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Systematic Review

Efficacy & safety of stem cell therapy for treatment of acute myocardial infarction: A systematic review & meta-analysis

Pravesh Aggarwal[1], Ranu R. Oza[1], Hitendrapal Solanki[2], Jaykaran Charan[1], Rimple Jeet Kaur[1], Surender Deora[3], Lokesh Saini[4], Deepak Kumar[2], Rahul Choudhary[3], Pankaj Bhardwaj[5], Tanuj Kanchan[6] & Siddhartha Dutta[7]

Departments of [1]Pharmacology, [2]Medicine, [3]Cardiology, [4]Paediatrics, [5]Community Medicine and Family Medicine, & [6]Forensic Medicine and Toxicology, All India Institute of Medical Sciences, Jodhpur, Rajasthan & [7]Department of Pharmacology, All India Institute of Medical Sciences, Rajkot, Gujarat, India

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***Background & Objectives*: Stem cell based therapeutic treatments have been used as a management strategy for acute myocardial infarction (AMI), a common primary factor causing death globally. We aimed to undertake a meta-analysis of studies including randomised controlled trials (RCTs) examining different stem cell preparations in AMI, as a definitive answer from this therapeutic approach is yet to emerge.**

***Methods*: Following PROSPERO registration (CRD42024628552), a systematic search was conducted through PubMed database, Embase, Cochrane, and Web of Science. Data was analysed using RevMan 5.4.1. Primary outcomes included all-cause mortality, recurrent myocardial infarction (Re-MI), severe adverse events (SAEs), hospitalisation for heart failure, cancer incidence, and left ventricular ejection fraction (LVEF). A fixed-effect model was used to assess six outcomes: all-cause mortality, Re-MI, SAEs, heart failure hospitalisation, cancer incidence, and stroke. A model based on random effects depending on heterogeneity was used to assess LVEF.**

***Results*: From 9,516 records, 48 studies were included for analysis based on available endpoints. No notable changes in all-cause mortality were observed between patients receiving stem cell therapy and those in the control group, according to the meta-analysis. [Risk Ratio (RR) 0.73], SAEs (RR 0.93), Re-MI (RR 0.67), HF-related hospitalisation (RR 0.79), cancer (RR 0.82), or stroke (RR 0.81). Echocardiographic LVEF improved significantly at study end [Mean difference (MD) 2.53%] and difference from baseline (MD 3.89%), with high heterogeneity (I^2 - 76%). MRI-assessed LVEF showed no significant change at study end (MD 0.83%) but improved from baseline (MD 1.37%). Heterogeneity was low except for LVEF, with serious bias risk for most outcomes and very serious for Re-MI and SAEs, though their objective nature limits bias**

***Interpretation & conclusions*: Analysis done found no significant benefit of stem cell-based therapies on clinical endpoints in AMI patients.**

Key words Meta analysis - myocardial infarction - stem cells - stem cell therapy - systematic review

Based on the available data globally, the leading cause of mortality is cardiovascular disease[1]. Acute myocardial infarction (AMI) can cause persistent illness and is the cause of death among the different

cardiac tissue-related diseases. Present therapy for treatment of the current episode and prevention of re-myocardial infarction (Re-MI) is not much efficacious. Each episode of MI has high mortality and there are high chances of recurrence in the survivors[2]. The available treatment options do not reverse tissue damage occurring during the episode, and there is a need for novel methods or interventions that may affect the pathology at the molecular level to reverse the changes in the heart due to ischemia. Numerous strategies, including gene therapy, cardiac tissue engineering, cell reprogramming, and biomaterial-based delivery methods, are being researched to treat AMI. Numerous clinical trials have explored the use of stem cell based therapeutic approaches. Stem cells are primitive, unspecialized cells capable of self-renewal throughout an organism's lifespan. Their therapeutic potential in myocardial infarction primarily stems from their paracrine effects, which facilitates the transformation of stem cells into heart muscle and endothelial cells and triggers the stimulation and migration of the heart's own stem cells[3].

Many clinical studies were conducted to evaluate the effects of therapeutic strategies of stem cell for treating acute AMI. Several studies have reported improvements in functional parameters such as end-diastolic volume (EDV), end-systolic volume (ESV), left ventricular ejection fraction (LVEF), and infarct size (IS). Additionally, some trials have reported reductions in clinical outcomes like mortality and recurrent myocardial infarction (Re-MI); however, the findings across studies have not been consistent, with some reporting conflicting results[4]. Updated Cochrane review published in 2015 showed moderate evidence of no effect, with the caveat that further studies may change the scenario[5].

Given the inconsistent results reported in previous studies, we undertook this systematic review and performed meta-analysis to address the research question stating: 'What does the existing evidence reveal about the safety and effectiveness of stem cell therapies in managing acute myocardial infarction (AMI)?' Our review seeks to include recently published trials while adhering to a methodology aligned with earlier systematic reviews[5].

Materials & Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary table I) while conducting this systematic review the protocol of which was registered in the PROSPERO database (number CRD42024628552). Methodological guidance was also drawn from the 'Cochrane Handbook for Systematic Reviews of Interventions'[6]. Randomised Controlled Trials (RCT) satisfying all of the following requirements were included: (*i*) population: individuals with a myocardial infarction diagnosis,(*ii*) stem cells as an intervention, and (*iii*) comparison: inclusion of a placebo (Supplementary table II). For the syntheses, studies with the same endpoint were grouped.

A thorough and methodical search of the literature was conducted, and papers were evaluated for eligibility using established criteria for selecting and excluding studies. Two authors developed a strategy for the advanced search using keywords related to the study population (myocardial infarction), intervention (stem cells), and comparison (placebo or no treatment alongside standard care). From the beginning until October 27, 2023, two researchers (PA, RO) separately searched four main databases: Medline (PubMed), Cochrane, Web of Science, and Embase for relevant material. They did this without regard to language limitations. Supplementary material 1 lists the specific search tactics for each database. To find more research, computerized searches were supplemented by a manual screening of narrative reviews, systematic reviews, and reference lists of pertinent trials. Five reviewers independently examined the abstracts and titles for possible inclusion after deleting duplicate records. Full-text articles of the selected studies, along with any supplementary materials and protocols, were retrieved and assessed. The reasons for exclusion at each stage were systematically recorded. Detailed characteristics of the included studies are presented in table I. The type and method of administering stem cells, the length of follow up, and patient attributes such as age and gender were taken into consideration when extracting data. Although it was originally intended to get in touch with the original study authors to enquire about any missing data, this step was unnecessary because the included studies contained all the information that was needed. In studies that used a single control group to compare against multiple intervention arms, the control group's participant count was halved to prevent duplication in the analysis.

Outcome measure: The primary outcomes included all-cause mortality, recurrent myocardial infarction (Re-MI), serious adverse events (SAEs), hospitalisation due to heart failure, cancer incidence, and changes in

Table 1. This table summarizes characteristics of all the included studies in the systematic review

