Autologous bone marrow stem cell transplantation for patients undergoing coronary artery bypass grafting: a meta-analysis of 22 randomized controlled trials

Juelin Song†, Kang He† and Jianglong Hou*

Abstract

Background: Although the safety and feasibility of coronary artery bypass grafting (CABG) and bone marrow stem cell (BMSC) transplantation have been established, the effectiveness of this approach compared with CABG alone remains controversial. The aim of this updated meta-analysis of randomized controlled trials was to evaluate the efficacy of this procedure.

Methods: A random-effects meta-analysis was conducted using studies sourced from the PubMed, Embase, and Cochrane literature databases to compare patients who received isolated CABG (CABG group) and BMSC transplantation with CABG (BMSC group). 22 studies were included.

Results: A total of 22 relevant publications with 820 patients were included. 432 patients received BMSC transplantation with CABG and 388 patients received isolated CABG. Compared with the CABG group, the BMSC transplantation group exhibited an improvement in the left ventricular (LV) ejection fraction (mean difference (MD) = 3.87%; 95% confidence interval (CI): 1.93–5.80%; P < 0.001).

Conclusion: The present evidence suggests that autologous BMSC transplantation for patients undergoing CABG appears to be associated with an improvement in LV function compared with CABG alone. However, heterogeneity in the data suggests that patients respond differently to this therapy. Further research is needed to understand these differences.

Keywords: Bone marrow, Stem cell, Coronary artery bypass, Meta-analysis, Randomized controlled trial

Introduction

Ischemic heart disease (IHD) remains one of the leading causes of morbidity and mortality worldwide, imposing both economic and healthy burdens on either developed and developing countries [1–3]. Myocardial ischemia often results in irreversible loss of viable myocardium and replacement by noncontractile scar tissue, leading to the impairment of left ventricular and cardiac dysfunction. Despite the advances in revascularization techniques and pharmacological treatment, patients with poor cardiac function struggle to achieve desirable outcomes. The aim of bone marrow stem cells (BMSCs) therapy is to repair damaged myocardium, prevent ventricular remodeling, and improve overall cardiac function [1].

Bone marrow cells are the first choice for bypass combined stem cell transplantation because they are autologous and readily available. The efficacy of CABG...
combined with BMSC transplantation remains controversial. Studies have shown that CABG combined with BMSC transplantation is beneficial to cardiac function without adverse reactions, and is a safe and feasible clinical adjuvant therapy [4–14]. However, other studies have reported no effect of CABG combined with BMSC transplantation on overall left ventricular function and clinical symptoms [13, 15–24]. Since the publication of these meta-analyses, several new randomized controlled trials (RCTs) have been published [11, 14, 22–24]. The purpose of this meta-analysis was to reevaluate the efficacy of CABG combined with BMSC transplantation by incorporating updated RCTs results.

Methods
Search strategy
The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [25] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (no. CRD42021276095). The PubMed, Cochrane Library and EMBASE were searched from inception to August 16, 2021. Detailed search strategies are shown in Additional file 1: Tables S1, Additional file 2: Table S2, Additional file 3: Table S3. The studies were not restricted by language, date of publication, or setting. To enhance detection, the reference lists of all selected published articles, relevant meta-analyses, systematic reviews, and editorials were hand-searched for other relevant articles.

Selection criteria
Studies were included based on the following criteria: (1) RCTs comparing CABG in combination with BMSC transplantation and CABG alone for IHD; (2) follow-up for at least 3 months after stem cell therapy. The exclusion criteria were as follows: (1) catheter-based stem cell injection methods; (2) the published data did not include LVEF.

Quality assessment
The quality of the selected RCTs was independently assessed by 2 reviewers (J. S. and K. H.) according to the Cochrane risk of bias criteria [26], with each quality item classified as low risk, high risk, and unclear risk. The 6 items used to evaluate bias in each trial included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

Data extraction and outcomes
Two reviewers (J. S. and K. H.) extracted the following relevant data from each study independently: First author; year of publication; country of origin; study population, including BMSC and CABG group; follow-up time; participant characteristics, including age and sex; type of stem cells; the dose of stem cells; route of stem cell administration; treatment of CABG group; outcome measurement method; LV ejection fraction (LVEF), including baseline (LVEFbaseline), follow-up (LVEFfollow-up), and LVEF change from baseline to follow-up for the BMSC (LVEFBMSC change) and CABG groups (LVEFCABG change), and similarly, related data of LV end-diastolic volume (LVEDV), LV end-diastolic volume index (LVEDVI), LV end-systolic volume (LVEDS), LV end-systolic diameter (LVESD), and 6-min walk test (6MWT). Because magnetic resonance imaging (MRI) is more accurate than echocardiography [27], MRI data are preferred in statistical analysis. Any disagreements between the reviewers were resolved by attending to a consensus.

