

REVIEW ARTICLE

Stem Cell-Derived Exosomes as a Therapeutic Option for Spinal Cord In-

juries; a Systematic Review and Meta-Analysis

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Abstract: Introduction: Exosomes function as cell signaling carriers and have drawn much attention to the cell-free treatments of regenerative medicine. This meta-analysis aimed to investigate the efficacy of mesenchymal stem cell-derived (MSCderived) exosomes in animal models of spinal cord injuries (SCI). Methods: A comprehensive search was conducted in Medline, Embase, Scopus, and Web of Science to attain related articles published by January 31, 2023. The eligible keywords were correlated with the spinal cord injury and MSC-derived exosomes. The evaluated outcomes were locomotion, cavity size, cell apoptosis, inflammation, neuro-regeneration, and microglia activation. A standardized mean difference was calculated for each sample and a pooled effect size was reported. Results: 65 papers fully met the inclusion criteria. Treatment with MSC-derived exosomes ultimately improved locomotion and shrunk cavity size (p<0.0001). The administration of MSC-derived exosomes enhanced the expression of beta-tubulin III, NF200, and GAP-43, and increased the number of NeuN-positive and Nissl-positive cells, while reducing the expression of glial fibrillary acidic protein (p<0.0001). The number of apoptotic cells in the treatment group decreased significantly (p<0.0001). Regarding the markers of microglia activation, MSC-derived exosomes increased the number of CD206- and CD68-positive cells (p=0.032 and p<0.0001, respectively). Additionally, MSC-derived exosome administration significantly increased the expression of the anti-inflammatory interleukin (IL)-10 and IL-4 (p<0.001 and p=0.001, respectively) and decreased the expression of the inflammatory IL-1b, IL-6, and TNF-a (p<0.0001). Conclusions: MSC-derived exosome treatment resulted in a significantly improved locomotion of SCI animals through ameliorating neuroinflammation, reducing apoptosis, and inducing neuronal regrowth by facilitating a desirable microenvironment.

Keywords: Exosomes; Mesenchymal stem cells; Spinal cord injury

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1. Introduction

Traumatic spinal cord injury (SCI) is a devastating pathophysiological state that could result in sensory, motor, and autonomous deficits. The incidence and burden of spinal cord injuries have increased over the last 30 years, with about 0.9 million new incidents and 20.6 million prevalent cases in 2019 [1]. Injury to the spinal cord initiates consecutive inflammatory cascades that ultimately lead to the formation of scar tissue and axonal loss [2]. Based on the location of the neuronal interruption, a broad range of clinical syndromes are expected, and a comprehensive course of management is often required [3-5]. Pre-clinical studies have shown promising results of stem cell therapy in recovering neurodegenerative conditions through neuroprotection, immunomodulation, neuronal relay formation, and myelin regeneration [6, 7]. In addition to their immunomodulatory properties, stem cells also participate in the cell replenishment of neurons. Recent studies have highlighted the neuro-regenerative effects of their secretory components such as cytokines, chemokines, and extracellular vehicles (EVs) [8-12].

EVs are classified into exosomes (30-200 nanometers (nm)), micro-vesicles (100-1000 nm), and apoptotic bodies (>1000 nm) [13]. Although exosomes were originally hypothesized to contain unwanted cellular products [14], it was later discovered that these vesicles contain lipids, proteins, deoxyribonucleic acids (DNAs), and ribonucleic acid (RNA) subtypes such as messenger RNAs and non-coding RNA species [15, 16].

Exosomes function as cell signaling carriers and have drawn much attention to the cell-free treatments of regenerative medicine due to their high biocompatibility, stability in circulation, and low immunogenicity [17-21].

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Several sources serve as the origin of EVs; to date, mesenchymal stem cells (MSC) are the most frequently studied source of EVs [22]. MSCs are abundantly present in the adipose tissue, umbilical cord, and bone marrow [23-26]. These cells are easily available, cultured, and manipulated in addition to having favorable differentiation capacities and immunomodulatory properties [27-29]. Research shows that the MSCs' secretory products exhibit regenerative effects similar to the engraftment of MSCs themselves [30].

Since exosomes contain various constituents from the cell of origin and MSCs have previously shown remarkable effects on tissue recovery in spinal cord injuries, several studies have examined the neuro-regenerative potentials of MSC-derived exosomes in spinal cord injuries [31-33].

Three recent meta-analyses published in the past three years primarily focused on the functional outcomes of injured animals following exosome administration, not taking into account important outcomes such as inflammatory response or histopathological findings [35-37]; even though Zhang et al. [37] assessed other outcomes, the number of experiments was limited. Additionally, the overall number of studies included was notably lower. Considering that research in this field is still up-and-coming, and no consensus has been reached regarding the matter [34], the present systematic review and meta-analysis aimed to investigate the efficacy of MSC-derived exosomes in SCI.

2. Methods

- Study design and setting

The purpose of this study was to summarize the evidence on the efficacy of MSC-derived exosomes administered in SCI. We defined the population as the spinal cord-injured animals, the intervention was the administration of MSCderived exosomes, and the comparison was made with the spinal cord-injured control group who did not receive the intervention. The evaluated outcomes were locomotion, cavity size, cell apoptosis, inflammation, neuro-regeneration, and microglia activation.

- Search strategy

We designed search strategies based on the Medline, Embase, Scopus, and Web of Science guidelines to obtain their indexed publications by January 31, 2023. The eligible keywords were correlated with the spinal cord injury and MSCderived exosomes. Appropriate tags and Boolean operators were applied to these keywords for the final search. Ultimately, we manually searched the grey literature (Google and Google Scholar) and the references section of the included studies to avoid missing articles. The search strategies of all databases and the keywords are presented in Appendix 1.

- Selection criteria

The inclusion criteria were the original pre-clinical studies on the effectiveness of MSC-derived exosomes in SCI. The exclusion criteria were in-vitro studies, non-traumatic SCI, non-exosome therapies (such as conditioned mediums), treatment with exosomes derived from sources other than MSCs, articles with insufficient data about the exosomes' preparation and administration methods, combination therapies, articles without a spinal cord-injured group that did not receive treatment, articles with no reports of the desired outcomes, review studies, and retracted articles.

- Data collection

Non-duplicate records were examined by two independent researchers. The titles and abstracts of the obtained records were reviewed in the initial screening process. In the next step, the full text of the relevant articles was studied in detail, and the final included articles were selected. The extracted data from each article was re-evaluated by at least one other independent researcher. The data were entered into a checklist based on the PRISMA guideline [38]. The recorded variables were the last name of the first author, publication year, baseline characteristics of the included animals, sample size, model of SCI, the origin of MSC-derived exosomes, the volume or dose of the administered exosomes, the method of exosome administration, the time interval between injury and exosome administration, and outcomes. Figurative data were extracted using the Plot Digitizer software.

- Quality assessment

The quality of the included articles was assessed based on the SYRCLE's risk of bias assessment tools [39]. In case of any disagreements in data collection or the quality assessment, the conflict was resolved through discussions or with the help of a third researcher.

- Statistical analyses

Data were recorded as mean \pm standard deviation (SD) and were analyzed in the STATA 17.0 statistical program. A standardized mean difference (SMD) was calculated for each study and a pooled effect size was reported. Heterogeneity between studies was calculated with the I2 test. In the case of heterogeneity, subgroup analyses were performed to determine the source of heterogeneity. Funnel plots with 95% confidence intervals were used to report the publication bias, using the proposed method in the study of Doleman et al. [40]. The Galbraith plot was utilized for outlier evaluation, and experiments exerting significant effects on heterogeneity or publication bias were excluded from the analysis to ensure the robustness of the findings.

3. Results

- Article selection process

Out of the 1009 obtained articles from the systematic search, 507 were duplicates and were therefore removed. 502 articles entered the screening process, and the full texts of 156 were reviewed in detail. 65 articles met the inclusion criteria. No additional articles were found in our manual search in grey literature. Excluded studies were reviews (52 records), studies on condition mediums (5 records), combination therapies (8 records), in vitro studies (4 records), studies without a control group (2 records), studies with no reports of desired outcomes (1 record), retracted studies (1 record), studies on non-traumatic spinal cord injuries (3 records), studies

without a mesenchymal stem cell-origin of the exosomes (4 records), a study with insufficient data (1 record) and duplicate studies (10 records) (Figure 1).

- Study characteristics

The included articles wielded strains of rats (52 records) and mice (13 records). The spinal cord was injured in the thoracic region in all included articles. The model of injury was contusion in 45 articles, compression in 11 articles, and transection in 7 articles. The exosomes were isolated from bone marrow-derived MSCs (BMMSC) in 40 articles, human umbilical cord-derived MSCs (hUCMSC) in 11 articles, adipose-derived MSCs (ADMSC) in 7 articles, human placenta-derived MSCs (hPMSC) in 3 articles, human Wharton's jelly-derived MSCs (hWJMSC) in 1 article, human dental-pulp MSCs (hDpMSC) in 1 article, and mouse umbilical cord MSCs (MUMSCs) in 1 article. In 1 article, exosomes were isolated from human MSCs (hMSC) of unreported origin. Apart from 10 articles including a range of treatment administration time intervals, the first injection of MSC-derived exosomes took place in the first 24 hours post-injury. The route of administration was intravenous in 46 articles, intrathecal in 6 articles, into the injury site in 6 articles, intranasal in 1 article, into the injured hind limbs in 1 article, subcutaneously near the back wound in 1 article, under the dura in 1 article, and in both the injury site and tail vein in 1 article (Table 1).

Meta-analysis on the effect of MSC-derived exosomes on post-SCI outcomes

- Locomotion

Locomotion was reported with the scales of Basso, Beattie, and Bresnahan (BBB) or the Basso Mouse Scale (BMS). The data from 72 separate analyses were pooled, and an overall effect size was obtained. MSC-derived exosome administration ultimately improved the locomotion of SCI animals (SMD = 2.31, 95%CI: 1.95 to 2.66, p<0.0001; Figure 2).

Subgroup analyses and meta-regressions were conducted to identify the source of heterogeneity (Table 2). Meta-regression demonstrated that rats showed greater improvement in locomotion compared to mice (meta-coefficient = 1.09, 95% CI: 0.31 to 1.88, p = 0.006). Therefore, the animals' species is a possible source of heterogeneity among the studies.

- Cavity size

Pooling data from 26 separate analyses demonstrated that the administration of MSC-derived exosomes reduced the cavity size post-treatment (SMD = -2.75, 95%CI: -3.69 to -1.80, p<0.0001; Figure 3).

Subgroup analysis showed that using exosomes from ADM-SCs didn't significantly reduce cavity size (SMD = -5.95, 95% CI: -14.06, 2.17, p = 0.151; Table 3). However, meta-regressions didn't show notable subgroup differences in cavity size reduction following exosome treatment.

- Neural tissue regeneration

The expression of beta-tubulin III (SMD = 3.21, 95% CI: 2.01 to 4.42, p<0.0001) and the number of NeuN-positive cells

(SMD = 4.46, 95%CI: 2.56 to 6.36, p<0.0001) were significantly increased in the treatment group. Moreover, pooling data from 13 different analyses showed that the number of NF200-positive cells was significantly higher after MSC-derived exosome administration (SMD = 3.55, 95%CI: 2.43 to 4.67, p<0.0001). The analysis showed a significantly higher level of GAP-43 (SMD = 2.37, 95%CI: 0.7 to 4.05, p<0.0001) and more Nissl-positive cells (SMD = 3.13, 95%CI: 1.60 to 4.66, p<0.0001) post-treatment (Figure 4). Also, GFAP expression was significantly decreased in the intervention group (SMD = -2.80, 95%CI: -3.74 to -1.85, p<0.0001; Figure 5).

Subgroup analyses showed that the improvement in GFAP was significant in almost every subgroup, except the 3 experiments that used ADMSCs as the source of exosome (SMD = -0.66, 95%CI: -2.36 to 1.04, p=0.447). Meta-regressions revealed that the variation in administration protocol (single dose vs. multidose) is a source of heterogeneity since multi-dose exosome therapy causes a significantly higher effect size compared to single-dose therapy (meta-regression coefficient=2.14; 95%CI: 0.57 to 3.70; p=0.007). Additionally, according to meta-regression analyses, the administration of exosome in the acute phase of SCI, as opposed to the immediate phase, showed significant differences (metaregression coefficient=-3.58; 95%CI: -5.21 to -1.95, p<0.0001) and the use of hWJMSC as the origin of exosomes (versus BMMSC) also contributed to heterogeneity (meta-regression coefficient=-3.05; 95%CI: -5.46 to -0.63, p=0.013; Table 4).

- Apoptosis

The expression of the pro-apoptotic Bax protein diminished in the treatment group (SMD = -4.36, 95%CI: -5.78 to -2.94, p<0.0001). On the other hand, Bcl-2 expression was significantly higher in the intervention group (SMD = 3.68, 95%CI: 2.26 to 5.11, p<0.0001). The expression of Caspase 1 (SMD = -3.16, 95%CI: -5.57 to -0.74, p=0.042) and Caspase 3 (SMD = -2.46, 95%CI: -3.15 to -1.78, p=0.003) significantly decreased in the animals of the treatment group (Figure 6).

In addition, pooled data analysis on 23 separate experiments demonstrated that the number of apoptotic cells was significantly lower post-treatment (SMD = -4.29, 95%CI: -5.24 to -3.35, p<0.0001; Figure 7).

Subgroup analyses showed no differences in all subgroups, while meta-regression analyses demonstrated significantly fewer apoptotic cells in a follow-up duration of 28 days and more compared to less than 28 days (meta-regression coefficient=-1.97 [95% CI: -3.88, -0.07], p = 0.042; Table 5). Hence, follow-up duration might be the source of heterogeneity.

- Microglia activation

Treatment with MSC-derived exosomes did not have a meaningful effect on the expression of Arg1 (SMD = 1.80; 95%CI: -0.37 to 3.97, p=0.206). Nonetheless, the number of CD206positive cells (SMD = 3.35, 95%CI: 0.28 to 6.42, p=0.032) and CD68-positive cells (SMD = -6.26; 95%CI: -8.06 to -4.47, p<0.0001) were significantly increased in the treatment group. Pooled data analysis exhibited a significantly decreased Iba-1 expression in the treatment group (SMD = - 2.44, 95%CI: -3.78 to -1.10, p<0.0001; Figure 8).

