Clinical Lessons of MSC Therapy Over the Past 15 Years: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: Despite increasing clinical investigations in emphasizing the safety of MSC therapy in different populations with different diseases, recently, no article overall reviewed the side events in all populations.

Aim: To evaluate the safety of MSC therapy in all populations receiving MSC therapy and explore the potential heterogeneities influencing the clinical application of MSC.

Methods: The databases of PubMed, Embase, Web of Science and Scopus were searched from onset until March 1st, 2021.

Results: All side events were displayed as odds ratio (OR) and 95% CI (confidential intervals). Totally, 62 randomized clinical trials (RCTs) that enrolled 3546 participants diagnosed with various diseases (about 20 kinds of diseases) treated with intravenous or local implantation vs placebo, or no treatment were included. All studies were high quality, neither serious publication bias nor serious adverse events (such as death and infection) were discovered across included studies. The pooled analysis demonstrated that MSC administration was extremely associated with transient fever [OR, 3.65, 95% CI: 2.05 to 6.49, $p<0.01$], administration site conditions [OR, 1.98, 95% CI: 1.01 to 3.87, $p=0.05$], constipation [OR, 2.45, 95% CI: 1.01 to 5.97, $p=0.05$], fatigue [OR, 2.99, 95% CI: 1.06 to 8.44, $p=0.04$], and sleeplessness [OR, 5.90, 95% CI: 1.04 to 33.47, $p=0.05$]. Interestingly, MSC administration trended to lower rather than boost the incidence rate of arrhythmia [OR, 0.62, 95% CI: 0.36 to 1.07, $p=0.09$].

Conclusions: Conclusively, MSC administration was safe in different populations compared with the other placebo modalities.

Introduction

Mesenchymal stromal cells (MSCs), a class of highly heterogeneous cells, that can be isolated from bone marrow, adipose, umbilical cord, and placenta, are primarily discovered in 1974 by Friedenstein[1]. Over these years, exogenous MSCs are amazingly found to have a therapeutic effect on many diseases (e.g., myocardial infarction, liver cirrhosis, limb ischemia and spinal cord injury)[2-5].

Deferring from multipotent stem cells, the potency of MSCs is restricted but MSCs can be induced into osteoblasts, chondrocytes and adipocytes in vitro. Universally, MSCs exert their favourable effects by immunomodulatory regulation and paracrine manners[6, 7]. Clinically, MSCs have been applied in many refractory diseases, such as cerebral palsy[8], spinal cord injury[9] and systemic lupus erythematosus[10]. However, MSCs easily flock together forming the core of the clot and leading to vascular disorders. Additional, MSCs are tumorigenic as a result of their reproductive capacity and potentially cause acute or chronic immunogenicity of the cells themselves as foreign matters[11-13]. A large number of studies, most of which are small samples, have been investigating the safety of MSCs transplantation, but no article overall reviews these studies to characterize the side events closely associated with MSCs administration over the past 9 years.

We performed this systematic review and meta-analysis to identify all treatment-related side events concerning MSCs administration and explore the safety of MSCs in clinical utilization.

Methods And Materials

Search results

This meta-analysis was limited to published articles assessing the safety of MSC administration and was performed by searching PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Library databases (from inception to 1stt March 2021). The search strategy is as follows: ((MSC [title/abstract]) OR (mesenchymal stem cell [title/abstract]) OR (Wharton's jelly [title/abstract])) AND ((safety [title/abstract]) OR (side event [title/abstract]) OR (side effect [title/abstract]) OR (adverse event [title/abstract]) OR (adverse effect [title/abstract])). The reference lists of the included articles were also browsed to identify potential studies. To perform a comprehensive search, we did not limit the "study type"; retrospective studies were excluded during the study selection process. The detailed database search strategy is provided in **Additional file 1**.

Article selection

Primarily, duplicates of all articles were excluded. Two participants initially screened all titles and abstracts to preclude articles that were irrelated to our research objectives. Then, we carefully read the full manuscripts and selected the eligible ones.

Eligibility criteria

The selection process strictly obeyed the PICOS (participants, interventions, comparison, outcome and study) principles and these principles were listed in **Table 1**.

Data extraction

Two skilled reviewers (YW and HX Y) independently extracted data from all articles according to pre-set criteria. We retrieved 12 characteristic entries from the original articles, including author, year, and study type, location, disease, and cell type, administration method, study phrase, and language, dose, follow-up day, and the NO. of the patient in each group. Conflicts were resolved in consultation with a third referee.

Quality assessment

Risk of bias in individual study and across studies were performed by using the Cochrane Collaboration's tool for assessing the risk of bias.

Outcome definition

Totally, we reported 17 side events appeared during MSC therapy, and of which 9 events (death, infection, diarrhea, central nervous system disorders, arrhythmia, urticaria/dermatitis, vascular disorders) were classified into major events, and 8 events (anemia, constipation, metabolism disorders, fatigue, nausea, seizure, sleepless, vomiting) were classified into minor events. One event would be considered as a major event if it was reported by more than 5 studies or life-threatening judged by our clinician; otherwise, it should be sorted into a minor event. Among these events, some events were not specifically clinical symptoms but referred to a series of correlated symptoms, such as central nervous system disorders, vascular disorders, infection, arrhythmia, administration site conditions, metabolism and nutrition disorders. These side events were redefined in **Table 2**. Other entries were retrieved from the original definitions.

Statistical analysis

All data were synthesized by using R software version 4.0.3 (University of Auckland, New Zealand). All results presented in this article were presented as odds ratio (OR) with 95% CIs for outcomes. A random-effect model was used to analyze the data when heterogeneity was significant (p<0.05 or I^2>50%); otherwise, a fixed-effect model was used. Publication bias was tested by Egger's and Begg's tests were utilized to analyze the publication bias of the included articles with R software version 4.0.3 (meta package). Subgroup analysis was also conducted to seek potential heterogeneous factors.