Study ID	Country	Patient details	Age: Mean (SD/ SEM)	% Male	No. of participants in intervention (n)/ comparator	Follow up	Route of cell administration	Cell type	Procedure to obtain cells	Suspension media	Dose (cells)	Comparator (placebo or control)
Angeli 2012	Brazil	STEMI, LVEF<45%	Not reported	Not reported	11 /11	12 Months	Injection intracoronary through balloon	BMMNC	Not reported	Not reported	260(160) million BMMNC; 1.4 (1.5) % CD34+	Medium
Assmus 2014	Germany	Acute STEMI, LVEF<45%	Intervention: 57 (11) Control: 55(11)	82%, 82%	101/103	60 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	10 ml of X VIVO 10 media	236(174) million	Patient's own serum
Attar 2023	Iran	STEMI, LVEF < 40%.	Intervention: 53.25 (5.05); Repeated intervention: 56.05 ± 7.48 Control: 56.53 (7.95)	Intervention: 100 (%); Repeated intervention: 80% Control: 73.3	50/25	6 Months	Injection intracoronary through balloon	hWJMSC allogeneic	BM aspiration	0.9% normal saline	10 million	Standard treatment
Cao 2009	China	STEMI	Intervention: 50.7 (1.1) Mean (SEM) Control: 51 (1)	Intervention: 95.1 (%) Control: 93.3	41/45	48 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	Heparinized saline	50(12) million BMMNC; 1.8(0.6) % CD34+	Heparinized saline
Chen 2004	China	Acute MI	Intervention: 58 (7) Mean (SD) Control: 57 (5)	Intervention: 94 (%) Control: 97	34/35	6 Months	Injection intracoronary through balloon	BMMSC	BM aspiration	Heparinized saline	48,000 (60,000) million	Heparinized saline
Choudry 2016	Multicentre	Acute AMI	Intervention (n = 55) 56.4+10.4; Control (n = 45) 56.7+10.7	Intervention: 84% Control: 91%	55/45	12 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	0.9% normal saline with autologous whole bone marrow	59.8(59.9) million BMMNC; 1.9(1.5) million CD34+	10 mL sterile 0.9% NaCl mixed with 33 mL autologous whole bone marrow.
Chullikana 2015	India	STEMI, LVEF 30-50%	Intervention 47.31 (12.1); control 47.79 (6.48)	Intervention: 100 (%) Control: 80	10/10	24 Months	Anticubital vein of forearm	BM-MSC allogeneic	BM aspiration	35 ml of multiple electrolytes (PLASMA-LYTE A)	2 million cells/kg body weight; 0.14% CD34+	Multiple electrolytes injection (Plasma-Lyte A).
Colombo 2011	Italy	STEMI, LVEF < 45%	Intervention: 54 (47-60) Median (Range) Control: 56 (44 - 58)	Intervention: 100 (%) Control: 100	5/5	12 Months	Injection intracoronary through balloon	CD133+ cells	BM aspiration, selection to isolate CD133-positive cells	0.9% saline with 10% human serum albumin.	Median (range): 5.9 (4.9 to 13.5) million	Standard treatment
Delewi 2011	Netherlands	STEMI	Intervention: 56 (9) Control: 55 (10)	Intervention: 84 (%) Control: 86	69/65	60 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	Heparinised saline & 4 % human serum albumin	296 (164) million cells	Standard treatment
Dill 2009	Germany		Intervention: 57 (11) Control: 55(11)	82%, 82%	101/103	24 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	10 ml of X VIVO 10 medium	236(174) million	Standard treatment

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Study ID	Country	Patient details	Age: Mean (SD/ SEM)	% Male	No. of participants in intervention (n)/ comparator	Follow up	Route of cell administration	Cell type	Procedure to obtain cells	Suspension media	Dose (cells)	Comparator (placebo or control)
F. Aviles 2018	SPAIN, Belgium	STEMI, LVEF ≤45%	Intervention 56(12); Control 55±8	Intervention: 88% Control: 100	33/16	12 Months	Injected intracoronary through balloon	Cardiac stem cells- Allogenic	Human heart biopsies	saline solution with 5% human serum albumin	35 million	Standard treatment
Gao 2013	China	STEMI	Intervention: 55 (1.6 SEM) Control: 58.6 (2.4 SEM)	Intervention: 100 (%) Control: 86.4	21/22	24 Months	Injected intracoronary through balloon	BM-MSC	BM aspiration	Heparinised saline	3.08 (0.52) million cells	Standard treatment
Gao 2015	China	Acute STEMI	intervention - 57.3+/-1.3; control - 56.7+/-1.7	Intervention: 55%; Control 51%	58/58	18 Months	Injected intracoronary through balloon	WJ-MSCS	Umbilical cord	10 ml heparinized saline	6 million	Placebo
Ge 2006	China	STEMI	Intervention: 58 (11 SD) Control: 59 (8 SD)	Intervention: 80 (%) Control: 100	10/10	6 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	Heparinized saline	40 million cells; 4.7% CD34+	Placebo, BM supernatant mixed with heparinized saline
Grajek 2010	Poland	Anterior AMI	Intervention: 49.9 (8.4 SD) Control: 50.9 (9.3 SD)	Intervention: 87 (%) Control: 86	31/14	12 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	X-vivo 15 medium & 2% autologous plasma	410 (180) million	Standard treatment
Haddad 2020	Canada	Acute STEMI, LVEF 25% - 50%	50.5 (median age, n=37)	89%; 82.4% in intervention and 95% in placebo	17/20	8.5 yr IQR [7.9, 10.0]	Injected intracoronary through balloon	CD133+	BM aspiration	Normal saline containing 10% autologous plasma	10 million cells except in one patient (5.2 million)	placebo
Hare 2009	USA	MI; LVEF 30-60%	Intervention: 59 (12.3); Control: 55.1 (10.2)	I: 82.4%) C: (78.9%)	39/21	12 Months	Intravenous	hMSC-allogenic	BM aspiration	.9% human serum albumin, & 3.8% dimethyl sulfoxide in PlasmaLyte A	5 million hMSCs/kg body weight	solution of 1.9% human serum albumin with 3.8% dimethyl sulfoxide in PlasmaLyte A.
Huikuri 2008	Finland	STEMI	Intervention: 60 (10 SD) Control: 59 (10 SD)	Intervention: 90 (%) Control: 85	40/40	6 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	Heparinised saline & 50% autologous serum	402 (196) million cells; 2.6 (1.6) million CD34+	Placebo (heparinised saline & 50% autologous serum)
Janssens 2006	Belgium	STEMI	Intervention: 55.8 (11) Control: 57.9 (10)	Intervention: 82 (%) Control: 82	33/34	4 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	Heparinised saline & 5% autologous serum albumin	172 (72) million cells; 2(1.3) million CD34+	Placebo heparinised saline & 50% autologous serum
Kaminek 2008	Czech Republic.	Acute STEMI	intervention -54+/- 9; Control - 56+/- 9	Control- 89%; Intervention- 86%	31/31	12 Months	Injected intracoronary through balloon	BMMNC	BM aspiration		100 million	control
Kim 2018	SOUTH KOREA	Anterior MI, LVEF ≤ 40%	Intervention 55.3 ± 8.6; control 57.8 ± 8.9	Intervention: 100 (%) Control: 100	14/12	12 Months	Injection intracoronary through balloon	BM-MSC	BM aspiration	Heparinised saline & 5% autologous serum albumin	72(9) million	Standard treatment

