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Efficacy and safety of stem cell therapy in ischemic stroke patients: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background Stem cell (SC) transplantation is a promising therapeutic approach for ischemic stroke (IS). However, the current literature lacks robust evidence substantiating its efficacy and safety. This systematic review aims to evaluate the efficacy and safety profile of SC therapy in patients who had an IS.

Methods References up to November 2025 were sourced from OVID Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, Web of Science and ClinicalTrials.gov. Eligibility criteria followed a Population, Intervention, Comparator, Outcome framework: adult patients with image-confirmed IS, any human SC therapy (non-neural or neural), placebo or standard medical care and functional or neurological outcomes (modified Rankin Scale (mRS), Barthel Index (BI), National Institutes of Health Stroke Scale (NIHSS)), mortality or adverse events at ≥6 months. Only randomised controlled trials were considered. Random-effects meta-analyses compared efficacy and safety between SC and control groups. Study heterogeneity was measured using the I^2 statistic, and risk of bias was assessed using the Cochrane Risk-of-Bias V.2 tool.

Results 17 RCTs involving 999 patients (SC therapy: 495; control: 504) were included. A pooled analysis showed that SC therapy was associated with significant improvements in mRS scores (mean difference (MD)=−0.27, 95% CI −0.51 to −0.03, p=0.027, I^2=42.2%), BI scores (MD=7.78, 95% CI 0.50 to 15.06, p=0.036, I^2=53.0%) as well as reduced mortality rates (relative risk=0.64 (95% CI 0.42 to 0.98), p=0.040, I^2=0%). No significant effect was observed for NIHSS scores. The incidence of AE was comparable between groups. The included trials exhibited moderate heterogeneity and a moderate risk of bias.

Conclusion SC therapy shows potential to improve functional outcomes and survival in patients who had an IS without significant safety concerns. However, the observed effect on disability is fragile, as statistical significance was lost in leave-one-out analyses, and the substantial heterogeneity and moderate methodological quality limit definitive conclusions.

PROSPERO registration number CRD42024567397.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Stem cell (SC) therapy has gained attention as a potential treatment for ischemic stroke (IS), supported by numerous preclinical studies demonstrating its ability to reduce neuronal damage and promote functional recovery. However, clinical evidence remains inconsistent, with limited high-quality trials and high variability in outcomes and treatment protocols.

WHAT THIS STUDY ADDS

⇒ This meta-analysis demonstrates that SC therapy is associated with significant improvements in modified Rankin Scale and Barthel Index (BI) scores and reduced mortality in patients who had an IS, without an increase in adverse events. However, these functional benefits are fragile, as statistical significance, particularly for the BI, was lost in sensitivity analyses, and no significant improvement in neurological impairment (National Institutes of Health Stroke Scale) was observed, highlighting the need for further high-quality evidence to establish the therapy's overall clinical efficacy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings underscore the ongoing need for large-scale, high-quality phase III trials to validate the safety and efficacy of SC therapy, investigating the ideal dosage, administration route and SC type.

INTRODUCTION

Stroke is the second leading cause of morbidity and mortality worldwide,[1 2] with ischemic stroke (IS) accounting for approximately 85% of all cases.[3] The primary goal of currently established therapies for IS is reperfusion, achieved through intravenous recombinant tissue plasminogen activator administration or endovascular mechanical thrombectomy.[4] However, these therapies are limited by a narrow therapeutic window and strict eligibility criteria, leaving many patients ineligible for treatment.[5] Consequently, once brain damage after ischemia occurs in these patients, the only therapies available are rehabilitative therapy and pharmacological management of comorbidities, which often result in limited functional recovery and impose substantial healthcare and societal costs.[6 7] Although numerous pharmacological

and biological treatment options have shown promise in preclinical models, none have demonstrated clear clinical benefits.[8] Therefore, there is an urgent need for novel therapeutic strategies to improve treatment and, thereby, prognosis for patients suffering from IS.

Over the past two decades, numerous preclinical studies have demonstrated the potential of stem cell (SC) transplantation in IS models.[9–13] Rather than directly replacing lost neurons, SCs exert their effects through indirect mechanisms, including trophic support, reduction of apoptosis, enhancement of brain plasticity, suppression of peri-infarct inflammation and promotion of angiogenesis.[9–11 14 15] However, despite the completion of several randomised controlled trials (RCT), the safety and efficacy of SC therapy in patients who had an IS remain uncertain and the absence of standardised therapeutic protocols further complicates clinical translation.[9 11] The present meta-analysis aims to systematically evaluate the therapeutic efficacy and safety profile of clinical SC therapy in patients who had an IS, providing a comprehensive overview of the currently available evidence.

METHODS

A systematic review was conducted to identify RCTs evaluating the use of non-neural or neural human SC in patients who had an IS. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[16] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42024567397).

Search strategy

A comprehensive database-specific search strategy was developed in collaboration with a medical information specialist (online supplemental file 1).[17–19]

OVID Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, Web of Science and ClinicalTrials.gov were searched through 30 November 2025. References were managed in Rayyan.ai for duplicate removal and screening.[20] Title and abstract screening, full-text review and final article inclusion were conducted independently by two reviewers (AS and DdW). Discrepancies were addressed through consensus or, when required, by consulting the senior author (RG).

Inclusion and exclusion criteria

Eligibility was defined using Population, Intervention, Comparator, Outcome, Study Design.[21] The study population consisted of adult patients with image-confirmed IS (CT or MRI). The intervention of interest encompassed both non-neural and neural human SC transplantation; trials evaluating SC-mobilising agents without cell transplantation were excluded. The comparator included a control group that received either optimal medical treatment or a placebo intervention. Eligible outcomes comprised stroke metrics using one of the following: modified Rankin Scale (mRS), Barthel Index (BI) or National Institutes of Health Stroke Scale (NIHSS). Studies were excluded if they were preclinical or were published solely as abstracts, commentaries, editorials or reviews, or were non-English.

Data extraction

Reviewers used a standardised data extraction form based on the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions[22] to extract the following information: first author, year of publication, disease phase (acute phase: up to 7 days after IS, subacute phase: 8 days to 3 months after IS, chronic phase: more than 3 months), type and origin of SC therapy, SC dosage, administration route, timing of intervention, follow-up duration, sample size, efficacy and safety outcome data at the end of the follow-up period.

Quality assessment and risk of bias

The risk of bias in the included studies was independently assessed by two reviewers using the Cochrane Risk-of-Bias tool V.2.[23] Risk-of-bias graphs were created using the robvis visualisation tool.[24]

Outcomes

The primary outcome was efficacy, assessed by the mRS, BI and NIHSS at 6 months or later. Secondary outcomes were mortality and adverse events (AE), including neurological worsening (≥4-point NIHSS increase without recurrent stroke), infections, neoplastic transformation, symptomatic intracranial haemorrhage (SICH), recurrent stroke/transient ischemic attack (TIA) and seizures.

Statistical analysis

All statistical analyses were conducted using RStudio (V.2024.12.0, Build 467, Posit, PBC, Massachusetts, USA). Heterogeneity was assessed using the I^2 statistic. Due to observed heterogeneity, random-effects models were used. Mean differences (MDs) with 95% CIs were calculated for continuous outcomes. Relative risks (RRs) with 95% CIs were used for dichotomous outcomes. Publication bias was evaluated using funnel plots and Egger's test. Post hoc sensitivity analyses were conducted using Baujat diagnostics and leave-one-out analysis. P values of <0.05 were considered statistically significant.

