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REVIEW

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Mid- to long-term efficacy and safety of stem cell therapy for acute myocardial infarction: a systematic review and meta-analysis

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Abstract

Background This comprehensive systematic review and meta-analysis investigated the mid- to long-term efficacy and safety of stem cell therapy in patients with acute myocardial infarction (AMI).

Methods The study encompassed 79 randomized controlled trials with 7103 patients, rendering it the most up-to-date and extensive analysis in this field. This study specifically focused on the impact of stem cell therapy on left ventricular ejection fraction (LVEF), major adverse cardiac events (MACE), and infarct size.

Results Stem cell therapy significantly improved LVEF at 6, 12, 24, and 36 months post-transplantation compared to control values, indicating its potential for long-term cardiac function enhancement. A trend toward reduced MACE occurrence was observed in the intervention groups, suggesting the potential of stem cell therapy to lower the risk of cardiovascular death, reinfarction, and stroke. Significant LVEF improvements were associated with long cell culture durations exceeding 1 week, particularly when combined with high injected cell quantities (at least 10^8 cells). No significant reduction in infarct size was observed.

Conclusions This review highlights the potential of stem cell therapy as a promising therapeutic approach for patients with AMI, offering sustained LVEF improvement and a potential reduction in MACE risk. However, further research is required to optimize cell culture techniques, determine the optimal timing and dosage, and investigate procedural variations to maximize the efficacy and safety of stem cell therapy in this context.

Keywords Cell therapy, Acute myocardial infarction, Systematic review

Background

Despite significant prognostic advancements over the past decade, acute myocardial infarction (AMI) remains a significant contributor to global morbidity and mortality [1]. AMI continues to emerge as the primary driver of heart failure (HF), with a substantial impact on the patient's quality of life and healthcare costs [2]. Thus, emphasizing heart function preservation in patients with AMI is crucial, considering its implications for patient survival and the economic burden associated with HF progression [3].

Existing conventional treatments effectively and temporarily control the disease, underscoring the need for

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innovative methods aimed at preventing and reversing heart dysfunction. Stem cell therapy has significant regenerative potential in addressing the short-term effects of cardiac damage following AMI [4]. Research on this treatment method is ongoing, and although short-term effects (6 months) on cardiac function have been reported [4, 5], long-term evaluations ranging from 18 months to 3 years have yielded inconsistent data on whether cell transplantation improves cardiac function because of the small number of patients recruited in individual studies [6, 7].

It has been reported that there is an effective improvement in cardiac function as the number of injected stem cells increases [8]. However, the administration of a substantial number of stem cells necessitates a significant harvest from either the patient's blood or bone marrow (BM), a task often fraught with difficulty owing to the challenge of securing an adequate quantity of stem cells. In autologous stem cell transplantation, concerted efforts have been made to increase the quantity of stem cells through in vitro cultivation and proliferation. The duration of isolation and culture, and the timing of subsequent administration are also considered to influence stem cell therapy outcomes in patients with AMI [5, 9]. However, there is a lack of clarity regarding the optimal number of cells. Moreover, the effects of therapy and the appropriate length of time for cell culture to enable the injection of a large number of cells have not yet been discussed.

Administering stem cell therapy before complete myocardial damage may be an effective alternative to current treatment methods [10]. However, injecting stem cells too early can increase the procedural risks. Therefore, questions have been raised regarding the optimal time required from primary percutaneous coronary intervention (PCI) to cell infusion to ensure safe and effective treatment.

Traditionally, the primary outcomes used to evaluate the effectiveness of stem cell infusion include left ventricular ejection fraction (LVEF), left ventricle end-diastolic volume, and infarct size. However, these indicators often involve subjective interpretations by evaluators, as is the case with echocardiography, which cannot be eliminated in most studies [11]. Therefore, increasing attention has been paid to major adverse cardiac events (MACEs) as the patient outcomes, with a focus on observable events. A MACE is a composite endpoint event that includes cardiovascular death, reinfarction, and stroke [12]. As a critical composite endpoint, MACE has frequently been used to evaluate the safety and efficacy of treatment strategies in patients with acute coronary syndrome [13]. MACE significantly contributes to the morbidity and mortality of patients with AMI [13].

Through this systematic review, we aim to evaluate the mid- to long-term effectiveness of stem cell therapy in patients with AMI. We also intend to determine the appropriate cell quantity and optimal transplantation time to maximize treatment efficacy while ensuring safety.

Methods

The protocol for this review has been prospectively registered in the PROSPERO systematic review database (CRD42023422818). The protocol was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol checklist. The final report was prepared and submitted according to the Cochrane Handbook for Systematic Reviews of Interventions.

Search strategy

In this systematic review, searches were performed in the following databases: Ovid-MEDLINE, Ovid-EMBASE, Cochrane Library, KoreaMed, KMBASE, KISS, RISS, and DBpia, up to May 11th, 2023, to find relevant studies. The search terms included Medical Subject Headings in the titles and abstracts. We used the following keywords: "myocardial infarction," "ST elevation myocardial infarction," "non-ST elevated myocardial infarction," "angina pectoris," "myocardial ischemia," coronary artery disease," "coronary occlusion," "coronary stenosis," "acute coronary syndrome," "STEMI," "NSTEMI," "stem cells," "bone marrow cells," "mesenchymal stem cells," "mononuclear cells," "mesenchymal stromal cells," "pluripotent stromal cells," "embryonic stromal cells," and "cardiac progenitor cells." We applied the "removes records about animal" and "RCT" filters and English language limitations. Only peer-reviewed studies were included in this analysis.

Study selection criteria

The intervention groups included patients with AMI who underwent PCI and received stem cell therapy by injection into the coronary arteries, myocardium, or veins. Patients with AMI who underwent PCI intervention but did not receive stem cell therapy comprised the control group.

We included the following study types: (1) randomized controlled trials (RCTs); (2) studies including patients diagnosed with AMI as per the International Classification of Diseases, Eleventh Edition, definition (myocardial infarction specified as acute or with a stated duration of 4 weeks [28 days] or fewer from onset) within the specified timeframe; (3) clinical trials in which allogenic or autologous stem cells were transplanted; and (4) studies in which more than one proper clinical outcome (LVEF, MACE, infarct size, etc.) was reported. Studies were

excluded if they were: (1) non-human or pre-clinical studies; (2) non-original articles (systematic reviews, editorials, letters, comments, opinion pieces, reviews, guidelines, notes, news articles, etc.); (3) non-RCT trials; (4) continuous or duplicate studies; or (5) not available with the complete original text.

Study identification was performed by two independent reviewers (HSL and SHL). Any discrepancies and/or disagreements were resolved by discussion with a third reviewer (YJH). We eliminated duplicate studies and conducted a screening based on titles and abstracts. Subsequently, we identified potentially relevant studies and examined their full text. Finally, 79 RCTs were selected for inclusion in the systematic review. Sixty-nine RCTs were included in the meta-analysis.

Data extraction

Data were collected by two reviewers (HSL and YJH) using standardized forms. Data on publication characteristics (year of publication, journal, country, and corresponding author), study populations (eligibility criteria, age, and sex), intervention details (diagnosis, cell type, cell dose, culture period, injection route, time from the onset of myocardial infarction to the first intervention [cell injection], and number of injected cells), study designs (methods, sample size, and follow-up months), and clinical endpoints (efficacy and safety) were recorded.

Outcome measures

Primary outcomes

The primary outcomes of our study were post-treatment efficacy indices, such as LVEF, infarct size, and MACEs, which are defined as composite outcomes of cardiovascular death, and non-fatal myocardial infarction or stroke [12]. In several studies, cardiac function was measured using more than one modality; however, we included only one modality per study for the analysis of LVEF outcomes. If a single study reported LVEF using multiple modalities, we analyzed the data based on echocardiography, which is the commonly used method in most studies. In the absence of echocardiographic results, we analyzed results from magnetic resonance imaging (MRI) followed by single-photon emission computed tomography (SPECT). A subgroup meta-analysis was conducted to identify the differences in results based on the methods (echocardiography, MRI, SPECT, angiography) used to measure efficacy.

A subgroup analysis was conducted to analyze the differences in LVEF improvement based on various stem cell characteristics. The following subgroups were defined by baseline characteristics: (1) whether the cells were cultured, (2) length of time the cells had been cultured, and (3) measurement methods. The cut-off points for the length of time the cells were cultured [14] and the number of injected cells were based on the results of previous cell therapy studies [15, 16].

The secondary outcome was safety, assessed based on the occurrence of adverse events (AEs). We defined procedure-related AEs as complications that occurred during hospitalization in patients receiving stem cell injections. Whereas, non-procedure-related AEs were the events that developed during the follow-up period after hospital discharge for patients receiving stem cell injections. For procedure-related AEs, we analyzed events such as death, obstruction and/or thrombus of the related artery, coronary dissection, coronary spasm, and arrhythmia. We also investigated procedure-related complications associated with BM suppression or granulocyte colony-stimulating factor administration. Safety outcomes during the follow-up period included mortality, rehospitalization, stroke, cancer, and restenosis of the related artery.

Quality assessment

A single reviewer (HSL) assessed the selected studies for quality, and a second reviewer (YJH) confirmed the evaluation using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials. The assessment criteria included random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessments, incomplete outcome data, and selective reporting (Additional file 1).

Statistical analysis

We performed a meta-analysis using Review Manager version 5.4 from the Cochrane Library. Odds ratios (ORs) for dichotomous variables and mean differences and standardized mean differences for continuous variables were computed using a fixed-effects model. Statistical heterogeneity among the selected studies was evaluated using the chi-square test, with a significance level set at $p < 0.10$, and I^2 statistics were used to quantify the degree of heterogeneity.

Results

Search and selection of stem cell studies

We identified 14,912 potentially relevant studies and screened them for eligibility, selecting 121 pertinent stem cell therapy studies for full-text review. Of the 121 studies, 42 were excluded because they did not describe AMI ($n=9$), were not RCTs ($n=19$), were duplicate reports ($n=3$), were irrelevant interventions ($n=10$), or had insufficient outcomes ($n=1$). Finally, 79 RCTs with 7,103 patients were included in the review [11, 14, 17–93] and 69 RCTs were included in the meta-analysis (Fig. 1).

