Systematic Review and Meta-Analysis

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The efficacy and safety of salvianolic acids on acute cerebral infarction treatment

A protocol for systematic review and meta analysis

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Abstract

Background: Salvianolic acids (SA) has been widely used for the treatment of acute cerebral infarction (ACI) combined with basic western medicine therapy in China. This study was aimed to evaluate the efficacy and safety of SA on ACI treatment and its influence on neurological functions, activity of daily living, and cognitive functions.

Methods: We retrieved related articles from PubMed, the Cochrane Center Controlled Trials Register, EMBASE, Medline, Ovid, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Database without date and language restrictions. Finally, 58 randomized controlled trials were included from 239 retrieved records. Two researchers extracted the basic information and data from included articles and assessed the quality and analysis of data by using Review Manager 5.3.

Results: The administration of SA significantly increased the total clinical effective rate of ACI treatment ($P < .001$) and improved the National Institute of Health Stroke Scale scores, modified Rankin Scale scores, and Barthel Index scores after treatment and 3 months after ACI ($P < .05$). The activities of daily living scores in the SA group were significantly increased after treatment ($P < .001$), whereas they were remarkably decreased 3 months after ACI ($P < .001$) compared with that in the control group. Besides, SA profoundly promoted the recovery of Montreal Cognitive Assessment scores ($P < .001$). However, the use of SA increased the risk of adverse events occurrence ($P = .007$).

Conclusion: SA combined with basic western medicine treatment could promote neurological functions, daily living activities, and cognitive functions recovery of ACI patients. Although SA increased the risk of adverse events occurrence, these adverse events were easily controlled or disappeared spontaneously.

Abbreviations: ACI = acute cerebral infarction, ADL = activities of daily living, BDNF = brain-derived neurotrophic factor, BI = Barthel Index, CG = control group, CNS = central nervous system, CT = computed tomography, DALYs = disability-adjusted life-years, EG = experiment group, FDA = Food and Drug Administration, GBD = Global Burden of Disease, MCAO = middle cerebral artery occlusion, MMSE = mini-mental state examination, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, mRS = modified Rankin Scale, MT = mechanical thrombectomy, NGF = nerve growth factor, NIHSS = National Institute of Health Stroke Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline, RCTs = randomized controlled trials, RR = relative risk, rt-PA = recombinant tissue plasminogen activator, SA = salvianolic acids, WM = western medicine.

Keywords: acute cerebral infarction, acute ischemic stroke, efficacy, meta-analysis, safety, salvianolic acids

1. Introduction

Stroke is the second leading cause of mortality after ischemic heart diseases and the third most common cause of disability all over the world, in which ischemic stroke caused by cerebral artery occlusion accounts for ~80% of strokes.[1,2] Global Burden of Disease (GBD) 2013 Study showed that there were 25.7 million stroke survivors (71% with ischemic stroke), 6.5 million deaths

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The authors have no conflicts of interest to disclose.

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from stroke (51% due to ischemic stroke), 113 million disability-adjusted life-years (DALYs) due to stroke (58% due to ischemic stroke), and 10.3 million incidence (67% ischemic stroke).[3] Various mechanisms are involved in the injury postischemic stroke, including glutamate excitotoxicity, calcium overload, oxidative stress, inflammation, and so on.[4–6] Nowadays, the thrombolytic recombinant tissue plasminogen activator (rt-PA) is still the only validated agent for the clinical treatment of ischemic stroke approved by the Food and Drug Administration (FDA).[7,8] Mechanical thrombectomy (MT) is also a validated strategy for selective patients with acute cerebral infarction (ACI) and has demonstrated substantial rates of partial or complete arterial recanalization and improved outcomes compared with IV rtPA or other medical treatment alone in multiple randomized clinical trials.[9] However, the clinical use of rt-PA and MT is limited for its narrow therapeutic time window, patient enrollment criterion, and risk of hemorrhage. Therefore, the development of agents for ischemic stroke treatment is urgently needed.

Salvia Miltiorrhiza Bunge, also known as Danshen in Chinese, is a traditional Chinese medicinal herb which is used for the treatment of hepatitis, myocardial infarction, ischemic stroke, etc.[10] Salvianolic acids (SA) for injection are made of extracts from *Salvia Miltiorrhiza* Bunge, which mainly contains salvianolic acids (B, D, Y), rosmarinic acid, and alkannic acid.[11] In recent years, SA for injection has been widely used for the treatment of acute ischemic stroke combined with basic western medicine therapy in China. It has been reported that SA for injection can attenuate infarction volume through suppressing inflammation response and microglia activation in a rat middle cerebral artery occlusion (MCAO) model.[11] A clinical trial also demonstrated SA could increase the perfusion of hypo-perfused brain tissue to improve neurological functions postischemic stroke.[12]

More and more investigations indicate that SA might improve the prognosis of acute ischemic stroke.[12,13] In this systematic review, we are aimed to evaluate the effect and safety of SA on ACI patients as well as its impact of neurological functions, daily activities, and cognitive levels recovery after ACI.

2. Methods

We conducted the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (PRISMA). The data used in the analysis were not original but were based on the published clinical studies with ethical approvals. So ethical approval was not necessary.

2.1. Inclusion criteria

2.1.1. Study type. Clinical randomized controlled trials (RCTs) used SA as the adjuvant treatment of ACI. Included studies shared similar research methods and have consistent evaluation index with completed data.

2.1.2. Participants. ACI patients were diagnosed by the standard formulated on the fourth Chinese National Cerebrovascular Disease Conference in 1995 or the World Health Organization criteria.[14] Diagnoses were validated using computed tomography (CT) or magnetic resonance imaging (MRI). Patients were experiencing the first onset of ACI and were admitted to the hospital within 72 hours after ACI. The age and gender of patients were not restricted.

2.1.3. Intervention. Patients in the control group (CG) accepted normal western medicine (WM) treatment, while patients in the experiment group (EG) accept SA treatment based on WM. WM treatment included thrombolytic therapy, antiplatelet therapy, and cerebral protection, etc. There was no limitation of SA dosage form, treatment courses, and drug manufacturers.

2.1.4. Outcomes. Total clinical effective rate and adverse drug reactions rate were used to evaluate the efficacy and safety of SA respectively. National Institute of Health Stroke Scale (NIHSS) (range 0–42), modified Rankin Scale (mRS) (range 0–5), activities of daily living (ADL) (range 0–100) and Barthel Index (BI) (range 0–100) were used to assess the neurological functions and daily living activities of patients. The cognitive functions of patients have been evaluated by mini-mental state examination (MMSE) (range 0–30) and Montreal Cognitive Assessment (MoCA) (range 0–30).

2.2. Exclusion criteria

Patients with hemorrhagic stroke. Patients with severe complications, such as severe cardiopathy, liver, or kidney diseases. Patients who were anaphylactic to SA. Patients using other Chinese traditional medicines or therapies, which could influence the effect of SA. Researches that did not report any evaluation indexes mentioned above. Researches with incorrect, incomplete, or unavailable data.

