Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Mesenchymal stem cell transplantation as an effective treatment strategy for ischemic stroke in Asia: a meta-analysis of controlled trials

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Ping Xue
Min Wang
Guanhua Yan

Department of Neurology, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, Liaocheng, People's Republic of China

Objective: The aim of this study was to evaluate the efficacy and safety of the mesenchymal stem cell (MSC) therapy in patients with ischemic stroke (IS).

Materials and methods: Clinical trials involved in this research were searched from PubMed, Web of Science, Cochrane Library, Embase, Wanfang and CNKI database. Therapeutic effects of MSC therapy were assessed according to National Institutes of Health Stroke Scale (NIHSS), Barthel index (BI), Fugl-Meyer Assessment (FMA) and Functional Independence Measure (FIM), and its safety was evaluated based on adverse events.

Results: This research covered 23 trials including 1,279 IS patients. Based on our analysis, the overall condition of IS patients significantly improved after MSC therapy, indicated by decreased NIHSS and increased BI, FMA and FIM scores. Our analysis also showed that the treatment effects in the MSC transplantation group were superior to those in the control group (routine medication therapy) with statistical significance for NIHSS (1 month after therapy: odds ratio [OR]=–1.92, CI=–3.49 to –0.34, P=0.02; 3 months after therapy: OR=–2.65, CI=–3.40 to –1.90, $P<0.00001$), BI (1 month after therapy: OR=0.99, CI=0.19–1.79, P=0.02; 6 months after therapy: OR=10.10, CI=3.07–17.14, P=0.005), FMA (3 months after therapy: OR=10.20, CI=3.70–16.70, P=0.002; 6 months after therapy: OR=10.82, CI=6.45–15.18, $P<0.00001$) and FIM (1 month after therapy: OR=15.61, CI=–0.02 to 31.24, P=0.05; 6 months after therapy: OR=16.56, CI=9.06–24.06, $P<0.0001$). No serious adverse events were reported during MSC therapy.

Conclusion: MSC therapy is safe and effective in treating IS by improving the neurological deficits, motor function and daily life quality of patients.

Keywords: mesenchymal stem cells, routine medication, ischemic stroke, meta-analysis

Introduction

Stroke is the most lethal and second most incident disease, together with cancer and cardiovascular disease.[1,2] Ischemic stroke (IS) and intracerebral hemorrhage account for about 85% and 15%, respectively, of all stroke events.[3] The main pathological manifestation of IS is temporary brain tissue ischemia.[1] Ischemia results in reduced neuron number and interrupted neural axon network, and formation of a defected environment around the ischemic region, which prohibits brain self-healing, eventually resulting in the permanent loss of nerve tissue or disabled brain function.[1,4,5] Over 50,000,000 people are suffering from IS of various degrees in the world.[6] The annual mortality rate is close to 10%, and nearly 50% of stroke survivors are left with disabling sequelae.[1,2,4] Poststroke rehabilitation therapy is scant, and currently the most efficient medicine for IS in clinical settings is tissue plasminogen activator.[1,7]

Correspondence: Guanhua Yan
Department of Neurology, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, No 67 Dongchang West Road, Liaocheng 252000, Shandong, People's Republic of China
Tel +86 152 6688 9065
Email guahuayan65@163.com

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However, it functions mainly at the early stage of ischemia with a short time window, which may increase the risk of cerebral hemorrhage, and therefore, its clinical application is severely limited.[7]

Stem cell therapy, using hematopoietic stem cells (HSCs),[8,9] neural stem cells (NSCs),[10,11] endothelial progenitor cells (EPCs)[12] and other types of stem cells,[13,14] was considered a promising treatment for IS as it may reduce injury and promote rehabilitation after stroke. Mesenchymal stem cells (MSCs) are derived from mesoderm and have the capacity of regeneration and differentiation. MSCs can differentiate into various lineages such as NSCs, which can further differentiate into neurons, astrocytes, oligodendrocytes and so on,[4,15,16] with low immunogenicity and high histocompatibility.[1,15] Compared with other types of stem cells, such as NSCs, EPCs and HSCs, MSCs are more accessible as they can be easily obtained from umbilical cord, bone marrow, fat and other tissues, and can proliferate rapidly in vitro with little ethical constraints.[15] Preliminary preclinical studies using MSCs to treat IS have shown beneficial effects.[17–19] In animal models, researchers found the transplanted cells migrated to lesions, secreted neurotrophic factors, remitted inflammatory response and promoted plasticity and revascularization thereby minimizing the damage.[18–20]

Although both preclinical studies and studies with experimental models regarding MSC transplantation therapies for IS have been carried out,[17–19] the clinical application of MSCs still has a long way to go due to its unverified safety and therapeutic effects. To address this issue, we conducted a meta-analysis of published clinical trials treating IS with MSCs, to provide scientific references for upcoming research and future clinical application.

Materials and methods

Search strategy and selection criteria

Studies were identified from PubMed, Web of Science, Cochrane Library, Embase, Wanfang and CNKI database, with key terms ("mesenchymal stem cells" or "MSC") and ("ischemic stroke" or "cerebral infarction" or "cerebral ischemia" or "brain ischemia"), without language restriction. The last search was performed in October 2017.

Studies were included if they fulfilled the following inclusion criteria: case-controlled trials involving IS patients; participants were diagnosed with IS and without malignant tumor, pregnancy and lactation; and patients in the experimental group received both MSC transplantation and IS routine treatment (RT; including conventional medical therapy and rehabilitation training treatment) combined therapy, and those in control group were treated by RT alone.

Data extraction and quality assessment

All data collection and extraction were performed by two authors (PX and MW) independently. The following information was summarized: author's names, years of publication, locations, type of IS, samples sizes, patients' ages, study parameter types, therapeutic regimens, administration routes, MSC dosages and adverse events during the MSC therapy. Trials' quality was assessed for risk of bias following the instruction of Cochrane Handbook.[21]

Outcome definition

Treatment efficacy was assessed in terms of National Institutes of Health Stroke Scale (NIHSS), Barthel index (BI), Fugl-Meyer Assessment (FMA) and Functional Independence Measure (FIM). The frequencies of adverse events were gathered and assessed for MSC therapy safety.

Statistical analysis

This meta-analysis was performed using Review Manager 5.3 (Cochrane Collaboration). The therapeutic efficacy was evaluated by odds ratio (OR) and presented with 95% CI. $P<0.05$ indicates differences with statistical significance. The appropriate analysis model was determined by analyzing the heterogeneity between trials by Cochran's Q test.[22] Studies with $I^2<50\%$ or $P>0.1$ were considered homogenous.

Publication bias was evaluated based on funnel plots. Sensitivity analysis on subgroups was also performed to assess the impact of MSC types, cell administration methods and patients' characteristics on clinical outcomes.

Results

Search results

A total of 2,998 articles were initially identified, and 2,921 were excluded for lacking clinical trials (n=2,693), duplication and repetition (n=177) or being unrelated (n=51). The later detailed assessment further excluded 18 articles with insufficient data, 23 reviews or case reports or meta-analyses and 13 articles without control group. A total of 23 trials[23–45] with 1,279 IS patients were finally identified meeting the restrict inclusion criteria of this research (Figure 1).

Study and patient characteristics

After selection, all included trials were found to have been conducted in Asia. Two studies were conducted in Korea,[23,35]

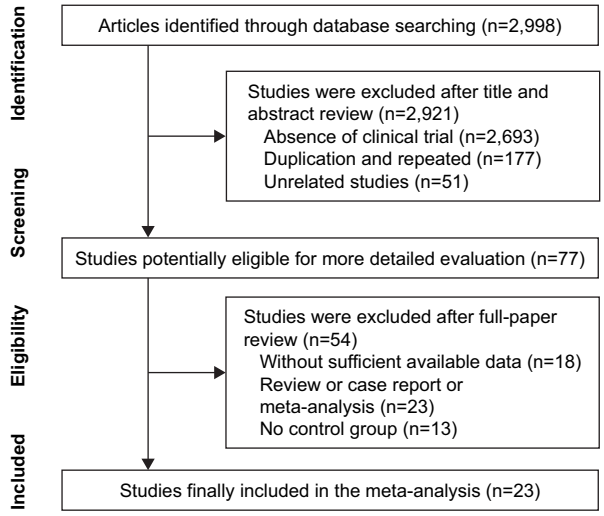

Figure 1 Flow diagram of the selection process.

two in India[24,25] and the rest of the included studies in China. MSCs were obtained from bone marrow in 18 studies,[23–30,32,35–37,40–45] from umbilical cord in three studies[33,34,38] and from umbilical cord blood in two studies.[31,39] Cells were administered through peripheral vein in 14 studies,[23–27,30,32,34,35,37,40–43] subarachnoid in five studies,[28,29,36,44,45] intrathecal in three studies[31,33,39] and intracarotid artery in one study.[38] In total, 625 IS patients accepted MSC and RT combined therapy, and 654 patients were treated by RT alone. Detailed information about the involved studies and participants is summarized in Tables 1 and 2.

Quality assessment

Bias risk of involved trials is shown in Figure 2. Sixteen studies were determined as low risk, five researches were not truly randomized controlled trials and the other two studies did not have clear illustration of randomization procedures. Seven trials did not provide clear description of allocation and performance concealment. All the included studies were free of detection risk. Three trials missing the follow-up study were considered as high risk, and one study with selective reporting was considered as unclear risk.

