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Review Article

Bone marrow stem cell therapy in heart failure patients with low ejection fraction: a systematic review

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Abstract: The association of bone marrow stem cells (BMSCs) with cardiac function outcomes and treatment outcomes in heart failure (HF) patients with low ejection fraction (EF) has been heterogeneous across studies. This systematic review aimed to investigate the effect of BMSCs on functional, clinical, quality of life, and major adverse cardiovascular events (MACE) outcomes in HF patients with low EF. PubMed, Scopus, Clinicaltrial.gov, Cochrane Library, Google Scholar, and Web and reference databases were searched for articles that examined the effect of BMSCs therapy on improving cardiac outcomes in patients with low EF, from 2000 to 2024. Differences in left ventricular ejection fraction (LVEF), MACE, echocardiographic indices (left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV)), 6-min walk test (6-MWT), New York Heart Association (NYHA) class and immunologic responses were defined as outcomes. Low EF was defined as an EF <45%. Finally, 14 RCTs involving 710 HF patients with low EF were included. BMSCs transplantation was associated with improvements in echocardiographic parameters, EF rate, and NYHA class in most studies (9 of 14) compared to the control group, regardless of the time of outcome assessment (3 or 6 months). It also significantly improved the 6-MWT in most studies. Improvements in parameters and functional outcomes were similar at both evaluation periods, 6 and 12 months. The BMSCs transplantation was not significantly associated with the incidence of MACE and immunological responses. The results of this systematic review supported the positive role of BMSCs transplantation in improving echocardiographic parameters, EF rate, NYHA class, and 6-MWT in HF patients with low EF. BMSCs transplantation was not significantly associated with the incidence of MACE and immunological responses.

Keywords: Chronic heart disease, low ejection fraction, heart failure, bone marrow stem cell

Introduction

Chronic heart disease (CHD) is one of the most common causes of death worldwide, which challenges health systems [1-3]. Despite the development of new strategies to treat these patients, CHD remains a leading cause of death worldwide, particularly in developing countries, and this trend is expected to increase with the aging population and the increase in chronic diseases such as hypertension and diabetes [4-7]. More than half of these patients die within five years [8].

Heart failure (HF) is a life-threatening clinical condition that is one of the leading causes of death from heart disease. In recent years, HF societies globally have reached a consensus on a standard definition of HF as "a clinical syndrome characterized by symptoms and/or signs resulting from a structural and/or functional cardiac irregularity, verified by increased levels of natriuretic peptides and/or objective signs of pulmonary or systemic congestion". Additionally, there is a standardized classification into HF with reduced ejection fraction (EF) (HFrEF) (left ventricular [LV] EF [LVEF]: ≤40%), HF with mildly reduced EF (HFmrEF) (LVEF: 41% to 49%), HF with preserved EF (HFpEF) (LVEF: ≥50%), and HF with improved EF [9]. EF is a key measure of how well the heart pumps blood, and changes in it indicate heart failure, which helps doctors diagnose and treat patients [10]. A reduced LVEF and an LVEF below 45% are

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indicators of unfavorable outcomes and higher mortality in an inpatient environment, respectively [11]. Therefore, any treatment that improves EF can help reduce the mortality and burden of this patient.

There is currently no consensus on a specific treatment strategy for patients with HFrEF [12]. For patients with HFrEF, treatment typically involves a combination of medications, including ACE inhibitors (or ARNIs), beta-blockers, renin angiotensin-aldosterone system (RAAS) blockers, mineralocorticoid receptor antagonists (MRAs), SGLT2 inhibitors, diuretics, and digoxin. In some cases, implantable devices such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices may also be used [12, 13]. However, there is no evidence to suggest that any one of these treatments is superior in managing patients with heart failure. Cardiac regeneration and restoration of cardiac function are not fully achieved with traditional medical therapy as routine treatments [14-16]. In recent years, researchers have focused on the role of stem cell therapy in myocardial regeneration and the restoration of cardiac function [17, 18].

Bone marrow stem cells (BMSCs), primarily comprising hematopoietic stem cells and mesenchymal stem cells, can differentiate into mesodermal and ectodermal tissues when provided with the right conditions [19]. Due to their convenience, safety, ease of in vitro cultivation, and potential for autologous replantation, BMSCs have emerged as a significant source of cells for tissue engineering [20].