2.3. Literature search

Two independent researchers performed a systematic literature search in different electronic databases including PubMed, the Cochrane Center Controlled Trials Register, EMBASE, Medline, Ovid, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Database without any restrictions of languages and date. In the English database, "salvianolic acid" was used as an initial research term in title/abstract. Retrieved articles were further restricted by term "ischemic stroke" or "cerebral infarction" or "brain infarction" in title/abstract. In the Chinese database, the term "Dan Shen Duo Fen Suan" was used as subject terms for the initial search in title/abstract. "Que Xue Xing Nao Cu Zhong" or "Nao Geng Si" was used to further retrieval among the above results.

2.4. Quality assessment and statistical analysis

The quality assessment of included RCTs was conducted by Cochrane Risk of Bias Summary Tool in Review Manager 5.3 (Cochrane Collaboration, Oxford, UK), which contains 7 items including sequence generation (selection bias), allocation concealment (selection bias), blinding of patients and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcomes data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias.[15]

The information and data of included articles were collected by 2 reviewers. The collected data were synthesized and analyzed by Review Manager 5.3. Relative risk (RR) and mean difference were chosen to evaluate dichotomous outcomes and continuous outcomes respectively. The difference in each outcome between experimental and control groups was presented with 95% confidence interval. Z test was conducted to evaluate the combined effect values. Heterogeneity between RCTs was

Table 1

The characteristics of included studies.

Study ID	Year	Sex (M/F)	N (EG/CG)	Age (EG/CG)	Intervention		Duration (d)	Outcomes	Allocation sequence
					EG	CG			
Peng et al [12]	2018	117/42	85/74	60.07±12.96/61.36±12.98	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)	Unclear
Zhang et al [69]	2018	18/7	15/10	42–71/45–75	SA (100 mg/d)+WM (3)	WM	10 d	(1)(2)	Unclear
Zhang [68]	2018	110/90	100/100	57.54±8.12/58.21±7.64	SA (100 mg/d)+WM (1)	WM	Unclear	(1)(3)	Unclear
Dong et al [19]	2015	63/47	55/55	63±8/63±6	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(5)	I
Lu et al[20]	2018	52/28	40/40	33–75	SA (100 mg/d)+WM (1)	WM	14 d	(1)	II
Huang et al [70]	2015	47/41	44/44	56.9±4.3/57.4±4.2	SA (100 mg/d)+WM (2)	WM	14 d	(1)(2)(4)(5)(6)	Unclear
Kang et al [64]	2016	50/36	43/43	57.1±5.1/58.7±4.5	SA (? mg/d)+WM (2)	WM	14 d	(1)(2)(4)(5)(6)(8)	Unclear
Yan et al [65]	2017	51/45	48/48	55.34±5.67/56.16±6.39	SA (100mg/d)+WM (1)	WM	14 d	(1)(2)(4)(5)(6)(8)	Unclear
Zhang et al [21]	2015	42/28	35/35	37–79	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(4)(5)(6)(8)	II
Hou et al [38]	2015	114/86	100/100	66.28±10.25/68.23±11.72	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)	Unclear
Liu et al [39]	2017	65/23	46/42	60.02±12.96/60.93±13.19	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(7)	Unclear
Xu et al [22]	2015	30/18	24/24	62.75±7.92/63.31±7.26	SA (100 mg/d)+WM (1)	WM	14 d	(1)	I
Hao et al [75]	2014	52/42	47/47	55.86±14.42/58.92±13.90	SA (300 mg/d)+WM (3)	WM	14 d	(4)	Unclear
Wang et al [40]	2017	39/43	42/40	67.12±8.63/67.73±10.64	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(4)(6)(7)	Unclear
Li et al [41]	2019	71/55	64/62	62.2±6.3/61.7±5.9	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	Unclear
He et al [23]	2018	45/33	39/39	57.2±6.2/56.8±6.4	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)(8)	I
Wei et al [42]	2017	128/72	100/100	58.95±8.25/58.88±7.45	SA (100 mg/d)+WM (1)	WM	14 d	(1)(3)(7)(8)	Unclear
Cui et al [76]	2016	58/42	45/45	38–74	SA (100 mg/d)+WM (1)	WM	14 d	(4)	Unclear
Yan et al [43]	2018	92/84	88/88	58.26±10.18/57.54±8.46	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	Unclear
Zhang et al [71]	2018	46/20	34/32	58.92±10.10/60.69±9.55	SA (100 mg/d)+WM (1)	WM	10 d	(1)	Unclear
Pei et al [24]	2017	34/26	30/30	59.40±7.43/58.83±7.32	SA (200 mg/d)+WM (3)	WM	14 d	(1)	I
Zhang et al [25]	2019	Unclear	56/56	Unclear	SA (200 mg/d)+WM (3)	WM	14 d	(1)(7)(8)	I
Xu et al [72]	2015	Unclear	53/53	Unclear	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(4)	Unclear
Liang et al [26]	2018	48/50	49/49	66.8±9.4/64.8±9.0	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)	I
Zhang et al [27]	2016	40/40	40/40	61.89±8.71/62.62±8.21	SA (200 mg/d)+WM (2)	WM	14 d	(1)(4)(7)(8)	I
Wang et al [28]	2016	57/33	42/48	61.5±3.3/61.7±3.5	SA (? mg/d)+WM (3)	WM	14 d	(1)	I
Liu et al [74]	2017	Unclear	46/42	Unclear	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)	Unclear
Song et al [44]	2019	Unclear	38/38	55–85	SA (100 mg/d)+WM (1)	WM	14 d	(2)(4)(7)	Unclear
Gao et al [29]	2019	58/38	48/48	72.24±5.44/71.82±5.38	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)	II
Zhang et al [45]	2019	114/86	100/100	66.28±10.25/68.23±11.72	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)	Unclear
Yu et al [30]	2019	51/41	46/46	64.17±8.13/65.26±7.04	SA (100 mg/d)+WM (1)	WM	14 d	(1)(3)(7)	III
Si et al [31]	2019	32/28	30/30	64±6.09/63±6.70	SA (100 mg/d)+WM (1)	WM	14 d	(1)	II
Ren et al [46]	2019	26/14	20/20	64.35±8.58/64.75±9.34	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)	Unclear
Xiang et al [47]	2018	70/48	59/59	67.72±10.45/62.7±11.4	SA (100 mg/d)+WM (1)	WM	14 d	(7)(8)	Unclear
Liu et al [48]	2017	56/30	43/43	62.4±3.0/62.3±3.1	SA (100 mg/d)+WM (1)	WM	14 d	(1)(5)(6)(7)(8)	Unclear
Liu et al [49]	2019	38/33	36/35	61.16±10.76/60.00±9.75	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(7)	Unclear
Sheng et al [66]	2019	57/41	49/49	60.86±3.19/61.13±3.28	SA (200 mg/d)+WM (1)	WM	14 d	(1) (8)	Unclear
Guan et al [32]	2019	39/29	34/34	64±5.34/64±6.57	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)(8)	I
Tan et al [50]	2019	54/48	51/51	62.82±8.05/63.22±7.51	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(7)(8)	Unclear
Wang et al [73]	2019	45/47	50/42	61.12±9.6/60.31±10.3	SA (100 mg/d)+WM (1)	WM	14 d	(1)(2)(4)	Unclear
Zheng et al [33]	2018	52/34	43/43	64.00±12.06/64.09±10.28	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	I
Chang et al [51]	2017	10/10	10/10	69.8±6.9/70.4±5.3	SA (100 mg/d)+WM (1)	WM	15 d	(7)	Unclear
Qian et al [67]	2017	42/68	55/55	64.36±10.47/65.07±9.43	SA (100 mg/d)+WM (1)	WM	14 d	(1)(3)(8)	Unclear
Li et al [52]	2016	88/72	80/80	58.17±8.48/59.16±7.29	SA (100 mg/d)+WM (1)	WM	14 d	(1)(3)(7)(8)	Unclear
Chen et al [53]	2015	41/23	32/32	54.23±9.6/53.67±10.3	SA (100 mg/d)+WM (1)	WM	14d	(1)(3)(7)(8)	Unclear
Yang et al [34]	2019	31/29	30/30	63.2±2.5/64.1±2.9	SA (100 mg/d)+WM (1)	WM	14 d	(1)(3)(6)(7)(8)	II
Jiang et al [54]	2019	53/47	50/50	65.4±5.5/64.4±4.6	SA (100 mg/d)+WM (1)	WM	14 d	(4)(7)(8)	Unclear
Liu et al [35]	2019	39/41	40/40	61.31±4.35/60.31±5.71	SA (100 mg/d)+WM (1)	WM	14 d	(1)(7)(8)	I
Chen et al [36]	2019	39/25	32/32	66.9±4.4/65.7±4.6	SA (100 mg/d)+WM (1)	WM	14 d	(7)(8)	I
An et al [55]	2016	45/35	40/40	65.32±9.34/65.31±9.35	SA (100 mg/d)+WM (1)	WM	14 d	(7)	Unclear
Yang et al [56]	2019	43/37	40/40	59.85±7.33/59.43±7.41	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	Unclear
Li et al [57]	2015	65/35	50/50	62.4±4.5/60.3±4.3	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	Unclear
Zhao et al [58]	2019	73/51	62/62	59.92±11.34/59.52±11.75	SA (100 mg/d)+WM (1)	WM	14 d	(1)(4)(7)(8)	Unclear
Wang et al [37]	2016	49/31	40/40	64.8±3.2/65.2±3.4	SA (100 mg/d)+WM (3)	WM	14 d	(1)(4)(7)(8)	II
Gao et al [59]	2019	57/43	50/50	53.23±6.45/56.63±6.58	SA (100 mg/d)+WM (1)	WM	14 d	(7)(8)	Unclea
Dong et al [60]	2018	62/38	50/50	64.75±6.36/63.46±5.33	SA (100 mg/d)+WM (1)	WM	28 d	(7)	Unclear
Fang et al [61]	2017	66/84	75/75	57.83±7.79/56.91±7.62	SA (100 mg/d)+WM (1)	WM	14 d	(7)(8)	Unclear
Xu et al [62]	2019	82/58	70/70	56.1±6.2/55.2±6.5	SA (100 mg/d)+WM (3)	WM	14 d	(7)(8)	Unclear