Results

The items of this meta-analysis were reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (**Additional file 2)**.

Article selection process

Approximately, 2078 articles were identified after the initial search. 1898 irrelevant articles were eliminated through browsing titles and abstracts, and 118 articles were excluded due to unexpected outcomes and interventions. Finally, 62 clinical trials, including 2 trials from the reference list, were taken into the analysis even if the elimination of 2 systematic reviews (**Figure 1**).

Baseline of included studies

The data were purified from studies performed over the past 11 years. Only 2 studies were prospective and the rest were randomized controlled trials (RCTs) ranging from study phrase 1/2 to study phrase 3. Asia was ranked first in the NO. of studies, and then North America and Europe. The MSC used in these studies were mainly isolated from bone marrow, adipose and umbilical cord. The injection dose ranged from 4×10^7 to 1.2×10^9 cells. The follow-up day was from 6 months to 2 years.

Pooled analysis of all studies

Totally, 62 clinical trials, containing populations with different characteristics, were included into analysis (**Figure 2A**). We discovered that MSC administration would not induce major side events, such as vascular disorders (1.17, 95% CI: 0.52-2.62, p=0.70), urticaria/dermatitis (0.93, 95% CI: 0.93-1.07, p=0.70), central nervous system disorders (1.13, 95% CI: 0.61-2.12, p=0.69), diarrhea (0.90, 95% CI: 0.49-1.63, p=0.73), death (0.99, 95% CI: 0.66-1.49, p=0.96), infection (1.03, 95% CI: 0.70-1.53, p=0.87). However, our analysis demonstrated that transient fever (3.65, 95% CI: 2.05-6.49) will occur within 48 hours if people receive MSC administration. Meanwhile, MSC injections also potentially caused administration site conditions (1.98. 95% CI: 1.01-3.87, p<0.01). Populations trended to benefit from receiving MSC therapy as they were like to have a lower rate of arrhythmia (0.62, 95% CI: 0.36-1.07, p=0.05).

As for minor side events, MSC presumably caused sleeplessness (5.90, 95% Ci: 1.04-33.47, p=0.05), constipation (2.45, 94% CI:1.01- 5.97, p=0.05), and fatigue (2.99, 1.06-8.44, p=0.05). Other minor side events, including, anemia (1.25, 95% CI: 0.39-4.07, p=0.71), metabolism and nutrition disorders (0.69, 95% CI: 0.20-2.43, p=0.56), nausea (2.00, 95% CI: 0.81-4.93, p=0.13), seizure (2.27, 94% CI: 0.79-6.56, p=0.13), vomiting (1.87,95% CI: 0.22-7.94, p=0.40), were non-significantly intimate to MSC treatment (**Figure 2B**).

Subgroup analysis of all studies

Subsequently, we dissected potential factors, including administration (method), age, methodology (analysis) of the article, cell type, population (disease), gender proportion, location, study phrase and publication date (year), influencing the major side events **(Figure 3A**). We identified that the non-significance of death, infection and diarrhea, which were not treatment-related side events of MSC therapy, were not altered in the slightest by any of the analyzed factors. MSC therapy was demonstrated to reduce the incidence of arrhythmia in the population with the age <60 years (p<0.01), PP analysis (p=0.01) and beyond 5 years (p<0.01). Despite the non-significant central nervous system disorders (head and dizziness) proved by pooled analysis, AD-MSC (p<0.01), placenta MSC (p<0.01) and uc-MSC (p<0.01) were more easily to cause headache and dizziness. Meanwhile, a population with degenerative joint diseases (p<0.01) and digestive diseases (p<0.01) could have headache and dizziness symptoms while receiving MSC implantation. Urticaria significantly occurred when the data were analyzed by PP analysis exclusively (p<0.01). As for vascular disorders, Asian people more easily had vascular disorders (p<0.01) after MSC treatment. Administration site conditions preferred to occur in populations with the age < 60 years (p=0.02), heart related diseases (p=0.01), the male proportion >60% (p=0.08), in study phrase 1/2 (p=0.01), and within 5 years (p=0.05). Even though transient fever was conspicuously associated with MSC treatment, populations with the age > 60 years (p=0.86), the male proportion < 60% (p=0.7), receiving local implantation (p=0.76), in North America (p=0.82) and study phrase 1 (p=0.15), had a lower risk of transient fever over the period MSC of therapy.

In terms of the minor side events, only five side events, including anemia, constipation, metabolism and nutrition disorders and nausea, were analyzed (**Figure 3B**). Similarly, the interactions between the 9 predicted factors and seldomly reported side events were dissected. Contrary to pooled analysis, neither constipation nor fatigue was a significant side event in these subgroup analyses. Similar to pooled analysis, both metabolism and nutrition disorders and nausea were non-impacted by these factors and were non-significant side events. Interestingly, we found that populations with the age < 60 years trended to have transient anemia (p=0.07) post-MSC treatment.

Pooled analysis of high-quality studies

After the elimination of low-quality articles (Kim 2018; Koh 2012; Lee 2017; Lin 2012; Oh 2018; Shi 2012; Sponer 2018; Wang 2006; Wang 2014; Wang 2016; Xie 2007; Zeng 2015; Xiao 2012; Skyler 2015), only seven major side events and one minor side event left (**Figure 4**). We merely found a close relationship between transient fever (3.08, 95% CI: 1.67-1.48, p=0.01) and MSC administration. Other side events, such as metabolism and nutrition disorders (0.49, 95% CI: 0.11-2.10, p=0.33), infection (1.05, 95% CI: 0.59-1.61, p=0.83), death (0.99, 95% CI: 0.66-1.48, p=0.96), arrhythmia (0.58, 95% CI: 0.33-1.03, p=0.06), central nervous system disorders (0.96, 95% CI: 0.49-1.88, p=0.91), vascular disorders (0.85, 95% CI: 0.30-2.45, p=0.77), and administration site conditions (2.15, 95% CI: 0.98-4.73, p=0.06) were not significantly impacted by MSC administration.

