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Efficacy and clinical outcomes of bone-marrow mononuclear cell therapy in chronic heart failure: a systemic review and meta-analysis

Jingjing Wu[1†], Yanqiu Shi[2†], Suxia Han[1*] and Xue Yang[1*]

Abstract

Background Over the past decade, there has been no clear evidence regarding the comparative effectiveness of bone-marrow mononuclear cell (BMMNC) therapy in patients with chronic heart failure (HF).

Methods We retrieved eligible randomized controlled trials (RCTs) of bone marrow mononuclear cells (BMMNCs) in patients with heart failure (HF) using a systematic approach of PRISMA guideline and focusing on studies published between 2015 and 2025. We performed a meta-analysis on clinical outcomes, including major adverse cardiovascular events (MACE), hospitalization for HF, and mortality, as well as echocardiographic indices, such as left ventricular ejection fraction (LVEF). The analysis was conducted using a random-effects model. Risk ratios (RR) or mean differences (MD) with corresponding 95% confidence intervals (CI) were pooled based on the type of outcome.

Results The analysis pooled data from 379 patients from 7 RCT studies, including 189 patients experienced BM-MNC and 190 patients in control group. While the stem cell group showed a slight improvement in left ventricular ejection fraction (LVEF) [MD=-0.73, 95%CI (-2.14,0.68), $P=0.31$] at both 3 months [MD = 2.34, 95%CI (-1.94,6.62), $P=0.28$] and 1 year [MD = 1.69, 95%CI (-2.29,5.66), $P=0.41$] compared to controls, these differences did not reach statistical significance ($P>0.05$). Furthermore, stem cell therapy demonstrated no significant benefits in reducing morbidity [RR = 0.99, 95%CI (0.40, 2.49), $P=0.99$], mortality [RR = 1.55, 95%CI (0.50,4.85), $P=0.45$], rehospitalization rates [RR = 1.09, 95%CI (0.63,1.88) $P=0.75$], or major adverse cardiac events (MACE) [RR = 0.59, 95%CI (0.14, 2.46), $P=0.47$], as well as injection route used ($P>0.05$ for all outcomes).

Conclusion The analysis of 7 RCTs found no statistically significant benefits of stem cell therapy on LVEF, clinical outcomes, or MACE, regardless of injection route. Current evidence does not support its routine use; further research is warranted.

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Keywords Chronic heart failure, Stem cell therapy, Bone-marrow mononuclear cells, RCT

Introduction

Heart failure is a significant global health issue, affecting millions of individuals and posing a substantial burden on healthcare systems [1]. Despite advances in medical therapy, the prognosis for patients with heart failure remains poor, highlighting the need for innovative and effective treatments [2]. One promising avenue of research has been the use of cell-based therapies, specifically bone marrow mononuclear cells (BMMNCs), to improve cardiac function and outcomes in patients with heart failure [3].

Over the past decade, numerous studies have explored the therapeutic potential of BMMNCs in the context of heart failure. BMMNCs are a heterogeneous population of cells derived from bone marrow that include hematopoietic stem cells and other progenitor cells. These cells have demonstrated potential benefits in improving cardiac function through mechanisms such as neovascularization and anti-inflammatory effects [4]. For instance, a recent meta-analysis of 36 RCTs (1549 HF patients receiving stem cells and 1252 patients in the control group) showed that BMMNC transplantation resulted in a significant improvement in left ventricular ejection fraction (LVEF) [MD (95% CI) = 3.05 (1.11; 4.99)]. However, stem cell therapy did not lead to a significant change in the risk of major adverse cardiovascular events (MACE) [RR (95% CI) = 0.59 (0.31; 1.13)]. There was a marginally decreased risk of all-cause death [RR (95% CI) = 0.84 (0.54; 1.32)] and rehospitalization [RR (95% CI) = 0.77 (0.61; 0.98)] with no significant difference among the cell types [5].

Several randomized controlled trials (RCTs) have been conducted to compare the efficacy and safety of BMMNC transplantation versus control treatments in patients with heart failure. A study published in 2021 found that BMMNCs demonstrated significant restorative effects on right ventricular (RV) hemodynamics and vascular remodeling in a monocrotaline (MCT) model of pulmonary arterial hypertension [6]. Another study reported that a single dose of CardiAMP Cell Therapy, which utilizes BM-MSCs, showed increased survival and reduced major adverse cardiac and cerebrovascular events (MACCE) in patients with ischemic heart failure [7].

Given these findings, there is a need for a comprehensive meta-analysis to synthesize the available evidence and provide a more definitive answer regarding the comparative effectiveness of BMMNC transplantation versus control treatments in heart failure. In this meta-analysis, we aim to systematically review and synthesize the data from RCTs published between 2015 and 2025 that compare the efficacy and safety of BMMNC transplantation versus control treatments in patients with heart failure. By pooling the results of these studies, we hope to provide a clearer understanding of the relative benefits and risks of BMMNC transplantation, thereby informing clinical practice and guiding future research directions in the field of regenerative medicine for heart failure.

Materials and methods

Inclusion and exclusion criteria

We included randomized controlled trials (RCTs) comparing single BMMNC to heart failure, published in between 2015 and 2025, and available in full text from SCOPUS, Cochrane Library, and PubMed. Studies were required to report LVEF 3 months to 1 year, MACE, morbidity, mortality and route of injection.

We excluded non-RCTs, studies lacking relevant outcome data, duplicate or overlapping data, non-comparative studies, non-human studies, and unpublished data. These criteria ensured the included studies were methodologically sound and relevant to our research question.

Data collection and methodology

We used the PRISMA standards in this study to make sure that the process of selecting articles was rigorous and organized [8]. Two separate reviewers who performed thorough searches in SCOPUS, MEDLINE, the Cochrane Library, and PubMed were part of our process. In order to make sure that our meta-analysis contained only reliable, peer-reviewed data, we eliminated conference papers and case reports because of their poor generalizability.

PICO

Population

Patients with chronic heart failure (HF).

Intervention

Bone-marrow mononuclear cell (BMMNC) therapy.

Comparison

Control group receiving standard care without BMMNC therapy.

Outcome

The primary outcomes include major adverse cardiovascular events (MACE), hospitalization for heart failure, and mortality, while the secondary outcome focuses on improvement in left ventricular ejection fraction (LVEF) as measured by echocardiography

Data extraction

Two researchers independently searched the included studies. A unified data extraction table was developed to extract the main data. The relevant information included the first author, publication year, country, sample size (BMMNC and Control), mean age (BMMNC and Control), and percentage of male (BMMNC and Control), and route of delivery (Intracoronary or Intramyocardial) as shown in Table 1. Two researchers resolved differences conferring with each other, and, if necessary, disagreements were settled by a third reviewer or by reaching a consensus. avoiding deviations caused by subjective factors of the extractors.

Statistical analysis

We conducted our meta-analysis using RevMan 5.4. For dichotomous outcomes, we used the Mantel-Haenszel method to calculate pooled risk ratios (RR) with 95% CIs, weighting studies by the inverse of their variance to account for sample size and variability differences. For continuous outcomes, we applied the inverse variance method to estimate pooled mean differences (MD) and 95% CIs. Both approaches prioritize studies with lower variance, enhancing precision in the meta-analysis. Heterogeneity was assessed using Q statistics for detection and I^2 values for quantification, with a significance threshold set at $P < 0.05$.

