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Efficacy and safety of stem cells in the treatment of ischemic stroke

A meta-analysis

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Abstract

Background: Stem cell therapy on ischemic stroke has long been studied using animal experiments. The efficacy and safety of this treatment in ischemic stroke patients remain uncertain.

Methods: We searched for all clinical randomized controlled trials published before October 2023, on PubMed, EMBASE, and the Cochrane Library using predetermined search terms, and performed a meta-analysis of the efficacy of stem cell therapy in ischemic stroke patients.

Results: 13 studies that included 592 ischemic stroke patients were reviewed. The mRS (MD −0.32, 95% CI −0.64 to 0.00, I^2 = 63%, P = .05), NIHSS (MD −1.63, 95% CI −2.69 to −0.57, I^2 = 58%, P = .003), and BI (MD 14.22, 95% CI 3.95–24.48, I^2 = 43%, P = .007) showed effective stem cell therapy. The mortality (OR 0.42, 95% CI 0.23–0.79, I^2 = 0%, P = .007) showed improved prognosis and reduce mortality with stem cell therapy.

Conclusion: Stem cell therapy reduces mortality and improves the neurological prognosis of ischemic stroke patients. However, due to the different types of stem cells used and the limited data in the reported studies, the safety of clinical applications of stem cells in patients with ischemic stroke must be carefully evaluated. Future randomized controlled trials with large sample sizes from controlled cell sources are warranted to validate this finding.

Abbreviations: BI = Barthel index, mRS = modified Rankin scale, MSCs = mesenchymal stem cells, NIHSS = National Institutes of Health Stroke Scale, RCT = randomized controlled trial.

Keywords: ischemic stroke, meta-analysis, mortality, randomized controlled trials, stem cells

1. Introduction

Ischemic stroke due to cerebral ischemia and hypoxia is a cerebrovascular disease with a high rate of disability. Ischemic stroke represents the main cause of disability and death worldwide.[1] The mortality rate of ischemic stroke within 30 days has been reported to range from 5% to 15%, and the disability rate may exceed 50%.[2,3] More than 40% of survivors experience ischemic stroke again, with even higher mortality and disability rates.[2,4] To date, recombinant tissue plasminogen activator standard intravenous thrombolytic therapy represents the only clinically approved drug therapy for acute cerebral infarction. However, this treatment has limitations, mostly linked to its application within a short window period of 4.5 hours following onset of symptoms.[5–7] Endovascular interventional therapy is also being increasingly used, but remains only applicable to patients with large vascular occlusions.[8,9] The disability rates for patients not eligible for either thrombolytic therapy or thrombectomy are even higher. Although rehabilitation treatment contributes to the recovery of neurological function, its curative effect remains limited.[10,11]

To date, a large number of preclinical studies have shown that stem cells can improve the recovery of neurological function after a cerebral ischemic injury through a variety of mechanisms. This includes the inhibition of inflammation, promotion of axonal regeneration, and neuroprotective effects.[12–19] Nevertheless, there have been few clinical trials on the treatment of ischemic stroke with stem cells.[20] In this study, we conducted meta-analyses of previously published clinical randomized controlled trials to determine the efficacy and safety of stem cells in the treatment of ischemic stroke.

YX, XG, WG, and CK contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

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2. Materials and methods

2.1. Search strategy

Two researchers (Y.X and F.Z) independently searched the PubMed, EMBASE, and Cochrane Library databases for any clinical randomized controlled trials published before October 2023. Keywords used in the search strategies included "stem cells," "ischemic stroke," and "randomized controlled trials" (MeSH and Entry Terms). The keywords used in this search strategy included "Randomized Controlled Trial" AND ("Progenitor Cells" OR "Mother Cells" OR "Colony-Forming Unit" OR "Stem Cells") AND ("Ischemic Stroke" OR "Cryptogenic Ischemic Stroke" OR "Cryptogenic Stroke" OR "Cryptogenic Embolism Stroke" OR "Wake-up Stroke" OR "Acute Ischemic Stroke" OR "Ischemic Stroke"). Repeated literature, case reports, summary meetings, animal experiments, other reviews and meta-analyses, ongoing experiments, and failed experiments were excluded for various reasons. Prior to the final data analysis, we ran a search algorithm for any new relevant publications. A flow chart of the specific search strategy is included in Figure 1 (Appendices Figures). The review was not registered. Ethical approval is not used for this study.

2.2. Inclusion criteria and exclusion criteria

The inclusion criteria of the eligible studies were as follows: ischemic stroke was diagnosed by computed tomography or magnetic resonance imaging (regardless of whether the disease was acute or chronic); intervention was stem cell therapy (regardless of type, dose, and injection mode); outcome indicators were the National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS), Barthel index (BI), and safety results, including mortality and other complications; and the study was a clinical randomized controlled trial (RCT).

The exclusion criteria were as follows: interventions were not stem cells; other diseases; outcome indicators did not meet; only one group of data available or data could not be extracted or the data were incomplete; and follow-up failed due to various reasons.

2.3. Study selection

Two researchers (Y.X and F.Z) preliminarily screened studies that met the inclusion criteria according to the title and summary of the study. The full text of the preliminary study was then retrieved to assess whether they qualified for inclusion. Discrepancies were resolved through discussions.

2.4. Data extraction

Researcher Y.X used the pre-designed standardized form to extract data and the data was checked by the second researcher (F.Z) to evaluate the bias risk and evidence quality of individual included studies. The extracted information included the study country, study type, details of interventions, specific classification of diseases, treatment methods, outcome indicators, and other data u sed to assess the risk of bias and quality of evidence. Whenever possible, missing data were obtained by directly emailing the study authors.

2.5. Assessment quality

The Cochrane Risk Bias Assessment Tool was used to assess the bias of each study. The degree of bias risk (low risk, unknown risk, high risk) was evaluated from 7 aspects (random sequence generation, allocation concealment, blinding researchers and participants, integrity of outcome data, blind evaluation of research outcome, selective reporting of research result, and other sources of bias), so as to reflect the quality of each research.

