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ORIGINAL ARTICLE

# Preventive Effect of Bone Marrow Mononuclear Cell Transplantation on Acute Myocardial Infarction-Induced Heart Failure: A Meta-analysis of Randomized Controlled Trials

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## Abstract

**Purpose** Heart failure (HF) is a major complication of acute myocardial infarction (AMI). Transplantation of bone marrow mononuclear cells (BM-MNC) in the setting of AMI has been proposed as a means for myocardial tissue regeneration. Several trials have explored the outcomes of these cells on surrogate end points such as left ventricular ejection fraction (LVEF) in patients with AMI. However, the data regarding the clinical efficacy are infrequent. Here, we performed a meta-analysis investigating the effect of BM-MNCs injection on the rate of hospitalization for HF in the long-term follow-up period.

**Methods** PubMed, Scopus, and Cochrane databases were queried with various combinations of keywords through May 2, 2022. A random-effects meta-analysis was performed to calculate risk ratio (RR) and 95% confidence interval (CI) of hospitalization for HF, all-cause mortality, and stroke rate. Subgroup analyses for hospitalization based on time and cell dose were performed.

**Results** A total of 2150 patients with AMI across 22 trials were included for quantitative synthesis. At long-term follow-up, AMI patients treated with an intracoronary injection of BM-MNCs were less likely to be hospitalized for heart failure compared to the control group receiving standard treatment (RR = 0.54, 95% CI = [0.37; 0.78], $p = 0.002$). There was no association between BM-MNC therapy and all-cause mortality (RR = 0.69, 95% CI = [0.47; 1.01], $p = 0.05$) and stroke (RR = 1.12, 95% CI= [0.24; 5.21], $p = 0.85$).

**Conclusion** Autologous injection of BM-MNC in the setting of AMI may be associated with decreased risk of hospitalization of heart failure in the long term. However, its effect on all-cause mortality and stroke rate is questionable.

**Keywords** Stem cell · Myocardial infarction · Heart failure · Bone marrow mononuclear cell

## Introduction

Accumulating evidence suggests that the occurrence of heart failure (HF) following acute myocardial infarction (AMI) is a strong predictor of both all-cause mortality and cardiac-related mortality [1]. In addition to the patients diagnosed with in-hospital HF after AMI, 13–30% of cases develop HF in the first year after hospital discharge [2]. Introduction of percutaneous coronary intervention (PCI) in the setting of AMI has been associated with decreased incidence of HF since early invasive reperfusion therapy can prevent myocardial necrosis by restoring the blood flow to the compromised tissue [3]. Various variables and risk factors such as advanced age, female gender, previous history of infarction, several biochemical markers, and systolic function indices have been linked to increased risk for post AMI-HF [2]. It has been demonstrated that a 5% decline in left ventricular ejection fraction (LVEF) appears to be a predictor of HF in AMI (hazard ratio = 1.07 (1.03–1.11)) [4].

Due to its remarkable regeneration properties for myocardial tissue [5], stem cell therapy has entered clinical studies in patients with AMI to investigate its potential effects on left ventricular function indices and clinical events. Although the results from a previous meta-analysis have shown that BM-MNC therapy in the setting of AMI is

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associated with an increase of LVEF by 2.5% compared to controls [6], it remains unclear if improvement in cardiac function indices can be translated into prevention of HF in a long–term follow-up period. Also, the probable effect of timing and dosage of stem cell therapy on the outcomes is not fully elucidated. Thus, conducting a meta-analysis on the potential preventive effect of BM-MNC therapy after AMI on clinical outcomes is imperative.

## Methods

**Search Strategy** Digital databases, including PubMed, Scopus, and Cochrane, were queried using the combination of medical subject headings (MeSH) and keywords for identification of potential relevant studies. These keywords included "acute myocardial infarction," "stem cell," "bone marrow mononuclear cell," "heart failure," and "hospitalization." The search was not restricted with any time frame. Based on our PICO (participants, intervention, comparison, and outcome) approach to the search, the potentially eligible studies were all the randomized controlled trials (RCT) investigating the long-term effect of autologous intracoronary injection of BM-MNCs in AMI participants on hospitalization for heart failure. Eligible participants were all the patients > 18 years, diagnosed with ST-segment acute myocardial infarction and treated with either successful coronary angioplasty with stent implantation or thrombolytics. The intervention group should be compared to a control group of patients diagnosed with AMI receiving standard therapy for AMI based on guidelines with/without intracoronary injection of placebo. The primary study endpoint for this study was long-term rates of hospitalization due to heart failure in AMI patients. Other outcomes of interest included all-cause mortality, stroke, and in short-term (4–6 months) change in left ventricular ejection fraction (LVEF) after stem cell therapy. Titles and abstracts of the extracted studies were screened by two authors, AH and HH. Then full text reviewing of the eligible studies were performed. Any disagreements through the screening process were resolved with consensus and discussion with AA.

**Data Extraction** Raw data comprising the primary and secondary outcomes were extracted from the eligible RCTs by two authors (AH and HH) and disagreements were resolved through discussion. Detailed study characteristics included the name of first author, publication year, trial design, type of therapy used for control arm (placebo vs. no placebo), time and dosage of stem cell therapy, follow-up period, data related to sex and age, number of events in both intervention and control group at the longest available follow-up, values of LVEF at baseline, final, and the absolute change after 4–6 months of follow-up. All the data were validated by the corresponding author.