Results

Patient characteristics

Using the search terms "Bone marrow," "Mononuclear cell," and "RCT," we identified 7,316 records from PubMed, Scopus, MEDLINE, and Cochrane Library. After removing 5,393 duplicates, 1,923 articles underwent title/abstract screening. Of these, 1,916 were excluded for irrelevance (e.g., non-comparative studies, case reports, books, or inappropriate study designs). The remaining 7 full-text articles were retrieved for eligibility assessment (Fig. 1).

Risk of bias in studies

The risk of bias was assessed by two independent reviewers using the built-in Risk of Bias tool in RevMan [16], including random sequence generation, allocation concealment, binding of participant and personnel, binding of outcome assessment, incomplete outcome data, selective reporting and overall risk of bias as shown in Figs. 2 and 3.

Morbidity

We conducted a meta-analysis of three studies reporting morbidity, defined as the occurrence of ≥ 1 post-operative complication (e.g., surgical site infection, pneumonia, or sepsis). The analysis included 60 patients in the BM-MNC group and 60 patients in the control group. However, the results did not reach statistical significance, with a heterogeneity of 0%. The relative risk ratio (RR) was 0.99, with a 95%CI of (0.40, 2.49), and a *p*-value of 0.99 (Fig. 4A, B).

Mortality

Data from two studies were analyzed to assess mortality, with a total of 30 patients in the BM-MNC group (6 events) and 33 patients in the control group (4 events). However, the comparison between the two groups did not yield a statistically significant result. The relative risk (RR) was 1.55, with a 95% (CI) (0.50, 4.85) and a *p*-value of 0.45. Additionally, the heterogeneity was 0%, as illustrated in Fig. 5A and B.

Rehospitalization

Data from seven studies were pooled to compare rehospitalization rates between the BM-MNC group and the control group. A total of 189 patients were included in the BM-MNC group, with 22 rehospitalizations, and 190 patients were in the control group, with 20 rehospitalizations. However, the analysis did not reveal a statistically significant difference between the two groups. The relative risk (RR) was 1.09, with a 95% confidence interval (CI) of (0.63, 1.88) and a *P*-value of 0.75. Moreover, the heterogeneity across the studies was 0% as shown in Fig. 6A and B.

Table 1 Characteristics of the included studies

Study	Year	Country	Sample size		Mean age		Percentage of male		Route of delivery
			BMMNC	Control	BMMNC	Control	BMMNC	Control	
Hamshere [9]	2015	United Kingdom	15	15	57.7 ± 12.3	54.9 ± 10.9	67	60	Intracoronary
Lehtinen [10]	2015	Finland	20	19	69.3 ± 9.9	69.0 ± 11.2	NA	NA	Intramyocardial
Martino [11]	2015	Brazil	82	78	51 ± 11	49.6 ± 11.1	73	68	Intracoronary
Trifunovic [12]	2015	Serbia	15	15	53.8 ± 10.1	60 ± 6.8	93	93	Intramyocardial
Wang [13]	2015	China	17	16	65.6 ± 4	65.5 ± 5.6	45	45	Intramyocardial
Choudhury [14]	2017	United Kingdom	30	30	63.7 ± 9.5	61.6 ± 10.8	97	97	Intracoronary
Mann [15]	2019	Netherland	19	20	65.0 ± 7	65 ± 8	100	95	Intramyocardial

BMMNC Bone-marrow mononuclear cell, *NA* not available

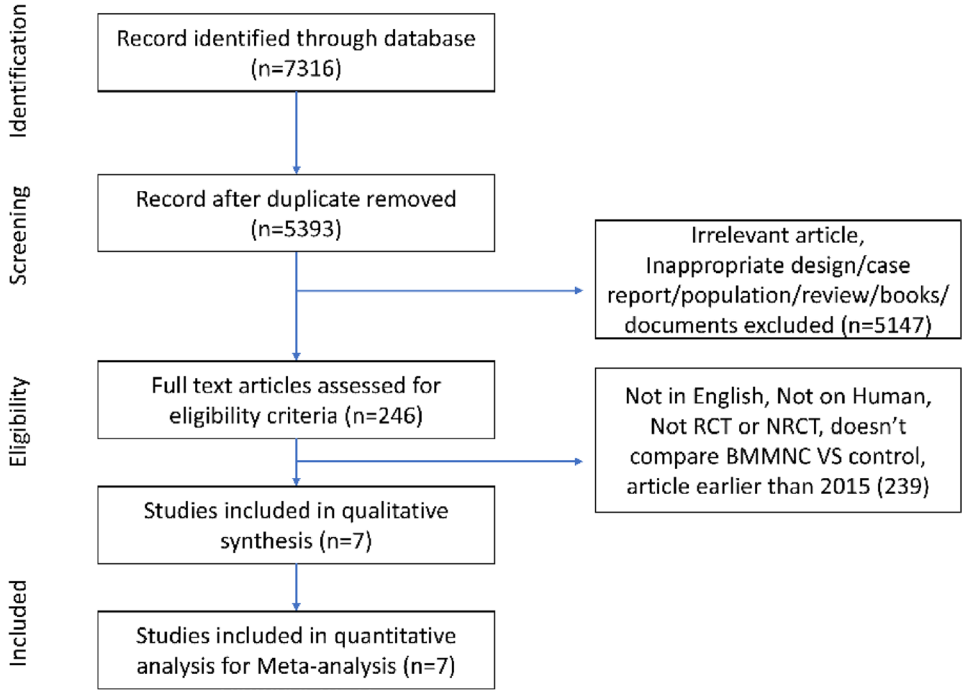

Fig. 1 Prisma flow chart

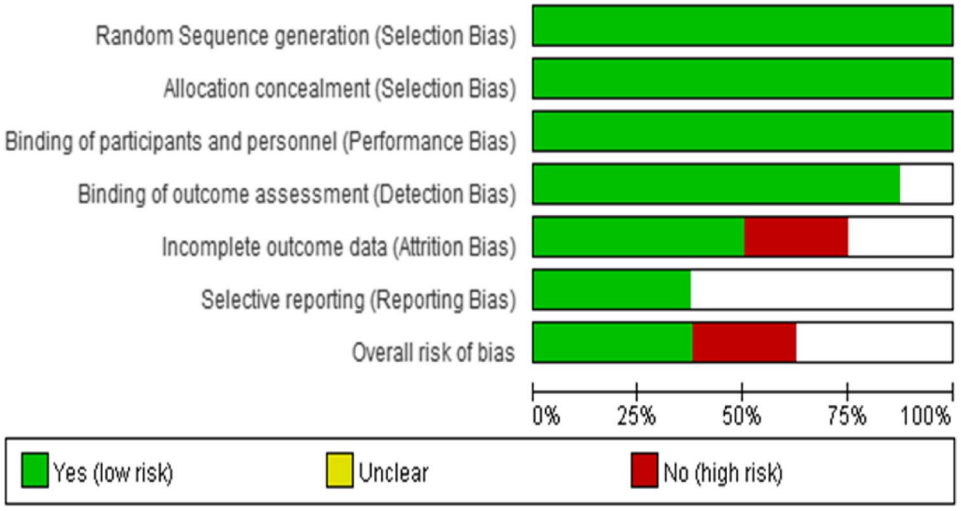

Fig. 2 Risk of bias

Major adverse cardiovascular events MACE (route of injection)

We evaluated Major Adverse Cardiovascular Events (MACE) based on the route of injection using data from two selective studies. A total of 43 patients received BM-MNC injections, with 2 experiencing MACE, while 44 patients were in the control group, with 4 experiencing MACE. The results indicated no significant difference between the groups, with a relative risk (RR) of 0.59, a 95%CI of (0.14, 2.46), and a *P*-value of 0.47. Additionally, the heterogeneity was 0%, as shown in Fig. 7A and B.

