

# Effects of epinephrine for out-of-hospital cardiac arrest

## A systematic review and meta-analysis of randomized controlled trials

Lu Huan, MD<sup>a</sup>, Fei Qin, MD<sup>b</sup>, Yin Wu, MD<sup>c,\*</sup>

### Abstract

**Aim:** Our objective is to assess the effects of epinephrine for out of hospital cardiac arrest.

**Background:** Cardiac arrest was the most serious medical incidents with an estimated incidence in the United States of 95.7 per 100,000 person years. Though epinephrine improved coronary and cerebral perfusion, improving a return of spontaneous circulation, potentially harmful effects on the heart lead to greater myocardial oxygen demand. Concerns about the effect of epinephrine for out-of-hospital cardiac arrest were controversial and called for a higher argument to determine whether the effects of epinephrine is safe and effective for short and long terms outcomes.

**Method:** Searching databases consist of all kinds of searching tools, such as Medline, the Cochrane Library, Embase, PubMed, etc. All the included studies should meet our demand of this meta-analysis. In the all interest outcomes blow we take the full advantage of STATA to assess, the main measure is Risk Ratio (RR) with 95% confidence, the publication bias are assessed by Egger Test.

**Result:** In current systematic review and meta-analysis of randomized trials investigating epinephrine for out of hospital cardiac arrest, we found that epinephrine was associated with a significantly higher likelihood of ROSC (RR = 3.05,  $I^2 = 23.1\%$ ,  $P = .0001$ ) and survival to hospital discharge (RR = 1.40,  $I^2 = 36.3\%$ ,  $P = .008$ ) compared with non-adrenaline administration. Conversely, epinephrine did not increase CPC 1 or 2 (RR = 1.15,  $I^2 = 40.5\%$ ,  $P = .340$ ) and hospital admission (RR = 2.07,  $I^2 = 88.2\%$ ,  $P = .0001$ ).

**Conclusion:** In conclusion, in this systematic review and meta-analysis involving studies, the use of epinephrine resulted in a significantly higher likelihood of survival to hospital discharge and ROSC than the non-epinephrine administration, but, there was no significant between group difference in the rate of a favorable neurologic outcome.

**Abbreviations:** CI = confidence interval, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, MeSH = medical subject heading, OHCA = out-of-hospital cardiac arrest, PEA = pulseless electrical activity, RCTs = randomized controlled trials, ROSC = return of spontaneous circulation, RR = risk ratio.

**Keywords:** cardiac arrest, epinephrine, hospital discharge, resuscitation, return of spontaneous circulation

### 1. Introduction

Cardiac arrest was the most serious medical incidents with an estimated incidence in the United States of 95.7 per 100,000

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person years,<sup>[1,2]</sup> it is a great challenge for cardiovascular physicians and emergency physicians. For more than 50 years, treatment strategies have included the use of various drugs, but there is limited evidence that such treatments are effective.<sup>[3]</sup> Early in 1960s animal study revealed that epinephrine improved coronary and cerebral perfusion, improving a return of spontaneous circulation (ROSC) through the constriction of arterioles mediated by  $\alpha$ -adrenergic receptors.<sup>[4-6]</sup> But for all this, potentially harmful effects on the heart lead to greater myocardial oxygen demand through  $\beta$ -adrenergic receptors and aggravate recurrent cardiac arrest.<sup>[7]</sup> Therefore, it makes sense to investigate the role of epinephrine in out-of-hospital cardiac arrest (OHCA).

In previous studies they considered epinephrine did improve ROSC with out of hospital cardiac arrest, but exasperate the neurologic outcome.<sup>[8]</sup> In addition, Belletti<sup>[9]</sup> deemed only a combination of adrenaline, vasopressin, and methylprednisolone was associated with improved survival with a good neurologic outcome compared with any other drug or placebo. However, Perkins<sup>[10]</sup> considered that there was no significant difference in the rate of a favorable neurologic outcomes. Myocardial dysfunction, impaired cerebral micro-circulation, increase in ventricular arrhythmia, and increased oxygen consumption are also still non-negligible.<sup>[11-14]</sup>

Until now, evidence in humans is limited, with most studies being observational studies with inconsistent results on short term outcomes including ROSC or hospital admission and long term outcomes including hospital discharge.<sup>[15–17]</sup>

Despite several systematic reviews<sup>[9,18,19]</sup> have been published, there is still a need for further discussion and analysis on account of some reasons as followed. One earlier research Lin<sup>[18]</sup> implemented a systematic review that included randomized controlled trial (RCT), in that study their major purpose was to compare standard doses of epinephrine with some other drugs that are placebo, vasopressin and high dosage of adrenaline in out of hospital cardiac arrest patients. Respect to the pool of adrenaline and no adrenaline administration there was only one RCT<sup>[20]</sup> included, even they failed to find any advantages of adrenaline over placebo, adrenaline and vasopressin combination, or vasopressin alone, in survival to discharge or neurological outcomes after OHCA. Finally, not long ago Belletti<sup>[9]</sup> conducted a network meta-analysis and considered there was no significant randomized evidence to support neither discourage the use of adrenaline during cardiac arrest.

Recently increasing literature have been implemented after the aforementioned studies. Hence, we perform a systematic review and meta-analysis which places emphasis on comparing epinephrine with placebo in several respects (such as, ROSC, hospital admission, hospital discharge and cerebral performance category (CPC) 1 or 2) for the patients in out of hospital cardiac arrest.

## 2. Materials and methods

Ethical approval or patient consent was not required because the present study was a review of previous published literature.