CG=control group, EG=experimental group, F=female, M=male, SA=salvianolic acid, WM=western medicine therapies.

Salvianolic acids in intervention: Tasly Pharmaceutical Group Co, Ltd, Tianjin, China; Shang Hai Green Valley Pharmaceutical Company; unclear.

Outcomes: (1) National Institute of Health Stroke Scale (NIHSS), (2) Modified Rankin Scale (mRS), (3) Activities of daily living (ADL), (4) Barthel Index (BI), (5) Mini-Mental State Examination (MMSE), (6) Montreal Cognitive Assessment (MoCA), (7) Total clinical effective rate, (8) Adverse events.

Allocation sequence: I random figure table, II random queue insertion, III random draw.

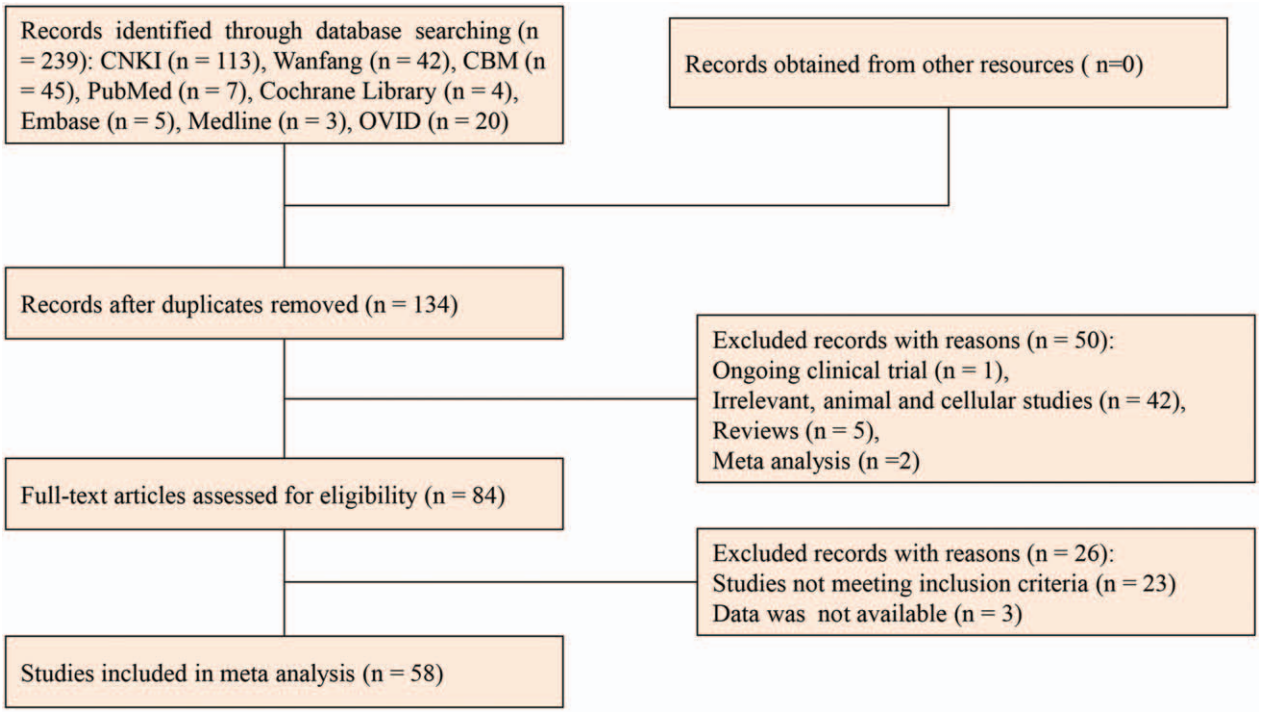

Figure 1. Flow chart of study search and selection.