2.6. Outcome measures

Mortality was the primary outcomes. The secondary outcomes included mRS, mRS ≤ 2, NIHSS, BI, and related complications. Patients with mRS ≤ 2 are generally considered to be non-disabling stroke patients with good prognosis.[21]

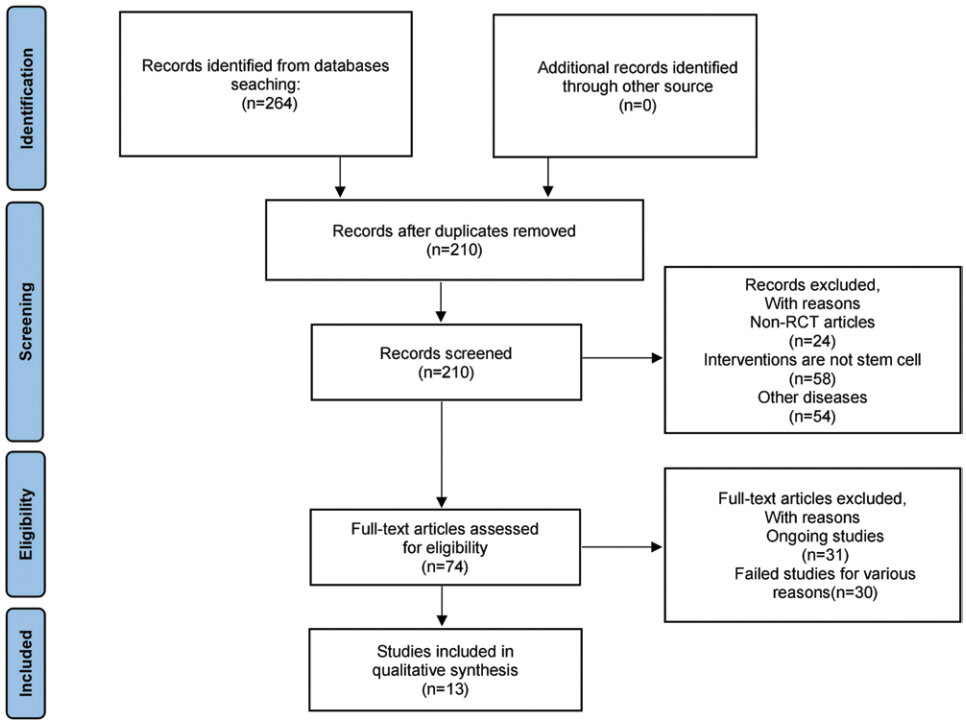

Figure 1. Flow chart of the search algorithm.

Table 1

The characteristics of the 13 included studies.

Author	Country	Year	Age	Type	Blind	Immuno-suppressive treatment	Rehabilitation	Stem cell group	Control group (Saline)	Cell type	Route of administration	Outcomes scale
Bang[24]	Korea	2012	30-75	Phase III	Yes	NR	NR	5	25	Autologous MSCs	Intravenous Injection	BI, mRS
Bhasin[25]	India	2016	33-61	NR	Incomplete	NR	Yes	10	10	Autologous MNCs	Intravenous Injection	SAE, mBI, FM, VEFG, MRC, BDNF
Bhatia[26]	India	2018	20-80	NR	Yes	NR	NR	10	10	Autologous MNCs	Arterial Injection	mRS, NIHSS, SAE
Chen[27]	CHINA	2014	35-75	Phase II	NR	NR	Yes	15	15	PBSC	NR	NIHSS, mRS
Chung[28]	Korea	2021	30-75	Phase II	Yes	NR	Yes	39	15	Autologous MSCs	Intravenous Injection	mRS, SAE, MI, FMA, FAC
Fang-1[29]	CHINA	2018	18-80	Phase I/IIa	Incomplete	NR	NR	5	6	Autologous EPCs	NR	BI, mRS, NIHSS, SAE, SSS
Fang-2[29]	CHINA	2018	18-80	Phase I/IIa	Incomplete	NR	NR	5	6	Autologous MSCs	NR	BI, mRS, NIHSS, SAE, SSS
Hess[30]	England USA	2017	18-83	Phase II	Yes	NR	NR	65	61	Allogenic MAPCs	Intravenous Injection	mRS, NIHSS, BI, SAE
Jaillard[31]	France	2020	18-70	NR	Incomplete	NR	Yes	16	15	Autologous MSCs	Intravenous Injection	NIHSS, mRS, BI, SAE, FMS
Jin[35]	CHINA	2017	NR	NR	NR	NR	NR	10	10	Autologous MNCs	NR	NIHSS, BI, mRS, SAE, FIM
Lee[32]	Korea	2010	30-75	NR	Incomplete	NR	NR	16	36	Autologous MSCs	Intravenous Injection	mRS, SAE, SDF-1a
Prasad[21]	India	2014	18-75	Phase II	Yes	NR	NR	60	60	Autologous MNCs	Intravenous Injection	mRS, BI, NIHSS, IV
Savitz[33]	USA	2019	30-83	Phase II	Yes	NR	NR	29	16	Autologous BM ALD-401 cell	Arterial Injection	mRS, BI, NIHSS, SAE, DWI, ALDH
Xie[34]	CHINA	2016	45-71	NR	NR	NR	NR	12	10	Allogeneic UCMSCs	NR	SAE, MMSE, HAMA, HRSD, UPDRS

ALDH = aldehyde dehydrogenase, BDNF = brain-derived neurotrophic growth factor, BI = Barthel index, DWI = diffusion-weighted imaging, EPCs = endothelial progenitor cells, FAC = functional ambulatory category, FIM = functional independence measure, FM = Fugl Meyer scale, FMA = Fugl-Meyer Assessment, FMS = Fugl-Meyer Score, HAMA = Hamilton Anxiety Rating Scale, HRSD = Hamilton Rating Scale for Depression, IV = infarct volume, MAPCs = multipotent adult progenitor cells, MI = motricity index, MMSE = mini-mental state examination, MNCs = marrow mononuclear cells, mRS = modified Rankin Scale, MSCs = mesenchymal stem cells, NIHSS = National Institute of Health stroke scale, NR = none reported, PBSC = peripheral blood stem cells, SAE = severe adverse events, SDF-1a = stromal cells derived factor-1a, SSS = Scandinavia Stroke Scale, UCMSCs = umbilical cord mesenchymal stem cells, UPDRS = Unified Parkinson's Disease Rating Scale, VEGF = vascular endothelial growth factor.

2.7. Statistical analyses

The meta-analysis of data was carried out using the REVMAN software. We obtained the 95% CI and *P* value of each study by measuring the MD of the continuous variable and the OR of the binary variable. Q-value statistics and I^2 value statistics were used to assess the heterogeneity of the study. According to the recommendations of the Cochrane Statistical Methods Group, the heterogeneity *P* value was set to .1, and the I^2 statistic was interpreted as: 0% to 40%-low heterogeneity, 30% to 60%-moderate heterogeneity, 50% to 90%-substantive heterogeneity, 75% to 100%-obvious heterogeneity. If there was substantial heterogeneity ($I^2 \geq 50\%$), researchers performed a sensitivity analysis or created a Galbraith plot (STATA) to identify the source of heterogeneity.[22] For the outcome indicators of more than 10 patients, researchers developed a funnel plot (STATA) to assess publication bias.[23] Egger and Begg's test was used to evaluate the asymmetry of the funnel plot, and a value of $P > .05$ was considered reflective of the absence of any publication bias.

