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REVIEW ARTICLE

Stem Cell-Derived Exosomes as a Therapeutic Option for Spinal Cord Injuries; 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 (MSC-derived) 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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a) The first and second authors have identical contributions.

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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 MSC-derived 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 MSC-derived 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 ± 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

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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 ADMSCs 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 (meta-regression 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 CD206-positive 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 de-

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creased 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 meta-analysis 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 post-injury. 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

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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 anti-inflammatory 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 pro-inflammatory 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 blood-spinal 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 post-treatment. 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/b-catenin 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

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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 follow-up 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 SCI	Model of SCI	Exosome origin	Exosome dose/ volume	SCI to treatment interval	Site of injection
Chang	2021	SD Rat	M	220- 260 g	T10	Contusion	BMMSC	200 l	1 hour	Intrathecal
Chen	2021	SD Rat	M	N/R	T10	Compression	BMMSC	200 g	Immediately	Intravenous
Fan	2021	SD Rat	M	200–250 g	T10	Contusion	BMMSC	200 l	Daily for 7 consecutive days	Intravenous
Gu	2020	SD rat	M	220–260g	T10	Contusion	BMMSC	200 g	1 hour	Intravenous
Han	2021	Wistar Rat	F	200–250 g	T10	Contusion	BMMSC	100 l	Daily for 3 consecutive days	Intrathecal
Huang	2020	SD Rat	M	180–220g	T10	Contusion	AMSC	100 g	Immediately	Intrathecal
Huang	2020	SD Rat	M	180–220g	T10	Contusion	BMMSC	250 g	30 minutes	Intravenous
Huang	2017	SD Rat	M	180–220g	T10	Contusion	BMMSC	100g	30 minutes	Intravenous
Huang	2021	SD Rat	M	80-100 g	T10	Contusion	BMMSC	200 g	Daily for 7 consecutive days	Intravenous
Huang	2021	SD Rat	F	200–250 g	T10	Contusion	BMMSC	200 g	Daily for 5 consecutive days	Intravenous
Ji	2019	SD Rat	M	150–180g	T10	Compression	BMMSC	100mg	24 hours	Intravenous
Jia	2021	SD Rat	M	230-250 g	T10	Contusion	BMMSC	200 l	1 hour	Intravenous
Jiang	2021	SD Rat	M	180–220g	T9/T10	N/R	BMMSC	100 g	30 minutes	Intravenous
Li	2019	Wistar Rat	M	150–200g	T9–T11	Contusion	BMMSC	200g	Every 3 days for 27 days	N/R
Li	2020	SD Rat	M	N/R	T10	Compression	BMMSC	100g	24 hours	Intravenous
Li	2018	SD Rat	M	250–300g	T10	Compression	BMMSC	100g	24 hours	Intravenous
Liu	2020	C57BL/6	M	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
Lu	2021	SD Rat	F	170–220g	T10	Contusion	BMMSC	200 g	Immediately	Intravenous
Nakazaki	2021	SD Rat	M	185-215 g	T9	Contusion	BMMSC	4 g	Daily for 9 consecutive days	Intravenous
Nie	2021	SD Rat	N/R	180-220 g	T10	Transection	BMMSC	100g	24 hours	Intravenous
Noori	2021	Wistar Rat	M	210-280 g	T10	Compression	hWJMSC	1-3 g	24 hours	Intrathecal
Ren	2019	SD Rat	M	250-350 g	T10	Compression	AMSC	N/R	N/R	N/R
Romanelli	2021	F344 Rat	F	140–190 g	T8	Contusion	hUCMSC	1.5×10^9 particles	Immediately	Intravenous
Romanelli	2019	F344 Rat	F	140–190 g	T8	Contusion	hUCMSC	N/R	Immediately & 24 hours	Intravenous
Ruppert	2018	SD Rat	M	225–250g	T10	Contusion	hUCMSC	10^9 particles	3hours	Intravenous
Shao	2020	C57BL/6 mouse	N/R	6W	T8/T9	Compression	AMSC	200 g	Immediately	Intravenous
Sheng	2021	C57BL/6 mouse	F	6-8 W	T10	Contusion	BMMSC	200 g	Immediately	Injury site
Sun	2018	C57BL/6 mouse	F	17–22g	T11/T12	Contusion	hUCMSC	20 g	30minutes	Intravenous
Wang	2021	Rat	F	230 g	T10	Transection	AMSC	100 ng	Immediately	Injury site
Wang	2018	SD Rat	M	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	M	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 mouse	M	30-35 g	T8/T9	Contusion	hUCMSC	20 g	Daily for 10 consecutive days	Injury site
Zhang	2021	SD Rat	M	200-280 g	T10	Contusion	BMMSC	50 g	5 minutes	Injury site + Intravenous
Zhang	2020	Mouse	M	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 days & 14 days	Intravenous
Zhou	2021	SD Rat	F	200-220 g	T11	Transection	hPMSC	50 g	Immediately &1 hour & 2 weeks	Intravenous

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Table 1: Characteristics of the included articles (continue)

Name	Year	Animal	Gender	Weight/Age	Level of SCI	Model of SCI	Exosome origin	Exosome dose/ volume	SCI to treatment interval	Site of injection
Zhou	2019	Wistar Rat	M	200–250g	T10	Transection	BMMSC	100g	1hour	Intravenous
Guo	2019	SD Rat	F	200–250g	T10	Transection	BMMSC	40 l	23 hours & daily for 5 consecutive days	Intranasal
Zhou	2022	SD Rat	M	200–250 g	T10	Contusion	BMMSC	40 g	30 minutes & 24 hours	Intravenous
Xin	2021	SD Rat	F	220–250g	T9	Contusion	BMMSC	100 g	Immediately & daily for 7 consecutive days	Subcutaneous
Pinho	2022	C57BL/6 mouse	F	10-15 w	T8-9	Compression	AMSC	100 l	Daily for 3 days & once a week afterwards	Intravenous
Huang	2022	SD Rat	M	200-220 g	T10	Contusion	BMMSC	40 g	30 minutes & 24 hours	Intravenous
Xie	2022	SD Rat	M	180–220g	T10	Contusion	BMMSC	10 g	2 hours & every 2 days for 3 injections	Intravenous
Yan	2019	SD Rat	M	220 250 g	T10	Contusion	BMMSC	40 g	2 hours & every 2 days for 3 injections	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	M	7-8 w	T10	Contusion	BMMSC	N/R	3 days	Into the injured hind limbs
Suang	2022	SD Rat	F	220 g	T9	Compression	AMSC	10^9 particles	Immediately & 3 days	Intravenous
He	2022	SD Rat	N/R	220 g	T10	Contusion	BMMSC	100 g	Daily for 7 consecutive days	Intravenous
Kang	2022	SD Rat	F	170–220 g	T10	Contusion	hUCMSC	200 g	Immediately	N/R
Cheshmi	2023	SD Rat	M	200-250 g	T9	Contusion	hPMSCs	200 g	30 min	Intravenous
Han	2022	Wistar Rat	F	200-250 g	T10	Contusion	BMSC	72 l	continuous injection for 3 days	under the dura
Hu	2022	SD Rat	F	200-250 g	T6, T7	Transection	hUCMSC	50 l	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 consecutive days	Intravenous
Wang B	2022	C57BL/6J mice	F	20-25 g	T11, T12	Contusion	hUCMSC	50 g	N/R	Intravenous
Wang Y	2022	Wistar Rat	F	NR	T10	Contusion	BMSCs	25 l	continuous injection for 3 days	Intrathecal
Xiong	2023	C57BL/6J mice	M	20-25 g	T10	Transection	MUMSCs	4 l	4 times every 7 days	Injury site
Yin	2022	C57BL/6J 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