analyzed by Cochrane's Q-statistic and I^2 tests.[16] The random effects model was used if evidence of significant heterogeneity was found ($P < .05$ or $I^2 > 50\%$). Otherwise, the fixed effects model was employed.[17,18]

3. Results

3.1. Included studies

A total of 239 articles were retrieved from different databases. After removal of duplicates, we retrieved 134 records from the literature search. We screened the titles and the abstracts of those citations and excluded records with reasons including: Ongoing clinical trial (n=1), reviews (n=5), meta-analysis (n=2), irrelevant studies (n=42), data was not available (n=3), studies not meeting inclusion criteria (n=23). Finally, 58 RCTs were included (Table 1) after removing duplicated articles and studies not meet inclusion criteria (Fig. 1). All included RCTs were conducted in China. The 58 RCTs included 2663 cases in EG and 2646 cases in CG. The sample size of included studies varied from 25 to 200. The daily dose of SA ranged from 100 to 300 mg and the duration of treatments ranged from 10 to 28 days. The number of RCTs related to the corresponding scores (NIHSS, mRS, ADL, BI, MMSE, MoCA) was shown in Fig. 2.

3.2. Quality of the included studies

We use the Cochrane Risk of Bias Summary Tool to evaluate the quality of the included studies (Fig. 3). Among these studies, 19 RCTs[19–37] described the method to generate the allocation sequence, in which 12 RCTs[19,22–28,32,33,35,36] used random figure table, 6 RCTs[20,21,29,31,34,37] used random queue insertion, and 1 RCTs[30] used random draw. Other RCTs did not mention the method to generate the allocation sequence. All of the included studies did not describe the information about blinding. In general, the overall quality of included RCTs was not high.

3.3. Outcomes

3.3.1. Total clinical effective rate. In total 37 RCTs[23,25–27,29,30,32–62] reported the total effective rate. NIHSS decreased by 91% to 100% was considered to be recovered. NIHSS decreased by 46% to 90% was considered to be significantly improved.

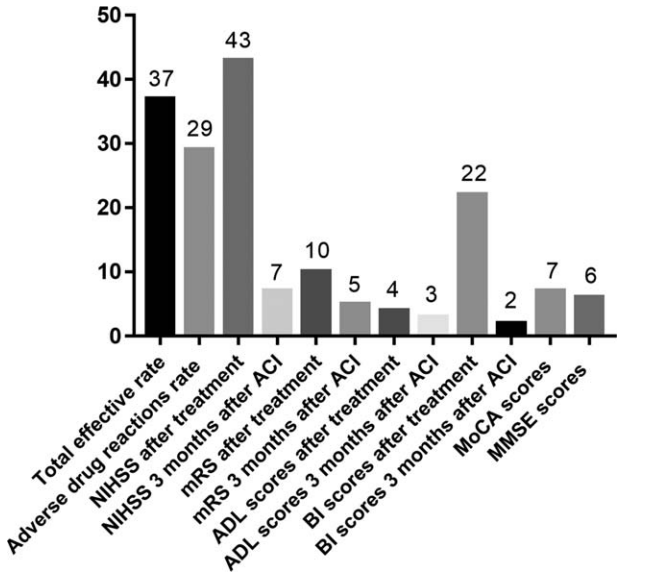

Figure 2. The number of RCTs related to the corresponding scores. RCTs = randomized controlled trials.

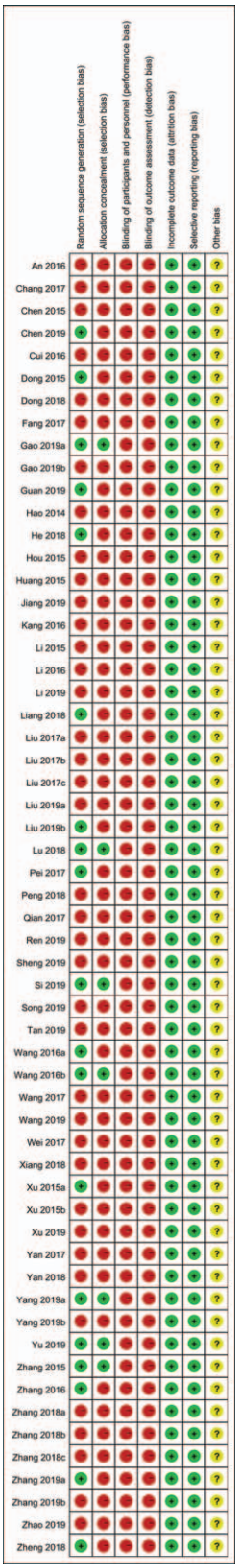

Figure 3. Risk of bias summary.

NIHSS decreased by 18% to 45% was considered to be improved. No change or worsen was determined as NIHSS decreased by less than 17%. Total clinical effective rate (%)= (number of recovered patients + number of patients with significant improvement + number of patients with improvement)/total number × 100%.[63] The results of the meta-analysis indicated that the total clinical effective rate in EG was significantly higher in comparison with that in CG by the fixed effects model ($P < .001$) (Fig. 4). Funnel plot on publication bias for total clinical effective rate (Fig. 5) presented a general symmetry and the studies included gathered in the upper part of the funnel plot. Since several patients have accepted thrombolytic therapy, we divided the cases into 2 subgroups, namely thrombolysis subgroup, and nonthrombolysis group. In both thrombolysis and nonthrombolysis subgroups, EG showed a higher total clinical effective rate in comparison with CG (Fig. 6). The Funnel plot on publication bias for total clinical effective rate in thrombolysis and nonthrombolysis groups was shown in Fig. 7.

3.3.2. Adverse drug reactions rate. A total of 29 studies[21,23,25,27,32–37,41–43,47,48,50,52–54,56–59,61,62,64–67] reported adverse drug reactions, in which 8 studies[25,32–35,37,66,67] reported that there were no adverse drug reactions in both groups. Meta-analysis showed that the adverse drug reaction rate was remarkably higher in EG compared with that in CG ($P = .007$) (Fig. 8). Adverse drug reactions include headache, dizziness, hemorrhage of digestive tract or skin and mucosa, liver or kidney injury, and so on. We found that there is no difference in the incidence of hemorrhage of digestive tract or mucosa, headache or dizziness, chest discomfort or palpitation, nausea, vomiting or diarrhea, and itchy skin or rash (Fig. 9). However, the occurrence of liver and kidney injury is more frequent in EG (Fig. 9). The adverse drug reactions could be eliminated after the termination of SA treatment or controlled easily by symptomatic treatment, such as liver protection therapy for liver injury.

