Mesenchymal stromal cells and their exosomes as acute therapeutic interventions for traumatic brain injury in pre-clinical studies: A systematic review and meta-analysis

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Abstract. The present systematic review and meta-analysis aimed to evaluate the efficacy of mesenchymal stromal cells (MSCs) and MSC-derived exosomes administered in the acute phase after traumatic brain injury (TBI), comparing neurological, histopathological and biochemical outcomes in pre-clinical models. For this purpose, pre-clinical studies involving MSCs or MSC-derived exosomes administered to animal models of TBI were reviewed. The present study analyzed functional outcomes, lesion volume and cognitive recovery. Meta-analytic techniques (RevMan Web) were used to calculate effect sizes for each outcome. A total of 46 studies were included with 1,558 animals for analysis. Both MSC-based therapies and MSC-derived exosomes significantly improved neurological function [pooled mean difference (MD), -2.09; 95% confidence interval (CI), -3.06 to -1.13; P<0.0001], cognitive performance (pooled MD, -16.72; 95% CI, -22.87 to -10.58; P<0.00001) and reduced lesion volume (pooled MD, -0.15; 95% CI, -0.16 to -0.14; P<0.00001). Subgroup analyses revealed that MSC-derived exosomes, particularly intravenously administered, had the largest effects on cognitive recovery and lesion volume reduction. High heterogeneity (I^2=100%) was observed due to variations in study designs, intervention types and delivery routes. On the whole, as demonstrated herein, MSC-based therapies and MSC-derived exosomes demonstrate significant neuroprotective effects in TBI, with intravenous MSC-derived exosomes exhibiting the most promising results. These findings highlight the role of paracrine mechanisms in MSC-mediated neuroprotection and support further investigations into cell-free therapies for the treatment of TBI.

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Introduction

Traumatic brain injury (TBI) remains a leading cause of mortality and long-term disability worldwide, particularly among young adults and military personnel (1,2). In 2019, an estimated 27-69 million new cases occurred globally, with the highest burden in low- and middle-income countries (3). Acute TBI initiates primary mechanical injury followed by secondary cascades including neuroinflammation, blood-brain barrier disruption, excitotoxicity, oxidative stress and progressive neuronal loss (4,5). Despite extensive research, no pharmacological agent has yet proven unequivocal efficacy in large phase III trials, leaving supportive care and surgery as standard management (6,7).

Mesenchymal stromal cells (MSCs) and their secreted exosomes have emerged as promising regenerative and immunomodulatory therapeutic candidates for acute TBI (8,9). MSCs exert pleiotropic effects primarily through paracrine mechanisms (anti-inflammatory cytokines, neurotrophic factors and extracellular vesicles) (10,11). Exosomes, small membrane-bound vesicles (30-150 nm) containing proteins, lipids and nucleic acids, can cross the blood-brain barrier, modulate microglial polarization, reduce apoptosis, promote angiogenesis and enhance endogenous repair processes without the risks associated with cell engraftment (12-15).

Pre-clinical rodent studies using controlled cortical impact or fluid percussion models have consistently demonstrated that MSCs and MSC-derived exosomes, administered ≤7 days post-injury, significantly reduce lesion volume and cerebral edema, while preserving neurological function and improving cognitive outcomes (13,16,17). These beneficial effects appear to be mediated predominantly by immunomodulation and restoration of blood-brain barrier integrity (13,18,19).

Early-phase clinical trials evaluating intravenous (IV) or intracerebroventricular (ICV) MSC administration in patients with severe TBI have reported preliminary safety and signals of efficacy (20,21). However, the clinical translation of exosome-based therapy remains in its infancy, with no registered trials specifically addressing acute TBI as of 2024, at least to the best of our knowledge (22).

Despite the growing body of evidence, considerable heterogeneity exists regarding cell/exosome source, dose, timing, route of administration and outcome measures across studies. Furthermore, systematic synthesis comparing the relative efficacy and safety of whole MSCs vs. their exosomes in acute TBI has not yet been performed, at least to the best of our knowledge. Such an analysis is critical to guide clinical trial design and regulatory decision-making.

Therefore, the objectives of the present systematic review and meta-analysis were the following: i) To comprehensively evaluate the efficacy of MSCs and MSC-derived exosomes administered in the acute phase following TBI in pre-clinical (animal) studies; ii) to quantitatively compare neurological, histopathological and biochemical outcomes between MSC and MSC-derived cell-free-based interventions; and iii) to identify optimal therapeutic parameters and knowledge gaps for future translational research.

Data and methods

International prospective register of systematic reviews (PROSPERO) registration. The present systematic review was prospectively registered in PROSPERO (CRD420251236846) under the title 'Mesenchymal Stromal Cells and MSC-Based Cell-Free as Acute Traumatic Brain Injury Therapy: Systematic Review and Meta-Analysis of preclinical studies'. The protocol is publicly available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420251236846. All methods were pre-defined in the registered protocol to minimize reporting bias and ensure methodological transparency. Any deviations from the protocol will be clearly documented in the final publication.

Literature search strategy. A systematic literature search was conducted on November 21, 2024 across four major electronic databases: PubMed, MEDLINE, Scopus and Cochrane Library. The search combined controlled vocabulary (MeSH) and free-text keywords with Boolean operators. The search utilized a combination of MeSH terms and free-text keywords as demonstrated in Table I.

To ensure comprehensive coverage, reference lists of retrieved articles were manually screened through backward and forward citation searching for additional relevant studies. To capture contemporary evidence, the search was restricted to studies published over the past decade (January 1, 2015 to the search date) with no language restrictions. The review was written and published in English.

Inclusion and exclusion criteria. Studies were included if they met all of the following: Investigated MSCs and/or MSC-derived exosomes (MSC-derived cell-free products, conditioned medium) administered ≤7 days post-injury (defined as the acute phase, aligned with the secondary injury cascade in TBI); pre-clinical *in vivo* animal models of TBI (any severity or model); and reported quantitative data for at least one pre-defined efficacy outcome (Fig. 1). Comparators comprised vehicle, sham, saline, or standard care. Both randomized and non-randomized study designs were included. The timing of administration was extracted from the Methods section of each study and independently verified by two reviewers (DRA and AP) to ensure compliance with the ≤7-day criterion. Articles not meeting these criteria were excluded (non-traumatic brain injury models, *in vitro*-only studies and reviews).

Screening and selection process. The initial search yielded a broad range of articles, which were filtered based on publication year, relevancy and study type. Of note, two reviewers (C and TS) independently screened the titles and abstracts of all records identified through the systematic search and manual reference checking. Full-text reports of any record considered potentially relevant by at least one reviewer (C) were retrieved and independently evaluated for inclusion by the same two reviewers (DRA and AP). Any discrepancies between reviewers (DRA and AP) during title/abstract screening or full-text assessment were first resolved by discussion. Persistent disagreements were adjudicated by a third reviewer (C). Exclusions at the full-text stage were categorized and recorded. A PRISMA flow diagram was created to illustrate the study selection process (Fig. 1).

Data extraction and synthesis. Selected articles with key data were systematically extracted, including the title and authors of the articles, year of publication, study objectives and methodology, sample size and study population (animal species demographics), intervention details (MSC and/or exosome source, route of administration), comparators, and key findings related to efficacy and safety outcomes. Primary outcomes were the following: i) Neurological function: Assessed by the modified neurological severity score (mNSS; score 0-18, lower scores indicate better function); ii) cognitive performance: Evaluated using the Morris water maze (MWM) test (typically reported as mean escape latency in seconds or percentage time spent in the target quadrant); iii) histopathological outcome: Lesion volume (mm^3), hematoxylin and eosin staining or magnetic resonance imaging (MRI).

Statistical analysis. Data were extracted independently by two reviewers (C and TS) using a standardized Excel form. Disagreements were resolved by discussion or a third reviewer (C). Extracted items included study details, intervention characteristics, sample sizes and results. Continuous outcomes data were used directly or converted as the mean and SD. Graphs were digitized using WebPlotDigitizer (v4.5) when needed and sensitivity analyses tested earliest or all time points. Data synthesis was conducted using RevMan Web, aggregating quantitative data for the meta-analysis where applicable, using random-effects models. Heterogeneity was assessed with I^2. Authors were contacted to provide any required data not available in published reports.

Data analysis and interpretation. Extracted data were analyzed to identify recurring themes, magnitude of treatment effects, optimal therapeutic parameters and research gaps.

Table I. Key word search strategy and strings.

Database	Search term
Pubmed	('Brain Injuries, Traumatic' OR 'traumatic brain injury' OR TBI) AND ('Mesenchymal Stem Cells' OR 'mesenchymal stromal cells' OR MSC OR 'Exosomes' OR 'extracellular vesicles' OR 'conditioned medium') AND (acute OR 'acute phase' OR 'early administration' OR '7 days'OR '≤7 days')
MEDLINE	('Brain Injuries, Traumatic' OR 'traumatic brain injury' OR TBI) AND ('Mesenchymal Stem Cells' OR 'mesenchymal stromal cells' OR MSC OR 'Exosomes' OR 'extracellular vesicles' OR 'conditioned medium') AND (acute OR 'acute phase' OR 'early administration' OR '7 days'OR '≤7 days')
Scopus	TITLE-ABS-KEY ('traumatic brain injury' OR TBI) AND ('mesenchymal stem cells' OR 'mesenchymal stromal cells' OR msc OR exosomes OR 'extracellular vesicles' OR 'conditioned medium') AND (acute OR 'acute phase' OR 'early administration' OR 'within 7 days' OR '≤7 days')
Cochrane Library	('Brain Injuries, Traumatic' OR 'traumatic brain injury' OR TBI) AND ('Mesenchymal Stem Cells' OR 'mesenchymal stromal cells' OR MSC OR 'Exosomes' OR 'extracellular vesicles') AND (acute OR 'acute phase' OR 'early administration')

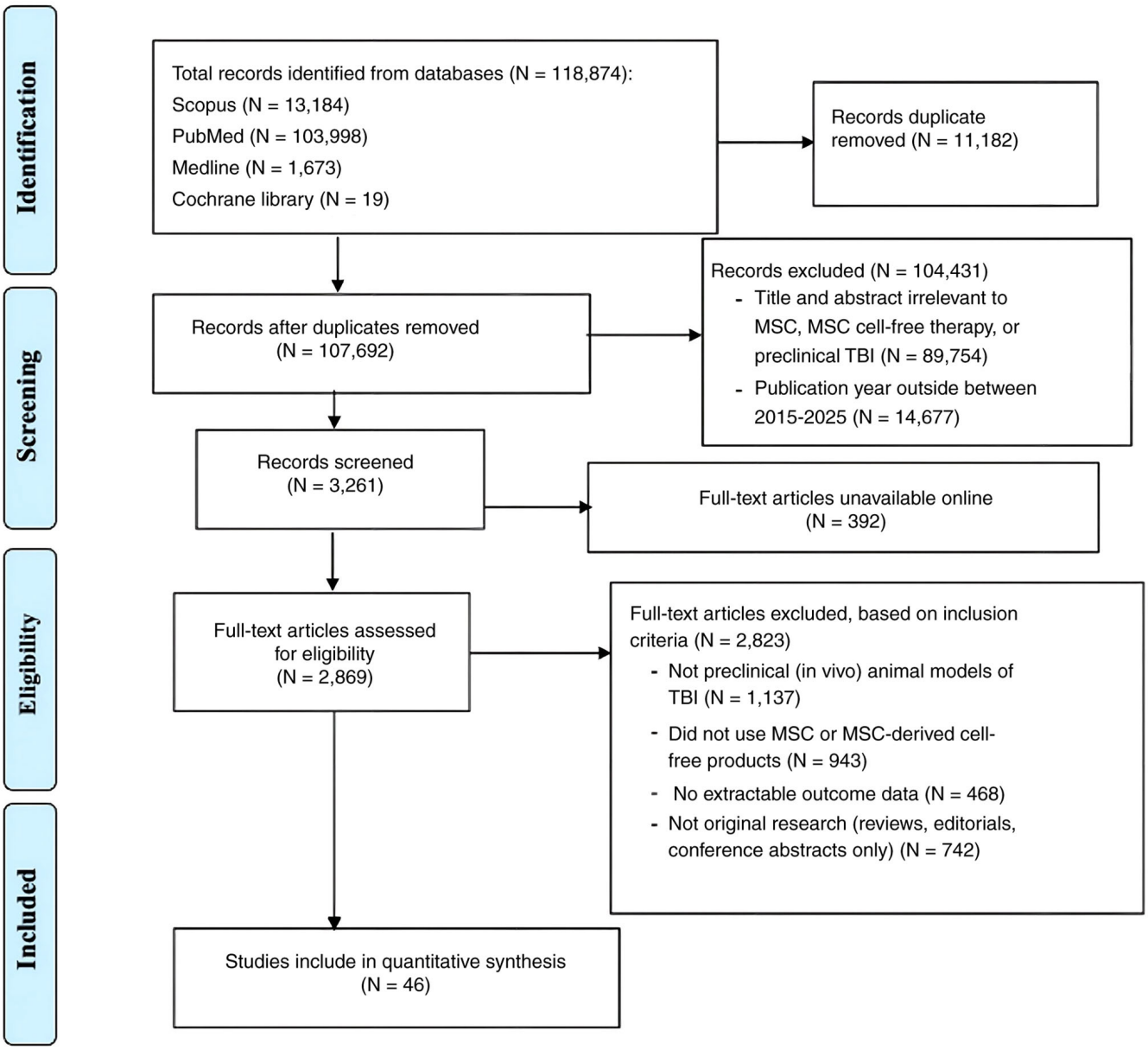

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process for the present systematic review.

Similarities and differences across pre-clinical and clinical studies were evaluated to assess the translational potential of MSCs and/or MSC-derived exosomes administered within 7 days following TBI. Meta-analytic techniques included the calculation of pooled effect sizes with 95% confidence intervals (CIs) for continuous outcomes (standardized mean difference) and dichotomous outcomes (risk ratio), with heterogeneity assessed using the I^2 statistic. Subgroup analyses based on study type, intervention (MSC vs. exosome), timing, dose, route and TBI severity, along with funnel plot assessments for publication bias, were conducted to strengthen the validity of conclusions. The certainty of findings was assessed using the Cochrane RoB Tools 2.0 checklist to assess the risk of bias within the studies included in the present systematic review. The assessment was integrated into the systematic review and meta-analysis process, which adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols and The Cochrane Handbook. This approach ensures a rigorous evaluation of the evidence, aligning with the standards of high-quality systematic reviews that employ established criteria to determine confidence in the body of evidence for key outcomes.

