Safety of intravenous mesenchymal stem cell therapy: a meta-analysis of randomized controlled trials

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Abstract

Previous preclinical research and human trials have demonstrated that intravenous cell administration is a safe and successful treatment method for improving the quality of life in patients with a variety of illnesses. The purpose of this study was to evaluate the safety profile of mesenchymal stem cells administered intravenously. We explored PubMed, ScienceDirect, Web of Science, ClinicalTrials.gov, and the Cochrane Library for published research from their creation through December 2024, following PRISMA 2020 guidelines. Two researchers independently assessed the study's inclusion and exclusion criteria, data extraction, and risk of bias assessment. Our meta-analysis includes 36 studies on mesenchymal stem cell therapy by intravenous method. The safety profile of mesenchymal stem cell therapy was evaluated across various adverse event categories using meta-analyses of randomized controlled trials. Twenty-two randomized controlled trials assessed general disorders and administration site conditions, showing no statistically significant increase in adverse event risk in the mesenchymal stem cell group compared to controls (log odds ratio [OR]: 0.29, 95% confidence interval [CI]: –0.15 to 0.73, P = 0.201). Similarly, analyses of musculoskeletal/connective tissue disorders (four randomized controlled trials, log OR: –0.26, 95% CI: –1.81 to 1.29, P = 0.742) and renal/urinary disorders (five randomized controlled trials, log OR: 0.30, 95% CI: –0.59 to 1.19, P = 0.511) revealed non-significant results. Conversely, a statistically significant increase in nervous system disorders was observed (thirteen randomized controlled trials, log OR: 0.54, 95% CI: –0.05 to 1.13, P = 0.072). Infection-related adverse events, evaluated in twenty randomized controlled trials, showed a slight but significant elevated risk in the mesenchymal stem cell group (log OR: –0.32, 95% CI: –0.61 to-0.02, P = 0.036). Gastrointestinal disorders (five randomized controlled trials, log OR: 0.00, 95% CI: –0.33 to 0.33, P = 0.988), respiratory/thoracic disorders (eight randomized controlled trials, log OR: –0.12, 95% CI: –0.67 to 0.42, P = 0.652), and immune system disorders (three randomized controlled trials, log OR: –0.97, 95% CI: –2.42 to 0.49, P = 0.193) did not show significant risk increases. Injury and procedural complications (five randomized controlled trials) also demonstrated a non-significant trend. Heterogeneity was minimal across all analyses, and no substantial publication bias or influential studies were identified. While most findings support the safety of mesenchymal stem cell therapies, significant results for nervous system and infection-related adverse events warrant further investigation. We conclude that intravenous delivery of mesenchymal stem cells is safe for many conditions. However, large-scale randomized controlled trials are required to confirm the findings.

Key Words: clinical trials; intravenous; mesenchymal stem cell therapy; meta-analysis; regenerative medicine; stem cell therapy

Introduction

Mesenchymal stromal cells (MSCs) are a diverse group of cells that can be obtained from various sources, including bone marrow, adipose tissue, the umbilical cord, and the placenta. These cells were first identified by Friedenstein in 1974.[1] While commonly referred to as "adult stem cells," MSCs possess limited cellular differentiation potential. Instead, preclinical studies indicate that their therapeutic benefits primarily arise from their immunomodulatory and paracrine properties.[2] MSCs have the ability to migrate to sites of inflammation and secrete bioactive molecules, making them potentially valuable in the treatment of proinflammatory conditions. Recently, a growing body of literature shows the great therapeutic effects of MSCs in many diseases and their clinical applicability in refractory diseases such as cerebral palsy,[3] spinal cord injury,[4,5] systemic lupus erythematosus,[6] acute myocardial infarction,[7] liver cirrhosis,[8] hematological malignancies, and graft versus host diseases.

The application of MSCs in the treatment of pulmonary diseases like chronic obstructive pulmonary disease and critical illnesses such as acute respiratory distress syndrome has garnered attention. However, the successful translation of MSCs into viable clinical therapy is hindered by significant safety concerns. These concerns encompass various aspects, including the potential for neoplastic transformation due to the proliferative nature of MSCs and an increased susceptibility to infections resulting from their immunomodulatory effects. Additionally, there is a risk of cell embolism, zoonotic infections associated with cell culture reagents, and the potential for acute or chronic immunogenic reactions elicited by the cells themselves. Addressing these safety concerns is crucial for the successful implementation of MSC-based therapies in clinical settings. The predominant methods for MSC transplantation, apart from tissue engineering-based approaches, include intravenous or intra-arterial infusion, as well as direct intra-tissue injection.[9] The most convenient mode of MSC transplantation is the intravenous route. In most cases, MSCs were primarily distributed to the lungs. Although intravenous injection is convenient, its pulmonary distribution characteristics may pose a risk of embolism. The distributed MSCs were also found in the spleen, liver, bone marrow, thymus, kidney, and skin.

In various preclinical models and preliminary clinical studies, systemic intravenous delivery of MSCs has demonstrated clinical safety and effectiveness. Interestingly, this safety and efficacy appears to be consistent regardless of the cell source's autologous or allogeneic nature. Notably, positive clinical outcomes seem to occur independently of long-term engraftment of

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MSCs at the specific target site, suggesting that interactions with non-target tissues, such as the spleen and liver, may play a significant role.[9]

We performed this meta-analysis to identify all treatment-related adverse events (AEs) in randomized control trials concerning MSC administration intravenously and explore the safety of MSCs in clinical utilization.

Methods

Search strategy

This meta-analysis was limited to published randomized control clinical trials assessing the safety of MSC administration intravenously and was performed by searching numerous directories for eligible studies, including the Cochrane Library, PubMed, ScienceDirect, Web of Science, and ClinicalTrials.gov (from inception to 31st December 2024). We used a combination of keywords such as: ((MSC [title/abstract]) OR (mesenchymal stem cell [title/abstract]) OR (Wharton's jelly [title/abstract])) AND ((safety [title/abstract]) OR (side event [title/abstract]) OR (side effect [title/abstract]) OR (adverse event [title/abstract]) OR (adverse effect [title/abstract])). The reference lists of the included articles were also browsed to identify potential studies. The exploration was strictly limited to published studies involving human subjects and written in English; unpublished studies were excluded. Studies published in languages other than English were excluded due to feasibility constraints, including the lack of accessible translations. We acknowledge this as a potential source of language bias.

Eligibility criteria

The selection process adhered closely to the participants, interventions, comparison, outcome, and study (PICOS) principles, which are outlined in **Table 1**.

Literature selection and data extraction

Two researchers (UEH and SS) worked independently on the comprehensive literature screening and data retrieval. In cases where discrepancies arose during the study selection process, a third reviewer (NK) was consulted. We retrieved the 12 characteristics entries from the selected studies including the first author's name, year of publication, sample size, disease/condition to be treated, study type, phase of the study, mean patient age in years, mean dose of injected cells, treatment (route and source), location(s) of trial, and timeframe of follow-up duration in months (**Table 2**).

Adverse event definition

Prerequisites focused on the main endpoint outcomes for evaluating safety: referencing AEs. An AE is considered a negative medical event that happens in a patient; its association or non-association with the intravenous administration of MSCs will not be discussed. Serious AEs refer to those causing death, immediate life-threatening conditions, hospitalization and/or prolongation of hospitalization, or permanent disability or incapacity. Complications due to intravenous MSC treatments were considered AEs in this study. AEs were reported both in terms of their frequency and severity according to the CTCAE version 5.0. The occurrence and documentation of AEs were also assessed based on the CONSORT guidelines for harm reporting to include systematic coverage of expected AEs regarding their type, frequency, and follow-up under the methods section.

Table 1 | **Inclusion and exclusion criteria**

Item	Inclusion criteria	Exclusion criteria
Intervention/ treatment	Using MSCs as treatment via intravenous route, regardless of sources of MSCs (e.g. from the adipose, bone marrow, and umbilical cord)	The interventions utilized various cell types such as NSCs, ESCs, olfactory neurons, Schwann cells, human induced pluripotent stem cells, and stem cells from body fluids (e.g., saliva, urine, serum, and tears), while MSCs were employed as the specific treatment
Population	Populations including diseased people	healthy population
Comparison	Comparison of MSCs group with the placebo (control group)	Studies predicting the role of MSCs in diseased populations only
Outcome/ results	(1) Any side events associated with MSC treatment; (2) one side event reported by more than one study; (3) regardless of the efficacy of MSC therapy for any diseases	Studies with no adverse events reported
Study type	RCT only	Case reports; single-arm study; retrospective controlled study; cross-controlled study; n-RCTs

ESC: Embryonic stem cells; n-RCTs: non-randomized control trials; NSCs: neural stem cells; RCT: randomized control trial.

Statistical analysis

This meta-analysis evaluated the association between intrathecal administration of MSCs and an increased probability of AEs, categorized using the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).[10] The analysis was conducted using Jamovi (version 2.3),[11] with results presented through forest plots. A random-effects model employing the DerSimonian-Laird method, adjusted for zero-count cells, was utilized to analyze the data. Dichotomous outcomes were summarized as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Heterogeneity among randomized controlled trials (RCTs) was assessed using the I^2 statistic, with values of 25%, 50%, and 75%–100% indicating low, moderate, and high heterogeneity, respectively. A random-effects model was applied when substantial heterogeneity was detected ($I^2 > 50\%$ and $P < 0.10$), as this accounts for variability across studies. In contrast, a fixed-effects model was used when heterogeneity was low ($I^2 \leq 50\%$) and the assumption of a common effect size across studies was reasonable.[12] Heterogeneity was further evaluated using Cochrane's Q-test and I^2 statistics. Bias was assessed using funnel plots, Fail-Safe N analysis, Rank correlation, and Begg's and Egger's regression tests. The Risk of Bias (RoB) within the included studies was summarized graphically. This comprehensive approach ensured rigorous evaluation of the data, enhancing the reliability and validity of the findings.

Results

Search results

The search strategy identified 987 articles from selected databases and prior bibliographies. Following a review of the titles and abstracts, 780 studies were eliminated due to their lack of relevance in terms of purpose, goal, intervention, and/or measures. After a thorough evaluation of the remaining 207 papers, 169 were excluded. In total, 36 randomized clinical trials met the inclusion criteria and were embraced in the quantitative data analysis for the safety study (**Table 2**). The selection process of studies is often presented in a flow diagram, which may be visualized in **Figure 1**. This diagram provides an overview of the steps taken to identify, screen, and include studies in a systematic review or meta-analysis.

Meta-analysis of adverse events related to general disorders and administration site conditions

A meta-analysis of twenty-two RCTs evaluated AEs such as rehospitalization, chest pain, fatigue, fever, self-limiting fever (37–38°C), multi-organ failure, swelling at the injection site (19%), hematoma (12%), site mass (13%), pain (6%), puncture site, fever; 1–4 weeks, fever; 5–24 weeks, anorexia, surgical complication, general transient fever, chills, cryptogenic, anaphylaxis, pyrexia, and lower extremity edema (**Table 3**). Results did not demonstrate a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = 1.28, $P = 0.201$; average log odd ratio [OR] difference: 0.29; 95% CI: –0.15 to 0.73; **Figure 2**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes ($Q = 46.512$, $P = 0.092$, $\tau^2 = 0.3754$, $I^2 = 24.75\%$), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±3.197, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. A rank correlation test did not identify funnel plot asymmetry ($P = 0.182$), though this finding was not corroborated by the regression test ($P = 0.044$). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to musculoskeletal and connective tissue disorders

A meta-analysis of four RCTs[13-16] evaluated AEs, such as flank pain, musculoskeletal connective tissue, pain: myalgia (musculoskeletal) and back pain (**Table 3**). Results did not demonstrate a