3.3.3. Neurological function and activities of daily living. A total of 43 researches[19–35,37,38,40–43,45,46,48–50,52,53,56–58,64–73] mentioned NIHSS after treatment and 7 researches[12,39,42,52,67,73,74] reported NIHSS 3 months after ACI. NIHSS after treatment ($P < .001$) and 3 months after ACI ($P < .001$) in EG were significantly lower than that in CG (Table 2). Among included RCTs, 10 studies described mRS after treatment[21,40,44,49,50,64,65,70,72,73] and 5 studies[12,39,68,73,74] mentioned mRS 3 months after ACI. Modified Rankin Scale both after treatment ($P = .01$) and 3 months after ACI ($P < .001$) were remarkably decreased in EG in comparison with that in CG (Table 2). In total 4 articles[30,34,53,68] reported ADL scores after treatment and 3 articles[42,52,67] mentioned ADL scores 3 months after ACI. ADL scores after treatment were significantly increased ($P < .001$) while ADL 3 months after ACI was remarkably decreased ($P < .001$) in EG compared with that in CG (Table 2). In total 22 researches[19,21,27,33,37,38,40,41,43–45,54,56–58,64,65,70,72,73,75,76] reported BI scores after treatment and 2 articles[19,73] mentioned BI scores 3 months after ACI. BI scores after treatment ($P < .001$) and 3 months after ACI ($P = .02$) were both higher in EG than that in CG (Table 2).

3.3.4. Cognitive functions. A total of 6 RCTs[19,21,48,64,65,70] reported MMSE scores after treatment and 7 articles[21,34,40,48,64,65,70] mentioned MoCA scores after treatment. The results of meta-analysis showed that there is no significant difference in MMSE scores between EG and CG ($P = .08$) (Table 3). However, MoCA scores were remarkably higher in EG compared with that in CG ($P < .001$) (Table 3).

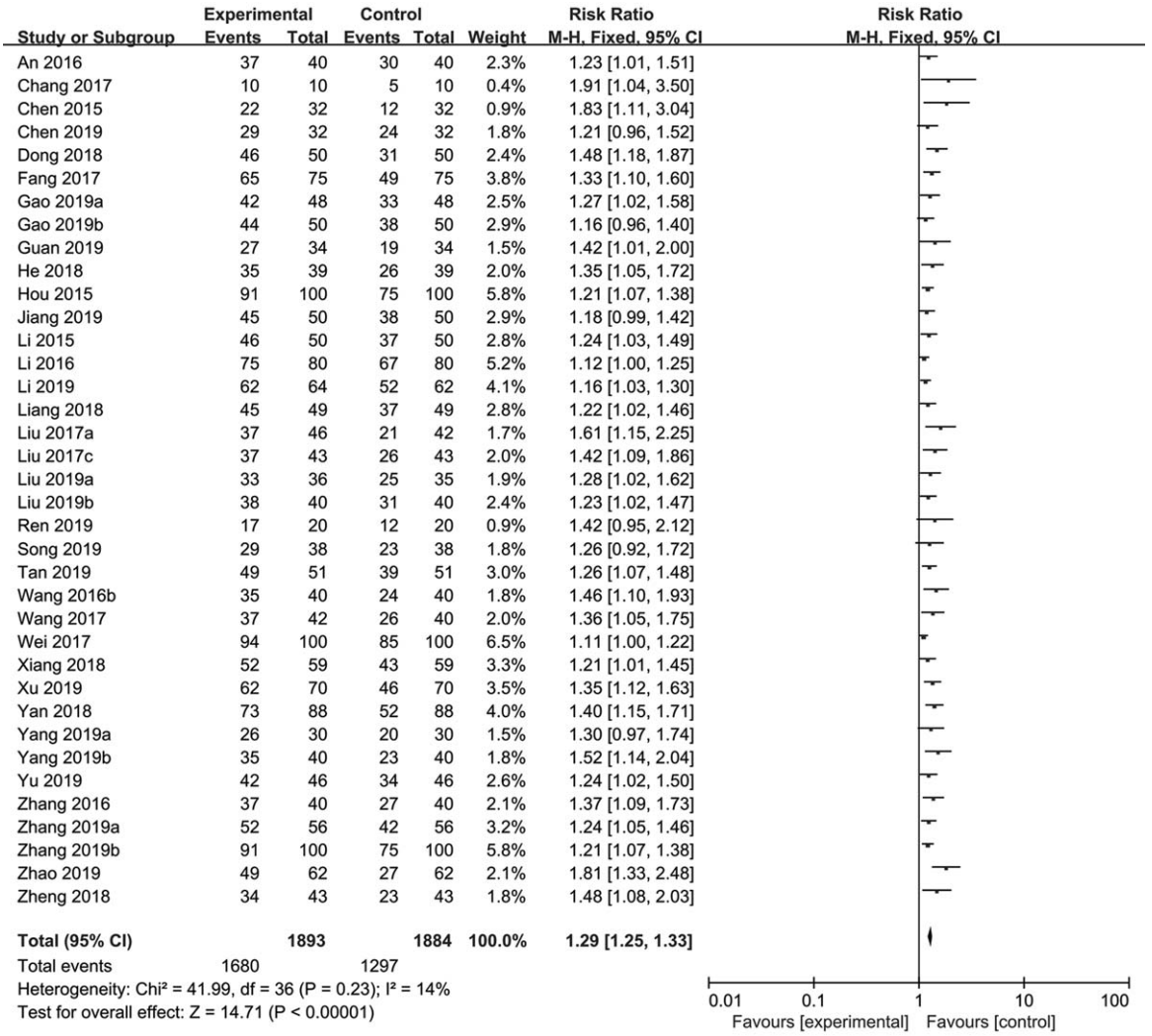

Figure 4. Meta-analysis of comparison of total effective rate between EG and CG. CG = control group, EG = experimental group.

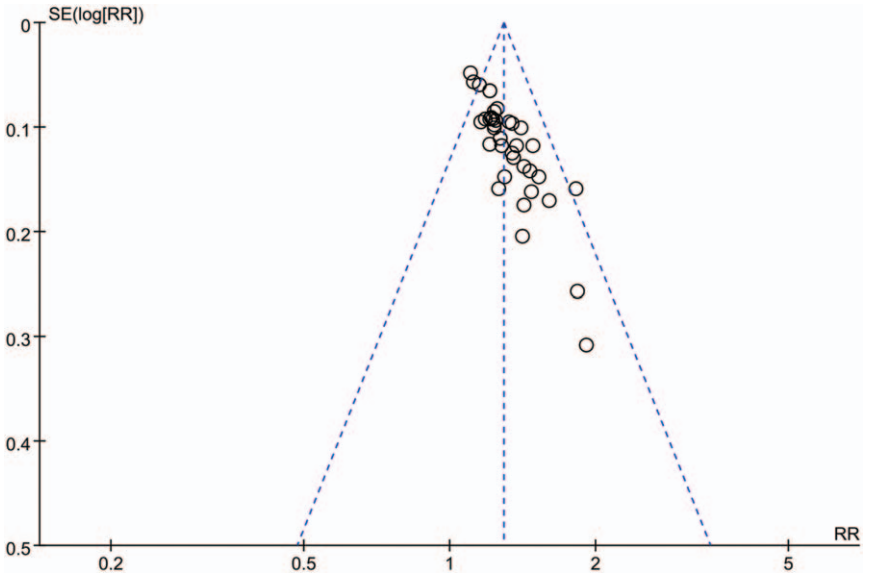

Figure 5. Funnel plot of publication bias for RCTs reported total effective rate. RCTs = randomized controlled trials.