Risk of bias and certainty of evidence. Risk of bias was assessed independently by two reviewers (C and TS) using SYRCLE's tool for animal studies. Domains were rated low, high, or unclear risk. Disagreements were resolved by consensus or a third reviewer (C). Certainty for primary outcomes (mNSS, MWM, lesion volume) was evaluated using an adapted GRADE approach for pre-clinical studies and the results are shown in Table SI. Beginning from 'high', downgrades were applied for risk of bias (SYRCLE), inconsistency (high I^2), indirectness, imprecision and publication bias (funnel plots/Egger's test).

Results

A total of 118,874 records were identified through database searching (Scopus, PubMed, Medline, and Cochrane Library). The PRISMA diagram of the study selection process is illustrated in Fig. 1. Duplicate entries were removed, titles and abstracts were screened, and records irrelevant to MSC, MSC-derived cell-free therapy, or pre-clinical TBI models were excluded; additional exclusions were due to unavailable full texts and failure to meet the inclusion criteria. Ultimately, 46 studies were included in the quantitative synthesis (Fig. 1).

Within this final set of studies, 27 pre-clinical studies that evaluated MSC-based cellular therapies in animal models of TBI were identified; these are presented in Table II (23-49). In addition, 19 pre-clinical studies that investigated MSC-derived cell-free products (such as exosomes or conditioned medium) were identified; these are presented in Table III (12,13,50-66). On the whole, these pre-clinical studies provide the core data for comparing the efficacy of whole-cell MSC therapy and MSC-derived cell-free approaches on functional outcomes, lesion volume, and relevant histopathological and molecular markers.

The total number of animals across all 46 included studies was 1,558; not all studies reported every primary outcome (Fig. S1): The mNSS was reported in studies contributing 403 animals; MWM outcomes were available from studies with 408 animals; and lesion volume data came from studies involving 403 animals. This discrepancy arises as some studies measured only one or two of the three primary outcomes. All analyses were restricted to studies providing the relevant outcome data, ensuring transparency.

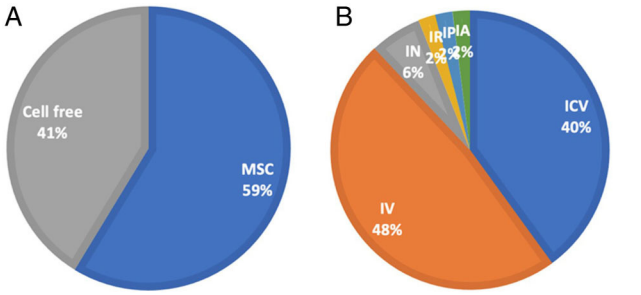

Figure 2. Characteristics of the 46 preclinical studies, with (A) MSC therapy vs. cell-free therapy; and (B) injection route from all studies. MCS, mesenchymal stem cell; IN, intranasally; IR, intra-retrobulbar; IP, intraperitoneal; IA, intra-arterial; IV, intravenous; ICV, intracerebroventricular.

Characteristics of the pre-clinical studies. The key characteristics of the included interventions are summarized in Fig. 2. Among the 46 pre-clinical studies, a greater proportion of experiments used MSC-based cell therapy than MSC-derived cell-free products (59 vs. 41%; Fig. 2A). As regards the delivery route, almost half of the interventions were administered IV (48%), followed by ICV injection in 40% of the studies (Fig. 2B). Only a small minority used alternative routes, such as intranasal delivery (6%) or other less frequently applied approaches (intra-arterial, intraperitoneal and intra-retrobulbar; ≤2% each), indicating that the current pre-clinical evidence is dominated by systemic IV and ICV administration strategies.

Risk of bias. The SYRCLE risk-of-bias assessment across all 46 included pre-clinical studies is summarized in Fig. 3. Overall, the majority of studies had at least one domain with an unclear or high risk of bias. In total, 43% of the assessments were rated as low risk, 53.5% as unclear risk and 3.5% as high risk. Domains related to random sequence generation, allocation concealment, random housing and blinding of caregivers or investigators were predominantly judged as unclear risk due to insufficient reporting. By contrast, the domains of incomplete outcome data, selective reporting and other sources of bias were mostly assessed as low risk.

Publication bias. The visual inspection of funnel plots for the three main outcomes is illustrated in Fig. 4. For mNSS (Fig. 4A), the funnel plot appeared mildly asymmetric, with a relative paucity of small, imprecise comparisons reporting null or detrimental effects and a cluster of small studies favoring MSC-based therapies, suggesting the presence of small-study effects and possible publication bias. A similar pattern of moderate asymmetry was observed for lesion volume (Fig. 4C), where several imprecise studies reported very large reductions in lesion size without a corresponding number of small studies showing neutral effects. By contrast, the funnel plot

Table II. MSC therapy in models of TBI.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
1	Fu, 2015	Rats, 5 groups: Sham; TBI; TBI + BMSC; TBI + OEC; TBI + BMSC + OEC (co-graft), (n=16 per group)	Moderate TBI, weight-drop contusion over right parietal cortex	Acute intracerebral injections of BMSC and/or OEC around the lesion	BMSC, OEC and co-graft significantly reduced NSS, increased $NeuN^+$ neuronal counts and $GAP\text{-}43^+$ axonal sprouting, decreased $GFAP^+$ reactive astrocytes vs. TBI alone; co-graft showed greatest neuronal preservation (all $P<0.05$).	NR	(23)
2	Silachev, 2015	Rats, Sham n=6; TBI + saline IV n=11; TBI + MSC IV n=9; TBI+MSC intra-arterial (IA) n=8	Open-skull weight-drop TBI to left sensorimotor cortex	Single dose 1.5x10□ MSC 24 h after TBI via jugular vein (IV) or internal carotid artery (IA); saline IV control	Intra-arterial and intravenous MSC reduced MRI lesion volume (trend), significantly improved limb-placing scores (IA > IV from day 4) and reduced forelimb asymmetry in cylinder test vs. saline (all $P<0.05$).	NR	(24)
3	Turtzo, 2015	Rats, Total 177 rats; 4 group, rMSC IV vs. saline (total n=34), rMSC IC vs. saline (total n=24), hMSC IV vs. saline (total n=24), hMSC IC vs. saline (total n=28)	Focal controlled cortical impact (CCI) to left frontal motor cortex	rMSC or hMSC $5x10^6$ IV on days 3, 5, and 7 post-TBI; or $1x10^6$ IC 15 min after TBI; all compared with saline	hMSC IV showed no significant reduction in MRI lesion volume or hemispheric loss at days 2-30, no improvement in NSS-R or foot-fault test vs. saline, and <0.0005% cells homed to brain (most trapped in lung/spleen).	No increase in mortality or specific toxicities attributed to MSC; hemorrhagic MRI changes reflect expected CCI evolution in all groups.	(25)
4	Kota, 2016	Rats, 207 male Sprague-Dawley rats divided across sub-cohorts; MWM sub-study: 5 groups (Sham, CCI, CCI + Pro, CCI + MSC, CCI + Pro + MSC) with n=6 per group; BBB cohort n=71.	Moderate-severe CCI to right temporoparietal cortex	Propranolol 10 mg/kg IP at 1 h after CCI; MSC 10^7 cells/kg IV at 72 h; groups: CCI only, CCI + Pro, CCI + MSC, CCI + Pr o+ MSC, Sham	Progesterone significantly reduced brain edema at 24 h and BBB permeability at 96 h; MSC and Pro+MSC increased DCX^+ neurogenesis at day 7 vs. CCI alone ($P<0.05$); no improvement in MWM learning at day 120.	A total of 3 rats died acutely from the primary CCI and were excluded; no additional mortality of MSC treatment.	(26)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
5	Shen, 2016	Rats, 3 groups: Sham; TBI; TBI + BMSC (n=16/ group)	Moderate-severe TBI with modified Feeney CCI to right temporo-parietal cortex	Acute stereotactic intracerebral BMSC (GFP-labeled) injections into pericontusional cortex at 4 sites immediately after TBI; all animals received cyclosporine A	BMSC transplantation significantly improved NSS at days 7 (4.4±1.3 vs. 5.2±1.2) and 14 (2.6±1.2 vs. 4.1±0.8), increased GDNF expression, reduced TUNEL-positive neurons, and enhanced GAP-43 and synaptophysin levels vs. TBI alone (all $P<0.05$).	NR	(27)
6	Danilina, 2017	Rat TBI model: Sham; TBI; TBI + BMSC (N=19)	TBI rat model; MSCs preconditioned with pro-inflammatory factors (e.g., LPS, leukocytes) before transplantation	MSCs with or without inflammatory preconditioning transplanted after TBI	Lesion volume: smaller lesion size; inflamed-MSC group shows greatest reduction. Neurological outcome: better functional scores; inflammatory preconditioning further improves neurological outcome; exact NSS). Cytokines (IL-1α, IL-6, TNF-α) and MMP-2/9 inflammatory priming significantly increases secretion of these factors.	NR	(28)
7	Feng, 2017	105 rats; 3 groups (Sham, TBI, TBI+ BMSC), (N=35/ group)	Weight-drop TBI to right parietal cortex	IV BMSC ($3x10^6$ cells in 1 ml) via tail vein 30 min after TBI	Rotarod: TBI + BMSC vs. TBI (significantly longer fall-latency at post-injury time points; $P<0.05$. mNSS: TBI+BMSC vs. TBI (significantly lower deficit scores at post-injury time points; $P<0.05$). Viable neuron counts significantly increases surviving neurons compared with TBI ($P<0.05$). Donor-derived neurons (SRY^+/ $NeuN^+$): more double-positive cells in BMSC group than TBI ($P<0.05$).	NR	(29)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
8	Guo, 2017	60 male C57BL/6 mice; 4 groups: Control, Sham, TBI, BMSC (n=15/ group)	Controlled cortical impact TBI in mice (4-mm craniotomy, 20 mg weight, 50 cm height, 1 mm deformation)	IV tail-vein injection of BMSCs ($2x10^6$ cells) after TBI (single dose)	BMSC significantly reduced NSS and MWM escape latency, decreased $TUNEL^+$ and $caspase\text{-}3^+$ cells, upregulated VEGF/ Ang-1 expression, and increased microvessel density ($CD34^+$) vs. TBI alone (all $P<0.05$).	NR	(30)
9	Li, 2017	30 male Wistar rats (300-350 g): 4 main TBI groups - saline 6 h (n=5), saline 1 week (n=5), hMSC 6 h (n=10), hMSC 1 week (n=10) after TBI	Controlled cortical impact (CCI) TBI	IV injection of 1 ml saline or ~$3x10^6$ human BMSCs at either 6 h or 1 week post-TBI; all animals underwent serial MRI and behavioral testing up to 3 weeks	hMSC (particularly 6 h post-TBI) accelerated sensorimotor recovery and enhanced peri-lesional white matter reorganization with increased FA and entropy along lesion boundary vs. later administration and control groups.	NR	(31)
10	Bonilla Horcajo, 2018	Severe TBI rat model; four groups established 2 months post-TBI: saline; PRP scaffolds (PRPS) alone; MSCs in saline; MSCs in PRPS; exact number of rats per group not reported in accessible abstract	Severe TBI induced by weight-drop impact to right cerebral hemisphere	At 2 months post-TBI (chronic phase), intralesional transplantation through a small burr hole into the brain lesion cavity: saline; PRPS alone; MSCs in saline; MSCs embedded in PRPS; animals followed for 12 months	Functional outcome: greatest and most sustained functional improvement observed in the MSCs + PRPS group over 12-month follow-up; MSCs alone and PRPS alone produced smaller benefits. Chronic brain damage: PRPS enhanced the benefit of delayed MSC therapy in established severe TBI	NR	(32)
11	Hu, 2018	50 male SD rats total; EG (BM-MSC); CG (saline) (n=25/group)	Craniocerebral injury (CI) induced by free-fall weight (20 g from 15 cm)	EG: intraventricular injection of BM-MSCs 12 h after CI (10 μl, $1x10^4$ cells/rat) into left lateral ventricle; CG:	EPCs, cells/200,000 mononuclear cells, n=12/group. CD31 at 7 days, EG vs. CG (40.10±3.00 vs. 31. 23±2.38; $P<0.05$). NSE: at 7 days, EG vs. CG (44.29±5.29 vs. 30. 03±4.88; $P<0.05$). Microvessel	NR	(33)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
			onto exposed dura over right parietal lobe (3-mm craniotomy)	saline injection (route stated as intraperitoneal)	density: 7 days, EG vs. CG (79.38±2.00 vs. 55.51±3.89; P<0.05); 3 days, EG vs. CG (65.45±3.02 vs. 53.57±2.33; P<0.05). mNSS: reduced.		
12	Shi, 2018	TBI mice divided into groups receiving SOD2-overexpressing BM-MSCs, BM-MSCs, or vehicle; plus *in vitro* BM-MSC cultures), (n=NA)	Traumatic brain injury mouse model (details in full text; abstract specifies ipsilateral cortex and BBB assessment)	BM-MSCs genetically modified to over-express SOD2, transplanted intravenously after TBI; comparator groups included unmodified BM-MSCs and non-MSC controls	SOD2-overexpressing BM-MSCs vs. unmodified BM-MSCs vs. TBI control: reduced apoptosis (*in vitro*), attenuated neuroinflammation, increased SOD and glutathione, decreased MDA, preserved BBB integrity, and improved rotarod performance (all significant).	NR	(34)
13	Hao, 2019	Rats, 26 adult SD rats total: 2 donors for BMSCs; 24 rats with TBI divided into 4 groups: BMSC-Sox2, BMSC, Sox2, PBS (control), (n=8/group)	Controlled cortical injury (CCI) TBI: 1.0-cm craniotomy lateral to sagittal suture; 20-mg steel rod (4-mm diameter) dropped from 30 cm to produce standardized parietal contusion	BMSCs transduced with lentiviral Sox2 (BMSC-Sox2) vs. BMSC alone vs. Sox2 lentivirus alone vs. PBS. Seven days after TBI, 50 μl of BMSC-Sox2, BMSC, Sox2, or PBS injected into injured brain area using Hamilton syringe (cell density $1x10^5$ cells/μl for BMSC-containing groups)	Sox2-BMSCs enhanced neuronal differentiation *in vitro* ($Tuj1^+$/GFP^+, neuron-like morphology) and provided greatest motor recovery at day 7 (NSS: 3.35±0.40 vs. BMSC 4.01±0.50 vs. Sox2 4.97±0.29 vs. PBS 6.26±0.36; (P<0.05)	NR	(35)
14	Hu, 2019	Male Sprague-Dawley rats (200-240 g) randomly assigned	Focal TBI induced by weight-drop onto right parietal	MDL28170 (calpain inhibitor) 50 mM, 1 μl intracranial injection at lesion	MDL28170 + BMSCs significantly reduced pro-inflammatory cytokines, microglial activation, and lesion volume; increased	NR	(36)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
		to: Sham, TBI, TBI + vehicle (20% DMSO), TBI + MDL28170, TBI+ GFP-BMSCs, TBI + MDL28170 + GFP-BMSCs;	cortex after 5 mm craniotomy (50 g hammer, 30 cm drop); sham rats underwent craniotomy without impact.	center, 30 min post-TBI; GFP-BMSCs locally transplanted into lesion site 24 h post-TBI; groups: TBI only, vehicle, MDL28170 only, BMSCs only, MDL28170 + BMSCs.	BMSC survival/proliferation and IL-10; produced greater mNSS improvement at days 7 and 14 compared with BMSCs alone or MDL28170 alone (all $P<0.05$).		
15	Peruzzaro, 2019	39 male Sprague-Dawley rats: TBI + vehicle (HBSS) n=10, TBI+MSCs n=10, TBI+MSCs+ IL-10 n=9, Sham + vehicle n=10; subset used for histology: TBI + vehicle n=7, TBI + MSCs n=7, TBI+MSCs+IL-10 n=6, Sham + vehicle n=7.	CCI to medial frontal cortex (6 mm craniotomy, 3 mm anterior to bregma; depth 2.5 mm, velocity 2.25 m/sec, duration 0.5 sec); sham rats received scalp incision without impact. Rats pair-housed with standard conditions.	At 36 h post-TBI: stereotaxic bilateral transplantation into perilesional cortex. Four injection sites per rat (AP +3.0, ML ± 3.5, DV -3.0 and -1.5 mm); each site 2 μl containing 100,000 MSCs/μl (total 8 μl; 800,000 cells/rat). Groups: TBI + vehicle (HBSS only), TBI + MSCs (GFP-MSC), TBI + MSCs+IL-10 (MSCs engineered via lentivirus to overexpress IL-10), Sham + vehicle (HBSS). Behavioral tests up to 3 weeks (MWM, ladder rung, rotarod).	IL-10-overexpressing MSCs reduced GFAP$^+$ astrocytes, CD86$^+$ microglia, TNF-α, and shifted microglia to CD163$^+$ phenotype, improved ladder rung motor coordination, and provided partial cognitive benefit in MWM reversal vs. MSCs alone and vehicle ($P<0.05$)	Histology showed sparse GFP/Hoechst-labeled transplanted cells near injection tracks, but no evidence of tumorigenesis or overt toxicity	(37)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
16	Wu, 2019	C57BL/6 mice, randomly divided into 5 groups: Sham; TBI only; TBI + GFP-BMSCs; TBI + GFP-NT3-BMSCs; TBI + GFP-NT3P75-2-BMSCs. Behavioral tests: mNSS and rotarod. Brain edema evaluation: Immuno-fluorescence (Iba1, GFAP, GFP): (N= 10 per group)	Mouse CCI TBI model: impact velocity 4 m/sec, depth 2.0 mm, diameter 3 mm over right hemisphere (AP -5 mm, ML + 5 mm from bregma).	At 24 h post-TBI, GFP-labelled BMSCs (GFP only, GFP-NT3, or GFP-NT3P75-2) were locally transplanted into the lesion core. Groups: Sham (no TBI, no cells); TBI (no treatment); TBI + GFP-BMSCs; TBI+GFP-NT3-BMSCs; TBI + GFP-NT3P75-2-BMSCs.	NT3P75-2-BMSCs significantly increased graft survival, reduced brain edema and lesion volume, improved mNSS and rotarod performance, decreased microglial/astrocyte activation, and inhibited P75/JNK/Bax-mediated apoptosis vs. GFP-BMSCs and GFP-NT3-BMSCs (all $P<0.05$).	NR	(38)
17	Yan, 2019	Wistar rats,Total: 44 adult male (250 g) used for TBI model and treatment allocation. Animals were divided into 4 groups: A: TBI + immunosuppressor + BMSCs/scaffold; B: TBI + BMSCs/ scaffold; C: TBI + BMSCs stereotactic injection; D: (n=8/group)	Rat TBI model based on Feeney's free-fall method: 10-mm cranio-tomy adjacent to sagittal suture between lambda and bregma, intact dura; weight-drop impact produced cortical contu-sion; all rats anesthetized with 10% chloral hydrate.	Groups A and B: at 72 h post-TBI, collagen-chitosan porous scaffold seeded with BrdU-labelled BMSCs ($2x10^6$ cells/μl, cultured 48 h) was placed directly into the lesion cavity (A with immuno-suppressor, B without). Group C: single stereotactic injection of BMSCs (no scaffold). Group D: TBI	BMSC/scaffold transplantation reduced neuronal necrosis, promoted neurogenesis (↑BrdU/ NSE+ and BrdU/GFAP+ cells at days 7-14), increased VEGF expression in hippocampus, and significantly improved mNSS recovery and MWM spatial learning/memory (shorter escape latency) vs. BMSC injection alone or vehicle (all superior in scaffold groups).	NR	(39)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
				model only (no cells, no scaffold). All animals underwent behavioral testing (mNSS, Morris Water Maze) and histology (HE, BrdU/NSE, BrdU/ GFAP, VEGF IHC).			
18	Huang, 2021	C57BL/6 male mice (15-20 g, SPF). Mice were randomly assigned to 4 groups: TBI + PBS; TBI+ BMMSCs; TBI + BMMSCs-shLuci, (n=8)	Mouse CCI TBI model: 4-mm diameter craniotomy over right parietal cortex; maximum depression depth 3 mm at impact velocity 4 m/s, 90° angle; impact site 2.5 mm lateral to sagittal suture and 3.5 mm posterior to bregma.	Model ischemic stress; transduced with shRNA lentiviruses targeting Rac1, p22-phox, p47-phox, or p67-phox. *In vivo*: at 24 h post-TBI, 5 μl cell suspension ($5x10^5$ BMMSCs) was injected into lesion center	Rac1-silenced BMMSCs strongly reduced OGD-induced ROS *in vitro*, significantly improved mNSS and rotarod performance days 3-21, decreased apoptosis/ $TUNEL^+$ cells and oxidative stress, upregulated VEGFA/ MMP-2, and provided superior neuroprotection vs. non-silenced BMMSCs and PBS (all $P<0.05$).	NR	(40)
19	Song, 2020	Adult Sprague Dawley rats: Sham, TBI, TBI + MH, TBI + BMSCs, TBI + MH + tsBMSCs (n=25/ group)	Adult Sprague-Dawley rats with severe TBI; groups: sham, TBI, TBI + mild hypothermia (MH), TBI + BMSCs, TBI + MH + tsBMSCs	Combination of mild hypothermia and temperature-sensitive BMSC transplantation after severe TBI vs. TBI alone and single-treatment groups (MH or BMSCs).	mNSS and brain edema: TBI + MH + tsBMSCs vs. TBI (significantly lower mNSS and brain water content at measured time points, $P<0.05$; better than single MH or BMSC). Serum biomarkers: S100β, NSE, LDH, CK and blood glucose signifi-cantly reduced vs. TBI and single-treatment groups. TUNEL: lowest apoptotic index in combination group. GLUT-3 expression modulated toward sham levels compared with TBI.	NR	(41)