- Inflammation

Treatment with exosomes significantly increased the expression of the anti-inflammatory IL-10 (SMD = 2.41, 95%CI: 1.38 to 3.45, p=0.001).

Pooled data analysis demonstrated a similar result for IL-4 (SMD = 3.44, 95%CI: 1.38 to 5.49, p=0.006; Figure 9).

In the analysis of the level of IL-1b, we pooled 27 out of 28 experiments. One experiment was excluded due to its outlier status, as it significantly influenced publication bias. The level of this inflammatory marker was significantly lower in the treatment group (SMD = -3.30, 95%CI: -4.15 to -2.45, p<0.0001; Figure 10). The result was similar for IL-6 (SMD = -2.04, 95%CI: -2.74 to -1.34, p<0.0001). Regarding IL-18, its expression meaningfully dropped in the treatment group (SMD = -3.02, 95%CI: -5.27 to -0.78, p=0.021). Nonetheless, IL-1a levels were not significantly different between the treatment and control groups (SMD = -2.44, 95%CI: -5.17 to 0.28, p=0.096). Also, there were no significant differences between the treatment and control groups in terms of NLRP3 (SMD = -1.90, 95%CI: -4.24 to 0.44, p=0.276) and MCP-1 levels (SMD = -2.56, 95%CI: -5.24 to 0.11, p=0.061; Figure 11).

Subgroup analyses and meta-regressions were performed to detect sources of heterogeneity. Meta-regressions showed that the extent of reduction in IL-1b level is significantly greater in animals with compression models of SCI (meta-regression coefficient=-0.62, 95%CI: -2.49 to 1.24, p=0.008) in comparison to contusion models (Table 6).

Out of 31 experiments assessing TNF-a, 3 studies were excluded due to their outlier status and impact on heterogeneity. The results from 28 separate analyses revealed that the expression of TNF-a was significantly less in the treatment group (SMD = -2.59, 95%CI: -3.22 to -1.95, p<0.0001; Figure 12).

Subgroup analyses demonstrated that the improvement in TNF-a was significant in all subgroups except for the injection of exosomes in the acute phase of SCI (SMD = -4.74, 95%CI: -9.59 to 0.11, p=0.056) which was investigated only in 4 experiments. In meta-regression analyses, we observed a larger effect size in experiments involving the local administration of exosomes compared to the systemic administration (meta-regression coefficient=-1.52; 95%CI: -2.91 to 0.13; p=0.024; Table 7).

-Quality control

It is noteworthy that housing randomization and random selection of animals for outcome assessment are infrequently narrated in animal interventional studies, and similarly, none of our included articles adequately disclosed the aforementioned items. The risk of bias in allocation concealment was low in 2 articles and unclear in others, and only 8 articles addressed incomplete outcome data. Conclusively, the overall risk of bias for the present systematic review and metaanalysis was considered fair (Supplementary Table 1). **Publication bias** No publication bias was observed among the included articles in the markers of apoptosis (p=0.745), number of apoptotic cells (p=0.083) cavity size (p=0.118), locomotion (p=0.416), IL-4 and IL-10 (p=0.066), inflammatory ILs (IL-18, IL1a, IL6, MCP-1, NLRP3) (p=0.481), IL-6 (p=0.479), IL-1b (p=0.211), TNF-a (p=0.657), and microglia activation markers (p=0.079). The articles that reported neural regeneration markers, displayed evidence of a possible publication bias (p=0.024) (Supplementary Figure 1).

4. Discussion

Neuronal damage after SCI has a complex pathogenesis that could be categorized into irreversible primary damage from mechanical injury followed by an amenable secondary injury resulting from neuroinflammation, apoptosis, ischemia, and excitotoxicity [41, 42]. During the last two decades, stem cell transplantation has gained considerable attention as a novel therapeutic strategy in the management of central nervous system injuries by mitigating secondary injury and promoting neuronal regeneration [43]. Originally, it was believed that functional recovery ensued by the transplantation of MSCs in neuronal injuries is derived greatly from the differentiation of engrafted stem cells to neurons and oligodendrocytes [44]. However, recent research endeavors have proposed that stem cell therapy's regenerative efficacy is largely driven by the intercellular communication of transplanted stem cells with surviving neurons and microglial cells [45-47]. Exosomes, as nano-sized extracellular vesicles containing lipids, proteins, and nucleic acids, play a crucial role in the paracrine interaction of MSCs with neighboring cells at the injury site in addition to the trafficking of biomaterials such as messenger RNAs and microRNAs into the recipient cells [48, 49]. Since the cell-free extracellular vesicles' administration circumvents the limitations of direct stem cell transplantation such as the immunological rejections, low viability of the transplanted cells at the injury site, tumorigenesis, and microvasculature blockade, this approach drew great interest from researchers as a potential treatment for neurodegenerative conditions [50]. The current systematic review and meta-analysis demonstrated that treatment with exosomes in animal models of SCI was associated with significantly improved motor function, smaller cavity size, higher nervous tissue regeneration markers, lower apoptosis rate, and attenuated inflammation.

Neuroinflammation after SCI is cardinal, aggravating secondary neuronal damage and hindering cellular repair processes. Microglia activation is a key factor in mounting inflammatory responses and neurogenesis which could act as a double-edged sword, depending on its polarization postinjury. Our review revealed that the exosomes' administration doesn't reduce the overall number of macrophages, demonstrating the levels of the pan-macrophage marker CD68. However, there were significantly fewer activated macrophages with an incline towards the anti-inflammatory M2 phenotype polarization, deducted from lessened Iba-1

and increased CD206 expression. Recent studies highlighted the temporal alterations of the micro-RNA profile as pivotal in the pathogenesis and functional recovery of SCIs [51, 52]. miRNAs are noncoding single-stranded RNAs that regulate genes' expressions at a post-transcription level, binding to their targeted mRNA's 3' untranslated region, causing either mRNA degradation or lessened translation [53]. Exosomes were shown to contain miRNA-125a, miRNA-216a, and miRNA-23b, which contribute to the M2 polarization of macrophage cells and cause subsequent release of antiinflammatory cytokines IL-4, Il-10, and TGF-B [54, 55]. Exosomes were also demonstrated to harbor short interfering RNAs (siRNA) that could downregulate the inflammasomes' activation in innate immune cells [56]. Inflammasomes consist of complex proteins that are responsible for the processing and secretion of proinflammatory cytokines such as IL-1b and IL-18 [57, 58]. Additionally, exosome treatment can suppress the NF-KB signaling pathway, which is crucial in governing immune cells' activation and production of proinflammatory cytokines of TNF-a, IL-6, and IL-1b [59-62]. By suppressing the NF-KB pathway and inhibiting pericyte migration, exosomes could stabilize the integrity of the bloodspinal cord barrier [63]. As another component of the glial system, astrocyte activation and the following glial scar formation affect the secondary injury progression and thus, the subsequent recovery. Although glial formation could restrict the inflammation and spare the adjacent survived neurons from neurotoxic effects in the epicenter of injury, overactivation of astrocytes could impede neuro-regenerative processes by preventing the regrowth of axons and establishment of additive connections across the formed boundaries of previously developed scars [64, 65]. Our results revealed that exosome treatment was associated with lower activated astrocytes deducible from the reduced GFAP levels posttreatment. A similar astrogliosis-regulating effect was previously reported in the treatment of stroke and brain injuries with MSCs [66, 67]. Analogous to the pro-inflammatory M1 and anti-inflammatory M2 macrophages, there are two phenotypes of activated astrocytes. A1 astrocytes pre-dominate after SCI and exacerbate secondary injury by the release of chemokines and neurotoxic compounds. Instead, A2 astrocytes release anti-inflammatory cytokines and neuroprotective materials which aid in neurological recovery [68]. Although we didn't investigate the effects of exosomes on the polarization of activated astrocytes, there is convincing evidence claiming that exosomes could shift astrocytes' activation towards the A2 phenotype [44, 69, 70].

The disintegration of the vascular network is one of the immediate changes that follow the mechanical force in SCI. Disrupted blood flow after CNS injuries causes ischemia and secondary damage becomes inevitable, contributing to impaired functional recovery [71]. Previously, MSCs were demonstrated to induce angiogenesis in ischemic injuries and thus were proven to be promising in the treatment of stroke and coronary artery diseases [72, 73]. Some studies indicate that the exosome treatment promotes angiogenesis and the scaffold microvasculature apparatus at the injury site [45, 70, 74]. Altogether, these favorable biological alterations could potentially provide a microenvironment conducive to neuronal regeneration and functional recovery after SCI. Concordantly, our review showed higher beta-tubulin III, NF200, and GAP-43 levels, along with more NeuN-positive cells, representing improved neuronal viability, axonal regrowth, and synaptic plasticity after the exosome treatment in SCI.

Based on our results, exosome administration was associated with higher neuroprotection through its anti-apoptotic properties. Exosomes changed the balance against apoptosis through upregulation of the anti-apoptotic protein Bcl-2 and a reduced expression of the pro-apoptotic Bax protein and cleaved Caspase-3 [75]. Besides reducing the inflammatory mediators that promote programmed cell death, exosome treatment could directly regulate apoptosis-associated genes and signaling pathways. Once again, recent studies shed light on the role of miRNAs, especially miRNA-21 and miRNA-19, as exosomes' constituents in suppressing the multiplex apoptosis genes, including programmed cell death 4 protein (PDCD4) and phosphatase and tensin homolog (PTEN) in targeted tissues [65, 76-78]. The involvement of the Wnt/bcatenin signaling pathways in axonal regrowth and apoptosis inhibition in neural injuries was recognized in previous studies [79, 80]. As another underlying mechanism, the study by Li et al. showed that the exosome treatment could activate the Wnt/b-catenin signaling pathways in rat SCI models, thus hindering apoptosis [81]. According to the present review, alleviating neuronal apoptosis and necrosis is validated morphologically by diminished cavity size ensued by treatment with exosomes.

Owing to high viability in the target tissue and their enhanced stability, exosomes have the capacity to be loaded with concentrated mediators such as nucleic acids and proteins through transfection. Although we didn't investigate the therapeutic effects of exosomes when employed as carriers of genetic materials or drugs, some studies endorsed the improved regenerative efficacy of miRNA- or siRNA-modified MSC-derived exosomes in SCI management [82-84]. Additionally, it is noteworthy that the exosomes' contents could be manipulated by the alteration of their ingenious stem cells' conditioning processes, which could add to their therapeutic efficacy. For instance, a study by Liu et al. demonstrated that exosomes derived from MSCs pre-treated in a hypoxic environment exerted a better functional recovery than the conventionally normoxic cultured cells in the SCIs [55, 85]. Similarly, MSC-derived exosomes that were isolated in an inflammatory agent-induced stimulation process, showed enhanced sensory recovery and higher mechanical force threshold than the conventionally MSC-derived exosomes in rat SCI [86].

Although the majority of studies in our review administrated exosomes shortly after SCI, there is evidence that a fractioned

multiple-dose administration of exosomes outperforms the therapeutic efficacy of a single injection [87]. This highlights the demand for further research to clarify the best dosage and timing of exosome treatment in SCI. Finally, although our results were in favor of the restorative efficacy of the exosome treatment in SCI, there was a lack of evidence about its long-term adverse effects. As exosomes could regulate genes' expression and biomaterials' trafficking, a long-term followup seems reasonable to ascertain this treatment modality's safety.

There have been three recent meta-analyses that evaluated the effect of exosome administration on the improvement of functional outcomes following spinal cord injury. Our findings regarding functional outcomes align with these analyses, which demonstrated that stem cell-derived exosomes have a significant therapeutic effect. Yi et al.[36] conducted a pooled data analysis of locomotion scores from 35 studies using BBB and BMS scoring scales in rats and mice, respectively. They found a significant improvement in locomotion scores for rats (SMD=3.21) and for mice (SMD=2.46). They also noted that exosomes derived from neural stem cells and PC12 cells had an earlier therapeutic effect than those from BMSC, evaluated on the third day post-injury. Shang et al. [35] observed significant recovery in BBB scores after exosome administration from ADMSC (SMD=3.73), BMMSC (SMD=3.65), hUMSC (SMD=2.74), and NSC (SMD=4.54), with NSC-derived exosomes showing the greatest therapeutic value overall (SMD=3.60). Zhang et al.[37] found that BBB scores of BMSC-derived exosomes were significantly better than the control group (SMD=3.89). Additionally, they evaluated other outcomes, including apoptotic factors and inflammatory response. They found that the expression level of Bax in the exosome group was significantly lower than the control group (SMD=-0.70), while the expression level of Bcl-2 was significantly higher than the control group (SMD=0.45). Furthermore, pooled data analysis showed that the expression levels of pro-inflammatory factors IL-1b (SMD=-158.37) and TNFa (SMD=-259.92) were significantly lower in the exosome group, while the expression levels of anti-inflammatory factors IL-4 (SMD=33.77) and IL-10 (SMD=46.47) were better in the exosome group.

5. Limitations

Although we tried to perform a comprehensive analysis of all behavioral and histopathological aspects of exosome treatment in SCI, the number of studies included in some analyses was limited; therefore, we recommend performing more studies on the effect of exosome administration on inflammation and apoptosis. In addition, since the method of measuring the outcomes varied among included studies, we decided to calculate SMD instead of the weighted mean difference. In addition, in the investigation of neural regeneration markers, evidence of possible publication bias was observed; therefore, it is recommended to interpret the findings of these markers with more caution.

6. Conclusions

MSC-derived exosome administration resulted in a significantly improved locomotion of SCI animal models, mainly through ameliorating neuroinflammation, reducing apoptosis, and inducing neuronal regrowth by facilitating a desirable microenvironment. These findings could be considered as potential evidence to design and conduct future clinical trials.

7. Declarations

7.1. Acknowledgments

None.

7.2. Authors complications

Study design: MY, AT; Data gathering: SJ, PP, PG; Analysis: MY, SJ, PP; Interpretation: All authors; Drafting: SJ, PP, AT, SR; Revised: All authors. All authors read and approved the final version.

7.3. Availability of data

The data and statistical codes used in this study are available from the corresponding author upon reasonable request.

7.4. Informed consent

Not applicable.

7.5. Funding and supports

This study was supported by the Iran University of Medical Sciences (Grant number: 99-1-32-17205).

7.6. Conflict of interests

The authors declare that they have no conflict of interest.

