



## Research Paper

# Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: An updated systematic review and meta-analysis

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## ABSTRACT

**Background:** Characterization of the mesenchymal stromal cell (MSC) safety profile is important as this novel therapy continues to be evaluated in clinical trials for various inflammatory conditions. Due to an increase in published randomized controlled trials (RCTs) from 2012–2019, we performed an updated systematic review to further characterize the MSC safety profile.

**Methods:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science (to May 2018) were searched. RCTs that compared intravascular delivery of MSCs to controls in adult populations were included. Pre-specified adverse events were grouped according to: (1) immediate, (2) infection, (3) thrombotic/embolic, and (4) longer-term events (mortality, malignancy). Adverse events were pooled and meta-analyzed by fitting inverse-variance binary random effects models. Primary and secondary clinical efficacy endpoints were summarized descriptively.

**Findings:** 7473 citations were reviewed and 55 studies met inclusion criteria ( $n = 2696$  patients). MSCs as compared to controls were associated with an increased risk of fever (Relative Risk (RR) = 2.48, 95% Confidence Interval (CI) = 1.27–4.86;  $I^2 = 0\%$ ), but not non-fever acute infusional toxicity, infection, thrombotic/embolic events, death, or malignancy (RR = 1.16, 0.99, 1.14, 0.78, 0.93; 95% CI = 0.70–1.91, 0.81–1.21, 0.67–1.95, 0.65–0.94, 0.60–1.45;  $I^2 = 0\%$ ,  $0\%$ ,  $0\%$ ,  $0\%$ ,  $0\%$ ). No included trials were ended prematurely due to safety concerns.

**Interpretations:** MSC therapy continues to exhibit a favourable safety profile. Future trials should continue to strengthen study rigor, reporting of MSC characterization, and adverse events.

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## 1. Introduction

Mesenchymal stromal cells (mesenchymal stem cells; MSCs) are multipotent stem cells that can be isolated from many adult tissues (e.g. bone marrow, adipose tissue). First described in 1974 [1], they

have recently received attention in a number of different clinical fields for their potential therapeutic effects. While often described as ‘adult stem cells’, MSCs have limited cellular differentiation ability as compared to other types of stem cells. Pre-clinical evidence suggests that MSCs exert their beneficial effects primarily through immunomodulatory and paracrine mechanisms. MSCs target sites of inflammation and secrete bioactive molecules [2] and there is a growing body of literature demonstrating the efficacy of MSC therapy in a

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## Research in context

### *Evidence before this study*

Several small clinical trials have investigated the efficacy and safety of MSCs in diseases, including chronic heart failure, acute myocardial infarction, hematological malignancies, graft versus host disease and the acute respiratory distress syndrome, and found some benefit with MSC therapy compared to controls. A previous systematic review examined the safety of intravascular administration of MSC therapy in heterogeneous adult patient populations. The review included eight RCTs and identified fever as the only adverse event that was significantly associated with MSC therapy. Since that publication in 2012, several reviews of MSC efficacy and or safety have included safety as part of the review objective. However, only one review included a detailed and systematic examination of the efficacy and safety of intravascular MSC administration that was limited to acute myocardial infarction and ischemic heart failure conditions and found no association between MSC therapy and acute adverse events (less than 24 h after study treatment); however MSC therapy compared to controls was associated with delayed neurological events.

### *Added value of this study*

In our updated systematic review that now includes over 40 additional RCTs and over 2000 additional patients, aside from fever, we continue to detect no significant reported safety signals associated with MSC treatment.

### *Implications of all the available evidence*

Our findings suggest that with the accumulation RCT evidence, the administration of MSCs continues to appear safe. The findings from our review should provide additional assurance to researchers, clinicians, health regulators and patients and families that, with this updated evidence, the administration of MSCs continues to appear safe. Future trials should continue to strengthen study rigor, reporting of MSC characterization and functionality, and adverse events as clinical indications as well as manufacturing processes evolve and second generation MSC products make their way to clinical trials.

patients) and identified fever as the only adverse event that was significantly associated with MSC therapy [8]. Given the increase in published RCTs and patients enrolled in MSC trials since that time, we decided to conduct and update our systematic review to further characterize the safety profile of MSC-based therapy and descriptively summarize primary and secondary efficacy outcomes in MSC RCTs.

## 2. Methods

The methods of this systematic review and meta-analysis are similar to our previously published review [8] with a few modifications; these are the addition of key words in our search strategy to capture placenta derived MSC trials, the inclusion of only randomized controlled trials, a focus on reporting adverse events that were pre-specified and that are potentially relevant to MSC administration, the addition of one additional pre-specified adverse event category (thrombotic and thromboembolic events) and one additional subgroup analysis according to placental MSCs, documentation of all reported serious adverse events and their relatedness to study treatment (in the MSC or control group), pooling of pre-specified adverse event estimates according to relative risks and 95% confidence intervals, and a descriptive summary of primary and secondary efficacy outcomes in the included RCTs. This report follows the PRISMA guidelines (complete checklist can be found in Appendix 2) [9] and because our review is an update of a previously published review, no protocol was registered.

### 2.1. Search strategy and selection criteria

We conducted electronic searches of Ovid MEDLINE (1950 to April 2019), EMBASE (1980 to April 2019) and Cochrane Central Register of Controlled Trials (April 2019). Given the non-standard terminology associated with MSCs, a number of terms were used (Appendix I, search strategy). ClinicalTrials.gov was searched for ongoing or recently completed trials. Abstracts and proceedings from clinical conferences were identified and searched using Web of Science (April 2019). Bibliographies of retrieved articles and relevant reviews were manually searched. All searches were performed without any language restrictions; if included, any non-English studies were subsequently translated for data extraction.

We included RCTs that examined the intravascular (venous and arterial) administration of MSCs compared to a control group that did not receive MSCs in adult populations. We excluded studies that exclusively used non-intravascular routes of administration (e.g. injection into a joint), *ex vivo* differentiated MSCs, or MSCs co-administered with other experimental cells or treatments.

Study screening and selection, data extraction and risk of bias assessments were all performed in duplicate by three independent reviewers (DW, MT, ED) using standardized forms.

### 2.2. Data analysis

Data were extracted under the following subheadings using a standardized spreadsheet: RCT characteristics and patient populations, MSC preparation and administration, assessment of risk of bias, and primary (safety) and secondary (efficacy) outcome measures. We recorded primary and secondary efficacy endpoints as reported in the RCTs. We contacted authors via email correspondence when data relevant to our systematic review was not reported in the included studies.

Safety was examined according to pre-specified incident adverse events according to the following categories: (1) immediate events (i.e., fever and non-fever acute infusional toxicity that occurred within 24 h of study drug administration) that captured the potential for MSCs to embolize or cause hypersensitivity reactions, (2) infection events that occurred at any time post-infusion because MSCs are known to immune-modulate in pre-clinical models, (3) thrombotic

variety of pre-clinical models, including acute lung injury [3,4], sepsis [5] and acute myocardial infarction [6]. Indeed, evidence of the immune-modulatory ability of MSC therapy in pre-clinical models has led to interest in the possible therapeutic role for MSCs in a variety of acute and chronic inflammatory conditions.

To date, several small clinical trials have investigated the efficacy and safety of MSCs for a variety of conditions including chronic heart failure, acute myocardial infarction, hematological malignancies, graft versus host disease and acute respiratory distress syndrome. While the results of some trials suggest benefit, larger trials with clinically important endpoints are needed before more definitive conclusions can be drawn. Thus, as more and more patients are being asked to participate in the studies, the safety of MSC therapy is of increasing importance and any risk of adverse events could represent a significant barrier to their successful translation into clinical practice. These potential risks include neoplastic potential due to MSCs' proliferative capacity, susceptibility to infection given their immunomodulatory effects, embolism of the cells, zoonoses associated with cell culture reagents, and acute or chronic immunogenicity of the cells themselves [7]. A previous systematic review published by our group in 2012 included eight randomized controlled trials (RCTs) ( $n = 369$

or thrombo-embolic events because MSCs can express or secrete tissue factor and other coagulation proteins [10–14] and therefore there is a theoretical risk of activation of coagulation and consequent adverse clinical events (i.e. deep venous thrombosis, pulmonary embolism, arterial thrombosis etc.), and (4) longer-term events including death and malignancy, the latter of which was captured due to the theoretical risk that MSCs could engraft.

Adverse event data were extracted based on the longest follow-up point. Adverse event data from RCTs with more than one MSC study arm (ex: dose escalation trial) were combined into one MSC study group. Meta-analyses for each pre-specified adverse event category was performed using OpenMetaAnalyst (for Windows 7). Data were analyzed using DerSimonian-Laird random effects models with a correction factor of 0.5 added to both arms for studies with 0 counts. Pooled events were described using Relative Risks (RR) and 95% confidence intervals (95% CI).

For all pre-specified adverse events we documented whether the events were reported as serious and if they were related to the study treatment (in either the MSC group or control group); we also captured other serious adverse events that were not pre-specified in our review and their reported relatedness to the study treatment. Finally, we captured the number of studies that were aborted pre-maturely due to safety concerns.

We used the CONSORT approach to harm reporting as a guide to capture the quality of adverse event reporting [15]. Specifically, we examined whether the reported approach to monitoring/recording adverse events (*a priori* plan to monitor events, types of events, frequency, and follow-up duration for events) were defined in the methods sections of the included studies.

Data related to MSC characterization as defined by the Dominici criteria were also recorded [16]. These included MSC cell source and origin, tri-lineage differentiation potential, cell surface markers, and cell morphology and adherence to plastic. We also described measures of MSC production (MSC viability, MSC potency, culture medium, and cryopreservation technique) because these measures could potentially impact both therapeutic efficacy and safety.