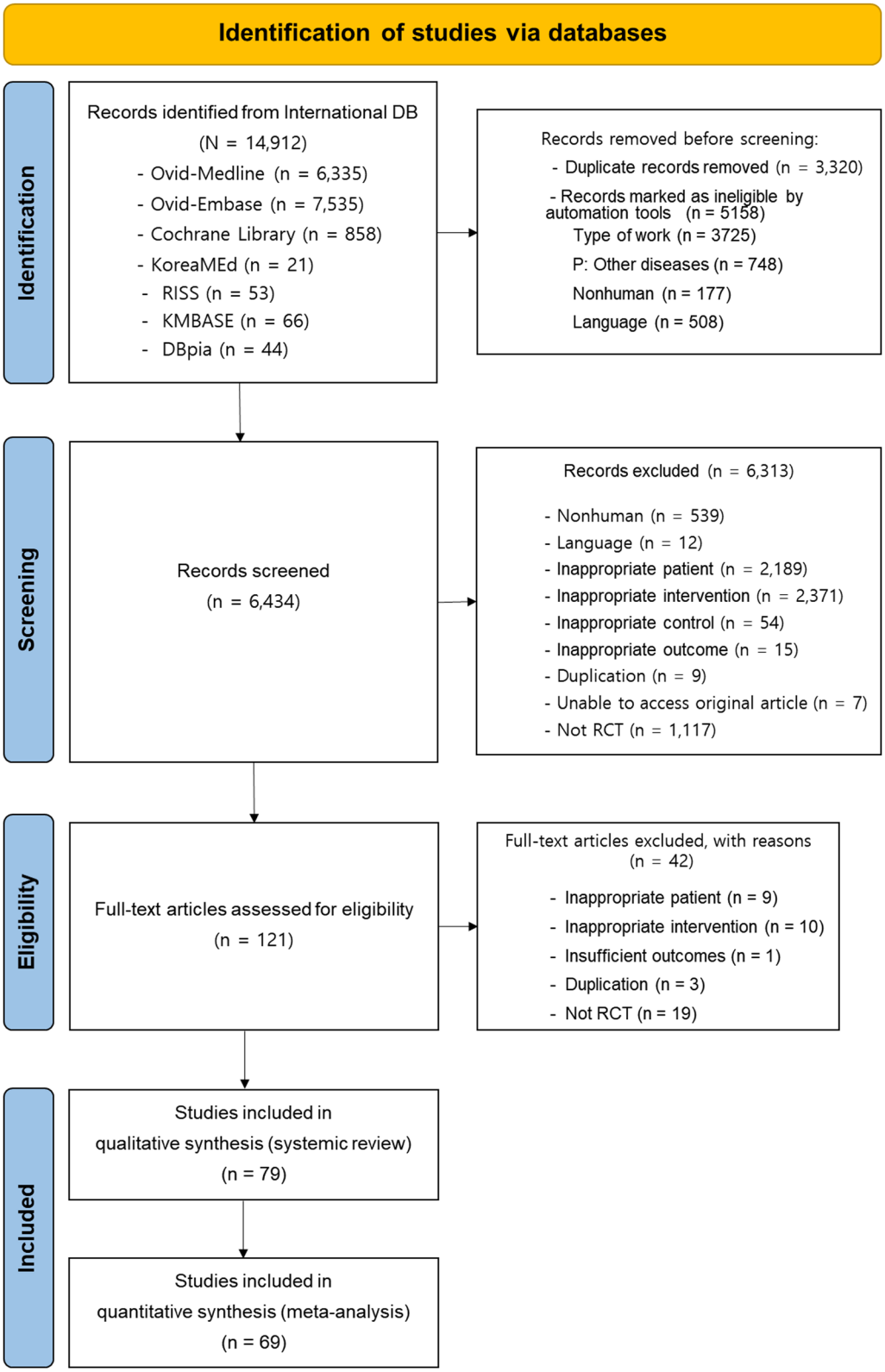


Fig. 1 Flow diagram of the literature selection process. DB, database, RCT, randomized controlled trial

Study characteristics

Table 1 shows the characteristics of all the included studies. The selected studies were published between 2004 and 2022. The study size ranged from 15 to 375 patients, and the follow-up duration ranged from 1 to 60 months. Of the 79 studies, 49 were conducted in Europe, 9 in China, 7 in the USA, 5 in Korea, 3 in Iran, 2 in India, 2 in Brazil, 2 in Pan-Europe, and 1 in Russia. Among the 7103 patients, 4014 received stem cell therapy, and 3,120 were in the control group. Of the 79 studies, 75 used autologous stem cells and 4 used allogeneic stem cells [17–20].

Of the 75 studies using autologous stem cells, 66 used BM cells (BMCs), 3 used granulocyte colony-stimulating factor-mobilized peripheral blood stem cells (PBSCs) via leukapheresis [87–89], and 4 used both BMCs and PBSCs [90–93]. One study used umbilical cord-derived cells [19] and human cardiac stem cells [17]. Most studies used mononuclear cells (MNCs) ($n=63$), and nine studies used mesenchymal stem cells (MSCs) cultured from BM aspirates. Two studies used BM-derived cluster of differentiation (CD)133+cells [55, 56], one study used CD34+and C-X-C chemokine receptor (CXCR)4+cells [73], and one used both CD133+and CD34+cells [68]. Two studies used progenitor cells [53, 67]. Twenty-one studies have conducted cell culture, out of which, thirteen employed cell culture duration exceeding seven days.

Most cell injections ($n=75$) were performed through intra-coronary infusion within 28 days of the primary PCI using the stopped-flow technique. Two studies infused cells intravenously after PCI [18, 20], and two other studies injected cells intramuscularly through the epicardium during coronary artery bypass graft operations [39, 40]. Except for one study [74] where stem cells were infused at 3–7 days and after 3 months, all studies infused a single injection of stem cells. The total numbers of injected cells are listed in Table 1. In 53 studies, cells were injected at quantities equal to or greater than 10^8. The comparisons included standard treatment ($n=40$) and placebo ($n=30$) groups. Seven studies did not report interventions received by the control group.

Left ventricular ejection fraction

Analyses based on a fixed-effects model for differences in LVEF, MACE, and infarct size are shown in Fig. 2. Stem cell therapy for patients with AMI improved LVEF at 6 months (2.91% increase; $p<0.001$), 1 year (2.22% increase; $p<0.001$), 2 years (2.61% increase; $p<0.001$), and 3 years (2.50% increase; $p=0.005$) compared with that in the control group (Fig. 2A–D). One study reporting a 5-year follow-up found no significant difference in LVEF between the intervention and control groups (Fig. 2E). In the subgroup analysis based on cell culture, studies with and without cell culture demonstrated a greater improvement in the intervention group than in the control group at 6 and 12 months of observation (Fig. 2F, G). After 24 months of observation, studies with cell culture showed a significant improvement in the intervention group compared to control values (5.11% increase; $p<0.001$), whereas those without cell culture showed no significant difference (1.28% decrease; $p=0.23$) (Fig. 2H).

This analysis focused on cell culture studies, specifically examining the mean change in LVEF based on the duration of the cell culture. Among the studies with a cell culture period exceeding 1 week, the intervention group showed a significant improvement in LVEF at 6 months (4.32% increase; $p<0.001$), 12 months (1.89% increase; $p<0.001$), and 24 months (5.23% increase; $p<0.001$) (Fig. 2I–K). However, in studies with a cell culture period of 1 week or less, there was a significant improvement only at 6 months (3.38% increase; $p<0.001$), with no significant differences between the intervention and control groups at 12 months (1.40% increase; $p=0.46$) or 24 months (1.96% increase; $p=0.66$).

Cell type-based analyses showed a significant increase in LVEF in the intervention group compared with that of the control group at 6 and 12 months for treatment with MNCs and MSCs (Fig. 2L, M), which were the most commonly used cells. At 6 months, there was a 2.35% ($p<0.001$) and a 4.47% ($p<0.001$) increase in LVEF during MNC and MSC treatments, respectively. However, at 12 months, we observed a 1.87% ($p<0.001$) and a 2.43% ($p=0.001$) increase in LVEF during MNC and MSC treatments, respectively. At 24 months, there was no significant difference in LVEF for MNC treatment ($p=0.29$), whereas a meta-analysis of two studies using MSCs (5.23% increase; $p<0.001$) showed a significant improvement in LVEF in the intervention group compared to that in the control group (Fig. 2N).

Major cardiac adverse events

No significant difference in MACE occurrence was observed between the intervention and control groups at the 6-month observation point (OR 0.78; 95% confidence interval [CI]: 0.46, 1.31; $p=0.34$; Fig. 3A). At the 12-month observation point (OR 0.62; 95% CI 0.38, 1.01; $p=0.05$; Fig. 3B) and between 18 and 36 months (OR 0.63; 95% CI 0.39, 1.02; $p=0.06$; Fig. 3C), the intervention group showed a tendency toward a lower risk of MACE than that shown by the control group. However, at the 60-month observation point (Fig. 3D), there was no significant difference in MACE occurrence between the intervention and control groups (OR 1.00; 95% CI 0.58, 1.72; $p=0.99$).

Table 1 General characteristics of selected studies ($n=79$)

Author	Year of publication	Country	Cell origin	Type of cell	Sample size		Mean age		Sex (Male%)		Control treatment	Route of delivery	Cell dose (10^7)	Culture duration	Injection time (days)	Follow-up duration
					Intervention	Control	Intervention	Control	Intervention	Control						
Allogeneic cultured																
Fernández et al. [17]	2018	Spain	Human CSC		33	16	56 ± 12	55 ± 8	29 (87.9)	16 (100)	Placebo	IC	3.5	5 passages	5–7	6/12
Chullokana et al. [18]	2015	India	BMC	MSC	10	10	47.31 ± 12.10	47.79 ± 6.48	10 (100)	8 (80)	Placebo	IV	0.2/kg	passage 1	2	6/24
Gao et al. [19]	2015	China	WJMSCs		58	58	56.7 ± 1.7	57.3 ± 1.3	51 (87.9)	55 (94.8)	Placebo	IC	0.6	6 passages	5–7	12/24
Hare et al. [20]	2009	USA	BM-hMSC		39	21	59.0 ± 12.3	55.1 ± 10.2	28 (82.4)	15 (78.9)	Placebo	IV	0.05–0.5/kg	30 days	1–10	6
Autologous cultured																
Zhang et al. [14]	2021	China	BMC	MSC	21	22	59.3 ± 9	58.6 ± 11	20 (95.2)	19 (90.5)	Standard	IC	(0.1–0.2)/ml × 2 ml	3 days	< 30	6/12
Kim et al. [21]	2018	Korea	BMC	MSC	14	12	55.3 ± 8.6	57.8 ± 8.9	14 (100)	12 (100)	Standard	IC	7.2 ± 9	25.0 ± 2.4 days	28	6/12
Lamirault et al. [22]	2017	France	BMC	MNC	52	49	56 ± 12	55 ± 11	42 (80.8)	44 (89.8)	Standard	IC	9.8 ± 0.87	14 days	9.3 ± 1.7	12
Manrique et al. [23]	2016	France	BMC	MNC	43	40	55.6 ± 10.5	55.1 ± 12.3	35 (81)	38 (95)	Standard	IC	9.8 ± 0.87	14 days	9.3 ± 1.7	–
Lee et al. [11]	2014	Korea	BMC	MSC	30	28	53.9 ± 10.5	54.2 ± 7.7	27 (90.0)	25 (89.3)	Standard	IC	7.2 ± 9	7–10 days	3.8 ± 1.5 (aspiration) + 7–10 culture	6
Wang et al. [24]	2014	China	BMC	MSC	28	28	58 ± 10.2	56.1 ± 9.8	19 (67.9)	16 (53.3)	Placebo	IC	20	14 days	25	6
Gao et al. [25]	2013	China	BMC	MSC	21	22	55.0 ± 1.6	58.6 ± 2.5	21 (100)	19 (86.4)	Standard	IC	0.308 ± 5.2	14.6 ± 0.7 days	17	6/12/24
Jazi et al. [26]	2012	Iran	BMC	MNC	16	16	48 ± 2.48	45.20 ± 3.16	11 (66)	14 (90)	N/A	IC	246 ± 84	overnight	30	6
Quyyumi et al. [27]	2011	USA	BMC	MNC	15	15	52 (median)	52 (median)	14 (88)	13 (87)	Standard	IC	1	14 days	8.3	6
Roncalli et al. [28]	2011	France	BMC	MNC	52	49	56 ± 12	55 ± 11	42 (80.8)	44 (89.8)	Standard	IC	9.8 ± 0.87	14 days	9.3 ± 1.7	6
Kaminek et al. [29]	2010	Czech	BMC	MNC	37	36	54 ± 9	56 ± 9	32 (86)	32 (89)	Standard	IC	10	overnight	5–9	6/12
Grajek et al. [30]	2010	Poland	BMC	MNC	31	14	49.9 ± 8.4	50.9 ± 9.3	27 (87.1)	12 (85.7)	Placebo	IC	234 ± 12	overnight	5–6	6/12
Meluzín et al. [31]	2008	Czech	BMC	MNC	I1: 20 I2: 20	20	I1: 54 ± 2 I2: 54 ± 2	55 ± 2	I1: 19 (95) I2: 18 (90)	18 (90)	Standard	IC	I1:1 I2:10	overnight	5–9	6/12
Kaminek et al. [32]	2008	Czech	BMC	MNC	31	31	55 ± 8	54 ± 8	26 (84)	28 (90)	Standard	IC	10	overnight	5–9	6