Statistical analysis
All statistical analyses were implemented with Review Manager 5.4 (RevMan, The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) and Stata version 16.0 (StataCorp, College Station, TX, USA). A meta-analysis was performed to calculate the mean difference (MD) LVEF change (MD LVEFchange = LVEFBMSC change − LVEFCABG change), LVEFBMSC change = LVEFBMSC follow-up − LVEFBMSC baseline, and similarly, the MD LVEDVchange, MD LVEDVIchange, MD LVESDchange, MD LVESVchange, MD LVESVIchange, MD LVEDDDchange, 6MWTchange as well as their 95% confidence intervals (CIs).

Most studies reported the mean and standard deviation (SD). In three studies [20, 21, 24], LV volume and ejection fraction values were expressed as mean and standard error (SE). In one study [24], the distance of 6MWT was expressed as mean and SE. The SD was calculated by the formula SD = SE × \sqrt{n}, where n is the sample size. In two studies [7, 19], the LV volume and ejection fraction values were expressed as the median and interquartile range. In two studies [7, 18], distance of 6MWT was expressed as the median and interquartile range. Median and interquartile range were converted into the mean by the method introduced by Luo et al. [28] and converted into the SD by the method introduced by Wan et al. [29].

In addition, some studies [4, 6, 8–11, 13, 18, 30] did not directly report the mean and SD of LVEFBMSC change and LVEFCABG change. The mean of the LVEFBMSC change and LVEFCABG change can be calculated by the difference between the means of the LVEFbaseline and LVEFfollow-up. The SD of LVEFBMSC change and LVEFCABG change was calculated by the following formula: 

\[ SD_{change} = \sqrt{SD_{baseline}^2 + SD_{follow-up}^2 - 2 \times Corr \times SD_{baseline} \times SD_{follow-up}} \]
The SD of \( \text{LVEF}_{\text{BMSC change}} \) and \( \text{LVEF}_{\text{CABG change}} \) in the study by Hendriks et al. [15] were used to calculate the Corr values by using the following formula:

\[
\text{Corr} = \frac{\text{SD}_{\text{baseline}} \times \text{SD}_{\text{follow-up}}}{\text{SD}_{\text{change}}^2 + \text{SD}_{\text{follow-up}}^2 - 2 \times \text{SD}_{\text{baseline}} \times \text{SD}_{\text{follow-up}} \text{SD}_{\text{change}}}. 
\]

The Corr value of the BMSC group and CABG group was calculated to be 0.6. The mean and SD of the LV volume change values were calculated in the same manner.

A random-effects model was used to pool the data and I^2 statistics were used to assess statistical heterogeneity between summary data. All tests were two-tailed and \( P<0.05 \) was considered to indicate a statistically significant difference.

To evaluate whether the effectiveness of CABG combined with BMSC transplantation in IHD patients was influenced by the clinical characteristics, subgroup analyses were performed based on (1) follow-up time (>6 or ≤6 months); (2) method to determine the outcome measure [echocardiography (ECHO), MRI OR single-photon emission computed tomography (SPECT)]; (3) type of stem cells [bone marrow mononuclear cells (BMMNCs), bone marrow cells (BMCs) or other selected cell populations (CD133+ and CD34+ cells)]; (4) route of injection [intramyocardial (IM) or intracoronary (IC)]; (5) dose of stem cells \([≥10^8 \text{ or < } 10^8 \text{ cells (10^8 was the median number of BMSCs injected)}\]; (6) baseline LVEF <30 or ≥30%. Analyses were performed to evaluate whether the differences between the subgroups were statistically significant. Leave-one-out sensitivity analysis of the primary outcome LVEF was performed.

**Results**

**Search results**

A total of 436 studies were identified from the electronic database search. Finally, 20 independent RCTs were included in the analysis according to our search strategy. There were 2 relevant randomized controlled trials identified after researching the reference list of relevant literature (n=2). These 4 literature [13, 31–33] reports one trial. The final analysis included 22 independent RCTs [4–24, 30]. A flow chart for the study selection process is presented in Fig. 1.

**Study characteristics**

A total of 22 studies were included in the present meta-analysis. A total of 914 participants were assessed for the baseline of the studies. The ‘BMSC group’ (n=484) included participants who had received CABG combined with BMSC transplantation, while the ‘CABG group’ (n=430) included patients who had only received CABG. The follow-up period was range from 4 to 60 months. The mean age of the participants ranged from 51.7 to 66.8 years, and the percentage of male patients ranged from 70 to 100%. A total of 7 studies were performed in China, 3 in Germany and 1 each in Argentina, UK, Canada, Serbia, Spain, Finland, France, Iran, Netherlands, Indonesia, Turkey and Belgium. The baseline characteristics of the included studies are summarized in Table 1.