Several clinical trials have shown that BMSCs therapy can be associated with improved cardiac function restoration and better treatment outcomes in patients with low EF [18, 21-23]. The association of BMSCs therapy with improved cardiac functional outcomes, clinical outcomes, tissue regeneration, and quality of life in patients with severe to low EF has been heterogeneous [19, 21, 23-25].

The inconsistency in these research results could be attributed to several factors, including the limited sample size, the underlying cause of the cardiomyopathy, the stage of the disease, the type of cells utilized in the transplantation, and the duration of treatment and follow-up. To our knowledge, the effect of BMSCs therapy on treatment outcomes in patients with low EF has not been investigated in a comprehensive review. This systematic review aimed to investigate the effect of BMSCs therapy on cardiac remodelling, quality of life, and adverse events in patients with low EF.

Methods for literature search

This systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).

Search strategy

PubMed, Scopus, Clinicaltrial.gov, Cochrane Library, Google Scholar, and Web and reference databases were searched for articles that examined the effect of BMSCs therapy on improving cardiac outcomes in patients with low EF, from 2000 to 2024. The protocol number for the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42024607064. Two independent investigators with the following database-appropriate terms conducted the literature search. “Chronic ischemic heart disease”, “ischemic heart disease”, “low ejection fraction”, “cardiomyopathy”, “Myocardial Disease”, “Heart Failure”, “Heart Decompensation”, “stem cell”, “bone marrow”, “mononuclear cell”, “mesenchymal cell”, “myocardial infarction” and “acute myocardial infarction”.

Eligibility criteria

In this systematic review, we included all studies that examined the effect of BMSCs therapy on cardiac outcomes in patients with heart failure with low EF, Patients with chronic heart failure or cardiomyopathy, administration of BMSCs, studies with a minimum follow-up of 3 months and reporting clinical outcomes or echocardiographic indices. Low EF was defined as an EF <45%. Administration of other stem cells, letters to the editor, interventional studies, experimental studies, review and meta-analysis articles and lack of access to the full text of the article were defined as exclusion criteria.

Outcomes

Differences in left ventricular ejection fraction (LVEF), major adverse cardiovascular events

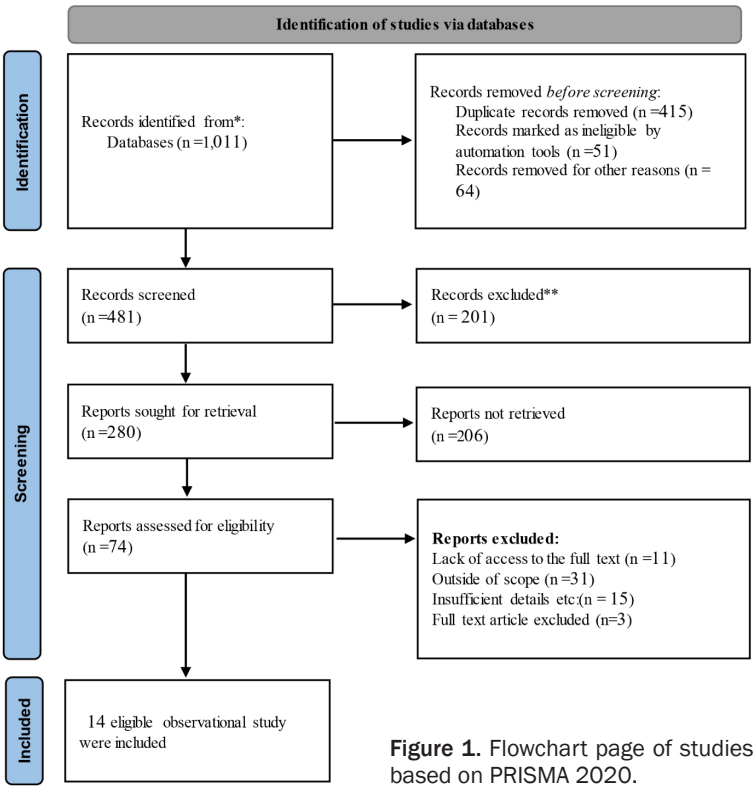

Figure 1. Flowchart page of studies based on PRISMA 2020.

(MACE), echocardiographic indices (left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV)), 6-min walk test (6-MWT), New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLHFQ) score and Immunologic Responses were defined as outcomes.