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Study ID	Country	Patient details	Age: Mean (SD/ SEM)	% Male	No. of participants in intervention (n)/ comparator	Follow up	Route of cell administration	Cell type	Procedure to obtain cells	Suspension media	Dose (cells)	Comparator (placebo or control)
Laguna 2018	SPAIN	AMI, LVEF < 50%	Intervention 62.63 (8.35); Control 64.78 (11.48)	Intervention (n=8) 87.5; Control (n=9) 88.9	10/10	9 Months	Direct intramyocardial injection	BMMNC	BM aspiration	heparinized Ringer's lactate solution	1 million cells per millilitre	Saline and CABG
Lezo J S D 2007	Spain	Anterior STEMI	Intervention: 52 (12) Control: 55 (11)	BMMNC: 80% Control: 70%	10/10	3 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	0.9% normal saline with 0.1% heparin	900 (300) million; 17(13) million CD34+	Heparinised saline
Lee 2014	South Korea	STEMI	Intervention: 53.9 (10.5) Control: 54.2 (7.7)	Intervention: 90 (%) Control: 89.3	40/40	6 Months	Injected intracoronary through balloon	BM-MSC	BM aspiration	NR	72 (9) million cells	Standard treatment
Lunde 2007	Norway	Ant. STEMI	Intervention: 58.1 ± 8.5; Control 56.7 ± 9.6	Intervention: 84 (%) Control: 84	50/50	6 months	Injected intracoronary through balloon	BMMNC	BM aspiration	0.9% normal saline with 20% heparin plasma	68 (IQR 54-130) million	Standard treatment
Mathur 2020 (BAMI)	Multicentre	STEMI, LVEF <45%	Intervention: 59 (11); Control 60 (11)	Intervention: 83.7 (%) Control: 77.3	185/190	24 Months	Injected intracoronary through balloon	BMMNC	BM aspiration	X-Vivo 10 medium	25-500 million	Standard treatment
Meyer 2009	Germany	STEMI	Intervention 53·4 (14·8); Control 59·2 (13·5)	Intervention 20 (67%); Control 22 (73%)	30/30	5 yr	Injected intracoronary through balloon	BMMNC	BM aspiration	saline with heparin.	2460(940) million, 9.5(6.3) million CD34+	Standard treatment
Naseri 2018	Tehran, Iran	STEMI, LVEF: 20-45%	Placebo group n=26: 55.5 (8.54) CD133+ group n=21: 53.14 (8.56) MNC group n=30: 51.45 (7.49)	Placebo group n=26: 88.5% CD133+ group n=21: 91.5% MNC group n=30: 90%	51/26	18 Months	Direct intramyocardial injection	BMMNC; CD133+	BM aspiration	2 ml normal saline with 2% autologous serum.	564.63 million (± 69.35) MNC cells; 8.19 million (± 4.26) CD133+ cells	2 ml normal saline supplemented with 2% autologous serum.
Ostovaneh 2021		MI, LVEF <45%	intervention (n=83): 54.7 (11.1); Control (n=41): 53.5 (10.2);	Placebo (n=41): 87.8% CAP-1002 group (n=83): 86.7%	95/47	12 Months	Intracoronary infusion	allogeneic cardiosphere-derived cells (CDCs) [CAP-1002]	Donor hearts at the time of cardiac transplantation	NR	25 million	
Penicka 2007	Czech Republic	Anterior STEMI, LVEF < 50%	Intervention: 61 (14) Control: 54 (10)	Intervention: 71 (%) Control: 100	17/10	24 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	NR	2640 (IQR 1960-3300) million	Standard treatment
Piepoli 2010	Italy	STEMI	intervention (n= 19) 63.1+/- 2.4; Control (n=19)- 67+/- 2.7	13 (68.4) in C; 13 (68.4) in BM	19/19	12 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	7 ml of PBS-EDTA buffer containing 3 ml of human albumin 5% W/V.	248 million BMMNC, 2 million CD34+	control
Plewka 2009	Poland	STEMI, LVEF <40%	intervention: 59 (9) Contol: 56 (8)	BMMNC 68% Control: 78%	40/20	24 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	heparinised saline	144 (49) million cells	Standard treatment

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Study ID	Country	Patient details	Age: Mean (SD/ SEM)	% Male	No. of participants in intervention (n)/ comparator	Follow up	Route of cell administration	Cell type	Procedure to obtain cells	Suspension media	Dose (cells)	Comparator (placebo or control)
Quyyumi 2011	USA	Acute STEMI & LVEF ≤ 50%	$CD34^+$ levels (median, IQR): HD 50.5 (45–53), MD 63 (57–66), LD 52 (51–52); treated pooled 52 (47.5–63.5), control pooled 52 (47–57).	CD34+: 100% (HD), 80% (MD), 80% (LD) Control: 87%	16/15	12 Months	Injection intracoronary through balloon	CD34+ cells	BM aspiration, selection to isolate CD34+ cells	Heparinised phosphate buffered saline, 40% autologous serum & 1% human serum albumin	LD: 4.8 (0.4) million cells MD: 9.9 (0.7) million cells HD: 14.3 (1.6) million cells	Standard treatment
Quyyumi 2017	USA	STEMI LVEF ≤48%	Intervention: 57.1 ± 10.1 Control: 56.4 ± 10.1	Intervention: 85% Control: 80%	100/95	6 Months	Injection intracoronary through balloon	CD34+ cells	BM aspiration, selection to isolate CD34+ cells	10 ml phosphate buffered saline supplemented with autologous serum & human serum albumin	14.9 ± 8 million cells (range 8 to 43.8)	phosphate buffered saline, autologous serum & HAS without cells.
Roman 2015	Spain	AMI	BMMC (n=30): 54 +/- 11; G-CSF (n=30); 57 +/- 9 BMMC + G-CSF (n=29): 56 +/- 8 Control (n = 31): 57 +/- 11	BMMC (n=30): 97%; G-CSF (n=30); 83% BMMC + G-CSF (n=29): 86% Control (n = 31): 90	59/61	12 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	heparinized saline	560 million	
Roncalli 2011	France	Acute STEMI, LVEF ≤ 45%;	BMMNC: 56 (12) Control: 55 (11)	BMMNC: 80.8% Control: 89.8%	52/49	3 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	4% human serum albumin solution	98.3 (8.7) million cells	Standard treatment
Srimahachota 2011	Thailand	STEMI, LVEF < 50%	Inervention 52 + 12.9; Control 54.1 + 14.7	Intervention 81.8; Control 83.3	11/12	6 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	saline with 2% autologous serum	420 (221) million cells	Standard treatment
Surder 2016	Switzerland	STEMI, LVEF < 45%	BMMNC: median 55 (IQR 15) (E), 62 (IQR 15) (L) Control: median 56 (IQR 14.5)	BMMNC: 86.2% (E), 82.5 (L) Control: 83.6%	133/67	12 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	20% of autologous serum	E: 159.7 (125.8) million cells; L: 139.5 (120.5) million cells	Standard treatment
Tendra 2009	Multicentre	Anterior AMI, LVEF ≤ 40%	CD34/CXCR4+: median 58 BMMNC: median 55 Control: median 59	CD34/CXCR4+: 63.7% BMMNC: 70.6% Control: 75%	160/40	6 Months	Injection intracoronary through balloon	Selected cells (S): CD34+/ CXCR4+ cells Unselected cells (U): BMMNC	BM aspiration; Selected cells: immunomagnetic selection to isolate CD34+/ CXCR4+ cells	Phosphate-buffered saline	S: 1.9 million cells U: 178 million cells	Standard treatment
Traverse 2010	USA	STEMI; LVEF <50%	BMMNC: median 52.5 (IQR 43 - 64) Control: median 57.5 (IQR 54 - 59)	BMMNC: 83.3% Control: 60%	30/10	15 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	0.9% saline solution & 5% human serum albumin	100 million cells	0.9% saline solution & 5% human serum albumin

