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Therapeutic Potential of Endothelial Progenitor Cells in Angiogenesis and Cardiac Regeneration: A Systematic Review and Meta-Analysis of Rodent Models

Samaneh Narimani[1], Reza Rahbarghazi[1, 2*], Hanieh Salehipourmehr[3], Maryam Taghavi Narmi[2], Hamid Lotfimehr[2], Robab Mehdipour[3]

[1]Department of Applied Cell Sciences, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Purpose: Myocardial infarction (MI), the leading cause of human mortality, is induced by a sudden interruption of blood supply. Among various stem cell types, endothelial progenitor cells (EPCs) are novel and valid cell sources for the restoration of vascularization in the ischemic tissue. The present study aimed to evaluate the regenerative properties of EPCs in rodent models of MI.

Methods: A comprehensive systematic search was implemented in Cochrane Library, Embase, PubMed, Scopus, and Web of Science databases without language limitation in Sep 2024. Of the 67 papers pooled, 42 met the inclusion criteria and were subjected to multiple analyses.

Results: Compared to the MI group, the overall effect size was confirmed in the groups receiving EPC with enhanced angiogenesis (SMD: 2.02, CI 95%: 1.51-2.54, $p<0.00001$; I2: 82%), reduced fibrosis (SMD: -1.48; 95% CI − 2.15, -0.81; $p < 0.0001$; I2: 88%), improved ejection fraction (EF; SMD: 1.72; 95% CI − 1.21, 2.23; $p < 0.00001$; I2: 87%), and fractional shortening (FS; SMD: 1.58; 95% CI − 1.13, 2.03; $p < 0.00001$; I2: 82%). Data confirmed significant improvements in the cardiac tissue parameters after intramyocardial injection of EPCs.

Conclusion: These data showed that EPC transplantation is an alternative therapy to ameliorate ischemic myocardium in rodents via the stimulation of angiogenesis, reduction of fibrosis, and improvement of fractional shortening and ejection fraction.

***Corresponding Authors:**
Reza Rahbarghazi, Email: rezarahbardvm@gmail.com, ORCID: 0000-0003-3864-9166

Introduction

Ischemic heart disease (IHD) is a global leading cause of human mortality and disability in the clinical setting.[1] Typically, MI occurs following partial or complete occlusion of a coronary artery leading to massive cardiomyocyte damage, inflammation, and subsequent fibrotic changes.[2] Notably, the contraction of fibroblasts and collagen fibers at the healing site can contribute to the thinning of the left ventricle (LV). Over time, the reduction of ejection fraction (EF) and lethal arrhythmias in an ischemic heart can be life-threatening.[3] Currently, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are clinical modalities for the restoration of blood and reduction of cardiomyocyte injury.[4] Unfortunately, these approaches are not fully effective, and the development and application of *de novo* therapeutic strategies are highly recommended.[5]

In recent decades, the discovery and application of stem cells in various pathological conditions have revolutionized regenerative medicine.[6] It has been shown that stem cells can promote the healing of ischemic myocardium via the release of cytokines, growth factors, and direct differentiation into cardiomyocytes.[6,7] Besides, these cells can accelerate the regeneration of injured myocardium via juxtacrine interaction and production of pro-angiogenesis factors.[8,9]

According to recent data, it has been confirmed that EPCs are valid cell sources for restoring dysfunctional endothelium via various reparative functions, especially promoting angiogenesis and vasculogenesis.[10] In this regard, EPCs alone or in combination with other stem cells or mature cells have been used in different studies to accelerate regenerative outcomes and circumvent limitations associated with the administration of single stem cell type alone.[11,12] Proteomic analyses have proved the existence of common specific surface molecules such as CD133, CD34, vascular endothelial growth factor-2 (VEGFR-2), Tie-2, and Sca-1 between EPCs and hematopoietic stem cells.[13] Following various pathologies and hypoxic conditions, EPCs are recruited from the bone marrow niche, the primary storage site in adults, to the circulation system.[14] Circulating EPCs migrate toward the injury sites in a cytokine gradient manner where they gradually lose their stemness features (CD133↓, and CD34↓) and mature into endothelial cells (ECs; CD31↑ and vWF↑).[15] Besides differentiation capacity, EPCs release several proangiogenesis factors (IGF-1, VEGF, HGF, FGF-2, etc.) to expedite the formation of new blood vessels in the hypoxic areas.[16] Data have indicated that the injection of EPCs in several animal models of MI can improve the healing of myocardium through the stimulation of angiogenesis, regulation of inflammation, and control of extracellular matrix (ECM) remodeling.[12]

In the present systematic review, the application of EPCs in the rodent model of MI and their potential in the restoration of injured myocardium mainly via angiogenesis was explored. To the best of our knowledge, there are few reports related to systematic review and metanalysis of EPCs in humans and different animal models of MI. Most of the studies have investigated the diagnostic properties of EPCs under certain pathological conditions such as ischemic diseases in humans or there are several reposts related to separate applications of EPCs in certain MI models in animals.[17-19] Although the reparative properties of EPCs have been proved in different MI animal models, it is imperative that data from various experiments with similar objectives be combined and assessed to minimize the possible bias and make logic in the interpretation of the obtained data.[20] In the last decades, rodents have been widely used for different experiments related to the MI model due to inherent advantages like small body mass and easy handling pre- and post-MI induction with minimal space and resources. Besides, researchers can have access to various rodents with similar genetic characteristics which facilitates high repeatability.[21] It seems that data from this study can provide invaluable data about the eligibility of EPC application in the alleviation of MI in the clinical setting.

Material and methods

The current systematic review and meta-analysis were conducted based on the PRISMA 2020 statement guideline. The used protocol was registered in the PROSPERO database (CRD42024571517).

Search strategy

A comprehensive systematic search was implemented in Cochrane Library, Embase, PubMed, Scopus, and Web of Science databases without the limitations of language and date in Sep 2024. After the completion of the systematic search, collected articles, experiments, and contacted authors were carefully monitored and validated for subsequent evaluations. The abstracts from the international congresses were also monitored. The strategy used in this study is shown in **Supplementary Table 1**.

Study design considerations

All preclinical studies associated with the application of EPCs in rodent models of MI, including mice and rats were reviewed. Rodents with experimentally induced MI in any age in both genders were included. EPCs transplantation in human counterparts, and other species (*i.e.*, rabbits, porcine, canines, etc.), and *in vitro* experiments were excluded from the present analysis. Data related to the administration of EPCs alone, but not in combination with other stem cell types, were collected. Also, studies related to the use of EPC exosomes in rodent models of MI were not included. Articles with no access to their full texts were not considered. In **Table 1**, inclusion and exclusion criteria are outlined.

The primary outcome indicators were “angiogenesis”, and “infarct size”. The secondary outcome indicators were “LVEF”, and “fractional shortening (FS)”. For the meta-analysis, the data containing at least one of the outcomes measured between 1- and 8 weeks post-EPC transplantation were used. If studies contained more than one set of data for primary or secondary outcome analysis, the selection was done based on the more relevant and common data.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Preclinical studies about EPCs as therapy on rodent models (mice and rats), with cardiac infarction in any age or gender • Endothelial progenitor cells • Studies including the combination therapy with EPC such as scaffold, miRNA, growth factors, and other type of stem cells • Studies with CD34+ cells transplantation • All experimental studies (preclinical)	• Not an animal study • Other animal study rather than rodents • Not a myocardial infarction model • Clinical studies on humans • In vitro studies • Other types of stem cells • Studies with CD133+ cells transplantation • Studies including combination therapy with EPC and other types of stem cells • Not transplantation of EPC and just mobilization investigation • EPCs-derived exosome transplantation • Other study type • In vitro studies • Studies without any access to the full text, or studies in the other languages, and retracted studies

Study selection

Once the databases were searched for the relevant papers, all collected citations were uploaded to EndNote 18 software with duplicate studies being deleted. Two separate reviewers blindly screened the titles and abstracts to

ensure the eligibility of the studies in terms of the inclusion and exclusion criteria. Any discrepancy was re-checked again by a third blind reviewer.

Data collection

The collected data from multiple search databases were organized using PRISMA guidelines. For this purpose, articles were entered into an Excel spreadsheet. The process was continued by an independent review of the selected abstracts by the same reviewers. Any disagreements were critically assessed until a precise decision was made and the opinion of a third reviewer was obtained if it was required.

Evaluation of methodological quality

Using the modified CAMARADES checklist, two independent reviewers monitored the methodological validity of the quantitative publications selected for retrieval before their inclusion in the systematic review. Again, any disagreements were resolved through consultation with a third reviewer.

Statistical analysis

The results of the selected data were analyzed using RevMan 5.4.1. Data are presented as mean ± SD with a 95% confidence interval (CI). Statistical heterogeneity was analyzed using the I2 value and the chi-square test. In this study, $p<0.05$ and $I2>50\%$ were considered statistical heterogeneity. Fixed and mixed models were used for low and high heterogeneity in the parameters analysis. The subgroup analysis was performed if needed. Publication bias was assessed using funnel plots and more formally with both Begg and Mazumdar's rank correlation test (Kendall's tau) and Egger's regression test. Begg's test assesses the correlation between the effect estimates and their variances, while Egger's test examines the relationship between the effect estimates and their standard errors. A p-value of less than 0.05 was indicative of statistically significant publication bias.

Results

Description of studies and risk of bias

The flow chart for data selection and handling is presented in **Figure 1**. Here, a modified CAMARADES quality checklist was used to assess the collected experiments. Of all peer-reviewed articles, 67 declared compliances with animal welfare regulations. It is worth mentioning that random allocation to different groups was detected in 28 studies and 42 experiments expressed a conflict-of-interest statement. Furthermore, 6 articles had blinded induction of MI in the rodent models and 30 studies benefitted from both animal exclusion criteria and blind outcome assessment based on our evaluation. In the selected articles, no study declared the methodology related to sample size calculation (**Figure 2**). All articles were included for quality synthesis (**Table 2**).

Table 2. Characteristics of included and excluded studies

Author (s)	Year	Study group	Species	Sex	Age (weeks)	Weight	status	Type of Disease	Intervention	The time between injury induction and the start of medication	Administration route	Cell type	Markers for cell characterization	EPC count
Atluri, P.[22]	2013	1: control (coronary ligation alone, n = 14), 2: implant of decellularized ECM (n = 13), 3: implant of ECM seeded with EPCs (n = 12), 4: implant of the engineered construct (n=9).	Wistar rat	Male	Adult	250-300 g	Healthy	MI	LAD ligation	After LAD ligation	Implanted	EPC from the bone marrow of Wistar rats' long bones	CD34, VEGFR2, DiL-Ac-LDL, isolectin, Aminoactinomycin D	5×10^6 cells/cm 2
Burghoff, S.[23]	2010	1: Controls (n = 3), 2: Control/+ phytohemagglutinin (n = 3), 3: MI (n = 3), 4: MI/+phytohemagglutinin (n = 2).	Wistar rat	Male	ND	350 g	Healthy	MI	LAD ligation for 2 h	4 days after LAD ligation	Intracoronary transplantation	EPCs from human peripheral blood	BS-1, DiL-AcLDL, vWF, CD31, CD144, CD3, CD34	1×10^6 hEPCs in 500 µl
Chang, Z.[24]	2018	1: healthy control, 2: sham-operated (only strung without the ligation of the artery; PBS injection), 3: model (subjected to LAD ligation and PBS injection), 4: EPC group (injection of immunofluorescence-confirmed EPC in the MI). (n = 10/group)	Sprague-Dawley rat	Male	6 weeks	300-350 g	Healthy	AMI	LAD ligation	2-3 min surgery completion	Intramyocardial injection	EPC from rats' peripheral blood	CD133, Flk-1	200 µL of 5×10^5/µl EPCs
Fang, Y.[25]	2018	1: experimental (ESCs injection) (n=10), 2: negative control groups (PBS only) (n=10).	Sprague-Dawley rat	Female	6-8 weeks	200-220 g	Healthy	AMI	Rats were injected with vitamin D3 once every 30 days (2x106 U/kg) and	Following anaesthetizing	Intramyocardial injection	Autologous ESCs	ND	1×10^4 ESCs in 100 µl