In addition to cardiac imaging studies, efficacy assessments in the primary studies included a standardized 6-minute walk test, measured by a cardiologist [26]. The NYHA classification system comprises four categories: Class I indicates no limitations in physical activity; Class II signifies a slight limitation; Class III denotes a significant limitation; and Class IV reflects an inability to engage in any physical activity without experiencing symptoms [27].

To evaluate the impact of heart failure on patients' quality of life, the MLHFQ was utilized [1]. Each question on the questionnaire has a response scale ranging from 0 (no impact) to 5 (very much). The total score is calculated by adding the responses to 21 questions, resulting in a possible score that ranges from 0 (no impact) to 105 (a strong impact of heart failure on daily life). This instrument is recognized as both valid and effective. An increase of over 10% in the score between two assessments indicates that patients may be at high risk for adverse outcomes in the following 12 months.

Screening

During the initial database search using the specified search terms, 1,011 studies were identified. Duplicate articles between databases were identified using EndNote version 22. Two independent investigators for inclusion criteria assessed the remaining articles. The initial evaluation was based on the title and abstract of the articles. The full text of 74 articles was reviewed for final evaluation based on the research question and objectives. Finally, 14 clinical trials were included (**Figure 1**).

Data extraction

Two independent researchers extracted data using Excel software in two separate files. A checklist of key variables was designed based on a literature review and in consultation with a cardio-oncologist and an epidemiologist. A third researcher resolved any discrepancies for variable extraction. The variables of this systematic review include the first author, publication and county of the study, the study design, total heart failure patients, number of patients undergoing BMSCs therapy, baseline EF, mean EF disorder before and after treatment, mean difference in 6-MWT, imaging modality, cell type (Allo/Auto), follow-up period, gender (male), outcomes studied, and study results.

Quality assessment

The quality of the eligible studies was evaluated using the Cochrane Collaboration's tool for assessing bias in randomized trials [28]. Each of the included RCTs underwent a quality evaluation and was categorized as having a high,

Table 1. Characteristics of patients in the studies and the quality of the included studies

Author	Country	Study design	Sample size	Age	Cell Type	EF %	sex (Male)	Follow up (Month)	Risk of bias assessment
SLMA Beeres (2007) [24]	Netherlands	RCTs	15	63.2	Auto	<35	14	3	High
M Tendera (2009) [23]	Poland	RCTs	200	59.1	Auto	<40	51	6	Low
A Rivas-Plata (2010) [36]	Peru	RCTs	30	62.1	Auto	<40	25	26	Some concerns
S Hu (2011) [25]	China	RCTs	20	56.6	Auto	<35	8	6	Some concerns
JM Hare (2012) [21]	USA	RCTs	30	63.1	Allo/Auto	<40	26	12	Some concerns
AW Heldman (2014) [19]	USA	RCTs	40	57.1	Auto	<45	17	12	Some concerns
BA Nasseri (2014) [35]	Germany	RCTs	60	62.7	Auto	<35	27	6	Some concerns
EC Perin (2015) [34]	USA	RCTs	60	62.2	Allo	<45	27	12	Some concerns
AB Mathiasen (2015) [22]	Denmark	RCTs	60	66.1	Auto	<40	35	6	Some concerns
Z Qi (2015) [33]	China	RCTs	42	57.88	Auto	<35	23	6	High
W Xiao (2017) [32]	China	RCTs	37	51.6	Auto	<40	15	12	Low
TW Soetisna (2020) [30]	Indonesia	RCTs	26	54.6	Auto	<35	12	6	Some concerns
AB Mathiasen (2020) [31]	Denmark	RCTs	60	66.1	Auto	<45	38	12	Low
TW Soetisna (2021) [29]	Indonesia	RCTs	30	64.2	Auto	<35	26	6	Some concerns

low, or some concerns regarding the risk of bias across different domains.

Statistical analysis

Descriptive statistics were used to analyze qualitative variables. The results were presented in a table. The mean difference in EF rate and 6-MWT before and after treatment was estimated using Stata version 17 software. Quantitative variables, such as age, difference in EF, and difference in 6-MWD, were reported with means and standard deviations. Frequency and % were used to report categorical variables such as NYHA classification.

Results

Fourteen RCT studies [19, 21-25, 29-36] including 710 (BMSCs therapy (393 patients and control (317 patients)) with severe to low EF were included in this meta-analysis. The mean age of the patients was 61.6 ± 2.9 years. 88% of patients were male. Most of the studies were conducted in developed countries. Most studies were of moderate quality. The characteristics of the studies included in this meta-analysis are reported separately in **Table 1**.