Table 1 (continued)

Author	Year of publication	Country	Cell origin	Type of cell	Sample size		Mean age		Sex (Male%)		Control treatment	Route of delivery	Cell dose (10^7)	Culture duration	Injection time (days)	Follow-up duration
					Intervention	Control	Intervention	Control	Intervention	Control						
Meluzín et al. [33]	2006	Czech	BMC	MNC	I1: 22 I2: 22	22	I1: 55 ± 5 I2: 55 ± 5	55 ± 2	I1: 22 (100) I2: 19 (86)	20 (91)	Standard	IC	I1:1 I2:10	overnight	5–9	–
Ge et al. [34]	2006	China	BMC	MNC	10	10	58 ± 11	59 ± 8	8 (80)	10 (100)	Placebo	IC	4	overnight	24 h	6
Chen et al. [35]	2004	China	BMC	MSC	34	35	58 ± 7	57 ± 5	32 (94.1)	34 (97.1)	Placebo	IC	(800–1000)/ml × 6 ml	7–10 days	18	6
Autologous non-cultured																
Mathur et al. [36]	2022	UK	BMC	MNC	46	39	56.6 ± 9.6	56.3 ± 10.0	39 (84.8)	37 (94.9)	Placebo	IC	5.98	–	< 18 h after primary PCI	60
Mathur et al. [37]	2020	pan-European	BMC	MNC	185	190	59 ± 11	60 ± 11	155 (83.8)	147 (77.4)	Standard	IC	2.5–50 (median 1.4)	–	2–6	24
Yang et al. [38]	2020	China	BMC	MNC	I1: 20 I2: 17 I3: 20	19	I1: 57.0 ± 12.7 I2: 50.1 ± 13.0 I3: 52.9 ± 13.8	51.7 ± 9.1	I1: 18 (90) I2: 15 (88.2) I3: 17 (85.0)	18 (94.7)	Placebo	IC	언급 없음	–	14–28	12
Laguna et al. [39]	2018	Spain	BMC	MNC	8	9	62.63 ± 8.35	64.78 ± 11.48	7 (87.5)	8 (88.9)	Standard	IM	1	–	10–15	12
Naseri et al. [40]	2018	Iran	BMC	MNC	I1: 30 I2: 21	26	I1: 51.45 ± 7.49 I2: 53.14 ± 8.56	55.50 ± 8.54	I1: 27 (90) I2: 19 (90.5)	23 (88.5)	Placebo	IM	I1:56.463 I2:0.819	–	30	18/24
Nicolau et al. [41]	2018	Brazil	BMC	MNC	66	55	59.23 ± 9.44	58.72 ± 9.30	53 (80.30)	45 (81.81)	Placebo	IC	10	–	6–9	6
Traverse et al. [42]	2018	USA	BMC	MNC	58	27	55.9 ± 11.0	56.4 ± 10.4	51 (87.9)	23 (85.2)	Placebo	IC	15	–	3–7	6/12/24
Quyyumi et al. [43]	2017	USA	BMC	MNC	78	83	57.1 ± 10.1	56.4 ± 10.1	66 (85)	66 (80)	Placebo	IC	1.49	–	9–10	6/12/24
Choudry et al. [44]	2016	UK	BMC	MNC	55	45	56.4 ± 10.4	56.7 ± 10.7	46 (83.6)	41 (91.1)	N/A	IC	5.98	–	< 18 h after primary PCI	12
Surder et al. [45]	2016	Switzerland	BMC	MNC	I1: 65 I2: 63	55	I1: 55 ± 15 I2: 62 ± 15	56 ± 14.5	I1: 56 (86.2) I2: 52 (82.5)	46 (83.6)	Standard	IC	5–50	–	I1: 5–7 I2: 3–4 weeks	6/12
Nair et al. [46]	2015	India	BMC	MNC	125	125	48.07 ± 9.68	48.98 ± 9.76	111 (88.8)	109 (87.2)	Standard	IC	55.8 (median)	–	7–21 (median 15)	6
San Roman et al. [47]	2015	Spain	BMC	MNC	I1: 30 I2: 30 I3: 29	31	I1: 54 ± 11 I2: 57 ± 9 I3: 56 ± 8	57 ± 11	I1: 29 (97) I2: 25 (83) I3: 25 (86)	28 (90)	Standard	IC	0.5/ml × (3–6) ml	–	4–6	12
Assmus et al. [48]	2014	Germany	BMC	MNC	101	103	55 ± 11	57 ± 11	83 (82)	84 (82)	Placebo	IC	0.1	–	4	60
Surder et al. [49]	2013	Switzerland	BMC	MNC	I1: 65 I2: 63	67	I1: 55 ± 15 I2: 62 ± 15	56 ± 14.5	I1: 56 (86.2) I2: 52 (82.5)	56 (83.6)	Standard	IC	5–50	–	I1: 5–7 I2: 3-4 weeks	4
Wöhrle et al. [50]	2013	Germany	BMC	MNC	29	13	61.0 ± 8.1	61.1 ± 9.3	26(90)	8 (62)	Placebo	IC	32.4	–	7	6/12/24/36

Table 1 (continued)

Author	Year of publication	Country	Cell origin	Type of cell	Sample size		Mean age		Sex (Male%)		Control treatment	Route of delivery	Cell dose (10^7)	Culture duration	Injection time (days)	Follow-up duration
					Intervention	Control	Intervention	Control	Intervention	Control						
Skalicka et al. [51]	2012	Czech	BMC	MNC	17	10	61 ± 14	54 ± 10	12 (71)	10 (100)	N/A	IC	264	–	4–11 after PCI	6/24
Traverse et al. [52]	2012	USA	BMC	MNC	79	41	56.9 ± 11.05	57 ± 10.2	69 (87.3)	36 (87.8)	Placebo	IC	15	–	3–7	6
Turan et al. [53]	2012	Germany	BMC	progenitor cell	42	20	61 ± 15	60 ± 11	28 (66.7)	14 (70)	Standard	IC	9.6 ± 3.2/ml × (3–5)ml	–	7	12
Beitnes et al. [54]	2011	Norway	BMC	MNC	48	49	61.2 ± 8.4	59.7 ± 9.8	42 (87.5)	42 (85.7)	Standard	IC	6.8	–	4–7	–
Colombo et al. [55]	2011	Italy	BMC	MNC (CD133 +)	I1: 5 I2: 5	5	I1: 53.75 ± 3.65 I2: 48.75 ± 9.48	53.5 ± 3.93	I1: 5 (100) I2: 4 (80)	5 (100)	Standard	IC	0.49–1.35	–	10–14	12
Mansour et al. [56]	2011	Iran	BMC	MNC (CD133 +)	20	20	51 ± 5	57 ± 4	18 (95)	16 (87)	Placebo	IC	0.15–3.36	–	3–7 after PCI (11.6 +− 1.4 after the infarction)	12
Miettinen et al. [57]	2011	Finland	BMC	MNC	40	40	60 ± 10	59 ± 10	36 (90)	34 (85)	Placebo	IC	40.2 ± 19.6	–	2–6	–
Plewka et al. [58]	2011	Poland	BMC	MNC	40	20	56 ± 9	56 ± 9	27 (67.5)	15 (75)	Standard	IC	14.4 ± 4.9	–	7 (3–11)	24
Traverse et al. [59]	2011	USA	BMC	MNC	58	29	57.6 ± 11	54.6 ± 11	46 (79.3)	26 (89.7)	N/A	IC	14.7 ± 1.7	–	2–3 weeks	6
Assmus et al. [60]	2010	Germany	BMC	MNC	101	103	55 ± 11	57 ± 11	83 (82)	84 (82)	Placebo	IC	0.1	–	4	24
Piepoli et al. [61]	2010	Italy	BMC	MNC	19	19	63.1 ± 2.4	67.0 ± 2.7	13 (68.4)	13 (68.4)	Standard	IC	41.8	–	4–7	12
Schaefer et al. [62]	2010	Germany	BMC	MNC	28	28	53 ± 14.8	59.2 ± 13.5	19 (67)	22 (73)	Standard	IC	2500 ± 200	–	4.8	6
Wöhrle et al. [63]	2010	Germany	BMC	MNC	29	13	61 ± 8.1	61.1 ± 9.3	26 (89.7)	8 (61.5)	Placebo	IC	38.1 ± 13	–	5–7	6
Beitnes et al. [64]	2009	Norway	BMC	MNC	50	50	58.1 ± 9.6	56.7 ± 9.6	42 (84)	42 (84)	Standard	IC	6.8	–	4–7	6/12/36
Cao et al. [65]	2009	USA	BMC	MNC	41	45	50.7 ± 1.1	51.0 ± 1.0	39 (95.1)	42 (93.3)	Placebo	IC	12.5 (5 ± 12/ml)	–	7	6/12/48
Dill et al. [66]	2009	Germany	BMC	MNC	27	27	57.9 ± 10.7	54.6 ± 11.4	24 (88.9)	25 (92.6)	Placebo	IC	0.1	–	4	6/12
Herbots et al. [67]	2009	Belgium	BMC	progenitor cell	33	34	55 ± 11	58 ± 10	27 (81.8)	28 (82.4)	Placebo	IC	30.4 ± 12.8 (nucle-- ated) + 17.2 ± 7.2 (MNC)	–	1	6
Lipiec et al. [68]	2009	Poland	BMC	MNC (CD34 +, CD133 +)	26	10	57 ± 9	59 ± 9	18 (69.2)	7 (70)	Standard	IC	0.369	–	4–11	6

Table 1 (continued)