									received a high-fat diet containing 2% cholesterol, 3% lard oil, 0.5% sodium cholate, 0.2% propylthiouracil and 94.3% basic diet supplemented with vitamin D3 (1.25x106 U/kg) to establish acute myocardial infarction.					
Gaffey, A. C.[26]	2015	1: control (LAD coronary artery ligation with the injection of PBS), 2: EPCs alone, 3: STG alone, 4: STG-EPC construct. (n=41)	Wistar rat	Male	Adult	250-300 g	Healthy	MI	LAD ligation with suture	After LAD ligation	Intramyocardial injection of EPCs alone/ Treatment with the STG-EPC construct	EPC from the bone marrow of Wistar rats' long bones	DiL-LDL, VEGFR2, CD34	7×10^5 cells in 100 µl
Gaffey, A. C.[27]	2019	1: control (LAD ligation with injection of PBS, n = 10), 2: EPCs alone (n = 9),3: blank STG (n = 9), 4: STG + EPC construct (n = 11).	Wistar rat	Male	Adult	250-300 g	Healthy	AMI	LAD ligation	After LAD ligation	Intramyocardial injection of EPCs alone/ treatment with the STG-EPC construct	EPC from the bone marrow of Wistar rats' long bones	DiL-LDL, VEGFR2, CD35	7×10^5 cells in 100 µl
Quan, Z.[28]	2017	1: control (injection of PBS), 2: EPC (injection of PBS containing EPCs), 3: Tβ4-EPC (administration of EPCs pre-treated with Tβ4. (n = 8/group)	Sprague-Dawley rat	Female	Adult	200±20 g	Healthy	MI	Permanent LAD ligation	After the establishment of MI	Intramyocardial injection	EPC from the bone marrow of Sprague-Dawley rat's femurs and tibias	CD34, CD133, VEGFR2	2×10^6 EPCs in 100 µl

Schuh, A.[29]	2012	1: injection of SDF-1a infected EPCs (n = 8) intramyocardial or intracoronary, respectively (n = 8), 2: injection of non-transduced EPCs (intramyocardial (n = 8) and intracoronary (n = 8)), 3: medium as control group (n = 10).	Sprague-Dawley rat	Female	Adult	200-250 g	Healthy	MI	LAD ligation for 90 min	90 min after LAD	Intramyocardial and intracoronary	EPC from Sprague-Dawley rats' spleen	PECAM1, vWF	1 x 10^6 EPCs in 100 µl
Schuh, A.[30]	2008	1: BrdU-labelled EPCs (n = 12), 2: SDF-1a (n = 8), 3: EPCs+SDF-1a (n = 8), 4: (placebo control) only culture medium (n = 12).	Sprague-Dawley rat	Female	Adult	200-250 g	Healthy	AMI	LAD ligation	4 weeks after LAD ligation	Intramyocardial injection	EPC from human peripheral blood	Dil-Ac-LDL, VEGFR2, lectin, vWF	1 x 10^6 EPCs in 100 µl
Sen, S.[31]	2010	1: EPCs transduced by AAV-IGF-1, 2: or AAV-lacZ.	Sprague-Dawley rat	Male	7- 8 weeks	ND	Healthy	MI	LAD ligation	Immediately after LAD ligation	Intramyocardial injection	Autologous EPC from peripheral blood	Cell culture only	1 × 10^4 cells in 20 µl
She, Q.[32]	2012	1: Dil-ac-LDL fluorescence-labeled p6HRE-CMV-VEGF165-transfected EPCs, 2: pCMV-VEGF165-transfected EPCs, 3: EPCs, 4: normal saline, 5: sham surgery (control). (n = 10/group)	Sprague-Dawley rat	Male	Adult	180-230 g	Healthy	AMI	Permanent LAD ligation	After the establishment of MI	Tail vein injection	EPC from the bone marrow of Sprague-Dawley rats' femurs	CD34, CD133, VEGFR2, Dil-ac-LDL	2 x 10^7 cells/ml
Zhao, Y.[33]	2018	1: sham (surgery without LAD ligation), 2: EPC (EPC re-suspended in EGM-2), 3: Tβ4-EPC (Tβ4 pre-treated human EPCs), 4: control blank EGM-2 without cells. (n = 40)	Sprague-Dawley rat	Male	8 weeks	200-250 g	Healthy	MI	LAD ligation	After LAD ligation	Intramyocardial injection	EPC from human peripheral blood	VE-cadherin, KDR, CD34, AC133, Dil-LDL, lectin	1 x 10^6 in 150 µl

Boyle, A. J.[34]	2005	1: (MI, n=5) no treatment, 2: (ACE/BB, n=5) quinapril and metoprolol in drinking water, 3: (EPCs, n=5) human CD34+ cells, 4: (ACE/BB + EPCs, n=5) quinapril, metoprolol, and EPCs.	Rowett (mu/mu) athymic nude rat	Male	10 weeks	ND	Nude	AMI	LAD ligation	2 days after LAD ligation	Intravenous injection	CD34+ cells from human peripheral blood	CD34	2 x10^6 cells
Chaudeurge, A.[35]	2012	1: iron-loaded EPCs, and magnetic guidance (n = 14), 2: iron-loaded EPCs, without magnetic guidance (n = 10), 3: culture medium alone (n = 7).	Wistar rat	Femal e	ND	250 g	Immuno competent	MI	LAD ligation for 30 min, followed by 20 min of reperfusion + aorta cross-clamping	20 min after LAD ligation	Intramyocardial injection	EPC from human umbilical cord blood	CD31, CD144, VEGFR2, vWF	5 x10^5
Demetz, G.[36]	2017	1: IGF-2-transfected EPC-derived cells, 2: vector-only-transduced EPCs, 3: Control (PBS only).	Athymic nude rat	Male	6- 8 weeks	ND	Nude	AMI	LAD ligation for 30 min	30 min after LAD ligation	Intramyocardial injection	EPC from human umbilical cord blood	CD34	1 × 10^6 cells in 100 µL
Frederick, J. R.[37]	2010	1: control (n = 22), 2: ECM alone (ECM, n = 13), 3: ECM stimulated with SDF (ECM+SDF, n = 11), 4: ECM seeded with cells but not activated with SDF (ECM+EPC, n = 15), 5: ECM seeded with EPCs and activated with SDF (EPCM, n=21).	Lewis rat	Male	ND	250-300 g	Healthy	MI and progression to cardiomyopathy	LAD ligation	Following LAD ligation	Sutured to the anterolateral LV	EPC from Lewis rats' bone marrow	Dil-Ac-LDL, I-isolectin B4, CD3, 7AAD, CD45, VEGFR2, CXCR4	ND
Li, H.[38]	2018	1: control (n = 22), 2: blank vector (n = 24), 3: miR-126-3p transfection (n = 20).	Nude rat	ND	ND	200-250 g	Nude	ICM (Ischemic Cardio myopat	LAD ligation	4 weeks after LAD ligation	Intramyocardial injection	EPC from human peripheral blood	Ac-LDL, CD34, CD133	3 × 10^6 EPCs

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Mehmood, A.[39]	2015	1: serum-free medium injected, 2: untreated EPCs transplanted, 3: DZ treated EPCs (DZ EPCs) transplanted. (n = 6 survived rats in each group)	Wistar rat	Male	ND	200-250 g	Healthy	MI	Permanent LAD ligation	Immediately after LAD ligation	Intramyocardial injection	EPC from bone marrow	CD34, VEGFR2, eNOS, vWF, VE-cadherin	10^6 EPCs in 70 µl
Li, S. H.[40]	2015	1: Control (PBS injection), 2: EPCs, 3: transfection group (hTERT-EPCs).	Sprague-Dawley rat	Male and Female	4 weeks	80-100 g	Healthy	MI	LAD ligation for 1 h	ND	Intramyocardial injection	EPC from the bone marrow of SD rats Femur, humerus, tibias	CD31, CD34, CD133, VWF, FLK-1	ND
Lian, F.[41]	2008	1: the implantation (n = 60) received Dil-labelled EPCs, 2: the control (n = 60) received IMDM.	Sprague-Dawley rat	Male	8-10 weeks	300-350 g	Healthy	AMI	LAD ligation	After LAD ligation	Intramyocardial injection	Autologous EPC from rats' peripheral blood	CD31, CD34, VWF, FLK-1, Ac-LDL	2×10^5 EPCs
Poh, K. K.[42]	2020	1: Tβ4-treated EPCs (n = 7), 2: non-Tβ4 treated EPCs (n = 6), 3: medium alone injected (n = 6).	Zucker diabetic fatty rat	ND	20 weeks	ND	Diabetic	AMI	Permanent LAD ligation	10 min after MI	Intramyocardial injection	EPC from blood collected from cardio-puncture of Zucker diabetic fatty rats	CD34, KDR	1×10^6 in 200 µL
Yao, Y.[43]	2011	a) MI (n=60): 1: SPIO-labeled EPCs, 2: unlabeled EPCs, 3: PBS, b) sham MI group (n=10).	Sprague-Dawley rat	ND	ND	250±30 g	Healthy	AMI	LAD ligation	After LAD ligation	Intramyocardial injection	EPC from Sprague–Dawley rats tibias and femurs	KDR/Flk-1, eNOS, CD31, UEA-1-lectin, Ac-LDL-Dil, CD34	1×10^6 EPCs
Garikipati, V. N.[44]	2015	1: GFP+ WT-BMPAC (n = 22), 2: IL-10 KO-BMPAC (n = 12) BMPAC with or without miR-375 knockdown.	Wild-type and IL-10 knockout mice of C57BL/6J background	Male	8 weeks	ND	Wild-type and IL-10 knockout	AMI	LAD ligation	Immediately after LAD ligation	Intramyocardial injection	EPC from wild-type and IL-10 knockout mice of C57BL/6J background bone marrow	Cell culture only	1×10^5 cells in 15 µL
Ahmadi, A.[45]	2014	1: GFP+ CACs, 2: collagen matrix only, 3: GFP+ CACs + collagen	C57BL6/J mice	Female	9 weeks	ND	Healthy	MI	LAD ligation	1 week after MI	Ultrasound-guided closed-chest procedure	Circulating angiogenic cells (CACs) from eGFP mice	CD34, CD133, c-kit, CXCR4	5×10^5 cells in 50 µL

		matrix, 4: PBS (Sigma) as control.									intramyocardial injection	(C57BL/6-Tg (CAG-EGFP)) bone marrow		
Brunt, K. R.[46]	2012	1: medium, 2: EPC, 3: Akt EPCs, 4: HO-1 EPC, 5: Akt/HO-1 EPCs.	Nude mice	Female	ND	18-20 g	Nude	MI	Permanent LAD ligation	At the time of occlusion	Intramyocardial injection	Late outgrowth EPCs from human peripheral blood	Cell culture only	5 x10^5 in 15 µL
Chen, X.[47]	2013	1: sham (n = 15), 2: medium (n = 15), 3: lenti-eNOS (n = 15), 4: control EPCs (n = 15), 5: eNOS-EPCs (n = 15).	C57BL/6 mice	Male	6-10 weeks	ND	Healthy	AMI	LAD ligation	1 h after MI	Intramyocardial injection	EPC from C57BL/6 mice bone marrow	CD34, CD133, KDR, CD45	1 × 105 cells in 20 µL
Cheng, Y.[48]	2012	1: PBS (vehicle, n = 12), 2: PBS containing EGFP-EPCs (EPC, n = 18), 3: PBS containing recombinant human EPO (EPO, n = 12), 4: PBS containing EGFP-EPCs and recombinant human EPO (EPC + EPO, n = 18).	Wild-type BALB/c mice	Male	12-14 weeks	ND	Healthy	MI	Permanent LAD ligation	Before the heart was replaced into the intrathoracic space	Intramyocardial injection	EPC from the bone marrow of EGFP-transgenic BALB/c mice tibias and femurs	UEA-1, ac-LDL, CD34, Flk	5 × 10^4 cells in 15 µL
Hu, C. H.[49]	2010	1: EPC (n = 16), 2: control (medium, n = 17).	Wistar rat	Male	ND	191±7.5 g	Healthy	AMI	LAD ligation	Immediately after LAD	Intramyocardial injection	EPC from human umbilical cord blood	CD34, CD133, KDR, Dil-Ac-LDL, UEA-l	1 × 10^6 cells in 100 µL
Iwasaki, H.[50]	2006	1: low group, 2: mid group, 3: high group CD34+ cells resuspended with PBS, 4: PBS without cells. (n =12/group when the first patient's cells were used; n = 4/group for the second patient's cells)	Athymic nude rat	Female	7-8 weeks	130-145 g	Nude	MI	LAD ligation	20 min after MI	Intramyocardial injection	CD34+ cells from human peripheral blood	CD34, CD133, KDR, CD45, CD31, VE-cadherin, SMA	1 × 10^3 or 1 × 10^5 or 5 × 10^5 cells in 120 µL