**Quality of the Included Studies** We employed Cochrane Collaboration's tool for assessing risk of bias in randomized trials [7] for risk assessment of the included RCTs. Each included study was closely investigated in terms of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), outcome assessment blinding (detection bias), presence of incomplete outcome data (attrition), and selective reporting of outcomes (reporting bias). For each type of bias, studies were marked as low, high, or unclear risk of bias. The overall quality of the studies were summarized and entered into Review Manager (RevMan 5.1.7) Software. All the studies with moderate and high risk were included for quantitative synthesis.

**Statistical Analysis** Random-effects meta-analysis was performed for all the included analyses. For dichotomous data, risk ratio (RR) with 95% confidence interval (CI) were calculated using the Mantel-Haenszel (MH) method. Prespecified subgroup analyses based on the time of injection (early: BM-MNC therapy ≤ 10 days after diagnosis of AMI, late: BM-MNC therapy after 10 days of the diagnosis of AMI) and stem cell dose (high dose: ≥ $10^8$ cells injected, low dose: < $10^8$ cells injected) were performed for the primary outcome. Another subgroup analysis was performed for LVEF based on the imaging modality used in each trial. For continuous data, the absolute change of LVEF from baseline after 4–6 months was extracted. In case of missing an absolute change, this endpoint was calculated with the correlation coefficient formula using the baseline and final values of the endpoint. Then, the mean difference (MD) and its 95% CI were computed using the inverse variance (IV) method. Pooled effects with CI that did not cross the zero line ($p<0.05$) were considered to be statistically significant. For assessing the rate of heterogeneity, the $I^2$ statistical method was observed, and in the case of $p < 0.05$, heterogeneity was labeled as statistically significant. We assessed the publication bias graphically by illustrating the funnel plot and numerically by Egger's test, in which a $p<0.05$ was considered to have publication bias. This meta-analysis was carried out using RStudio Software Version 1.3.959.

## Results

**Search Results and Study Characteristics** The initial comprehensive search through PubMed, Cochrane databases, and Scopus identified 2983 records for further screening. After removal of 536 duplicates and 2224 irrelevant studies, full texts of 223 studies were retrieved for the final stage of

screening. Of these, 201 articles were excluded based on the inclusion criteria. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the step-by-step search strategy.

A total of 2150 patients diagnosed with ST-segment elevation MI pooled from 22 trials were included in the study, of these 1271 (59%) received intracoronary injection of BM-MNCs and 879 (41%) participants were placed in the control group who had standard care for AMI according to guidelines with or without placebo injection. The mean (95% CI) age of patients was 57.28 (56.09–58.47) versus 57.66 (56.25–59.08) years for the intervention and control group, respectively. The mean (95% CI) baseline LVEF was 44.91% (42.36–47.46) and 45.26% (42.43–48.08) for the intervention and control group, respectively. The follow-up duration for clinical events ranged between 6–60 months. The comparator arm received the standard treatment for AMI in 12 trials [8–19], whereas in other studies the control group received an injection of placebo with or without undergoing bone marrow aspiration (Tables 1 and 2).

**Risk of Bias in Individual Studies** Although the eligible studies were chosen from randomized controlled trials, several trials lacked a specific method mentioned for random sequence generation and also allocation concealment. Thus, the overall selection bias was rated as low or unclear. The majority of the studies blinded the groups from outcome assessors, except one study [20], contrary to blinding of patients and personnel in which masking was not done for either patients, personnel or both in at least seven trials [9, 12, 13, 16–18, 20], which were scored as high risk for performance bias. Attrition bias or incomplete outcome data was at high risk for six of the included studies [13, 15, 17, 18, 20, 21], and the rest of the studies were at low risk. Also, except two studies [8, 22], the rest of the trials were at low risk of selective reporting of the data. The visual assessment of the risk of bias is depicted in Fig. 2.

**Rate of Hospitalization Due to Heart Failure** The pooled estimate from 1217 patients receiving intracoronary BM-MNCs and 865 participants in the control group receiving standard therapy for AMI showed that BM-MNC therapy was associated with a significantly lower rate of hospitalization for heart failure in the long-time follow-up compared to the control arm (RR = 0.54, 95% CI = [0.37; 0.78], $p = 0.0025$) with no level of heterogeneity ($I^2 = 0.00\%$, $p = 0.74$) (Fig. 3A). Subgroup analyses of time and cell dosage revealed that BM-MNC therapy was more effective when performed before 11 days after AMI (early) and with high dosage ($\geq 10^8$ cells) as the group with early injection of

