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REVIEW ARTICLE

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Clinical effects and safety of edaravone in treatment of acute ischaemic stroke: A meta-analysis of randomized controlled trials

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Abstract

What is known and objective: Edaravone is a new antioxidant and hydroxyl radical scavenger. Although there is evidence that it improves clinical outcomes of patients with acute ischaemic stroke (AIS), it is not yet widely accepted for treatment of AIS in Western countries. We further investigated the efficacy and safety of edaravone through this meta-analysis of randomized controlled clinical trials (RCTs).

Method: Pubmed, Embase, Web of Science and Cochrane Library were screened up to December 2020 for original articles from SCI journals that published in English. RCTs that compared edaravone versus placebo or no intervention in adult patients and reported the efficacy or safety of edaravone were regarded as eligible. Mortality was regarded as the primary outcome and the improvement of neurological impairment was regarded as the secondary outcome. Safety evaluation was conducted according to the incidence of adverse events. Review Manager 5.3 was employed to perform the assessment of the risk of bias and data synthesis. The Cochrane risk of bias tool for randomized controlled trials was employed to assess the risk of bias.

Results and discussion: Seven randomized controlled trials with 2069 patients were included. For the incidence of mortality, the pooled RR for studies that evaluated edaravone after three-month follow-up was 0.55 (95% CI, 0.43-0.7, $I^2 = 0$, $P < 0.01$). The pooled RR for improvement of neurological impairment at the three months follow-up was 1.54 (95% CI, 1.27-1.87, $I^2 = 0$, $P < 0.01$) in four RCTs. On subgroup analysis of studies that were conducted in Asia, the RR was 1.56 (95% CI, 1.27-1.90, $I^2 = 0\%$; $P < 0.01$); the pooled RR for studies that conducted in Europe was 1.32 (95% CI, 0.64-2.72; $P = 0.45$); the pooled RR for studies that used edaravone for two weeks was 1.42 (95% CI, 1.10 to 1.83, $I^2 = 0\%$; $P < 0.01$); the pooled RR for studies that used edaravone for one week was 1.64 (95% CI, 1.24-2.16, $I^2 = 0\%$; $P < 0.01$); the pooled RR for studies that conducted in patients with mean age equal to or over 60 years was 1.52 (95% CI, 1.24-1.87, $I^2 = 0\%$; $P < 0.01$); and the pooled RR for studies that conducted in patients with mean age less than 60 was 1.80 (95% CI, 1.05-3.08, $I^2 = 0\%$; $P = 0.03$). For the

Chongyue Chen and Mingkai Li contributed equally to this study.

incidence of any treatment-related adverse events, the pooled RR for studies that evaluated edaravone during treatment was 0.83 (95% CI, 0.51-1.34, I^2 = 0, P = 0.43). The difference of the incidence of any treatment-related adverse events between two groups was not statistically significant.

What is new and conclusion: The limited studies indicate that edaravone can improve neurological impairment with a survival benefit at three-month follow-up, regardless of the mean age and course of treatment. It is worthy of promotion in the clinical treatment of AIS in Asian countries. More well-designed RCTs with larger sample sizes are needed to determine the benefits of edaravone in patients from Western countries.

KEYWORDS
acute ischaemic stroke, edaravone, efficacy and safety, meta-analysis, randomized controlled clinical trials

1 | WHAT IS KNOWN AND OBJECTIVE

Cerebrovascular disease is a major cause of death and disability worldwide.[1] Acute ischaemic stroke (AIS) is the most common type of cerebrovascular disease. Despite the availability of antithrombotic drugs and endovascular treatment in most cases, AIS remains a major public health issue that poses a significant health burden.[2] Brain ischaemia is regarded as a process of delayed neuronal cell death. Diminished cerebral blood flow triggers the "ischaemic cascade" that results in intracellular calcium overload, an increased number of abnormal free radicals and cytotoxic oedema to facilitate cell destruction.[3] To interrupt the process that ischaemic neurons undergo as part of the ultimate common pathway of cell death remains a hot topic of neuroprotection.

As the first free radical scavenger for acute ischaemic stroke, edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is produced by Mitsubishi Tanabe Pharma Corporation (Japan). Edaravone was approved for sale in Japan in 2001 and has been widely accepted for clinical use in Japan, China and India.[4] Edaravone was first regarded to express a favourable performance in animal models of stroke in the late 1980s.[5-7] There exist three underlying antioxidative mechanisms of edaravone. Firstly, edaravone was reported to inhibit both lipid-soluble and water-soluble peroxyl radical-induced peroxidation systems.[8] Secondly, non-enzymatic lipid peroxidation and lip-oxygenase pathways are halted by the utilization of edaravone.[9] Lastly, quenching hydroxyl radical (OH) can suppress the OH-dependent and OH-independent lipid peroxidation.[10] Since edaravone expresses powerful antioxidative performance and it was validated in clinical application, the Japanese Guidelines for the Management of Stroke in 2009 suggested edaravone for AIS as a grade B recommendation.[11] Though edaravone is widely accepted in many Asian countries, it has not been approved for clinical application in Western countries.[12] Although a previous meta-analysis has confirmed the favourable outcomes of edaravone applied in acute stroke patients, the quality of included studies of edaravone for acute stroke was generally poor. Most of the included trials were conducted in Asia and only focused on the short-term improvement of neurological deficit.[13] Due to the reported liver and kidney dysfunction associated with edaravone,[14] its safety should also be carefully taken into consideration. To further determine efficacy and safety of edaravone, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate its clinical effect of edaravone in treatment of AIS.