Li, H. Q.[51]	2013	1: saline without cells or with non-preconditioned EPC (control group), 2: E2 preconditioned EPC (E2 group), 3: AMD3100 treated EPC (AMD group), or 4: EPC pre-treated with E2 plus AMD3100 (E2+AMD group). (n= 11)	BALB/C mice	Female	6 weeks	ND	Healthy	AMI	LAD ligation	3 days after LAD ligation	Intravenous injection	EPC from the bone marrow of BALB/C mice tibias and femurs	DiI-Ac-LDL, lectin, VEGFR-2, Sca-1	3×10^6 cells
Cheng, Y.[52]	2013	1: PBS (n=12), 2: EPCs (n=12), 3: PBS + wortmannin (n=6), 4: EPCs + wortmannin (n=6).	BALB/C mice	Male	12-14 weeks	ND	Healthy	AMI	LAD ligation	After LAD ligation	Intramyocardial injection	EPC from the bone marrow of Balb/c mice tibias and femurs	DiI-Ac-LDL, UEA-1 lectin, CD309, CD34	5×10^4 cells in 15 μL
Hamada, H.[53]	2006	1: WT E2+ (WT BMT to WT mouse with E2 pellet (n = 12)), 2: WT E2- (WT BMT to WT mouse with placebo pellet (n = 12)), 3: ERαKO E2+ (ERαKO BMT to WT mouse with E2 pellet (n = 8)), 4: ERβKO E2+ (ERβKO BMT to WT mouse with E2 pellet (n = 8)).	C57BL6/J mice	Female	9-10 weeks	ND	Wild-type mice underwent Ovariectomy at Day -28, together with splenectomy at day -7. Seven Days later (day 0), animals underwent MI surgery.	AMI	Permanent LAD ligation	Immediately after MI surgery	Intravenous injection	EPC from the bone marrow of mouse tibias and femurs	Cell culture only	5×10^5 cells
Botta, R.[54]	2004	1: CD34+ cells, 2: MNCs, 3: CD34+ KDR+, 4: CD34+ KDR- cells after MI, 5: Sham, 6: PBS	NOD-SCID mice	Male	7-9 weeks	ND	NOD-SCID	MI	LAD ligation	After LAD ligation	Intramyocardial injection	Human umbilical cord blood cd34+	CD34, HPCA-2, KDR+, KDR-	(2×10^5 CD34+ cells or MNCs; 2×10^3

		control. (n = 4-9/group)												CD34+KDR+ or CD34+KDR– cells) in 15 µl
Deutsch, M. A.[55]	2020	1: ECFCs, 2: saline solution.	(SCID)beige mice	Male	8-12 weeks	ND	SCID	AMI	LAD ligation	Immediately after LAD ligation	Intramyocardial injection	Endothelial colony-forming cells (ECFCs) from human peripheral blood	CD34, CD105, CD144, CD45, vWF, VEGF-R2, Flt1, Flt4, Tie-2, CD146	5×10^5 cells in 15 µL
Moldenhauer, L. M.[56]	2015	1: PBS (MI), 2: EXnaEFCs (expanded for 6–8 days) in PBS, 3: control (Control rats did not undergo surgery). (n = 3–6/group).	CBH-Rnu rat	Male	ND	ND	Healthy	AMI	Permanent LAD ligation	After LAD ligation	Transepicardial injection	Primary HUVECs from human umbilical veins	CD34, CD117, CD133, CD31, CD144, CD146, VEGFR2, CD14, CD38, CD45, IL3RA, Dil-Ac-LDL, UEA-l lectin	1×10^6 cells in 100 µL
Gunetti, M.[57]	2011	1: sham-operated, 2: PBS 4 h after CAL (CAL+PBS), 3: BMbCD34+ cells 4 h after CAL (CAL+BMbCD34+), 4: BMbCD34+ cells 4 h after CAL, and 5: BMeCD34+ cells 7 days after CAL (CAL+BMbeCD34+). (n = 61)	Non-obese diabetic (NOD)/SCID mice	Male	ND	20-23 g	NOD/SCID	AMI	Permanent Left coronary artery ligation (CAL)	4 h after the MI	Percutaneously injection into LV	CD34+ from healthy donors' bone marrow	CD34, CD14, CD31, CD105, KDR, CD146	0.3×10^6 cells in 100 µL
Saucourt, C.[58]	2019	1: sham-operated, 2: placebo (PBS/2% HSA alone), 3: bCD34+ SC (basal-CD34+), 4: eCD34+ (expanded cells).	Athymic rat	Male	least 9 weeks	247-339 g	Nude	AMI	Left anterior descending coronary artery ligation (CAL)	1 week after CAL	Intramyocardial injection	bCD34+ or eCD34+ cells from healthy donors' peripheral blood	CD133, CD34, CD45, CD14, CD56, CD2, CD3, CD19, CD20, CD15	5×10^5 cells in 100 µL
Sheng, Z.[59]	2018	4 groups [1: AMI, 2: EPCs treatment, 3: TWEAK pre-treated EPCs, 4: sham; n=8/group] or 6 groups (1: AMI, 2:	C57Bl/6 mice	Male	10-12 weeks	20-22 g	Healthy	AMI	LAD ligation	15 min after LAD ligation	Intramyocardial injection	EPC from C57Bl/6 mice tibiofibular bone marrow	CD34, KDR, CD45, CD133, CD146	1×10^6 cells in 30 µL

		EPC treatment, 3: TWEAK pre-treated EPC group, 4: TWEAK pre-treated Fn14 siRNA EPC, 5: TWEAK pre-treated Bay 11-7082 EPC, 6: sham; n=10/group).												
Sheng, Z.[60]	2013	1: basal medium without hEPCs (Con group), 2: containing non-PC hEPCs (EPCs group), 3: BK PC hEPCs (BK PC group), 4: BK PC hEPCs pre-treated with HOE140 (BK PC/HOE group), 5: LY294002 (BK PC/LY group), 6: L-NAME (BK PC/LN group). A total of 112 nude mice were used in this experiment. During the operation, 28 mice died. This experiment was divided into 2 subgroups, the day 2 group (n = 50) and the day 10 group (n = 62). Each subgroup had 7 groups; 5-6 live nude mice were used in each group.	BALB/C nude mice	Male	ND	20-22 g	Nude	AMI	LAD ligation	10 min after LAD ligation	Intramyocardial injection	EPC from human umbilical cord blood	DiI -Ac-LDL, UEA-1-lectin, CD34, B1R, B2R, CD133, VEGFR2	1×10^6 cells in 30 μL
Sheng, Z. L.[61]	2015	1: basal medium without hEPCs (Con group), 2: basal medium containing non-PC hEPCs (EPCs group), 3: bradykinin-preconditioned hEPCs (BK-PC-hEPCs; BK	Nude mice	Male	ND	20-22 g	Nude	AMI	LAD ligation	10 min after LAD ligation	Intramyocardial injection	EPC from human umbilical cord blood	Dil-Ac-LDL, UEA-1-lectin, CD34, B1R, B2R, CD68, VEGFR2, CD45, CD105	2×10^6 cells in 30 μL

		PC group), 4: BK-PC-hEPCs pre-treated with HOE140 (BK PC/HOE group), 5: LY294002 (BK PC/LY group), 6: sham group.												
Shintani, S.[62]	2006	1: the combination therapy group (n = 9) Human CD34+ cells and phVEGF2 resuspended with saline, 2: the cell therapy group (n = 8) CD34+ cells and empty plasmid, 3: the gene therapy group (n = 9) CD34– cells and phVEGF2, 4: the control group (n = 8) CD34– cells and empty plasmid.	Athymic nude rat	Female	6-8 weeks	ND	Nude	MI	LAD ligation	30 min after induction of MI	Intramyocardial injection	CD34+ cells from human peripheral blood	CD34	1×10^4 cells in 100 ml
Sondergaard, C. S.[63]	2009	1: CD34+ cells (n = 5), 2: Transplantation control (medium only (mock), n = 4).	Athymic nude rat	Male	5-10 weeks	ND	Nude	AMI	LAD ligation	After LAD ligation	Intramyocardial injection	CD34+ cells from human peripheral blood	CD34	2×10^6 cells in 100 µL
Stein, A.[64]	2010	1: eEPC (n = 9), 2: eEPC + Epo (n = 9), 3: Epo (n = 8), 4: control (PBS alone, n = 8).	Athymic nude rat	Male	ND	ND	Nude	AMI	LAD ligation for 30 min	After reperfusion was initiated by the release of the ligation	Intramyocardial injection	eEPCs from human umbilical cord blood	CD34	1×10^6 cells in 150 µL
Sun, Z.[65]	2008	ACPs or culture media into infarcted myocardium (1: M-Cell, n= 9; 2: M-Control, n= 5) or into the coronary artery via the aorta (3: C-Cell, n= 9; 4: C-Control, n= 5). 2 rats died during the LAD ligation procedure, and 2 rats died shortly	Athymic nude rat	Male	ND	200-250 g	Nude	MI	LAD ligation	6 days after LAD ligation	Intramyocardial injection and intracoronary cell implantation	Angiogenic cell precursors (ACPs) from human peripheral blood	CD117, CD31, CD34	1.5×10^6 cells in 50 µL

		after the procedure. 3 rats were excluded from the study because they did not meet the infarct size criteria for inclusion (2 because the scars were too small; 1 because the scar was too large). 2 rats died following intramyocardial media injection, and 1 rat died following intramyocardial cell injection.												
Thal, M. A.[66]	2012	1: mouse EPCs, 2: CD34+ cells, 3: Saline group (PBS only).	Nude mice	ND	8-10 weeks	ND	Nude	AMI	LAD ligation	Immediately after LAD ligation	Intramyocardial injection	Lin-Sca1+CD31+ EPCs from femurs, tibiae, and hip-bones bone marrow of C57BL/6J or eGFP transgenic mice human CD34+ cells	CD3e, CD11b, B220, Ter119, Ly6G/C, Sca-1, CD31	2.0×10^5 mouse EPCs, 2.5 or 5×10^4 CD34+ cells in 20μL
Xin, Z.[67]	2008	1: CEPC, 2: BM-EPC, 3: control (EBM-2 only). (n = 10/group)	Sprague-Dawley rat	Female	ND	250-300 g	Healthy	AMI	Permanent LAD ligation	1 h after LAD ligation	Intramyocardial injection	Circulating EPC (peripheral blood); and BM-EPCs from SD rats' femurs and tibias	vWF, Dil-Ac-LDL, UEA-1, CD14, CD133	1×10^6 cells in 200 μL
Xue, Y.[68]	2020	2: sham, 2: CME, 3: CME+EPC (low), 4: CME+EPC (high) (n = 8/group)	Wistar rat	Male	ND	220-240 g	Healthy	Coronary artery microembolization (CME)	A microembolism suspension was injected into the LV during 10- s occlusion of the ascending aorta	During 10- s occlusion of the ascending aorta	Injected into the LV	EPCs from the bone marrow of rats' femurs and humerus	VEGFR2, CD34	2×10^6 or 2×10^5 cells in 300 μL

