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REVIEW

Safety and Efficacy of Mesenchymal Stem Cell Therapy in Multiple System Atrophy: Systematic Review

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Objective: To systematically evaluate the efficacy and safety of mesenchymal stem cell (MSC) therapy for patients with Multiple System Atrophy (MSA) by synthesising available clinical trial evidence and clarifying signals of disease modification.

Background: MSA is a rapidly progressive and fatal neurodegenerative disorder for which no disease-modifying therapies exist. MSC therapy has emerged as a potential treatment, with mechanisms centered on neuroprotection and clinical benefit through anti-inflammatory and trophic effects rather than direct cell replacement.

Methods: We systematically searched PubMed, Scopus, the Cochrane Library, and Web of Science for studies on mesenchymal stem cell (MSC) therapy in adults with probable or confirmed multiple system atrophy (MSA). Eligible studies included single-arm trials or comparisons with placebo or usual care. The primary outcome was safety and tolerability, assessed by the type and severity of adverse events. Secondary outcomes included the rate of disease progression measured by UMSARS total, Part I, and Part II scores.

Results: A total of 123 participants from seven studies were included. MSCs were administered through multiple routes, and adverse events occurred in 65–70% of participants but were mostly mild and transient. No serious MSC-related toxicity was reported. Several studies suggested slower disease progression following MSC therapy. For example, in Singer et al (2019), patients receiving high-dose MSCs showed a markedly lower rate of UMSARS total score progression compared with a matched historical control group (0.40 ± 0.59 vs 1.44 ± 1.42 points/month, $p = 0.004$), suggesting a possible dose-dependent effect. However, treatment effects varied across studies depending on dose, administration route, and disease stage.

Conclusion: MSC therapy shows potential for disease modification in MSA by slowing neurological deterioration. The treatment was well tolerated, supporting the need for larger, definitive trials with standardised protocols and longer follow-up to confirm clinical benefit.

Plain Language Summary: Multiple System Atrophy (MSA) is a rare, rapidly worsening brain disorder that affects movement, balance, and automatic body functions, and there are currently no treatments that can slow its progression. Mesenchymal stem cell (MSC) therapy has been suggested as a possible treatment because it may protect nerve cells and reduce inflammation rather than replace damaged neurons. We reviewed all clinical trials testing MSC therapy in adults with MSA to evaluate safety and possible effectiveness. Major medical databases were searched, and studies reporting side effects and changes in disease severity over time using a standard clinical rating scale were included. Seven studies with 123 patients were included. MSCs were given through different routes, including blood vessels, spinal fluid, or near the brain. Most patients experienced mild, short-term side effects, such as fever or headache, and no serious treatment-related problems were reported. Across studies, patients receiving MSC therapy showed slower worsening of symptoms than expected, particularly in earlier stages of MSA. While these findings are encouraging, the included studies were small and varied in design, which limits the strength of the conclusions. Larger, well-designed clinical trials are needed to

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determine whether MSC therapy can provide sustained clinical benefits for patients with MSA.

Keywords: cerebellar dysfunction, immunomodulation, mesenchymal stem cells, multiple system atrophy, neurodegeneration, neuroprotection, Parkinsonism

Introduction

Multiple system atrophy (MSA) is a rare, progressive neurodegenerative disorder characterized by autonomic dysfunction, parkinsonism, and cerebellar ataxia[1] with an estimated prevalence of approximately 7.2 per 100,000 persons[2] and incidence rates ranging from 0.6 to 3 per 100,000 person-years globally.[3] The disease affects men more frequently than women, with prevalence rates of 2.75 versus 1.19 per 100,000 persons.[4] MSA typically manifests in the sixth decade of life, with a mean age at onset of approximately 56-year-old.[3]

MSA presents with two major clinical phenotypes: the parkinsonian subtype (MSA-P) and the cerebellar subtype (MSA-C). MSA-P is characterized predominantly by bradykinesia, rigidity, and parkinsonian motor symptoms, whereas MSA-C is dominated by gait ataxia, limb incoordination, dysarthria, and other cerebellar features.[3] Epidemiological studies indicate that MSA-P appears to be more common than MSA-C in many European and U.S. cohorts, and both subtypes generally show poor responsiveness to levodopa treatment.[5]

The median survival range after symptoms appearance is usually 6–10 years.[6] Although overall survival appears broadly similar between the two phenotypes, differences in disease progression have been reported. Some studies suggest that MSA-C may present earlier[5] and demonstrate faster early functional decline, including an earlier need for walking assistance, whereas MSA-P may exhibit greater responsiveness to dopaminergic therapy, although disease progression remains rapid in both forms.,[7] although disease progression remains rapid in both forms. Despite these differences in clinical trajectory, many cohorts report comparable overall survival between the two phenotypes, generally remaining less than 10 years from disease onset.[5,8]

Diagnosis of MSA also remains challenging. According to consensus criteria, probable MSA requires a sporadic, progressive adult-onset disorder with rigorously defined autonomic failure accompanied by poorly levodopa-responsive parkinsonism or cerebellar ataxia.[9] However, even when the second consensus diagnostic criteria are applied, only 62% of cases meet pathological confirmation, highlighting the diagnostic heterogeneity and clinical complexity of the disorder.[10]

The pathological hallmark of MSA is defined by the accumulation of misfolded alpha-synuclein protein within oligodendrocytes, leading to the formation of filamentous inclusions called glial cytoplasmic inclusions (GCIs).[11,12] This synucleinopathy is accompanied by severe, system-specific neurodegeneration primarily affecting the striatonigral system (MSA-P phenotype) and the olivopontocerebellar system (MSA-C phenotype).[13]