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

	Number of experiments	Subgroup analysis			Meta-regression	
		Weight/ AgeSMD [95%CI]	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 administrations						
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

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

	Number of experiments	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 administrations						
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

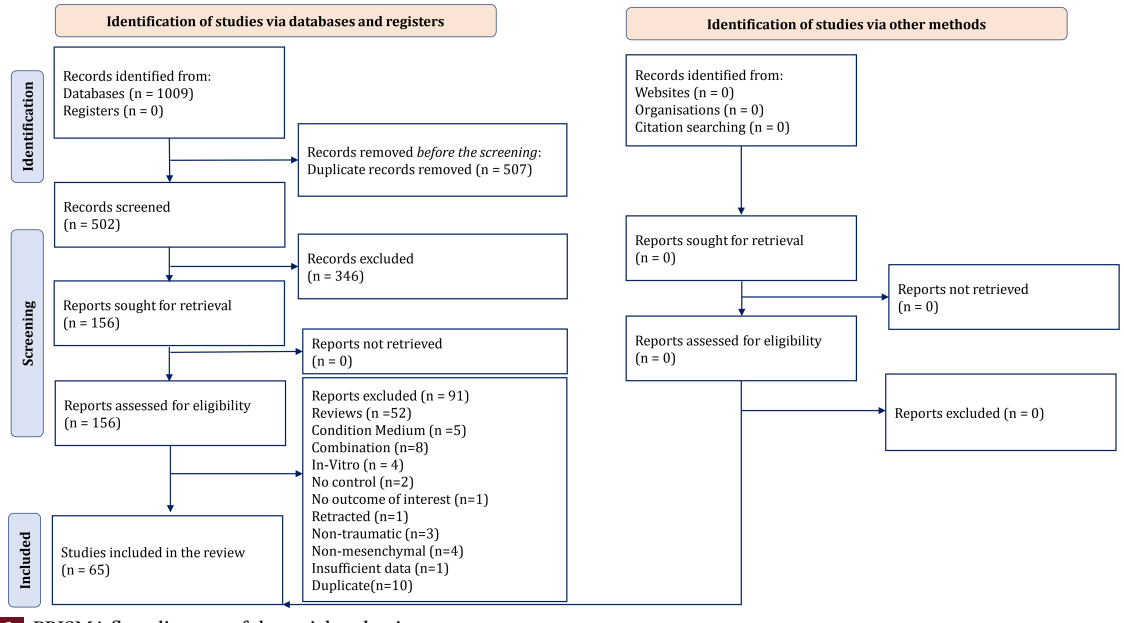

Figure 1: PRISMA flow diagram of the article selection process.

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

	Number of experiments	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 administrations						
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

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

	Number of experiments	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 administrations						
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

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

	Number of experiments	Subgroup analysis			Meta-regression	
		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 administrations						
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

Low: low risk of bias

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

	Number of experiments	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 administrations						
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

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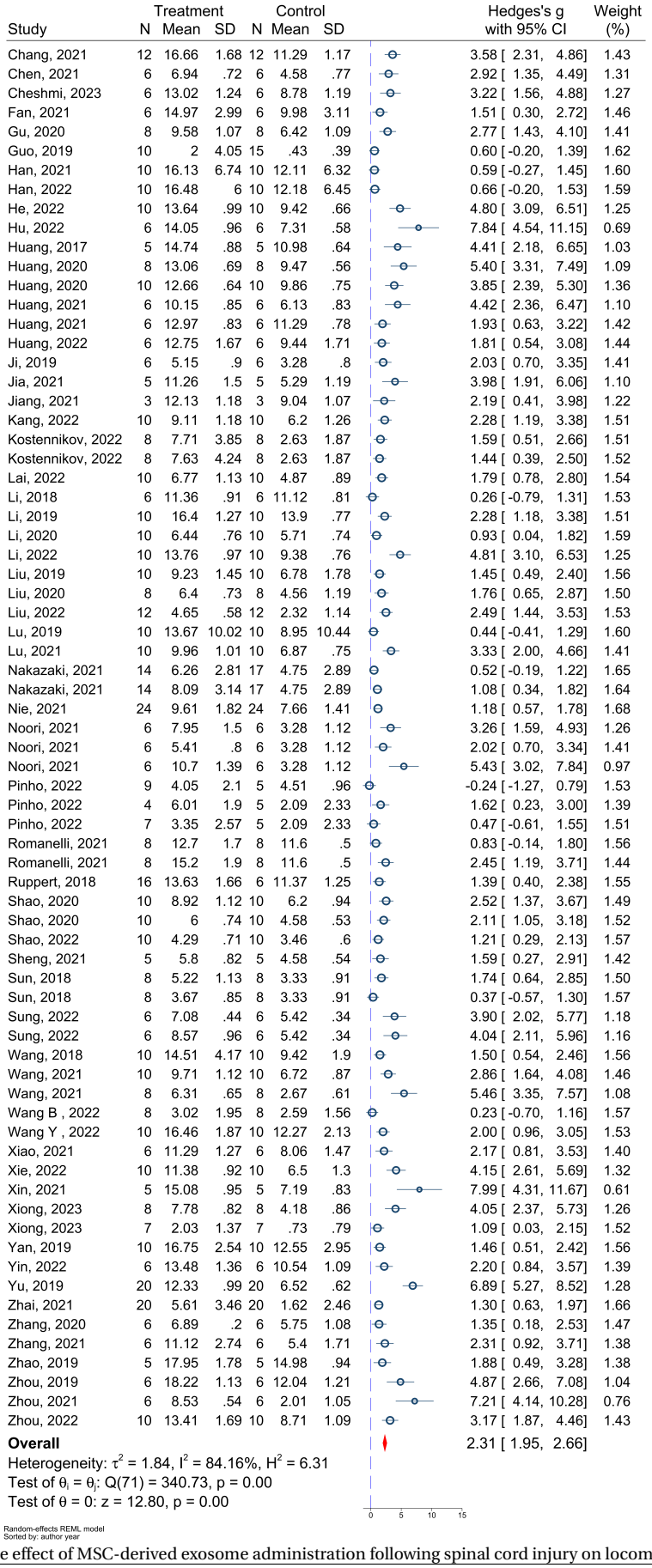

Figure 2: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on locomotion.