**Risk of bias assessment**

Of the 22 studies, 12 (54.5%) adequately generated their randomization sequence, 10 (45.4%) concealed allocation, 16 (72.7%) blinded participants and personnel, 9 (40.9%) blinded outcome assessment,17(77.3%) studies had a low risk of incomplete outcome data and 13(59.1%) studies had a low risk of selective reporting. The detailed information on the risk of bias is presented in Figs. 2 and 3.

**LV function**

LVEF has been reported in all 22 studies, including a total of 820 participants. The difference in the change of the LVEF between the BMSC and CABG groups was statistically significant (MD=3.87%; 95% CI: 1.93 to 5.80%; \( P<0.001 \); Fig. 4). There was no statistical difference in the overall change of LVEDV from baseline to follow-up between the BMSC and CABG groups (MD=−3.68 ml; 95% CI: −15.43 to 8.08 ml; \( P=0.54 \); Fig. 5). The difference in the change of the LVEDVI between the BMSC and CABG groups was statistically significant (MD=−10.57 ml/m^2; 95% CI: −19.86 to −1.28 ml/m^2; \( P=0.03 \); Fig. 6).

There was no statistical difference in the overall change of LVESV from baseline to follow-up between the BMSC and CABG groups (MD=−2.13 ml; 95% CI: −15.58 to 11.32 ml; \( P=0.76 \); Fig. 7). There was a statistical difference in the overall change of LVESVI from baseline to follow-up between the BMSC and CABG groups (MD=−9.49 ml/m^2; 95% CI: −16.95 to −2.03 ml/m^2; \( P=0.01 \); Fig. 8).

A total of 3 studies with 298 participants reported a change in LVESD after the treatment. There was a statistical difference in the overall change of LVESD from baseline to follow-up between the BMSC and CABG groups (MD=−3.50 mm; 95% CI: −5.58 to −1.42 mm; \( P=0.001 \); Fig. 9). A total of 4 studies with 164 participants reported a change in LVEDD after the treatment. There was no statistical difference in the overall change of LVEDD from baseline to follow-up between the BMSC and CABG groups (MD=−2.49 mm; 95% CI: −7.27 to 2.28 mm; \( P=0.31 \); Fig. 10).

**6MWT**

A total of 4 studies with 154 participants reported a change in 6MWT after the treatment. There was no statistical difference in the overall change of 6MWT from
baseline to follow-up between the BMSC and CABG groups (MD = 7.44 m; 95% CI: -24.80 to 39.67 m; \( P = 0.65 \); Fig. 11).

**Publication bias**

To exclude potential publication bias, funnel plots for publication bias were performed. No publication bias
Table 1  Baseline characteristics of the included studies