Table 2 | **Study characteristics of randomized control trials**

Study	Country	Condition	Patient (*n*)	Intervention			Patients evaluated *n* (%male)		Age (yr)*		Dose (T)	Phase	Follow-up (mon)	NCT#
				Source	Route	Control	T	C	T	C				
Ning et al., 2008[38]	PRC	Hematological malignancy	30	Matched, allogenic	Central venous	Stem cell transplant alone	10 (90)	15 (87%)	36 ± 11	39 ± 12	3.4×10^5/kg	Early phase	36.6	NA
Hare et al., 2009[41]	USA	Acute MI	60	Unmatched allogeneic hMSCs	IV	vehicle solution, IV	34 (82)	19 (79%)	59 ± 12	55 ± 10	0.5, 1.6, and 5×10^6 cells/kg	I	6	NCT00114452
Lee et al., 2010[20]	ROK	Ischemic stroke	85	Autologous MSCs	IV	alone	16 (50)	36 (72%)	64 ± 12	65 ± 15	5×10^7	I, II	60	NA
Zhang et al., 2012[31]	PRC	Decompensated liver cirrhosis	45	Allogenic UCMSCs	IV	Saline	26	14	48 (25–64)	47 (29–64)	0.5×10^6/kg	I, II	12	NCT0120492
Shi et al., 2012[29]	China	ACLF	43	Allogenic UCMSCs	IV	Saline	20 (83.3)	15 (78.9%)	24–59	26–62	0.5×10^6/kg	I, II	12	NCT01218464
Weiss et al., 2013[25]	USA	COPD	62	Non-HLA matched allogeneic MSCs (Prochymal)	IV	Vehicle	18 (60)	18 (56)	68.1	64.1	1×10^8 cells	I	24	NCT00683722
Zheng et al., 2014[43]	China	ARDS	12	Allogeneic adipose-derived MSC	IV	Placebo	6 (100)	5 (83.3)	66.7 ± 20.4	69.8 ± 9.1	1×10^6 cells/kg	I	1	NCT01902082
Lublin et al., 2014[21]	USA (6 sites)	MS	16	Human placental-derived MSCs	IV	Placebo	2 (33; 1(17)	2 (50)	52.5 (41–5); 47.5 (36–56)	47.5 (40–52)	1.5×10^8 cells; 6×10^8 cells	Ib	12	NA
Skyler et al., 2015[36]	Canada (2)	T2DM		Allogenic MPCs	IV	placebo	10 (66.7); 9 (60.0); 9 (60.0)	12 (75.0)	57.7 ± 8.2; 55.3 ± 11.4; 57.2 ± 6.6	58.7 ± 7.3*	0.3×10^6/kg; 1.0×10^6/kg; 2.0×10^6/kg	Ib-CHECK	24	NCT01576328
Zhang et al., 2017[30]	USA (18 sites)	ITBL	82	Allogenic UCMSCs	IV	Placebo (saline)	1 /11	12/58	47.3 ± 10.1	42.8 ± 11.5	1.0×10^6/kg ($n = 6$)	I	24	NCT02223897
Dhere et al., 2016[32]	China	Refractory Crohn's disease	12	Autologous BM-MSCs	IV	Placebo	6 (50)	No data shown	18–52	18–52	2.0×10^6/kg; 5.0×10^6/kg; 10.0×10^6/kg	I	2.25	NCT01659762
Álvaro-Gracia et al., 2017[44]	USA	Refractory rheumatoid arthritis	53	Allogenic AD-MSCs	IV	Placebo	46	7	50.33–57.40	58.43	1, 2, 4 million per kg	phase Ib/IIa	24 weeks	NCT01663116
Tompkins et al., 2017[15]	Spain	Aging frailty	30	AllogeniC	IV	Placebo	20 (60)	10 (60%)	75.0 ± 7.4; 76.3 ± 8.4	75.3 ± 6.8	All-100 M/kg; Allo-200 M/kg	I/II	6	NCT02065245
Lin et al., 2017[37]	Florida, USA	ACLF	110	human MSCs	IV	Placebo	51 (91.1)	53 (98.2%)	40.0 ± 9.9	42.8 ± 8.4	10×10^5 cells/kg	N/A	6	NCT01322906
Bartolucci et al., 2017[39]	China	Heart Failure	30	Allogenic BM-MSCs	IV	Placebo	12 (80.0)	14 (93.3)	57.33 ± 10.05	57.20 ± 11.64	1×10^6 UC-MSCs/kg of body weight	I/II	12	NCT01739777
Huang et al., 2018[33]	Chile	CP	54	Allogenic UC-MSCs	IV	Normal saline	27 (81.5)	21 (77.8%)	7.3 ± 0.483	7.5 ± 0.443	5×10^7 cells	N/A	24	NCT01988584
Fernández et al., 2018[45]	China	MS	34	Allogenic hUCB-MSCs	IV	Placebo	Low doe: 10 (40) High dose: 9 (22)	3 (27)	44.8 ± 8.0; 47.8 ± 9.7	46.3 ± 8.9	1×10^6 cells/kg; 4×10^6 cells/kg	I/II	12	NCT01056471
Erpicum et al., 2019[27]	Spain	KTR	20	Autologous AD-MSCs	IV	Placebo	10 (70)	10 (40%)	63 (54–67)	64 (51.5–68.7)	–2.4 × 10^6/kg	I-II	12	NCT01429038
Averyanov et al., 2020[17]	Russia	IPF	20	Third- party BM-MSCs	IV	Placebo	10 (50)	10 (60)	59.4 ± 11.5	62.5 ± 6.4	4 doses (1.6×10^9)	I/II	12	NCT02594839
Jaillard et al., 2020[34]	France	Subacute Ischemic Stroke	31	Allogenic BM-MSCs	IV	Placebo	16 (68.8)	15 (73.3)	55 (46–58) IQ*	53 (45–63) IQR*	Low dose (1–10): 100 M; High dose (11–20): 300 M	I/II	24	NCT 00875654
Gu et al., 2020[40]	China	CP	39	Autologous BM-MSCs	IV	Placebo	19 (70)	20 (70)	3.830 ± 0.459	4.755 ± 0.644	$4.5–5.5 \times 10^7$		12	ChiCTR1800016554
Dawson et al., 2020[18]	USA	ASD	180	Autologous and allogenic hUCB	IV	Placebo	Ato: 56 (16.1); Allo: 63 (19.0)	61 (26.2)	Auto: 509 (2.74–7.99); Allo: 5.33 (2.39–8.00)	5.24 (2.31–8.1)	2.7×10^7 cells/kg; 3.8×10^7 cells/kg (adjusted > 2.5×10^7 cells/kg)	II	6	NCT02176317
Meng et al., 2020[35]	China	COVID-19	18	Allogenic UC-MSCs	IV	Placebo	9 (70)	9 (40)	34–64	33–67	3×10^7	I	7 days	NCT 04252118
Shi et al., 2012[29]	China	DLC	219	Allogenic UC-MSCs	IV	Placebo	108 (97.0)	111 (86.48)	21–65	19–65	$1–2 \times 10^6$ cells/kg	I/II	75	NCT01220492

Table 2 | **Continued**

Study	Country	Condition	Patient (*n*)	Intervention		Control	Patients evaluated *n* (%male)		Age (yr)*		Dose (T)	Phase	Follow-up (mon)	NCT#
				Source	Route		T	C	T	C				
Casiraghi et al., 2021[13]	Italy	Liver transplant recipients	20	Third-party BM-derived MSC	IV	Control	10 (70)	10 (60)	60.2 (57.8–65.9)	60.5 (53.8–66.6)	1–2 × 10^6 cells/kg	Ib/IIa	12	NCT02260375
Lan et al., 2021[19]	China	Severe aplastic anemia	18	Allogenic UC-MSCs	IV	Control	9 (30)	9 (50)	1–10	3–9	1 × 10^6/kg per week for 3 weeks	IV	48	NCT02218437
Lanzoni et al., 2021[46]		COVID-19 ARDS	24	Allogenic UC-MSCs	IV	Control	12 (50)	12 (80)	58.58 ± 15.93	58.8 ± 11.61	2 doses; 0 and 3rd day: 100 ± 20 × 10^6		1	NCT04355728
Law et al., 2021[42]	Malaysia	Subacute middle cerebral artery infarct	17	Autologous BM-MSCs	IV	Control	9	8	54.6	64.0	2 million/kg	Phase 2	12	NCT01461720
Karyana et al., 2022[14]	Indonesia	COVID-19	9	DW-MSCs	IV	Control	Low dose: 3 (100); High dose: 3 100)	3 (90)	32–38; 31–47	34–43	Low doe: 5.0 × 10^7 cells; High dose: 1.0 × 10^8	I	28 d	NCT04535856
Monsel et al., 2022[22]	France	COVID-19 associated ARDS	47	Allogenic UC-MSCs	IV	Control	21 (81)	24 (83.3)	64	63.2	3 doses: 10^6 cells/kg	Phase 2b	28 d	NCT04333368
Shi et al., 2022[24]	China	Severe COVID-19	100	Allogenic UC-MSCs	IV	Placebo	65 (56.92)	35 (54.29)	60.72	59.94	3 doses: 4.0 × 10^7 cells	Phase 2	12	NCT04288102
Zang et al., 2022[26]	China	T2DM	91	Allogenic UC-MSCs	IV	Placebo	45 (62.22)	46 (68.18)	50.00 ± 9.38	50.45 ± 8.03	3 doses: 1 × 10^6/kg	Phase 2	11.03	NCT02302599
Perico et al., 2023[23]	3 European sites	T2DM	16	allogeneic BM-MSCs	IV	Placebo	12	4	–	–	80 × 10^6, 160 × 10^6, 240 × 10^6 cells	Phase 1b/2a	18	NCT02585622
Ichikado et al., 2023[47]	29 centers in Japan	ARDS	30	allogeneic BM-MSCs	IV	standard group	20 (80)	10 (100)	69.2 ± 13.2	66.5 ± 10.8	9.0 × 10^8	Phase 2	28 d	NCT03807804
Zhu et al., 2024[16]	China	Aging frailty	30	hUC-MSCs	IV	Placebo	15 (33.33)	15 (46.67)	67.27 ± 5.23	69.27 ± 5.02	1 × 10^6/kg	Phase I/II	6 mon	NCT04314011
Laterre et al., 2024[48]	Belgium, France	Community-acquired bacterial pneumonia	83	Cx611	IV	Placebo	42	41	61.1 ± 11.2	63.4 ± 10.4	2 doses: 1.6 × 10^8 cells	Phase 1b/2a	3 mon	NCT03158727

*Data are expressed as the mean±SD. ACLF: Acute-chronic liver failure; ARDS: acute respiratory distress syndrome; ASD: autism spectrum disorder; C: control; COPD: Chronic obstructive pulmonary disorder; CP: cerebral palsy; DLC: decompensated liver cirrhosis; IPF: idiopathic pulmonary fibrosis; ITBL: Ischemic-type biliary lesions; IV: intravenous; KTR: kidney transplant recipients; MI: myocardial infarction; MS: multiple sclerosis; NA: not applicable; T: treatment; T2DM: type 2 diabetes mellitus.

Table 3 | **Frequency of adverse events in randomized controlled trials**

Source	Reported adverse events	Frequency in treatment group	Frequency in control group
General disorders and administration site conditions			
Hare et al., 2009 (a)[41]	Rehospitalization	9/34	7/19
Hare et al., 2009 (b)[41]	Chest pain, fatigue	14/34	13/19
Lee et al., 2010[20]	Fever	1/16	0/36
Shi et al., 2012[29]	Self-limiting fever (37–38°C)	2/24	0/19
Zheng et al., 2014[43]	Multi-organ failure	1/6	1/6
Lublin et al., 2014 (a)[21]	Swelling at injection site (19%), hematoma (12%), site mass (13%), pain (6%)	6/12	0/4
Lublin et al., 2014 (b)[21]	Puncture site	2/12	0/4
Skyler et al., 2015[36]	General	6/45	3/16
Zhang et al., 2016[49]	Self-limiting fever (37.6°C)	1/12	0/70
Lin et al., 2017 (a)[37]	Fever; 1–4 weeks	15/56	12/54
Lin et al., 2017 (b)[37]	Fever; 5–24 weeks	10/56	1/54
Lin et al., 2017 (c)[37]	General	14/56	24/54
Álvaro-Gracia et al., 2017[44]	Fever	9/46	0/7
Huang et al., 2018[33]	Mental; anorexia	3/20	1/18
Erpicum et al., 2019 (a)[27]	Surgical complication	0/10	1/10
Erpicum et al., 2019 (b)[27]	General	3/10	1/10
Averyanov et al., 2020 (a)[50]	Transient fever	4/10	1/1
Averyanov et al., 2020 (b)[50]	Chills	2/10	0/10
Jaillard et al., 2020[34]	Fever; cryptogenic	0/16	1/15
Gu et al., 2020[40]	Fever	7/19	4/20
Meng et al., 2020 (a)[35]	Transient fever; no more than 38°C	5/9	2/9
Meng et al., 2020 (b)[35]	Fatigue	4/9	5/9
Shi et al., 2021[51]	self-limiting fever 37–38°C	7/108	0/111