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Study ID	Country	Patient details	Age: Mean (SD/ SEM)	% Male	No. of participants in intervention (n)/ comparator	Follow up	Route of cell administration	Cell type	Procedure to obtain cells	Suspension media	Dose (cells)	Comparator (placebo or control)
Traverse 2011	USA	STEMI, LVEF ≤ 45%; PCI	BMMNC: 57.6 (11) Control: 54.6 (11)	BMMNC: 79% Control: 90%	58/29	6 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	0.9% saline solution & 5% human serum albumin	147 (17) million cells	0.9% saline solution and 5% human serum albumin
Traverse 2018	USA	anterior STEMI, LVEF ≤45%	BMC 55.9 (11) C 56.4 (10.4)	BMC 88%, C 85%	79/41	12 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	0.9% saline solution & 5% human serum albumin	146.1(20.1) million	5% ALBUMIN IN NS with 100 ul oh whole blood
Wang 2014	China	Acute STEMI	Intervention: 58 (10.2) Control: 56.1 (9.8)	Intervention: 67.9% Control: 53.3%	28/30	6 Months	Injection intracoronary through balloon	BM-MSC	BM aspiration and culture of MSC	Heparinized saline	100 million cells	Heparinized saline
Wen X 2012	China	AMI	BM-MSC: 60.4 (8.9) Control: 58.6 (10)	BM-MSC: 58.8% Control: 61.9%	17/21	3 Months	Injection intracoronary through balloon	BM-MSC	BM aspiration	NR	460 (160) million cells	heparinised saline
Wohrle 2010	Germany	AMI	Intervention: 61.0 (8.1) Control: 61.1 (9.3)	Intervention: 90% Control: 62%	29/13	36 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	0.9% saline solution,2% human serum albumin & 0.1% autologous erythrocytes	381 (130) million cells	0.9% saline solution, 2% human serum albumin and 0.1% autologous erythrocytes)
Wollert 2017	Germany, Norway	STEMI LVEF < 52%	55 ± 10	86.6	loBMC (n = 38) hiBMC (n =33) loBMCi (n =25) hiBMCi (n= 31) Comparator = 26	6 Months	Injection intracoronary through balloon	BMMNC	BM aspiration	serum-free DMEM (Dulbecco's modified eagle medium)	loBMC (Nucleated cells - 700 ± 290 million; CD34 cells - 2.9 ± 2.1 million); hiBMC (Nucleated cells - 2060 ± 770 million; CD34 cells - 8.2 ± 5.3 million)	Pure red blood cell suspension
Yao 2009	China	STEMI, LVEF 20-39%	Intervention: 52.1 (6.3) (SD), 51.3 (7.4) (DD) Control: 52.7 (7.8)	Intervention: 83.3 & (SD), 80% (DD) Control: 91.7%	27 (15 SD, 12 DD); Control 12	12 Months	Injection intracoronary through balloon	BMMNC	BM Aspiration	Heparinised plasma	SD: 410 million cells; DD: 190 (SE 120) million cells	Heparinised plasma
Zhang 2021	China	STEMI	BMC: 59.3+/-9: placebo 58.6+/-11	BMC: 95.2% Placebo: 86.36%	21/22	12 Months	Injection intracoronary through balloon	BM-MSC	BM Aspiration	2 ml normal saline	2-5 million cells	

LVEF assessed by MRI and echocardiography. Two researchers independently extracted the data, and a subject matter expert was consulted to settle any differences.

Statistical analysis: Authors collected and compiled the detailed outcome data from all the studies included and pooled estimates were visually represented using forest plots generated in Review Manager (RevMan) version 5.4, developed by The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, 2020. Statistical significance was defined as a $P<0.05$. The dichotomous and continuous data were analysed using relative risks (RRs) and mean difference (MD) respectively with their confidence intervals (CIs). The I^2 statistic was used to assess heterogeneity across studies, with values over 50 per cent considered indicative of substantial heterogeneity. Depending on the degree of heterogeneity, a fixed-effects model was used for low heterogeneity, whereas a random-effects model was employed when heterogeneity was substantial. Subgroup analyses were performed based on factors such as the timing of outcome assessment, type of stem cells used, autologous *versus* allogeneic sources, administration route and timing, sample size, and cell dose to identify potential sources of heterogeneity. Means and standard deviations were estimated from medians and ranges using the approach outlined by Hozo *et al*[7] (2005). Additionally, RevMan calculator was used for conversion of data from one form to another.

Risk of bias assessment: The risk of bias for each included study was independently evaluated by two reviewers (PA, RO). Differences in opinion were resolved through discussion, and, if needed, a third reviewer was consulted. The Cochrane Collaboration's Risk of Bias 2 (ROB-2) tool was used to assess the methodological quality of the randomized controlled trials (RCTs). Based on the assessment, studies were grouped into categories of low risk, some concerns, or high risk of bias[8,9]. The ROBVIS tool was utilized to graphically present the risk of bias evaluations. Potential bias from selective reporting or missing results in the synthesis was specifically evaluated through Domain 5 of the ROB-2 tool, which addresses bias due to selective outcome reporting. By using this approach, a transparent and complete evaluation of the methodological quality of the studies was achieved.

Recommendations: The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was employed to assess the overall certainty of the synthesized evidence. For each outcome, this method evaluates the quality of evidence across multiple studies and classifies it into four levels: high, moderate, low, and very low certainty. While randomised controlled trials (RCTs) generally begin as high-certainty evidence, factors such as publication bias, indirectness, imprecision, inconsistency, and risk of bias can lead to downgrading their certainty level. On the other hand, in some circumstances, a large effect size or a dose-response connection, among other factors, might improve the certainty[10-12]. This was done by two independent assessors. They resolved disagreements amongst themselves and if it persisted, they followed a third independent assessor.

Results

The screening process *via* the PRISMA flowchart[13] can be visualized in flowchart figure 1. After a systematic search across four databases, we identified 9516 records initially, retrieved 218 full texts and selected 48 articles for comprehensive review and quantitative synthesis.

We extracted all relevant results reported across the included studies. It included data from different measures, time points, and analyses. However, to prevent unit of analysis issue, endpoints reported at the longest follow up were considered for the analysis and a subgroup analysis was done based on trial duration.

Mortality: All-cause mortality was reported in 30 clinical trials[14-42] having 2879 participants (1633 in stem cell and 1246 in control). The findings demonstrated that stem cell therapy had no significant effect on reducing all-cause mortality in patients with AMI (RR = 0.73; 95% CI: 0.50–1.05; $P = 0.09$) with uniform findings among the studies ($I^2 = 0\%$; Fig. 2). Furthermore, subgroup analyses stratified by the timing of outcome assessment revealed no significant differences, further supporting the absence of a clear mortality benefit associated with stem cell therapy (trial period up to 6 months, trial period up to 12 months, trial period more than 12 months; Supplementary Fig. 1A), cell type (mononuclear, mesenchymal, both; Supplementary Fig. 1B), route of administration (intracoronary, direct intramyocardial, antecubital vein of forearm; Supplementary Fig. 1C), autogenic *vs*. allogenic; Supplementary Fig. 1D), time of cell