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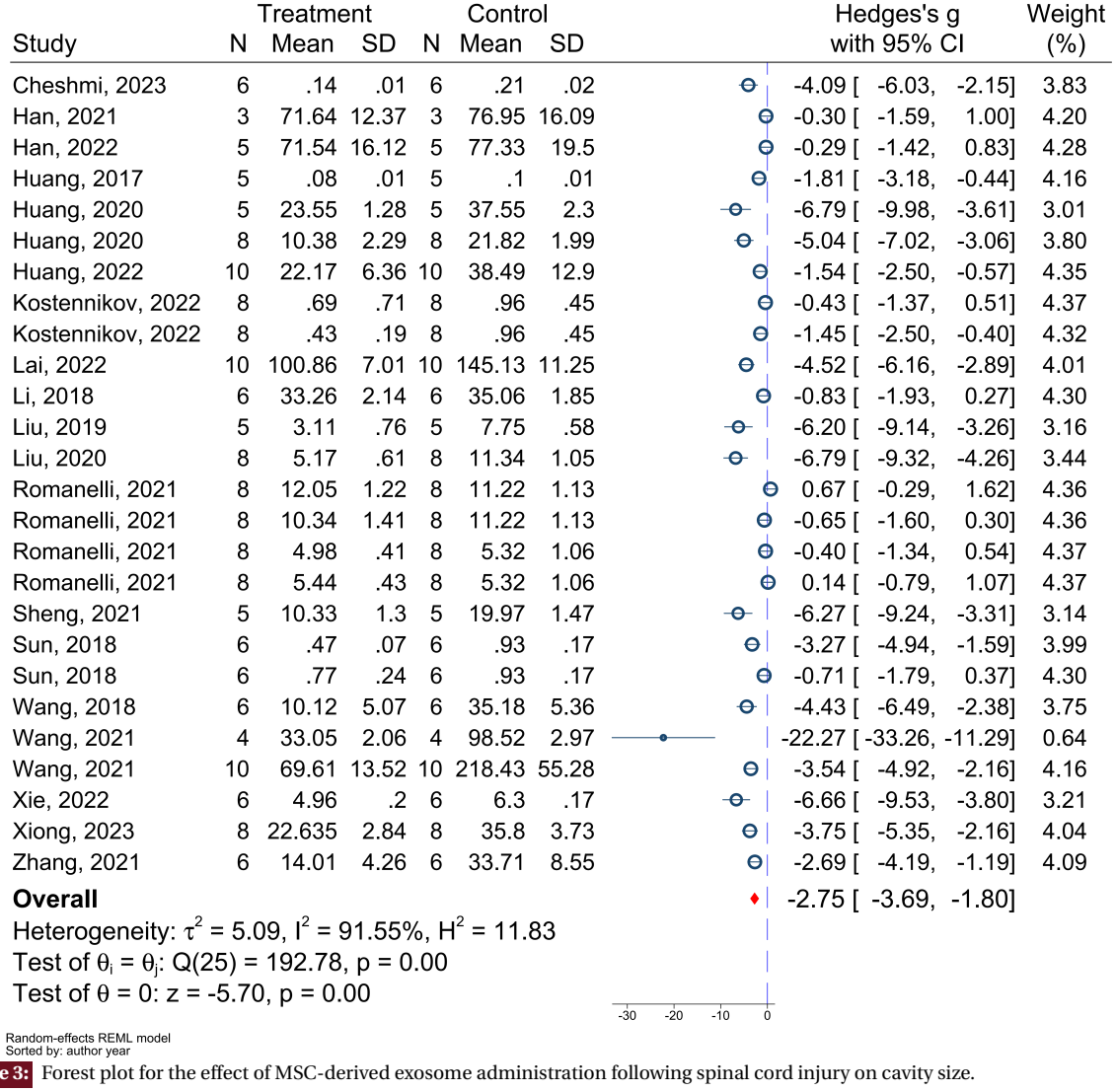

Figure 3: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on cavity size.

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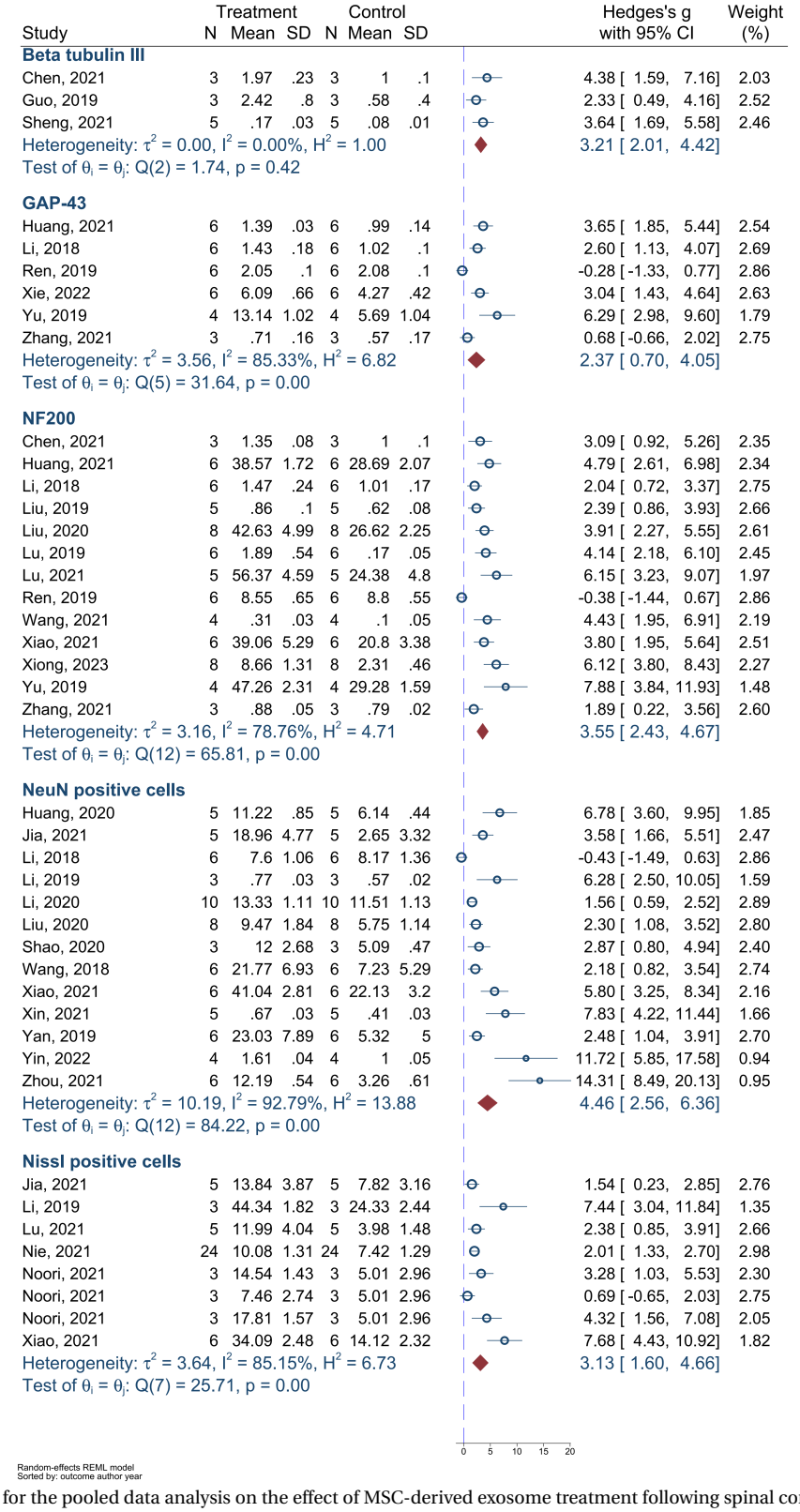

Figure 4: Forest plot for the pooled data analysis on the effect of MSC-derived exosome treatment following spinal cord injury on markers of neural tissue regeneration.

