Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Early Administration of Adrenaline for Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis

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BACKGROUND: The use of adrenaline in out-of-hospital cardiac arrest (OHCA) patients is still controversial. This study aimed to determine the effects of early pre-hospital adrenaline administration in OHCA patients.

METHODS AND RESULTS: PubMed, EMBASE, Google Scholar, and the Cochrane Library database were searched from study inception to February 2019 to identify studies that reported OHCA patients who received adrenaline. The primary outcome was survival to discharge, and the secondary outcomes were return of spontaneous circulation, favorable neurological outcome, and survival to hospital admission. A total of 574 392 patients were included from 24 studies. The use of early pre-hospital adrenaline administration in OHCA patients was associated with a significant increase in survival to discharge (risk ratio [RR], 1.62; 95% CI, 1.45–1.83; $P<0.001$) and return of spontaneous circulation (RR, 1.50; 95% CI, 1.36–1.67; $P<0.001$), as well as a favorable neurological outcome (RR, 2.09; 95% CI, 1.73–2.52; $P<0.001$). Patients with shockable rhythm cardiac arrest had a significantly higher rate of survival to discharge (RR, 5.86; 95% CI, 4.25–8.07; $P<0.001$) and more favorable neurological outcomes (RR, 5.10; 95% CI, 2.90–8.97; $P<0.001$) than non-shockable rhythm cardiac arrest patients.

CONCLUSIONS: Early pre-hospital administration of adrenaline to OHCA patients might increase the survival to discharge, return of spontaneous circulation, and favorable neurological outcomes.

REGISTRATION: URL: https://www.crd.york.ac.uk/PROSPERO; Unique identifier: CRD42019130542.

Key Words: adrenaline ■ early pre-hospital administration ■ out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) remains a major public health problem in developed countries.[1,2] Approximately 40 000 cases in Canada and 420 000 cases in the United States occur annually.[3,4] Based on 81 864 cases in CARES (Cardiac Arrest Registry to Enhance Survival) 2018, the rate of survival to hospital discharge after OHCA treated by emergency medical services was 10.4%, with only 8.2% surviving with good functional status.[5] The routine administration of adrenaline upon cardiac arrest has been recommended since 1974.[6] The current American Heart Association and European Resuscitation Council guidelines for adult cardiac arrest state that 1 mg of adrenaline should be given every 3 to 5 minutes during resuscitation.[7]

The rationale for the use of adrenaline is that adrenaline was shown to increase aortic blood pressure and coronary perfusion pressure during chest compressions in animals,[8,9] and this result was also confirmed in humans.[10] However, in recent years, the use of adrenaline has been brought into question because it may be associated with poor neurological outcomes, overall rates of return of spontaneous circulation (ROSCs) and survival to discharge.[11–14]

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014330

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This meta-analysis evaluated the efficacy of early application of adrenaline and compared the outcomes between patients with initial shockable and non-shockable rhythms.
- Our data show that early pre-hospital administration of adrenaline to out-of-hospital cardiac arrest patients might increase the rate of survival to discharge, return of spontaneous circulation and favorable neurologic outcomes.
- Cardiac arrest patients with an initial shockable rhythm had a significantly higher rate of survival to discharge and more favorable neurological outcome than cardiac arrest patients with a non-shockable rhythm.

What Are the Clinical Implications?

- Our finding highlights that early use of adrenaline may be useful for out-of-hospital cardiac arrest patients.
- When evaluating the effects of adrenaline, patients should be stratified by initial cardiac arrest rhythm; otherwise, this difference may influence the outcomes.

Nonstandard Abbreviations and Acronyms

OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
RR	risk ratio
RCTs	randomized controlled trials

Three systematic reviews have been conducted,[15–17] and the results did not support adrenaline administration in OHCA patients. However, the association between outcomes and the time of adrenaline administration was unknown. The timing of adrenaline administration plays a key role in cardiac arrest resuscitation strategies. Observational studies have previously reported that the potential benefits of adrenaline may be limited for early-phase administration.[18–23] It is believed that emphasis should be placed on the "time-dependent" effectiveness of adrenaline administration.[24] Therefore, we conducted a systematic review and meta-analysis, aiming to determine the efficacy of early (time to adrenaline ≤10 minutes) pre-hospital adrenaline administration in OHCA patients.

METHODS

The authors declare that all supporting data, analytic methods, and study materials within the article and the online supporting information are available to other researchers. This systematic review was performed in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The PRISMA checklist is provided in Table S1. The study was registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42019130542). Institutional Review Board approval was not required for this systematic review and meta-analysis.

Search Strategy and Study Eligibility

A systematic search of the scientific literature was performed. The search was conducted from inception to February 2019 in PubMed, EMBASE, Google Scholar, and the Cochrane Library database. The terms used for the search were as follows: ("heart arrest" OR "out-of-hospital cardiac arrest" OR "ventricular fibrillation" OR "pulseless electrical activity" OR "PEA" OR "asystole" OR "cardiac arrest") AND ("epinephrine" OR "adrenaline").

Studies were selected by 2 independent reviewers if they met the following inclusion criteria: (1) patients with OHCA were enrolled; (2) the patients were treated with epinephrine; (3) when multiple studies from the same institute were available, to avoid overlapping information, only the study with the largest sample size was included for each analysis; (4) randomized controlled trials (RCTs) or observational studies; and (5) the study outcomes were stated. Inter-reviewer agreement was determined using Cohen kappa coefficients.

Data Extraction

Data were extracted by 2 independent reviewers (L.Y.R., J.L.L.). Any disagreement was discussed with the senior author (W.H.). Study and participant characteristics were extracted. In addition, clinical data including initial cardiac rhythms, dose of adrenaline administered, presumed cardiac origin, witnessed cardiac arrest and bystander cardiopulmonary resuscitation status were also extracted.

Outcomes

The primary outcome was survival to discharge. The secondary outcomes were ROSC, favorable neurological outcome at hospital discharge/1 month according to a cerebral performance category of 1 or 2,[26,27] and survival to hospital admission.

Risk of Bias Assessment

The Newcastle-Ottawa scale, which assesses the quality of non-randomized studies,[28] was used to assess the risk of bias according to 3 aspects: selection, comparability, and outcome. Higher numbers of stars indicate better quality; the study quality was characterized as low (0–4 stars), moderate (5–6 stars), or high (7–9 stars). *The Cochrane Handbook of Systematic Reviews*