Hospital based (route of injection)

Data from two studies hospital-based were analyzed to compare the outcomes of different routes of injection. A total of 30 patients received BM-MNC injections, with 6 experiencing the event of interest, while 33 patients were in the control group, with 4 experiencing the event. The analysis revealed no significant difference between the two groups, with a relative risk (RR) of 1.55, a 95% confidence interval (CI) of (0.50, 4.85), and a *p*-value of 0.45. Additionally, the heterogeneity across the studies was 0%, as illustrated in Fig. 8A and B.

Fig. 3 Risk of bias graph summary

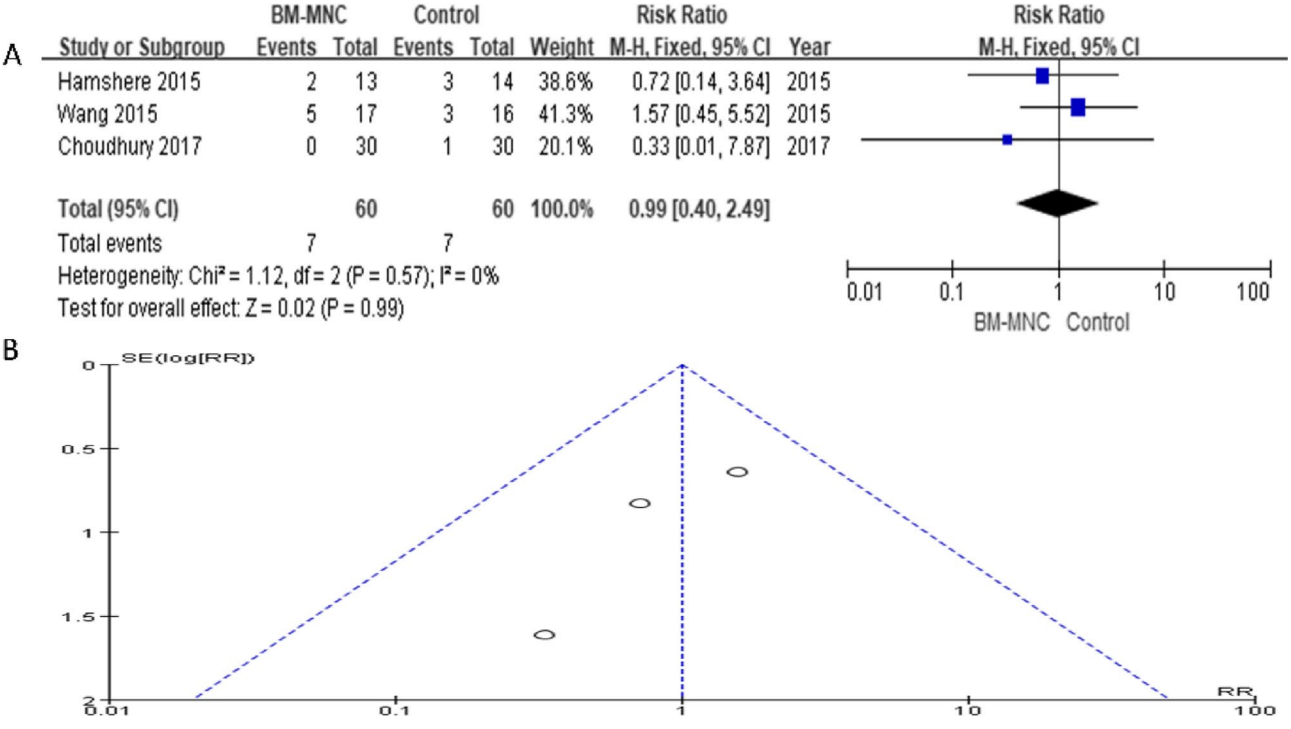

Fig. 4 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 7/60 patients in the BM-MNC group and 7/60 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 0.99, 95%CI (0.40,2.49), *P* = 0.99]. **B** Funnel plot for morbidity.

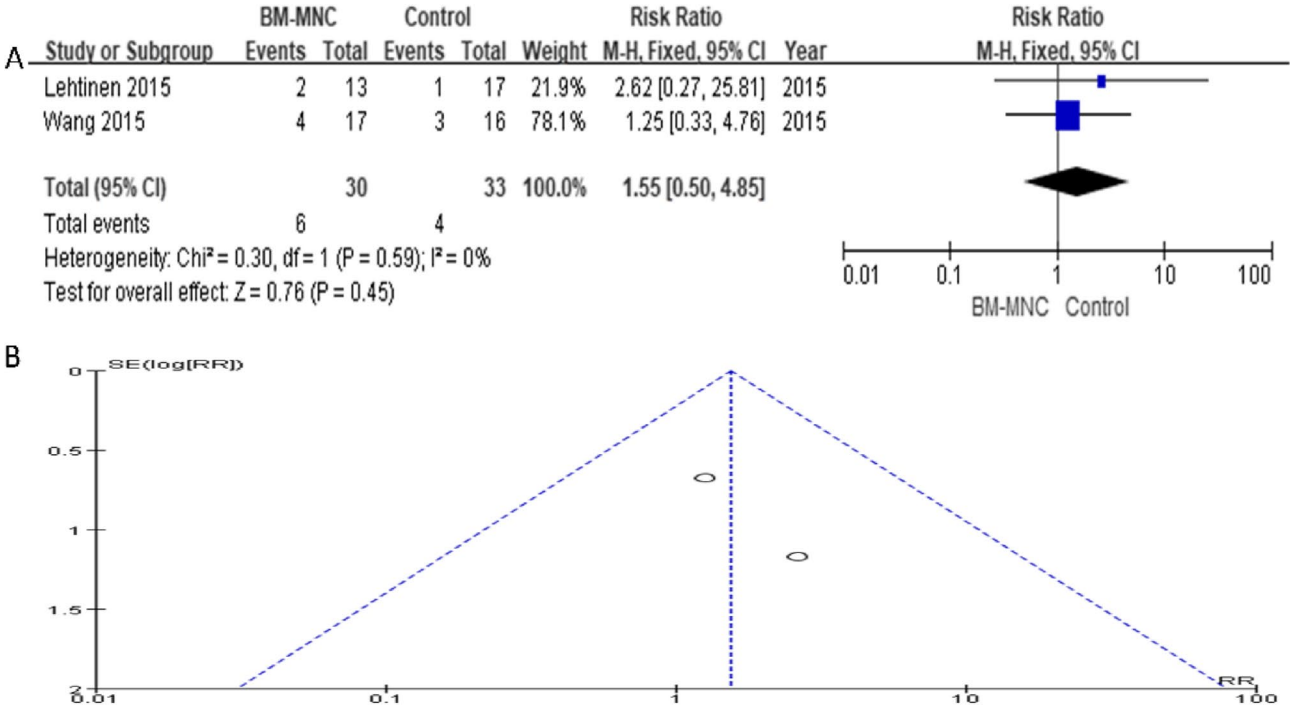

Fig. 5 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 6/30 patients in the BM-MNC group and 4/33 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 1.55, 95%CI (0.50,4.85), *P* = 0.45]. **B** Funnel plot for mortality