Therapeutic efficacy assessments

Effectiveness of MSCs assessed by the NIHSS score

The analysis of involved trials showed that after MSC therapy, the NIHSS score was reduced in the first, second,

Table 1 Clinical information from the eligible trials in the meta-analysis

Included studies	Country	Type of stroke: acute/chronic	Patients: control/experimental	Age (years)		Parameter types
				Control	Experimental	
Bang et al[23]	Korea	Acute	25/5	ND	ND	BI
Bhasin et al[24]	India	Chronic	20/20	45.2±11.8	45.1±12.1	FMA, BI
Bhasin et al[25]	India	Chronic	6/6	46.5±6.3	42±9.3	FMA, BI, AE
Cai et al[26]	China	Chronic	21/21	62.7±6.9	61.4±6.7	FMA, FIM, BI
Cheng et al[27]	China	Acute	18/18	68.1±2.5	69.1±1.2	FIM, BI
Chen et al[28]	China	ND	43/43	ND	ND	FMA, FIM
Chen et al[29]	China	ND	30/30	57.4±9.6	49.3±20.8	NIHSS
Deng et al[30]	China	ND	15/15	ND	ND	NIHSS
Feng et al[31]	China	ND	50/50	60.2±11.8	61.4±11.3	NIHSS
He[32]	China	ND	18/20	54.3±8.7	56.4±7.9	NIHSS, BI
Hu et al[33]	China	ND	60/60	59.2±13.8	60.8±15.2	FMA, FIM
Ji et al[34]	China	ND	60/60	ND	ND	FMA, BI
Lee et al[35]	Korea	Acute	36/16	64.9±14.5	64.0±11.6	AE
Liu et al[36]	China	ND	29/29	56.9±4.4	55.3±3.6	NIHSS, FMA, BI
Meng et al[37]	China	ND	30/30	52.9±8.3	52.7±7.9	FMA, FIM
Shen[38]	China	Acute	16/16	ND	52±10.4	FIM
Song et al[39]	China	ND	28/28	65.4	63.2	NIHSS
Sun et al[40]	China	Acute	22/20	58.9±7.4	57.8±8.9	NIHSS, BI
Sun et al[41]	China	ND	15/20	30.9±16.9	29.5±9.4	FMA
Tsang et al[42]	Hong Kong	Chronic	4/5	51.5	53.4	FIM, BI, AE
Wang et al[43]	China	ND	60/60	ND	ND	FIM
Xie et al[44]	China	ND	30/30	53.7±6.1	51.4±7.2	NIHSS, BI
Zhao et al[45]	China	ND	18/23	53.3±18.9	50.2±20.0	NIHSS

Note: Data are presented as mean±SD or median.
Abbreviations: ND, nondetermined; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure; AE, adverse event.

Table 2 Information of MSC therapy

Included studies	Therapeutic regimen		Administration route	Cell dose (cycles)	Enrollment period	Follow-up (months)	Adverse events
	Experimental	Control					
Bang et al[23]	Con Reg+BMSC	RM+G-CSF	IVE	5×10^7 (2 cycles)	ND	52	No obvious adverse reactions
Bhasin et al[24]	Con Reg+BMSC	RM	IVE	$5–6\times10^7$ (1 cycle)	ND	6	No obvious adverse reactions
Bhasin et al[25]	Con Reg+BMSC	RM	IVE	$5–6\times10^7$ (1 cycle)	ND	6	Fever (1); pain (2)
Cai et al[26]	Con Reg+BMSC	RM	IVE	$0.5–2\times10^8$ (3 cycles)	2014.1–2015.1	6	ND
Cheng et al[27]	Con Reg+BMSC	RM	IVE	$0.5–2\times10^8$ (3 cycles)	2011.1–2012.12	3	ND
Chen et al[28]	Con Reg+BMSC	RM	SUB	1×10^6/kg (1 cycle)	2009.12–2011.8	5	ND
Chen et al[29]	Con Reg+BMSC	RM	SUB	$3–5\times10^6$ (2 cycles)	2009.1–2011.5	6	Low-grade fever (3); headache (4)
Deng et al[30]	Con Reg+BMSC	RM+SM	IVE	$1–5\times10^7$ (3 cycles)	ND	1	No obvious adverse reactions
Feng et al[31]	Con Reg+UBMSC	RM	IT, IVE	3×10^7 (6 cycles)	2010.9–2013.2	3	Low-grade fever (1)
He[32]	Con Reg+BMSC	RM	IVE	1×10^8 (1 cycle)	2010.4–2012.2	3	ND
Hu et al[33]	Con Reg+UCMSC	RM	IT+IVE	1×10^8 (1 cycle)	2011.4–2012.6	3	Low-grade fever (12); headache (5); flank soreness (10)
Ji et al[34]	Con Reg+UCMSC	RM	IVE	1×10^7 (1 cycle)	2009–2010	6	No obvious adverse reactions
Lee et al[35]	Con Reg+BMSC	RM	IVE	5×10^7 (2 cycles)	2003.7–2005.12	60	No obvious adverse reactions
Liu et al[36]	Con Reg+BMSC	RM	SUB	1×10^7/kg (4 cycles)	2010.12–2012.12	3	No obvious adverse reactions
Meng et al[37]	Con Reg+BMSC	RM	IVE	2.97×10^9 (1 cycle)	2003.6–2008.6	6	Low-grade fever (4); headache (3)
Shen[38]	Con Reg+UCMSC	RM	IC	ND	2012.1–2013.12	3	ND
Song et al[39]	Con Reg+UBMSC	RM	IT+IVE	ND	2009–2010	1	Low-grade fever (5)
Sun et al[40]	Con Reg+BMSC +G-CSF	RM	IVE	$1.4\pm0.6\times10^8$ (1 cycle)	2006.8–2007.6	3	ND
Sun et al[41]	Con Reg+BMSC	RM	IVE	ND (3 cycles)	2011.8–2012.8	3	Low-grade fever (2)
Tsang et al[42]	Con Reg+BMSC	RM	IVE	4.57×10^7 (1 cycle)	ND	15	No obvious adverse reactions
Wang et al[43]	Con Reg+BMSC	RM	ND	$1–2\times10^8$ (1 cycle)	2009.1–2010.6	6	No obvious adverse reactions
Xie et al[44]	Con Reg+BMSC	RM	SUB	2×10^7 (1 cycle)	2011.1–2012.7	6	Low-grade fever (3); headache (4)
Zhao et al[45]	Con Reg+BMSC	RM	SUB	ND	ND	1	Fever (1)

Abbreviations: Con Reg, control group regimen; RM, routine medication; MSC, mesenchymal stem cell; BMSC, bone marrow mesenchymal stem cell; UBMSC, umbilical cord blood mesenchymal stem cell; UCMSC, umbilical cord mesenchymal stem cell; ND, nondetermined; SM, *Salvia miltiorrhiza*; G-CSF, granulocyte colony-stimulating factor; IVE, intravenous; IT, intrathecal; SUB, subarachnoid; IC, intracarotid.

third and sixth month after treatment (1 month: OR=−5.20, CI=−6.52 to −3.87, $P<0.00001$; 2 months: OR=−6.46, CI=−7.86 to −5.06, $P<0.00001$; 3 months: OR=−7.50, CI=−9.59 to −5.40, $P<0.00001$; 6 months: OR=−9.19, CI=−11.77 to −6.60, $P<0.00001$; Figure S1). As shown in Figure 3, compared to the control group, the NIHSS score of the experimental group was lower in the first (OR=−1.92, CI=−3.49 to −0.34, $P=0.02$) and third month (OR=−2.65, CI=−3.40 to −1.90, $P<0.00001$).

Effectiveness of MSCs assessed by the BI score

The postoperative BI score was increased after combined therapy in the first, second, third and sixth month and after 12 months (1 month: OR=30.14, CI=29.34–30.94, $P<0.00001$; 2 months: OR=15.50, CI=2.99–28.01, $P=0.02$; 3 months: OR=29.66, CI=24.12–35.20, $P<0.00001$; 6 months: OR=27.76, CI=13.24–42.28, $P=0.0002$; after 1 year: OR=45.79, CI=37.32–54.25, $P<0.00001$; Figure S2). In the comparison between patients treated by combined therapy and RT alone, the BI score in the combined therapy group was higher in the first and sixth month (1 month: OR=0.99, CI=0.19–1.79, $P=0.02$; 6 months: OR=10.10, CI=3.07–17.14, $P=0.005$; Figure 4).

Effectiveness of MSCs assessed by the FMA score

The FMA score after combined therapy was significantly increased in the first, second, third and sixth month, and