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Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
20	Yuan, 2020	Adult male C57BL/ 6J mice, (H-BMSC group) (n=8/group)	Adult male C57BL/6J mice with CCI-induced TBI; groups: sham, control (TBI + DMEM), normoxic BMSCs (N-BMSC), hypoxic BMSCs (H-BMSC); n=8 per group.	Hypoxia-preconditioned BMSCs (1% O_2 for 8 h) transplanted 24 h after TBI vs. DMEM vehicle; normoxic BMSCs as comparator.	Hypoxia-preconditioned BMSCs (H-BMSC) significantly improved wire-hanging, grid-walking, cylinder and MWM performance (escape latency 18 vs. 28 sec N-BMSC vs. >55 sec control), reduced lesion volume, enhanced remyelination (↑MBP/NF200, ↑NG2+/BrdU+ OPCs and APC+/ BrdU+ oligodendrocytes), and activated mTOR/HIF-1α/VEGF pathway vs. normoxic BMSCs and control (p	NR	(42)
21	Li, 2021)	C57BL/6 mouse: Sham, TBI, TBI + GH/MSC (n=6/group)	C57BL/6 mouse moderate TBI model (controlled cortical impact) with cortical lesion and econdary ischemia, oxidative stress, and neuroinflam-mation.	Injectable dual-enzymatically cross-linked gelatin hydrogel (HRP + ChOx) used as 3D scaffold to load BMSCs; *in vivo* implantation of BMSC-laden soft GH into TBI lesion cavity vs. BMSC alone, GH alone, and TBI only.	GH/BMSC implants significantly increased BMSC viability, neural differentiation, and neurotrophin secretion *in vitro*; reduced lesion volume, inflammation, and neuronal apoptosis; increased endogenous neural cell survival/ proliferation; and improved mNSS and MWM performance (shorter escape latency, better spatial learning/memory) vs. TBI and GH-only groups (P<0.05).	NR	(43)
22	Deng, 2021	mice: Sham, TBI BMMSC-shRac1 group) (n=8/group)	Controlled cortical impact TBI in mice	Intravenous trans-plantation 24 h post-TBI of BMMSCs with Rac1 knockdown (BMMSCs-shRac1), compared with BMMSCs, BMMSCs-shLuci, or PBS	mNSS: BMMSCs-shRac1 vs. PBS (lower scores from day 3-21 post-TBI, P<0.01); rotarod: longer latency to fall vs. PBS and BMMSCs-shLuci (P<0.01); lesion volume ratio: BMMSCs-shRac1 vs. PBS (smaller cavity at day 21, P<0.05); brain water content: reduced vs. PBS at days 7 and 21 (P<0.05); BMMSC-shRac1 enhanced migration to lesion site and increased neuronal survival markers vs. control groups	NR	(44)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
23	Ma, 2021	Rats: Sham, TBI, NR (BMSCs/SA/ Col/SDF-1 (n=8/group)	Rat TBI model with lesion cavity and hostile micro-environment (oxidative stress, inflammation, poor cell survival).	Sodium alginate/ collagen type I hydrogel incorporating SDF-1 (SA/Col/ SDF-1) loaded with BMSCs, implanted into TBI lesion; sustained SDF-1 release and SDF-1/ CXCR4 activation.	SA/Col/SDF-1 scaffold + BMSCs significantly improved motor/ cognitive function, reduced anxiety/depressive-like behavior, esion size, neuronal death and lneuroinflammation, enhanced BMSC recruitment and neurogenesis via SDF-1/CXCR4-FAK/ PI3K/AKT pathway vs. other groups (P<0.05).	NR	(45)
24	Chen, 2020	Sprague-Dawley rats: Sham-operated control, TBI, TBI + HUCDMSC (n=10/group)	Acute traumatic brain injury in adult male Sprague-Dawley rats	Intravenous injection of HUCDMSC ($1.2x10^6$ cells) at 3 h post-TBI	Treatment group significantly improved corner/inclined plane tests, reduced ischemic volume, apoptosis (↓Bax/cleaved-caspase3/PARP), fibrosis (↓Smad3/TGF-β), oxidative stress (↓NOX-1/2/p22phox), brain edema/ DNA-damage (↓AQP4/γ-H2AX), inflammation (↓CD14/GFAP/ F4/80); increased angiogenesis (↑VEGF/SDF-1α/CXCR4) and neural integrity (↑NeuN/nestin/ DCX) vs. TBI alone (all P<0.001-0.0001).	NR	(46)
25	Zhou, 2016	Sprague-Dawley rats: TBI, UC-MSCs, HBO, UC-MSCs + HBO (n=40/group)	Severe traumatic brain injury in Sprague-Dawley rats	UC-MSC intravenous injection via tail vein ($1x10^6$ cells/ml, 1 ml) combined with HBO therapy (0.2 MPa, 4 times/ day for 4 days)	UC-MSC + HBO combination therapy most effectively reduced AQP4, improved neurological scores and MWM performance (shorter escape latency, more platform crosses), reduced lesion cavities/scarring, increased GAP-43 and grafted cell survival (54.21±14.52 vs. 30.53±9.43 in UC-MSC alone) vs. monotherapy and TBI groups.	NR	(47)

Table II. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/ Model	Treatment	Results	Adverse effects	(Refs.)
26	Li, 2019	Wistar rats: Saline, hMSCs (n=10/group)	Traumatic brain injury in Wistar rats	Human bone marrow stromal cells (hMSCs) intravenous injection (~3x10^6 cells) at 1 week post-TBI	hMSC treatment accelerated recovery of FA and AWF in corpus callosum/external capsule (significant from 3-5 weeks vs. saline), increased MK at 3 weeks, reversed RK decline earlier, and significantly improved spatial memory in mMWM vs. saline group (all P<0.05).	NR	(48)
27	Bayat Tork, 2025	Male Wistar rats: Sham, TBI, TBI + PBS, TBI + Nano-SDF, TBI + NSCs, TBI + Nano-SDF + NSCs (n=10/group)	Traumatic brain injury induced by controlled cortical impact in male Wistar rats	Implantation of nano-scaffold containing SDF-1 (PLLA-PCL with Young's modulus 3.21 kPa) loaded with NSCs into lesion cavity post-TBI	SDF-1 scaffold + NSC significantly increased proliferation (2.1-fold), migration (1.8-fold), neuronal differentiation (NeuN + 45% vs. 28%), graft survival (62 vs. 38%), neurite outgrowth, synaptogenesis (PSD-95/Syn 1.7-fold), mNSS (12→5 at 28 days), and MWM latency (↓35%) vs. control scaffold (all P<0.05-0.001).	NR	(49)

MSC, mesenchymal stem cell; TBI, traumatic brain injury; BMSC, bone marrow-derived mesenchymal stem cell; OEC, olfactory ensheathing cell; MWM, Morris water maze; CCI, controlled cortical impact; Pro, propranolol; LPS, lipopolysaccharide; EPCs, endothelial progenitor cells; NA, not available; NR, not reported.

Table III. MSC-derived cell-free therapy in models of TBI.