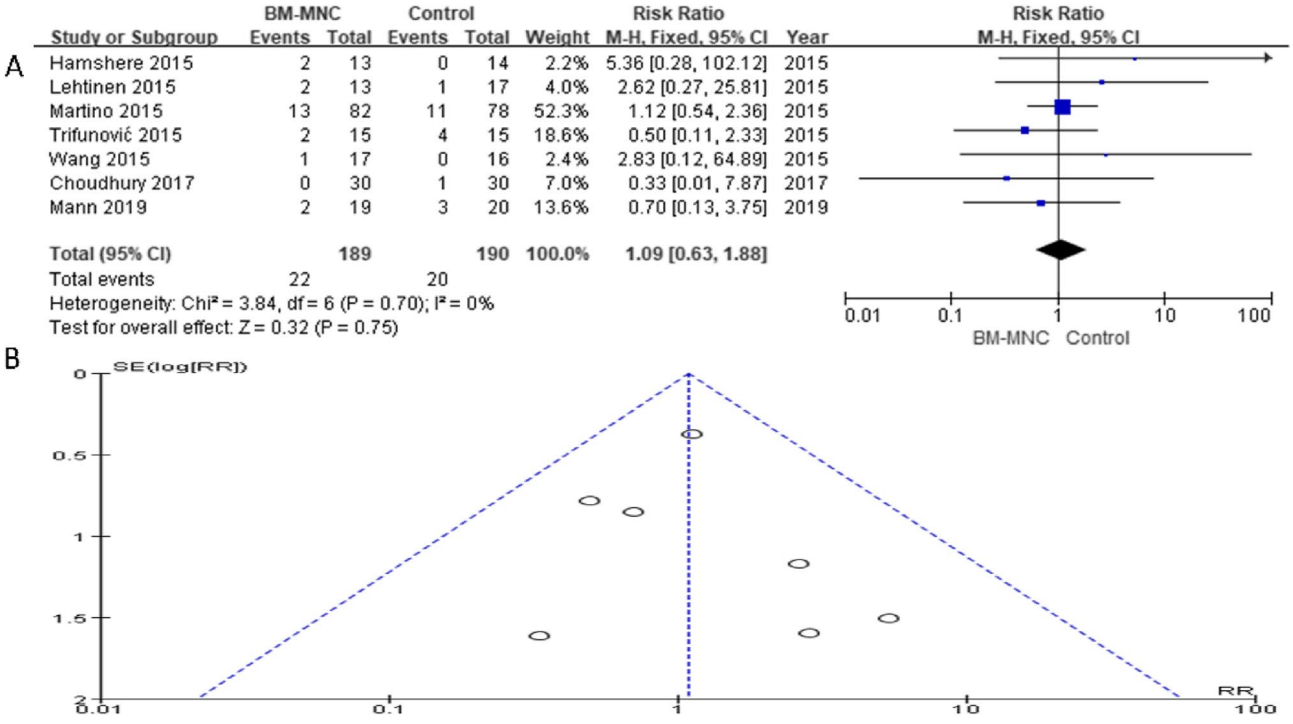

Fig. 6 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 22/189 patients in the BM-MNC group and 20/190 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 1.09, 95%CI (0.63,1.88) *P* = 0.75]. **B** Funnel plot for rehospitalization.

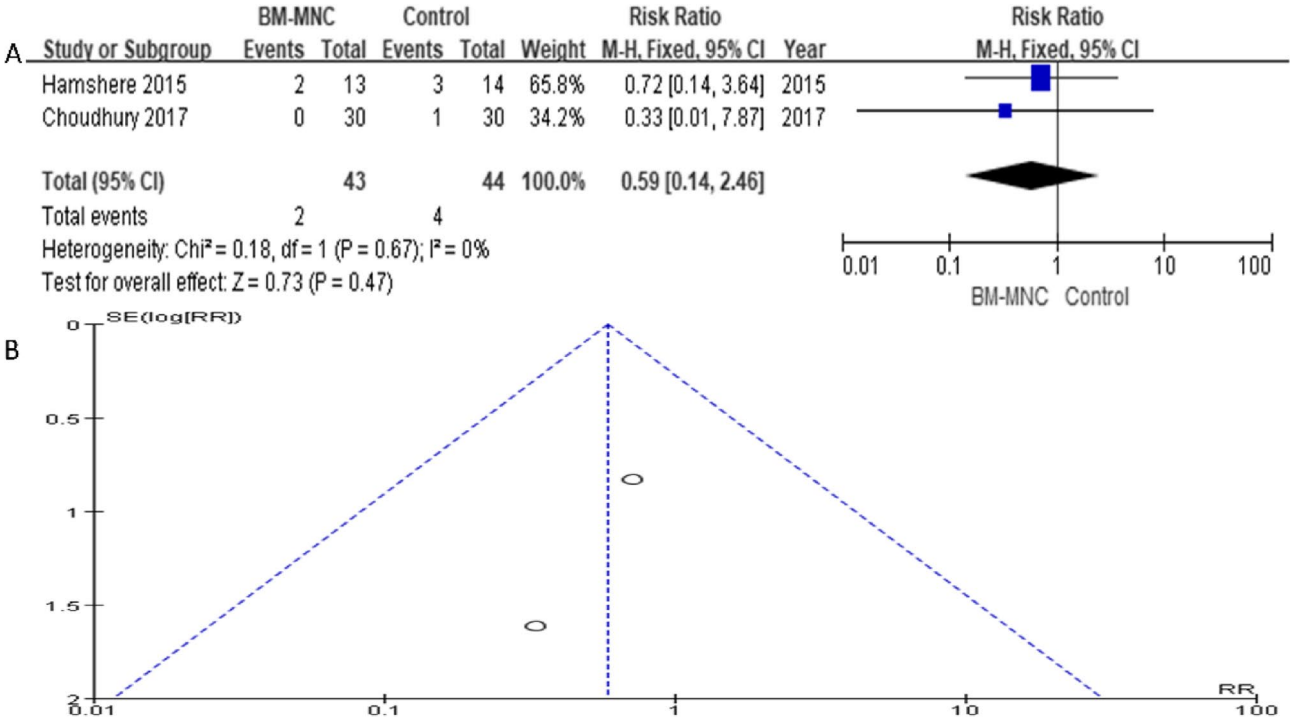

Fig. 7 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 2/43 patients in the BM-MNC group and 4/44 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 0.59,95% (0.14, 2.46), *P* = 0.47]. **B** Funnel plot for MACE based on route of injection