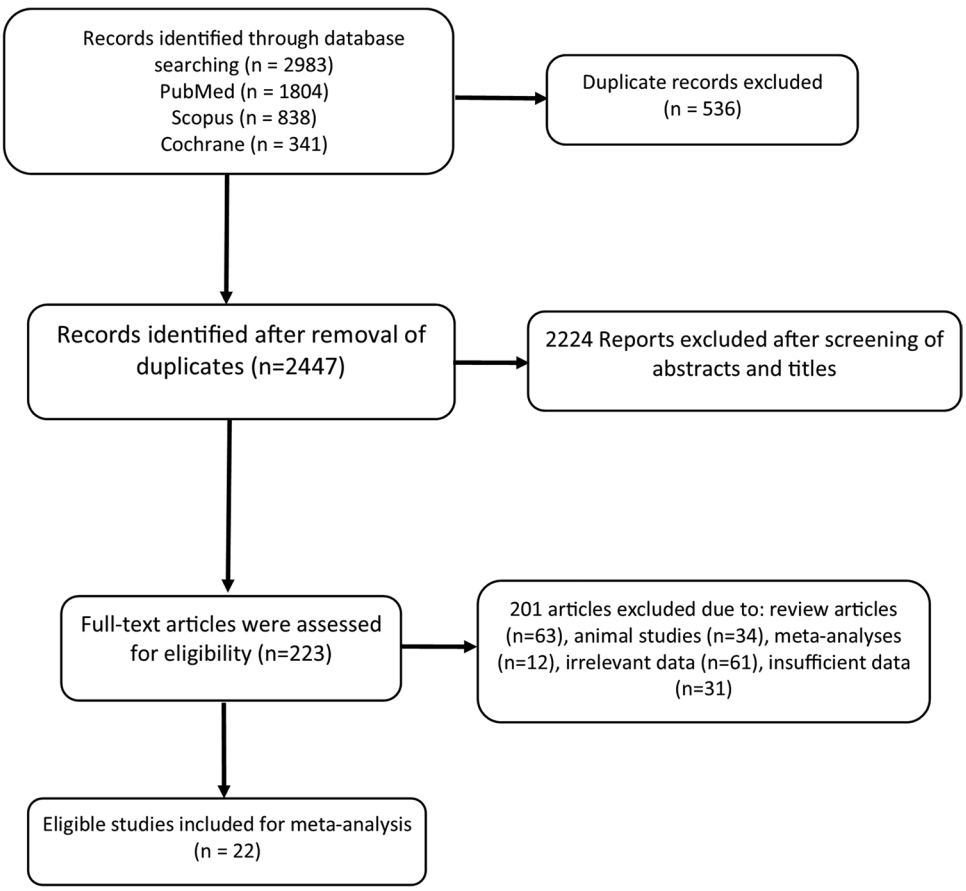


**Fig. 1** PRISMA flow diagram of the search strategy

**Table 1** Characteristics of the studies included in meta-analysis

| Study | Trial design | Comparator arm | Number of participants | | Age (mean±SD) | | Male (%) | | LVEF change | Follow-up duration (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | BM-MNC | Control | BM-MNC | Control | BM-MNC | Control | | |
| Assmus et al. 2014 [25] | PC, DB, MC | Bone marrow aspiration + placebo injection | 101 | 103 | 55±11 | 57±11 | 82 | 82 | ↑ | 60 |
| Beitnes et al. 2009 [11] | Randomized, controlled, two centers | Standard treatment | 50 | 50 | 58.1±8.5 | 56.7±9.6 | 84 | 84 | ↑ | 36 |
| Benedek et al. 2014 [26] | PC, SC | Placebo injection (saline solution) | 9 | 9 | 53.5±15.1 | 61±10.1 | 77.8 | 55.5 | ↑ | 48 |
| Delewi et al. 2014 [12] | Randomized, non-blinded, MC | Standard treatment | 69 | 65 | 56±9 | 55±10 | 84 | 86 | ↑ | 60 |
| Hu et al. 2015 [10] | Randomized, DB | Standard treatment | 22 | 14 | 60.4±11.4 | 60.6±10.8 | 86.5 | 64 | → | 12 |
| Huang et al. 2015 [20] | PC, SC, non-blinded | Saline infusion after PCI | 79 | 25 | 58.5±8.7 | 58.8±8.4 | 91 | 88 | ↑ | 12 |
| Huikuri et al. 2008 [27] | PC, DB, two centers | Placebo injection | 40 | 40 | 60±10 | 59±10 | 90 | 85 | ↑ | 6 |
| Lamirault et al. 2016 [9] | MC, open-label blinded | State-of-the-art therapy | 59 | 42 | 56±12 | 55±11 | 80.8 | 89.8 | ↑ | 12 |
| Mathur et al. 2020 [16] | MC, open-label blinded | Standard treatment | 185 | 190 | 59±11 | 60±11 | 83.8 | 77.4 | - | 24 |
| Mathur et al. 2022 [33] | PC, DB, MC | Placebo injection (saline solution) | 46 | 39 | 56.6±9.6 | 56.3±10 | 85 | 95 | ↑ | 60 |
| Meluzín et al. 2008 [8] | SC, SB | Standard treatment | 40 | 20 | 54±2 | 55±2 | 92.5 | 90 | ↑ | 12 |
| Meyer et al. 2009 [14] | SC, SB | Standard treatment | 30 | 30 | 53.4±14.8 | 59.2±13.5 | 67 | 73 | → | 61 |
| Piepoli et al. 2009 [19] | SC, SB | Standard treatment | 19 | 19 | 63.1±2.4 | 67±2.7 | 68.4 | 68.4 | ↑ | 12 |
| Plewka et al. 2011 [15] | Randomized, SC | Standard treatment | 40 | 20 | 56±9 | 56±9 | 67 | 75 | ↑ | 24 |
| San Roman et al. 2015 [18] | MC, SB, open-label | Standard treatment | 30 | 31 | 54±11 | 57±11 | 97 | 90 | → | 12 |
| Skalicka et al. 2012 [13] | SC, non-blinded | Standard treatment | 17 | 10 | 61±14 | 54±10 | 71 | 100 | ↑ | 24 |
| Sürder et al. 2016 [17] | MC, non-blinded, open-label | Standard treatment | 133 | 67 | 58.5±14.8 | 56±14.5 | 84 | 83.6 | → | 12 |
| Traverse et al. 2010 [24] | PC, DB, SC | Bone marrow aspiration + saline/albumin infusion | 30 | 10 | 52.5±15.6 | 57.5±3.7 | 83 | 60 | ↑ | 6 |
| Traverse et al. 2011 [28] | PC, DB, MC | Bone marrow aspiration + saline/albumin infusion | 58 | 29 | 57.6±11 | 54.6±11 | 79 | 90 | → | 6 |
| Traverse et al. 2018 [23] | PC, DB, MC | Bone marrow aspiration + saline/albumin infusion | 58 | 27 | 55.9±11 | 56.4±10.4 | 88 | 86 | → | 24 |
| Wöhrle et al. 2010 [22] | PC, DB | Bone marrow aspiration + placebo injection | 29 | 13 | 61±8.1 | 61.1±9.3 | 90 | 62 | → | 6 |
| Wollert et al. 2017 [21] | PC, DB, MC | Bone marrow aspiration + placebo injection | 127 | 26 | 55.5±9.8 | 55±9 | 85 | 92 | ↑ | 6 |

