

Rational Route of Delivery Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction (AMI) and Chronic Ischemic Cardiomyopathy (ICM): a Systematic Review and Meta-analysis

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Abstract

Background: Recent studies suggest that mesenchymal stem cells (MSCs) may have therapeutic potential for both acute myocardial infarction (AMI) and chronic ischemic cardiomyopathy (ICM). However, the rational route of delivery MSC therapy has not reached consensus. We performed a systematic review of clinical trials evaluating the rational route of delivery MSCs for AMI or ICM.

Methods: Databases including Embase, PubMed, and Cochrane Central Register of Controlled Trials were searched from inception to February 2021. Studies that examined the use of MSCs in adults with AMI or ICM were eligible. Bias of included studies were assessed by the Cochrane risk of bias tool. The primary outcome was cardiac function assessed by left ventricular ejection fraction (LVEF) and the secondary outcome was cardiac remodeling which was assessed by left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV), we also explored the safety between different routes.

Results: 18 studies fulfilled eligibility criteria, which consist of 11 studies evaluated AMI and 7 studies evaluated ICM. In AMI group, only when patients received intracoronary infusion(IC) can improve LVEF (SMD 0.88, 95% CI 0.64-1.12), and there was a decrease in LVEDV&LVESV when administered IC or intravenous infusion (IV). While in ICM group, no significant difference in LVEF was noted no matter administered which route, and transendocardial stem cell injection(TESI) seems to be effective in decreasing LVEDV&LVESV. Safety appeared no difference between different routes.

Conclusions: Results from our systematic review suggest that intracoronary infusion seems more effective for MSC's delivery in AMI group, while in ICM group, TESI better.

Background

Cardiovascular disease caused by ischemic injury represent a major cause of mortality worldwide^[1]. Currently, no therapeutic solutions are available for long-term management except for heart transplant, indicating the demand for new approaches to prevent and reverse cardiac dysfunction^[2]. Display remarkable promise for myocardial regeneration, cell-based therapy has gained a lot of attention in the last few decades^[3]. Recent studies has suggested that mesenchymal stem cells (MSCs) may be more effective than other cell types^[4, 5], and MSCs therapy ischemic heart disease appears to be safe and effective^[6, 7]. The basic mechanisms are suggested to include: (1) differentiate and incorporate into the host tissue^[8]; (2) paracrine effect, which can ameliorate oxidative stress and inflammation^[9-11], induce neovascularization^[12], anti-apoptosis^[13], reduce collagen deposition^[14]. However, there is still debate regarding the best patient group, source of cells, timing of administration, and the optimal route. Compared to other factors, the rational route was less discussed. Up to today, the route of delivery MSCs included intracoronary infusion (IC), directly intramyocardial injection (DI), transendocardial/transepical stem cell injection(TESI) and intravenous infusion (IV). The route of delivery makes a major influence on grafting efficiency and survival of transplanted cells in the infarcted

region of the heart, which means that finding an optimal route can lead to better clinical outcomes for cell therapy. Thus, we try to explore the optimal route of Mesenchymal Stem Cell(MSC) delivery.

Methods

Search strategy

We searched for trials in databases including PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) registry of the Cochrane Collaboration until February 2021. The following search terms were used alone or in combination: mesenchymal stromal cells, mesenchymal stem cells, MSCs, mesenchymal stem cell transplantation, multipotent mesenchymal stromal cells, bone marrow mesenchymal stem cells, adipose-derived mesenchymal stem cells, Wharton's Jelly Cells, Myocardial Infarction, Myocardial Ischemia, Cardiovascular Stroke, Heart Attack, Ischemic Heart Disease. Two review authors identified all studies independently. The search was limited to controlled studies with a comparator arm. No language limit was applied. Any disagreement relating to the eligibility of a particular study was settled through discussion with senior reviewers.

Eligibility criteria

Inclusion criteria for this analysis were as follows: (1) Only unmodified MSCs were included, any pretreated, genetically engineered, or transfected cell were excluded; (2) The resources (bone marrow, umbilical cords, or adipose tissue) and administration route were unrestricted; (3) studies that were conducted in patients who had Ischemic cardiomyopathy; (4) Both cell groups and control arms should receive standard therapy, the control arm did not receive stem cells.

Data extraction and quality assessment

A standardized data extraction form was used to extract data from the included studies. Information extracted included: study setting (publication year and country); demographics and baseline characteristics of the study population; details of the intervention and control conditions, such as cell delivery route, resource, dose, time interval between PCI to injection, change in LVEF, LVESV, LVEDV, follow-up duration; information for assessment of the risk of bias. Data was extracted independently by two review authors, discrepancies identified were settled by discussion with senior reviewers.

Summary measures

Change in LVEF is our primary outcome measures, many methods were used measuring LVEF(% EF), echocardiography data were used in preference unless MRI data were available. Change in LVEDV and LVESV were used as secondary outcome measures. In addition, we explore safety within different routes.

Method for meta-analysis

The data were analysed using Stata 16.0 (Stata Corporation, College Station, TX). The mean difference (MD) was used for continuous variables, while Forest plots were used to present the results of our meta-analysis. When studies that contained more than two treatment arms, only control and MSC groups were analyzed. Values pooled together using mean, standard deviation, and size for studies conducting more than one experimental group containing MSCs. $P < 0.05$ was considered statistically significant and two-sided 95%CI were reported throughout the study. Chi-square-based Q test and I² tests were used to assess the quantity of heterogeneity among these studies. When $I^2 < 50\%$, $p > 0.1$, the pieces of evidences were thought to be acceptable heterogeneity, the fixed-effects model would be used. Otherwise, the random-effects model was applied.

Results

Search results

Ultimately, 18 clinical trials which investigating the effect of MSC therapy on AMI and ICM were included in the meta-analysis ($n = 1055$)^[15–32]. Characteristics of the enrolled clinical studies are shown in Table 1.