7.7. Ethical statement

The ethics committee of Iran University of Medical Sciences (IR.IUMS.REC.1398.1165) approved the current study.

7.8. Using artificial intelligence chatbots

The authors declare that no artificial intelligence chatbots were used.

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 Table 1:
 Characteristics of the included articles

Name	Year	Animal	Gender	Weight/Age	Level of	Model of SCI	Exosome	Exosome	SCI to treatment	Site of injec-
			ounder		SCI		origin	dose/	interval	tion
					001		ongin	volume	lintervui	tion
Chang	2021	SD Pat	м	220 260 g	T10	Contusion	PMMSC	2001	1 hour	Introthogol
Chang	2021	SD Rat	IVI M	220-200 g	T10	Contusion	DMMSC	2001	I IIOUI	Intratilecal
Cnen	2021	SD Rat	M	N/K	110	Compression	BMMSC	200 g	Immediately	Intravenous
Fan	2021	SD Rat	M	200–250 g	110	Contusion	BMMSC	2001	Daily for 7 con-	Intravenous
	0000				TT1 0		D) () (0.0	000	secutive days	x
Gu	2020	SD rat	M	220–260g	110	Contusion	BMMSC	200 g	I hour	Intravenous
Han	2021	Wistar	F	200–250 g	T10	Confusion	BMMSC	1001	Daily for 3 con-	Intrathecal
		Rat							secutive days	
Huang	2020	SD Rat	М	180–220g	T10	Contusion	AMSC	100 g	Immediately	Intrathecal
Huang	2020	SD Rat	М	180–220g	T10	Contusion	BMMSC	250 g	30 minutes	Intravenous
Huang	2017	SD Rat	М	180–220g	T10	Contusion	BMMSC	100g	30 minutes	Intravenous
Huang	2021	SD Rat	М	80-100 g	T10	Contusion	BMMSC	200 g	Daily for 7 con-	Intravenous
									secutive days	
Huang	2021	SD Rat	F	200–250 g	T10	Contusion	BMMSC	200 g	Daily for 5 con-	Intravenous
									secutive days	
Ji	2019	SD Rat	М	150–180g	T10	Compression	BMMSC	100mg	24 hours	Intravenous
Jia	2021	SD Rat	М	230-250 g	T10	Contusion	BMMSC	2001	1 hour	Intravenous
Jiang	2021	SD Rat	М	180–220g	T9/T10	N/R	BMMSC	100 g	30 minutes	Intravenous
Li	2019	Wistar	М	150–200g	T9-T11	Contusion	BMMSC	200g	Every 3 days for	N/R
		Rat						Ū	27 days	
Li	2020	SD Rat	М	N/R	T10	Compression	BMMSC	100g	24 hours	Intravenous
Li	2018	SD Rat	М	250–300g	T10	Compression	BMMSC	100g	24 hours	Intravenous
Liu	2020	C57BL/6	М	6-8 w	T10	Contusion	BMMSC	200 g	Immediately	Intravenous
Liu	2019	SD Rat	F	170-220g	T10	Contusion	BMMSC	200 g	Immediately	Intravenous
Lu	2019	SD Rat	M	200–250 g	T10	Contusion	BMMSC	200 g	30 minutes	Intravenous
Iu	2010	SD Rat	F	170_220g	T10	Contusion	BMMSC	200 g	Immediately	Intravenous
Nakazaki	2021	SD Rat	M	185-215 g	ТО	Contusion	BMMSC	200 g	Daily for 9 con-	Intravenous
INAKAZAKI	2021	SD hat	111	105-215 g	15	Contusion	DIVINISC	48	secutive days	muavenous
Nio	2021	SD Pat	N/D	190 220 g	T10	Transaction	BMMSC	100g	24 hours	Intravonous
Noori	2021	Wietar	M	210-220 g	T10	Compression	bWIMSC	1.3 g	24 hours	Intrathecal
	2021	Pat	141	210-200 g	110	Compression	1100 10130	1-5 g	24 110013	muaniccai
Bon	2010	SD Pot	м	250 250 g	T10	Comprossion	AMSC	N/D	N/D	N/D
Refi	2019	SD Rat	Г	250-550 g	T10	Compression	LUCMOC	N/K	IN/K	IN/K
Romanelli	2021	F344 Kat	г	140–190 g	18	Contusion	nucmsc	$1.5 \times 10^{\circ}$	Immediately	Intravenous
D112	2010	E244 D-4	Г	140,100 -	TO	Contraion	LUCMO	particles	In the second	T 4
Romanelli	2019	F344 Kat	г	140–190 g	18	Contusion	nucmsc	N/K	immediately &	Intravenous
D (0010			005 050	T 10		1.1101406	109	24 nours	T /
Ruppert	2018	SD Rat	М	225–250g	110	Contusion	hUCMSC	10 ⁵ parti-	3hours	Intravenous
		0						cles		-
Shao	2020	C57BL/6	N/R	6W	18/19	Compression	AMSC	200 g	Immediately	Intravenous
		mouse								
Sheng	2021	C57BL/6	F	6-8 W	T10	Contusion	BMMSC	200 g	Immediately	Injury site
		mouse								
Sun	2018	C57BL/6	F	17–22g	T11/T12	Contusion	hUCMSC	20 g	30minutes	Intravenous
		mouse								
Wang	2021	Rat	F	230 g	T10	Transection	AMSC	100 ng	Immediately	Injury site
Wang	2018	SD Rat	М	200–250g	T10	Contusion	BMMSC	40 g	30minutes	Intravenous
Wang	2021	SD Rat	F	6-7 W	N/R	N/R	hUCMSC	N/R	N/R	Intravenous
Xiao	2021	SD Rat	М	150–200g	T10	Compression	hUCMSC	100mg	24 hours	Intravenous
Xu	2019	SD Rat	N/R	180–220g	T9/T10	Contusion	hMSC	N/R	N/R	Intravenous
Yu	2019	SD Rat	F	230–250g	T10	Contusion	BMMSC	100 g	1 hour	Intravenous
Zhai	2021	ICR	М	30-35 g	T8/T9	Contusion	hUCMSC	20 g	Daily for 10 con-	Injury site
		mouse		0				0	secutive days	, , , , , ,
Zhang	2021	SD Bat	М	200-280 g	T10	Contusion	BMMSC	50 g	5 minutes	Injury site + In-
8								0		travenous
Zhang	2020	Mouse	М	8 W	T10	Contusion	hPMSC	200 g/l	N/R	Injury site
Zhang	2021	SD Rat	M	200–230 g	T10	Contusion	BMMSC	200 g	30 minutes & 7	Intravenous
Linung	2021	ob nat	.,,	200 200 g	110	Contasion	DivitivioC	200 6	dave & 14 dave	muuvenous
Zhou	2021	SD Pat	F	200-220 g	T11	Transaction	hPMSC	50 g	Immediatoly 0.1	Intravenous
Zilou	2021	SD hat	1	200-220 g	111	mansection	in wise	50 g	hour & 2 wooko	muavenous
									nour & 2 weeks	

Name	Year	Animal	Gender	Weight/Age	Level of	Model of SCI	Exosome	Exosome	SCI to treatment	Site of injec-
					SCI		origin	dose/ volume	interval	tion
Zhou	2019	Wistar Rat	М	200–250g	T10	Transection	BMMSC	100g	1hour	Intravenous
Guo	2019	SD Rat	F	200–250g	T10	Transection	BMMSC	401	23 hours & daily for 5 consecutive days	Intranasal
Zhou	2022	SD Rat	М	200–250 g	T10	Contusion	BMMSC	40 g	30 minutes & 24 hours	Intravenous
Xin	2021	SD Rat	F	220–250g	Т9	Contusion	BMMSC	100 g	Immediately & daily for 7 con- secutive days	Subcutaneous
Pinho	2022	C57BL/6 mouse	F	10-15 w	T8-9	Compression	AMSC	1001	Daily for 3 days & once a week af- terwards	Intravenous
Huang	2022	SD Rat	М	200-220 g	T10	Contusion	BMMSC	40 g	30 minutes & 24 hours	Intravenous
Xie	2022	SD Rat	М	180–220g	T10	Contusion	BMMSC	10 g	2 hours & every 2 days for 3 injec- tions	Intravenous
Yan	2019	SD Rat	М	220 250 g	T10	Contusion	BMMSC	40 g	2 hours & every 2 days for 3 injec- tions	Intravenous
Liu	2022	C57BL/6 mouse	F	17.4-22 g	T11–12	Contusion	hDPMSC	200 g	30 minutes	Intravenous
Shao	2022	C57BL/6 mouse	М	7-8 w	T10	Contusion	BMMSC	N/R	3 days	Into the injured hind limbs
Suang	2022	SD Rat	F	220 g	Т9	Compression	AMSC	10 ⁹ parti- cles	Immediately & 3 days	Intravenous
Не	2022	SD Rat	N/R	220 g	T10	Contusion	BMMSC	100 g	Daily for 7 con- secutive days	Intravenous
Kang	2022	SD Rat	F	170–220 g	T10	Contusion	hUCMSC	200 g	Immediately	N/R
Cheshmi	2023	SD Rat	М	200-250 g	T9	Contusion	hPMSCs	200 g	30 min	Intravenous
Han	2022	Wistar Rat	F	200-250 g	T10	Contusion	BMSC	721	continuous in- jection for 3 days	under the dura
Hu	2022	SD Rat	F	200-250 g	T6, T7	Transection	hUCMSC	501	Immediately	Injury site
Kostennikov	/2022	Wistar Rat	F	250-300 g	T8	Contusion	Ad- MSCs	10, 50 g	30 min	Intravenous
Lai	2022	SD Rat	F	NR	T10	Compression	hUCMSC	200 g	N/R	Intravenous
Li	2022	SD Rat	N/R	220 g	T10	Contusion	BMSCs	100 g	Daily for 7 con- secutive days	Intravenous
Wang B	2022	C57BL/6 mice	F	20-25 g	T11, T12	Contusion	hUCMSC	50 g	N/R	Intravenous
Wang Y	2022	Wistar Rat	F	NR	T10	Contusion	BMSCs	251	continuous in- jection for 3 days	Intrathecal
Xiong	2023	C57BL/6 mice	М	20-25 g	T10	Transection	MUMSCs	41	4 times every 7 days	Injury site
Yin	2022	C57BL/6 mice	F	8 weeks	T8-T10	Contusion	BMSCs	N/R	N/R	Intrathecal
Zhao	2023	SD Rat	N/R	6-8 weeks	T10	Contusion	BMSCs	200 g	1 hour	Intravenous

Table 1: Characteristics of the included articles (continue)

	Number of ex- periments	Subgroup analys	is			Meta-regression		
		Weight/ [95%CI]	AgeSMD	P value	I ² (p value)	Coefficient [95%CI]	P value	
Locomotion								
Species								
Mice	17	1.44 [0.99, 1.86]		< 0.0001	66.03 (<0.0001)	Reference		
Rat	55	2.61 [2.18, 3.05]		< 0.0001	85.30 (<0.0001)	1.09 [0.31to 1.88]	0.006	
Model of SCI								
Transection	8	3.73 [1.82, 5.64]		< 0.0001	94.12 (<0.0001)	Reference		
Contusion	45	2.24 [1.81, 2.66]		< 0.0001	83.89 (<0.0001)	-1.038 [-2.28 to 0.20]	0.101	
Compression	17	1.99 [1.37, 2.60]		< 0.0001	74.28 (<0.0001)	-1.25 [-2.63 to 0.12]	0.074	
Severity of SCI								
Moderate	40	2.24 [1.77, 2.71]		< 0.0001	84.71 (<0.0001)	Reference		
Severe	25	2.65 [1.94, 3.36]		< 0.0001	87.55 (<0.0001)	0.33 [-0.45, 1.12]	0.403	
Origin of Exosome								
BMMSC	41	2.28 [1.81, 2.74]		< 0.0001	84.84 (<0.0001)	Reference		
ADMSC	11	2.40 [1.34, 3.47]		< 0.0001	86.10 (<0.0001)	0.074 [-0.97, 1.12]	0.890	
UCMSC	13	1.89 [1.21, 2.57]		< 0.0001	79.33 (<0.0001)	-0.032 [-1.28, 0.64]	0.517	
hWJMSC	3	3.35 [1.52, 5.17]		< 0.0001	69.20 (0.048)	1.07 [-0.87, 3.02]	0.279	
hPMSC	3	3.67 [0. 48, 6.86]		0.024	89.32 (0.001)	1.03 [-0.95, 3.02]	0.308	
hDpMSC	1	NA		NA	NA	NA	NA	
Number of administra- tions								
Single dose	43	2.33 [1.88, 2.77]		< 0.0001	82.87 (<0.0001)	Reference		
Multi dose	29	2.28 [1.69, 2.87]		< 0.0001	86.28 (<0.0001)	-0.08 [-0.81, 0.64]	0.828	
Time of injection after SCI								
Immediate (<3 hours)	56	2.55 [2.13, 2.97]		< 0.0001	84.20 (<0.0001)	Reference		
Acute (24 to 72 hours)	9	1.77 [1.02, 2.51]		< 0.0001	74.72 (0.002)	-0.67 [-1.71, 0.38]	0.213	
Subacute (>24 hours)	2	NA		NA	NA	NA	NA	
Route of administration								
Systemic	54	2.24 [1.85, 2.64]		< 0.0001	83.36 (<0.0001)	Reference		
Local	17	2.57 [1.70, 3.44]		< 0.0001	88.07 (<0.0001)	0.24 [-0.62, 1.09]	0.586	
Follow up duration								
<28 days	11	2.36 [1.46, 3.26]		< 0.0001	80.44 (<0.0001)	Reference		
≥28 days	61	2.30 [1.91, 2.68]		< 0.0001	84.92 (<0.0001)	-0.082 [-1.09, 0.93]	0.873	

 Table 2:
 Subgroup analyses and meta-regressions for different variables in locomotion recovery

	Number of ex- periments	Subgroup analysis			Meta-regression		
		Weight/ AgeSMD [95%CI]	P value	I ² (p value)	Coefficient [95%CI]	P value	
Cavity size							
Species							
Mice	5	-3.93 [-6.10, -1.76]	< 0.0001	86.55 (<0.0001)	Reference		
Rat	21	-2.46 [-3.48, -1.43]	< 0.0001	91.72 (<0.0001)	1.462696 [-0.9082156, 3.833608]	0.227	
Severity of SCI							
Moderate	13	-3.52 [-4.80, -2.25]	< 0.0001	86.46 (<0.0001)	Reference		
Severe	9	-2.50 [-4.55, -0.44]	0.017	95.58 (<0.0001)	1.32 [-0.72, 3.37]	0.205	
Origin of Exosome							
BMMSC	12	-3.43 [-4.95, -1.91]	< 0.0001	90.46 (<0.0001)	Reference		
ADMSC	4	-5.95[-14.06, 2.17]	0.151	99.09 (<0.0001)	0.18 [-2.87, 3.23]	0.907	
UCMSC	9	-1.69 [-2.95, -0.42]	0.009	90.67 (<0.0001)	1.68 [47, 3.82]	0.125	
hPMSC	1	NA	NA	NA	NA	NA	
Number of administra- tions							
Single dose	19	-2.66 [-3.89, -1.44]	< 0.0001	93.25 (<0.0001)	Reference		
Multi dose	7	-3.08 [-4.48, -1.68]	< 0.0001	84.25 (<0.0001)	-0.55 [-2.68, 1.58]	0.612	
Rout of administration							
Systemic	18	-2.78 [-3.86, -1.7]	< 0.0001	90.91 (<0.0001)	Reference		
Local	8	-2.95 [-5.29, -0.61]	0.013	94.93 (<0.0001)	0.17 [-1.96, 2.3]	0.873	
Follow up duration							
<28 days	6	-4.10 [-6.28, -1.91]	< 0.0001	89.66 (<0.0001)	Reference		
≥28 days	20	-2.32 [-3.31, -1.34]	< 0.0001	90.64 (<0.0001)	1.68 [-0.53, 3.88]	0.136	

Table 3: Subgroup analyses and meta-regressions for different variables in cavity size



Figure 1: PRISMA flow diagram of the article selection process.