Study no.	First author, year of publication	Animal	Pre-condition/model	Treatment	Results (condensed, with exact numbers where reported)	Adverse effects	(Refs.)
1	Zhang, 2015	Wistar rat: TBI + MSC-exosomes; TBI +vehicle; sham (n=8/group)	Wistar rat moderate TBI (controlled cortical injury/ contusion model)	Single IV tail-vein injection of 100 μg MSC-derived exosomal protein at 24 h post-TBI; vehicle control	MSC-derived exosomes significantly shortened MWM escape latency, reduced mNSS and foot-fault errors days 14-35, decreased lesion volume, increased angiogenesis ($BrdU^+/EBA^+$) and neurogenesis($BrdU^+/DCX^+$ & $BrdU^+/NeuN^+$) vs. vehicle (all $P<0.05$).	NR	(50)
2	Zhang, 2017	Wistar rats; exosomes in 2D or 3D, liposomes (n=8/group)	Controlled cortical impact (CCI) TBI in Wistar rats	Single IV tail-vein injection at 24 h post-TBI: exosomes from 2D-hMSC culture, exosomes from 3D collagen scaffold-grown hMSCs, or liposome control; behavioral follow-up to day 35	2D- and 3D-exosomes significantly improved MWM spatial learning, reduced NSS and foot-fault errors days 14-35, increased angiogenesis and neurogenesis, decreased neuroinflammation vs. liposome control (all $P<0.05$); 3D-exosomes superior to 2D in MWM performance; no difference in lesion volume.	NR	(51)
3	Ni, 2019	59 male C57BL/ 6 mice (12-14 weeks): Sham + PBS n=17, TBI + PBS n=21, TBI + exosomes; n=21.	Controlled cortical impact (CCI) to right hemisphere (velocity 4 m/sec, depth 1.0 mm, 150 msec duration) after 4 mm cranio-tomy; sham: same surgery without impact.	Single retro-orbital IV injection 15 min post-TBI: TBI + exosomes group received 30 μg total protein of BMSC-derived exosomes in 150 μl PBS; TBI + PBS and Sham + PBS received equal volume PBS.	MSC exosomes significantly improved mNSS and rotarod at days 7-14, reduced lesion area at day 14, decreased apoptosis (↑Bcl-2, ↓Bax), early inflammation (↓IL-1β/TNF-α), and shifted microglia to M2 phenotype (↓iNOS, ↑Arg1/CD206) vs. PBS (all $P<0.05$-0.01).	NR	(12)
4	Xu, 2020	Rats: sham group, PBS group, MSCs-Exo group, BDNF-induced MSCs-Exo group (n=12/group)	Adult rats with TBI induced by electric controlled cortical impact; groups: sham (n=12), PBS (TBI + PBS, n=12), MSCs-Exo (n=12), BDNF-induced MSCs-Exo (n=12).	Single tail-vein injection of BDNF-induced MSC exosomes (100 μg total protein in 0.5 ml PBS) 24 h post-TBI vs. PBS injection; standard MSC exosomes as additional comparator.	BDNF-engineered exosomes significantly reduced mNSS days 7-28, shortened MWM escape latency and increased target quadrant time days 31-35, decreased TUNEL+ cells, improved neuronal morphology and neuro-regeneration markers vs. standard MSC-Exo and PBS (all $P<0.05$; effects mediated by miR-216a-5p).	NR	(52)

Table III. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/model	Treatment	Results (condensed, with exact numbers where reported)	Adverse effects	(Refs.)
5	Zhang, 2020	Adult male Wistar rats: Exo-100 μg, D1 group used here as Exp (n=8 /group)	Adult male Wistar rats with unilateral moderate CCI to left parietal cortex (6-mm tip, 4 m/s, 2.5-mm depth), causing cortical lesion, hippocampal damage and white-matter injury.	Single IV tail-vein injection of human MSC-derived exosomes (100 μg protein in 0.5 ml PBS) at 1 day post-TBI (Exo-100, D1) vs. PBS; study also tested 50/200 μg and 100 μg at days 4 or 7.	MSC exosomes (50-200 μg) dose-dependently improved mNSS, foot-fault and MWM performance days 7-35 (optimal at 100 μg), reduced hippocampal neuronal loss, increased vascular density/$BrdU^+$/EBA^+ cells, and decreased $CD68^+$ microglia/macrophages and $GFAP^+$ astrocytes vs. PBS (all $P<0.05$; best effects when given day 1).	NR	(13)
6	Zhang, 2021	Young male Wistar rats: TBI + Exo-17-92 (n=8/group)	Young male Wistar rats with unilateral moderate cortical contusion (CCI); 24 TBI animals + 8 sham; no mortality during 35-day follow-up.	Single IV injection of 100 μg exosomes (Exo-17-92 cluster-enriched) in 0.5 ml PBS at 24 h post-TBI; comparators: Exo-empty (100 μg) and Vehicle PBS.	miR-17-92-enriched exosomes significantly improved mNSS (77% vs. 63% reduction), foot-fault (65 vs. 48%), adhesive-removal (58 vs. 21%), and MWM performance; reduced DG/CA3 neuronal loss, increased angiogenesis/neurogenesis, and decreased $CD68^+$/$GFAP^+$ cells more effectively than empty exosomes and vehicle (all $P<0.05$)	NR	(53)
7	Wen, 2022	C57BL/6J male mice, (TBI + Exo, various timepoints) (n=5/group)	C57BL/6J male mice with lateral fluid percussion TBI; microglia-mediated neuroinflammation and neuronal apoptosis present.	Tail-vein injection of BMSC-derived exosomes (200 μl, $6.3x10^{10}$ particles/ml) daily after TBI (1-7 days) vs. saline additional lentiviral modulation of miR-181b (up/down) in separate TBI cohorts.	BMSC-exosomes significantly shifted microglia to M2 phenotype (↑CD206+, ↓CD86+), reduced IL-1β/IL-6/TNF-α, increased IL-10/TGF-β *in vitro*; decreased cortical apoptosis, neuroinflammation and promoted M2 polarization *in vivo* via miR-181b-mediated IL-10/STAT3 pathway.	NR	(54)
8	Zhang, 2024	C57BL/6 wild-type mice: Sham, TBI, TBI + antagomir 9-5p (n=8/group)	Traumatic brain injury-induced acute lung injury in C57BL/6 wild-type mice	Injection of brain-derived exosomes (100 μg via tail vein) or antagomir 9-5p treatment	TBI induced pulmonary ferroptosis (↑ROS/MDA/Fe^{2+}, ↑miR-9-5p, ↓Scd1); miR-9-5p antagomir significantly reduced ferroptosis markers, normalized ferroptosis-related proteins, decreased inflammatory cytokines/cells in BALF, and attenuated acute lung injury severity vs. TBI alone (all $P<0.05$).	NR	(55)

Table III. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/model	Treatment	Results (condensed, with exact numbers where reported)	Adverse effects	(Refs.)
9	Wang, 2025	Mice: Sham; PBS; NExo; SeNExo (n=NA)	Traumatic brain injury and spinal cord injury in murine models	Intravenous administration of SeNExo (selenized neural stem cell-derived exosomes)	SeNExo significantly enhanced ROS scavenging and BBB penetration, reduced cerebral lesion size, alleviated neuronal apoptosis, restored glia homeostasis, remodeled glia-neuron networks, decreased neuronal loss, and improved neurological/locomotor function vs. control in TBI and SCI models (all P<0.01).	NR	(56)
10	Qian, 2024	Sprague Dawley rats: Sham, TBI, TBI + miR-148a-5p agomir, TBI + miR-148a-3p antagomir (n=20/group)	Traumatic brain injury in male Sprague Dawley rats	Intracerebroventricular infusion of miR-148a-3p agomir (5 nmol, 20 μl) or antagomir (5 nmol, 20 μl) 20 min after TBI	miR-148a-3p-enriched exosomes promoted M2 polarization (↑Arg-1/IL-4/IL-10, ↑CD206, ↓CD32/iNOS), reduced IL-1β/IL-6/TNF-α, inhibited p-ERK/NF-κB, decreased brain edema, mNSS and lesion area v.s TBI control (all P<0.05-0.001).	NR	(57)
11	Wang, 2024	Mice: Sham, rmTBI, rmTBI + EXO, rmTBI + EXO-124 (n=8/group)	Repetitive mild traumatic brain injury in adult male C57BL/6J mice	Intranasal delivery of microglia-derived exosomes overexpressing miR-124-3p (100 μg total, 3 doses at 24 h intervals) post-rmTBI	miR-124-3p-overexpressing microglial exosomes significantly suppressed ER stress markers (GRP78/p-IRE1α/XBP1s/CHOP/cleaved caspase-12/3) and neuronal apoptosis *in vitro* and *in vivo* via direct targeting of IRE1α vs. control exosomes (all P<0.0001).	NR	(58)
12	Liu, 2023	Sprague-Dawley rats: Sham, TBI, 3D-CC-NExos, 3D-CC-INExos (n=30/group)	Traumatic brain injury in male Sprague Dawley rats	Implantation of 3D-printed collagen/chitosan scaffolds (2 mm diameter, 2 mm height) loaded with IGF-1-pretreated NSC exosomes into lesion cavity post-TBI	3D-CC-INExos scaffold significantly shortened MWM escape latency, reduced mNSS at day 28, decreased lesion cavity, increased nestin/NF/MBP/NeuN/MAP2/SYP/CD31/α-SMA, reduced CD68/Iba-1/TUNEL, and improved neuronal/myelin ultrastructure vs. 3D-CC-NExos and TBI groups (all P<0.05-0.01).	NR	(59)

Table III. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/model	Treatment	Results (condensed, with exact numbers where reported)	Adverse effects	(Refs.)
13	Liu, 2025	Mice: Injury (n=4-11); Injury + A-Exo (n=4-11); Injury + Y-Exo (n=11/group)	Repeated mild traumatic brain injury in C57BL/6 mice	Intranasal administration of brain-derived exosomes from aged mice (A-Exo) post-rmTBI	Y-Exo significantly improved Y-maze alternations, MWM crossings/latency/target time, reduced TUNEL^{+} apoptotic neurons, increased cell viability, and decreased apoptosis vs. A-Exo; Tnfrsf25 knockdown and desoxycortone/propantheline inhibitors reversed A-Exo-induced apoptosis (all P<0.05-0.0001).	NR	(60)
14	Kim, 2025	Mice: Sham, TBI, TBI + NI-Exo ($1x10^4$ particles/ml), TBI + NI Exo ($1x10^5$ particles/ml) (n=30/group)	Traumatic brain injury in C57BL/6 mice	Intracerebroventricular injection of NI-Exo ($1x10^4$ or $1x10^5$ particles/ml) 1 h post-TBI	NI-Exo significantly reduced IL-6/IL-1β/TNF-α, increased IL-4/IL-10, improved rotarod/EBST/cylinder performance, enhanced cell viability/NeuN/MAP2, decreased p53/ROCK1/Bax/p-ERK/p-p38/p-NF-κB vs. TBI alone (all P<0.001).	NR	(61)
15	Moss, 2021	Mice: Sham (n=15); TBI (n=30); TBI + EXO (n=21); TBI + EXO-M (n=21)	Traumatic brain injury induced by controlled cortical impact in mice	Intranasal delivery of hASC-derived exosomes (hASCexo) containing MALAT1 at 48 hours post-TBI; exosomes depleted of MALAT1 as control	MALAT1-enriched exosomes significantly improved EBST motor recovery, RAWM cognitive performance, reduced cortical damage and MHCII^{+} microglia, and modulated inflammation/NRTK3-TrkC expression vs. TBI and MALAT1-depleted exosomes (all P<0.05).	NR	(62)
16	Zhang, 2021	Sprague-Dawley rats: Sham, Sham + AS-Exo, TBI, TBI + AS-Exo (n=15/group rats)	Traumatic brain injury in adult male Sprague-Dawley rats and C57BL/6 mice ($Nrf2^{+/+}$ and Nrf2-KO)	Intravenous injection of astrocyte-derived exosomes (AS-Exos, 100 μg) via tail vein 30 min post-TBI	AS-Exo significantly reduced mNSS, brain edema, lesion volume, ROS/mitochondrial H_2O_2 and apoptosis (↓TUNEL/CC-3/Bax), improved forelimb placement, rotarod, MWM performance and increased viable neurons, SOD/CAT/GSH, Nrf2/HO-1 vs. TBI (all P<0.05-0.01); effects abolished in Nrf2-KO mice.	NR	(63)

Table III. Continued.

Study no.	First author, year of publication	Animal	Pre-condition/model	Treatment	Results (condensed, with exact numbers where reported)	Adverse effects	(Refs.)
17	Pischiutta, 2025	Mice: TBI saline, TBI NB, TBI CM, TBI SYNT (n=8/group)	Traumatic brain injury in mice	Intravenous administration of MSC-conditioned medium (CM) or synthetic cocktail (SYNT: prostaglandins and kynurenine) post-TBI	SYNT and CM significantly reduced *in vitro* neuronal death, improved sensorimotor function and memory up to 4-6 months, decreased microglia activation/astrogliosis at 6 months; CM additionally reduced contusion volume at 5 months vs. saline (all P<0.05).	NR	(64)
18	Chen, 2020	Sprague-Dawley rats, Sham-operated control; TBI; TBI + HUCDMSC (n=10/group)	Traumatic brain injury in male Sprague-Dawley rats (hydraulic injury model)	Intracerebroventricular injection of astrocytes-derived exosomes carrying GJA1-20k (10 μg) post-TBI	GJA1-20k exosomes significantly increased neuronal uptake, reduced apoptosis 22%, improved mitochondrial function (ATP ↑1.5-fold, ROS ↓40%) *in vitro*; reduced lesion volume 35%, increased neuronal survival 1.8-fold, decreased TUNEL$^+$ apoptosis 28% and Bax/Bcl-2 ratio *in vivo* vs. control exosomes (all P<0.05-0.01).	NR	(65)
19	Zhuang, 2023	Male Sprague-Dawley rats: Sham, TBI + Vehicle, TBI + BMSCs-Exos, TBI + SB203580, TBI + BMSCs Exos miR-124-3p, TBI + BMSCs Exos miR-124-3p inhibitor (n=22/group)	Traumatic brain injury in male Sprague-Dawley rats	Intravenous injection of BMSCs-derived exosomes enriched with miR-124-3p (BMSCs-Exos^ miR-124-3p, 200 μg) at 24 h post-TBI	miR-124-3p was downregulated in TBI and directly targeted p38 MAPK. miR-124-3p-enriched BMSC-derived exosomes reduced apoptosis and p38 MAPK expression while increasing GLT-1 *in vitro*. *In vivo*, they decreased lesion volume and neuronal cell death, enhanced neuronal survival, and improved cognitive performance, with effects comparable to the p38 inhibitor SB203580.	NR	(66)

MSC, mesenchymal stem cell; TBI, traumatic brain injury; Exo, exosome; BMSC, bone marrow-derived mesenchymal stem cell; OEC, olfactory ensheathing cell; MWM, Morris water maze; CCI, controlled cortical impact; Pro, propranolol; LPS, lipopolysaccharide; NA, not available; NR, not reported.