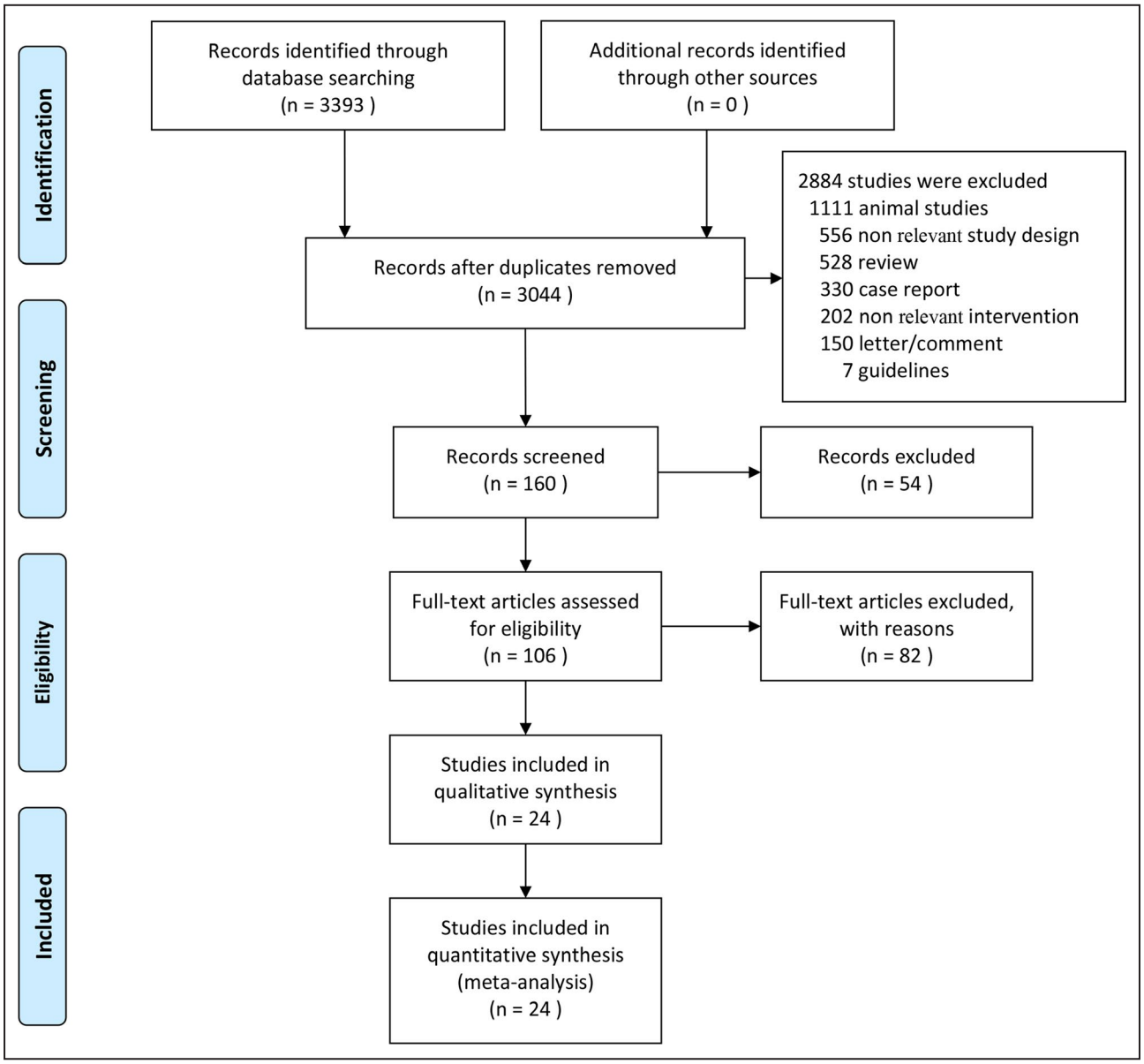

Figure 1. Flow diagram of the study selection.

for intervention tool[29] was used to assess the risk of bias in each RCT. This tool evaluates the biases of 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We assessed the risk of bias for each domain as low, unclear, or high risk of bias.

Statistical Analysis

The efficacy was estimated for each study by the risk ratio (RR) along with its 95% CI. $P<0.05$ were considered significant. Heterogeneity was assessed based on the I^2 test ($I^2>50$, implying substantial heterogeneity). Across the studies, if no significant heterogeneity (defined as $I^2<50\%$) was found, the results were combined with the fixed-effects model (Mantel–Haenszel)[30]; otherwise, the random-effects model (DerSimonian-Laird)[31] was used. A sensitivity analysis was performed by serially excluding each study to determine its influence. STATA version 12.0 (StataCorp, College Station, TX) was used to evaluate the outcomes. Finally, the quality of evidence was assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach,[32] to provide reliable evidence for clinical selection.

Subgroup Analysis

A subgroup analysis was performed, and the patients administered adrenaline were stratified by shockable

Table. Characteristics of Included Studies

Study	Country	Study Period	Design	Sample	Age, y	Initial Cardiac Rhythm n (%)		Cardiac cause (%)	Witnessed Arrest (%)	Bystander CPR (%)	Intervention	Comparator
						Shockable	Non-Shockable					
Callaham et al, 1992[38]	United States	1990–1992	RCT, MC	816	65±18.6	24.4	75.6	NA	52.3	16.4	Adrenaline	No adrenaline
Cantrell et al, 2013[34]	United States	2009	Cohort, MC	660	63.1±16.8	24.2	75.8	NA	53	46	Administration of adrenaline <10 min	Administration of adrenaline >10 min
Dumas et al, 2014[12]	France	2000–2012	Cohort, SC	1556	59.8±16	54.3	45.7	NA	84.6	43.8	Adrenaline	No adrenaline
Ewy et al, 2015[33]	United States	2005–2013	Cohort, MC	3469	66.3±15.1	41.8	58.2	100	100	49.4	Administration of adrenaline in shockable rhythm	Administration of adrenaline in non-shockable rhythm
Fisk et al, 2018[39]	United States	2008–2016	Cohort, SC	2255	63.7±17.7	24.6	75.4	NA	36.6	52.7	Administration of adrenaline in shockable rhythm	Administration of adrenaline in non-shockable rhythm
Funada et al, 2018[35]	Japan	2011–2014	Cohort, SC	124 856	77±14.8	0	100	52.5	100	48.5	Adrenaline	No adrenaline
Gotoet al, 2013[40]	Japan	2009–2010	Cohort, MC	209 577	74±16.1	7.4	92.6	56.7	35.7	45.7	Adrenaline	No adrenaline
Gueugniaud et al, 1998[41]	France and Belgium	1994–1996	RCT, MC	3327	65.6±15	17	83	71.6	78.8	9.8	Standard doses of adrenaline	High doses of adrenaline
Gueugniaud, 2008[42]	France	2004–2006	RCT, MC	2894	61.5±15	9.2	90.8	35.9	75.2	26.8	Adrenaline	Adrenaline+ vasopressin
Guyette et al, 2004[43]	United States	2002–2003	Cohort, SC	298	63.8±15.1	26.8	68.8	NA	44	28.2	Adrenaline	No adrenaline
Hansen et al, 2018[52]	United States, Canada	2011–2015	Cohort, MC	32 101	68+19.5	0	100	8.5	40.2	40.9	Administration of adrenaline <10 min	Administration of adrenaline >10 min
Hayashi et al, 2012[18]	Japan	2007–2009	Cohort, MC	3161	73.3+15.2	16	84	67.3	100	41.6	Adrenaline	No adrenaline
Holmberg et al, 2002[44]	Sweden	1990–1995	Cohort, MC	10 966	67.3	56.7	43.3	NA	66.8	32.2	Adrenaline	No adrenaline
Hubble and Tyson, 2017[36]	United States	2012–2014	Cohort, MC	1917	66.3±14.8	31	69	NA	100	52	Administration of adrenaline <10 min	Administration of adrenaline >10 min
Jacobs et al, 2011[45]	Australia	2006–2009	RCT, SC	534	64.6±17.4	49	51	91.4	55.8	51.1	Adrenaline	Placebo

(*Continued*)