3. Results

3.1. Search results

A total of 264 studies were identified using the search method, and 210 articles were included after removing duplicate articles. Another 136 articles were excluded during primary screening (because they were unrelated to the ailments studied or were meta-analyses, reviews, conference summaries, or animal experiments). Following a full review of the remaining 74 studies, 31 ongoing studies and 30 failed studies were excluded for various reasons (due to withdrawal of a large number of participants during the experiment and insufficient recruitment). The retrieval strategy was repeated before data analysis, and no additional studies were identified in the update. Finally, 13 studies[21,24–35] involving 592 patients were included. The overall characteristics of the 13 studies and specific information on the individual studies are represented in detail in Table 1

3.2. Risk of bias in included studies

The Cochrane risk bias assessment tool was used to assess the quality of the included 13 RCTs. Among these, 11 studies[21,24–32,35] specified the process of generating random sequences, including random number tables, computer random number generation, coin throwing, and double-blind lottery. Two studies did not specify the randomization process.[33,34] Six studies[24–26,30,33,35] mentioned blindness for participants and major researchers, and 2 studies[27,29] only considered single blindness. Four studies[21,31,32,34] were not blinded to the researchers or participants (open label) and one study[28] did not elaborate on blindness. There were follow-up losses in the 13 studies; due to the small number of missing follow-ups, the number was balanced between groups, which was insufficient to impact the intervention effect. The results of the bias risk assessment are represented in Figures S1 and 2, Supplemental Digital Content, http://links.lww.com/MD/L843; http://links.lww.com/MD/L870 (Appendices Figures).

3.3. Outcomes

We included a total of 13 studies (Fang's study used 2 cell types; Fang-1 and Fang-2), of which mesenchymal stem cells (MSCs) were reported in 6,[24,28,29,31,32,34] marrow mononuclear cells (MNC) in 4,[21,25,26,35] peripheral blood stem cells in 1,[27] endothelial progenitor cells in 1,[29] multipotent adult progenitor cells in 1[30] and ALD-401 cells in 1.[33] Included studies were divided into the "MSCs" group, "MNCs" group and "Other" group, and we performed subgroup analysis based on the different stem cell types.

3.3.1. Mortality. At the end of the follow-up period, 13 studies[21,24–32,35,36] reported the number of deaths, and the data showed that the mortality in the stem cell intervention group was lower than that in the control group (OR 0.42, 95% CI 0.23–0.79, I^2 = 0%, P = .007, Fig. 2B). Our subgroup analysis revealed that MSCs (OR 0.25, 95% CI 0.07–0.83, I^2 = 0%, P = .02) and other types of stem cells (OR 0.33, 95% CI 0.12–0.88, I^2 = 0%, P = .03) had a significant effect on the mortality in patients with ischemic stroke, while MNCs (OR 0.88, 95% CI 0.30–2.58, I^2 = 0%, P = .82) had no significant effect on mortality (Fig. 2B).

3.3.2. mRS. The mRS scores at the end of the follow-up were reported in 10 studies.[21,24,26–32,35] The data showed that stem cell intervention had a beneficial trend for patients with ischemic stroke (MD −0.32, 95% CI −0.64, 0.00, I^2 = 63%, P = .05, Fig. 3A). Based on different stem cell types, subgroup analysis showed that MSCs (MD −0.10, 95% CI −0.42, 0.22, I^2 = 0%, P = .55), MNCs (MD −0.57, 95% CI −1.58, 0.44, I^2 = 83%, P = .27), and other types of stem cells (MD −0.32, 95% CI −0.91, 0.28, I^2 = 80%, P = .30) had no significant effect on mRS scores in patients with ischemic stroke (Fig. 3A). Statistically, there was significant heterogeneity between studies (I^2 > 50%), and the analysis by Galbraith diagram showed that 2 studies[27,35] significantly contributed to heterogeneity (Figure S3, Supplemental Digital Content, http://links.lww.com/MD/L844) (Appendices Figures).

3.3.3. mRS ≤ 2. Four studies[21,28,30,32] reported an mRS ≤ 2 score at the end of follow-up. There was no significant difference between the stem cell intervention group and the control group (OR 1.07, 95% CI 0.67–1.73, I^2 = 0%, P = .77, Fig. 3B). Based on different stem cell types, subgroup analysis showed that MSCs (OR 0.66, 95% CI 0.19–2.27, I^2 = 0%, P = .51), MNCs (OR 1.31, 95% CI 0.63–2.73, P = .46), and other types of stem cells (OR 1.04, 95% CI 0.50–2.14, P = .92) had no significant effect on ischemic stroke patients with mRS ≤ 2 (Fig. 3B).

3.3.4. NIHSS. NIHSS scores were reported in 8 studies[21,26,27,29–31,34,35] at the end of the follow-up. Significant differences were detected between the 2 groups in favor of stem cell intervention (MD −1.63, 95% CI −2.69 to −0.57, I^2 = 58%, P = .003, Fig. 4A). Based on different stem cell types, subgroup analysis showed that MNCs had a significant effect on NIHSS score in patients with ischemic stroke (MD −1.68, 95% CI −2.63, −0.72, I^2 = 0%, P < .001), while MSCs (MD −1.69, 95% CI −3.81, 0.43, I^2 = 38%, P = .12) and other stem cell types (MD −1.57, 95% CI −4.81, 1.66, I^2 = 90%, P = .34) did not (Fig. 4A). Again, significant heterogeneity was observed between the included studies (P > 50%). A sensitivity analysis of the 8 studies found that heterogeneity decreased significantly with little effect on the pooled result, as summarized in Figure 3B (MD −2.02, 95% CI −2.96 to −1.08, I^2 = 35%, P < .001, Fig. 4B).

3.3.5. BI. Five studies[21,24,31,34,35] reported the BI scale at the end of the follow-up, and data showed that there was a significant difference in the BI scale favoring stem cell intervention (MD 14.22, 95% CI 3.95–24.48, I^2 = 43%, P = .007, Fig. 2A). Subgroup analysis on different stem cell types showed that MSCs (MD 9.74, 95% CI 0.15–19.33, I^2 = 1%, P = .05) and MNCs (MD 24.20, 95% CI 11.57–36.83, P < .001) had a significant effect on BI score in patients with ischemic stroke (Fig. 2A).