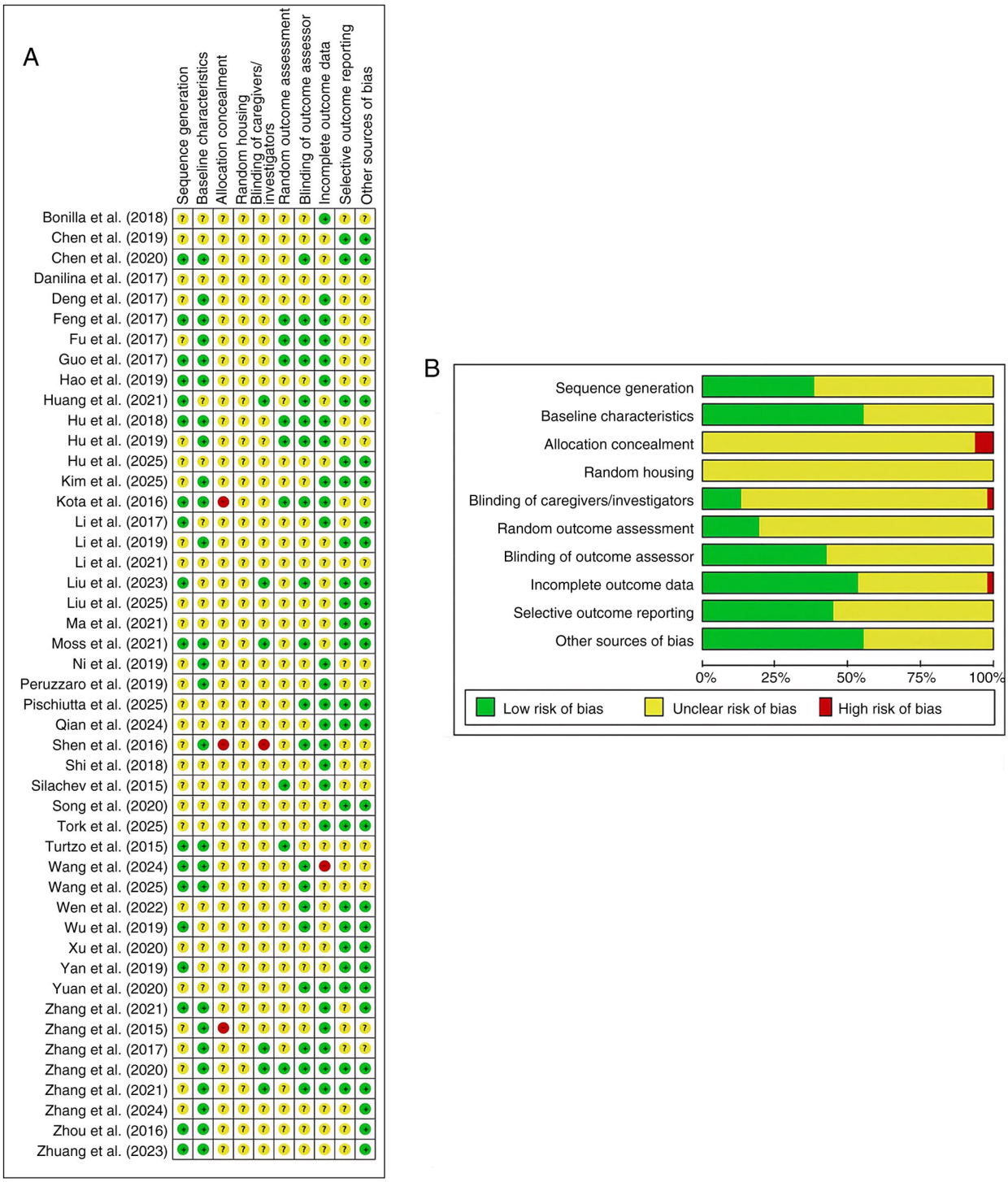

Figure 3. Risk of bias assessment with SYRCLE of (A) from all MSC and MSC-derived cell-free therapy studies; (B) percentage of high risk (red), unclear risk (yellow), low risk (green). MCS, mesenchymal stem cell.

for MWM (Fig. 4B) was more symmetric around the pooled effect line, providing no strong visual evidence of publication bias. Nevertheless, given the high between-study heterogeneity and the experimental nature of the included studies, all pooled estimates should be interpreted with caution, particularly for mNSS and lesion volume.

Stratified meta-analysis. The meta-analysis was then stratified by outcome domain. For global neurological function, 92 comparisons reporting mNSS were pooled. Using a random-effects model with the Hartung-Knapp adjustment, MSC-based and MSC-derived cell-free therapies significantly reduced mNSS scores compared with the control (95% CI; $P<0.0001$; $I^2=100\%$), indicating improved neurological recovery. The corresponding pooled and stratified effects are presented in Fig. 5.

For cognitive performance, 51 comparisons reporting MWM outcomes were combined. The pooled analysis demonstrated substantially lower (improved) MWM scores in the treatment groups than in the controls [overall mean

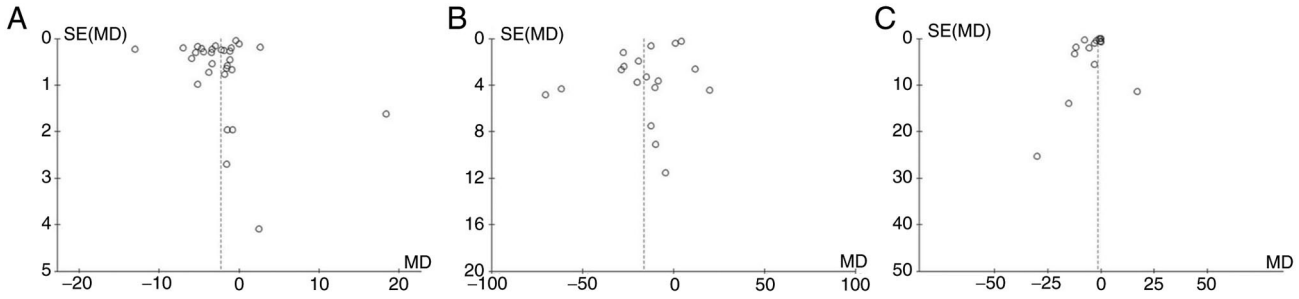

Figure 4. Funnel plots for all groups for (A) the modified neurological severity score, (B) Morris water maze test, and (C) lesion volume. MD, mean difference.

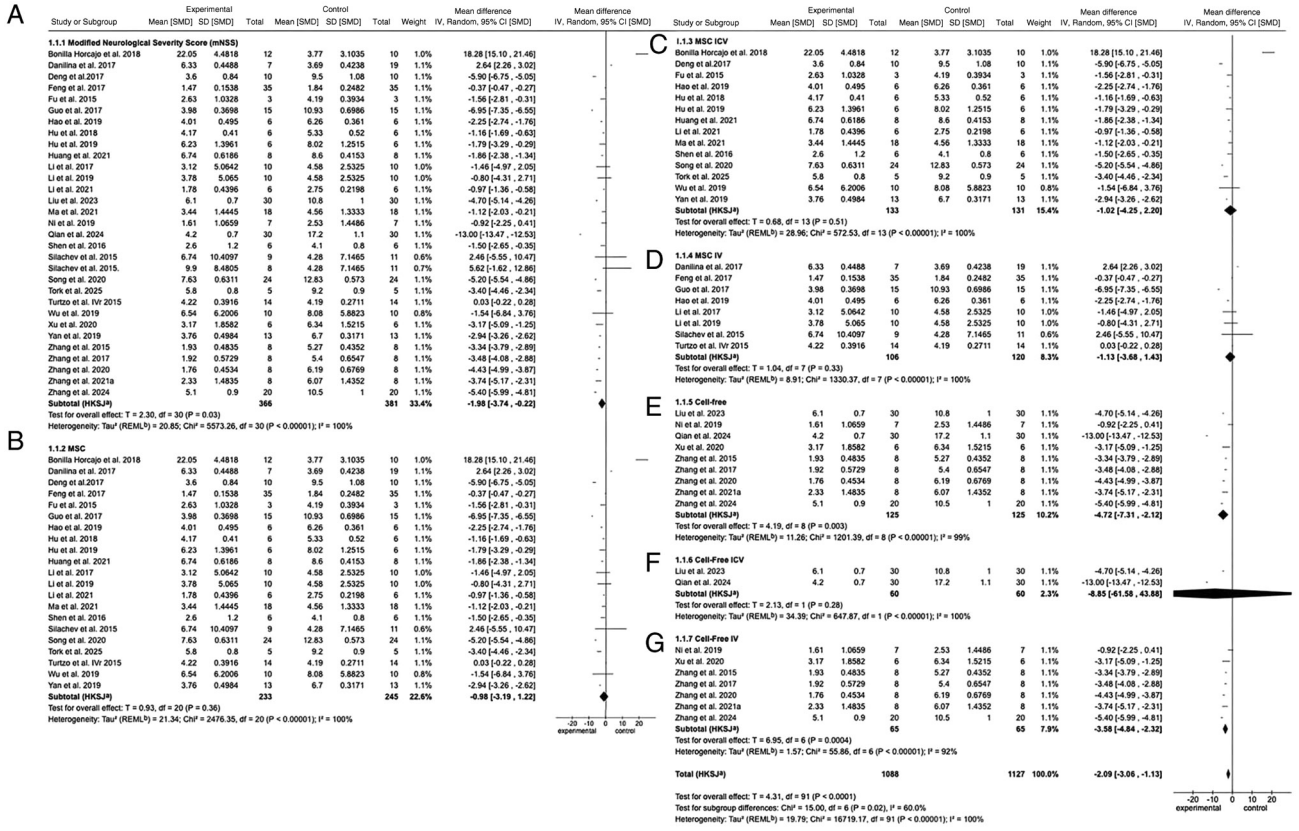

Figure 5. Forest plots demonstrating mean effect size and 95% CI values of mNSS for (A) all routes from MSC and cell-free groups; (B) MSC groups; (C) MSC ICV route groups, (D) MSC IV route groups, (E) cell-free groups, (F) cell-free ICV route groups, and (G) cell-free IV route groups. CI, confidence interval; mNSS, modified neurological severity score; MCS, mesenchymal stem cell; ICV, intracerebroventricular; IV, intravenous.

difference (MD), -16.72; 95% CI, -22.87 to -10.58; P<0.00001; I^2=100%], these findings are presented in Fig. 6. For structural brain damage, 50 comparisons reporting lesion volume were analyzed and a robust reduction in lesion volume was observed in the treated animals compared with the controls (overall MD, -0.15; 95% CI, -0.17 to -0.14; P<0.00001; I^2=98%) (Fig. 7). Overall, across neurological deficit (mNSS), cognition (MWM) and lesion volume, stratified analyses consistently favored MSC-based or MSC-derived cell-free therapies in pre-clinical TBI models, albeit with considerable between-study heterogeneity.

Subgroup analysis (cell-based vs. cell-free and route of administration). Subgroup analyses were then performed according to product type (MSC vs. MSC-derived cell-free products) and route of administration (ICV, IV or other routes). For mNSS, subgroup analyses suggested that the magnitude of benefit varied across intervention types (test for subgroup differences: P=0.02; I^2=60%). As shown in Fig. 5, larger pooled improvements for MSC-derived cell-free products were observed in mNSS (MD, ~-4.7) compared with MSC-based cellular therapies, while the ICV delivery of cell-free products yielded very imprecise estimates with wide confidence intervals due to the small number of experiments. Despite this variability, all subgroups favored treatment over the control.

For MWM, consistent cognitive benefits were observed across subgroups as shown in Fig. 6. Both MSC-based and cell-free interventions, delivered either ICV or IV, improved MWM performance to a similar extent, and the test for subgroup differences was not significant (P=0.78; I^2=0%).

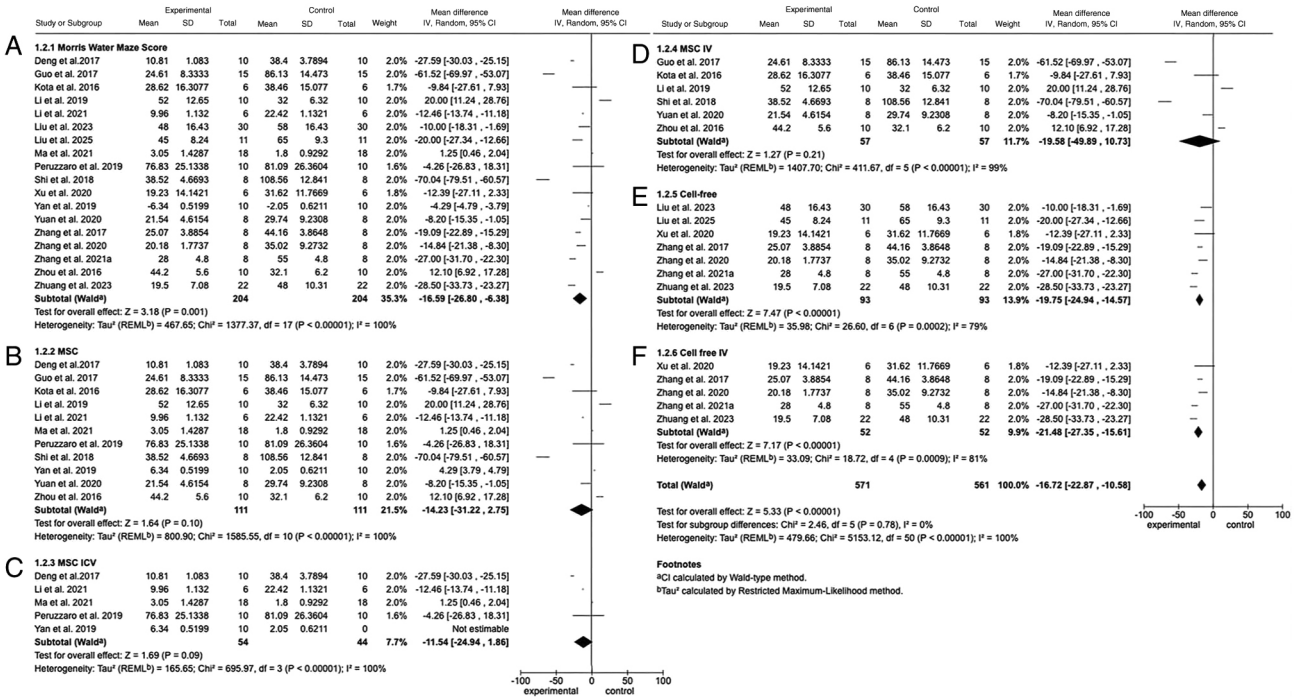

Figure 6. Forest plots demonstrating mean effect size and 95% CI values of MWM for (A) all routes from MSC and cell-free groups; (B) MSC groups; (C) MSC ICV route groups, (D) MSC IV route groups, (E) cell-free groups, and (F) cell-free IV route groups. CI, confidence interval; MWM, Morris water maze test; MCS, mesenchymal stem cell; ICV, intracerebroventricular; IV, intravenous.