In included trials, intracoronary infusion (IC)($n = 9$) was the most common route of delivery stem cells, followed by transendocardial stem cell injection(TESI)($n = 6$), intravenous infusion (IV) ($n = 2$) and directly intramyocardial injection (DI) ($n = 1$). Most of studies ($n = 13$) applied autologous/ allogeneic adult human bone marrow-derived mesenchymal cells^[16, 17, 19–25, 27–29, 32]. 3 study investigated the use of autologous adipose tissue-derived mesenchymal cells^[15, 30, 31]. The remaining studies utilised varied allogeneic cell sources such as mesenchymal cells from umbilical cord blood ($n = 2$)^[18, 26]. We performed a further meta-analysis on 11 AMI clinical trials ($n = 550$ patients)^[15–25], characteristics of which are presented in Table 2, and performed on 7 ICM clinical trials($n = 505$)^[26–32], characteristics of which are depicted in Table 3.(More detailed information outlined in Supporting Information Appendix 1&2)

Primary outcomes——cardiac function

Left Ventricular Ejection Fraction (LVEF)

Compared to control, Patients receiving MSCs had a significantly increased in LVEF (SMD 0.37, 95% CI 0.23–0.50, $I^2 = 94.3\%$). MSC administered through intracoronary(IC), transendocardial stem cell injection(TESI), intravenous(IV) and directly intramyocardia(DI) have shown the potential to increase LVEF, when referring to the optional administration route, MSCs increased LVEF only when applied intracoronary injection (SMD 0.69, 95% CI 0.47–0.91, $I^2 = 96.6\%$)(Fig. 1), while when we performed a further meta-analysis within AMI and ICD patients, statistically significant difference was found in LVEF when administered different route

LVEF subgroup analysis

In AMI clinical trials, MSCs increased LVEF only when intracoronary injection was applied (SMD 0.88, 95% CI 0.64-1.12, $I^2 = 96.8\%$), and no difference in LVEF whether administered TESI (SMD 0.40, 95% CI -0.37-1.17) or intravenously (SMD 0.01, 95% CI -0.44-0.47). While in ICD clinical trials, it seems no difference in the increase in LVEF no matter applied which route. (SMD 0.10, 95% CI 0.09-0.29, $I^2 = 84.3\%$).

Using a sensitivity analysis, significant heterogeneity was found in the trials reported by Wang^[22] and Gao et al.^[18]. I^2 decreased from 95.7% to 68.7% when the data from Wang^[22] and Gao et al.^[18] were excluded.

Secondary outcomes——cardiac remodeling

LVEDV & LVESV

A total of 7 AMI studies and 4 ICD studies provided data on LVEDV. Patients who underwent intravenous or intracoronary decreased LVEDV significantly in AMI clinical trials. While in ICD clinical trials, the route included in was only TESI way, which limited our assessment of other pathways, and TESI displayed an effective role on reducing cardiac remodeling (SMD -0.23, 95% CI -0.43- -0.03). The above results were also appeared in LVESV.

Tertiary Outcomes——safety

Mortality

9 AMI studies and 5 ICM studies reported mortality. Patients no matter AMI or ICM showed no difference in mortality (RR 0.90, 95% CI 0.56-1.43), the same result was observed no matter administered which route.

Sever adverse event

3 AMI studies and 4 ICM studies reported Sever adverse event. No significant difference in the risk of mortality between MSC and control groups, no matter in which group or administered which route. Interestingly, there was seems a trend to reduce sever adverse event when TESI was applied in ICM group, though it was not statistically significant.

Rehospitalization

6 AMI studies and 3 ICM studies provided data on readmission. In these trials, AMI group included IC and IV way, while only TESI is incorporate in ICM group, which makes it difficult to analysis the optimal route for reducing readmission between AMI or ICM group. Under such limited condition, we found that TESI showed a subtle advantage on reducing rehospitalization (SMD 0.6, 95% CI 0.37-0.96).

Other outcomes

WMSI

In AMI group, WMSI was more significantly decreased when use IC than TESI injection, and there were no significant differences between MSC-and placebo-treated patients when applied IV injection(data not shown).WMSI was rarely reported in ICD group, thus we can't know its real efficacy.

6min-walk

A total of 4 studies reported 6min-walk in ICD group, there were no significant differences between MSC- and placebo-treated patients when use DI or TESI way. 6min-walk was rarely reported in AMI group and it limit our conclusion.

No comparisons are made between other outcomes like infarct size, myocardial perfusion, NYHA class, quality of life due to its insufficient reports in studies included.

Risk of Bias Assessment

Two studies met all seven criteria for low risk of bias. Two studies fulfilled six of seven risk of bias criteria. Seven studies described a low risk of bias in randomization procedures. Four studies underwent allocation concealment with low risk of bias. For Double-blinding procedures, six studies met low risk of bias. One study had a high risk of bias due to incomplete outcome data reporting and three study had an unclear risk of bias for selective reporting. None of the studies were considered to be at high risk for other biases.

Discussion

During the past decades, mesenchymal stem cell(MSC) have been extensively used in various forms of restorative and preventive medicine, which have shown conflicting and inconclusive effects in ischemic cardiomyopathy, reasons for this owing to vast differences within various clinical trials, like patient profiles, cell phenotypes, dosing, routes of delivery, study endpoints and design, making it challenge to figure out an optimal intervention. Our systematic review try to assess the optimal route of MSC therapy for AMI and ICM. We major focused our review on cardiac performance and cardiac remodeling, and we found that In AMI group, only when patients received intracoronary infusion(IC) can improve LVEF (SMD 0.88, 95% CI 0.64-1.12), and there was a decrease in LVEDV&LVESV when administered IC or intravenous infusion (IV). While in ICM group, no significant difference in LVEF was noted no matter administered which route, and transendocardial stem cell injection(TESI) seems to be effective in decreasing LVEDV&LVESV. Safety appeared no difference between different routes. Results from our systematic review suggest that intracoronary infusion seems more effective for MSC's delivery in AMI group, while in ICM group, TESI better.

There is a large heterogeneity in our study, I^2 decreased from 95.7% to 68.7% when the data from Wang^[22] and Gao et al. ^[18] were excluded. When we tried to figure out the source of heterogeneity in these studies, we found that these trials were different from other studies in the transplantation timing and dosage. The cell dosage used in most studies ranged from $10^6 \sim 10^7$, which was the rational cell dosage

suggested from Zi Wang^[33]'s meta-analysis, while Wang et al.^[22] used 2×10^8 cells, this may be one of the reasons why this study had little effect on the improvement of LVEF. The time interval from PCI to injection in most studies is 15~30 days, Gao et al.^[18] only used 5 days, the best transplantation timing reported by Zi Wang^[33], this may can explain why the improvement in cardiac function from this studies was more noticeable.

The finding above is different from Kanelidis^[34] et al. study, one potential explanation for these results is that only 6 clinical trials were included, which makes it difficult to make firm conclusions. In addition to including more studies, we took chronic ischemic myopathy patients into account, and it turn out to be a completely different result on cardiac function and cardiac remodeling when compared with AMI clinical trials, which seems to indicate distinct mechanisms between both AMI and ICD when administered different route of MSC delivery.

Intramyocardial injection(IM) consists of DI and TESI. DI requires directly injecting stem cells into and around the infarcted area of the heart under thoracotomy, which would increase risks for complications, morbidity and mortality. TESI means injecting stem cells into the myocardium directly through the endocardium, which is a minimally invasive surgery. All studies included use the NOGA system (Biosense Webster) for imaging. IV refers to the cells infused from peripheral vein, cells will migrate toward the injured myocardium depending on preponderance of physiological homing signals. IC means delivering MSCs through the coronary vessel to the infarcted myocardial regions. The route of delivery makes a major influence on grafting efficiency and survival of transplanted cells in the infarcted region of the heart.