Environmental risk factors potentially include occupational exposure to metal dusts and fumes, plastic[14] monomers and additives, organic solvents, and pesticides though these associations have not been definitively confirmed.[15] Interestingly, smoking appears to be a protective factor in MSA, similar to its effect in Parkinson's disease.[16]

Despite advances in understanding MSA pathophysiology, therapeutic options are largely symptomatic and palliative, with no disease-modifying treatments currently available.[17] Because of this gap, regenerative medicine techniques have been investigated, especially mesenchymal stem cell (MSC) therapy, which has shown promise in treating neurodegenerative illnesses.[18]

Over the past decade, clinical trials have explored MSC therapy in MSA using different cell sources (bone marrow, adipose tissue, umbilical cord), administration routes (intravenous, intrathecal, intracerebral), and dosing regimens. Given the variability in study design, outcome measures, and reported results, synthesizing this evidence is crucial to clarify MSC safety and potential clinical effects in MSA, as well as to highlight gaps for future research.

Materials and Methods

This review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD420251137238.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 guidelines.[19]

Literature Search

Four major databases, PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched up to September 16, 2025. MeSH terms and free-text terms covering Multiple system atrophy, mesenchymal stem cell and different interventions were used without date restrictions (see Additional File 1 for full search strategies). The results were imported into Rayyan software, where duplicates were automatically eliminated before screening.

Eligibility Criteria

The study protocol was established as a priori with predefined eligibility criteria based on the PICO framework. We included comparative studies (randomized and non-randomized controlled trials) evaluating patients diagnosed with Multiple System Atrophy (MSA). Adult patients diagnosed with probable or confirmed MSA based on established clinical criteria were included. Eligible interventions comprised mesenchymal stem cell (MSC) transplantation administered through various routes, including intra-arterial, intrathecal, intravenous, and lateral atlanto-occipital space puncture (LASP). We planned to analyze different administration routes separately if sufficient data were available. Cell types included autologous bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived autologous MSCs, allogeneic adipose tissue-derived MSCs from healthy donors, and human umbilical cord blood mononuclear cells (hUCB-MNCs). The primary outcome was safety and tolerability, assessed by severity (mild, moderate, severe), type, and frequency of adverse events across different administration routes. Secondary outcomes included the rate of disease progression measured via Unified Multiple System Atrophy Rating Scale (UMSARS) total, Part I, and Part II scores. Patients with other neurodegenerative or systemic diseases that could confound outcomes, and those with a Mini-Mental Status Examination (MMSE) score of 24 or less were excluded. Studies were also excluded if they were noncomparative, lacked safety or clinical outcome data, or were observational in design (eg., case series or reviews).

Study Selection

Two reviewers independently evaluated all identified records by examining titles and abstracts against the predefined inclusion criteria. Articles meeting these preliminary criteria underwent full-text assessments of potentially eligible studies. To ensure methodological consistency, any discrepancies between reviewers were resolved through discussion.

Data Collection Process

For the included studies, two reviewers independently extracted data on study characteristics (design, country, sample size, follow-up duration), patient demographics (age, gender, symptom duration, diagnostic criteria), and Intervention details included various MSC delivery techniques and administration routes, such as intra-arterial infusion, intrathecal injection, intravenous infusion, and LASP. Specific procedural parameters, including injection volume, frequency, and total number of treatment sessions, were recorded when available. Outcome measures included safety and tolerability of profiles, categorized by the type, frequency, and severity of adverse events. Additional secondary clinical efficacy outcomes included changes in the Unified Multiple System Atrophy Rating Scale (UMSARS) total, Part I, and Part II scores, as well as overall functional improvement and patient-reported symptom changes following MSC transplantation. Discrepancies or unclear information were resolved and discussed through consensus among the reviewers.

This is a systematic review built upon secondary data made available through selected articles, with no form of personal interest whatsoever, this research did not present any risk of violating normative ethical rights and, therefore, did not need to be submitted to the Ethics Committee on Research with Human Beings.

Risk of Bias Assessment

The risk of bias for each included study was independently assessed by two reviewers using an appropriate tool based on study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, while non-

randomized studies were assessed using the ROBINS-I tool.[19] Discrepancies were resolved through consensus. Publication bias assessment using funnel plots and statistical tests would be performed if more than 10 studies were available.

Results

Description of Eligible Studies

The systematic search across multiple databases identified a total of 951 records, including PubMed (n = 81), Scopus (n = 760), Web of Science (n = 97), and the Cochrane Library (n = 13). After removing 259 duplicate records automatically through Rayyan, 796 unique citations were screened by title and abstract. A total of 775 records were excluded based on the exclusion criteria, and 21 potentially eligible reports underwent full-text review. Ultimately, seven studies were included in the final qualitative synthesis. The study selection process is visually summarized in the PRISMA 2020 flow diagram[19] (Figure 1).

