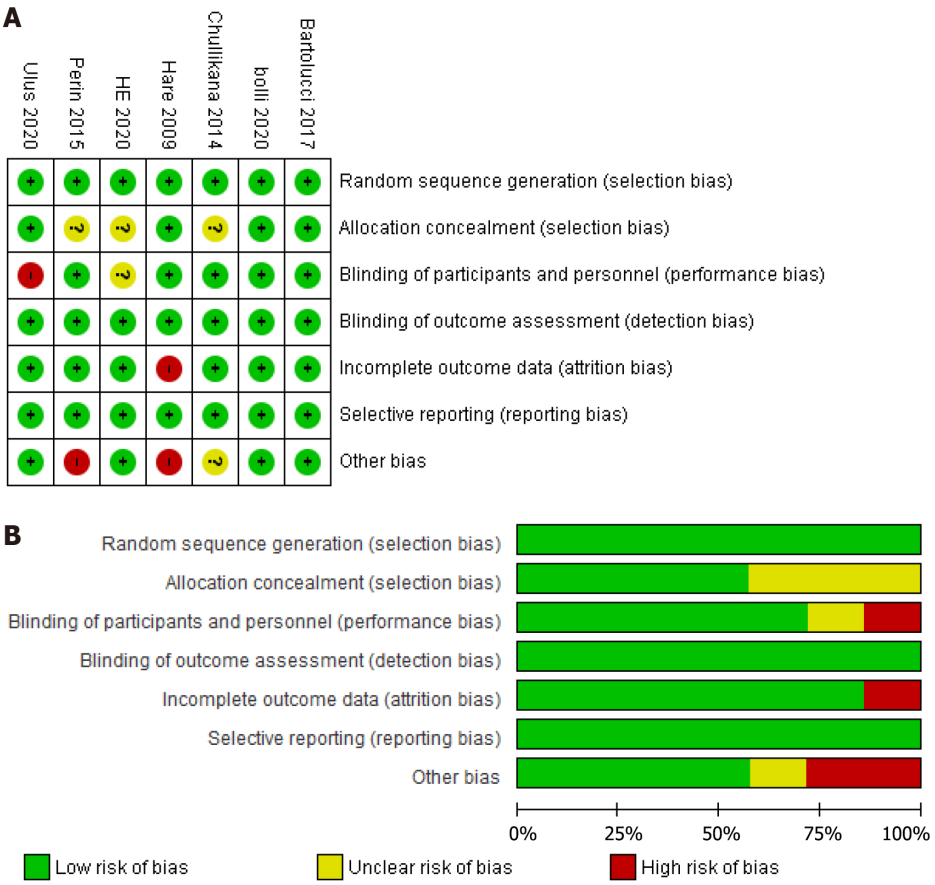

Figure 2 Risk of bias summary and graph. A: Risk of bias summary; B: Risk of bias graph. Symbols: (+) low risk of bias, (?) unclear risk of bias, (-) high risk of bias.

The functional outcome

LVEF: Seven studies[15-21] reported changes in LVEF after six months of [Cryo]MSCs-based treatment, including three studies[19-21] using UC-MSCs and four studies[15-18] using BM-MSCs. The pooled analysis showed a significant 2.11% improvement in LVEF in the MSC treatment groups compared to the control [WMD (95%CI) = 2.11 (0.66-3.56), $P = 0.004$, $I^2 = 1\%$]. In the subgroup analysis by cell type, the pooled 6-month LVEF changes recorded a significant 3.53% increase in the UC-MSCs studies [WMD (95%CI) = 3.53 (1.38-5.67), $P = 0.001$, $I^2 = 0\%$]. At the same time, the BM-MSCs treatment did not demonstrate any significant improvement compared to the control [WMD (95%CI) = 0.92 (-1.03 to 2.88), $P = 0.35$, $I^2 = 0\%$] (Figure 3A). Seven studies measured the LVEF change before and after 12 months of [Cryo]MSCs treatment, including 3 UC-MSCs and 4 BM-MSCs studies. However, the pooled change in the treatment group was a 1.99% improvement compared to the control, which was not statistically significant [WMD (95%CI) = 1.99 (-0.02 to 3.99), $P = 0.05$, $I^2 = 14\%$) (Figure 3B).

In the subgroup analysis based on post-thaw viability, the group with more than 80% post-thaw viable cells demonstrated a significant 3.44% increase in LVEF after six months of follow-up compared to the placebo group [WMD (95%CI) = 3.44 (1.46-5.43), $P = 0.0007$, $I^2 = 0\%$]. On the contrary, the group with less than 80% post-thaw viable cells did not show a significant difference at six months [WMD (95%CI) = 0.37 (-2.89 to 2.14), $P = 0.77$, $I^2 = 0\%$] (Figure 4A). Moreover, at the 12-month follow-up, neither the > 80% viable cell group nor the < 80% viable cell group showed any statistically significant improvement in LVEF compared to the control group [WMD (95%CI) = 2.25 (-1.36 to 5.86), $P = 0.22$, $I^2 = 53\%$] and [WMD (95%CI) = 0.79 (-3.74 to 5.32), $P = 0.73$] respectively (Figure 4B).