For patients with acute myocardial infarction, Forest VF et al.^[35] reported a significant cell fraction retained within the heart after intracoronary injection, whereas no cardiac homing was observed in IV group. In addition, study from Hayashi M^[36] showed that the survival of BMCs in the infarcted area was significantly higher in the IM group than in the IV groups. Therefore, IV route means the least cell implantation and retention. In theory, retention of BMCs in the IM group should be higher than IC group^[37], however, Fukushima S et al.^[38] found that the IM and IC groups showed a similar survival of donor cell, which may due to the harsh microenvironment in infarcted heart. The hypoxic–ischemic and inflammatory microenvironments in the ischemic myocardium lowers survival and viability of MSCs^[39], besides, exosomes from injured cardiomyocytes accelerates transplanted bone marrow mesenchymal stem cells injury^[40]. Distinct cell clusters were found from immunohistochemistry when stem cell injection through intramyocardial, containing donor-derived cells and accumulated host-derived inflammatory cells in the infarct border zone^[41, 42] showed that the cells were engulfed in macrophages that had infiltrated the injection areas. In contrary, IC cell injection provided more homogeneous donor cell dissemination with less inflammation and without disrupting the native myocardial structure.^[38], indicating that IC cell injection results in less mechanical injury or biochemical stress to donor cells than IM cell injection does.

For patients with chronic ischemic myopathy, mesenchymal stem cell therapy has no significant effect on increasing cardiac function probably due to different pathophysiological mechanism from this vulnerable population. MSCs are thought to work primarily because of their anti-inflammatory effects, so it is perhaps not surprising that MSCs had little impact in chronic disease such as ICM, where the level of inflammatory burden is much lower. In the aspect of cardiac remodeling, exosomes derived from Mesenchymal Stem Cells can promote Fibroblast-to-Myofibroblast differentiation in Inflammatory Environments and benefit cardioprotective effects^[14]. Interestingly, our studies found that TESI used in ICM group show a tendency in reducing mortality when compared to DI, which may due to its minimally invasive.

Limitations

Of note, the studies we included mainly focused on small randomized controlled studies, there are few study compared all the route directly, limiting our conclusions. Therefore, further experimental and clinical studies, which contain large-scale, rigorously conducted, randomized, adequately powered, placebo-controlled, blinded designs with outcome measures based on clinically relevant markers, are required to explore direct comparison of transmission pathways.

Apart from that, outcomes were not available in all studies included, like adverse reactions, readmission rates, which led us can not compare the safety of the different routes more comprehensively. We hope that studies in the future can provide more data on safety and provide longer follow-up data so that we can understand MSC therapy's safety over time.

Conclusions

Our study reveal that in AMI clinical trials, IC appears to be the most rational route of delivery due to its reduction in cardiac remodeling and improvement of LVEF, while in ICD clinical trials, none of any route can affect cardiac function, but TESI can reduce cardiac remodeling.

List Of Abbreviations

AMI Acute myocardial infarction

ICD Chronic ischemic cardiomyopathy

MSC Mesenchymal stromal cell

LVEF Left ventricular ejection fraction

LVEDV Left ventricular end-diastolic volume

LVESV Left ventricular end-systolic volume

IC Intracoronary

TESI Transendocardial stem cell injection

IV Intravenous

DI Directly intramyocardia

IM Intramyocardial injection

PCI Percutaneous coronary intervention

MRI Magnetic resonance imaging

CI Confidence interval

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Available data in this study exist in the above clinical trials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HYT and LZ contributed to the conception and design of the study. YXB and CSQ were responsible for the collection of data. HYT and LWZ performed the statistical analysis and manuscript preparation. GK,LZS,XML and SYW were responsible for checking the data. All authors were responsible for the drafting of the manuscript and read and approved the final version.

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Tables

Table 1. Disposition of study design

study variable	Studies(n)	Subjects(n)
studies included	18	1055
country		
china	6	371
united states	5	412
south korea	2	84
india	1	20
Denmark	1	60
Turkey	1	41
the Netherlands	2	67
Study design		
RCT	15	915
Non-RCT(case-control design)	3	140
disease type		
chronic ischemic cardiomyopathy (ICM)	7	505
acute myocardial infarction (AMI)	11	550
stem cell characteristics		
Cell source		
Allogeneic	4	230
Autologous	14	825

Table 2. Study characteristics for AMI clinical trials

	number(n)	age(years)	Time interval between PCI to injection (days)	MSC source	cell type	MSCs No.	Route	Follow-up
Houtgraaf 2012	13	59.2 ± 5	N/A	autologous	adipose tissue-derived	2~4x10 ⁷	IC	6months
Hare 2009	53	57.6 ± 11.6	N/A	allogeneic	bone marrow-derived	0.5、1.6、5 × 10 ⁶	IV	6months
Chullikana 2015	20	47.6 ± 9.5	N/A	allogeneic	bone marrow-derived	4x10 ⁶	IV	24months
chen 2004	69	57.5 ± 6	18.3 ± 0.4	autologous	bone marrow-derived	8~10 × 10 ⁹	IC	6months
Rodrigo 2013	54	60.2 ± 10.7	21~31	autologous	bone marrow-derived	< 1 × 10 ⁷	TESI	12months
Wang 2004	55	57 ± 10	15 ± 0.5	autologous	bone marrow-derived	20X10 ⁷	IC	6months
Gao 2015	116	57 ± 1.5	5	allogeneic	Umbilical	6 × 10 ⁶	IC	18months
Kim 2018	26	56.5 ± 8.7	30 ± 1.3	autologous	bone marrow-derived	7.2 ± 0.90 × 10 ⁷	IC	12months
Zhang 2021	43	58.9 ± 11	14.07 ± 9.53	autologous	bone marrow-derived	2~5x10 ⁶	IC	12months
Lee 2014	58	54 ± 9.2	25.0 ± 2.4	autologous	bone marrow-derived	7.2 ± 0.90 × 10 ⁷	IC	6months
Gao 2013	43	56.8 ± 2.8	N/A	autologous	bone marrow-derived	3.1 ± 0.5X10 ⁶	IC	24months

Table 3. Study characteristics for ICD clinical trials

	number(n)	age(years)	MSC characteristics			Route	Follow-up
			MSC source	cell type	MSCs No.		
Henry 2016	31	64.8 ± 7.7	autologous	adipose tissue-derived	4 ± 0.9 × 10 ⁷	TESI	6 months
perin 2014	27	63.6 ± 7.5	autologous	adipose tissue-derived	4.2 × 10 ⁷	TESI	18 months
CHART-1 2017	271	61.9 ± 8.7	autologous	bone marrow	60 × 10 ⁷	TESI	12 months
HUC-HEART	41	63.2 ± 9	allogeneic	Umbilical	2.1 ~ 2.6 × 10 ⁷	DI	12 months
TAC-HFT 2014	30	58.2 ± 11	autologous	bone marrow	N/A	TESI	12 months
MSC-HF trial 2015	60	65.5 ± 8.7	autologous	bone marrow	7.8 ± 6.8 × 10 ⁷	TESI	6 months
Chen 2006	45	58.5 ± 7.0	autologous	bone marrow	0.5 × 10 ⁷	IC	3 months