Yang, K.[69]	2020	1: negative control, 2: miR-125b mimic. (n = 6–8/group)	Mice	ND	ND	ND	Healthy	MI	LAD ligation	After LAD ligation	Intramyocardial injection	EPC from the mouse bone marrow	Cell culture only	2×10^5 cells in 20 µL
Yao, Y. Y.[70]	2013	1: sham surgery, 2: medium-treated group, 3: Ad.Null-hEPCs-treated group, 4: Ad.hTK-hEPC-treated group. (n = 12/group)	Nude mice	Male	ND	20-22 g	Nude	AMI	LAD ligation	10 min after LAD ligation	Intramyocardial injection	EPC from Human umbilical cord blood	Dil-Ac-LDL, UEA-1-lectin, VEGFR2, CD34, BK B2 receptor	5×10^5 cells in 30 µL
Yoo, C. H.[71]	2013	1: WT, 2: MI, 3: MI + Cell. (n=6/group were used for morphological analysis)	BALB/cAnNCrljOri mice	Male	8 weeks	ND	Nude	MI	LAD ligation	After occlusion	Injected around the occluded region	CD34+ EPCs (2F-hEPCs) from human dental pulp-derived iPS cells	CD105, CD31, CD34, calponin, SM22a, vWF, VE-cadherin, elastin, a-SMA	1×10^6 cells in 20 µL
Yuan, Z. Z.[72]	2018	1: saline without cells or with non-preconditioned EPCs (control group), 2: E2- preconditioned EPCs (E2 group), 3: EPCs preconditioned with E2 and MMP (E2 + MMP group), 4: EPCs preconditioned with E2 and AMD (E2 + AMD group), 5: EPCs preconditioned with E2 and MMP plus AMD (E2 + MMP + AMD group).	BALB/C mice	Female	6 weeks	ND	Wild-type mice underwent ovariectomy at day - 28.	AMI	LAD ligation	3 days after LAD ligation	Intravenous injection	EPC from the bone marrow of mice tibias and femurs	Dil-Ac-LDL, lectin 1, Sca-1, Flk-1	3×10^6 cells
Zhou, W.[73]	2021	1: EPC wt, 2: EPC Rab, 3: MI.	Mice	Male	ND	ND	Healthy	MI	LAD ligation	After the MI model was successfully conducted	Intramyocardial injection	EPCs from mouse bone marrow	Dil-AcLDL, UEA-1, CD34, VEGFR2	4×10^5 cells in 10 µL
Atluri, P.[74]	2014	1: control (coronary ligation alone), 2: implant of a fibrin patch without cells (10 mg/mL [FIB 10] or 20 mg/mL [FIB	Wistar rat	Male	Adult	250-300 g	Healthy	AMI	LAD ligation	Following LAD ligation	Intramyocardial injection +implant	EPC from the bone marrow of syngeneic Wistar rats' long bones	Dil-LDL, VEGFR2, CD34	17 x 10^6 or 7×10^6 EPCs/mL with fibrin or

		20]), 3: injection of EPCs (IC, 2 million cells/in 250 mL PBS), or 4: implant of EPC-fibrin hydrogel (a: 10 mg/ mL fibrin 7 × 106 EPCs/mL, b: 10 mg/mL fibrin 17 × 106 EPCs/mL, c: 20 mg/mL fibrin 7 × 106 EPCs/mL, d: 20 mg/mL fibrin 17 × 106 EPCs/mL).												$2x10^6$ EPCs/in 250 mL PBS
Yang, J.[75]	2011	1: KSL, 2: KL, 3: SL, 4: CD34+ cells, 5: PBS control.	B6;129SGt [ROSA] 26Sor/J mice	Male	8–12 weeks	ND	Healthy	MI	LAD ligation	3 days after MI	Systemically injected	KSL, KL, SL, and CD34+ cells (EPCs) from the bone marrow of mouse hipbones, femurs, tibiae, shoulder bones, ulnas, vertebrae, and sternum	CD34, lineage markers, Sca-1, c-Kit, streptavidin	5×10^4 SL, KL, KSL and CD34 cells together with PBS control
Park, J. H.[76]	2011	1: EPC, 2: PBS, 3: sham.	C57BL/6J mice and ubiquitous eGFP-expressing transgenic mice with a C57 background	ND	6-10 weeks	ND	Healthy	AMI	LAD ligation	After induction of MI	Intramyocardial injection	EPCs from mouse bone marrow	Cell culture only	5×10^5 cells in 50 µl
Huang, H.[77]	2013	1: PBS, 2: EPCs, 3: EPC null, 4: EPCDll-4+, 5: EPCDll-4-. (n = 20/group)	C57BL/6 mice	ND	8 weeks	20±2 g	Healthy	MI	LAD ligation	1 week	Intravenous injection in the tail vein	EPC from the bone marrow of C57BL/6 mice tips of the hind legs	KDR, hAC133, hCD31, hCD34	5×10^6/100 µl cells in PBS or 50 µl

														PBS only
Li, X.[78]	2019	1: miR-326-5p-EPCs, 2: miR-326-5p-EPCs+ Wnt1 agonist, 3: EPCs-NC, 4: PBS/control. (n = 15/group)	C57BL/ 6 mice	Femal e	8-10 weeks	ND	Healthy	AMI	Permanent LAD ligation	Following LAD ligation	Intramyocar dial injection	EPC from the bone marrow of C57BL/6 mice femurs and tibias	CD11b, CD31, CD45, CD133, VE-cadherin, Flk-1, DiI-ac-LDL	ND
Zhang, B. F.[79]	2019	1: SO (sham-operated), 2: MI control, 3: MI+EPC, 4: MI+EPC+M, 5: MI+(Fe-EPC), 6: MI+(Fe-EPC) +M; M: magnet. (n=10/group)	Sprague -Dawley rat	Femal e	ND	200-250 g	Healthy	MI	LAD ligation	1 week	Intravenous injection in the tail vein	EPC from the bone marrow of SD rats' long bones	Dil-Ac-LDL, UEA-1, CD133, CD34, VEGFR	5 x 10^6 cells in 100 µl
Xiao, Q.[80]	2019	1: CON-EPC-Null, control EPCs modified by control adenovirus, 2: DM-EPC-Null, diabetic EPCs modified by control adenovirus, 3: DM-EPC-Shh, diabetic EPCs modified by Shh-overexpressing adenovirus, 4: PBS. (n = 5/group)	C57BL/ 6 mice	Male	6-8 weeks	20±2 g	Diabetic	AMI	LAD ligation	Immediately after LAD ligation	Intramyocar dial injection	EPC from the bone marrow of C57/B6 mice tibias and femurs	Dil-Ac-LDL, UEA-1, CD31, CD34	2 x 10^2 cells
Sun, Y. Y.[81]	2014	1: PBS, 2: DiI-labelled WT, or 3: per2-/- mouse bone-marrow EPCs	C57BL/ 6 mice	Male	8–12 weeks	25-30 g	Healthy	MI	LAD ligation	Immediately after surgery	Intramyocar dial injection	EPC from the bone marrow of WT and per2-/- mice tibias and femurs	Dil-Ac-LDL, UEA-1, CD34, CD45, Flk1	5 x 10^5 cells in 30 µl
Wu, Y.[82]	2006	1: DiI-EPCs pre-treated with anti-CD18 (EPCs-CD18 mAb group), 2: control IgG (EPCs-IgG group), 3: equal volume of PBS (PBS group), 4: sham group	Athymic nude mice	Femal e	8-10 weeks	ND	Nude	AMI	Permanent LAD ligation	1 hour after MI	left ventricular intracavity injection	EPC from the bone marrow of Balb/C mice and SD rats tibias and femurs	CD11a, CD11b, CD18, CD31, CD34, c-kit, Tie-2, VE-cadherin, Flk-1, DiI-Ac-LDL	0.5 x 10^6 cells

		underwent open chest surgery without coronary artery.												
Chang, Z. T.[83]	2013	MI: a) EPC treatment (n = 28): 1: EPC, 2: EPCs transfected with Tβ4 short hairpin RNA (shRNA), 3: EPCs transfected with scrambled (SC) shRNA, 4: Tβ4; b) control (MI, n = 28)/ Ischemia-reperfusion: (n = 40).	Sprague -Dawley rat	Male	7-10 weeks	230-350 g	Healthy	MI, ischemic reperfusion	LAD/LAD ligation for 40 min	ND/35 min after MI	Intramyocardial injection	Peripheral blood EPCs SD rats' peripheral blood	Dil-LDL, lectin, VE-cadherin, KDR, CD34, AC133	5×10^6 cells in 150 µL
Hu, C. H.[84]	2009	1: EPC group (n = 20), 2: control group (control group was injected with equivalent cell-free medium, n = 20), 3: sham group (in the sham group, the LAD was left unligated, n = 15).	Wistar rat	Male	ND	190±8 g	Healthy	AMI	LAD ligation	After LAD ligation	Intramyocardial injection	EPC from human umbilical cord blood	DiI-Ac-LDL, lectin	1×10^6 cells in 100 µL
Mackie, A. R.[85]	2012	Treatment groups included 1: Saline (n = 16), 2, 25K unmodified CD34 cells (CD34NM) (n = 8), 3: 25K CD34 cells transfected with an empty vector (CD34EV) (n =7), 4: 25K CD34 cells transfected with an Shh-coding vector (CD34Shh) (n = 13), 5: 25K CD34NM and 200ng Shh protein (n=7), 6: 50K CD34NM (n = 9).	Nude/Jor NOD-SCID mice	Male	8 weeks	ND	Nude/Jor NOD-SCID	AMI	LAD ligation	Following verification of induced ischemia	Intramyocardial injection	CD34+ cells from human peripheral blood	CD34	2.5×10^4 (25K) cells/mouse, or 5.0×10^4 (50K) in 2 - 10 µl

Murasawa, S.I.[86]	2005	1: intramyocardial (intramuscular) EPC injection, 2: systemic EPC injection, 3: control (PBS injection). (n = 5/group)	Athymic nude rat	ND	8 weeks	135-140 g	Nude	MI	LAD ligation	After operatively induced MI	Intramyocardial (intramuscular) or systemic injection	EPC from human peripheral blood and cultured with H9C2 Cell Line	ND for peripheral blood/ CD31, CD34 for cultured EPC	1×10^6 or 2.5×10^5 cells in 25 µL
Rong, Q.[87]	2007	1: MI surgical manipulation (n = 3), 2: sham surgery (n = 3) was injected with the same number of nonviral infected EPCs (normal intervened); 3: MI + HBV treated EPC (n=15).	Sprague -Dawley mice	Male	ND	150-250 g	Healthy	MI	LAD ligation	4 h after MI induction	Intravenous injection in the testicle vein	EPC from human umbilical cord blood	CD34, KDR, CD133, DiI-Ac-LDL, vWF, CD34	2.5×10^6 cells
Toeg, H. D.[88]	2013	1: PBS only (n = 8), 2: CACs only (n = 10), 3: SIS-ECM only (n = 10), 4: SIS-ECM + CACs (n = 10); small intestine submucosal extracellular matrix (SIS-ECM); circulating angiogenic cells (CACs).	C57BL/ 6J mice	Femal e	9-10 weeks	ND	Healthy	AMI	LAD ligation	7 days after ligation	Echocardiographically guided intramyocardial injection	EPC from the bone marrow of C57BL/6J mice femurs and tibias	Cell culture only	5×10^5 cells in 20 µl