*BM-MNC, bone marrow mononuclear cell; SD*, standard deviation; *PCI*, percutaneous coronary intervention; *LVEF*, left ventricular ejection fraction; *PC*, placebo-controlled; *DB*, double-blinded; *SB*, single-blinded; *MC*, multicenter; *SC*, single center, LVEF change; ↑, significant change in LVEF in the intervention group; →, no significant change in LVEF in the intervention group)

**Table 2** Characteristics of intracoronary autologous BM-MNC therapy

| Study | Time from PCI to stem cell therapy | Injected cell dose (million) |
|---|---|---|
| Assmus et al. 2014 [25] | 4.2±0.2 d | 315±43 |
| Beitnes et al. 2009 [11] | 4-8 d | 68 |
| Benedek et al. 2014 [26] | 3w-3m | 166±32 |
| Delewi et al. 2014 [12] | 6 d | 296±164 |
| Hu et al. 2015 [10] | ~6 d | 100 |
| Huang et al. 2015 [20] | 1.6±9h – 11.1±3.3d | 486±260 |
| Huikuri et al. 2008 [27] | 70±36 h | 402±196 |
| Lamirault et al. 2016 [9] | 7–11 d | 98.3 |
| Mathur et al. 2020 [16] | 2–8 d | 140 |
| Mathur et al. 2022 [33] | < 10 h | 236±174 |
| Meluzín et al. 2008 [8] | 6.9 d | 10–100 |
| Meyer et al. 2009 [14] | 4.8±1.3 | 2460±940 |
| Piepoli et al. 2009 [19] | 4-7 d | 248.78 |
| Plewka et al. 2011 [15] | 7 d | 144±49 |
| San Roman et al. 2015 [18] | 3-5 d | 83 |
| Skalicka et al. 2012 [13] | 4–11 d | 2640 |
| Sürder et al. 2016 [17] | 5–7 d, 3–4 w | 160 |
| Traverse et al. 2010 [24] | 3-10 d | 100 |
| Traverse et al. 2011 [28] | 17.4 d | 150 |
| Traverse et al. 2018 [23] | 3–7 d | 150 |
| Wöhrle et al. 2010 [22] | 6.6±1.5 d | 381±130 |
| Wollert et al. 2017 [21] | 7–10 d | 610–2080 |

*BM-MNC*, bone marrow mononuclear cell; *PCI*, percutaneous coronary intervention

BM-MNCs was less likely to be hospitalized for heart failure compared to late group (early group: RR = 0.51, 95% CI = [0.34; 0.77], $I^2$ = 0.00% and late group: RR = 0.78, 95% CI = [0.28; 2.21], $I^2$ = 0.00%) (Fig. 3B) and also an injection of a high dose of cells was associated with lower hospitalization rate contrary to the low dose group (high-dose group: RR = 0.50, 95% CI = [0.34; 0.73], $I^2$ = 0.00% and low-dose group: RR = 0.92, 95% CI = [0.20; 4.30], $I^2$ = 0.00%) (Fig. 3C).

**All-cause Mortality** A total of 20 trials [9–28] reported the data regarding all-cause mortality rate in the follow-up period with a total of 2022 AMI patients comprising 1177 patients in the intervention group and 845 patients in the control group. Two of the included trials reported no case of mortality during the follow-up period [20, 24]. There was no significant difference between the intervention and control groups in terms of all-cause mortality with no sign of heterogeneity (RR = 0.69, 95% CI = [0.47; 1.01], $p$ = 0.05, $I^2$ = 0.00%) (Fig. 4).