3.3.6. Complications. Complications were recorded in the context of 13 studies[21,24–35] at the end of the follow-up. Three studies[25,27,34] reported no early or late complications during or after transplantation. The data showed that there was no significant difference in the incidence of complications between the stem cell intervention and control groups (OR 0.58, 95% CI 0.21–1.63, I^2 = 13%, P = .31, Fig. 5A). Among the studies included in the present meta-analysis, recurrent ischemic stroke or transient ischemic attack (TIA), infection, and seizures were the most common complications. Therefore, we further performed a subgroup analysis. The data showed that there was no significant difference in the incidence of recurrent ischemic stroke or TIA (OR 0.80, 95% CI 0.23–2.83, I^2 = 14%, P = .73, Fig. 5B), infection (OR 0.77, 95% CI 0.45–1.29, I^2 = 0%, P = .32, Fig. 2B), and seizure (OR 1.09, 95% CI 0.41–2.90, I^2 = 6%, P = .86, Fig. 5B) between the treatment group and the control group. The specific complications in each study are represented in Table 2. Distribution of the complications is shown in Figure 6.

4. Discussion

In this study, 13 studies that met the inclusion criteria were assessed to evaluate the efficacy and safety of stem cells in the treatment of ischemic stroke by examining mortality, mRS, NIHSS, BI, and complications. The mRS, NIHSS, and BI scores are majorly used to evaluate the severity of ischemic stroke in the clinical setting, of which the mRS is utilized to evaluate the functional independence of patients, NIHSS to accurately assess the severity of neurological defects, and BI to evaluate the quality of daily life and the degree of disability.[37] MRS ≤ 2 was linked to patient prognosis.[28] An mRS ≤ 2 is considered to have an overall better prognosis in the absence of severe disability.

Overall, compared with the control group, stem cell treatment had a significant effect on patients with ischemic stroke (P < .05), which was manifested by a decrease in mortality in the stem cell intervention group and an improvement in mRS, NIHSS, and BI scores.

The mRS ≤ 2 showed no significant difference across the stem cell intervention and control groups. However, different stem cell types were used in different studies, including MSCs, MNC, peripheral blood stem cells, endothelial progenitor cells, multipotent adult progenitor cells and ALD-401 cells. We divided the included studies into the "MSCs" group, the "MNCs" group, and "Other" group, and performed subgroup analysis on all the outcomes. Data analysis showed that the application of MSCs could improve the BI score of patients with ischemic stroke and reduce mortality but showed no effect on mRS and NIHSS scores. The application of MNCs can improve the NIHSS score and BI score of patients, but has no effect on mRS score and mortality. The application of stem cells from the "Other" group can reduce the mortality of patients but has no effect on mRS and NIHSS scores. The differences in results of the overall and subgroup analyses may be related to the different types of stem cells used, the different evaluation criteria of mRS, NIHSS, and BI scores, and the basic scores of the patient population. The factors owing to these differences should be explored further.

Complications are linked to many factors, including the severity of the disease, injection route of stem cells, type of stem cells, dose of stem cells, and duration of administration. Among the 411 reported complications, 1 study reported drug-related injuries (20 cases),[30] 4 studies reported recurrent ischemic stroke (8 cases),[28,29,31,32] 4 studies reported infection (67 cases),[26,30,32] 1 study reported transient ischemic attack (1 case),[28] and 2 studies reported epileptic seizures (10 cases).[29,32] Subgroup analysis

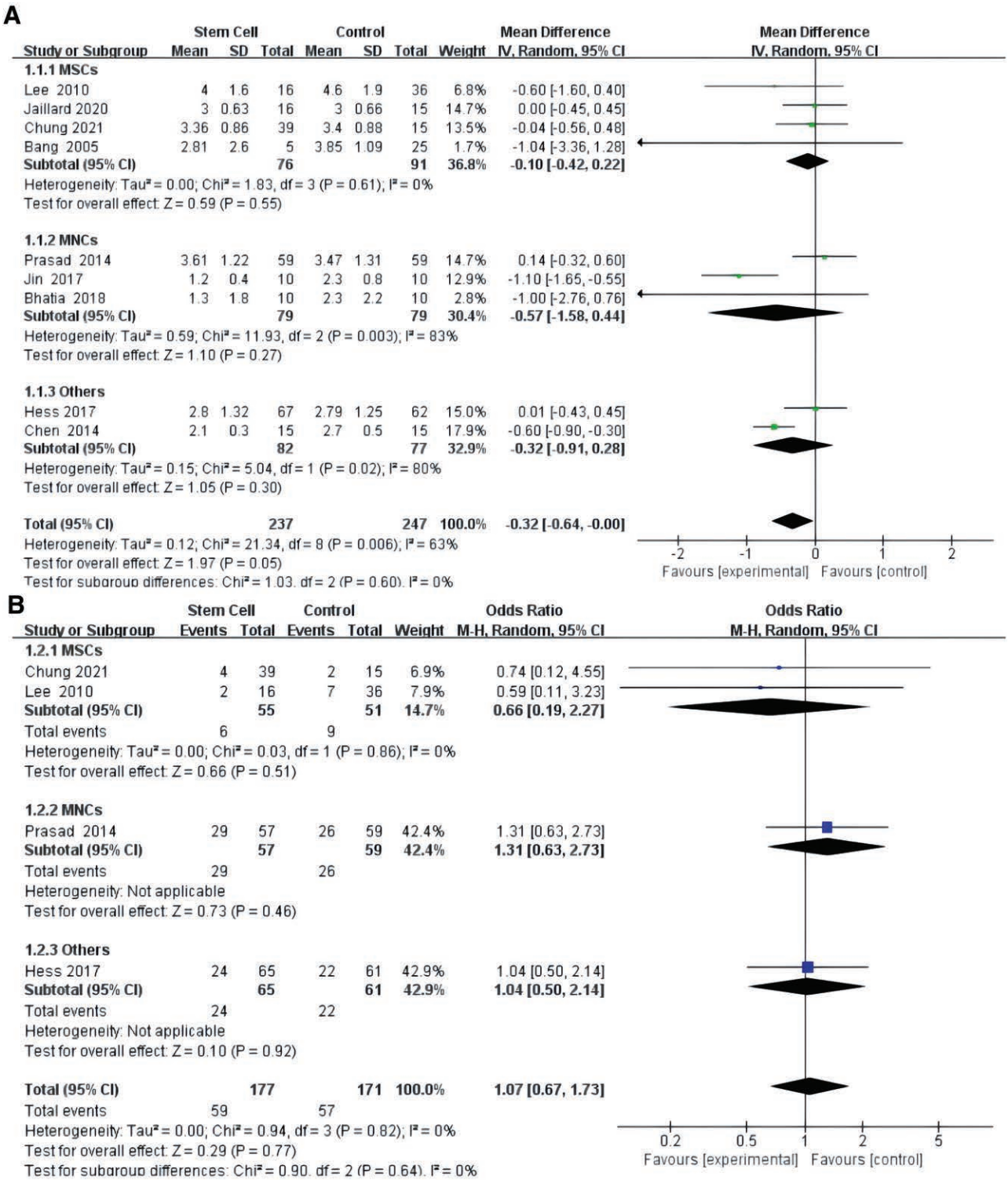

Figure 2. Meta-analysis of the effect of stem cells on ischemic stroke with Barthel index (A). Meta-analysis of the effect of stem cells on mortality in patients with ischemic stroke (B).

