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Safety and efficacy of edaravone combined with alteplase for patients with acute ischemic stroke: A systematic review and meta-analysis

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Early administration of edaravone for acute ischemic stroke patients (AIS) receiving intravenous thrombolysis (IVT) has a potential neuroprotective effect. This study aimed to estimate the safety and efficacy of edaravone for AIS patients receiving IVT. We searched PubMed, Embase, Cochrane Library and Chinese Databases (CNKI database, Weipu database, and Wanfang database) for randomized controlled trials (RCT) from the inception of the database to 20 July 2020. Efficacy outcome was reduced National Institutes of Health Stroke Scale (NIHSS) score before and after treatment. Safety outcomes were intracranial hemorrhage (ICH) and mortality. Review Manager 5.3 and Stata 14.0 was used to perform the meta-analysis. A total of 1877 AIS patients from 17 studies were included, 939 (50.03%) patients received edaravone combined with alteplase treatment. Compared with alteplase alone, combined treatment reduced the NIHSS score (MD=3.95,95% CI 2.92-4.99, I^2= 92%) and ICH (OR=0.44,95% CI 0.29-0.66, I^2=0%) during hospitalization. There was no significant association between combined treatment and mortality during follow-up (OR=0.43,95% CI 0.13-1.42, I^2=0%). Conclusions: Edaravone combined with alteplase seems to be safe and effective for AIS patients' short term outcomes.

1. Introduction

Stroke is the most common cause of death and a major cause of disability worldwide (Lopez et al. 2006; Feigin et al. 2010). For patients with acute ischemic stroke (AIS), intravenous recombinant tissue plasminogen activator (rt-PA) remains the effective treatment (Powers et al. 2018). However, a prior study indicated that there were only 33% AIS patients who had vascular recanalization with rt-PA alone (Seners et al. 2016), which suggested that the therapeutic effect of rt-PA alone is limited. Some animal and human studies demonstrated that edaravone, a free radical scavenger, could enhance thrombolytic effects by increasing recanalization rate and improving neurological recovery (Yamashita et al. 2015; Kiyoshi et al. 2017; Takenaka et al. 2014; Lee and Xiang 2018). Moreover, other studies suggested that edaravone may reduce reperfusion injury following rt-PA by lower oxygen radical levels (Sandoval and Witt 2008; Yamamoto et al. 2009; Takenaka et al. 2014). These findings suggested that edaravone has a potential neuroprotective effect for AIS patients treated with rt-PA. In this study, we aimed to systematically investigate the safety and efficacy of edaravone for thrombolysis-treated AIS patients.

2. Investigations and results

2.1. Study selection and characteristics

A flowchart of the screening procedure is shown in Fig. 1. A total of 679 articles were identified. After excluding the duplicates, reviewing the abstract and the full text, we included 17 studies (Chen et al. 2012; Zhang et al. 2008; Li 2018; Huang et al. 2018; Chen et al. 2017; Li et al. 2019; Chen 2018; Wang and Zhang 2018; Ye and Jiang 2019; Zhang et al. 2016; Yue and Zhang 2019; Yue 2016; Yu 2016; Fan 2019; Chang 2017; Luo and Zhang 2019; Li et al. 2019) involving a total of 1877 participants, of whom 939 (50.03%) were receiving edaravone. Study characteristics and quality assessment are shown in the Table.

2.2. Results

2.2.1. Stroke severity

Fifteen studies (Chen et al. 2012; Zhang et al. 2008; Li 2018; Huang et al. 2018; Chen et al. 2017; Li et al. 2019; Chen 2018; Wang and Zhang 2018; Ye and Jiang 2019; Zhang et al. 2016; Yue and Zhang 2019; Fan 2019; Chang 2017; Luo and Zhang 2019; Li et al. 2019) involving 1719 patients reported stroke severity score at baseline and in-hospital follow-up. Compared with using rt-PA alone, the meta-analysis demonstrated that rt-PA combined with edaravone treatment was associated with an reduced NIHSS score (MD=3.95,95% CI 2.92-4.99; Fig. 2), while significant heterogeneity was detected between the studies (P <0.00001; I^2 = 92%). We further performed a subgroup analysis by treatment days. The subgroup analysis demonstrated that treatment for 7 days (MD=5.11,95% CI 2.84-7.37, P <0.0 0001; I^2=95%; Fig.2) and treatment for 14 days (MD=3.11,95% CI 2.23-3.99, P <0.00001; I^2=80%; Fig.2) both significantly reduced NIHSS score.