6MWD test: The 6MWD test results were reported in four included studies, one involving UC-MSCs and three involving BM-MSCs. The pooled analysis demonstrated no significant difference in 6MWD between the MSCs group and control group [WMD (95%CI) = 20.73 (-3.40.10 to 44.86), $P = 0.09$, $I^2 = 0\%$] for either the UC-MSCs studies [WMD (95%CI) = 28.36 (-37.10 to 93.82), $P = 0.40$] or the BM-MSCs studies [WMD (95%CI) = 19.53 (-6.43 to 45.49), $P = 0.14$, $I^2 = 0\%$] (Figure 5A). Furthermore, the subgroup analysis according to cellular post-thaw viability demonstrated no significant difference in 6MWD between the intervention and control groups, regardless of whether the viable cells were > 80% [WMD (95%CI) = 14.15 (-33.31 to 61.60), $P = 0.56$, $I^2 = 0\%$] or < 80% [WMD (95%CI) = 22.74 (-9.09 to 54.57), $P = 0.16$, $I^2 = 22\%$] (Figure 5B).

The safety outcomes

Rehospitalization: The rehospitalization incidence was reported during the follow-up period in two UC-MSCs and two BM-MSCs studies. The analysis showed no significant reduction in the overall OR of rehospitalization [OR (95%CI) = 0.51 (0.20-1.28), $P = 0.15$, $I^2 = 0\%$] for both UC-MSCs and BM-MSCs treated groups compared to the respective control groups