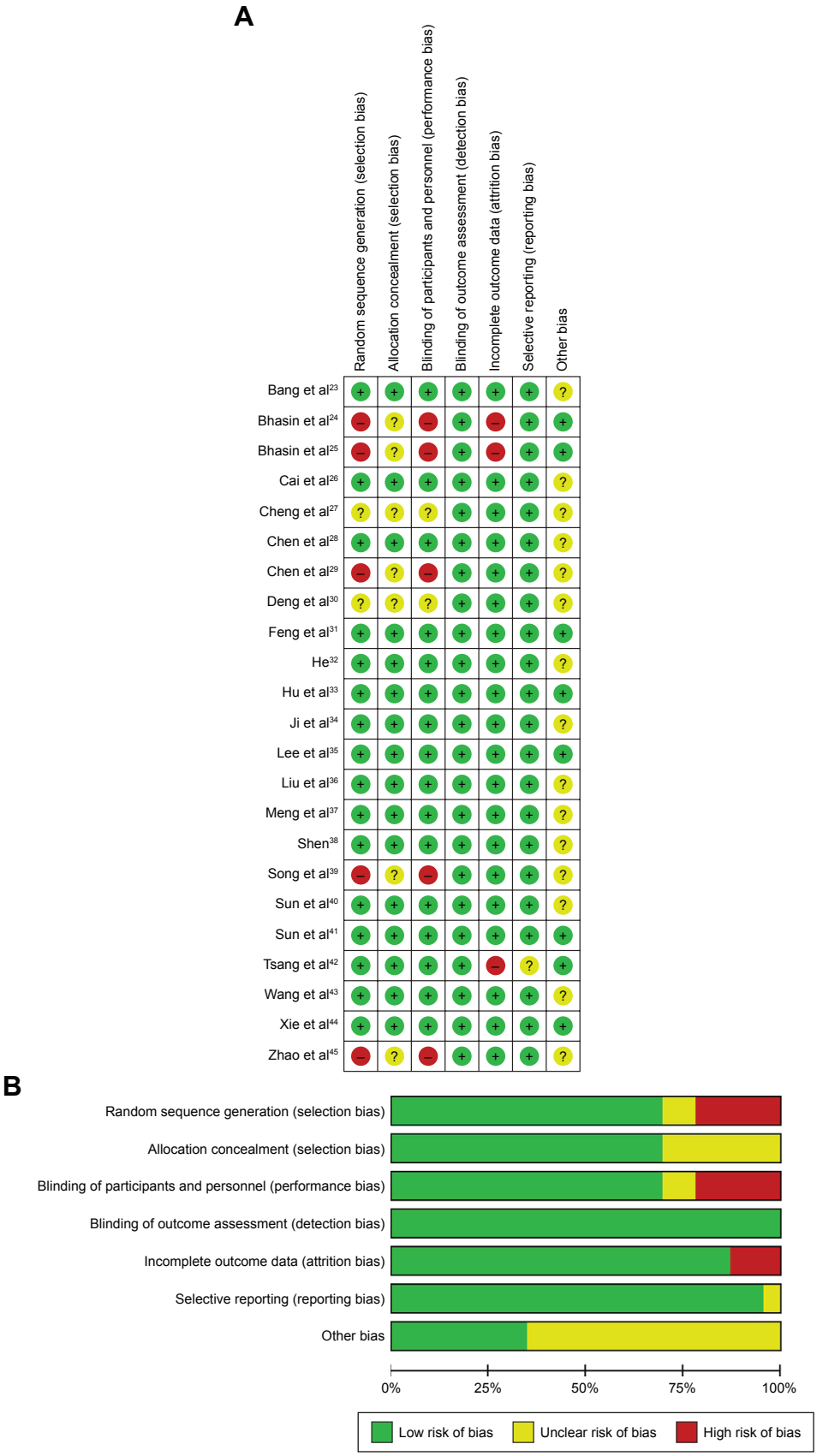

Figure 2 (**A**) Risk-of-bias summary: review of authors' judgments about each risk-of-bias item for included studies. (**B**) Risk-of-bias graph: review of authors' judgments about each risk-of-bias item presented as percentages across all included studies.
Note: Each color represents a different level of bias.

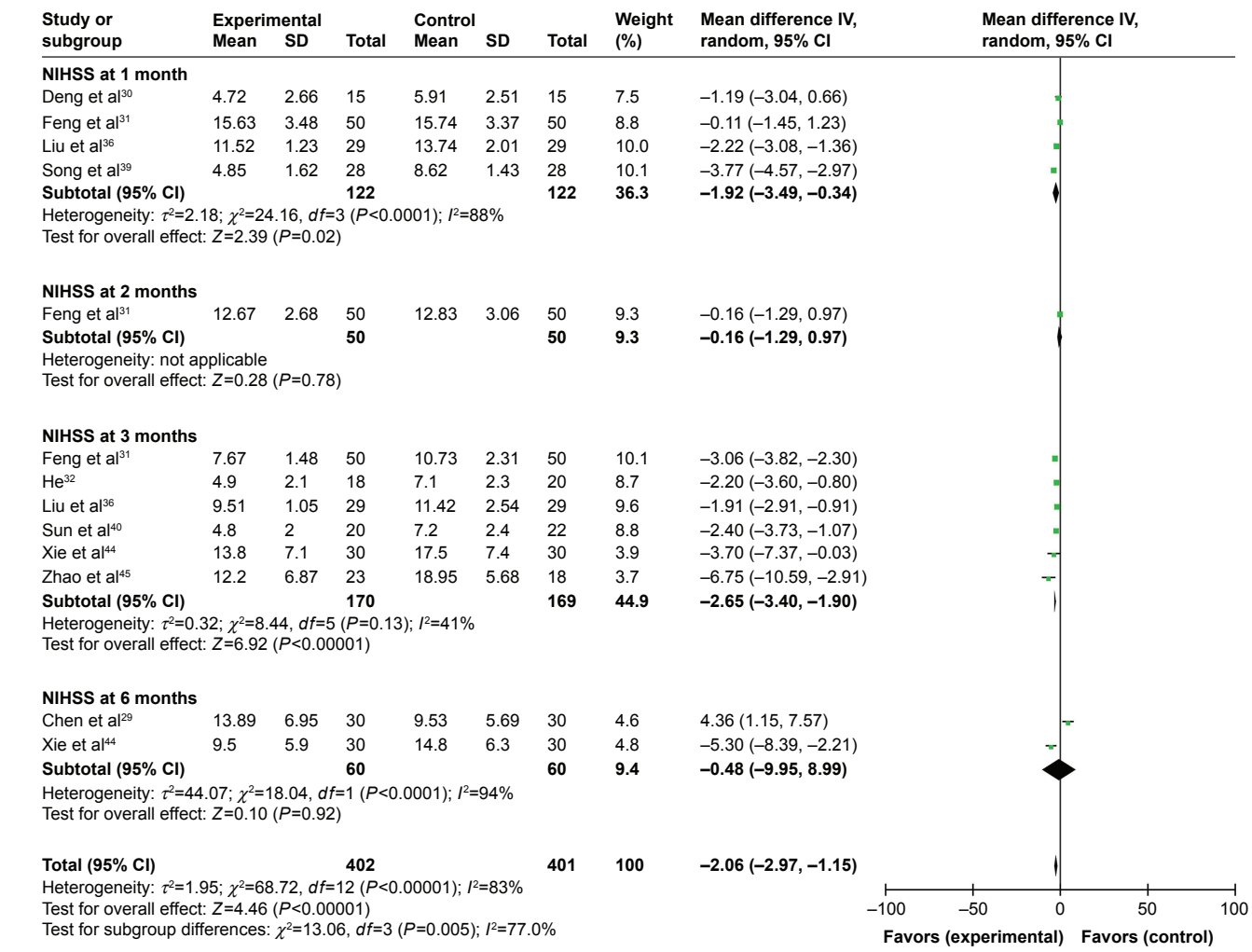

Figure 3 Forest plot of the comparison of NIHSS scores between the experimental and control groups.
Notes: Control group, RT alone group; experimental group, RT plus MSC therapy. The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; NIHSS, National Institutes of Health Stroke Scale; RT, routine treatment; MSC, mesenchymal stem cell.

after 12 months (1 month: OR=15.49, CI=7.51–23.47, P=0.0001; 2 months: OR=18.46, CI=7.11–29.82, P=0.001; 3 months: OR=27.00, CI=19.78–34.23, $P<0.00001$; 6 months: OR=39.26, CI=25.85–52.67, $P<0.00001$; after 1 year: OR=36.40, CI=29.31–43.49, $P<0.00001$; Figure S3). A comparison between the two groups indicated a significantly increased FMA score in the third and sixth month postoperation in the combined therapy group (3 months: OR=10.20, CI=3.70–16.70, P=0.002; 6 months: OR=10.82, CI=6.45–15.18, $P<0.00001$; Figure 5).

Effectiveness of MSCs assessed by the FIM score

As shown in Figure 3, the FIM score was increased after combined therapy, especially in the first, third and sixth month postoperation (1 month: OR=24.47, CI=7.14–41.80, P=0.006; 3 months: OR=24.05, CI=6.56–41.54, P=0.007; 6 months: OR=48.13, CI=32.04–64.23, $P<0.00001$; Figure S4). Meanwhile, the FIM score in the combined therapy group was higher than that of the control group in the first and sixth month (1 month: OR=15.61, CI=–0.02 to 31.24, P=0.05; 6 months: OR=16.56, CI=9.06–24.06, $P<0.0001$; Figure 6).

Adverse event assessment

We evaluated the safety of MSC therapy in this meta-analysis. The most common side effects of MSC treatment were headache and fever, which usually subsided within 24 hours without treatment. No serious adverse events were reported in the involved studies (Table 1). However, the incidence of side effects in experimental and control groups was not compared in most included trials. Three studies[25,35,42] conducted the comparison of adverse events including

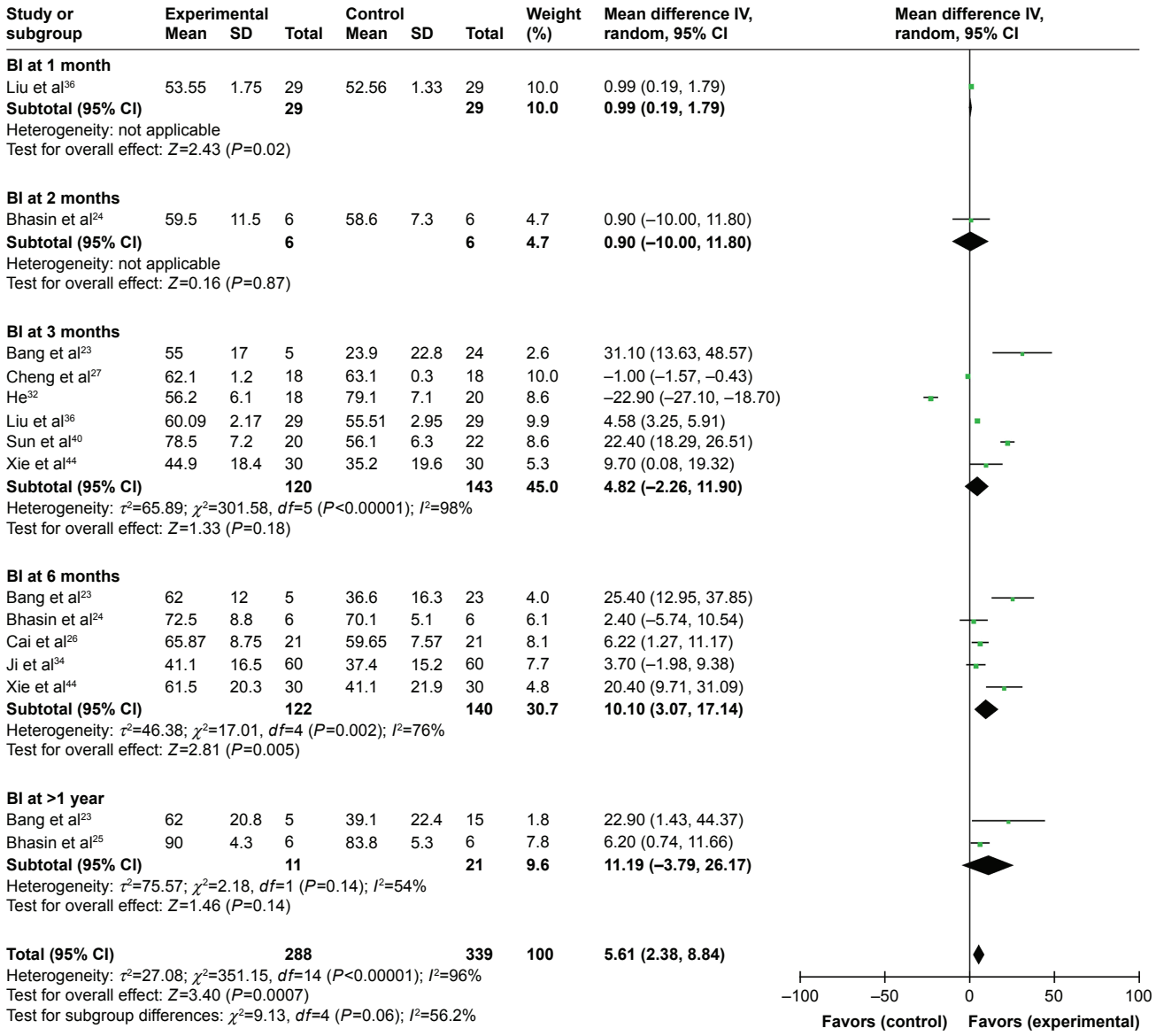

Figure 4 Forest plot of the comparison of the BI scores between the experimental and control groups.
Notes: Control group, RT alone group; experimental group, RT plus MSC therapy. The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; BI, Barthel index; RT, routine treatment; MSC, mesenchymal stem cell.