Table. Continued

Study	Country	Study Period	Design	Sample	Age, y	Initial Cardiac Rhythm n (%)		Cardiac cause (%)	Witnessed Arrest (%)	Bystander CPR (%)	Intervention	Comparator
						Shockable	Non-Shockable					
Bar-Joseph et al, 2005[46]	Israel	1990–1992	RCT, MC	2122	65.7	49.4	49	NA	NA	42	Adrenaline and low sodium bicarbonate	Adrenaline and high sodium bicarbonate
Koscik et al, 2013[19]	United States	2005–2011	Cohort, MC	686	69±17	25	75	NA	47	NA	Administration of Adrenaline <10 min	Administration of Adrenaline >10 min
Mukoyama et al, 2009[47]	Japan	2001–2006	RCT, SC	336	65.4±17	24	76	100	44.3	15.1	Adrenalin	Vasopressin
Nakahara et al, 2012[37]	Japan	2007–2008	Cohort, MC	49 165	76±15	16.4	83.6	67.5	100	45.7	Adrenaline	No adrenaline
Olasveengen et al, 2012[11]	Norway	2003–2008	RCT, SC	848	66±18	33.5	66.5	71	65.3	100	Adrenaline	No adrenaline
Ong et al, 2007[48]	Singapore	2002–2004	Cohort, MC	1296	64±16	20.3	79.7	NA	67.3	19.4	Adrenaline	No adrenaline
Ong et al, 2012[49]	Singapore	2006–2009	RCT, MC	727	65±15	7.7	88.2	86.2	72.9	15.4	Adrenaline	Vasopressin
Tanaka et al, 2016[21]	Japan	2006 –2012	Cohort, MC	119 639	71±14	23.7	76.3	100	100	45	Adrenaline	No adrenaline
Wenzel et al, 2004[50]	Austria, Germany, Switzerland	1999 –2002	RCT, MC	1186	66±14	39.8	60.2	60.6	77.6	18.4	Adrenaline	Vasopressin

CPR indicates cardiopulmonary resuscitation; MC, multiple centers; NA, not applicable; Non-shockable, pulseless electrical activity and asystole; RCT, randomized controlled trial; SC, single center; and Shockable, ventricular fibrillation and pulseless ventricular tachycardia.

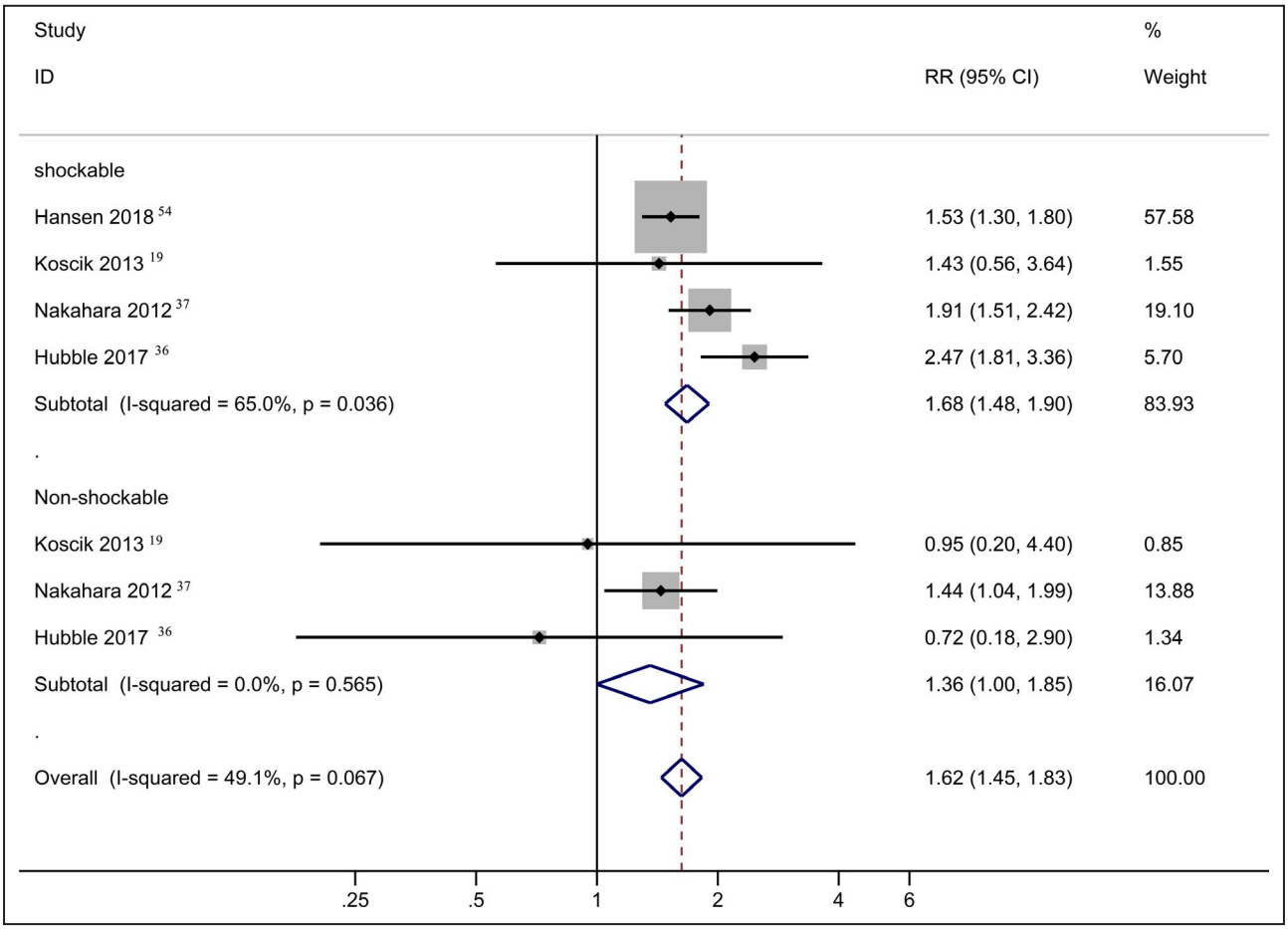

Figure 2. Effects of early (<10 minutes vs >10 minutes) pre-hospital adrenaline administration on survival to discharge/1 month.
RR indicates risk ratio.

rhythm (ventricular fibrillation and pulseless ventricular tachycardia) and non-shockable rhythm (pulseless electrical activity and asystole).

RESULTS

Study Selection

Of the 3393 studies retrieved by the literature search, 349 duplicates were removed, leaving 3044 studies available for screening. After screening the title and abstract, 160 studies underwent full-text review. Of these studies, 9 randomized clinical trials and 15 observational studies were included. The search strategy is shown in Figure 1. The inter-reviewer agreement for the 5 inclusion criteria during the second review phase ranged from "good" to "very good" (κ: 0.768–1.000; Table S2).

Study Characteristics

The basic characteristics of the studies are summarized in Table. A total of 574 392 participants were included. Twenty-two studies included patients with shockable and non-shockable rhythms, and only 2 studies included patients with non-shockable rhythms.[23,33] Eighteen studies only enrolled patients administered adrenaline; and 4 studies compared adrenaline to vasopressin. Eight studies reported outcomes where the time to adrenaline administration was within 10 minutes[18,19,21,23,34–37]; 19 studies compared the outcomes between shockable and non-shockable rhythm patients.[11,12,18,33,34,36,38–50] Four studies were based on data from the All-Japan Utstein Registry.[21,35,37,40]

Risk of Bias Assessment

Fifteen adult cohorts were assessed for risk of bias using the Newcastle-Ottawa scale (Table S3). All studies were categorized as high quality. The potential sources of bias in RCTs are summarized in Figure S1 and displayed in Figure S2. Two RCTs were assessed as "low risk of bias", 7 RCTs were assessed as having "unclear risk of bias" for at least 1 domain, and no study was assessed having a "high risk of bias".