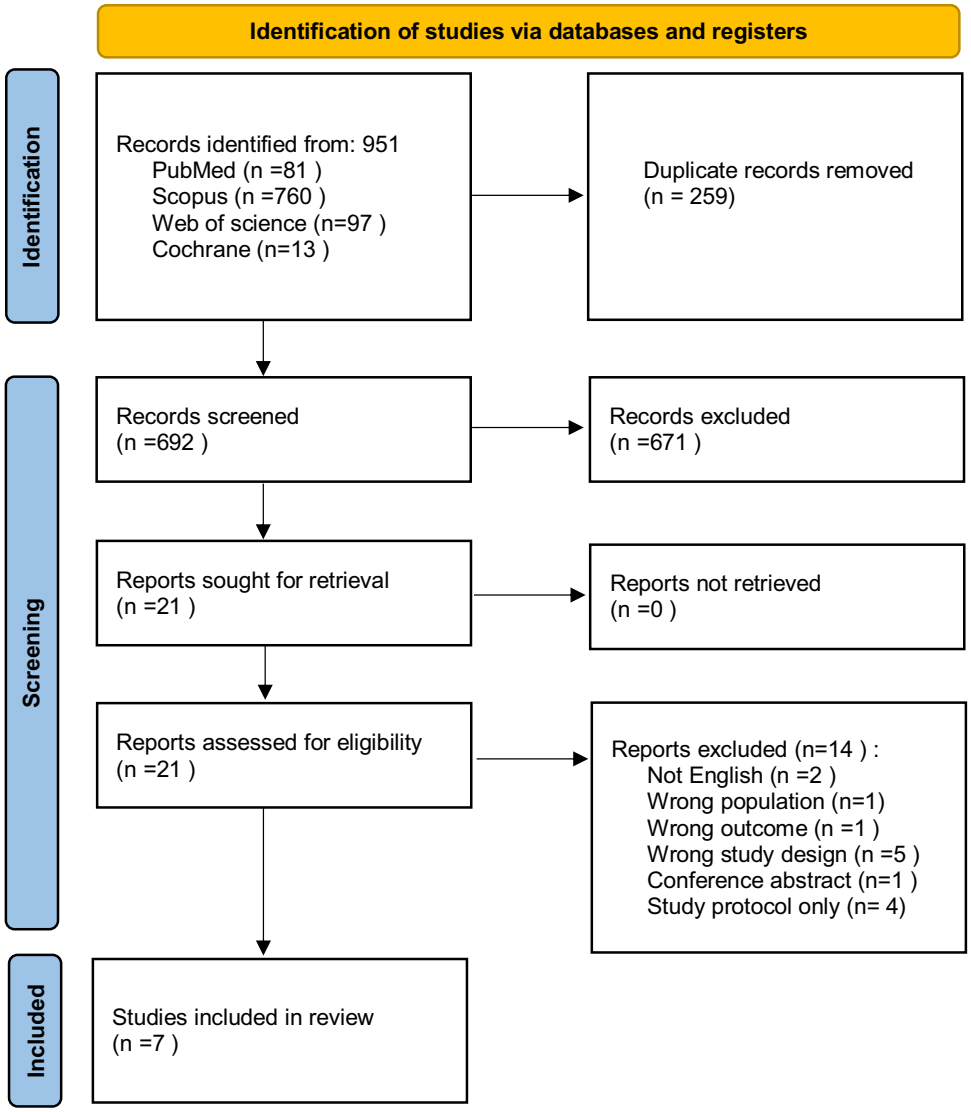

Figure 1 PRISMA 2020 flowchart diagram of the study selection for a systematic review on Safety and Efficacy of Mesenchymal Stem Cell Therapy in Multiple System Atrophy.

Risk of Bias Assessment

The risk of bias assessment revealed significant concerns across the included studies, largely caused by their design. Only two studies[20,21] were randomized controlled trials. When evaluated using the Cochrane RoB 2 tool,[22] Lee et al (2012) trial was judged to have "some concerns" overall While the randomization process itself was low risk, concerns were raised due to the potential for deviations from the intended interventions during the unblinded intra-arterial procedure, missing outcome data for several secondary endpoints, and the subjective components of the primary clinical rating scale. In contrast, Lee et al (2008) was judged to have a high risk of bias, mainly due to deviations from intended interventions and concerns regarding outcome measurement (Figure 2).

The other five studies[23–27] were non-randomized, using single-arm or other controlled designs, which were evaluated using the ROBINS-I tool,[22] and all were classified as having a Serious or Critical risk of bias. The main source of bias was confounding. The lack of a concurrent randomized control group made it impossible to determine whether the observed effects were due to the intervention or to confounding factors such as the natural history of the disease, regression to the mean, concomitant treatments, or placebo effects. Another concern was bias in measurement of outcomes, as the open-label design meant that patients and outcome assessors were not blinded, introducing potential for expectation bias, particularly for subjective clinical scores (Figure 3).

A summary comparison of the overall risk-of-bias profiles across all seven included studies, integrating both RoB 2 and ROBINS-I assessments, is presented in (Figures 2 and 3), illustrating the consistent methodological limitations that reduce confidence in the observed treatment effects. Formal assessment of publication bias was not feasible because fewer than 10 studies were available for analysis.