### 2.1. Searching strategy

The following ways were used to search all the literature. We performed medical subject heading (MeSH) and key words, such as “Heart Arrest” (mesh), “Heart Arrest” (title/abstract), “cardiac arrest”(title/abstract), these words were in conjunction with “epinephrine”(mesh), “epinephrine” (title/abstract), “adrenaline” (title/abstract). In addition we performed the same similar words about epinephrine and cardiac arrest those belonged to the same meaning with different description type. In this way, we searched from PubMed, EMBASE and Cochrane library to confirm the relevant studies. These words were connected with AND or OR. Besides, we searched the correlative article to assess whether was available to the current study. (Fig. 1)

### 2.2. Selection criteria

Two authors (Lu Huan and Fei Qin) screened the searching studies repeatedly, if they had divergences, another person would reassess it. Any RCT published in English was included if it met the following selection criteria: first of all, the studies should be RCTs; all the articles in patients with OHCA, compared concerns between epinephrine and no administration, and had one or more outcomes of interest: ROSC, hospital admission, hospital discharge, favorable neurologic outcome at hospital discharge or cerebral performance category (CPC) 1 or 2, CPC scores are defined as: I–normal function, II–mild to moderate disability, III–severe disability, IV–vegetative state, and V–dead.<sup>[20]</sup>; maybe in

some literature they didn't perform epinephrine but the meaning was as same as epinephrine, we also included it.

### 2.3. Data extraction

The data which was based on a standardized collection was extracted by two independent reviewers (Lu Huan and Fei Qin). If the design of study belonged non-RCT, we would exclude. The following data were our collection: the year of publication, mean age year, number of patients. In addition, clinical data including initial cardiac rhythms, dose and routes of adrenaline administration, presumed cardiac etiologies. Any divergence was discussed with the senior author (Yin Wu).

### 2.4. Evaluation of quality

The evaluation of quality was according to the Cochrane Handbook. We performed low, high and unclear to assess the quality in 7 pools which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective outcome reporting and other sources of bias. (Figs. 2 and 3)

### 2.5. Data synthesis and statistical analysis

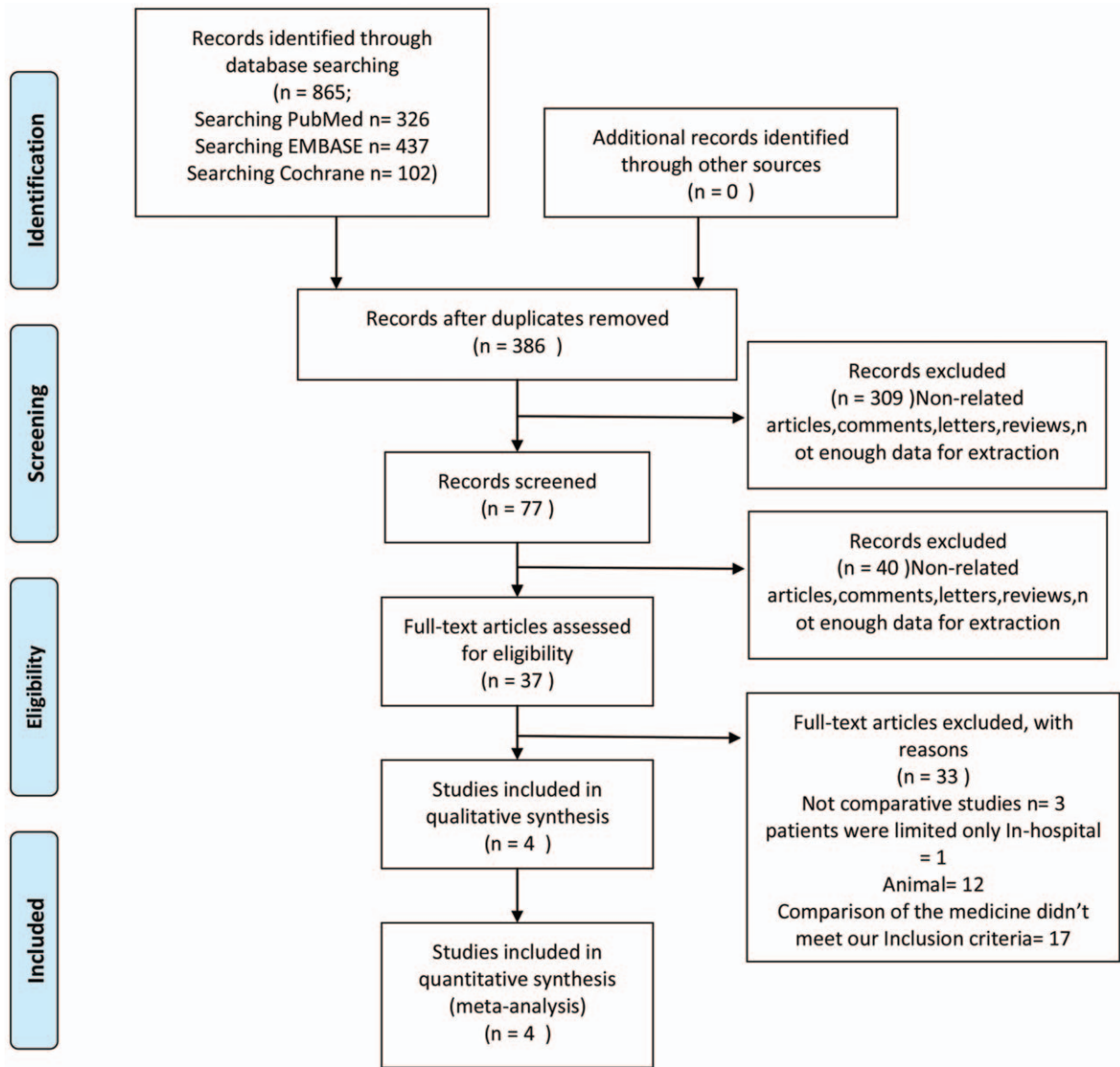
We performed STATA software to complete all the data synthesis, except for that applied the Review Manager 5 software to assess the quality of including studies. In the outcomes of interest, they belonged to dichotomous variables which were described as risk ratio (RR) along with its 95% confidence interval (CI) and the effects pooled using a random effects model or fixed effects model that was based on their own heterogeneity for the primary and secondary outcomes. When  $I^2$  levels was less than or equal to 25% when it was regarded as low, the  $I^2$  ranged between 25% and 50% when it was moderate, the  $I^2$  levels was greater than 50% when it was high.<sup>[21]</sup> The RR was pooled across studies applying the random-effect model if heterogeneity was present,<sup>[22]</sup> otherwise a fixed-effects model was performed. When the grade of heterogeneity was high, we used random-effects model, to test the heterogeneity which represented the proportion of between study variation two researchers (Fei Qin and Lu Huan) independently affiliated the data into Stata, this is variation due to differences in study design, interventions, or populations.