infection, tumor formation, seizures, psychological illness, death and fever. Except death, no significant difference was found for other indicators between the two groups (infection: OR=0.69, CI=0.16–2.99, *P*=0.62; tumor formation: OR=0.72, CI=0.03–18.56, *P*=0.84; seizures: OR=1.02, CI=0.26–3.93, *P*=0.98; psychological illness: OR=1.69, CI=0.53–5.33, *P*=0.37; death: OR=0.24, CI=0.06–0.88, *P*=0.03; fever: OR=5.03, CI=0.48–52.71, *P*=0.18; Figure 7).

Publication bias

Based on the NIHSS,[31,32,36,40,44,45] BI,[23,24,26,27,32,34,36,40,42,44] FMA[28,31,33,36,37,41] and FIM[27,28,33,37,38,42] data, funnel plots were drawn for the studies. The funnel plots were symmetrical, indicating no existence of publication bias (Figures 8 and S5).

Sensitivity analysis

To further evaluate the effects of clinical variables including cell types and different administration routes on clinical efficacy of patients with different characteristics, we performed subgroup analysis. Results showed that MSC therapy was more effective when infusion was performed through vein, and autogenous MSCs were superior to those derived from other sources, indicated by increased BI, FMA and FIM scores (Table 3).

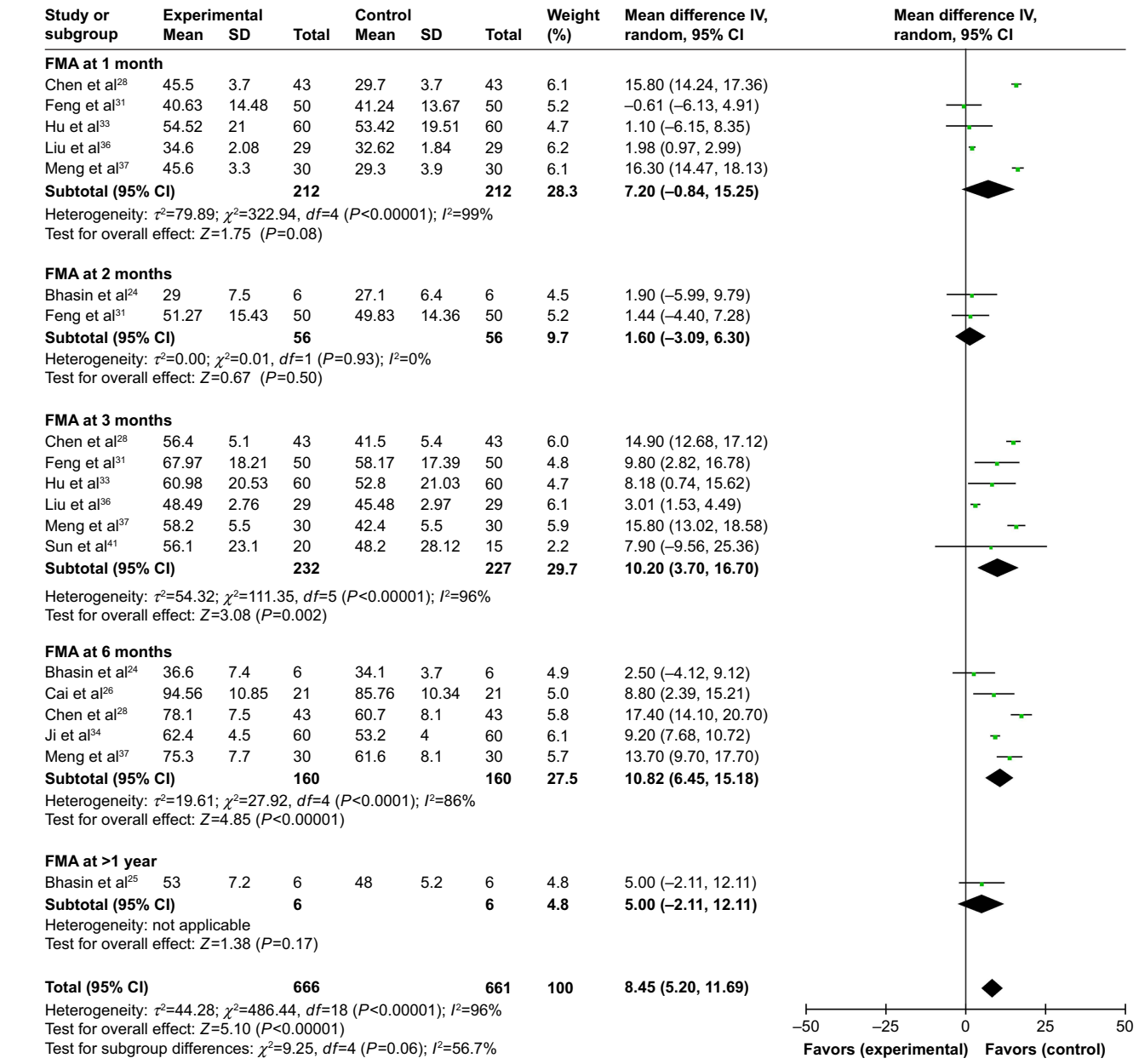

Figure 5 Forest plot of the comparison of FMA scores between the experimental and control groups.
Notes: Control group, RT alone group; experimental group, RT plus MSC therapy. The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; FMA, Fugl-Meyer Assessment; RT, routine treatment; MSC, mesenchymal stem cell.

Discussion

MSC transfusion has been considered as a promising option to treat IS due to its unique biological characteristics. Transfused MSCs can migrate to infarction area and induce angiogenesis,[46,47] reduce neuron apoptosis,[48,49] enhance axonal regeneration and rebuild synapses. Upon stimulating the release of cytokines and neurotrophic factors,[3,50] such as brain-derived neurotrophic factor,[3] basic fibroblast growth factor[15] and vascular endothelial growth factor,[3,51] MSCs also promote the differentiation of endogenous neural stem and progenitor cells. Most importantly, the low immunogenicity of MSCs reduces the possibility of graft-versus-host reaction.[1,15]

In recent years, several studies reported that MSC therapy is a safe and feasible treatment option for IS,[23–45] but different clinical protocols among studies may bring different therapeutic effects. In this study, we performed an extensive and systematic analysis of published clinical trials to assure statistical reliability. Our meta-analysis revealed that compared to IS patients treated by RT alone, those treated by

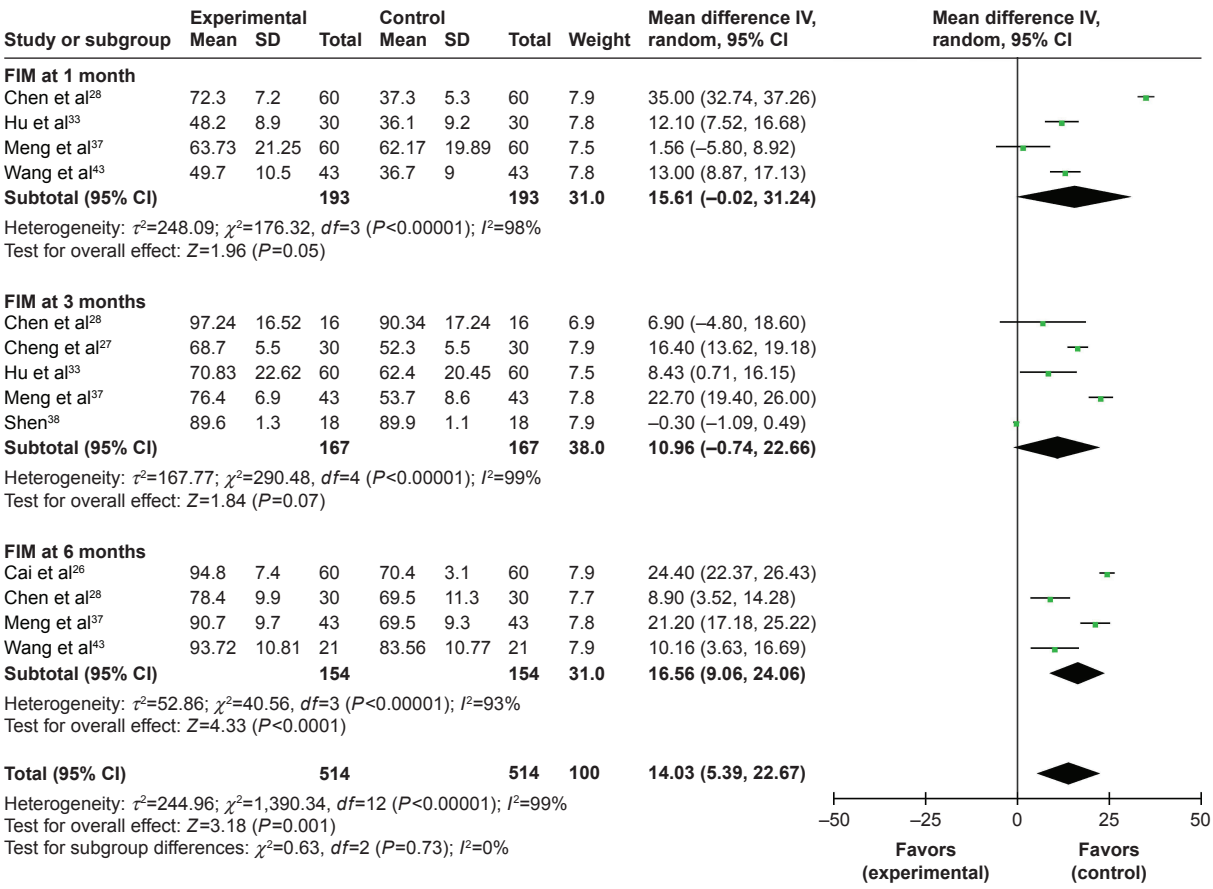

Figure 6 Forest plot of the comparison of the FIM scores between the experimental and control groups.
Notes: Control group, RT alone group; experimental group, RT plus MSC therapy. The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; FIM, Functional Independence Measure; RT, routine treatment; MSC, mesenchymal stem cell.