of common complications, including recurrent ischemic stroke or TIA, infection, and seizure, showed that there was no significant difference between the experimental and control groups. Therefore, future studies should assess whether genetic charge affect the prognosis of patients following stem cell therapy. In addition, further research may focus on the reduction of the incidence of complications during stem cell transplantation, which currently remains a clinical challenge.[38] Furthermore, the socioeconomic value and cost-effectiveness of stem cells in the treatment of ischemic stroke should also be evaluated, as the financial and social burden of the disease plays a prominent role in long-term outcomes.[39]

Several preclinical animal experiments have demonstrated that stem cell transplantation following ischemic stroke may significantly improve neurological deficits.[40,41] In addition to directly replacing cells, stem cells are associated with

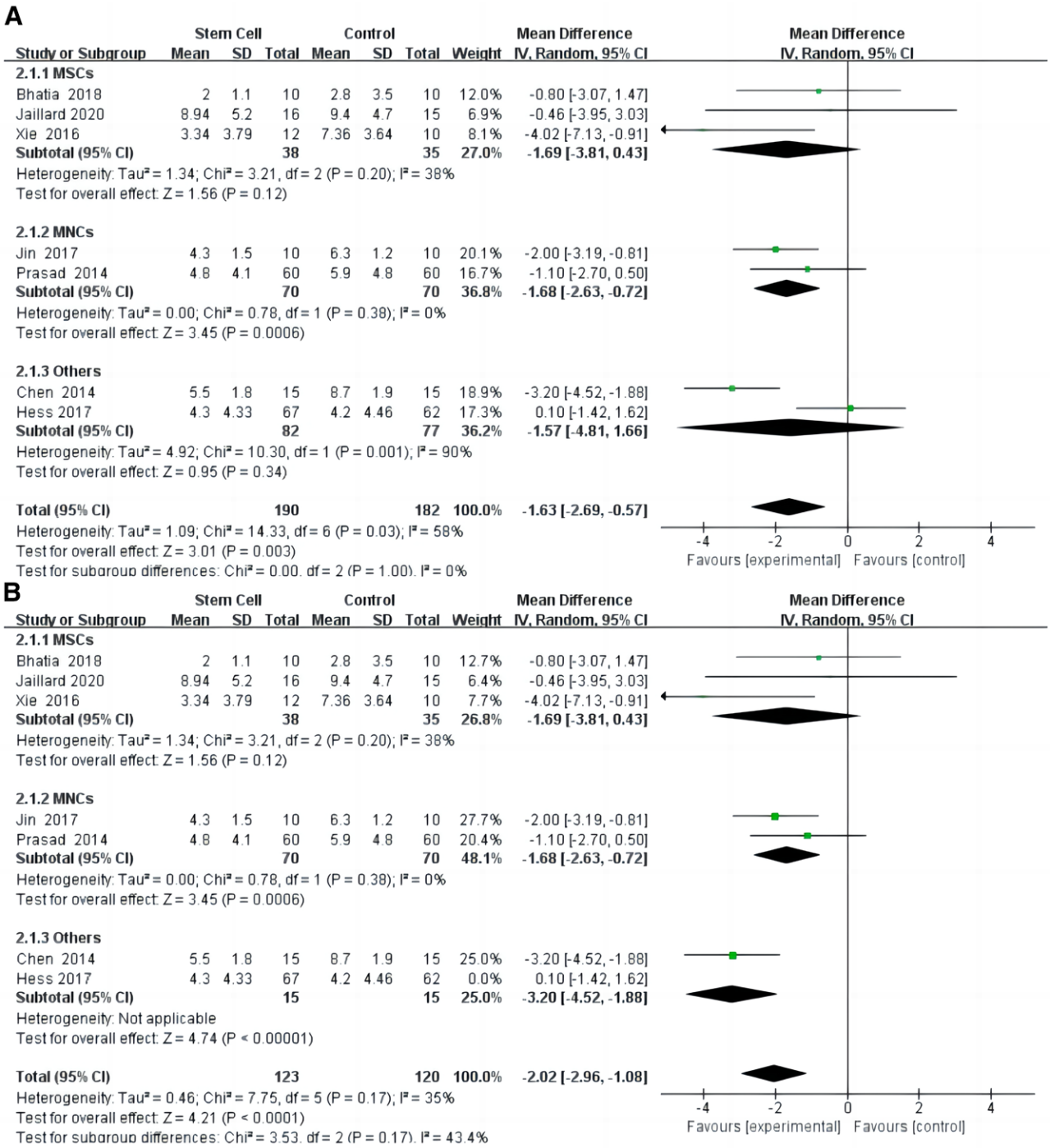

Figure 3. Meta-analysis of the effect of stem cells on ischemic stroke, with modified Rankin Scale (A) and modified Rankin Scale ≤ 2 (B).

anti-inflammatory effects, neuroprotective effects, promotion of axonal regeneration, promotion of angiogenesis, and other post-stroke processes (Fig. 7).[42,43] Currently, the timing of stem cell infusion remains uncertain, and stem cell infusion is usually at the minimum dose in the safe range obtained from dose gradient experiments.[44] The main methods of stem cell therapy are intravenous and arterial infusions. However, the optimal route of administration remains to be determined. Meanwhile, bone MSCs are the most commonly used stem cells in published studies.[45] This may be due to their overall physiological characteristics, including easy access, sufficient autologous sources, low immunogenicity, and self-renewal.[46,47] It is also the most efficient stem cell to produce exosomes, an important substance for stem cells to exert their effects.[48] Exosomes are speculated to be able to transmit proteins, genetic information, and cytokines to target cells, thereby regulating the key physiological and pathological activities of target cells.[49]