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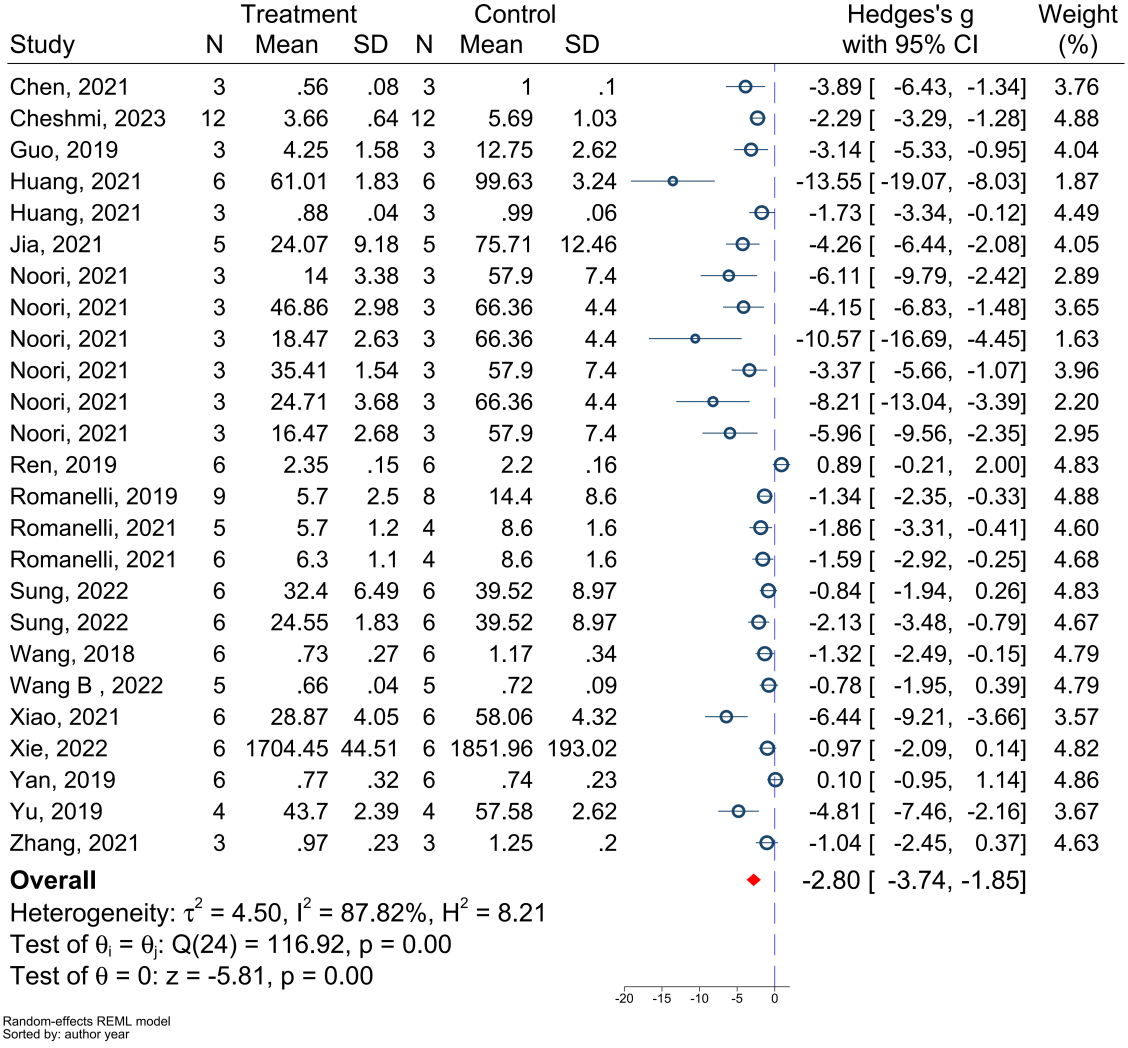

Figure 5: Forest plot for the pooled data analysis on the effect of MSC-derived exosome treatment following spinal cord injury on the expression of GFAP.

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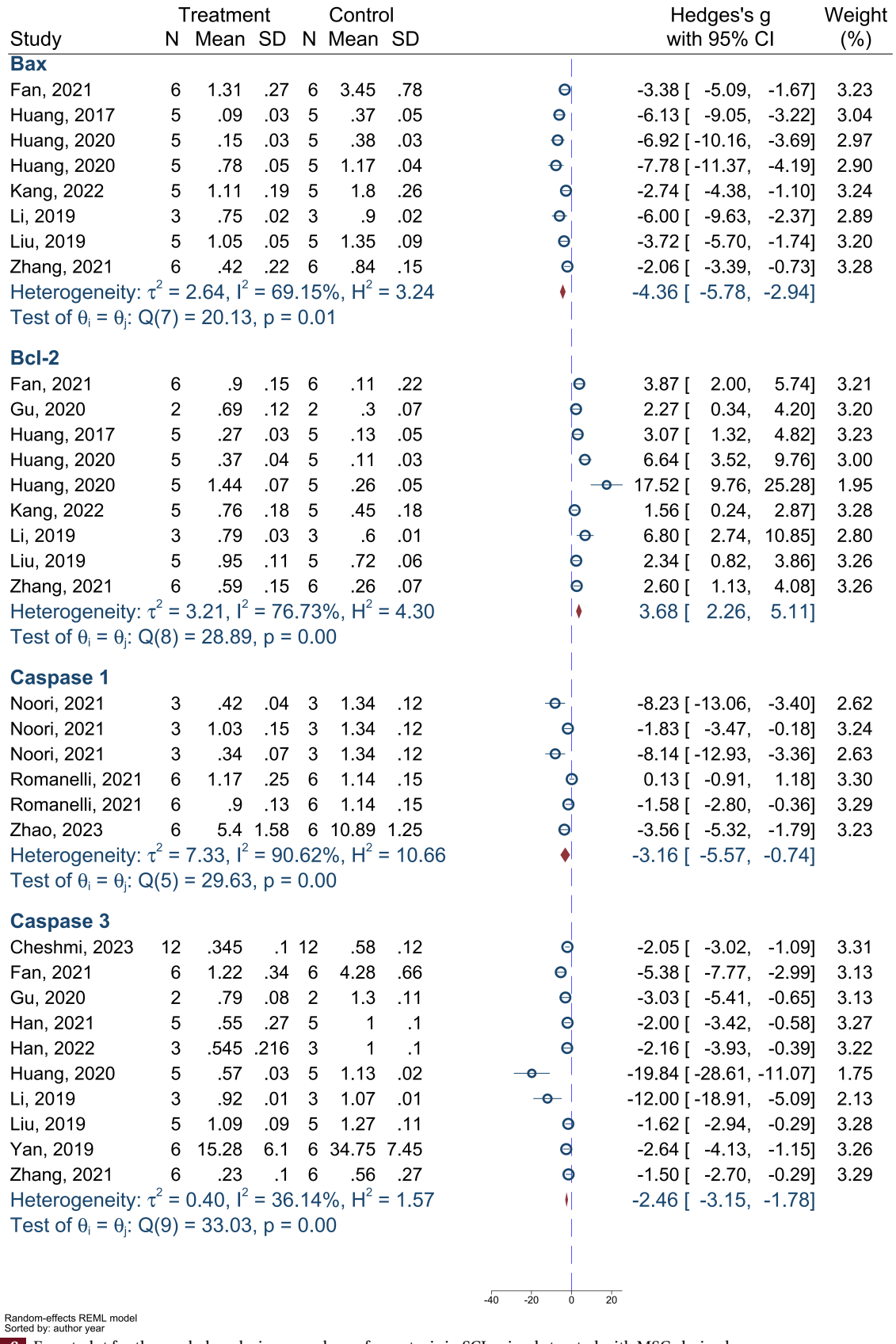

Figure 6: Forest plot for the pooled analysis on markers of apoptosis in SCI animals treated with MSC-derived exosomes.