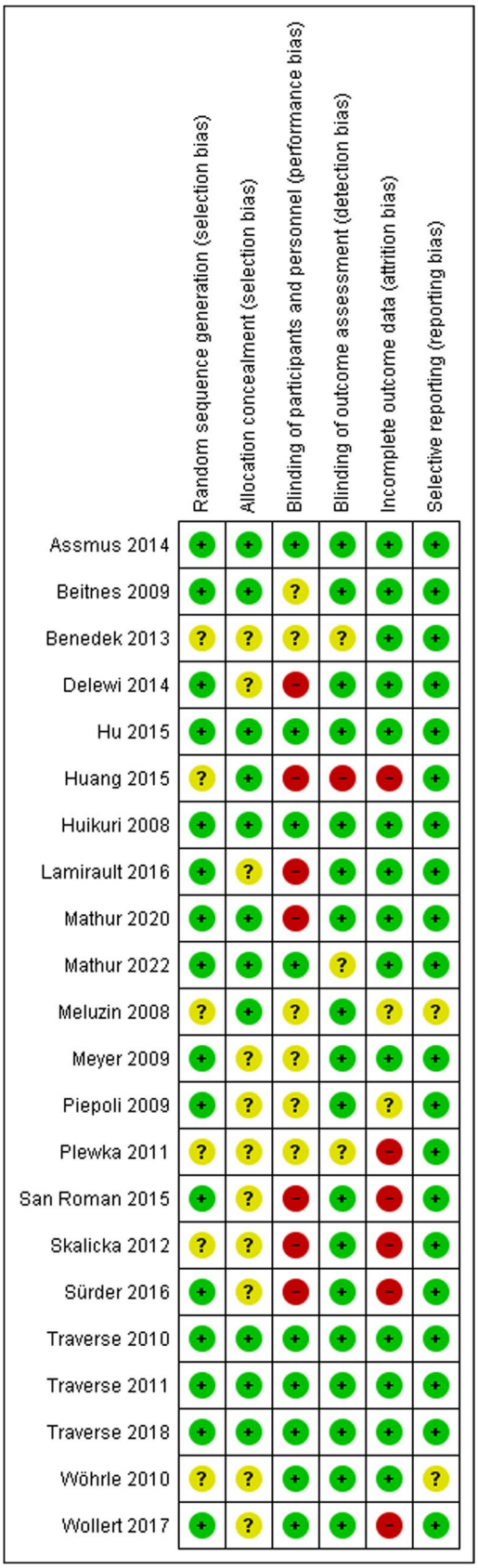


**Fig. 2** Risk of bias assessment of the included studies with the Cochrane Collaboration's tool

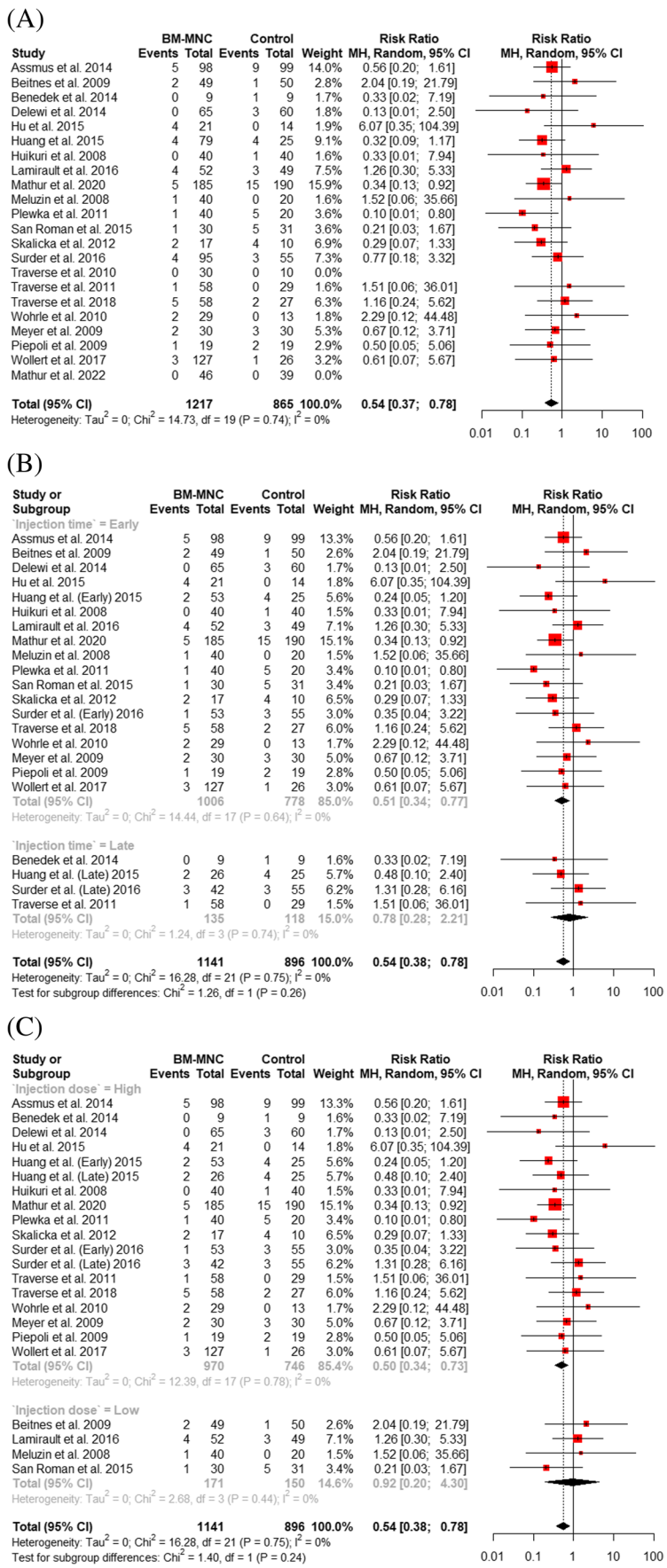


**Fig. 3** (**A**) Forest plot of risk ratio (RR) with 95% confidence interval (CI) of long-term hospitalization rate for heart failure in AMI patients receiving intracoronary BM-MNCs compared to the control group receiving optimal medical treatment with/without placebo injection; (**B**) Subgroup analysis of RR of hospitalization based on time of the injection after PCI (Early, transplantation of BM-MNCs ≤10 days; Late >10 days); (C) Subgroup analysis of RR of hospitalization based on BM-MNC dosage (High $\geq 10^8$ cells; Low $<10^8$ cells)