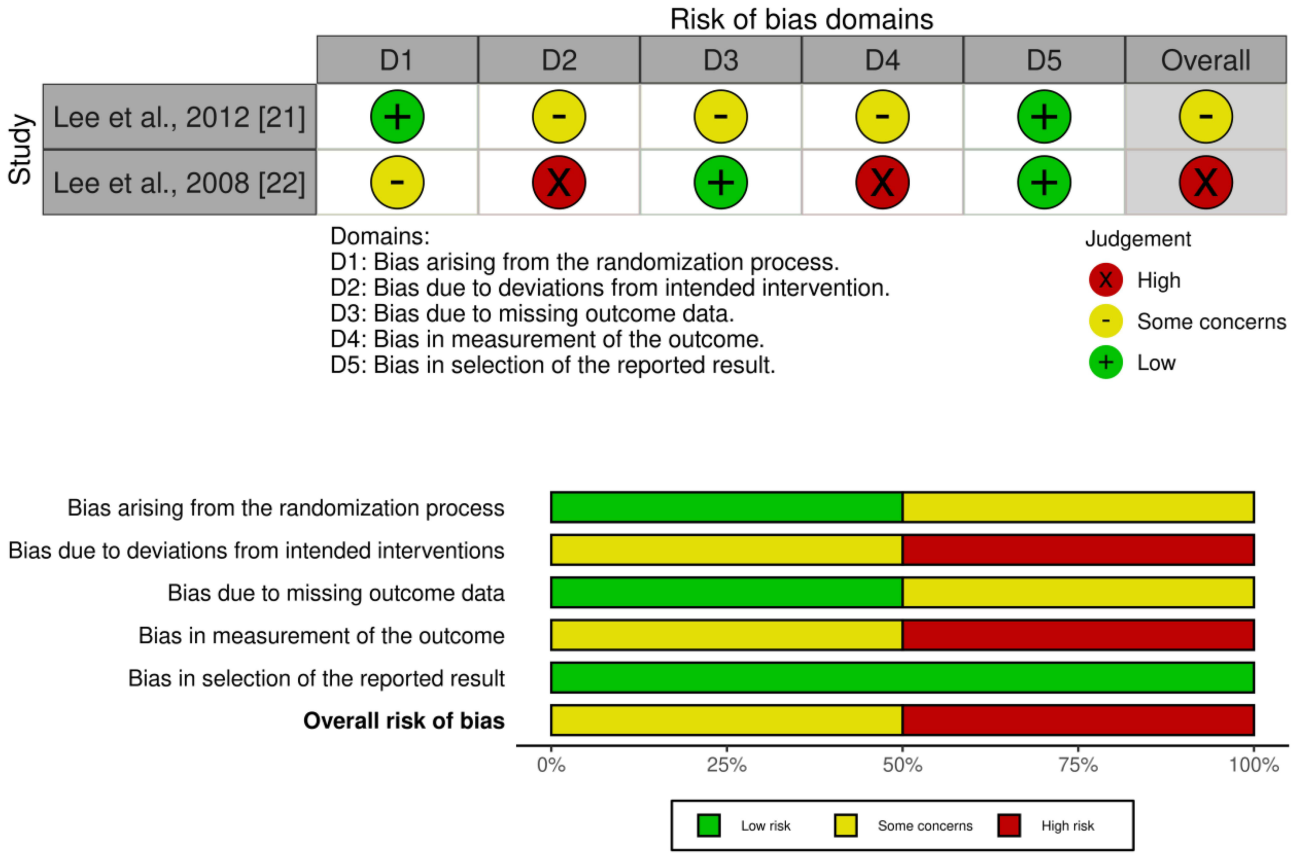

Figure 2 Risk of bias assessment of randomized controlled trials using the RoB 2 tool; five domains evaluated independently by two reviewers.

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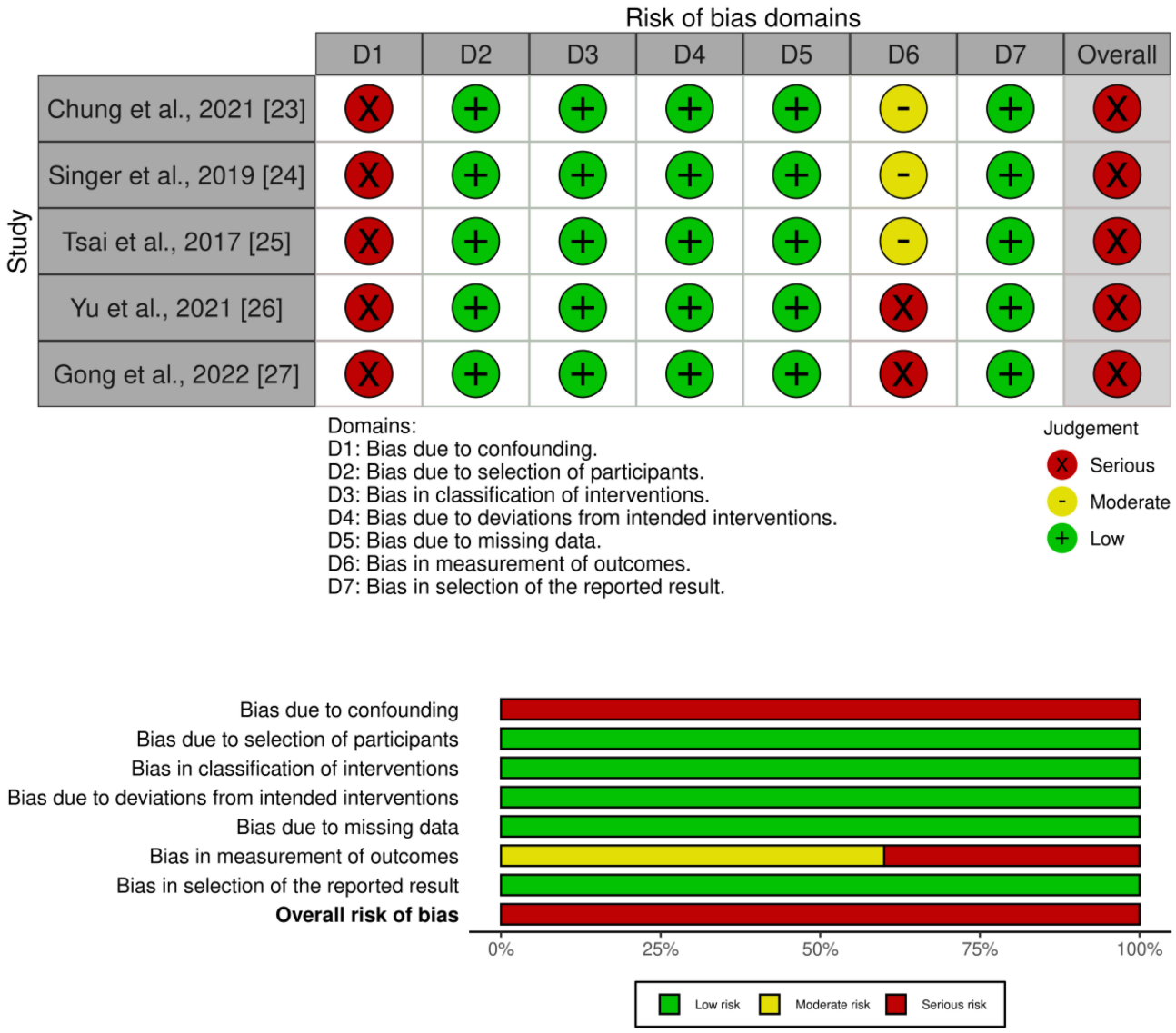

Figure 3 Risk of bias assessment of non-randomized studies using the ROBINS-I tool; seven domains evaluated independently by two reviewers.