2 | METHODS

2.1 | Search strategy

The specific search strategy is listed in Table S1. Four authorized online databases, namely Pubmed/Medline, Embase, the Web of Science, and the Cochrane Library were screened up to December 2020 utilizing the following key words: edaravone, MCI-186, stroke, brain infract, cerebral infraction, cerebrovascular disease, brain attack.

2.2 | Inclusion and exclusion criteria

Original articles were considered initially eligible if they met the following criteria: (i) randomized controlled trials comparing edaravone versus placebo or no intervention in adult patients. These patients were clinically diagnosed as AIS in accordance with the WHO case definition or the Fourth National Cerebrovascular Disease Conference of China. (ii) The original articles need to be published in English and could be screened in SCI journals. The following situations were considered as the exclusion criteria: (i) studies on children or animal; (ii) when patients with transient ischaemic attacks (TIAs), intracerebral haemorrhage or subarachnoid haemorrhage were included; (iii) when patients with severe liver or renal dysfunction were included; and (iv) when patients with previous edaravone allergy were included.

2.3 | Outcomes assessed

Mortality at 3 months follow-up reported in each RCT was regarded as the primary outcome. The secondary outcome we assessed was the improvement of neurological impairment. Improvement of neurological impairment was identified with the modified Rankin Scale (mRS) grade 0-2, the evident reduction of NIH Stroke Scale (NIHSS) or the authors' own judgements. Safety outcomes included reported adverse events. The adverse events related with edaravone were extracted from the original articles.

2.4 | Data extraction and quality assessment of the included articles

Two experienced researchers (CC and SC) were invited to screen the online databases and make preliminary selections. The eligibility and quality of each article were cautiously screened by each investigator. Two researchers then extracted the targeted data separately. Basic and technical characteristics of the included studies were summarized in our predesigned forms. According to the criteria listed in the Cochrane Handbook for Systematic Reviews of Interventions,[15] two experienced reviewers (CC, QZ) conducted the methodological quality assessment of the eligible RCTs using the Cochrane tool for assessing the risk of bias with Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). A third reviewer (ML) was invited to assess the disagreements between the two researchers.

2.5 | Statistical analysis

2.5.1 | Measurement of outcomes

The continuous data were presented as mean ± standard deviation (SD). Review Manager 5.3 was introduced to perform the

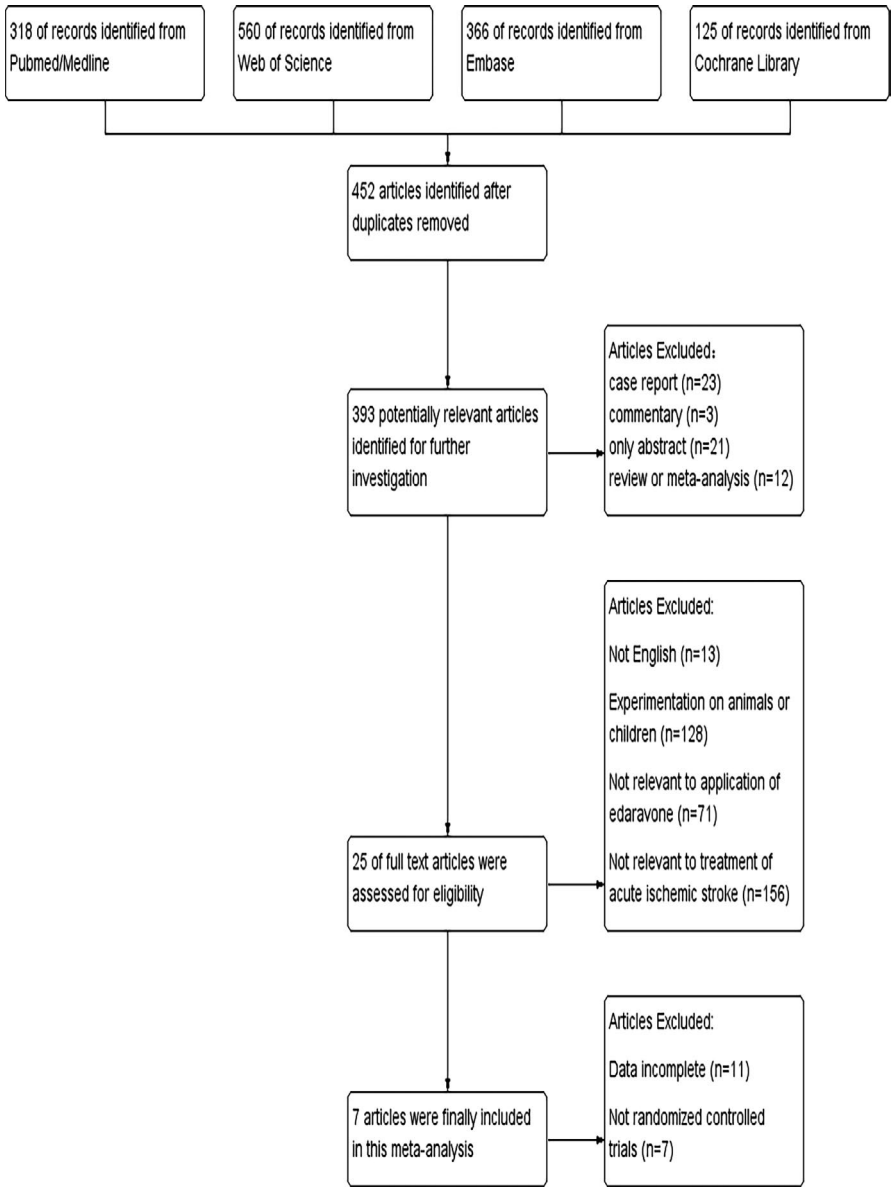


FIGURE 1 Flow diagram of the study selection.150 × 200 mm (300 × 300 DPI)