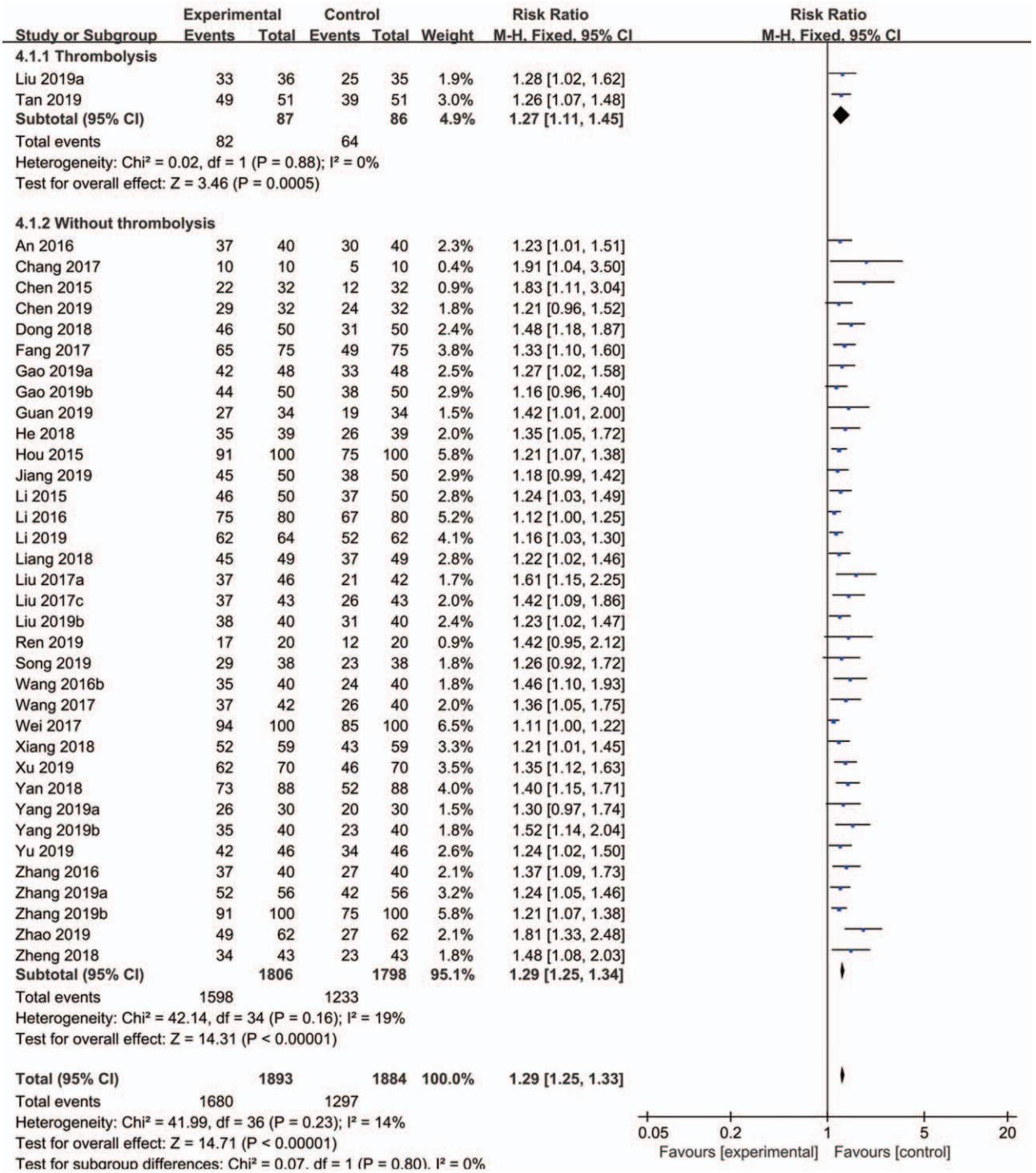

Figure 6. Meta-analysis of comparison of total effective rate between EG and CG in thrombolysis and nonthrombolysis subgroups. CG = control group, EG = experimental group.

4. Discussion

In this meta-analysis, 58 RCTs including 5309 patients were included. The results indicated that SA combined with WM play a beneficial role for ACI patients. SA significantly the increased total clinical effective rate of ACI treatment on the basis of WM. In addition, it improved neurological and cognitive functions profoundly. As for daily living activity, SA remarkably increased ADL and BI scores just after treatment. BI scores 3 months after treatment in EG were also significantly higher in comparison with that in CG. However, ADL scores 3 months after ACI were remarkably decreased in EG. ADL and BI are scaled using similar items to appraise patients' daily living activity. These results suggest that the influence of SA on the daily living activity of ACI

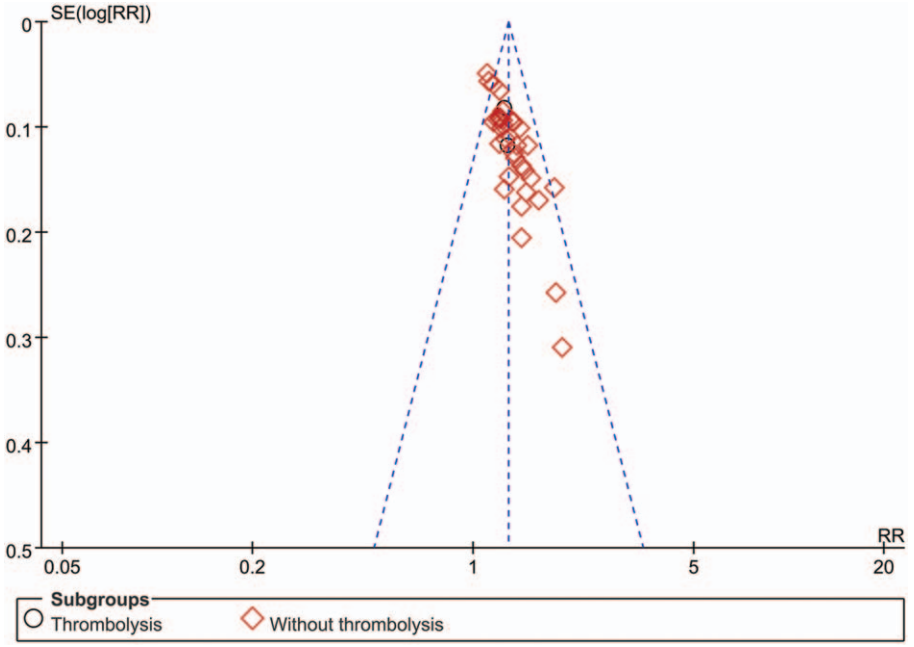

Figure 7. Funnel plot of publication bias for RCTs reported total effective rate in thrombolysis and nonthrombolysis groups. RCTs = randomized controlled trials.