Study Characteristics

A total of seven studies (n = 123) were included in this review, comprising five single-arm trials[23–27] and two randomized controlled trials[20,21] published between 2008 and 2022. The key characteristics of these studies, including country, last follow up, design or setting, study population, diagnostic criteria, intervention details, total number of patients, mean of age, and disease duration, are summarized in Table 1.

The primary outcome across the included studies was safety and tolerability, assessed by the type, frequency, and severity of adverse events. Secondary outcomes included the rate of disease progression, measured through the Unified Multiple System Atrophy Rating Scale (UMSARS) total, Part I, and Part II scores. Final outcomes, including adverse effects, and UMSARS results, are presented in Table 2.

Safety Outcomes

The seven included studies were categorized according to the source of mesenchymal stem cells (MSCs) used. Three studies utilized BM-MSCs: Lee 2008,[21] Lee et al 2012,[20] and Chung et al 2021,[23] Two studies used adipose tissue-

Table 1 Characteristics of Included Studies

Study (Year), Country	Setting/Design	Last Follow-Up	Total N	MSC Population (=n)	Age Mean ± SD	Diagnostic Criteria	Source of MSC	Route of Administration	Disease DURATION in MSC Group
Chung et al,[23] 2021 South Korea	Single-center, open-label Phase I clinical trial	For adverse event: 28 days For UMSARS: 3 months	9	9 (MSA-C)	57.1 ± 7.4	Second consensus statement (Gilman et al, 2008)[9]	Autologous BM-MSCs	Intra-arterial administration	<5 years since diagnosis
Singer et al,[24] 2019 USA	Phase I/II study with dose-escalation design (pilot)	12-month primary outcome; survival at 24 months	24	24 (19 MSA-C, 5MSA-P)	57.3 ± 6.3	Second consensus statement (Gilman et al, 2008)[9]	Adipose-derived autologous MSCs	Intrathecal administration	2-5.4 years
Tsai et al,[25] 2017 Taiwan	Open-label phase I/IIa clinical study	1-year follow-up	7	6 SCA3 and 1 MSA-C	One MSA patient age 52	Not explicitly mentioned	Allogeneic adipose tissue-derived MSCs	Intravenous administration	3 years
Yu et al,[26] 2021 China	Single-center	6 months	20	(17 MSA-C, 3 MSA-P)	55.4 ± 3.9	Second consensus statement (Gilman et al, 2008)[9]	Human umbilical cord blood-mononuclear cells (hUCB-MNCs)	Through lateral atlanto-occipital space puncture	1.5–5 years
Gong et al,[27] 2022 China	Prospective, Single-Arm, Uncontrolled trial	3 to 5 years	7	7 (5 MSA-C, 2 MSA-P)	57.6 ± 5	Second consensus statement (Gilman et al, 2008)[9]	Human umbilical cord blood-mononuclear cells (hUCB-MNCs)	Lateral atlanto-occipital space puncture (LASP)	1.5–4 years
Lee et al,[21] 2008 South Korea	Open label, Randomized Controlled Trial, Prospective	1 year	29 (11 MSC, 18 Control)	11 (9 MSA-C, 2 MSA-P)	MSC: 57.5 ±6.5; Control: 57.2 ± 6.5	Second consensus statement (Gilman et al, 2008)[9]	Autologous BM-MSCs	Intra-arterial infusion and intravenous infusion of MSCs	4.1–7.1 years
Lee et al,[20] 2012 South Korea	Randomized, Double-Blind, Placebo-Controlled Trial	1 year	33 (16 MSC, 17 Placebo)	16 (MSA-C)	MSC: 55.8 ±6.1; Placebo: 56.1 ± 8.9	Second consensus statement (Gilman et al, 2008)[9]	Autologous BM-MSCs	Intra-arterial and Intravenous injections administration	1.9–4.3 years

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Table 2 Final Outcomes and Adverse Effects of Included Studies