| Fist author (year) | Country | Sample size (n) | BMSC group (n) | CABG group (n) | Follow-up (months) | Age (years) | Sex, (male/ female) | Type of stem cells | Dose of stem cells | Route of cell administration | Treatment of control group | Method for determining outcome measure |
|-------------------|---------|----------------|----------------|----------------|-------------------|-------------|---------------------|-------------------|-------------------|--------------------------|--------------------------|----------------------------------|
| Patel et al. (2005) | Argentina | 20 | 10 | 10 | 6 | 64.8 ± 3.9 | 63.6 ± 4.9 | 8/2 | CD 34+ | 22.0 × 10^6(median) | IM | off-pump | CABG-only | ECHO |
| Hendrikx et al. (2006) | Belgium | 20 | 10 | 10 | 4 | 63.2 ± 8.5 | 66.8 ± 9.2 | 10/0 | BMSC | 60.25 ± 3.15 × 10^6 | IM | CABG-only | MRI | |
| Stamm et al. (2007) | Germany | 40 | 20 | 20 | 12 | 62 ± 10.2 | 63.5 ± 8.4 | 15/5 | CD 133+ | 5.0 ± 10^6(median)(range 1.08 × 10^6 to 8.35 × 10^7) | IM | CABG-only | ECHO | |
| Ang et al. (2008) | UK | 62 | 21/21a | 20 | 6 | 64.7 ± 8.7/62.1 ± 8.7 | 61.3 ± 8.3 | 15/6/19/2 | 18/2 | BMSC | 84 ± 56 × 10^6/115 ± 73 × 10^6 | IM/C | CABG-only | MRI | |
| Zhao et al. (2008) | China | 36 | 18 | 18 | 6 | 60.3 ± 10.4 | 59.1 ± 15.7 | 15/3 | BMWNC | 6.59 ± 5.12 × 10^8 | IM | CABG+ placebo | ECHO | |
| Hu et al. (2011) | China | 60 | 31 | 29 | 6 | 56.61 ± 9.72 | 58.27 ± 8.86 | NA | NA | BMWNC | 13.17 ± 10.66 × 10^7 | IC | CABG+ placebo | MRI | |
| Maurer et al. (2012) | France | 14 | 7 | 7 | 6 | 58 ± 10 | 57 ± 10 | 7/0 | 6/1 | BMWNC | NA | IM | CABG-only | MRI | |
| Lu et al. (2013) | China | 50 | 25 | 25 | 12 | 58.0 ± 7.8 | 57.0 ± 8.3 | 22/3 | 24/1 | BMWNC | 13.38 ± 8.14 × 10^7 | IC | CABG+ placebo | MRI | |
| Nasseri et al. (2014) | Germany | 60 | 30 | 30 | 6 | 61.9 ± 7.3 | 62.7 ± 10.6 | 28/2 | 29/1 | CD 133+ | 5.1 ± 1.017 × 10^6(median)(IQR 3.0 × 10^6 to 9.1 × 10^6) | IM | CABG+ placebo | MRI | |
| Patla et al. (2014) | Finland | 39 | 20 | 19 | 12 | 65(57–73)(median) | 64(58–70)(median) | 19/1 | 18/1 | BMWNC | 8.4 × 10^8(median)(IQR 5.2 × 10^8 to 13.5 × 10^8) | IM | CABG+ placebo | MRI | |
| Trifunović et al. (2015) | Serbia | 30 | 15 | 15 | 60(median) | 53.8 ± 10.1 | 60 ± 6.8 | 14/1 | 14/1 | BMWNC | 70.7 ± 32.4 × 10^6 | IM | CABG-only | ECHO | |
| Wang et al. (2015) | China | 90 | 45 | 45 | 6 | 61.4 ± 7.45 | 62.9 ± 6.93 | 37/8 | 35/10 | BMSC | 5.21 ± 0.44 × 10^8 | IM | CABG+ placebo | ECHO | |
| Noiseux et al. (2016) | Canada | 33 | 19 | 14 | 6 | 66.4 ± 6.5 | 63.1 ± 7.2 | 17/2 | 13/1 | CD 133+ | 6.5 ± 3.1 × 10^6 | IM | CABG+ placebo | MRI | |
| Wang et al. (2016) | China | 33 | 17 | 16 | 24 | 65.6 ± 3.97 | 65.5 ± 5.6 | NA | NA | BMWNC | 98.5 ± 48.3 × 10^6 | IM | CABG-only | ECHO | |
| Lu et al. (2017) | China | 40 | 20 | 20 | 24 | 51.7 ± 2.5 | 52.6 ± 3.8 | 8/12 | 12/8 | CD 34+ | NA | IM | CABG-only | ECHO | |
| Steinhoff et al. (2017) | Germany | 58 | 28 | 30 | 6 | 64.0 ± 7.20 | 63.6 ± 7.75 | 26/2 | 26/4 | CD 133+ | 2.29 ± 1.42 × 10^6 | IM | CABG+ placebo | MRI |
| Fist author (year) | Country | Sample size (n) | BMSC group (n) | CABG group (n) | Follow-up (months) | Age (years) | Sex, (male/female) | Type of stem cells | Dose of stem cells | Route of cell administration | Treatment of control group | Method for determining outcome measure |
|---------------------|--------|----------------|---------------|---------------|------------------|-------------|------------------|-------------------|------------------|------------------------|-----------------------|-----------------------------|
| Laguna et al. (2018) | Spain  | 17             | 8             | 9             | 9                | 62.63±8.35 | 64.78±11.48 | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | IM | CABG+ placebo | ECHO |
| Naseri et al. (2018) | Iran   | 77             | 21/30b       | 26            | 18               | 53.14±8.56/51.45±7.49 | 55.50±8.54 | 19/2, 27/3 | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | 19/2, 27/3 | MNC/CD 133+ | IM | CABG+ placebo | SPECT |
| Oi et al. (2018)     | China  | 42             | 24            | 18            | 12               | 57.88±8.52 | 56.56±9.09 | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | IM | CABG+ placebo | SPECT |
| Mann et al. (2019)   | Netherlands | 39          | 19            | 20            | 12               | 65±7        | 65±8       | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | IM | CABG+ placebo | SPECT |
| Soetisna et al. (2020) | Indonesia | 26          | 13            | 13            | 6                | 54.61±8.07 | 57.46±6.33 | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | IM | CABG+ placebo | SPECT |
| Ulus et al. (2020)   | Turkey | 28             | 12            | 16            | 12               | 56.9±1.5(SE) | 65.3±1.7(SE) | BMSC Group | BMSC Group | CABG Group | BMSC Group | CABG Group | BMSC Group | CABG Group | IM | CABG+ placebo | SPECT |

Values are expressed as the mean ± standard deviation

a Three arms for the study: IM BMSC injection vs IC BMSC injection vs CABG alone

b Three arms for the study: MNC injection vs CD 133+ injection vs CABG alone
was evident for the studies included in the LVEF, LVEDV, LVESV, LVESD, LVEDD and 6MWT meta-analysis. But publication bias may exist for the studies included in the LVEDVI and LVESVI according to funnel plots.