RESULTS

Search results

A total of 2049 unique articles were screened by title and abstract. Of these, 25 were included for full-text screening, resulting in the inclusion of 17 trials[25–41] (figure 1). A total of 999 patients were included in the meta-analysis, with 495 receiving SC interventions and 504 serving as controls.

Study characteristics

The included studies were published between 2005 and 2025. The IS disease phase varied among the studies, with seven studies (41%) focusing on the acute phase, eight studies (47%) on the subacute phase and two studies

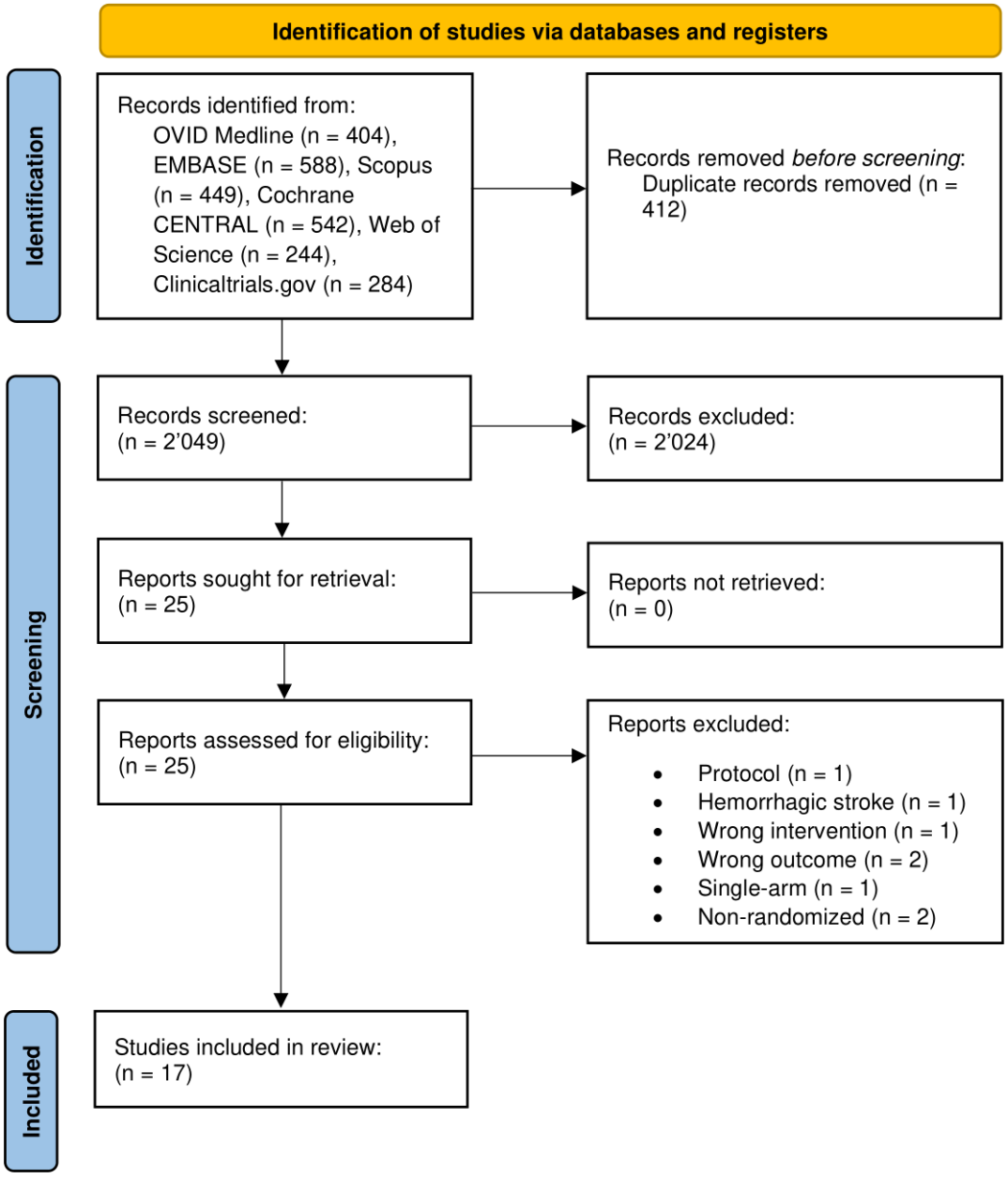

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrating the systematic article selection and screening process.

(12%) on the chronic phase. Follow-up periods ranged from 6 months to 7 years (table 1). Table 2 additionally presents the baseline characteristics of the patients in the included studies.

Regarding the origin of SC therapy, 13 studies (76%) used autologous SC, while 4 studies (24%) employed allogenic SC. Bone marrow-derived mesenchymal SC (BM-MSC) (n=3, 18%) and mononuclear cells (BM-MNC) (n=4, 24%) were the most frequently used cell types. Other SC types included CD34+ haematopoietic stem/progenitor cells (n=2, 12%), multipotent adult progenitor cells (n=2, 12%), adipose tissue-derived mesenchymal SC (n=1, 6%), mesenchymal stromal cells (n=1, 6%), an enriched population of aldehyde dehydrogenase-SC (ALD-401) (n=1, 6%) and a combination of bone marrow-derived mesenchymal stromal cells and endothelial progenitor cells (n=1, 6%). One study used a combination therapy with embryonic-derived neural stem cells and umbilical cord-derived mesenchymal stem cells (n=1, 6%).

The administration route varied across the studies. Intravenous delivery was the most common method, used in 10 studies (59%), followed by intra-arterial (IA) delivery, which was used in four studies (24%). Two studies (12%) administered SC intrathecally via lumbar puncture, and one study (6%) used intracerebral delivery by stereotactic insertion of a needle delivering SC intracerebrally.

Cell dosages varied substantially across the included studies, with regimens based either on body weight (n=4, 24%) or fixed doses (n=13, 76%).