TABLE 1 Basic characteristics of the included studies

Author	Year	Region	Methods of randomization	Number of the patients (Tre/Con)	Mean age, y (Tre/Con)	Male, Sex % (Tre/Con)	Time window (h)	Dose range (mg/d)	Duration of treatment (d)	Duration of follow-up (d)	Evaluation criterion
Kaste	2013	Europe	Unclear	25/11	63.5/69	76/72.7	≤24	12 patients: 1.52 mg/kg; 11 patients: 3.04 mg/kg	3	90	mRS/NIHSS/BI
Li	2019	China	Unclear	48/48	60.5/62.5	52.1/60.4	≤48	60	14	14	NIHSS/ADL
Miyaji	2015	Japan	Unclear	1129/313	73.2/76.9	55.8/56.9	≤24	60	7	90	mRS
Otomo	2003	Japan	Random Table	125/125	66.3/66.1	65.6/67.2	≤72	60	14	365	mRS
Sharma	2011	India	Random Table	25/25	58.1/56	64/60	≤72	60	14	90	mRS/BI
Sun	2019	China	Random Table	65/65	52.4/51.3	56.9/61.5	Unclear	60	14	14	NIHSS/ADL/FMA
Zheng	2015	China	Random Table	35/30	63.4/59.8	57.1/53.3	≤24	60	14	14	NIHSS/BI

TABLE 2 Quality assessment of the included studies

Author	Year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Kaste	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Li	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Miyaji	2015	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Otomo	2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sharma	2011	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Sun	2019	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Zheng	2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

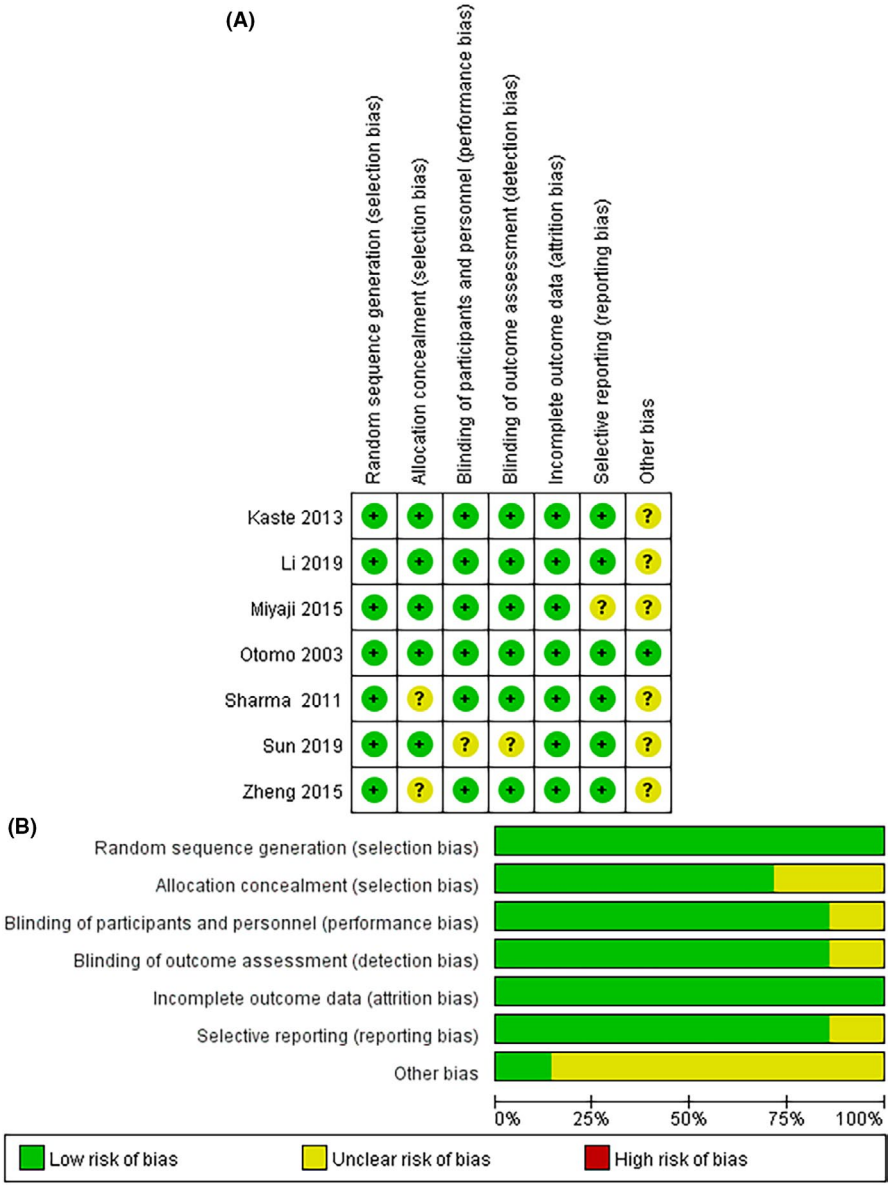


FIGURE 2 Summary of risk of bias assessment of 7 studies according to Cochrane risk of bias tool for randomized controlled trials. (A) Overall and (B) study level of bias. 150 × 200 mm (300 × 300 DPI)

statistical analysis. The relative risk (RR) and 95% CI that associated with the candidate outcomes in each group were pooled utilizing the DerSimonian and Laird random-effects or fixed model according to the potential heterogeneity.[16]

2.5.2 | Assessment of heterogeneity

We judged the heterogeneity by the Q-I^2 statistic presented in the forest plots generated by Review Manager 5.3. An I^2>50% was regarded as a threshold for determining substantial statistical heterogeneity.[17]