We analyzed the influence of each study to confirm the heterogeneity or to reassess the stable of primary outcome and used Egger test to assess the publication bias. A sensitivity analysis was applied by excluding candidate studies suspected to be a source of heterogeneity or by Galbraith plot for heterogeneity performed by STATA. Owing to the number of including studies was < 10, there was no funnel plot in each pool.

## 3. Result

### 3.1. Characteristics of included studies

There were only 4 studies<sup>[10,20,23,24]</sup> that satisfied criteria for inclusion in the systematic review and meta-analysis. Of these, all of them were RCTs. The flow of the search process and inclusion of studies is shown in Figure 1. Details regarding each study are provided in Table 1. Among these studies included with 9061



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Figure 1. Flow diagram showing the selection of randomized controlled trials.

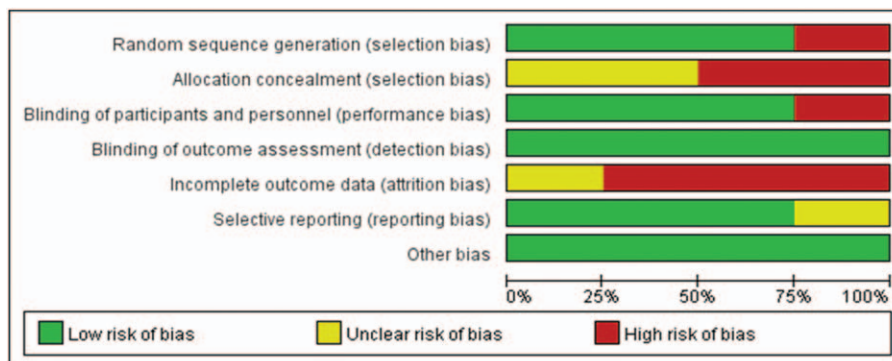
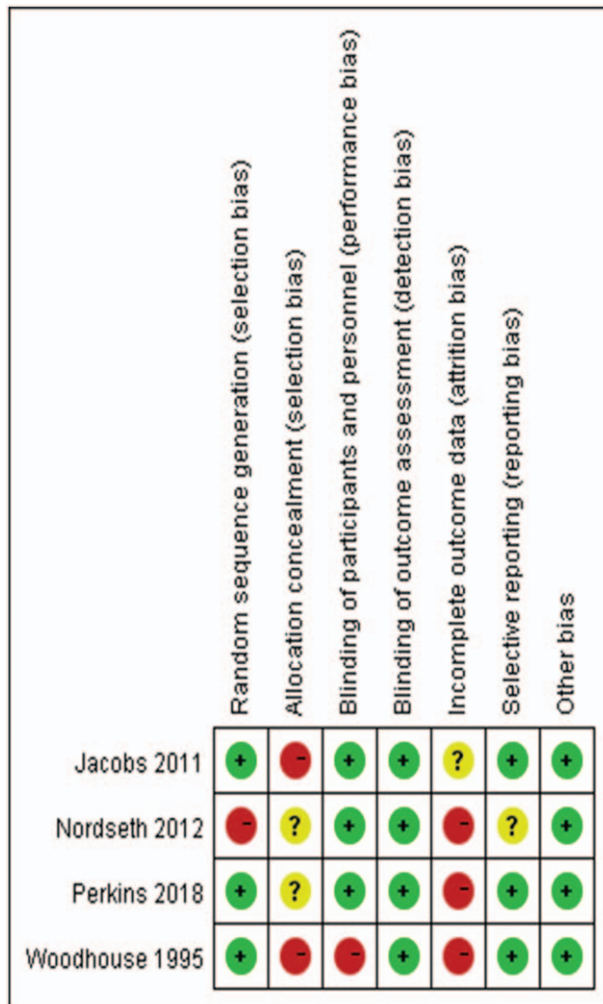


Figure 2. Risk bias of graph. Each risk of bias item presented as percentages across all of the included trials, which indicated the proportion of different level risk of bias for each item.