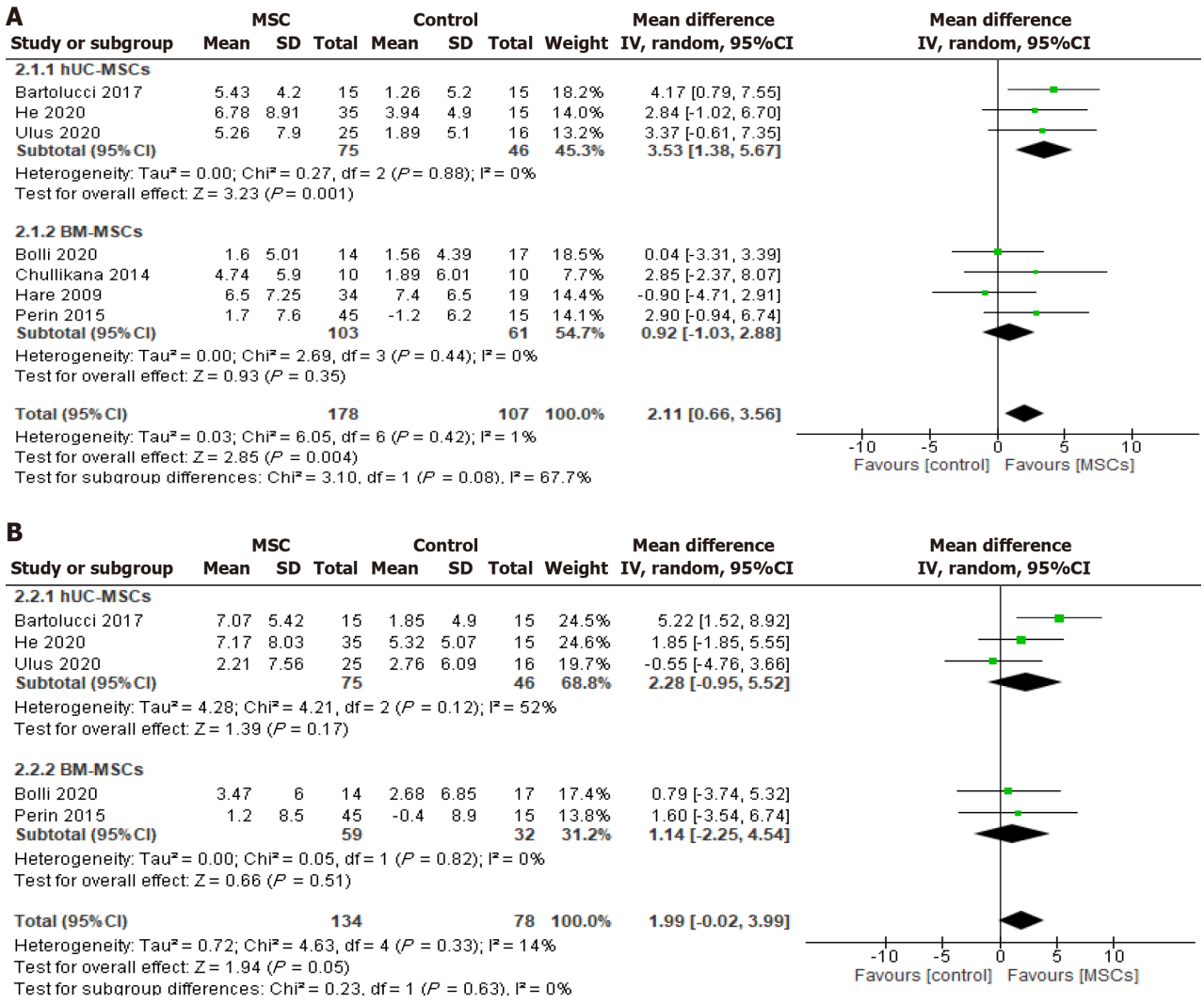

Figure 3 Effect of cryopreserved mesenchymal stem cell therapy on left ventricular ejection fraction sub-grouped according to cell source: Umbilical cord-derived mesenchymal stem cells and bone marrow-derived mesenchymal stem cells. A: Change from the baseline to six months of follow-up; B: Change from the baseline to twelve months of follow-up; hUC-MSC: Human umbilical cord-derived mesenchymal stem cell; BM-MSC: Bone marrow-derived mesenchymal stem cell.

[OR (95%CI) = 0.64 (0.09-4.72), P = 0.66, I^2 = 9%] and [OR (95%CI) = 0.47 (0.16-1.38), P = 0.17, I^2 = 0%] (Figure 6A).

Mortality: Two UC-MSCs RCTs and three BM-MSCs RCTs reported mortality from the included RCTs (Figure 6B). There were no significant differences in the OR of mortality between the intervention group and control group with either UC-MSCs studies [OR (95%CI) = 0.79 (0.10-5.95), P = 0.82, I^2 = 0%] and BM-MSCs studies [OR (95%CI) = 0.64 (0.17-2.35), P = 0.50, I^2 = 0%].

MACEs

Six included studies reported the incidence of MACE, 2 UC-MSCs studies, and 4 BM-MSCs studies, such as ventricular tachycardia, supraventricular tachycardia, and angina and revascularization of myocardial infarction. The pooled analysis did not show a statistically significant difference in the overall MACE [OR (95%CI) = 0.80 (0.39-1.67), P = 0.56, I^2 = 0%] between the [Cryo]MSCs and the control group. Similarly, no statistically significant effect was seen when sub-grouping into UC-MSCs and BM-MSCs compared to the control [OR (95%CI) = 0.90 (0.24-3.33), P = 0.87, I^2 = 0%] and [OR (95%CI): 0.72 (0.24-2.12), P = 0.55, I^2 = 29%] respectively (Figure 6C).

The effect of cellular post-thaw viability on adverse events

Based on cellular post-thaw viability, a subgroup analysis was conducted on adverse events, including rehospitalization, mortality, and MACE. The analysis found no significant differences between the MSCs and the control groups for either the > 80% viable cells or < 80% viable cells groups regarding rehospitalization, mortality, or MACE (Figure 7).