Table 3 | **Continued**

Source	Reported adverse events	Frequency in treatment group	Frequency in control group
Lan et al., 2021 (a)[19]	Anaphylaxis (including drug fever)	4/9	0/9
Lan et al., 2021 (b)[19]	Fatigue	0/9	0/9
Monsel et al., 2022 (a)[22]	Fever 38.2°C	0/21	1/24
Monsel et al., 2022 (b)[22]	Fever	0/21	1/24
Monsel et al., 2022 (c)[22]	Fever 39.1°C	1/21	0/24
Monsel et al., 2022 (d)[22]	Fever 39.5°C	1/21	0/24
Zang et al., 2022[26]	Chest pain	2/12	0/4
Perico et al., 2023 (a)[23]	Fever of unknown origin	0/12	1/4
Perico et al., 2023 (b)[23]	Fatigue	1/12	0/4
Perico et al., 2023 (c)[23]	Pain (right heel)	0/12	1/4
Ichikado et al., 2023 (a)[47]	Pyrexia	6/20	0/10
Ichikado et al., 2023 (b)[47]	Chills	2/20	0/10
Zhu et al., 2024[16]	Lower extremity edema	0/15	1/15
Musculoskeletal and connective tissue disorders			
Tompkins et al., 2017[15]	Flank pain	1/20	0/10
Casiraghi et al., 2021[13]	Musculoskeletal and connective tissue	2/10	1/10
Karyana et al., 2022[14]	Pain: Myalgia (musculoskeletal)	0/6	1/3
Zhu et al., 2024[16]	Back pain	0/15	1/15
Nervous system disorder			
Lee et al, 2010[20]	Local complications	0/16	0/36
Weiss et al., 2013 (a)[25]	Dizziness	2/30	1/32
Weiss et al., 2013 (b)[25]	Nervous system dysfunction	6/30	7/32
Weiss et al., 2013 (c)[25]	Lethargy	2/30	0/32
Lublin et al., 2014[21]	Headache	3/12	0/4
Averyanov et al., 2020 (a)[50]	Headache	2/10	2/10
Averyanov et al., 2020 (b)[50]	Weakness	4/10	1/10
Dawson et al., 2020 (a)[18]	Concussion	1/56	0/61
Dawson et al., 2020 (b)[18]	Neuropsychiatric disorders associated with streptococcal infection	1/63	0/61
Casiraghi et al., 2021[13]	Nervous system	4/10	5/10
Lan et al., 2021[19]	Headache	0/9	0/9
Monsel et al., 2022[22]	Neurological	2/21	2/24
Shi et al., 2022 (a)[24]	Dizziness	2/65	0/35
Shi et al., 2022 (b)[24]	Anemia	3/65	0/35
Zang et al, 2022[26]	Cerebral infarction	1/45	0/46
Perico et al., 2023[23]	Headache	1/12	0/4
Ichikado et al., 2023[47]	Anemia	5/20	0/10
Zhu et al., 2024[16]	Dizziness	1/15	0/15
Infections and infestations			
Ning et al., 2008[38]	Infection (early/mid-phase)	4/10	5/15
Hare et al., 2009[41]	Infection	11/34	5/19
Lee et al., 2010[20]	Pneumonia, urinary tract infection	3/16	9/36
Weiss et al., 2013 (a)[25]	Urinary tract infection	3/30	2/32
Weiss et al., 2013 (b)[25]	Upper respiratory tract infection	1/30	4/32
Weiss et al., 2013 (c)[25]	Skin infections	0/30	2/32
Zheng et al., 2014[43]	Sepsis	0/6	1/6
Skyler et al., 2015 (a)[36]	Urinary tract infection	1/45	0/16
Skyler et al., 2015 (b)[36]	Upper respiratory tract infection	2/45	0/16
Skyler et al., 2015 (c)[36]	Fungal	1/45	0/16
Skyler et al., 2015 (d)[36]	Folliculitis	1/45	0/16
Tompkins et al., 2017[15]	Renal and urinary	1/20	0/10
Lin et al., 2017 (a)[37]	Urinary tract infection	1/56	0/54
Lin et al., 2017 (b)[37]	Bacterial peritonitis	13/56	20/54
Lin et al., 2017 (c)[37]	Bile tract infection	13/56	22/54
Lin et al., 2017 (d)[37]	Bacterial pneumonia	6/56	7/54
Lin et al., 2017 (e)[37]	Fungal pneumonia	0/56	2/54
Lin et al., 2017 (f)[37]	Digestive tract fungal infection	2/56	5/54
Lin et al., 2017 (g)[37]	Sepsis	1/56	1/54
Álvaro-Gracia et al., 2017[44]	Urinary tract infection	6/46	0/7
Huang et al., 2018[33]	Upper respiratory tract infection	9/20	8/18
Fernández et al., 2018 (a)[45]	Urinary	3/23	3/11
Fernández et al., 2018 (b)[45]	Respiratory	1/23	3/11
Erpicum et al., 2019 (a)[27]	CMV	3/10	0/10
Erpicum et al., 2019 (b)[27]	Polyoma BK viremia	3/10	4/10
Erpicum et al., 2019 (c)[27]	Pneumocystis pneumonia	1/10	0/10
Averyanov et al., 2020 (a)[50]	URTI	2/10	2/10
Averyanov et al., 2020 (b)[50]	LRTI	2/10	2/10
Jaillard et al., 2020 (a)[34]	UTI	3/16	2/15
Jaillard et al., 2020 (b)[34]	Pneumonia	2/16	3/15

Table 3 | **Continued**

Source	Reported adverse events	Frequency in treatment group	Frequency in control group
Gu et al., 2020[40]	URTI	10/19	14/20
Casiraghi et al., 2021[13]	Infections	4/10	1/10
Lan et al., 2021[19]	Infections	1/9	1/9
Law et al., 2021[42]	pneumonia	0/8	1/8
Karyana et al., 2022 (a)[14]	Right lobe pneumonia	1/6	0/3
Karyana et al., 2022 (b)[14]	Cutaneous candidiasis	0/6	1/3
Monsel et al., 2022 (a)[22]	Bacteremia related to cocci Gram+ bacteria	1/21	0/24
Monsel et al., 2022 (b)[22]	Healthcare-associated pneumonia	0/21	1/24
Monsel et al., 2022 (c)[22]	Lymphangitis	0/21	1/24
Monsel et al., 2022 (d)[22]	Right arm lymphangitis	0/21	1/24
Monsel et al., 2022 (e)[22]	Urinary	1/21	1/24
Shi et al., 2022 (a)[24]	Urinary tract infection	1/65	0/35
Shi et al., 2022 (b)[24]	Bacterial infection	1/65	0/35
Shi et al., 2022 (c)[24]	Pharyngitis	1/65	0/35
Renal & urinary disorders			
Weiss et al., 2013[25]	Glycosuria and hematuria (renal & urinary disorders)	3/30	4/32
Casiraghi et al., 2021[13]	Renal and urinary	5/10	4/10
Lan et al., 2021[19]	Renal failure	0/9	0/9
Law et al., 2021[42]	Acute Renal failure	2/8	1/8
Ichikado et al., 2023[47]	Renal	3/20	1/10
Monsel et al., 2022[22]	Acute renal failure	2/21	1/24
Immune system disorders			
Ning et al., 2008 (a)[38]	GVHD (acute)	1/10	8/15
Ning et al., 2008 (b)[38]	GVHD (chronic)	1/10	4/15
Hare et al., 2009[41]	Immune	2/34	0/19
Respiratory, thoracic, and mediastinal disorders			
Weiss et al., 2013 (a)[25]	Cough	3/30	2/32
Weiss et al., 2013 (b)[25]	Emphysema	0/30	2/32
Weiss et al., 2013 (c)[25]	Chronic obstructive pulmonary disorder	14/30	12/32
Averyanov et al., 2020[50]	Cough	2/10	2/10
Meng et al., 2020 (a)[35]	Cough	4/9	8/9
Meng et al., 2020 (b)[35]	Shortness of breath	1/9	5/9
Meng et al., 2020 (c)[35]	Severe hypoxemia	1/9	0/9
Casiraghi et al., 2021 (a)[13]	Respiratory, thoracic, mediastinal	1/10	0/10
Casiraghi et al., 2021 (b)[13]	Respiratory, thoracic and mediastinal	3/10	4/10
Monsel et al., 2022 (a)[22]	Respiratory	2/21	2/24
Monsel et al., 2022 (b)[22]	Pulmonary	1/21	0/24
Monsel et al., 2022 (c)[22]	Refractory acute respiratory distress syndrome and multiple organ failure	0/21	1/24
Monsel et al., 2022 (d)[22]	Oropharyngeal	1/21	0/24
Shi et al., 2022[24]	Cough	2/65	1/35
Perico et al., 2023[23]	Cough	2/12	1/4
Laterre et al., 2024[48]	Worsening respiratory conditions	1/42	3/41
Gastrointestinal disorders			
Hare et al., 2009[41]	Gastrointestinal and renal	9/34	4/19
Weiss et al., 2013[25]	Gastrointestinal	3/30	5/32
Zheng et al., 2014[43]	Diarrhea	1/6	1/6
Skyler et al., 2015[36]	Gastrointestinal viral	0/45	1/16
Tompkins et al., 2017[15]	Gastroenteritis	0/20	1/10
Lin et al., 2017 (a)[37]	Diarrhea; 1–4 weeks	7/56	7/54
Lin et al., 2017 (b)[37]	Diarrhea; 5–24 weeks	0/56	0/54
Lin et al., 2017 (c)[37]	Gastrointestinal; bleeding	1/56	3/54
Lin et al., 2017 (d)[37]	Gastrointestinal; bleeding	1/56	2/54
Álvaro-Gracia et al., 2017 (a)[44]	Nausea	5/46	0/7
Álvaro-Gracia et al., 2017 (b)[44]	Vomiting	3/46	0/7
Álvaro-Gracia et al., 2017 (c)[44]	Diarrhea	2/46	0/7
Huang et al., 2018 (a)[33]	Diarrhea	5/20	5/18
Huang et al., 2018 (b)[33]	Constipation	2/20	2/18
Erpicum et al., 2019[27]	Gastrointestinal symptoms	0/10	2/10
Averyanov et al., 2020[50]	Nausea	2/10	2/10
Gu et al., 2020 (a)[40]	Vomiting	5/19	3/20
Gu et al., 2020 (b)[40]	Constipation	1/19	3/20
Gu et al., 2020 (c)[40]	Diarrhea	6/19	9/20
Dawson et al., 2020[18]	Viral gastroenteritis, dehydration, aggression	0/119	3/61
Casiraghi et al., 2021 (a)[13]	Gastrointestinal	2/10	0/10
Casiraghi et al., 2021 (b)[13]	Gastrointestinal	6/10	5/10
Lan et al., 2021 (a)[19]	Nausea	0/9	0/9
Lan et al., 2021 (b)[19]	Diarrhea	0/9	0/9