	Number of ex- periments	Subgroup analysis			Meta-regression		
		Weight/ AgeSMD [95%CI]	P value	I ² (p value)	Coefficient [95%CI]	P value	
Expression of GFAP							
Model of SCI							
Contusion	13	-1.79 [-2.53, -1.06]	< 0.0001	72.19 (<0.0001)	Reference		
Transection	1	NA	NA	NA	NA	NA	
Compression	11	-3.97 [-5.77, -2.16]	< 0.0001	87.14 (<0.0001)	-1.64 [-3.61, 0.33]	0.103	
Severity of SCI							
Moderate	10	-1.91 [-3.21, -0.60]	< 0.0001	89.06 (<0.0001)	Reference		
Severe	15	-3.59 [-4.96, -2.22]	< 0.0001	86.40 (<0.0001)	-1.55 [-3.43, 0.34]	0.107	
Origin of Exosome							
BMMSC	10	-2.76 [-4.34, -1.18]	0.001	88.63 (<0.0001)	Reference		
ADMSC	3	-0.66 [-2.36, 1.04]	0.447	84.06 (0.002)	1.90 [-0.58, 4.37]	0.133	
UCMSC	5	-2.07 [-3.59, -0.55]	0.007	83.16 (0.008)	0.44 [-1.68, 2.57]	0.684	
hWJMSC	6	-5.41 [-7.15, -3.66]	< 0.0001	33.08 (0.165)	-3.05 [-5.46, -0.63]	0.013	
hPMSC	1	NA	NA	NA	NA	NA	
Number of administra- tions							
Single dose	15	-3.61 [-4.69, -2.52]	<0.0001	76.13 (<0.0001)	Reference		
Multi dose	10	-1.36 [-2.39, -0.33]	0.009	82.98 (<0.0001)	2.14 [0.57, 3.70]	0.007	
Time of injection after SCI							
Immediate (<3 hours)	16	-1.96 [-2.62, -1.30]	< 0.0001	69.15 (<0.0001)	Reference		
Acute (24 to 72 hours)	7	-5.54 [-7.03, -4.05]	< 0.0001	28.42 (0.195)	-3.58 [-5.21, -1.95]	< 0.0001	
Route of administration							
Systemic	16	-2.36 [-3.30, -1.43]	< 0.0001	84.56 (<0.0001)	Reference		
Local	8	-4.32 [-6.27, -2.37]	< 0.0001	77.42 (0.001)	-1.69 [-3.67, 0.30]	0.095	
Follow up duration							
<28 days	13	-2.59 [-4.01, -1.65]	< 0.0001	90.42 (<0.0001)	Reference		
≥28 days	12	-3.05 [-4.33, -1.78]	< 0.0001	84.05 (<0.0001)	-0.59 [-2.51, 1.33]	0.548	

 Table 4:
 Subgroup analyses and meta-regressions for different variables in the expression of GFAP

	Number of ex- periments	Subgroup analysis			Meta-regression		
		Weight/ AgeSMD [95%CI]	P value	I ² (p value)	Coefficient [95%CI]	P value	
Number of apoptotic cells							
Model of SCI							
Contusion	15	-4.07 [-5.29, -2.86]	< 0.0001	83.49 (<0.0001)	Reference		
Transection	1	NA	NA	NA	NA	NA	
Compression	6	-4.30 [-5.73, -2.87]	< 0.0001	54.56 (0.060)	-0.45 [-2.68 to 1.78]	0.692	
Severity of SCI							
Moderate	14	-4.31 [-5.46, -3.19]	< 0.0001	75.97 (<0.0001)	Reference		
Severe	8	-4.41 [-6.48, -2.34]	< 0.0001	86.28 (<0.0001)	0.12 [-2.00, 2.24]	0.910	
Origin of Exosome							
BMMSC	15	-4.49 [-5.66, -3.31]	< 0.0001	78.77 (<0.0001)	Reference		
ADMSC	1	NA	NA	NA	NA	NA	
UCMSC	3	-4.94 [-7.09, -2.78]	< 0.0001	54.62 (0.112)	-0.57 [-3.43, 2.30]	0.699	
hWJMSC	3	-4.07 [-6.66, -1.49]	0.002	60.68 (0.083)	0.34 [-2.62, 3.31]	0.819	
hPMSC	1	NA	NA	NA	NA	NA	
Number of administra- tions							
Single dose	16	-3.95 [-5.04, -2.86]	<0.0001	79.20 (<0.0001)	Reference		
Multi dose	6	-5.21 [-6.92, -3.49]	< 0.0001	70.31 (0.007)	-1.28 [-3.37, 0.81]	0.231	
Time of injection after SCI							
Immediate (<3 hours)	16	-4.29 [-5.53, -3.04]	< 0.0001	84.07 (<0.0001)	Reference		
Acute (24 to 72 hours)	5	-4.62 [-6.55, -2.68]	< 0.0001	64.59 (0.032)	-0.46 [-2.95, 2.04]	0.719	
Route of administration							
Systemic	17	-4.22 [-5.39, -3.05]	< 0.0001	83.55 (<0.0001)	Reference		
Local	5	-4.74 [-6.60, -2.88]	< 0.0001	58.33 (0.043)	-0.65 [-3.12, 1.83]	0.608	
Follow up duration							
<28 days	16	-3.60 [-4.59, -2.61]	< 0.0001	73.50 (<0.0001)	Reference		
≥28 days	7	-5.67 [-7.45, -3.90]	< 0.0001	75.48 (0.001)	-1.97 [-3.88, -0.07]	0.042	

 Table 5:
 Subgroup analyses and meta-regressions for different variables in the number of apoptotic cells

	Number of ex-	Subgroup analysis			Meta-regression		
	periments	Weight/ AgeSMD [95%CI]	P value	I ² (p value)	Coefficient [95%CI]	P value	
IL-1b							
Species							
Mice	6	-2.02 [-3.27, -0.77]	0.002	79.39 (0.001)	Reference		
Rat	21	-3.78 [-4.86, -2.71]	< 0.0001	86.01 (<0.0001)	-1.60 [-3.53 to 0.33]	0.105	
Model of SCI							
Contusion	18	-2.98 [-4.00, -1.97]	< 0.0001	87.51 (<0.0001)	Reference		
Transection	1	NA	NA	NA	-9.1 [-15.22 to -2.98]	0.512	
Compression	7	-3.13 [-4.08, -2.19]	< 0.0001	27.04 (0.074)	-0.62 [-2.49 to 1.24]	0.008	
Severity of SCI							
Moderate	16	-2.75 [-3.49, -2.00]	< 0.0001	70.18 (<0.0001)	Reference		
Severe	10	-4.91 [-7.50, -2.32]	< 0.0001	95.18 (<0.0001)	-1.3 [-3.35, 0.57]	0.166	
Origin of Exosome							
BMMSC	12	-3.29 [-4.69, -1.89]	< 0.0001	89.75 (<0.0001)	Reference		
ADMSC	4	-3.66 [-5.22, -2.10]	< 0.0001	57.27 (0.070)	-0.58 [-3.27, 2.12]	0.676	
UCMSC	8	-2.80 [-4.41, -1.20]	0.001	87.31 (<0.0001)	0.44 [-1.66, 2.54]	0.683	
hWJMSC	3	-5.19 [-8.97, -1.41]	0.007	72.18 (0.018)	-1.70 [-5.08, 1.68]	0.325	
Number of administra- tions							
Single dose	15	-3.30 [-4.33, -2.27]	< 0.0001	79.47 (<0.0001)	Reference		
Multi dose	12	-3.28 [-4.77, -1.80]	< 0.0001	90.03 (<0.0001)	0.24 [-1.53, 2.00]	0.793	
Time of injection after SCI							
Immediate (<3 hours)	21	-3.47 [-4.38, -2.55]	< 0.0001	83.04 (<0.0001)	Reference		
Acute (24 to 72 hours)	4	-3.93 [-7.17, -0.68]	0.018	88.03 (0.001)	-0.02 [-2.62, 2.58]	0.987	
Route of administration							
Systemic	19	-2.93 [-3.82, -2.05]	< 0.0001	83.25 (<0.0001)	Reference		
Local	8	-4.61 [-6.90, -2.32]	< 0.0001	88.67 (<0.0001)	-1.24 [-3.22, 0.75]	0.223	
Follow up duration							
<28 days	19	-3.37 [-4.30, -2.44]	< 0.0001	79.07 (<0.0001)	Reference		
≥28 days	8	-3.24 [-5.42, -1.06]	0.004	94.31 (<0.0001)	0.47 [-1.42, 2.35]	0.627	

 Table 6:
 Subgroup analyses and meta-regressions for different variables in pro-inflammatory marker IL-1b

	Number of ex- periments	Subgroup analysis			Meta-regression			
	-	Weight/ AgeSMD [95%CI]	P value	I ² (p value)	Coefficient [95%CI]	P value		
TNF-a								
Species								
Mice	8	-2.79 [-4.46, -1.12]	0.001	89.45 (<0.0001)	Reference			
Rat	20	-2.49 [-3.14, -1.84]	< 0.0001	72.10 (<0.0001)	0.01 [1.43, 1.45]	0.987		
Model of SCI								
Contusion	18	-2.43 [-3.07, -1.79]	< 0.0001	72.21 (<0.0001)	Reference			
Transection	1	NA	NA	NA	-6.29 [-10.25, -2.33]	NA		
Compression	8	-2.08 [-3.27, -0.90]	0.001	75.23 (<0.0001)	0.47 [-0.79, 1.71]	0.469		
Severity of SCI								
Moderate	20	-2.30 [-2.94, -1.67]	< 0.0001	75.10 (<0.0001)	Reference			
Severe	7	-4.26 [-7.02, -1.49]	< 0.0001	93.38 (<0.0001)	-0.95 [-2.59, 0.70]	0.260		
Origin of Exosome								
BMMSC	11	-2.75 [-3.67, -1.83]	< 0.0001	75.95 (<0.0001)	Reference			
ADMSC	4	-2.21 [-3.60, -0.81]	0.002	68.80 (0.043)	0.50 [-1.60, 2.60]	0.642		
UCMSC	9	-2.27 [-3.67, -0.87]	< 0.0001	88.38 (<0.0001)	0.62 [-0.99, 2.23]	0.449		
hWJMSC	3	-6.57 [-12.00, -1.14]	0.018	80.24 (0.005)	-2.29 [-5.34, 0.75]	0.139		
hPMSC	1	NA	NA	NA	NA	NA		
Number of administra- tions								
Single dose	18	-2.90 [-3.73, -2.08]	<0.0001	78.60 (<0.0001)	Reference			
Multi dose	10	-2.07 [-3.05, -1.09]	< 0.0001	79.27 (<0.0001)	0.81 [-0.49, 2.11]	0.223		
Time of injection after SCIv								
Immediate (<3 hours)	22	-2.66 [-3.28, -2.04]	<0.0001	73.01 (<0.0001)	Reference			
Acute (24 to 72 hours)	4	-4.74 [-9.59, 0.11]	0.056	94.09 (<0.0001)	-0.87 [-2.22, 2.05]	0.936		
Route of administration				. ,				
Systemic	19	-2.09 [-2.70, -1.48]	<0.0001	72.63 (<0.0001)	Reference			
Local	9	-4.18 [-6.02, -2.34]	< 0.0001	87.37 (0.001)	-1.52 [-2.91, -0.13]	0.032		
Follow up duration								
<28 days	21	-2.25 [-2.86, -1.63]	<0.0001	71.22 (<0.0001)	Reference			
≥28 days	7	-3.59 [-5.44, -1.74]	< 0.0001	88.65 (<0.0001)	-1.00 [-2.48, 0.47]	0.183		

Table 7: Subgroup analyses and meta-regressions for different variables in pro-inflammatory marker TNF-alpha

