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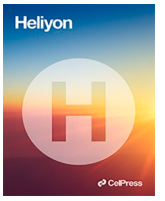

Research article

Effects of bone marrow mesenchymal stromal cells-derived therapies for experimental traumatic brain injury : A meta-analysis

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ABSTRACT

Background: Bone-marrow-derived mesenchymal stromal (stem) cells [also called MSC(M)] and their extracellular vesicles (EVs) are considered a potentially innovative form of therapy for traumatic brain injury (TBI). Nevertheless, their application to TBI particularly remains pre-clinical, and the effects of these cells remain unclear and controversial. Therefore, an updated meta-analysis of preclinical studies is necessary to assess the effectiveness of MSC(M) and MSC (M) derived EVs in clinical trials.

Methods: The following databases were searched (to December 2022): PubMed, Web of Science, and Embase. In this study, we measured functional outcomes based on the modified neurological severity score (mNSS), cognitive outcomes based on the Morris water maze (MWM), and histo-pathological outcomes based on lesion volume. A random effects meta-analysis was conducted to evaluate the effect of mNSS, MWM, and lesion volume.

Results: A total of 2163 unique records were identified from our search, with Fifty-five full-text articles satisfying inclusion criteria. A mean score of 5.75 was assigned to the studies' quality scores, ranging from 4 to 7. MSC(M) and MSC(M) derived EVs had an overall positive effect on the mNSS score and MWM with SMDs −2.57 (95 % CI -3.26; −1.88; $p < 0.01$) and - 2.98 (95 % CI -4.21; −1.70; $p < 0.01$), respectively. As well, MSC(M) derived EVs were effective in reducing lesion volume by an SMD of - 0.80 (95 % CI -1.20; −0.40; $p < 0.01$). It was observed that there was significant variation among the studies, but further analyses could not determine the cause of this heterogeneity.

Conclusions: MSC(M) and MSC(M) derived EVs are promising treatments for TBI in pre-clinical studies, and translation to the clinical domain appears warranted. Besides, large-scale trials in animals and humans are required to support further research due to the limited sample size of MSC(M) derived EVs.

Abbreviations: CAMARADES, collaborative approach to meta-analysis and review of animal data from experimental studies; EVs, extracellular vesicles; IA, intra-arterial; IC, intracardiac; ICV, intracranial; IR, retro-orbital injection; IV, intravenous; MSC(M): bone marrow called mesenchymal stromal (stem) cells, mNSS:modified neurological severity score; MWM, cognitive outcomes based on the Morris water maze; PRISMA, preferred reporting items for systematic review and meta-analyses; SD, standard deviation; SE, standard error; SMD, standardized mean difference; TBI, traumatic brain injury.

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1. Introduction

Traumatic brain injury (TBI) is becoming a significant concern for the public health due to the high mortality and morbidity rates associated with such injuries [1]. The disease affects people of all ages, especially adolescents and young adults [2]. After a traumatic brain injury, most people experience a long period of cognitive impairment, motor impairment, and neuropsychiatric deficits [3]. TBI causes both primary and secondary brain damage [4]. The following is the mechanism by which brain damage occurs after a TBI. A direct mechanical impact caused the major injury, which occurred approximately minutes following a traumatic brain injury [5]. In addition, secondary brain injury may be caused by apoptosis, elevated levels of calcium within the cells, excitotoxicity, elevated levels of calcium within the cells, oxidative stress, inflammation, and mitochondrial dysfunction [6]. Presently, treatment is limited to supportive management, such as monitoring intracranial pressure, maintaining cerebral perfusion, and maximizing cerebral oxygenation. The aim is to reduce the extent of secondary injury. Although tremendous efforts have been made to understand the pathophysiology process of TBI, these approaches have not proven sufficiently effective in promoting functional recovery following TBI. Accordingly, it is important to explore novel therapeutic approaches from the perspective of evidence-based medicine.

In recent years, stem cell transplantation has attracted considerable attention. Researchers have demonstrated the effectiveness of mesenchymal stem cells (MSCs) and their ability to improve recovery following strokes, Alzheimer's disease, and brain injuries [7,8]. A variety of tissues can be used to produce this cell, including bone marrow, umbilical cord, olfactory mucosa, placenta, and adipose tissue. In preclinical studies, the mesenchymal stromal stem cells (MSCs) derived from the bone marrow [also called as MSC(M)] have been studied extensively in comparison with other MSCs [9]. There has been evidence to suggest that MSC(M) and MSC(M) derived extracellular vesicles (EVs) diminish neuroinflammation, decrease blood-brain barrier breakdown, and alleviate neurological deficits in animal models of TBI after traumatic brain injury [10–12]. In comparison with other types of MSCs, MSC(M) are easily accessible and associated with fewer immunological reactions [13], as well as being easily reproduced in large quantities, making them suitable for clinical applications [14]. Recently, growing pieces of evidence have emerged to evaluate MSC(M) and MSC(M)-EVs transplantation's effectiveness for TBI, but the administration route, dose, and time window remain controversial.

In the clinical field, systematic reviews and meta-analyses comprise the gold standard for objectively and thoroughly studying interventions [15,16]. Using scientific methods in systematic reviews can provide a more accurate assessment of outcomes in contrast to traditional reviews. Moreover, meta-analyses can provide valuable insight into treatment outcomes, identify research gaps, and contribute to the advancement of medical science [17,18]. In previous meta-analyses, either the approach was applied to all types of MSC therapy [19] or data were not updated [20]. Another meta-analysis in 2016 provided evidence of the beneficial effects of treatment with progenitor cells in animal models of TBI [21]. However, the authors did not perform a meta-analysis of the relevant studies to determine the effectiveness both functionally and histopathologically of MSC(M) transplantation after TBI. Hence, in this article, Our objective was to conduct an updated meta-analysis of MSC(M) particularly and focused on the functional outcome as well as histopathological outcome following TBI in animals.

2. Materials and methods

2.1. Literature search

We identified studies of MSC(M) in in vivo models of TBI by searching the following databases (Web of Science, EMBASE, and PubMed) by December of 2022. The search strategy in detail is shown in Additional file 1. Additionally, we searched the reference lists of the studies that were eligible for inclusion. Furthermore, lists of references of eligible studies were screened to identify any additional relevant publications.

2.2. Inclusion and exclusion criteria

We included all experimental studies that compared MSC(M) and MSC(M) derived EVs to no treatment in rodent models of TBI, characterized by the neurobehavioral score or lesion volume. A list of inclusion criteria was compiled to prevent publication bias: (1) The article should be published in an English-language peer-reviewed journal. (2) Animal studies were performed to determine if MSC (M) and MSC(M) derived EVs were effective in treating TBI, with no restrictions placed on the animal species, weight, gender, sample size, and age of the animal. (3) Measures of outcome that rely on neurobehavioral scores or lesion volumes. (4) Experimental studies with saline, PBS, vehicle, or no treatment as the control group, and with xenogenic or allogeneic or syngeneic MSC(M) therapy as the experimental group, the dose of MSC(M) and MSC(M) derived EVs, as well as the initial duration of treatment, were not restricted. We considered all articles reporting on the same sample as one study. The abstracts were reviewed independently by Chunli Chen and Cuiying Peng, with conflicting comments resolved by a third reviewer (Lite Ge). The exclusion criteria were as follows: (1) Research involving stem cells that have been substantially manipulated, such as stem cells that have been differentiated into mature cells, or stem cells that have been combined with another treatment, or stem cells that have been transfected with genes that are overexpressed or underexpressed. (2) The number of animals, mean outcomes, and standard deviations of each group were not obtained in studies. (3) Studies that untested MSC(M). (4) MSC(M) or MSC(M) derived EVs administered before TBI.

2.3. Data collection

Chunli Chen and Cuiying Peng separately retrieved from the eligible studies the following items. We obtained information from these articles: general study information (year of publication and first author), animal species, type of anesthesia used, number of subjects enrolled, TBI induction method, type of stem cells used and dosage, delivery route, follow-up interval, and a functional outcome based on neurological severity scores (mNSS or Morris water maze (MWM)), histopathological result (lesion volume), and study quality index. Data were extracted from each publication separately when there was more than one experiment or more than one individual comparison in the same article. Data were collected for the longest time every time neurobehavioral tests were conducted at different times. For cases in which the standard deviation (SD) was not provided directly, we calculated the SD by multiplying the standard error (SE) by the square root of the number of participants included in the study. Whenever data were presented only graphically, the mean and standard deviation were calculated from the graphs using GetDataGraph (version 2.26). The data associated with mean and SD are extracted from both the control and treatment groups for each comparison to determine the size of the effect of stem cells. Finally, figures in the text were created using Figdraw software.