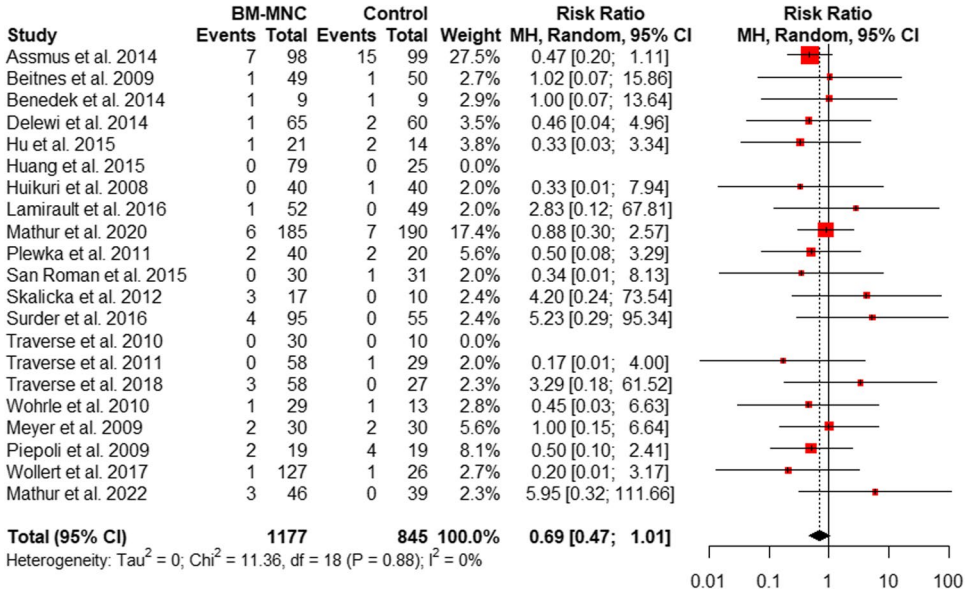


**Fig. 4** Forest plot of risk ratio (RR) with 95% confidence interval (CI) of long-term all-cause mortality in AMI patients receiving intracoronary BM-MNCs compared to the control group receiving optimal medical treatment with/without placebo injection

**Stroke** Using a pooled analysis from seven trials [9–12, 16, 17, 25] with 1082 patients, no significant difference was observed in stroke rate for AMI patients with or without stem cell therapy (RR = 1.12, 95% CI = [0.24; 5.21], $p$= 0.85, $I^2 = 13.9\%$) (Fig. 5).

**Left Ventricular Ejection Fraction** Studies used different modalities for measuring ventricular indices such as echocardiography [9–11, 13, 15, 20, 26, 27], cardiac magnetic resonance (CMR) [12, 14, 17, 18, 21–24, 28], left ventricular (LV) angiography [25], and single photon emission computed tomography (SPECT) [8, 19]. The most frequent modality used for assessing the cardiac function was CMR followed by echocardiography. Based on the results of 20 studies (1593 participants), BM-MNC therapy revealed a treatment benefit in terms of LVEF improvement compared with control arm (MD = 1.47%, 95% CI = [0.39; 2.55], $p$ = 0.01, $I^2 = 44.0\%$) (Fig. 6).

**Publication Bias and Sensitivity Analysis** Visual assessment of the funnel plot illustrated for the primary endpoint showed an overall symmetrical distribution of the studies on each side of the vertical axis (Fig. 7). Also, Egger's test showed no sign of publication bias for asymmetry intercept ($p = 0.33$). For sensitivity analysis, we removed each single study from all the analyses to see their impact on the summary of results and no significant change was observed for all the endpoints.

## Discussion

Here, we have conducted a meta-analysis specifically focused on clinical outcomes of BM-MNCs therapy after AMI. The results of our study showed that this intervention both improved the myocardial function indices and reduced the HF incidence. However, the effect on all-cause mortality appeared to be marginally non-significant.

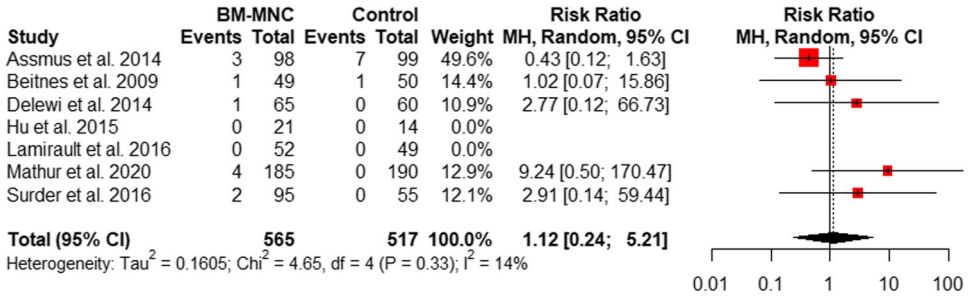


**Fig. 5** Forest plot of risk ratio (RR) with 95% confidence interval (CI) of long-term stroke rate in AMI patients receiving intracoronary BM-MNCs compared to control group receiving optimal medical treatment with/without placebo injection