2.5.3 | Data synthesis

DerSimonian and Laird random-effects model and Mantel-Haenszel (M-H) methods were applied if there was substantial statistical heterogeneity. Otherwise, a fixed-effects model was the preferred choice to perform meta-analysis. Funnel plots were generated by Review Manager 5.3 for the evaluation of publication bias of the included studies (Figure S1). A $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics and the quality of the retrieved studies

A total of 1369 records were retrieved utilizing our primary search strategies. 452 articles were identified after duplications removed. After excluding commentaries, conference abstracts, reviews and meta-analyses, non-English articles, non-SCI studies, and studies not related to the application of edaravone or MCI-186 in the treatment

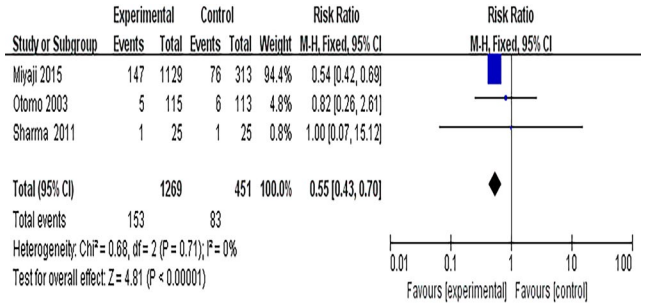


FIGURE 3 Edaravone's effect on acute ischaemic stroke patients' death at 3 months follow-up. 150 × 100 mm (300 × 300 DPI)

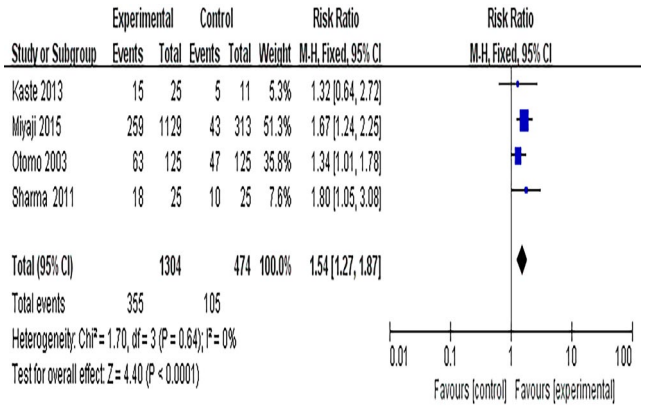


FIGURE 4 Neurological impairment improvement of edaravone for ischaemic stroke patients according to the authors' judgements at 3-month follow-up. 150 × 100 mm (300 × 300 DPI)

of stroke, brain infract, cerebral infraction, cerebrovascular disease or brain attack, 25 articles were downloaded for further selection. Finally, 7 studies[18-24] were included for this meta-analysis. The flow diagram of the study selection is presented in Figure 1. Table 1 shows the characteristics of these studies. A multicentre, double-blind, placebo-controlled RCT enrolled AIS patients from Europe.[18] The other six RCTs was conducted in Asia. 2069 subjects (mean age, 70.1 years; 58.0% male) were included, of whom 1425 patients (mean age, 70.6 years; 57.1% male) were exposed to edaravone. The other 617 patients (mean age, 69.1 years; 60.0% male) were regarded as the control group. All RCTs focused on the comparison of edaravone plus conventional therapy with routine treatment alone. Three RCTs[18,20,22] investigated patients with a treatment time window within 24 h, and three RCTs[19,21,22] investigated patients with stable vital signs who were admitted to hospitals during 24-72 hours after the onset of stroke. Five RCTs[19,21-24] investigated patients treated with edaravone for two weeks and the other two RCTs included patients treated with edaravone for one week. Four RCTs[18,20-22] evaluated outcome at the long-term follow-up, namely three months or later. The other three RCTs[19,23,24] made an assessment at two weeks follow-up. The detailed quality assessment of the included studies is presented in Table 2 and Figure 2.