Subgroup analysis of high-quality studies

We examined whether the potential factors significantly influenced the terminal outcomes (7 major side events) reported by high-quality studies (**Figure 5**). MSC administration would not directly lead to death, death, central nervous disorders (headache and dizziness), or vascular disorders. Populations with the age <60 years (p<0.01), receiving BMSC injection (p=0.04), in study phrase 3 (p=0.04), and beyond 5 years (p<0.01) seemed to have a lower incidence of arrhythmia and benefit from MSC administration. When it came to transient fever, MSC administration would not trigger fever in populations with the age > 60 years (p=0.86), the male proportion <60% (p=0.70), from Europe (p=0.82), in study phrase 2 (p=0.15), beyond 5 years (p=0.11), and receiving local implantation (p=0.76).

Sensitivity analysis

Leave-one meta-analysis was performed for administration site conditions, arrhythmia, death, dermatitis, diarrhea, transient fever, infection, central nervous system disorders, and vascular disorders, and fatigue, metabolism and nutrition disorders, anemia, constipation, and nausea from all studies (**Additional file 3-16**), and for administration site conditions, arrhythmia, death, transient fever, infection, central nervous system disorders, and vascular disorders from high-quality studies (**Additional file 17-23**).

Publication bias and article quality

We assessed the article quality by using the Cochrane Collaboration's tool for assessing the risk of bias (**Figure 6**). We concluded that most studies' design was suitable and high quality. Only 14 studies were considered as low quality because they had more than two entries marked as high risk and less than four entries evaluated as low risk. There was performance bias, selection bias, detection bias, and attrition bias potentially lowering the integral quality of included studies. Furtherly, we tested the publication bias for administration site conditions, arrhythmia, death, dermatitis, diarrhea, transient fever, infection, central nervous system disorders, and vascular disorders (**Additional file 24-32**) from all studies. Publication bias for administration site conditions, arrythmia, death, fever, infection, central nervous system disorders, and vascular disorders (**Additional file 33-39**) from high-quality studies were conducted as well.

Discussion

Summary of evidence

The association between the side events and MSC administration is first reported by M. Lalu[14] and the association between MSC administration and the infusional toxicity, organ system complications, infection, death was not explored due to limited clinical researches. However, aside from these side events above, which were analyzed in this systematic review, more side events are described in recent trials with the expansion of population. In addition to transient fever, which is the most frequently reported by researchers, other side events such as constipation, fatigue, administration site conditions and sleeplessness can be induced by MSC administration as well. As for arrhythmia, MSC seems to benefit patients with cardiac diseases.

We were unable to discover the conspicuous association between MSC administration and the rest side events (vascular disorders, urticaria/dermatitis, dizziness/headache, diarrhea, infection, death, anemia, metabolism and nutrition disorders, nausea, seizure, and vomiting). Neither, there was direct proof suggesting that the MSC administration is tumorigenic. Up to date, the malignance of MSC was merely reported by Ning[15] despite the potential of tumorigenesis of MSC.

After the elimination of the low-quality studies, eight side events were actually analyzed, including metabolism and nutrition disorders, infection, fever, and death, arrhythmia, dizziness/headache, vascular disorders, and administrations. Among these side events, transient fever was exclusively associated with MSC administration. Arrhythmia and administration site conditions trended to be significant after MSC administration. Other side events had no relevance to MSC administration.

Furtherly, we analyzed each side events in various sub-populations to dissect by which side event was determined. We discovered that age, gender proportion, location, and year, analysis, disease, study phrase, cell type, and administration method were the main factors impacting the final side event. Take the definite side event fever as an instance, the aged were not susceptible to MSC administration and this may be because of blunt reactions of the organism to acute

inflammation triggered by MSC[16]. The female more easily suffers from transient fever and the estrogen level is under serious doubt[17]. The population in North America less undergo transient fever compared to other regional populations and this may suggest the racial discrepancy of MSC administration.

Strengths and weakness

This meta-analysis removes studies of low-grade evidence (retrospective study, single-arm study, and case) and included 62 prospective studies. All results suggest the strong association between MSC administration and transient fever, and administration site conditions. Moreover, more side events that were not reported before (e.g., anemia constipation and vomiting) are gradually being discovered[18-20]. Theoretically, the side events of MSC administration should be under stringent surveillance in case of occurrence of other side events that were not reported before along with the expansion of clinical trials. We also notice that the longest follow-up is 5 years, which may be a shorter time considering the fact that we are using cell products. We should be cautious that longer term events in the farther future possibly impend.

Our research has limitations. First, we synthesized the data across heterogeneous disease states. Despite subgroup analysis of disease, it was difficult to distinguish whether one side event was specifically disease-related owing to the limited number of studies. Second, some studies presented their data in the form of abstract prior to formal publication which may impose an unknown effect on the interpretation of the outcomes. These data are difficult for us to obtain because many ongoing trials are in the middle stage and the performers would not like to release these data. Third, serval side events are merely comprehensive conceptions rather than specific clinic symptoms and we contend that it is important to record these obscure descriptions (e.g., metabolism and nutrition disorders and gastrointestinal dysfunction). Fourth, we are not informed of whether cell dose is closely associated with these side events as a result of the lack of dose-dependent trials. If possible, a Bayesian network meta-analysis should be conducted to explore the puzzlement. Finally, tumorigenesis, which theoretically exists in MSC therapy, is rarely reported by researchers. And this interesting point should raise our attention.