Adrenaline Administration Within 10 Minutes Versus Adrenaline Administration After 10 Minutes

The results of 4 studies[19,23,36,37] were pooled to examine the effects of early adrenaline administration on survival to discharge, with a sample size of 28 700 in the shockable rhythm group and 5989 in the non-shockable rhythm group (Figure 2). A fixed-effects model was used; the pooled RR in the shockable rhythm group was 1.68 (95% CI, 1.48–1.90; $P<0.001$, $I^2=65.0\%$); in the non-shockable rhythm group, the pooled RR was 1.36 (95% CI, 1.00–1.85; $P=0.053$, $I^2=0.0\%$), indicating that a patient with shockable rhythm cardiac arrest receiving pre-hospital adrenaline within 10 minutes was 1.68 times more likely to survive to discharge than one receiving pre-hospital adrenaline after 10 minutes. The quality of the evidence was assessed as low (Figure S3).

Data from 4 studies[19,21,34,36] were pooled for the analysis of pre-hospital ROSC, with a total of 6403 patients with shockable rhythm cardiac arrest and 17 179 patients with non-shockable rhythm cardiac arrest (Figure 3). A fixed-effects model was used, and the pooled RR in the shockable rhythm group was 1.58 (95% CI, 1.38–1.81; $P<0.001$, $I^2=80.8\%$); a sensitivity analysis was performed because of the significant heterogeneity when excluding the study[21] that included only cardiac arrest patients. The heterogeneity decreased to 42.9%, with a pooled RR of 1.35 (95% CI, 1.15–1.60; $P<0.001$). In the non-shockable rhythm group, the pooled RR was 1.44 (95% CI, 1.23–1.68; $P<0.001$, $I^2=0.0\%$), indicating a greater likelihood of experiencing pre-hospital ROSC in patients administered pre-hospital adrenaline within 10 minutes. The quality of the evidence was assessed as low (Figure S3).

We included 5 studies[18,21,35–37] in a pooled analysis of favorable neurological outcomes (cerebral performance category 1–2), with a total of 6302 patients with shockable rhythm cardiac arrest and 33 454 patients with non-shockable rhythm cardiac arrest (Figure 4). A fixed-effects model was used; the pooled RR in the shockable rhythm group was 3.21 (95% CI, 2.54–4.05, $P=0.000$; $I^2=55.2\%$), and the

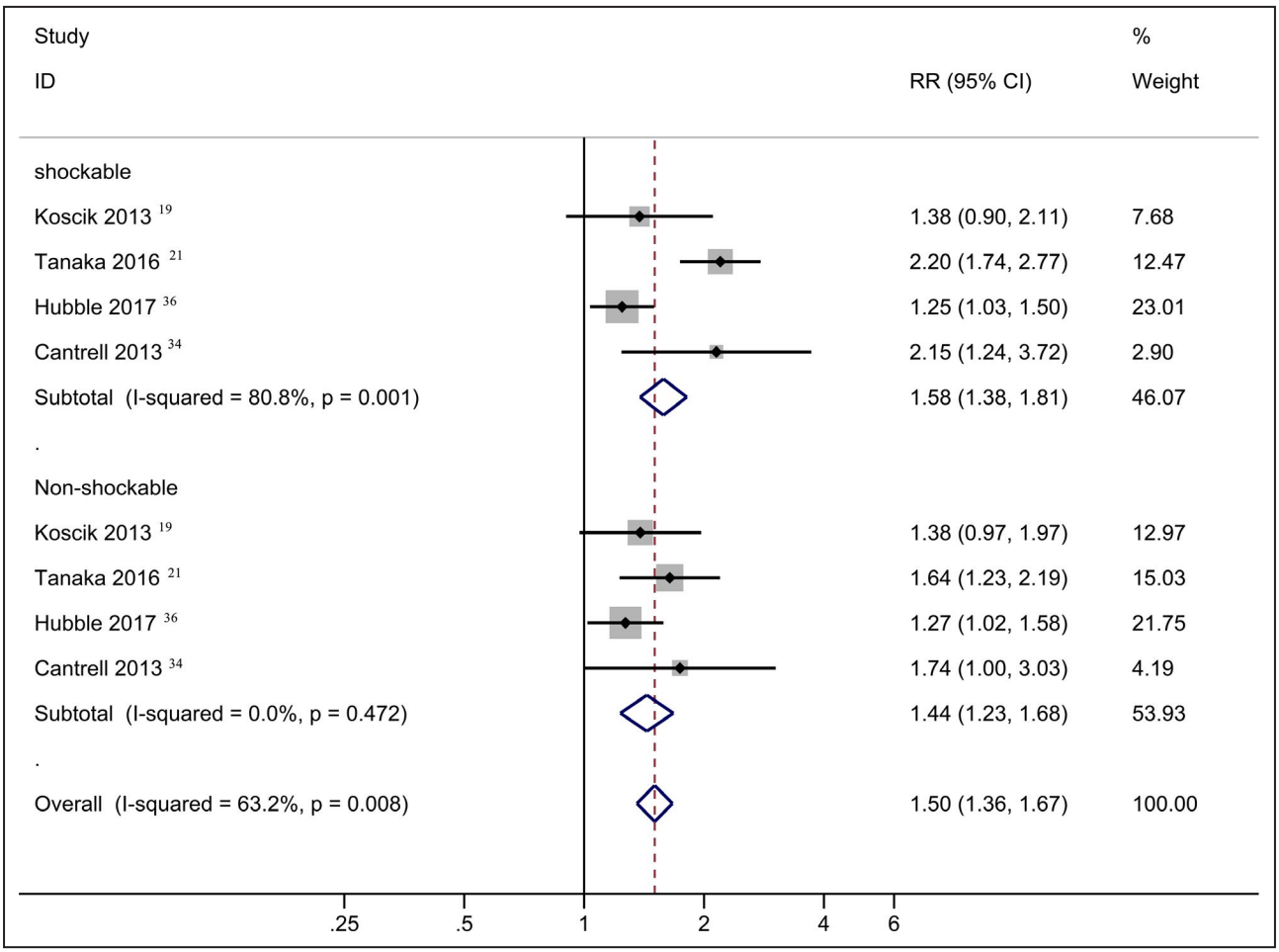

Figure 3. Forest plot for pooling the effects of early (<10 minutes vs >10 minutes) pre-hospital adrenaline administration on return of spontaneous circulation.
ROSC indicates return of spontaneous circulation; and RR, risk ratio.