MSC and RT combined therapy exhibited more favorable therapeutic efficacy, indicated by decreased NIHSS and increased BI, FMA and FIM scores.

MSC therapy has been applied to treat refractory diseases for years with satisfied safety record,[52–55] and our analysis showed that MSCs were safe in treating IS as well. No serious adverse events have been reported during MSC therapy. Most common side effects, including fever and headache, usually resolved naturally. However, relevant studies were insufficient, and the potential long-term toxicity and the risk of tumor formation are unknown, which usually take years to occur. More research evidence will be required to support the safety of combined therapy.

Therapeutic effects of MSC therapy may be affected by infusion routes, cell dosages, cell types and patients' characteristics. We found that intravenous infusion is generally superior to subarachnoid injection in therapeutic effects, but there were also contradicted conclusions drawn from different researches. There are articles that claimed that local subarachnoid injection may deliver a larger number of transplanted MSCs to the stroke lesion thereby promoting nerve recovery and regeneration.[2,56] However, the different routes of cell infusion did not make big difference in other researches,[57] which speculated that MSCs treat IS through releasing growth factors and antiapoptotic factors instead of homing to the nerve system.[3,58] The treatment effect varies at different time points of detection, and dosages of transfused MSCs are a key factor in therapeutic strategy optimization. There are studies that showed that increased number of infused cells contributed to favorable clinical efficacy,[57] but currently published literature is still not sufficient to perform reliable statistical analysis. Sources of MSC may also associate with treatment outcomes. Based on our extracted data, autogenous MSCs were associated with increased BI and FIM score, indicating a better therapeutic effect than allogenic MSCs for IS. However, our data were not sufficient, and more research evidence is needed to support this conclusion. The optimal conduction time of cell delivery is also undetermined

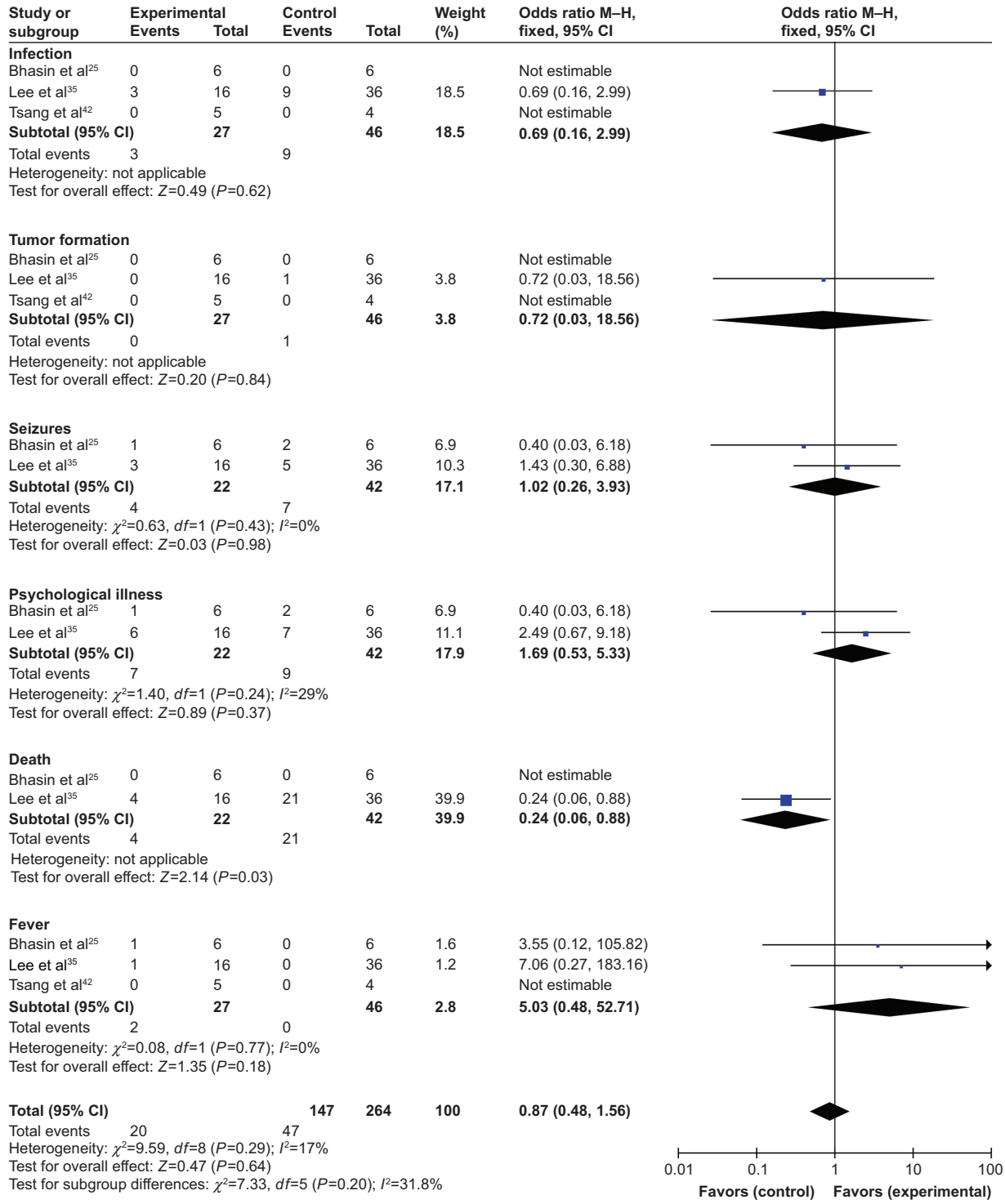

Figure 7 Forest plot of the comparison of adverse events between the experimental and control groups.
Notes: Control group, RT alone group; experimental group, RT plus MSC therapy. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.
Abbreviations: M–H, Mantel–Haenszel; RT, routine treatment; MSC, mesenchymal stem cell.

yet. Preclinical studies showed that early intervention leads to an obvious relief of neurological defects.[2,59] Our subgroup analysis suggested no significant difference in outcomes between the acute and chronic phases of stroke.

Limitations

There are some limitations in this analysis. First of all, the numbers of involved studies and patients were small and the follow-up period was short, which may cause publication

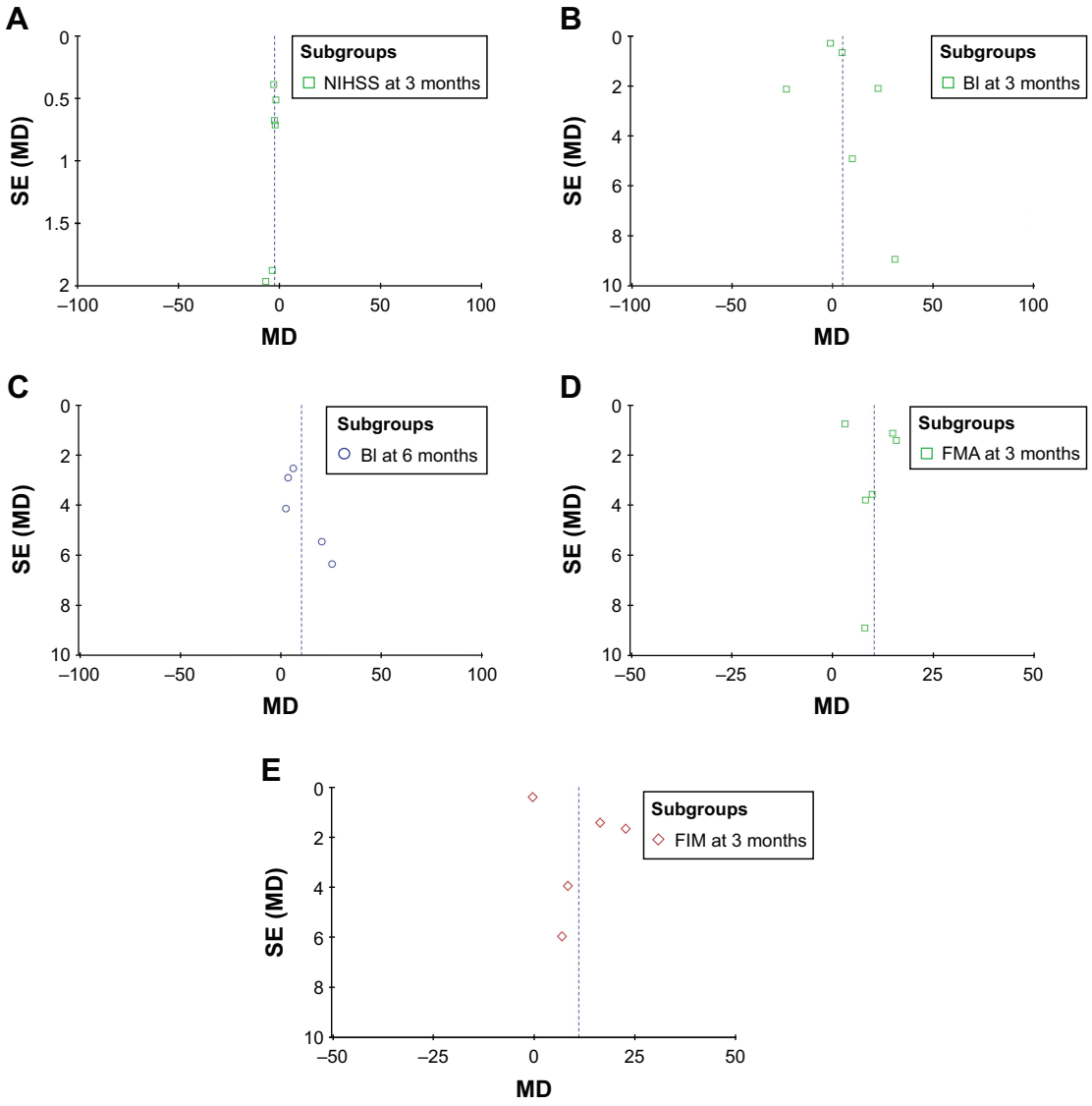

Figure 8 Funnel plot of the NIHSS (**A**), BI (**B** and **C**), FMA (**D**) and FIM (**E**) scores between the experimental and control groups.
Note: Parameters were discussed in over five studies which were included in bias analyses.
Abbreviations: SE, standard error; MD, mean difference; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure.