3.2 | Outcome evaluation

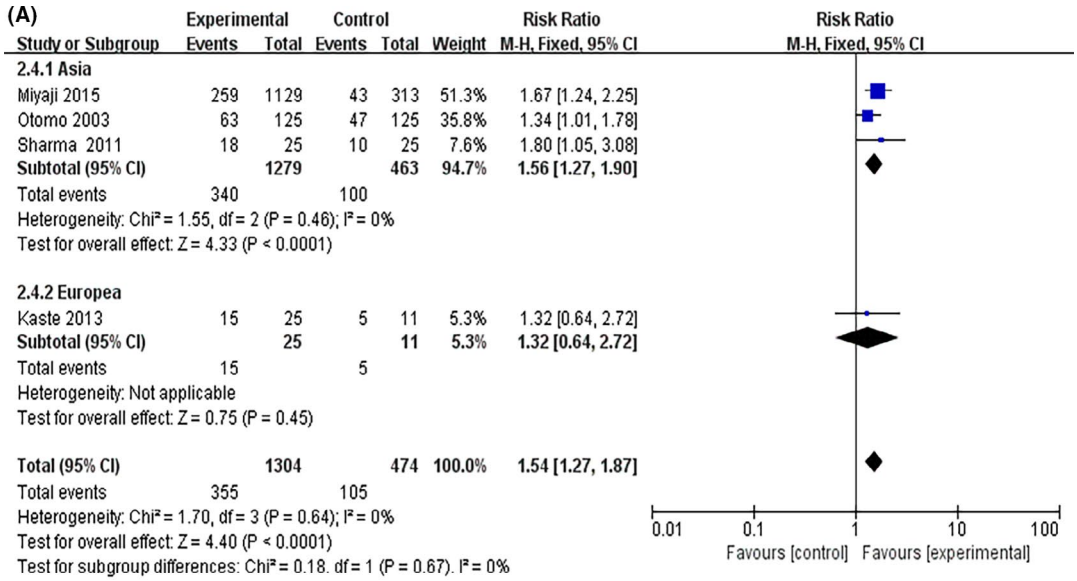
3.2.1 | Mortality

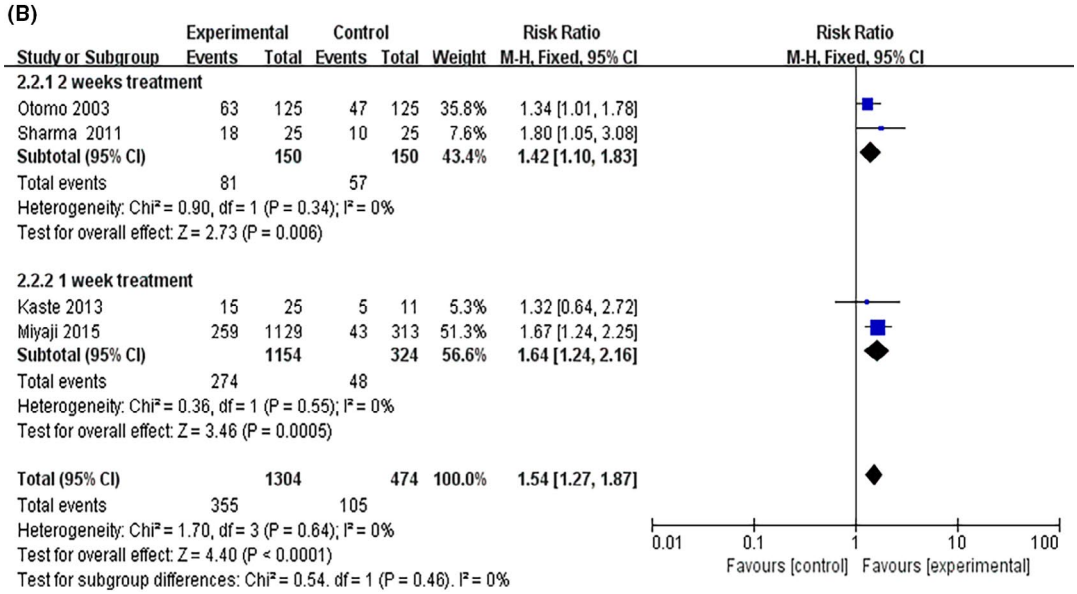
Three RCTs[20-22] including 1720 patients reported the mortality at three months follow-up. In the control group, 83 (18.4%) deaths occurred among 451 participants. Regarding the edaravone group, at three months follow-up 153 (12.1%) patients died. The results showed that the I^2 value and P value for evaluation of mortality were 0 and 0.71, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 3, a significant reduction of mortality was observed in the edaravone group than in the control group (RR = 0.55, 95% CI, 0.43-0.70, I^2 = 0%; p < 0.01). Figure S1 shows that there was no evidence of publication bias for assessment of the mortality at three-month follow-up.

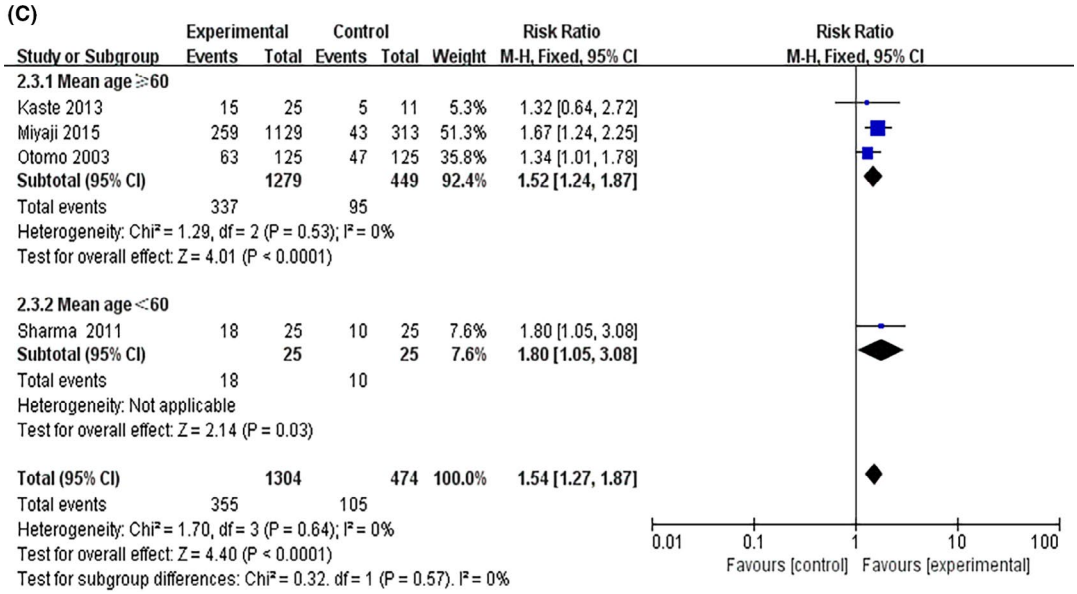
3.2.2 | Improvement of neurological impairment