Conclusions

We summarized all side events potentially related to the application of MSC and no serious safety signals other than transient fever, administration site conditions, sleeplessness, and constipation were discovered. Many population characteristics, including age, analysis, cell type, disease, gender, location, study phrase, year, and administration method possibly impacted the occurrence of one side event. The safety of MSC administration should be under sustained observation despite the innovative therapy appears safe.

Abbreviations

OR, odds ratio; CI; confidential intervals; RCTs, randomized clinical trials; MSCs, mesenchymal stromal cells; PICOS, participants, interventions, comparison, outcome and study; NO., number; PRISMA, Systematic Review and Meta-Analysis; pp, per-protocol; ESC, embryonic stem cell; NSC, neuronal stem cell; h-IPS, human induced pluripotent stem cell; PSVT, paroxysmal supraventricular tachycardia; VT, ventricular tachycardia；COPD, chronic obstructive pulmonary disease; BMSC, bone marrow-derived human umbilical cord mesenchymal stromal cell; AD-MSC, adipose-derived human umbilical cord mesenchymal stromal cell; NA, not available.

Declarations

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Authors' contributions

Conceptualization, YC S and Y W; Methodology, Y W and HX Y; Investigation, Y W and HX Y; Software, Y W; Formal analysis, Y W and HX Y; Writing—original draft, Y W and YC S; Writing—review & editing, YC S; Funding acquisition, HX Y; Supervision, Y W and YC S. All authors read and approved the final manuscript.

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Consent for publication

The publication of this manuscript is approved by all authors.

Competing interests

No conflicts of interests are declared.

Consent to participate

Not applicable.

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Tables

Table 1. Inclusion and exclusion principles.

Principle	Inclusion criteria	Exclusion criteria
Population	Any populations including the healthy people and the diseased people	NA
Intervention	Using MSC as treatment, regardless of the administration methods (e.g. local implannation and injection) and sources of MSC (e.g. from the adipose, bomarrow marrow and gum)	Using NSC, ESC, olfactory neuron, schwann cell, h-IPS and stem cell from body fluids (e.g. saliva, urine, serum and tears) etc but MSC as interventions
Comparison	Placeebo treatment, non-treatment or basic treatment both utilized in the control and the intervention groups	Merely using traditional treatment (surgery and drug) in the control group but not in the intervention group
Outcome	1) Any side events associated with MSC treatment; 2) one side event reported by more than one study; 3) regardless of the efficacy of MSC therapy for any diseases	No side events reported
Study	1) RCT; 2) prospective controlled study	1) Case report (series); 2) single arm study; 3) retrospective controlled study; 4) cross controlled study; 5) study protocol

ESC, embryonic stem cell; MSC, mesenchymal stromal cells ; NSC, neuronal stem cell; h-IPS, human induced pluripotent stem cell; NA, not available.

Table 2. Outcome definition.

Side event	Definition
Vascular disrders	1) Vascular thrombosis including venous and aterial thrombosis; 2) vasculitis
Arhythmia	1) PSVT; 2)VT; 3) atrial fibrillation; 4) ventricular fibrillation
Central nervous disorders	1) dizzy; 2) headache
Diarrhea	Non-infectious diarrhea
Infection	1) non-injection site infection; 2) respiratory system infection; 3) urinary system infection; 4) biliary tract; 5) digestive tract and spontaneous peritonitis
Fever	Transient fever (low-grade, 37.3-38°C) within 48 hours
Administration site conditions	1) Injection site bleeding; 2) injection site swelling; 3) injection site pain; 4) injection site itchy; 5) injection site infection
Anemia	Defined by Hb<110g/L
Metabolism and nutrition disorders	Mainly refer to malnutrition

PSVT, paroxysmal supraventricular tachycardia; VT, ventricular tachycardia.