Functional status, cardiac remodelling and pulmonary function

The effect of BMSCs on EF changes before and after treatment was examined in 14 studies [23, 24]. In nine studies, BMSCs was significantly associated with improved EF rate [22-25, 29-32, 36]. BMSCs therapy improved the EF rate by an average of 6.01%, with a range of 1.1% to 10.9% in different studies. In a clinical trial, A Rivas-Plata et al. [36], investigated the effect of BMSCs on improving cardiac outcomes in 34 patients with chronic heart failure and low EF in two groups (23 bypass graft plus BMSCs (23 patients) and vascular graft (11 patients)), showed that at 26 months follow-up, BMSCs was associated with a significantly improved EF rate compared to the control group (10.9% vs. 2.3%). BMSCs was associated with a significantly improved EF (10.9% vs. 2.3%). They also demonstrated that the rate of improvement in functional class was significantly greater in the BMSCs group compared to the control group. SLMA Beeres et al. [24], also reported similar results. S Hu et al. [25] showed, in a 6-month follow-up, that CABG + BMSCs was significantly associated with an improved EF rate (more than 10%) and a lower left ventricular end-systolic volume index compared with the control group. Z. Qi et al. [33] also reported similar results. AB Mathiasen et al. [22], showed that BMSCs therapy was associated with an improvement in LVEF (mean difference: 6.2%), stroke volume (mean difference: 18.4 ml), and myocardial mass (mean difference: 5.7 g) compared to placebo. In another study, TW Soetisna et al. [29], evaluated the effect of CABG + CD133 treatment on improving cardiac outcomes compared with CABG alone in 30 patients with ischemic heart disease with EF. They showed that CABG + CD133 therapy was associated with improvement in EF and wall motion score. However, there was no significant association with improvement in left

Table 2. Outcomes and important notes of the reported studies

Author	Imaging modality	Difference in EF	Difference in 6-MWD	Final clinical outcomes	Key Finding
SLMA Beeres (2007) [24]	Echo/CT/MRI	4.3%	NA	NYHA class, LV ejection fraction, regional wall thickening and perfusion score	BMSCs transplantation was safe in patients with chronic myocardial infarction and severe EF dysfunction and may be associated with a reduction in heart failure symptoms and improvement in LV function.
M Tendera (2009) [23]	Echo/CT/MRI	5.4%	NA	LV ejection fraction and major cardiovascular event	BMSCs could be associated with LVEF improvement in patients with baseline LVEF <37%.
A Rivas-Plata (2010) [36]	Echo/CT/MRI	10.9%	NA	NYHA class, LV ejection fraction and LV end-systolic volume index	In patients with chronic heart failure and low EF, BMSCs transplantation was safe and may be associated with improved ventricular systolic function and functional class.
S Hu (2011) [25]	CMR	10.62%	45.1	LV ejection fraction, LV end-systolic volume index, wall motion index score and 6-MWT	CABG + BMSCs was significantly associated with improved cardiac outcomes in patients with prior MI and chronic heart failure.
JM Hare (2012) [21]	Echo/CT	1.98%	46.53	LV ejection fraction, 6-MWT, and MLHFQ score, EED, sphericity index, and LV end-diastolic volume	BMSC injection had a positive effect on improving patient functional outcomes, quality of life, and ventricular remodeling.
AW Heldman (2014) [19]	Echo/CT/MRI	-1.23%	32.3	LV ejection fraction, regional myocardial function, Minnesota Heart Failure Lifespan score and 6-MWT, LV end-systolic volume index and major cardiovascular event	In patients with chronic ischemic cardiomyopathy and LV dysfunction, BMSCs were safe. BMSCs may be associated with improvements in quality of life and 6-minute walk distance, but were not significantly associated with improvements in functional outcomes and EF rate.
BA Nasseri (2014) [35]	Echo/MRI	2.1%	12.7	LV ejection fraction, 6-MWT, NYHA index and scar mass and MLHFQ score, EED, sphericity index, and LV end-diastolic volume	Intramyocardial injection of CD133 + BMSCs, although it may be associated with improvements in some indices, including scar size and regional perfusion, had no significant effect on global LV function and clinical symptoms.
EC Perin (2015) [34]	Echo/MRI	1.1%	26.3	LV ejection fraction and major cardiovascular event	Transendocardial injection of allogeneic BMSCs in low EF patients is safe and may be associated with improvement functional outcomes.
AB Mathiasen (2015) [22]	Echo/CT/MRI	5.01%	20.1	LV ejection fraction, LV end-systolic volume index, wall motion index score and 6-min walking test.	In patients with severe ischemic heart failure, 6 months after treatment, intramyocardial injection of autologous expanded mesenchymal stem cell cultures was safe and improved myocardial function.
Z Qi (2015) [33]	Echo/CT/MRI	1.4%	NA	LV ejection fraction and major cardiovascular event	CABG + BMSCs compared to CABG was significantly associated with better cardiac outcomes.
W Xiao (2017) [32]	Echo/SPECT	6.9%	NA	LV ejection fraction, NYHA index and myocardial perfusion	In patients with EF <40 (severe), intracoronary bone marrow stem cell transplantation may be associated with improved cardiac outcomes.
TW Soetisna (2020) [30]	Echo/MRI	8.69%	113.15	LV ejection fraction, wall motion score, scar size, 6-MWT, NYHA index and MLHFQ score	In patients with low EF coronary artery disease, combined CD133 + BMSCs transplantation during bypass grafting significantly improved cardiac function compared with bypass grafting alone.
AB Mathiasen (2020) [31]	Echo/CT/MRI	6.2%	NA	LV ejection fraction, LV end-systolic volume index, stroke volume, myocardial mass wall, motion index score and 6-MWT	MSC infusion was associated with improvements in myocardial function and myocardial mass in patients with ischemic heart failure.
TW Soetisna (2021) [29]	Echo/MRI	8.69%	NA	LV ejection fraction, myocardial function, exercise capacity and 6-MWT	In patients with low EF, transplantation of CD 133+ stem cells combined with CABG improved myocardial function and indirectly improved functional exercise capacity and quality of life.