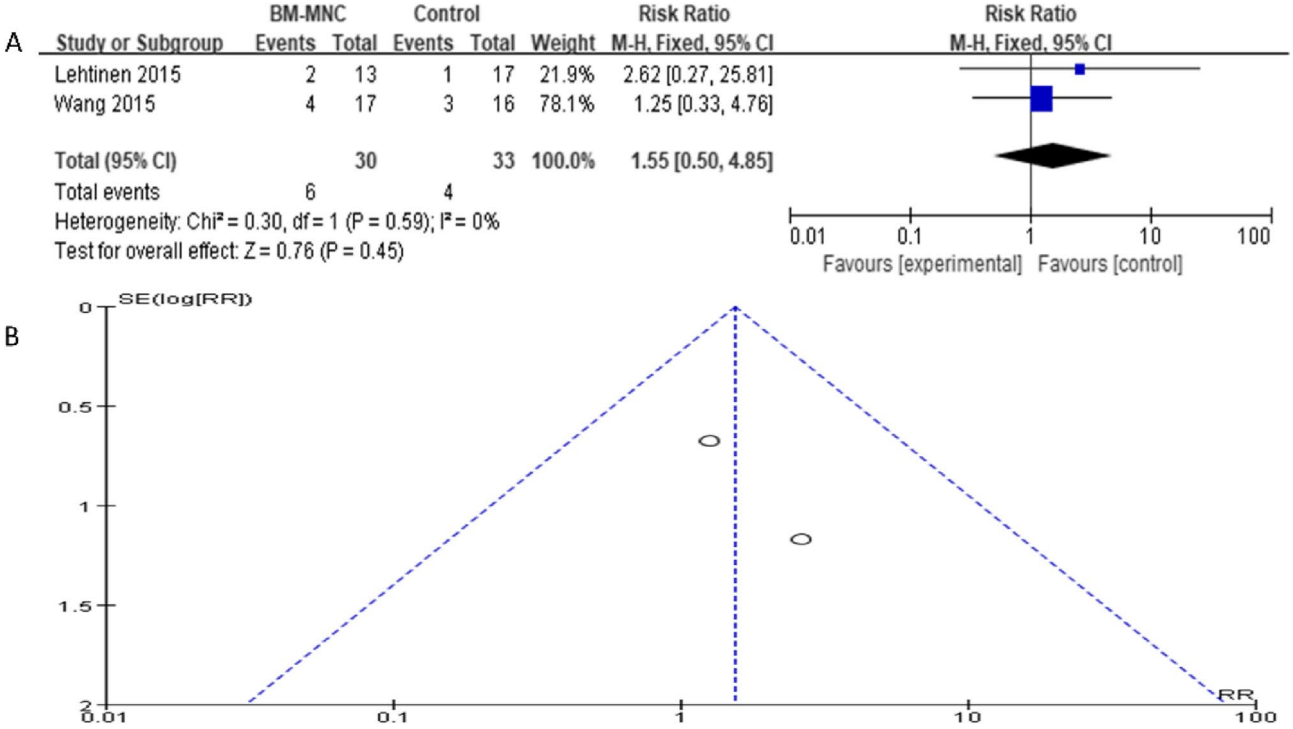

Fig. 8 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 6/30 patients in the BM-MNC group and 4/33 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 1.55, 95%CI(0.50,4.85), *P* = 0.45]. **B** Funnel plot for hospital based on route of injection

Death (route of injection)

Data from seven studies were analyzed to compare the outcomes of different routes of injection based on mortality. A total of 189 patients received BM-MNC injections, with 22 deaths, while 190 patients were in the control group, with 20 deaths. The analysis did not reveal a statistically significant difference between the two groups, with a relative risk (RR) of 1.09, a 95% confidence interval (CI) of (0.63, 1.88), and a *p*-value of 0.75. Additionally, the heterogeneity across the studies was 0% as shown in Fig. 9A and B.

LVEF

Data from six studies were analyzed to compare left ventricular ejection fraction (LVEF). A total of 163 patients received BM-MNC injections, while 158 patients were in the control group. The analysis did not reveal a statistically significant difference between the two groups [MD=−0.73, 95%Cl (−2.14,0.68), $P=0.31$]. Additionally, the heterogeneity across the studies was 0% as shown in Fig. 10A and B.

After 3–6 months

Data from four studies were analyzed to compare left ventricular ejection fraction (LVEF) after 3 months postoperative. A total of 132 patients received BM-MNC injections, while 126 patients were in the control group. The analysis reveals no statistically significant difference between the two groups [MD = 2.34, 95%Cl (−1.94,6.62), $P=0.28$]. Additionally, the heterogeneity across the studies was 78% as shown in Fig. 11A and B.

LVEF after 1 year

Data from four studies were analyzed to compare left ventricular ejection fraction (LVEF) after 1 year postoperative. A total of 126 patients received BM-MNC injections, while 120 patients were in the control group. The analysis reveals no statistically significant difference between the two groups [MD = 1.69, 95%Cl (−2.29,5.66), $P=0.41$]. Additionally, the heterogeneity across the studies was 78% as shown in Fig. 12A and B.

BMI

Data from four studies were analyzed to compare body mass index (BMI). A total of 64 patients received BM-MNC injections, while 64 patients were in the control group. The analysis didn't reveal a statistically significant difference between the two groups [MD=−0.20, 95%Cl (−1.70,1.29), $P=0.79$]. Additionally, the heterogeneity across the studies was 78% as shown in Fig. 13A and B.