Heterogeneity between RCTs was evaluated using the  $I^2$  as well as the P-value from  $\chi^2$  test. Sub group analyses for each pre-specified adverse event category were planned according to the individual patient populations (cardiovascular, neurological, hematological/oncological, endocrine, renal, liver, respiratory, infectious, immune-deficient/inflammatory, other), MSC characteristics (type, origin, source), and MSC preparation (fresh versus cryopreserved, xenogenic versus xeno-free culture media). No adjustments for multiple comparisons were made for these sub group analyses as they were considered exploratory. A post-hoc sensitivity analysis of the pre-specified adverse event pooled estimates that excluded studies published in abstract form only was also conducted to evaluate the robustness of the study findings. The secondary efficacy outcomes were not pooled but rather summarized descriptively in table format for the reader.

RCTs that met inclusion criteria were assessed for risk of bias according to the Cochrane Collaboration methods [17].

### 2.3. Role of funding source

The funders had no role in the analysis, interpretation of the study results, or drafting of the manuscript. The authors independently designed the study, collected data, had access to the raw data, did the statistical analysis, and were responsible for the decision to submit for publication.

## 3. Results

Our search identified 7473 unique titles and 55 RCTs met inclusion criteria (see Fig. 1 for PRISMA flow diagram). All 55 RCTs were included for review ( $n = 2696$  patients) [18–66] (Table 1); six of the 55 RCTs

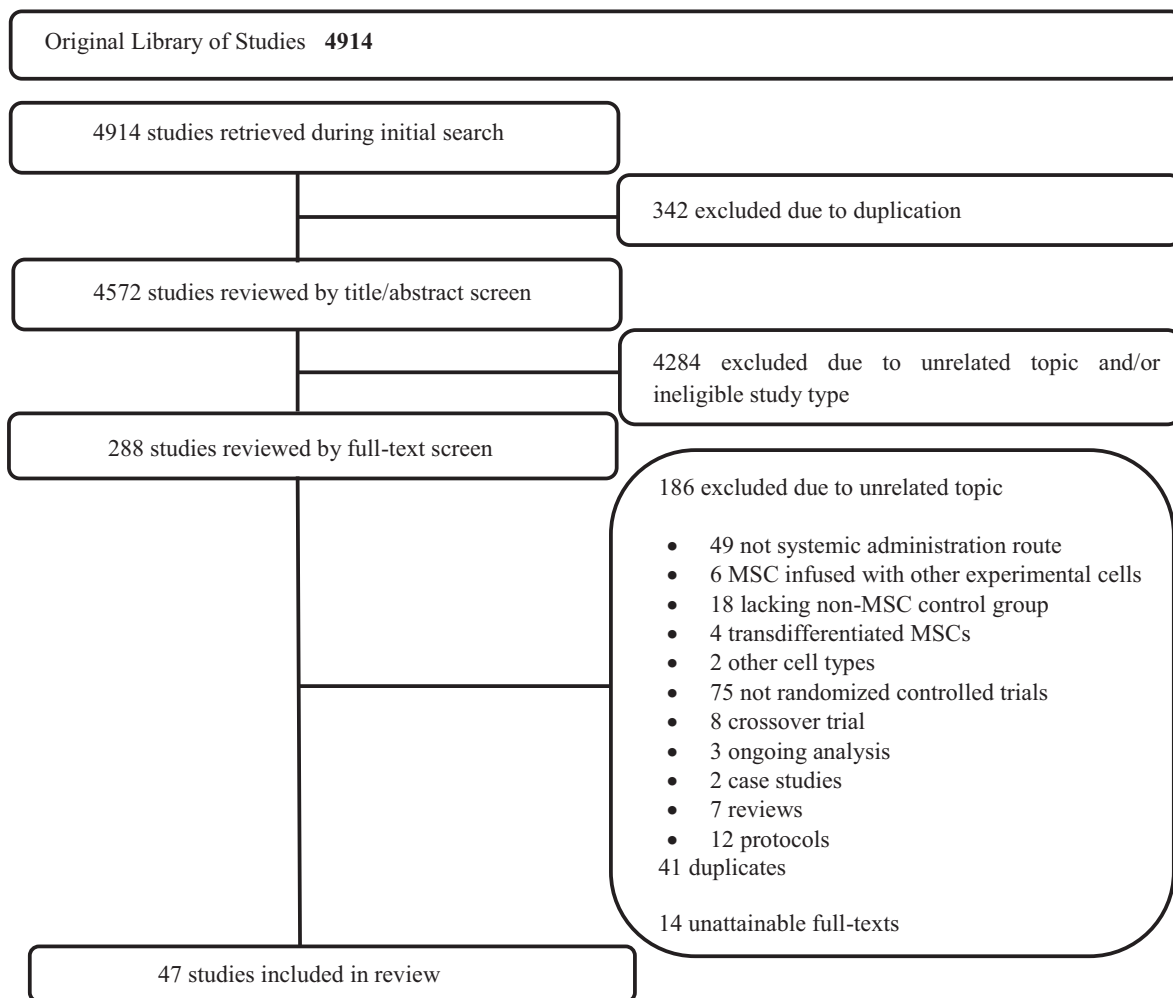
were published in abstract form only [19,45,61,64,65,67]. Included RCTs were conducted in 12 different countries and 20 (36.4%) were multi-center [20–23,26,27,29,38,40,46,47,49,55,62–64,66,68–70]. Sample sizes ranged from nine to 135 patients ( $49.9 \pm 31.3$ , mean  $\pm$  standard deviation). The follow-up period ranged from one day to 60 months ( $14.2 \pm 13.5$ , mean  $\pm$  standard deviation). Thirteen (23.6%) reported funding from a for-profit manufacturer of MSCs (i.e. Osiris Therapeutics, Inc., FCB-Pharmacell Company Limited, Celgene Cellular Therapeutics, etc.) [20–23,27,29,49,52,55,56,65,69,70].

Patient populations were diverse and included cardiovascular (12 trials,  $n = 612$  patients) [21,24–27,29,37,40,42,44,49,58], neurological (10 trials,  $n = 242$  patients) [30–32,36,45,48,57,62,65,69], renal (three trials,  $n = 177$  patients) [55,63,67], liver (seven trials,  $n = 404$  patients) [35,43,47,53,54,59,66], respiratory (three trials,  $n = 134$  patients) [18,23,68] and endocrine diseases (four trials,  $n = 169$  patients) [22,28,39,50], hematological/oncological malignancies (five trials,  $n = 318$  patients) [33,34,41,46,71], immune deficient or inflammatory conditions (nine trials,  $n = 544$  patients) [20,38,51,52,60,61,64,70,72], general frailty (one trial,  $n = 30$  patients) [56], and severe sepsis in severely neutropenic patients with hematologic malignancies (one trial,  $n = 30$  patients) [19].

With respect to MSC preparation and administration, of the 55 included RCTs, 31 (56.4%) examined bone marrow [19,21–27,29–34,36,39,41–43,45,47,53,55–59,61,66,68,71], 16 (29.1%) umbilical cord [28,35,38,40,44,46,48–52,54,60,63,65,72], four (7.3%) adipose-derived MSCs [18,20,62,64], two (3.6%) placenta-derived cells [69,70]; and in two RCT (3.6%) the source of MSCs was unclear [37,67]. See Supplementary Table 1 for expanded detail. Twenty (36.4%) RCTs used autologous MSCs [24–26,29–32,36,37,39,42,43,45,47,57–59,61,62,66], 29 (52.7%) used third party unmatched allogeneic MSCs [18–23,27,28,35,38,40,44,46,48–56,60,63–65], and four (7.3%) used allogeneic MSCs from matched donors [33,34,41,67]. Two (3.6%) RCTs used placenta-derived mesenchymal-like cells [69,70] and one (1.8%) RCT used mesenchymal precursor cells (MPC) rather than MSCs [22]. Twelve (21.8%) RCTs cultured the MSCs in a xeno-free medium [21,27,28,39,41,49,50,52,55,58,59,71], whereas the remainder either used a xenogenic product (40.0%,  $n = 22$ ) [18,22,23,25,26,29–35,42,46,47,53,56,57,60,62,66,68] or did not report the medium used (38.1%,  $n = 21$ ) [19,20,24,36–38,40,43–45,48,51,54,61,63–65,67,69,70,72]. Fifteen (27.3%) RCTs cryopreserved MSCs prior to administration [19–23,27,30,39,52,53,55,56,60,69,70], 32 (58.2%) used fresh MSCs [18,24–26,28,29,31–35,38,40,42–44,46–51,54,57–59,62–64,66,68,72], two (3.6%) used both a fresh and cryopreserved product [41,71] and in six (10.9%) it was unclear [36,37,45,61,65,67]. One trial that used both a fresh and cryopreserved product (1.8%) [71] and five of the 32 RCTs that used fresh MSCs (9.1%) used a cryopreserved cell product that was thawed and cultured prior to injection for a fresh cell product [18,47,49,68,72]. Of the 22 RCTs that reported cryopreserving their product, 14 (25.6%) used dimethyl sulfoxide as the cryoprotectant solution at a concentration of 10% or less [18,19,21–23,27,41,47,52,55,56,60,68,71]; the type cryoprotectant was unclear for the eight other RCTs (14.5%). Seven (12.7%) of the included RCTs reported all three Dominici criteria for MSC characterization [20,21,40,41,68,71,72]. Twenty-nine (52.7%) RCTs reported on cell viability [20–23,25,26,29–33,37,39,40,43,47–49,52,54–58,62,68,71,72] and eight (14.5%) reported on a measure of MSC potency [20,22,23,25,29,47,62,68].

A description and frequency of the pre-specified incident adverse events defined in our systematic review (infusional toxicity: fever and non-fever, infection, thrombotic or thromboembolic events, death and malignancy) for each included RCT is provided in Supplementary Table 2 and a summary of pooled data presented as forest plots for each pre-specified adverse event category are summarized in Figs. 2A–F.