Study (Year), Country	Dosage	Total UMSARS		UMSARS Part I		UMSARS Part II		ADVERSE EVENT
		Baseline (Mean ± SD)	Last Follow-Up (Mean ± SD)	Baseline (Mean ± SD)	Last Follow-Up (Mean ± SD)	Baseline (Mean ± SD)	Last Follow-Up (Mean ± SD)	
Chung et al,[23] 2021 South Korea	Low dose: 3.0×10^5 cells/kg	43†	55.3 ± 5.1^	20†	26.7 ±3.1^	20.3†	25.3 ± 2.4^	(N = 13), 1 BBB breakdown, 1 photopsia, 1 constipation, 1 abdominal distension, 1 increased blood pressure, 1 weight increase, 1 herpes zoster, 1 urinary tract infection, 2 injury, poisoning, and procedural, disorders, 1 anxiety, 1 depression.
	Medium dose: 6.0×10^5 cells/kg	35.7†	40.8 ± 3.6^	16.3†	20.2 ±2.2^	18.3†	18.3 ± 1.7^	No adverse events were reported
	High dose: 9.0×10^5 cells/kg	39.7†		18.7†		18.7†		(N = 2), 1 headache, and 1 constipation.
Singer et al,[24] 2019 USA	Single dose of 100×10^5 cells	31.4 ± 7.7	37.4***	14.0 ± 3.0	17.2***	17.5 ± 5.4	20.4***	(N=50) 7 related to the underlying disease, 9 to spinal taps, and 26 to the MSC product, and 8 nonspecific AEs attributed as probably or not related to study procedures.
	2 doses of 500×10^5 1 month (±4 days) apart		35***		16***		18.8***	
	2 doses of 1000×10^5 cells each 1 month apart		36.2 ± 8		17.1±3.2		19.4 ±5.5	
	Historical control group		48.2***		21.3 ***		27.1 ***	
Tsai et al,[25] 2017 Taiwan	10×10^5 cells/kg	NR						(N=1) worsening of preexisting rigidity and depression
Yu et al,[26] 2021 China	5 mL of hUCB-MNC suspension (2000–3000) × 10^5 cells/mL	NR		23.5 ± 4.7	19.4 ± 4.1	30.2 ± 5.6	24.3 ± 5.1	(N=4) 3 mild headache, 1 slight fever
Gong et al,[27] 2022 China	5 mL of hUCB-MNC suspension (2000–3000) × 10^5 cells/mL	42.6 ± 8.0	35.1 ± 18.2	NR		19.1 ± 5.2	16.4 ± 10.4	(N=2) 1 fever, 1 pain and discomfort at the puncture site.
Lee et al,[21] 2008 South Korea	1600×10^5 cells	NR	−5.4 ± 10**	NR				(N = 13), 6 fever, 7 small spotty lesions without neurological deficits in diffusion-weighted MRI (2 patients exhibited multiple spotty lesions and 5 patients had a single lesion). No delayed adverse effects were related to MSC infusion during the 12-month follow-up.
	Control Group		12.1± 15.5**					NR

Lee et al,[20] 2012 South Korea	Single intra-arterial injection (400 × 10^5 cells) Followed by 3 intravenous injections (400 × 10^5 cells) at 1, 2, 3 months	40.1 ± 8.5	49.6 ± 10.1*	NR	19.6 ± 4.1	24.6 ± 4.6*	(N = 14) 2 skin rash, 4 acute cerebral ischemic lesions, 1 transient dystonic attack, 3 syncope, 1 general myalgia, 1 pathological laughing or crying, 2 urinary tract infections, 1 hypertension, 2 leg edema, 1 chest discomfort, 1 pain on buttock, 1 dysuria, 1 contusion, 1 scarlet spot on neck, 1 hypoxic brain damage, 1 laceration.
	Placebo group	39.5 ± 6.2	55.8 ± 7.7 *		17.7 ± 2.9	26.2 ± 3.7*	(N = 17) 2 skin rash, 6 acute cerebral ischemic lesions, 0 transient dystonic attack, 5 syncope, 2 general myalgia, 1 personality change, 1 delusion, 1 pathological laughing or crying, 2 nausea, 1 vomiting, 1 headache, 2 pain in both legs, 2 urinary tract infections, 2 hypertension, 1 chilling sensation, 1 itching sensation, 1 pneumonia.

Notes: Values are presented as mean ± standard deviation (SD) unless otherwise specified. Cell doses from all studies were standardized and reported as $\times 10^5$ cells to allow comparison across trials. * Final mean and SD are calculated from reported baseline and change values. **Data reported in the original study as mean change with standard error (SE) rather than absolute baseline and follow-up values. ***Final mean from baseline and change; SD not calculated due to lack of repeated-measures data. ^p > 0.05 for the comparison between baseline and last follow-up. † Mean value calculated from reported data, as baseline means were not explicitly provided, and standard deviations were not reported in the original study.

Abbreviations: NR, Not Reported; BBB, Blood–Brain Barrier; UMSARS, Unified Multiple System Atrophy Rating Scale; hUCB-MNC, Human umbilical cord blood–derived mononuclear cells; AE, Adverse events.

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derived MSCs: Singer et al 2019,[24] Tsai et al[25] The remaining two studies employed hUCB-MNCs: Yu et al 2021,[26] and Gong et al2022,[27]

Across the seven included studies, adverse events were generally mild and procedure related. In Chung et al, one patient in the low-dose group developed leptomeningeal enhancement after intra-arterial MSC infusion, while no ischemic lesions were observed in the medium- or high-dose groups. In Singer et al, small spotty ischemic lesions occurred at a similar frequency in both MSC-treated and placebo groups, and MRI changes involving thickened or mildly enhancing cauda equina roots were observed in all patients in the medium- and high-dose tiers, with only half reporting mild back discomfort; no neurological deficits or serious infusion-related events were noted. Tsai et al reported 10 adverse events over 12 months, none severe or related to allogeneic MSC infusion. In contrast, studies using hUCB-MNCs observed fewer and generally milder adverse events: Yu et al reported three mild headaches and one transient fever among four participants, all resolving within hours to days, while Gong et al[27] reported one transient fever and one puncture-site discomfort among two participants, also resolving without complications. In Lee et al[21] small spotty ischemic lesions occurred after intra-arterial infusion without neurological deficits. Lee et al,[20] ischemic lesions were observed at similar frequency in MSC and placebo groups, and no serious immediate or delayed adverse effects were attributed to MSCs during follow-up.