Table 3 | **Continued**

Source	Reported adverse events	Frequency in treatment group	Frequency in control group
Monsel et al., 2022 (a)[22]	Vomiting	1/21	0/24
Monsel et al., 2022 (b)[22]	Diarrhea	0/21	1/24
Monsel et al., 2022 (c)[22]	Liquid diarrhea	1/21	0/24
Monsel et al., 2022 (d)[22]	Nausea and diarrhea	1/21	0/24
Monsel et al., 2022 (e)[22]	Pseudomonas aeruginosa-related ventilator-associated pneumonia	1/21	0/24
Shi et al., 2022 (a)[24]	Nausea	1/65	0/35
Shi et al., 2022 (b)[24]	Vomiting	1/65	0/35
Shi et al., 2022 (c)[24]	Diarrhea	4/65	0/35
Shi et al., 2022 (d)[24]	Abdominal distension	2/65	0/35
Shi et al., 2022 (e)[24]	Abdominal pain	1/65	0/35
Shi et al., 2022 (f)[24]	Functional gastrointestinal disorder	1/65	0/35
Perico et al., 2023 (a)[23]	Vomiting	1/12	0/4
Perico et al., 2023 (b)[23]	Diarrhea	3/12	0/4
Laterre et al., 2024 (a)[48]	constipation	9/42	9/41
Laterre et al., 2024 (b)[48]	Diarrhea	9/42	9/41
Injury, poisoning, and procedural complications			
Lee et al., 2010[20]	Local complications	0/16	0/36
Skyler et al., 2015[36]	Procedural complication, injury	2/45	2/16
Casiraghi et al., 2021[13]	Injury, procedural complications	2/10	2/10
Monsel et al., 2022[22]	Acute pulmonary embolism	0/21	1/24
Laterre et al., 2024	Pulmonary embolism	1/42	2/41
Cardiac disorders			
Ning et al., 2008[38]	Infusion toxicity	0/10	0/15
Lee et al, 2010 (a)[20]	Cardiac	1/16	2/36
Lee et al, 2010 (b)[20]	Arrhythmia	0/16	0/36
Weiss et al., 2013[25]	Congestive heart failure	5/30	6/32
Bartolucci et al., 2017 (a)[39]	Nonsustained ventricular tachycardia	7/15	7/15
Bartolucci et al., 2017 (b)[39]	Heart failure	1/15	3/15
Bartolucci et al., 2017 (c)[39]	Myocardial infarction	0/15	1/15
Erpicum et al., 2019 (a)[27]	Cardiac event	1/10	0/10
Erpicum et al., 2019 (b)[27]	Cardiac event	2/10	0/10
Casiraghi et al., 2021[13]	Cardiac	0/10	2/10
Lan et al., 2021 (a)[19]	Heart failure	0/9	0/9
Lan et al., 2021 (b)[19]	Arrythmia	0/9	0/9
Law et al., 2021[42]	Cardiovascular	2/8	2/8
Lanzoni et al., 2021[46]	Arrythmia (bradycardia)	1/12	1/12
Monsel et al., 2022[22]	Cardiac	2/21	0/24
Shi et al., 2022[24]	Cardiac failure	1/65	0/35
Hematological or oncological disorders			
Fernández et al., 2018[45]	Hematological disorder (anemia)	3/23	2/11
Monsel et al., 2022[22]	Hematological	1/21	2/24
Skin and subcutaneous tissue disorders			
Weiss et al., 2013[25]	Skin	0/30	2/32
Zheng et al., 2014[43]	Rash in chest area	1/6	0/6
Lin et al., 2017 (a)[37]	Rash; 1–4 weeks	5/56	3/54
Lin et al., 2017 (b)[37]	Rash; 5–24 weeks	3/56	4/54
Álvaro-Gracia et al., 2017[44]	Rash	2/46	0/7
Huang et al., 2018[33]	Urticaria	0/20	1/18
Erpicum et al., 2019[27]	Graft dysfunction	4/10	1/10
Averyanov et al., 2020[50]	Skin rash	0/10	1/10
Jaillard et al., 2020[34]	Foot skin	0/16	1/15
Meng et al., 2020[35]	Facial flushing	2/9	0/9
Casiraghi et al., 2021[13]	Skin and subcutaneous tissue	4/10	2/10
Karyana et al., 2022[14]	Rash	1/6	0/3
Shi et al., 2022[24]	Rash	1/65	0/35
Ichikado et al., 2023[47]	Skin exfoliation	2/20	0/10
Laterre et al., 2024[48]	Macular rash	0/42	1/41
Vascular disorders			
Lee et al, 2010 (a)[20]	Vascular disorders (recurrent stroke)	2/16	1/36
Lee et al, 2010 (b)[20]	Peripheral artery occlusive disease	1/16	0/36
Weiss et al., 2013[25]	Vascular disorders	5/30	4/32
Tompkins et al., 2017[15]	Vascular disorders	0/20	1/10
Erpicum et al., 2019[27]	Infantile hemangiomas	1/10	0/10
Casiraghi et al., 2021 (a)[13]	Vascular disorders	0/10	1/10
Casiraghi et al., 2021 (b)[13]	Vascular disorders	4/10	6/10
SAEs deaths			
Ning et al., 2008[38]	Death	6/10	5/15
Tompkins et al., 2017[15]	Death	1/20	0/10

Table 3 | **Continued**

Source	Reported adverse events	Frequency in treatment group	Frequency in control group
Lin et al., 2017 (a)[37]	Death	9/56	18/54
Lin et al., 2017 (b)[37]	Hepatic coma	4/56	7/54
Bartolucci et al., 2017[39]	Cardiovascular	0/15	1/15
Fernández et al., 2018[45]	Death	0/23	2/11
Averyanov et al., 2020 (a)[50]	Death	2/10	2/2
Averyanov et al., 2020 (b)[50]	Ischemic stroke	1/10	0/10
Jaillard et al., 2020 (a)[34]	Death	0/16	1/15
Jaillard et al., 2020 (b)[34]	Ischemic stroke	0/16	2/15
Lanzoni et al., 2021 (a)[46]	Failed endotracheal intubation	1/12	0/12
Lanzoni et al., 2021 (b)[46]	Acute respiratory failure	1/12	1/12
Lanzoni et al., 2021 (c)[46]	Multi-organ dysfunction syndrome	0/12	6/12
Hepatobiliary disorders			
Lee et al., 2010[20]	Hepatic	1/16	2/36
Casiraghi et al., 2021[13]	Hepatobiliary	1/10	2/10
Lan et al., 2021[19]	Hepatotoxicity	0/9	0/9
Ichikado et al., 2023[47]	Hepatic	4/20	1/10
Karyana et al., 2022[14]	Hepatobiliary disorder	0/6	1/3
Neoplasms benign and malignant disorders			
Ning et al., 2008[38]	Tumor/malignancy (relapse)	6/10	3/15
Hare et al., 2009[41]	Tumor/malignancy	0/34	0/19
Tompkins et al., 2017[15]	Tumor/malignant (Glioblastoma)	0/20	1/10
Bartolucci et al., 2017[39]	Tumor/malignant	1/15	1/15
Casiraghi et al., 2021[13]	Neoplasms benign, malignant and unspecified	0/10	1/10
Zang et al.,2022 (a)[26]	Prostate cancer	0/45	1/46
Zang et al.,2022 (b)[26]	Papillary thyroid carcinoma	0/45	1/46

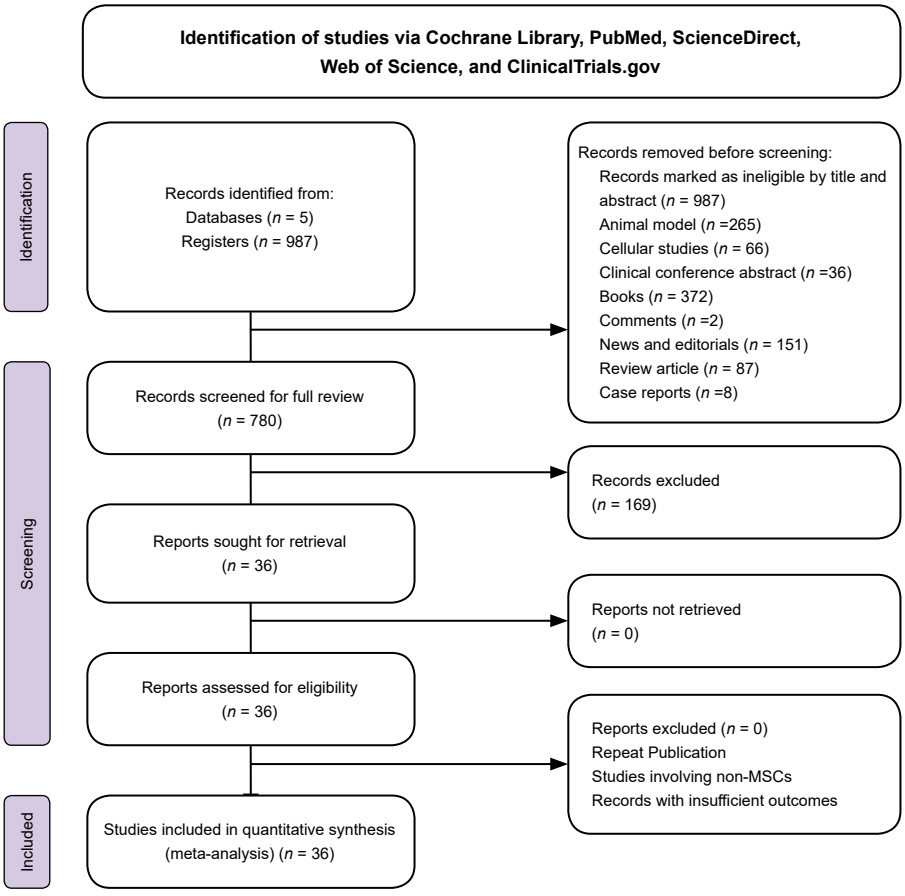

Figure 1 | **Flow diagram illustrating the identification, screening, and selection of the eligible clinical trials/studies for meta-analysis**
MSCs: Mesenchymal stem cells.

statistically significant, very slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = –0.329, P = 0.742; estimated average log OR difference: –0.26; 95% CI: –1.81 to 1.29; **Figure 3**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 2.147, P = 0.542, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.4977, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.3333 and 0.2439, respectively). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to nervous system disorders

A meta-analysis of thirteen RCTs[13,16-26] evaluated AEs such as local complications, dizziness, nervous system dysfunction, lethargy, headache, weakness, concussion, neuropsychiatric disorders associated with streptococcal infection, nervous system, neurological, anemia, and cerebral infarction (**Table 3**). Results demonstrated a slightly elevated but not statistically significant risk of AEs in the MSC group compared to the control group (Z-test = 1.80, P = 0.072; average log OR difference: 0.54; 95% CI: –0.05 to 1.13; **Figure 4**). Since the CI crosses zero, the findings indicate that the observed increase in AEs may not be statistically significant, and caution should be exercised in interpreting these results.

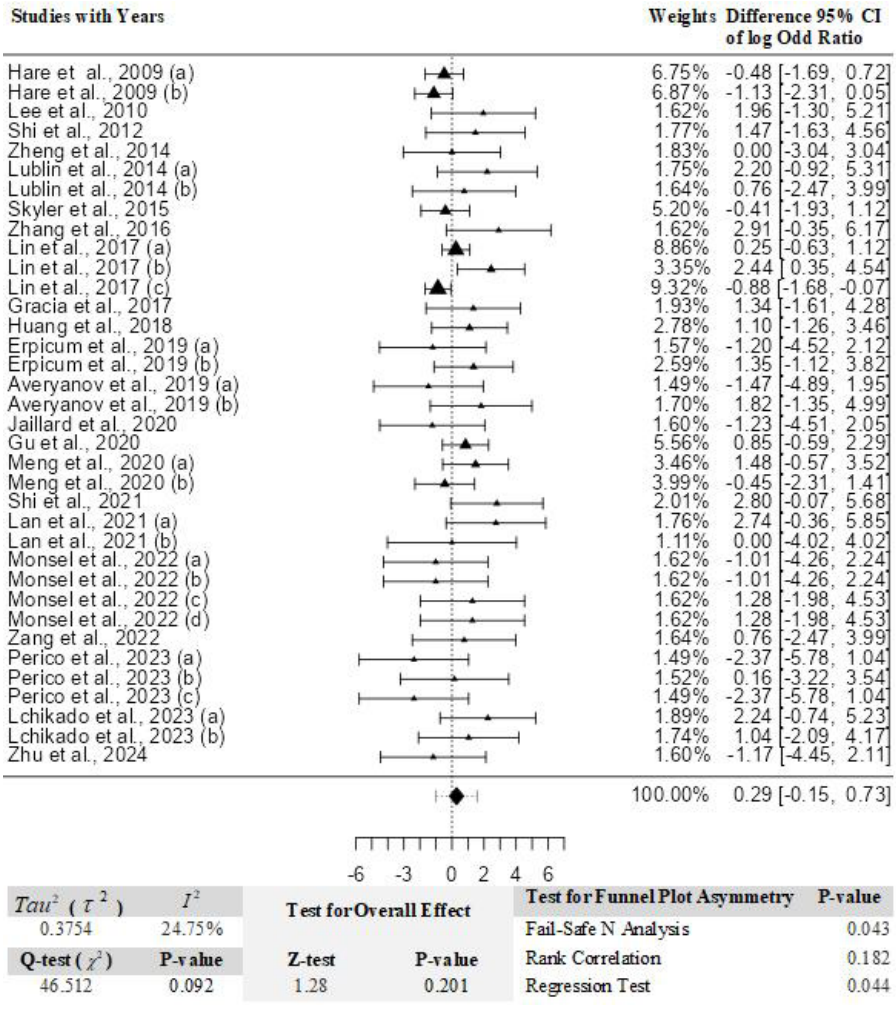

Figure 2 | **Meta-analysis of adverse events related to general disorders and administration site conditions.**
CI: Confidence interval.