With respect to the occurrence immediate adverse events, a total of 19 RCTs ( $n = 880$  patients) reported on fever infusional toxicity [20,31,32,35–38,43,47–51,57,59,60,63,71,72]. In the pooled analysis,



**Fig. 1.** Literature search and study inclusion. MSC= mesenchymal stem cell; \*Figure is reflective of search data from 2012 to present and does not include search data from the prior publication, including the 8 RCTs previously included.

the risk of fever was significantly greater in the MSC group as compared to the control group (Relative Risk (RR) = 2.48, 95% Confidence Interval (CI) = 1.27–4.86,  $I^2 = 0\%$ ; see Fig. 2a). Pooled analysis of reported non-fever infusional toxicity events in a total of 32 RCTs ( $n = 1525$  patients) however did not reveal any significant increase in risk for the MSC as compared to the control group (RR = 1.16, 95% CI = 0.70–1.91,  $I^2 = 0\%$ ; see Fig. 2b) [18,21–23,25–27,29,30,33,34,37,39,40,44,46,48–54,56–60,63,68–70].

A total of 27 RCTs ( $n = 1315$  patients) reported on infection [19–23,27,30–34,38–40,47,50,52–57,62,63,69,70,72]. In the pooled analysis, there was no significant increase in the risk of infection for the MSC as compared to the control group (RR = 0.99, 95% CI = 0.81–1.21,  $I^2 = 0\%$ ; see Fig. 2c).

The occurrence of thrombotic or thrombo-embolic events were reported in a total of 24 RCTs ( $n = 1112$  patients) [20,21,26,29,32,33,37,40,50,56,58,60,63,66,69,70]. In the pooled analysis there was no significant increase in the risk of thrombotic/thrombo-embolic events for MSCs as compared to the control group (RR = 1.14, 95% CI = 0.67–1.95,  $I^2 = 0\%$ ; see Fig. 2d).

A total of 40 ( $n = 1991$  patients) and 19 ( $n = 1015$  patients) RCTs reported on death [18–21,23–27,29,31–37,40–42,44–46,48–53,55,56,58,59,62,63,66,68–71] and malignancy and/or ectopic tissue formation respectively [20,27,31–34,38–41,44,47,49,53,55–57,70,71]. In the pooled analysis, the risk of death was significantly lower for the MSC group as compared to the control group

(RR = 0.78, 95% CI = 0.65–0.94,  $I^2 = 0\%$ ; see Fig. 2e). There was no significant increase found in the risk of malignancy or ectopic tissue formation for the MSC as compared to the control group (RR = 0.93, 95% CI = 0.60–1.45,  $I^2 = 0\%$ ; see Fig. 2f).

The results of the risk of bias assessment found that only six (10.9%) RCTs fulfilled all six criteria for low risk of bias (Table 2) [23,27,30,40,49,62]. Nine (16.4%) RCTs met five of six primary criteria [21,28,32,46,50,52,56,68,69]. The allocation lists were concealed in 24 (43.6%) [21–23,27,28,30–32,39,40,46,47,49,50,52,53,55,56,59,60,62,63,68,69]; 21 (38.1%) were double blinded [18,21,23,27,28,30,40,46,49–52,55–57,62,64,65,68–70] and three (5.5%) had an open label intervention but blinded outcome measures [29,32,54]. In terms of other potential sources of bias, 35 (63.6%) of the RCTs were registered with either clinicaltrials.gov or their own regional registration program [18–23,26,29,30,35,38–41,43,46–49,51–57,60,62–66,68,70,72]. Thirty-eight (69.0%) RCTs did not report an *a priori* sample size calculation or provide a rationale for the sample size [18,19,21,24–28,31–39,41,42,44,45,48–52,54,57–59,61,64–67,69,71,72].

Sub-groups were meta-analyzed for the six pre-specified adverse event outcome categories and are summarized in Supplementary Table 3. Briefly, the risk of fever related acute infusional toxicity in the MSC group was increased in the neurological and immune/inflammatory populations, when unmatched allogeneic and autologous, bone marrow, umbilical, or fresh MSCs were administered, and when the MSC culture medium was xenogenic or unclear. The risk of



**Table 1**  
Characteristics of included RCTs.

Source	Country	Patient Population (Sample Size)	Single-center vs multi-center (Number of centers)	Follow Up Duration (months)	Intervention	Control Comparison	Patients Evaluated (n (% male))		Age (years ± SD)	
							T	C	T	C
<b>Cardiovascular</b>										
Chen et al., 2004	PRC	Acute myocardial infarction (69)	Single-center	6	Autologous BM-MSCs	Saline, IC	34 (94)	35 (97)	58 ± 7	57 ± 5
Chen et al., 2006	PRC	Ischemic heart failure (45)	Single-center	12	Autologous BM-MSCs	Maximal medical therapy	22 (88)	23 (92)	59 ± 7	57 ± 7
Chullikana et al., 2015	India	Acute ST-elevation myocardial infarction (20)	Multi-center (4)	24	Unmatched allogeneic BM-MSCs	Multiple electrolytes (Plasma-lyte A), IV	10 (100)	10 (80)	47.3 ± 12.1	47.8 ± 6.5
Gao et al., 2013	PRC	Acute ST-elevation myocardial infarction (43)	Multi-center (4)	24	Autologous BM-MSCs	Routine therapy	21 (100)	22 (86)	55.0 ± 1.6	58.6 ± 2.5
Gao et al., 2015	PRC	Acute ST-elevation myocardial infarction (116)	Multi-center (11)	18	Unmatched allogeneic UC-MSCs	Saline with heparin, IC	58 (95)	58 (88)	57.3 ± 1.3	56.7 ± 1.7
Hare et al., 2009	USA	Acute myocardial infarction (53)	Multi-center (10)	6	Unmatched allogeneic BM-MSCs	Vehicle, IV	34 (82)	19 (79)	59 ± 12	55 ± 10
Lee et al., 2014	ROK	Acute myocardial infarction (58)	Multi-center (3)	6	Autologous BM-MSCs	Standard treatment	30 (90)	28 (89)	53.9 ± 10.5	54.2 ± 7.7
Wang et al., 2006**	PRC	Idiopathic dilated cardiomyopathy (24)	Single-center	6	Autologous MSCs	Saline, IC	12 (75)	12 (67)	54 ± 11	58 ± 11
Wang et al., 2014	PRC	Acute myocardial infarction (58)	Single-center	6	Autologous BM-MSCs	Saline, IC	28 (68)	30 (53)	58.0 ± 10.2	56.1 ± 9.8
Zhao et al., 2015	PRC	Chronic systolic heart failure (59)	Single-center	6	Unmatched allogeneic UC-MSCs	No IC injection, only drug therapy alone	30 (80)	29 (66)	52.9 ± 16.3	53.2 ± 11.5
Bartolucci et al., 2016/2017	Chile	Stable heart failure (30)	Multi-center (2)	12	Unmatched allogeneic UC-MSCs	Placebo NR	15 (80.0)	15 (93.3)	57.33 ± 10.05	57.20 ± 11.64
Xiao et al., 2017	PRC	Dilated cardiomyopathy (37)	Single-center	12	Autologous BM-MSCs	Placebo (saline)	17 (70.6)	20 (70.0)	51.6 ± 12.2	54.4 ± 11.6
<b>Neurological</b>										
Ibrahim et al., 2016*	Malaysia	Acute middle cerebral artery stroke (17)	NR	12	Autologous BM-MSCs	Standard treatment	NR	NR	NR	NR
Lee et al., 2008	ROK	Multiple system atrophy (29)	Single-center	12	Autologous BM-MSCs	NR	11 (73)	18 (67)	58 ± 7	57 ± 7
Lee et al., 2010	ROK	Ischemic stroke (52)	Single-center	60	Autologous BM-MSCs	Rehabilitation alone	16 (50)	36 (72)	64 ± 12	65 ± 15
Lee et al., 2012	ROK	Multiple system atrophy (31)	Single-center	12	Autologous BM-MSCs	Saline, IV and IA	14 (65)****	17 (63)****	56.1 ± 8.9****	55.8 ± 6.1****
Xie et al., 2007**	PRC	Spinal cord injury (24)	Single-center	3	Autologous BM-MSCs	Rehabilitation alone	11 (81)	13 (77)	(18–49)	(21–53)
Xie et al., 2016	PRC	Encephalopathy (22)	Single-center	6	Unmatched allogeneic UC-MSCs	Saline, IV	12 (67)	10 (60)	58.0 ± 7.4	63.3 ± 6.11
Fernandez et al., 2018	Spain	Secondary progressive multiple sclerosis (30)	Multi-center (2)	12	Autologous Adipose-MSCs	Placebo (Ringer's lactate)	10 (40)**** 9 (22)****	11 (27)****	44.8 ± 8.0**** 47.8 ± 9.7****	46.3 ± 8.9****
Tsang et al., 2017	PRC	Chronic stroke/vegetative state (9)	Single-center	Day of or day after	Autologous BM-MSCs	Placebo (5% normal human albumin)	5 (40)	4 (75)	52.8 (48–56)	51.5 (41–59)
Kim et al., 2018*	ROK	Cerebral infarction (12)	Single-center	6	Unmatched allogeneic UC-MSCS	Placebo	8 (NR)	4 (NR)	NR	NR
Lublin et al., 2014	USA/Canada	Multiple sclerosis (16)	Multi-center (8)	12	Placenta-derived mesenchymal-like cells	Placebo	6 (33) 6 (17)	4 (50)	52.5 (41–58) 47.5 (36–56)	47.5 (40–52)

(continued on next page)

Table 1 (Continued)