ventricular end-systolic volume and left ventricular end-diastolic volume 6 months after treatment (**Table 2**).

Five studies did not report a significant association between BMSCs and EF improvement [19, 21, 33-35]. M Tendera et al. [23] reported that six months after treatment, BMSCs was not significantly superior to the control group in improving LVEF, left ventricular end-systolic volume, and left ventricular end-diastolic volume compared to the control group. Whereas, BMSCs could be associated with LVEF improvement in patients with a baseline LVEF <37%. BMSCs was not significantly associated with major cardiovascular events (death, reinfarction, stroke, or target vessel revascularization), suggesting that BMSCs plays a positive role in improving EF in patients with severe EF decline. In another trial, JM Hare et al. [21] reported no significant association between BMSCs therapy and improvement in EF. These results were confirmed in other studies [19, 33-35].

SLMA Beeres. [24], also reported that BMSCs was associated with improvements in regional wall thickness and perfusion score. AW Heldman et al. [19], showed that BMSCs therapy was associated with improvement in regional myocardial function as measured by peak peripheral Eulerian pressure at the site of injection (more than 5%). These results were confirmed in other studies [35].

New York heart association class

NYHA class was reviewed in seven studies after the BMSCs [22, 24, 25, 31, 33, 35, 36]. Five studies reported that NYHA class improved after BMSCs treatment in patients with severe to moderate EF [24, 25, 33, 35]. A Rivas-Plata et al. [36] showed that the rate of improvement in functional class was significantly greater in the BMSC group than in the control group. While AB Mathiasen et al. [22] did not report a significant association between BMSC therapy and improvement in NYHA class.

Quality of life

Eleven studies reported that the 6-min walking test improved after BMSCs treatment in patients with low EF [19, 21, 22, 25, 29-35]. S Hu et al. [28] and Z Qi et al. [29] demonstrated in a 6-month follow-up that BMSCs therapy was significantly associated with improved results on the 6-min walking test. JM Hare et al. [21] showed that treatment with BMSCs was associated with improvements in the 6-MWT and MLHFQ scores. While AB Mathiasen et al. [22] did not report a significant association between BMSCs therapy and improvement in the 6-MWT and MLHFQ. They demonstrated that CABG combined with CD133 therapy was associated with an improvement in the 6-MWT. However, there was no significant association with improvement in MLHFQ parameters at 6 months after treatment [30].

Major adverse cardiovascular events

The frequency of MACE as well as the composite endpoint of death, reinfection, stroke, and TVR was similar among patients in the BMSCs group and the control groups [19, 21, 23-25, 32, 35, 36]. The incidence of MACE was approximately 33.3% and ranged from 22% to 43%.