**Subgroup analysis and sensitivity analysis of LVEF**

No statistical differences have been found within subgroups based on follow-up period, type of stem cells, route of cell administration, dose of stem cells and baseline LVEF, except the subgroups of measurement method for the LVEF (ECHO, SPECT or MRI) \( (P = 0.05; \text{Table 2}) \). Leave-one-out sensitivity analysis indicated that the results were not markedly affected by the exclusion.

**Discussion**

In this meta-analysis, CABG combined with BMSC transplantation showed an improved cardiac function in patients with IHD compared with CABG alone. The change of LVEF from baseline to follow-up in the BMSC group increased by 3.87% (CI: 1.93–5.80%) compared with that in the CABG group. But the results were highly heterogeneous \( (I^2 = 80\%) \). A detailed subgroup analysis was performed to explore differences in LVEF change and revealed that these results were consistent regardless of the follow-up time, type of stem cells, route of cell injection (IM or IC), dose of stem cells and baseline LVEF.

Subgroup analysis of LVEF measurements (echocardiography, SPECT, or MRI) showed that the choice of method influenced the determined effectiveness of CABG combined with BMSC transplantation in IHD patients. Method of LVEF measurements was revealed as a significant factor contributing to the heterogeneity of the results. In addition, subgroup analysis of echocardiographic tests demonstrated higher values of LVEF improvement but poor homogeneous results. However, subgroup analysis of MRI did not show any significant improvement of LVEF and more homogeneous results. Echocardiography, SPECT and MRI have important diagnostic value in assessing cardiac function. Nonetheless, echocardiographic measurements are affected by the ultrasonographer, whereas MRI and SPECT are more reliable and accurate for measuring cardiac function in IHD patients. The source of heterogeneity in these results cannot be identified sufficiently. Although the subgroup analysis showed the method of LVEF and SPECT assessment as significant factors, this finding could not clinically explain the differences in the outcomes reported by different trials. The high SD values in some trials may demonstrate that the cause of the different outcomes reported by the trials might be due to variation in patient response to BMSC transplantation.

Subgroup analysis suggested that the use of BMMNCs or BMCs may lead to a more pronounced improvement in LVEF compared to CD133+ or CD34+ cells, that 2 of the 7 studies that included CD133+ or CD34+ cells in the meta-analysis had an unfavorable MD, and 2 of the 10 studies using BMMNCs or BMCs had an unfavorable MD. But the study of Naseri et al. [12] suggested that CD133+ cells had slightly greater efficacy compared to BMMNCs. Naseri et al. [12] have commented that the heterogeneous population of the BMMNCs may affect homing of the desired cells and previous human studies have shown that intracoronary transplantation with a small concentration of bone marrow progenitor cells has a sevenfold higher homing ability compared to larger numbers of BMMNCs. Noisieux et al. [20] suggested that selected CD133+, CD34+, CD45+ hematopoietic
progenitor cells have vasculogenic properties that may improve perfusion in ischemic cardiomyopathy. However, results may be limited by the small sample size of groups treated with CD133+ or CD34+ cells and autologous cell agents are medical products characterized by the complexity of cell isolation protocols and cell product storage, and the methods used to evaluate the results may be inhomogeneous. These factors may affect the effectiveness of cell therapy in improving heart function. In addition, subgroup analysis of dose of stem cells demonstrated that the number of injected BMSCs was not a significant factor affecting the heterogeneity of the data, and the change of LVEF may be independent of the dose of BMSCs.