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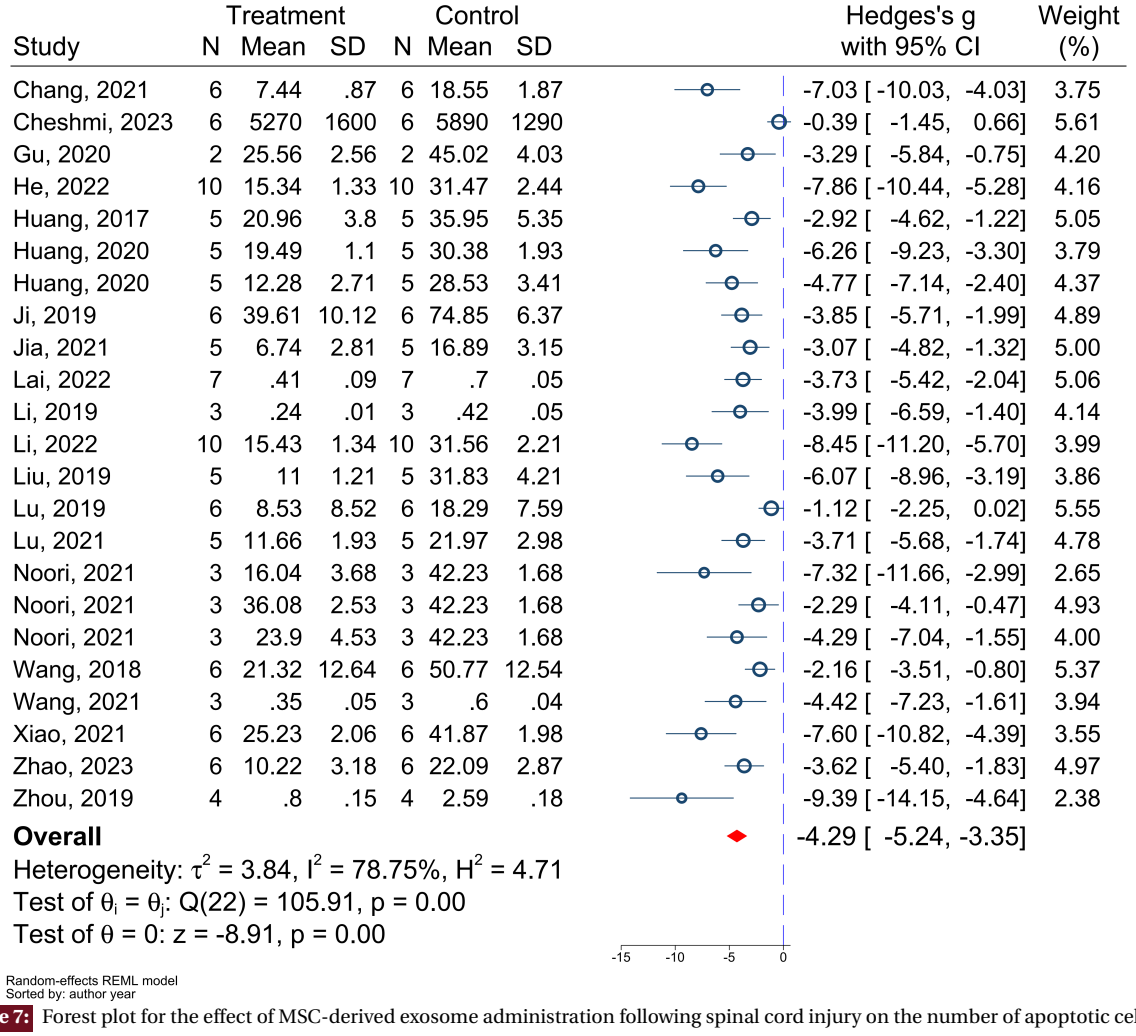

Figure 7: Forest plot for the effect of MSC-derived exosome administration following spinal cord injury on the number of apoptotic cells.

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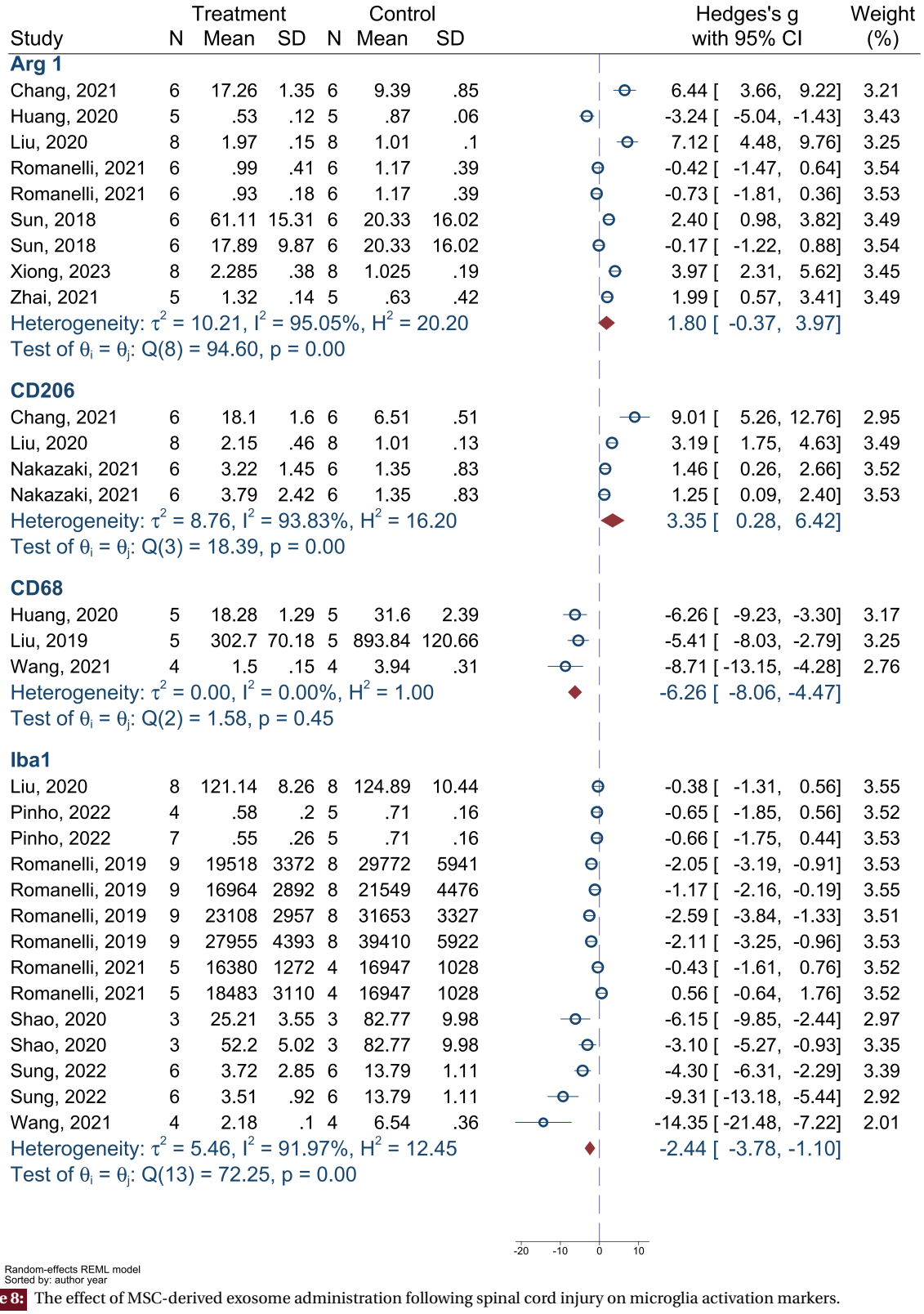

Figure 8: The effect of MSC-derived exosome administration following spinal cord injury on microglia activation markers.