Immunologic responses

In the majority of studies, BMSCs therapy did not induce significant donor-specific immune responses [21, 22, 29, 30, 32].

Discussion

The relevance of cell therapy, such as BMSCs and mesenchymal stromal cell (MSC), in heart failure in patients with preserved EF has been investigated in comprehensive studies [37, 38]. However, the effect of BMSC may differ in heart failure patients with low and severe EF compared to those with preserved EF. In this study, we investigated for the first time in a systematic review the effect of BMSCs therapy on improving cardiac parameters, quality of life, and MACE in patients with EF <45% in 14 RCTs, including 710 patients with a mean age of 61 years.

The results of this systematic review showed that BMSCs therapy in the majority of studies (9/14) in patients with EF <45% was significantly associated with improvement in EF and echocardiographic parameters, regardless of the time of assessment (6 or 12 months). BMSCs therapy also significantly improved 6-MWT in the majority of studies. NYHA class improved significantly after BMSCs therapy in the majority of studies. Improvement in parameters

and functional outcomes was similar at both assessment periods, 6 and 12 months. BMSCs therapy was not significantly associated with the incidence of MACE and immunologic responses, and the incidence of MACE ranged from 22 to 43%.

In a meta-analysis, in 2024, A Hosseinpour et al. [38], (2024) compared the efficacy of MSC versus bone marrow BMSCs in heart failure patients with preserved EF. They demonstrated that both types of stem cells were effective in improving EF, with no significant difference between the cells. The incidence of MACE was similar in both cell types and was not associated with a risk reduction. In a meta-analysis, R. Xu et al. [39] demonstrated that the improvement in LVEF rate was significantly higher in patients who received BMSCs transplantation compared to the control group, particularly in those with a lower baseline LVEF. In another systematic review, V Jeevanantham et al. [40] Showed that BMSCs transplantation was significantly associated with improved LV function, infarct size, and remodelling in patients with ischemic heart disease compared with standard care. They also showed that the reduction in mortality, recurrent myocardial infarction, and stent thrombosis was greater in patients who received BMSCs transplantation than in the control group. In our study, no significant association was observed between BMSCs therapy and reduced MACE and mortality, which could be explained by the differences in the populations studied in the two studies. In another study, Y. Wang et al. [41] reported that stem cell transplantation was significantly associated with improvements in LVEF, NYHA class, CCS grade, and LVESV, while having no significant effect on mortality. In a systematic review, A. Hosseinpour et al. [42] demonstrated that BMSCs transplantation was significantly associated with a reduced risk of acute myocardial infarction and long-term HF hospitalization. In a meta-analysis, Y Jiang et al. [43] reported that in patients with HF with reduced EF, BMSCs transplantation during CABG may be associated with better outcomes and improve LELV function.

Various populations of autologous and allogeneic stem cells have been examined in preclinical and clinical contexts of heart failure for their ability to repair or regenerate the damaged myocardium [44]. Initially, it was believed that the primary mechanism of cell therapy involved directly replacing injured cardiomyocytes with new, cell-derived ones through a process of transdifferentiation. Although this mechanism has been demonstrated in preclinical heart failure models, its clinical applicability has not been definitively proven [45]. Current evidence suggests that the principal reparative mechanisms of cell therapy in the failing myocardium are primarily driven by paracrine effects that influence myocardial neurohumoral activation, inflammation, fibrosis, apoptosis, Ca2+ handling and metabolism, stimulation of neovascularization, and activation of endogenous cardiac-resident cells [46, 47]. These mechanisms could lead to favourable outcomes in HFpEF by enhancing angiogenesis, reducing fibrosis, and lowering inflammation.

Limitations

Our study had strengths and weaknesses that should be noted. First, most primary studies were conducted in developed countries, and the the generalization of the results to other countries should be done with caution. The studies were conducted in a specific group of patients, and generalization of the results to other groups should be done with caution. The investigationinvestigation of the effect of BMSCs on functional, clinical, quality of life outcomes, and MACE in HF patients with low EF in a systematic review was the most important strength of our study.

Conclusion

The results of this systematic review supported the positive role of BMSCs transplantation in improving echocardiographic parameters, EF rate, NYHA class, and 6-MWT in HF patients with low EF. BMSCs transplantation was not significantly associated with the incidence of MACE and immunological responses. RCTs in large sample sizes can help clarify the role of BMSCs transplantation in these patients.

Disclosure of conflict of interest

None.

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