Table 3. Study characteristics

Author	Year	Study type	Location	Disease	Cell	Administration	Analysis	Study phrase	Language	Dose
Emadedin	2018	RCT	Iran	Knee osteoarthritis	BMSC	Local implanation	pp	1/2	English	40×10^6 cells
Gao	2013	RCT	China	Acute myocardial infarction	BMSC	Intracoronary injection	PP	3	English	$(3.08 \pm 0.52) \times 10^6$ cell
Gupta	2013	RCT	India	Critical limb ischemia	BMSC	Local injection	ITT	1/2	English	2×10^6 cells/kg
Lee	2010	RCT	South Korea	Ischemic stroke	BMSC	Intravenous injection	PP	3	English	1×10^8 cells
Zollino	2018	RCT	Italy	Chronic leg ulcers	BMSC	Local injection	PP	2	English	NA
Weiss	2013	RCT	USA	COPD	BMSC	Intravenous injection	PP	3	English	100 × 1 cells
Xiao	2017	RCT	China	Dilated cardiomyopathy	BMSC	Intracoronary injection	PP	3	English	$(4.9 \pm 1 \times10^8$ ce
Hare	2009	RCT	USA	Acute myocardial infarction	BMSC	Intravenous injection	PP	3	English	0.5, 1.6, and 5 $\times10^6$ cells/kg
Huang	2018	RCT	China	Cerebral palsy	uc-MSC	Intravenous injection	PP	3	English	5×10^7 cells
Centeno	2014	RCT	USA	Knee osteoarthritis	BMSC	local implanation	PP	3	English	75% BMSC, 12.5% PRP, an 12.5% PBS
FernaÂndez	2018	RCT	Spain	Multiple sclerosis	AD-MSC	Intravenous injection	ITT	1/2	English	1×10^6 cells/kg 4×10^6 cells/kg
Vangsness	2014	RCT	USA	Partial medial meniscectomy	BMSC	local implanation	PP	3	English	50 × 10 cells
Lin	2017	RCT	China	Liver failure	BMSC	Intravenous injection	PP	3	English	1.0-10×10^5 cells/kg
Molendijk	2015	RCT	USA	Crohn's disease	BMSC	Local implanation	PP	3	English	1-9×10 cells
Tompkins	2017	RCT	USA	Aging frailty	BMSC	Intravenous injection	PP	2	English	100-200×10 cells
Li	2013	RCT	China	Leg ischemia	BMSC	Local implanation	PP	3	English	1×10^7 cells/m
Lee	2007	RCT	South Korea	Multiple system atrophy	BMSC	Intravenous injection	PP	3	English	4×10^7 cells
Jaillard	2020	RCT	France	Ischemic stroke	BMSC	Intravenous injection	ITT	3	English	100-300×10 cells
Mathiasen	2019	RCT	Denmark	Ischaemic heart failure	BMSC	Intramyocardial injection	ITT	3	English	0.2 mL
Bartunek	2016	RCT	USA	Ischaemic heart failure	BMSC	Intramyocardial injection	ITT	3	English	24×10^6 cells
Bartunek	2013	RCT	Belgium	Heart failure	BMSC	Intramyocardial injection	PP	3	English	600 -12 $\times 10^6$ ce
Powell	2012	RCT	USA	Critical limb ischemia	BMSC	Local implanation	PP	3	English	0.5 ml
Olivera	2017	RCT	Brazil	Pulmonary emphysema	BMSC	Intravenous injection	ITT	1	English	10^8 cell

Sponer	2018	Prospective study	Czech	Femoral bone defects	BMSC	Local implanation	PP	3	English	(15± 4.5 × 10^6 ce
Wang	2016	RCT	China	knee osteoarthritis	uc-MSC	Local implanation	PP	3	Chinses	2 -3×10 cells
Teraa	2015	RCT	Netherlands	Limb ischemia	BMSC	Local implanation	ITT	3	English	144-500 ×10^6 ce
Bhansali	2016	RCT	USA	Diabetes mellitus	BMSC	Intravenous injection	PP	3	English	1×10^6 cells /kg
Panes	2016	RCT	Spain	Crohn's disease	AD-MSC	Intralesional injection	ITT	3	English	120×10 cells
Averyanov	2019	RCT	Russia	Idiopathic pulmonary fibrosis	BMSC	Intravenous injection	PP	3	English	2 × 10^8 cells
Skyler	2015	RCT	USA	Type 2 diabetes	BMSC	Intravenous injection	ITT	3	English	0.3-2×1 cells/kg
Shi	2010	RCT	China	Chronic liver failure	BMSC	Intravenous injection	PP	3	English	0.5 ×10 cells/kg
Lublin	2014	RCT	USA	Multiple sclerosis	Placenta-Derived MSc	Intravenous injection	ITT	3	English	600×10 cells
Zhang	2011	RCT	China	Liver cirrhosis	uc-MSC	Intravenous injection	PP	3	English	0.5 × 10 cells/kg
Winkler	2018	RCT	Germany	Hip arthroplasty	Placenta-Derived MSc	Local implanation	ITT	3	English	1.5-3.0×10^8 cells
Kim	2018	RCT	South Korea	Myocardial infarction	BMSC	Intracoronary injection	PP	3	English	(7.2 ± 0.90) × 10^7 cell
Tan	2012	RCT	China	Kidney transplants	BMSC	Intravenous injection	PP	3	English	1-2×10^6/k
Hauzeur	2017	RCT	Belgium	Osteonecrosis	BMSC	Local implanation	PP	3	English	50 ml
Noriega	2017	RCT	Spain	Intervertebral disc regeneration	BMSC	Local implanation	PP	3	English	25×10^6 cells
Gao	2015	RCT	China	Myocardial infarction	uc-MSC	Intracoronary injection	PP	3	English	6 × 10^6 cells
Ascheim	2014	RCT	USA	Left ventricular assist device patients	BMSC	Intramyocardial injection	PP	3	English	25×10^6 cells
Koh	2012	RCT	South Korea	Knee osteoarthritis	BMSC	Local implanation	PP	3	English	1.89×10 cells
Berry	2019	RCT	USA	Amyotrophic lateral sclerosis	BMSC	Local implanation	PP	2	English	125 × 1 cells
Chullikana	2014	RCT	India	Acute myocardial infarction	BMSC	Intracoronary injection	PP	1/2	English	6.0×10^7 cells
Oh	2018	RCT	Republic of Korea	Amyotrophic lateral sclerosis	BMSC	Intrathecal injections	ITT	3	English	1×10^6 cells/kg
Hess	2017	RCT	USA	Acute ischaemic stroke	BMSC	Intracerebral injection	ITT	2	English	1200 ×1 cells
Bartolucci	2017	RCT	Chile	Heart failure	uc-MSC	Intravenous injection	PP	1/2	English	1×10^6 cells/kg
Wang	2017	RCT	Australia	Anterior cruciate ligament reconstruction patients	BMSC	local implanation	ITT	3	English	150 ×10 cells
Wang	2014	RCT	China	Lyocardial infarction	BMSC	Intracoronary injection	PP	3	English	1×10^8 cells/m
Gu	2020	RCT	China	Cerebral palsy	uc-MSC	Intravenous injection	PP	3	English	4.5-5.5 × 10^7 cell