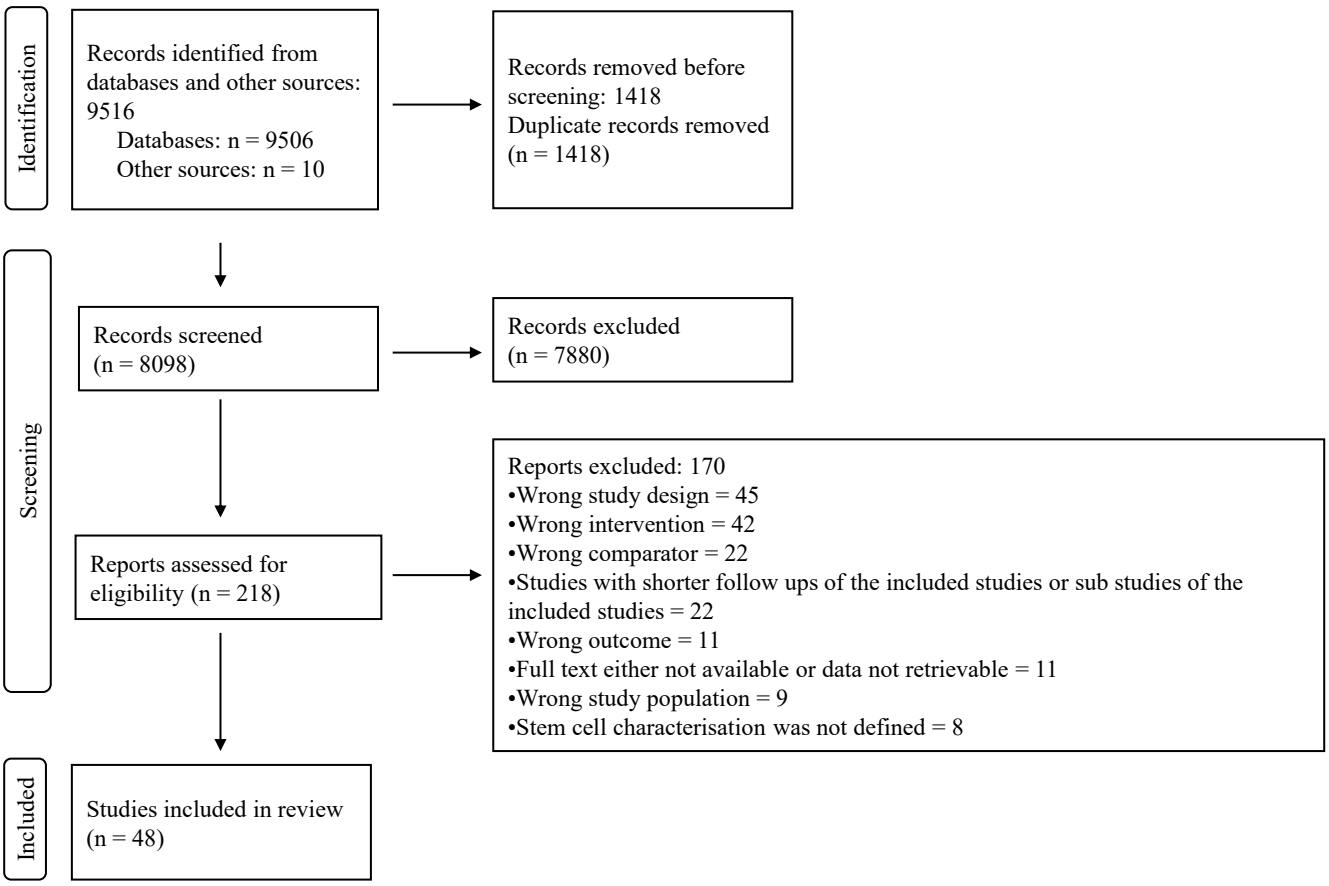

Fig. 1. PRISMA flow diagram illustrating the study selection process according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

administration (administration < 24 h, administration 1 - 21 days, not mentioned; Supplementary Fig. 1E), sample size (<100 and ≥100) Supplementary Fig. 1F), and dose of cell administered (< 500 million and ≥ 500 million; Supplementary Fig. 1G).

Serious adverse events: SAEs were reported in 12 trials[14,17,21,23-25,29,31-33,41,43] having 1161 participants (571 in the stem cell intervention group and 590 in control group). There was no significant difference in the occurrence of SAEs between the stem cell group and the control group [RR = 0.93 (0.76-1.14) *P*=0.51, I^2=0%; Supplementary Fig. 2A. No significant differences were obtained on subgroup analysis based on time of assessment (Supplementary Fig. 2B), cell type (Supplementary Fig. 2C), route of administration (Supplementary Fig. 2D), autogenic *vs*. allogenic (Supplementary Fig. 2E), time of cell administration (Supplementary Fig. 2F), sample size (Supplementary Fig. 2G), and dose of cell administered (Supplementary Fig. 2H).

Recurrent-myocardial infarction: Incidences of re-MI were reported in 18 trials[14,16,18,20-23,25-28,32,34,35,37,44,45] having 1981 participants (1158 in intervention group and 823 in control). Stem cell treatment has no favourable effect on preventing myocardial infarction [RR = 0.67 (0.43 – 1.05), *P*=0.08, I^2 = 0%; Fig. 3]. No significant differences were obtained on subgroup analysis based on time of assessment (Supplementary Fig. 3A), cell type (Supplementary Fig. 3B), route of administration (Supplementary Fig. 3C), time of cell administration (Supplementary Fig. 3D), sample size (Supplementary Fig. 3E), and dose of cell administered (Supplementary Fig. 3F).

Hospitalisation due to heart failure: Nineteen trials[14,15,18-20,22,26,27,29,31-34,37,39,40,44,46,47] reported occurrences of hospitalisation caused by heart failure (total participants = 1641, 928 in the stem cell group *vs*. 713 in the control group). No significant difference in hospitalisation due to heart failure was observed between the intervention and control groups [RR = 0.79

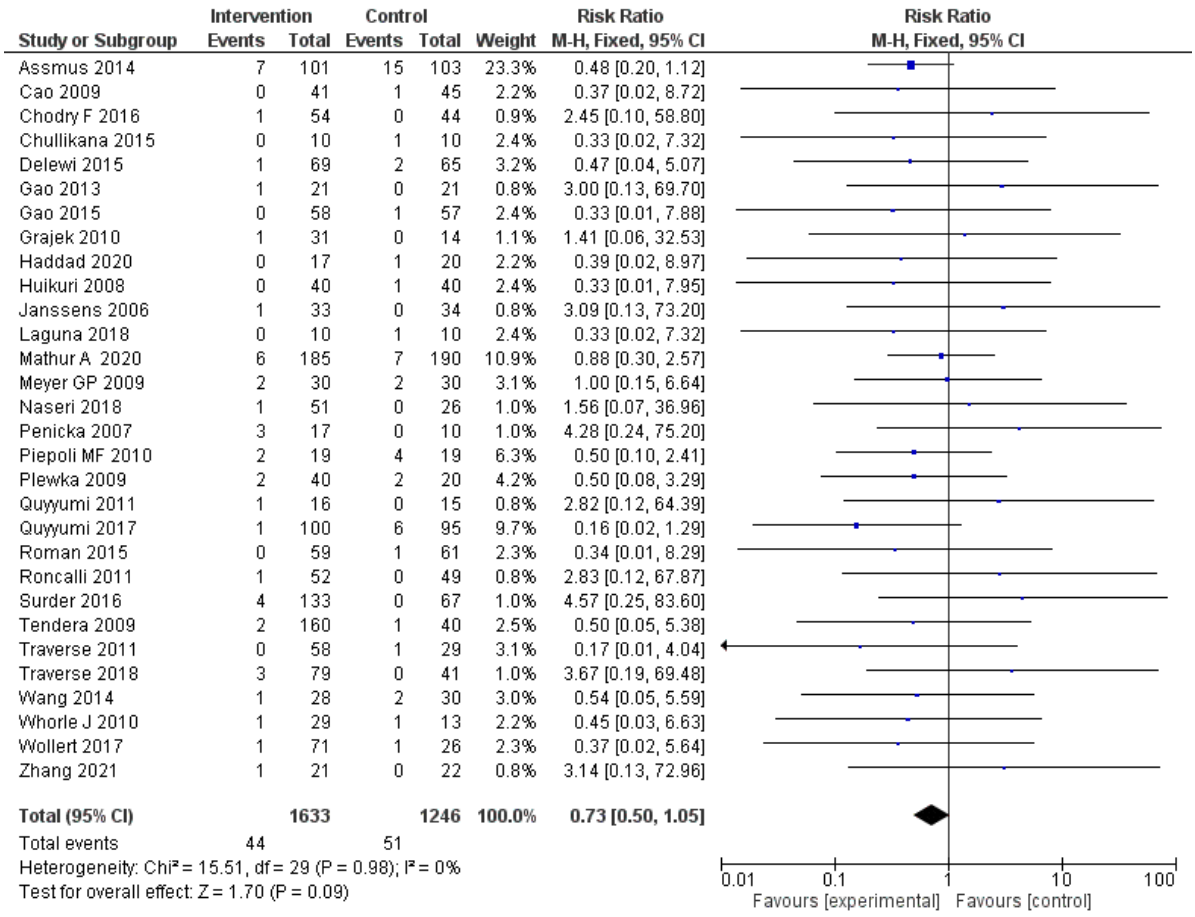

Fig. 2. This forest plot shows all-cause mortality incidence between stem cell therapy and control groups, with pooled effect estimates.