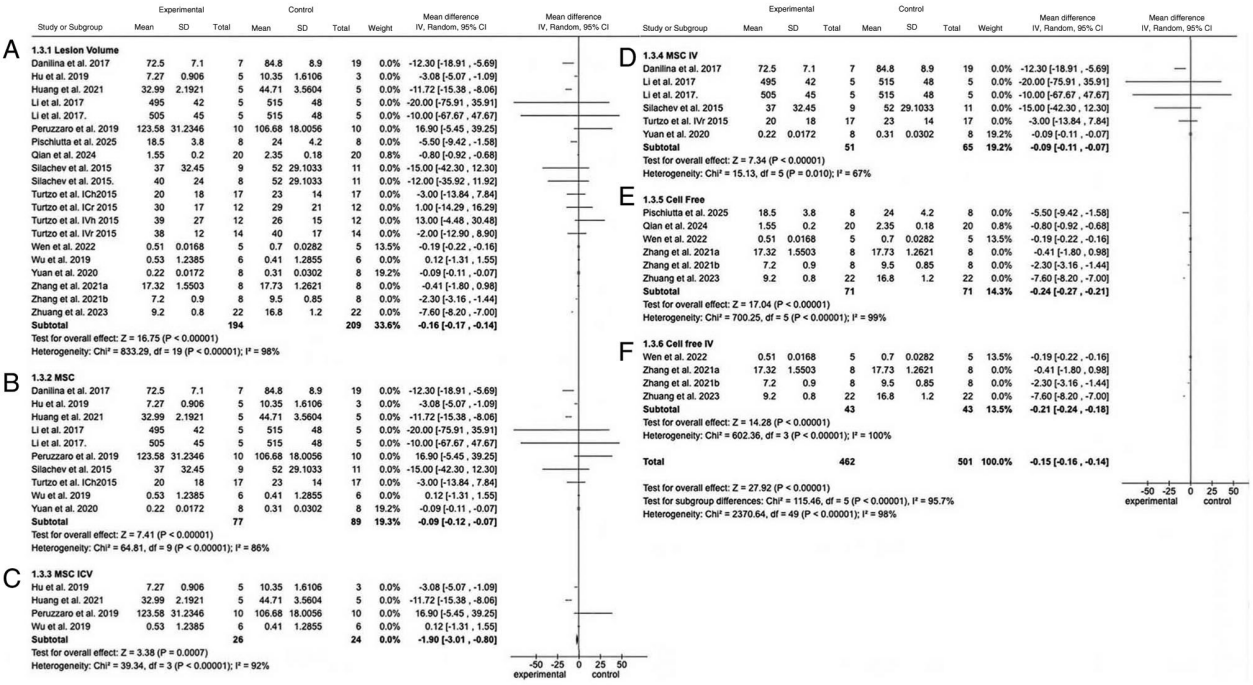

Figure 7. Forest plots demonstrating mean effect size and 95% CI values of lesion volume for (A) all routes from MSC and cell-free groups; (B) MSC groups, (C) MSC ICV route groups, (D) MSC IV route groups, (E) cell-free groups, and (F) cell-free IV route groups. CI, confidence interval; MCS, mesenchymal stem cell; ICV, intracerebroventricular; IV, intravenous.

This finding suggests that, for cognitive recovery, the beneficial effect is relatively robust to the choice of MSC product type and delivery route.

For lesion volume, subgroup analyses revealed clearer differences between modalities (test for subgroup differences: $P<0.00001$; $I^2=95.7\%$), As shown in Fig. 7, MSC-derived cell-free therapies produced the largest reductions in lesion volume, particularly when delivered intravenously (pooled MD, -0.21 to -0.24), whereas MSC-based cellular therapies exhibited, minimal, but still significant effects (pooled MD, -0.09). Nevertheless, each subgroup exhibited a shift in favor of treatment compared with the control, indicating that both

MSC and MSC-derived cell-free approaches confer structural neuroprotection, with cell-free products, particularly via IV administration, tending to provide the greatest lesion-reducing effect.

Taken together, these subgroup findings support a consistent neuroprotective signal across different MSC-based strategies, while also suggesting that MSC-derived cell-free products and IV delivery may be particularly promising for optimizing functional and structural outcomes after experimental TBI.

Heterogeneity and interpretation. All primary outcomes exhibited high heterogeneity (I^2=98-100% for mNSS, lesion volume and MWM), typical in pre-clinical TBI meta-analyses due to variations in animal species, TBI models, injury severity, MSC/exosome sources, isolation methods, doses, administration routes (IV vs. ICV) and follow-up durations. Sensitivity analyses (leave-one-out analysis) confirmed that pooled estimates remained directionally consistent and significant in favor of treatment, with no single outlier dominating the results (Figs. 5-7). Pre-specified subgroup analyses by product type (MSC vs. cell-free) and route (IV vs. ICV vs. other) partially accounted for heterogeneity; notably, IV cell-free interventions showed larger effects on lesion-reducing effect (subgroup difference P<0.05 for lesion volume). Residual heterogeneity remained high within subgroups, likely due to unmeasured factors such as exosome characterization and preconditioning.

Meta-regression was not conducted owing to insufficient studies per covariate and a very high baseline heterogeneity. The most robust conclusion is the consistent directional benefit across diverse pre-clinical settings: MSC-based therapies and, particularly IV. MSC-derived (exosomes) demonstrate clear neuroprotective signals in neurological function, cognition, and lesion volume. These results underscore paracrine mechanisms and emphasize the urgent need for standardized protocols in future pre-clinical studies to facilitate clinical translation.

Discussion

MSC and cell-free efficacy on functional outcomes. In the present meta-analysis, 403 animals contributed mNSS data (194 experimental and 209 controls). Across all product types and routes, MSC-based interventions significantly improved global neurological function following experimental TBI, as shown by a lower mNSS in treated animals (P<0.0001). This indicates a consistent neuroprotective effect on composite motor, sensory, reflex and balance deficits, and aligns with pre-clinical studies in which systemic MSC administration upregulated neurotrophic factors [brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and nerve growth factor (NGF)] in the peri-lesional cortex, reduced apoptosis, and improved behavioral recovery (12).

The overall neuroprotective effect is largely attributable to paracrine mechanisms, whereby MSCs secrete anti-inflammatory cytokines, neurotrophic factors and extracellular vesicles that modulate the post-injury microenvironment without requiring long-term cellular engraftment. MSC-derived exosomes, as key paracrine mediators, carry bioactive cargo including proteins (BDNF and VEGF for neuroprotection and angiogenesis) and miRNAs (miR-133b for axonal growth and synaptic plasticity, miR-216a-5p for inhibiting neuroinflammation via BDNF pathways, miR-124-3p for suppressing Rela/Apolipoprotein E to mitigate neurodegeneration). Recent studies (2024-2025) confirm that these cargoes enable exosomes to cross the blood-brain barrier efficiently, deliver targeted payloads to neurons and glia, and regulate transcriptional/translational processes for repair (67,68).

Immunomodulation is central. Exosomes shift microglial polarization from pro-inflammatory M1 (iNOS, TNF-α, IL-1β and IL-6) to reparative M2 phenotype (Arg-1, CD206 and IL-10), downregulating NF-κB/MAPK pathways and reducing oxidative stress/apoptosis (68,69). The study by Liu *et al* (67) highlighted exosomal miR-133b and miR-22 upregulation under hypoxic conditions to facilitate nerve repair, while Xiong *et al* (68) emphasized neurorestoration via anti-apoptotic and anti-inflammatory cargo. These mechanisms explain greater mNSS improvements with cell-free products, particularly IV exosomes, as they provide concentrated, standardized delivery without cell survival issues (8,10-12). Beyond immunomodulation, both MSCs and MSC-derived exosomes attenuate neuronal apoptosis, promote angiogenesis, support neurogenesis and enhance synaptic plasticity, all of which contribute to the restoration of cortical and subcortical networks that mediate motor and sensory functions (11,12). These effects align with the longstanding view that MSCs exert their therapeutic effects predominantly through paracrine signaling rather than direct cell replacement, a concept supported by accumulating pre-clinical and early clinical evidence in TBI (13,70).

However, high heterogeneity (I^2=100%) substantially limits the precise interpretation of pooled estimates. Sources include variability in TBI models controlled cortical impact (CCI) and fluid percussion injury (FPI), injury severity, MSC sources (bone marrow vs. umbilical cord), exosome isolation/characterization methods, doses, timing (≤7 days), routes (IV vs. ICV) and follow-up durations. This heterogeneity reflects real-world translational challenges, but also underscores the robustness of directional benefits across diverse settings (70). Future studies are required to standardize protocols Minimum Information for Studies of Extracellular Vesicles (MISEV) guidelines for exosome characterization, consistent dosing in particle number or protein content) to reduce variability and facilitate meta-regression or clinical trial design. Sensitivity analyses confirmed directional consistency, but residual heterogeneity within subgroups suggests unmeasured factors (preconditioning, miRNA cargo profiling) as key contributors.

Although almost all point estimates favored treatment over control, statistically significant gains were driven mainly by MSC-derived cell-free preparations, particularly when delivered intravenously, whereas MSC subgroups exhibited similar directions, but wider confidence intervals. This pattern suggests that IV cell-free products, particularly exosomes, may provide larger and more reliable benefits, likely due to better bioavailability and targeted immunomodulation.

MSC and cell-free efficacy on cognitive outcomes. For cognitive outcomes, 408 animals with MWM data were included. Cognitive recovery is a central target for TBI therapies, and tje pooled MWM analysis revealed that MSC-based interventions

significantly improved spatial learning and memory compared with the controls, despite marked between-study heterogeneity ($P<0.00001$; $I^2=100\%$). This indicates that, at a global level, MSC-centered strategies do not only reduce gross neurological deficits, but also confer measurable benefits on higher-order functions that rely on hippocampal integrity and neuroplasticity.

Both MSCs and MSC-derived cell-free products act on multiple levels of hippocampal circuitry. Pre-clinical TBI research has demonstrated that intravenous MSC-derived exosomes enhance spatial learning by increasing dentate gyrus neurogenesis ($BrdU^+/DCX^+$ and $BrdU^+/NeuN^+$ cells), promoting synaptic plasticity (upregulation of GAP-43, synaptophysin and PSD-95), and reducing neuronal loss in CA1-CA3, changes that parallel improved MWM performance (50). BDNF-induced MSC exosomes further augment these effects by delivering miR-216a-5p and other neurotrophic cargos that support neuronal survival and dendritic complexity, thereby accelerating recovery of spatial learning following TBI (13). In parallel, hypoxia-preconditioned MSCs promote oligodendrogenesis and remyelination, restore white-matter integrity, and activate mTOR/HIF-1α/VEGF signaling, which together improve network connectivity and result in better cognitive outcomes in MWM testing (42).

Cell-free preparations appear particularly effective as they concentrate the paracrine signals that drive hippocampal plasticity. MSC-derived exosomes modulate microglial phenotypes in the hippocampus, shifting from pro-inflammatory M1 to anti-inflammatory M2 via miR-181b/IL-10-STAT3 signaling, leading to reduced IL-1β, IL-6 and TNF-α, less synaptic pruning, and improved MWM performance (13,52,54). Other exosomal cargos, such as the long non-coding RNA MALAT1 have been shown to activate pro-regenerative and synaptogenic pathways, and to attenuate chronic neuroinflammation when delivered intranasally following TBI, again translating into improved motor and cognitive scores (62). Together with broader evidence that MSC-based therapies enhance neurogenesis, angiogenesis and network-level plasticity across neurological models, these data provide a biological rationale for the finding of the present study that the majority of MSC-based and MSC-derived cell-free interventions improve spatial learning and memory, with the most robust and consistent cognitive gains arising from standardized exosome-based strategies (71).

Subgroup analyses revealed that almost all point estimates favored treatment, indicating a broadly consistent trend toward better MWM performance with both MSC and MSC-derived cell-free products. However, statistically significant improvements were largely driven by the cell-free subgroup ($P<0.00001$), whereas MSC subgroups (overall MSC, MSC-ICV and MSC-IV) exhibited effects in the same direction but failed to reach conventional significance (all $P>0.05$), reflecting wide confidence intervals and substantial heterogeneity. The test for subgroup differences was not significant ($P=0.78$, $I^2=0\%$), meaning that confidence intervals overlapped and formal interaction testing does not prove clear superiority of one modality over another. Practically, these findings suggest that the majority of MSC-based and cell-free strategies tend to improve cognitive performance, with the strongest and most statistically robust signal arising from cell-free interventions. This aligns with the concept that post-TBI cognitive recovery depends heavily on synaptic remodeling, neurogenesis and network-level plasticity driven predominantly by the paracrine cargo of MSC-derived secretome and extracellular vesicles, while the very high overall heterogeneity and variable methodological quality emphasize the need for more standardized MWM protocols, predefined treatment timing, and rigorous blinding in future pre-clinical studies.

MSC and cell-free efficacy on structural outcomes. For structural outcomes, 403 animals contributed lesion volume data, with 194 animals in the experimental groups and 209 in the control groups. Lesion volume provides a structural correlate of tissue preservation and is closely linked to long-term functional outcome following TBI. The meta-analysis demonstrated a very robust and highly significant reduction in lesion volume in animals treated with MSC-based interventions compared with controls ($P<0.00001$, $I^2=98\%$). This magnitude of effect indicates that MSC-centered strategies consistently limit the extent of brain tissue loss across diverse experimental models, injury severities, and treatment protocols.