Table 1 Study characteristics of included trials

Study	Disease phase	SC origin	SC type	Administration route	FU period (months)	Outcome measure	Delivery medium	Dosage
Bang *et al, 2005* [37]	Subacute	Autologous	BM-MSC	Intravenous	12	mRS; NIHSS; BI	Saline	5×10^7 cells administered two times (at 4–5 weeks and 7–9 post stroke)
Lee *et al*, 2010[36]	Subacute	Autologous	BM-MSC	Intravenous	60	mRS	Saline	5×10^7 MSCs per infusion, two doses 2 weeks apart
Chen *et al, 2010*[38]	Chronic	Autologous	$CD34^+$	Intracerebral	12	mRS; NIHSS	Saline	3–8 $CD34^+$ 10^6 cells
Prasad *et al, 2014*[25]	Subacute	Autologous	BM-MNC; $CD34^+$	Intravenous	12	mRS; NIHSS; BI	Phosphate-buffered saline	Mean dose: 2.81×10^8 total cells including 2.9×10^6 $CD34^+$
Jin *et al*, 2017[41]	Subacute	Autologous	BM-MNC	Lumbar subarachnoid	84	mRS; NIHSS; BI	Saline	1×10^7 cells
Hess *et al, 2017*[27]	Acute	Allogenic	MAPC	Intravenous	12	mRS; NIHSS; BI	PlasmaLyte-A and serum albumin	4×10^8 or 1.2×10^9 cells, depending on group
Bhatia *et al, 2018*[26]	Subacute	Autologous	BM-MNC; $CD34^+$	Intraarterial	6	mRS; NIHSS	No medium used	6.1×10^8 total cells, including 1.02×10^7 $CD34^+$ cells
Savitz *et al, 2019*[30]	Subacute	Autologous	ALD-401-bright	Intraarterial	12	mRS; NIHSS; BI	Suspension	Mean dose: 3.08×10^6 cells
Fang *et al, 2019*[33]	Acute	Autologous	Mesenchymal stromal cells; EPC	Intravenous	48	mRS; NIHSS; BI	Saline	5×10^6 cells/kg, in two doses of 2.5×10^6 cells/kg each
Jaillard *et al, 2020*[32]	Subacute	Autologous	BM-MSC	Intravenous	24	mRS; NIHSS; BI	No medium used	Low dose: 1×10^8 cells; high dose: 3×10^8 cells
Law *et al, 2021*[34]	Subacute	Autologous	Mesenchymal stromal cells	Intravenous	12	mRS; NIHSS; BI	Saline-based medium	2×10^6 cells/kg
Chung *et al, 2021*[35]	Chronic	Autologous	Mesenchymal SC	Intravenous	12	mRS	Autologous serum	1×10^6 cells/kg
de Celis-Ruiz *et al, 2022*[31]	Acute	Allogenic	AD-MSC	Intravenous	24	mRS; NIHSS	Glucosaline and Ringer's lactate	1×10^6 cells/kg
Moniche *et al, 2023*[28]	Acute	Autologous	BM-MNC	Intraarterial	6	mRS; NIHSS; BI	Ringer lactate solution with 1% heparin and 2.5% glucose	Low dose: 2×10^6 cells/kg; high dose: 5×10^6 cells/kg
Houkin *et al, 2024*[29]	Acute	Allogenic	MAPC	Intravenous	12	mRS; NIHSS; BI	No medium used	1.2×10^9 cells
Lin *et al, 2024*[39]	Acute	Autologous	CD34+	Intraarterial	6	mRS; NIHSS; BI	Plasma	3×10^7 cells
Yang *et al, 2025*[40]	Acute	Allogenic	NSC and UC-MSC	Intrathecal	6	NIHSS; BI	No medium used	NSCs: 5×10^6 and MSCs: 1×10^7

AD-MSC, adipose tissue-derived mesenchymal stem cells; ALD-401, aldehyde dehydrogenase stem cells; BI, Barthel Index; BM-MNC, bone marrow-derived mononuclear cells; BM-MSC, bone marrow-derived mesenchymal stem cells; EPC, endothelial progenitor cell; FU, follow-up; MAPC, multipotent adult progenitor cells; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSC, neural stem cell; SC, stem cell; UC-MSC, umbilical cord-derived mesenchymal stem cells.

Table 2 Overview of baseline characteristics for intervention and control groups in the included studies

Study	Total (n)	Control (n)	Intervention (n)	Control type	Mean age (y)±SD	Baseline NIHSS	Baseline mRS	Baseline BI	IVT rate and EVT rate	ASPECTS or infarct volume (mL)
Bang *et al*[37]	30	25	5	Open-label standard of care	59.3±11.5 vs 63.0±7.5	11.6±4.9 vs 10.6±2.6	4.6±0.7 vs 4.8±0.5 (measured on 7th day)	13.4±22.2 vs 9.0±20.1 (measured on 7th day)	IVT: 5/25 (20%) vs 1/5 (20%) EVT: n/a	89.1±77.4 vs 127.4±60.3 (DWI lesion volume)
Lee *et al*[36]	52	36	16	Open-label standard of care	64.9±14.5 vs 64.0±11.6	10.17±3.67 vs 10.63±3.03 (measured on 7th day)	4.4±0.9 vs 4.8±0.5 (measured on 7th day)	n/a	IVT: 12/36 (33.3%) vs 6/16 (37.5%) EVT: n/a	90.1±86.8 vs 115.7±95.2
Chen *et al*[38]	30	15	15	Open-label standard of care	52.8±9.0 vs 50.1±7.7	9.6±1.3 vs 9.3±0.5	2.8±0.4 vs 2.9±0.3	n/a	n/a	n/a
Prasad *et al*[25]	120	60	60	Open-label standard of care	52.5±12.1 vs 50.7±11.6	13 (IQR 6) vs 11 (IQR 6)	n/a	27.5 (IQR 25) vs 25 (IQR 28.7)	IVT: 0% vs 0% EVT: 0% vs 0%	111.7±72.4 vs 86.9±57.2
Jin *et al*[41]	20	10	10	Open-label standard of care	53.10±13.07 vs 50.8±17.43	10.7±3.71	4.1±0.99 vs 4.6±0.70	15.00±8.50 vs 14.50±13.01	n/a	n/a
Hess *et al*[27]	126	61	65	Sham infusion	62.6±11.4 vs 61.8±11.4	13.3±3.7 vs 13.4±3.6	n/a	n/a	IVT: 29/61 (48%) vs 29/65 (45%) EVT: 12/61 (20%) vs 17/65 (26%) Both: 9/61 (15%) vs 8/65 (12%)	50.9±41.3 vs 43.7±26.9
Bhatia *et al*[26]	20	10	10	Open-label standard of care	66.0±7.3 vs 57.0±12.2	10.6 vs 10.5	n/a	n/a	IVT: 0 (0%) vs 1 (10%) EVT: n/a	n/a
Savitz *et al*[30]	48	19	29	Sham infusion	62.9±10.81 vs 59.3±10.03	10 vs 11	n/a	n/a	IVT: 2/19 vs 1/29 Thrombectomy: 4/19 vs 5/29 Stent: 2/19 vs 4/29 CEA: 0/19 vs 1/29	n/a
Fang *et al*[33]	16	6	EPCs: 5 BM-MSCs: 5	Sham bone marrow aspiration and intravenous saline infusion	52.83±14.95 vs 50.80±14.11 (EPCs) vs 49.40±10.85 (BMSCs)	15.50±3.02 vs 12.20±4.92 vs 17.60±5.59 (7th day after onset)	3.67±0.82 vs 3.40±0.89 vs 4.00±1.22	25.00±20.00 vs 39.00±24.60 vs 27.00±30.74	IVT: 0/6 vs 0/5 vs 0/5 EVT: n/a	n/a
Jaillard *et al*[32]	31	15	16	Open-label standard of care	55 (IQR 46–58) vs 53 (IQR 45–63)	17 (IQR 14.5–21.5) vs 17 (IQR 14–21)	4 (IQR 3.5–4) vs 4 (IQR 4–4)	47.5 (IQR 10–75) vs 45 (IQR 15–65)	IVT: 4/16 (25%) vs 8/15 (53.3%)	92 (IQR 39–121) vs 113 (IQR 65)
Law *et al*[34]	17	8	9	Open-label standard of care	64.0±13.9 vs 54.6±13.2	15 (IQR 10–21.5) vs 16 (IQR 14.5–21.0)	4.5 (IQR 4–5) vs 4 (IQR 4–5)	5 (IQR 0–27.5) vs 10 (IQR 5–27.5)	Patients with thrombolysis were excluded	38.0±30.1 vs 68.2±41.0