Zhang	2016	RCT	China	Liver transplantation	uc-MSC	Intravenous infusion	PP	3	English	1.0 × 1(cells/ k(
Suk	2016	RCT	South Korea	Alcoholic cirrhosis	BMSC	Hepatic arterial injection	PP	2	English	5×10^7 cells
Zheng	2014	RCT	China	Acute respiratory distress syndrome	AD-MSC	Intravenous infusion	PP	3	English	1×10^6 cells/kg
Matas	2019	RCT	Chile	Knee Osteoarthritis	AD-MSC	Local implanation	PP	1/2	English	2×10^7 c(
Wang	2006	RCT	China	Dilatedcardiomyopathy	BMSC	intracoronary injection	ITT	3	Chinses	8×10^7 cells
Lin	2012	RCT	China	Liver fibrosis	uc-MSC	Intravenous infusion	ITT	3	Chinses	0.5-1 ×1 cells/kg
Xie	2007	RCT	China	Spinal cord injury	BMSC	Intrathecal injection	ITT	3	Chinses	20.56-58.87 $\times10^8$ ce
Xiao	2012	RCT	China	Myocardial infarction	BMSC	Intracoronary injection	ITT	3	Chinses	1-10×1(cells
Erpicum	2018	RCT	Belgium	Kidney transplantation	BMSC	Intravenous injection	PP	1/2	English	2×10^6 cells/kg
Shadmafar	2017	Prospective study	China	Liver fibrosis	uc-MSC	Hepatic artery injection	ITT	3	English	(42 ± 4) $\times10^6$ ce
Zeng	2015	RCT	Iran	Rheumatoid arthritis	BMSC	Local implanation	PP	1/2	Chinese	6.0-7.0×10^7 cells/kg
Ning	2008	RCT	China	Hematologic malignancy	BMSC	Intravenous injection	NA	NA	English	1.0-2.0 $\times10^6$ cells/kg
José	2020	RCT	Spain	Knee osteoarthritis	BMSC	Local implanation	ITT	2	English	100 ×1(cells

uc-MSC, human umbilical cord mesenchymal stromal cell; BMSC, bone marrow-derived human umbilical cord mesenchymal stromal cell; AD-MSC, adipose-derived human umbilical cord mesenchymal stromal cell; PP, per-protocal; ITT, intention to treat; RCT, randomized clinical trial; COPD, chronic obstructive pulmonary disease.