Study	N	Treatm Mean	ent SD N	Conti Mean	ol SD		Hedges's g W with 95% Cl	Veight (%)
Chang, 2021	12	16.66	1.68 12	11.29	1.17	-0-	3.58 [2.31, 4.86]	1.43
Chen, 2021	6	6.94	.72 6	4.58	.77	-0-	2.92 [1.35, 4.49]	1.31
Cheshmi, 2023	6	13.02	1.24 6	8.78	1.19	-0-	3.22 [1.56, 4.88]	1.27
Fan, 2021	6 8	14.97	2.99 6	9.98 6.42	3.11	•	1.51 [0.30, 2.72]	1.46
Guo, 2019	10	3.30 2	4.05 15	.43	.39	0	0.60 [-0.20, 1.39]	1.62
Han, 2021	10	- 16.13	6.74 10	12.11	6.32	Ð	0.59 [-0.27, 1.45]	1.60
Han, 2022	10	16.48	6 10	12.18	6.45	θ	0.66 [-0.20, 1.53]	1.59
He, 2022	10	13.64	.99 10	9.42	.66	-0-	4.80 [3.09, 6.51]	1.25
Hu, 2022	6	14.05	.96 6	7.31	.58		7.84 [4.54, 11.15]	0.69
Huang, 2017 Huang, 2020	5 8	13.06	.00 0	947	.04		4.41 [2.16, 0.05] 5 40 [3 31 7 49]	1.03
Huang, 2020	10	12.66	.64 10	9.86	.75	-0-	3.85 [2.39, 5.30]	1.36
Huang, 2021	6	10.15	.85 6	6.13	.83	-0-	4.42 [2.36, 6.47]	1.10
Huang, 2021	6	12.97	.83 6	11.29	.78	-0-	1.93 [0.63, 3.22]	1.42
Huang, 2022	6	12.75	1.67 6	9.44	1.71	•	1.81 [0.54, 3.08]	1.44
JI, 2019 Jia: 2021	5	5.15	.9 6	3.28	.8 1 1 0	-0-	2.03 [0.70, 3.35]	1.41
Jiang, 2021	3	12.13	1.18 3	9.04	1.07	-0-	2.19 [0.41, 3.98]	1.22
Kang, 2022	10	9.11	1.18 10	6.2	1.26	-0-	2.28 [1.19, 3.38]	1.51
Kostennikov, 2022	8	7.71	3.85 8	2.63	1.87	•	1.59 [0.51, 2.66]	1.51
Kostennikov, 2022	8	7.63	4.24 8	2.63	1.87	0	1.44 [0.39, 2.50]	1.52
Lai, 2022	10	6.77	1.13 10	4.87	.89	ð	1.79 [0.78, 2.80]	1.54
Li, 2019	10	16.4	1.27 10	13.9	.01	Ĭ _e	2.28 [1.18, 3.38]	1.55
Li, 2020	10	6.44	.76 10	5.71	.74	Θ	0.93 [0.04, 1.82]	1.59
Li, 2022	10	13.76	.97 10	9.38	.76	-0-	4.81 [3.10, 6.53]	1.25
Liu, 2019	10	9.23	1.45 10	6.78	1.78	Ð	1.45 [0.49, 2.40]	1.56
Liu, 2020	8	6.4	.73 8	4.56	1.19	· 0 ·	1.76 [0.65, 2.87]	1.50
Liu, 2022	12	4.05	.58 12	8.95	1.14	₽	2.49 [1.44, 3.53] 0.44 [-0.41 1.29]	1.53
Lu, 2021	10	9.96	1.01 10	6.87	.75	ĭ	3.33 [2.00, 4.66]	1.41
Nakazaki, 2021	14	6.26	2.81 17	4.75	2.89	θ	0.52 [-0.19, 1.22]	1.65
Nakazaki, 2021	14	8.09	3.14 17	4.75	2.89	θ	1.08 [0.34, 1.82]	1.64
Nie, 2021	24	9.61	1.82 24	7.66	1.41	θ	1.18 [0.57, 1.78]	1.68
Noori 2021	6	7.95	1.5 C	3.20	1.12	-0-	3.20 [1.59, 4.93] 2.02 [0.70 3.34]	1.20
Noori, 2021	6	10.7	1.39 6	3.28	1.12	_ 	5.43 [3.02, 7.84]	0.97
Pinho, 2022	9	4.05	2.1 5	4.51	.96	•	-0.24 [-1.27, 0.79]	1.53
Pinho, 2022	4	6.01	1.9 5	2.09	2.33	-0-	1.62 [0.23, 3.00]	1.39
Pinho, 2022	7	3.35	2.57 5	2.09	2.33	0	0.47 [-0.61, 1.55]	1.51
Romanelli 2021	0 8	15.2	1.7 0	11.0	.5	Ф	0.83 [-0.14, 1.80] 2 45 [1 19 3 71]	1.50
Ruppert, 2018	16	13.63	1.66 6	11.37	1.25	Ð	1.39 [0.40, 2.38]	1.55
Shao, 2020	10	8.92	1.12 10	6.2	.94	-0-	2.52 [1.37, 3.67]	1.49
Shao, 2020	10	6	.74 10	4.58	.53	O -	2.11 [1.05, 3.18]	1.52
Shao, 2022	10	4.29	.71 10	3.46	.6 54	0	1.21 [0.29, 2.13]	1.57
Sun 2018	5 8	5.22	.02 :	3.33	.04 91	ф (1.59[0.27, 2.91]	1.42
Sun, 2018	8	3.67	.85 8	3.33	.91	•	0.37 [-0.57, 1.30]	1.57
Sung, 2022	6	7.08	.44 6	5.42	.34	- o -	3.90 [2.02, 5.77]	1.18
Sung, 2022	6	8.57	.96 6	5.42	.34	-0-	4.04 [2.11, 5.96]	1.16
Wang, 2018	10	14.51	4.17 10	9.42	1.9	•	1.50 [0.54, 2.46]	1.56
Wang, 2021 Wang, 2021	8	6.31	.65 8	2.67	.61	_0_	5.46 [3.35, 7.57]	1.08
Wang B , 2022	8	3.02	1.95 8	2.59	1.56	•	0.23 [-0.70, 1.16]	1.57
Wang Y , 2022	10	16.46	1.87 10	12.27	2.13	- O -	2.00 [0.96, 3.05]	1.53
Xiao, 2021	6	11.29	1.27 €	8.06	1.47	- 0 -	2.17 [0.81, 3.53]	1.40
Xie, 2022	10	11.38	.92 10	6.5	1.3	-0-	4.15 [2.61, 5.69]	1.32
Xin, 2021 Xiona, 2023	5 8	7 78	.95 5	4 18	.03 86	-0-	4 05 [2 37 5 73]	1.26
Xiong, 2023	7	2.03	1.37 7	.73	.79	0	1.09 [0.03, 2.15]	1.52
Yan, 2019	10	16.75	2.54 10	12.55	2.95	Ð	1.46 [0.51, 2.42]	1.56
Yin, 2022	6	13.48	1.36 6	10.54	1.09	-0-	2.20 [0.84, 3.57]	1.39
Yu, 2019 Zhai: 2024	20	12.33	.99 20	6.52	.62	-0-	6.89 [5.27, 8.52]	1.28
∠nai, 2021 Zhang 2020	∠∪ 6	0.01 6.80	3.40 20 2 P	5.75	∠.40 1.08	0	1.30 [0.03, 1.97] 1.35 [0.18 2.53]	1.00 1.47
Zhang, 2021	6	11.12	2.74 6	5.4	1.71	-0-	2.31 [0.92, 3.71]	1.38
Zhao, 2019	5	17.95	1.78 5	14.98	.94	-0-	1.88 [0.49, 3.28]	1.38
Zhou, 2019	6	18.22	1.13 6	12.04	1.21	-0-	4.87 [2.66, 7.08]	1.04
Zhou, 2021	6	8.53	.54 6	2.01	1.05	-0	7.21 [4.14, 10.28]	0.76
2110U, 2022	10	13.41	1.09 10	σ./1	1.09	-0-	3.17 [1.87, 4.46]	1.43
Uverall Heterogeneity: 7 ²	= 1 0	R4 I ² −	84 16%	H ² = 6	31		2.31[1.95, 2.66]	
Test of $\theta_i = \theta_i$: Q(7)	- 1.0 (1) =	340.73	3, p = 0.0	– 0. 10	51			
Test of θ = 0: z =	12.8	0, p = 0	0.00				7	
						0 5 10	15	

Random-effects REML model Sorted by: author year

Figure 2: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on locomotion. This open-access article distributed under the terms of the Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0). Downloaded from: https://journals.sbmu.ac.ir/aaem/index.php/AAEM/index

Studv	N	Treatme Mean	ent SD	N	Contr Mean	ol SD		Hedges's with 95% (g Cl	Weight (%)
Cheshmi 2023	6	14	01	6	21	02	A	-4.09[-6.03	-2 151	3.83
Han 2021	3	71 64	12.37	3	76 95	16.09	Ŭ O	-0.30 [-1.59	1 001	4 20
Han 2022	5	71.54	16 12	5	77.33	19.5	Å	-0.29[-1.42	0.831	4 28
Huang, 2017	5	.08	.01	5	.1	.01	0	-1.81 [-3.18.	-0.441	4.16
Huang, 2020	5	23.55	1.28	5	37.55	2.3	-0-	-6.79 [-9.98.	-3.611	3.01
Huang, 2020	8	10.38	2.29	8	21.82	1.99	Ð	-5.04 [-7.02.	-3.061	3.80
Huang, 2022	10	22.17	6.36	10	38.49	12.9	Θ	-1.54 [-2.50,	-0.57]	4.35
Kostennikov, 2022	8	.69	.71	8	.96	.45	0	-0.43 [-1.37,	0.51	4.37
Kostennikov, 2022	8	.43	.19	8	.96	.45	Θ	-1.45 [-2.50,	-0.40]	4.32
Lai, 2022	10	100.86	7.01	10	145.13	11.25	Θ	-4.52 [-6.16,	-2.89]	4.01
Li, 2018	6	33.26	2.14	6	35.06	1.85	Θ	-0.83 [-1.93,	0.27]	4.30
Liu, 2019	5	3.11	.76	5	7.75	.58	-0-	-6.20 [-9.14,	-3.26]	3.16
Liu, 2020	8	5.17	.61	8	11.34	1.05	-0-	-6.79 [-9.32,	-4.26]	3.44
Romanelli, 2021	8	12.05	1.22	8	11.22	1.13	0	0.67 [-0.29,	1.62]	4.36
Romanelli, 2021	8	10.34	1.41	8	11.22	1.13	•	-0.65 [-1.60,	0.30]	4.36
Romanelli, 2021	8	4.98	.41	8	5.32	1.06	e	-0.40 [-1.34,	0.54]	4.37
Romanelli, 2021	8	5.44	.43	8	5.32	1.06	φ	0.14 [-0.79,	1.07]	4.37
Sheng, 2021	5	10.33	1.3	5	19.97	1.47	-0-	-6.27 [-9.24,	-3.31]	3.14
Sun, 2018	6	.47	.07	6	.93	.17	Ð	-3.27 [-4.94,	-1.59]	3.99
Sun, 2018	6	.77	.24	6	.93	.17	•	-0.71 [-1.79,	0.37]	4.30
Wang, 2018	6	10.12	5.07	6	35.18	5.36	Ð	-4.43 [-6.49,	-2.38]	3.75
Wang, 2021	4	33.05	2.06	4	98.52	2.97	o	-22.27 [-33.26,	-11.29]	0.64
Wang, 2021	10	69.61	13.52	10	218.43	55.28	θ	-3.54 [-4.92,	-2.16]	4.16
Xie, 2022	6	4.96	.2	6	6.3	.17	-0-	-6.66 [-9.53,	-3.80]	3.21
Xiong, 2023	8	22.635	2.84	8	35.8	3.73	θ	-3.75 [-5.35,	-2.16]	4.04
Zhang, 2021	6	14.01	4.26	6	33.71	8.55	Θ	-2.69 [-4.19,	-1.19]	4.09
Overall							•	-2.75 [-3.69,	-1.80]	
Heterogeneity: τ^2 :	= 5.0	$09, I^2 = 9$	91.55%	%,⊦	$H^2 = 11.$	83		-	-	
Test of $\theta_i = \theta_i$: Q(2	5) =	192.78	, p = 0	.00			i i			
Test of θ = 0: z = -	.5.70	p = 0.	00							
							-30 -20 -10 0			

Random-effects REML model Sorted by: author year

Figure 3: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on cavity size.