Continued

Table 2 Continued

Study	Total (n)	Control (n)	Intervention (n)	Control type	Mean age (y)±SD	Baseline NIHSS	Baseline mRS	Baseline BI	IVT rate and EVT rate	ASPECTS or infarct volume (mL)
Chung *et al*[35]	54	15	39	Open-label standard of care	64.3±13.3 vs 63.0±14.4	14.5±5.3 vs 11.4±5.2	4.5±0.8 vs 4.3±0.8	19.8±25.5 vs 28.3±26.6	IVT: 5/15 (33%) vs 11/39 (28%) Angioplasty/stenting: 1/15 (7%) vs 1/39 (3%)	96.5±74.3 vs 91.0±79.6
de Celis-Ruiz *et al*[31]	19	10	9	Sham infusion	76 (69–80.25) vs 78 (70.5–82)	10.5 (9.5–14) vs 12 (9–17.5)	n/a	n/a	IVT: 1/10 (10%) vs 1/9 (11.1%) EVT: 4/10 (40%) vs 0/9 (0%) Both: 1/10 (10%) vs 1/9 (11.1%)	88.2 (55.1–130.8) vs 43.22 (37.6–94.0)
Moniche *et al*[28]	77	38	Low dose: 20, high dose: 19	Open-label standard of care	66.0 (54–72) vs 63.0 (55–72) (low dose) vs 66.0 (52–76) (high dose)	12.3±4.5 vs 12.4±4.4 vs 12.7±3.4	n/a	n/a	IVT: 16/38 (42%) vs 10/20 (50%) vs 9/19 (47%) EVT: 33/38 (87%) vs 16/20 (80%) vs 14/19 (74%) Both: 14/38 (37%) vs 7/20 (35%) vs 7/19 (37%)	79 (41–108) vs 68 (46-90) vs 69 (55-98)
Houkin *et al*[29]	206	102	104	Sham infusion	76.2±10.6 vs 76.7±10.4	13.9±3.9 vs 13.7±3.9	n/a	n/a	Any reperfusion therapy: 52/102 (51%) vs 56/104 (53.8%) IVT: 12/102 (11.8%) vs 24/104 (23.1%) EVT: 40/102 (39.2%) vs 32/104 (30.8%)	54.3±57.0 vs 42.0±48.4
Lin *et al*[39]	28	14	14	Open-label standard of care	64.5±9.6 vs 65.2±8.2	n/a	n/a	n/a	Patients with IVT or EVT were excluded	n/a
Yang *et al*[40]	156	78	78	Open-label standard of care	57.5±6.5 vs 59.0±7.8	10.2±3.2 vs 10.8±2.9	n/a	41.0±7.1 vs 39.2±8.4	Patients with a history of IVT were excluded	n/a

Data are presented as n (%), mean (SD), or median (IQR) IVT: Intravenous thrombolysis; EVT: Endovascular thrombectomy; ASPECTS: Alberta Stroke Program Early CT Score; DWI: Diffusion-Weighted Imaging; CEA: Carotid Endarterectomy
BI, Barthel Index; BM-MSC, Bone marrow-derived mesenchymal stem cell; EPCs, endothelial progenitor cells; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Risk-of-bias assessment

Overall, 3 studies (18%) were deemed to have a low risk of bias, 13 studies (76%) were assessed as having a moderate risk of bias, and 1 study (6%) was identified as having a high risk of bias (figure 2).

Primary outcomes

Clinical outcome assessment

Modified Rankin Scale (mRS)

16 (94%) included trials reported the mRS as an outcome measure at the end of the follow-up period. However, mRS data were unavailable for one study (6%), and additional data requests by email were unsuccessful.[30] The analysis of 15 trials comprising 824 patients demonstrated that patients in the SC therapy group achieved significantly better outcomes in mRS scores at the end of their respective follow-up periods compared with the control group (MD=−0.27, 95% CI −0.51 to −0.03, p=0.027, I^2=42.2%) (figure 3A).

Barthel Index (BI)

12 studies (71%) reported BI outcomes at the end of their follow-up periods.[25 27–30 32–34 37 39–41] BI data could not be retrieved for three studies (18%), and data request to the corresponding authors were unsuccessful.[28–30] A pooled analysis of nine trials involving 525 patients showed a significant difference in BI scores between the SC therapy group and the control group (MD=7.78, 95% CI 0.50 to 15.06, p=0.036, I^2=53.0%) (figure 3B).

National Institutes of Health Stroke Scale (NIHSS)

The NIHSS was reported as an outcome measure in 15 (88%) studies.[25–34 37–41] However, NIHSS data from three trials (18%) were unavailable, and data requests were unsuccessful.[29 30 37] The pooled analysis of 12 trials, including 583 patients, showed no favourable outcome in NIHSS scores for patients receiving SC therapy compared with the control group at the end of the follow-up period (MD=−0.65, 95% CI −1.73 to 0.42, p=0.24, I^2=71.7%) (figure 3C).

Safety assessment

Mortality

Mortality data were reported in all but one of the included studies (n=16, 94%). A pooled analysis revealed significantly lower mortality rates in the SC therapy groups compared with the control groups (RR=0.64, 95% CI 0.42 to 0.98, p=0.040, I^2=0%) (figure 4).

Adverse events

No cases of severe neurological worsening without recurrent stroke or instances of neoplastic transformation of the ischemic lesion were reported within any of the included studies. The analysis of AE showed no significant differences between the SC therapy and control groups for all AE (figure 5).

Subgroup analysis

Subgroup analysis was performed for (a) route of administration, (b) timing of injection and (c) cell type (table 3).

A. Intrathecal delivery was associated with significant improvement in mRS and BI, but not in NIHSS. Intracerebral administration was also associated with significant improvements in mRS and NIHSS; however, its effect on BI scores was not assessed (online supplemental figure 1).
B. Treatment during the subacute phase improved BI. Furthermore, NIHSS scores improved significantly when administered in the acute and chronic phases (online supplemental figure 2).
C. Subgroup analysis by cell type demonstrated that autologous SC therapy was associated with significant improvements in both mRS and BI (online supplemental figure 3). In addition, allogenic SC therapy produced a significant benefit on the NIHSS.

Publication bias

Funnel plots demonstrated minimal to no publication bias (online supplemental figure 4). Egger's test did not indicate significant publication bias or funnel asymmetry for the mRS (intercept=0.44, SE=0.77, t=0.57, p=0.58), BI (intercept=0.21, SE=0.77, t=0.27, p=0.79) and NIHSS (intercept=−0.20, SE=0.76, t=−0.27, p=0.79),

Sensitivity analysis

The Baujat diagnostic analysis for the mRS identified Jin *et al* (Cochran's Q: 40.8%)[41] and Prasad *et al* (13.2%)[25] as the principal sources of overall heterogeneity (online supplemental figure 5A). Excluding Jin *et al* rendered the effect non-significant and reduced heterogeneity (MD=−0.20, 95% CI −0.41 to 0.02, p=0.069, I^2=27.2%). The exclusion of Prasad *et al* maintained a significant effect size while moderately reducing heterogeneity (MD=−0.33, 95% CI −0.56 to −0.09, p=0.0076, I^2 = 39.1%).