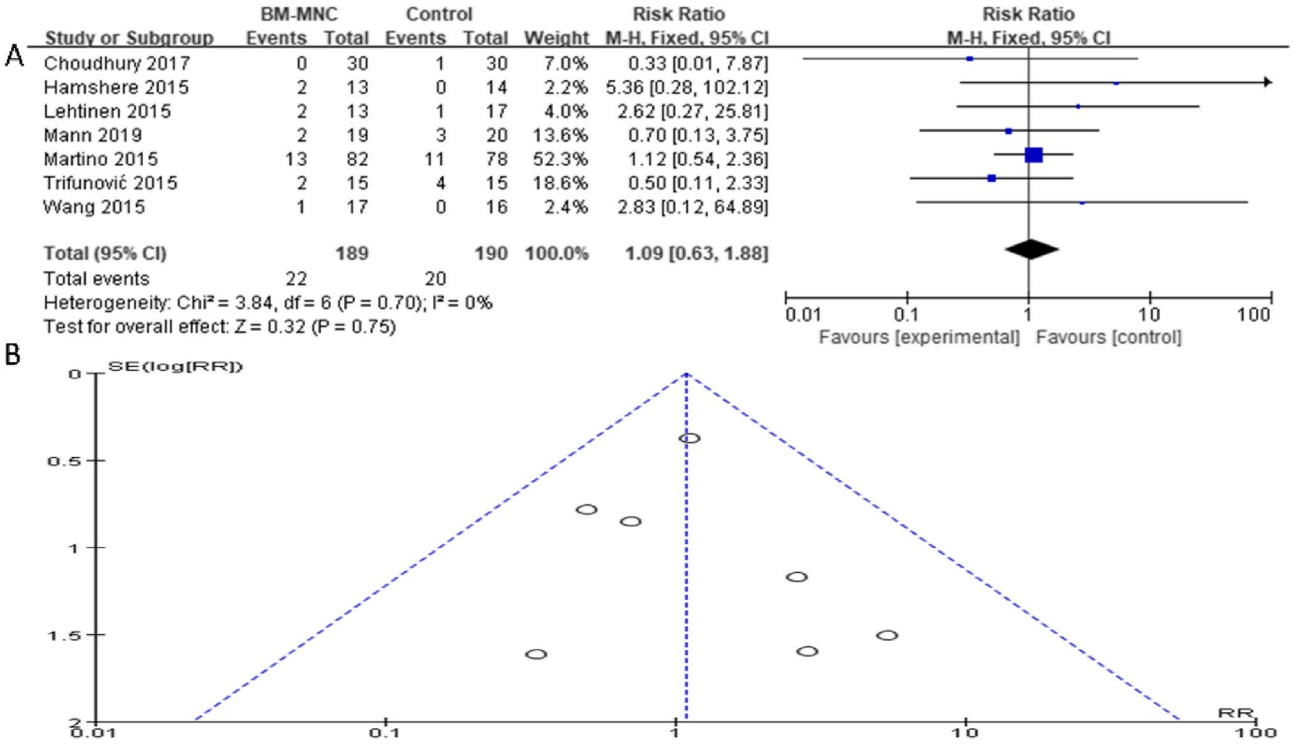

Fig. 9 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 22/189 patients in the BM-MNC group and 20/190 patients in the control group. Risk ratio gives the estimated standardized mean difference and its [RR = 1.09, 95%Cl (0.63,1.88), $P=0.75$]. **B** Funnel plot for death based on route of injection

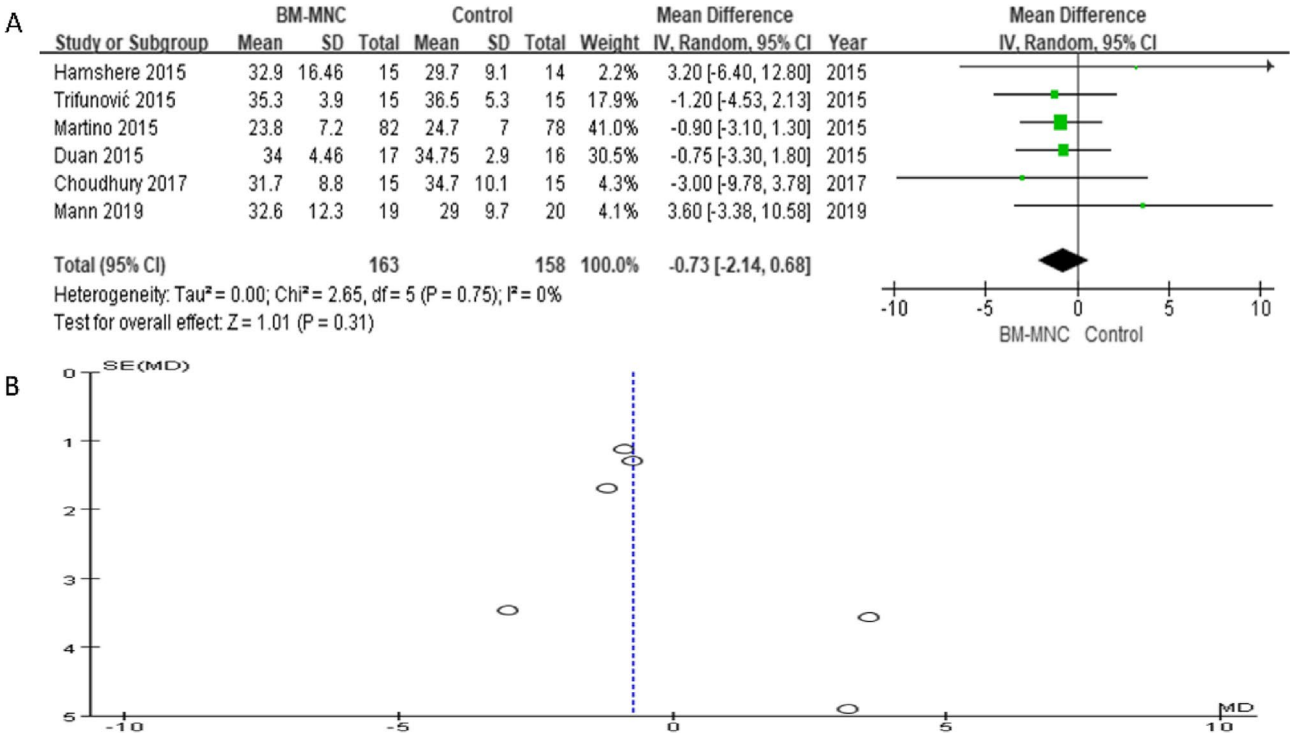

Fig. 10 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 163 patients in the BM-MNC group and 158 patients in the control group. [MD=−0.73, 95%CI (−2.14,0.68), *P* = 0.31]. **B** Funnel plot for LVEF