Characteristics of studies

All the included studies from 2004 to 2021 with access to full text were selected. The systematic review focused on rodent models of MI consisting of rat (N=37; 55.22%) and mouse (N=30; 44.78%) models of MI (**Supplementary Table 2**). Data indicated that a greater number of experiments were done on male rats/mice (N=41; 61.19%), while 17 (25.37%) studies were conducted on female models Interestingly, in one study both genders were used. Rodents in 36 studies (53.73%) aged between 4 to 20 weeks. In 8 experiments (11.94%), the term “adult” was used to describe rodent age. In just one experiment (1.49%), "at least 9-week-old" rodents were used for the MI model. Rats and mice subjected to MI models weighed 80-350, and 18-250 grams, respectively. 58.21% of rats and mice were in healthy status (N=39). Nude animals constituted 25.37% (N=17) of the experiments. In 3 studies (4.48%), MI was inducted on diabetic models. Animals with severe combined immunodeficiency including NOD-SCID (N=2; 2.99%), SCID (N=1; 1.49%), and a combination of Nude/J or NOD-SCID (N=1; 1.49%) were employed. Immunocompetent experimental models were 1.49% of collected studies (N=1). In one study (1.49%), the models underwent ovariectomy together with splenectomy; while in one experiment just ovariectomy was conducted (1.49%). Experiments with both wild-type and IL-10 knockout models comprised 1.49% (N=1) of the studies. Protocols consisting direct left anterior descending coronary artery (LAD) ligation (N=64; 95.52%); injection of vitamin D3 in high‑fat diet-fed rodents (N = 1; 1.49%), intramyocardial administration of microembolism suspension following the occlusion of the ascending aorta (N=1; 1.49%), and LAD ligation followed by reperfusion besides aorta cross-clamping (N=1; 1.49%) were used to induce experimental MI models. Based on the analysis, MI (N = 63; 94.03%), progressive MI to cardiomyopathy (N = 1; 1.49%), MI with ischemic reperfusion (N=1; 1.49%), coronary artery microembolization (CME) (N = 1; 1.49%), and ICM (ischemic cardiomyopathy model) (N = 1; 1.49%) were pathological conditions in rodent models. In the selected articles, EPCs were collected from different sources as follows; Bone marrow (N = 32; 47.76%), peripheral blood (N = 19; 28.36%), umbilical cord blood (N=11; 16.42%), direct cardio-puncture (N = 1; 1.49%), spleen (N = 1; 1.49%), dental pulp (N=1; 1.49%), and both peripheral blood and bone marrow (N = 1; 1.49%). EPCs were administrated as doses between 2×10^2 and 2×10^7 in most of the experiments (N=59; 88.06%). In contrast to studies using single EPC injection, 8 experiments (11.94%) were conducted based on multiple EPC administrations. Timing of EPC injection varied from immediate to delayed administration (until 4 weeks) following MI induction. Different introduction approaches and terms were found in different studies such as intramyocardial injection (N = 44; 65.67%), intravenous injection (N=9; 13.43%), intramyocardial injection and subsequent treatment with the construct (N=3; 4.48%), simultaneous intramyocardial and intracoronary injections (N=2; 2.99%), injection into the LV (N=2; 2.99%), transepicardial injection (N=1; 1.49%), anterolateral LV surface suture (N=1; 1.49%), implantation (N=1; 1.49%), intracoronary injection (N=1; 1.49%), percutaneously injection into LV (N=1; 1.49%), injection to the border of occluded region (N=1; 1.49%), and intramyocardial (intramuscular) or systemic injection (N=1; 1.49%).

EPC transplantation effect on angiogenesis potential

A random-effects model was applied to find differences in angiogenesis potential in 32 eligible studies (**Figure 3a**; SMD: 2.02, CI 95%: 1.51-2.54, p<0.00001; I2: 82%). The subgroup analysis of EPC injection in different time points (1, 2, 3, 4, 6, and 8) indicated an improved angiogenesis potential after MI induction. Of note, these changes reached statistically significant levels post EPC injection after one week (SMD: 1.29, CI 95%: 0.27-2.31, p=0.01; I2: 0%; N=2), two weeks (SMD: 2.61, CI 95%: 1.95-3.27, p<0.00001; I2: 0%; N=4), four (SMD: 1.72,

CI 95%: 1.19-2.26, p<0.00001; I2: 73%; N=18), and eight weeks (SMD: 5.98, CI 95%: 0.25-11.70, p=0.04; I2: 89%; N=2). The other features were not statistically significant compared to the control group.

EPC transplantation effect on myocardial fibrosis

Data confirmed the reduction of myocardial fibrosis in 28 studies after EPC transplantation compared to the control group (SMD: -1.48; 95% CI − 2.15, -0.81; p < 0.0001; I2: 88%). Subgroup analysis revealed significant differences of post-EPC administration after one week (SMD: -0.97; 95% CI − 1.88, -0.07; p = 0.04; I2: 0%; N=2), two weeks (SMD: − 1.89; 95% CI − 2.93, -0.85; p = 0.0004; I2: 0%; N=2), three weeks (SMD: − 1.73; 95% CI − 2.78, -0.68; p = 0.001; I2: 62%; N=3), and four weeks (SMD: -2.05; 95% CI, − 3.00, -1.10; p < 0.0001; I2: 89%; N=18) (**Figure 3b**).

EPC transplantation effect on cardiac ejection fraction

Random-effects model for differences in LVEF values is shown in **Figure 3c**. Data showed the efficiency of EPC transplantation in the improvement of LVEF after one week (SMD: 0.70; 95% CI − 0.14, 1.27; p = 0.01; I2: 52%; N=8), two weeks (SMD: 3.98; 95% CI 1.36, 6.61; p = 0.003; I2: 95%; N=6), three weeks (SMD: 1.08; 95% CI 0.60, 1.57; p < 0.0001; I2: 0%; N=2), four weeks (SMD: 2.02; 95% CI 1.18, 2.86; p < 0.00001; I2: 88%; N=17), and eight weeks (SMD: 1.07; 95% CI 0.09, 2.04; p = 0.03; I2: 10%; N=2) compared to the control group. Despite these results, two experiments reported the lack of statistically significant differences in LVEF parameters after 6 weeks post-EPC administration between the control and EPC groups.

EPC transplantation effect on cardiac FS

Data obtained from a random-effects model indicated significant differences in cardiac FS following EPC therapy in rodent models of MI. To be specific, statistically significant differences were found in FS parameter after one week (SMD: 0.65; 95% CI 0.26, 1.03; p = 0.0010; I^2: 6%; N=7), two weeks (SMD: 2.65; 95% CI 0.87, 4.43; p = 0.004; I^2: 91%; N=6), four weeks (SMD: 1.91; 95% CI 1.18, 2.64; p < 0.00001; I^2: 82%; N=13), and eight weeks (SMD: 1.12; 95% CI 0.52, 1.72; p = 0.0002; I^2: 0%; N=3) in EPC group as compared with the control group (**Figure 3d**).

Different EPC injection approaches

The regenerative efficacy of the EPC injection route was also assessed in rodent MI models. Intramyocardial route is the commonly used approach for the introduction of EPCs into the ischemic myocardium with the angiogenesis potential (SMD 1.91, 95% CI- 1.39-2.43, P<0.00001, I^2: 80%; N=27; **Figure 4a**); reduction of fibrosis (SMD -1.16, 95% CI- -1.96, -0.36, P =0.004, I^2: 90%; N=25; **Figure 4b**); improving EF (SMD:1.53, 95% CI- 0.92-2.15, P<0.00001, I^2: 86%; N=24; **Figure 4c**), and FS values (SMD:1.58, 95% CI- 1.04-2.12, P<0.00001, I^2: 80%; N=21; **Figure 4d**).

Various EPC doses

Based on EPC dose, studies were categorized into 5 groups as follows; up to 0.5×10^6, 0.5 to 1×10^6, 1 to 2×10^6, 2 to 5×10^6, and more than 5×10^6 groups. The weighted applied dose to EPC transplantation is dose 1 (up to 0.5×10^6), which demonstrated significant angiogenesis effects (SMD 7.16, 95% CI- 4.30-10.01, P<0.00001, I^2: 92%; N=12; **Figure 5a**), reduced fibrosis (SMD -10.31, 95% CI- -18.72, -1.90, P=0.02, I^2: 98%; N=15; **Figure 5b**), improved EF (SMD 11.33, 95% CI- 2.44-20.22, P=0.01, I^2: 98%; N=11; **Figure 5c**), and FS (SMD 5.58, 95% CI- 2.80-8.37, P<0.0001, I^2: 92%; N=11; **Figure 5d**) compared to the other doses.

Various EPC sources

Based on our data, it was confirmed that bone marrow EPCs exerted significant angiogenesis effects (SMD 6.88, 95% CI- 4.57-9.19, P<0.00001, I^2: 88%; N=16; **Figure 6a**); reduced fibrosis (SMD -15.28, 95% CI- -20.40, -10.16, P<0.00001, I^2: 95%; N=16; **Figure 6b**); improved EF (SMD:10.63, 95% CI- 7.53-13.73, P<0.00001, I^2: 86%; N=17; **Figure 6c**), and FS (SMD: 6.93, 95% CI- 4.25-9.61, P<0.00001, I^2: 89%; N=15; **Figure 6d**) in comparison with EPC types.

Publication bias

Four funnel plots were developed using RevMan 5.4.1 to assess the publication bias among the selected experiments on each outcome (**Figures 7a-d**). For angiogenesis potential, Begg and Mazumdar's test revealed Kendall's tau of 0.546 (z = 4.395, p = 0.00001), and Egger's regression test indicated a significant intercept of 5.79 (SE = 0.855, p = 0.00000). For anti-fibrosis properties, Begg and Mazumdar's test yielded Kendall's tau of -0.576 (z = 4.211, p = 0.00003) with Egger's regression of -4.62 (SE = 1.407, p = 0.00300). In terms of EF, Kendall's tau of 0.522 (z = 4.481, p = 0.00001) was obtained by Begg and Mazumdar's test, and a noteworthy intercept of 5.43 (SE = 1.011, p = 0.00001) was evaluated by Egger's regression test. Finally, in the FS parameter, Begg and Mazumdar's test demonstrated Kendall's tau of 0.460 (z = 3.637, p = 0.00028) and an intercept of 4.27 (SE = 1,113, p = 0.00062) after Egger's regression test. These results suggest publication bias based on both the visual inspection of the funnel plot and the statistical tests in all outcomes.

Discussion

MI is a debilitating pathological condition with a high rate of mortality in societies.[89] Therapeutic strategies targeting the increase of vascularization and blood perfusion are beneficial to alleviate the adverse effects of MI. In this regard, in-time blood vessel formation can significantly reduce scar formation, abnormal LV remodeling, and massive cardiomyocyte damage.[90] Emerging *in vitro*, preclinical, and clinical data have indicated the potency of various stem cell types, especially EPCs, in the restoration of vascularization into the ischemic sites. It was suggested that both maturation into functional ECs, and the release of several proangiogenesis factors can expedite the process of healing in the ischemic sites.[13] Of note, *in vitro*, *ex vivo* experiments, preclinical studies, and *in silico* analyses are required to evaluate the efficacy and safety of cells or drug candidates before application in the human counterpart.[91] In this regard, the current systemic review and meta-analysis included preclinical experiments and aimed to explore the effectiveness of EPCs in rodent (rat and mouse) models of MI. Features such as angiogenesis, fibrosis, EF, and SF were monitored in MI animals following the administration of EPCs and compared to the control MI group.