2.4. Methodological quality of included studies

According to the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) checklists, the methodological quality of the studies includedwas evaluated in the following manner: (1) peer-reviewed publications. (2) Controlled temperatures were maintained. (3) The treatment group and the control group were assigned randomly. (4) the induction of the TBI model was blinded. (5) the assessment of outcome was blinded. (6) drugs that are used as anesthetics do not possess a marked neuroprotective effect or action such as ketamine. (7) examined an animal model with pertinent comorbidities (diabetic, elderly, or hypertensive). (8) calculation of the number of samples required. (9) Laws about the welfare of animals must be adhered to, and (10) potential conflicts of interest must be disclosed.

2.5. Statistical analysis

Stata software (version 12.1) and R software (version 4.0.2) performed all statistical analyses. Effective sizes were calculated using means, standard deviations, and sample sizes. Continuous variables include standard mean difference (SMD) and 95 % confidence intervals. Random effects models were applied because we hypothesized that between-study and within-study moderators would result in different effect sizes. Comparing the effect size of MSC(M) and MSC(M) derived EVs on the mNSS, MWM, and lesion volume between the treatment and control groups was conducted. Furthermore, if a higher outcome value indicated a more favorable outcome, this value was multiplied by -1. If one study was excluded at a time, we tested for sensitivity to combined effect sizes. Using I^2 statistics, it was possible to estimate the percentage of heterogeneity across the studies. If the I^2 statistic is below 25 %, it indicates small heterogeneity, ranging from 25 % to 50 % indicating moderate heterogeneity, and >50 % represents significant heterogeneity. The funnel plot was used to assess publication bias. Moreover, Egger's test and trim-and-fill methods were applied to evaluate funnel plot asymmetry. Lastly, we conducted a final analysis to stratify the effect size based on the pre-specified subgroups: delivery routes (retro-orbital injection (IR), intracardiac (IC), intravenous (IV), intra-arterial (IA), or intracranial (ICV)), cell sources (autologous, allogeneic, or xenogeneic), species (rat or mouse), model (controlled cortical impact (CCI) or weight-drop model), gender (male or female), time of delivery post-TBI induction ($\leq$24 h, >24 h < 7 D, $\geq$7 D), number of times (repeated doses or single dose), and therapy type (MSC or EV). We performed a Q-test based on variance analysis to determine whether there was a difference between subgroups of studies. All data were analyzed using the $p < 0.05$ statistical significance level, except where noted. Standard 95 % confidence intervals for all results were calculated.

3. Results

3.1. Study selection and characteristics

We identified seven English publications focusing on MSC(M) derived therapy for treating TBI in compliance with preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines [22]. Fig. 1 illustrates the selection process in detail. After reviewing the literature, 2163 potential studies were discovered: 1138 in Web of Science, 1042 in Embase, and 404 in PubMed. There were 138 full-text articles remaining after review and exclusion, of which 65 did not meet the inclusion criteria (Fig. 1). An overall total of 55 studies were included in the meta-analysis) [23–77].

In 2001, Lu et al. published the first study of MSC(M). Since then, the number of publications per year has been increasing, especially in 2013 when the number of publications reached its peak (Fig. 2A & Table 1). Across countries, the largest contribution came from China (n = 24), and the USA (with 20 studies) followed by Spain (n = 4), South Korea (n = 2), Iran (n = 2), Russia (n = 2), and Italy (n = 1) (Fig. 2B). Controlled cortical impact (CCI, n = 37) and weight drop (WD, n = 18) impact injuries were the most frequently used TBI models (Fig. 2C). Among the 53 studies, 36 studies used allogeneic stem cells, 15 studies used xenogeneic stem cells, and 4 studies syngeneic stem cells (Fig. 2C). Among the two main routes of MSC-EV delivery, intravenous injection (IV) (n = 28) and intraventricular injection (ICV) (n = 25) delivery were most commonly used, other options include intraarterial injection (IA) (n = 1), and retro-orbital injection (IR) (n = 1) (Fig. 2C). For the time of delivery post-TBI induction, most studies suggest that MSC(M) or MSC(M) derived EVs are injected within 24 h (including 24 h) (n = 40) of TBI modeling. Rats (n = 43), mainly Wistar (n = 23) or

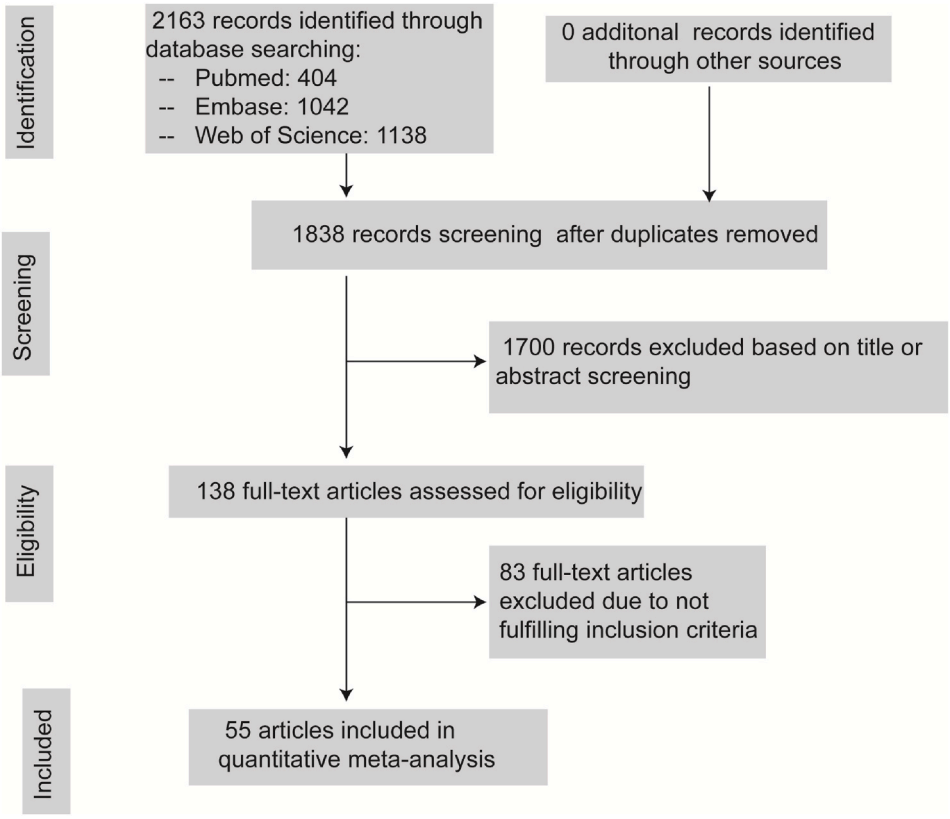

Fig. 1. Flow diagram of literature search and study selection.

Sprague Dawley (n = 19) were used in most of the studies, mice in the remainder (n = 10) (Fig. 2C). Rodents were predominantly male (n = 42) (Fig. 2C). However, only 38.2 % of MSC(M) or MSC (M) derived EVs were characterized by quantification (N = 21), surface marker expression (N = 14, MSC(M) = 9, EVs = 5), differentiation ability for MSC(M) (N = 2), size distribution for EVs (N = 7), morphological analysis for EVs (N = 4) and in most studies (Table S1). Only four studies accurately characterized their EV therapies to meet the MISEV 2018 recommendations. More importantly, most studies failed to demonstrate the presence of EVs by examining negative markers.

3.2. Quality score

Table 2 summarizes the quality assessment of the included studies. The study scores ranged from 4 to 8 following the analysis of each study (Fig. 2D). The studies were all published in peer-reviewed journals with a compliance statement. Among the studies evaluated, only 3.64 % reported calculating the sample size, 78.2 % described assigning randomized treatments, 7.27 % described concealing allocation, and 65.5 % reported blinding the outcome assessment. In addition, 83.6 % of studies avoided using neuroprotective anesthetic agents, 69.1 % mentioned temperature control, as well as 74.5 % disclosed conflicts of interest.

3.3. Sensitivity analysis

Further sensitivity analysis was performed by omitting the order of each study as a way of assessing the robustness of the results. It can be seen from Fig. 3A,B and C that in the pooled analysis of combined effect value.