Author	Year of publication	Country	Cell origin	Type of cell	Sample size		Mean age		Sex (Male%)		Control treatment	Route of delivery	Cell dose (10^7)	Culture duration	Injection time (days)	Follow-up duration
					Intervention	Control	Intervention	Control	Intervention	Control						
Meyer et al. [69]	2009	Germany	BMC	MNC	30	30	53 ± 14.8	59.2 ± 13.5	20 (67)	22 (73)	Standard	IC	2500 ± 200	–	4.8	6/24/60
Nogueira et al. [70]	2009	Brazil	BMC	MNC	I1: 14 I2: 10	6	I1: 59.7 ± 14.3 I2: 53.6 ± 8.3	57.2 ± 10.8	I1: 10 (71) I2: 7 (70)	4 (67)	Standard	IC	10	–	I1: 5.5 ± 1.28 I2: 6.1 ± 1.37	6
Plewka et al. [71]	2009	Poland	BMC	MNC	38	18	56 ± 9	56 ± 8	26 (68.4)	14 (77.8)	Standard	IC	14.4 ± 4.9	–	7 (3–11)	6
Schächinger et al. [72]	2009	Germany	BMC	MNC	95	92	55 ± 12	57 ± 11	77 (81)	78 (85)	Placebo	IC	0.1	–	4	–
Tendera et al. [73]	2009	Poland	BMC	MNC (CD34 +, CDCR4 +)	I1: 80 I2: 80	40	I1: 55 (37–74) I2: 58 (30–75)	59 (37–73)	I1: 56 (70.6) I2: 51 (63.7)	30 (75)	N/A	IC	17.8	–	7 (3–12)	6
Yao etal. [74]	2009	China	BMC	MNC	I1: 12 I2: 15	12	I1: 52.1 ± 6.3 I2: 51.3 ± 7.4	52.7 ± 7.8	I1: 10 (83.3) I2: 12 (80)	11 (91.7)	Placebo	IC	19 ± 13	–	3–7	6/12
Huikuri et al. [75]	2008	Finland	BMC	MNC	40	40	60 ± 10	59 ± 10	90 (36)	34 (85)	Placebo	IC	40.2 ± 19.6	–	2–6	6
Lunde et al. [76]	2007	Norway	BMC	MNC	50	50	58.1 ± 9.6	56.7 ± 9.6	42 (84)	42 (84)	Standard	IC	0.68	–	4–7	–
Suárez et al. [77]	2007	Spain	BMC	MNC	10	10	52 ± 12	55 ± 11	8 (80)	7 (70)	Standard	IC	90 ± 30	–	5–12	6
Janssens et al. [78]	2006	Belgium	BMC	MNC	33	34	55.8 ± 11	57.9 ± 10	27 (82)	28 (82)	Placebo	IC	17.2 ± 7.2	–	–	6
Lunde et al. [79]	2006	Norway	BMC	MNC	50	50	58.1 ± 8.5	56.7 ± 9.6	42 (84)	42 (84)	Standard	IC	6.8	–	6	6
Meyer et al. [80]	2006	Germany	BMC	MNC	30	30	53 ± 14.8	59.2 ± 13.5	20 (67)	22 (73)	Standard	IC	2500 ± 200	–	4.8	18/24
Schächinger et al. [81]	2006	Germany	BMC	MNC	101	103	55 ± 11	57 ± 11	83 (82)	84 (82	Placebo	IC	23.6 ± 17.4	–	3–7	6
Schächinger et al. [82]	2006	Germany	BMC	MNC	101	103	55 ± 11	57 ± 11	83 (82)	84 (82)	Placebo	IC	0.1	–	4	12
Schaefer et al. [83]	2006	Germany	BMC	MNC	30	29	53 ± 14.8	59 ± 3	20 (67)	21 (71)	Standard	IC	2500 ± 200	–	4.8	–
Karpov et al. [84]	2005	Russia	BMC	MNC	22	22	55.2 ± 8.6	52.1 ± 9.2	20 (90)	16 (73)	N/A	IC	8.85 ± 4.92	–	7–21	–
Ruan et al. [85]	2005	China	BMC	MNC	9	11	61 ± 8	58 ± 6	8 (88.9)	11 (100)	Placebo	IC	언급없음	–	–	6
Wollert et al. [86]	2004	Germany	BMC	MNC	30	30	53 ± 14.8	59.2 ± 13.5	20 (67)	22 (73)	Standard	IC	2500 ± 200	–	4.8	6

Table 1 (continued)

Author	Year of publication	Country	Cell origin	Type of cell	Sample size		Mean age		Sex (Male%)		Control treatment	Route of delivery	Cell dose (10^7)	Culture duration	Injection time (days)	Follow-up duration
					Intervention	Control	Intervention	Control	Intervention	Control						
Kang et al. [87]	2012	Korea	PBSC	MNC	57	60	57.5 ± 10.9	57.5 ± 11.9	48 (84)	43 (72)	Standard	IC	110 ± 5	–	< 14	6/24
Chang et al. [88]	2008	Korea	PBSC	MNC	20	20	56.6 ± 13.1	57.1 ± 11.9	17 (85)	16 (80)	Standard	IC	100–200	–	< 14	6
Kang et al. [89]	2006	Korea	PBSC	MNC	50	25	60.6 ± 10.6	59.4 ± 12.3	20 (80)	20 (80)	Standard	IC	140 ± 5	–	< 14	6
Delewi et al. [90]	2015	Nether-lands	BMC, PBSC	MNC	I1: 69 I2: 66	65	I1: 56 ± 9 I2: 57 ± 9	55 ± 10	I1: 58 (84) I2: 56 (85)	56 (86)	Standard	IC	29.6 ± 16.4	–	3–8	6/24
Robbers et al. [91]	2014	Nether-lands	BMC, PBSC	MNC	I1: 52 I2: 47	45	I1: 56 ± 9 I2: 56 ± 9	54 ± 10	I1: 44 (85) I2: 47 (85)	40 (89)	N/A	IC	29.6 ± 16.4	–	3–8	–
Hirsch et al. [92]	2011	Nether-lands	BMC, PBSC	MNC	I1: 69 I2: 66	65	I1: 56 ± 9 I2: 57 ± 9	55 ± 10	I1: 58 (84) I2: 56 (85)	56 (86)	N/A	IC	29.6 ± 16.4	–	3–8	6
van der Laan et al. [93]	2011	Nether-lands	BMC, PBSC	MNC	I1: 23 I2: 18	19	I1: 55.2 ± 8.8 I2: 54.6 ± 11.0	54.2 ± 7.4	I1: 19 (83) I2: 14 (78)	17 (90)	Standard	IC	I1:29.1 ± 17.3 I2:28.8 ± 9.1	–	3–8	–

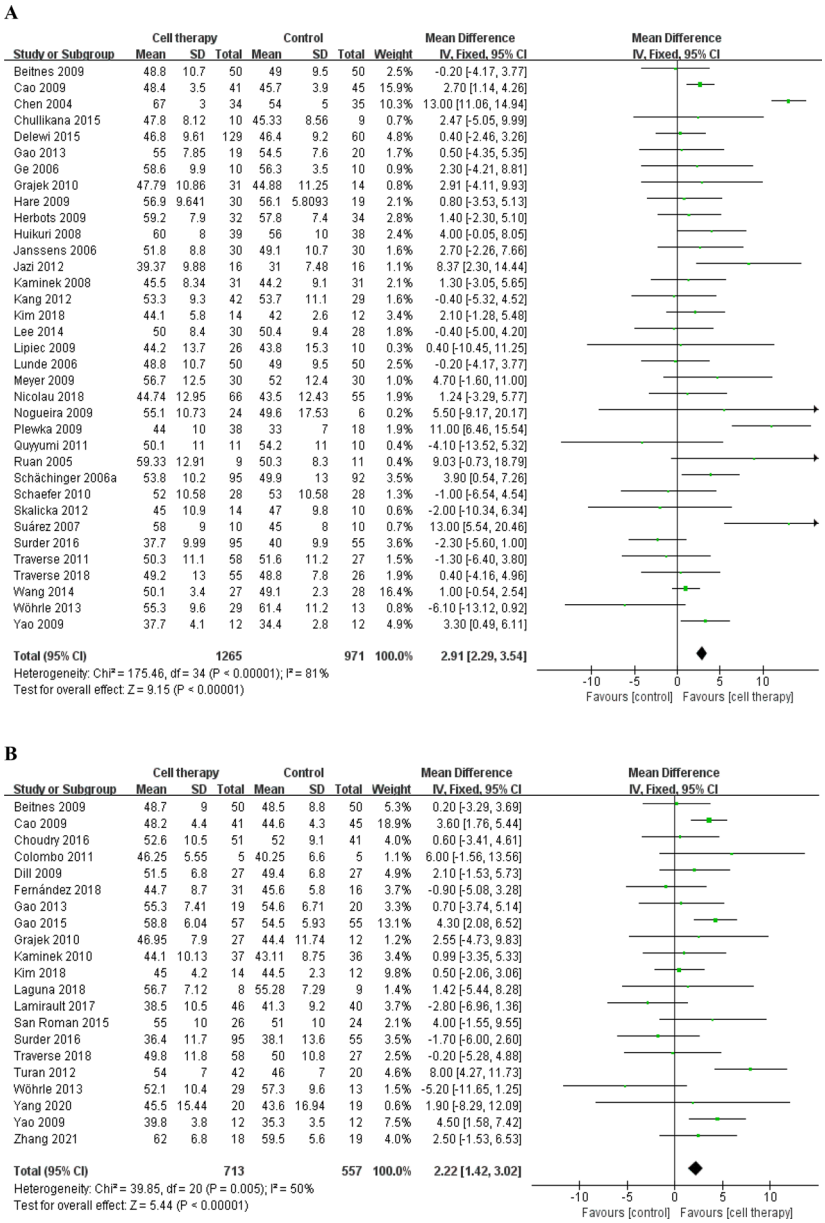
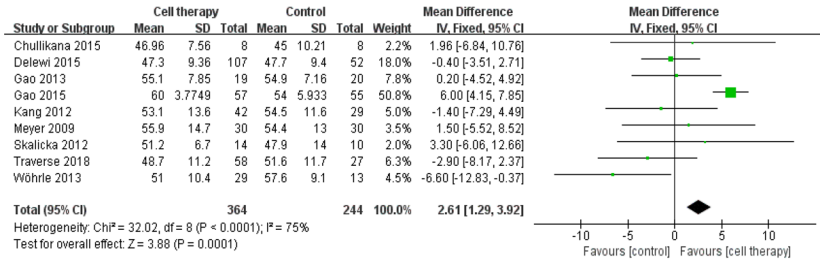


Fig. 2 Forest plots of left ventricular ejection fraction (LVEF) improvement. **A–E** Forest plots for LVEF at the **A** 6-, **B** 12-, **C** 24-, **D** 36-, and **E** 60-month follow-ups. **F–H** Subgroup comparisons of LVEF between the cultured cell therapy and non-cultured cell therapy groups at the **F** 6-, **G** 12-, and **H** 24-month follow-ups. **I–K** Subgroup analyses of LVEF based on the length of cell culture time at the **I** 6-, **J** 12-, and **K** 24-month follow-ups. **L–N** Subgroup comparisons of LVEF between patients treated with mononuclear cells (MNCs) and mesenchymal stem cells (MSCs) at the **L** 6-, **M** 12-, and **N** 24-month follow-ups

Risk analysis of MACE, according to cell type, showed no significant difference between the intervention group and the control group at 6 months for either MNC (OR 0.58; 95% CI 0.30, 1.13; $p=0.11$) or MSC (OR 1.23; 95% CI 0.52, 2.91; $p=0.63$; Fig. 3E) treatment. At 12 months and between 18 and 36 months, the intervention group that received MNCs showed a significantly lower MACE risk than the control group (12 months OR 0.57; 95% CI 0.34, 0.97; $p=0.04$) (18 and 36 months OR 0.61; 95% CI 0.37, 0.98; $p=0.04$; Fig. 3F); whereas the group that received MSCs showed no significant difference in MACE risk from the control group (12 months OR 1.05; 95% CI 0.25, 4.36; $p=0.95$) (18 and 36 months OR 3.15; 95% CI 0.12, 81.74; $p=0.49$; Fig. 3G).