For BI, Jin *et al* (36.6%)[41] and Hess *et al* (16.0%)[27] accounted for over half of the heterogeneity (online supplemental figure 5B). Removing Jin *et al* reduced heterogeneity and produced a non-significant effect (MD=4.97, 95% CI −0.57 to 10.51, p=0.08, I^2=32.1%), while excluding Hess *et al* retained significance with minor heterogeneity reduction (MD=9.75, 95% CI 2.06 to 17.44, p=0.013, I^2=53.4%).

For NIHSS, Jin *et al* (35.5%)[41] and Chen *et al* (31.7%)[38] contributed most to heterogeneity (Suponline supplemental figure 5C). Excluding Jin *et al* rendered a significant NIHSS improvement and reduced heterogeneity (MD=−1.01, 95% CI −1.96 to −0.05, p=0.038, I^2=59.2%). Excluding Chen *et al* resulted in a moderate change in effect size heterogeneity (MD=−0.18, 95% CI −1.10 to 0.74, p=0.70, I^2=57.7%).

DISCUSSION

Despite intravenous thrombolysis and mechanical thrombectomy having revolutionised treatment for acute IS, nearly 29% of survivors suffer from moderate

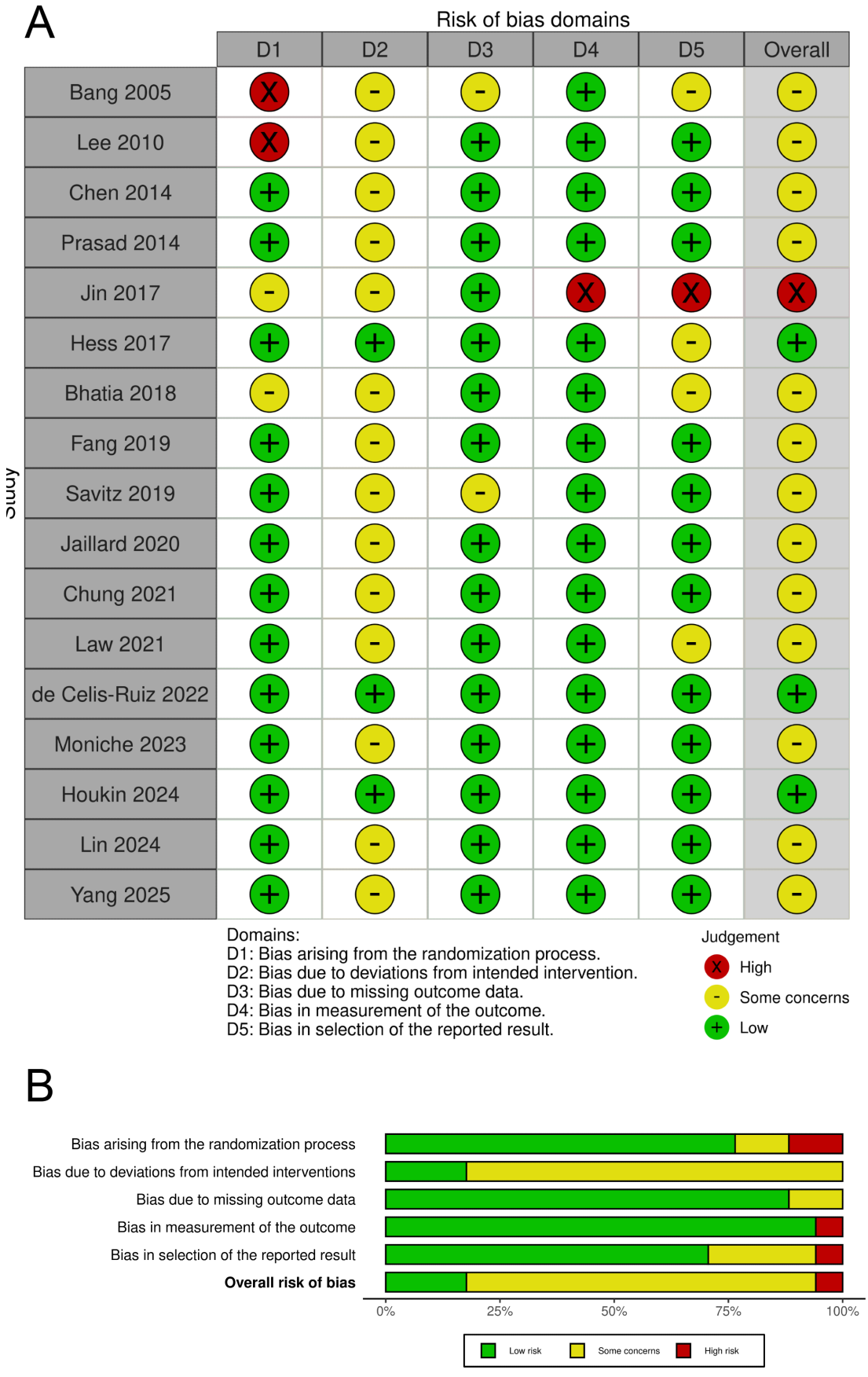

Figure 2 Risk-of-bias assessment using the Cochrane Risk-of-Bias tool, presented as: (A) traffic light plot for individual included studies, (B) summary plot showing risk-of-bias dimensions across all studies.