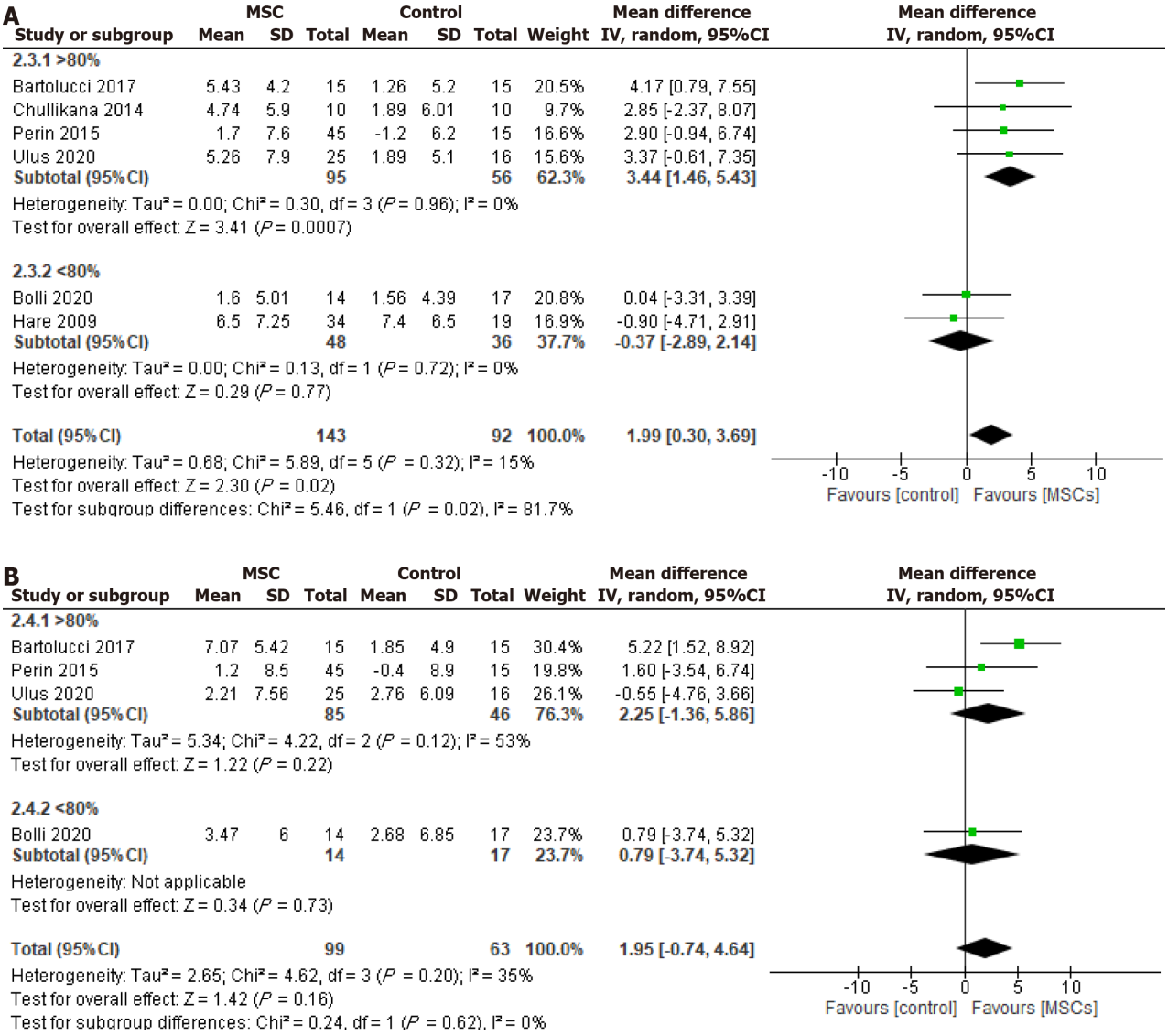

Figure 4 Effect of cryopreserved mesenchymal stem cell therapy on left ventricular ejection fraction sub-grouped according to cellular post-thaw viability as > 80% and < 80%. A: Change from the baseline to 6 mo of follow-up; B: Change from the baseline to 12 mo of follow-up. MSC: Mesenchymal stem cell; CI: Confidence interval.

DISCUSSION

Our systematic review and meta-analysis are aimed at evaluating the safety and efficacy of the [Cryo]MSCs for treating patients with myocardial infarction and heart failure. The significant findings of our study are: (1) [Cryo]MSC treatment resulted in an overall 2.11% improvement in LVEF during 6 mo of follow-up compared to the control group; (2) The LVEF improvement was higher when using UC-MSCs or [Cryo]MSCs with more than 80% post-thaw viability; (3) The functional benefits of treatment with [Cryo]MSCs were not sustained during the 12-mo follow-up; (4) Treatment with [Cryo]MSCs did not result in a statistically significant improvement of the 6MWD test compared to control; (5) Treatment with [Cryo]MSCs was safe, as there was no significant difference in the incidence of MACE compared to the control group; and (6) No significant effects on mortality and readmission were observed in the [Cryo]MSC group compared to the control group.

Unlike conventional drugs, which are mostly natural or synthetic, and modern-day biologics, which are substances of biological origin, pharmacology has advanced to the next generation of drugs: The living biodrugs, *i.e.*, a novel fast-emerging group of medications for which product viability is a primary requirement. Depending upon their subsequent therapeutic application, living biodrugs can also be genetically modified to enhance their efficacy, such as chimeric antigen receptors-T cells nick-named TRUCKs and hematopoietic progenitor cells-based Food and Drug Administration-approved products (Allocord, Hemacord, Ducord, *etc*)[22]. MSCs are novel living biodrugs that may be used naïve or modified to deliver transgenes and drugs as payloads[23]. Logistic considerations for living biodrugs, especially off-the-shelf ready-to-use availability, differ from conventional pharmaceuticals and impede their clinical progress. Firstly, such an arrangement will mainly necessitate an allogenic source of cells. Although the published clinical data supports the use of allogenic MSCs on par with their autologous counterparts[24,25], the donor-related factors affecting their biology and functional heterogeneity, especially for long-term benefits, add to the potential uncertainty about their clinical outcome