Subgroup analysis of IC injection demonstrated higher values of LVEF improvement but poor homogeneous results [MD 5.07% (2.34 to 7.80%), I²=0%], while MD of IM injection group is 3.80%(1.53 to 6.06, I²=84%). Hu et al. [7] have commented that stem cells in the process of operation were shipped to the myocardial, mainly around the infarction area, while a large number of transplanted cells by intramyocardial in situ, but a large number of cells during ischemia or infarction area reducing survival and impairing proliferation ability, in addition, the uneven distribution of delivery within myocardial cells, some parts need to cell therapy can't reach. In their study [7], the aorta was open 5 min after cell injection, extending the contact time between BMMNCs and small coronary vessels and enhancing the adhesion of BMMNCs, thereby reducing the number of BMMNCs washed out of the heart. They [7] hypothesized that in a cardiac arrest, capillaries dilate and blood vessel permeability increases, so transplanted cells attached to the blood vessel wall migrate easily to the myocardium. Naseri et al. [12] hold the opposite view that intramuscular injection was the most effective method because cells are more reliably located in the heart by direct visualization and delivery to the target site, while many of the injected cells deliver to the lungs or liver with intracoronary injections. More high-quality research is needed to determine which approach is better.

LVESVchange and LVEDVchange decreased in the BMSC group, but the difference was not statistically significant compared with the CABG group. Our meta-analysis demonstrated that there was a statistical difference in LVEDVchange (MD = −10.57 ml/m²; 95% CI: −19.86 to −1.28 ml/m²; P = 0.03) and LVESVchange (MD = −9.49 ml/m²; 95% CI: −16.95 to −2.03 ml/m²; P = 0.01) between the BMSC and CABG groups, while the meta-analysis of Wu et al. [1] with 14 RCTs revealed no statistically difference between two groups. These indexes are more reflective regarding the heart function compared with LVEDV and LVESV, as each individual's
**Fig. 4** Forest plot of the difference in the change from baseline in the LVEF between the BMSC and CABG groups

**Fig. 5** Forest plot of the difference in the change from baseline in the LVEDV between the BMSC and CABG groups

**Fig. 6** Forest plot of the difference in the change from baseline in the LVEDVI between the BMSC and CABG groups
body surface area is different. This may be one of the reasons for the difference in LVEDV and LVESV not being statistically significant.

LVESD change and LVEDD change decreased in the BMSC group compared with the CABG group. There was a statistically difference in LVESD change (MD = −3.50 mm;
95% CI: $-5.58$ to $-1.42$ mm; $P=0.001$) and no statistically difference in LVEDD\textsubscript{change} (MD $=-2.49$ mm; 95% CI: $-7.27$ to $2.28$ mm; $P=0.31$). This meant the BMSC group may benefit more than the CABG group in LVESD.

There are some points of view in previous studies. Wang et al. [30] have commented that paracrine effects of BMMNCs transplantation and the intervention time may play a key role in the outcome, the left ventricular remodeling is more likely to be prohibited and the left ventricular systolic function obtains the opportunity to improve steadily in the long term while transplanted at the acute myocardial infarction setting, limited reduction in MI size, short-term improvement in LV function, and disappearance of paracrine effects over time when BMMNCs is transplanted at old myocardial infarction setting in which the left ventricular remodeling has already developed and the paracrine effect of BMMNCs is mainly acting on the transitional zone of old myocardial infarction. Wang et al. [10] suggested that transplantation during off-pump coronary artery bypass grafts could reduce ischemia and reperfusion injury and restore vascular supply, thereby increasing stem cell survival rate and avoiding inflammation, loss of survival signal of extracellular matrix components and release of ischemic cardiac cytotoxic factors leading to high mortality of stem cells after transplantation.

BMSCs are an ideal cell resource for cell therapy. BMSCs are easy to harvest, and the biological characteristics are not affected after isolation. There are several important subclasses, such as endothelial progenitor cells, mesenchymal stem cells, and hemopoietic progenitor cells; each type may be capable of improving heart function [7].
The detailed mechanism of autologous bone marrow stem cell transplantation for patients undergoing coronary artery bypass grafting has not been fully elucidated. The role of CD133+ cells in reducing nonviable segments, improving LVEF and wall thickening is unclear. Nasre et al. [12] have commented that previous animal experiments have shown that the transplanted cells integrate into the new environment and form new vasculature and myocardium. Wang et al. [30] have commented that a series of experimental studies have shown that BMMNCs can express a large number of cytokines, prevent cardiomyocyte apoptosis, promote angiogenesis, and recruit endogenous stem cells for cell regeneration and fusion. Wang et al. [10] have suggested that the suppression of fibrosis and the improvement of ventricular remodeling induced by BMSCs transplantation may play important roles in improving cardiac function. Lu et al. [11] have commented that autologous BMMNCs transplantation increased viable myocardium and improved microcirculation of infarcted myocardium. Previous animal studies have suggested that exogenous Shh protein may promote the improvement of cardiac function of CD34+ cells after bone marrow stem cell transplantation [11]. Previous studies have shown that erythropoietin combined with granulocyte-colony-stimulating factor can enhance vascular formation and reduce infarct area after bone marrow stem cell transplantation in myocardial infarction area by increasing endothelial progenitor cell mobilization and up-regulating vascular endothelial growth factor and other microenvironments [11].