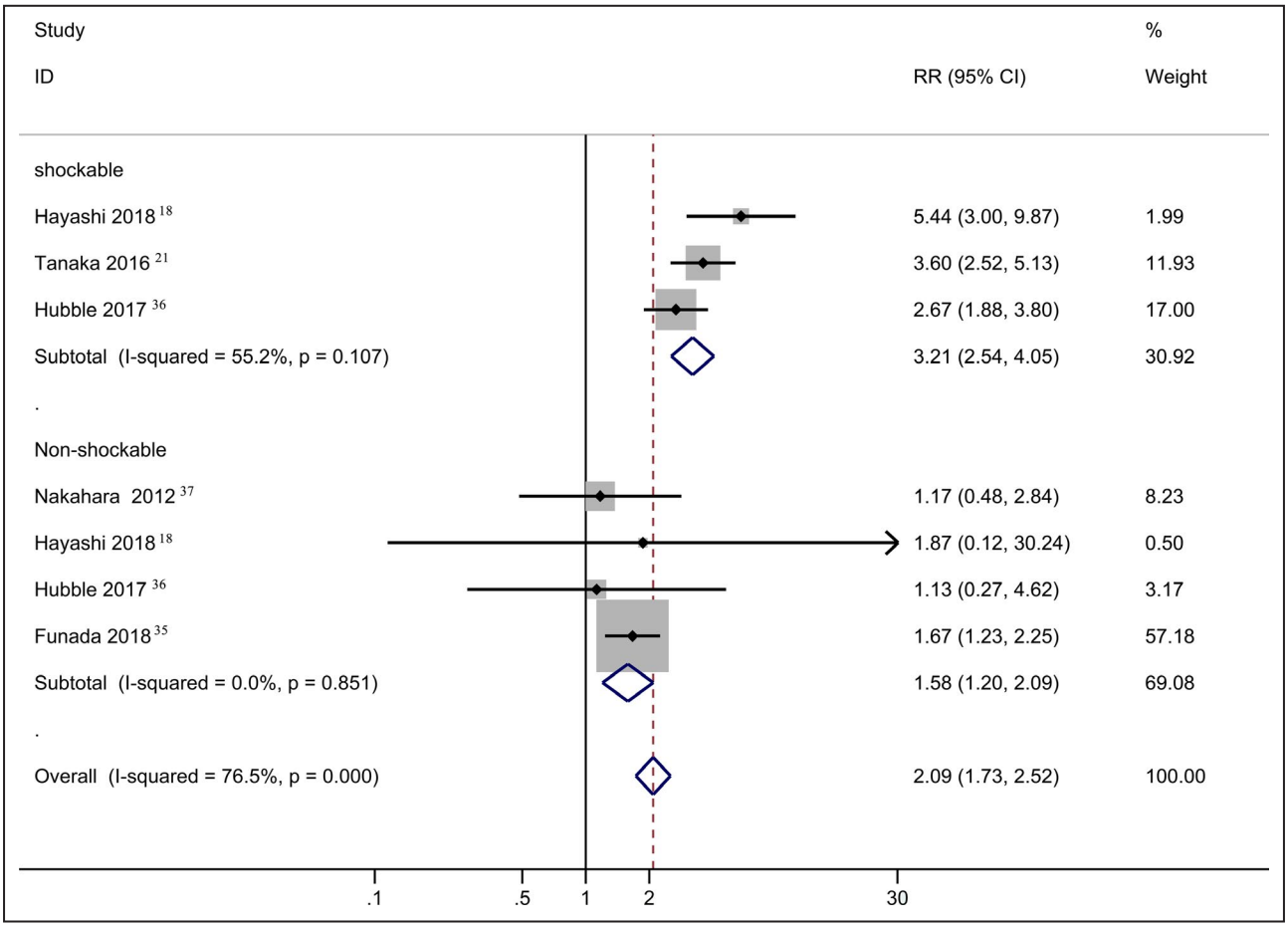

Figure 4. Forest plot for pooling the effects of early (<10 minutes vs >10 minutes) pre-hospital adrenaline administration on achieving a cerebral performance category of 1 to 2.
CPC indicates cerebral performance category; and RR, risk ratio.

pooled RR in the non-shockable rhythm group was 1.58 (95% CI, 1.20–2.09; P=0.001, I^2=0.0%). This result suggested that a patient with shockable rhythm cardiac arrest receiving pre-hospital adrenaline within 10 minutes was 3.21 times more likely to experience a favorable neurological outcome than one receiving pre-hospital adrenaline after 10 minutes. The quality of the evidence was assessed as moderate (Figure S3). One study[12] did not report initial cardiac rhythm separately; when the study was included, the pooled overall RR was 2.03 (95% CI, 1.73–2.39; P<0.001, I^2=81.2%) (Figure S4).

Shockable Rhythm Versus Non-Shockable Rhythm

Fourteen studies were included to observe the pooled effect of adrenaline administration on survival to discharge, with a sample size of 21 844 patients with shockable rhythm cardiac arrest and 208 284 patients with non-shockable rhythm cardiac arrest (Figure 5A). A random-effects model was used; the pooled RR was 5.86 (95% CI, 4.25–8.07; P<0.001, I^2=89.6%), which indicated that a patient with shockable rhythm cardiac arrest was 5.86 times more likely to survive to discharge than one with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

Fourteen studies were included to observe the pooled effects of adrenaline administration on pre-hospital ROSC, with a sample size of 19 480 patients with shockable rhythm cardiac arrest and 205 671 patients with non-shockable rhythm cardiac arrest (Figure 5B). A random-effects model was used; the pooled RR was 1.51 (95% CI, 0.91–2.50; P=0.11, I^2=99.5%), and there was no significant difference between the groups. The quality of the evidence was assessed as high (Figure S5).

Eight studies were included to observe the pooled effects of adrenaline administration on favorable neurological outcome (cerebral performance category 1–2), with a sample size of 7317 patients with shockable rhythm cardiac arrest and 27 411 patients with non-shockable rhythm cardiac arrest (Figure 6A). A