bias. Second, all trials included in this paper were mainly conducted in Asian countries. There were indeed several trials conducted in non-Asian countries included upon the first retrieve. However, no paper meeting our inclusion criteria has been produced based on these trials, and studies were excluded due to insufficient data, and being case reports, unrelated to MSC therapy or without control group. We will keep paying close attention to global studies in this field and carry out further analyses in our later studies. Third, our data were partly extracted from published papers rather than original patient records, which means we were not able to avoid the analytical bias based on the information presented in them. In addition, different trials evaluated the treatment efficacy by different outcomes, which have to be summarized using various scales when assessed in this study, leading to small sample sizes in each statistical analysis. Due to above limitations, future studies and generated data will be valuable to further verify the safety and efficacy of MSC therapy.

Conclusion

In summary, our analysis verified the safety and efficacy of MSC therapy for IS. It significantly mitigated neurological defects and improved life quality of IS patients, without causing serious adverse events. Therefore, MSC therapy is a promising treatment option for IS patients.

Table 3 Subgroup analyses of NIHSS, BI, FMA and FIM between the experimental and control groups

Parameter (TP after surgery)	Factors at study level	Experimental group	Control group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
		No. of patients (n)	No. of patients (n)		I^2 (%)	*P*-value			
NIHSS (Month 3)	**Cell type**								
	Auto-MSC	120	119	Random	37	0.18	−2.49	−3.45 to −1.54	<0.00001
	Allo-MSC	50	50	Random			−3.06	−3.82 to −2.30	<0.00001
	Route of delivery								
	Subarachnoid	82	77	Random	68	0.04	−3.66	−6.53 to −0.80	0.01
	Intravenous	38	42	Random	0	0.84	−2.30	−3.27 to −1.34	<0.00001
BI (Month 3)	**Route of delivery**								
	Subarachnoid	59	59	Random	6	0.30	4.83	2.66–7.01	<0.0001
	Intravenous	61	84	Random	99	<0.00001	6.02	−10.58 to 22.63	0.48
BI (Month 6)	**Cell type**								
	Auto-MSC	62	80	Random	80	0.002	12.48	3.01–21.94	0.010
	Allo-MSC	60	60	Random			3.70	−1.98 to 9.38	0.20
	Route of delivery								
	Subarachnoid	30	30	Random			20.40	9.71–31.09	0.0002
	Intravenous	92	110	Random	72	0.01	7.70	0.96–14.44	0.03
	Patients' characteristics								
	Acute stroke	5	23	Random			25.40	12.95–37.85	<0.0001
	Chronic stroke	27	27	Random	0	0.43	5.19	0.96–9.42	0.02
FMA (Month 3)	**Cell type**								
	Auto-MSC	122	117	Random	97	<0.00001	10.76	2.38–19.14	0.01
	Allo-MSC	110	110	Random	0	0.76	9.04	3.95–14.13	0.0005
	Route of delivery								
	Subarachnoid	72	72	Random	99	<0.00001	8.92	−2.73 to 20.58	0.13
	Intravenous	50	45	Random	0	0.38	15.60	12.86–18.35	<0.00001
FIM (Month 3)	**Cell type**								
	Auto-MSC	89	89	Random	84	0.002	17.28	11.01–23.55	<0.00001
	Allo-MSC	78	78	Random	79	0.03	3.19	−5.19 to 11.57	0.46
	Route of delivery								
	Subarachnoid	16	16	Random			6.90	−4.80 to 18.60	0.25
	Intravenous	73	73	Random	88	0.004	19.49	13.31–25.66	<0.00001

Abbreviations: TP, time point; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure; auto-MSC, autogenous mesenchymal stem cell; allo-MSC, allogenic mesenchymal stem cell.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
NIHSS at 1 month								
Deng et al[1]	4.72	2.66	15	10.8	3.65	15	7.2	–6.08 (–8.37, –3.79)
Feng et al[2]	15.63	3.48	50	19.13	4.28	50	8.7	–3.50 (–5.03, –1.97)
Liu et al[3]	11.52	1.23	29	16.23	0.94	29	10.1	–4.71 (–5.27, –4.15)
Song et al[4]	4.85	1.62	28	11.36	1.18	28	9.9	–6.51 (–7.25, –5.77)
Subtotal (95% CI)			**122**			**122**	**35.9**	**–5.20 (–6.52, –3.87)**
Heterogeneity: τ^2=1.40; χ^2=20.13, *df*=3 (*P*=0.0002); I^2=85%								
Test for overall effect: *Z*=7.67 (*P*<0.00001)								
NIHSS at 2 months								
Feng et al[2]	12.67	2.68	50	19.13	4.28	50	8.9	–6.46 (–7.86, –5.06)
Subtotal (95% CI)			**50**			**50**	**8.9**	**–6.46 (–7.86, –5.06)**
Heterogeneity: not applicable								
Test for overall effect: *Z*=9.05 (*P*<0.00001)								
NIHSS at 3 months								
Feng et al[2]	7.67	1.48	50	19.13	4.28	50	9.1	–11.46 (–12.72, –10.20)
He[5]	4.9	2.1	18	10.2	2.3	18	8.8	–5.30 (–6.74, –3.86)
Liu et al[3]	9.51	1.05	29	16.23	0.94	29	10.1	–6.72 (–7.23, –6.21)
Sun et al[6]	4.8	2	20	10.1	2.2	20	9.1	–5.30 (–6.60, –4.00)
Xie et al[8]	13.8	7.1	30	19.1	11.5	30	3.5	–5.30 (–10.14, –0.46)
Zhao et al[9]	12.2	6.87	23	23.13	5.32	23	5.1	–10.93 (–14.48, –7.38)
Subtotal (95% CI)			**170**			**170**	**45.8**	**–7.50 (–9.59, –5.40)**
Heterogeneity: τ^2=5.56; χ^2=66.70, *df*=5 (*P*<0.00001); I^2=93%								
Test for overall effect: *Z*=7.01 (*P*<0.00001)								
NIHSS at 6 months								
Chen et al[10]	13.89	6.95	30	22.89	5.26	30	5.7	–9.00 (–12.12, –5.88)
Xie et al[8]	9.5	5.9	30	19.1	11.5	30	3.7	–9.60 (–14.23, –4.97)
Subtotal (95% CI)			**60**			**60**	**9.5**	**–9.19 (–11.77, –6.60)**
Heterogeneity: τ^2=0.00; χ^2=0.04, *df*=1 (*P*=0.83); I^2=0%								
Test for overall effect: *Z*=6.96 (*P*<0.00001)								
Total (95% CI)			**402**			**402**	**100**	**–6.73 (–7.85, –5.61)**
Heterogeneity: τ^2=3.16; χ^2=126.51, *df*=12 (*P*<0.00001); I^2=91%								
Test for overall effect: *Z*=11.77 (*P*<0.00001)								
Test for subgroup differences: χ^2=8.68, *df*=3 (*P*=0.03); I^2=65.4%								

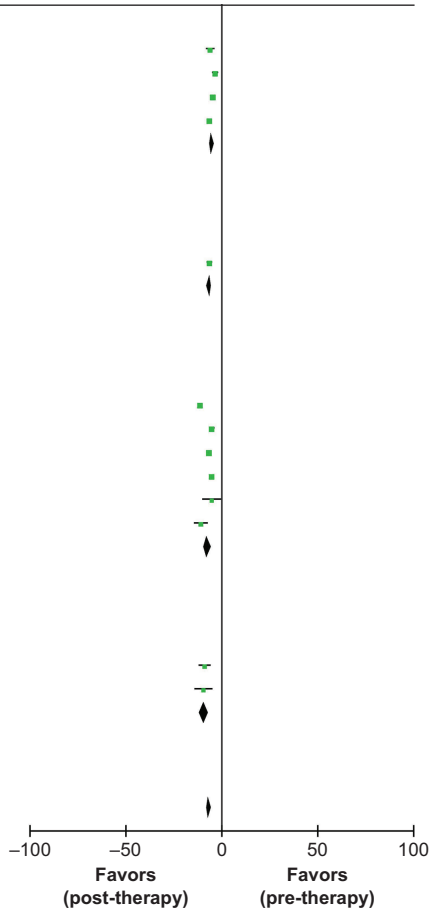

Figure S1 Forest plot of the comparison of NIHSS scores pre- and post-therapy.
Note: The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; NIHSS, National Institutes of Health Stroke Scale.