Four RCTs[18,20-22] including 1778 patients evaluated the improvement of neurological impairment according to the authors' judgements at three-month follow-up. For comparison of outcome, they divided patients into two groups with favourable (mRS0-2) and poor (mRS3-6) outcomes. In the control group, 105 (22.2%) patients exhibited neurological improvement among 474 participants. Regarding the edaravone group, at three-month follow-up 355 (27.2%) patients reported neurologic improvement. The results showed that the I^2 value and P value for evaluation of improvement of neurological impairment were 0 and 0.64, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 4, a significant improvement of neurological impairment was observed in the edaravone group than in the control group (RR = 1.54, 95% CI, 1.27-1.87, I^2 = 0%; P < 0.01). Subgroup analysis of the patients from different continents included three studies that assessed the efficacy of edaravone in Asian patients (RR, 1.56; 95% CI, 1.27-1.90, I^2 = 0%; P < 0.01) and one study that evaluated edaravone in European patients (RR, 1.32; 95% CI, 0.64-2.72; P = 0.45) (Figure 5A). The second subgroup analysis was based on the duration of the treatment of edaravone, namely 1 week and 2-week treatment. The pooled RR for patients treated with edaravone for 2 weeks was 1.42 (95%

FIGURE 5 Subgroup analysis of neurological impairment improvement of edaravone for ischaemic stroke patients at 3-month follow-up. (A) Subgroup analysis of the patients from different continents. (B) Subgroup analysis was performed based on the course of treatment. (C) Subgroup analysis was performed based on the mean age. 150 × 250 mm (300 × 300 DPI)


(A)
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.4.1 Asia
Miyaji 2015 259 1129 43 313 51.3% 1.67 [1.24, 2.25]
Otomo 2003 63 125 47 125 35.8% 1.34 [1.01, 1.78]
Sharma 2011 18 25 10 25 7.6% 1.80 [1.05, 3.08]
Subtotal (95% CI) 1279 463 94.7% 1.56 [1.27, 1.90]
Total events 340 100
Heterogeneity: Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)
2.4.2 Europea
Kaste 2013 15 25 5 11 5.3% 1.32 [0.64, 2.72]
Subtotal (95% CI) 25 11 5.3% 1.32 [0.64, 2.72]
Total events 15 5
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)
Total (95% CI) 1304 474 100.0% 1.54 [1.27, 1.87]
Total events 355 105
Heterogeneity: Chi² = 1.70, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.40 (P < 0.0001)
Test for subgroup differences: Chi² = 0.18. df = 1 (P = 0.67). I² = 0%
0.01 0.1 1 10 100
Favours [control] Favours [experimental]


(B)
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.2.1 2 weeks treatment
Otomo 2003 63 125 47 125 35.8% 1.34 [1.01, 1.78]
Sharma 2011 18 25 10 25 7.6% 1.80 [1.05, 3.08]
Subtotal (95% CI) 150 150 43.4% 1.42 [1.10, 1.83]
Total events 81 57
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)
2.2.2 1 week treatment
Kaste 2013 15 25 5 11 5.3% 1.32 [0.64, 2.72]
Miyaji 2015 259 1129 43 313 51.3% 1.67 [1.24, 2.25]
Subtotal (95% CI) 1154 324 56.6% 1.64 [1.24, 2.16]
Total events 274 48
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)
Total (95% CI) 1304 474 100.0% 1.54 [1.27, 1.87]
Total events 355 105
Heterogeneity: Chi² = 1.70, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.40 (P < 0.0001)
Test for subgroup differences: Chi² = 0.54. df = 1 (P = 0.46). I² = 0%
0.01 0.1 1 10 100
Favours [control] Favours [experimental]


(C)
Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.3.1 Mean age ⩾60
Kaste 2013 15 25 5 11 5.3% 1.32 [0.64, 2.72]
Miyaji 2015 259 1129 43 313 51.3% 1.67 [1.24, 2.25]
Otomo 2003 63 125 47 125 35.8% 1.34 [1.01, 1.78]
Subtotal (95% CI) 1279 449 92.4% 1.52 [1.24, 1.87]
Total events 337 95
Heterogeneity: Chi² = 1.29, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)
2.3.2 Mean age <60
Sharma 2011 18 25 10 25 7.6% 1.80 [1.05, 3.08]
Subtotal (95% CI) 25 25 7.6% 1.80 [1.05, 3.08]
Total events 18 10
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Total (95% CI) 1304 474 100.0% 1.54 [1.27, 1.87]
Total events 355 105
Heterogeneity: Chi² = 1.70, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.40 (P < 0.0001)
Test for subgroup differences: Chi² = 0.32. df = 1 (P = 0.57). I² = 0%
0.01 0.1 1 10 100
Favours [control] Favours [experimental]

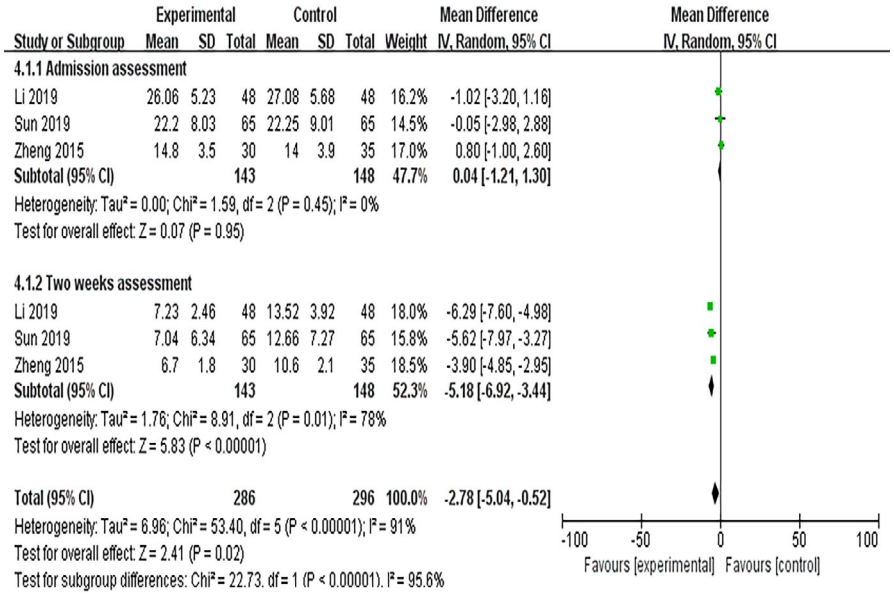


FIGURE 6 Neurological impairment improvement of edaravone for ischaemic stroke patients according to the NIHSS scores at 3-month follow-up. 150 × 100 mm (300 × 300 DPI)