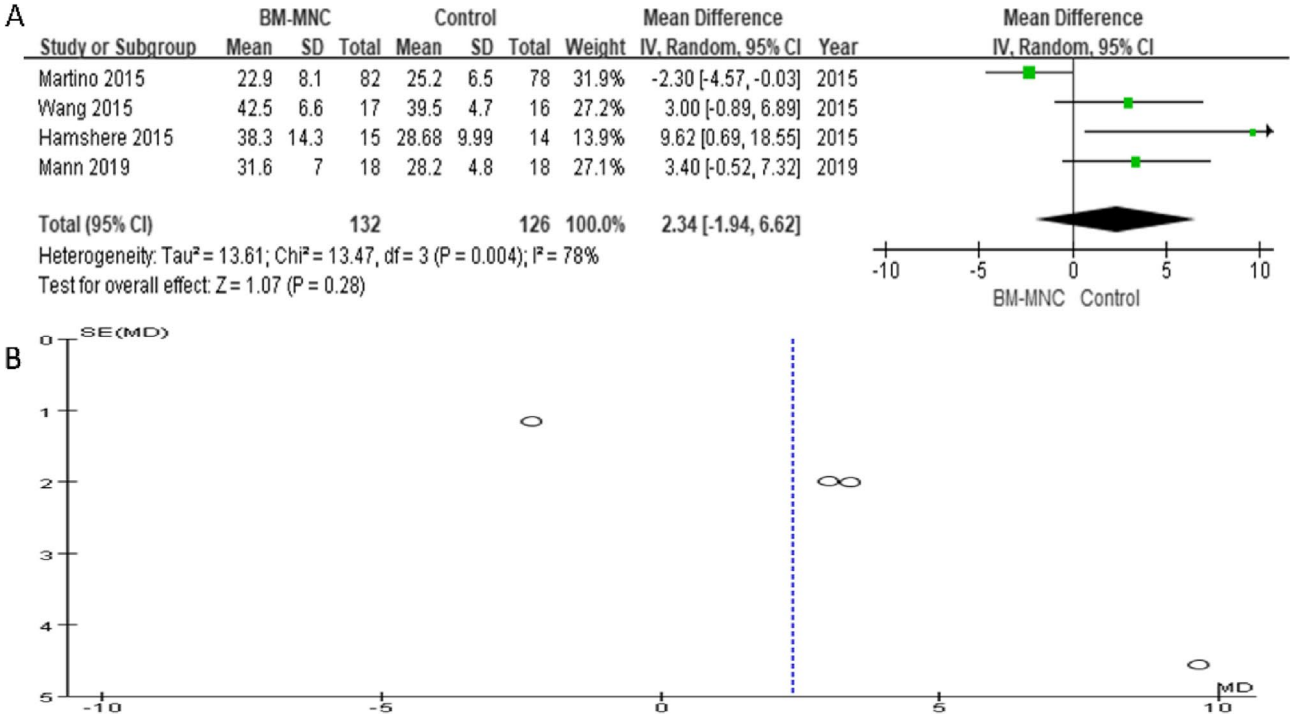

Fig. 11 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 132 patients in the BM-MNC group and 126 patients in the control group. [MD = 2.34, 95%CI (−1.94,6.62), *P* = 0.28]. **B** Funnel plot for LVEF after 3 months

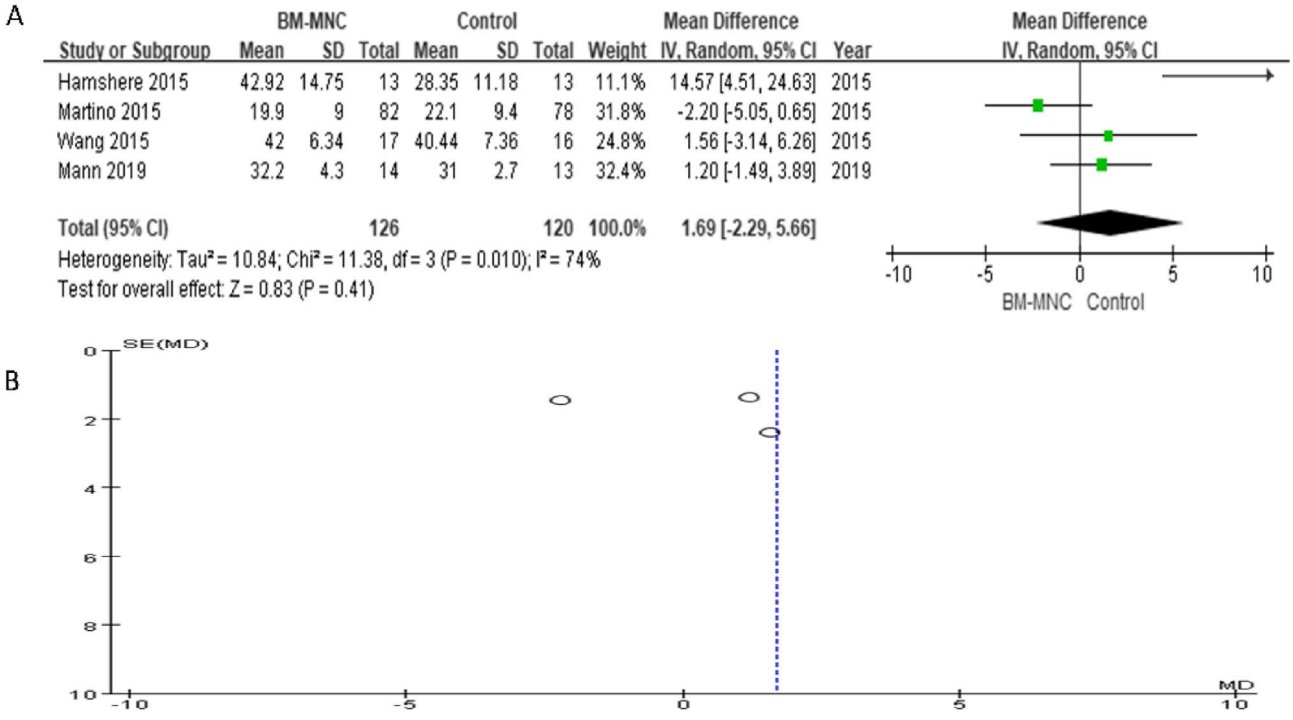

Fig. 12 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 126 patients in the BM-MNC group and 120 patients in the control group. [MD = 1.69, 95%CI (−2.29,5.66), *P* = 0.41]. **B** Funnel plot for LVEF after one year.