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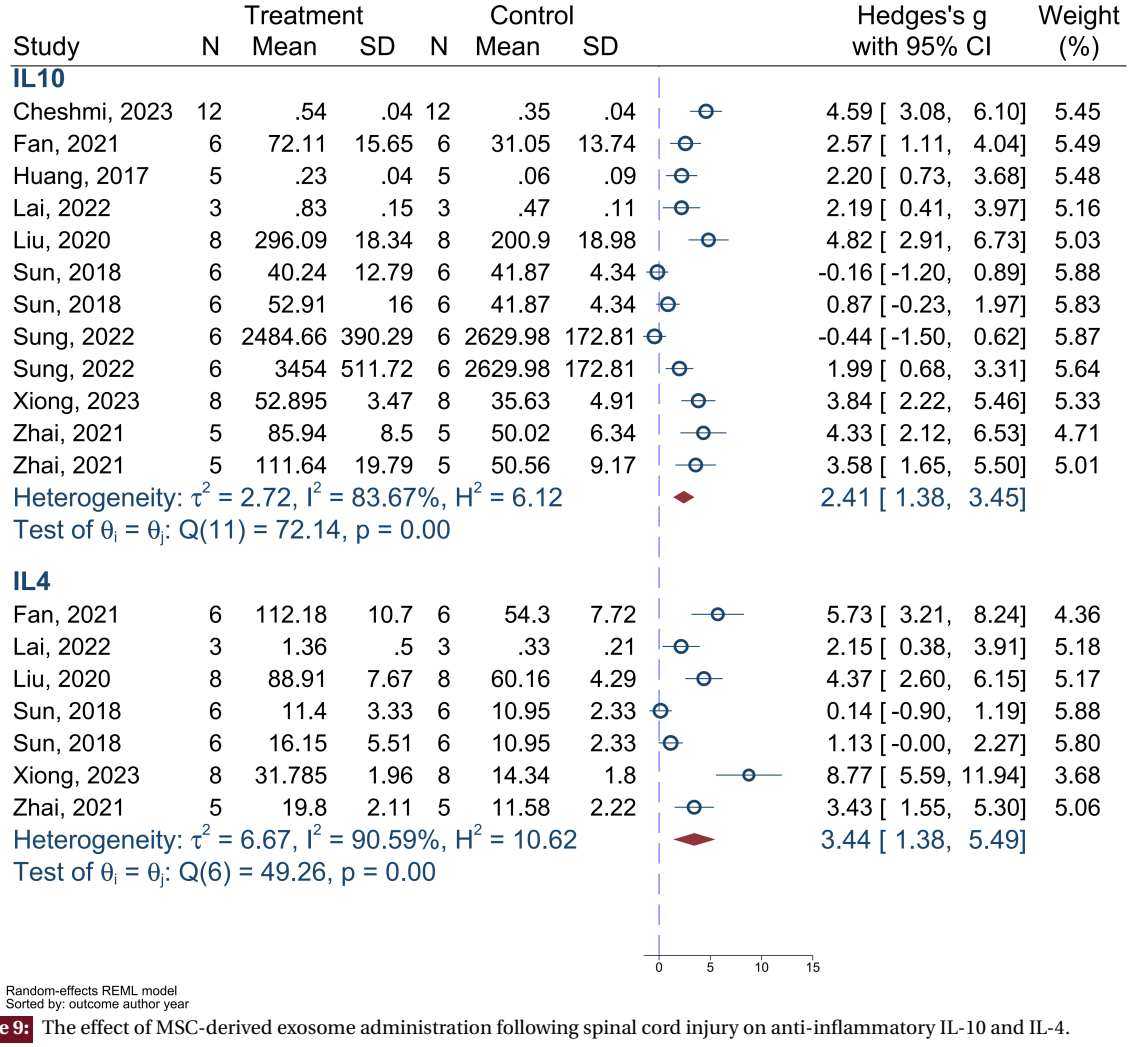

Figure 9: The effect of MSC-derived exosome administration following spinal cord injury on anti-inflammatory IL-10 and IL-4.

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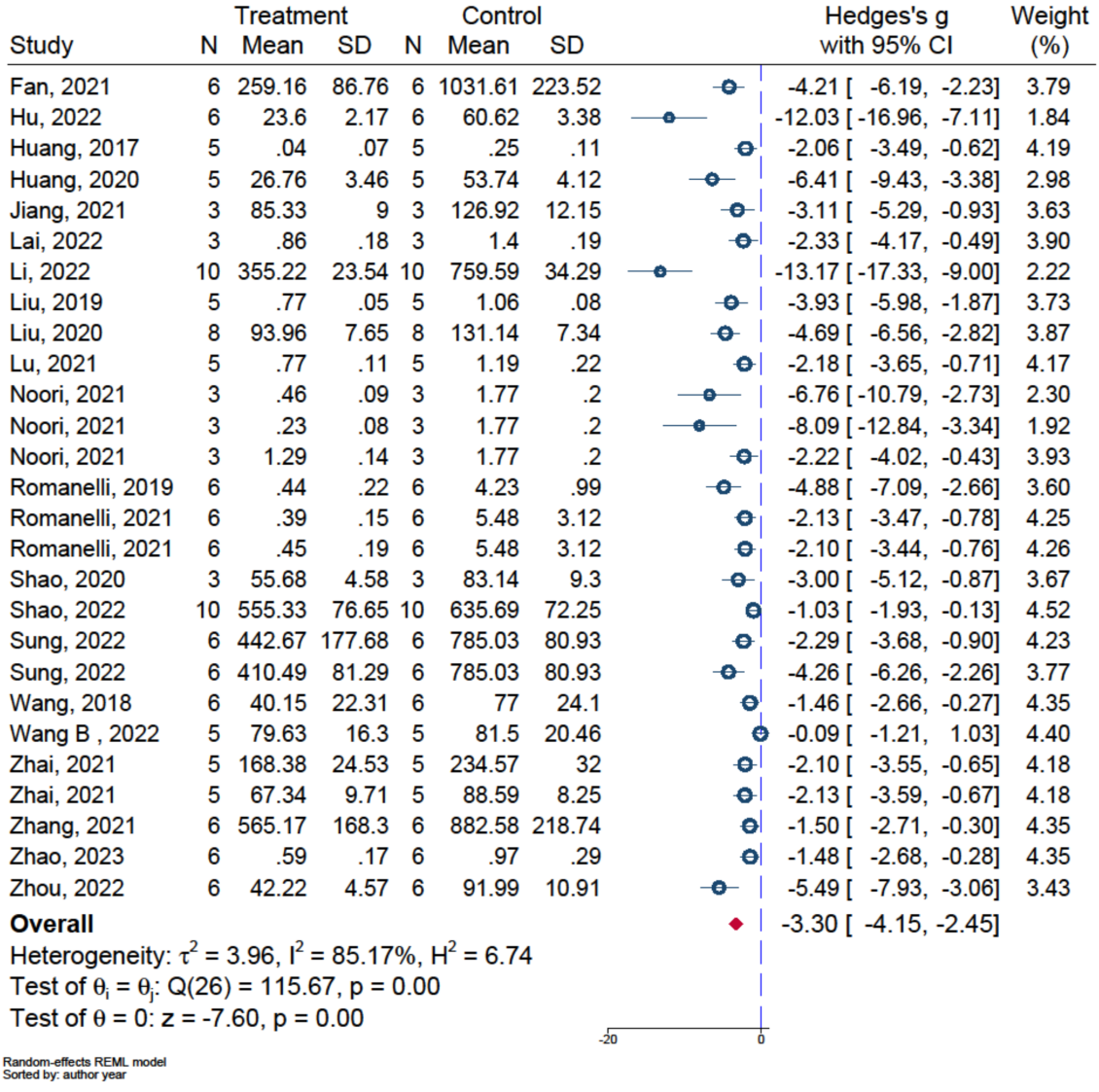

Figure 10: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker IL-1b.