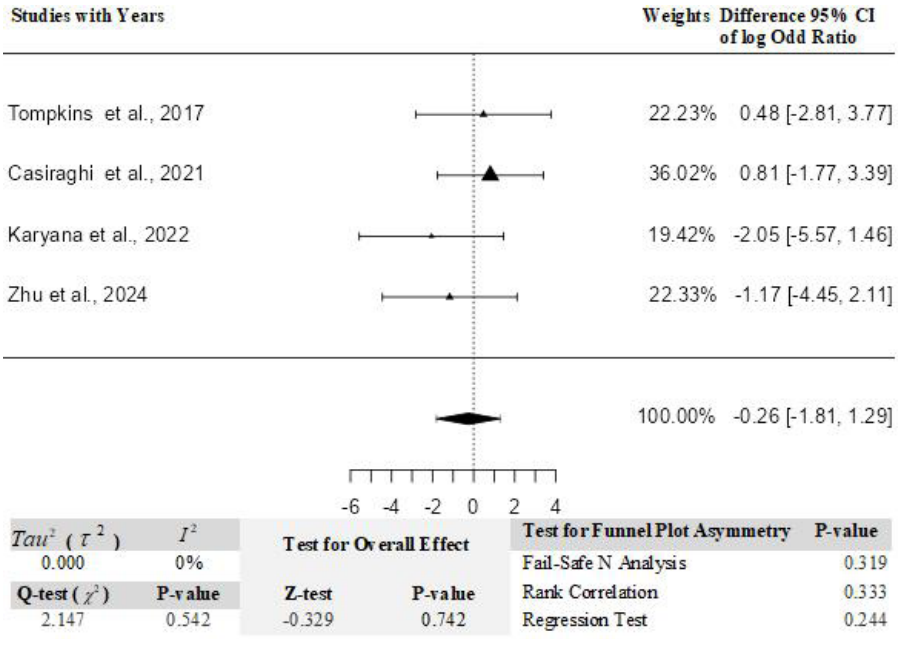

Figure 3 | **Meta-analysis of adverse events related to musculoskeletal and connective tissue disorders.**
CI: Confidence interval.

The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 6.377, P = 0.990, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.9913, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.6540 and 0.0892, respectively). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to infections and infestations

A meta-analysis of 20 RCTs evaluated AEs such as infection (early/mid-phase), infection, pneumonia, urinary tract infection, urinary tract infection, upper respiratory tract infection, skin infections, sepsis, urinary tract infection, upper respiratory tract infection, fungal, folliculitis, renal, urinary, urinary tract infection, bacterial peritonitis, bile tract infection, bacterial pneumonia, fungal pneumonia, digestive tract fungal infection, sepsis, urinary tract infection, upper respiratory tract infection, respiratory, CMV, polyoma BK viremia, pneumocystis pneumonia, URTI, LRTI, UTI, pneumonia, infections, right lobe pneumonia, cutaneous candidiasis, bacteremia related to cocci gram+ bacteria, healthcare-associated pneumonia, lymphangitis, right arm lymphangitis, urinary, urinary tract infection, bacterial infection, and pharyngitis (**Table 3**). Results demonstrated a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = –2.10, P = 0.036; average log OR difference: –0.32; 95% CI: –0.61 to –0.02; **Figure 5**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 24.072, P = 0.991, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. A rank correlation test did not identify funnel plot asymmetry (P = 0.598), though this finding was confirmed by the regression test (P = 0.181). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings. An analysis of studentized residuals revealed no values exceeding ±3.2544, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential.

Meta-analysis of adverse events related to renal and urinary disorders

A meta-analysis of five RCTs evaluated AEs such as glycosuria and hematuria (renal & urinary disorders), renal and urinary, renal failure, and acute renal failure (**Table 3**). Results did not establish a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = 0.657, P = 0.511; average log OR difference: 0.30; 95% CI: –0.59 to 1.19; **Figure 6**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 0.895, P = 0.917, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.6383, indicating no potential

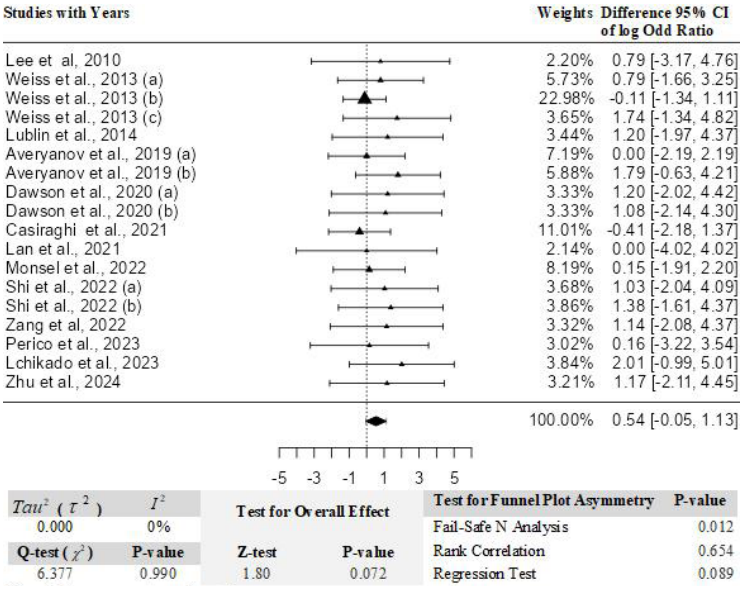

Figure 4 | **Meta-analysis of adverse events related to nervous system disorders.**
CI: Confidence interval.

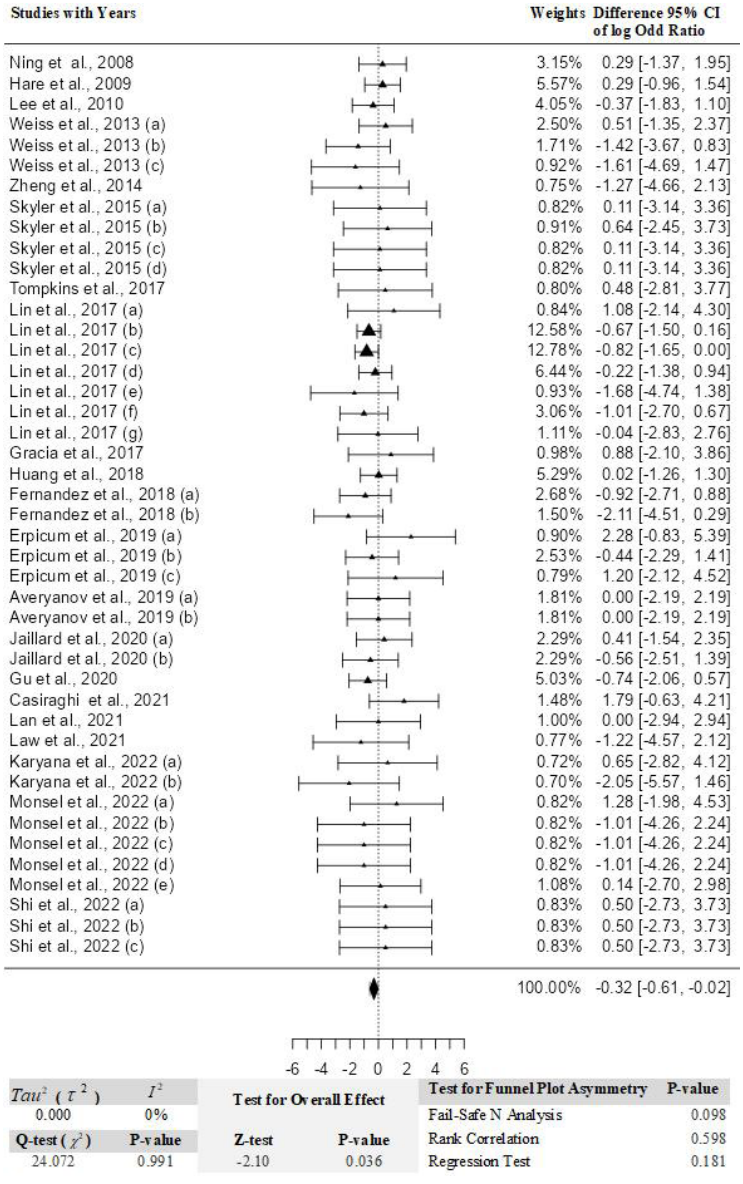

Figure 5 | **Meta-analysis of adverse events related to infections and infestations.**
CI: Confidence interval.

outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.4694 and 0.6560, respectively).

Meta-analysis of adverse events related to immune system disorders

A meta-analysis of three RCTs evaluated AEs such as graft-versus-host disease (GVHD) (acute), GVHD (chronic), immune, and allergy (**Table 3**). Results did not demonstrate a statistically significant, raised minor risk of AEs in the MSC group compared to the control group (Z-test = –1.30, P = 0.193; average log OR difference: –0.97; 95% CI: –2.42 to 0.49; **Figure 7**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 3.325, P = 0.344, τ^2 = 0.2214, I^2 = 9.76%), suggesting homogeneity among the included studies. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.3333 and 0.1865, respectively). An analysis of studentized residuals revealed no values exceeding ±2.4977, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential.

Meta-analysis of adverse events related to respiratory, thoracic, and mediastinal disorders

A meta-analysis of eight RCTs evaluated AEs such as cough, emphysema, chronic obstructive pulmonary disorder, cough, shortness of breath, severe hypoxemia, respiratory, thoracic, mediastinal, respiratory, thoracic, mediastinal, respiratory, pulmonary, refractory acute respiratory distress syndrome and multiple organ failure, oropharyngeal, and worsening respiratory conditions (**Table 3**). Results explained a statistically non-significant, elevated slightly risk of AEs in the MSC group compared to the control group (Z-test = –0.451, P = 0.652; average log OR difference: –0.12; 95% CI: –0.67 to 0.42; **Figure 8**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 12.336, P = 0.653, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.8567 and 0.4733, respectively). An analysis of studentized residuals revealed no values exceeding ± 2.9552, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to gastrointestinal disorders

A meta-analysis of five RCTs evaluated AEs such as gastrointestinal renal, gastrointestinal, diarrhea, gastrointestinal viral, gastroenteritis, diarrhea; 1–4 weeks, diarrhea; 5–24 weeks, gastrointestinal; bleeding, nausea, vomiting, constipation, gastrointestinal, vomiting, viral gastroenteritis, dehydration, aggression, liquid diarrhea, pseudomonas aeruginosa-related ventilator-associated pneumonia, abdominal distension, and abdominal pain (**Table 3**).

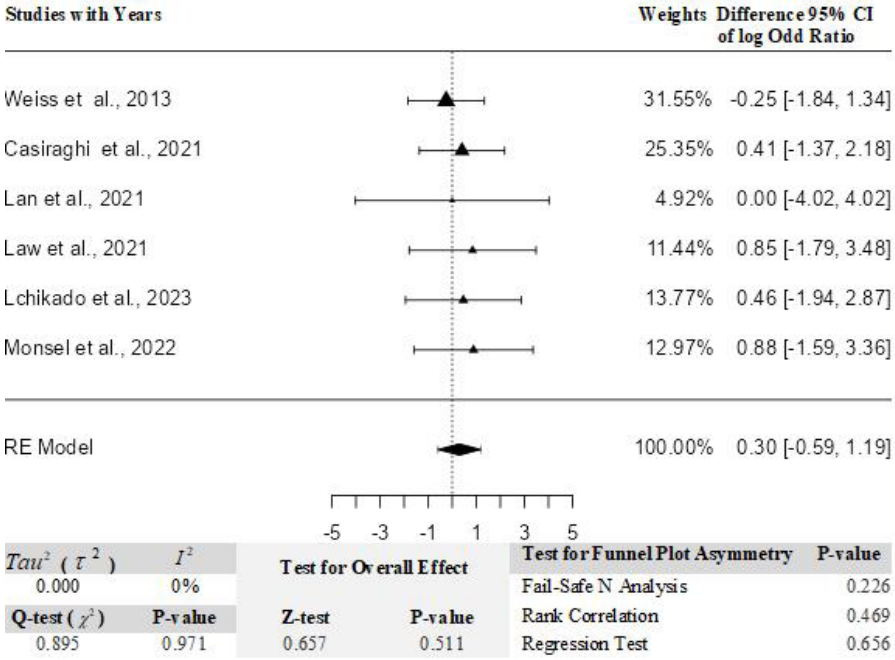

Figure 6 | **Meta-analysis of adverse events related to renal and urinary disorders.**
CI: Confidence interval.