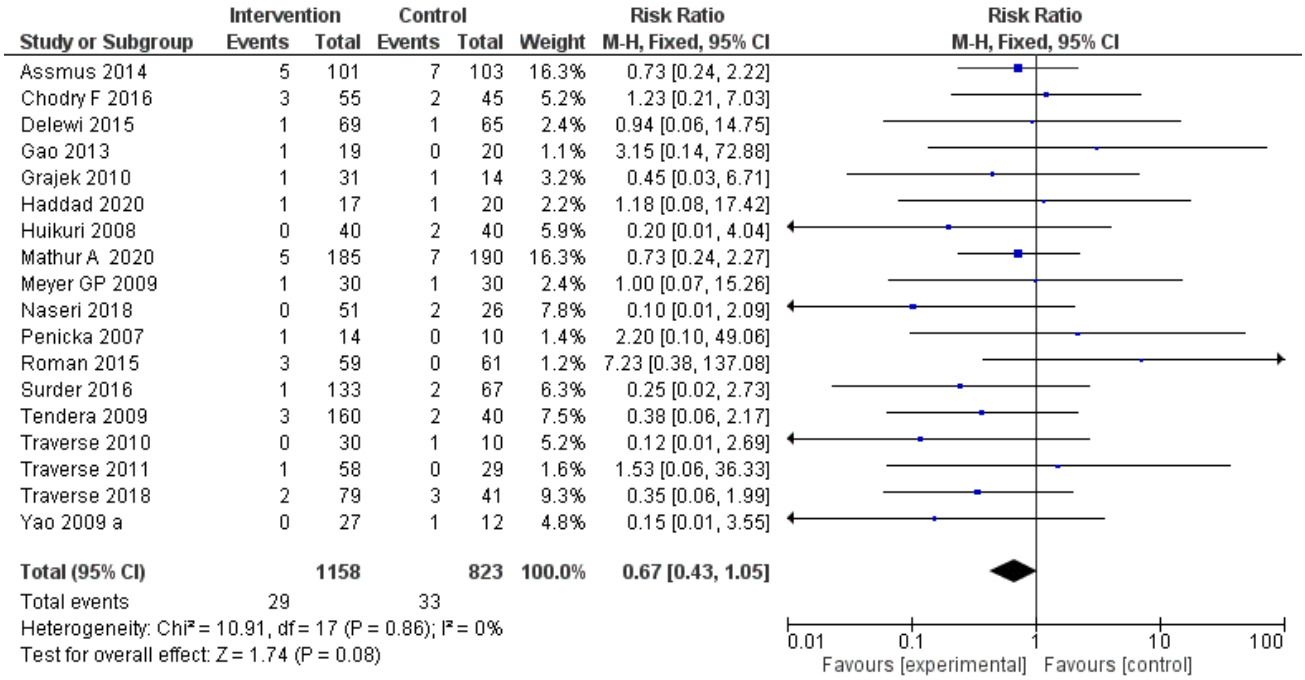

Fig. 3. This forest plot presents the overall effect of stem cell therapy on the incidence of re-myocardial infarction.

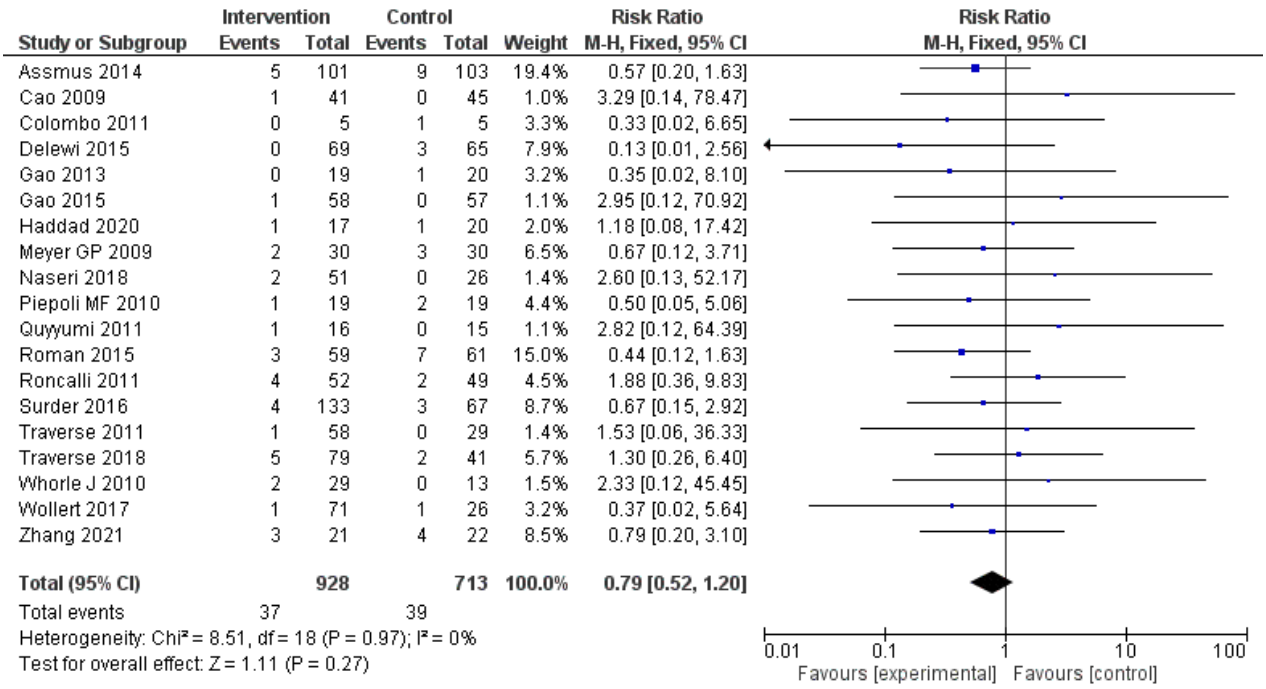

Fig. 4. This forest plot presents effect of stem cell therapy on hospitalisation due to heart failure in comparison with control.

(0.52–1.20), $P = 0.27$, $I^2 = 0\%$; Fig. 4]. No significant differences were obtained on subgroup analysis based on time of assessment (Supplementary Fig. 4A), cell type (Supplementary Fig. 4B), route of administration (Supplementary Fig. 4C), autogenic *vs*. allogenic (Supplementary Fig. 4D), time of cell administration (Supplementary Fig. 4E), sample size (Supplementary Fig. 4F), and dose of cell administered (Supplementary Fig. 4G).

Cancer incidence: Cancer incidences were reported in six trials[14,20,22,25,28,48] having 807 participants (411 in cell group, 396 in control). No extra cancer incidences were reported in the stem cell group compared to control [RR = 0.82 (0.43 – 1.55) P=0.54, $I^2 = 0\%$; Fig. 5]. No significant differences were obtained on subgroup analysis based on the time of assessment (Supplementary Fig. 5A), cell type (Supplementary Fig. 5B), route of administration (Supplementary Fig. 5C), autogenic *vs*. allogenic (Supplementary Fig. 5D), time of cell administration (Supplementary Fig. 5E), sample size (Supplementary Fig. 5F), and dose of cell administered (Supplementary Fig. 5G). In this analysis, studies with a follow up period of 12 months or longer had a median duration of 24 months (range: 18–104 months); see table I for details.

Stroke incidence: Stroke incidences were reported in eight trials[14,18,22,24,25,31,34,37] (1121 participants, 610 stem cell group, and 511 control group). No statistically significant difference was observed in stroke incidences reported in the stem cell group compared to control [RR = 0.81 (0.41 – 1.60), $P = 0.55$, $I^2 = 0\%$; Fig. 6]. No significant differences were observed in subgroup analyses based on time of assessment (Supplementary Fig. 6A), cell type (Supplementary Fig. 6B), route of administration (Supplementary Fig. 6C), autogenic *vs*. allogenic (Supplementary Fig. 6D), time of cell administration (Supplementary Fig. 6E), and sample size (Supplementary Fig. 6F).