CI, 1.10-1.83, I^2 = 0%; P < 0.01), and the pooled RR for patients treated with edaravone for 1 week was 1.64 (95% CI, 1.24-2.16, I^2 = 0%; P < 0.01) (Figure 5B). The third subgroup analysis was based on the mean age of patients. Three RCTs were conducted in patients with mean age equal to or over 60 years (RR = 1.52, 95%CI, 1.24-1.87, I^2 = 0%; P < 0.01), and one study was conducted in patients with mean age less than 60 (RR = 1.80, 95% CI, 1.05-3.08; P = 0.03) (Figure 5C). There was moderate evidence supporting the use of edaravone associated with an improvement of neurological impairment based on the European patients. However, the result was limited by the study size (20 events in 36 patients).

Additionally, as presented in Figure 6, three RCTs, with a total of 291 patients, including 143 patients in the observation group, evaluated the prognosis through NIHSS scores. The results showed that the I^2 value and P value of the subgroup after treatment were 78% and 0.01, respectively, indicating a moderate heterogeneity. Hence, the random-effects model was applied for meta-analysis. As a result, regarding the baseline NIHSS scores evaluated before treatment, no significant difference was observed between two groups (MD = 0.04, 95% CI: −1.21 to 1.30, P = 0.95). As predicted, regarding the NIHSS scores evaluated at two weeks follow-up, a significant improvement was observed between two groups (MD = −5.18, 95% CI −6.92 to −3.44, P = 0.01). Figure S1 shows that there was no evidence of publication bias for assessment of the improvement of neurological impairment at three months follow-up.

3.2.3 | Adverse events

Four RCTs[18,21-23] including 466 patients reported the incidence of adverse events during the treatment. In the control group, any treatment-related adverse events were found in 29 (12.1%) patients among 226 participants. Regarding the edaravone group, various adverse effects were observed in 28 (12.4%) patients among 240 participants.

The results showed that the I^2 value and P value for evaluation of any treatment-related adverse events were 0 and 0.64, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 7A, there was no significant difference in the incidence of adverse reactions between two groups (RR = 0.83, 95% CI: 0.51-1.34, P = 0.43). Figure S1 shows that there was no evidence of publication bias for assessment of the incidence of adverse events.

Furthermore, the synthesis of data resulted in no significant differences between two groups in terms of occurrence of nausea (RR: 1.31, 95% CI: 0.33-5.29, P = 0.7; Figure 7B), skin rash (RR: 1.05, 95% CI: 0.33-3.36, P = 0.93; Figure 7C) and abnormal liver function (RR: 0.65, 95% CI: 0.22-1.91, P = 0.43; Figure 7D). Most reported treatment-related adverse events were of mild or moderate severity. Only two severe treatment-related adverse events were reported.[18] In fact, this was a severe treatment-related adverse event (gout flare) reported twice in the same patient.

4 | DISCUSSION

Along with the rapidly increasing ageing population and the constant rise of cardiovascular diseases, the incidence rate of acute ischaemic stroke has continued to rise year by year, posing a significant health burden.[25] The progress of the acute ischaemic stroke would trigger local blood flow disorder, tissue ischaemia, hypoxia, and eventually, nerve cell necrosis. At this time, patients tend to present with various clinical symptoms such as hemiplegia and aphasia, indicating clinically gradual deterioration.[26] Penumbra was proposed for the first time on the basis of a research conducted by Abstrup.[27] In the early stage of ischaemia, cells in the ischaemic penumbra region