A recent meta-analysis of a clinical study on stem cells in the treatment of ischemic stroke revealed that the application of stem cells can improve neurological deficits and activities of daily living in patients with ischemic stroke; however, its benefits remain limited.[50] Therefore, our meta-analysis further analyzed the correlation between stem cell therapy for ischemic stroke and the prognosis (neurological function recovery, quality of life, and mortality) of patients. All 13 studies included in the present analysis were RCTs, which are currently the highest-level

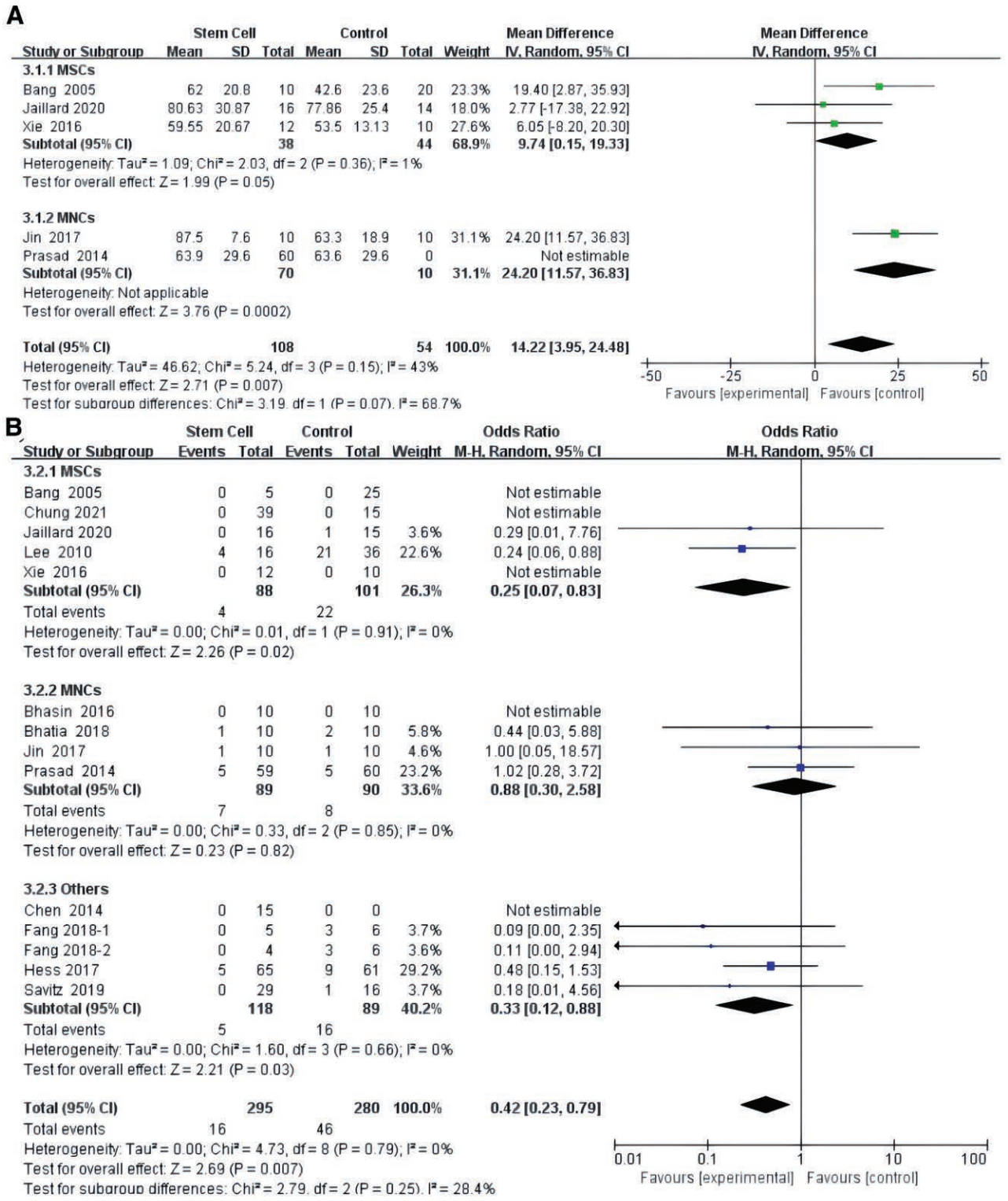

Figure 4. Meta-analysis (A) and sensitivity analysis (B) of the effects of stem cells on ischemic stroke, with National Institute of Health stroke scale.

evidence of evidence-based medicine on this topic.[51] The results demonstrated that there were significant differences in the mRS score, NIHSS score, BI score, and mortality, favoring stem cell treatment. This result supports the notion that the use of stem cells can improve the prognosis and quality of life of patients with ischemic stroke.

Stem cells have been used in many preclinical studies and some clinical trials since their development, producing some encouraging results. However, stem cell therapy has not yet translated into clinical practice. Current clinical applications of stem cells have limitations including optimal cell source, preparation of autologous stem cells that fully meet transplantation conditions, dose, time window and route of transplantation, and monitoring and management of adverse events during stem cell transplantation.[52] These limitations must be overcome to ensure the safety and efficacy of stem cells. Because of the safety