3.4. Meta-analysis and effect evaluation

A total of 54 studies used the mNSS scores to assess the changes in neurobehavioral function in TBI rodent models. Comparing MSC (M) and EV derived from MSC(M) with the control group, the pooled analysis revealed that MSC(M) and EVs showed better improvement in neurological functions (SMD = −2.57; 95 % CI -3.26; −1.88; Fig. 4A) with statistically significantly heterogeneous among comparisons (I_2 = 91 %, $p < 0.01$). Twenty-one studies used the MWM test to assess the cognitive function changes in TBI animal models. The statistical pooled analysis found a significant effect through the evaluation of escape latency, which is how long it takes an animal to discover the hidden platform (SMD = −2.98, 95 % CI -4.21; −1.70; Fig. 4B). A noticeable heterogeneity was

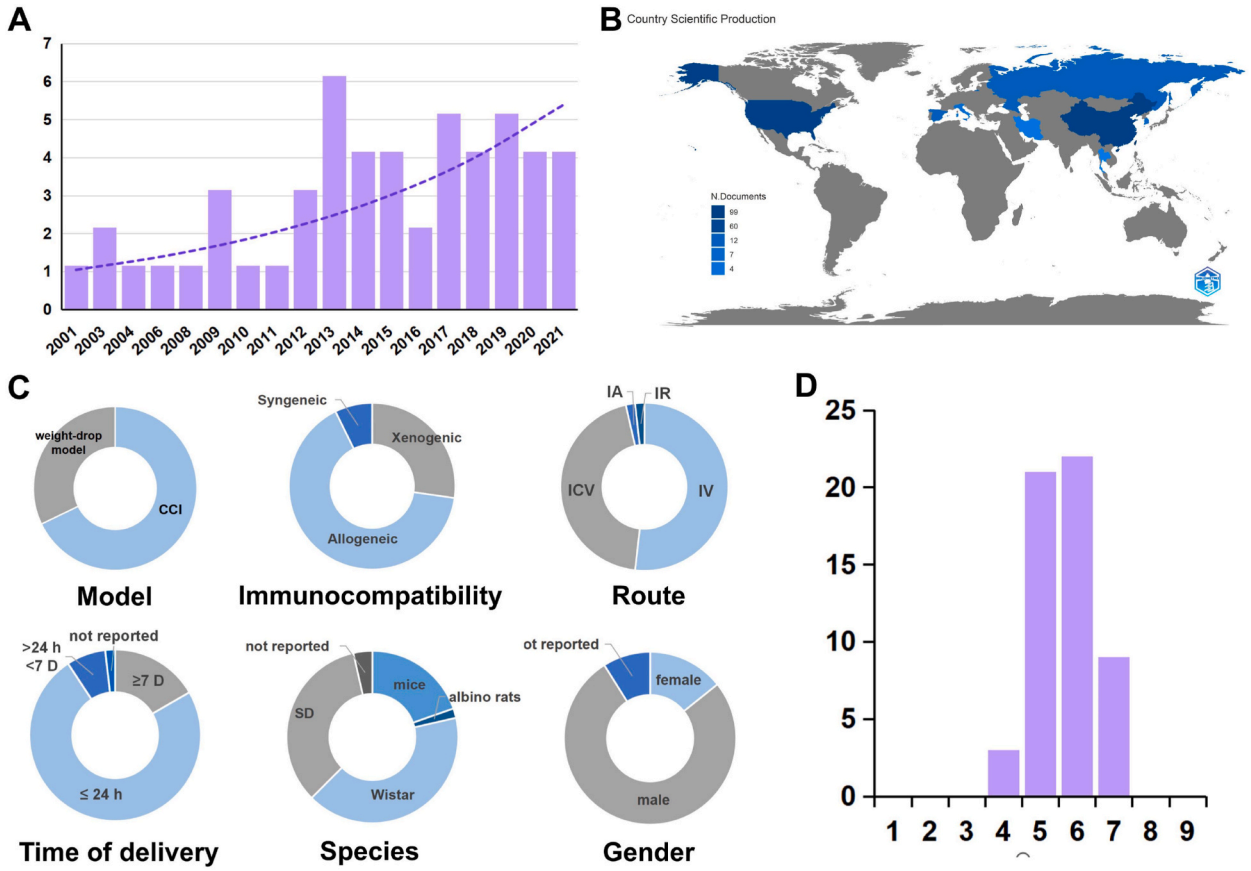

Fig. 2. Characteristics of the 53 studies in the qualitative synthesis, and quality score. A: Number of publications per year. B: World map with a color scale indicating the number of papers published in each country (image adapted from Bibliometrix package in R 4.1.3). C: Pie charts of features of publications related to model, immunocompatibility, delivery route, time of administration, gender, and species. D: Distribution of quality scores.

observed across studies ($I_2 = 90$ %, $p < 0.01$). In addition, twenty-three studies analyzed brain lesion volume. MSC(M) and MSC(M)-derived EVs significantly reduced the brain lesion volume with an SMD of −0.80 (95 % CI -1.20; −0.40; Fig. 4C), with a statistically significant heterogeneity ($I^2 = 69$ %, $p < 0.01$).

3.5. Publication bias

This study evaluated the publication bias of the included studies using funnel plots, indicating that significant publication bias for the mNSS, the MWM test, and the lesion volume (Fig. 5A, B, C), and Egger test results confirmed these findings ($p < 0.01$). After adding the missing studies to the pooled estimation, we recalculated it using the trim-and-fill method. However, there were no significant differences in the overall results (Fig. 5D,E,F), suggesting that there were no "missing" studies.

3.6. Subgroup analysis

An assessment of multiple meta-analysis examined the model type of TBI, the recipient rodents' sex, the recipient rodents'strain, immunocompatibility, the route of administration, and administration time for mNSS(Additional file 2), MWM (Additional file 3), and brain lesion volume (Additional file 4) respectively. For mNSS, based on the stratified analysis no significant differences in effect sizes were observed with respect to type of TBI model ($p = 0.97$) (Fig. S2.1), rodent gender ($p = 0.99$) (Fig. S2.2), donor species ($p = 0.40$) (Fig. S2.3), immunocompatibility ($p = 0.13$) (Fig. S2.4), and therapy type ($p = 0.25$) (Fig. S2.5). However, the route of admission was associated with significant differences in effect sizes ($p < 0.01$) (Fig. S2.6), administration time ($p < 0.01$) (Fig. S2.7), and numbers of times ($p < 0.01$) (Fig. S2.8). For WMM, subgroup analyses showed that no significant differences in effect sizes were observed relative to the model type of TBI ($p = 0.68$) (Fig. S3.1), donor species ($p = 0.31$) (Fig. S3.3), immunocompatibility ($p = 0.22$) (Fig. S3.4), therapy type ($p = 0.68$) (Fig. S3.5) and route of admission ($p = 0.16$) (Fig. S3.6), but significant differences related to the rodent gender ($p < 0.01$) (Fig. S3.2), and administration time ($p < 0.01$) (Fig. S3.7). For brain lesion volume, there was no significant difference in effect sizes observed between all stratified groups including the type of TBI model when conducting the stratified analysis ($p = 0.97$)

Table 1
|Summary of study characteristics of all included articles.