Study	ר N	reatme Mean	ent SD	N	Contro Mean	ol SD		Hedges's with 95%	s g Cl	Weight (%)
Beta tubulin III Chen, 2021	3	1.97	.23	3	1	.1	-0	4.38 [1.59,	7.16]	2.03
Guo, 2019	3	2.42	.8	3	.58	.4	-0-	2.33 [0.49,	4.16]	2.52
Sheng, 2021	5	.17	.03	5	.08	.01	-0-	3.64 [1.69,	5.58]	2.46
Heterogeneity: $\tau^2 = 0.0$ Test of $\theta_i = \theta_j$: Q(2) = τ	00, 1.74	l ² = 0.0 , p = 0.	0%, ⊦ 42	1 ² =	1.00		•	3.21 [2.01,	4.42]	
GAP-43										
Huang, 2021	6	1.39	.03	6	.99	.14	-0-	3.65 [1.85,	5.44]	2.54
Li, 2018	6	1.43	.18	6	1.02	.1	- O -	2.60 [1.13,	4.07]	2.69
Ren, 2019	6	2.05	.1	6	2.08	.1	0	-0.28 [-1.33,	0.77]	2.86
Xie, 2022	6	6.09	.66	6	4.27	.42	- - -	3.04 [1.43,	4.64]	2.63
Yu, 2019 Zhang 2021	4	13.14	1.02	4	5.69	1.04		0.29 [2.98,	9.60]	1.79
Heterogeneity: $\tau^2 = 3.8$ Test of $\theta_i = \theta_j$: Q(5) = 3	56, 31.6	l ² = 85. 4, p = 0	33%, 0.00	H ²	= 6.82	.17		2.37 [0.70,	4.05]	2.75
NF200										
Chen, 2021	3	1.35	.08	3	1	.1	-0-	3.09 [0.92,	5.26]	2.35
Huang, 2021	6	38.57	1.72	6	28.69	2.07	-0-	4.79 [2.61,	6.98]	2.34
Li, 2018	6	1.47	.24	6	1.01	.17	Φ	2.04 [0.72,	3.37]	2.75
Liu, 2019	5	.86	.1	5	.62	.08	- O -	2.39 [0.86,	3.93]	2.66
Liu, 2020	8	42.63	4.99	8	26.62	2.25	•	3.91 [2.27,	5.55]	2.61
Lu, 2019	6	1.89	.54	6	.17	.05	-0-	4.14 [2.18,	6.10]	2.45
Lu, 2021	5	56.37	4.59	5	24.38	4.8	-0-	6.15 [3.23,	9.07]	1.97
Ren, 2019	6	8.55	.65	6	8.8	.55	0	-0.38 [-1.44,	0.67]	2.86
Wang, 2021	4	.31	.03	4	.1	.05	-0-	4.43 [1.95,	6.91]	2.19
Xiao, 2021	6	39.06	5.29	6	20.8	3.38	-0-	3.80 [1.95,	5.64]	2.51
Xiong, 2023	8	8.66	1.31	8	2.31	.46	-0-	6.12[3.80,	8.43]	2.27
Yu, 2019 Zhang 2021	4	47.20	2.31	4	29.28	1.59		7.88 3.84,	2 561	1.48
Heterogeneity: $\tau^2 = 3$	3 16	.00 ² – 78	.05	о Ц ²	- 1 71	.02		3 55 [2 /3	3.30j	2.60
Test of $\theta_i = \theta_j$: Q(12) =	65	.81, p =	0.00		- 4.71			5.55 [2.45,	4.07]	
NeuN positive cells										
Huang, 2020	5	11.22	.85	5	6.14	.44	-0-	6.78 [3.60,	9.95]	1.85
Jia, 2021	5	18.96	4.77	5	2.65	3.32	-0-	3.58 [1.66,	5.51]	2.47
Li, 2018	6	7.6	1.06	6	8.17	1.36	0	-0.43 [-1.49,	0.63]	2.86
Li, 2019	3	.77	.03	3	.57	.02	-0	6.28 [2.50,	10.05]	1.59
Li, 2020	10	13.33	1.11	10	11.51	1.13	Θ	1.56 [0.59,	2.52]	2.89
LIU, 2020	8	9.47	1.84	8	5.75	1.14	O	2.30 [1.08,	3.52]	2.80
Snao, 2020	3	12	2.08	3	5.09	.47	-0-	2.87 [0.80,	4.94]	2.40
Viany, 2010 Xiao, 2021	6	Z1.77 A1 04	2.83	6	22 13	3.29		2.10[0.02, 5.80[3.25	3.34j 8.3/1	2.74
Xia0, 2021 Xin 2021	5	67	2.01	5	22.13 41	03		7 83 [4 22	11 441	1.66
Yan, 2019	6	23.03	7.89	6	5.32	.00	- 0 -	2.48 [1.04.	3.911	2.70
Yin. 2022	4	1.61	.04	4	1	.05		11.72 [5.85.	17.58]	0.94
Zhou, 2021	6	12.19	.54	6	3.26	.61		- 14.31 [8.49,	20.13]	0.95
Heterogeneity: $\tau^2 = 10$.19	$I^2 = 92$	2.79%	, н	² = 13.	88	•	4.46 [2.56,	6.36]	
Test of $\theta_i = \theta_j$: Q(12) =	84	.22, p =	0.00						-	
NissI positive cells										
Jia, 2021	5	13.84	3.87	5	7.82	3.16	θ	1.54 [0.23,	2.85]	2.76
Li, 2019	3	44.34	1.82	3	24.33	2.44		7.44 [3.04,	11.84]	1.35
Lu, 2021	5	11.99	4.04	5	3.98	1.48	- 0 -	2.38 [0.85,	3.91]	2.66
Nie, 2021 Naari, 2021	24	10.08	1.31	24	1.42	1.29	θ	2.01 [1.33,	2.70]	2.98
NOOFI, 2021	3	14.54	1.43	3	5.01	2.96	- 0 -	3.28 [1.03,	5.53	2.30
NOOFI, 2021	3	17.46	2.74	3	5.01	2.96	₩	0.09[-0.65,	2.03	2.15
Xiao 2021	د د	11.01	1.07	с С	1/ 10	∠.७0 २.२२		4.32 [1.30,	10 021	2.00
Heterogeneity: $\tau^2 = 2.4$	34	34.09 $1^2 = 85$	∠.40 15%	о µ ²	= 6.72	2.32		7.00 [4.43, 3 13 [1 60	4 661	1.02
Test of $\theta_i = \theta_j$: Q(7) = 2	25.7	'1, p = (0.00	r1	- 0.73			5.15[1.00,	4.00]	
								-		
							0 5 10 15 2	20		

Random-effects REML model Sorted by: outcome author year

Figure 4: Forest plot for the pooled data analysis on the effect of MSC-derived exosome treatment following spinal cord injury on markers of neural tissue regeneration.

		Treatme	ent		Contr	ol		Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Chen, 2021	3	.56	.08	3	1	.1	-0-	-3.89 [-6.43, -1.34]	3.76
Cheshmi, 2023	12	3.66	.64	12	5.69	1.03	θ	-2.29 [-3.29, -1.28]	4.88
Guo, 2019	3	4.25	1.58	3	12.75	2.62	-0-	-3.14 [-5.33, -0.95]	4.04
Huang, 2021	6	61.01	1.83	6	99.63	3.24	— o —	-13.55 [-19.07, -8.03]	1.87
Huang, 2021	3	.88	.04	3	.99	.06	0	-1.73 [-3.34, -0.12]	4.49
Jia, 2021	5	24.07	9.18	5	75.71	12.46	-0-	-4.26 [-6.44, -2.08]	4.05
Noori, 2021	3	14	3.38	3	57.9	7.4	—o —	-6.11 [-9.79, -2.42]	2.89
Noori, 2021	3	46.86	2.98	3	66.36	4.4	-0-	-4.15 [-6.83, -1.48]	3.65
Noori, 2021	3	18.47	2.63	3	66.36	4.4	— —	-10.57 [-16.69, -4.45]	1.63
Noori, 2021	3	35.41	1.54	3	57.9	7.4	-0-	-3.37 [-5.66, -1.07]	3.96
Noori, 2021	3	24.71	3.68	3	66.36	4.4	—o —	-8.21 [-13.04, -3.39]	2.20
Noori, 2021	3	16.47	2.68	3	57.9	7.4	— o —	-5.96 [-9.56, -2.35]	2.95
Ren, 2019	6	2.35	.15	6	2.2	.16		∂ 0.89 [-0.21, 2.00]	4.83
Romanelli, 2019	9	5.7	2.5	8	14.4	8.6	θ	-1.34 [-2.35, -0.33]	4.88
Romanelli, 2021	5	5.7	1.2	4	8.6	1.6	Ð	-1.86 [-3.31, -0.41]	4.60
Romanelli, 2021	6	6.3	1.1	4	8.6	1.6	Φ	-1.59 [-2.92, -0.25]	4.68
Sung, 2022	6	32.4	6.49	6	39.52	8.97	Θ	-0.84 [-1.94, 0.26]	4.83
Sung, 2022	6	24.55	1.83	6	39.52	8.97	Φ	-2.13 [-3.48, -0.79]	4.67
Wang, 2018	6	.73	.27	6	1.17	.34	θ	-1.32 [-2.49, -0.15]	4.79
Wang B , 2022	5	.66	.04	5	.72	.09	Θ	-0.78 [-1.95, 0.39]	4.79
Xiao, 2021	6	28.87	4.05	6	58.06	4.32	-0-	-6.44 [-9.21, -3.66]	3.57
Xie, 2022	6	1704.45	44.51	6	1851.96	193.02	Θ	-0.97 [-2.09, 0.14]	4.82
Yan, 2019	6	.77	.32	6	.74	.23	e	0.10 [-0.95, 1.14]	4.86
Yu, 2019	4	43.7	2.39	4	57.58	2.62	-0-	-4.81 [-7.46, -2.16]	3.67
Zhang, 2021	3	.97	.23	3	1.25	.2	Ð	-1.04 [-2.45, 0.37]	4.63
Overall							•	-2.80 [-3.74, -1.85]	
Heterogeneity:	$\tau^2 = 4$	4.50, I ² =	87.82	%,	$H^2 = 8.2^{\circ}$	1			
Test of $\theta_i = \theta_j$: Q	(24)	= 116.9	2, p = (0.0	C				
Test of θ = 0: z	= -5.	.81, p = 0	0.00			2	0 15 10 5 5		
Random-effects REML model Sorted by: author year						-2	v -10 -10 -0 L	,	

Figure 5: Forest plot for the pooled data analysis on the effect of MSC-derived exosome treatment following spinal cord injury on the expression of GFAP.

Study	T N	reatme Mean	nt SD	N	Contro Mean	ol SD		Hedges's with 95% (g Cl	Weight (%)
Bax										
Fan, 2021	6	1.31	.27	6	3.45	.78	θ	-3.38 [-5.09,	-1.67]	3.23
Huang, 2017	5	.09	.03	5	.37	.05	θ	-6.13 [-9.05,	-3.22]	3.04
Huang, 2020	5	.15	.03	5	.38	.03	θ	-6.92 [-10.16,	-3.69]	2.97
Huang, 2020	5	.78	.05	5	1.17	.04	Ð	-7.78 [-11.37.	-4.19]	2.90
Kang, 2022	5	1.11	.19	5	1.8	.26	Θ	-2.74 [-4.38.	-1.10]	3.24
Li. 2019	3	.75	.02	3	.9	.02	Ð	-6.00 [-9.63.	-2.371	2.89
Liu 2019	5	1.05	.05	5	1.35	09	Θ	-3.72 [-5.70	-1.74]	3.20
Zhang 2021	6	42	22	6	84	15	0	-2.06 [-3.39	-0 731	3.28
Heterogeneity: τ	$^{2} = 2$	$^{0}64 I^{2}$	= 69	15	% $H^2 =$	= 3.24		-4.36 [-5.78	-2 941	0120
Test of $A = A : O($	(7) =	04,1	- 00	. 10 0 0	70, TT - 11	- 0.24	•	-4.00 [-0.70,	-2.04]	
$1 = S_i \cup U_j = U_j \cdot U_j$	(7) -	- 20.15	, p –	0.0						
BcI-2										
Fan. 2021	6	.9	.15	6	.11	.22	Θ	3.87 [2.00.	5.741	3.21
Gu. 2020	2	.69	.12	2	.3	.07	θ	2.27 [0.34.	4.201	3.20
Huang 2017	5	27	03	5	13	05	Ð	3.07 [1.32	4 821	3.23
Huang, 2020	5	.27	.00	5	.10	.00		6.64 [3.52,	9.761	3.00
Huang, 2020	5	1 1 1	.04	5	26	.05		- 17.52 [0.76	25 281	1 05
Kang 2022	5	76	.07	5	.20	.05		156[0.24	20.20]	2.20
Kany, 2022	0	.70	. 10	0	.45	.10		1.50 [0.24,	2.07]	3.20
LI, 2019	3	.79	.03	3	0. 70	.01	•	0.80 [2.74,	10.85	2.80
LIU, 2019	5	.95	.11	5	.72	.06	Ð	2.34 [0.82,	3.86]	3.26
Zhang, 2021	26	.59	.15	6	.26	.07	Θ	2.60 [1.13,	4.08]	3.26
Heterogeneity: τ	- = 3	3.21, I ⁻	= 76	.73	%, H⁻ =	= 4.30	•	3.68 [2.26,	5.11]	
lest of $\theta_i = \theta_j$: Q((8) =	= 28.89	, p =	0.0	0					
Casnase 1										
Noori 2021	3	12	04	3	1 3/	10	~	8 23 [13 06	3 401	2 62
Noori, 2021	с С	.42	.04	່ ວ	1.04	.12	Ŭ,	-0.23 [-13.00,	-3.40]	2.02
Noori, 2021	ა ი	1.03	.10	ა ი	1.04	.12		-1.03 [-3.47,	-0.10]	3.24
Noori, 2021	3	.34	.07	3	1.34	.12	T	-8.14[-12.93,	-3.30]	2.03
Romanelli, 2021	6	1.17	.25	6	1.14	.15	e	0.13[-0.91,	1.18]	3.30
Romanelli, 2021	6	.9	.13	6	1.14	.15	e	-1.58 [-2.80,	-0.36]	3.29
Znao, 2023	ь 2 -	5.4	1.58	6	10.89	1.25	Θ	-3.56 [-5.32,	-1.79]	3.23
Heterogeneity: τ	_ = /	∕.33, I ⁻	= 90	.62	%, H ⁻ =	= 10.66	j ♦	-3.16[-5.57,	-0.74]	
Test of $\theta_i = \theta_j$: Q((5) =	29.63	, p =	0.0	0					
Casnase 3										
Chochmi 2022	10	245	1	12	59	10		2051 202	1 001	2 21
Ene 2021	12	1 22	24	12	.00	.12	ď	-2.05[-3.02,	2 001	2.21
Fall, 2021	0	1.22	.34	0	4.20	.00	0	-3.30[-7.77,	-2.99]	3.13
Gu, 2020	2	.79	.08	2	1.3	.11	Ð	-3.03 [-5.41,	-0.65]	3.13
Han, 2021	5	.55	.27	5	1	.1	θ	-2.00 [-3.42,	-0.58]	3.27
Han, 2022	3	.545	.216	3	1	.1	θ	-2.16[-3.93,	-0.39]	3.22
Huang, 2020	5	.57	.03	5	1.13	.02	—O —	-19.84 [-28.61,	-11.07]	1.75
Li, 2019	3	.92	.01	3	1.07	.01	-0-	-12.00 [-18.91,	-5.09]	2.13
Liu, 2019	5	1.09	.09	5	1.27	.11	Ø	-1.62 [-2.94,	-0.29]	3.28
Yan, 2019	6	15.28	6.1	6	34.75	7.45	Θ	-2.64 [-4.13,	-1.15]	3.26
Zhang, 2021	6	.23	.1	6	.56	.27	ø	-1.50 [-2.70,	-0.29]	3.29
Heterogeneity: τ	² = ().40, I ²	= 36	.14	%, H ² =	= 1.57	•	-2.46 [-3.15,	-1.78]	
Test of $\theta_i = \theta_j$: Q((9) =	: 33.03	, p =	0.0	0					
								_		
							-40 -20 0 20	-		

Random-effects REML model Sorted by: author year

Figure 6: Forest plot for the pooled analysis on markers of apoptosis in SCI animals treated with MSC-derived exosomes.