The occurrence of AEs related to stem cell injection resulted in one death each in three studies [19, 27, 82];

C



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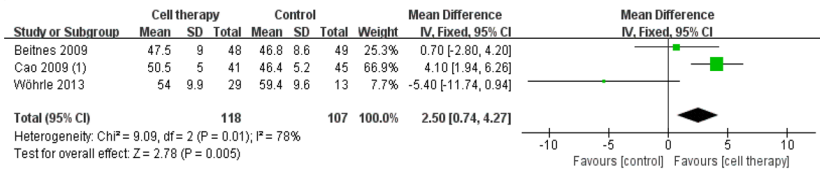
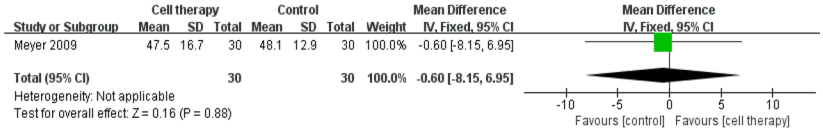


Footnotes
(1) 48 months f/u

E



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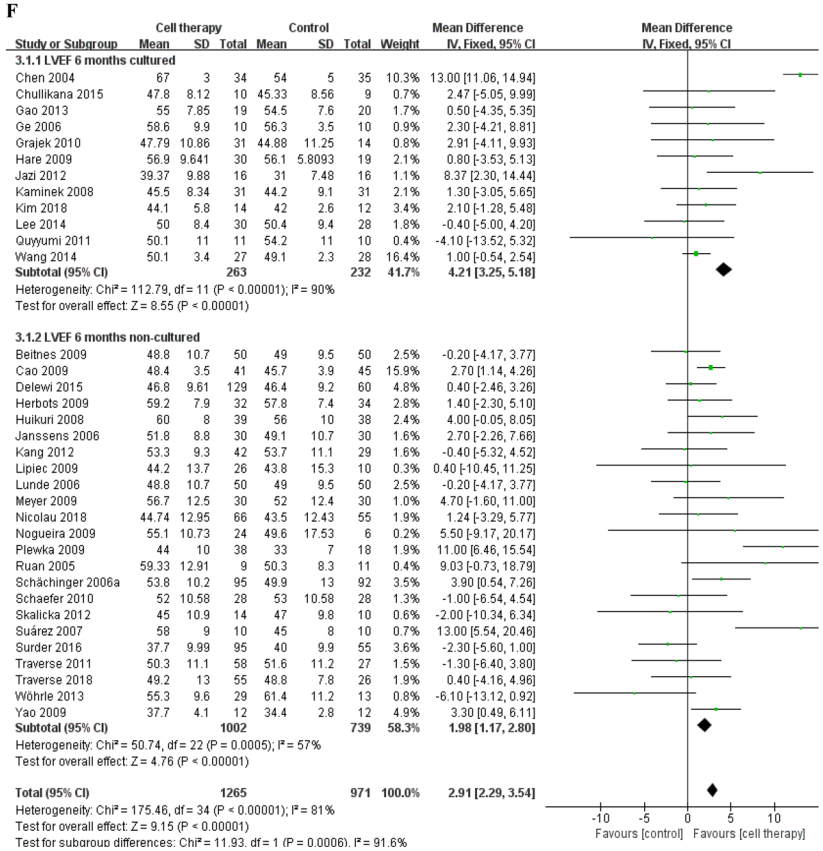

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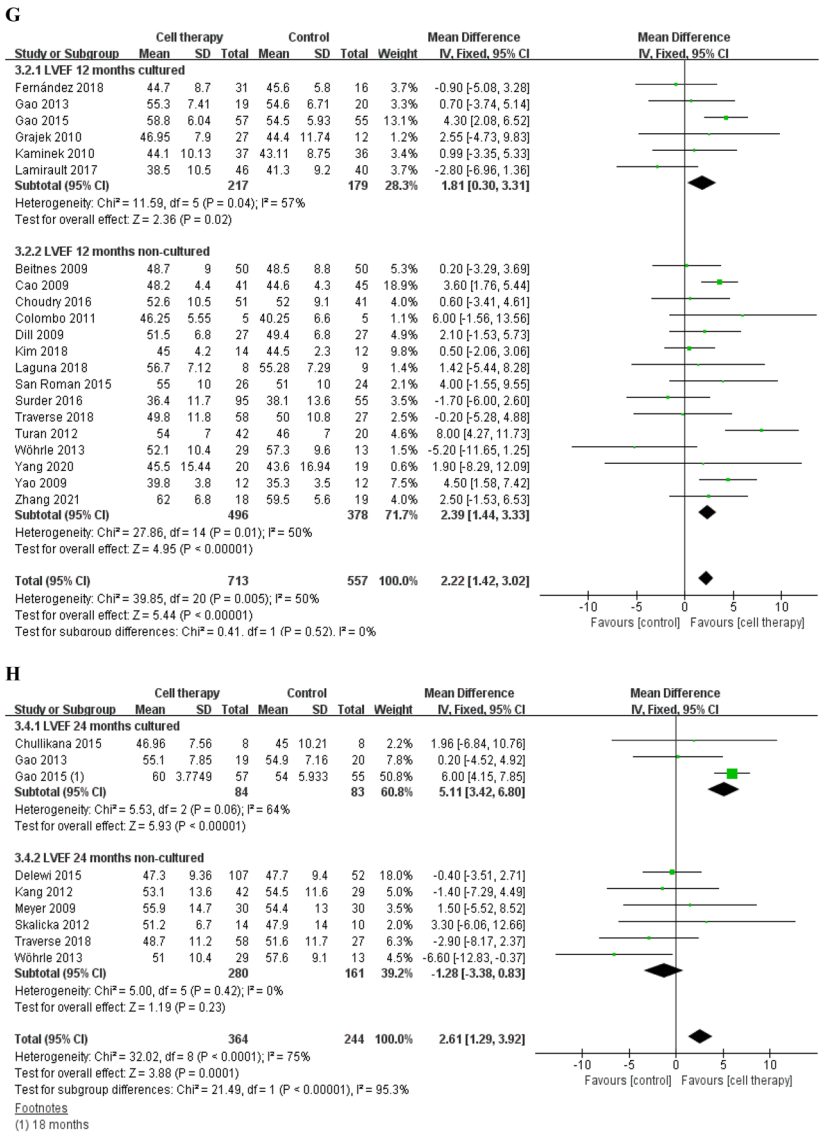

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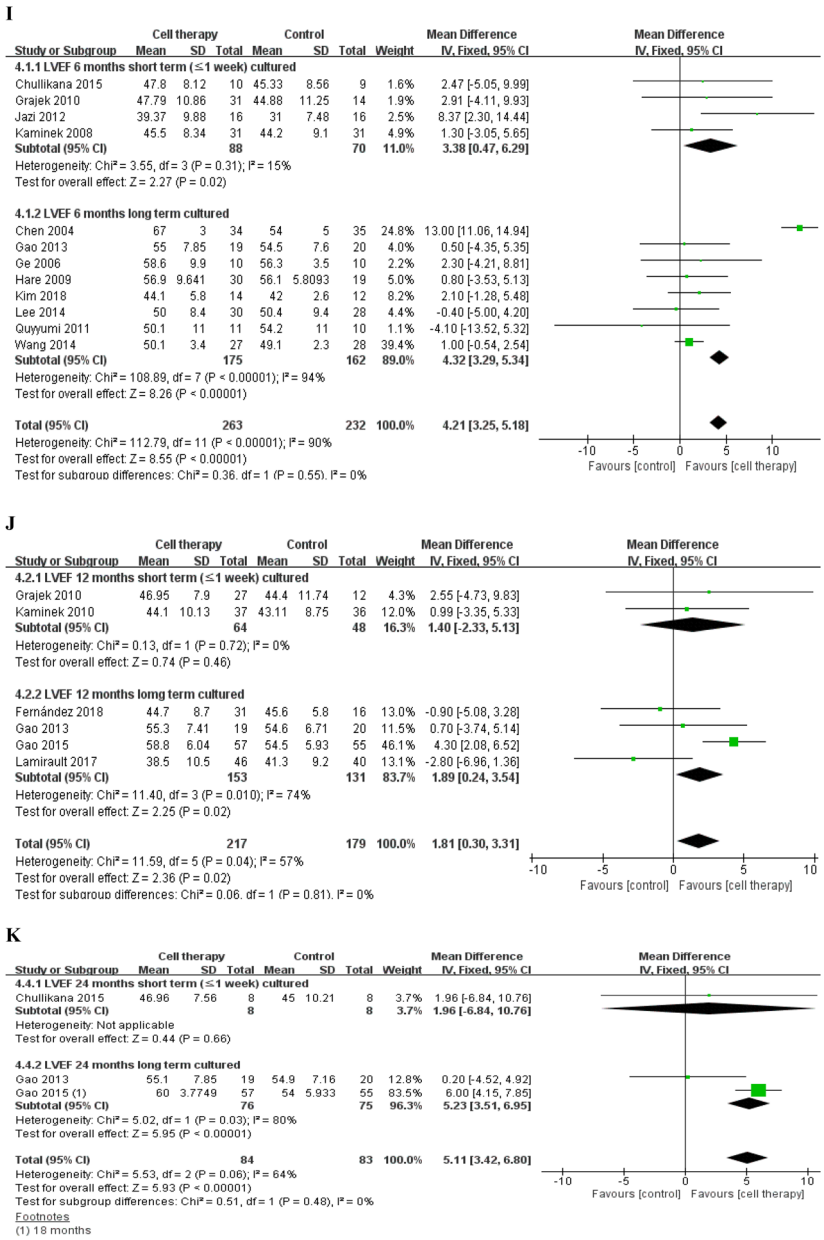
however, there were either no controls or no significant differences from the control group in AE occurrence. Additionally, cases of coronary artery restenosis, thrombosis, and coronary artery dissection were reported, but all were successfully treated.

Infarct size

Infarct size after stem cell therapy in patients with AMI showed no significant difference between the intervention and control groups at the 6-month (−0.02; 95% CI −0.14, 0.10; $p=0.75$; Fig. 4A), 1-year (−0.29; 95% CI −0.29, 0.06; $p=0.19$; Fig. 4B), 2-year (0.12; 95% CI, −0.26, 0.50; $p=0.53$; Fig. 4C), and 3–4-year observation points (0.01; 95% CI, −0.44, 0.46; $p=0.95$; Fig. 4D).