number	title	Author year Country	Species	Strain	Gender	model	MSC (M) or EV	MSC(M) source	Compatibility MSC Dose	Time of delivery post-TBI induction	MSC route
1	Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome	Lu et al. (2001) USA [23]	rats	Wistar	male	CCI	MSC	Allogeneic	2*10^6	6 h , 7 d	IV
2	Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells	Mahmood et al. (2003) USA [24]	rats	Wistar	male	CCI	MSC	Allogeneic	1*10^6/2*10^6	24 h	IV
3	Global test statistics for treatment effect of stroke and traumatic brain injury in rats with administration of bone marrow stromal cells	Lu et al. (2003) USA [25]	rats	Wistar	male	CCI	MSC	Allogeneic	1*10^6/2*10^6/ 4*10^6	24 h	IV
4	Marrow stromal cell transplantation after traumatic brain injury promotes cellular proliferation within the brain	Mahmood et al. (2004) USA [26]	rats	Wistar	male	CCI	MSC	Allogeneic	1*10^6/2*10^6	24 h	ICV
5	Long-term recovery after bone marrow stromal cell treatment of traumatic brain injury in rats	Mahmood et al. (2006) USA [27]	rats	Wistar	female	CCI	MSC	Allogeneic	2*10^6/4*10^6/ 8*10^6	24 h	IV
6	Treatment of Traumatic Brain Injury in Mice with Marrow Stromal Cells	Qu et al. (2008) USA [28]	mice	C57BL/ 6 J	female	CCI	MSC	Allogeneic	3*10^5	7 d	IV
7	Delayed intralesional transplantation of bone marrow stromal cells increases endogenous neurogenesis and promotes functional recovery after severe traumatic brain injury	Bonilla et al. (2009) Spain [29]	rats	Wistar	female	weight-drop model	MSC	Allogeneic	5*10^6	24 h	ICV
8	Intravenous mesenchymal stem cell therapy for traumatic brain injury	Harting et al. (2009) USA [30]	rats	SD	male	CCI	MSC	Allogeneic	2*10^6/4*10^6	2 month	IV
9	Comparison of Transplantation of Bone Marrow Stromal Cells (BMSC) and Stem Cell Mobilization by Granulocyte Colony Stimulating Factor after Traumatic Brain Injury in Rat	Bakhtiary et al. (2010) Iran [31]	rats	Wistar	male	CCI	MSC	Allogeneic	2*10^6	24 h	IV
10	Therapeutic Effects of Human Mesenchymal Stem Cells on Traumatic Brain Injury in Rats: Secretion of Neurotrophic Factors and Inhibition of Apoptosis	Kim et al. (2010)Korea [32]	rats	SD	male	CCI	MSC	Xenogenic	2*10^6	72 h	IV
11	Treatment of Traumatic Brain Injury in Mice with Bone Marrow Stromal Cell-Impregnated Collagen Scaffolds	Qu et al. (2010) USA [33]	mice	C57BL/ 6 J	male	CCI	MSC	Xenogenic	3*10^5	24 h	ICV/IV
12	Transplantation of Marrow Stromal Cells Restores Cerebral Blood Flow and Reduces Cerebral Atrophy in Rats with Traumatic Brain Injury: In vivo MRI Study	Li et al. (2011) USA [34]	rats	Wistar	male	CCI	MSC	Xenogenic	3*10^6	24 h	IV
13	Transplantation of autologous bone marrow-derived mesenchymal stem cells for traumatic brain injury	Jiang et al. (2012)China [35]	rats	SD	male	weight-drop model	MSC	Allogeneic	1*10^6	5 d	ICV
14	Failure of Delayed Intravenous Administration of Bone Marrow Stromal Cells after Traumatic Brain Injury	Bonilla et al. (2012) Spain [36]	rats	Wistar	female	weight-drop model	MSC	Allogeneic	1.5 *10^7	24 h	IV

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Table 1 (*continued*)

number	title	Author year Country	Species	Strain	Gender	model	MSC (M) or EV	MSC(M) source	Compatibility MSC Dose	Time of delivery post-TBI induction	MSC route
15	MRI measurement of angiogenesis and the therapeutic effect of acute marrow stromal cell administration on traumatic brain injury	Li et al. (2012)China [37]	rats	Wistar	male	CCI	MSC	Xenogenic	3*10^6	2 month	IV
16	Effects of treating traumatic brain injury with collagen scaffolds and human bone marrow stromal cells on sprouting of corticospinal tract axons into the denervated side of the spinal cord	Mahmood et al. (2013) USA [38]	rats	Wistar	male	CCI	MSC	Xenogenic	3*10^6	6 h	ICV
17	Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury	Zhang et al. (2013)China [39]	rats	Wistar	male	CCI	MSC	Allogeneic	4*10^6	24 h	IV
18	Protective Effects of BDNF Overexpression Bone Marrow Stromal Cell Transplantation in Rat Models of Traumatic Brain Injury	Wang et al. (2013)China [40]	rats	SD	female	CCI	MSC	Allogeneic	1*10^6	2 h	ICV
19	Transplantation of human mesenchymal stem cells loaded on collagen scaffolds for the treatment of traumatic brain injury in rats	Guan et al. (2013)China [41]	rats	SD	male	CCI	MSC	Xenogenic	3*10^6	6 h	ICV
20	Injection Time-Dependent Effect of Adult Human Bone Marrow Stromal Cell Transplantation in a Rat Model of Severe Traumatic Brain Injury	Han et al. (2013)South Korea [42]	rats	SD	male	CCI	MSC	Xenogenic	1*10^6	7 d	ICV
21	Administration of TSG-6 improves memory after traumatic brain injury in mice	Watanabe et al. (2013) USA [43]	mice	C57BL/6j	male	CCI	MSC	Xenogenic	1 *10^6	24 h/7 d	IV
22	Is the subarachnoid administration of mesenchymal stromal cells a useful strategy to treat chronic brain damage?	Bonilla et al. (2014) Spain [44]	rats	Wistar	female	weight-drop model	MSC	Allogeneic	2*10^6	6 h	ICV
23	Intravenous transplantation of bone marrow mesenchymal stem cells promotes neural regeneration after traumatic brain injury	Anbari et al. (2014)Iran [45]	rats	Wistar	male	weight-drop model	MSC	Allogeneic	3*10^6	0 h	IV
24	Study of co-transplantation of SPIO labeled bone marrow stromal stem cells and Schwann cells for treating traumatic brain injury in rats and in vivo tracing of magnetically labeled cells by MR	Xu et al. (2014)China [46]	rats	SD	male	weight-drop model	MSC	Allogeneic	1 *10^5	24 h	ICV
25	Immunosuppression does not affect human bone marrow mesenchymal stromal cell efficacy after transplantation in traumatized mice brain	Pischiutta et al. (2014) Italy [47]	mice	C57Bl/6	male	CCI	MSC	Xenogenic	1.5 *10^5	48 h	ICV
26	Intra-Arterial Administration of Multipotent Mesenchymal Stromal Cells Promotes Functional Recovery of the Brain after Traumatic Brain Injury	Silachev et al. (2015) Russia [48]	rats	not reported	not reported	weight-drop model	MSC	Allogeneic	1.5 *10^6	24 h	IV/IA
27	Combined Bone Mesenchymal Stem Cell and Olfactory Ensheathing Cell Transplantation Promotes Neural Repair Associated With CNTF Expression in Traumatic Brain-Injured Rats	Fu et al. (2015)China [49]	rats	Wistar	male	weight-drop model	MSC	Syngeneic	not reported	24 h	ICV
28	Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury	Zhang et al. (2015)USA [50]	rats	Wistar	male	CCI	EV	Allogeneic	100 μg in 0.5 mL PBS	0 h	IV

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Table 1 (*continued*)

number	title	Author year Country	Species	Strain	Gender	model	MSC (M) or EV	MSC(M) source	Compatibility MSC Dose	Time of delivery post-TBI induction	MSC route
29	Failure of Intravenous or Intracardiac Delivery of Mesenchymal Stromal Cells to Improve Outcomes after Focal Traumatic Brain Injury in the Female Rat	Turtzo et al. (2015) USA [51]	rats	Wistar	female	CCI	MSC	Allogeneic	5*10^6	24 h	IV
30	Bone Marrow Stromal Cells Promote Neuronal Restoration in Rats with Traumatic Brain Injury: Involvement of GDNF Regulating BAD and BAX Signaling	Shen et al. (2016)China [52]	rats	SD	not reported	CCI	MSC	Xenogenic	1*10^7	3\5\7 d (IV) , 0 h (intracardiac)	ICV
31	Propranolol and Mesenchymal Stromal Cells Combine to Treat Traumatic Brain Injury	Kota et al. (2016) USA [53]	rats	SD	male	CCI	MSC	Xenogenic	1*10^6	0 h	IV
32	Diffusion-Derived Magnetic Resonance Imaging Measures of Longitudinal Microstructural Remodeling Induced by Marrow Stromal Cell Therapy after Traumatic Brain Injury	Li et al. (2017) USA [54]	rats	Wistar	male	CCI	MSC	Xenogenic	3*10^6	72 h	IV
33	Transplantation of bone mesenchymal stem cells promotes angiogenesis and improves neurological function after traumatic brain injury in mouse	Guo et al. (2017) China [55]	mice	C57BL/6	male	weight-drop model	MSC	Allogeneic	2*10^6	not reported	IV
34	Bone marrow stromal cells promote neuromotor functional recovery, via upregulation of neurotrophic factors and synapse proteins following traumatic brain injury in rats	Feng et al. (2017) China [56]	rats	SD	male	weight-drop model	MSC	Allogeneic	3*10^6	30 min	IV
35	Platelet-rich plasma-derived scaffolds increase the benefit of delayed mesenchymal stromal cell therapy after severe traumatic brain injury	Horcajo et al. (2014) Spain [57]	rats	Wistar	female	weight-drop model	MSC	Allogeneic	5*10^6	0 h	ICV
36	Effects of SDF-1/CXCR4 on the Repair of Traumatic Brain Injury in Rats by Mediating Bone Marrow Derived Mesenchymal Stem Cells	Deng et al. (2017)China [58]	rats	SD	male	CCI	MSC	Allogeneic	not reported	0 h	ICV
37	The Influence of Proinflammatory Factors on the Neuroprotective Efficiency of Multipotent Mesenchymal Stromal Cells in Traumatic Brain Injury	Danilina et al. (2017)Russia [59]	rats	albino rats	not reported	weight-drop model	MSC	Allogeneic	3*10^6	24 h	IV
38	Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury	Zhang et al. (2017)USA [60]	rats	Wistar	male	CCI	EV	Xenogenic	100 μg in 0.5 mL PBS	24 h	IV
39	The impact of bone marrow-derived mesenchymal stem cells on neovascularisation in rats with brain injury	Hu et al. (2018) China [61]	rats	SD	male	weight-drop model	MSC	Allogeneic	1 *10^4	12 h	ICV
40	Effects of over-expression of SOD2 in bone marrow-derived mesenchymal stem cells on traumatic brain injury	Shi et al. (2018)China [62]	mice	Balb/c	not reported	CCI	MSC	Allogeneic	1 *10^6	6 h	IV
41	Collagen-chitosan scaffold impregnated with bone marrow mesenchymal stem cells for treatment of traumatic brain injury	Yan et al. (2018)China [63]	rats	Wistar	male	weight-drop model	MSC	Allogeneic	2*10^6	24 h	ICV