Efficacy Outcomes

UMSARS progression outcomes varied across the studies. In Singer et al (2019), the rate of UMSARS total score progression was markedly lower in MSC-treated patients compared to a matched historical control group (0.40 ± 0.59 vs 1.44 ± 1.42 points/month, $p = 0.004$) with an apparent dose-dependent effect. Yu et al (2021) reported a statistically significant decrease in total UMSARS from a baseline of 23.50 ± 4.72 to 19.40 ± 4.11 at follow-up and in Part II from 30.15 ± 5.63 to 24.25 ± 5.05. In Chung et al (2021), compared to the low-dose group, the medium- and high-dose groups exhibited a slower rate of increase in UMSARS Part II (group × time, $p = 0.131$) and total scores (group × time, $p = 0.096$); these trends did not reach statistical significance due to the small number of patients in each group. Gong et al (2022) reported a statistically significant improvement at the timepoint of best effect (3–6 months post-treatment), with the total UMSARS score decreasing from a baseline of 42.57 ± 7.96 to 25.71 ± 11.87 ($p = 0.001$). However, scores subsequently increased from this nadir to a last follow-up value of 35.14 ± 18.21. Tsai et al (2017) did not provide numerical UMSARS scores.

In Lee et al (2012), the MSC group demonstrated a smaller increase in total and Part II UMSARS scores compared with placebo ($p = 0.047$ and $p = 0.008$, respectively), with the effect more pronounced in Part II, which reflects objective neurological assessments. Similarly, Lee et al (2008) reported significantly greater improvements in UMSARS scores in MSC-treated patients compared with controls at all visits throughout the 12-month study period. Studies using hUCB-MNCs, including Yu et al (2021) and Gong et al (2022), also showed significant reductions in UMSARS scores; for instance, Yu et al (2021) observed a decrease in Part II scores from 30.15 ± 5.63 to 24.25 ± 5.05.

Discussion

Overview of Principal Findings

This systematic review demonstrates that MSC therapy for MSA is associated with a favorable safety profile and signals of potential clinical efficacy, particularly when administered in early disease stages and within defined post-treatment windows. Across the included studies, patients with multiple system atrophy were enrolled at defined disease stages, with baseline UMSARS scores typically ranging from 30 to 65, consistent with early to moderate disease severity. Across all seven included studies, reported benefits were generally modest, time-dependent, and heterogeneous, reflecting differences in dosing strategies, disease stage at enrollment, routes of administration, and study design.[20,21,23–27]

Overall, the safety profile of MSC therapy across early-phase studies appears acceptable, particularly when considered in the context of the rapid and disabling progression of MSA. Adverse events were predominantly mild and procedure-related, with no consistent evidence of serious MSC-related toxicity. Ischemic lesions were reported in several studies using intra-arterial delivery; notably, Lee et al (2012) observed similar frequencies of such lesions in both MSC

and placebo groups, supporting a procedure-related rather than cell-related mechanism. These lesions were typically small, asymptomatic, and without long-term neurological sequelae.[20]

In intra-arterial and intrathecal studies (Chung et al, Singer et al, Lee et al 2008 and 2012), ischemic lesions were consistently attributed to angiographic catheterization, contrast exposure, or procedural manipulation, rather than direct MSC toxicity. Intrathecal administration in Singer et al was associated with reactive MRI changes of the cauda equina and mild, self-limited back discomfort in approximately half of participants, without neurological deficits or serious infusion-related events.[24] Overall, intrathecal delivery appeared safe within defined dosing thresholds, with MRI evidence of mild reactive changes but minimal clinical symptoms.[20,21,23,24] Minor adverse events across studies, including transient fever, headache, and puncture-site discomfort, resolved spontaneously without complications. Additionally, Tsai et al reported no severe or treatment-related adverse events following allogeneic MSC administration over 12 months of follow-up.[25]

Only one potential MSC-related adverse event was reported, leptomeningeal enhancement in a low-dose patient in Chung et al This finding may reflect increased blood–brain barrier permeability facilitating cellular migration. Importantly, it was not observed in the medium- or high-dose cohorts, suggesting that adverse effects are not clearly dose-dependent.[23]

Across efficacy outcomes, several studies reported slowing of disease progression, although effect sizes varied. Singer et al demonstrated substantially slower monthly UMSARS progression in MSC-treated patients compared with historical controls.[24] Chung et al reported non-significant trends toward slower progression in UMSARS Part II and total scores in medium- and high-dose groups[23] Chung et al, Singer et al, Lee et al (2012), and Gong et al, a consistent trend toward slower disease progression was observed, with medium- or high-dose MSC groups demonstrating relatively favorable UMSARS Part II and total scores compared with placebo or historical controls.[20,23,24,27] Yu et al reported post-treatment improvement in UMSARS total and Part II scores, while Gong et al described marked improvement at 3 to 6 months followed by partial attenuation, suggesting a time-limited neuroprotective effect.[26,27] Consistent with this temporal pattern, Lee et al (2012) demonstrated that the treatment effect became statistically apparent around day 240 and declined thereafter, implying that repeated MSC administration may be required to sustain therapeutic benefit.[20] Collectively, these findings support the hypothesis that MSCs exert short- to medium-term neuroprotective effects, potentially mediated by neurotrophic and anti-inflammatory mechanisms. Furthermore, both Chung et al and Gong et al identified stronger responses among patients with earlier disease stages, lower baseline UMSARS scores, and presumed preserved blood–brain barrier integrity, facilitating more efficient MSC homing to affected neural tissue (.[23,27] These observations support the concept that MSC therapy may be most effective when administered prior to advanced neurodegeneration, consistent with preclinical and mechanistic evidence.

Comparison across cellular sources further illustrates the heterogeneity of treatment responses. In the hUCB-MNC study by Gong et al (2022), total UMSARS scores decreased by 17.5% from baseline, suggesting possible symptomatic or neuroprotective effects. Conversely, adipose-derived autologous MSCs (Singer et al, 2019) were associated with a 15.3% increase from baseline in the treatment group, though this represented substantially slower progression than the 53.5% worsening observed in historical controls. Bone marrow-derived autologous MSCs demonstrated variable outcomes: Chung et al (2021) reported near-stabilization with only a 2.9% increase from baseline, while Lee et al (2012) showed a 23.7% increase in MSC-treated patients compared to 41.3% worsening in placebo controls. These divergent trajectories likely reflect not only differences in cell source but also variations in disease stage at enrollment, route of administration, and follow-up duration, precluding direct head-to-head comparisons of cell type efficacy. Lee et al (2008), Yu et al (2021), and Tsai et al (2017) did not report total UMSARS scores and/or baselines for comparison.