Left ventricular ejection fraction:

a) LVEF measured by echocardiography (end of the study): End of the study, LVEF measured by echocardiography was reported by 19[15,17,19-21,23,28,33,40,43,46,49-55] clinical trials with 20 comparisons (909 participants, 480 in the stem cell group, and 429 in the control group). LVEF (%) at the study's end was significantly higher in the treatment group compared to controls [MD = 2.53 (0.95–4.10); $P < 0.001$], with high heterogeneity ($I^2 = 76\%$, $P < 0.001$; Supplementary Fig. 7A). Significant results were observed in subgroup analyses based on trial duration (up to 12

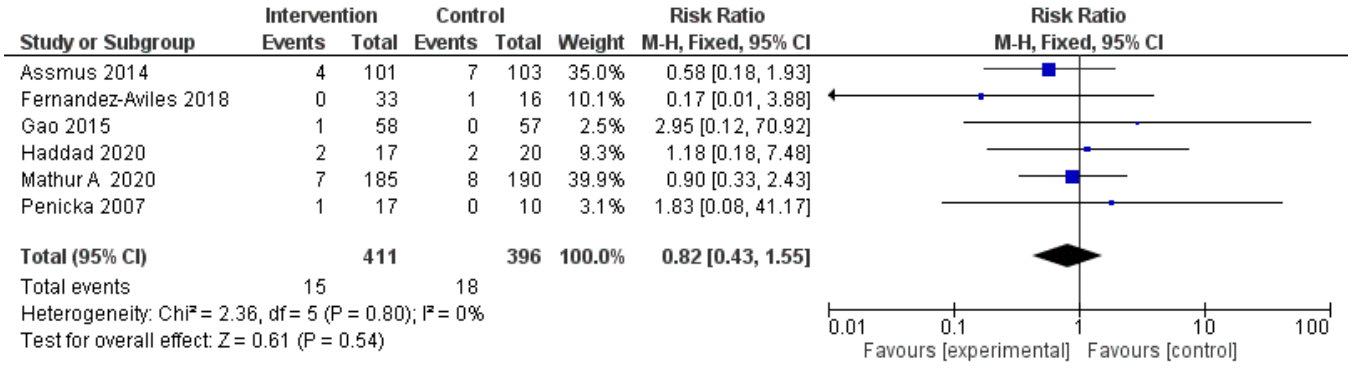

Fig. 5. This forest plot shows the cancer incidence between stem cell therapy recipients and control participants.

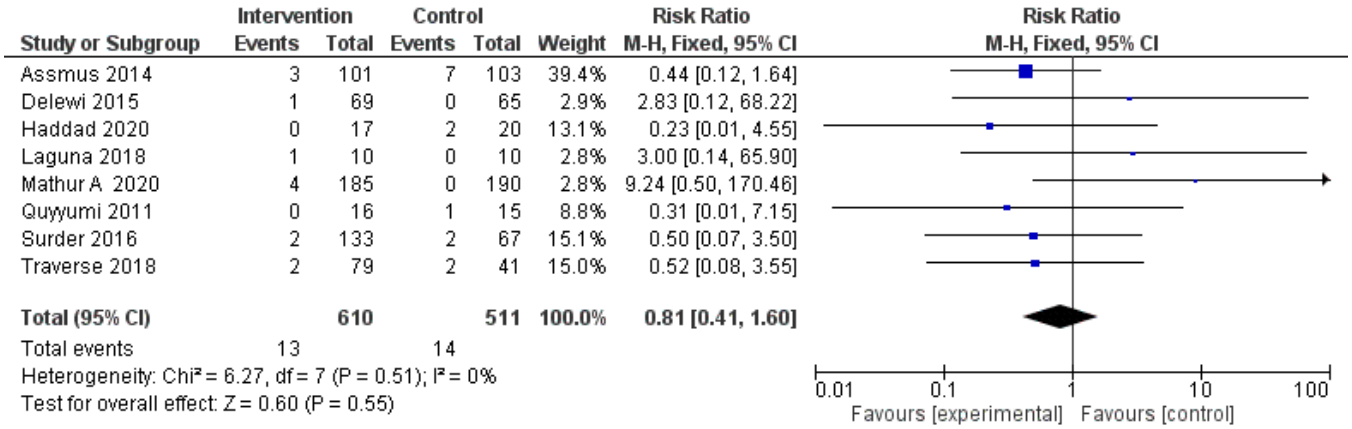

Fig. 6. Forest plot comparing the incidence of stroke between patients receiving stem cell therapy and controls.

months, and >12 months; (Supplementary Fig. 7B), cell type (mesenchymal; (Supplementary Fig. 7C), administration route (intracoronary; (Supplementary Fig.7D), autologous *vs.* allogeneic cells (Supplementary Fig.7E), timing of cell administration (administration <24 hand 1-21 days; Supplementary Fig.7F), sample size (<100; Supplementary Fig. 7G) and dose administered (<500 million; Supplementary Fig. 7H).

b) LVEF measured by echocardiography (difference from the baseline): Differences from baseline LVEF were reported in 8 clinical trials[15,19,20,23,50,52-54] with nine comparisons (486 participants, 251 in the stem cell group, and 235 in the control group). The difference from baseline LVEF was significantly greater in the stem cell group as compared to the control group [MD=3.89 (2.32 – 5.46), P <0.001]. The trials exhibited high heterogeneity (I^2 = 80%, P<0.001; Supplementary Fig. 8A). Significant differences were obtained on subgroup analysis based on time of assessment (Supplementary Fig. 8B), cell type (Supplementary Fig. 8C), route of administration (Supplementary Fig. 8D), autogenic *vs.* allogenic (Supplementary Fig. 8E), time of cell administration (Supplementary Fig. 8F), and sample size (Supplementary Fig. 8G).

LVEF measured by MRI:

a) LVEF measured by MRI (end of the study): End of the study, LVEF measured by MRI was reported by 19 clinical trials[16,18,24,26,31-33,35,37,39,41,44,45,48,50,54,56,57], reporting 24 comparisons with control (1340 participants, 809 in the stem cell group, and 531 in the control group). LVEF (%) at the end of the study was not significantly different from that of the control group [MD=0.83 (-0.73 – 2.38), P = 0.3]. The trials exhibited high heterogeneity (I^2 = 60%, P<0.001; Supplementary Fig. 9A). No significant differences were obtained on subgroup analysis based on time of assessment (Supplementary Fig. 9B), cell type (Supplementary Fig. 9C), route of administration (Supplementary Fig. 9D), autogenic *vs*. allogenic (Supplementary Fig. 9E), time of cell administration (Supplementary Fig. 9F), sample size (Supplementary Fig. 9G), and dose of cell administered (Supplementary Fig. 9H).

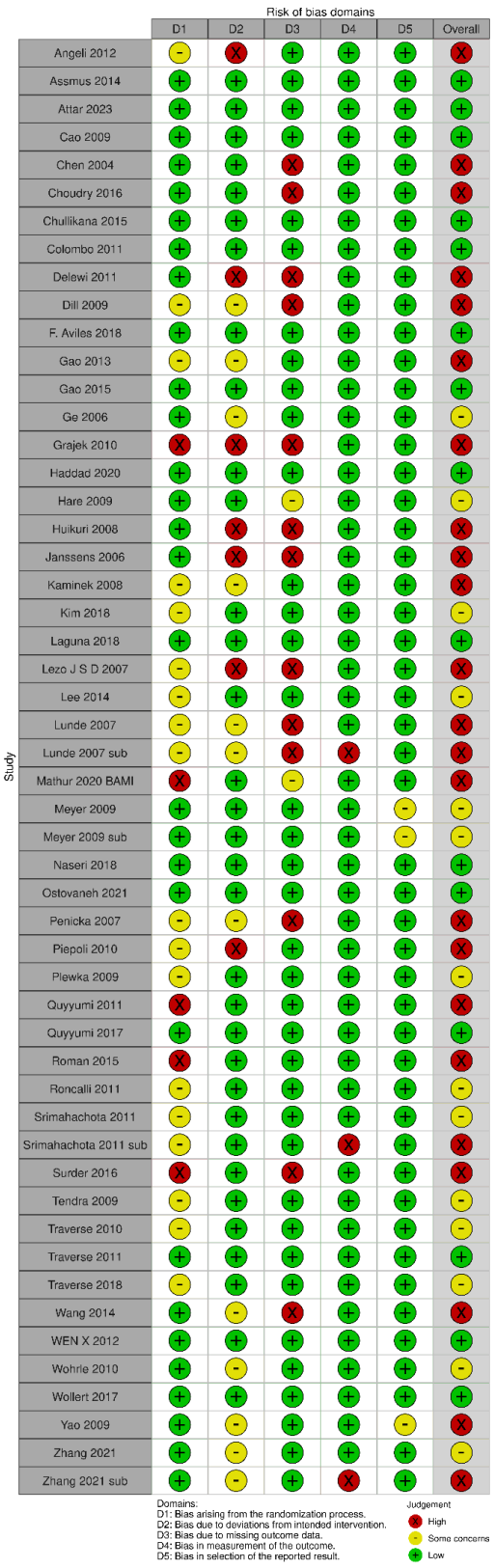

Fig. 7. This visual representation uses a 'traffic light' system (green = low risk, yellow = some concerns, red = high risk) to show the risk of bias for each included study.