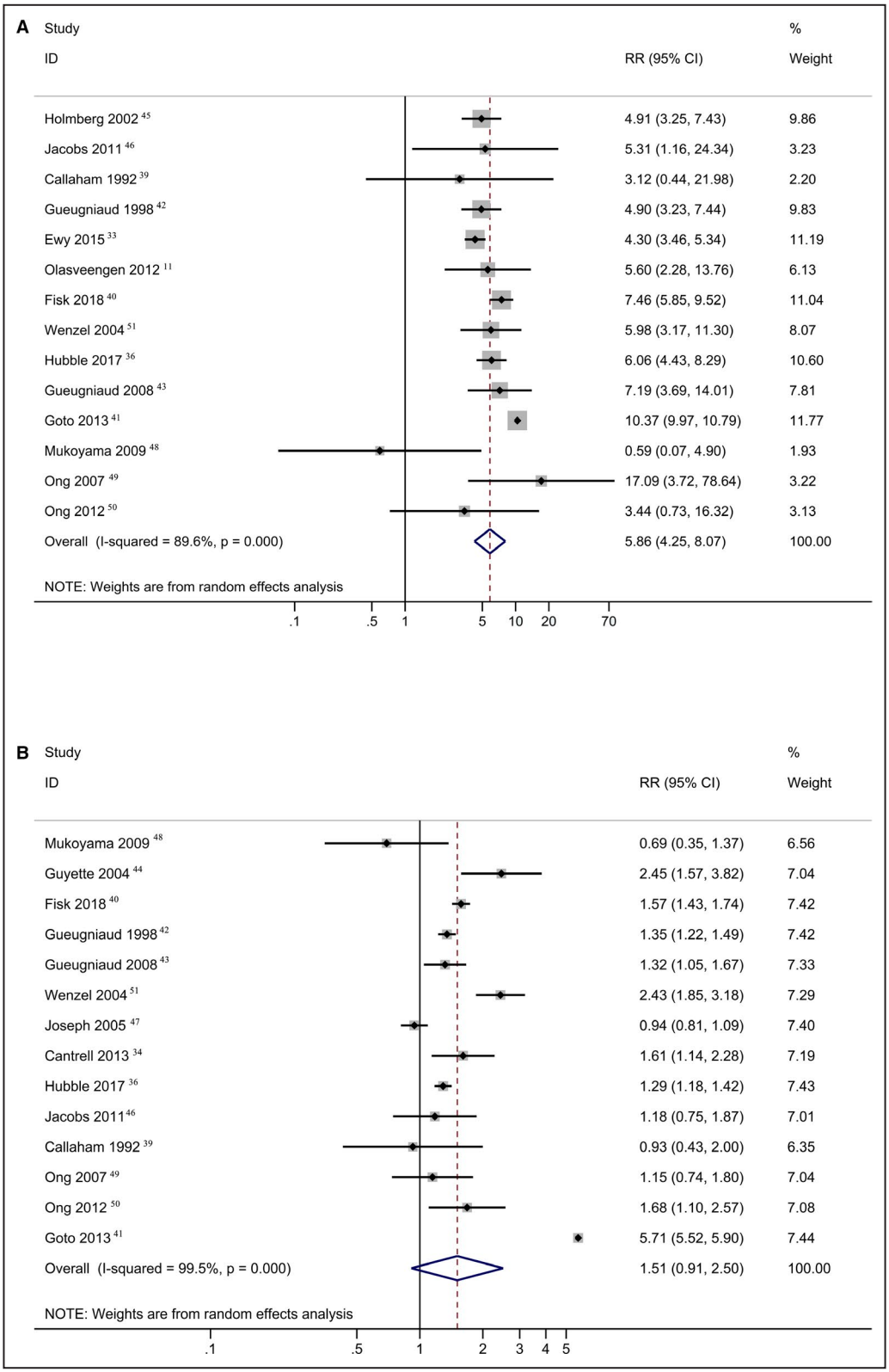

Figure 5. A, Forest plot comparing survival to discharge between patients who had shockable and non-shockable rhythm cardiac arrest; B, Forest plot comparing return of spontaneous circulation between patients who had shockable and non-shockable rhythm cardiac arrest.
ROSC indicates return of spontaneous circulation; and RR, risk ratio.

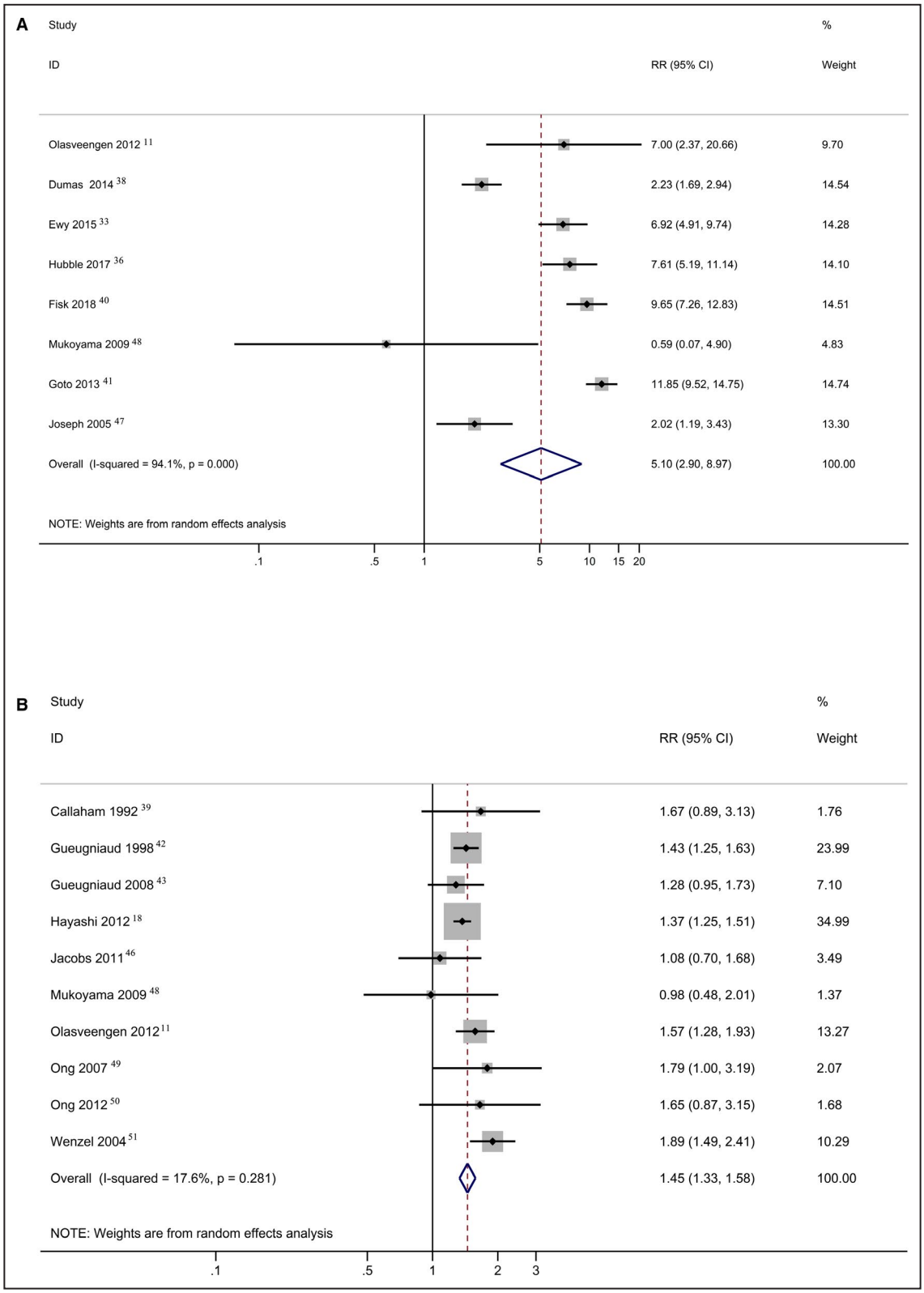

Figure 6. A, Forest plot comparing the effects of a cerebral performance category of 1 to 2 between patients who had shockable and non-shockable rhythm cardiac arrest; B, Forest plot comparing survival to admission between patients who had shockable and non-shockable rhythm cardiac arrest.
RR indicates risk ratio.

random-effects model was used; the pooled RR was 5.10 (95% CI, 2.90–8.97; $P<0.001$, $I^2=94.1\%$), indicating that a patient with shockable rhythm cardiac arrest was 5.10 times more likely to experience a favorable neurological outcome than one with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

Ten studies were included to observe the pooled effects of adrenaline administration on survival to admission, with a sample size of 2359 patients with shockable rhythm cardiac arrest and 9655 patients with non-shockable rhythm cardiac arrest (Figure 6B). A random-effects model was used; the pooled RR was 1.45 (95% CI, 1.33–1.58; $P<0.001$, $I^2=17.6\%$), suggesting a higher rate of survival to admission in patients with shockable rhythm cardiac arrest than in patients with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

DISCUSSION

In this systematic review and meta-analysis, we evaluated the effects of early pre-hospital administration of adrenaline in OHCA patients. Our results indicated that the administration of adrenaline within 10 minutes significantly increased the survival to discharge, ROSC, and favorable neurological outcomes. In addition, compared with non-shockable cardiac arrest patients, shockable cardiac arrest patients seemed to have a significantly improved prognosis, especially in terms of survival to discharge and favorable neurological outcome.

The use of adrenaline has been reported to result in severe neurological impairment. In a recent randomized, double-blind trial,[14] Perkins et al found that severe neurologic impairment was more frequent in the adrenaline group than in the placebo group (31.0% versus 17.8%). Although a more favorable neurologic outcome at discharge was observed in the adrenaline group than in the placebo group, the difference was not significant (2.2% versus 1.9%). In addition, these authors also reported a significantly higher rate of 30-day survival in the adrenaline group than in the placebo group. In another double-blind randomized controlled trial, Jacobs et al[45] reported that although pre-hospital ROSC was significantly improved, the outcomes, including survival to discharge and favorable neurological survival, did not differ.