2.2.2. ICH

Eight studies (Chen et al. 2012; Li 2018; Li et al. 2019; Ye and Jiang 2019; Zhang et al. 2016; Yue and Zhang 2019; Fan 2019; Chang 2017) with 946 patients reported ICH. Five studies (Chen et al. 2012; Li 2018; Ye and Jiang 2019; Yue and Zhang 2019; Chang 2017) indicated that edaravone treatment could not reduce the rate of intracranial hemorrhage, while another three studies (Li et al. 2019; Zhang et al. 2016; Fan 2019) reported a significant reduction of ICH in the edaravone group. Pooled analysis found that edaravone treatment was associated with a lower risk of ICH (OR=0.44, 95%CI 0.29-0.66, P <0.00001, P=0.93, I^2=0%; Fig. 3).

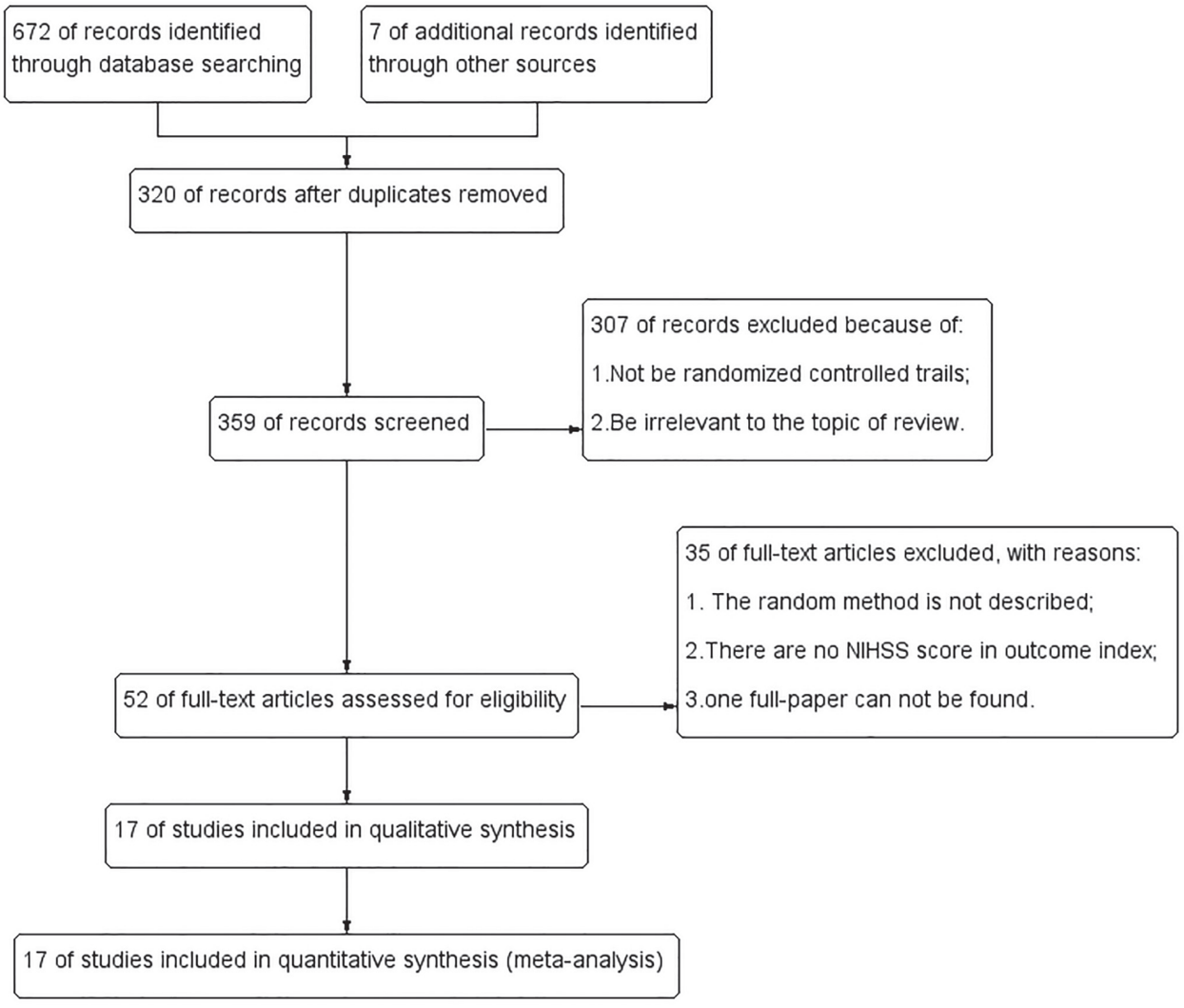

Figure 1. Study Flowchart

2.2.3. *Mortality*

Four studies (Chen et al. 2012; Zhang et al. 2008; Li et al. 2019; Ye and Jiang 2019) involving 442 patients investigated the all-cause mortality during follow-up. Pooled analysis demonstrated that no significant relationship between edaravone treatment and mortality could be shown (OR=0.43, 95%CI 0.13-1.42, P=0.87, I^2=0%; Fig. 3).

2.2.4. *Publication bias*

A funnel plot was constructed to assess the publication bias for the gender that had been investigated in 17 studies. The visual inspection of the funnel plot and Begg's test (p=0.843) indicated no evidence of publication bias.

3. Discussion

Our study including AIS patients from 17 RCTs demonstrated that compared with rt-PA treatment alone, edaravone combined with rt-PA treatment improved the short-term neurological deficit and was associated with a lower risk of ICH during hospitalization.