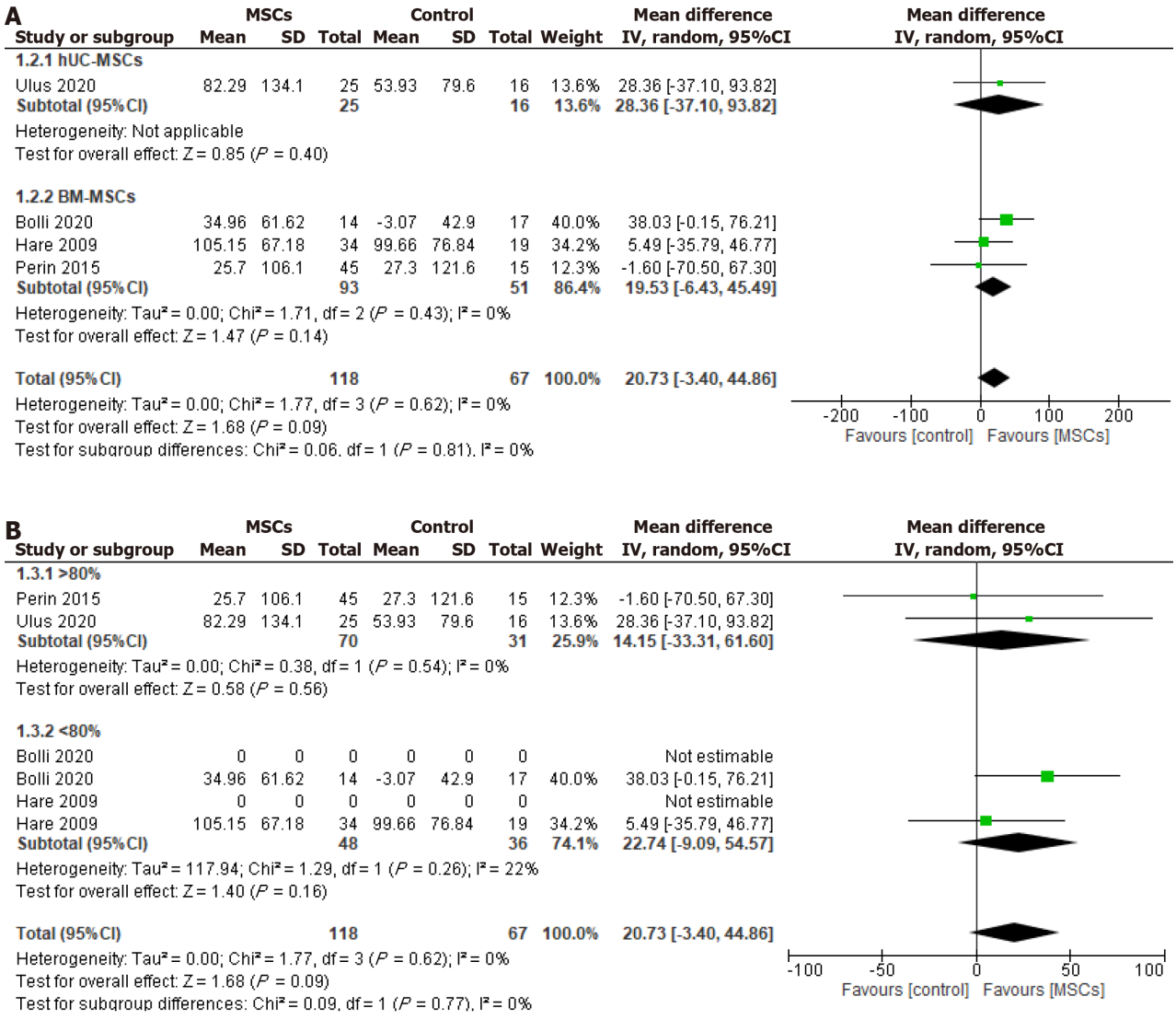

Figure 5 Effect of cryopreserved mesenchymal stem cell therapy on 6 min walk distance sub-grouped according to cell source. A and B: Umbilical cord-derived mesenchymal stem cells (A) and bone marrow-derived mesenchymal stem cells (B) cellular post-thaw viability as > 80% and < 80%. MSC: Mesenchymal stem cell; CI: Confidence interval; hUC-MSC: Human umbilical cord-derived mesenchymal stem cell; BM-MSC: Bone marrow-derived mesenchymal stem cell.

[26]. Their cryopreservation increases the uncertainty regarding their post-transplantation performance.