In contrast, in recent years, several studies have reported that a potential benefit of adrenaline was only seen with early administration.[18–20,22,51,52] In a multicenter observational study,[19] Hayashi et al reported that among shockable rhythm cardiac arrest patients, 66.7% of the patients who received adrenaline within 10 minutes had neurologically intact 1-month survival; however, the rate decreased to 24.9% in patients without adrenaline administration. Fukuda et al[22] performed a similar propensity score-matched study of 237 068 patients; compared with the patients who did not receive adrenaline administration, the patients who received adrenaline within 15 minutes had a significantly higher rate of survival to 1 month and favorable neurological survival, regardless of whether the patients had shockable or non-shockable rhythm cardiac arrest. Our results are consistent with the results of these previous studies. In the present study, our findings supported the effects of early adrenaline administration on increasing survival to discharge, overall ROSC, and favorable neurological outcome.

The American Heart Association guidelines[53] recommend that for cardiac arrest with a shockable rhythm, it may be reasonable to administer epinephrine after initial defibrillation attempts have failed. In our subgroup analysis stratified by initial cardiac arrest rhythm, early administration of adrenaline improved the outcomes in both shockable and non-shockable rhythm cardiac arrest patients. The patients with shockable rhythm cardiac arrest were found to have significantly higher rates of survival to discharge, favorable neurological outcomes and survival to admission than patients with non-shockable rhythm cardiac arrest in the adrenaline administration group. The different outcomes between the shockable and non-shockable rhythm groups might be because of the fact that defibrillation plays an important role in the prognosis of patients with shockable rhythm cardiac arrest; this difference indicates that when evaluating the effects of adrenaline, the initial cardiac rhythm should be considered a key factor for predicting the outcomes, and the patients should be stratified by initial cardiac arrest rhythm. Otherwise, this difference may influence the outcomes.

There were several potential limitations in this meta-analysis. First, our primary and secondary outcomes were based on a maximum of 3 to 4 studies, and only a few of the studies reported the effects of early adrenaline administration. Consequently, more studies are needed to confirm this conclusion. Second, most of the studies that were included were observational studies, making it difficult to adjust for confounders such as the number of doses provided, witnessed arrest, bystander cardiopulmonary resuscitation, emergency medical service response time, and the use of cointerventions. Third, interventions performed in the hospital, such as targeted temperature management and percutaneous coronary intervention, could not be measured or accounted for. Finally, because of insufficient data, we could not perform a comparison with a no adrenaline group; further studies are needed for this comparison.

Despite these limitations, the present study included a large sample size from 13 countries, which may help to increase the reliability of the results.

CONCLUSIONS

This systematic review and meta-analysis suggested that early pre-hospital administration of adrenaline in OHCA patients might increase the rate of survival to discharge, ROSC, and favorable neurologic outcomes. However, large randomized, controlled studies are needed to further confirm the results.

ARTICLE INFORMATION

Received August 19, 2019; accepted April 8, 2020.

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Sources of Funding

This work is supported by the National Natural Science Foundation of China (81170188 and 30971212).

Disclosures

None.

Supplementary Materials

Tables S1–S3
Figures S1–S5
References 12, 18, 19, 21, 33, 35–40, 44, 45, 49, and 54

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SUPPLEMENTAL MATERIAL

Table S1. PRISMA checklist.

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table S2. Inter-reviewer Agreement.

Criterion	Kappa	Standard error	P-value
Patients with OHCA	1.000	-	-
Treated with epinephrine	0.949	0.036	0.000
Study population	1.000	-	-
RCT or observational study	1.000	-	-
Study outcome stated	0.768	0.070	0.000

Table S3. Newcastle-Ottawa Scale quality assessment scores for the included studies.

First Author	Selection (0-4)	Comparability (0-2)	Outcome (0-3)	Total stars
Cantrell, 2013[39]	★★★	★★	★★★	8
Dumas, 2014[38]	★★★	★★	★★★	8
Ewy, 2015[33]	★★★	★★	★★★	8
Fisk, 2018[40]	★★★	★★	★★★	8
Funada, 2018[35]	★★★★	★★	★★★	9
Goto, 2013[41]	★★★★	★★	★★★	9
Guyette, 2004[44]	★★★	★★	★★★	8
Hansen, 2018[54]	★★★	★★	★★★	8
Hayashi, 2012[18]	★★★★	★★	★★★	9
Holmberg, 2002[45]	★★★	★★	★★★	8
Hubble, 2017[36]	★★★	★★	★★★	8
Koscik, 2013[19]	★★★	★★	★★★	8
Nakahara, 2012[37]	★★★	★★	★★★	8
Ong, 2007[49]	★★★★	★★	★★★	9
Tanaka, 2016[21]	★★★★	★★	★★★	9