Figures

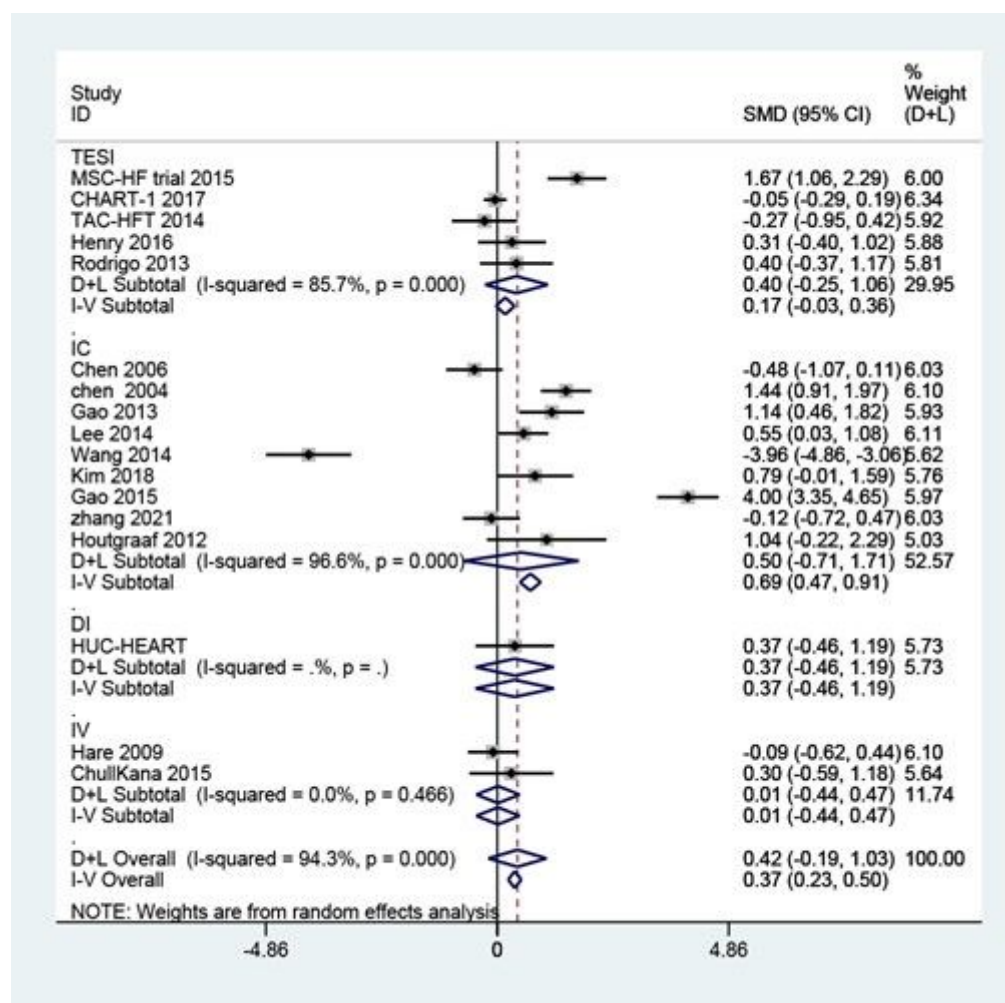


Figure 1

Impact of route of delivery MSC on LVEF. Forest plot of standardized mean difference(SMD) on LVEF compared with control. IC intracoronary, TESI transendocardial stem cell injection, IV intravenous, DI directly intramyocardia, CI confidence interval