Discussion

This systematic review included 79 RCTs that investigated stem cell therapy in patients with AMI. Our work is the most recent and comprehensive systematic review. Additionally, this is the only study that has conducted an analysis based on the duration of cell culture and discusses the adequacy of infused cell counts and the appropriate timing of stem cell injection. The major finding of this study is the enhancement of LVEF in patients undergoing stem cell therapy, as compared to the control group, at 6 and 12 months, and 24 and 36 months durations. Additionally, the intervention groups undergoing stem cell transplantation had a lower MACE risk as compared to the control groups. Moreover, significant



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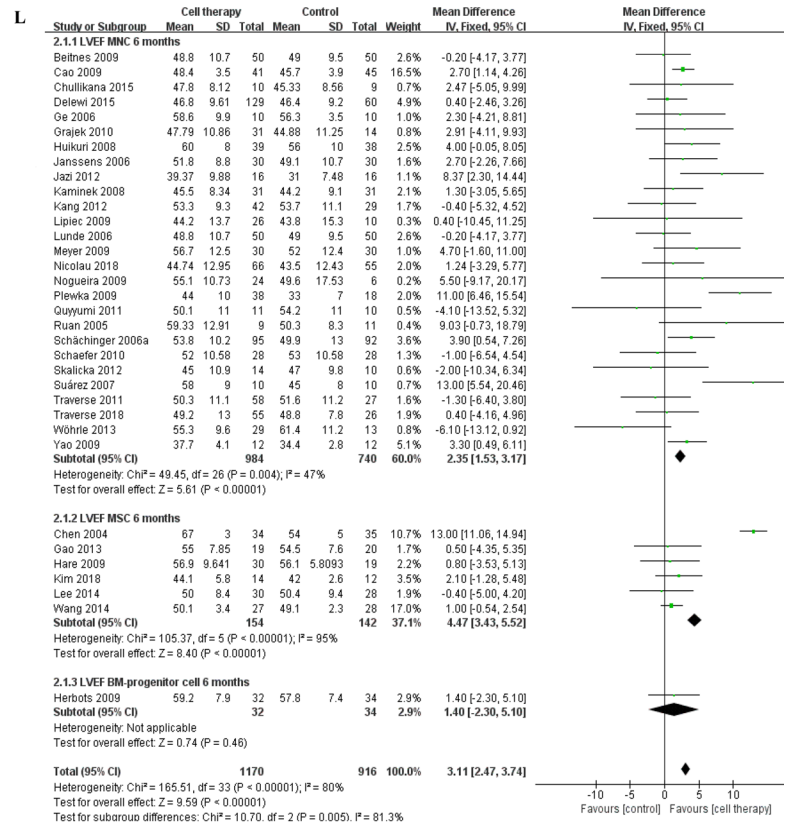
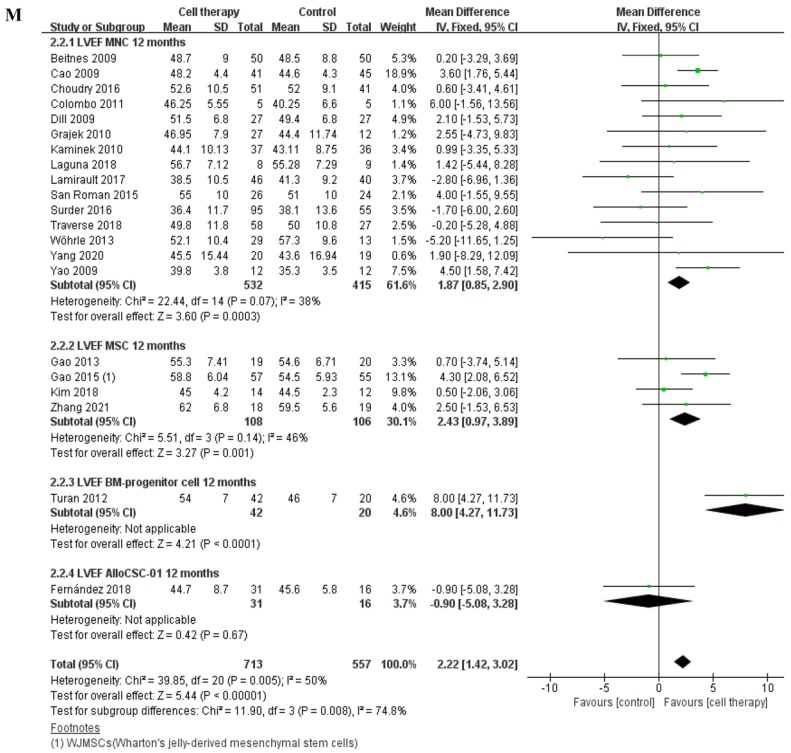
enhancements in LVEF were observed in studies employing cell culture, especially when the culture duration exceeded 1 week and the cell quantity of at least 10^8 was administered.

Mid- to long-term improvement in LVEF with stem cell therapy

We found that the intervention group showed modest improvements in LVEF at 6, 12, 24, and 36 months compared to the control group. Additionally, these improvements were more pronounced in patients receiving MSC injections. Previous systematic reviews have reported only the short-term (approximately 6 and 12 months) effectiveness of stem cell therapy. The studies evaluating patients from 18 months to 3 years are limited, resulting in inconsistent data on whether cell transplantation improves cardiac function [4, 6]. The current systematic review indicates that the effect of stem cell therapy on LVEF in patients with AMI may last up to 3 years. However, the effects at 5 years remain unclear as a limited number of studies report the follow-up results up to 5 years after stem cell injection.





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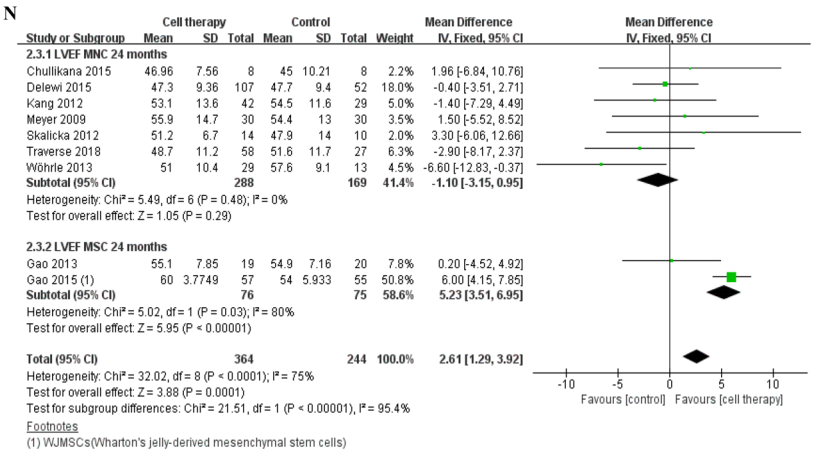

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In contrast to the improvement in LVEF, the reduction in infarct size showed no significant difference between the intervention and control groups in the observed 6- to 48-month period, indicating unclear recovery of the infarcted area in AMI with stem cell injection. The improvements in LVEF and lack of improvements in infarct size are consistent with the findings of previous systematic reviews [4]. The observed improvement in infarct-related regional wall motion abnormalities did not correspond to a significant change in infarct size, rendering this discrepancy difficult to explain. Infarct size measurement involves various modalities, such as MRI, echocardiography, and SPECT, leading to limitations owing to the lack of consistency in measurement techniques.

Potential role of stem cell therapy in reducing MACE risk

Our systematic review revealed a trend toward fewer MACEs in the intervention group than in the control group at 12 ($p=0.05$) and 18–36 months ($p=0.06$) after stem cell transplantation. In recent years, there has been significant emphasis on reporting MACEs as objective clinical outcomes in patients with heart disease. However, there is a notable scarcity of systematic reviews reporting MACEs as indicators of the efficacy or safety of stem cell transplantation for patients with AMI. Few studies have reported a reduction in MACE incidence after stem cell therapy. This could be attributed to the low incidence of MACEs in intervention groups when compared with that in the well-treated control groups receiving standard therapy that is highly effective. Another possibility is that patients with severe AMI might not have been recruited for stem cell therapy. Considering these points, although not statistically significant, the observed trends in cardiovascular death, non-fatal reinfarction, and non-fatal stroke are noteworthy given the difficulty in demonstrating improvement with cell therapy [7]. Thus, comprehensive analyses that integrate the results from additional studies are necessary to ascertain the true efficacy of cell-based treatments. When analyzed by cell type, the intervention group that received MNCs showed a significant reduction in MACE occurrence compared to the control group at 12 and 18–36 months. However, studies involving MSC injections did not show a significant difference in MACE risk between intervention and control groups. Due to the limited number of studies and MACE occurrences in MSC therapy research, it is difficult to conclude the incidence of MACEs in patients receiving MSC injections based on this meta-analysis. Further research is needed to validate these findings and provide more robust evidence for the effectiveness of stem cell transplantation in reducing MACE risk in patients with AMI.

Although reports of mortality and recurrent myocardial infarction within the hospitalization period exist for patients with AMI who received stem cell injections, no significant difference in frequency was found compared with that in the control group. Moreover, the reported rates of in-hospital mortality after PCI in previous studies ranged from 0.53 to 2.0% [94, 95], and the myocardial infarction recurrence rate was 0.7% [96], which was not significantly higher than control values, indicating relative safety. Most studies analyzed in this systematic review employed intra-coronary stem cell injection. In terms of complications, intra-coronary stem cell injection is generally considered safer than direct cell injection into the myocardium (trans-endocardial or trans-epicardial cell injection) [97].