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Table 1 (*continued*)

number	title	Author year Country	Species	Strain	Gender	model	MSC (M) or EV	MSC(M) source	Compatibility MSC Dose	Time of delivery post-TBI induction	MSC route
42	Calpain inhibitor MDL28170 improves the transplantation-mediated therapeutic effect of bone marrow-derived mesenchymal stem cells following traumatic brain injury	Hu et al. (2019) China [64]	rats	SD	male	weight-drop model	MSC	Allogeneic	1 *10^5	24 h	ICV
43	NT3P75-2 gene-modified bone mesenchymal stem cells improve neurological function recovery in mouse TBI model	Wu et al. (2019) China [65]	rats	not reported	male	CCI	MSC	Allogeneic	3*10^5	0 h	ICV
44	Bone marrow mesenchymal stem cells combined with Sox2 increase the functional recovery in rat with traumatic brain injury	Hao et al. (2019) China [66]	rats	SD	not reported	weight-drop model	MSC	Allogeneic	1 *10^5	72 h	ICV
45	Exosomes Derived From Bone Mesenchymal Stem Cells Ameliorate Early Inflammatory Responses Following Traumatic Brain Injury	Ni et al. (2019)USA [67]	mice	C57BL/6	male	CCI	EV	Syngeneic	30 mg total protein of BMSCs-exosomes in 150 mL PBS	15 min	retro-orbital injection (IR)
46	Transplantation of mesenchymal stem cells genetically engineered to overexpress interleukin-10 promotes alternative inflammatory response in rat model of traumatic brain injury	Peruzzaro et al. (2019) USA [68]	rats	SD	male	CCI	MSC	Allogeneic	1 *10^6	36 h	ICV
47	Temperature-sensitive bone mesenchymal stem cells combined with mild hypothermia reduces neurological deficit in rats of severe traumatic brain injury	Song et al. (2020) China [69]	rats	SD	male	CCI	MSC	Allogeneic	1 *10^6	6 h	ICV
48	Mesenchymal Stem Cell–Derived Exosomes Improve Functional Recovery in Rats After Traumatic Brain Injury: A Dose-Response and Therapeutic Window Study	Zhang et al. (2020)USA [70]	rats	Wistar	male	CCI	EV	Xenogenic	100 μg in 0.5 mL PBS	24 h	IV
49	Protective Effect of Mesenchymal Stromal Cell-Derived Exosomes on Traumatic Brain Injury via miR-216a-5p	Xu et al. (2020)China [71]	rats	SD	male	CCI	EV	Allogeneic	100 μg	24 h	IV
50	Hypoxic preconditioning enhances the differentiation of bone marrow stromal cells into mature oligodendrocytes via the mTOR/HIF-1α/VEGF pathway in traumatic brain injury	Yuan et al. (2020) China [72]	mice	C57BL/6	male	CCI	MSC	Allogeneic	2*10^6	24 h	IV
51	Transplanting Rac1-silenced bone marrow mesenchymal stem cells promote neurological function recovery in TBI mice	Huang et al. (2021) China [73]	mice	C57BL/6	male	CCI	MSC	Syngeneic	5*10^5	24 h	ICV
52	Dual-enzymatically cross-linked gelatin hydrogel promotes neural differentiation and neurotrophin secretion of bone marrow-derived mesenchymal stem cells for treatment of moderate traumatic brain injury	Li et al. (2021)China [74]	mice	C57BL/6	male	weight-drop model	MSC	Allogeneic	5*10^5	0 h	ICV
53	Sodium alginate/collagen/stromal cell-derived factor-1 neural scaffold loaded with BMSCs promotes neurological function recovery after traumatic brain injury	Ma et al. (2021)China [75]	rats	SD	male	weight-drop model	MSC	Syngeneic	3*10^6	0 h	ICV
54	MiR-17-92 Cluster-Enriched Exosomes Derived from Human Bone Marrow Mesenchymal Stromal	Zhang et al. (2021)USA [76]	rats	Wistar	male	CCI	EV	Xenogenic	100 μg (3.75 × 10^11 particles) in 0.5 mL in PBS	24 h	IV

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Table 1 (*continued*)

number	title	Author year Country	Species	Strain	Gender	model	MSC (M) or EV	MSC(M) source	Compatibility MSC Dose	Time of delivery post-TBI induction	MSC route
	Cells Improve Tissue and Functional Recovery in Rats after Traumatic Brain Injury										
55	Exosomes derived from bone marrow mesenchymal stem cells inhibit neuroinflammation after traumatic brain injury	Wen et al. (2021) China [77]	mice	C57BL/ 6 J	male	CCI	EV	Allogeneic	200 μL (6.3 × 10^10 particles/mL)	24 h\3 d\7 d	IV

Table legends: IA: intra-arterial; ICV: intracranial; IR: retro-orbital injection; IV: intravenous; MSC(M): bone marrow called mesenchymal stromal (stem) cells; CCI: controlled cortical impact; EV: extracellular vesicle; Sprague-Dawley: SD.

Table 2
Methodological quality of udies included in the meta-analysis.

Author year	peer reviewed publication	control of temperature	random allocation to treatment or control	blinded induction of haemorrhage allocation concealment	blinded assessment of outcome	use of anesthetic without marked intrinsic neuroprotective activity	animal model (aged, diabetic or hypertensive)	sample size calculation	compliance with animal welfare regulations	conflict of interests	total score
Lu et al. (2001) USA [23]	✓	✓	✓		✓	✓			✓	✓	7
Mahmood et al. (2003) USA [24]	✓	✓	✓		✓	✓			✓	✓	7
Lu et al. (2003) USA [25]	✓		✓		✓	✓			✓	✓	6
Mahmood et al. (2004) USA [26]	✓		✓		✓				✓	✓	5
Mahmood et al. (2006) USA [27]	✓	✓	✓		✓	✓			✓	✓	7
Qu et al. (2008) USA [28]	✓		✓			✓			✓	✓	5
Bonilla et al. (2009) Spain [29]	✓		✓			✓			✓	✓	5
Harting et al. (2009) USA [30]	✓	✓	✓		✓	✓			✓	✓	7
Bakhtiary et al. (2010) Iran [31]	✓	✓			✓	✓			✓	✓	6
Kim et al. (2010) Korea [32]	✓	✓	✓			✓			✓		5
Qu et al. (2010) USA [33]	✓		✓		✓	✓			✓	✓	6
Li et al. (2011) USA [34]	✓	✓	✓		✓	✓			✓		6
Jiang et al. (2012)	✓	✓			✓				✓	✓	5

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Table 2 (*continued*)

Author year	peer reviewed publication	control of temperature	random allocation to treatment or control	blinded induction of haemorrhage allocation concealment	blinded assessment of outcome	use of anesthetic without marked intrinsic neuroprotective activity	animal model (aged, diabetic or hypertensive)	sample size calculation	compliance with animal welfare regulations	conflict of interests	total score
China [35]											
Bonilla et al. (2012) Spain [36]	✓		✓		✓	✓			✓	✓	6
Li et al. (2012) China [37]	✓		✓			✓			✓	✓	5
Mahmood et al. (2013) USA [38]	✓	✓	✓			✓			✓	✓	6
Zhang et al. (2013) China [39]	✓	✓	✓		✓	✓			✓	✓	7
Wang et al. (2013) China [40]	✓		✓		✓	✓			✓	✓	6
Guan et al. (2013) China [41]	✓	✓	✓						✓	✓	5
Han et al. (2013) South Korea [42]	✓	✓			✓	✓			✓		5
Watanabe et al. (2013) USA [43]	✓	✓				✓			✓	✓	5
Bonilla et al. (2014) Spain [44]	✓		✓			✓			✓	✓	5
Anbari et al. (2014) Iran [45]	✓		✓		✓	✓			✓	✓	6
Xu et al. (2014) China [46]	✓	✓	✓			✓			✓	✓	6