**Figure 3.** Risk bias of summary. Judgments about each risk of bias item for each included trials. Green indicates low risk of bias. Yellow indicates unclear risk of bias. Red indicates high risk of bias.

patients, everyone reported survival to discharge that was primary outcome, three studies<sup>[10,20,23]</sup> reported ROSC, hospital admission and discharged with CPC 1 or 2. But One RCT<sup>[24]</sup> included patients with both in-hospital and OHCA, we still

included it to pool effects of epinephrine and focused on the heterogeneity and the influence of each study.

**3.2. Survival to discharge**

All the studies<sup>[10,20,23,24]</sup> included were applied for polling effects of adrenaline administration on survival to discharge. The pooled RR was 1.40 (95% CI: 1.09, 1.80) with a moderate degree of heterogeneity ( $I^2=36.3\%$ ,  $P=.008$ ). (Fig. 4) There was no evidence of publication bias as suggested by Egger test ( $P=.456 > 0.05$ ). This demonstrated that receiving epinephrine had a higher chance of discharge alive, despite this was of borderline significance. In addition, we performed an analysis to confirm the influence of individual study, all the spots located in 95% CI. (Fig. 5)

**3.3. Return of spontaneous circulation**

Three of all studies<sup>[10,20,23]</sup> were included for pooling epinephrine administration effects on ROSC with sample sizes of 4388 for epinephrine and 4334 for non-epinephrine groups. The heterogeneous was low across studies ( $I^2=23.1\%$ ,  $P=.0001$ ). A fixed-effects model was applied and generated a pooled RR of 3.05 (95% CI: 2.79, 3.34), suggesting that patients receiving epinephrine were more over three times more likely to ROSC than those non-epinephrine administration. (Fig. 6)

There was no evidence of publication bias as suggested by Egger test ( $P=.746 > .05$ ).

**3.4. Cerebral performance category (CPC) 1 or 2**

Three studies<sup>[10,20,23]</sup> were included for pooling epinephrine administration effects on CPC 1 or 2 with the sample sizes of 4380 for epinephrine and 4329 for non-epinephrine groups. Considering moderate heterogeneous ( $I^2=40.5\%$ ) a fixed-effects model was performed and yielded a pooled RR of 1.15 (95% CI: 0.86, 1.54), and there was no significant difference between the two groups ( $P=.340$ ). There was no evidence of publication bias as suggested by Egger test ( $P=.440 > .05$ ). (Fig. 7).

**3.5. Hospital admission**

Studies<sup>[10,20,23]</sup> assessed the relation between epinephrine administration and hospital admission. The effect of epinephrine

**Table 1**  
Characteristics of included studies.

Author, year [reference]	Country	Study Design	Sample Size	Patients	Mean Age, year	Initial cardiac rhythm (EPI: P)	Witnessed by bystander (%)	Bystander CPR (%)	EPI (mg)
Perkins, 2018 [10]	UK	RCT	EPI: 4015 P (0.9% saline): 3999	OHCA, ≥16 years	EPI: 69.7 P: 69.8	EPI: 65 P: 64.6 VF (716: 684) PVT (25: 20) PEA (955: 937)	EPI: 50.1 P: 49.2	EPI: 59.3 P: 58.7	1
Jacobs, 2011 [20]	Australia	RCT	EPI: 272 P (0.9% saline): 262	OHCA, ≥18 years	EPI: 64.3 P: 64.9	EPI: 71 P: 74.8 VF (119:126) PEA (91: 70)	EPI: 44.1 P: 52.7	EPI: 52.9 P: 49.2	5
Nordseth, 2012 [23]	Sweden	RCT	EPI: 101 P (no i.v drugs): 73	OHCA, ≥18 years	EPI: 74 P: 76	EPI: 62 P: 66 NA	EPI: 50 P: 65	EPI: 39 P: 42	NA
Woodhouse, 1995 [24]	Australia	RCT	EPI: 145 P (0.9% saline): 100	OHCA and In-hospital, No age limit	EPI: 68 P: 67	EPI: 71.9 P: 64.3 VF (88: 39)	NA	NA	1

EPI = epinephrine, i.v = intravenous injection, NA = not available, OHCA = out of hospital cardiac arrest, P = placebo, PEA = pulseless electrical activity, PVT = pulseless ventricular tachycardia, RCT = randomized controlled trial, VF = ventricular fibrillation.