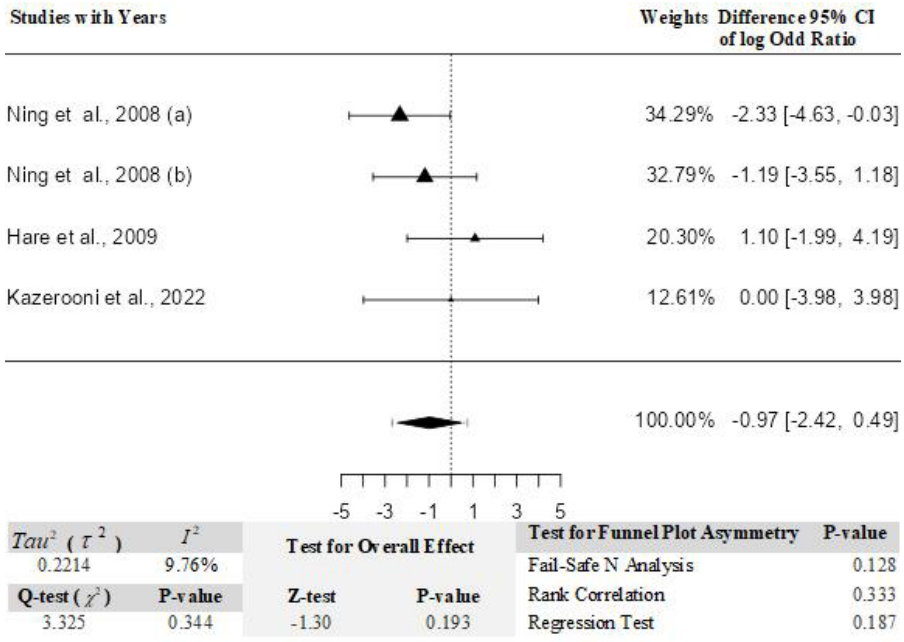

Figure 7 | **Meta-analysis of adverse events related to immune system disorders.**
CI: Confidence interval.

Results of the meta-analysis did not present a statistically significant, elevated minor risk of AEs in the MSC group compared to the control group (*Z*-test = –0.00272, *P* = 0.988; average log OR difference: –0.00; 95% CI: –0.33 to 0.33; **Figure 9**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (*Q* = 20.614, *P* = 0.993, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±3.2272, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (*P* = 0.4617 and 0.6742, respectively). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to injury, poisoning, and procedural complications

A meta-analysis of five RCTs evaluated AEs such as local complications, procedural complications, injury, procedural complications, acute pulmonary embolism, and pulmonary embolism (**Table 3**). Results demonstrated a non-significant, slightly elevated risk of AEs in the MSC group compared to the control group (*Z*-test = –0.974, *P* = 0.330; average log OR difference: –0.57; 95% CI: –1.70 to 0.57; **Figure 10**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (*Q* = 1.083, *P* = 0.897, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.5758, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (*P* = 0.4833 and 0.6435, respectively).

Meta-analysis of adverse events related to cardiac disorders

A meta-analysis of eleven RCTs evaluated AEs such as infusion toxicity, infusion toxicity, arrhythmia, cardiac, arrhythmia, congestive heart failure, non-sustained ventricular tachycardia, heart failure, myocardial infarction, cardiac event, cardiac, heart failure, arrythmia, cardiovascular, arrythmia (bradycardia), cardiac, and cardiac failure (**Table 3**). Results of the meta-analysis did not demonstrate a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (*Z*-test = –0.896, *P* = 0.370; average log OR difference: –0.23; 95% CI: –0.74 to 0.28; **Figure 11**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (*Q* = 11.055, *P* = 0.892, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (*P* = 0.6998 and 0.3825, respectively). An analysis of studentized residuals revealed no values exceeding ±3.0078, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to hematological or oncological disorders

A meta-analysis of two RCTs evaluated AEs such as hematological disorder (Anemia) and hematological (**Table 3**). Results demonstrated a statistically non-significant, slightly elevated risk of AEs in the MSC group compared to the control group (*Z*-test = –0.603, *P* = 0.547; average log OR difference: –0.47; 95% CI: –2.01 to 1.06; **Figure 12**). The *Q*-test for heterogeneity indicated no significant variability in the true effect sizes (*Q* = 0.016, *P* = 0.899, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ± 2.2414, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (*P* = 1.0000 and 0.8987, respectively).

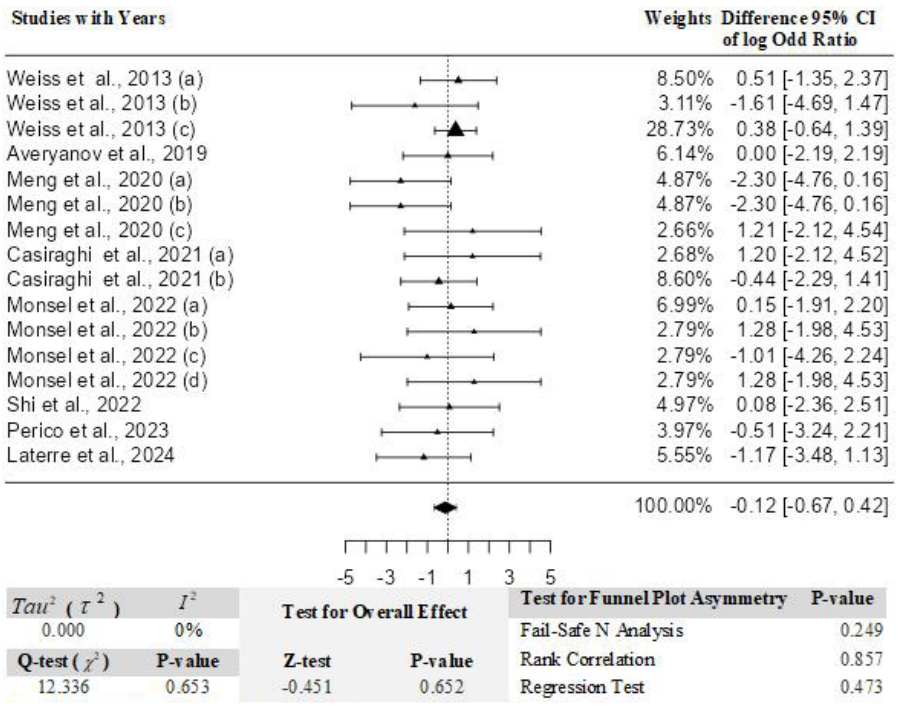

Figure 8 | **Meta-analysis of adverse events related to respiratory, thoracic, and mediastinal disorders.**
CI: Confidence interval.

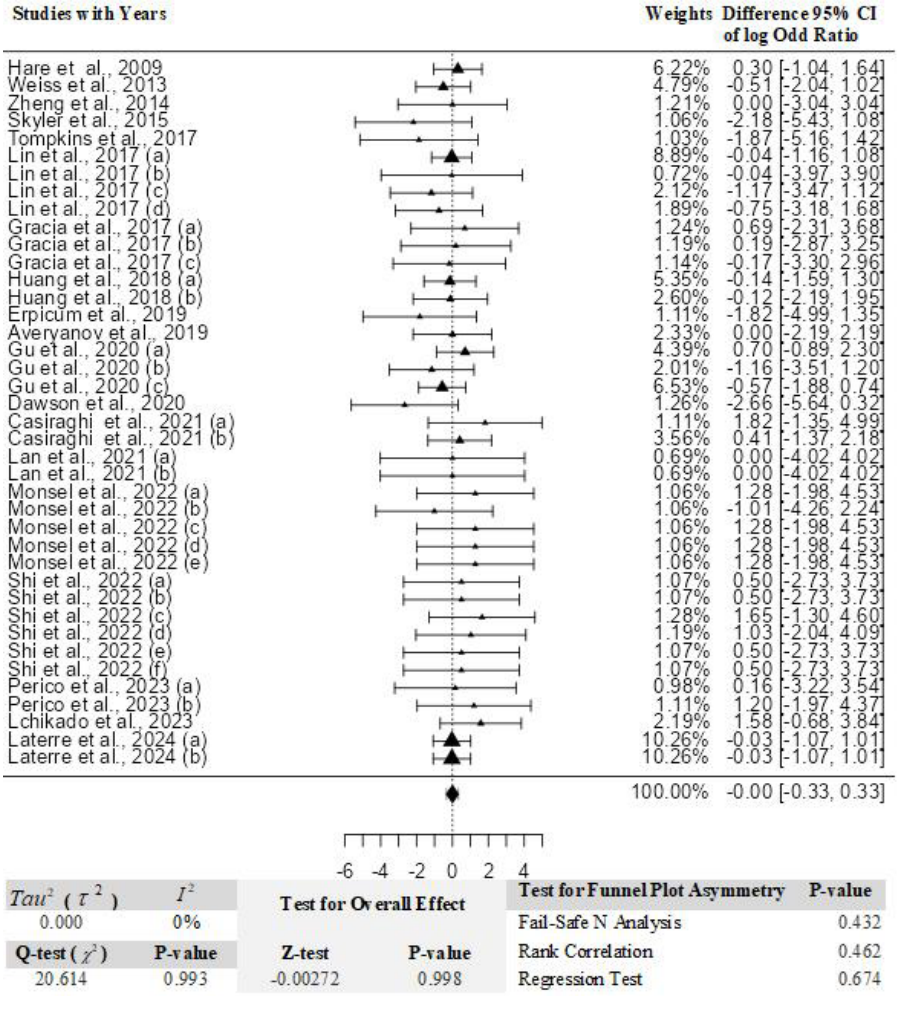

Figure 9 | **Meta-analysis of adverse events related to gastrointestinal disorders.**
CI: Confidence interval.

Meta-analysis of adverse events related to skin and subcutaneous tissue disorders

A meta-analysis of fourteen RCTs evaluated AEs such as skin, rash in the chest area, rash; 1–4 weeks, rash; 5–24 weeks, urticaria, graft dysfunction, skin rash, foot skin, facial flushing, skin and subcutaneous tissue, rash, skin exfoliation, and macular rash (**Table 3**). Results demonstrated a statistically non-significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = 0.640, P = 0.522; average log OR difference: 0.21; 95% CI: –0.44 to 0.87; **Figure 13**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 8.898, P = 0.838, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.9352, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.4351 and 0.6556, respectively).

Meta-analysis of adverse events related to vascular disorders

A meta-analysis of six RCTs evaluated AEs such as vascular disorders (recurrent stroke), peripheral artery occlusive disease, vascular disorders, vascular disorders, infantile hemangiomas, and local phlebitis (**Table 3**). Results did not present a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = 0.310, P = 0.756; average log OR difference: 0.13; 95% CI: –0.71 to 0.98; **Figure 14**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 6.152, P = 0.522, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ± 2.7344, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.7084 and 0.9265, respectively).

Meta-analysis of adverse events related to serious adverse event deaths

A meta-analysis of nine RCTs evaluated AEs such as death, hepatic coma, cardiovascular, ischemic stroke, failed endotracheal intubation, acute respiratory failure, and multi-organ dysfunction syndrome (**Table 3**). Results demonstrated a statistically non-significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = –2.09, P = 0.37; average log OR difference: –0.67; 95% CI: –1.30 to –0.04; **Figure 15**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 14.231, P = 0.358, τ^2 = 0.1241, I^2 = 8.65%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ±2.9137, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. A rank correlation test did not identify funnel plot asymmetry (P = 0.451), also this finding was

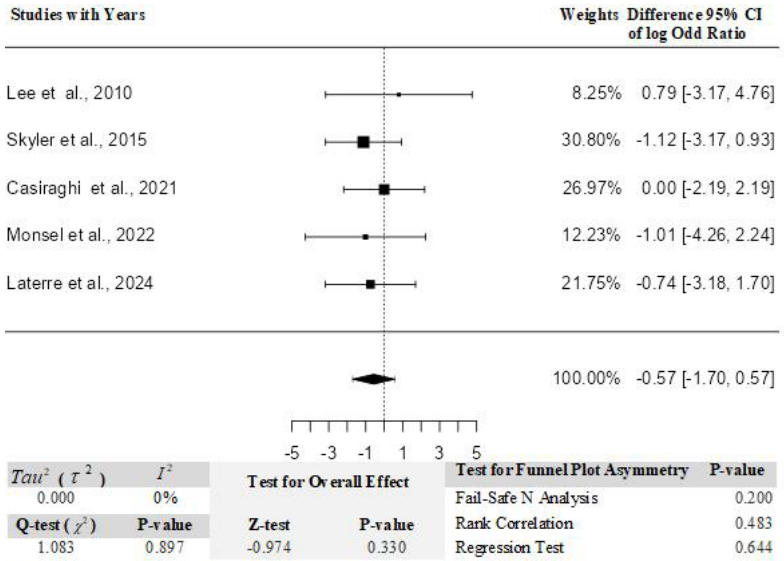

Figure 10 | **Meta-analysis of adverse events related to injury, poisoning, and procedural complications.**
CI: Confidence interval.