The factors affecting the safety and efficacy of cryopreserved cells encompass almost everything from tissue source[27] and cryo-banking to thawing and delivery. For example, whether the cryopreserved cells post-thaw be cultured or used directly after washing to remove the cryoprotectant remains an important consideration. Similarly, their viability post-thaw is critical to their safety and efficacy. The current study represents the first evaluation of [Cryo]MSCs' efficacy in patients with CVD and reveals a notable connection between MSCs viability post-thawing and their impact on LVEF. A subgroup analysis based on MSC type and post-thaw viability showed that treatment with UC-MSCs resulted in a significant 3.53% improvement in LVEF during 6 mo of follow-up compared to the control group. On the contrary, no significant LVEF change was observed after treatment with BM-MSCs. It is essential to mention that neither cell type significantly impacted the 12-mo follow-up, although UC-MSCs demonstrated better efficacy. The considerable variations in LVEF improvement observed between MSCs from two tissue sources may be attributed to the relatively primitive nature of UC-MSCs compared to the BM-MSCs[5,27]. These are significant findings as UC-MSCs, with their better efficacy, primitive nature, and non-invasive availability, are being widely cryopreserved to ensure ready-to-use obtainability. The preclinical studies support these data to indicate that MSCs isolated from healthy donors and cryopreserved in liquid nitrogen for extended periods can sustain their biology and stemness characteristics, *i.e.*, paracrine signaling, differentiation potential, and proliferation capabilities[10,28]. This underscores the potential of UC-MSCs for future cryopreservation efforts, instilling a sense of optimism and hope for further research and development.

Changes in LVEF remain a significant predictor of prognosis in heart failure patients. Previous studies have shown that the hazard ratio for all-cause mortality increases by 39% for every 10% reduction in LVEF below 45%[29]. Despite this, relatively few studies have assessed the effectiveness of heart failure medications in improving LVEF. One study demonstrated that beta-blocker treatment led to an LVEF improvement of 4% to 4.9% in patients with a baseline LVEF below 40% and 1.9% in those with a baseline LVEF between 40% and 50%[30]. Another study on the impact of renin-