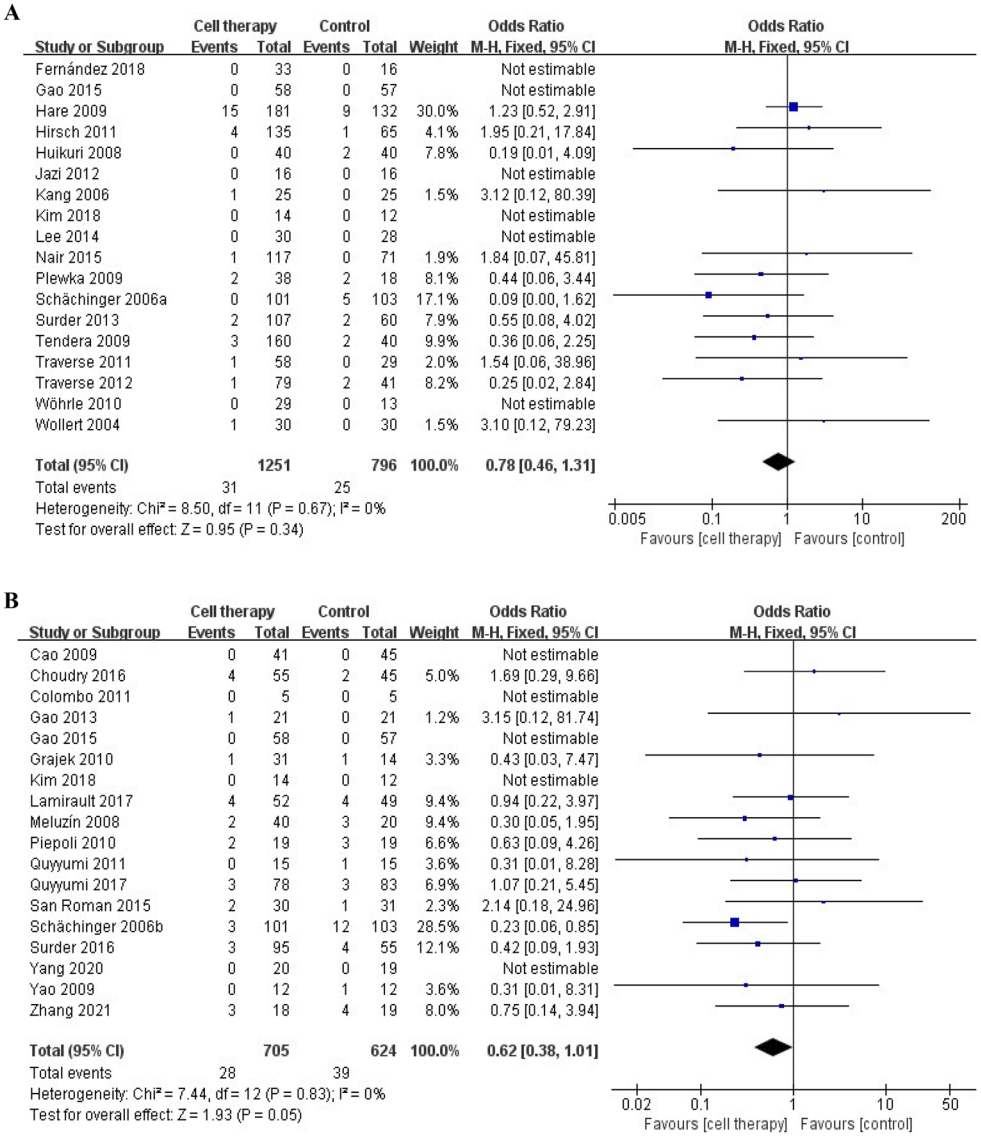
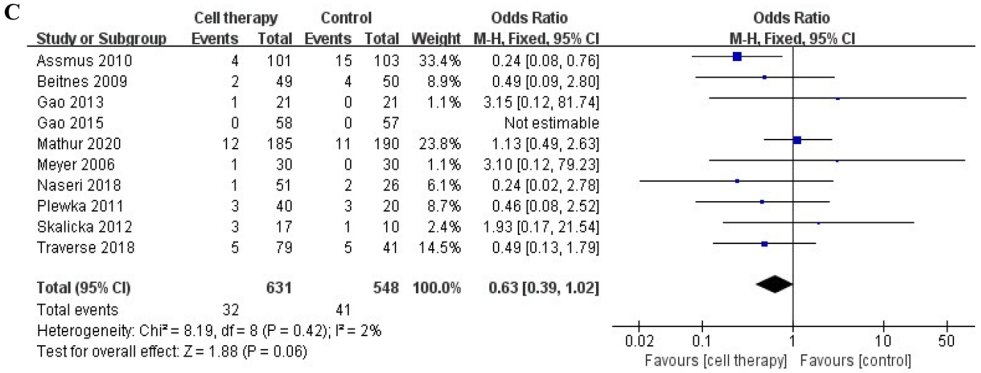


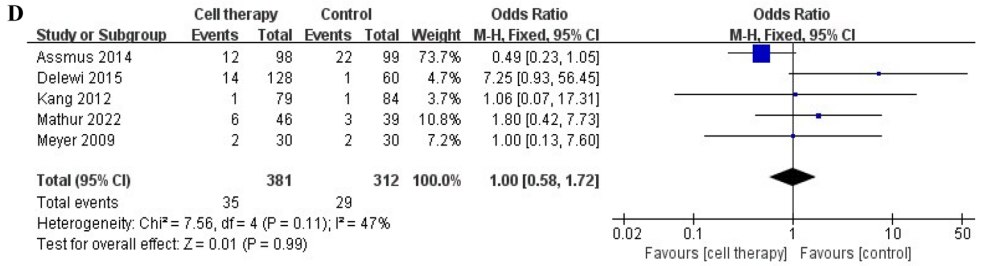
Fig. 3 Forest plots of major adverse cardiac events (MACEs). **A–D** Forest plots for MACE occurrence at the 6-, **B** 12-, **C** 18-, 24-, 36-, and **D** 60-month follow-ups. **E–G** Subgroup analyses of MACE occurrence between patients treated with mononuclear cells (MNCs) and mesenchymal stem cells (MSCs) at the **(E)** 6-, **F** 12-, and **G** 24-month follow-ups

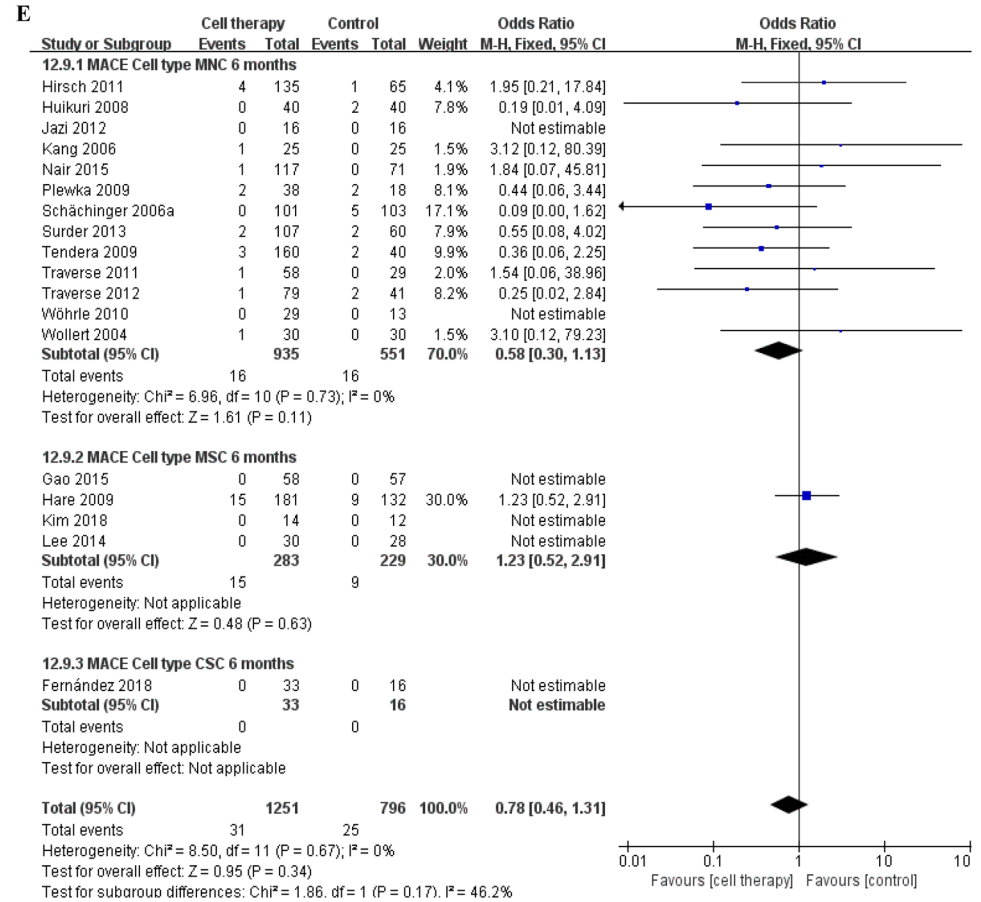
Role of cell culture in increasing cell numbers and appropriate number of injected stem cells

In this study, a subgroup analysis was conducted by distinguishing studies that did and did not perform cell culture, demonstrating a significant improvement in LVEF during the mid-term period (12–24 months) in patients when cell culture was performed. Furthermore, the analysis of various studies with cell culture periods of less than 1 week and those exceeding 1 week revealed a significant improvement in LVEF during the mid-term period (12–24 months) in studies with a culture period exceeding 1 week. To our knowledge, few studies have analyzed the effects of cell therapy on cardiac function improvement considering whether cell culture was conducted and for how long. The results of this systematic review suggest that enhancing the purity of injected cells has a positive impact on the preservation or recovery of cardiac function. Therefore, we hypothesize that achieving a homogeneous cell population through culture may enhance therapeutic efficacy.

Ensuring an adequate number of selected cells is important to ensure the sufficient recovery of cardiac function. Therefore, recent research on cell therapy for myocardial infarction treatment has also focused on using selected







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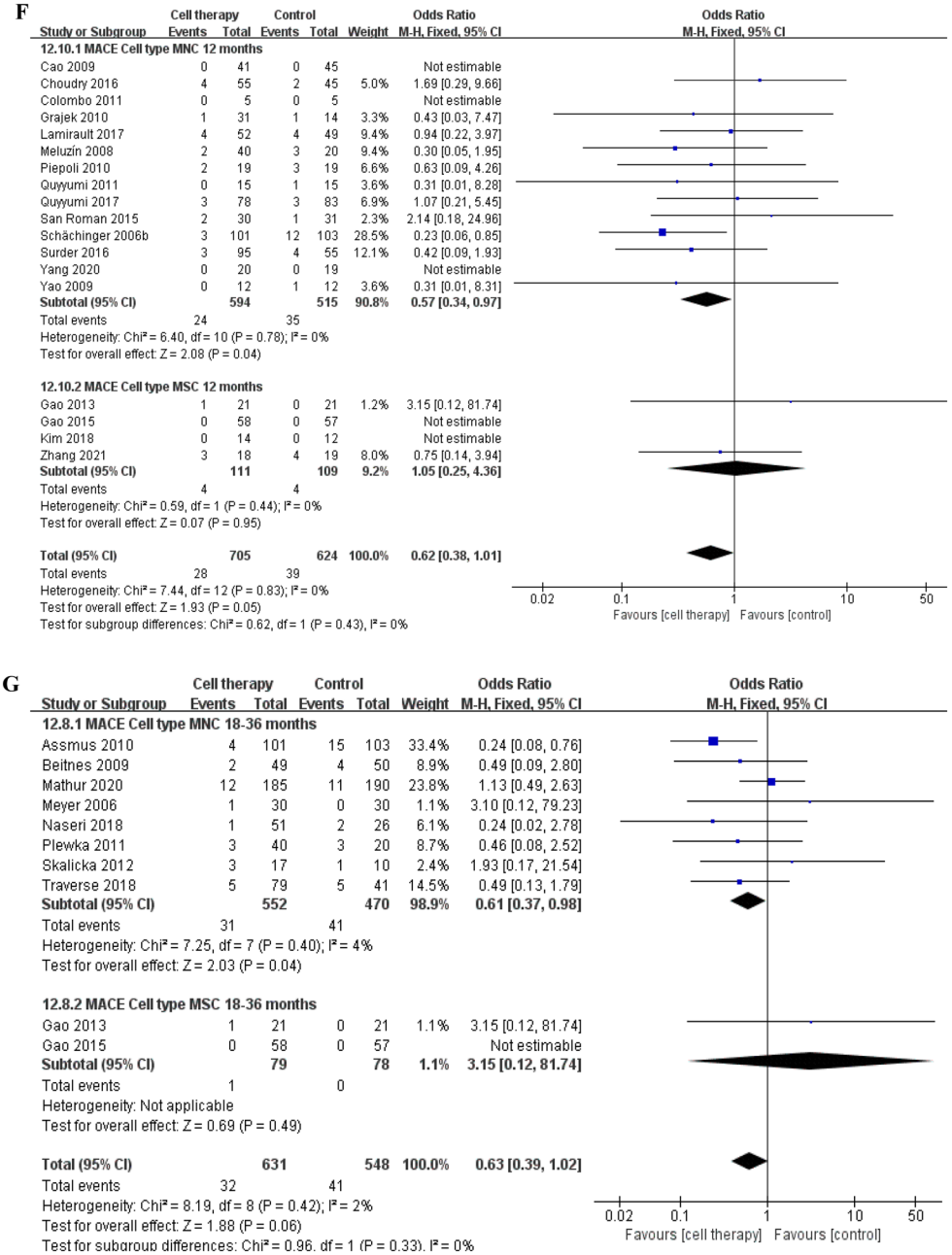

Fig. 3 continued

cell products such as MSCs and CD34+cells rather than BM-MNCs [7]. Although it is important to conduct cell processing and isolation effectively, increasing the number of cells may also be necessary. Therefore, in the context of autologous stem cell transplantation, efforts have been made to increase the number of stem cells selected through in vitro cultivation and proliferation.