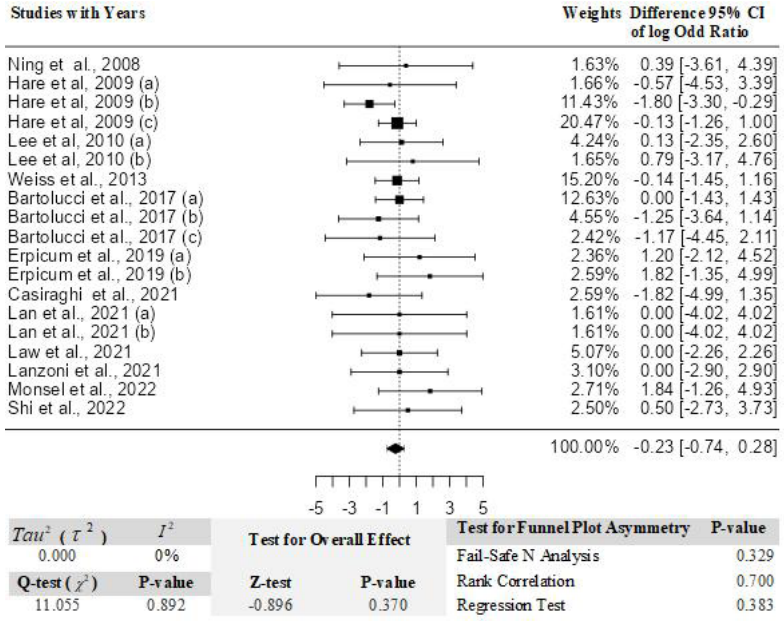

Figure 11 | **Meta-analysis of adverse events related to cardiac disorders.**
CI: Confidence interval.

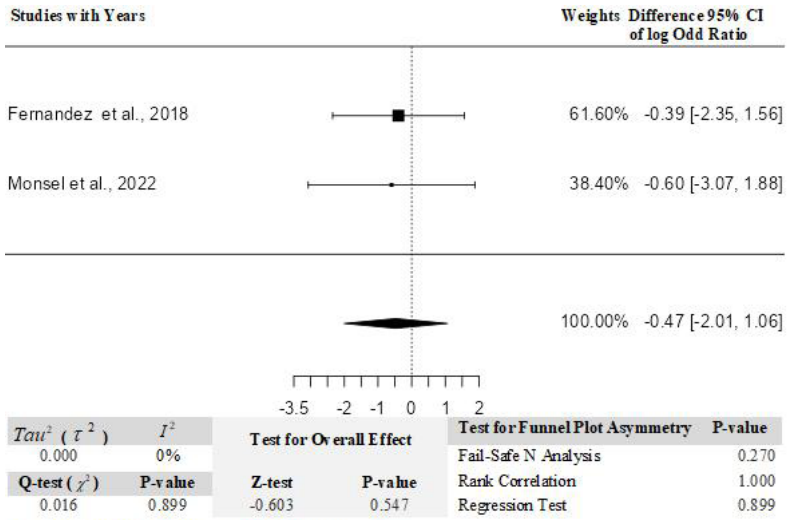

Figure 12 | **Meta-analysis of adverse events related to hematological or oncological disorders.**
CI: Confidence interval.

corroborated by the regression test (P = 0.694). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Meta-analysis of adverse events related to hepatobiliary disorders

A meta-analysis of five RCTs evaluated AEs such as hepatic, hepatobiliary, and hepatobiliary disorder (**Table 3**). Results did not demonstrate a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = –0.292, P = 0.771; average log OR difference: –0.19; 95% CI: –1.44 to 1.07; **Figure 16**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 2.076, P = 0.722, τ^2 = 0.0000, I^2 = 0%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ± 2.5758, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (P = 0.2333 and 0.4387, respectively).

Meta-analysis of adverse events related to neoplasms benign and malignant disorders

A meta-analysis of five RCTs evaluated AEs such as tumor/malignancy (relapse), tumor/malignant (glioblastoma), neoplasms benign, malignant, unspecified, prostate cancer, and papillary thyroid carcinoma (**Table 3**). Results did not show a statistically significant, slightly elevated risk of AEs in the MSC group compared to the control group (Z-test = –0.0993, P = 0.921; average log OR difference: –0.06; 95% CI: –1.20 to 1.08; **Figure 17**). The Q-test for heterogeneity indicated no significant variability in the true effect sizes (Q = 6.556, P = 0.364, τ^2 = 0.2072, I^2 = 8.49%), suggesting homogeneity among the included studies. An analysis of studentized residuals revealed no values exceeding ± 2.6901, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. The regression test indicated funnel plot asymmetry (P = 0.0183) but not the rank correlation test (P = 0.1245). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Risk of bias assessment

The quality of the articles was assessed by using the Cochrane Collaboration's Tool for assessing the risk of bias in the included studies is summarized in **Figure 18**. For the selection bias, five studies[27-31] were of slightly low quality because those had some high risk of bias due to random sequence generation (13.5%) and one study[32] had an unclear risk of bias (2.7%). Also, eight studies[17,27,29,31,33-36] had a high risk of bias (24.3%) and two studies[30,37] had an unclear risk of bias due to allocation concealment. For the performance bias, three studies[17,29,37] had high risk of bias (10.0%) and seven studies[27,30,31,33-36] had some unclear risk of bias (18.9%) due to blinding of participants and personnel. For the detection bias, three studies[14,30,35] had some unclear risk of bias (8.1%), and twelve studies[17,19,20,24,27,29,31,33-38] had a high

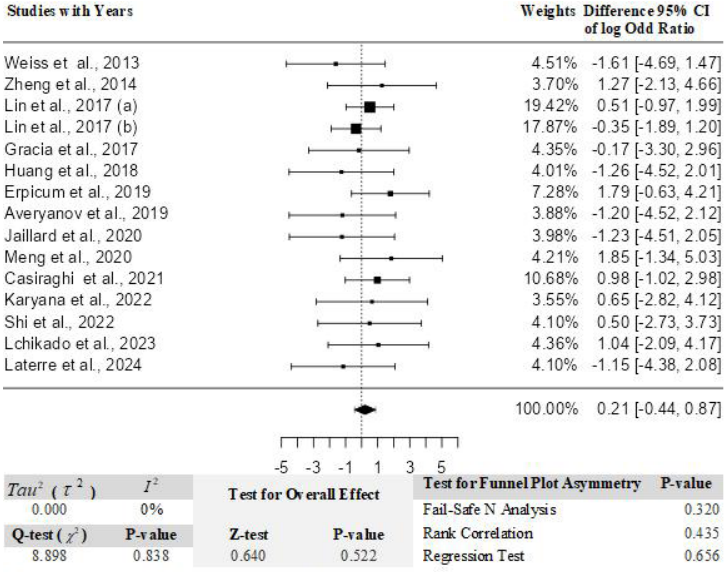

Figure 13 | **Meta-analysis of adverse events related to skin and subcutaneous tissue disorders.**
CI: Confidence interval.

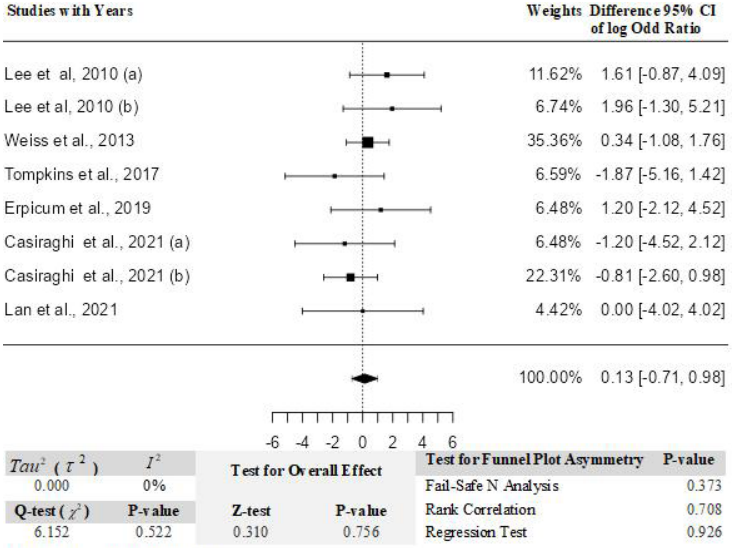

Figure 14 | **Meta-analysis of adverse events related to vascular disorders.**
CI: Confidence interval.

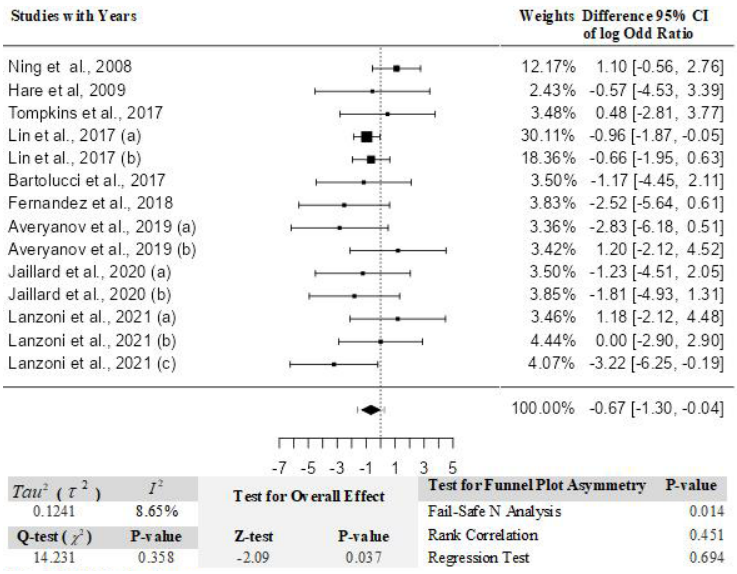

Figure 15 | **Meta-analysis of adverse events related to serious adverse event deaths.**
CI: Confidence interval.

risk of bias (35.1%) due to blinding of outcome assessment. For attrition bias, four studies[13,15,31,39] had some unclear risk of bias (10.8%) and the other four studies[17,24,25,40] had a high risk of bias (13.5%) due to incomplete outcome data. For the reporting bias, two studies[17,37] had some unclear risk of bias (5.4%) due to selective reporting and for other bias, two studies[29,35] had a high risk of bias (5.4%) due to other bias. For the other bias, only three studies[26,41,42] had some unclear risk of bias (8.1%) due to selective reporting and for other bias, one study[38] had a high risk of bias (2.7%) due to other bias. There were performance bias and detection bias potentially lowering the integral quality of the included studies. Overall, we concluded that most study designs were suitable and of high quality.

Publication bias

Publication bias was assessed using funnel plots (**Figure 19**) as well as through the analysis of studentized residuals revealed no values exceeding, indicating no potential outliers within this model. Similarly, Cook's distance values suggested that none of the studies were disproportionately influential. In the majority of AEs both the regression and rank correlation tests did not indicate funnel plot asymmetry ($P > 0.05$). These results underscore the need for further investigation into potential biases while supporting the overall robustness of the findings.

Discussion

To the best of our knowledge, this is the first study to assess the safety and efficacy of mesenchymal stem cell injection by intravenous method. Our findings provide support for the "Safe Cell" idea.

Our systematic review and meta-analysis were conducted utilizing a thorough methodology specifically designed to investigate the safety profile of MSC treatment. We employed a variety of electronic databases to avoid the possibility of publication bias and give a comprehensive assessment of the literature. While earlier systematic reviews have confirmed the safety of MSC therapy provided via various methods, our analysis stands out because it uses statistical tools to pool safety data linked to intravenous MSC delivery on a similar outcome across 36 RCTs.

In evaluating the AEs, some key factors come to consideration. Our results suggest that the intravenous MSC administration is to be considered generally safe; however, certain AE categories need further vigilance and consideration. Nervous system-related events showed a trend toward increased risk ($P = 0.072$), and infections were statistically significant ($P = 0.036$). These observations emphasize the need for continued research to better understand potential risks and assure patient safety. Given these observations, a more tempered interpretation would seem warranted Taken together with the interpretation of high safety in general terms, specific organ systems might require increased monitoring.

Furthermore, our mortality analysis suggests lower risk of death in the MSC-treated group. Such positive results validate the expected therapeutic benefits of MSC therapy and strengthen the argument for more extensive studies to confirm

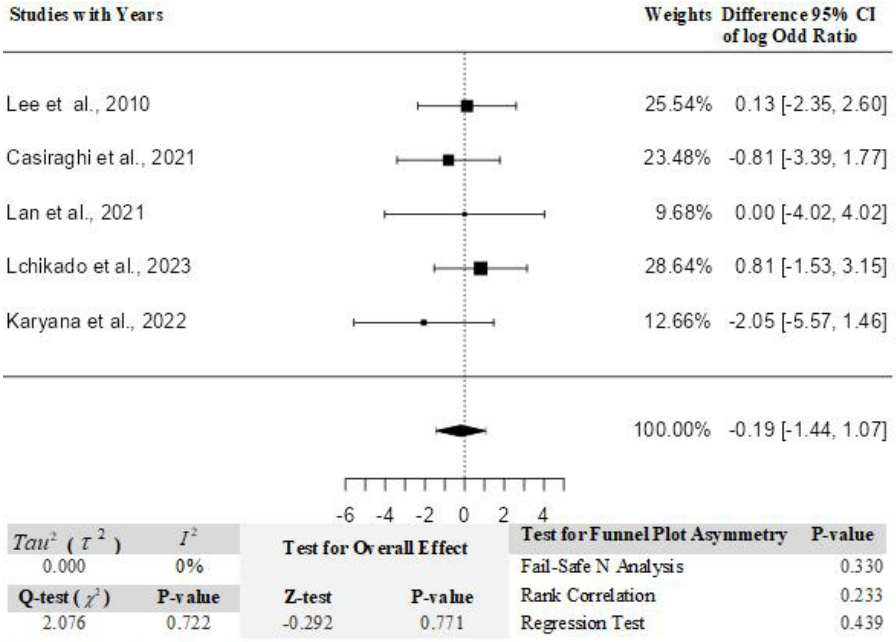

Figure 16 | **Meta-analysis of adverse events related to hepatobiliary disorders.**
CI: Confidence interval.