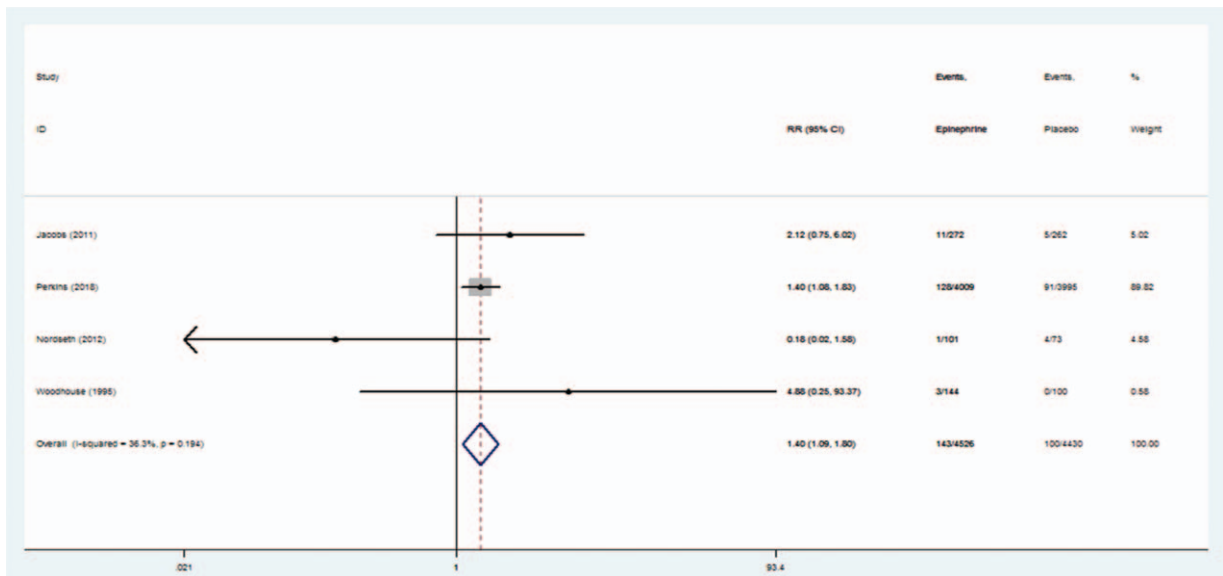


Figure 4. Forest plots of survival to discharge in patients with epinephrine therapy vs those without epinephrine administration for OHCA.

highly varied across studies ( $I^2=88.2\%$ ), it was not statistically valid ( $P=.0001$ ) with a pooled RR of 2.07 (95% CI: 1.28, 3.35). (Fig. 8) Therefore, we performed a sensitivity analysis by excluding the study<sup>[2,3]</sup> that was out of the interval in Galbraith plot for heterogeneous (Fig. 9) and the degree of heterogeneous wasn't improved ( $I^2=77.3\%$ ,  $P=.0001$ ) with a pooled RR of 2.51 (95% CI: 1.67, 3.76). After excluding another study<sup>[10]</sup> the degree of heterogeneous decreased intrinsically ( $I^2=31.2\%$ ,  $P=.0001$ ) with a pooled RR of 1.71 (95% CI: 1.31, 2.32).

A sensitivity analysis was performed by excluding the study<sup>[2,3]</sup> which specifically concerned with drug effects of adrenaline in

patients with initial pulseless electrical activity (PEA). The degree of heterogeneity did not improve the degree of heterogeneity ( $Q=4.41$ ,  $d.f.=1$ ,  $P=.04$ ,  $I^2=77\%$ ) and with a pooled RR of 2.98 (95% CI: 2.57, 3.22). Excluding another study<sup>[10]</sup> in which advanced life support was provided by trial-trained paramedics were eligible for inclusion decreased substantially ( $Q=1.45$ ,  $d.f.=1$ ,  $P=.23$ ,  $I^2=31\%$ ).

We, to some extent, just included two studies to analyze and the result wasn't statistical difference. Besides, some factors might affect the results though there was no compelling evidence, which included the patient's age, CPR implementer, initial cardiac rhythm and many more.