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
BI at 1 month								
Liu et al[3]	53.55	1.75	29	23.41	1.34	29	10.0	30.14 (29.34, 30.94)
Subtotal (95% CI)			**29**			**29**	**10.0**	**30.14 (29.34, 30.94)**
Heterogeneity: not applicable								
Test for overall effect: Z=73.64 (P<0.00001)								
BI at 2 months								
Bhasin et al[11]	59.5	11.5	6	44	10.6	6	4.4	15.50 (2.99, 28.01)
Subtotal (95% CI)			**6**			**6**	**4.4**	**15.50 (2.99, 28.01)**
Heterogeneity: not applicable								
Test for overall effect: Z=2.43 (P=0.02)								
BI at 3 months								
Bang et al[12]	55	17	5	9	20.1	5	1.9	46.00 (22.93, 69.07)
Cheng et al[13]	62.1	1.2	18	32.6	2.4	18	9.9	29.50 (28.26, 30.74)
He[5]	56.2	6.1	18	36.9	7.9	18	8.6	19.30 (14.69, 23.91)
Liu et al[3]	60.09	2.17	29	23.41	1.34	29	10.0	36.68 (35.75, 37.61)
Sun et al[6]	78.5	7.2	20	37.8	8.3	20	8.5	40.70 (35.88, 45.52)
Tsang et al[14]	33.4	35.4	5	31.6	33.5	5	0.6	1.80 (–40.92, 44.52)
Xie et al[8]	44.9	18.4	30	27.9	12.8	30	6.6	17.00 (8.98, 25.02)
Subtotal (95% CI)			**125**			**125**	**46.1**	**29.66 (24.12, 35.20)**
Heterogeneity: τ^2=37.45; χ^2=149.15, df=6 (P<0.00001); I^2=96%								
Test for overall effect: Z=10.50 (P<0.00001)								
BI at 6 months								
Bang et al[12]	62	12	5	9	20.1	5	2.3	53.00 (32.48, 73.52)
Bhasin et al[11]	72.5	8.8	6	44	10.6	6	5.1	28.50 (17.48, 39.52)
Cai et al[15]	65.87	8.75	21	32.41	4.05	21	8.8	33.46 (29.34, 37.58)
Ji et al[16]	41.1	16.5	60	36.1	12.4	60	8.2	5.00 (–0.22, 10.22)
Tsang et al[14]	38	37.1	5	31.6	33.5	5	0.6	6.40 (–37.41, 50.21)
Xie et al[8]	61.5	20.3	30	27.9	12.8	30	6.3	33.60 (25.01, 42.19)
Subtotal (95% CI)			**127**			**127**	**31.3**	**27.76 (13.24, 42.28)**
Heterogeneity: τ^2=265.36; χ^2=84.55, df=5 (P<0.00001); I^2=94%								
Test for overall effect: Z=3.75 (P=0.0002)								
BI at >1 year								
Bang et al[12]	62	20.8	5	9	20.1	5	1.6	53.00 (27.65, 78.35)
Bhasin et al[17]	90	4.3	6	44	10.6	6	6.0	46.00 (36.85, 55.15)
Tsang et al[14]	47	37.4	4	31.6	33.5	5	0.5	15.40 (–31.56, 62.36)
Subtotal (95% CI)			**15**			**16**	**8.1**	**45.79 (37.32, 54.25)**
Heterogeneity: τ^2=0.00; χ^2=1.92, df=2 (P=0.38); I^2=0%								
Test for overall effect: Z=10.60 (P<0.00001)								
Total (95% CI)			**302**			**303**	**100**	**29.27 (25.75, 32.80)**
Heterogeneity: τ^2=32.16; χ^2=320.06, df=17 (P<0.00001); I^2=95%								
Test for overall effect: Z=16.28 (P<0.00001)								
Test for subgroup differences: χ^2=18.48, df=4 (P=0.0010); I^2=78.4%								

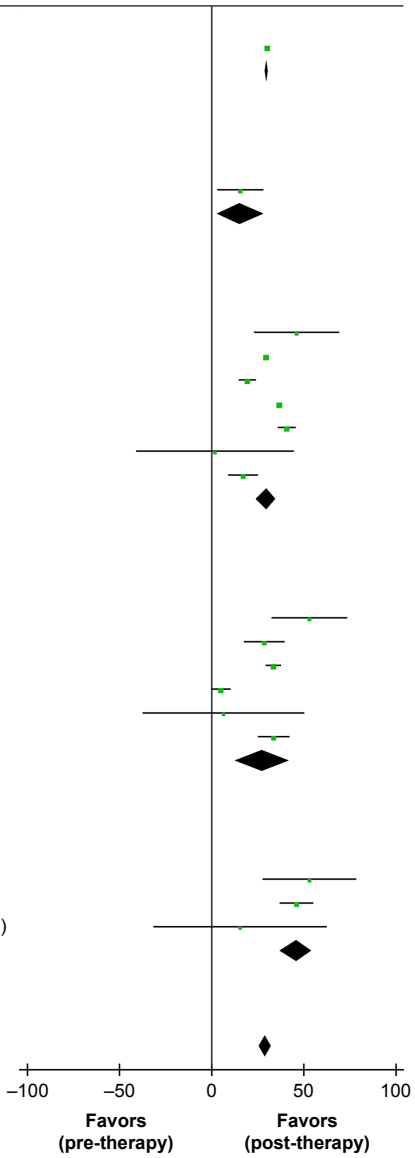

Figure S2 Forest plot of the comparison of BI scores pre- and post-therapy.
Note: The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; BI, Barthel index.

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
FMA at 1 month								
Chen et al[18]	45.5	3.7	43	21.2	2	43	5.5	24.30 (23.04, 25.56)
Feng et al[2]	40.63	14.48	50	27.27	12.09	50	5.3	13.36 (8.13, 18.59)
Hu et al[19]	54.52	21	60	52.02	18.52	60	5.1	2.50 (–4.58, 9.58)
Liu et al[3]	34.6	2.08	29	24.34	1.93	29	5.5	10.26 (9.23, 11.29)
Meng et al[20]	45.6	3.3	30	20.5	2.2	30	5.5	25.10 (23.68, 26.52)
Subtotal (95% CI)			**212**			**212**	**26.9**	**15.49 (7.51, 23.47)**
Heterogeneity: τ^2=78.94; χ^2=429.72, *df*=4 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=3.80 (*P*=0.0001)								
FMA at 2 months								
Bhasin et al[11]	29	7.4	6	16.6	5.3	6	5.1	12.40 (5.12, 19.68)
Feng et al[2]	51.27	15.43	50	27.27	12.09	50	5.3	24.00 (18.57, 29.43)
Subtotal (95% CI)			**56**			**56**	**10.3**	**18.46 (7.11, 29.82)**
Heterogeneity: τ^2=56.53; χ^2=6.26, *df*=1 (*P*=0.01); I^2=84%								
Test for overall effect: *Z*=3.19 (*P*=0.001)								
FMA at 3 months								
Chen et al[18]	56.4	5.1	43	21.2	2	43	5.5	35.20 (33.56, 36.84)
Feng et al[2]	67.97	18.21	50	27.27	12.09	50	5.2	40.70 (34.64, 46.76)
Hu et al[19]	60.98	20.53	60	52.02	18.52	60	5.1	8.96 (1.96, 15.96)
Liu et al[3]	48.49	2.76	29	24.34	1.93	29	5.5	24.15 (22.92, 25.38)
Meng et al[20]	58.2	5.5	30	20.5	2.2	30	5.5	37.70 (35.58, 39.82)
Sun et al[7]	56.1	23.1	20	50.5	21.8	20	4.2	5.60 (–8.32, 19.52)
Subtotal (95% CI)			**232**			**232**	**31.0**	**27.00 (19.78, 34.23)**
Heterogeneity: τ^2=71.84; χ^2=234.72, *df*=5 (*P*<0.00001); I^2=98%								
Test for overall effect: *Z*=7.33 (*P*<0.00001)								
FMA at 6 months								
Bhasin et al[11]	36.6	7.4	6	16.6	5.3	6	5.1	20.00 (12.72, 27.28)
Cai et al[15]	94.56	10.85	21	63.54	7.65	21	5.2	31.02 (25.34, 36.70)
Chen et al[18]	78.1	7.5	43	21.2	2	43	5.5	56.90 (54.58, 59.22)
Ji et al[16]	62.4	4.5	60	30	4.4	60	5.5	32.40 (30.81, 33.99)
Meng et al[20]	75.3	7.7	30	20.5	2.2	30	5.4	54.80 (51.93, 57.67)
Subtotal (95% CI)			**160**			**160**	**26.7**	**39.26 (25.85, 52.67)**
Heterogeneity: τ^2=228.89; χ^2=423.88, *df*=4 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=5.74 (*P*<0.00001)								
FMA at >1 year								
Bhasin et al[17]	53	7.1	6	16.6	5.3	6	5.1	36.40 (29.31, 43.49)
Subtotal (95% CI)			**6**			**6**	**5.1**	**36.40 (29.31, 43.49)**
Heterogeneity: not applicable								
Test for overall effect: *Z*=10.06 (*P*<0.00001)								
Total (95% CI)			**666**			**661**	**100**	**26.49 (20.51, 32.47)**
Heterogeneity: τ^2=169.09; χ^2=2,425.13, *df*=18 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=8.69 (*P*<0.00001)								
Test for subgroup differences: χ^2=20.12, *df*=4 (*P*=0.0005); I^2=80.1%								

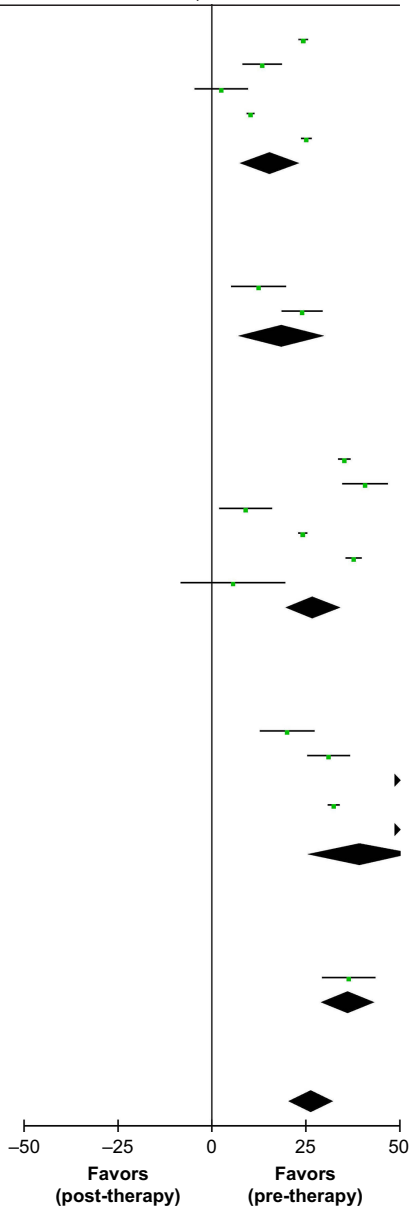

Figure S3 Forest plot of the comparison of FMA scores pre- and post-therapy.
Note: The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; FMA, Fugl-Meyer Assessment.