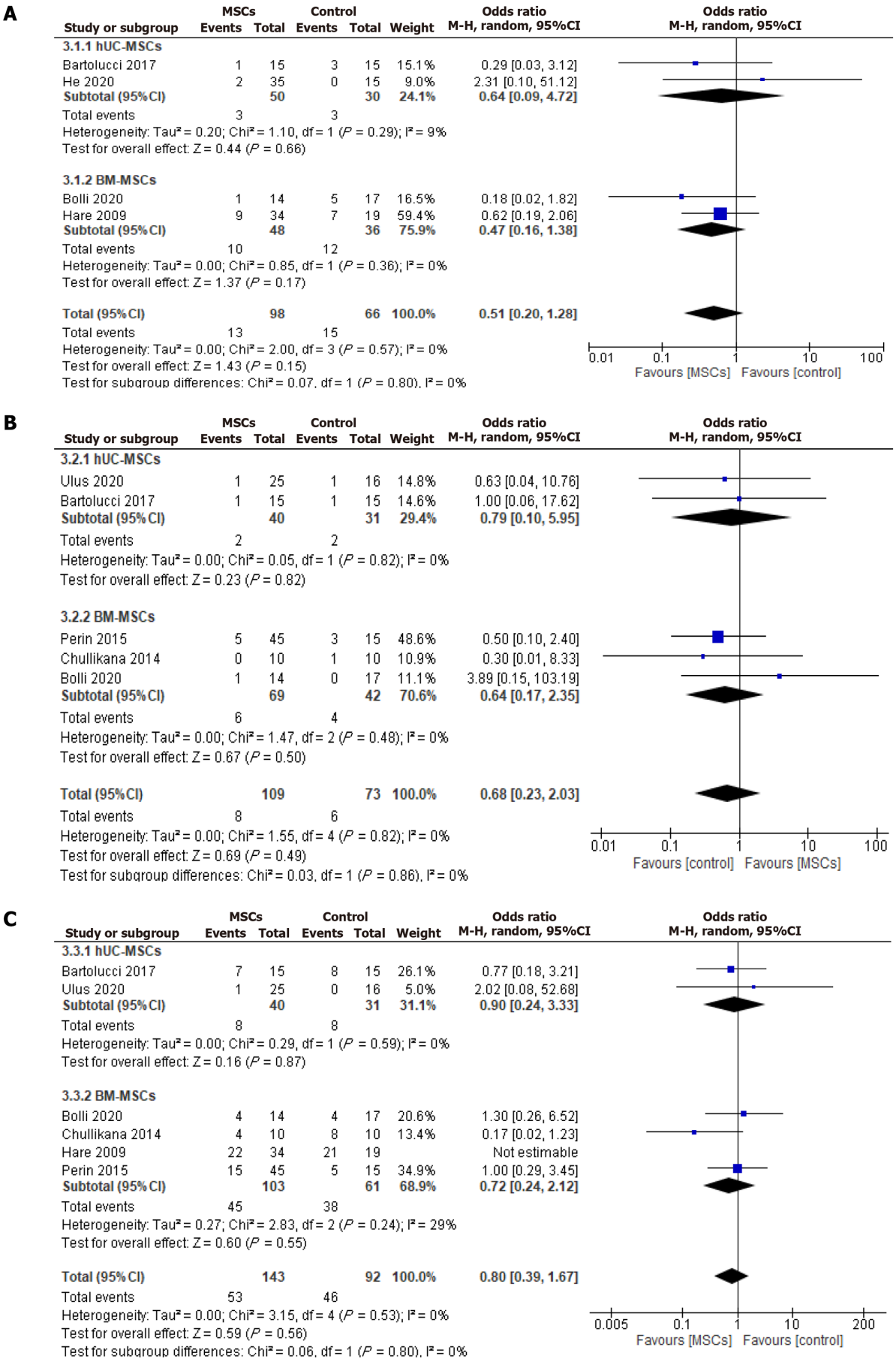

Figure 6 Odds ratio of the safety outcomes. A: Rehospitalization; B: Mortality; C: Major adverse cardiac events. MSC: Mesenchymal stem cell; CI: Confidence interval; hUC-MSC: Human umbilical cord-derived mesenchymal stem cell; BM-MSC: Bone marrow-derived mesenchymal stem cell.