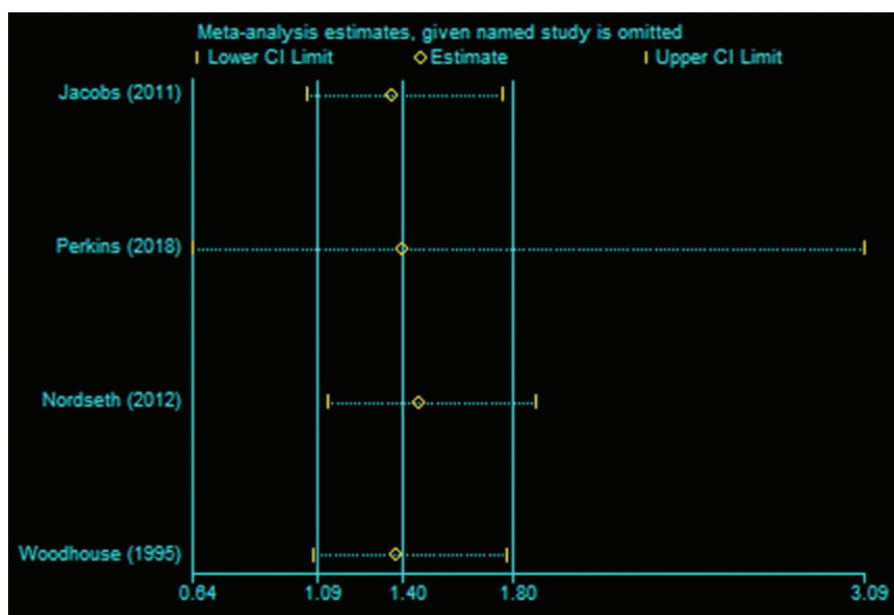
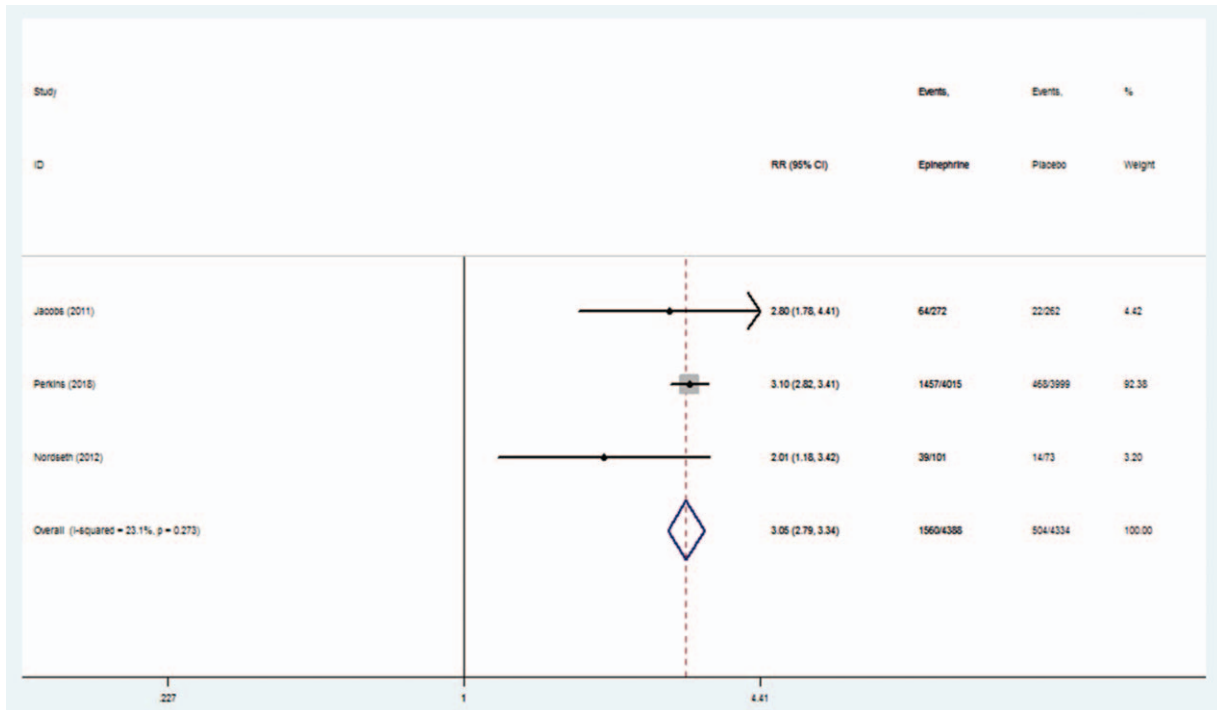
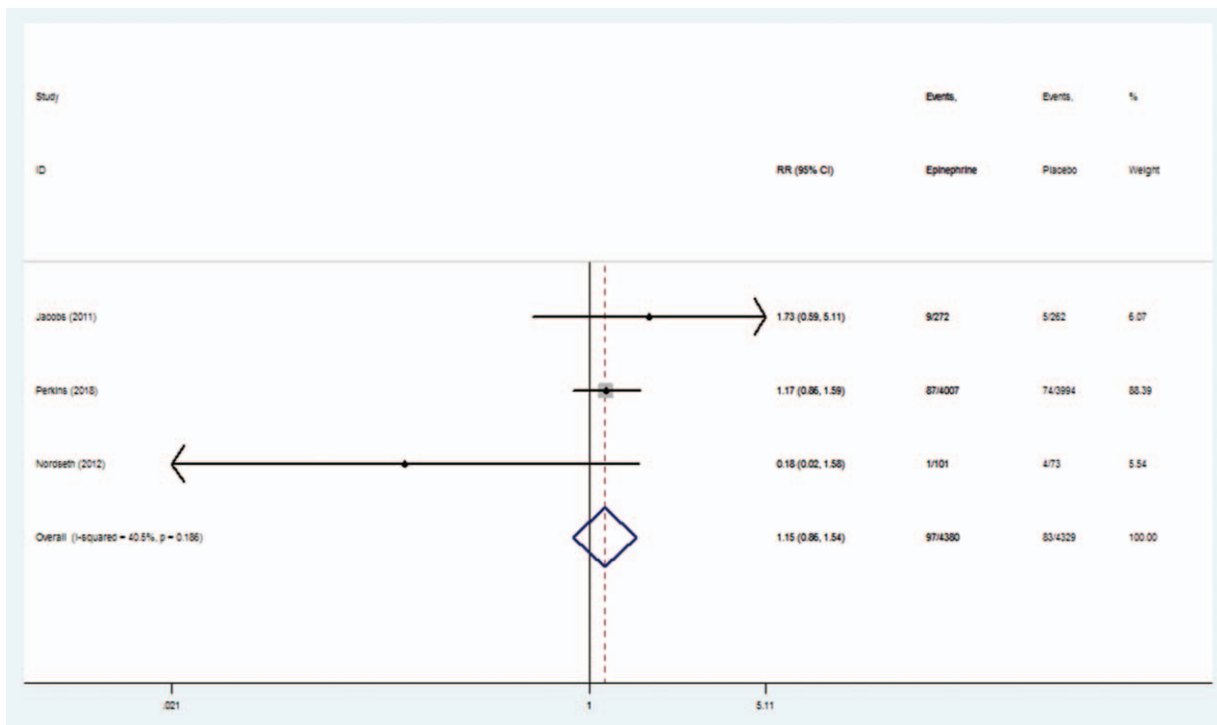