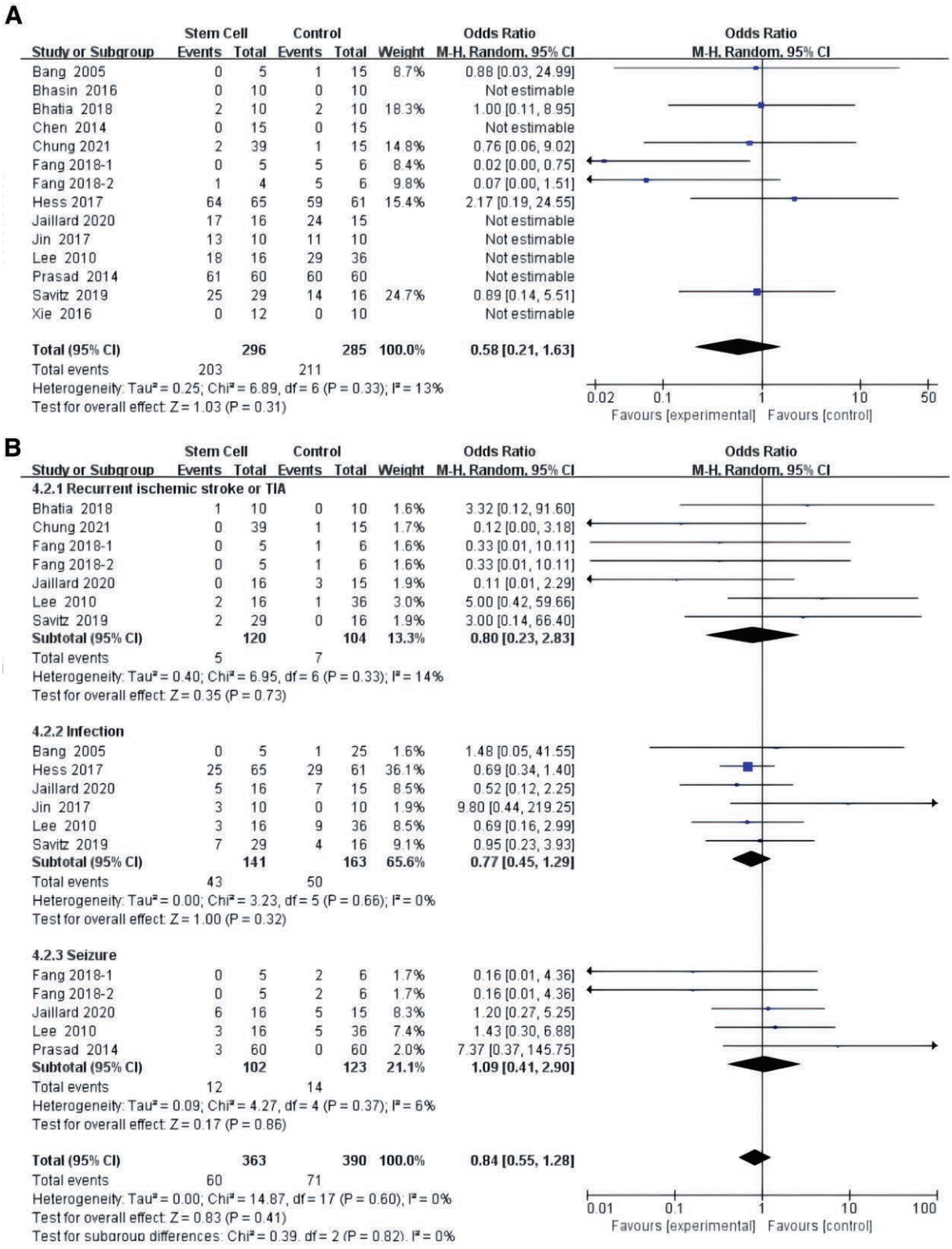

Figure 5. Meta-analysis of the effects of stem cells on all complications of ischemic stroke (A). Subgroup analysis of the effect of stem cells on complications of ischemic stroke (B).

risk associated with stem cell application and insufficient clinical data, stem cells should be considered carefully and be fully prepared by an experienced clinician.

Our study had several limitations. This study was based on a small number of clinical trials because stem cell therapy has recently made the jump from preclinical animal studies to an experimental clinical setting. Hence, the available literature on this topic is scarce. High heterogeneity existed in the NIHSS and BI outcomes. This may be due to the fact that the basic NIHSS score (3–30), gender (male > female), cerebral ischemia duration

Table 2

Complications reported in the studies included.

Author	Year	Cases	Complications (%)
Bang[24]	2005	1	Cellulitis (100%)
Bhasin[25]	2016	0	0
Bhatia[26]	2018	4	New infarct (25%), Death (75%)
Chen[27]	2014	0	0
Chung[28]	2021	3	Recurrent stroke or TIA (33.33%), Allergic reactions (33.33%), Systemic complications (33.33%)
Fang[29]	2018	7	Seizure (28.57%), Deep vein thrombosis (14.29%), Parkinson's syndrome (14.29%), Arrhythmia (14.29%), Recurrent stroke (14.29%), Cancer (14.29%)
Hess[30]	2017	123	Study drug-related (16.26%), Secondary infection (43.90%), Serious adverse events (37.40%)
Jaillard[31]	2020	41	Death (2.44%), Depression (4.88%), Recurrent ischemic stroke (4.88%), TIA (2.44%), Urinary tract infection (12.20%), Crytpogenic fever (2.44%), Algodystrophia (4.88%), Hip pain(2.44%), Humeral fracture (7.72%), Foot skin infection (2.44%), Epileptic seizures (26.83%), Deep lower limb venous thrombosis (2.44%), Pneumonia (12.20%), Gastrostomy (2.44%), Ankle sprain (2.44%), Atrial flutter (2.44%), Rotator cuff tear (2.44%), Kidney pain (2.44%)
Jin[35]	2017	25	Fever (8%), Pain in puncture site (80%), Pulmonary infection (4%), Death (8%)
Lee[32]	2010	47	Recurrent stroke (6.38%), Myocardial infarction or angina (6.38%), Peripheral artery occlusive disease (2.13%), Infection (pneumonia, urinary tract infection) (25.53%), Acute renal failure (2.13%), Liver enzyme elevation (6.38%), Systemic cancer (2.13%), Mass, benign (4.26%), Seizure (17.02%), Neuropyschological illness (27.66%)
Prasad[21]	2014	121	Haematological (24.79%), Hepatic (28.93%), Others (46.28)
Savitz[33]	2019	39	Mild (38.46%), Moderate (38.46%), Severe (23.07%)
Xie[34]	2016	0	0

TIA = transient ischemic attack.