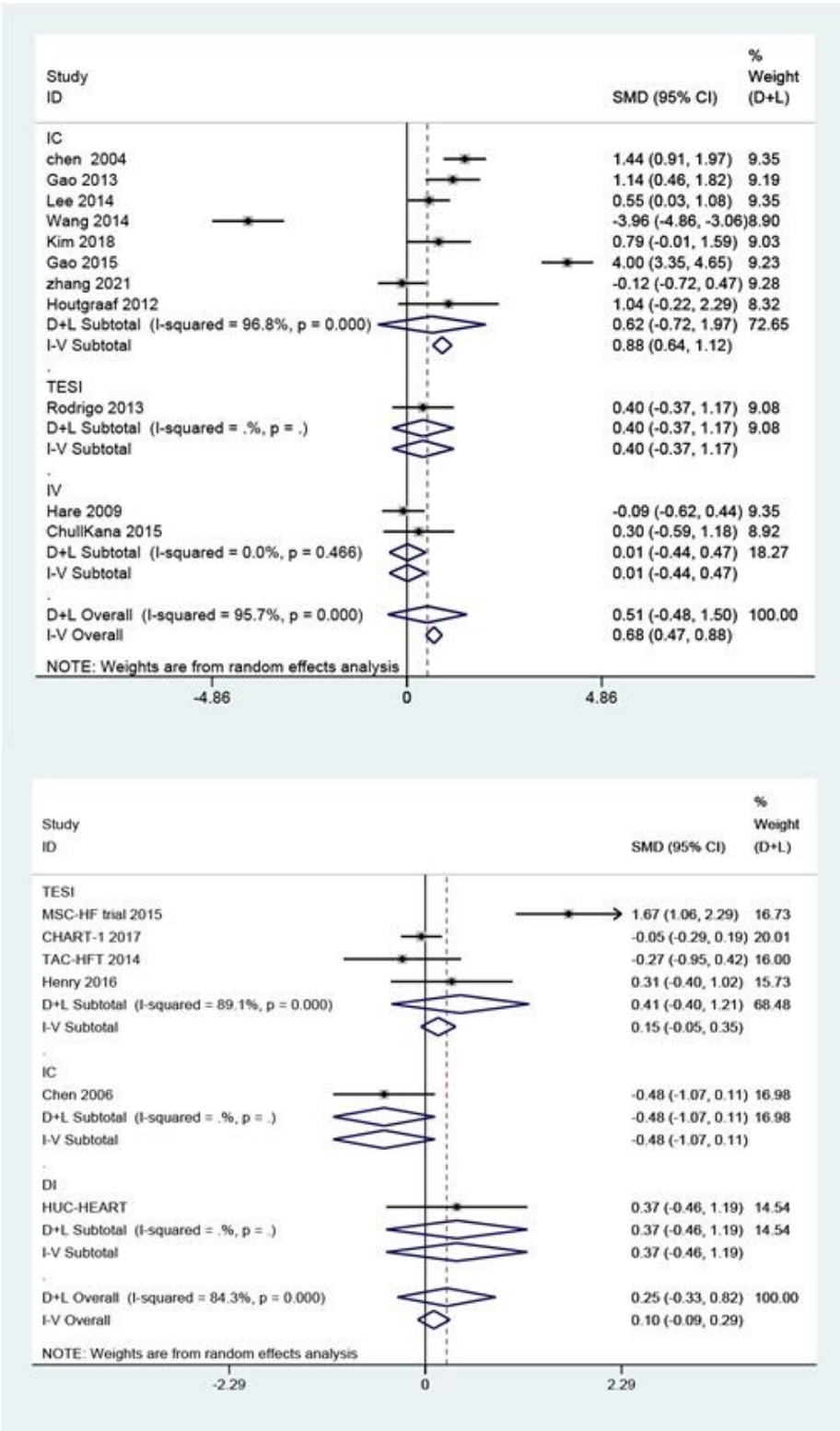


Figure 2

Impact of route of delivery MSC on LVEF within AMI or ICD patients. The figure above was in the AMI group, the below was in the ICD group.

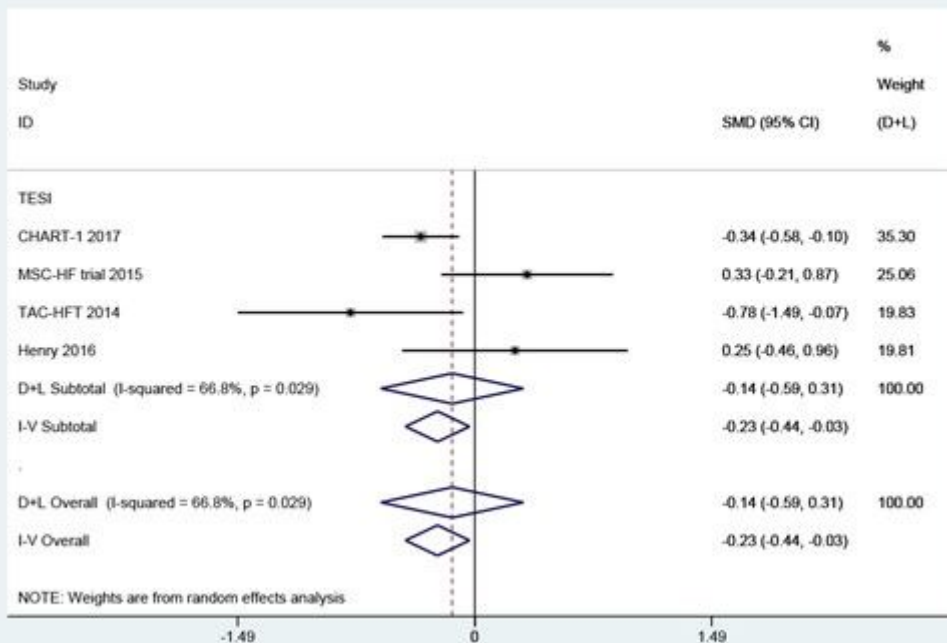
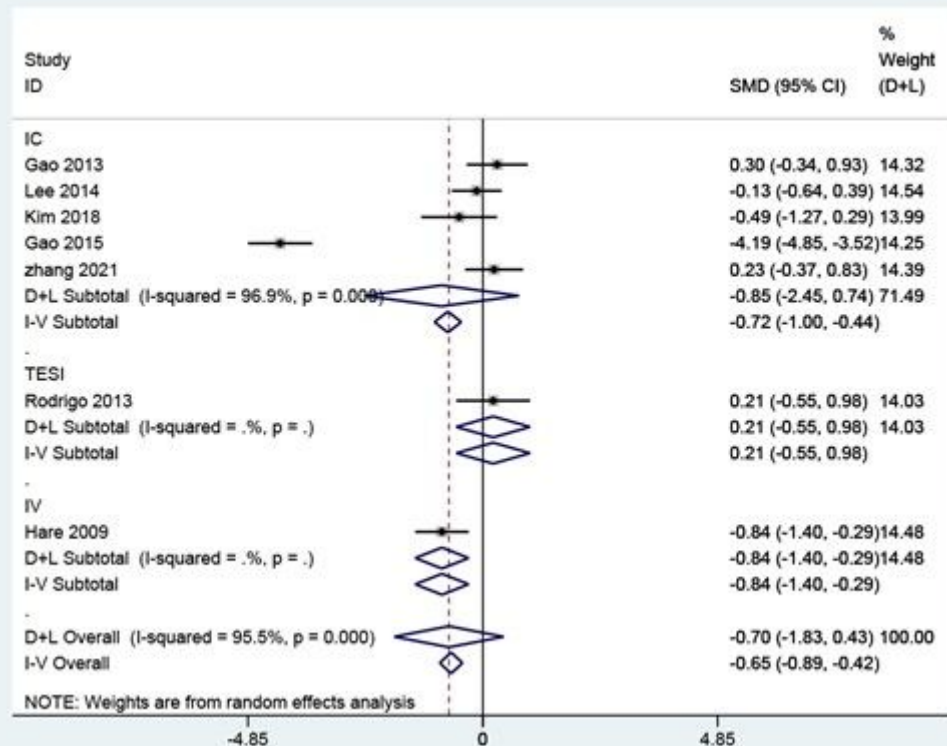


Figure 3

Impact of route of delivery MSC on LVEDV within AMI or ICD patients. The figure above was in the AMI group, the below was in the ICD group.