Figures

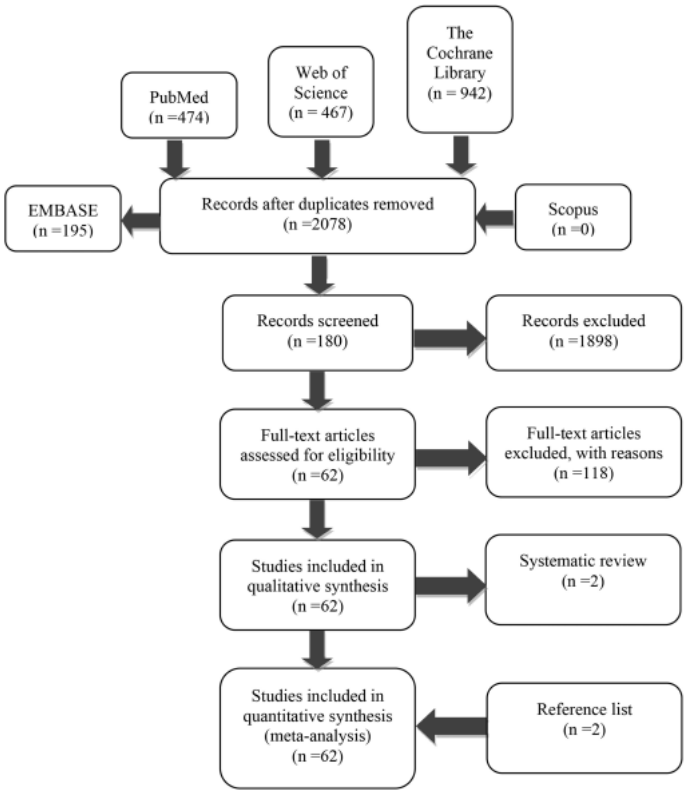

Figure 1

Article selection process

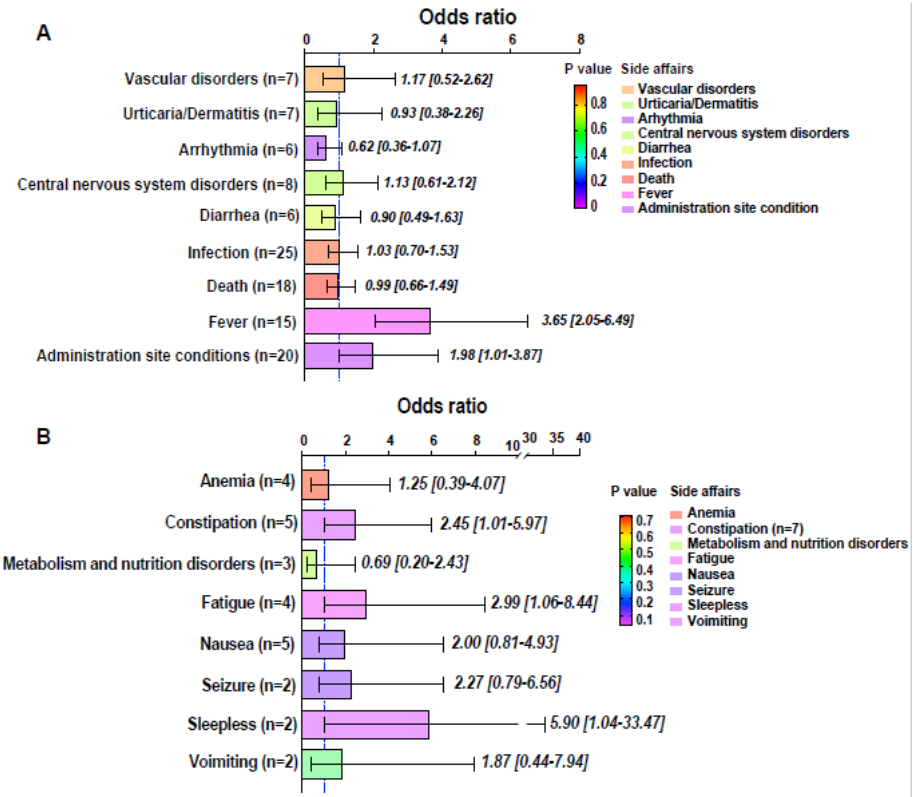

Figure 2

Bar plot for events of all articles. This figure depicted the significance of major events (A) and minor events (B) of all included articles. The OR value of each pooled event is presented as mean and 95% confidential intervals. The significance of each event is marked by different colors. The more the color approaches the bottom of the p value bar, the occurrence of the event is significant. Scarcely reported event (reported by single one article) was not collected and considered as minor event.

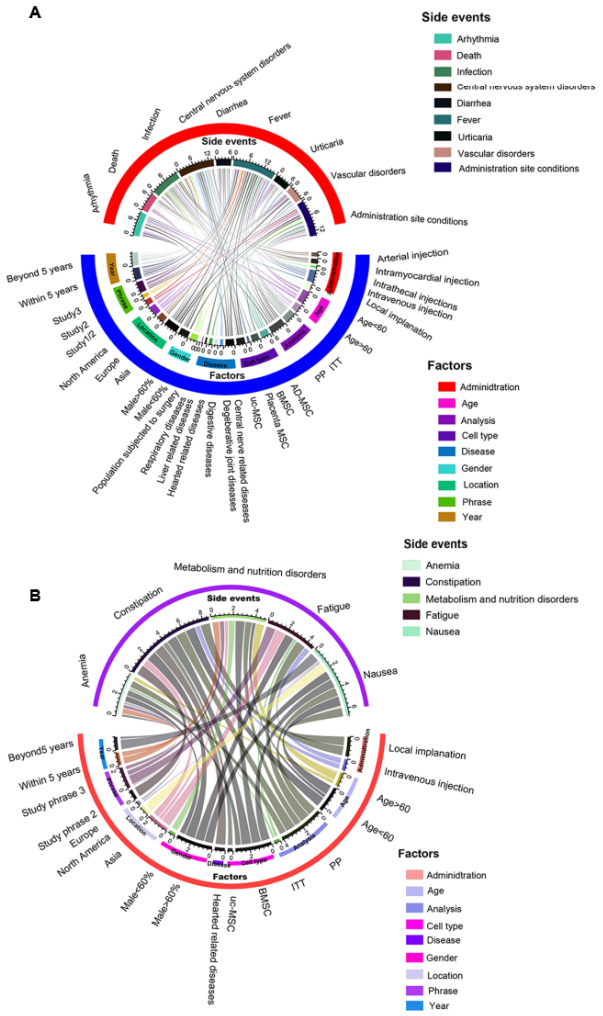

Figure 3

Bar plot for events of high-quality articles. This figure depicted the significance of major events (A) and minor events (B) of high-quality articles. The OR value of each pooled event is presented as mean and 95% confidential intervals. The significance of each event is marked by different colors. The more the color approaches the bottom of the p value bar, the occurrence of the event is significant. Scarcely reported event (reported by single one article) was not collected and considered as minor events.

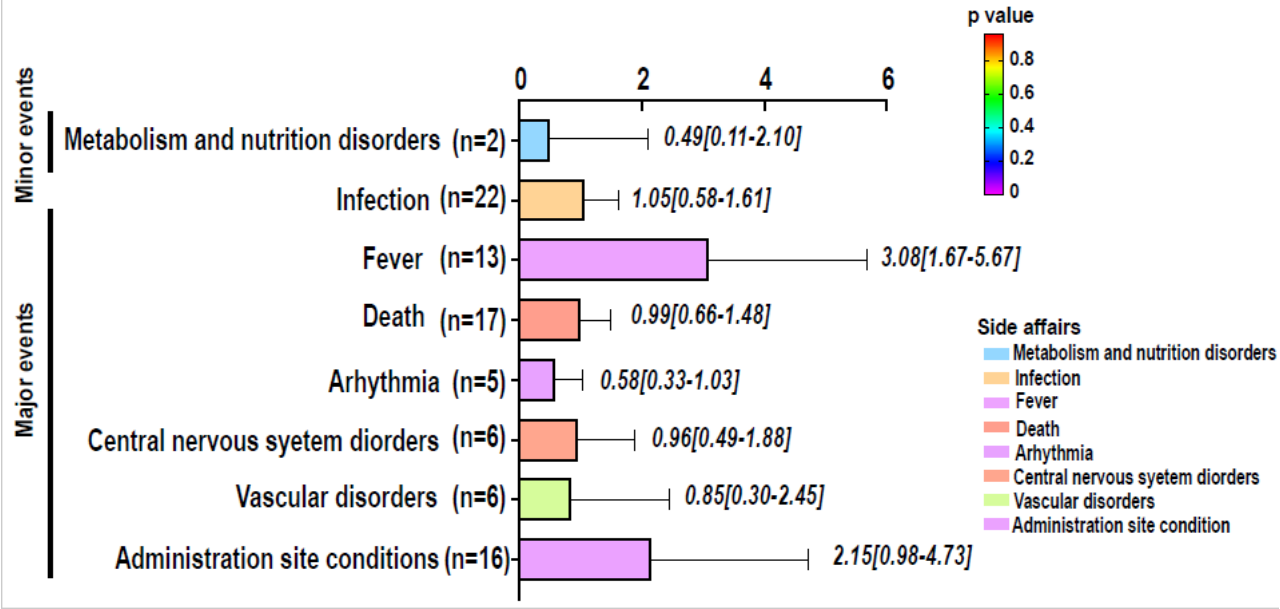

Figure 4

Circular net-work map for events of all articles. This figure depicted potential factors impacting major events (A) and minor events (B) of included articles. Each line connecting 2 color blocks indicates a potential interaction between the side affair and the factor. If no interaction exists between the factor and the side affair, the value was denoted as 1 by default. The area of the connecting line is proportional to the value of 1 minus p. The larger of the connecting line area, the likely the side affair is to be impacted by the factor.