The present data noted that EPC transplantation can influence primary outcomes such as angiogenesis and fibrosis in MI groups receiving only cell-free phosphate-buffered saline (PBS) or culture medium. Along with these changes, EPC administration led to improvements in cardiac function parameters, such as FS, and EF following MI induction. It has been assumed that several underlying molecular mechanisms are stimulated after the injection of EPCs into ischemic tissues.[92] For example, EPCs are capable of ensuring cardiac tissue regeneration via the reduction of oxidative stress.[93] Xue et al. found that moderate-to-high doses of EPCs blunt the oxidative stress (8-iso-prostaglandin F2α↓, and SOD↑), and endoplasmic reticulum stress (GRP78 and CHOP) in a rat model of acute MI.[94] Of course, prolonged exposure to insulting conditions contributes to the induction of oxidative stress in EPCs. Under such conditions, the function of EPCs and angiogenesis potential are fundamentally influenced. Hamed and co-workers found that diabetic circulating EPCs produce higher oxygen free radicals and exhibit higher SOD, NADPH oxidase activity with reduced NO bioavailability compared to normal EPCs.[95] Therefore,

attention should be given to the selection of appropriate EPCs to achieve optimal regenerative outcomes under varying pathological conditions.

It is hypothesized that direct physical contact between the EPCs and cardiac cells can stimulate several healing processes related to angiogenesis, ECM remodeling, and ventricular function.[12] Multiple cell death modes such as cardiomyocyte apoptosis, excessive autophagic death, and necrosis are diminished following the administration of EPCs.[96,97] Besides, EPCs exert anti-fibrotic properties through the modulation of the TGF-β signaling pathway and regulation of Smads.[98] Of course, the regenerative potential of EPCs is not limited to the above-mentioned mechanisms, and these cells can affect the bioactivity of multiple cardiac cells in a paracrine and juxtacrine manner.[99] For instance, the EPC secretome contains various signaling factors affecting the function of ECs after injury. In response to the EPC paracrine activity, the angiogenesis potential of ECs is promoted while simultaneously inflammatory damage is reduced in ECs.[100] One possible explanation for this effect is that the EPC-derived extracellular vesicles harbor high levels of pro-angiogenesis factors, such as VEGF and miR-183, which have the potential to activate the biological activity of ECs at the site of injury.[101] More interestingly, the differentiation of cardiac cells increases toward endothelial lineage once certain signaling pathways such as Shh are stimulated.[12] Abd El Aziz and co-workers found that intramyocardial transplantation of 5×10^6 human cord blood EPCs improves cardiac tissue function in a canine model of infarction via localization in the vascular units and direct differentiation into troponin I^+ cardiomyocytes.[102] The increase of endothelial nitric oxide synthetase and NO inside ECs is also associated with the paracrine activity of EPCs.[103] Likewise, both superoxide dismutase and catalase stimulation and the expression of Bcl-2 increase EC resistance to oxidative stress juxtaposed to ischemic myocardium.[12] Li et al found that shortly after ischemia induction in mice, donor EPCs can rapidly be recruited into the myocardium and elevate the local NO contents via the production of endothelial (eNOS) and inducible nitric oxide synthetase (iNOS).[104] In line with this, Cristóvão and co-workers indicated lower $CD34^+/KDR^+$ EPC levels in ischemic cardiomyopathy patients compared to healthy counterparts, indicating fast and appropriate recruitment of EPCs in response to hypoxic/ischemic conditions.[105]

Data have confirmed that the direct juxtacrine activity of EPCs can promote neointima formation via the regulation of pericyte migration, secretion capacity, and phenotypic switching.[106] Notably, EPCs can be genetically modified before transplantation to increase their regenerative potential.[107] For instance, miR-214 expressing EPCs efficiently can control calcium hemostasis in stressed cardiomyocytes and enhance survival rate.[12] Exosomal miR-1246 and miR-1290 driven EPCs upregulate ELF5 and SP1 in cardiac fibroblasts and increase endothelial differentiation.[108]

In addition to reducing fibrosis, the promotion of angiogenesis, activation of local cardiac progenitor cells, and increase in circulating progenitors within the infarcted myocardium collectively accelerate the healing process.[109] Therefore, EPC administration appears to promote cardiac tissues through both endogenous and exogenous mechanisms.[110]

Recent data affirm that the administration route influences the healing capacity and regenerative outcomes by affecting the on-target delivery, stem cell survival rate, and bioactivities.[111] According to the search we conducted, the direct intramyocardial injection yields better healing properties compared to the other administration routes. The systemic administration could lead to the sequestration of EPCs in certain tissues such as the liver, spleen, and lungs due to massive vascular beds while direct injection into the target tissues provides a higher delivery rate and retention time.[112] Therefore, the homing of systemically administrated EPCs into the myocardium is less due to low retention time and certain anatomical features of cardiac tissue.[113] Like intramyocardial injection, the intracoronary EPC infusion is considered to be widely administered. However, this modality requires higher cell

volume compared to direct intramyocardial injection. It is worth remembering that the intracoronary route can increase the probability of cell clustering, and embolism, resulting in the occlusion of supporting blood vessels into the affected sites.[114,115] Although intramyocardial injection ascertains higher cell delivery into the ischemic sites, this approach leads to the loss of a fraction of transplanted cells due to mechanical stress in solid organs such as cardiac tissue. Besides, iatrogenic inflammation and secondary tissue injuries can also occur when the cells are directly administrated into the myocardium.[116] Like transepicardial and intracoronary routes, the intramyocardial injection essentially requires thoracotomies, which is an invasive surgical approach and cannot be performed when multiple cell doses are required.[117] Despite the low targeting efficiency of EPC therapy via the systemic route, this approach is suitable for multiple-dose injection purposes.[110,117] Using special advanced technologies such as ultrasound-guided percutaneous injection, the high cell doses can be directly delivered into different parts of LV in a relatively non-invasive manner. To standardize this approach with minimum side effects, various studies must be conducted

The statistically significant results of Egger's and Begg's tests suggest the possibility of publication bias, implying that studies with statistically significant results may be more likely to be published than studies with null or negative findings. This could lead to an overestimation of the true effect size. Therefore, the results of this meta-analysis should be interpreted with caution. Future research, including studies with negative or null findings, would be valuable to clarify the true effect of EPCs in the restoration of cardiac function following experimentally induced MI in rodents.

This study has several limitations and future experiments should address them as much as possible. Even though this study made an effort to synthesize the available evidence rigorously, the high heterogeneity observed for most outcomes ($I^2 > 80\%$) suggests considerable variability between the included studies. Despite the conduction of subgroup analyses, it was not feasible to fully explore the potential sources of this heterogeneity due to limitations in the reported data of the original publications. Due to these features, it was not possible to draw firm conclusions about the specific factors influencing the effectiveness of EPC therapy. In addition, a small sample size related to some parameters would make the interpretation problematic. These limitations highlight the necessity of further experiments to address the gaps and flaws. Specifically, future studies should report detailed data in a more standardized and comprehensive manner in terms of EPC source, dosage, administration route, experimental conditions, and relevant outcome measures.

The micro-, and microanatomy structure of cardiac tissue and its kinetics profoundly vary in rodents compared to their human counterparts. It is estimated that rodents have high heart rates and short lifespans. Meanwhile, the expression of genes and factors in cardiac cells can in part but not completely differ as compared to the other mammals.[21] For instance, alpha isoform is the dominant type of myosin heavy chain in humans and large mammals atrium while this protein type is highly expressed in ventricles of mice and rats.[21] The prominent difference in cardiac tissue kinetics and parameters can lead to relatively incomparable outcomes in rodents receiving stem cells and progenitors compared to large-size mammal models and humans.[118] EPCs display high similarity with other cell lineages such as hematopoietic stem cells, thus the precise characterization, isolation, and purification of EPCs seem problematic. Besides, EPCs constitute 0.01 to 0.0001% of total bone marrow mononuclear cells, and *in vitro* expansion using different growth factors and supporting ECM components are necessary to yield EPCs in high quantities.[13,119] Regarding the limited number of EPCs in freshly collected samples, serial passages and prolonged culture time can contribute to the loss of EPC phenotype and functionality.[120] Although cryopreservation in part preserves the phenotype and biological activity, attention should be given to optimizing the cryopreservation protocols using suitable cryoprotectants to minimize the adverse effects of storage

temperature.[121] Based on the recent data, EPC type and maturation stage can influence the angiogenesis outcomes. Sieveking and co-workers found that later outgrowth EPCs can directly participate in the structure of vascular units better than that of early EPCs. It seems that early EPCs can promote the angiogenesis phenomenon indirectly via the release of angiogenesis factors at the site of injury.[122] The mobilization of EPCs in response to cytokine gradient increases simultaneous maturation and functional activity compared to the resident progenitors inside the bone marrow niche.[13] The circulating EPCs can lose their stemness features (CD133↓, and CD34↓) accompanied with the expression of certain markers such as CD31, and vWF with the reaching to the injured site.[13] These data confirm that bone marrow EPCs are putative progenitor cells in the induction of angiogenesis in the ischemic regions. Besides cell source, the number of graft stem cells can predetermine the angiogenesis outcomes, especially in tissue with chronic injuries. However, less and excessive stem cells can cause the disruption of the healing process via an imbalance in immune cell activity and normal development of resident cells and transplanted stem cells.[123] Taken together, the number and source of EPCs can be effective in the induction of angiogenesis in the ischemic myocardium.

Conclusion

The current systemic review and meta-analysis showed the eligibility of EPCs in the restoration of cardiac function following experimentally induced MI rodents, either rats or mice. The stimulation of angiogenesis and reduction of fibrosis along with the improvement of cardiac functional parameters (EF, and FS) are the main outcomes following EPC transplantation. Taken together, the current data provide new insights into the potential clinical application of EPCs and their regenerative properties in patients with MI.

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Authors' Contribution

Reza Rahbarghazi participated in all stages of the review and supervised the conduct of the study. Samaneh Narimani, Hamid Lotfimehr, Maryam Taghavi Narmi, and Robab Mehdipour collected the data and wrote the manuscript. Hanieh Salehipourmehr performed the statistical analysis, and wrote the relevant sections. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

Ethical Approval

All phases of this study were approved by local ethics committee of Tabriz University of Medical Sciences (ethical code: IR.TBZMED.REC.1400.175; Approval date: 2023-10-16) and NIMAD (National Institute for Medical Research Development) (ethical code: IR.NIMAD.REC.1402.031; Approval date: 2023-12-30) under research proposal entitled "Application of endothelial progenitor cells in the alleviation of cardiac infarction in rodent models".