The result of our meta-analysis is consistent with those of the included studies (Chen et al. 2012; Zhang et al. 2008; Li 2018; Huang et al. 2018; Chen et al. 2017; Li et al. 2019; Chen 2018; Wang and Zhang 2018; Ye and Jiang 2019; Zhang et al. 2016; Yue and Zhang 2019; Yue 2016; Yu 2016; Fan 2019; Chang 2017; Luo and Zhang 2019; Li et al. 2019), which demonstrated that edaravone improved neurological recovery in AIS patients treated with rt-PA. We are proposing the following underlying mechanism. Firstly, edaravone could enhance the effect of rt-PA-mediated effect by increasing vascular recanalization rate and function recovery (Kiyoshi et al. 2017). An *in-vitro* study indicated that oxidants could reduce the affinity between tissue plasminogen and fibrin (Feng and Hart 1995), this process can be suppressed by antioxidants like edaravone. This hypothesis has been proved by previous studies (Lee and Xiang 2018; Yu-Yo et al. 2014; Kimura et al. 2012) which demonstrated that rt-PA could improve vascular recanalization rate and reduce NIHSS score. Secondly, there is a vicious cycle between neurocyte damage and free radical releasing when AIS onset (Sun et al. 2018). By protecting neurocyte injury from free radicals, edaravone plays an important neuroprotective role during the process of AIS.

Our meta-analysis suggested that combined edaravone treatment associated with lower risk of ICH, which was inconsistent in previous studies (Chen et al. 2012; Li 2018; Ye and Jiang 2019; Yue and Zhang 2019; Chang 2017). This result may be partly explained by the fact that edaravone could reduce serum metalloprotease-9 (MMP-9) and interleukin-1β(IL-1β) level (Yagi et al. 2009; Onodera et al. 2013), which can reduce the ischemic injury