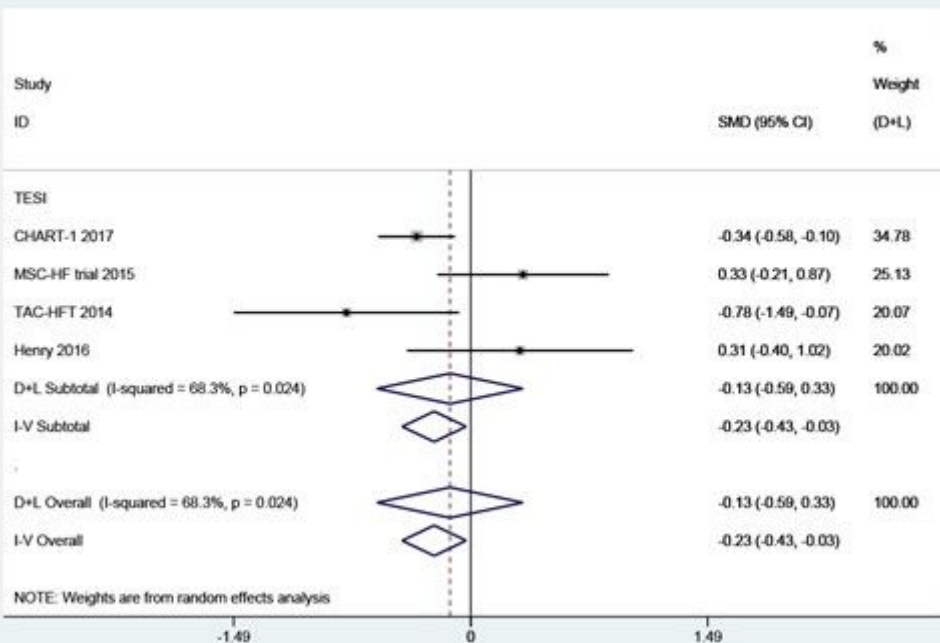
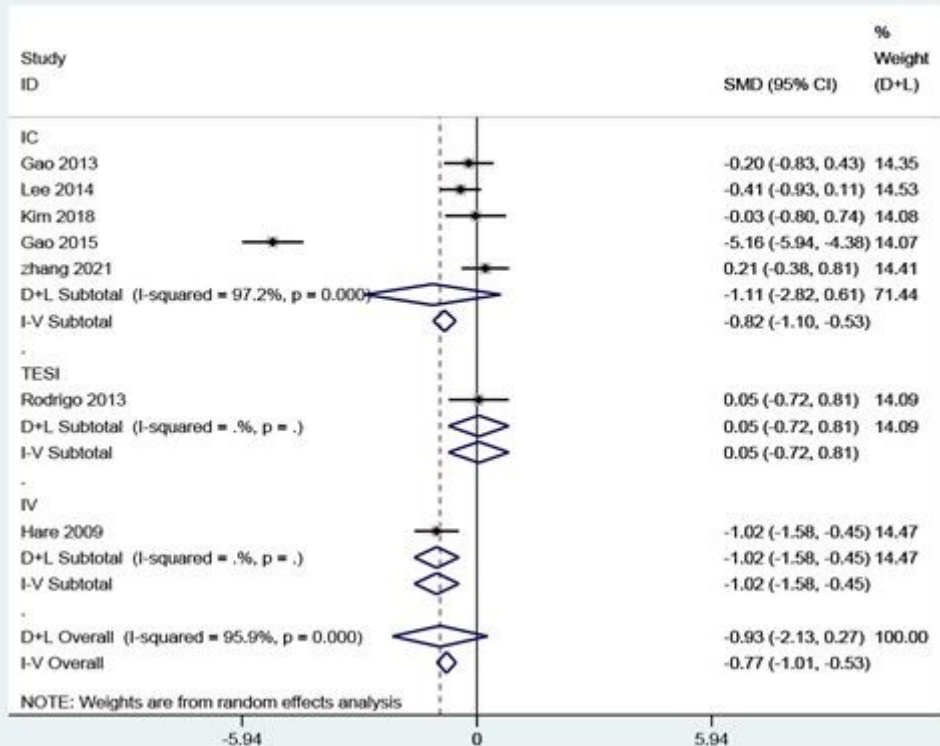


Figure 4

Impact of route of delivery MSC on LVESV within AMI or ICD patients. The figure above was in the AMI group, the below was in the ICD group.

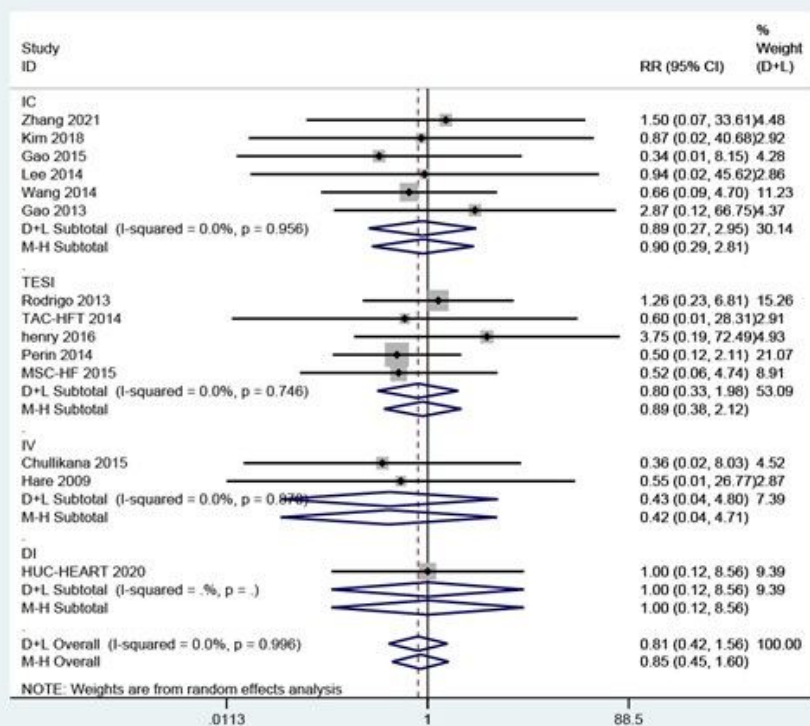
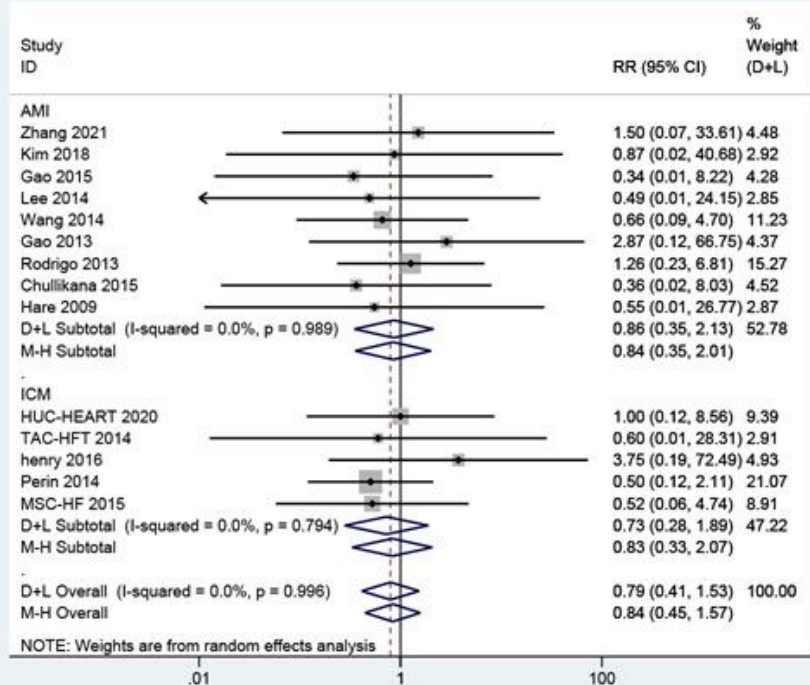


Figure 5

Impact of route of delivery MSC on mortality. The figure above explored the difference about mortality between AMI and ICD group, the below explored the difference about mortality when administered different route.