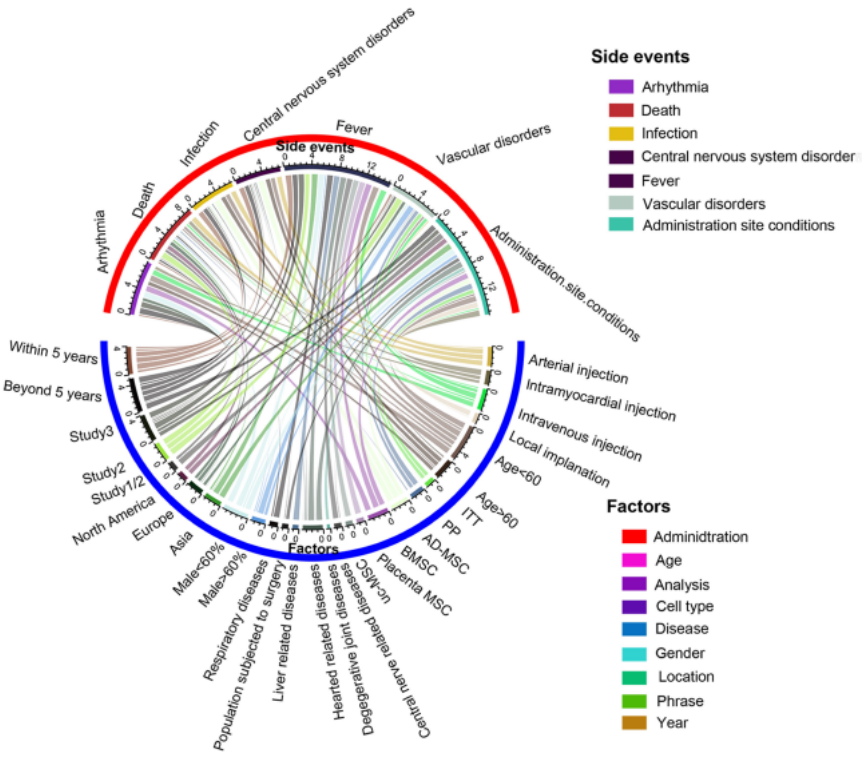

Figure 5

Circular net-work map for events of high qualities articles. This figure depicted potential factors impacting major events (A) and minor events (B) of high-quality articles. Each line connecting 2 color blocks indicates a potential interaction between the side affair and the factor. If no interaction exists between the factor and the side affair, the value was denoted as 1 by default. The area of the connecting line is proportional to the value of 1 minus p. The larger of the connecting line area, the likely the side affair is to be impacted by the factor.

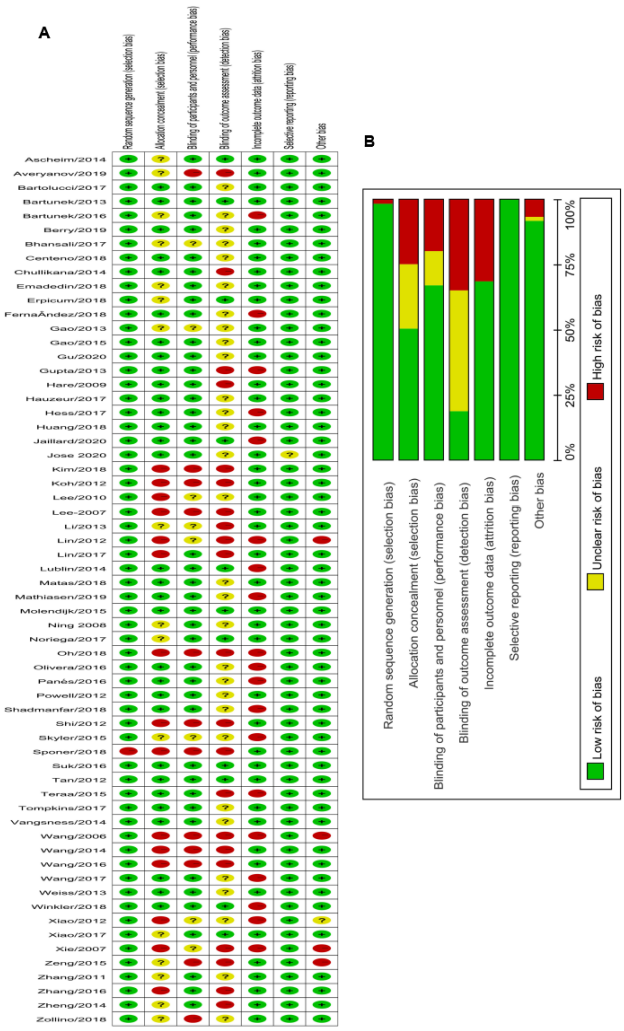

Figure 6

Quality assessment of included articles. A. Quality assessment of each article. B. Pooled result of quality assessment.

Supplementary Files

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