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Figures:

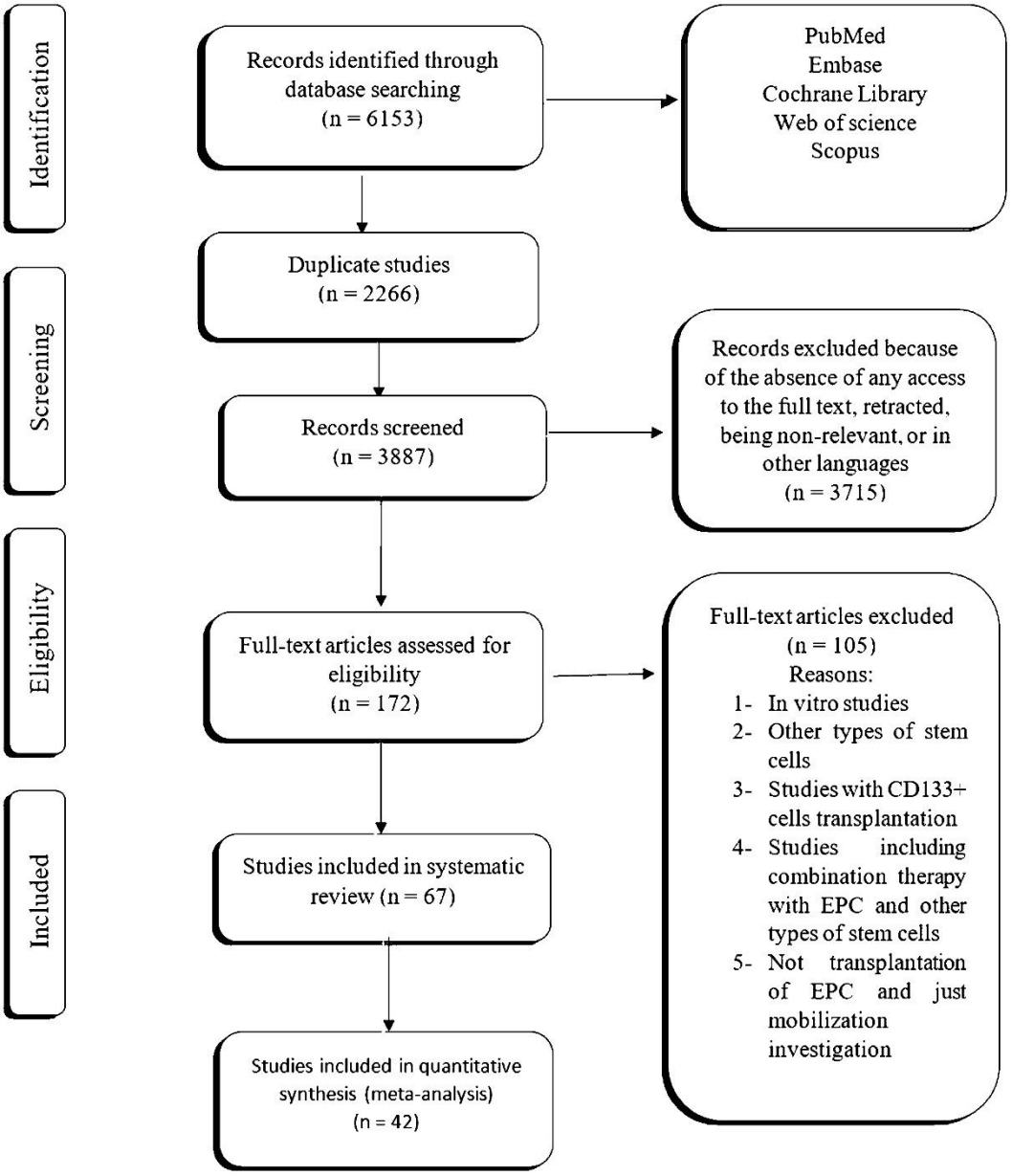

Figure 1. PRISMA diagram of the review process for the meta-analysis

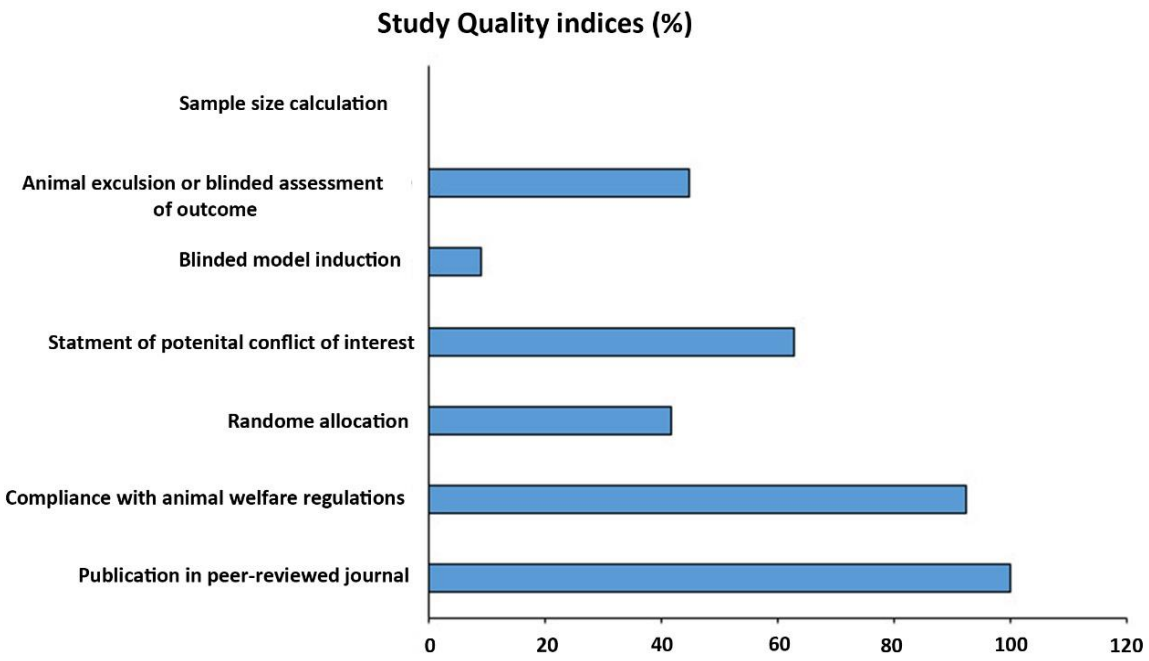

Figure 2. Percentage of selected experiments for each item in the modified version of the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) quality checklist.

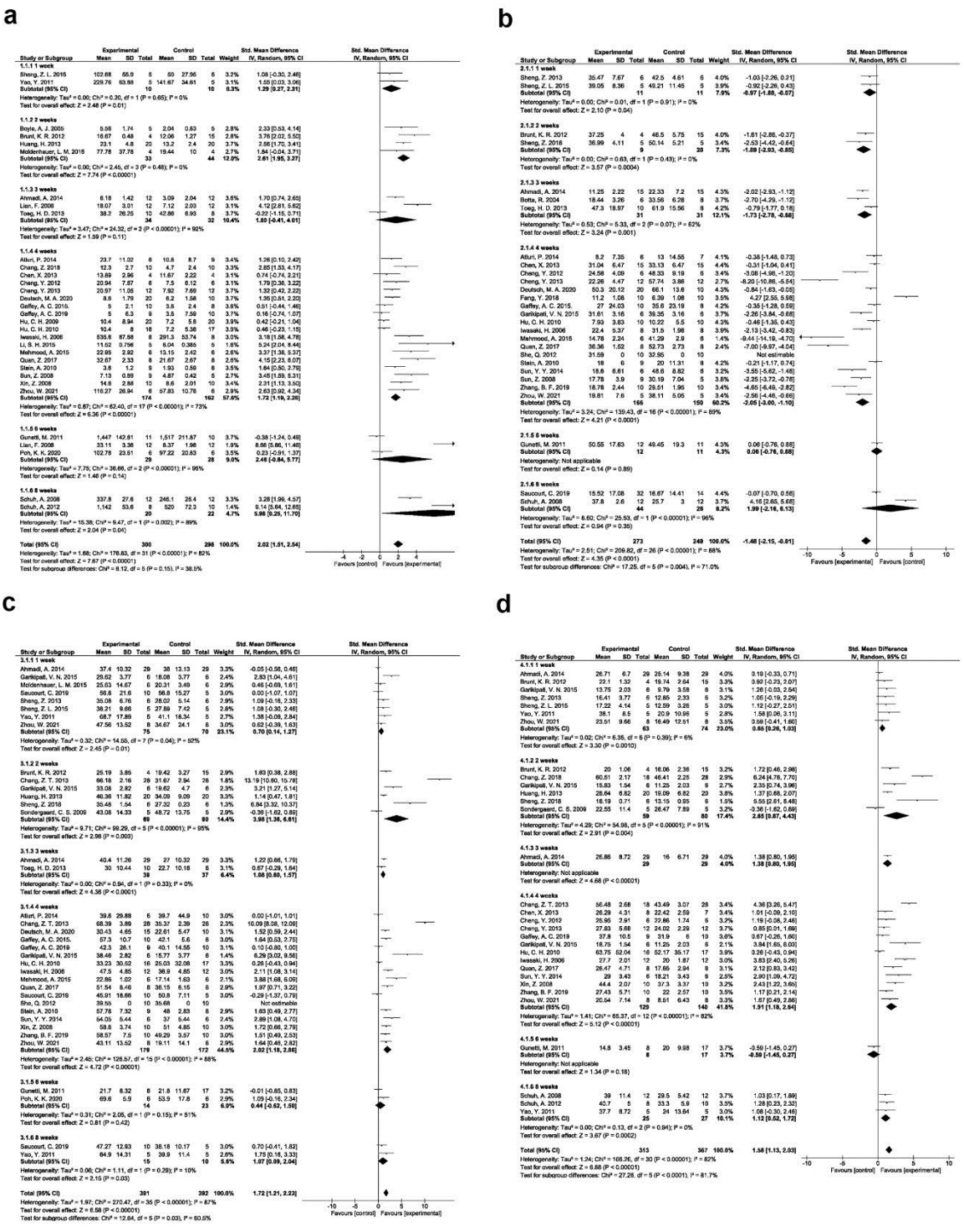

Figure 3. Angiogenesis improvement based on the time of results assessment (a). Fibrosis improvement based on the time of results assessment (b). Ejection fraction improvement based on the time of results assessment (c). Fractional shortening improvement based on the time of results assessment (d).

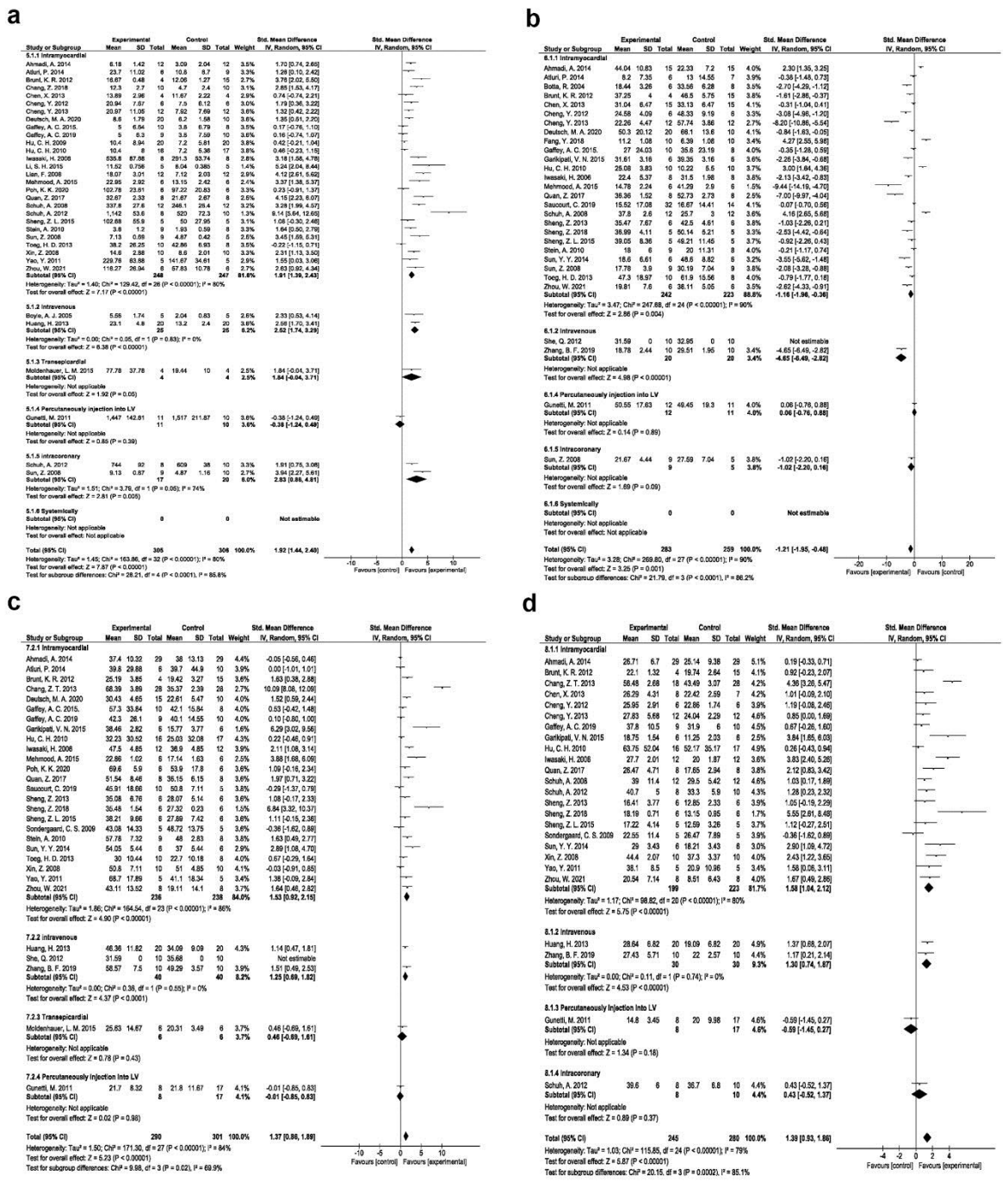

Figure 4. Angiogenesis improvement based on injection method (a). Fibrosis improvement based on injection method (b). Ejection fraction improvement based on injection method (c). Fractional shortening improvement based on injection method (d).