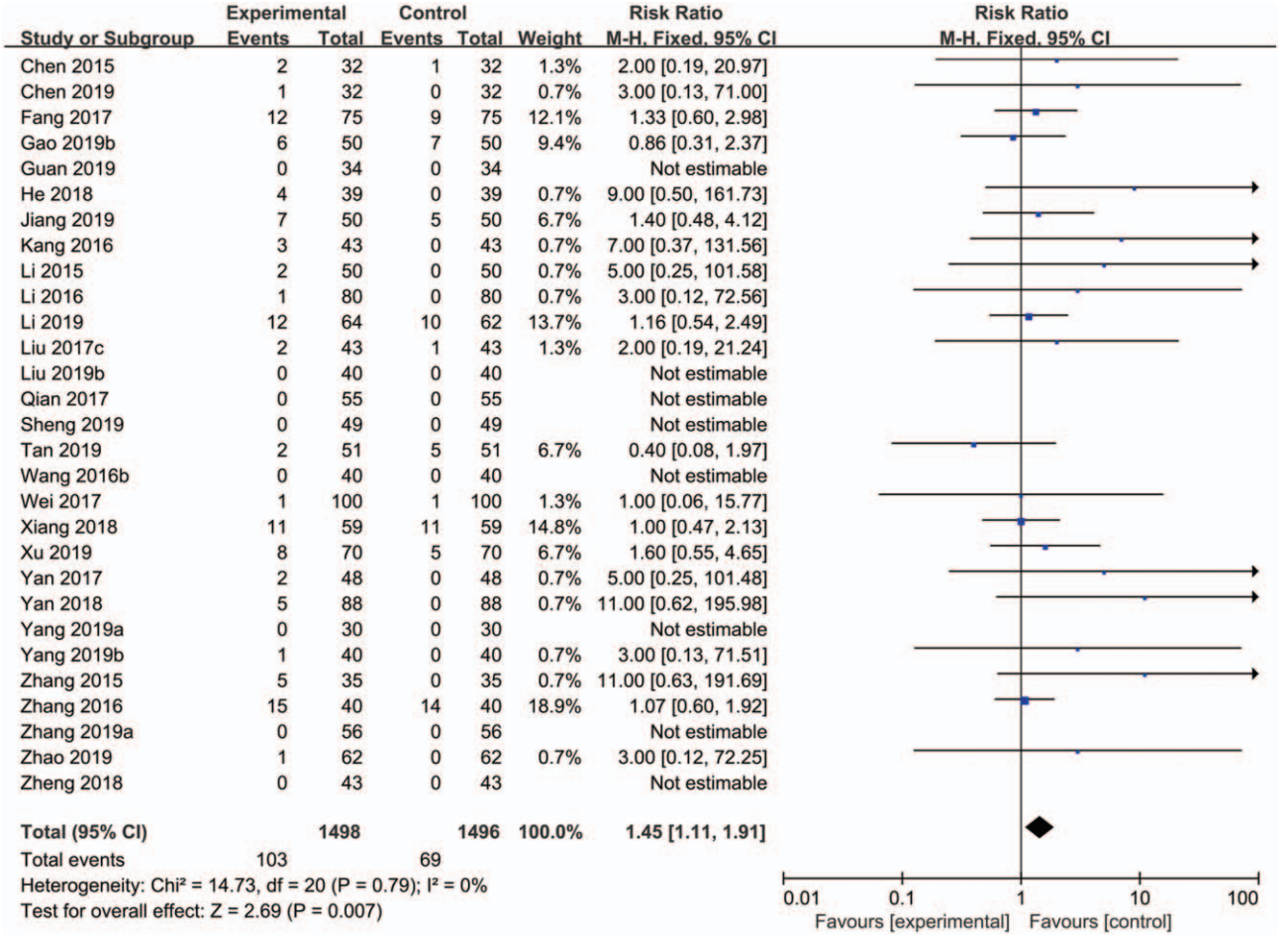

Figure 8. Meta-analysis of comparison of total drug adverse reactions rate between EG and CG. CG = control group, EG = experimental group.

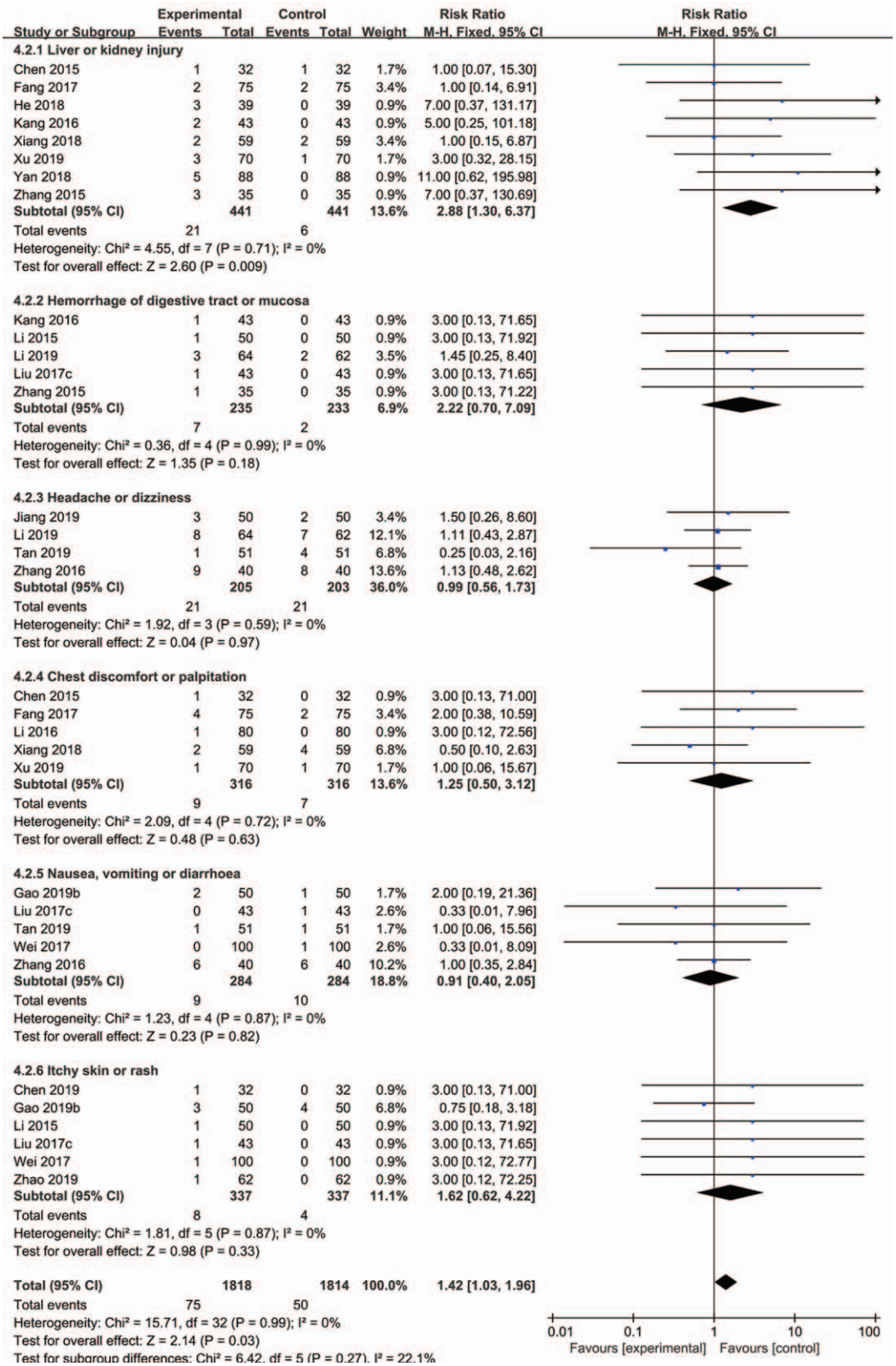

Figure 9. Meta-analysis of comparison of drug adverse reactions rate between EG and CG in different subgroups. CG = control group, EG = experimental group.