Study or subgroup	Post-therapy Mean	SD	Total	Pre-therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
FIM at 1 month								
Chen et al[18]	49.7	10.5	43	24.8	7	43	6.8	24.90 (21.13, 28.67)
Hu et al[19]	63.73	21.25	60	62.27	20.12	60	6.6	1.46 (–5.94, 8.86)
Meng et al[20]	48.2	8.9	30	24.6	9.4	30	6.7	23.60 (18.97, 28.23)
Wang et al[21]	72.3	7.2	60	25.3	6.6	60	6.8	47.00 (44.53, 49.47)
Subtotal (95% CI)			**193**			**193**	**27.0**	**24.47 (7.14, 41.80)**
Heterogeneity: τ^2=306.63; χ^2=220.03, *df*=3 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=2.77 (*P*=0.006)								
FIM at 3 months								
Chen et al[18]	89.6	1.3	18	72.6	2.1	18	6.8	17.00 (15.86, 18.14)
Cheng et al[13]	76.4	6.9	43	24.8	7	43	6.8	51.60 (48.66, 54.54)
Hu et al[19]	70.83	22.62	60	62.27	20.12	60	6.6	8.56 (0.90, 16.22)
Meng et al[20]	68.7	5.5	30	24.6	9.4	30	6.8	44.10 (40.20, 48.00)
Shen[22]	97.24	16.52	16	86.21	11.13	16	6.5	11.03 (1.27, 20.79)
Tsang et al[14]	58.2	28.6	5	56.2	26.8	5	4.4	2.00 (–32.35, 36.35)
Subtotal (95% CI)			**172**			**172**	**37.9**	**24.05 (6.56, 41.54)**
Heterogeneity: τ^2=436.97; χ^2=603.42, *df*=5 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=2.69 (*P*=0.007)								
FIM at 6 months								
Cai et al[15]	93.72	10.81	21	71.84	9.04	21	6.7	21.88 (15.85, 27.91)
Chen et al[18]	90.7	9.7	43	24.8	7	43	6.8	65.90 (62.32, 69.48)
Meng et al[20]	78.4	9.9	30	24.6	9.4	30	6.7	53.80 (48.91, 58.69)
Tsang et al[14]	64	31	5	56.2	26.8	5	4.2	7.80 (–28.12, 43.72)
Wang et al[21]	94.8	7.4	60	25.3	6.6	60	6.8	69.50 (66.99, 72.01)
Subtotal (95% CI)			**159**			**159**	**31.2**	**48.13 (32.04, 64.23)**
Heterogeneity: τ^2=296.79; χ^2=228.69, *df*=4 (*P*<0.00001); I^2=98%								
Test for overall effect: *Z*=5.86 (*P*<0.00001)								
FIM at >1 year								
Tsang et al[14]	59.2	32.5	4	56.2	26.8	5	3.9	3.00 (–36.58, 42.58)
Subtotal (95% CI)			**4**			**5**	**3.9**	**3.00 (–36.58, 42.58)**
Heterogeneity: not applicable								
Test for overall effect: *Z*=0.15 (*P*=0.88)								
Total (95% CI)			**528**			**529**	**100**	**30.32 (18.34, 42.30)**
Heterogeneity: τ^2=547.98; χ^2=2,453.32, *df*=15 (*P*<0.00001); I^2=99%								
Test for overall effect: *Z*=4.96 (*P*<0.00001)								
Test for subgroup differences: χ^2=7.42, *df*=3 (*P*=0.06); I^2=59.6%								

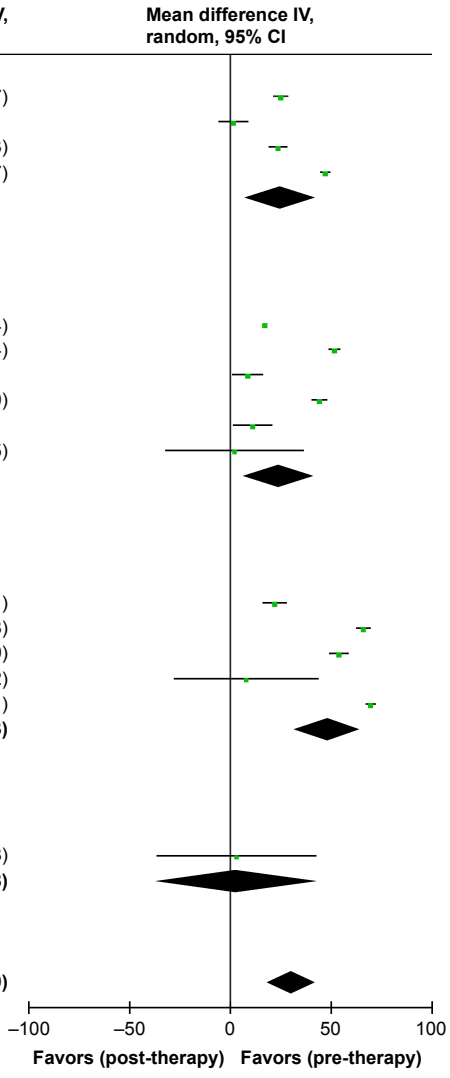

Figure S4 Forest plot of the comparison of FIM scores in pre- and post-therapy.
Note: The random-effects meta-analysis model (inverse variance method) was used.
Abbreviations: IV, inverse variance; FIM, Functional Independence Measure.

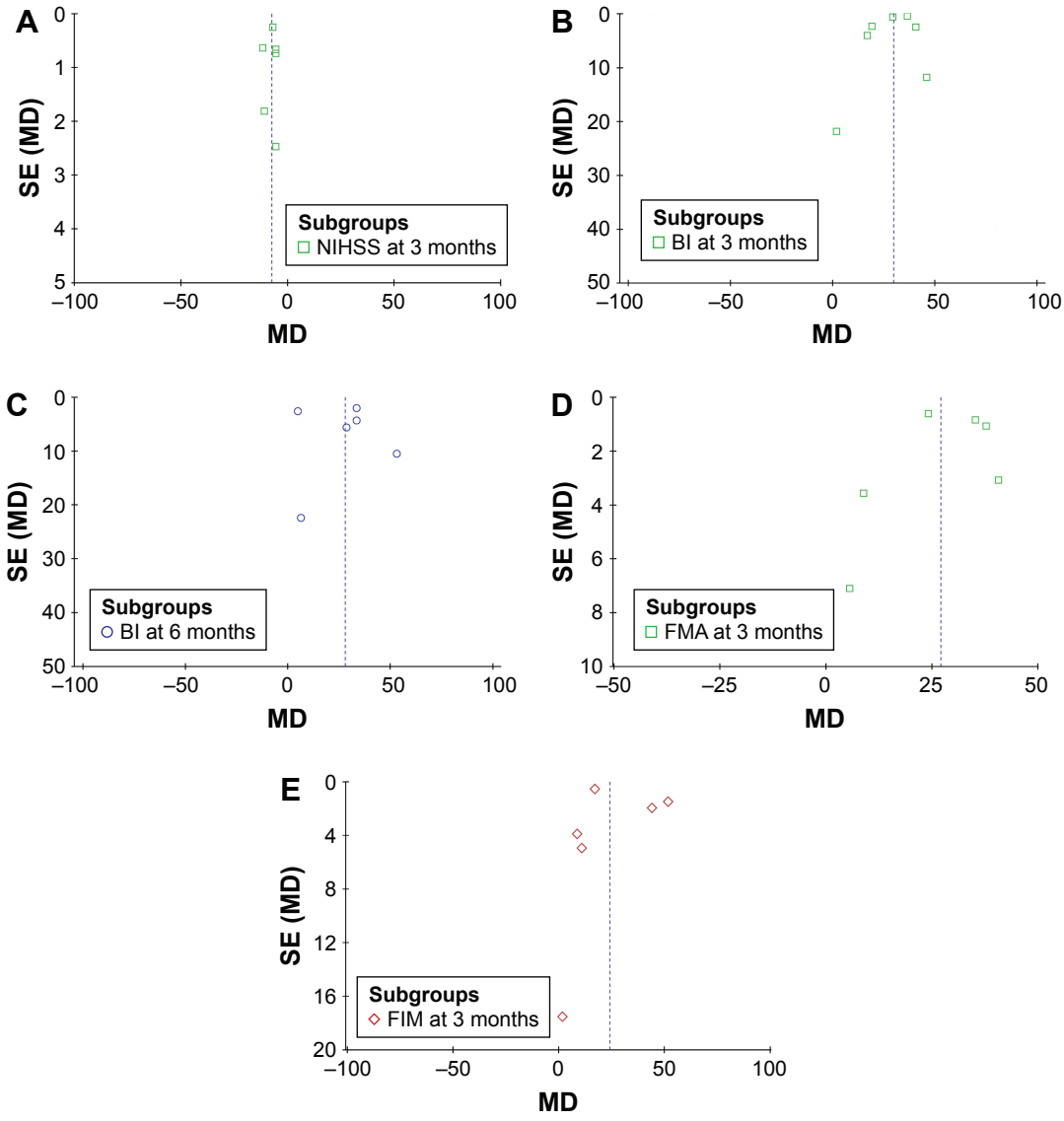

Figure S5 Funnel plot of the NIHSS (**A**), BI (**B** and **C**), FMA (**D**) and FIM (**E**) scores pre- and post-therapy.
Note: Parameters were discussed in over five studies which were included in bias analyses.
Abbreviations: SE, standard error; MD, mean deviation; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure.

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