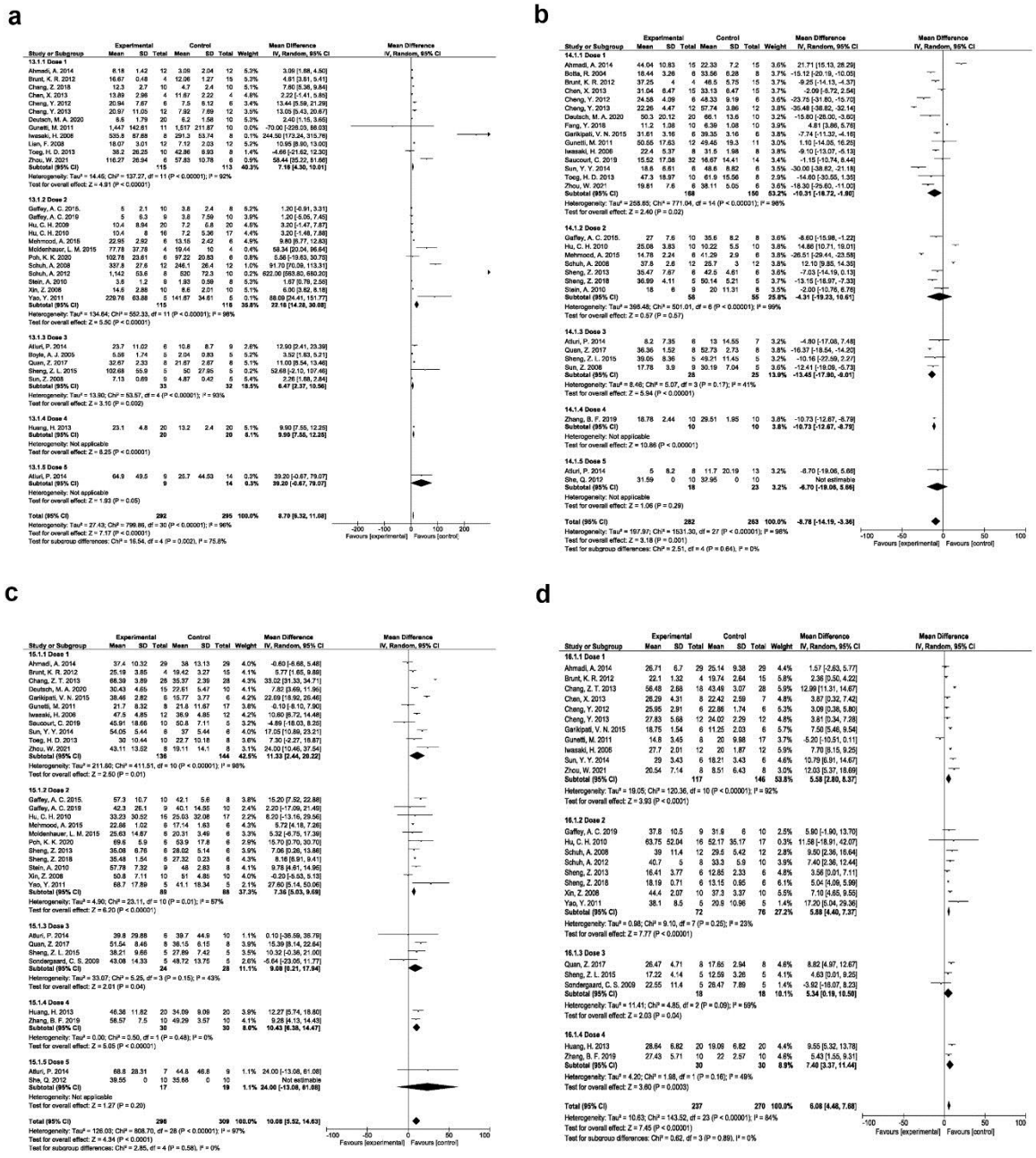

Figure 5. Angiogenesis improvement based on EPC dose (a). Fibrosis improvement based on EPC dose (b). Ejection fraction improvement based on EPC dose (c). Fractional shortening improvement based on EPC dose (d).

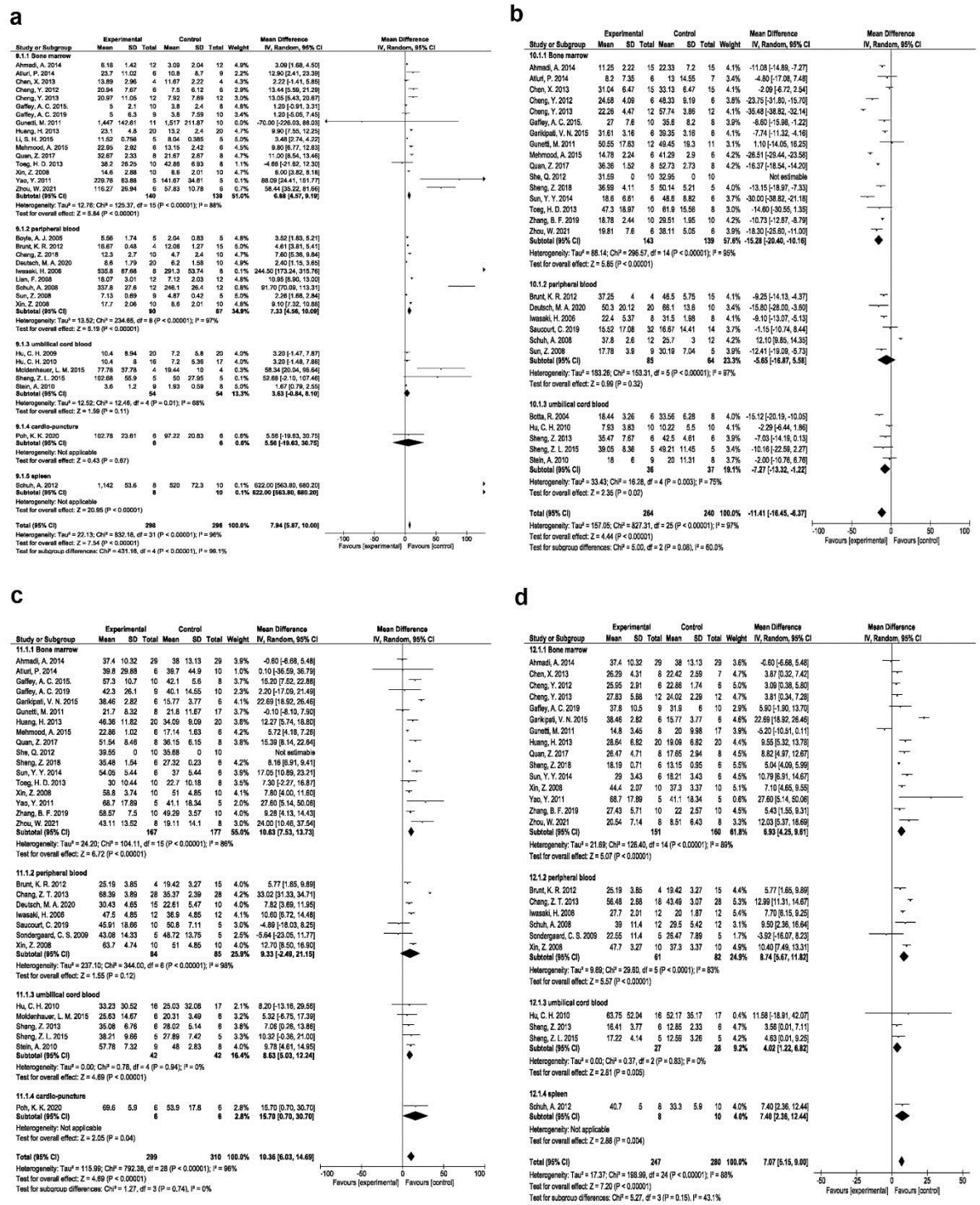

Figure 6. Angiogenesis improvement based on EPC source (a). Fibrosis improvement based on EPC source (b). Ejection fraction improvement based on EPC source (c). Fractional shortening improvement based on EPC source (d).

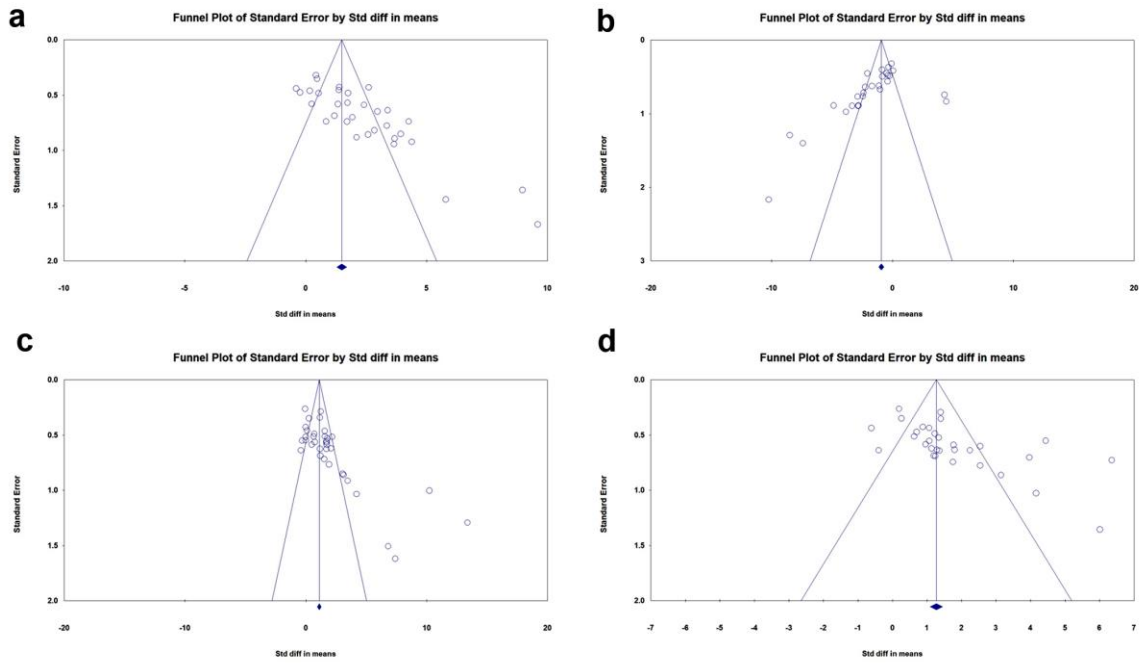

Figure 7. Funnel plot of standard error by the standard difference. Angiogenesis (a); Fibrosis (b); Ejection fraction (c); and Fractional shortening (d)