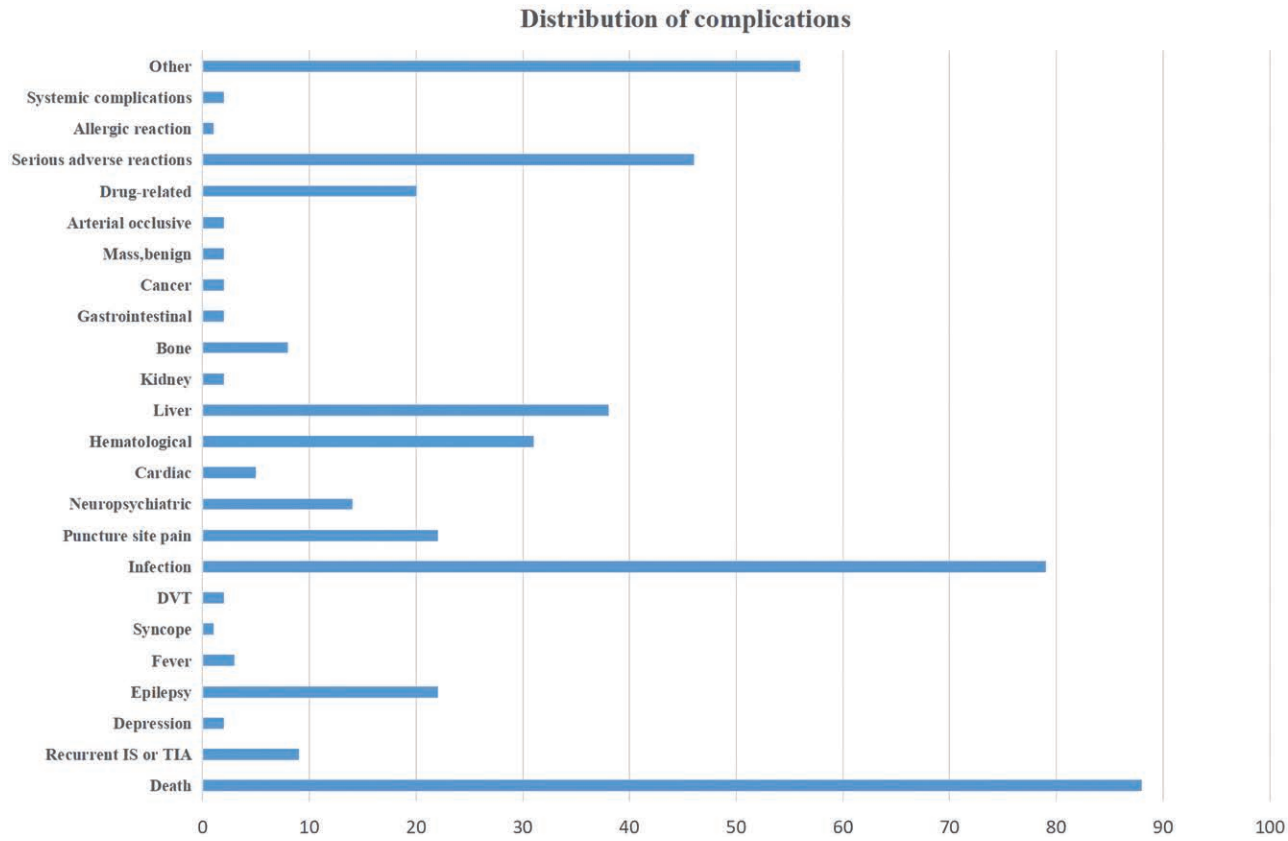

Figure 6. Distribution bar chart of clinical complications.

(acute, subacute, chronic), stem cell types, stem cell injection dose, drug administration (intra-arterial injection, intravenous injection) and recovery time of the patients included in the studies differed. After the sensitivity analysis, the heterogeneity significantly decreased, but without any change to the significant difference in the overall effect. Stroke of different severity may be associated with different complications, which may also affect the evaluation of efficacy and safety. Different types of stroke may have different treatments other than stem cell therapy, which may affect clinical outcomes and should be a limitation of the present study. In addition, this study protocol was not registered before it started, and records identified from the database was relatively small, which was also a limitation of the present study.

Figure 7 mechanism diagram of stem cell therapy for ischemic stroke.

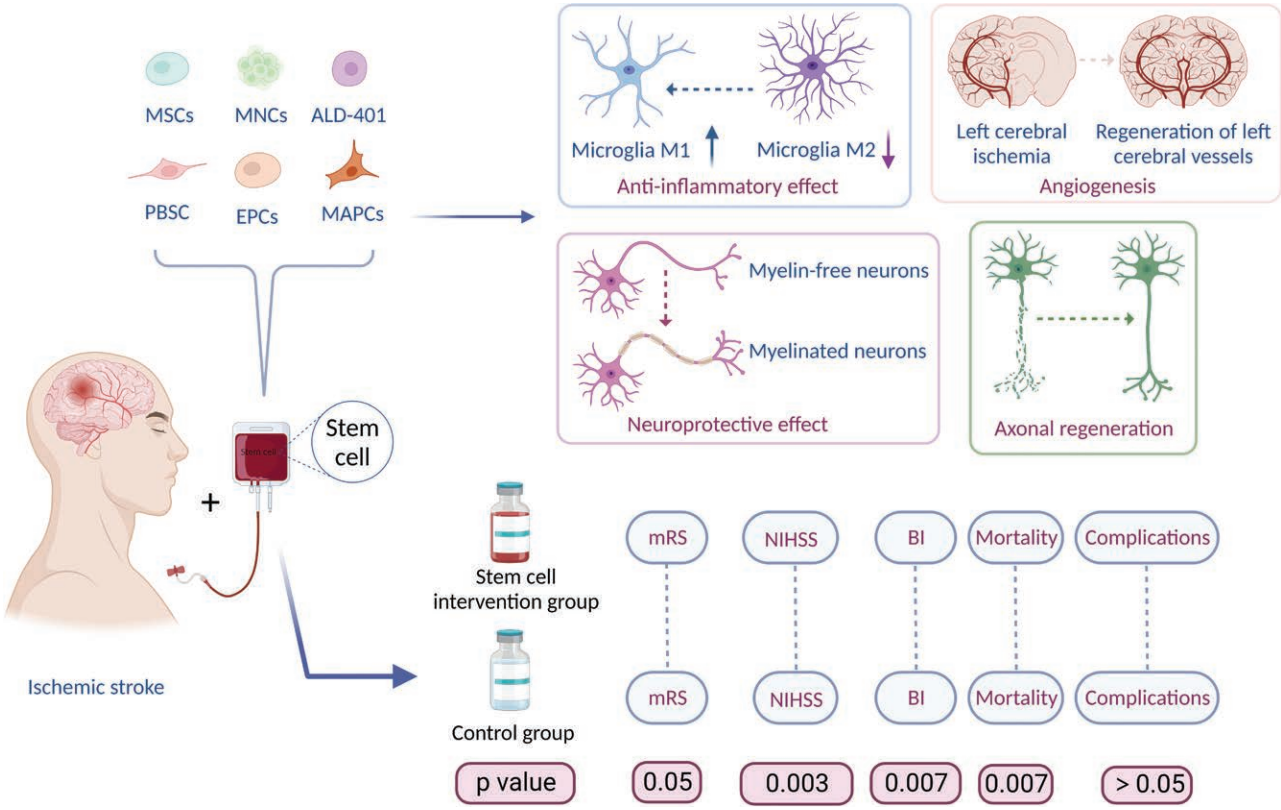

Figure 7. Preclinical study and meta-analysis of stem cells for ischemic stroke.

5. Conclusion

Stem cell therapy may reduce mortality and improve the neurological prognosis of ischemic stroke patients. However, due to the different types of stem cells used and the limited data in the reported studies, the safety of clinical applications of stem cells in patients with ischemic stroke must be carefully evaluated. Future randomized controlled trials with large sample sizes from controlled cell sources are warranted to validate this finding.

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