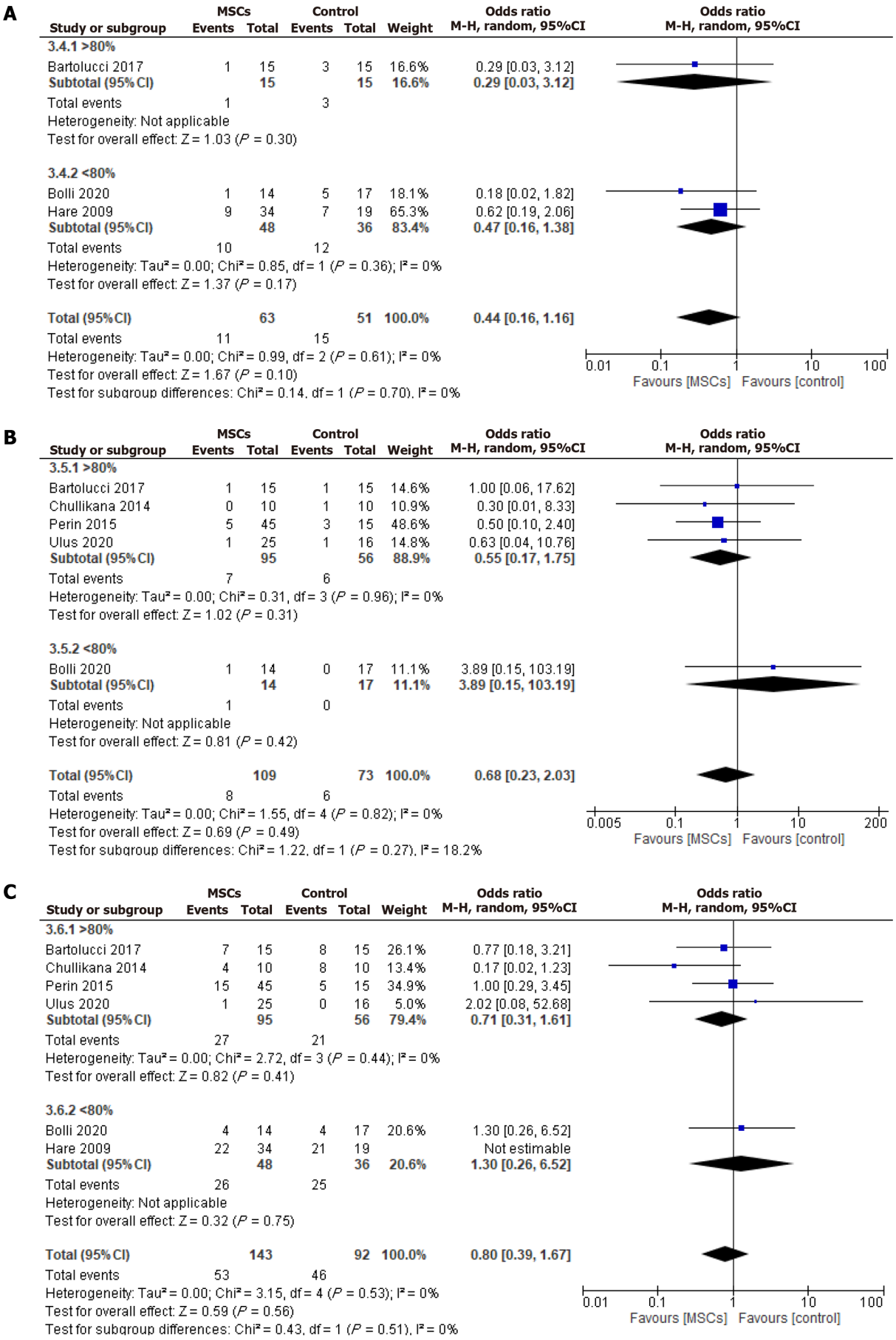

Figure 7 Odds ratio of the safety outcomes sub-grouped according to post-thaw cellular viability. A: Rehospitalization; B: Mortality; C: Major adverse cardiac events. MSC: Mesenchymal stem cell; CI: Confidence interval.

angiotensin system inhibition in heart failure with preserved LVEF found a significant LVEF improvement (2.18%) after treatment[31]. Based on this evidence, the improvements observed in our analysis with ^{Cryo}MSCs appear promising. However, it is important to note that in three of the included studies, both the intervention and control groups received standard therapy (*e.g.*, beta blockers and/or renin-angiotensin system inhibitors). Consequently, we found that treatment with ^{Cryo}MSCs resulted in a more sustained and pronounced improvement in LVEF compared to those receiving standard therapy alone. Moreover, it is difficult to delineate the effects of cell therapy from those of standard therapy during concomitant treatment.

The lack of sustained treatment effects with ^{Cryo}MSCs after 12 months suggests that a single dose is insufficient for long-term cardiac improvement, and administering a second dose may sustain long-term outcomes. Possible explanations for the lack of sustained long-term effects include the progressive nature of heart failure, which often worsens insidiously due to the underlying neurohormonal imbalance and endothelial dysfunction, even in the absence of overt clinical symptoms[32]. Secondly, the permanence of the long-term therapeutic benefits may require the sustenance of the cell graft. Loss of cell graft may contribute to the loss of therapeutic benefits, which can be benefited by repeated cell administration until the recovery from heart failure is reached. Moreover, some studies have employed intravenous administration of cells, which offers advantages such as safety, ease of administration, and lower cost than intracoronary or intramyocardial routes. Although these alternative routes may be more effective, there is a need for specialized centers and a 1%-2% risk of complications like perforation and tamponade that hamper their routine application. Intravenous administration is associated with lower engraftment, which can limit the therapeutic benefits, especially when a single dose is used[33]. Lastly, due to the clinical trial design of the included studies, labeling the injected cells and tracking their migration to the myocardium proved challenging[17]. These factors underscore the potential advantages of administering multiple doses over time. A recent study by Attar *et al*[34] showed that administering repeated MSC doses led to a 4% improvement in LVEF at 6 months compared to a single dose. Although there is no data on a second dose administered after 6 mo for myocardial infarction or heart failure patients, studies have shown that a second dose given 6 months after the first can lead to significant functional improvements in knee osteoarthritis patients compared to a single dose[35,36]. These findings emphasize the potential of repeated MSC doses at various intervals to optimize treatment in cardiac patients, sparking further interest and research. We did not find a significant difference in the adverse cardiac events between the ^{Cryo}MSCs and the control groups, suggesting the clinical safety of the cryopreserved cells. However, the included RCTs lack details regarding the cryopreservation methods, underscoring the need for further research.

Our study results were limited by the relatively small number of RCTs and the small sample size in the included RCTs. Another significant limitation of our study is the absence of RCTs that directly assess the clinical effectiveness of ^{Cryo}MSCs. Given the topic's significance, it is strongly recommended that future clinical studies explore this area further. Hence, there is a pressing need for more extensive RCTs to validate these findings and establish standardized cell preservation protocols. This urgent need for further research underscores the importance of our findings and the potential impact on cardiology and regenerative medicine.

CONCLUSION

In conclusion, our systematic review of the literature's meta-analysis reveals that ^{Cryo}MSCs significantly improved LVEF by an average of 2.11%, with superior outcomes observed when employing ^{Cryo}MSCs with post-thaw viability exceeding 80%. Furthermore, the safety profile of ^{Cryo}MSCs did not show a significant incidence of adverse events compared to the control. This suggests that ^{Cryo}MSCs hold promise as a viable cell product for off-the-shelf use in patients with CVD, offering a positive outlook for the future of this treatment[37]. This promising outlook should encourage further research and development in this area.

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, performed the data extraction and plotted and validated the extracted data, performed the quality assessment of the included trials, and conducted the statistical analysis; Safwan M and Haider KH drafted the first manuscript; Safwan M, Bourgleh MS, and Haider KH reviewed the final manuscript; and all the authors contributed to the final manuscript. All authors have read and agreed to the published version of the manuscript.

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