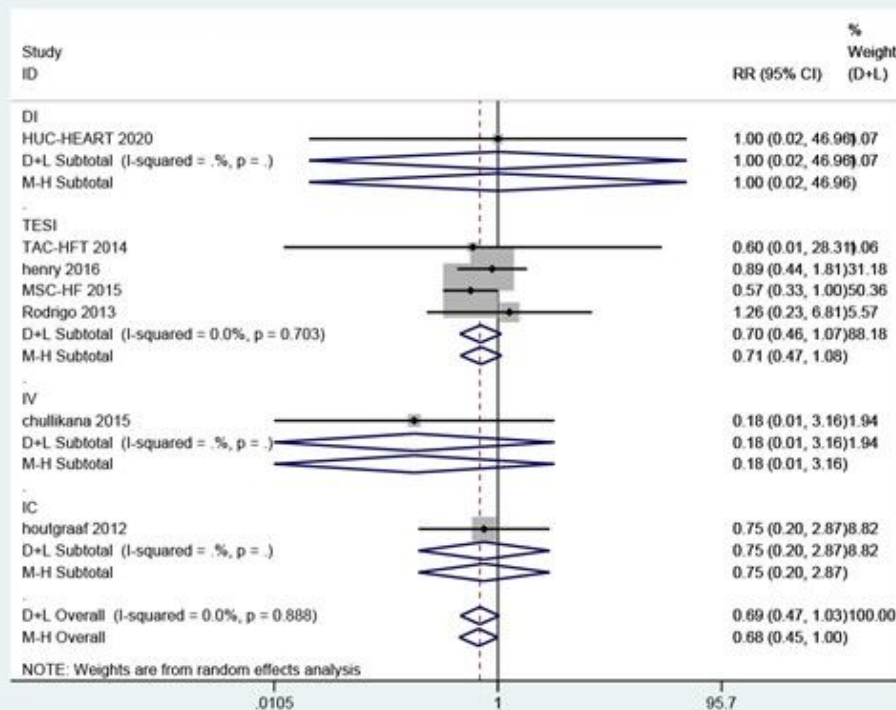
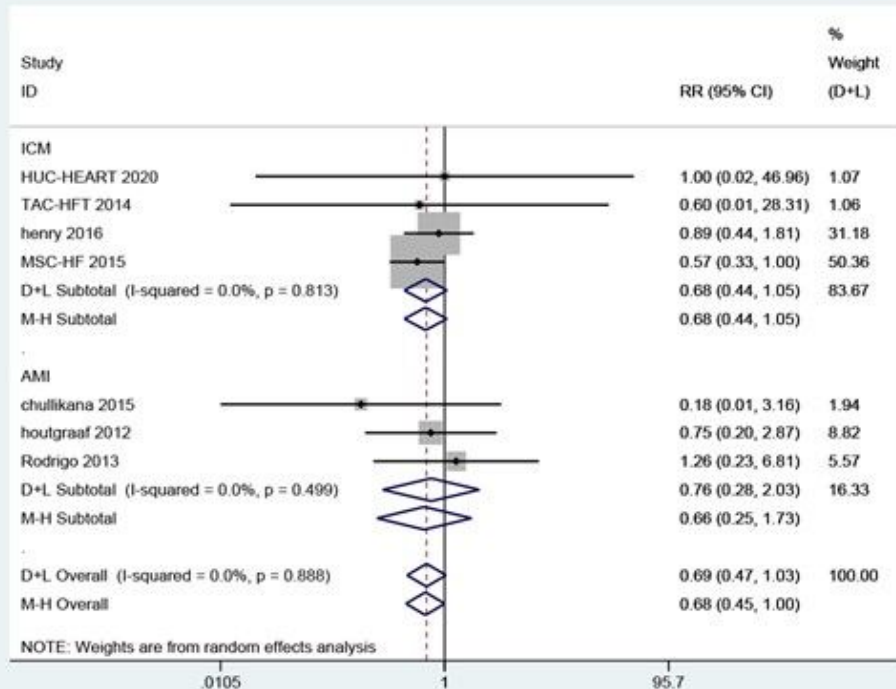


Figure 6

Impact of route of delivery MSC on Sever adverse event within AMI or ICD patients. The figure above explored the difference about Sever adverse event between AMI and ICD group, the below explored the difference about Sever adverse event when administered different route.

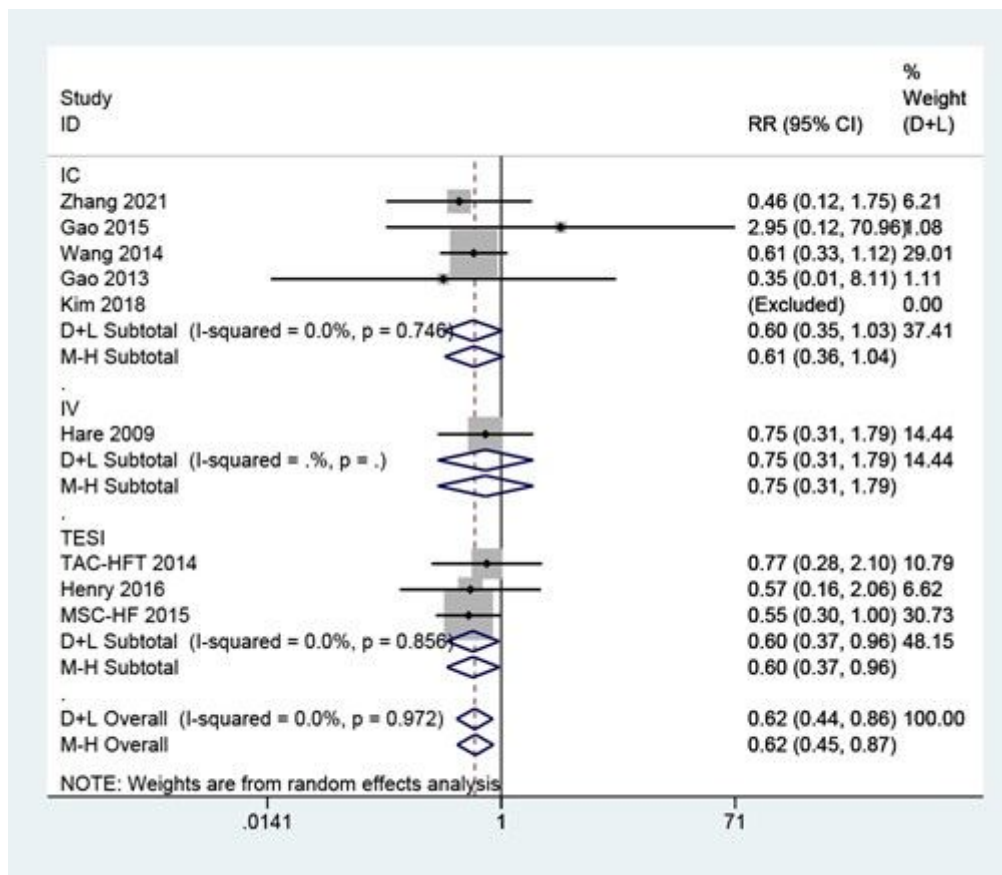


Figure 7

Impact of route of delivery MSC on readmission.