Source	Country	Patient Population (Sample Size)	Single-center vs multi-center (Number of centers)	Follow Up Duration (months)	Intervention	Control Comparison	Patients Evaluated (n (% male))		Age (years ± SD)	
							T	C	T	C
<b>Oncological/Hematological</b>										
Gao et al., 2016	PRC	Stem cell transplantation for hematologic malignancy (124)	Multi-center (5)	51 (24–70)	Unmatched allogeneic UC-MSCs	Saline, IV	62 (47)	62 (48)	NR	NR
Liu et al., 2011	PRC	Stem cell transplantation for leukemia (55)	Single-center	24	Matched allogeneic BM-MSCs	Stem cell transplant alone	27 (74)	28 (68)	30 (14–46)	31.5 (12–48)
Ning et al., 2008	PRC	Stem cell transplantation for hematologic malignancy (25)	Single-center	36	Matched BM-MSCS	Stem cell transplant alone	10 (90)	15 (87)	36 ± 11	39 ± 12
Kuzmina et al., 2012	Russia	Recipients of allogeneic bone marrow transplants for hematological malignancies (37)	Single-center	32	Unmatched BM-MSCs	Standard aGVHD prophylaxis	19 (42)	18 (39)	34 (20–63)	29 (19–60)
Shipounova et al., 2014	Russia	Recipients of allogeneic bone marrow transplants for hematological malignancies (77)	Single-center	60	Matched BM-MSCS	Standard aGVHD prophylaxis	39 (NR)	38 (NR)	NR	NR
<b>Endocrine</b>										
Carlsson et al., 2015	Sweden	Type 1 diabetes mellitus (18)	Single-center	12	Autologous BM-MSCs	Insulin-only treatment	9 (89)	9 (56)	24 ± 2	27 ± 2
Hu et al., 2013	PRC	Type 1 diabetes mellitus (29)	Single-center	24	Unmatched allogeneic UC-MSCs	Saline, IV	15 (60)	14 (57)	17.6 ± 8.7	18.2 ± 7.9
Hu et al., 2016	PRC	Type 2 diabetes mellitus (61)	Single-center	36	Unmatched allogeneic UC-MSCs	Saline, IV	31 (55)	30 (53)	52.43 ± 4.88	53.21 ± 8.22
Skyler et al., 2015	USA	Type 2 diabetes mellitus (61)	Multi-center (18)	3	Unmatched allogeneic BM-MPCs	Saline, IV	15 (67) 15 (60) 15 (60)	<b>16 (75)</b> 57.2 ± 6.6	57.7 ± 8.2 55.3 ± 11.4 57.2 ± 6.6	<b>58.7 ± 7.3</b>
<b>Renal disease</b>										
Swaminathan et al., 2018	USA	Patients undergoing cardiac surgery using cardiopulmonary bypass, who developed acute kidney insufficiency (135)	Multi-center (27)	3	Unmatched allogeneic BM-MSCs	Placebo	67 (65.7)	68 (82.4)	65.6 ± 11.9	67.0 ± 9.9
Korotkov et al., 2018*	Belarus	Renal transplantation (NR)	Single-center	7 days	Matched allogeneic MSCs	Standard treatment	NR	NR	NR	NR
Sun et al., 2018	PRC	Renal allograft (42)	Multi-center (3)	12	Unmatched allogeneic UC-MSCs	Standard treatment	21 (67)	21 (52)	40.8 ± 9.2	47.1 ± 10.2
<b>Liver disease</b>										
Suk et al., 2016	ROK	Alcohol-related liver cirrhosis (68)	Multi-center (12)	12	Autologous BM-MSCs	Standard treatment	21 (83)*** 23 (89)***	24 (94)*** 54.4 ± 7.9***	53.1 ± 8.7*** 54.4 ± 7.9***	53.7 ± 8.2***
Shi et al., 2012	PRC	Acute-on-chronic liver failure (43)	Single-center	18	Unmatched allogeneic UC-MSCs	Placebo (saline)	24 (83)	19 (79)	40 (24–59)	45 (26–62)
Salama et al., 2014	Egypt	Post-HCV end-stage liver disease (40)	Multi-center (2)	6	Autologous BM-MSCs	Antiviral therapy (no hepatic artery infusion)	20 (85)	20 (80)	50.27 ± 6.05	50.90 ± 7.23
Xu et al., 2014	PRC	Hepatitis B virus-related liver cirrhosis (56)	Single-center	6	Autologous BM-MSCs	Standard care	27 (65)***	29 (58)***	44 ± 12***	45 ± 10***
Lin et al., 2017	PRC	Hepatitis B virus-related acute-on-chronic liver failure (110)	Single-center	6	Unmatched allogeneic BM-MSCS	Standard treatment	56 (91.1)	54 (98.2)	40 ± 9.9	42.8 ± 8.4
Zhang et al., 2017	PRC	Liver fibrosis induced by hepatolenticular degeneration (60)	Single-center	3	Autologous BM-MSCs	Standard treatment	30 (53.3)	30 (56.7)	30.98 ± 11.25	32.1 ± 10.36
Shi et al., 2017	PRC	First cadaveric liver transplantation (27)	Single-center	6	Unmatched allogeneic UC-MSCs	Standard treatment	14 (92.9)	13 (92.3)	57 ± 12	55 ± 11

(continued on next page)

**Table 1** (Continued)

Source	Country	Patient Population (Sample Size)	Single-center vs multi-center (Number of centers)	Follow Up Duration (months)	Intervention	Control Comparison	Patients Evaluated (n (% male))		Age (years $\pm$ SD)	
							T	C	T	C
<b>Respiratory</b>										
Weiss et al., 2013	USA	Moderate to severe chronic obstructive pulmonary disease (62)	Multi-center (6)	24	Unmatched allogeneic BM-MSCs	Vehicle solution, IV	30 (60)	32 (56)	68.1 $\pm$ 7.54	64.1 $\pm$ 8.76
Zheng et al., 2014	PRC	Acute respiratory distress syndrome (12)	Single-center	1	Unmatched allogeneic adipose-MSCs	Saline, IV	6 (100)	6 (83)	66.7 $\pm$ 20.4	69.8 $\pm$ 9.1
Matthay et al., 2018	USA	Acute respiratory distress syndrome (60)	Multi-center (5)	2	Unmatched allogeneic BM-MSCs	Plasma-Lyte A, IV	40 (58)	20 (50)	55 (17)	55 (20)
<b>Infectious</b>										
Galstian et al., 2015/2016*	Russia	Patients with severe neutropenia and severe sepsis (30)	Single-center	3	Unmatched allogeneic BM-MSCs	Standard treatment	15 (43) ****	15 (54) ****	48 (30–75) ****	55 (33–81) ****
<b>Immune-deficient/auto-immune/inflammatory</b>										
Alvaro-Garcia et al., 2016	Spain	Refractory rheumatoid arthritis (53)	Multi-center (18)	6	Unmatched allogeneic adipose-MSCs	Lactated Ringer's solution, IV	20 (10) 20 (10) 6 (0)	7 (14)	54.15 $\pm$ 7.79 57.40 $\pm$ 11.01 50.33 $\pm$ 15.62	58.43 $\pm$ 14.25
Zhang et al., 2013	PRC	HIV-1 infection (13)	Multi-center (NR)	12	Unmatched allogeneic UC-MSCs	Saline, IV	7 (71)	6 (83)	30 (26–49)	38 (19–55)
Hu et al., 2016	PRC	Ulcerative colitis (70)	Single-center	24	Unmatched allogeneic UC-MSCs	Saline, IV and IA	34 (62)	36 (61)	42.9 $\pm$ 23.1	43.7 $\pm$ 28.7
Deng et al., 2017	PRC	Systemic lupus erythematosus (18)	Single-center	12	Unmatched allogeneic UC-MSCs	Placebo	12 (8)	6 (0)	29 $\pm$ 10	29 $\pm$ 7
Zhang et al., 2018	PRC	Crohn's disease (82)	Single-center	12	Unmatched allogeneic UC-MSCS	Standard treatment	41 (58.5)	41 (63.4)	34.3 (21–44)	32.7 (20–41)
Arturo et al., 2017*	Columbia	Crohn's disease (26)	Single-center	6	Autologous BM-MSCs	Standard treatment	NR	NR	NR	NR
Panes et al., 2017*	Spain	Crohn's disease (131)	Multi-center (NR)	12	Unmatched allogeneic adipose-MSCs	Placebo	70 (NR)	61 (NR)	NR	NR
Yang et al., 2018	PRC	Rheumatoid arthritis (105)	Single-center	11	Unmatched allogeneic UC-MSCs	Placebo	28 (25)	53 (19)	50.7	49.8
Melmed et al., 2015	USA	Crohn's disease (46)	Multi-center (NR)	24	Placenta-derived mesenchymal-like cells	Placebo	24 (21) 8 (53) 5 (33)	7 (44)	51.2 35.3 $\pm$ 14.0 36.2 $\pm$ 11.6	36.5 $\pm$ 7.3
<b>Other</b>										
Tompkins et al., 2017	USA	Frailty (30)	Single-center	12	Unmatched allogeneic BM-MSCs	Placebo	10 (60)	10 (60)	75.0 $\pm$ 7.4	75.3 $\pm$ 6.8

PRC= People's Republic of China; USA= United States of America; ROK= Republic of Korea; T= treatment; C= control; BM= bone marrow; UC= Umbilical cord; MSCs= mesenchymal stromal cells; MPCs= mesenchymal precursor cells; IA= intra-arterial; IC= intracoronary; IV= intravenous; NR= not reported.

\* Abstract form only.

\*\* Foreign language text only.

\*\*\* Age and gender demographic data reported only for patients that completed trial follow-up.

\*\*\*\* Age and gender demographic data reported for all patients randomized, not necessarily infused with study treatment.

\*\*\*\*\* Age and gender demographic data reported only in earlier abstract, not updated to current abstract.