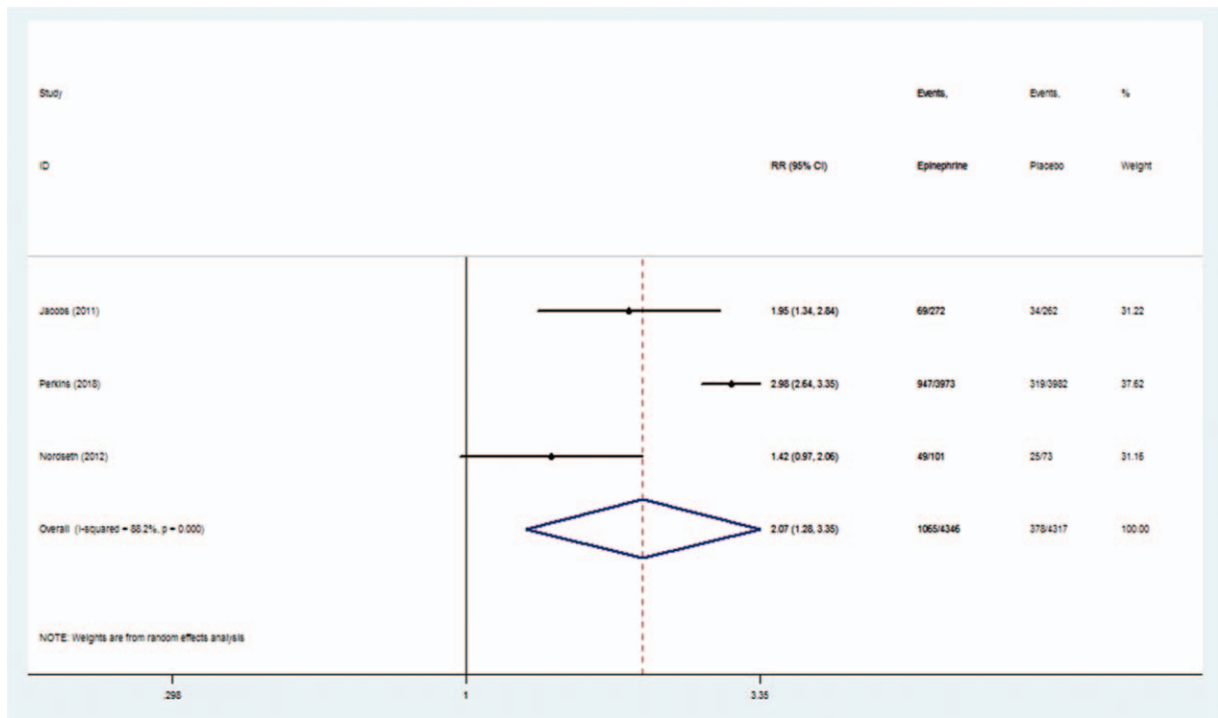
Figure 5. A analysis of individual study was to confirm the influence of each study for the result, all the spots located in 95% CI.



**Figure 6.** Forest plots of ROSC suggested Patients receiving epinephrine were more over three times more likely to ROSC than those non-epinephrine administration.



**Figure 7.** Forest plots of CPC 1 or 2 in patients with epinephrine vs those without epinephrine administration for OHCA demonstrated there was no significant difference between the two groups.



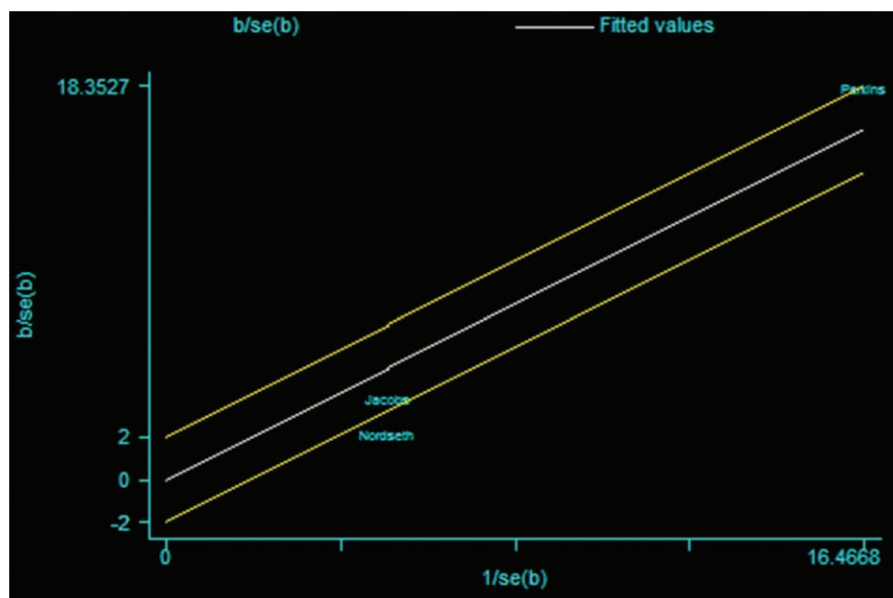
**Figure 8.** Forest plots of hospital admission suggested that the effect of epinephrine highly varied across studies and it was not statistically valid with a pooled RR of 2.07.

**4. Discussion**

In current systematic review and meta-analysis of randomized trials investigating epinephrine for out of hospital cardiac arrest, we found that epinephrine was associated with a significantly higher likelihood of ROSC (RR=3.05, I<sup>2</sup>=23.1%, P=.0001) and survival to hospital discharge (RR=1.40, I<sup>2</sup>=36.3%, P=.008) compared with non-adrenaline administration.

Conversely, epinephrine did not increase CPC 1 or 2 (RR= 1.15, I<sup>2</sup>=40.5%, P=.340) and hospital admission (RR=2.07, I<sup>2</sup>=88.2%, P=.0001).