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Table 2 (*continued*)

Author year	peer reviewed publication	control of temperature	random allocation to treatment or control	blinded induction of haemorrhage allocation concealment	blinded assessment of outcome	use of anesthetic without marked intrinsic neuroprotective activity	animal model (aged, diabetic or hypertensive)	sample size calculation	compliance with animal welfare regulations	conflict of interests	total score
Pischiutta et al. (2014) Italy [47]	✓	✓	✓		✓	✓			✓		6
Silachev et al. (2015) Russia [48]	✓	✓			✓	✓			✓		5
Fu et al. (201) China [49]	✓	✓	✓		✓				✓	✓	6
Zhang et al. (2015) USA [50]	✓		✓		✓	✓			✓	✓	6
Turtzo et al. (2015) USA [51]	✓	✓	✓		✓	✓			✓	✓	7
Shen et al. (2016) China [52]	✓		✓		✓	✓			✓	✓	6
Kota et al. (2016) USA [53]	✓	✓	✓						✓	✓	5
Li et al. (2017) USA [54]	✓	✓	✓			✓			✓	✓	6
Guo et al. (2017) China [55]	✓	✓				✓			✓		4
Feng et al. (2017) China [56]	✓	✓			✓	✓			✓	✓	6
Horcajo et al. (2014) Spain [57]	✓					✓		✓	✓		4
Deng et al. (2017) China [58]	✓	✓			✓	✓			✓		5
Danilina et al. (2017)	✓	✓	✓			✓			✓		5

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Table 2 (*continued*)

Author year	peer reviewed publication	control of temperature	random allocation to treatment or control	blinded induction of haemorrhage allocation concealment	blinded assessment of outcome	use of anesthetic without marked intrinsic neuroprotective activity	animal model (aged, diabetic or hypertensive)	sample size calculation	compliance with animal welfare regulations	conflict of interests	total score
Russia [59]											
Zhang et al. (2017) USA [60]	✓	✓	✓			✓			✓	✓	6
Hu et al. (2018) China [61]	✓	✓	✓			✓			✓		5
Shi et al. (2018) China [62]	✓	✓	✓			✓			✓		5
Yan et al. (2018) China [63]	✓	✓	✓		✓	✓			✓	✓	7
Hu et al. (2019) China [64]	✓	✓			✓	✓			✓		5
Wu et al. (2019) China [65]	✓	✓	✓		✓	✓			✓		6
Hao et al. (2019) China [66]	✓		✓		✓				✓	✓	5
Ni et al. (2019) USA [67]	✓				✓	✓			✓	✓	5
Peruzzaro et al. (2019) USA [68]	✓	✓	✓		✓	✓			✓	✓	7
Song et al. (2020) China [69]	✓	✓	✓			✓			✓		5
Zhang et al. (2020) USA [70]	✓	✓				✓			✓	✓	5
Xu et al. (2020)	✓	✓	✓	✓	✓				✓	✓	7

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Table 2 (*continued*)

Author year	peer reviewed publication	control of temperature	random allocation to treatment or control	blinded induction of haemorrhage allocation concealment	blinded assessment of outcome	use of anesthetic without marked intrinsic neuroprotective activity	animal model (aged, diabetic or hypertensive)	sample size calculation	compliance with animal welfare regulations	conflict of interests	total score
China [71]											
Yuan et al. (2020) China [72]	✓					✓			✓	✓	4
Huang et al. (2021) China [73]	✓	✓	✓	✓	✓	✓			✓	✓	8
Li et al. (2021) China [74]	✓		✓		✓	✓			✓	✓	6
Ma et al. (2021) China [75]	✓	✓	✓	✓	✓	✓			✓	✓	8
Zhang et al. (2021) USA [76]	✓		✓	✓	✓				✓	✓	6
Wen et al. (2021) China [77]	✓		✓					✓	✓	✓	6

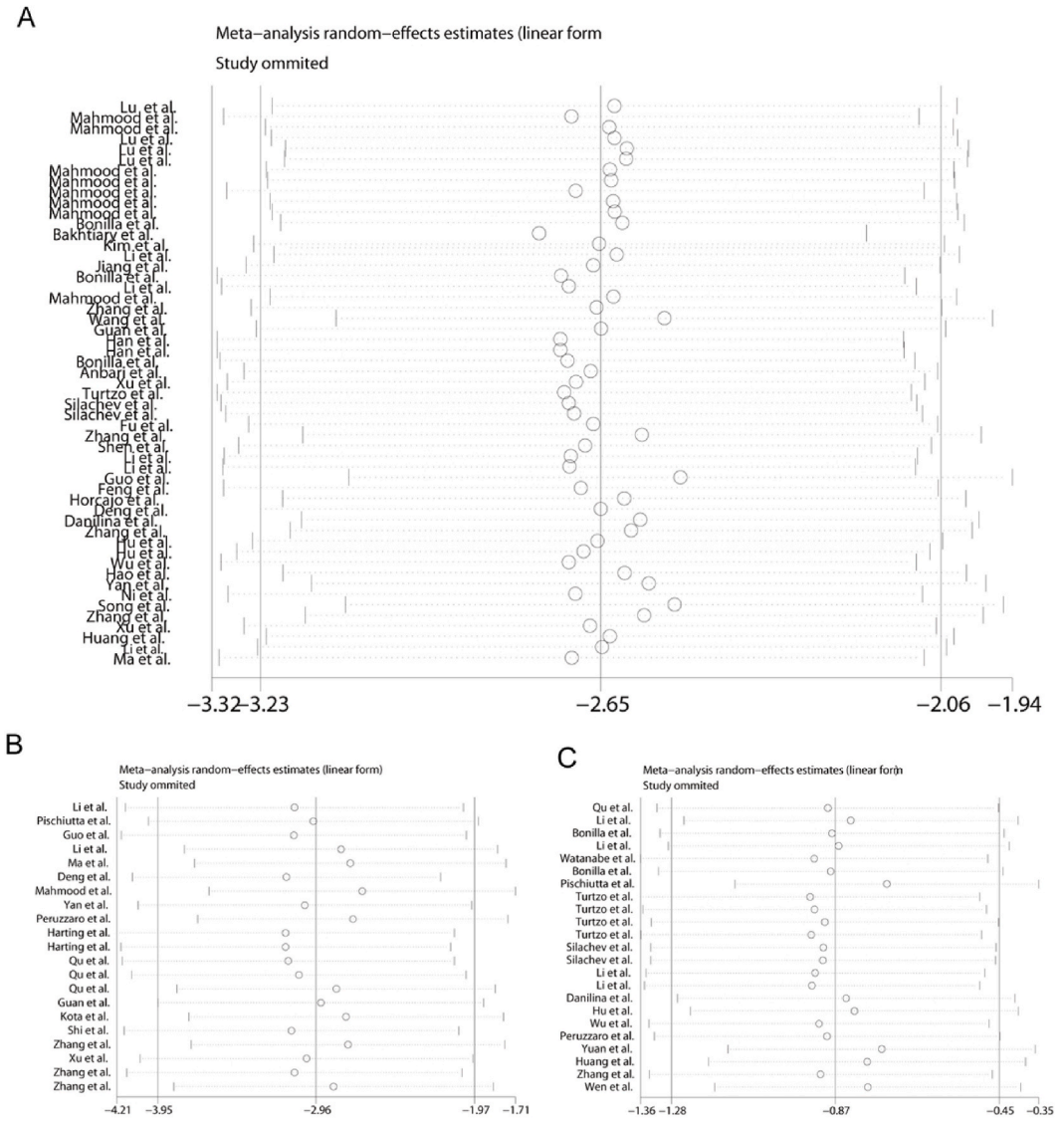

Fig. 3. Sensitivity analysis of included comparisons for functional and histopathological outcomes. Forest plot shows mean effect size and 95 % CI for (A) mNSS, (B) MWM, (C) lesion volume between MSC(M) derived therapy treatment group and control group in all studies.