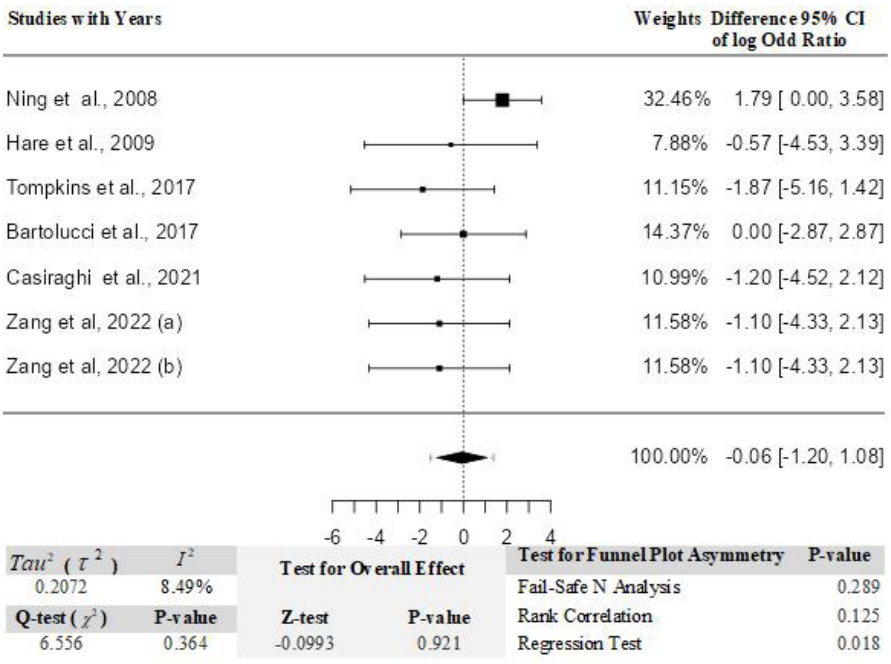

Figure 17 | **Meta-analysis of adverse events related to neoplasms benign and malignant disorders.**
CI: Confidence interval.

these findings. The mechanisms by which MSCs reduce mortality and their long-term effects will be a significant area of future research.

To address the observed significant increase in adverse nervous system events, we explored potential mechanisms that may contribute to this finding. One possible explanation is that MSC homing to the lungs may trigger an inflammatory response, which could have systemic effects leading to neurological symptoms. Additionally, interactions between MSCs and the immune system may modulate neuroinflammation, potentially affecting nervous system function. While our meta-analysis supports the overall safety of intravenous MSC administration, these findings emphasize the need for further research to better understand the biological mechanisms underlying nervous system-related AEs.

Long-term follow-up studies are needed to ensure the safety and efficacy of SCT for various disorders administered intravenously. Thus, more study with longer follow-up periods is required to better understand the effect of SCT on disease progression and patient outcomes. Further investigation is needed to elucidate the various follow-up stages and characterize the primary outcomes linked with the influence of SCT on disease morbidity and death. Additionally, future studies should focus on detailed mechanistic investigations to determine whether the observed nervous system-related AEs are transient or indicative of more serious concerns.

Limitations

Our study has various limitations that must be noted. Although we included 36 studies in our meta-analysis, the sample size for specific AEs differed between studies, potentially compromising the statistical power of our results. Furthermore, variety in trial designs, patient populations, MSC sources (autologous *vs.* allogeneic), treatment plans, and follow-up periods may have contributed to variability in the outcomes. Despite our efforts to include all relevant research, there is still a chance of publication bias, as unpublished unfavorable outcomes may influence the overall conclusions. Another significant drawback is a lack of long-term safety data, as several of the included trials had short follow-up periods, limiting our ability to assess the long-term effects of intravenous MSC delivery. Inconsistencies in AE reporting across trials may also have had an impact on outcome comparability and risk assessment accuracy. Moreover, while our major goal was to study the safety of MSC therapy, effectiveness outcomes were not thoroughly investigated, limiting the broader therapeutic implications of our findings.

Conclusion

The analysis indicates that MSCs are a safe option for stem cell transplantation. While short-term findings suggest that MSCs may be an effective treatment, further research is needed to evaluate their long-term effects. In the 36 studies reviewed, no significant adverse reactions or hypoglycemic events were observed in participants who received MSC treatment. This supports the view that MSC transplantation can be considered a safe therapeutic option for a range of diseases.

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Author contributions: *UEH led the development of the original draft, conducted formal analysis, conceptualized the study design, and followed up with the patient. DLG contributed to the conceptualization and design of the study, managed project administration, and secured funding. KA performed data curation, statistical analysis, investigation, methodology development, and software validation, along with visualization and review of the manuscript. SS compiled and formatted references and assisted with proofreading. NK and AU assisted in proofreading. All authors approved the final manuscript.*

Conflicts of interest: *The authors UEH, SS, NK, DLG, and AU were employed by the companies R3 Medical Research LLC, Pak-American Hospital Pvt. Ltd., and R3 Stem Cell LLC. The authors NK and DLG were employed by the company Bello Bio Labs and Therapeutics Pvt. Ltd. The remaining author declares that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

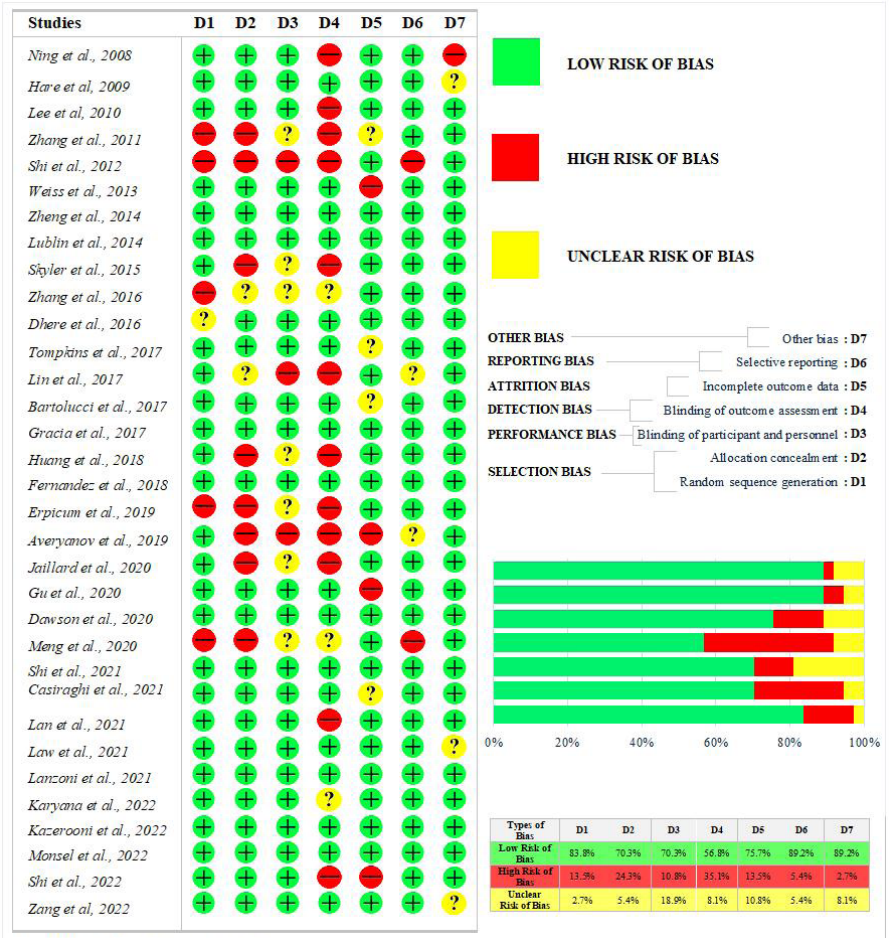

Figure 18 | **Risk of bias of the selected studies.**

Ethics committee approval: *Not applicable.*
Patient consent: *Not applicable.*
Data availability statement: *The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.*

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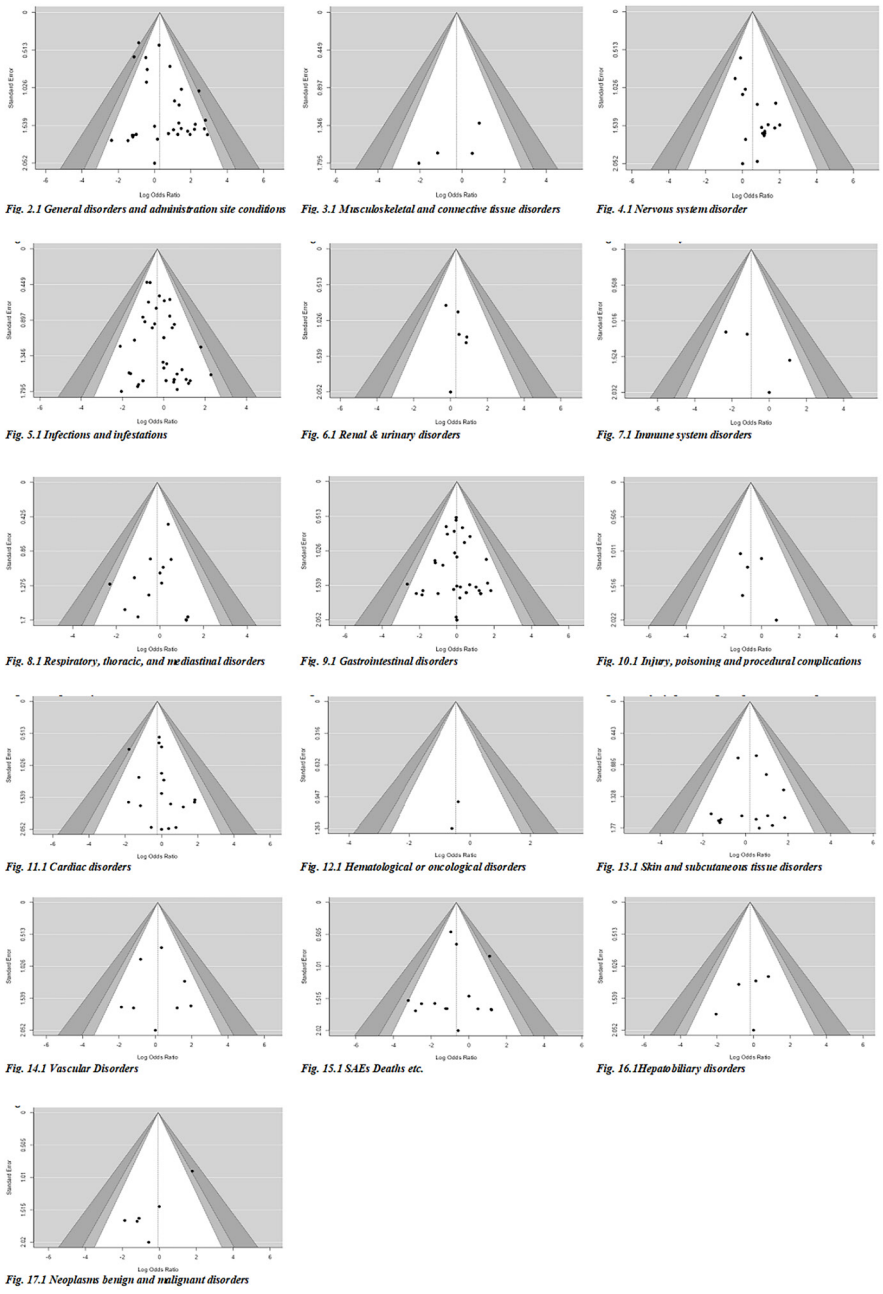

Figure 19 | **Funnel plots of adverse events categorized by Common terminology criteria for adverse events (CTCAE) version 5.0.**

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