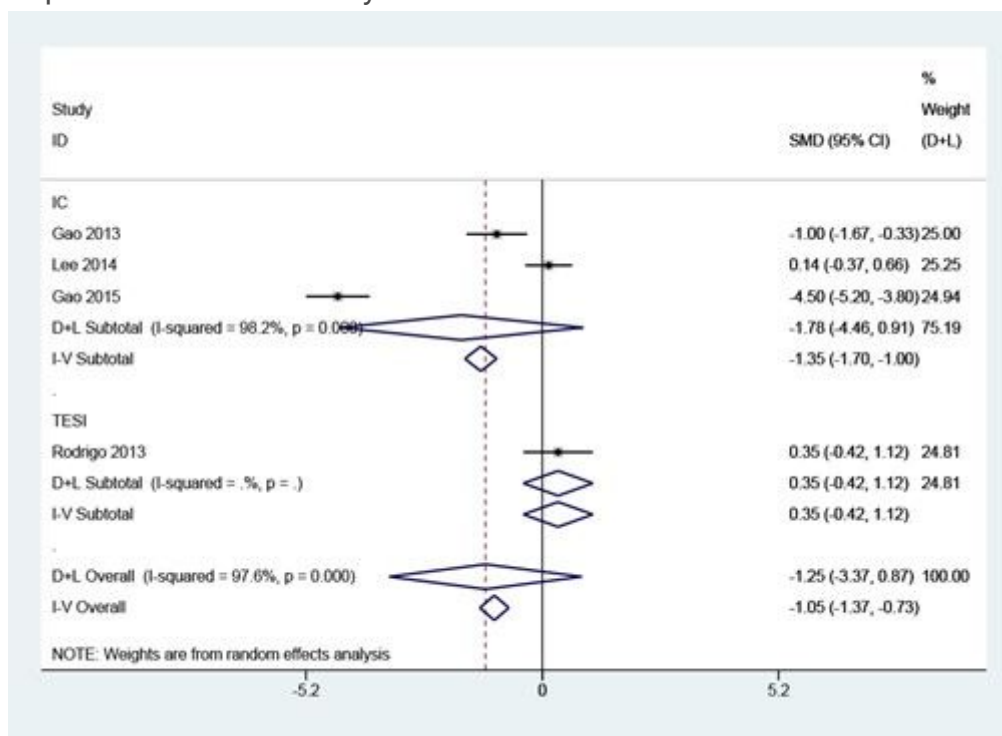


Figure 8

Impact of route of delivery MSC on WMSI.

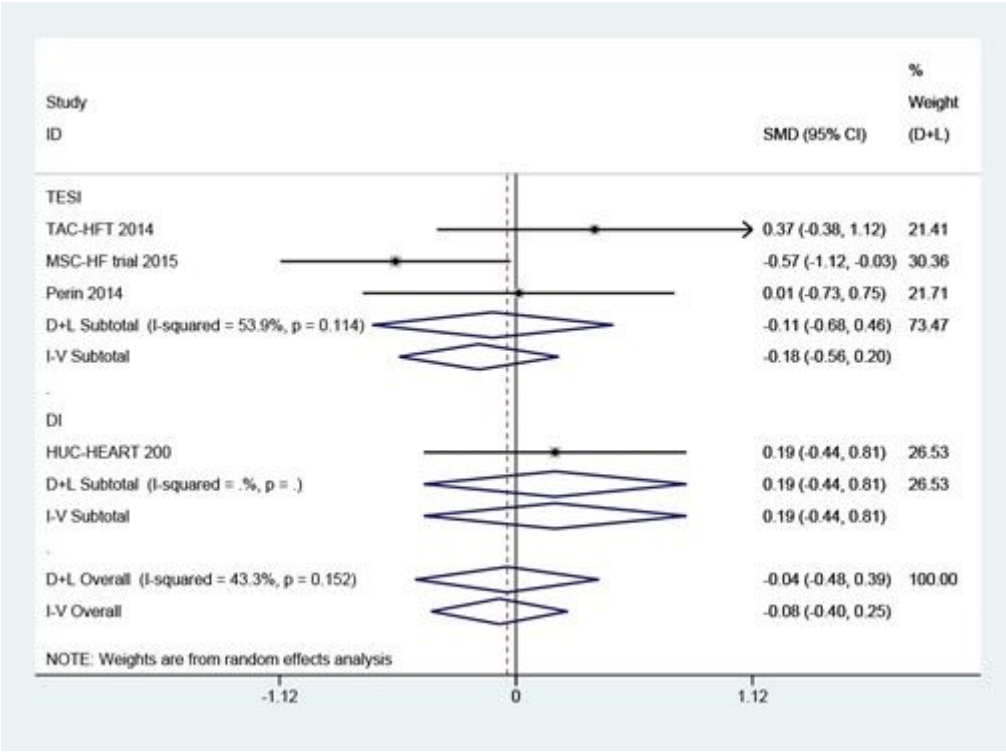


Figure 9

Impact of route of delivery MSC on 6min-walk.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CHART-1 2017	?	?	+	+	+	+	+
chen 2004	?	?	?	?	+	?	+
Chen 2006	?	?	?	?	+	?	+
Chullikana 2015	+	?	?	+	●	+	+
Gao 2013	+	?	●	+	+	?	+
Gao 2015	+	?	?	+	+	+	+
Hare 2009	+	+	+	+	+	+	+
henry 2016	?	+	+	+	+	+	+
houtgraaf 2012	?	?	?	?	+	+	+
HUC-HEART 2020	+	?	+	●	+	+	+
Kim 2018	?	?	●	●	+	?	+
Lee 2014	?	●	●	?	+	+	+
MSC-HF trial 2015	+	+	+	+	+	+	+
perin 2014	?	+	+	+	+	+	+
Rodrigo 2013	●	●	●	●	+	+	+
TAC-HFT 2014	●	?	+	+	+	+	+
Wang 2014	?	?	?	+	+	?	+
Zhang 2021	+	●	●	●	+	+	+

Figure 10

Risk of Bias Assessment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix1.xlsx](#)
- [Appendix2.xlsx](#)