(Fig. S4.1), immunocompatibility ($p = 0.06$) (Fig. S4.4), therapy type ($p = 0.68$) (Fig. S4.5), administration time ($p = 0.44$) (Fig. S4.7), and numbers of times ($p = 0.55$) (Fig. S4.8). but significant differences related to rodent gender ($p = 0.04$) (Fig. S4.2), donor species ($p = 0.02$) (Fig. S4.3), and the route of admission ($p = 0.04$) (Fig. S4.6). Overall, stratified analyses revealed significant differences between groups, however, the reasons for this heterogeneity cannot be identified.

4. Discussion

4.1. Summary of evidence

This meta-analysis focused on MSC(M) or MSC(M)-derived EV administered separately in a clearly defined disease model of TBI. To our knowledge, this is the most updated systematic review and meta-analysis of MSC(M)-derived therapies in experimental TBI models. The results confirmed that they improved neurological function, cognitive functions, and anatomical damage after TBI. Efficacy of mNSS, WMM, and lesion volume outcomes were robust when analyzed concerning MSC(M) source, time of administration, delivery route, species of recipients, gender, and the TBI models of different types, supporting the feasibility of further investigation of MSC(M) for TBI patients. In our study, we found that MSC(M) and MSC(M)-derived EVs displayed a high level of heterogeneity in their characterisation. Only one study met the international guidelines when describing MSC(M) in accordance with ISCT criteria [78], and

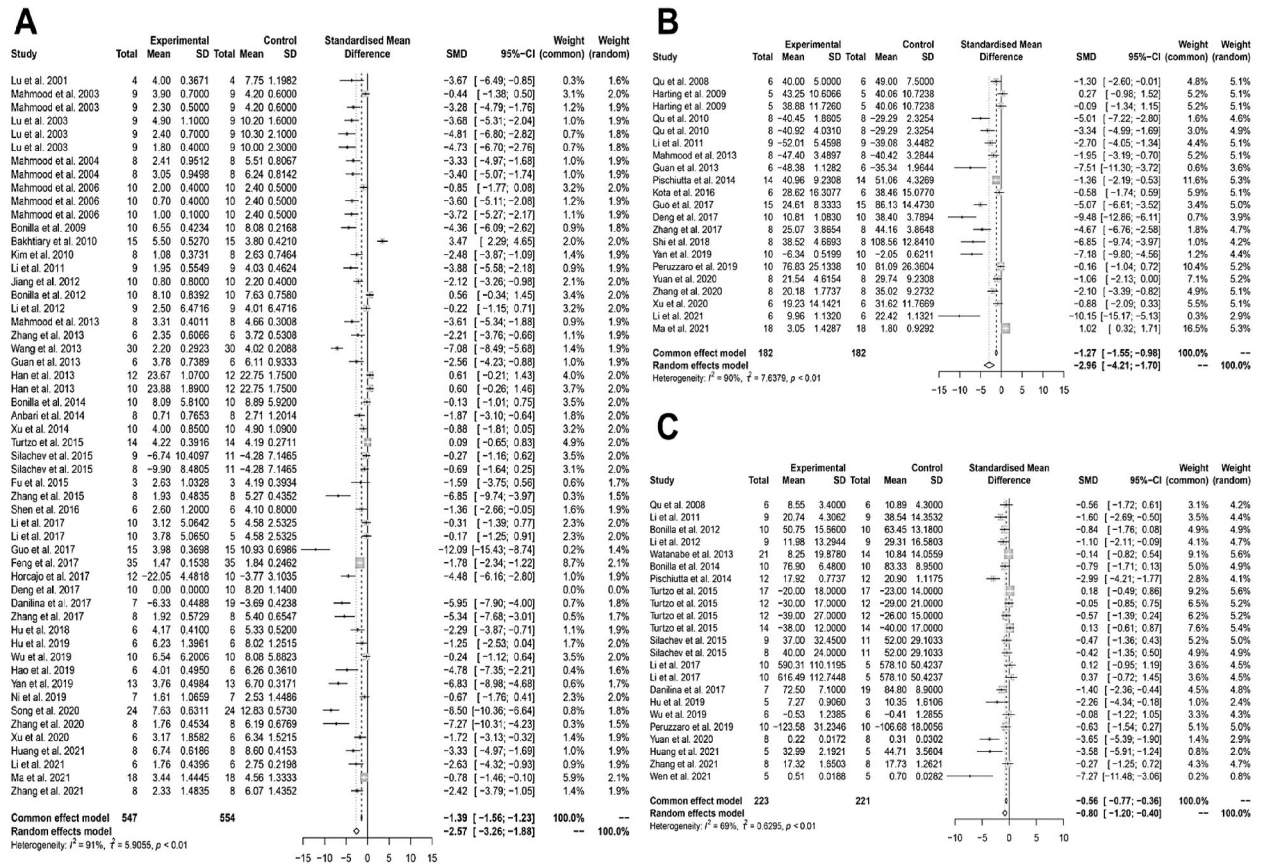

Fig. 4. Forest plot shows the mean effect size and 95 % confidence interval (CI) for mNSS(A), MWM (B), and lesion volume(C) between MSC(M) derived therapy treatment group and control group in all studies.

57 % of studies met the international guidelines when describing MSC(M)-derived EVs in accordance with MISEV 2018 [79]. Consequently, better characterisation of MSC(M) and MSC(M)-derived EVs will also enable the development of more effective and safe therapeutic protocols. Furthermore, none of the studies identified the expression of negative markers in EVs. More research is needed to identify potential biomarkers to assess the efficacy of MSC(M)-derived EV.

4.2. Interpretation of the stratified analysis

Numerous studies indicate that MSCs(M) can exert a positive effect primarily via their paracrine activity [80]. Based on the ability of MSC(M) derived EVs to cross the BBB and their ability to deliver targeted gene drugs, they might have a more promising therapeutic potential than MSC(M) as a treatment for diseases of the central nervous system [81]. Interesting to note is that there was no difference in mNSS scores, MWM scores or lesion volume outcomes associated with the treatment type (MSC or EV). There is, however, insufficient research on the safety and side effects of MSC(M) derived EVs. In the case of MSC(M) therapy, tumorigenicity, immunogenicity, as well as genomic mutability are the main concerns [82–84]. Research has shown that EVs exhibit characteristics similar to those of MSC(M) including minimal immunogenicity and can facilitate neuron regeneration [85]. Compared to MSC(M), EVs have the advantages of being more stable, less invasive, and less tumorigenic, which is extraordinary for their wide range of applications because they are free of ethical problems [86,87]. In addition, by using EVs, the safety risks associated with administering live cells, such as obstruction of the microvascular system and uncontrolled proliferation of the transplanted cells, are reduced [10]. However, proteomic analysis revealed differences between human MSC(M) and MSC(M) derived EVs [88,89]. MSC(M)-derived therapy may contribute to reducing TBI injury by promoting neuroprotection, and angiogenesis, suppressing oxidative stress and inflammation, enhancing mitochondrial function, and regulating immune function (Fig. 6). Consequently, further research will be necessary to determine which therapy (MSC(M) or EVs) would be most appropriate for treating TBI. Since that the number of studies included in this study was insufficient, larger and better designed studies in the preclinical stage are necessary to understand these issues more deeply.

Cell therapy efficiency is also affected by the route, timing of administration, and numbers of times. Stem cells have been transferred through a variety of routes, including intravenous (IV), intracranial (ICV), retro-orbital injection (IR), intracardiac (IC), intravenous (IV), and intra-arterial (IA). Previously, no experimental study compared the effectiveness of different transplantation