patients in the long term is controversial. These contrary results might be account of the limited sample size and evaluation errors since only 3 articles (470 patients included) reported ADL scores 3 months after ACI and 2 articles (201 patients included) mentioned BI scores 3 months after ACI, in which 4 researches did not describe allocation sequence generation method in detail

Table 2

Meta-analysis of comparison of neurological functions and activity of daily living between EG and CG.

Outcomes	Time	N (EG/CG)	Statistical heterogeneity	Results [MD (95% CI)]	*P* values
NIHSS	After treatment	2120/2106	$P<.001$, $I^2=93\%$	−2.38 (−2.80, −1.96)	<.001
	3 mo after ACI	462/435	$P=.03$, $I^2=57\%$	−1.44 (−1.97, −0.91)	<.001
mRS	After treatment	440/429	$P<.001$, $I^2=97\%$	−0.62 (−1.10, −0.14)	.01
	3 mo after ACI	242/210	$P=.92$, $I^2=0\%$	−0.88 (−1.11, −0.64)	< .001
ADL	After treatment	208/208	$P=.43$, $I^2=0\%$	9.20 (7.80, 10.60)	< .001
	3 mo after ACI	235/235	$P=.24$, $I^2=31\%$	−8.65 (−11.10, −6.20)	< .001
BI	After treatment	1177/1165	$P<.001$, $I^2=88\%$	11.77 (8.93, 14.61)	< .001
	3 mo after ACI	105/97	$P=.02$, $I^2=81\%$	17.29 (2.50, 32.08)	.02

ADL = activities of daily living, BI = Barthel Index, CG = control group, CI = confidence interval, EG = experimental group, MD = mean deviation, mRS = Modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale.

Table 3

Meta-analysis of comparison of cognitive functions between EG and CG.

Outcomes	N (EG/CG)	Statistical heterogeneity	Results [MD (95% CI)]	*P* values
MMSE	268/268	$P<.00001$, $I^2=95\%$	1.93 (−0.21, 4.07)	.08
MoCA	462/435	$P=.98$, $I^2=0\%$	2.27 (1.69, 2.86)	<.00001

CG = control group, CI = confidence interval, EG = experimental group, MD = mean deviation, MMSE = Mini-−Mental State Examination, MoCA = Montreal Cognitive Assessment.

and all researches did not mention the information of blinding. There were also some trials that record MMSE and MoCA scores, which is popularly used to evaluate cognitive functions of patients after ACI. The meta-analysis results displayed that the administration of SA profoundly improved MoCA scores rather than MMSE scores, indicating the protective role of SA for the cognitive function of ACI patients. Taken together, SA plays a beneficial role in the recovery of ACI patients. The result of our research is consistent with Jian et al's work, a meta-analysis included 14 studies and 1309 participants (650 cases in EG and 659 cases in CG). However, Jian et al did not analyze the difference of adverse drug events between EG and CG for the adverse drug events between EG and CG were described little in included studies. Our results showed that SA increased the risk of adverse events occurrence.[77] The main adverse events included headache, dizziness, hemorrhage of digestive tract or skin and mucosa, liver, or kidney injury etc, which could be controlled easily or eliminated after the termination of SA treatment. The main adverse drug events which are different between EG and CG are liver and kidney injury.

Various mechanisms, including promoting neurogenesis, inducing angiogenesis, suppressing inflammation poststroke, and inhibiting oxidation injury, might be involved in the protective role of SA to ACI patients. Zhang et al have demonstrated that SA could induce brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) production via activating Shh pathway to promote long-term neurological function recovery and neurogenesis in a mice MCAO model.[78] In addition, SA can promote angiogenesis in the peri-infarct area poststroke via activation of JAK2/STAT3 signaling pathway.[79] Our previous investigation has found that SA can also exert neuroprotective role via activating PI3K/AKT pathway and upregulating mitochondrial connexin 43 to suppress inflammation and oxidative stress response.[80] A pharmacokinetic and metabolomics analysis in rats transient MCAO models revealed that intravenous injected salvianolic acid A could enter central nervous system (CNS) massively to attenuate brain edema and protect neurological functions through enhancing the anti-inflammatory and antioxidant capacity via impairing NF-κB signaling.[81,82] In addition, salvianolic acid A can also promote neurogenesis by compromising GSK3β/Cdk5 activity.[82] Salvianolic acid B, the main component of salvianolic acids for injection, has also been reported to reduce infarction volume and improve neurological functions by alleviating inflammatory cytokines release in brain tissues through un-regulating SIRT1 and Bcl-2 signaling and down-regulating the expression of Ac-FOXO1 and Bax.[83] Xu et al have also revealed that salvianolic acids B can inhibit platelets activation through decreasing plasma soluble P-selectin and soluble CD40 ligand levels. All of these pieces of evidence indicated that SA plays a favorable role for ACI and might be a validated agent to improve the recovery of ACI patients.

5. Limitations

First, only 19 RCTs in included articles described the method to generate allocation sequence and there was no article describing the information about blinding, which might cause certain bias for assessment and reduce the grade of evidence. Second, as SA is an extract of a traditional Chinese medicine *Salvia Miltiorrhiza* Bunge, it is mainly used in China for ACI treatment. Therefore, all RCTs included in this meta-analysis were performed in China. More clinical trials in western populations are needed to identify the role of SA on ACI treatment in western populations.

6. Conclusion

Despite the limitation, we provide an evaluation for the efficacy and safety of SA on ACI treatment. SA can significantly improve the total clinical effective rate of ACI patients. The use of SA remarkably increased the neurological functions, short-term daily living ability recovery, and cognitive functions of ACI patients. However, the impact of SA on long-term daily living activity is still controversial. In addition, since SA could increase the risk of adverse events occurrence, physicians should pay close attention to patients' status and dispose of adverse events timely.

In spite of eliminating thrombus, restoring cerebral perfusion, and preventing the recurrence of ischemic stroke, the daily living quality of patients after ACI also needs enough attention to improve. Therefore, agents and other therapy strategies to improve the living quality of patients after ACI are urgently needed. This systematic review showed that SA could be a validated agent for ACI patients to improve living quality after ischemic stroke.

Supplementary Materials: http://links.lww.com/MD/E370

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