Table: Study characteristics

Author	Year	Sample size(T/C)	Therapeutics		Treatment days	Follow-up days	Drug dose (mg/d)	Outcomes	Jadad Score
			T	C					
Chang X	2017	38/38	A+R+E	A+R	14	14	60	NIHSS,Hematencephalon	3
Chen BL	2012	35/34	A+R+E	A+R	14	90	60	NIHSS,Hematencephalon, Mortality	4
Chen DL	2017	48/48	A+R+E	A+R	7	7	60	NIHSS	4
Chen JY	2018	28/28	A+R+E	A+R	7	7	60	NIHSS	3
Fan XH	2019	80/80	A+R+E	A+R	14	14	60	NIHSS, Hematencephalon	3
Huang Y	2018	98/99	A+R+E	A+R	14	14	60	NIHSS	4
Li JT	2019	100/100	A+R+E	A+R	14	14	60	NIHSS,Hematencephalon, Mortality	4
Li XJ	2018	35/35	A+R+E	A+R	14	14	60	NIHSS, Hematencephalon	4
Ye J	2019	42/43	A+R+E	A+R	30	30	60	NIHSS,Hematencephalon, Mortality	4
Wang Q	2018	54/54	A+R+E	A+R	10	10	60	NIHSS	3
Yue L	2019	42/42	A+R+E	A+R	14	90	60	NIHSS, Hematencephalon	4
Yue RH	2016	45/45	A+R+E	A+R	14	90	60	NIHSS	3
Yu ZY	2016	49/49	A+R+E	A+R	7	7	60	NIHSS	3
Zhang LF	2016	100/102	A+R+E	A+R	14	15	60	NIHSS,Hematencephalon, Mortality	4
Zhang XY	2008	45/44	A+R+E	A+R	7	90	60	NIHSS, Mortality	3
Luo DX	2019	47/47	A+R+E	A+R	7	7	60	NIHSS	4
Li L	2019	53/53	A+R+E	A+R	14	14	60	NIHSS	4

A, Alteplase; R, Routine therapy; E, Edaravone; T, Treatment group; C, Control group; NIHSS,National Institute of Health stroke scale

of vascular endothelial cell and blood-brain barrier (Deguchi et al. 2015; Lukic-Panin et al. 2010). However, due to the small sample size of the present study, further studies are required to verify this finding.

In a meta-analysis of four studies (Chen et al. 2012; Zhang et al. 2008; Li et al. 2019; Ye and Jiang 2019) involving 442 patients, we found that edaravone treatment was not associated with reduced mortality. Edaravone may be safe in thrombolysis patients, however, this finding should be explained with caution due to small sample size.

Our study has several limitations. First, most of the studies included did not clearly describe the potential risk of bias. Second, although we searched major databases, all the relevant RCTs were only confined to Chinese population, which limits the generalisation of the conclusion. Third, all studies included in the present meta-analysis did not report the 3-month follow-up modified Rankin Scale score, and thus we could not investigate the association between edaravone and long-term outcomes. Due to these weaknesses, further studies are needed to confirm our findings.

Given the risk of bias, these results should be explained with caution and verified by further high-quality RCTs with large sample size.

4. Experimental

4.1. Search method

The common evidence based medicine framework PICO (Patient population, Intervention, Control, Outcome) was used to specify the research question: is early edaravone treatment (intervention) effective or safe (outcome) compared to patients without edaravone (control) in acute ischemic stroke receiving rt-PA (patient population)? The systematic review and meta-analysis was prepared following the preferred reporting items for systematic reviews and meta-analyses (PRISMA). We retrieved by keywords "stroke alteplase edaravone", because there was no prior review specifically addressing our question. A search of titles and abstracts in PubMed, EMBASE, Cochrane Library, and Chinese databases (CNKI database, Weipu database, and Wanfang database) was conducted confined to human studies by two reviewers (Hu. Rz. and Guo. Yj.) from the inception to 20 Jul 2020. Reference lists from published journal articles were also reviewed to screen eligible studies. Search keywords were ischemic stroke AND (alteplase or rt-PA) AND edaravone.

4.2. Inclusion criteria and outcomes

Inclusion criteria were: (1) Studies investigated AIS patients treated with intravenous rt-PA combined with edaravone compared to patients without; (2) randomized controlled trials (RCTs); (3) Administration of edaravone before, or soon after intravenous rt-PA; (4) Reported data of safety or efficacy outcomes. Exclusion criteria were: (1) Studies that not reported the random method; (2) Duplicated articles based on the same datasets; (3) Reviews and abstracts, or no outcome of interest was reported. Efficacy outcome:(1) Change in National Institute of Health Stroke scale (NIHSS) during hospitalization; Safety outcomes: (1) any intracranial hemorrhage (ICH), evaluated by computerized tomography. (2) all-cause mortality during follow-up.