A systematic review comprising 40 randomized controlled trials reported a significant increase in LVEF when the BMC dosage exceeded 10^8 cells [6]. Another systematic review analyzing 41 RCTs also concluded that the mortality risk was reduced in patients who received $>10^8$ to $\leq 10^9$ cells [8], similar to our study findings. Given the hostile environment of AMI, higher doses may be necessary to counteract the initial cell death caused by hypoxia in transplanted cells [98]. MSC doses lower or higher than 10^7 cells did not show differential improvements in LVEF, and using even higher cell doses ($\geq 10^{10}$)

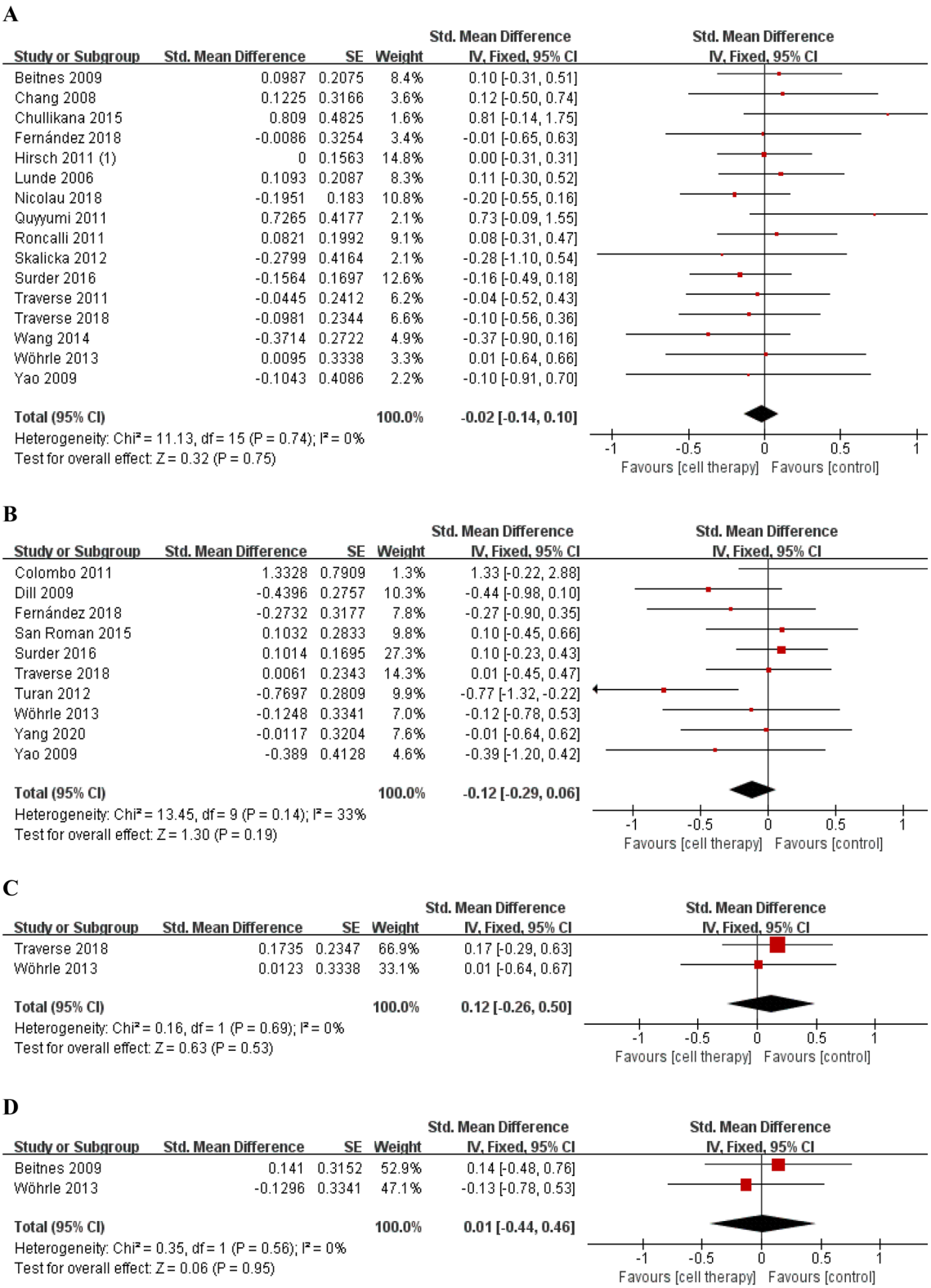

Fig. 4 Forest plots of infarct size. Forest plots of infarct size at the **A** 6-, **B** 12-, **C** 24-, and **D** 36–48-month follow-ups

did not significantly increase LVEF compared with that in the control group [6]. Administering a greater number of injections may pose a risk of myocardial damage, potentially diminishing the effectiveness of therapy and complicating the correlation between cell quantity and clinical benefits [98]. Considering the results of our study, injecting a cell quantity of at least 10^8 is preferable, whereas cell doses exceeding 10^{10} are unlikely to provide additional benefits. Moreover, when performing cell culture for cultivation and proliferation, ensuring a culture period of more than 1 week could be advantageous for increasing cell purity.

Additional research on methods to create purified cell populations is required and should include those employing processes such as cell culture that result in the selection of homogeneous cell populations. Moreover, further studies are required to improve the repair and regeneration functions of the stem cells. The methods for grafting the injected cells into damaged myocardial areas should also be investigated. Most studies included in this review involved autologous stem cells. However, the characteristics of each patient's stem cells were heterogeneous, and the results evaluated at the endpoint also exhibited a heterogeneous tendency. Subsequent studies should be conducted to inject sufficiently standardized allogeneic cells cultured from multiple patients and verify the outcomes.

Appropriate timing of stem cell injection for optimal effectiveness

In addition to cell dosage, the optimal timing of stem cell transplantation to achieve the greatest efficacy in improving cardiac function post-AMI has been investigated. Our study confirmed that ensuring a sufficient number of injected cells would help in the recovery of left ventricular function with an adequate culture period (more than 1 week). Similarly, some studies have suggested that the best transplantation time to secure an adequate culture period is between 7 and 14 days after PCI [14]. This strategy is advantageous because it allows time for the recovery of the damaged myocardium and coronary arteries.

However, contrary to our assertion, previous systematic reviews have suggested that the optimal timing for improving myocardial function is within 3–7 days post-AMI [15]. A systematic review of studies involving MSC transplantation post-AMI reported that, when performed during the first week [99], transplantation shows a higher efficacy in increasing LVEF, thereby improving the left ventricular end-systolic dimension and reducing the incidence of revascularization [100]. If stem cell transplantation is excessively delayed, its effectiveness may decrease due to myocardial cell loss and fibrosis [100]. However, this poses a risk of overlooking the inefficiency of excessively early stem cell transplantation and potential damage to the weakened heart. Immediately after AMI (1–2 days), an increased local apoptosis of transplanted stem cells is observed presumably due to significant myocardial ischemia and inflammation, post-reperfusion oxygen burst, and severe peroxidation injury. Therefore, the efficacy of stem cell therapy is poor [6]. The early injection of stem cells may be restricted owing to the risk of arrhythmias when cells are injected into a damaged heart with significant swelling, inflammation, and microvascular blockage, as well as potential coronary embolization and decreased blood flow. Additionally, the administration of heavy antiplatelet and anticoagulant medications can result in bleeding.

In our study, we have addressed crucial aspects of the previously reported optimal timing for stem cell transplantation, which is within 1 week of AMI. Further research is needed to explore the full extent of optimal timing for stem cell transplantation in patients post-AMI. Additionally, investigating potential strategies to mitigate the risks associated with early or delayed transplantation, such as minimizing AEs on coronary circulation, would be beneficial for enhancing the efficacy and safety of stem cell therapy.

In a study on repeated cell injection, when comparing 12 patients who received a single stem cell infusion at 3–7 days with 15 patients who received an initial infusion at 3–7 days followed by a second infusion at 3 months, the latter group showed more pronounced improvements in LVEF and reductions in infarct size, as assessed by MRI at 12 months, than the former group [74]. Further studies with larger patient populations are needed to draw definitive conclusions about the effectiveness of repeated stem cell infusions.

This study has some limitations. The analysis did not thoroughly scrutinize the procedural aspects of the stem cell therapy process, such as the cell collection technique or other preprocessing steps. Thus, further research is required to investigate whether variations in these processes lead to differences in efficacy. Moreover, the incidence of MACEs was too low in both the control and intervention groups to detect any statistically significant differences. Hence, further studies with larger sample sizes are necessary to elucidate the effects of stem cell transplantation on MACE occurrence. Long-term studies extending up to 5 years are warranted to provide a comprehensive understanding of the sustained effects of stem cell therapy on cardiac function post-AMI.

Conclusions

Our findings revealed the sustained enhancement of LVEF for up to 36 months post-transplantation and a trend toward decreased MACE risk in the intervention groups versus the control groups. Notably, significant

LVEF improvements were observed with longer cell culture durations and higher injected cell quantities. Nevertheless, no significant reduction in infarct size was noted, which is consistent with previous reviews. Future research should explore the optimal timing and dosages while addressing procedural variations to enhance the efficacy and safety of stem cell therapy in patients with AMI.

Abbreviations

AMI	Acute myocardial infarction
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
HF	Heart failure
PCI	Percutaneous coronary intervention
MRI	Magnetic resonance imaging
SPECT	Single-photon emission computed tomography
AE	Adverse event
OR	Odds ratio
RCT	Randomized controlled trial
BM	Bone marrow
BMC	Bone marrow cell
PBSC	Peripheral blood stem cell
MNC	Mononuclear cell
MSC	Mesenchymal stem cell
CD	Cluster of differentiation
CI	Confidence interval

Supplementary Information

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Additional file 1. Summary of the risk of bias in the included studies. Figures 1 and 2.

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Author contributions
SHL contributed to the concept and design of the study. HL and YH assisted in statistical analysis and administrative support. The first draft of the manuscript was written by HL, YH, and SHL. HL, HC, and SHL contributed to manuscript writing and preparing the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data underlying this research will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The protocol of this systematic review and meta-analysis was previously registered in PROSPERO (CRD42023422818). Since this study did not involve human participants, consent to participate was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interests.

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