Overall, the results of this meta-analysis should be interpreted with caution, especially the results of subgroup analyses, as the number of studies per subgroup is further reduced. Therefore, future meta-analyses must include more studies to obtain significant results.

Limitations
While the results of this study seem promising for the efficacy of BMSC transplantation, there were also certain limitations: There was significant heterogeneity in the present meta-analysis. Follow-up work in most studies is relatively short, and the continued efficacy of BMSC transplantation in patients treated with CABG remains to be demonstrated.

Conclusion
Based on current evidence, autologous BMSC transplantation in patients receiving CABG appears to be associated with improved LV function, and this improvement is beyond that achieved by CABG alone. BMSC transplantation seems to be beneficial for patients receiving CABG. However, the differences in patients’ responses to this treatment require further study. Future research should focus on patient profiling and response to treatment to identify the patient population that could benefit most from this approach and the mechanisms of action of BMSC transplantation.

Abbreviations
CABG: Coronary artery bypass grafting; BMSC: Bone marrow stem cell; LV: Left ventricular; MD: Mean difference; CI: Confidence interval; IHD: Ischemic heart disease; BMSCs: Bone marrow stem cells; RCTs: Randomized controlled trials; LVEF: LV ejection fraction; LVESV: LV end-systolic volume; LVEDV: LV end-diastolic volume; LVESVI: LV end-systolic volume index; LVEDVI: LV end-diastolic volume index; LVESD: LV end-systolic diameter; LVEDD: LV end-diastolic diameter; 6MWT: 6-Minute walk test; MRI: Magnetic resonance imaging; SD: Standard deviation; SE: Standard error; ECHO: Echocardiography; SPECT: Single-photon emission computed tomography; BMMNCs: Bone marrow mononuclear cells; BMSCs: Bone marrow cells; IM: Intramyocardial; IC: Intracoronary.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13019-022-01838-2.

Acknowledgements
Not applicable.

Author contributions
Jianglong Hou: Conceptualization, Methodology, Supervision; Juelin Song and Kang He: Writing- Original draft preparation. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
All data generated or analysed during this study are included in this published article [and its additional files].

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 25 October 2021   Accepted: 17 April 2022
Published online: 25 June 2022

References
1. Wu S, Yao L, Yan P, et al. Autologous bone marrow stem cell therapy for patients undergoing coronary artery bypass grafting: a meta-analysis of 14 randomized controlled trials. Exp Ther Med. 2019;17(4):2985–94.
2. Brunskill SJ, Hyde CJ, Doree CJ, Watt SM, Martin-Rendon E. Route of delivery and baseline left ventricular ejection fraction, key factors of bone marrow-derived cell therapy for ischaemic heart disease. Eur J Heart Fail. 2009;11(9):887–96.

3. Tian T, Chen B, Xiao Y, Yang K, Zhou X. Intramyocardial autologous bone marrow cell transplantation for ischaemic heart disease: a systematic review and meta-analysis of randomized controlled trials. Atherosclerosis. 2014;233(2):485–92.

4. Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005;130(6):1631–8.

5. Stamm C, Kleine HD, Choi YH, et al. Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies. J Thorac Cardiovasc Surg. 2007;133(3):717–25.

6. Zhao Q, Sun Y, Xia C, Chen A, Wang Z. Randomized study of mononuclear bone marrow cell transplantation in patients with coronary surgery. Ann Thorac Surg. 2008;86(6):1833–40.

7. Hu S, Liu S, Zheng Z, et al. Isolated coronary artery bypass graft combined with bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: a single-center, randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol. 2011;57(24):2409–15.

8. Lu M, Liu S, Zheng Z, et al. Pilot trial of autologous bone marrow mononuclear cell transplantation through grafting artery: a sub-study focused on segmental left ventricular function recovery and scar reduction. Int J Cardiol. 2013;168(3):2221–7.

9. Trifunovic Z, Obradovic S, Balint B, et al. Functional recovery of patients with ischemic cardiomyopathy treated with coronary artery bypass surgery and concomitant intramyocardial bone marrow mononuclear cell implantation: a long-term follow-up study. Vojnosanit Pregl. 2015;72(3):225–32.

10. Wang H, Wang Z, Jiang H, et al. Effect of autologous bone marrow cell transplantation combined with off-pump coronary artery bypass grafting on cardiac function in patients with chronic myocardial infarction. Cardiology. 2015;130(1):27–33.