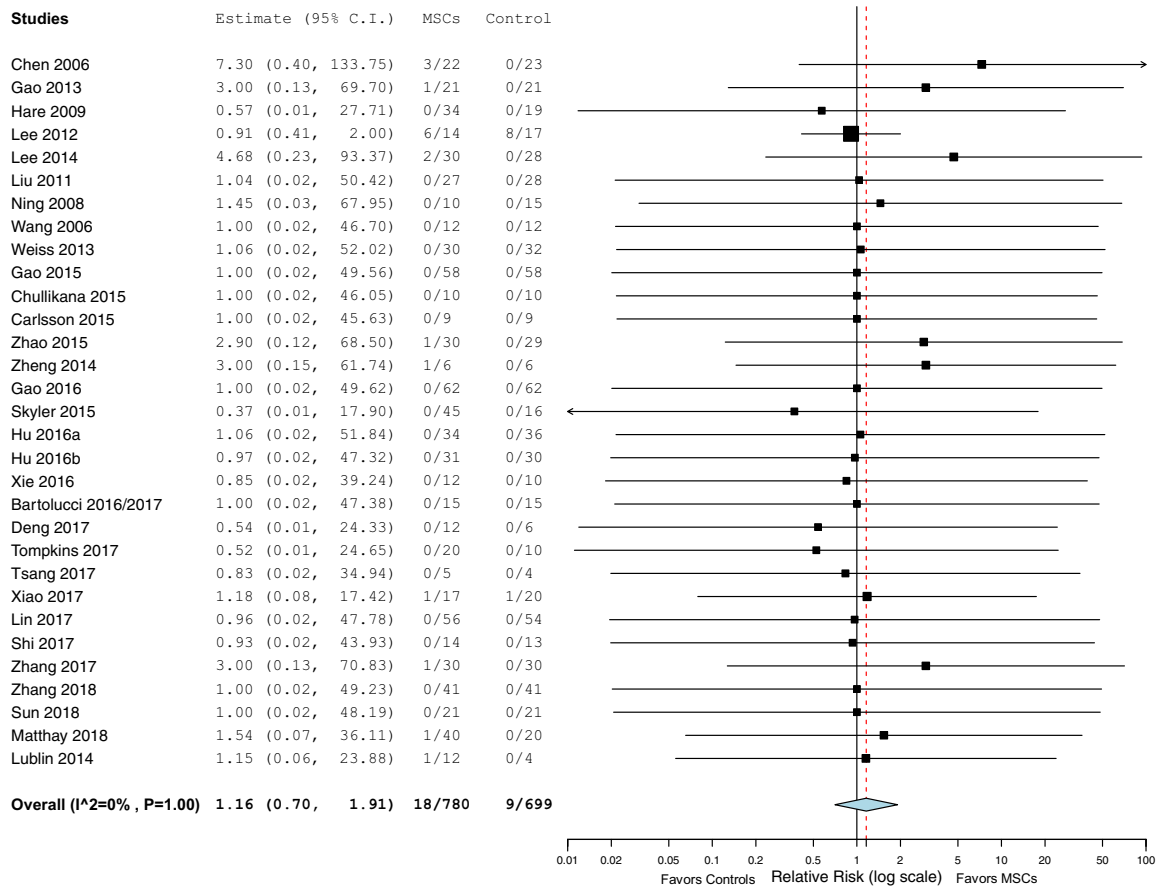
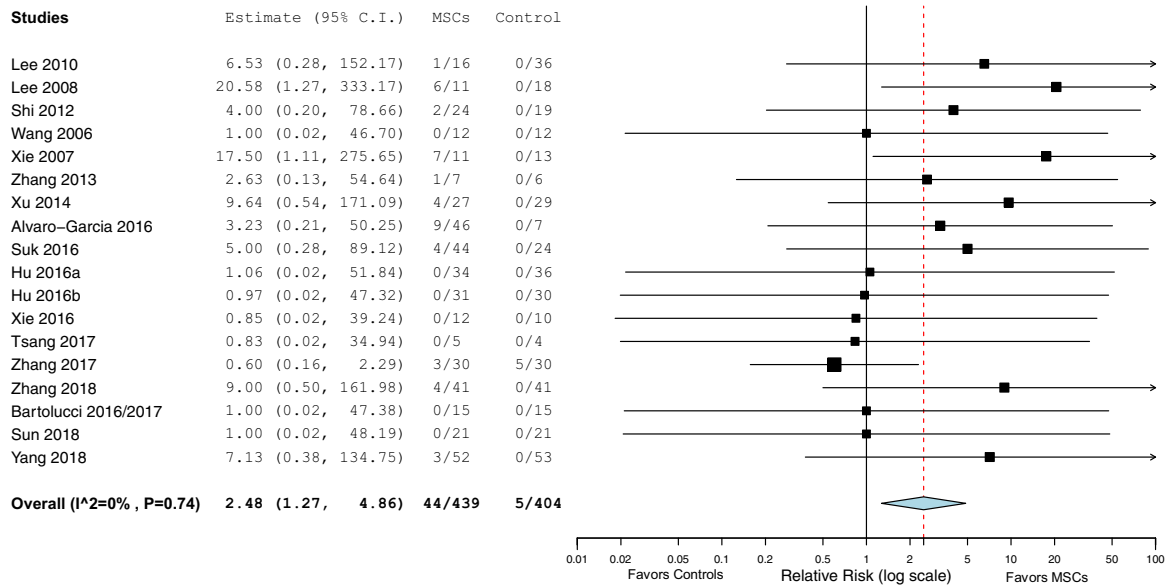


Fig. 2. a) Infusional toxicity: Fever. b) Infusional toxicity: Non-fever. c) Infection. d) Thrombotic/thrombo-embolic events. e) Mortality. f) Malignancy or ectopic tissue formation. RR, relative risk; CI, confidence interval; MSC, mesenchymal stem cell.



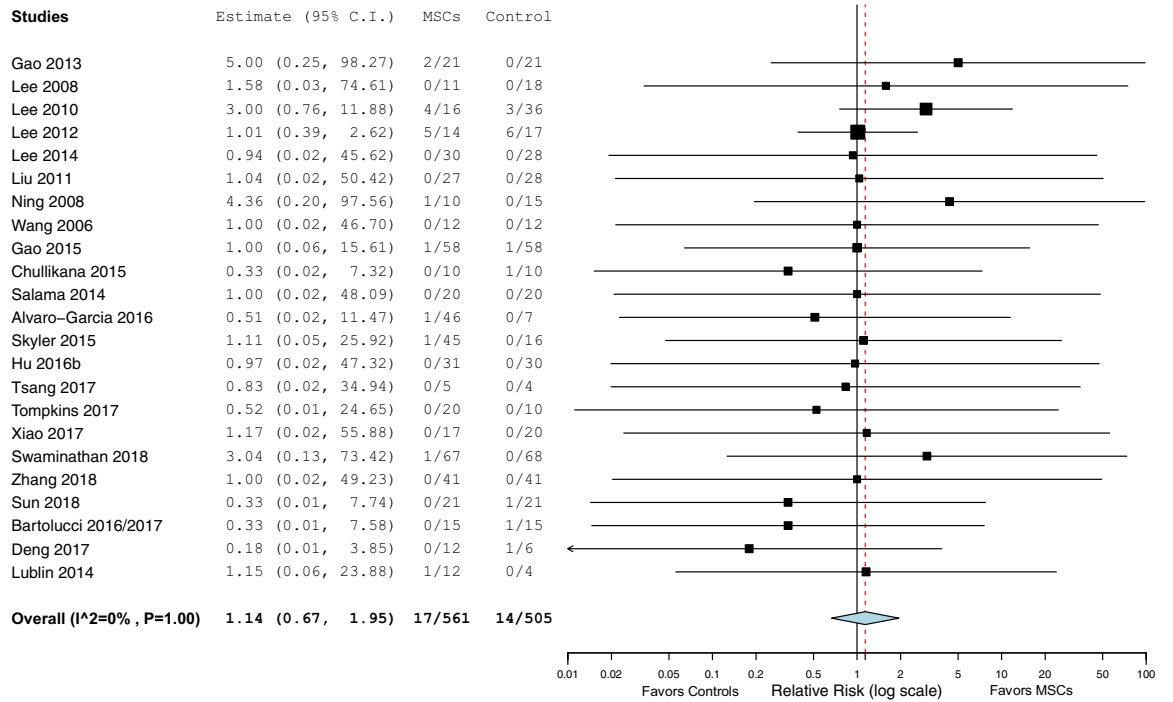
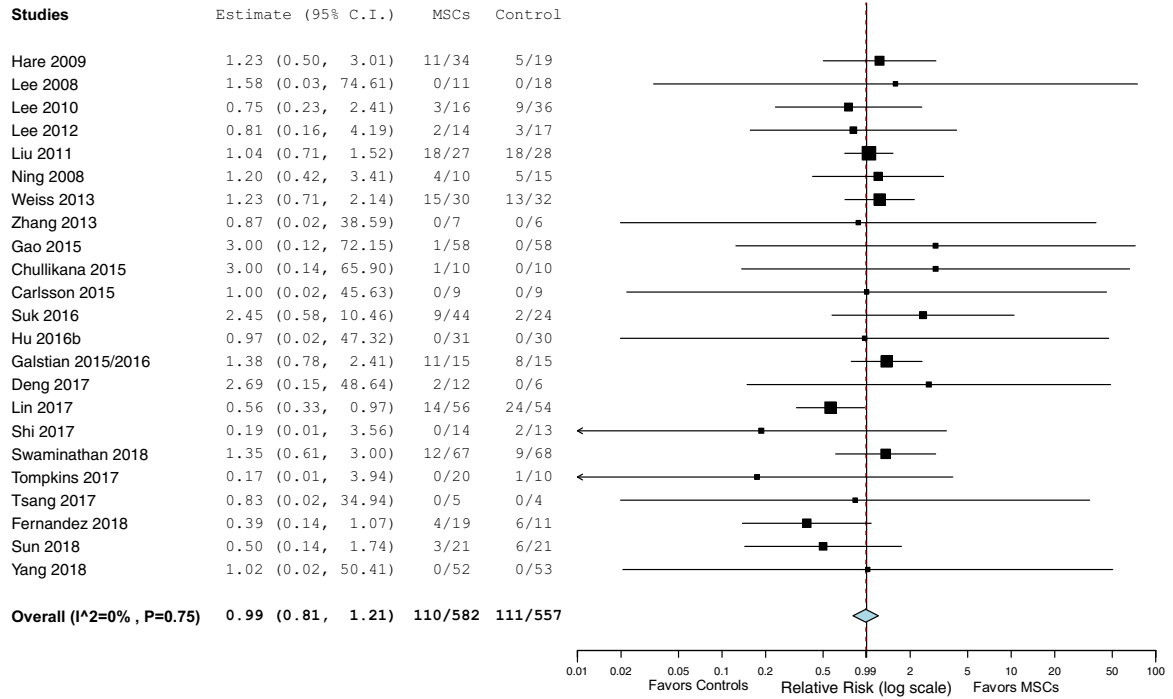