At the subgroup level, a markedly coherent pattern was observed: All subgroups (lesion volume, MSC, MSC-ICV, MSC-IV, cell-free and cell-free IV) exhibited highly significant reductions in lesion size ($P<0.001$). Thus, in contrast to the more variable statistical significance observed in mNSS and MWM, the structural endpoint of lesion volume exhibited a uniformly strong treatment signal across both cell-based and cell-free approaches. Nevertheless, the test for subgroup differences was highly significant, with very high heterogeneity between subgroups ($P<0.00001$, $I^2=95.7\%$), indicating that the magnitude of neuroprotection is not identical for all modalities.

This structural protection is consistent with pre-clinical evidence that MSCs and their extracellular vesicles primarily act by limiting secondary injury cascades in the peri-lesional 'penumbra' rather than reversing the primary mechanical damage (72). MSC-derived exosomes rapidly reach the injured cortex and hippocampus, where they modulate microglia/macrophage polarization from a pro-inflammatory M1 phenotype to a reparative M2 state, downregulating iNOS and pro-inflammatory cytokines, while upregulating Arg-1 and CD206 (12). By dampening neuroinflammation and oxidative stress, these vesicles reduce apoptotic cell death in neurons and oligodendrocytes and thereby preserve viable tissue, which translates into smaller cavitary lesions on histology and MRI (13,68).

In parallel, MSCs and MSC-derived extracellular vesicles enhance neurovascular remodeling and white-matter integrity, two additional processes that constrain lesion expansion. Hypoxia-preconditioned bone marrow-derived MSCs promote remyelination and reduce white-matter injury via mTOR/HIF-1α-dependent pathways, leading to reduced overall lesion volume in mice with TBI (42). MSC/EV therapies also stimulate angiogenesis and restore blood-brain barrier integrity, which decreases edema and secondary

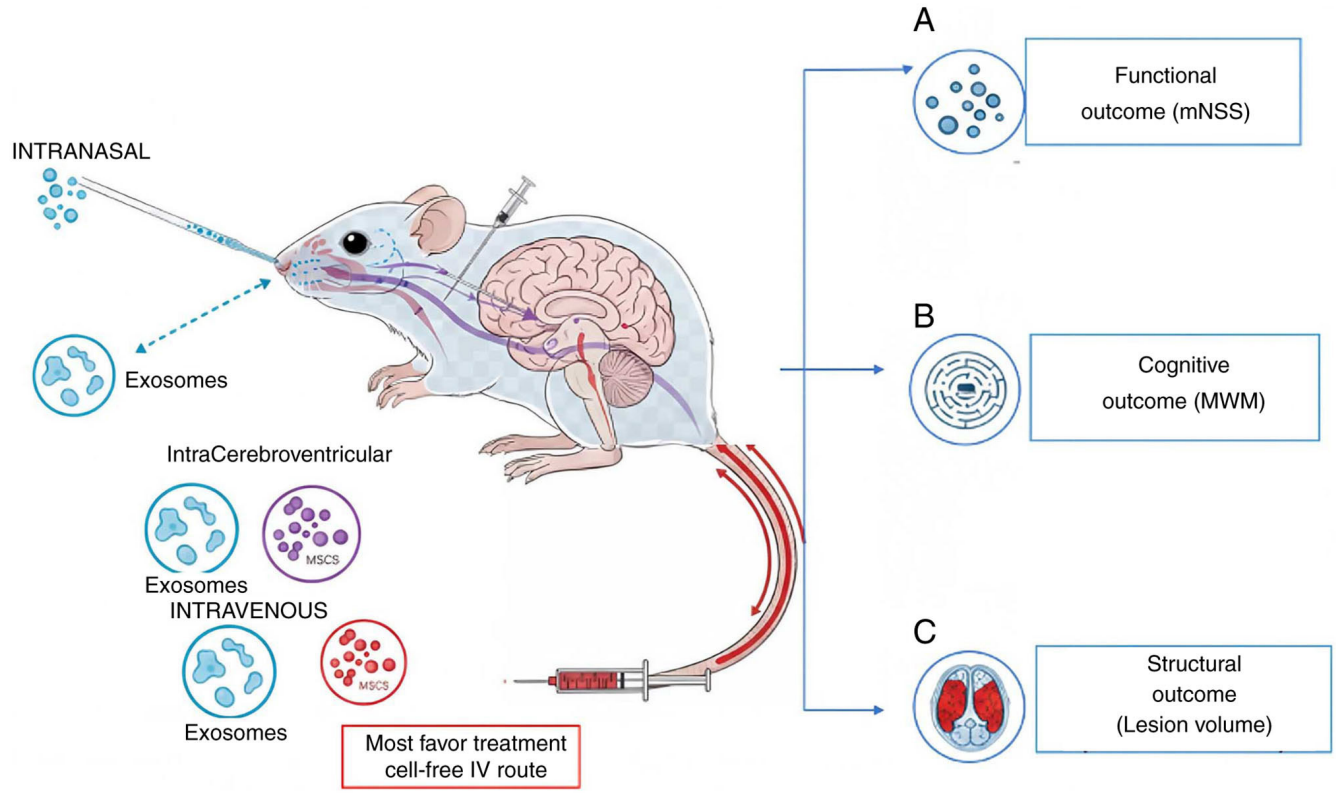

Figure 8. Illustration of the key findings of the present study demonstrating different administration routes of MSCs and exosomes, which affect: (A) Functional outcomes (mNSS), (B) cognitive outcomes, and (C) structural outcomes (lesion volume) in rodent models of traumatic brain injury. MCS, mesenchymal stem cell; mNSS, modified neurological severity score; MWM, Morris water maze test.

ischemic damage in the peri-contusional zone (73,74). Complementary data from broader extracellular vesicle research indicate that stem cell-derived exosomes can lower cortical and hippocampal water content and lesion volumes, while protecting against mitochondrial oxidative stress and apoptosis (75).

The findings of the present study are summarized by the illustration in Fig. 8 demonstrating different administration routes of MSCs and exosomes in rodent TBI models (IN, ICV and IV) and their effects on functional, cognitive and structural outcomes. Across all three panels, the bars indicate that MSC-derived cell-free products, particularly when administered IV, tend to produce the greatest improvement compared with whole-cell MSC therapy.

Although the present meta-analysis revealed consistent neuroprotective effects of MSC-based therapies and MSC-derived exosomes in acute pre-clinical TBI models, translation to clinical practice remains challenging, with no registered trials specifically for acute TBI using MSC-derived exosomes as of 2025. Key barriers include the lack of standardization in exosome production, characterization and cargo consistency (MISEV guidelines), undefined optimal dosing, therapeutic window (≤7 days in rodents vs. variable human timing), administration route (IV most promising), and long-term safety concerns (low immunogenicity). To advance translation, future efforts should prioritize large-animal models for better bridging to humans, standardized protocols, multicenter pre-clinical studies with long-term follow-up, and early-phase human trials focused on safety, biodistribution, and biomarkers (73).

In line with previous pre-clinical TBI meta-analyses, high statistical heterogeneity limits precise interpretation of pooled effect sizes, arising from variations in animal species, TBI models, injury severity, MSC/exosome sources, doses, routes, timing and follow-up durations; residual heterogeneity suggests unmeasured factors; thus, estimates should be viewed as directional summaries rather than protocol-specific predictions (73). The risk of bias (SYRCLE tool) was often unclear or high (43% low risk), particularly in randomization, blinding and allocation concealment, potentially inflating positive effects as indicated by funnel plot asymmetry. Translational limitations include fundamental differences between rodent models and human TBI (smaller brain size, distinct neurovascular/immune responses, absence of comorbidities such as age or polytrauma, and species-specific biodistribution/blood-brain barrier penetration), complicating direct extrapolation. Despite these constraints, the consistent directional benefit across settings supports the paracrine neuroprotective potential of MSC and exosome therapies, warranting standardized protocols for improved reproducibility and clinical relevance.

In conclusion, the present systematic review and meta-analysis demonstrates that MSC-centered interventions provide consistent neuroprotective effects in pre-clinical models of traumatic brain injury. Across the included experiments, treatment groups exhibited lower neurological deficit scores, improved performance on cognitive testing, and smaller lesion volumes than controls, indicating improvement at functional, cognitive and structural levels. Stratified and subgroup analyses

further suggested that MSC-derived cell-free products, particularly when administered intravenously, tended to yield larger and more precisely estimated benefits than whole-cell MSC preparations, particularly for cognitive recovery and lesion volume reduction. Taken together, these findings support a predominant role of paracrine mechanisms in MSC-mediated neuroprotection and identify intravenously delivered cell-free MSC therapies as the most promising MSC-based strategy in current pre-clinical TBI research.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DRA was involved in the conceptualization of the study, in the study methodology, formal analysis, data investigation, in the writing of the original draft, visualization and project administration. AP involved in the conceptualization of the study, in the study methodology, validation, in the writing of the draft, in the review and editing of the manuscript, and in study supervision. C was involved in data investigation, data curation and data validation. TS was involved in data validation, in the writing, reviewing and editing of the manuscript, and in study supervision. DRA and AP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, Aries M, Bashford T, Bell MJ, Bodien YG, *et al*: Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol 21: 1004-1060, 2022.
2. Capizzi A, Woo J and Verduzco-Gutierrez M: Traumatic brain injury: An overview of epidemiology, pathophysiology, and medical management. Med Clin North Am 104: 213-238, 2020.
3. James SL, Theadom A, Ellenbogen RG, Bannick M, Montjoy-Venning W, Lucchesi LR, Abbasi N, Suliankatchi RA, Niguse H, Adsuar JC, *et al*: Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol 18: 56-87, 2019.
4. Jassam YN, Izzy S, Whalen M, McGavern DB and El Khoury J: Neuroimmunology of traumatic brain injury: Time for a paradigm shift. Neuron 95: 1246-1265, 2017.
5. Simon DW, McGeachy MJ, Bayır H, Clark RSB, Loane DJ and Kochanek PM: Erratum: The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol 13: 572, 2017.
6. Vasudevan V, Amatya B and Khan F: Overview of systematic reviews: Management of common traumatic brain injury-related complications. PLoS One 17: e0273998, 2022.
7. Wright DW, Bauer ME, Hoffman SW and Stein DG: Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats. J Neurotrauma 18: 901-909, 2001.
8. Bonilla C and Zurita M: Cell-based therapies for traumatic brain injury: Therapeutic treatments and clinical trials. Biomedicines 9: 669, 2021.
9. Ghasempour E, Hesami S, Movahed E, keshel SH and Doroudian M: Mesenchymal stem cell-derived exosomes as a new therapeutic strategy in the brain tumors. Stem Cell Res Ther 13: 527, 2022.
10. Gnecchi M, Zhang Z, Ni A and Dzau VJ: Paracrine mechanisms in adult stem cell signaling and therapy. Circ Res 103: 1204-1219, 2008.
11. Keshtkar S, Azarpira N and Ghahremani MH: Mesenchymal stem cell-derived extracellular vesicles: Novel frontiers in regenerative medicine. Stem Cell Res Ther 9: 63, 2018.
12. Ni H, Yang S, Siaw-Debrah F, Hu J, Wu K, He Z, Yang J, Pan S, Lin X, Ye H, *et al*: Exosomes derived from bone mesenchymal stem cells ameliorate early inflammatory responses following traumatic brain injury. Front Neurosci 13: 14, 2019.
13. Zhang Y, Zhang Y, Chopp M, Zhang ZG, Mahmood A and Xiong Y: Mesenchymal stem cell-derived exosomes improve functional recovery in rats after traumatic brain injury: A dose-response and therapeutic window study. Neurorehabil Neural Repair 34: 616-626, 2020.
14. Xin H, Li Y, Buller B, Katakowski M, Zhang Y, Wang X, Shang X, Zhang ZG and Chopp M: Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells 30: 1556-1564, 2012.
15. Williams AM, Dennahy IS, Bhatti UF, Halaweish I, Xiong Y, Chang P, Nikolian VC, Chtraklin K, Brown J, Zhang Y, *et al*: Mesenchymal stem cell-derived exosomes provide neuroprotection and improve long-term neurologic outcomes in a swine model of traumatic brain injury and hemorrhagic shock. J Neurotrauma 36: 54-60, 2019.
16. Yarahmadi A, Dorri Giv M, Hosseininejad R, Rezaie A, Mohammadi N, Afkhami H and Farokhi A: Mesenchymal stem cells and their extracellular vesicle therapy for neurological disorders: Traumatic brain injury and beyond. Front Neurol 16: 1472679, 2025.
17. Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, Sandoval-Ávila S, Gomez-Pinedo U, Márquez-Aguirre AL, Vázquez-Méndez E, Padilla-Camberos E and Canales-Aguirre AA: Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res 14: 1626-1634, 2019.
18. Bao W, Lin Y and Chen Z: The peripheral immune system and traumatic brain injury: Insight into the role of T-helper cells. Int J Med Sci 18: 3644-3651, 2021.
19. Simon DW, McGeachy MJ, Bayır H, Clark RSB, Loane DJ and Kochanek PM: The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol 13: 171-191, 2017.