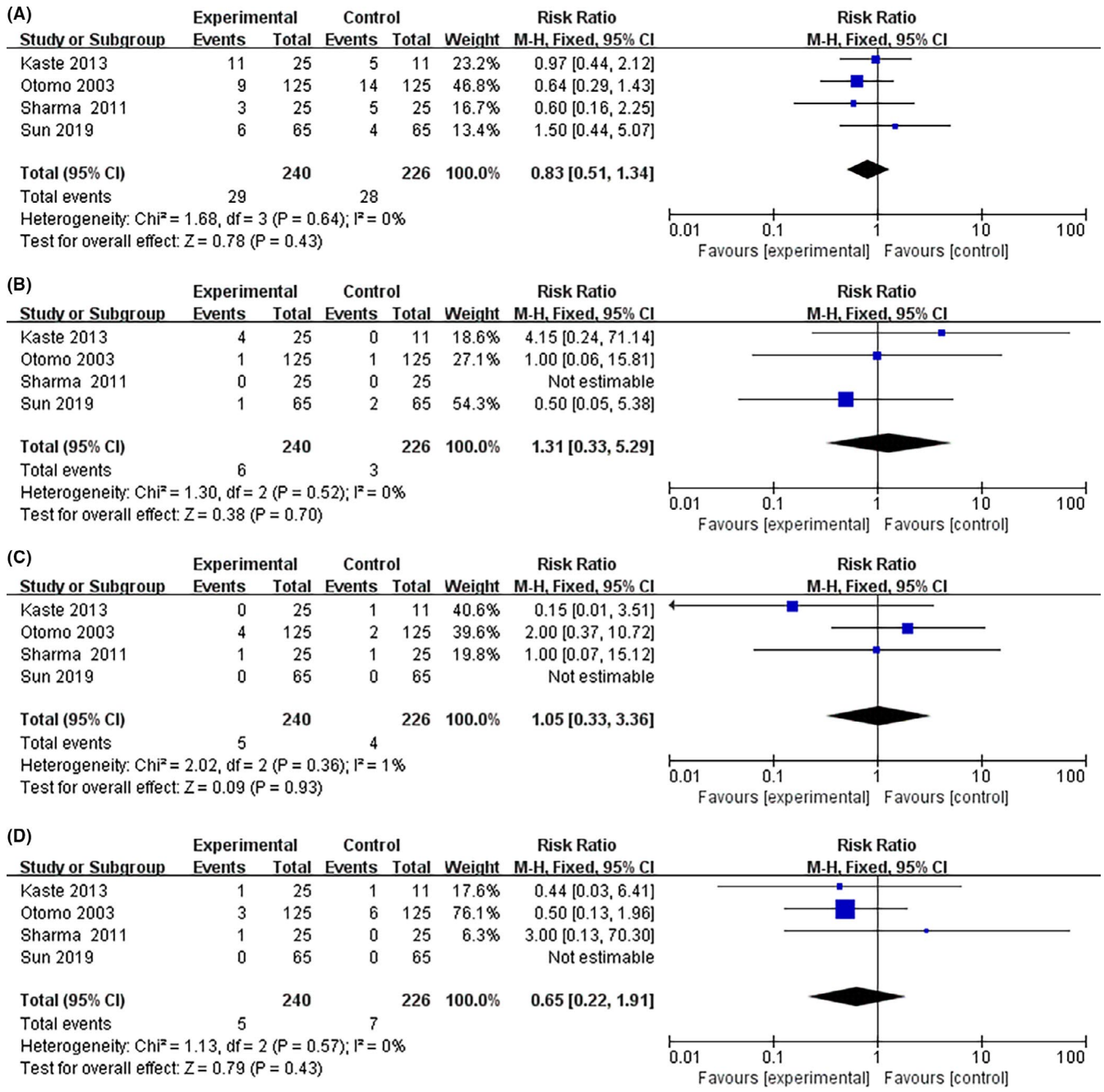


FIGURE 7 Incidence of adverse events during therapy-any treatment-related adverse events (A), nausea (B), skin rash (C), abnormal liver function (D). 150 × 150 mm (300 × 300 DPI)

will incur irreversible damage if blood flow cannot be recovered in time.[28] Hence, saving the ischaemic penumbra plays a vital role in the management of AIS.

It is acknowledged that the culprits of ischaemic cerebrovascular injury are free radicals, which are mainly produced by the peroxidation of unsaturated fat in phospholipids within the cell membrane, damaging the cell membrane and thus facilitating secondary brain tissue damage.[29] Edaravone is an antioxidant that has been produced in Japan since 2001 in the management of neurological and functional disorders as consequences of the acute ischaemic stroke. Theoretically, this antioxidant would scavenge free radical post-ischaemic events by alleviating the damage to neurons caused by oxidative stresses.[30]

In this meta-analysis of randomized controlled trials, we determined the efficacy and safety of edaravone in the treatment of AIS patients. As expounded in our results, seven randomized controlled trials studies with 2069 patients were included. The pooled RR for improvement of neurological impairment at the three-month follow-up was 1.54 (95% CI, 1.27-1.87, $I^2 = 0$, $P < 0.01$) in four RCTs. For the incidence of mortality, the pooled RR for studies that evaluated edaravone at the three-month follow-up was 0.55 (95% CI, 0.43-0.7, $I^2 = 0$, $P < 0.01$). For the incidence of any treatment-related

adverse events, the pooled RR for studies that evaluated edaravone during treatment was 0.83 (95% CI, 0.51-1.34, I^2 = 0, P = 0.43). We confirmed that edaravone improved the neurological impairment at three-month follow-up. A significant reduction of mortality was observed in the edaravone group at three-month follow-up. Additionally, there was no significant difference in the incidence of adverse reactions between the edaravone group and the control group. This current investigation indicates that edaravone is effective and safe in the management of AIS.

We acknowledge that there are still some limitations in the current investigation. First, only subjects from Asia and European countries were included in this investigation. We call for more reliable RCTs on the AIS patients from other continents. Second, due to the incomplete data, our meta-analysis did not focus on the specific ischaemic stroke subtype. More well-designed studies are required to explore the efficacy and safety of this antioxidant in different ischaemic stroke subtypes. Third, we acknowledge that our research included only one large RCT,[20] which itself had reporting bias and contributed the majority of the data. Hence, we call for more well-designed RCTs with larger sample sizes performed in Western countries. Last, only articles in English were included in this current research, which may contribute to information bias.

5 | WHAT IS NEW AND CONCLUSION

Collectively, our current study confirms that edaravone can improve neurological impairment with a definite effect at three-month follow-up, regardless of the mean age and course of treatment. Edaravone is also safe in the management of AIS. It is worthy of promotion in clinical treatment of AIS in Asian countries. More well-designed RCTs with larger sample sizes are needed to determine the benefits of edaravone in patients from Western countries.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

CC and ML contributed equally to this study. CC and ML planned the study. CC, SC and ML screened the literature and collected data. CC, SC and ML conducted the study quality assessment. ML, LL and YC performed the meta-analysis and wrote the manuscript. LH conducted the study supervision and critical revision.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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