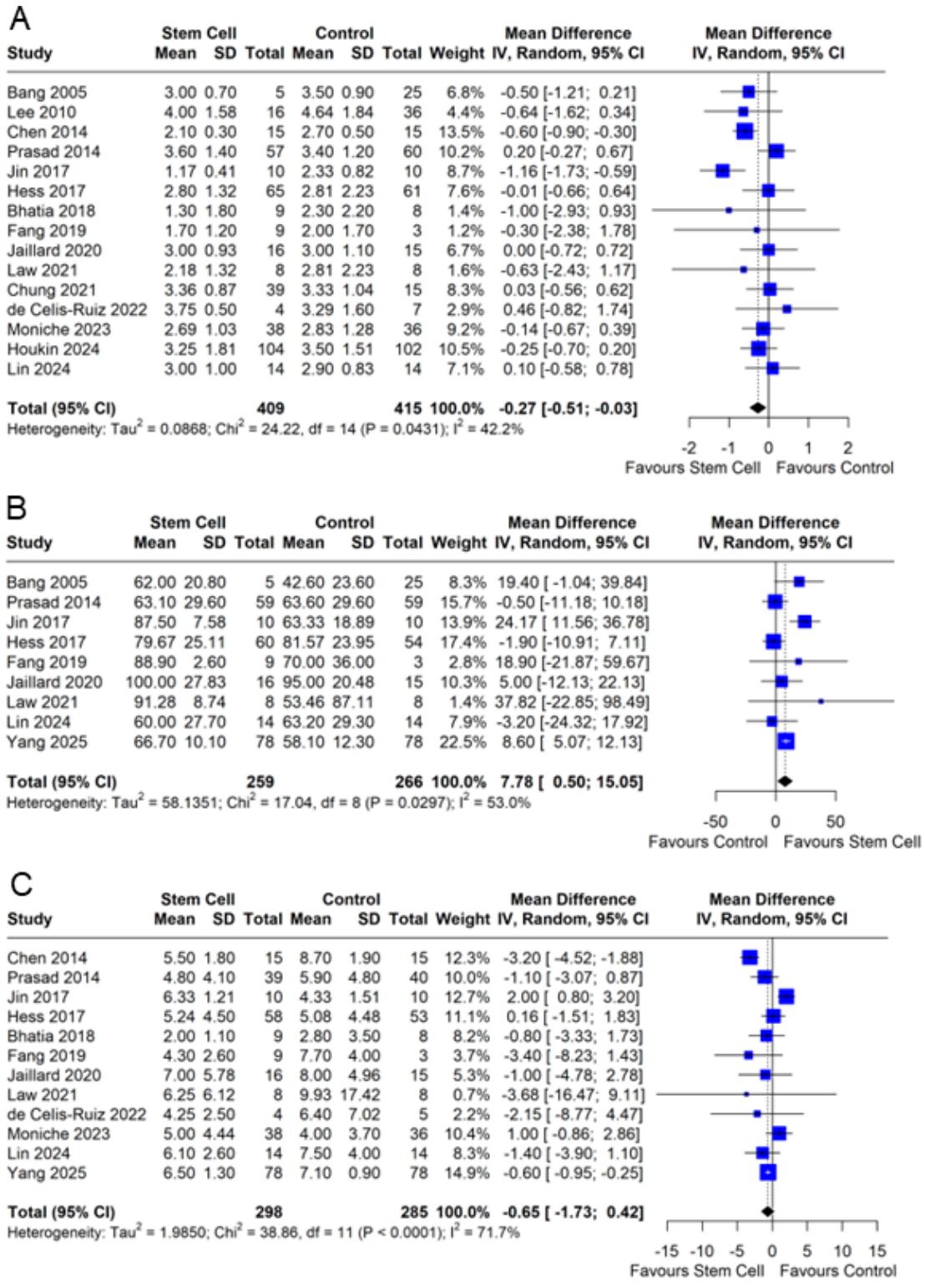

Figure 3 Forest plots illustrating the pooled effect sizes for clinical outcomes: (A) modified Rankin Scale, (B) Barthel Index and (C) National Institutes of Health Stroke Scale. IV, intravenous.

to severe disability.[42] Once the narrow therapeutic windows for these interventions are missed, patients are often left with limited rehabilitative strategies. As such, there is growing interest in post-acute and regenerative treatments, including SC therapies. Our meta-analysis of RCT revealed noteworthy benefits of SC therapy in IS, including significant enhancements in mRS and BI scores and a reduction in mortality rates compared with control groups. Nevertheless, no significant improvements were detected in NIHSS scores in the primary analysis. Importantly, SC therapy was not linked to serious safety issues.

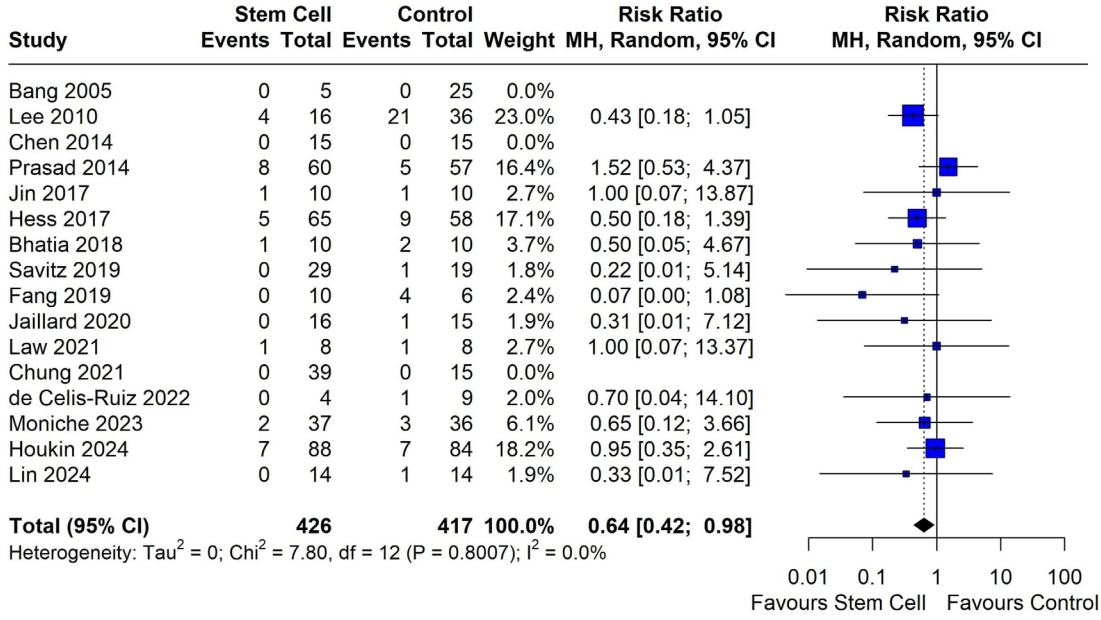

Figure 4 Forest plots showing pooled effect size for mortality. MH: Mantel Haenszel Test

Subgroup analyses further suggested enhanced efficacy with more targeted delivery methods (intrathecal and intracerebral). In addition, BI improved when SC therapy was applied during the subacute phase (8 days to 3 months after IS) and NIHSS improved when SC therapy was given in the acute (up to 7 days) or chronic phases (more than 3 months) of IS. Also, the use of autologous cell therapies was linked to significant improvements in mRS and BI, while allogenic SC were associated with improvements in NIHSS. Despite these findings, the high heterogeneity of the published data and moderate risk of bias across studies limit the strength of our analysis.

Efficacy

This meta-analysis showed favourable outcomes for the mRS and BI following SC therapy but found no significant improvements in NIHSS scores. The observed difference in outcomes may be explained by the broader scope of the mRS and BI, which assess overall functional recovery and daily living, whereas the NIHSS focuses on more specific neurological deficits.[43–45] Earlier meta-analyses reported broader benefits of SC therapy, but the inclusion of recent negative trials published and sourcing additional data from the study authors likely explains our more conservative findings.[46–48] It is also important to note that the pooled results are not robust but substantially influenced by individual studies.[27 41] Some variability in outcomes may also relate to the different SC types used across trials, as these differ in their immunomodulatory and regenerative capacities. Therefore, caution is warranted when interpreting the clinical efficacy of SC therapy.