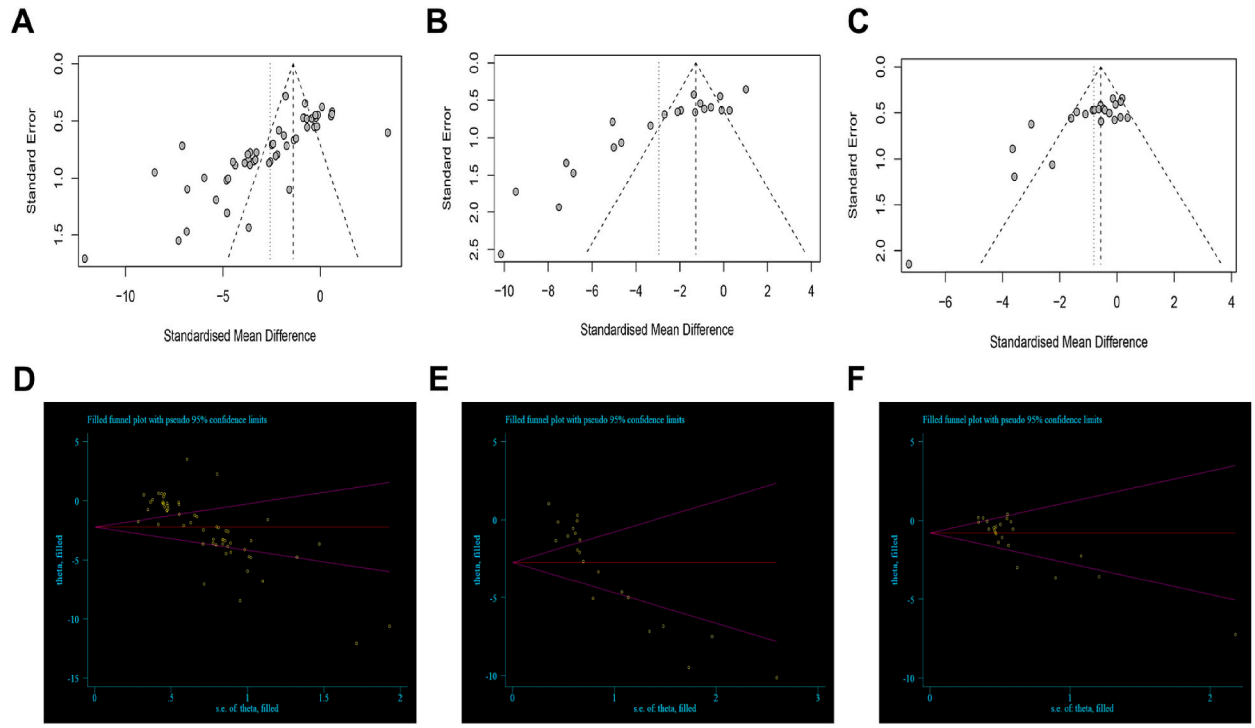

Fig. 5. The evaluation of publication bias. Funnel plots for mNSS(A), MWM (B), and lesion volume(C), with the y-axis signifying study quality and the x-axis showing the study results. (C) Trim-and-fill method was used to evaluate the missing studies in mNSS(D), MWM (E), and lesion volume(F) outcomes. SMD, standardized mean difference.

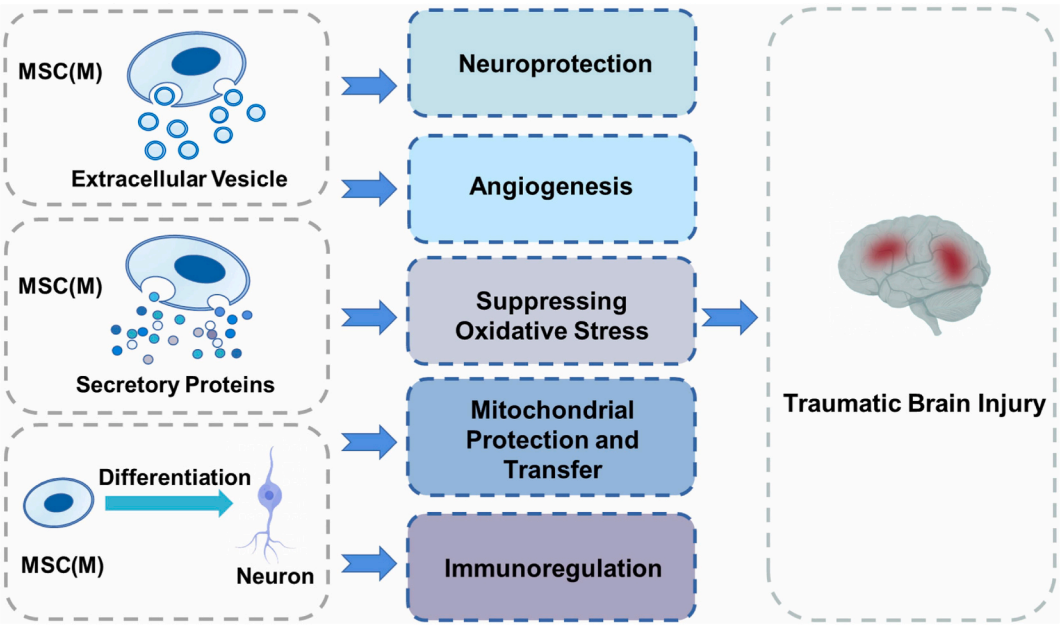

Fig. 6. The possible mechanisms of MSC(M) derived therapy for TBI.
MSC(M) derived therapy could alleviate neuropathology via multiple mechanisms, including neuroprotection, angiogenesis, suppressing oxidative stress, mitochondrial protection and transfer, and immunoregulation, as shown in TBI animal models.

routes and times. Our stratified analysis revealed that ICV injections improved neurobehavioral outcomes and reduced lesion volume more effectively than IV injections. However, ICV is an invasive procedure that can cause damage to brain tissue and is limited in terms of the number of transplanted cells. Recently, studies have shown that intranasal administration of EVs can bypass the BBB at the tissue level, and EVs accumulate more efficiently in the brain than those administered intravenously. In addition, EVs migrate actively to the site of the lesion. As a result, MSC(M)-derived EVs may be a promising therapeutic carrier for the treatment of traumatic brain injury. In terms of clinical applications, IV and IN appear to be the most attractive option. The timing of MSC delivery is also essential for efficient therapeutic effects. Our results found that MSC(M) and MSC(M) derived EVs administered in TBI 24 h had better neurobehavioral outcomes than those injected greater than 24 h after TBI induction. Han et al. found improvements in histological appearance and functional performance after treatment with human MSC(M) seven days after the injury instead of one day after the injury [39]. However, in human subjects, according to Tian et al. there is an advantage of transplanting MSC(M) after a TBI in the window of efficacy that is most likely to result in the best results [90]. A total of 97 TBI patients received MSC(M) transplantation at different times between the time of injury and the start of treatment. Results showed that patients who received the therapy within 1.51 months had better outcomes than patients who received it later [90]. Moreover, the motor function of patients treated with cell therapy within 1.35 months of injury onset improved significantly compared to those treated later in recovery [90]. Consequently, early implementation of MSC treatment resulted in greater efficacy. For the number of transplanted MSC(M), there may be a tendency to believe that the higher the number, the greater the extent of tissue repair will be, but that may not necessarily be the case. After rat brain injuries, Wu et al. [44]found that neurological functions were improved by infusion of 1×10^6 MSC(M), but the improvement did not improve with infusion of 3×10^6 cells. Few MSC(M) survive in the system and reach the brain after administration. According to Danielyan et al., 3×10^5 cells were injected intravenously into young mice, which resulted in 584 ± 184 cells in the olfactory bulb and 227 ± 47 cells in the cortex [91]. After TBI in human patients, Tian et al. transplanted 3.9×10^6 MSC(M) into the subarachnoid space by lumbar puncture technique, but they found no correlation between the number of cells transplanted and TBI outcome [90]. Regarding the number of injections, a single dose appeared to be more effective than a repeated dose in promoting restoration of neurological function. There were too few studies included in this study, and more comprehensive preclinical studies are necessary to address these issues. Overall, some stratified analyses revealed significant differences between the groups, however, sources of heterogeneity were not identified by these analyses. Furthermore, it should be noted that analyses of subgroups were only intended to provide hypotheses, not provide evidence to support them.

4.3. Limitations

Several potential limitations complicate the interpretation of this meta-analysis. (1) Despite performing subgroup and sensitivity analyses, the results may be unstable because of the inability to reduce heterogeneity between studies. (2) Although we included MSC (M) derived EVs and MSC(M), the number of studies involving EVs included in the review was insufficient, which may have also increased the heterogeneity. (3) The number of research studies that were retrieved may have been limited, leading to publication bias. (4) The extraction of data from graphics may have altered the original data, resulting in a different outcome.

5. Conclusions

Our meta-analysis indicates that MSC(M) derived therapies demonstrated beneficial effects in preclinical rodent TBI animals, by analyzing treatment outcomes such as mNSS score, MWM, and brain lesion volume. These findings provide valuable information for human clinical trials using MSC(M)-derived therapies. For further research, large animal studies and human trials are necessary.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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CRediT authorship contribution statement

Chunli Chen: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft. **Cuiying Peng:** Conceptualization, Data curation, Methodology. **Zhiping Hu:** Conceptualization, Supervision, Writing – review & editing. **Lite Ge:** Conceptualization, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We are thankful for the help of figdraw (figdraw.com) for Fig. 6.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25050.

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