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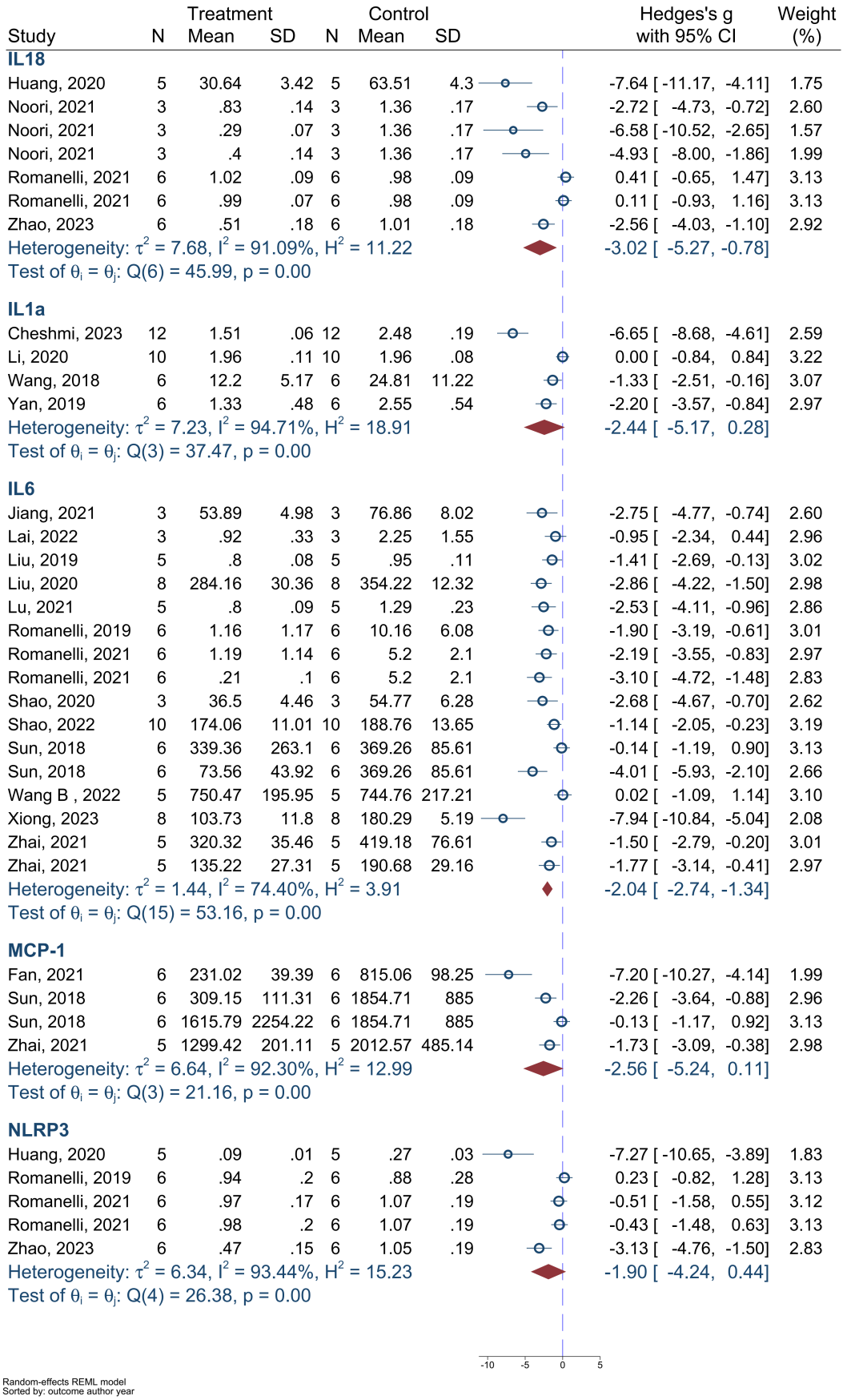

Figure 11: The effect of MSC-derived exosome administration following spinal cord injury on pro-inflammatory markers IL-18, IL-1a, IL-6, MCP-1 and NLRP3.

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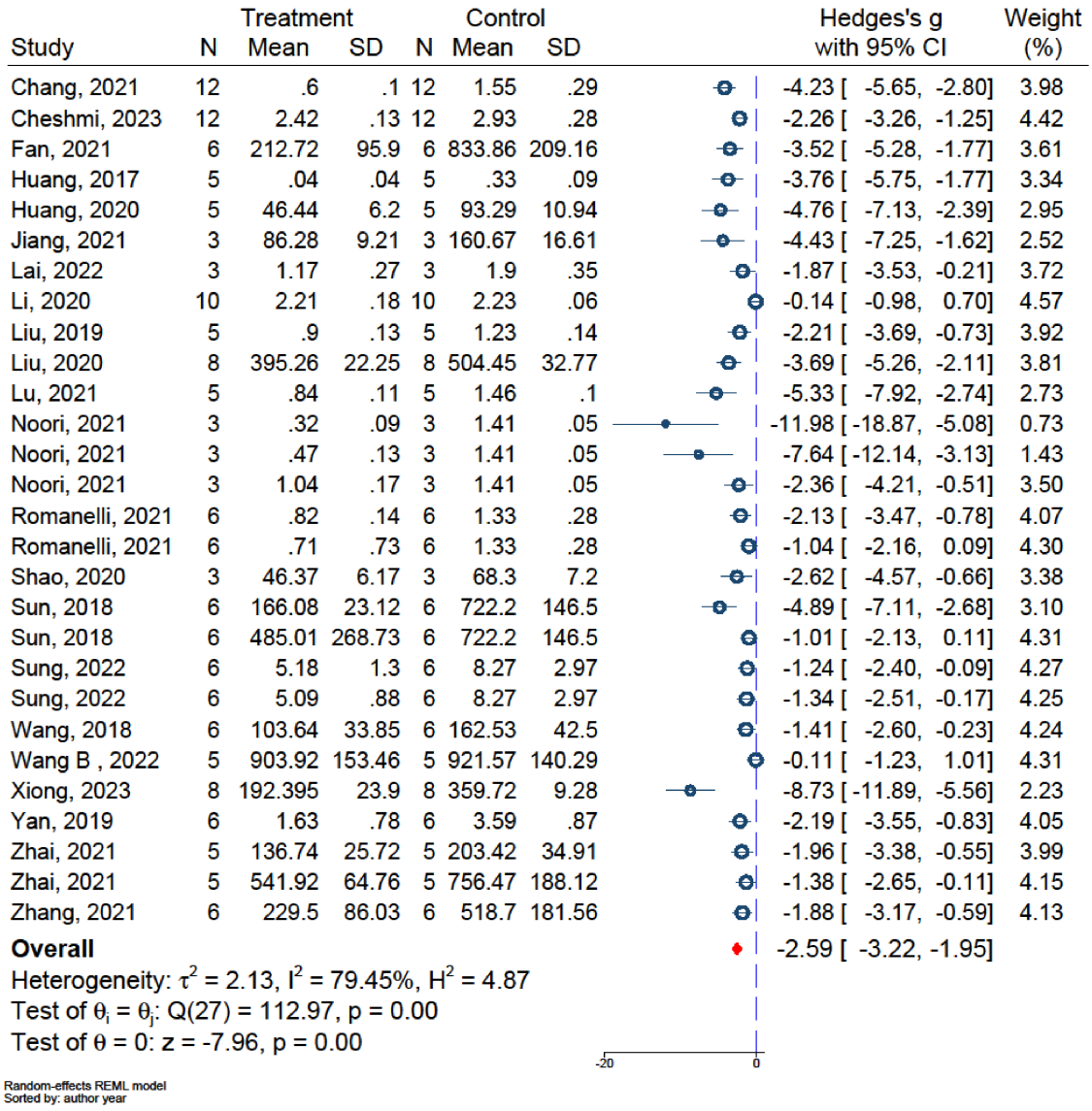

Figure 12: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.

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Supplementary Table 1: Quality control of the included studies

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

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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?