Fig. 2. Continued

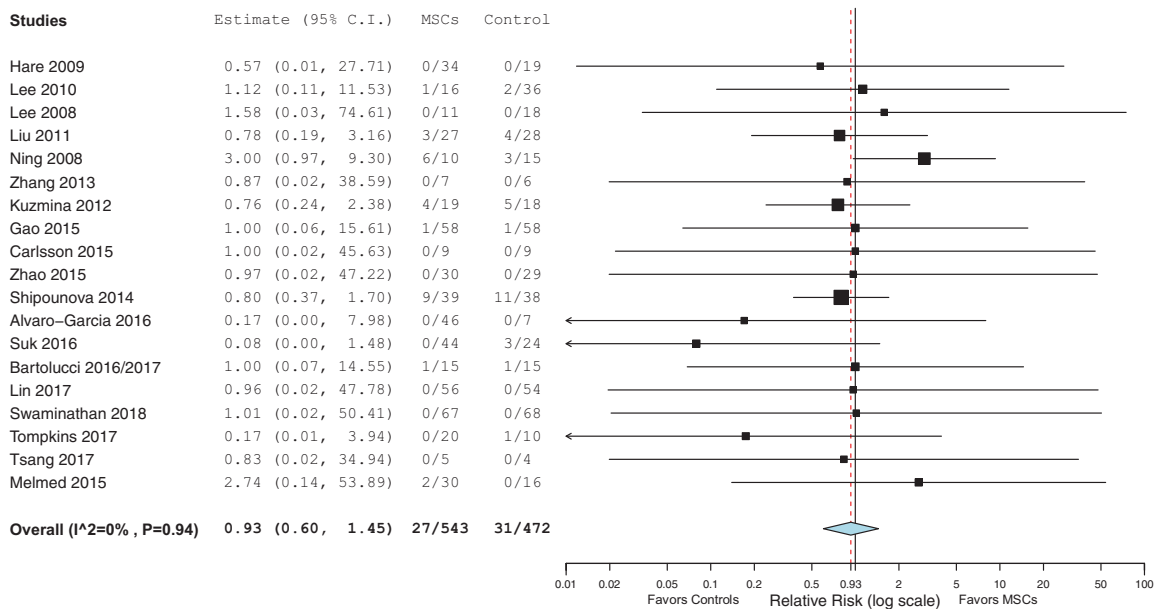
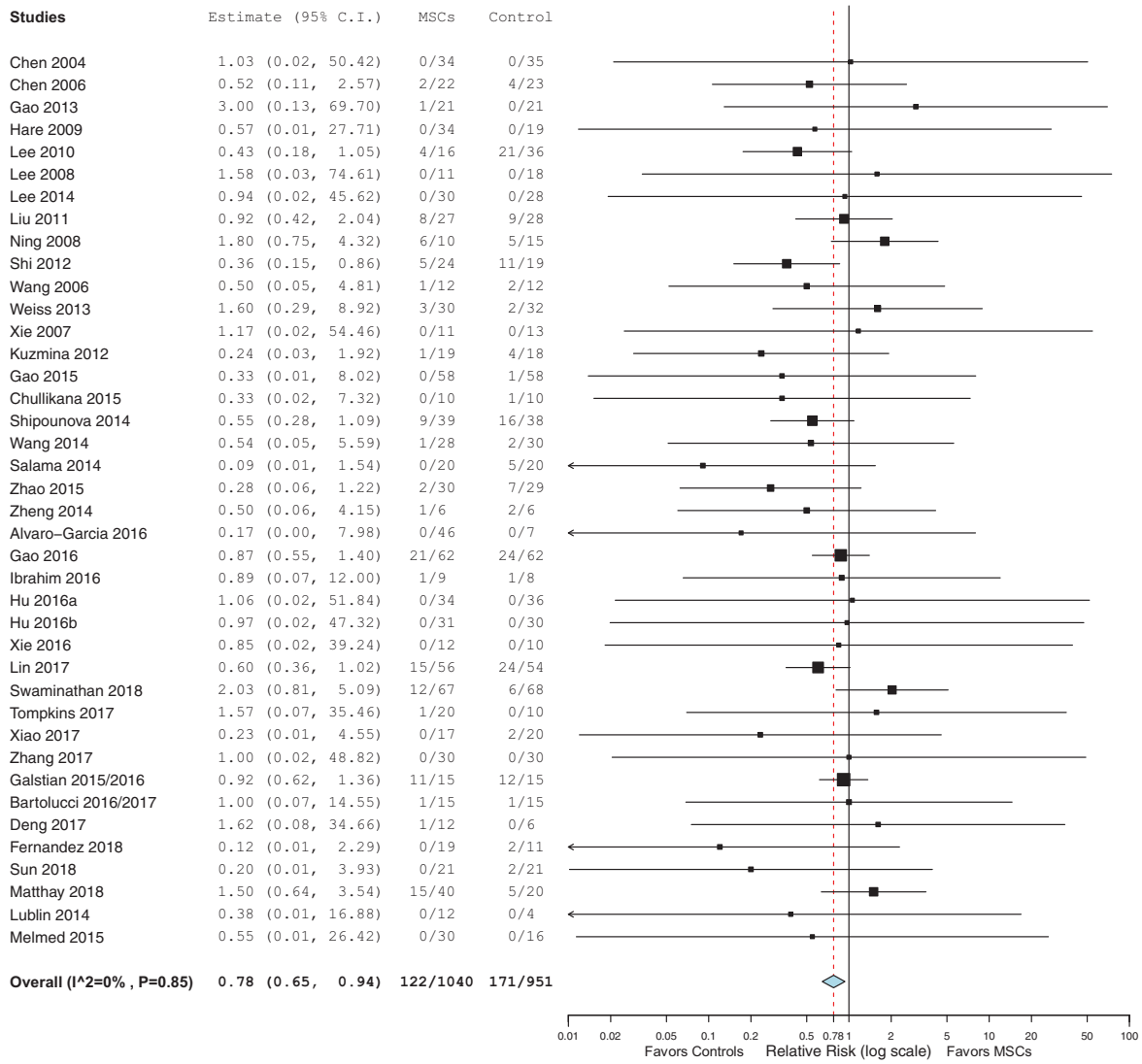


Fig. 2. Continued

**Table 2**  
Risk of bias assessments (expanded detail provided in Supplementary Table 2).

Author/Year	Selection bias		Performance bias			Reporting bias		Other Bias	
	1-Random sequence generation	2-Allocation concealment	3-ROB due to blinding: patients & personnel	4- ROB due to blinding: outcome assessor	5-Attrition: Incomplete outcome data	6-Selective outcome reporting	Registered Protocol (Y/N)	Apriori Sample Size Calculation for Primary Outcome in Methods	Industry or Biotech Sponsored
<b>Cardiovascular</b>									
Chen et al., 2004	Yellow	Yellow	Yellow	Green	Green	Green	Red	Red	Yellow
Chen et al., 2006	Yellow	Yellow	Red	Red	Green	Green	Red	Red	Yellow
Chullikana et al., 2015	Green	Green	Green	Green	Green	Green	Green	Red	Red
Gao et al., 2013	Red	Red	Green	Green	Red	Green	Green	Red	Green
Gao et al., 2015	Green	Green	Green	Green	Green	Green	Green	Green	Green
Hare et al., 2009	Green	Green	Green	Green	Green	Green	Red	Red	Red
Lee et al., 2014	Yellow	Yellow	Red	Green	Green	Green	Green	Green	Red
Wang et al., 2006**	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Red	Yellow
Wang et al., 2014	Yellow	Yellow	Yellow	Yellow	Red	Green	Red	Red	Green
Zhao et al., 2015	Yellow	Yellow	Yellow	Yellow	Green	Green	Red	Red	Green
Bartolucci et al., 2016/2017	Green	Green	Green	Green	Green	Green	Green	Red	Red
Xiao et al., 2017	Yellow	Yellow	Yellow	Green	Green	Green	Red	Red	Yellow
<b>Neurological</b>									
Ibrahim et al., 2016*	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Red	Yellow
Lee et al., 2010	Green	Green	Red	Green	Green	Green	Red	Red	Green
Lee et al., 2008	Green	Green	Red	Red	Red	Red	Red	Red	Green
Lee et al., 2012	Green	Green	Green	Green	Green	Green	Green	Green	Green
Xie et al., 2007**	Yellow	Yellow	Yellow	Yellow	Green	Yellow	Yellow	Red	Yellow
Xie et al., 2016	Yellow	Yellow	Red	Red	Green	Green	Green	Red	Green
Tsang et al., 2017	Yellow	Yellow	Yellow	Yellow	Green	Red	Green	Red	Green
Fernandez et al., 2018	Green	Green	Green	Green	Green	Green	Green	Green	Green
Kim et al., 2018*	Yellow	Yellow	Yellow	Yellow	Green	Yellow	Green	Red	Red
Lublin et al., 2014	Green	Green	Green	Red	Green	Green	Red	Green	Red
<b>Oncological/hematological</b>									
Gao et al., 2016	Green	Green	Green	Yellow	Green	Green	Green	Green	Green
Liu et al., 2011	Yellow	Yellow	Red	Red	Green	Green	Red	Red	Green
Ning et al., 2008	Green	Yellow	Red	Red	Green	Yellow	Red	Red	Green
Kuzmina et al., 2012	Yellow	Yellow	Yellow	Yellow	Green	Green	Red	Red	Green
Shipounova et al., 2014	Green	Yellow	Yellow	Yellow	Green	Green	Green	Red	Green
<b>Endocrine</b>									
Carlsson et al., 2015	Green	Green	Red	Red	Green	Green	Green	Red	Green
Hu et al., 2013	Green	Green	Green	Yellow	Green	Green	Red	Red	Green
Skyler et al., 2015	Green	Green	Red	Red	Green	Green	Green	Green	Red
Hu et al., 2016	Green	Green	Green	Yellow	Green	Green	Red	Red	Green
<b>Renal disease</b>									
Swaminathan et al., 2018	Red	Green	Green	Yellow	Green	Green	Green	Green	Red
Korotkov et al., 2018*	Yellow	Yellow	Red	Red	Yellow	Yellow	Yellow	Yellow	Yellow
Sun et al., 2018	Green	Green	Red	Yellow	Green	Green	Green	Green	Green