In previous meta-analyses, they considered that there were no significant difference in hospital discharge.<sup>[9,16,25]</sup> In contrast, respect to current study patients who have a cardiac arrest out of hospital and who are given adrenaline (epinephrine) by



**Figure 9.** The galbraith plot for heterogeneous was to find the sources of heterogeneity.

emergency medical services have more favorable survival to hospital discharge than those not given adrenaline, what made this was ascribed to  $\alpha$ -adrenergic receptors<sup>[4–6]</sup> and which was similar to a previous RCT<sup>[10]</sup> with large patients. What's more, our effect size was more precise than the finding by Belletti et al<sup>[9]</sup> because the pooling was based on RCT of included studies than Belletti, which was based on only one study. In addition, Nakahara et al conducted a retrospective cohort study comparing epinephrine vs. no epinephrine for patients with ventricular fibrillation, pulse-less electrical activity, or asystole,<sup>[26]</sup> which found higher overall survival with epinephrine (17.0% vs 13.4%) and was similar to us. On the contrary, the potential adverse effects of epinephrine include decreased total forward cardiac output, increased myocardial oxygen consumption, myocardial dysfunction postresuscitation,<sup>[5,27,28]</sup> and increased pulmonary shunting.<sup>[29]</sup> Even one study demonstrated Survival decrease with epinephrine (survival 0.43 (0.27–0.066) for shock-able, 0.30 (0.07–0.82) for nonshockable rhythms).<sup>[30]</sup> Also, another study suggested that patients with initially shock-able rhythm demonstrate worse outcomes if they receive epinephrine in terms of survival at 1 month.<sup>[26]</sup>

Comparing with non-epinephrine group it was seemed that epinephrine had some better influence on survival to hospital discharge. However, whether or not to use epinephrine regularly need more further studies that assessed the rate of disabled survival and severely disabled survival.<sup>[26]</sup> What is more, such post-resuscitation care as hypothermia should be put into considering.<sup>[31,32]</sup>

Epinephrine for OHCA caused constriction of peripheral vessels, increasing coronary and cerebral perfusion pressure.<sup>[6]</sup> Our findings support the effect of adrenaline in increasing prehospital ROSC, which is similar to a RCT Olasveengen et al,<sup>[33]</sup> systematic reviews by Atiksawedparit et al<sup>[25]</sup> and some other studies.<sup>[34,35]</sup> Besides, Kosciak et al retrospectively evaluated approximately 700 patients, finding earlier provision of epinephrine improves ROSC, from 21.5% to 48.6% (OR 3.45).<sup>[36]</sup> Considering including studies didn't report the starting time of epinephrine in detail and only one study<sup>[24]</sup> compared high-dose epinephrine with low-dose epinephrine, in addition, the studies included might apply different definitions of ROSC, therefore, owing to the insufficiency of the data, we couldn't set a subgroup to analyze further.

With respect to CPC 1 or 2, the result found there was no significant difference. We considered that epinephrine increased macroscopic cerebral blood flow, it, however, impaired cerebral microvascular blood flow, leading a potential to worsen brain injury.<sup>[37]</sup> Beyond that, what resulted in this might be that brain was more sensitive to ischemia and recovered poorly.<sup>[38]</sup>

In the case of epinephrine alone it might be not the most appropriate choice, some researcher considered vasopressin made an influence on a better survival for the patients with asystole, conversely, comparing with the combined-use of epinephrine epinephrine alone improved the survival to hospital discharge for patients with pulseless electrical activity.<sup>[39]</sup> Moreover, a combination regimen of epinephrine, vasopressin and steroids during in-hospital cardiac arrest was associated with better neurologically intact survival to hospital discharge, compared to epinephrine alone.<sup>[40]</sup> The study design which was the first RCT to demonstrate that medication was associated with more preferable long-term outcomes in patients with cardiac arrest evaluated the relative utility of the agents used in addition to epinephrine, rather than epinephrine itself. However, it

was important to note that it was not conducted in patients OHCA.

Hospital admission meant admission after out-of-hospital cardiac arrest, several studies<sup>[25,41]</sup> that included one published recently consider there was no significant difference in the pool of hospital admission, attributing to reason that adrenaline was intrinsically a short acting cardiovascular stimulant, which has a limited half-life, and it might be less likely to have a significant effect on long term outcomes for this reason.<sup>[42]</sup> However, we deemed the epinephrine improves the rate of hospital admission indeed and did not deny the significance of epinephrine.

There are numerous strengths in current study. We include all the relevant RCTs to analyze, which could adjust for some known and unknown confounders. Two independent reviewers used defined search terms and strategies to reduce selection bias. In addition, the number of included studies is small, it, however, is larger and more pervasive than other systematic reviews.<sup>[25]</sup>

Nonetheless, our meta-analysis has some limitations. Considering the small number of included studies and the lack of some data subgroups could not be accomplished, which also led limited exploration of sources of heterogeneity for pooled effects. In addition, we did not pool more results because of the data were insufficient, except for Hospital discharge, ROSC, CPC 1 or 2, Hospital admission. Meanwhile, 90% of the sample size came from one RCT<sup>[10]</sup> reported in 2018. The results might be skewed by this study, on the contrary, we did assess the stability of each result by changing the RR and considered the results were stable. Finally, we did not specifically address confounders such as differences/variation in witnessed arrest and bystander cardiopulmonary resuscitation (CPR) frequency, first shock, frequency of pulseless electrical activity, following guideline revision, and quality/intensity of post-ROSC care.

## 5. Conclusion

In conclusion, in this systematic review and meta-analysis involving studies, the use of epinephrine resulted in a significantly higher likelihood of survival to hospital discharge and ROSC than the non-epinephrine administration, but, there was no significant between group difference in the rate of a favorable neurologic outcome. In the future, there is a need for more high-quality RCTs to reassess or confirm this conclusion.

## Author contributions

**Methodology:** Lu Huan.

**Resources:** Lu Huan, Fei Qin.

**Software:** Lu Huan.

**Validation:** Fei Qin.

**Writing – original draft:** Lu Huan, Fei Qin.

**Writing – review & editing:** Fei Qin, Yin Wu.

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