Mechanistic Interpretation

The observed clinical effects are plausibly explained by several complementary biological mechanisms, including paracrine neurotrophic support (eg., BDNF, GDNF, VEGF release), immunomodulation leading to reduced glial activation and neuroinflammation, and activation of endogenous neural stem or progenitor cells, most evident in early treatment windows.[27] Enhanced MSC homing in early-stage disease, facilitated by preserved BBB permeability, may

further contribute to the observed efficacy. These mechanisms align with the temporal pattern of benefit peaking within 3–8 months and diminishing thereafter reported across multiple studies.[23]

Importantly, two of the included studies used hUCB-MNCs rather than purified MSC preparations. hUCB-MNCs represent a heterogeneous population of hematopoietic stem cells, immune cells, endothelial progenitor cells, and other mononuclear cell subsets and are therefore biologically distinct from culture-expanded MSC therapies.[28] The therapeutic effects of hUCB-MNC transplantation is thought to arise through partially different mechanisms, including modulation of immune responses, secretion of trophic and angiogenic factors, and stimulation of endogenous repair pathways.[28,29] Mononuclear cell populations within these preparations may contribute to neuroprotection by reducing neuroinflammation, enhancing microvascular perfusion, and promoting endogenous neural progenitor cell activity.[29,30] Given these biological differences, the mechanisms underlying clinical responses observed in studies using hUCB-MNCs may not be directly comparable to those of MSC-based therapies. Consequently, findings across these studies should be interpreted cautiously, and the inclusion of both intervention types represents an additional source of therapeutic heterogeneity within the current evidence base.

Methodological Limitations

All included studies were limited by small sample sizes, restricting statistical power and precluding robust subgroup analyses. Although dose-response trends were observed in Chung et al and Singer et al, these could not be confirmed statistically.[23,24] Several studies employed short follow-up durations, limiting the ability to capture the full natural trajectory of MSA.[23] The attenuation of treatment effect after day 240 in Lee et al (2012) highlights the need for longer-term follow-up and evaluation of repeated dosing strategies.[20] In Lee et al (2008), baseline total UMSARS scores were not separately reported; only mean change values with standard errors and final follow-up data were available, limiting direct baseline comparisons.[21]

Substantial heterogeneity in intervention protocols (including administration routes (intra-arterial, intrathecal, and intravenous), dosing regimens, number of injections, and sources of MSCs) complicated cross-study comparisons. Follow-up durations and study designs also varied considerably, and preferential enrollment of early-stage patients may have introduced selection bias, potentially overestimating treatment effects. In addition, outcome reporting was inconsistent across studies, with some presenting results as mean change with standard error, others lacking standard deviations, and some outcomes not reported numerically. As a result, there was insufficient consistent numerical data to permit reliable quantitative synthesis, and a formal meta-analysis was therefore not performed.

Only two studies were randomized controlled trials. Lee et al (2008) was judged to have a high risk of bias, primarily due to deviations from intended interventions and lack of blinded outcome assessment, while Lee et al (2012) had overall "some concerns" related to unblinded intra-arterial procedures, missing secondary outcome data, and the subjectivity of UMSARS.[20,21] The remaining non-randomized studies were assessed using ROBINS-I and demonstrated serious or critical risk of confounding, as the absence of concurrent randomized controls precluded differentiation of treatment effects from natural disease progression, regression to the mean, concomitant therapies, or placebo and expectation effects.[20,21] Finally, assessment of publication bias was not feasible, as the number of included studies was fewer than 10, precluding reliable funnel plot analysis or statistical testing.

Implications for Future Research

Future research in MSC based therapies for MSA should prioritize adequately powered Phase II and III randomized controlled trials to establish efficacy beyond placebo effects and natural disease variability. Standardization of MSC manufacturing, including cell source, culture conditions, dosing regimens, and delivery methods, is essential to enable reliable comparisons and identify optimal therapeutic strategies. Trials should focus on early-stage MSA, when neuroprotective interventions may be most effective, and include extended follow-up (≥24 months) to assess the impact of repeat MSC dosing, potentially at 6–8 months after initial administration. Integration of objective biomarkers, such as cerebrospinal fluid inflammatory markers, neurofilament light chain, and advanced neuroimaging, will be critical for mechanistic validation. Additionally, head-to-head comparisons of intrathecal versus intra-arterial delivery are warranted to optimize CNS bioavailability while minimizing procedural risk.

Conclusion

Mesenchymal stem cell (MSC) therapy represents a promising investigational approach for multiple system atrophy, a condition currently lacking disease-modifying treatments. Evidence from early clinical studies suggests that MSC administration may temporarily slow neurological deterioration, particularly when applied during earlier stages of the disease.

However, interpretation of these findings remains limited by small sample sizes, heterogeneity in treatment protocols, and methodological constraints across studies. Consequently, the current evidence is insufficient to establish definitive clinical efficacy. Future research should focus on adequately powered randomized controlled trials with standardized MSC preparation, optimized delivery strategies, longer follow-up periods, and incorporation of objective biomarkers to clarify therapeutic mechanisms and determine whether sustained disease modification can be achieved.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Noon Elimam, Shams Samih Albarari, Yara Shaalan, Shazaa Mahmoud Elsheikh, Ainaa A Alzamari, Nourhan Elmekkawi, Rahaf Mogahed, and Razan H Alghuweiri declare that they have no competing interests.

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