(continued)

Liver disease									
Xu et al., 2014									
Salama et al., 2014									
Suk et al., 2016									
Shi et al., 2012									
Lin et al., 2017									
Zhang et al., 2017									
Shi et al., 2017									
Respiratory									
Weiss et al., 2013									
Zheng et al., 2014									
Matthay et al., 2018									
Infectious									
Galstian et al., 2016*									
Immune-deficient/auto-immune/inflammatory									
Zhang et al., 2013									
Alvaro-Garcia et al., 2016									
Hu et al., 2016									
Deng et al., 2017									
Zhang et al., 2018									
Arturo et al., 2017*									
Panes et al., 2017*									
Yang et al., 2018									
Melmed et al., 2015									
Other									
Tompkins et al., 2017									
Green= low risk of bias; Yellow= unclear risk of bias; Red= high risk of bias; *Abstract form only; **Foreign language text only									

**Table 3**  
Comparison of 2012 versus 2019 Safety Outcomes and Quality of Safety Reporting Findings.

Safety Outcomes	2012 SafeCell SR		2018 SafeCell SR Update	
	# of RCTs*	Findings (RR, 95% CI)	# of RCTs*	Findings (RR, 95% CI)
Infusional toxicity- non-fever	4/8	2.01 (0.34–11.77)	32/55	1.16 (0.70–1.91)
Infusional toxicity- fever	4/8	9.28 (2.02–42.71)	19/55	2.48 (1.27–4.86)
Infection	4/8	1.09 (0.61–1.94)	27/55	0.99 (0.81–1.21)
Malignancy or ectopic tissue formation	4/8	2.21 (0.85–5.74)	19/55	0.93 (0.60–1.45)
Mortality	8/8	1.22 (0.71–2.10)	40/55	0.78 (0.65–0.94)
Thrombotic or embolic events	4/8**	2.71 (0.86–8.48)	24/55	1.14 (0.67–1.95)
<b>Quality of Safety Reporting</b>	# of RCTs*	Findings (%)	# of RCTs*	Findings (%)
A priori plan to monitor adverse events	3/8	37.5%	43/55	78.2%

\* That reported the adverse event.

\*\* Original review did not report on this outcome, but event rate is inserted for comparison purposes.

death was significantly reduced in the MSC group in three clinical populations (cardiovascular, neurological, and liver disease), and with autologous, umbilical and freshly cultured MSCs. The sensitivity analysis which excluded RCTs published in abstract form only did not affect the strength or direction of the pre-specified pooled adverse event estimates (see Table 4).

A description of all reported serious adverse events (pre-specified and not pre-specified in our review) and their relatedness to study treatment in the MSC or control group is also provided in Supplementary Table 4. Of all reported serious adverse events (SAEs), a total of 1

SAE in the control group (ventricular tachycardia post-infusion in a trial that administered study drug intravenously) [21] and 3 SAEs in the MSC group (treatment related fever [47], in-stent thrombosis with death and acute coronary artery occlusion [26], the latter two of which were also associated with intra-coronary injection of study drug) were considered related to study treatment. Four other SAEs in the MSC group (grade 1 anaphylactoid reaction [69], gastric ulcer perforation [70], hypersensitivity reaction [70], and anal cancer [70]) were also judged to be possibly related to study treatment [70]. None of the included RCTs were ended prematurely due to safety concerns.

**Table 4**  
Post-hoc sensitivity analysis of Safety Outcomes Reporting Findings in all studies versus only full-text publications.

Safety Outcomes	All studies		Only full-text publications	
	# of RCTs*	Findings (RR, 95% CI)	# of RCTs*	Findings (RR, 95% CI)
Infection	23/55	0.99 (0.81–1.21)	22/55	0.94 (0.76–1.17)
Mortality	40/55	0.78 (0.65–0.94)	38/40	0.74 (0.60–0.92)

\* That reported the adverse event.

A total of 43 (78.2%) of the 55 RCTs reported an *a priori* plan to monitor safety [18,20–23,26–35,38–40,42–44,46,47,49–51,53,55–60,62,63,65,67–72]; 20 (36.4%) of the RCTs also reported an *a priori* plan to monitor for expected adverse events to be monitored [26,29–32,35,38–40,42,46,49,50,53,55–58,63,68] (see Supplementary Table 4). Forty-five (81.8%) RCTs provided an *a priori* description of follow-up frequency for adverse events [18,20–35,38–40,42–44,47–53,55–60,62,63,65–70,72].

When comparing the pre-specified adverse event profile from 2012 compared to our updated systematic review, the risk of fever is the safety outcome that remains significantly associated with MSC administration (see Table 3). There now appears to be a reduction in the risk of death in association with MSC therapy. In comparison to 2012, our updated review found that more of the included RCTs reported an *a priori* plan to monitor for the occurrence of adverse events (37.5% versus 78.2%, respectively).

Thirty-five (63.6%) of the 55 RCTs included at least one efficacy outcome as a primary endpoint [21,24–26,28–31,35,36,38,39,41–47,49,52–55,57–61,63,64,66,67,70,71] where the remaining RCTs focused on safety alone. Of the 36 RCTs that reported efficacy outcomes, 23 (41.8%) found that MSCs were efficacious in at least one of the primary efficacy outcomes [24,28–31,35,38,43,44,46,47,49,52–54,58–60,64,66,67,70,71]. A more detailed description of each RCT's primary and secondary endpoints and their respective findings is provided in Supplementary Table 5.

#### 4. Discussion

In our updated systematic review that now includes over 40 additional RCTs and over 2000 additional patients, we continue to detect no associations between MSC treatment and the development of non-fever acute infusional toxicity, infection, or malignancy, nor did we detect associations between MSC treatment and the development of thrombotic or thrombo-embolic events. There does continue to be a significant association between MSC administration and reported fever. However of the 19 RCTs ( $n = 880$  patients) that reported on fever, only six were reported as serious, albeit all in MSC treated patients. In contrast, with an increase in the number of RCTs and patients in our updated review, the risk of death is now significantly reduced in the MSC as compared to the control group. In our updated review we also found that the approach to safety reporting was improved as many more authors reported an *a priori* plan to monitor for safety (78.2% versus 35.5%) and none of the trials were ended pre-maturely due to safety concerns. The findings of our updated review should provide additional assurance to researchers, clinicians, regulators, and patients and families that the administration of MSCs continues to appear safe.

Our systematic review will require future updates as scientists continue to unravel the multitude of mechanisms of actions associated with the cells, as the sources and origins of MSCs expand, and the manufacturing process and the development of second generation MSC products evolve. To illustrate, recent *in vitro*, pre-clinical, and clinical data has found that MSCs can express or increase secretion of proteins associated with coagulation (ex: tissue factor, thrombin anti-thrombin complexes) and with reports of thromboses

[10–14]. Depending on the clinical population this potential pro-coagulant effect could result in a beneficial or harmful clinical effect. In our updated review, we began to address this concern with the inclusion of thrombotic/thromboembolic events as a pre-specified adverse event category. Our findings suggest that these incident events reported in the included RCTs are rare (31 events in 24 RCTs and 1112 patients studied), were reported in both study groups ( $n = 17$  and 14 in the MSC and control groups respectively) and were not significantly associated with administration of MSCs. Although a significant association was not detected, it is likely that these events will be rare and as such we encourage investigators to *a priori* plan to monitor and report on these events to enable the detection of future thrombotic safety signals.

In contrast to our review from 2012, we found that safety reporting was improved in that more investigators reported an *a priori* plan to monitor for adverse events (78.2% versus 35.5% respectively). Serious adverse events that were reported as related to or as possibly related to study treatment (either in the MSC or control group) ( $n = 8$  out of 2634 patients studied) were very rare. This could be because these events are indeed rare or because it can be challenging if not impossible to attribute an event to study treatment, especially when the event does not occur during or shortly after completion of the infusion. To address this challenge in adverse event reporting, we sought to capture and synthesize pre-specified adverse events and any other SAE, irregardless of relatedness to study treatment in each of the RCTs. Even using this approach, safety signals other than fever generation were not detected.

A significant impediment to understanding whether MSCs are efficacious and safe relates to the quality of trial design and transparent reporting. Of the 55 included RCTs, only six trials met all six criteria for low risk of bias whereas none of the RCTs from the 2012 review met all six criteria. Although an improvement from 2012, it is important for investigators to address these risk of bias elements at the design phase of these clinical trials to maximize the internal validity of their research findings. With regard to MSC characterization, only seven trials reported on all three Dominici criteria [16] which aim to provide minimal and standardized criteria to define a MSC. Furthermore, only 29 of the included trials (52.7%) reported some measure of MSC viability during the manufacturing process and even fewer ( $n = 8$ , 14.5%) reported on a measure of MSC potency or functionality. We strongly assert that it is critical for investigators to transparently report on MSC characteristics, potency and viability in order to help readers, researchers, health regulators, and the community to better understand why a given trial may have succeeded or failed to meet study endpoints and with the ultimate aim to help move the field forward.