Safety

Regarding safety, our analysis found significantly lower mortality rates with SC therapy overall. Notably, only one study in our analysis reported a higher mortality rate in the SC group.[25] This aligns with previous meta-analyses.[48 49] The survival benefit of SC therapy may be attributed to its ability to mitigate secondary injury through neuroprotection, immune modulation and vascular repair.[50 51]

Importantly, no serious AE such as tumourigenicity, severe neurological worsening or SICH were observed in any patient receiving SC therapy. Other AE, including infections, recurrent stroke or TIAs and seizures, showed no significant differences between the SC and control groups. This result is consistent with the meta-analysis by Boncoraglio *et al*, which examined the same AE outcomes.[46] Nevertheless, the observed non-significant trend toward increased seizure risk among SC-treated patients emphasises the need for further safety evaluations, particularly in larger populations. No excess rates of AE were observed when comparing targeted versus systemic administration methods.

Although overall AE findings were encouraging, the largest RCTs reported more treatment emergent but non-serious events in SC groups,[27 29] while Prasad *et al* found comparable rates between groups.[25] These results highlight the need for further evaluation of treatment-emergent AE and long-term safety beyond 5 years.

Administration route, timing of treatment, SC type and dosage

Our subgroup analyses suggest that targeted delivery methods, such as lumbar subarachnoid or intracerebral approaches, may enhance functional recovery. This may be due to the higher local concentrations of therapeutic cells and bypassing the blood–brain barrier. This approach could be particularly effective for well-defined lesions (eg, small vessel occlusion or subacute/chronic phase), although current evidence is limited to small

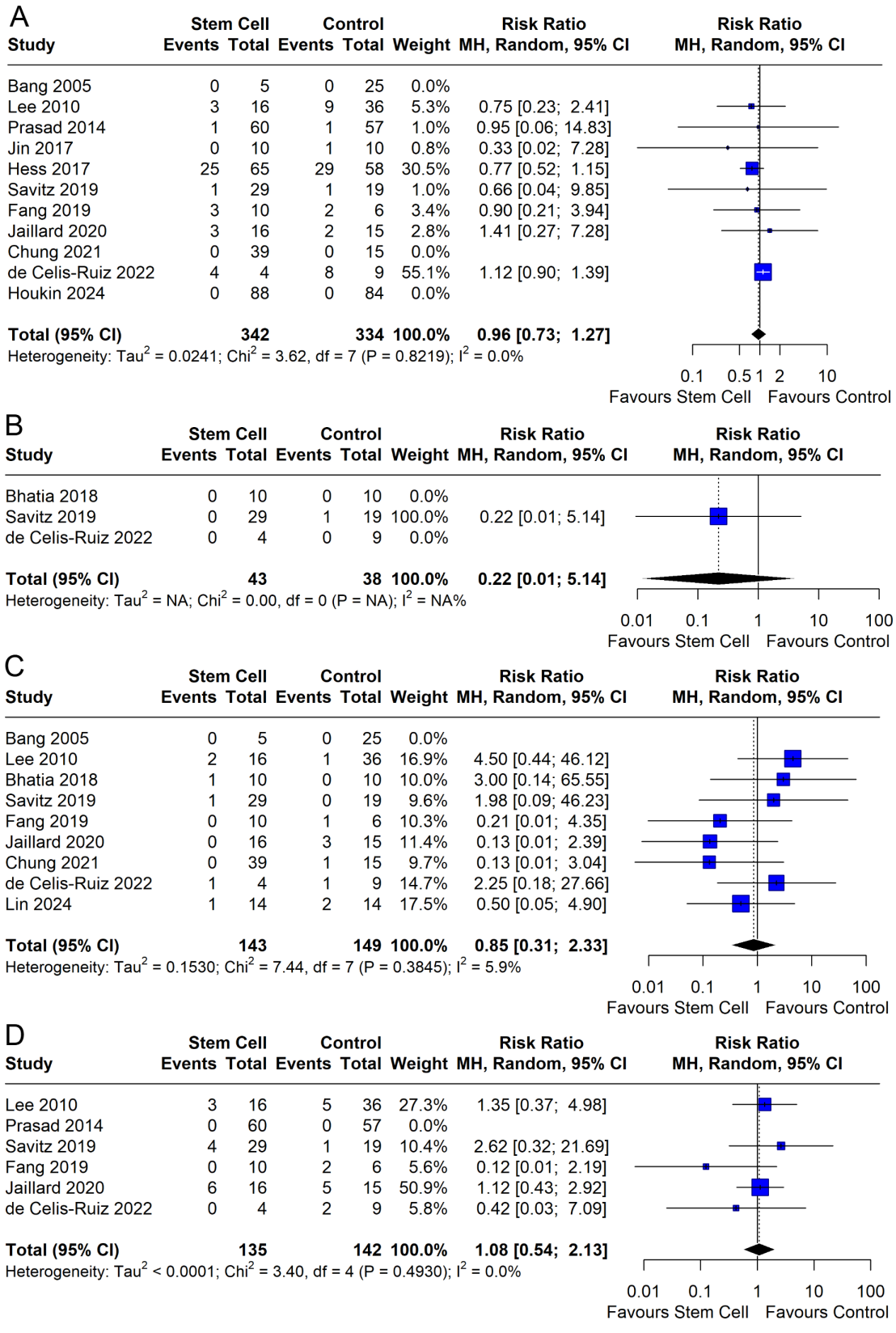

Figure 5 Forest plots showing effect size of adverse events: (A) infections, (B) symptomatic intracranial haemorrhages, (C) strokes and transient ischemic attacks, (D) seizures. MH: Mantel Haenszel Test

Table 3 Subgroup analyses of pooled effect sizes stratified by clinical outcome measures

Outcome measure	Variable	Studies (n)	MD (95% CI)	P value (MD)	Heterogeneity (%)	Heterogeneity (95% CI)	P value (subgroup differences)
Administration route							
mRS	Intracerebral	1 (single study)	−0.60 (−0.90 to −0.30)	<0.0001	–	–	0.0006
	Intrathecal	1 (single study)	−1.16 (−1.73 to −0.59)	<0.0001	–	–	
	Intravenous	10	−0.09 (−0.31 to 0.13)	0.41	0	0.00 to 0.62	
	Intra-arterial	3	−0.09 (−0.50 to 0.32)	0.66	0	0.00 to 0.90	
BI	Intrathecal	2	15.16 (0.09 to 30.22)	0.048	81.6	0.22 to 0.96	0.23
	Intravenous	6	2.03 (−3.96 to 8.03)	0.51	6.6	0.00 to 0.76	
	Intra-arterial	1	−3.2 (−24.32 to 17.92)	0.77	–	–	
NIHSS	Intracerebral	1 (single study)	−3.20 (−4.52 to −1.88)	<0.0001	–	–	0.004
	Intrathecal	2	0.63 (−1.9 to 3.18)	0.63	94.0	0.81 to 0.98	
	Intravenous	6	−0.68 (−1.83 to 0.47)	0.25	0	0 to 0.75	
	Intra-arterial	3	−0.20 (−1.80 to 1.36)	0.80	25.4	0.00 to 0.92	
Disease phase							
mRS	Chronic	2	−0.34 (−0.95 to 0.27)	0.27	71.2	0.00 to 0.94	0.41
	Subacute	7	−0.44 (−0.92 to 0.03)	0.06	60.0	0.08 to 0.83	
	Acute	6	−0.09 (−0.36 to 0.18)	0.49	0	0.00 to 0.11	
BI	Subacute	5	12.40 (0.19 to 24.61)	0.047	61.9	0.00 to 0.86	0.27
	Acute	4	4.1 (−3.97 to 12.18)	0.32	47.9	0.00 to 0.83	
NIHSS	Chronic	1 (single study)	−3.20 (−4.52 to −1.88)	<0.0001	–	–	0.0006
	Subacute	5	−0.006 (−1.80 to 1.78)	0.99	61.2	0.00 to 0.85	
	Acute	6	−0.51 (−0.97 to −0.05)	0.03	8.2	0.00 to 0.77	
Stem cell type							
mRS	Autologous	12	−0.32 (−0.61 to −0.03)	0.03	49.1	0.01 to 0.74	0.39
	Allogeneic	3	−0.12 (−0.48 to 0.24)	0.50	0	0.00 to 0.90	
BI	Autologous	7	10.46 (0.06 to 20.87)	0.049	50.7	0.00 to 0.79	0.40
	Allogeneic	2	4.2 (−5.95 to 14.36)	0.42	77.9	0.04 to 0.95	
NIHSS	Autologous	9	−0.78 (−2.22 to 0.65)	0.28	78.8	0.60 to 0.89	0.77
	Allogeneic	3	−0.57 (−0.92 to −0.23)	0.001	0	0.00 to 0.89	