	-	Treatm	ent		Contr	ol		Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Chang, 2021	6	7.44	.87	6	18.55	1.87	—o —	-7.03 [-10.03, -4.03]	3.75
Cheshmi, 2023	6	5270	1600	6	5890	1290	-0	-0.39 [-1.45, 0.66]	5.61
Gu, 2020	2	25.56	2.56	2	45.02	4.03	—o —	-3.29 [-5.84, -0.75]	4.20
He, 2022	10	15.34	1.33	10	31.47	2.44	—0 —	-7.86 [-10.44, -5.28]	4.16
Huang, 2017	5	20.96	3.8	5	35.95	5.35	-0-	-2.92 [-4.62, -1.22]	5.05
Huang, 2020	5	19.49	1.1	5	30.38	1.93	—o —	-6.26 [-9.23, -3.30]	3.79
Huang, 2020	5	12.28	2.71	5	28.53	3.41	-0-	-4.77 [-7.14, -2.40]	4.37
Ji, 2019	6	39.61	10.12	6	74.85	6.37	-0-	-3.85 [-5.71, -1.99]	4.89
Jia, 2021	5	6.74	2.81	5	16.89	3.15	-0-	-3.07 [-4.82, -1.32]	5.00
Lai, 2022	7	.41	.09	7	.7	.05	-0-	-3.73 [-5.42, -2.04]	5.06
Li, 2019	3	.24	.01	3	.42	.05	- o	-3.99 [-6.59, -1.40]	4.14
Li, 2022	10	15.43	1.34	10	31.56	2.21	— o —	-8.45 [-11.20, -5.70]	3.99
Liu, 2019	5	11	1.21	5	31.83	4.21	— o —	-6.07 [-8.96, -3.19]	3.86
Lu, 2019	6	8.53	8.52	6	18.29	7.59	θ	-1.12 [-2.25, 0.02]	5.55
Lu, 2021	5	11.66	1.93	5	21.97	2.98	-0-	-3.71 [-5.68, -1.74]	4.78
Noori, 2021	3	16.04	3.68	3	42.23	1.68	— o —	-7.32 [-11.66, -2.99]	2.65
Noori, 2021	3	36.08	2.53	3	42.23	1.68	-0-	-2.29 [-4.11, -0.47]	4.93
Noori, 2021	3	23.9	4.53	3	42.23	1.68	— o —	-4.29 [-7.04, -1.55]	4.00
Wang, 2018	6	21.32	12.64	6	50.77	12.54	-0-	-2.16 [-3.51, -0.80]	5.37
Wang, 2021	3	.35	.05	3	.6	.04	-0	-4.42 [-7.23, -1.61]	3.94
Xiao, 2021	6	25.23	2.06	6	41.87	1.98	—o —	-7.60 [-10.82, -4.39]	3.55
Zhao, 2023	6	10.22	3.18	6	22.09	2.87	-0-	-3.62 [-5.40, -1.83]	4.97
Zhou, 2019	4	.8	.15	4	2.59	.18	— • —	-9.39 [-14.15, -4.64]	2.38
Overall							•	-4.29 [-5.24, -3.35]	
Heterogeneity:	$\tau^2 =$	3.84,	² = 78	.75	%, H ² =	= 4.71			
Test of $\theta_i = \theta_i$: (ຸລ(22	2) = 10	5.91, p) = (00.0				
Test of $\theta = 0$: z	:=-8	3.91, p	= 0.00)				_	
							-15 -10 -5 0	1	

Random-effects REML model Sorted by: author year

Figure 7: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on the number of apoptotic cells.

Study	N	Treatme Mean	ent SD	N	Conti Mean	rol SD			Hedges' with 95%	s g ₀ CI	Weight (%)
Arg 1 Chang, 2021	6	17.26	1.35	6	9.39	.85		-0-	6.44 [3.66	6. 9.221	3.21
Huang, 2020	5	.53	.12	5	.87	.06	Ð	-	-3.24 [-5.04	i, -1.431	3.43
Liu, 2020	8	1.97	.15	8	1.01	.1		-0-	7.12 4.48	3, 9.76]	3.25
Romanelli, 2021	6	.99	.41	6	1.17	.39	e		-0.42 [-1.47	7, 0.64]	3.54
Romanelli, 2021	6	.93	.18	6	1.17	.39	e	•	-0.73 [-1.8	0.361	3.53
Sun, 2018	6	61.11	15.31	6	20.33	16.02		Θ	2.40 0.98	3, 3.82]	3.49
Sun, 2018	6	17.89	9.87	6	20.33	16.02	e	•	-0.17 [-1.22	2, 0.88]	3.54
Xiong, 2023	8	2.285	.38	8	1.025	.19		θ	3.97 [2.3	l, 5.62]	3.45
Zhai, 2021	5	1.32	.14	5	.63	.42		Θ	1.99 0.57	, 3.41]	3.49
Heterogeneity: τ	$^{2} =$	10.21, l ^é	² = 95.	05º	%, H ² =	20.20		•	1.80 [-0.37	, 3.97]	
Test of $\theta_i - \theta_j$. Q	(0)	- 94.00,	p – 0.	00							
CD206											
Chang, 2021	6	18.1	1.6	6	6.51	.51		-0-	9.01 [5.26	6, 12.76]	2.95
Liu, 2020	8	2.15	.46	8	1.01	.13		θ	3.19 [1.75	5, 4.63]	3.49
Nakazaki, 2021	6	3.22	1.45	6	1.35	.83		θ	1.46 [0.26	6, 2.66]	3.52
Nakazaki, 2021	6	3.79	2.42	6	1.35	.83		Θ	1.25 [0.09	9, 2.40]	3.53
Heterogeneity: T	2 =	8.76, I ²	= 93.8	3%	$H^2 = 1$	6.20		•	3.35 [0.28	3, 6.42]	
Test of $\theta_i = \theta_j$: Q((3)	= 18.39,	p = 0.	00							
CD68											
Huang, 2020	5	18.28	1.29	5	31.6	2.39	-0-		-6.26 [-9.23	3, -3.30]	3.17
Liu, 2019	5	302.7	70.18	5	893.84	120.66	-0-		-5.41 [-8.03	3, -2.79]	3.25
Wang, 2021	4	1.5	.15	4	3.94	.31	-0-		-8.71 [-13.15	5, -4.28]	2.76
Heterogeneity: T	² =	0.00, I ²	= 0.00	%.	$H^2 = 1.0$	00	•		-6.26 -8.06	6, -4.47]	
Test of $\theta_i = \theta_j$: Q((2)	= 1.58, j	o = 0.4	5						· 1	
lba1											
Liu. 2020	8	121.14	8.26	8	124.89	10.44	e	• •	-0.38 [-1.3	I. 0.561	3.55
Pinho. 2022	4	.58	.2	5	.71	.16	é	•	-0.65 [-1.8	5. 0.561	3.52
Pinho 2022	7	.55	26	5	71	16	e	•	-0.66 [-1.7	5 0 441	3.53
Romanelli 2019	9	19518	3372	8	29772	5941	0	T	-2.05 [-3.19	, <u>-091</u> 1	3.53
Romanelli 2019	9	16964	2892	8	21549	4476	e)	-1 17 [-2 16	3 -0 191	3 55
Romanelli 2019	9	23108	2957	8	31653	3327	A		-2.59[-3.84	,	3.51
Romanelli 2019	9	27955	4393	8	39410	5922	9		-2 11 [-3 2	5 -0.961	3 53
Romanelli 2021	5	16380	1272	4	16947	1028	e	•	-0.43[-1.6	, 0.00] 0.76]	3.52
Romanelli 2021	5	18483	3110	4	16947	1028		Í.	0.56[-0.64	1, 0.70] I 176]	3.52
Shao 2020	3	25 21	3 55	3	82 77	9 98	-0-	Ĩ	-6 15 [-9 8	5 -2 441	2 97
Shao, 2020	3	52.2	5.00	3	82 77	9.00	- -		-3 10 [-5 2]	7, <u>-</u> 0931	3 35
Sung 2022	6	3 72	2 85	6	13 70	1 11	4		-4.30 [-6.34	, 0.00] _2 201	3 30
Sung 2022	6	2.72	2.00 Q2	6	13.79	1 1 1				, -∠.∠3] } _5 //1	2 9 9
Mang 2021	1	2 18	.52	1	6.54	36			-14 35 [-21 49), -0.44] ≥ _7.221	2.92
Heterogonoity:	2 _	5.10	- 01 0	+ 70/	U.04 $U^2 = 1$	2 45	Ŭ	 	-74/1270	2, -1.22]	2.01
Test of $A = A \cdot O$	- (1२	(0, -0, -1) = 72.24	- 31.8 5 n = (י ⁄י חר	, – . 0	2.40	•	l I	-2.74 [-3.70	, -1.10]	
r_{ij} , v_{ij} , v_{ij} , v_{ij} , v_{ij}	(13) — 12.23	ο, μ – (5.0	0						
							-20 -10	D 10			

Random-effects REML model Sorted by: author year Figure 8: The effect of MSC-derived exosome administration following spinal cord injury on microglia activation markers.

		Treatme	ent		Contr	ol		Hedges's	Weight	
Study	N	Mean	SD	Ν	Mean	SD		with 95%	CI	(%)
IL10										
Cheshmi, 2023	12	.54	.04	12	.35	.04	−	4.59 [3.08,	6.10]	5.45
Fan, 2021	6	72.11	15.65	6	31.05	13.74	- O -	2.57 [1.11,	4.04]	5.49
Huang, 2017	5	.23	.04	5	.06	.09	- 0 -	2.20 [0.73,	3.68]	5.48
Lai, 2022	3	.83	.15	3	.47	.11	-O -	2.19[0.41,	3.97]	5.16
Liu, 2020	8	296.09	18.34	8	200.9	18.98	- O -	4.82 [2.91,	6.73]	5.03
Sun, 2018	6	40.24	12.79	6	41.87	4.34	•	-0.16 [-1.20,	0.89]	5.88
Sun, 2018	6	52.91	16	6	41.87	4.34	0	0.87 [-0.23,	1.97]	5.83
Sung, 2022	6	2484.66	390.29	6	2629.98	172.81	•	-0.44 [-1.50,	0.62]	5.87
Sung, 2022	6	3454	511.72	6	2629.98	172.81	- 0 -	1.99 [0.68,	3.31]	5.64
Xiong, 2023	8	52.895	3.47	8	35.63	4.91	- 0 -	3.84 [2.22,	5.46]	5.33
Zhai, 2021	5	85.94	8.5	5	50.02	6.34	- o -	4.33 [2.12,	6.53]	4.71
Zhai, 2021	5	111.64	19.79	5	50.56	9.17	-0-	3.58 [1.65,	5.50]	5.01
Heterogeneity:	$\tau^2 =$	2.72, I ²	= 83.67	%,	$H^2 = 6.12$	2	•	2.41 [1.38,	3.45]	
Test of $\theta_i = \theta_j$: C	ג(11) = 72.14	4, p = 0.	.00						
IL4										
Fan, 2021	6	112.18	10.7	6	54.3	7.72	— o —	5.73 [3.21,	8.24]	4.36
Lai, 2022	3	1.36	.5	3	.33	.21	- 0 -	2.15 [0.38,	3.91]	5.18
Liu, 2020	8	88.91	7.67	8	60.16	4.29	- 0 -	4.37 [2.60,	6.15]	5.17
Sun, 2018	6	11.4	3.33	6	10.95	2.33	•	0.14 [-0.90,	1.19]	5.88
Sun, 2018	6	16.15	5.51	6	10.95	2.33	0	1.13 [-0.00,	2.27]	5.80
Xiong, 2023	8	31.785	1.96	8	14.34	1.8	—0 —	8.77 5.59, 2	11.94]	3.68
Zhai, 2021	5	19.8	2.11	5	11.58	2.22	-0-	3.43 [1.55,	5.30]	5.06
Heterogeneity:	$\tau^2 =$	6.67. I ²	= 90.59	%.	$H^2 = 10.6$	62	-	3.44 [1.38.	5.491	
Test of $\theta_i = \theta_i$: C	Q(6)	= 49.26.	p = 0.0	0				L /	1	
· · · · · · · · · · · · · · · · · · ·				-						
							0 5 10	15		

Random-effects REML model Sorted by: outcome author year

Figure 9: The effect of MSC-derived exosome administration following spinal cord injury on anti-inflammatory IL-10 and IL-4.

		Treatm	ent		Contr	ol		Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Fan, 2021	6	259.16	86.76	6	1031.61	223.52	-0-	-4.21 [-6.19, -2.23]	3.79
Hu, 2022	6	23.6	2.17	6	60.62	3.38	— o —	-12.03 [-16.96, -7.11]	1.84
Huang, 2017	5	.04	.07	5	.25	.11	Ð	-2.06 [-3.49, -0.62]	4.19
Huang, 2020	5	26.76	3.46	5	53.74	4.12	-0-	-6.41 [-9.43, -3.38]	2.98
Jiang, 2021	3	85.33	9	3	126.92	12.15	-0-	-3.11 [-5.29, -0.93]	3.63
Lai, 2022	3	.86	.18	3	1.4	.19	-0-	-2.33 [-4.17, -0.49]	3.90
Li, 2022	10	355.22	23.54	10	759.59	34.29	-0-	-13.17 [-17.33, -9.00]	2.22
Liu, 2019	5	.77	.05	5	1.06	.08	-0-	-3.93 [-5.98, -1.87]	3.73
Liu, 2020	8	93.96	7.65	8	131.14	7.34	-0-	-4.69 [-6.56, -2.82]	3.87
Lu, 2021	5	.77	.11	5	1.19	.22	•	-2.18 [-3.65, -0.71]	4.17
Noori, 2021	3	.46	.09	3	1.77	.2	—0 —	-6.76 [-10.79, -2.73]	2.30
Noori, 2021	3	.23	.08	3	1.77	.2		-8.09 [-12.84, -3.34]	1.92
Noori, 2021	3	1.29	.14	3	1.77	.2	-0-	-2.22 [-4.02, -0.43]	3.93
Romanelli, 2019	6	.44	.22	6	4.23	.99	-0-	-4.88 [-7.09, -2.66]	3.60
Romanelli, 2021	6	.39	.15	6	5.48	3.12	•	-2.13 [-3.47, -0.78]	4.25
Romanelli, 2021	6	.45	.19	6	5.48	3.12	Ð	-2.10 [-3.44, -0.76]	4.26
Shao, 2020	3	55.68	4.58	3	83.14	9.3	-0-	-3.00 [-5.12, -0.87]	3.67
Shao, 2022	10	555.33	76.65	10	635.69	72.25	θ	-1.03 [-1.93, -0.13]	4.52
Sung, 2022	6	442.67	177.68	6	785.03	80.93	Ð	-2.29 [-3.68, -0.90]	4.23
Sung, 2022	6	410.49	81.29	6	785.03	80.93	-0-	-4.26 [-6.26, -2.26]	3.77
Wang, 2018	6	40.15	22.31	6	77	24.1	Ð	-1.46 [-2.66, -0.27]	4.35
Wang B , 2022	5	79.63	16.3	5	81.5	20.46	e	-0.09 [-1.21, 1.03]	4.40
Zhai, 2021	5	168.38	24.53	5	234.57	32	•	-2.10 [-3.55, -0.65]	4.18
Zhai, 2021	5	67.34	9.71	5	88.59	8.25	•	-2.13 [-3.59, -0.67]	4.18
Zhang, 2021	6	565.17	168.3	6	882.58	218.74	Ð	-1.50 [-2.71, -0.30]	4.35
Zhao, 2023	6	.59	.17	6	.97	.29	Ð	-1.48 [-2.68, -0.28]	4.35
Zhou, 2022	6	42.22	4.57	6	91.99	10.91	-0-	-5.49 [-7.93, -3.06]	3.43
Overall							•	-3.30 [-4.15, -2.45]	
Heterogeneity:	τ ² =	3.96, I ²	= 85.17	%,	$H^2 = 6.74$	4			
Test of $\theta_i = \theta_i$: C	(26)) = 115.0	67, p =	0.0	0				
Test of $\theta = 0$: z	= -7	.60, p =	0.00			ŗ	0		
Random-effects REML model Sorted by: author year						-2	u l	,	

Figure 10: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker IL-1b.