11. Liu G, Hao SH, Wang ZG, Zhang T, Wang HS, Zhang GX. Multiple imaging evaluation on the therapeutic efficacy of coronary artery bypass graft combined with autologous stem cell transplantation for myocardial infarction. Chin J Tissue Eng Res. 2017;21(33):5332–8.

12. Nasiri MH, Madani H, Ahmadi Tafti SH, et al. COMPARE CPM-RMI trial: intramyocardial transplantation of autologous bone marrow-derived CD133+ cells and MNCs during CABG in patients with recent MI: a phase II/III, multicenter, placebo-controlled, randomized, double-blind clinical trial. Cell J. 2018;20(2):267–77.

13. Qi Z, Liu S, Duan F. Effects of bone marrow mononuclear cells delivered through a graft vessel in patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular dysfunction. Med Ultrason. 2015;17(2):160–6.

14. Soetens EA, Sukmawan R, Setianto B, et al. Combined transapical and transseptal implantation of autologous CD 133+ bone marrow cells during bypass grafting improves cardiac function in patients with low ejection fraction. J Card Surg. 2020;35(4):740–6.

15. Hendrik M, Hensen K, Clijsters C, et al. Recovery of regional but not transmural function after peri-infarct autologous bone marrow transplantation: results from a randomized controlled clinical trial. Circulation. 2006;114(1 Suppl):I101-107.

16. Ang KL, Chin D, Leyva F, et al. Randomized, controlled trial of intramyocardial or intracoronary injection of autologous bone marrow cells into scarred myocardium during CABG versus CABG alone. Nat Clin Pract Cardiovasc Med. 2008;5(10):663–70.

17. Maureira P, Tran N, Dybalallah W, et al. Residual viability is a predictor of the perfusion enhancement obtained with the cell therapy of chronic myocardial infarction: a pilot multimodal imaging study. Clin Nucl Med. 2012;37(8):738–42.

18. Nasser EA, Ebelt W, Dandel M, et al. Autologous CD133+ bone marrow cells and bypass grafting for regeneration of ischaemic myocardium: the CARDIO133 trial. Eur Heart J. 2014;35(19):1263–74.

19. Patil A, Lehtinen M, Vento A, et al. Autologous bone marrow mononuclear cell transplantation in ischemic heart failure: a prospective, controlled, randomized, double-blind study of cell transplantation combined with coronary bypass. J Heart Lung Transplant. 2014;33(6):567–74.

20. Noiseux N, Mansour S, Weisel R, et al. The IMPACT-CABG trial: a multicenter, randomized clinical trial of CD133+ stem cell therapy during coronary artery bypass grafting for ischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2016;152(6):1582-1588.e1582.

21. Steinhoff G, Nesteruk J, Wolfien M, et al. Cardiac function improvement and bone marrow response: outcome analysis of the randomized PERFECT Phase III clinical trial of intramyocardial CD133+ application after myocardial infarction. EBioMedicine. 2017;22:208–24.

22. Laguna G, Maroto L, Fulquet E, Echevarría J, Revilla A, Urueta N, Sevilla T, Arnold R, Ramos B, Gutiérrez H, Serrador A. Effect of direct intramyocardial autologous stem cell grafting in the sub-acute phase after myocardial infarction. J Cardiovasc Surg (Torino). 2018;59(2):259–67.

23. Mann I, Tseng CCS, Rodrigo SF, et al. Intramyocardial bone marrow cell injection does not lead to functional improvement in patients with chronic ischaemic heart failure without considerable ischaemia. Neth Heart J. 2019;27(2):81–92.

24. Ulus AT, Mungan C, Kurtoglu M, et al. Intramyocardial transplantation of umbilical cord mesenchymal stem cells in chronic ischemic cardiomyopathy: a controlled, randomized clinical trial (HUC-HEART Trail). Int J Stem Cells. 2020;13(3):364–76.

25. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PloS Med. 2009;6(7):e1000100.

26. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 3.1.0 [updated March 2011]. The Cochrane Collaboration, 2011, England. Chichester, Available at: http://www.cochrane-handbook.org.

27. Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000;21(16):1387–96.

28. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805.

29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.

30. Wang R, Zhang L, Wang Y, et al. Long-term outcome of intra-myocardial injection of autologous bone marrow mononuclear cells combined with isolated coronary artery bypass grafting for patients with chronic ischemic heart failure. Heart Surg Forum. 2016;19(3):E131-138.

31. Qi Z, Duan F, Liu S, et al. Effects of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular function. Heart Surg Forum. 2014;17(2):160–6.

32. Qi Z, Liu S, Lv X, et al. Effects of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular remodelling. Mod Ultrasound. 2015;17(2):160–6.

33. Qi Z, Liu S, Lv X, et al. Effects of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left atrium function. Echocardiography. 2016;33(12):1835–43.