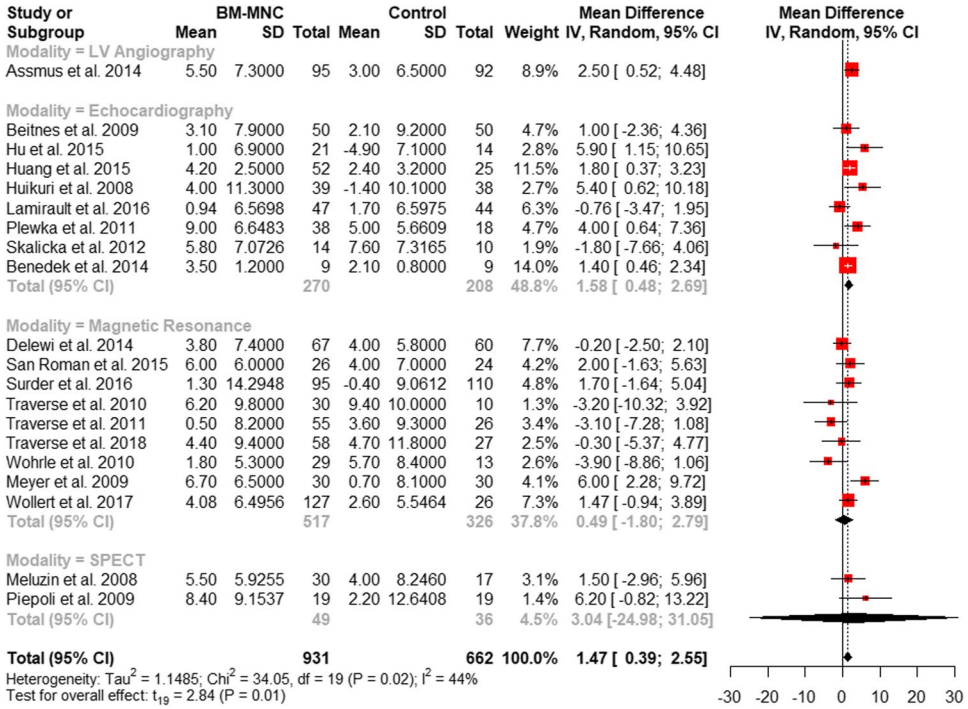


**Fig. 6** Forest plot of mean difference (MD) with 95% confidence interval (CI) of short-term (4–6 months) LVEF change in patients with AMI receiving intracoronary BM-MNCs compared to the control group receiving optimal medical treatment with/without placebo injection based on the imaging modality

Utilization of stem cells in clinical trials for AMI and HF has proposed favorable results on cardiac function. The most probable mechanism of action of stem cells for HF is by secreting cardio-protective factors that can induce vascular growth and remodeling and also prevent myocardial tissue fibrosis [29]. BM-MNC, which is the most frequent stem cell used in clinical trials for patients with AMI or HF, has shown promising effects on LVEF and LVESV. Results from a meta-analysis showed that in short term follow-up, BM-MNCs improve LVEF both in patients with AMI and also ischemic cardiomyopathy, particularly when injected with less than 600 million cells. Notably, this improvement in LVEF was not translated into decreased incidence of major adverse cardiovascular events (MACE) both in short and long term [30].

The major focus of the clinical studies investigating the impact of BM-MNCs in AMI has been on cardiac function indices such as LVEF and clinical outcomes have not been