		Treatm	ent		Contro	ol		Hedges's g	Weight
Study	Ν	Mean	SD	Ν	Mean	SD	1	with 95% CI	(%)
IL18	_								
Huang, 2020	5	30.64	3.42	5	63.51	4.3	— o —	-7.64 [-11.17, -4.11]	1.75
Noori, 2021	3	.83	.14	3	1.36	.17	-0-	-2.72 [-4.73, -0.72]	2.60
Noori, 2021	3	.29	.07	3	1.36	.17	o	-6.58 [-10.52, -2.65]	1.57
Noori, 2021	3	.4	.14	3	1.36	.17	— o —	-4.93 [-8.00, -1.86]	1.99
Romanelli, 2021	6	1.02	.09	6	.98	.09	Þ	0.41 [-0.65, 1.47]	3.13
Romanelli, 2021	6	.99	.07	6	.98	.09	· • ·	0.11 [-0.93, 1.16]	3.13
Zhao, 2023	6	.51	.18	6	1.01	.18	- O -	-2.56 [-4.03, -1.10]	2.92
Heterogeneity: τ	2 = 7	7.68, l ² =	91.09%,	H ²	= 11.22			-3.02 [-5.27, -0.78]	
Test of $\theta_i = \theta_j$: Q	(6) =	= 45.99, p	00.0 = 0						
IL1a									
Cheshmi, 2023	12	1.51	.06	12	2.48	.19	- o -	-6.65 [-8.68, -4.61]	2.59
Li, 2020	10	1.96	.11	10	1.96	.08	¢	0.00 [-0.84, 0.84]	3.22
Wang, 2018	6	12.2	5.17	6	24.81	11.22	0	-1.33 [-2.51, -0.16]	3.07
Yan, 2019	6	1.33	.48	6	2.55	.54	-0-	-2.20 [-3.57, -0.84]	2.97
Heterogeneity: τ	² = 7	7.23, $I^2 =$	94.71%,	H^2	= 18.91			-2.44 [-5.17, 0.28]	
Test of $\theta_i = \theta_i$: Q	(3) =	= 37.47, j	00.0 = c						
11.6									
liang 2021	3	53 89	4 98	3	76 86	8 02		-2 75 [-4 77 -0 74]	2 60
Lai 2022	3	92	33	3	2 25	1 55	-0	-0.95[-2.34_0.44]	2.00
Liu 2019	5	.02	.00	5	95	1.00		-1 41 [-2 69 -0 13]	3.02
Liu, 2013	8	284 16	30.36	8	354 22	12 32		-2.86 [-4.22 -1.50]	2.02
Liu, 2020	5	204.10	00.00	5	1 20	23	-0-1	-2.50 [-4.22, -1.50]	2.30
Romanelli 2010	6	1 16	1 17	6	10.16	6.08	-0-1	-1.00[-3.100.61]	2.00
Romanelli 2021	6	1.10	1.17	6	5.2	2 1		-2.10[-3.55 -0.83]	2.07
Romanelli 2021	6	21	1.14	6	5.2	2.1		-2.19[-3.03, -0.03]	2.37
Shao 2020	3	36.5	1 16	3	54 77	6.28		-2.68 [-4.67 -0.70]	2.00
Shao, 2020 Shao, 2022	10	174.06	11 01	10	199.76	13.65		-2.00[-4.07, -0.70]	2.02
Silao, 2022 Sup. 2018	6	330.36	263.1	6	360.70	85.61		-0.14[-2.05, -0.25]	3 13
Sun, 2010	6	72 56	42 02	6	260.26	95.61		4.01 [5.02 2.10]	2.13
Wang B 2022	5	750.47	105.05	5	744 76	217 21	Ŭ Á	-4.01[-3.93, -2.10]	2.00
Viang 2022	0 0	102 72	195.95	0	190.20	5 10		7.04 [10.94 5.04]	2.10
Alony, 2023	0	200.20	25.46	0	100.29	0.19 76.61		-7.94 [-10.04, -3.04]	2.00
Zhai, 2021	5	125.22	35.40	5	419.10	20.46	-0-	-1.50 [-2.79, -0.20]	3.01
Zhai, 2021	р 2	135.22	27.31	5 11 ²	190.68	29.16		-1.77 [-3.14, -0.41]	2.97
Heterogeneity: τ	= (4 E)	1.44, 1 =	74.40%,	Ч	= 3.91		•	-2.04 [-2.74, -1.34]	
Test of $\theta_i = \theta_j$: Q	(15)	= 53.16,	p = 0.00)					
MCP-1									
Fan, 2021	6	231.02	39.39	6	815.06	98.25	—0 —	-7.20 [-10.27, -4.14]	1.99
Sun, 2018	6	309.15	111.31	6	1854.71	885	-0-	-2.26 [-3.64, -0.88]	2.96
Sun, 2018	6	1615.79	2254.22	6	1854.71	885	•	-0.13 [-1.17, 0.92]	3.13
Zhai, 2021	5	1299.42	201.11	5	2012.57	485.14	-0-	-1.73 [-3.09, -0.38]	2.98
Heterogeneity: τ	² = (6.64, I ² =	92.30%,	H^2	= 12.99			-2.56 [-5.24, 0.11]	
Test of $\theta_i = \theta_j$: Q	(3) =	= 21.16, p	00.0 = c						
NLRP3									
Huang, 2020	5	.09	.01	5	.27	.03	o	-7.27 [-10.653 89]	1.83
Romanelli, 2019	6	.94	.2	6	.88	.28	-	0.23 [-0.82, 1.28]	3.13
Romanelli 2021	6	.04	.2 17	6	1 07	19	Å	-0.51 [-1.58 0.55]	3 12
Romanelli 2021	6	.07 QR		6	1 07	10	Å	-0.43 [-1.48 0.63]	3 13
Zhao 2023	6	.00 47	.2	6	1.07	19		-3 13 [-4 76 -1 50]	2.83
Heterogeneity: 7	² = 4	3 34 I ² -	93 41%	н ²	= 15.23	.13		_1 90 [_1 21 0 1 1 0	2.00
Test of $A = A \cdot O$	 - (<u>A</u>)	= 26 38 v	55.44 /0, 5 = 0.00		- 10.20			-1.30[-4.24, 0.44]	
$r_{ij} = v_j$. Q	()-	- 20.00,	5 - 0.00						
							-10 -5 0	5	

Random-effects REML model Sorted by: outcome author year

Figure 11: The effect of MSC-derived exosome administration following spinal cord injury on pro-inflammatory markers IL-18, IL-1a, IL-6, MCP-1 and NLRP3.

Study	N	Treatme	ent SD	N	Conti Mean	rol SD		Hedges's g with 95% CI	Weight
	19	wear	00	10	incuri	00			(70)
Chang, 2021	12	.6	.1	12	1.55	.29	- 0 -	-4.23 [-5.65, -2.80]	3.98
Cheshmi, 2023	12	2.42	.13	12	2.93	.28	θ	-2.26 [-3.26, -1.25]	4.42
Fan, 2021	6	212.72	95.9	6	833.86	209.16	•	-3.52 [-5.28, -1.77]	3.61
Huang, 2017	5	.04	.04	5	.33	.09	-0-	-3.76 [-5.75, -1.77]	3.34
Huang, 2020	5	46.44	6.2	5	93.29	10.94	-0-	-4.76 [-7.13, -2.39]	2.95
Jiang, 2021	3	86.28	9.21	3	160.67	16.61	-0-	-4.43 [-7.25, -1.62]	2.52
Lai, 2022	3	1.17	.27	3	1.9	.35	-0	-1.87 [-3.53, -0.21]	3.72
Li, 2020	10	2.21	.18	10	2.23	.06	ę	-0.14 [-0.98, 0.70]	4.57
Liu, 2019	5	.9	.13	5	1.23	.14	•	-2.21 [-3.69, -0.73]	3.92
Liu, 2020	8	395.26	22.25	8	504.45	32.77	•	-3.69 [-5.26, -2.11]	3.81
Lu, 2021	5	.84	.11	5	1.46	.1	-0-	-5.33 [-7.92, -2.74]	2.73
Noori, 2021	3	.32	.09	3	1.41	.05	•	-11.98 [-18.87, -5.08]	0.73
Noori, 2021	3	.47	.13	3	1.41	.05	e	-7.64 [-12.14, -3.13]	1.43
Noori, 2021	3	1.04	.17	3	1.41	.05	-0-	-2.36 [-4.21, -0.51]	3.50
Romanelli, 2021	6	.82	.14	6	1.33	.28	•	-2.13 [-3.47, -0.78]	4.07
Romanelli, 2021	6	.71	.73	6	1.33	.28	0	-1.04 [-2.16, 0.09]	4.30
Shao, 2020	3	46.37	6.17	3	68.3	7.2	-0-	-2.62 [-4.57, -0.66]	3.38
Sun, 2018	6	166.08	23.12	6	722.2	146.5	-0-	-4.89 [-7.11, -2.68]	3.10
Sun, 2018	6	485.01	268.73	6	722.2	146.5	9	-1.01 [-2.13, 0.11]	4.31
Sung, 2022	6	5.18	1.3	6	8.27	2.97	0	-1.24 [-2.40, -0.09]	4.27
Sung, 2022	6	5.09	.88	6	8.27	2.97	0	-1.34 [-2.51, -0.17]	4.25
Wang, 2018	6	103.64	33.85	6	162.53	42.5	0	-1.41 [-2.60, -0.23]	4.24
Wang B , 2022	5	903.92	153.46	5	921.57	140.29	e	-0.11 [-1.23, 1.01]	4.31
Xiong, 2023	8	192.395	23.9	8	359.72	9.28	-0-	-8.73 [-11.89, -5.56]	2.23
Yan, 2019	6	1.63	.78	6	3.59	.87	•	-2.19 [-3.55, -0.83]	4.05
Zhai, 2021	5	136.74	25.72	5	203.42	34.91	•	-1.96 [-3.38, -0.55]	3.99
Zhai, 2021	5	541.92	64.76	5	756.47	188.12	0	-1.38 [-2.65, -0.11]	4.15
Zhang, 2021	6	229.5	86.03	6	518.7	181.56	Θ	-1.88 [-3.17, -0.59]	4.13
Overall							•	-2 59 [-3 22 -1 95]	
Heterogeneity: 1	² = 2	$2 13 l^2 =$	79 45%	6 F	$1^2 = 4.87$	7		2.00 [0.22, 1.00]	
Test of $\theta = \theta$: Ω	(27)	= 112 9	7 n = 0	00					
Test of $\theta = 0.7$	= -7	96 n = 0							
		00, p - 0				-2	0 0	ī	

Random-effects REML model Sorted by: author year

Figure 12: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.

Study	Item 1	Item 2	Item 3	Item 14	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Overall
Chang 2021	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Chen 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Fan 2021	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Gu 2020	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Han 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Huang 2020	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Huang 2020	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Huang 2017	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Huang 2021	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Huang 2021	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Ji 2019	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Jia 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Jiang 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Li 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Li 2020	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Li 2018	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Liu 2020	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Liu 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Lu 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Lu 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Nakazaki 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Nie 2021	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Noori 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Romanelli 2021	Low	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Romanelli 2019	Low	Low	Low	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Ruppert 2018	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Shao 2020	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Sheng 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Sun 2018	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Wang 2021	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Wang 2018	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Wang 2021	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Xiao 2021	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Xu 2019	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Yu 2019	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Zhai 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Zhang 2021	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Zhang 2020	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Zhang 2021	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Zhao 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Zhou 2021	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Zhou 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Guo 2019	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Zhou 2022	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Xin 2021	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Pinho 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Huang 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Xie 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Yan 2019	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Liu 2022	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair

Supplementary Table 1: Quality control of the included studies

Supplementary Table 1: Subgroup analyses and meta-regressions for different variables in the expression of GFAP (continue)

Study	Item 1	Item 2	Item 3	Item 14	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Overall
Shao 2022	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Sung 2022	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
He 2022	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Kang 2022	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Cheshmi2023	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Han 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Hu 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Kostennikov 2022	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Lai 2022	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Li 2022	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Wang B 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Wang Y 2022	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Xiong 2023	Low	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair
Yin 2022	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Fair
Zhao 2023	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Fair

Low: low risk of bias

Item 1. Was the allocation sequence adequately generated and applied?

Item 2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?

Item 3. Was the allocation adequately concealed?

Item 4. Were the animals randomly housed during the experiment?

Item 5. Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?

Item 6. Were animals selected at random for outcome assessment?

Item 7. Was the outcome assessor blinded?

Item 8. Were incomplete outcome data adequately addressed?

Item 9. Are reports of the study free of selective outcome reporting?

Item 10. Was the study apparently free of other problems that could result in a high risk of bias?



Supplementary Figure 1: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.



Supplementary Figure 1: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.