Our systematic review has several strengths. We included a transparent search strategy, pre-defined a set of adverse events that were clinically relevant to MSC administration, and reported on all SAEs that were and were not identified as part of our *a priori* event categories irregardless of relatedness to study treatment to provide the most comprehensive and up to date evaluation of the safety profile of MSC therapy. Our review also has limitations. Six of the RCTs were published in abstract form only and as such contained limited information to populate in our review. However, we included these trials

so that the readership is aware of them and can further evaluate the efficacy and safety of study results when the full trials are published. Furthermore, the strength or direction of our pooled *a priori* adverse outcome estimates were not influenced by removal of studies that were published in abstract form only. As in our 2012 review, we pooled incident adverse events from RCTs from diverse adult clinical populations, MSC characteristics and MSC manufacturing in an effort to obtain signals for harm. However, to begin to address this diversity and due to the increased number of included RCTs in this review, we conducted several *a priori* derived sub group analyses to examine for heterogeneity in our *a priori* derived adverse event estimates and acknowledged that these analyses should be considered hypothesis generating. Only a few of the included trials (10.9%) met all six low risk of bias criteria which threatens the internal validity of the study findings from the perspectives of both safety and efficacy and we strongly encourage investigators to address these biases at the design stage and during the conduct of these RCTs. Finally, pooling efficacy outcomes for all of the included RCTs was not feasible within the scope of this safety review. However, in an attempt to provide some measure of efficacy information for the readership, we summarized the primary and secondary efficacy endpoints and associated results descriptively in Supplementary Table 5.

In conclusion, our review provides a systematic examination for incident adverse events related to the use of MSCs. Aside from fever, we did not identify any significant reported safety signals. Results from our systematic review provide further assurance to readers, investigators, health regulators, and our patients and communities that, with this updated evidence, MSC therapy continues to appear safe.

### Declaration of Competing Interests

LM reports grants from CIHR, OIRM and SCN during the conduct of this study. DJS and SHJM reports affiliations with Northern Therapeutics Inc., outside the submitted work. BH reports prior honoraria from Cornerstone Research Group for the provision of methodologic advice related to systematic review and meta-analysis, outside the submitted work. KRW reported grants for CIHR, outside the submitted work. No other authors have any affiliations to report in relation to this study.

### Acknowledgments

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### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2019.100249](https://doi.org/10.1016/j.eclinm.2019.100249).

### Appendix 1. Search strategy

#### Medline

Database: Ovid MEDLINE(R) ALL (1946 to September 23, 2019)  
Search Strategy:

1. exp Mesenchymal Stem Cells/ (33,741)
2. exp Mesenchymal Stem Cell Transplantation/ (10,675)
3. exp Multipotent Stem Cells/ (36,140)
4. exp Mesenchymal Stromal Cells/ (33,741)
5. (mesenchymal adj3 (stem or stroma\$1 or progenitor\*) and cell \$1).tw. (47,264)
6. (mesenchymal adj2 (stem or stromal or progenitor or multipotent or bone marrow or adipose or placenta\*)).tw. (47,000)
7. (MSC or MSCs or ADMSC or ADMSCs or BM-MSC or BM-MSCs or BMD-MSC or BMD-MSCs or BMDMSC or BMDMSCs).tw. (29,267)
8. ((multipotent or multi-potent) adj3 (stroma\$1 cell\$1 or stem cell\$1)).tw. (4521)
9. marrow stroma\$1 cell\$1.tw. (6975)
10. (colony-forming unit fibroblast\* or CFU-F\$1).tw. (844)
11. Mesoderm/cy (5710)
12. or/1-11 (71,482)
13. (ae or to or po or co).fs. (3,812,354)
14. (safe or safety).ti.ab. (723,468)
15. side effect\$.ti.ab. (236,090)
16. ((adverse or undesirable or harm\* or serious or toxic) adj3 (effect\* or reaction\* or event\* or outcome\*)).ti.ab. (494,272)
17. exp product surveillance, postmarketing/ (14,736)
18. exp adverse drug reaction reporting systems/ (7274)
19. exp clinical trials, phase iv/ (289)
20. exp poisoning/ (154,008)
21. exp substance-related disorders/ (269,073)
22. exp drug toxicity/ (111,624)
23. exp abnormalities, drug induced/ (14,457)
24. exp drug monitoring/ (19,962)
25. exp drug hypersensitivity/ (44,888)
26. (toxicity or complication\* or noxious or tolerability or hypersensitivity or abnormal\*).ti.ab. (1,919,833)
27. exp Postoperative Complications/ (525,174)
28. exp Intraoperative Complications/ (51,079)
29. or/13-28 (6,186,659)
30. 12 and 29 (10,413)
31. randomized controlled trial.pt. (489,730)
32. controlled clinical trial.pt. (93,263)
33. randomized.ab. (454,901)
34. placebo.ab. (200,750)
35. drug therapy.fs. (2,140,942)
36. randomly.ab. (318,366)
37. trial.ab. (476,933)
38. groups.ab. (1,955,339)
39. (clinical trial\* or multicenter study).pt. (747,085)
40. or/31-39 (4,746,525)
41. exp animals/ not humans/ (4,617,450)
42. 40 not 41 (4,135,721)
43. 30 and 42 (1815)
44. **limit 43 to yr="2012 -Current" (1346)**

### Cochrane

Search Name: McIntyre-Lauralynn-MSCS-Safety\_2019-09-25  
Date Run: 25/09/2019 19:04:03  
Comment:  
ID Search Hits

1. MeSH descriptor: [Mesenchymal Stem Cells] explode all trees 97
2. MeSH descriptor: [Mesenchymal Stem Cell Transplantation] explode all trees 183
3. MeSH descriptor: [Multipotent Stem Cells] explode all trees 99



4. (mesenchymal NEAR/3 (stem or stroma\$1 or progenitor\*)):ti,ab,kw 1250
5. (mesenchymal NEAR/2 (stem or stromal or progenitor or multipotent or bone marrow or adipose or placenta\*)):ti,ab,kw 1392
6. (MSC or MSCs or ADMSC or ADMSCs or BM-MS or BM-MSs or BMD-MS or BMD-MSs or BMDMS or BMDMSs):ti,ab,kw 989
7. (((multipotent or multi-potent) NEAR/3 (stroma\$1 cell\$1 or stem cell\$1))):ti,ab,kw 29
8. (marrow stroma\* cell\*):ti,ab,kw 281
9. (colony-forming unit fibroblast\*):ti,ab,kw 11
10. (cfu f):ti,ab,kw 155
11. (cfu fs):ti,ab,kw 2
12. MeSH descriptor: [Mesoderm] this term only and with qualifier (s): [cytology - CY] 3
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 1951
14. MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, toxicity - TO, poisoning - PO, complications - CO] 167,040
15. (safe or safety):ti,ab,kw 237,637
16. (side effect\*):ti,ab,kw 144,447
17. (((adverse or undesirable or harm\* or serious or toxic) NEAR/3 (effect\* or reaction\* or event\* or outcome\*)):ti,ab,kw 272,736
18. MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 194
19. MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 87
20. MeSH descriptor: [Clinical Trial, Phase IV] explode all trees 0
21. MeSH descriptor: [Poisons] explode all trees 31
22. MeSH descriptor: [Substance-Related Disorders] explode all trees 13,818
23. MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 3356 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees 47
24. MeSH descriptor: [Drug Monitoring] explode all trees 1685
25. MeSH descriptor: [Drug Hypersensitivity] explode all trees 955
26. (toxicity or complication\* or noxious or tolerability or hypersensitivity or abnormal\*):ti,ab,kw 291,059
27. MeSH descriptor: [Postoperative Complications] explode all trees 37,166
28. MeSH descriptor: [Intraoperative Complications] explode all trees 4123
29. #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 583,508
30. #13 AND #30 1141
31. **Limit from 2012 – September 25, 2019 1044**

**Web of Science – January 31, 2018**

5  
**169**  
 #4 AND #3  
 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI  
 Timespan=2017-2018  
 Edit  
 # 4  
 1207  
 ((TS= ((Mesenchymal) OR (Multipotent Stem Cell\*) OR (Stromal Cell\*))) AND DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper))  
 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI  
 Timespan=2017-2018  
 Edit  
 # 3

19,021  
 #2 OR #1  
 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI  
 Timespan=2017-2018  
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 # 2  
 13,741  
 ((CF=((American Heart Association) OR (American College of Cardiology) OR (Transcatheter Cardiovascular Therapeutics) OR (European Society of Cardiology) OR (International Society for Heart Research) OR (World Congress of Cardiology) OR (Heart Failure Society of America) OR (American Society of Hematology) OR (American Society for Blood and Marrow) OR (European Bone Marrow Transplant) OR (International Society of Cellular Therapy) OR (International Society for Experimental Hematology) OR (European Respiratory Society) OR (American Thoracic Society) OR (American College Chest Physicians) OR (British Thoracic Society) OR (Canadian Respiratory Conference) OR (Asia-Pacific Society of Respiriology) OR (International Union against Tuberculosis and Lung Disease) OR (Aspen Lung Conference) OR (American Academy of Neurology) OR (American Association of Neurologists) OR (European Federation of Neurological Societies) OR (World Federation of Neurology) OR (European Committee for Treatment and Research in Multiple Sclerosis) OR (Society of Critical Care Medicine) OR (International Symposium on Intensive Care and Emergency Medicine))) AND DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper))  
 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI  
 Timespan=2017-2018  
 Edit  
 # 1  
 16,768  
 ((Source = (Blood) OR Source = (Biology of Blood and Marrow Transplantation) OR Source = (Bone Marrow Transplantation) OR Source = (Cytotherapy) OR Source = (Experimental Hematology) OR Source = (Circulation) OR Source = (Journal of the American College of Cardiology) OR Source = (European Heart Journal) OR Source = (Journal of Molecular and Cellular Cardiology) OR Source = (Circulation) OR Source = (Journal of Cardiac Failure) OR Source = (European Respiratory Journal) OR Source = (American Journal of Respiratory and Critical Care Medicine) OR Source = (Chest) OR Source = (Thorax) OR Source = (Canadian Respiratory Journal) OR Source = (Respirology) OR Source = (International Journal of Tuberculosis and Lung Disease) OR Source = (Neurology) OR Source = (Annals of Neurology) OR Source = (European Journal of Neurology) OR Source = (Multiple Sclerosis) OR Source = (Critical Care Medicine) OR Source = (Critical Care))) AND DOCUMENT TYPES: (Meeting Abstract OR Proceedings Paper))  
 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI  
 Timespan=2017-2018

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