4.3. Data extraction

Two investigators independently extracted data from the eligible studies: (1) first author name, year of publication, and sample size; (2) random method, allocation concealment, blinding, and loss of follow-up; (3) therapeutics, drug dose, treatment days, follow-up days and outcomes. Disagreements were solved by consensus, and by a third reviewer if disagreement could not be solved.

4.4. Quality evaluation

As all included studies were RCTs, the risk of bias was assessed by the Jadad scale. High-quality study was defined as having a score of 3-5.

4.5. Statistical analysis

Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and Stata Software Package (V.14.0; Stata, College Station, Texas, USA) were used to perform analysis. We reported the results as odds ratio (OR) with 95% confidence interval (CI) for intracranial hemorrhage and mortality, and mean difference (MD) with 95% CI for Neurological impairment score. Heterogeneity among studies was assessed by Cochrane I^2 test. Between-study heterogeneity was estimated by the Cochrane I^2 value. If there was no significant heterogeneity among studies ($I^2 \leq 50\%$), we used fixed-effect model, when $I^2 > 50\%$, we used random-effects model. Subgroup analysis was performed by edaravone treatment days. Funnel plots was used to evaluate publication bias. Statistical significance was set as p value <0.05.

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Conflicts of interest: None declared.

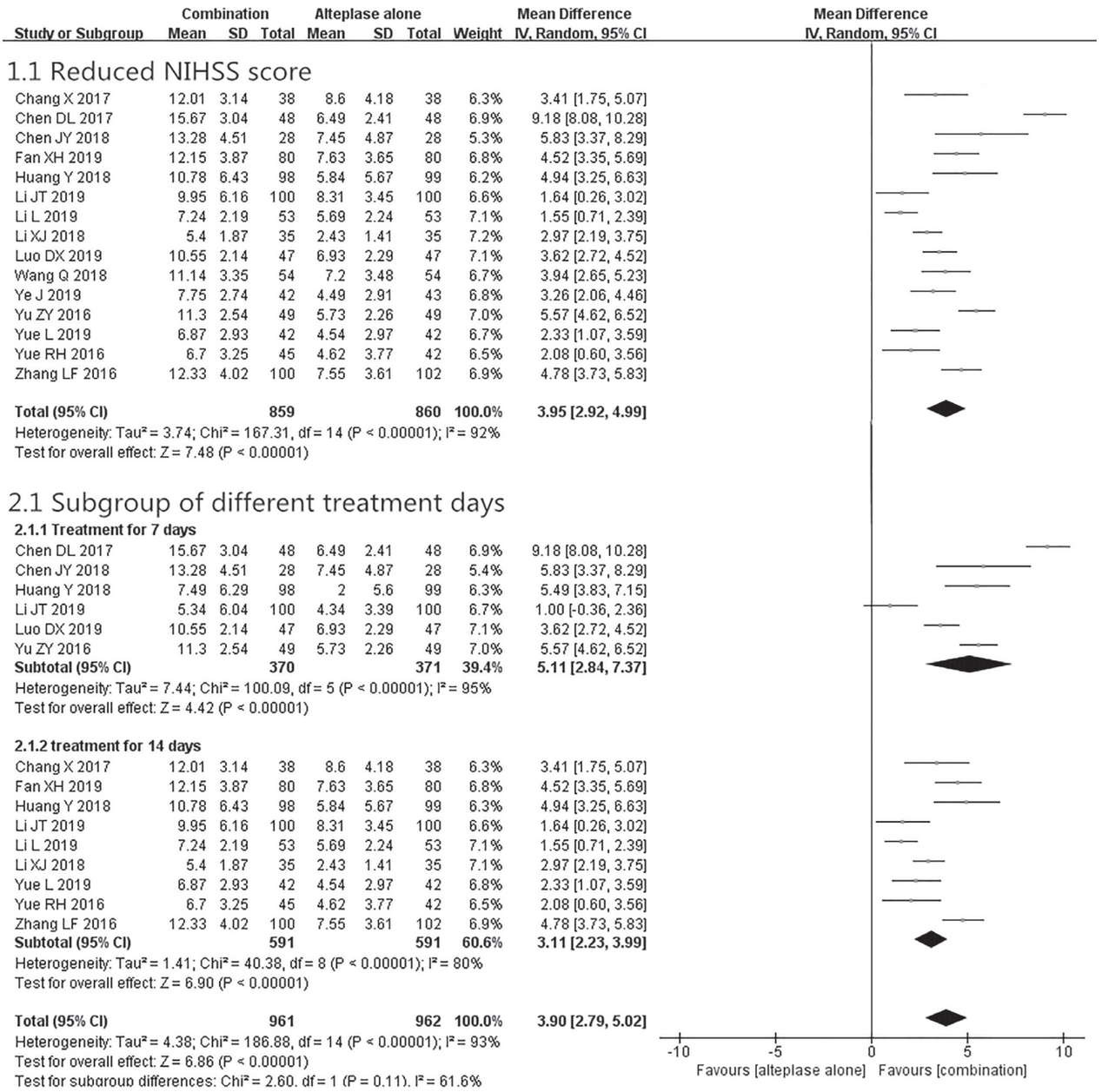

Figure 2. Efficacy outcome forest

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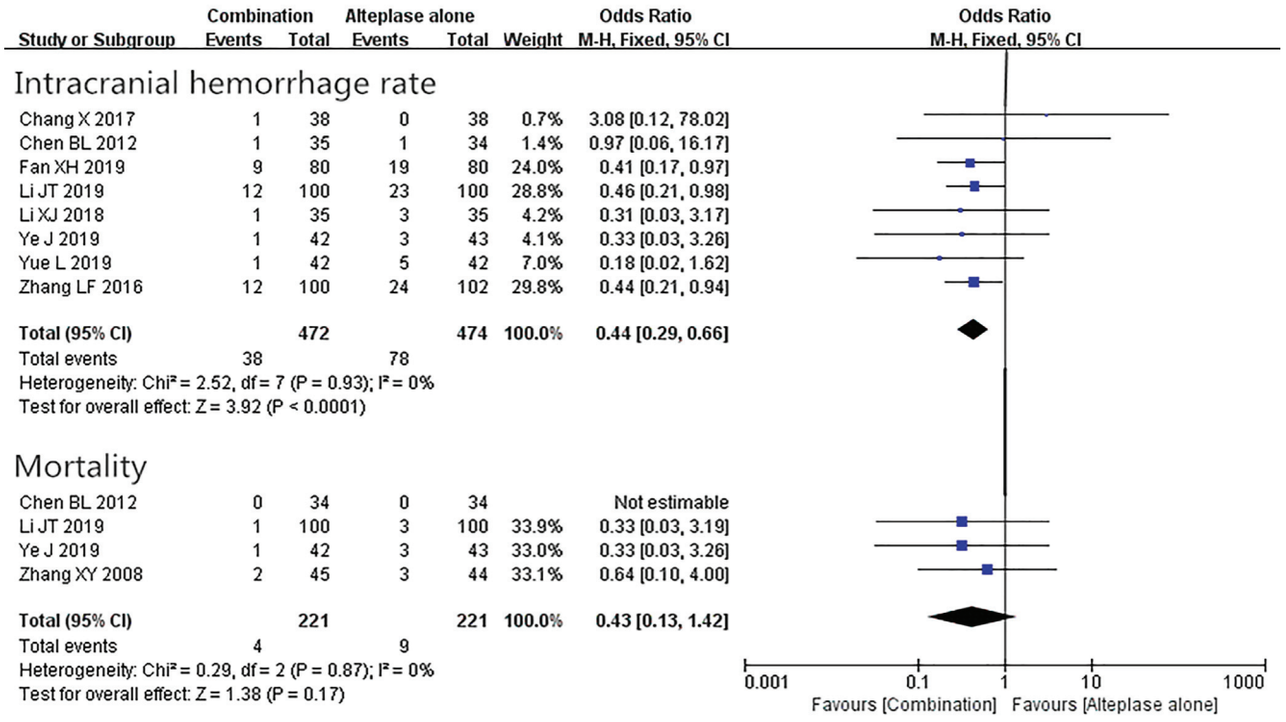

Figure 3. Safety outcome forest

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