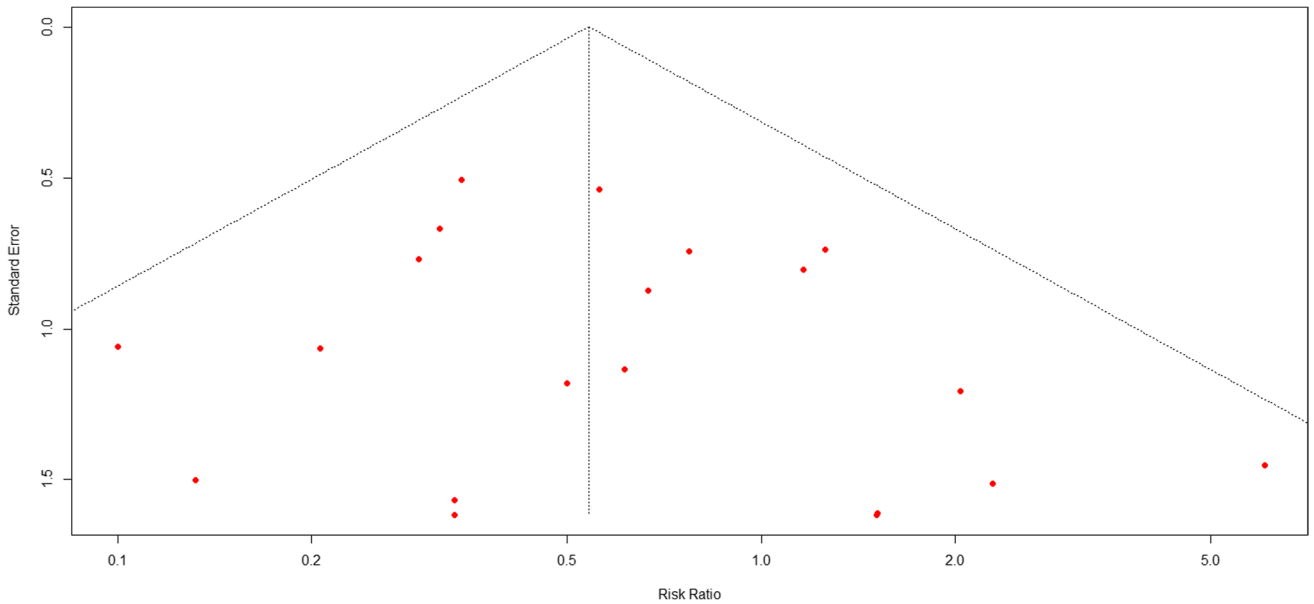


**Fig. 7** Funnel plot of the included studies for risk ratio (RR) of hospitalization for heart failure

the primary outcome of interest so far. BAMI trial was the first phase III randomized controlled trial recruiting a total of 375 patients, 185 patients in the intervention group receiving an intracoronary injection of BM-MNCs 2–8 days after PCI and 190 participants in the control arm who received only medical treatment, which primarily aimed to evaluate if stem cell therapy can reduce all-cause mortality and data regarding clinical outcomes, including all-cause mortality, hospitalization for heart failure, and stroke rate, were collected after 2 years of follow-up. The hazard ratio of all-cause mortality and rehospitalization for HF were both in favor of the BM-MNC group (0.85 vs. 0.33, respectively) [16]. The TIME trial was another RCT exploring the effect of BM-MNC therapy 3–7 days after PCI in 85 patients with anterior MI and moderate ventricular dysfunction (LVEF ≤ 45%) [23]. Contrary to the results of the BAMI trial, their 2-year cohort results revealed that hospitalization following HF was higher in the stem cell group compared to the placebo group (5 hospitalizations in the stem cell group and 2 in the placebo group). Considering these controversies, conducting a meta-analysis on this topic seemed essential to clarify the situation. Thus, we performed a meta-analysis on the effect of BM-MNC therapy on hospitalization rate for HF. Notably, we found that stem cell therapy can decrease the relative risk of HF hospitalizations by 46% in the longest available follow-up (median follow-up of 12 months) when compared to optimal medical treatment. This impact was more pronounced when BM-MNCs were infused shortly after AMI (≤ 10 days) and in higher doses (≥ $10^8$ cells). For other outcomes, BM-MNC therapy was not associated with a significant reduction in all-cause mortality (RR = 0.69) and stroke rate (RR = 1.12). In accordance with previous meta-analyses [6, 30], we detected an increase of LVEF by 1.46% after 4–6 months following AMI. The novel finding of this study was the fact that for the first time, improvement in LVEF was translated into a long-term clinical outcome, which was the incidence of HF needing hospitalization. Because the occurrence of HF is a strong predictor of mortality in patients with AMI [31], the main finding of this study supports the potential preventive effect of stem cells on heart failure after AMI. In a similar previous meta-analysis [32], stem cell transplantation with BM-MNCs did not result in a significant decreased odds of HF hospitalization (odds ratio = 0.84). There may be some explanations to this issue. Since the study by de Jong et al. [32], several new trials were conducted, and two of them [16, 25] had sample sizes of over 200 patients with long-term follow-up durations of 2 and 5 years. Also, in the mentioned study, the two groups were compared with a median follow-up duration of 6 months, whereas in our meta-analysis the median follow-up was 12 months. The longer follow-up periods for assessing the clinical events may provide more reliable and comprehensive results. Furthermore, the primary endpoint of that study was not HF incidence and consequently study selection and inclusion criteria were not based on that, while our study was specifically designed to answer this question.

There were some limitations to our analysis that should be taken into account. As with any meta-analysis, limitations to the method include heterogeneity across trials. In particular, there are differences in terms of treatment characteristics, including the cell dosage used, cell isolation protocols, storage methods, timing of delivery, and imaging modalities. There were heterogeneity among studies regarding trial designs and their methodology. Furthermore, the primary outcome of many studies was LVEF, and these studies were not designed specifically to monitor major cardiovascular events .

## Conclusion

In conclusion, injection of BM-MNC in patients with AMI may contribute to a significantly lower risk of long-term hospitalization for HF, especially when administered in high doses and shortly after the reperfusion therapy. However, this treatment does not reduce stroke rate and all-cause mortality. BM-MNC therapy could also result in significant improvements in LVEF in the short-term follow-up period compared to the patients receiving standard therapy. The results of this meta-analysis showed that transplantation of BM-MNCs can have a substantial effect on clinical outcomes although the great impact of advances in coronary angioplasty and medical therapy on lowering the rates of mortality and potentially other major cardiac events is undeniable.

**Authors' Contributions** AA contributed to the concept and design of the study. AH contributed to the screening process and statistical analysis. The first draft of the manuscript was written by AH and HH. AA and AH revised the final draft. AA, AH, and HH contributed to manuscript writing and preparing the final version of the manuscript.

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**Data Availability** The data underlying this article will be shared on reasonable request to the corresponding author.

## Declarations

**Ethics Approval** Not applicable.

**Consent to Publish** Not applicable

**Conflict of Interest** The authors declare that they have no conflict of interest.

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