b) LVEF measured by MRI (difference from the baseline): Differences from baseline LVEF were reported in 22 clinical trials[16,18,22,24,26,31,32,34,37,39,41-45,47,48,50,54,56,57] with 25 comparisons (1499 participants, 886 in the stem cell group, and 613 in the control group). Difference from baseline LVEF was significantly more in stem cell group as compared to control group [MD=1.37 (0.39 – 2.35), P =0.01]. The trials had a high heterogeneity (I^2 =56%, P<0.001; Supplementary Fig. 10A). Similar significant differences were obtained on subgroup analysis based on time of assessment (trial period up to 12 months (Supplementary Fig. 10B), cell type (mesenchymal; Supplementary Fig. 10C), route of administration (intravenous; Supplementary Fig. 10D), autogenic *vs.* allogenic (Supplementary Fig. 10E), time of cell administration (1-21 days; Supplementary Fig. 10F), sample size (<100; Supplementary Fig. 10G), and dose of cell administered (Supplementary Fig. 10H).

Risk of bias of the included studies: The risk of bias in the different studies is elaborated in figure 7. Around 28 studies were having high risk of bias. Most of these studies were either open blind or information about blinding and allocation concealment was missing, and there were dropouts in almost all studies (Supplementary table III). Most of the outcomes were very objective in nature; hence, the risk of bias, even if it existed, might have had limited influence on the overall results for these clinical outcomes. (Fig. 7).

Summary of finding table: Overall certainty of evidence remains low or very low for most outcomes. Grade assessment is shown in table II.

Publication bias: Outcomes with fewer than 10 trials were not eligible for publication bias assessment. For outcomes with ≥10 trials (mortality, SAE, Re-MI, hospitalisation due to heart failure, and LVEF differences), publication bias was evaluated and reported in supplementary figure 11.

Discussion

This systematic review and meta-analysis (SRMA) evaluated the efficacy and safety of stem cell therapy in patients with acute myocardial infarction (AMI). Based on the findings from 48 eligible studies, stem cell treatment did not demonstrate a significant improvement over standard care in major clinical outcomes, including all-cause mortality, serious adverse events (SAEs), recurrent myocardial infarction,

Table II. Grade assessment

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considera-tions	Cell	No cell	Relative (95% CI)	Absolute (95% CI)		
Mortality												
30	randomised trials	serious[a]	not serious	not serious	serious[b]	none	44/1633 (2.7%)	51/1246 (4.1%)	RR 0.73 (0.50 to 1.05)	11 fewer per 1,000 (from 20 fewer to 2 more)	⊕⊕◯◯ Low	CRITICAL
SAE frequency												
12	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	121/571 (21.2%)	143/590 (24.2%)	RR 0.93 (0.76 to 1.14)	17 fewer per 1,000 (from 58 fewer to 34 more)	⊕◯◯◯ Very low	CRITICAL
Re MI frequency												
18	randomised trials	very serious[d]	not serious	not serious	serious[b]	none	29/1158 (2.5%)	33/823 (4.0%)	RR 0.67 (0.43 to 1.05)	13 fewer per 1,000 (from 23 fewer to 2 more)	⊕◯◯◯ Very low	CRITICAL
Heart Failure Frequency												
19	randomised trials	serious[e]	not serious	not serious	serious[b]	none	37/928 (4.0%)	39/713 (5.5%)	RR 0.78 (0.50 to 1.20)	12 fewer per 1,000 (from 27 fewer to 11 more)	⊕⊕◯◯ Low	CRITICAL
Stroke frequency												
8	randomised trials	serious[a]	not serious	not serious	serious[b]	none	13/610 (2.1%)	14/511 (2.7%)	RR 0.81 (0.41 to 1.60)	5 fewer per 1,000 (from 16 fewer to 16 more)	⊕⊕◯◯ Low	CRITICAL
Cancer incidence												
6	randomised trials	not serious	not serious	not serious	serious[b]	none	15/411 (3.6%)	18/396 (4.5%)	RR 0.82 (0.43 to 1.55)	8 fewer per 1,000 (from 26 fewer to 25 more)	⊕⊕⊕◯ Moderate	CRITICAL

[a]only 33.3% of trials have low risk of bias; [b]Confidence interval crosses the point if no difference; [c]only 25% of trials have low risk of bias; [d]only 22% of trials have low risk of bias. CI, confidence interval; MD, mean difference; RR, risk ratio

hospitalisations due to heart failure, stroke incidence, or cancer occurrence. These results are consistent with the most current Cochrane review, which found that stem cell treatment does not enhance clinical outcomes for individuals with AMI after examining 41 trials[58].

Despite significant heterogeneity, our analysis showed a favourable change in LVEF as evaluated by echocardiography after the study and as a change from baseline in terms of functional outcomes. After the research, LVEF, as determined by MRI, did not significantly differ; however, it did demonstrate a notable improvement over baseline, albeit with significant heterogeneity. In this study, the improvement in LVEF (difference from baseline, measured by echocardiography) was 3.89 per cent, which falls below the five per cent threshold commonly cited in the literature as the Minimal Clinically Important Difference (MCID) for LVEF improvement[59,60]. This suggests that while the observed change may be statistically significant, its clinical relevance may be limited. These findings are consistent with the Cochrane review, further reinforcing the uncertainty regarding the clinical relevance of LVEF improvements. Overall, both our analysis and the Cochrane review suggest that stem cell therapy does not provide clinically meaningful benefits in the treatment of AMI. While modest improvements in LVEF were observed, their significance remains unclear due to high heterogeneity across studies.

The stem cell type, delivery method and timing, follow up periods, sample size, and cell dosage differed among the included trials. Subgroup analysis was performed to evaluate how these parameters affected the final outcome. Subgroup analysis based on sample size showed no significant differences in outcome direction between the two groups. Cell dose showed no overall effect, except for LVEF by echocardiography: doses <500 million improved outcomes, while >500 million, reported in one study, showed no effect—possibly by chance. However, a previous study reported improved LVEF with doses >500 million[61].

The overall quality of the evidence is moderate, reflecting some concerns about bias and confidence intervals, including the possibility of no effect. Seven outcomes were analysed, with heterogeneity observed in only one - LVEF. Subgroup analyses were performed to investigate differences based on cell type, dosage, and sample size. A few studies were excluded due to unclear reporting of stem cell characteristics. In this SRMA, it was found that in patients with AMI, the use of stem cells had no significant effect on mortality, current MI, or heart failure-related hospitalisations, except for LVEF. The evidence is of moderate quality; further clinical trials may change the estimate.

This meta-analysis suggests that stem cell therapy does not significantly impact mortality, current MI, or heart failure-related hospitalisations in AMI patients. While improvements in LVEF were noted, their clinical significance remained uncertain. The findings highlight the necessity of further large-scale, rigorously designed trials with long term follow-up to determine the potential role of stem cell therapy in AMI treatment.

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***Conflicts of Interest*:** None.

***Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation*:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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For correspondence: Dr Jaykaran Charan, Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur 342 005, Rajasthan, India
e-mail: dr.jaykaran78@gmail.com