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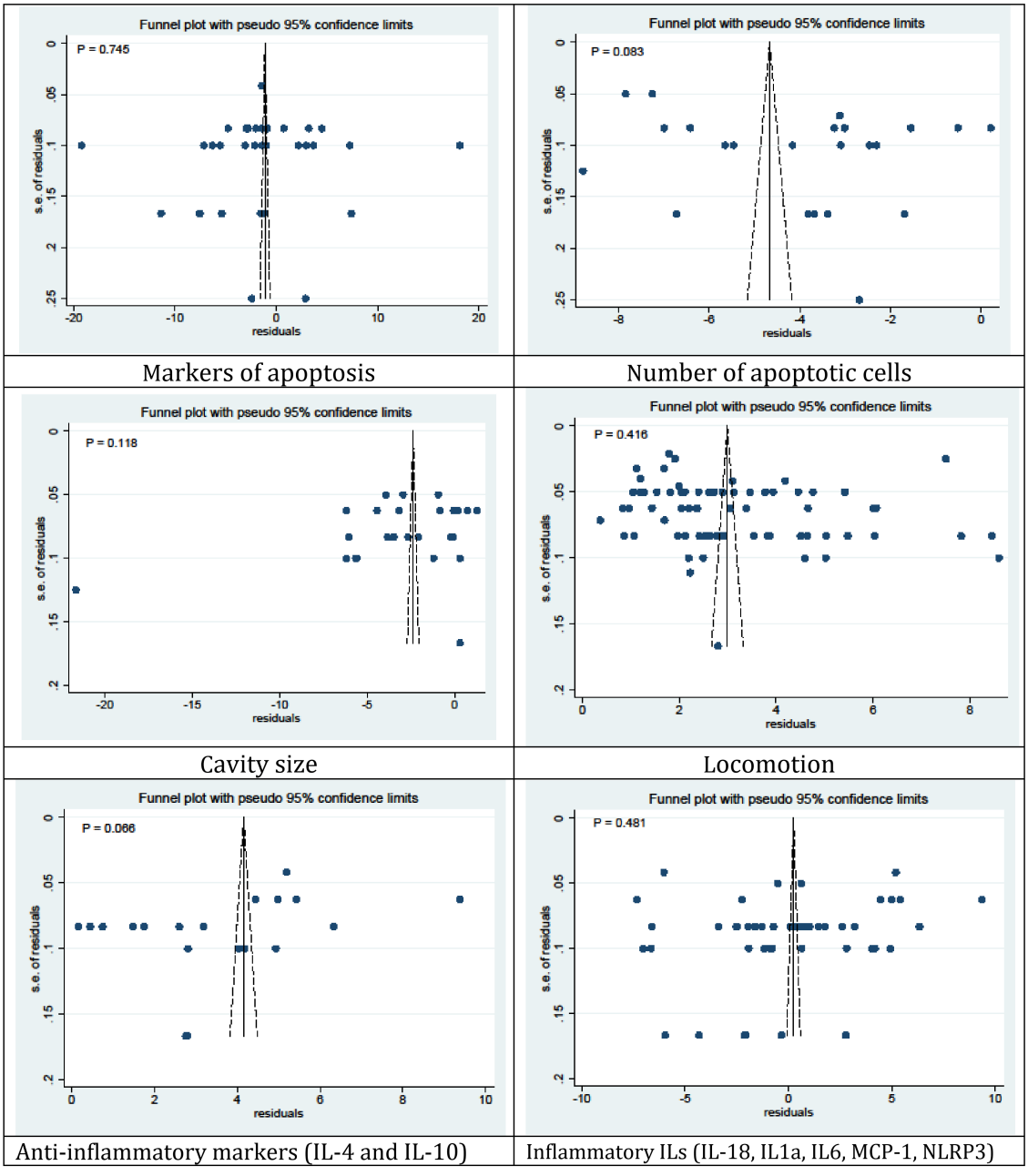

Supplementary Figure 1: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.

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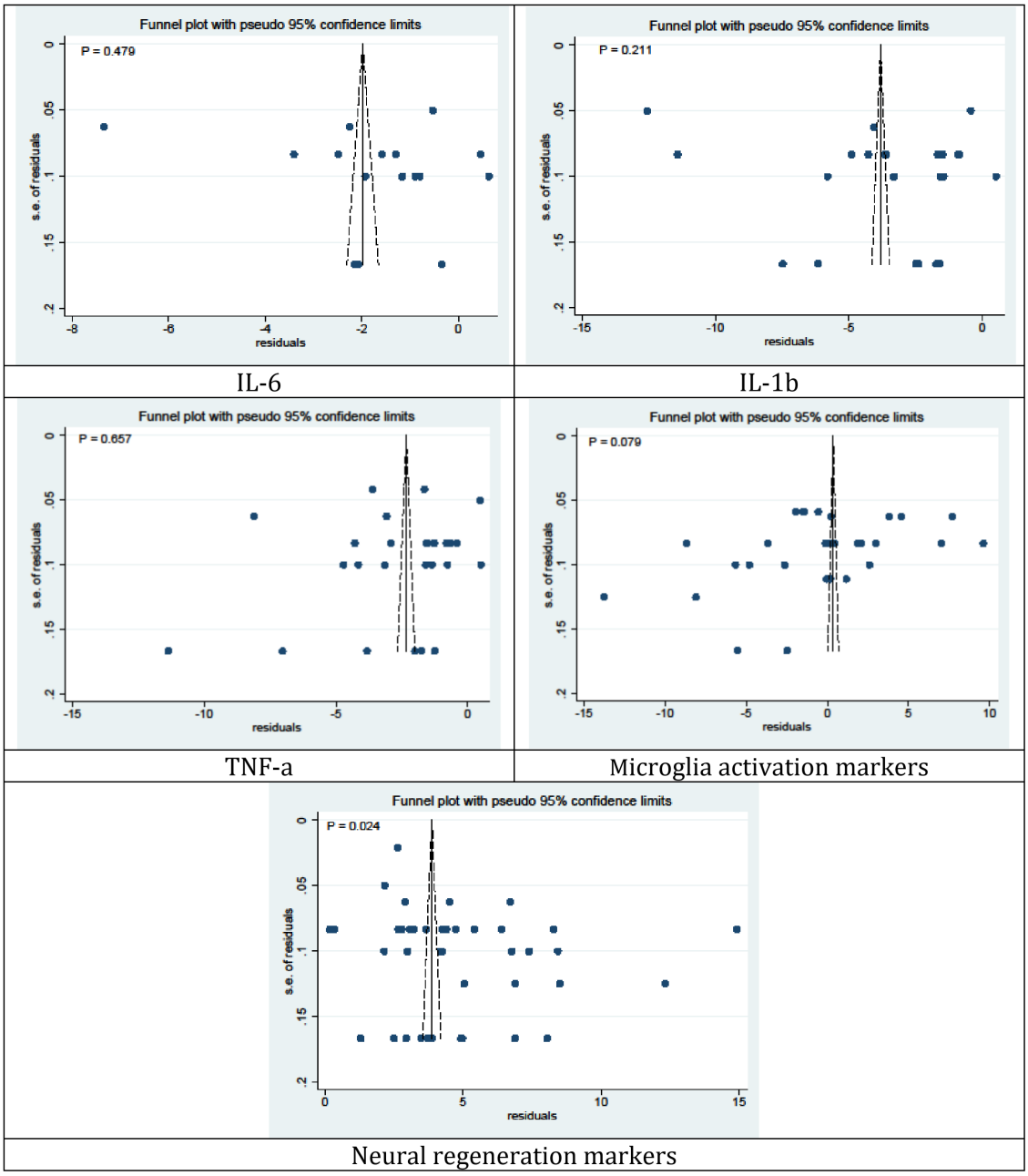

Supplementary Figure 1: The effect of MSC-derived exosome administration following spinal cord injury on the pro-inflammatory marker TNF-a.

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