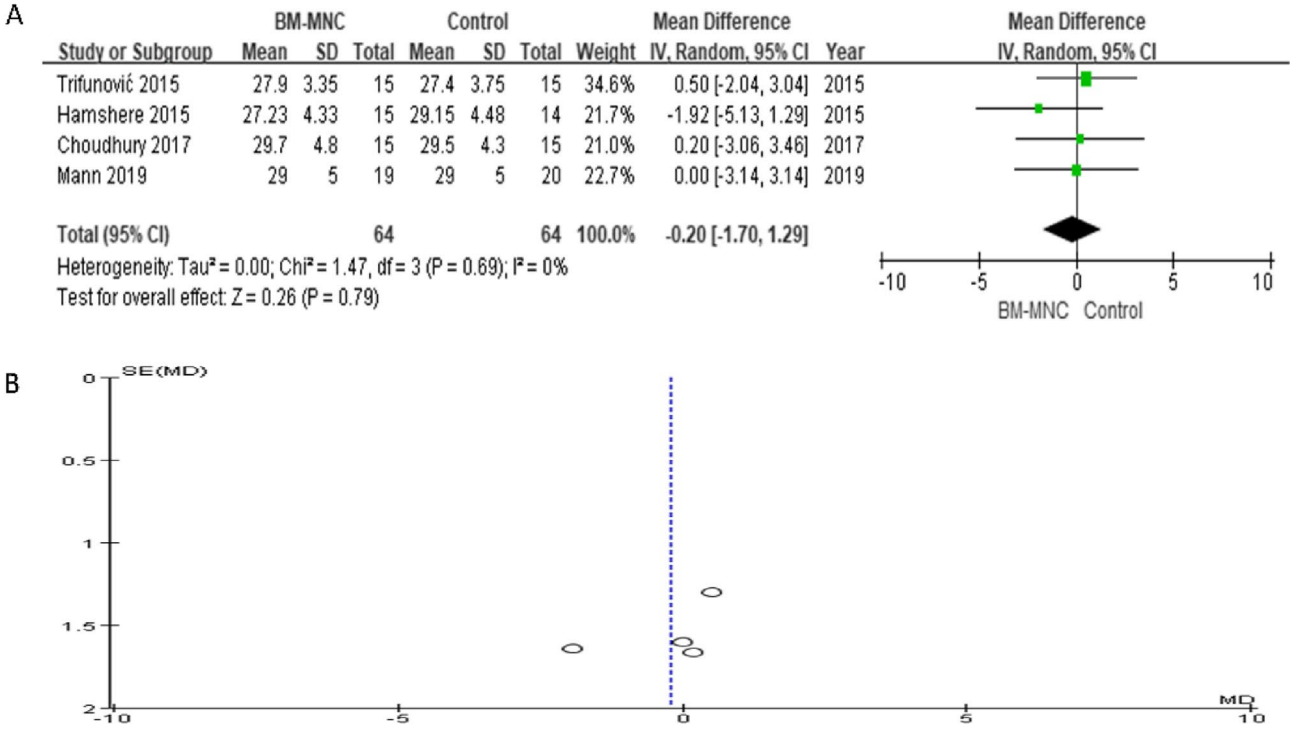

Fig. 13 **A** Forest plot for the comparisons between BM-MNC versus control group. In which total shown the total number of patient and event shown the performed procedure, 64 patients in the BM-MNC group and 64 patients in the control group. [MD=−0.20, 95%CI (−1.70,1.29), *P* = 0.79]. **B** Funnel plot for BMI.

Discussion

Our meta-analysis, focusing on studies from the last decade (2015–2025), identified a non-significant trend toward improved left ventricular ejection fraction (LVEF) in patients with chronic heart failure (HF) receiving bone-marrow mononuclear cell (BMMNC) therapy at 3 months and 1-year post-treatment. While this trend aligns with observations in other recent studies, the lack of statistical significance ($P > 0.05$) underscores the need for larger, standardized trials to confirm efficacy and assess clinically meaningful outcomes such as morbidity or mortality. For instance, a systematic review and meta-analysis by Yanbing Tang et al. (2023) demonstrated that BMMNC transplantation resulted in a statistically significant improvement in the National Institutes of Health Stroke Scale (NIHSS) scores at three months when compared with control groups, although no significant differences were observed at six months [17]. This suggests that while BMMNC therapy may have short-term benefits, its long-term efficacy remains uncertain.

However, our analysis also revealed that BMMNC therapy did not significantly impact major adverse cardiovascular events (MACE), hospitalization for HF, or mortality. This finding is supported by a recent meta-analysis comparing the effectiveness of BMMNCs and mesenchymal stem cells (MSCs) in HF patients, which found that while both types of stem cells significantly improved LVEF, neither led to a significant decrease in MACE or mortality [5]. This further supports the notion that while BMMNC therapy can enhance cardiac function, its broader clinical benefits are limited.

Bone marrow mononuclear cells (BMMNCs) improve heart failure primarily through paracrine effects by secreting growth factors and cytokines that promote angiogenesis, inhibit apoptosis, and reduce inflammation. They also enhance tissue repair by stimulating endogenous cardiac progenitor cells. Additionally, BMMNCs exhibit anti-apoptotic and anti-fibrotic properties, reducing cardiomyocyte death and myocardial fibrosis. They modulate the immune response to create a favorable environment for regeneration. While direct differentiation into cardiac cells is debated, clinical evidence shows BMMNC therapy can improve ejection fraction, reduce scar size, and enhance exercise capacity and quality of life in heart failure patients [18].

In addition, our meta-analysis did not find a significant correlation between BMMNC therapy and changes in body mass index (BMI). This aligns with findings from other studies that have investigated the impact of BMI on various therapeutic interventions. For example, a study on the impact of BMI on patient outcomes in acute myeloid leukemia found no significant differences in overall survival (OS) or event-free survival (EFS) between obese and non-obese patients [19]. Similarly, a meta-analysis on the relationship between BMI and the efficacy of immune checkpoint inhibitors (ICIs) in cancer patients found no significant association between BMI and the incidence of immune-related adverse effects (IRAEs) [20]. These studies suggest that BMI may not be a significant factor in determining the efficacy of BMMNC therapy in HF patients.

Furthermore, the heterogeneity of BMMNCs and the lack of standardized protocols for cell preparation and administration may contribute to the variability in treatment outcomes. BMMNCs are a heterogeneous group of cells, including progenitor cells such as hematopoietic stem cells (HSCs), mesenchymal stromal cells (MSCs), endothelial progenitor cells (EPCs), and immune cells such as monocytes, T cells, B cells, and natural killer cells [21]. Funnel plot asymmetry (Figs. 4, 5 and 6) may reflect heterogeneity in dosing protocols or patient selection, emphasizing the need for larger, standardized studies to clarify therapeutic potential. The optimal number of cells, route of administration, and number of doses of cells are still unclear, and further investigation is needed to determine the most effective treatment protocols.

While our analysis focused on BMMNCs in heart failure (HF), it is worth contextualizing their utility against other stem cell types, such as mesenchymal stem cells (MSCs) [22]. Unlike BMMNCs, which primarily promote angiogenesis and paracrine signaling, MSCs exhibit potent immunomodulatory effects (e.g., enhancing macrophage phagocytosis via migrasome-mediated pathways) that may better address inflammatory injury in acute myocardial infarction (AMI). In AMI, stem cell efficacy often correlates with acute biomarker modulation (e.g., IL-6, TNF-α suppression), whereas in chronic HF, structural repair via BMMNCs may dominate [23]. This dichotomy suggests stage-specific therapeutic roles: MSCs for acute inflammation and infarct stabilization, and BMMNCs for chronic remodeling. Future studies could explore combining these cells to target both phases of cardiac injury.

In summary, our meta-analysis, which included studies from the last 10 years, provides valuable insights into the efficacy of BMMNC therapy in chronic HF. While the therapy did not demonstrate significant improvement in LVEF, its impact on broader clinical outcomes was also limited. Future research should focus on exploring the potential synergistic effects of BMMNC therapy with other interventions, such as structured nursing care and advanced risk prediction models. Additionally, further studies should aim to improve the understanding of the long-term effects of BMMNC therapy and its integration into comprehensive HF management strategies. This multifaceted approach is essential to optimize patient outcomes and address the complex needs of patients with chronic heart failure.

Conclusion

The analysis of 7 RCTs found no statistically significant benefits of stem cell therapy on LVEF, clinical outcomes, or MACE, regardless of injection route. Current evidence remains insufficient to recommend routine clinical application at this time; further well-designed studies are needed to clarify potential benefits and optimize protocols.

Clinical trial number

Not applicable.

Authors' contributions

Jingjing Wu and Yanqiu Shi: Conceptualization, literature review, protocol development and manuscript writing, data extraction, revision, and submission. Suxia Han and Xue Yang: Supervision and final review.

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None.

Data availability

The meta-analysis presented here incorporates data extracted from articles that have been previously published, with pertinent details referenced throughout the manuscript. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

A Statement of Ethics is not applicable because this study is based exclusively on published literature.

Consent for publication

The manuscript is not under consideration for publication elsewhere.

Competing interests

The authors declare no competing interests.

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