BI, Barthel Index; MD, mean difference; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

cohorts. Similar benefits have been reported in previous clinical and preclinical meta-analyses.[12 46]

Systemic administration via IA or intravenous routes offers a less invasive and more readily available approach, but our analysis did not show a significant outcome for the mRS. This could be explained by cell sequestration in peripheral organs.[52 53]

Despite these challenges, systemic delivery remains a viable option, particularly in large vessel occlusions and the acute phase, where precise targeting is difficult. Among systemic approaches, IA appears more promising than intravenous by bypassing peripheral filtration and improving delivery efficiency.[53] When combined with real-time imaging, SC therapy can be delivered more precisely, thereby addressing one of its primary limitations.[54] Alternative routes, such as intranasal delivery, show encouraging results in animal models and could provide a less invasive method for targeting the brain.[55–57]

Regarding the disease phase, SC transplantation improved certain outcomes during the acute and subacute phase, which is consistent with preclinical evidence, suggesting that therapeutic benefits arise from modulation of the post-stroke microenvironment rather than neuronal replacement.[58 59] This underscores the potential of SC therapy as a viable treatment option in not only the acute but also both the subacute and possibly chronic stages of stroke, extending the therapeutic window.

Furthermore, autologous SC therapy was associated with significant improvements in mRS and BI, whereas allogenic SC showed a significant benefit on NIHSS, likely reflecting differences in biological mechanisms and the limited number of trials. While autologous SCs are

generally safer, allogenic SCs offer practical advantages, including immediate availability for acute treatment and avoidance of bone marrow aspiration challenges in patients on antiplatelet or anticoagulant therapy.[48] Moreover, SC quality declines with age, potentially reducing the therapeutic efficacy of autologous cells in older patients.[60] These differences likely reflect distinct underlying mechanisms, including variations in paracrine signalling, immune modulation and support of angiogenesis, which may guide future optimisation of cell type and timing.

Quality of evidence

The overall quality of evidence in this analysis was moderate, with three-quarters of the included studies classified as having a medium risk of bias and one study rated as high risk. The predominant source of bias was largely due to the single-blinded or open-label design of these trials. This pattern of moderate risk of bias aligns with findings from previous meta-analyses.[46 48 61]

Although our analysis did not identify any evidence of significant publication bias, substantial heterogeneity was observed across the included studies. The high heterogeneity in the primary outcome may stem from variations in SC sources, administration routes, treatment time windows and follow-up durations.

Baujat diagnostics and leave-one-out analyses identified key contributors to this heterogeneity, with Jin *et al*[41] emerging as the main source. Excluding this study substantially reduced heterogeneity and nullified the significant mRS and BI effect, indicating that its inclusion strongly influenced the overall outcome. This high heterogeneity likely stems from the study's unblinded outcome assessment and small, underpowered sample of 10 patients per group. Our findings highlight inconsistencies across trials and the need for more rigorous methods.

Future perspectives

The exact mechanisms underlying the therapeutic effects of SC therapy in IS remain poorly understood. While early studies suggested that SCs replace lost neurons,[62] accumulating evidence indicates they act primarily through the release of trophic factors that modulate inflammation, promote neurogenesis and facilitate angiogenesis.[58 59 62 63]

Despite promising findings, our meta-analysis indicates that SC therapy is not yet ready for routine clinical application. First, the choice of delivery method remains a critical issue. While targeted methods demonstrated more significant improvements compared with systemic administration, their feasibility for clinical application remains limited. Focused ultrasound and/or microbubble-assisted blood–brain barrier opening may improve systemic delivery by allowing SC to penetrate ischemic areas.[64 65] Additionally, the potential interactions between SC and standard stroke medications (eg, antiplatelets, antihypertensives, statins) require further preclinical investigation.[9]

Second, combining SC therapy with neurorehabilitation should be considered to enhance recovery, but the timing of rehabilitation is critical. Mistimed rehabilitation could diminish the benefits of SC therapy.[9] Differentiating the effects of rehabilitation from those of SC treatment complicates clinical trial design.

Third, optimising SC dosage is essential for achieving therapeutic efficacy while minimising risks. In these RCTs, dosing was typically extrapolated from preclinical animal models, with safety margins applied to reduce the risk of embolic stroke.[66] Nonetheless, current trials used a highly variable range of doses, spanning from three million to over one billion cells, with no established consensus on the optimal dose.[29 30] Two trials comparing low and high doses found no significant differences in efficacy or safety, underscoring the need for further preclinical dose-escalation studies.[28 32]

Finally, logistical and financial barriers remain significant obstacles to clinical translation. SC therapy requires specialised culture facilities, strict transportation protocols and standardised manufacturing processes to ensure reproducibility and quality control. The high cost of development and administration also poses a major challenge. Collectively, these gaps highlight the continuing need for large, phase III RCT with clear methodology, detailed reporting and publicly available outcome data to establish more definitive conclusions and enable the clinical translation of SC therapy in IS.

Limitations

This meta-analysis has several limitations. First, excluding unpublished trials and non-English studies may have introduced publication bias. Second, the high heterogeneity among studies, combined with small sample sizes and moderate-to-high risk of bias, likely reduced the reliability of the findings. Third, incomplete data from certain studies, due to non-responses from corresponding authors, further compromised the overall robustness of the analysis.

CONCLUSION

In summary, SC therapy holds promise for improving functional outcomes and mortality rates after IS. Nonetheless, variability in trial design, cell types, dosage and administration routes complicates definitive conclusions. Larger, rigorously conducted phase III trials with consistent protocols are necessary to establish standardised guidelines and confirm safety profiles over extended follow-up periods.

Contributors Conceptualisation: AS and RG. Data curation: DdW and AS. Formal analysis: DdW and AS. Resources: RG. Supervision: AS and RG. Visualisation: DdW and AS. Writing—original draft: DdW and AS. Writing—review and editing: All authors. Guarantor: RG. ChatGPT (model 4o, OpenAI) was used to refine sentence structure and wording.

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