20. Cox CS Jr, Hetz RA, Liao GP, Aertker BM, Ewing-Cobbs L, Juranek J, Savitz SI, Jackson ML, Romanowska-Pawliczek AM, Triolo F, *et al*: Treatment of severe adult traumatic brain injury using bone marrow mononuclear cells. Stem Cells 35: 1065-1079, 2017.
21. Cox CS Jr, Notrica DM, Juranek J, Miller JH, Triolo F, Kosmach S, Savitz SI, Adelson PD, Pedroza C, Olson SD, *et al*: Autologous bone marrow mononuclear cells to treat severe traumatic brain injury in children. Brain 147: 1914-1925, 2024.
22. Lin WY, Wu KH, Chen CY, Guo BC, Chang YJ, Lee TA, Lin MJ and Wu HP: Stem cell therapy in children with traumatic brain injury. Int J Mol Sci 24: 14706, 2023.
23. Fu XM, Liu SJ, Dan QQ, Wang YP, Lin N, Lv LY, Zou Y, Liu S, Zhou X and Wang TH: Combined bone mesenchymal stem cell and olfactory ensheathing cell transplantation promotes neural repair associated with CNTF expression in traumatic brain-injured rats. Cell Transplant 24: 1533-1544, 2015.
24. Silachev DN, Plotnikov EY, Babenko VA, Danilina TI, Zorov LD, Pevzner IB, Zorov DB and Sukhikh GT: Intra-arterial administration of multipotent mesenchymal stromal cells promotes functional recovery of the brain after traumatic brain injury. Bull Exp Biol Med 159: 528-533, 2015.
25. Turtzo LC, Budde MD, Dean DD, Gold EM, Lewis BK, Janes L, Lescher J, Coppola T, Yarnell A, Grunberg NE and Frank JA: Failure of intravenous or intracardiac delivery of mesenchymal stromal cells to improve outcomes after focal traumatic brain injury in the female rat. PLoS One 10: e0126551, 2015.
26. Kota DJ, Prabhakara KS, van Brummen AJ, Bedi S, Xue H, DiCarlo B, Cox CS Jr and Olson SD: Propranolol and mesenchymal stromal cells combine to treat traumatic brain injury. Stem Cells Transl Med 5: 33-44, 2016.
27. Shen Q, Yin Y, Xia QJ, Lin N, Wang YC, Liu J, Wang HP, Lim A and Wang TH: Bone marrow stromal cells promote neuronal restoration in rats with traumatic brain injury: Involvement of GDNF regulating BAD and BAX signaling. Cell Physiol Biochem 38: 748-762, 2016.
28. Danilina TI, Silachev DN, Pevzner IB, Gulyaev MV, Pirogov YA, Zorova LD, Plotnikov EY, Sukhikh GT and Zorov DB: The influence of proinflammatory factors on the neuroprotective efficiency of multipotent mesenchymal stromal cells in traumatic brain injury. Bull Exp Biol Med 163: 528-534, 2017.
29. Feng Y, Ju Y, Cui J and Wang L: Bone marrow stromal cells promote neuromotor functional recovery, via upregulation of neurotrophic factors and synapse proteins following traumatic brain injury in rats. Mol Med Rep 16: 654-660, 2017.
30. Guo S, Zhen Y and Wang A: Transplantation of bone mesenchymal stem cells promotes angiogenesis and improves neurological function after traumatic brain injury in mouse. Neuropsychiatr Dis Treat 13: 2757-2765, 2017.
31. Li L, Chopp M, Ding G, Qu C, Nejad-Davarani SP, Davoodi-Bojd E, Li Q, Mahmood A and Jiang Q: Diffusion-derived magnetic resonance imaging measures of longitudinal microstructural remodeling induced by marrow stromal cell therapy after traumatic brain injury. J Neurotrauma 34: 182-191, 2017.
32. Bonilla Horcajo C, Zurita Castillo M and Vaquero Crespo J: Platelet-rich plasma-derived scaffolds increase the benefit of delayed mesenchymal stromal cell therapy after severe traumatic brain injury. Cytotherapy 20: 314-321, 2018.
33. Hu W, Jiang J, Yang F and Liu J: The impact of bone marrow-derived mesenchymal stem cells on neovascularisation in rats with brain injury. Folia Neuropathol 56: 112-123, 2018.
34. Shi X, Bai Y, Zhang G, Liu Y, Xiao H, Liu X and Zhang W: Effects of over-expression of SOD2 in bone marrow-derived mesenchymal stem cells on traumatic brain injury. Cell Tissue Res 372: 67-75, 2018.
35. Hao Q, Zheng J, Hu Y and Wang H: Bone marrow mesenchymal stem cells combined with Sox2 increase the functional recovery in rat with traumatic brain injury. Chin Neurosurg J 5: 11, 2019.
36. Hu J, Chen L, Huang X, Wu K, Ding S, Wang W, Wang B, Smith C, Ren C, Ni H, *et al*: Calpain inhibitor MDL28170 improves the transplantation-mediated therapeutic effect of bone marrow-derived mesenchymal stem cells following traumatic brain injury. Stem Cell Res Ther 10: 96, 2019.
37. Peruzzaro ST, Andrews MMM, Al-Gharaibeh A, Pupiec O, Resk M, Story D, Maiti P, Rossignol J and Dunbar GL: Transplantation of mesenchymal stem cells genetically engineered to overexpress interleukin-10 promotes alternative inflammatory response in rat model of traumatic brain injury. J Neuroinflammation 16: 2, 2019.
38. Wu K, Huang D, Zhu C, Kasanga EA, Zhang Y, Yu E, Zhang H, Ni Z, Ye S, Zhang C, *et al*: $NT3^{P75\text{-}2}$ gene-modified bone mesenchymal stem cells improve neurological function recovery in mouse TBI model. Stem Cell Res Ther 10: 311, 2019.
39. Yan F, Li M, Zhang HQ, Li GL, Hua Y, Shen Y, Ji XM, Wu CJ, An H and Ren M: Collagen-chitosan scaffold impregnated with bone marrow mesenchymal stem cells for treatment of traumatic brain injury. Neural Regen Res 14: 1780-1786, 2019.
40. Huang D, Siaw-Debrah F, Wang H, Ye S, Wang K, Wu K, Zhang Y, Wang H, Yao C, Chen J, *et al*: Transplanting Rac1-silenced bone marrow mesenchymal stem cells promote neurological function recovery in TBI mice. Aging (Albany NY) 13: 2822-2850, 2020.
41. Song B, Wang XX, Yang HY, Kong LT and Sun HY: Temperature-sensitive bone mesenchymal stem cells combined with mild hypothermia reduces neurological deficit in rats of severe traumatic brain injury. Brain Inj 34: 975-982, 2020.
42. Yuan X, Luo Q, Shen L, Chen J, Gan D, Sun Y, Ding L and Wang G: Hypoxic preconditioning enhances the differentiation of bone marrow stromal cells into mature oligodendrocytes via the mTOR/HIF-1α/VEGF pathway in traumatic brain injury. Brain Behav 10: e01675, 2020.
43. Li J, Zhang D, Guo S, Zhao C, Wang L, Ma S, Guan F and Yao M: 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. Int J Biol Macromol 187: 200-213, 2021.
44. Deng QJ, Xu XF and Ren J: Correction to: Effects of SDF-1/CXCR4 on the repair of traumatic brain injury in rats by mediating bone marrow derived mesenchymal stem cells. Cell Mol Neurobiol 41: 617-618, 2021.
45. Ma S, Zhou J, Huang T, Zhang Z, Xing Q, Zhou X, Zhang K, Yao M, Cheng T, Wang X, *et al*: Sodium alginate/collagen/stromal cell-derived factor-1 neural scaffold loaded with BMSCs promotes neurological function recovery after traumatic brain injury. Acta Biomater 131: 185-197, 2021.
46. Chen KH, Shao PL, Li YC, Chiang JY, Sung PH, Chien HW, Shih FY, Lee MS, Chen WF and Yip HK: Human umbilical cord-derived mesenchymal stem cell therapy effectively protected the brain architecture and neurological function in rat after acute traumatic brain injury. Cell Transplant 29: 963689720929313, 2020.
47. Zhou HX, Liu ZG, Liu XJ and Chen QX: Umbilical cord-derived mesenchymal stem cell transplantation combined with hyperbaric oxygen treatment for repair of traumatic brain injury. Neural Regen Res 11: 107-113, 2016.
48. Li L, Chopp M, Ding G, Davoodi-Bojd E, Li Q, Mahmood A, Xiong Y and Jiang Q: Diffuse white matter response in trauma-injured brain to bone marrow stromal cell treatment detected by diffusional kurtosis imaging. Brain Res 1717: 127-135, 2019.
49. Bayat Tork MA, Saberifar M, Joneidi Yekta H, Hajinejad M, Hosseini Ravandi H, Gorji A and Sahab Negah S: Nano-scaffold containing functional motif of stromal cell-derived factor 1 enhances neural stem cell behavior and synaptogenesis in traumatic brain injury. Sci Rep 15: 5811, 2025.
50. Zhang Y, Chopp M, Meng Y, Katakowski M, Xin H, Mahmood A and Xiong Y: Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. J Neurosurg 122: 856-867, 2015.
51. Zhang Y, Chopp M, Zhang ZG, Katakowski M, Xin H, Qu C, Ali M, Mahmood A and Xiong Y: 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. Neurochem Int 111: 69-81, 2017.
52. Xu H, Jia Z, Ma K, Zhang J, Dai C, Yao Z, Deng W, Su J, Wang R and Chen X: Protective effect of BMSCs-derived exosomes mediated by BDNF on TBI via miR-216a-5p. Med Sci Monit 26: e920855, 2020.
53. Zhang Y, Zhang Y, Chopp M, Pang H, Zhang ZG, Mahmood A and Xiong Y: MiR-17-92 cluster-enriched exosomes derived from human bone marrow mesenchymal stromal cells improve tissue and functional recovery in rats after traumatic brain injury. J Neurotrauma 38: 1535-1550, 2021.
54. Wen L, Wang YD, Shen DF, Zheng PD, Tu MD, You WD, Zhu YR, Wang H, Feng JF and Yang XF: Exosomes derived from bone marrow mesenchymal stem cells inhibit neuroinflammation after traumatic brain injury. Neural Regen Res 17: 2717-2724, 2022.
55. Zhang Y, Sun C, Wang B, Gu A, Zhou Z and Gu C: Brain-derived exosomal miR-9-5p induces ferroptosis in traumatic brain injury-induced acute lung injury by targeting Scd1. CNS Neurosci Ther 30: e70189, 2024.

56. Wang W, Lu G, Guo P, Zhang H, Wang Y, Zheng D, Lyu C, Wang D, Li S, Li F, *et al*: Selenized neural stem cell-derived exosomes: A neotype therapeutic agent for traumatic injuries of the central nervous system. Cell Rep Med 6: 102319, 2025.
57. Qian Y, Li X, Li G, Liu H, Li Q, Liu X, Zhang Y, He Z, Zhao Y and Fan H: Astrocyte-derived exosomal miR-148a-3p suppresses neuroinflammation and restores neurological function in traumatic brain injury by regulating the microglial phenotype. eNeuro 11: ENEURO.0336-23.2024, 2024.
58. Wang Y, Li D, Zhang L, Yin Z, Han Z, Ge X, Li M, Zhao J, Zhang S, Zuo Y, *et al*: Exosomes derived from microglia overexpressing miR-124-3p alleviate neuronal endoplasmic reticulum stress damage after repetitive mild traumatic brain injury. Neural Regen Res 19: 2010-2018, 2024.
59. Liu XY, Feng YH, Feng QB, Zhang JY, Zhong L, Liu P, Wang S, Huang YR, Chen XY and Zhou LX: Low-temperature 3D-printed collagen/chitosan scaffolds loaded with exosomes derived from neural stem cells pretreated with insulin growth factor-1 enhance neural regeneration after traumatic brain injury. Neural Regen Res 18: 1990-1998, 2023.
60. Liu Y, Liu S, Yan B, Yin Z, Liao P, Wang Y, Li D, Han Z, Zhang S, Ge X, *et al*: Brain-derived exosomes from aged mice accelerate cognitive decline in repeated mild traumatic brain injury by activating neuronal Tnfrsf25. Exp Gerontol 211: 112931, 2025.
61. Kim D, Hwang J, Jang E, Cho HH, Kim BC, Jeong HS and Jang S: Therapeutic effect of neural induced-stem cell-derived exosomes by regulating ERK/p38/NF-κB in traumatic brain injury. Biomed Pharmacother 192: 118616, 2025.
62. Moss LD, Sode D, Patel R, Lui A, Hudson C, Patel NA and Bickford PC: Intranasal delivery of exosomes from human adipose derived stem cells at forty-eight hours post injury reduces motor and cognitive impairments following traumatic brain injury. Neurochem Int 150: 105173, 2021.
63. Zhang W, Hong J, Zhang H, Zheng W and Yang Y: Astrocyte-derived exosomes protect hippocampal neurons after traumatic brain injury by suppressing mitochondrial oxidative stress and apoptosis. Aging (Albany NY) 13: 21642-21658, 2021.
64. Pischiutta F, Tribuzio F, Magatti M, De Simone G, Moro F, Nattino G, Signorini F, Loose L, Caruso E, Bertani C, *et al*: Mesenchymal stromal cell secretome and its key bioactive metabolites induce long-term neuroprotection after traumatic brain injury in mice. Adv Sci (Weinh) 12: e15508, 2025.
65. Chen W, Zheng P, Hong T, Wang Y, Liu N, He B, Zou S, Ren D, Duan J, Zhao L and Feng J: Astrocytes-derived exosomes induce neuronal recovery after traumatic brain injury via delivering gap junction alpha 1-20 k. J Tissue Eng Regen Med 14: 412-423, 2020.
66. Zhuang Z, Liu M, Dai Z, Luo J, Zhang B, Yu H, Xue J and Xu H: Bone marrow stromal cells-derived exosomes reduce neurological damage in traumatic brain injury through the miR-124-3p/p38 MAPK/GLT-1 axis. Exp Neurol 365: 114408, 2023.
67. Liu MW, Li H, Xiong GF, Zhang BR, Zhang QJ, Gao SJ, Zhu YL and Zhang LM: Mesenchymal stem cell exosomes therapy for the treatment of traumatic brain injury: mechanism, progress, challenges and prospects. J Transl Med 23: 427, 2025.
68. Xiong Y, Mahmood A and Chopp M: Mesenchymal stem cell-derived extracellular vesicles as a cell-free therapy for traumatic brain injury via neuroprotection and neurorestoration. Neural Regen Res 19: 49-54, 2024.
69. Wu P, He B, Li X and Zhang H: Roles of microRNA-124 in traumatic brain injury: A comprehensive review. Front Cell Neurosci 17: 1298508, 2023.
70. Huang Y, Mei X, Jiang W, Zhao H, Yan Z, Zhang H, Liu Y, Hu X, Zhang J, Peng W, *et al*: Mesenchymal stem cell-conditioned medium protects hippocampal neurons from radiation damage by suppressing oxidative stress and apoptosis. Dose Response 19: 1559325820984944, 2021.
71. Isaković J, Šerer K, Barišić B and Mitrečić D: Mesenchymal stem cell therapy for neurological disorders: The light or the dark side of the force? Front Bioeng Biotechnol 11: 1139359, 2023.
72. Ollen-Bittle N, Roseborough AD, Wang W, Wu J liang D and Whitehead SN: Mechanisms and biomarker potential of extracellular vesicles in stroke. Biology (Basel) 11: 1231, 2022.
73. Chen C, Peng C, Hu Z and Ge L: Effects of bone marrow mesenchymal stromal cells-derived therapies for experimental traumatic brain injury: A meta-analysis. Heliyon 10: e25050, 2024.
74. Serrenho I, Ferreira SA and Baltazar G: Preconditioning of MSCs for acute neurological conditions: From cellular to functional impact-a systematic review. Cells 13: 845, 2024.
75. Wang J, Wang J, Li X and Shu K: Cell-derived exosomes as therapeutic strategies and exosome-derived microRNAs as biomarkers for traumatic brain injury. J Clin Med 11: 3223, 2022.