Figure S1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

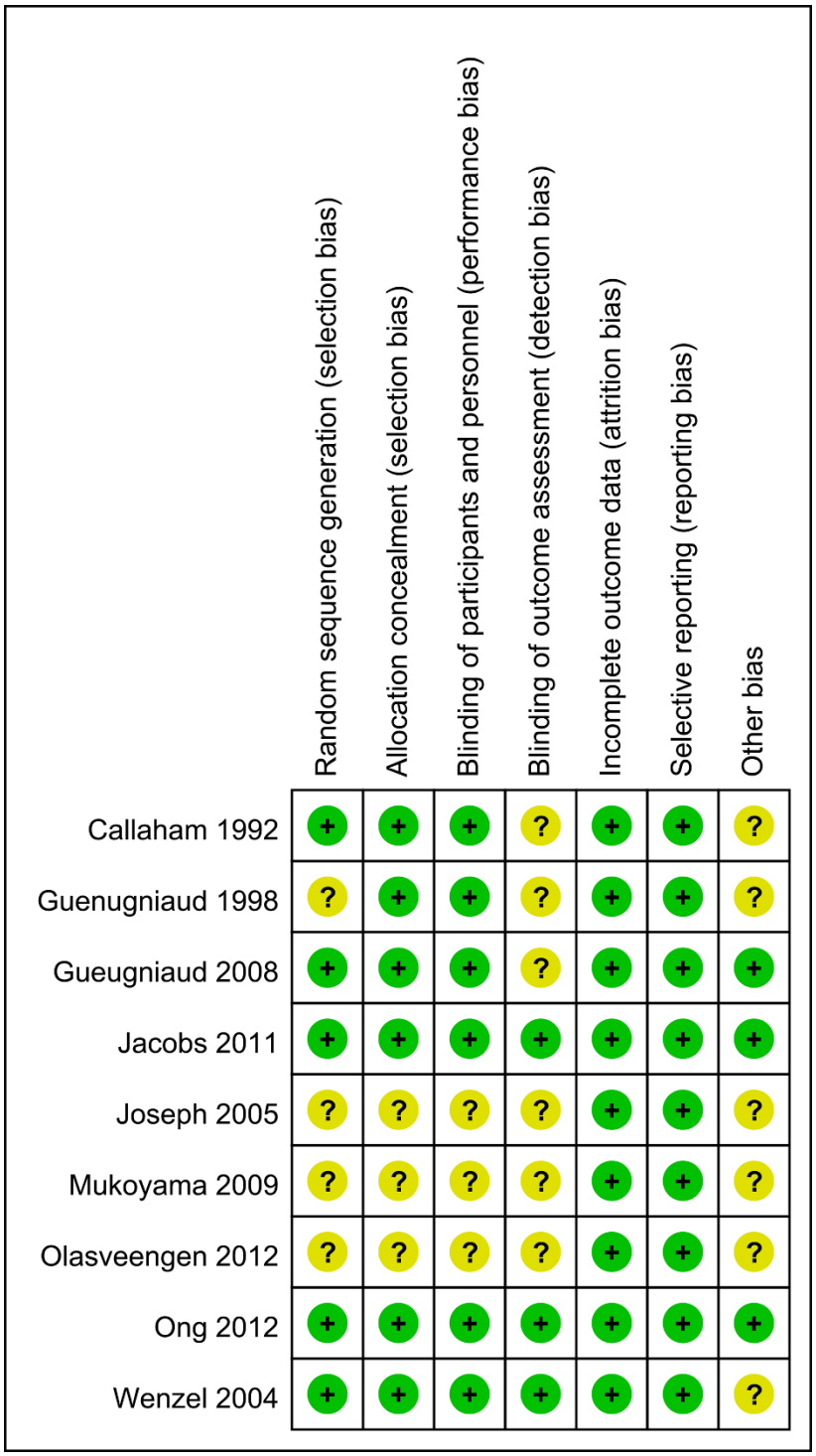


Figure S2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

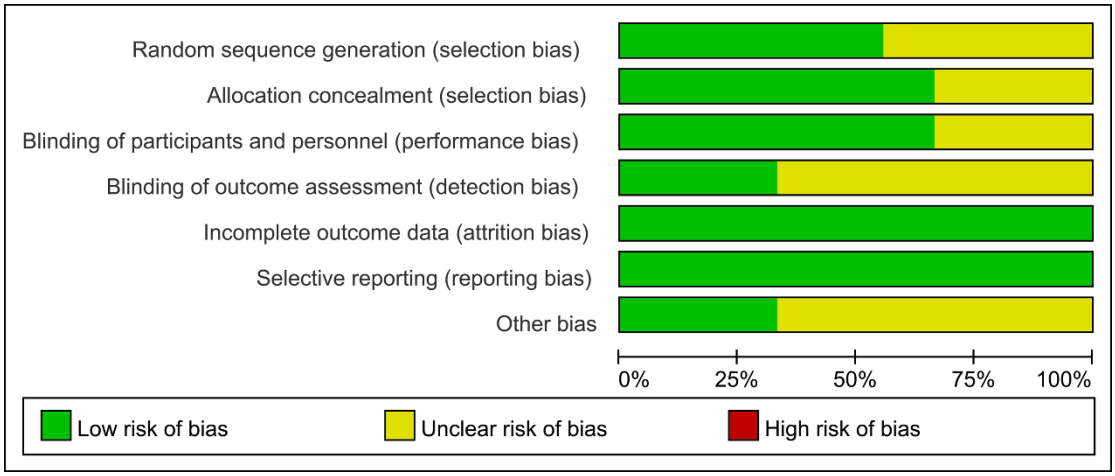
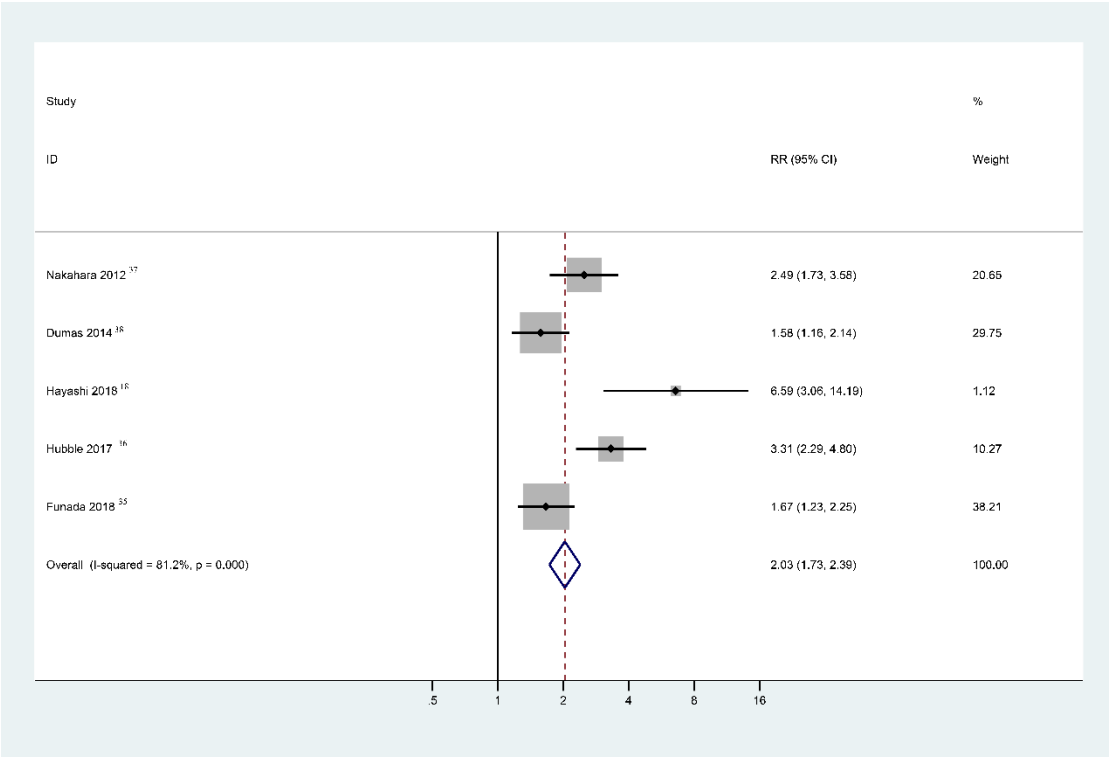


Figure S3. GRADE Assessment.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Time	placebo	Relative (95% CI)	Absolute (95% CI)		
ROSC												
4	observational studies	not serious	not serious	not serious	not serious	none	228/560 (40.7%)	4628/23025 (20.1%)	**RR 1.61** (1.27 to 2.05)	**123 more per 1,000** (from 54 more to 211 more)	⨁⨁◯◯ LOW	CRITICAL
CPC 1-2												
5	observational studies	not serious	not serious	not serious	not serious	strong association	187/9795 (1.9%)	879/46058 (1.9%)	**RR 3.08** (2.01 to 4.71)	**40 more per 1,000** (from 19 more to 71 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Survial to discharge												
4	observational studies	not serious	not serious	not serious	not serious	none	521/14062 (3.7%)	626/20636 (3.0%)	**RR 1.90** (1.44 to 2.51)	**27 more per 1,000** (from 13 more to 46 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Figure S4. Forest plot for pooling the effects of early (< 10 minutes vs. > 10 minutes) prehospital adrenaline administration on achievement of a CPC of 1-2.



CPC, cerebral performance category.

Figure S5. GRADE Assessment.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shockable	Non-shockable	Relative (95% CI)	Absolute (95% CI)		
CPC1-2												
8	randomised trials	not serious	not serious	not serious	not serious	very strong association	880/7317 (12.0%)	338/27411 (1.2%)	**RR 5.10** (2.90 to 8.97)	**51 more per 1,000** (from 23 more to 98 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ROSC												
14	randomised trials	not serious	not serious	not serious	not serious	none	5602/19417 (28.9%)	12320/205346 (6.0%)	**RR 1.51** (0.91 to 2.50)	**31 more per 1,000** (from 5 fewer to 90 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Discharge												
14	randomised trials	not serious	not serious	not serious	not serious	very strong association	4712/21844 (21.6%)	4963/208284 (2.4%)	**RR 5.86** (4.25 to 8.07)	**116 more per 1,000** (from 77 more to 168 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Admission												
10	randomised trials	not serious	not serious	not serious	not serious	none	762/2359 (32.3%)	2304/9655 (23.9%)	**RR 1.44** (1.34 to 1.54)	**105 more per 1,000** (from 81 more to 129 more)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio