Therapeutic Effects of Vasopressin in Cardiac Arrest: a Systematic Review and Meta-analysis

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Research Article

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Abstract

Objective: Our review aimed to demonstrate the therapeutic effect of vasopressin as alternative treatment for cardiac arrest.

Methods: PubMed, EMBASE, the Cochrane Library and Web of Science were searched for randomized controlled trials from inception until November 2021. Vasopressin use during cardiopulmonary resuscitation (CPR) in patients with in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) was compared to no vasopressin or placebo. The primary outcome was the return of spontaneous circulation (ROSC). The secondary outcomes included mild-term survival and mild-term good neurological outcome.

Results: Twelve studies (n=6718) were included, of which eight trials (n=5638) reported the data on patients with OHCA and four trials (n=1080) on patients with IHCA. There were no significant differences between intravenous vasopressin and placebo in the outcomes of ROSC (relative risk [RR]: 1.11; 95% confidence interval [CI]: 0.99–1.26), mild-term survival (RR: 1.23; 95% CI: 0.90–1.66), and mild-term good neurological outcome (RR,1.20; 95% CI: 0.77–1.87). However, in the subgroup analysis, intravenous vasopressin as part of the vasopressin, steroids and epinephrine (VSE) protocol can significantly improve the rate of ROSC (RR, 1.32; 95% CI: 1.18–1.47) but not the rate of mild-term survival (RR, 2.15; 95% CI:0.75–6.16) and mild-term good neurological outcome (RR,1.80; 95% CI, 0.81–4.01) for patients with IHCA. For patients with OHCA, there was no significant difference between groups in terms of ROSC (RR, 0.98; 95% CI, 0.91–1.07), mild-term survival (RR, 1.22; 95% CI, 0.86–1.72) and mild-term good neurological outcome (RR, 0.94; 95% CI: 0.55–1.61).

Conclusions: Our meta-analysis found that intravenous vasopressin may not significantly improve the rate of ROSC, mild-term survival and good neurological outcome. In the subgroup analysis, vasopressin as a part of VSE protocol is associated with the improvement of ROSC in patients with IHCA. However, no mild-term survival or mild-term good neurological outcome benefit has been demonstrated. Better-designed trials on a large group of patients should be conducted in the future to address the therapeutic effect of vasopressin or vasopressin-steroids-epinephrine in cardiac arrest.

Background

Cardiac arrest is a major contributor to morbidity and mortality worldwide. For more than 100 years, epinephrine has been administered during cardiopulmonary resuscitation (CPR) for patients in cardiac arrest(1). However, previous reports suggested that endogenous vasopressin levels in successfully resuscitated patients were significantly higher than those in patients who died, and that intravenous vasopressin during CPR may give better results than epinephrine(2–5). Based on a randomized controlled trial(5) and some small case series(6, 7), the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guidelines recommend vasopressin as an alternative to epinephrine for the treatment of cardiac arrest. However, the clinical benefit of vasopressin remains debated. A trial by Stiell et al.(8)

showed no obvious benefit of vasopressin over epinephrine for in-hospital cardiac arrest (IHCA). A clinical trial(9) demonstrated that a combination of vasopressin and epinephrine during CPR improves the outcome for patients with out-of-hospital cardiac arrest (OHCA). In addition, several studies have recently proposed that an emerging therapy using vasopressin, vasopressin, corticosteroid and epinephrine (VSE) protocol during CPR may improve the outcomes for cardiac arrest. To evaluate the impact of vasopressors in patients who had cardiac arrest, a meta-analysis indicated that there was no benefit from vasopressin with or without epinephrine(10). However, these trials were not included in this meta-analysis. Previous trials suggested that vasopressin may prove to benefit patients in ventricular fibrillation and asystole. Currently, there is no systematic review or meta-analysis that has evaluated the overall therapeutic effect of vasopressin (vasopressin only, vasopressin plus epinephrine, VSE) and the effect based on the initial rhythm, witnessed, and CPR by a bystander in cardiac arrest. Therefore, we performed a systematic review and meta-analysis to evaluate the therapeutic effect of vasopressin in cardiac arrest.

Methods

The methods and protocol of this meta-analysis were previously published in detail on the International Prospective Register of Systematic Reviews (registration number: CRD42021293347), following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines(11).

Eligibility criteria

Eligibility criteria were based on the Population, Intervention, Control, Outcomes and Study design (PICOS) framework as follows: (1) population: adult patients with cardiac arrest in any setting (IHCA or OHCA); (2) intervention: vasopressin administered during CPR; (3) control: non-vasopressin or placebo administered during CPR in the control group; (4) outcome: return of spontaneous circulation (ROSC), survival and good neurological outcome; and (5) study design: randomized controlled trials (RCTs). The following criteria determined the ineligible studies: (1) use of vasopressin not during CPR; (2) inappropriate study designs, single-arm trials, observational studies or non-RCTs (3) case reports or series and narrative and systematic reviews; (4) those with <20 patients; (5) those not reported in the English language; (6) studies with pregnant women or minors.

Search strategy

A systematic search of PubMed, EMBASE, the Cochrane Library and Web of Science was performed from database inception to November 2021 with English language restrictions by two authors (WQY and WHD). In addition, we conducted a hand search of references obtained from identified studies and known meta-analyses. We combined the following search terms: cardiac arrest, heart arrest, cardiopulmonary resuscitation, advanced cardiovascular life support, ventricle fibrillation, asystole, pulseless electrical activity, ACLS, CPR and vasopressin.

Data collection and data items

Two authors (WQY and XS) separately screened all retrieved citations by reviewing their titles and abstracts. Full-text articles were retrieved if either of the authors considered the abstract potentially suitable. Next, the same authors independently assessed each study's eligibility based on the inclusion criteria. Disagreements were resolved by discussion or consensus with a third author (ZC). Two reviewers (WHD and WQZ) independently extracted individual study data using a predefined data extraction form. Any disagreements between review authors were resolved by consultation with a third author (ZC). Data extracted included the name of the first author, date, country, study design, location, sample size, age, sex, rhythm, therapeutic methods in the two groups and outcomes.

Risk of bias in individual studies

Two reviewers evaluated studies for risk of bias using a previously piloted standardized form and the Cochrane Risk of Bias 2 tool(12) for RCTs. The following domains were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. The overall risk of bias for each included study was categorized into low risk of bias, some concern of bias, or high risk of bias. The risk of publication bias was assessed by visual interpretation of funnel plots if at least 10 studies could be identified reporting the outcome.

Outcomes and Subgroups

These outcomes included return of spontaneous circulation (ROSC), mild-term survival (at hospital discharge, 28 days, 30 days, or 1 month) and mild-term good neurological outcome (at hospital discharge, 28 days, 30 days, or 1 month). The good neurological outcome was measured by the Cerebral Performance Category (CPC). The CPC score has five categories as follows: (1) good cerebral performance, (2) moderate cerebral disability, (3) severe cerebral disability, (4) coma or vegetative state, and (5) death(13). A CPC score of 1–2 is considered a good neurological outcome.

We performed subgroup analyses of OHCA receiving vasopressin only or vasopressin plus epinephrine, IHCA receiving vasopressin only or vasopressin plus epinephrine, and IHCA receiving VSE. In addition, subgroup analyses were performed for patients based on the initial rhythm, witnessed, and CPR by a bystander.

Data Synthesis

Meta-analyses were conducted using the Review Manager 5.4 software (RevMan, The Cochrane Collaboration, 2020). Dichotomous data of ROSC, mild-term survival and mild-term good neurological outcome were represented as relative risk (RR) with 95% confidence intervals (CI). A random-effects model was used, and statistical significance was set at $P<0.05$ for all analyses. Heterogeneity was estimated visually in forest plots and statistically using I^2 tests, as recommended by the Cochrane Collaboration. We considered heterogeneity low if I^2 was <25%, moderate if 25–50%, and substantial if >50%. To examine heterogeneity, we performed subgroup analysis based on predefined moderator

variables, including the study year, study region, study quality, age, IHCA vs. OHCA and therapeutic methods. The primary outcome estimates for patients with shockable rhythms, with or without arrest witnessed and with or without CPR by a bystander, were also synthesized in the subgroup analysis.

Results

Study selection and Study characteristics

Our search strategy identified 12 randomized trials(5, 8, 9, 14–22), including 6,718 adult patients who met the eligibility criteria (Fig. 1; Additional file). All included studies were prospective randomized controlled trials and included patients between the years 1994 and 2021. Seven trials were performed in Europe, three in Asia, and two in North America. Eight trials (n=5,638) included patients with OHCA(5, 9, 14, 15, 17–19, 21) and four trials (n=1,080) included patients with IHCA(8, 16, 20, 22). One trial(21) did not provide the mean age, and the mean age of patients included in the other eleven trials ranged from 58 to 70 years. Four trials evaluated the efficacy of vasopressin only on patient outcomes in OHCA; four trials evaluated the efficacy of vasopressin and epinephrine in OHCA; three trials evaluated the efficacy of the VSE protocol in IHCA; and one trial evaluated the efficacy of vasopressin in IHCA. In the eight trials of OHCA, the patients of the two trials(5, 19) received one injection of 40 IU of vasopressin, and one trial(9) received two injections. The patients of the two trials(14, 21) received one injection of 40 IU vasopressin and 1 mg of epinephrine, one trial(15) received two injections and one trial(18) received three injections. The seven trials mentioned above received the study drugs, followed by additional treatment with the standard guideline if necessary. In addition, the patients of one trial(17) received a maximum of four injections of 40 IU of vasopressin after admission, and no combined injections of the vasopressors were administered in all groups. In the four trials of IHCA, one trial(8) received one injection of 40 IU of vasopressin, followed by an additional treatment with epinephrine if necessary. Patients of the three trials(16, 20, 22) who received VSE therapy were treated with the same regimen during the resuscitation period. The VSE drugs consisted of 20 IU of vasopressin and 40 mg of methylprednisolone administered as soon as possible after the first dose of epinephrine. Additional doses of vasopressin (20 IU) were administered after each epinephrine dose for a maximum of four doses (80 IU). In addition to VSE therapy during CPR, two of the three trials were treated with additional therapy that surviving patients in the study group with post-resuscitation shock received stress-dose hydrocortisone after resuscitation, but the remaining one trial did not.

Risk of bias in studies

The assessment of bias in the RCTs is listed in Fig. 2. Two trials(16, 21) were considered to have a high risk of bias, seven(5, 8, 9, 14, 17–19) were considered to have some concerns for risk of bias, and the remaining three(15, 20, 22) were considered to have a low risk of bias. Of the 12 RCTs, one trial(21) did not report methods of randomization and minimal baseline characteristics between groups; one(17) reported limited information on the process of randomization; and two(8, 19) reported some baseline imbalance between the groups.

Primary outcome

ROSC: As shown in Table 1, 11 trials(5, 8, 9, 14–20, 22) with 6,607 patients reported the rate of ROSC. There was no significant difference in patients with ROSC outcome between intravenous vasopressin and placebo (RR: 1.11; 95% CI: 0.99–1.26; Fig. 3). The statistical heterogeneity in this analysis was significant (P=0.004, I^2=62%; Fig. 3). Subgroup analyses were performed to examine the potential source of heterogeneity (Table 1). The quality of studies, setting, study period, study region, and the combination of the study drugs might be the source of heterogeneity.

When analysing the subgroups, intravenous VSE in IHCA patients was associated with significant increase in the rate of ROSC (RR, 1.32; 95% CI: 1.18–1.47; Fig. 3). There was no significant heterogeneity in the results (P=0.46, I^2=0%; Fig. 3). However, the use of VSE in IHCA patients increased the rate of ROSC but not with vasopressin only (RR, 1.09; 95% CI, 0.79–1.52; Fig. 3). There was no significant difference in the rate of ROSC (RR, 0.98; 95% CI: 0.91–1.07; Fig. 3) in OHCA patients. There was no significant heterogeneity in the results in OHCA (P=0.42; I^2=0.0%; Fig. 3). In addition, in the subgroup analyses, there was no significant difference in the rate of ROSC for patients of ventricular fibrillation (RR, 1.02; 95% CI: 0.84–1.25; Table 2), asystole (RR, 1.01; 95% CI: 0.90–1.14; Table 2), pulseless electrical activity (RR, 1.00; 95% CI: 0.82–1.21; Table 3), witnessed (RR, 1.04; 95% CI: 0.82–1.33; Table 2), and CPR by a bystander (RR, 1.22; 95% CI: 0.89–1.67; Table 2).

Secondary outcomes

Mild-term Survival: Eleven trials reported the survival rate at hospital discharge, and one trial(22) reported the rate of survival at 30 days. There was no significant difference in patients with mild-term survival outcome between intravenous vasopressin and placebo (RR: 1.23; 95%CI: 0.90–1.66; Fig. 4). Statistical heterogeneity in this analysis was moderate (P=0.08, I^2=39%; Fig. 4). There was no significant difference in the rate of mild-term survival for OHCA patients (RR: 1.22; 95% CI: 0.86–1.72; Fig. 4). Heterogeneity was not significant for this outcome (P=0.29; I^2=18%; Fig. 4). There was no significant difference in the rate of mild-term survival for IHCA patients who received vasopressin only (RR, 1.85; 95% CI: 0.41–1.78; Fig. 4). In addition, there was no important difference in the rate of mild-term survival for IHCA patients who received VSE (RR: 2.15; 95% CI: 0.75–6.16; Fig. 4) The test for heterogeneity was significant (P=0.01; I^2=76%; Fig. 4). After excluding one trial(22), the heterogeneity decreased significantly (I^2 value from 76–0%). The use of hydrocortisone after resuscitation might be the source of heterogeneity. Notably, no significant heterogeneity was observed between the two trials(16, 20) the study protocols were the same, and both were reported by the same study group. In addition, there was no significant difference in the rate of mild-term survival for patients with ventricular fibrillation in the subgroup analyses (RR: 0.51; 95% CI: 0.51–1.48; Table 2), asystole (RR: 1.29; 95% CI: 0.44–3.76; Table 2), pulseless electrical activity (RR: 0.62; 95% CI: 0.16–12.39; Table 2), witnessed (RR: 0.90; 95% CI: 0.39–2.07; Table 2) and CPR by a bystander (RR: 1.26; 95% CI: 0.64–2.46; Table 2).

Mild-term good neurological outcome: Six trials(8, 9, 16, 17, 20, 22) with 1,405 patients provided data to evaluate the effect of vasopressin on good neurological outcome. One trial(22) reported good neurological outcome at 30 days, and the remaining reported good neurological outcome at hospital discharge. There was no significant difference in patients with mild-term good neurological outcome between intravenous vasopressin and placebo (RR:1.20; 95% CI:0.77–1.87; Fig. 5). Statistical heterogeneity in this analysis was moderate (P=0.43, I^2=47%; Fig. 5). There was no significant difference for good neurological outcome in OHCA patients (RR: 0.94; 95% CI: 0.55–1.61; Fig. 5). Heterogeneity was not significant for this outcome (P=0.28; I^2=13%; Fig. 5). For IHCA patients receiving vasopressin only, there was no significant difference for good neurological outcome (RR: 71; 95% CI: 0.33–1.54; Fig. 5). The overall test for heterogeneity was significant (P=0.06; I^2=59%; Fig. 5). For IHCA patients, three trials of patients receiving VSE did not improve good neurological outcome (RR: 1.80; 95% CI: 0.81–4.01; Fig. 5). Statistical heterogeneity in the subgroup was significant (P=0.10; I^2=56%; Fig. 5). After excluding the 2021 trial(22), the heterogeneity decreased significantly (I^2 value from 76–0%). The use of hydrocortisone after resuscitation might also be the source of heterogeneity.

The plots for ROSC and mild-term survival were asymmetrical, which strongly imply publication bias (Fig. 6 and 7). Owing to the small number of included studies, a funnel plot did not allow assessment of the publication bias in terms of mild-term good neurological outcome.

Discussion

Our meta-analysis found that the administration of vasopressin during CPR, compared with epinephrine, did not significantly increase the rate of ROSC, mild-term survival and mild-term good neurological outcome in cardiac arrest. However, our subgroup analysis found that intravenous vasopressin as part of the VSE protocol during CPR for IHCA patients significantly increased the rate of ROSC, but not mild-term survival and mild-term good neurological outcome. In addition, subgroup analyses based on the initial rhythm, witnessed, and CPR by bystander did not reveal any significant differences in the outcomes of ROSC or mild-term survival.

The results of our meta-analyses are in concordance with the published meta-analysis(10), although we included the trials receiving VSE and did perform the subgroup analyses. Intravenous vasopressin may have no benefit in cardiac arrest patients. In a previous trial(5), Lindner et al. found that intravenous vasopressin during CPR significantly increased the benefit for OHCA patients with ventricular fibrillation. Moreover, one subgroup analysis of an RCT(8) showed that vasopressin was superior to epinephrine in OHCA patients with asystole, and that the use of vasopressin followed by epinephrine may be more effective than the use of epinephrine alone. However, we found no subgroup differences in patients with ventricular fibrillation, asystole, pulseless electrical activity, witnessed and CPR by a bystander (Table 3). We speculated on the reasons that vasopressin may have no benefit. First, 5,638 OHCA patients were included, which contributed to 84% of the study population. For OHCA patients, an early risk identification, high-quality CPR and emergency medical services (EMS) improved the outcomes among cardiac arrest

patients(23). As shown in Table 1, the small number of patients who received a bystander CPR included OHCA patients. All these factors led to the high mortality rate. High mortality may limit the certainty of the evidence for these comparisons. Second, our study included patients from different countries, and the results could have been affected by the ethnic differences, different resuscitation guidelines and EMS, leading to bias. In a planned subgroup analysis, the outcomes have no significant difference with respect to Europe, Asia and North America. However, the results of a previous meta-analysis(24) showed that the combination of vasopressin and adrenaline could improve the ROSC of OHCA in Asia, but patients from other regions did not achieve this result. The main reason for this inconsistency was that we did not include any RCT published in languages other than English. Finally, the effective dosage and course of vasopressin remain unclear. Vasopressin is a dose-response drug(9). In our analysis, the study protocols were not identical. Eight trials of OHCA included four trials of only one dose of vasopressin (40 IU), two trials had a maximum of two doses, one trial had a maximum of three doses, and one trial had a maximum of four doses. We could not obtain sufficient data to evaluate the effect of different doses. Inadequate dosing may have contributed to this negative result.

Using vasopressin is not entirely without benefit. The most significant finding was that vasopressin as a part of VSE did improve the rate of ROSC for IHCA patients but did not improve mild-term survival and mild-term good neurological outcome. The finding was inconsistent with the results of a previous meta-analysis(25) that suggested that VSE are associated with improved outcomes in cardiac arrest, including good neurologic outcome, survival to hospital discharge and ROSC. Three trials receiving VSE were included, and three trials used the same VSE protocol during CPR, as shown in the Table 1. Therefore, vasopressin may improve the rate of ROSC in IHCA patients. However, we cannot exclude the effects of corticosteroids. In addition, we speculated on the reasons for mild-term survival and mild-term good neurological outcome. First, the two trials by Mentzelopoulos(16, 20) that received VSE using glucocorticoids as an add-on treatment during the post-resuscitation period showed that VSE could improve mild-term survival and good neurological outcome. However, the VAM-IHCA trial(22) did not accept glucocorticoids during the post-resuscitation period and did not achieve better outcomes of mild-term survival and good neurological outcome. The use of glucocorticoids after ROSC, and not vasopressin or VSE, could directly improve the outcomes. In addition, in our analysis, the two trials reported survival at hospital discharge and good neurological outcome at hospital discharge as mild-term outcomes. However, the VAM-IHCA trial reported survival at 30 days and good neurological outcome at 30 days as mild-term outcomes. The two outcome measures may have an effect on the results of mild-term survival and good neurologic outcome.

In addition, although the objective was to demonstrate the therapeutic effect of vasopressin as an alternative treatment, we only found one trial(17) that used vasopressin without concomitant use of epinephrine. Once patients were randomized to the vasopressin group, they were never given epinephrine during CPR. This trial showed that vasopressin had no benefit. There was also no evidence of harmful effects from vasopressin administered during CPR(15, 26). Moreover, OHCA patients, constituting a significant proportion of the cases treated in the emergency department, were not included in the VSE

therapy studies. Therefore, better-designed trials on a large group of patients should be conducted in the future to address the therapeutic effect of vasopressin or VSE in cardiac arrest.

Our systematic review has several limitations. First, there are limited high-quality data to analyse the effect of vasopressin. Nine RCTs contained a high or unclear risk of bias in each domain. Second, data of the included patients were heterogeneous, based on baseline characteristics. The proportion of patients with ventricular fibrillation in each trial was different. Although we performed subgroup analysis of ventricular fibrillation, some trials did not provide data on outcomes of ventricular fibrillation. Third, despite finding vasopressin as part of VSE that may increase the ROSC, we cannot draw a firm conclusion that vasopressin has benefits in IHCA patients because we cannot exclude the effects of corticosteroids. Finally, whether the results of this meta-analysis can be generalized to all cardiac arrest patients remains uncertain. OHCA patients constituting a significant proportion of the study may influence the generalisability of our results. There are distinct differences in the treatment of patients who experience cardiac arrest in a hospital setting where disease processes, aetiologies and illness severity differ and medical response time is often shorter(23).

Conclusions

Intravenous vasopressin may not significantly improve the rate of return of spontaneous circulation, mild-term survival and good neurological outcome. However, in the subgroup analysis, we found that vasopressin, as part of the VSE protocol, is associated with the improvement of ROSC in IHCA patients. However, no benefit on mild-term survival or mild-term good neurological outcome has been demonstrated. Better-designed trials on a large group of patients should be conducted in the future to address the therapeutic effect of vasopressin or vasopressin-steroids-epinephrine in cardiac arrest.

Abbreviations

CPR: cardiopulmonary resuscitation; IHCA: in-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation; RR: relative risk; CI: confidence interval; VSE: vasopressin, steroids and epinephrine; AHA: the American Heart Association; ACLS: Advanced Cardiac Life Support; CPC: Cerebral Performance Category; EMS: emergency medical services.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WQY and XS wrote the draft. WQY and XS searched the database. WHD and WQZ assessed each study eligibility. WQY, WQZ, and WHD completed statistical analyses. ZC resolved discordant assessments and conflicting results. ZC conceived the idea and reviewed articles.

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Tables

Table 1 Results of the summary effect estimates for the outcome of return of spontaneous circulation

Analysis	Outcomes or variables	Number of included studies	RR (95%CI)	P	I^2, %	I^2, % (Subgroup difference)
The main analysis	ROSC	11	1.11 (0.99–1.26)	0.07	62%	-
The subgroup analysis						
Setting	OHCA	7	0.98(0.91-1.07)	0.68	0%	88.3%
	IHCA(VSE)	3	1.32(1.18-1.47)	<0.00001	0%	
	IHCA (vasopressin)	1	1.09(0.79-1.52)	0.60	-	
Study period	Before 2000	2	1.21(0.92,1.59)	0.17	4%	0%
	After 2000	9	1.10(0.96,1.25)	0.16	67%	
Study region	North America Europe	2	1.06(0.84,1.33)	0.63	0%	0%
	Europe	7	1.15(0.96,1.37)	0.13	77%	
	Asia	2	1.06(0.89,1.28)	0.51	0%	
Study quality	Low risk	3	1.16□0.93-1.43□	0.18	83%	74.7%
	Some concerns for risk	7	1.01□0.90-1.13□	0.89	3%	
	High risk	1	1.56□1.17-2.10□	0.03	-	
Study drug	Vasopressin only	5	1.03(0.90-1.18)	0.68	22%	87.6%
	Vasopressin and Epinephrine	4	0.97(0.87-1.08)	0.57	0%	
	VSE	3	1.32(1.18,1.47)	<0.00001	0%	

ROSC: return of spontaneous circulation; OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine; RR: relative risk.

Table 2 Results of subgroup subgroup analyses about return of spontaneous circulation and mild-term survival

Outcomes	Subgroup	Number of included studies	RR (95%CI)	P	I^2, %
ROSC	OHCA				
	VT/VF	6	1.02 [0.84, 1.25]	0.81	30%
	PEA	4	1.00 [0.82, 1.21]	0.99	0%
	Asystole	4	1.01 [0.90, 1.14]	0.81	0%
	With witnessed	4	1.04 [0.82, 1.33]	0.73	59%
	CPR by bystander	3	1.22 [0.89, 1.67]	0.21	38%
Mild-term survival	OHCA				
	VT/VF	5	0.87 [0.51, 1.48]	0.61	35%
	PEA	3	0.62 [0.16, 2.39]	0.48	46%
	Asystole	3	1.29 [0.44, 3.76]	0.64	57%
	With witnessed	4	0.90 [0.39, 2.07]	0.81	41%
	CPR by bystander	3	1.26 [0.64, 2.46]	0.51	0%

ROSC: return of spontaneous circulation; OHCA: out-of-hospital cardiac arrest; VF/VT: Ventricular Fibrillation /Tachycardia; PEA: pulseless electrical activity; CPR: cardiopulmonary resuscitation.

Figures

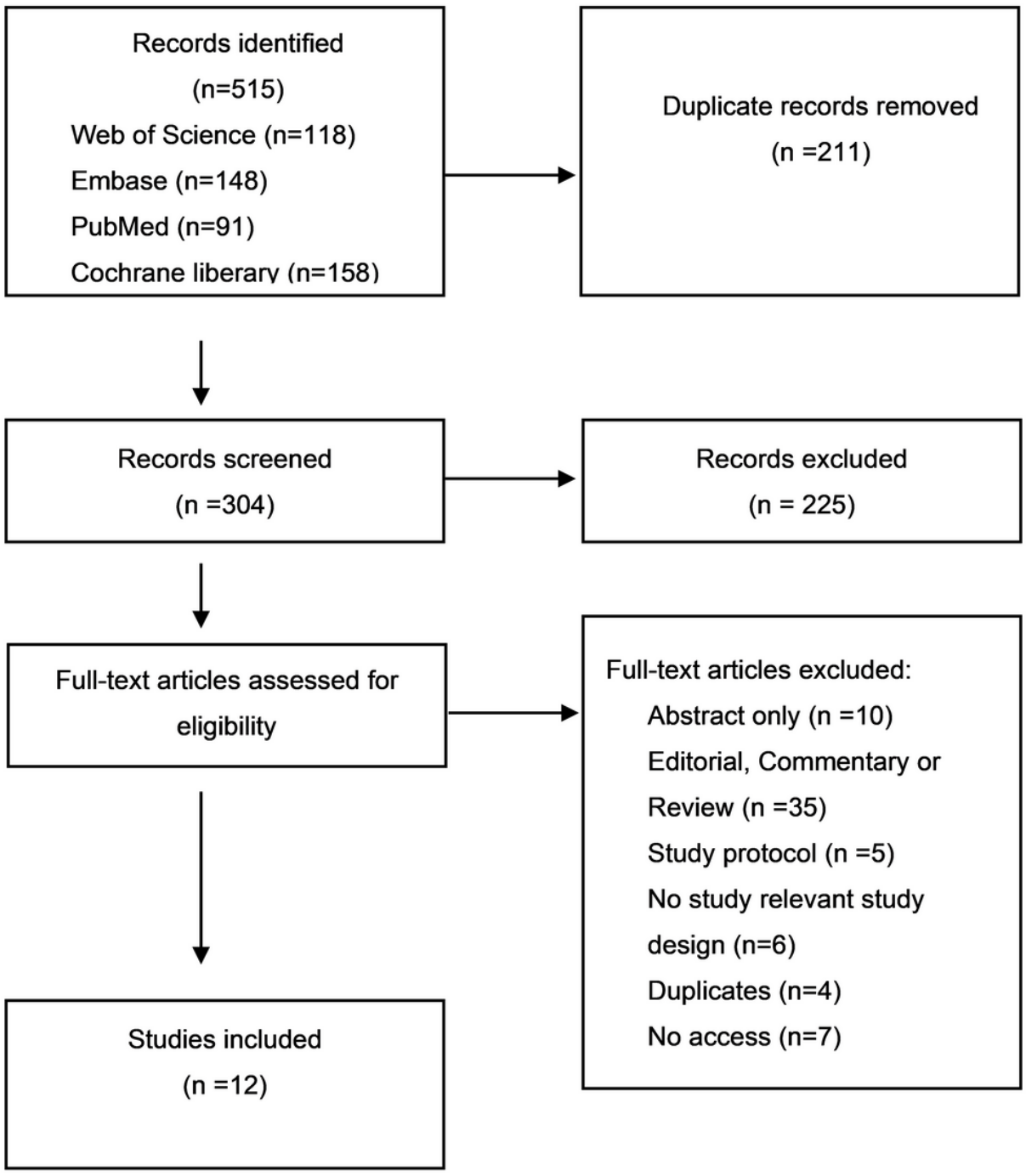

Figure 1

Literature search and study selection flow diagram

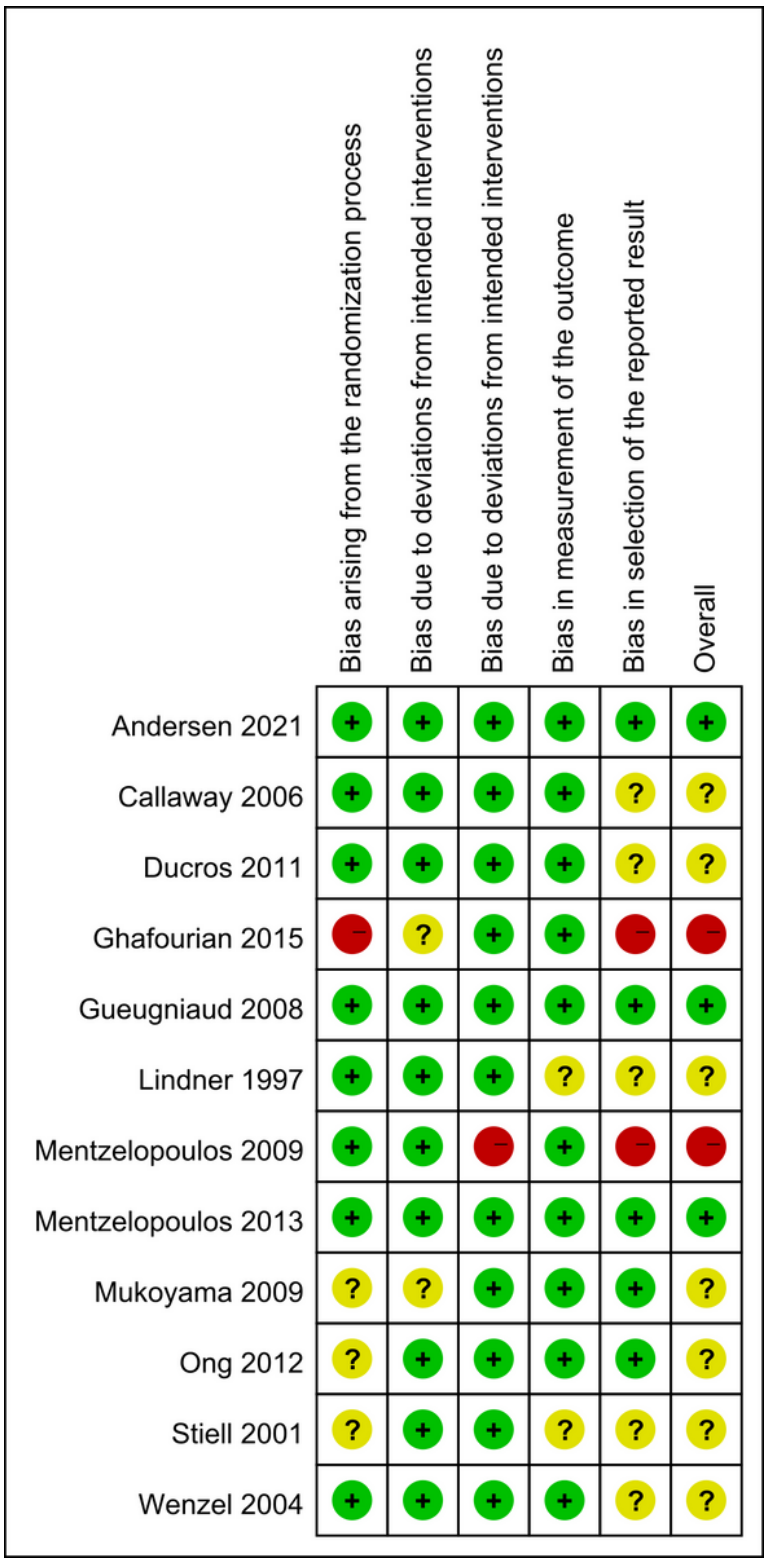

Figure 2

Risk of bias summary

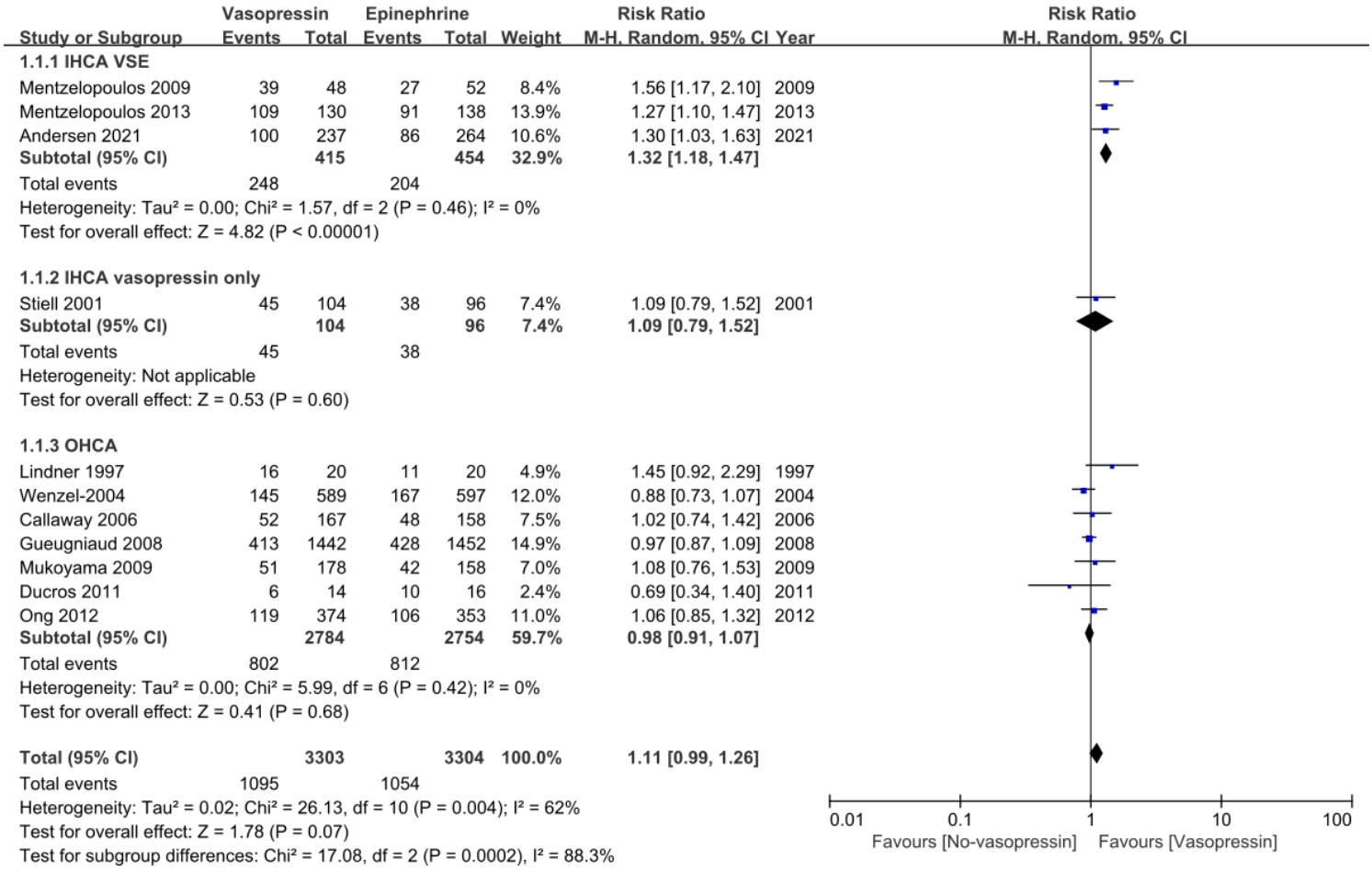

Figure 3

Forest plot of return of spontaneous circulation

Legend section: IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine; OHCA: out-of-hospital cardiac arrest.

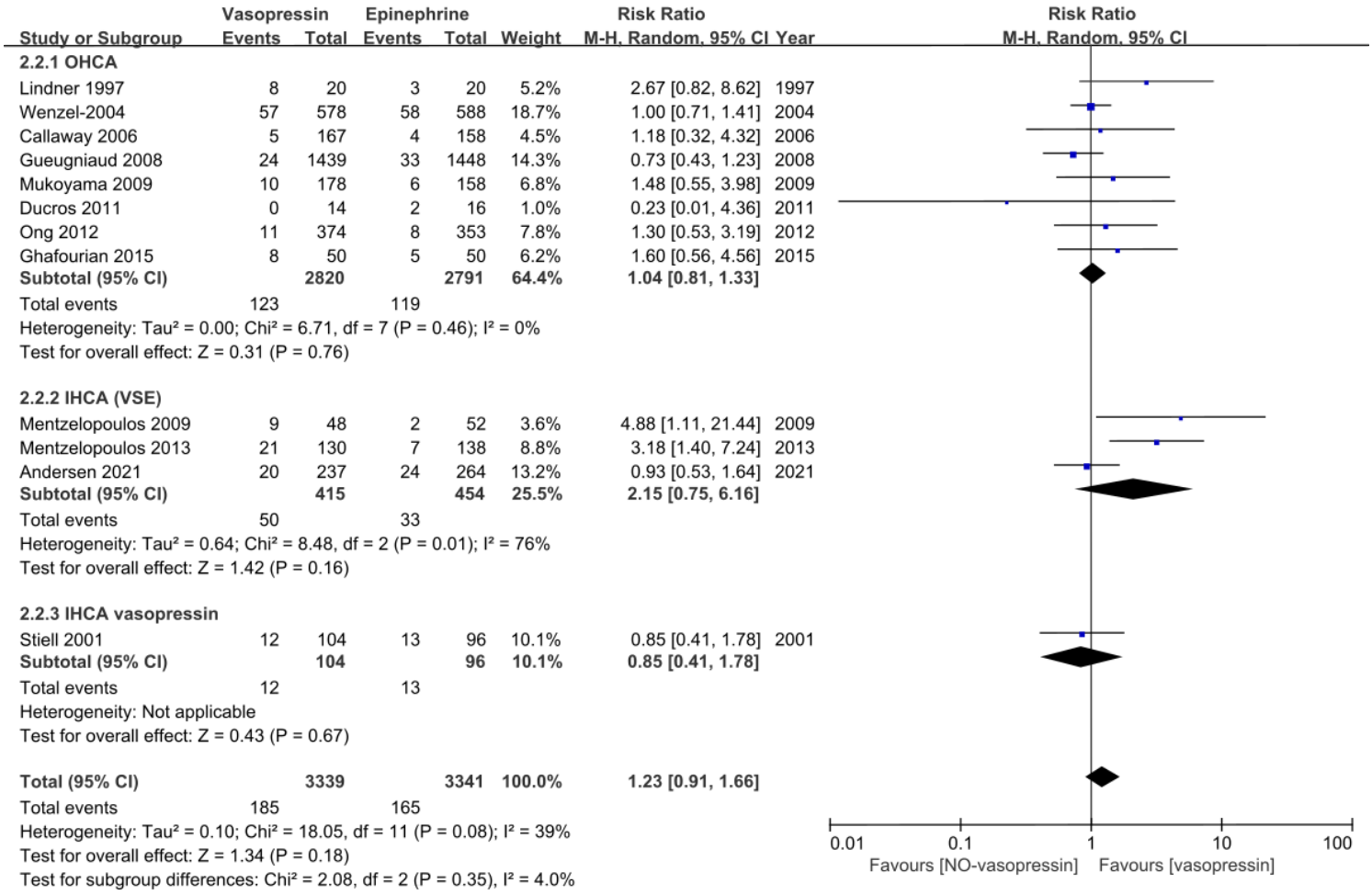

Figure 4

Forest plot of mild-term survival

Legend section: OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine.

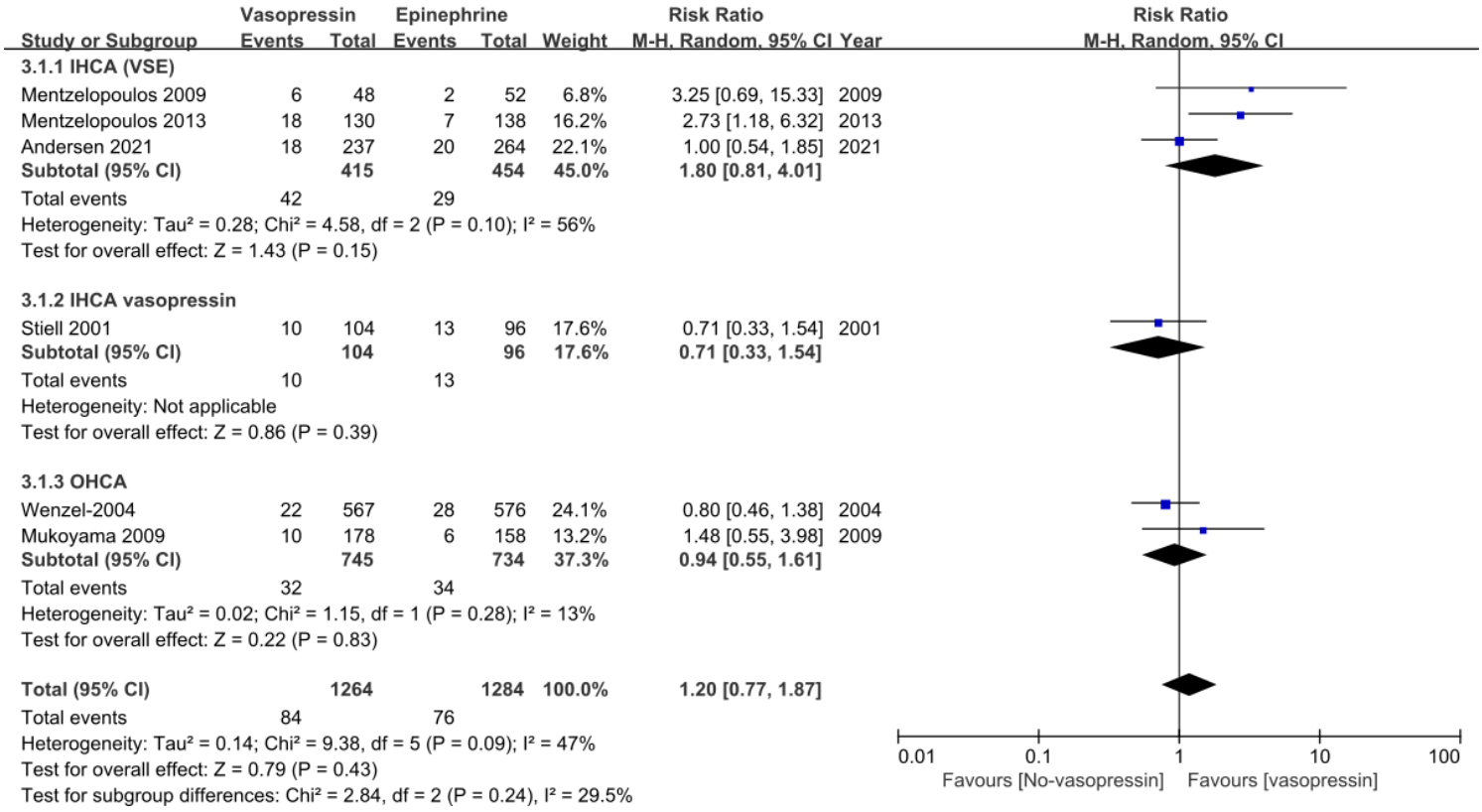

Figure 5

Forest plot of mild-term good neurological outcome

Legend section: IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine; OHCA: out-of-hospital cardiac arrest.

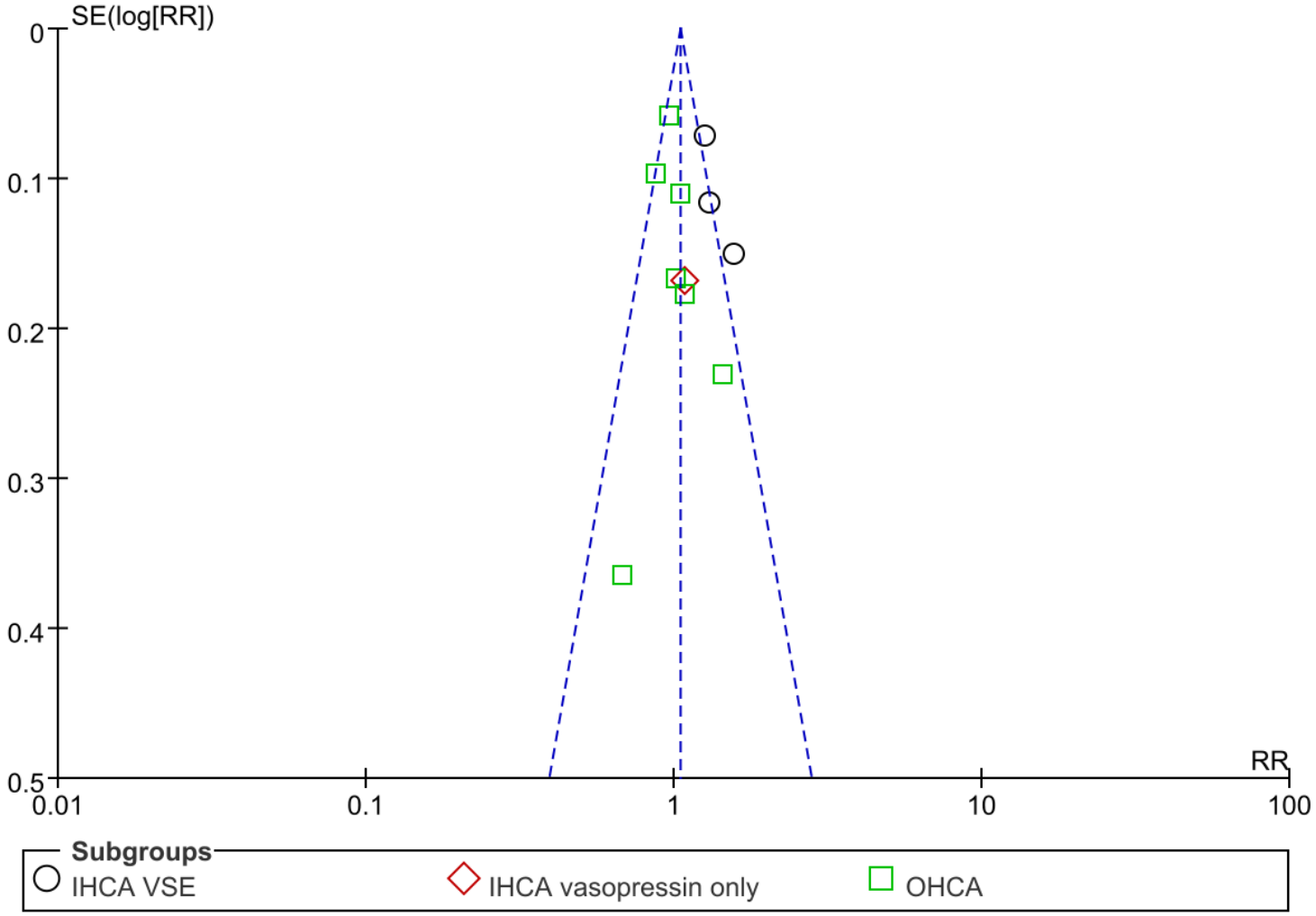

Figure 6

Funnel plot of return of spontaneous circulation

Legend section: IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine; OHCA: out-of-hospital cardiac arrest.

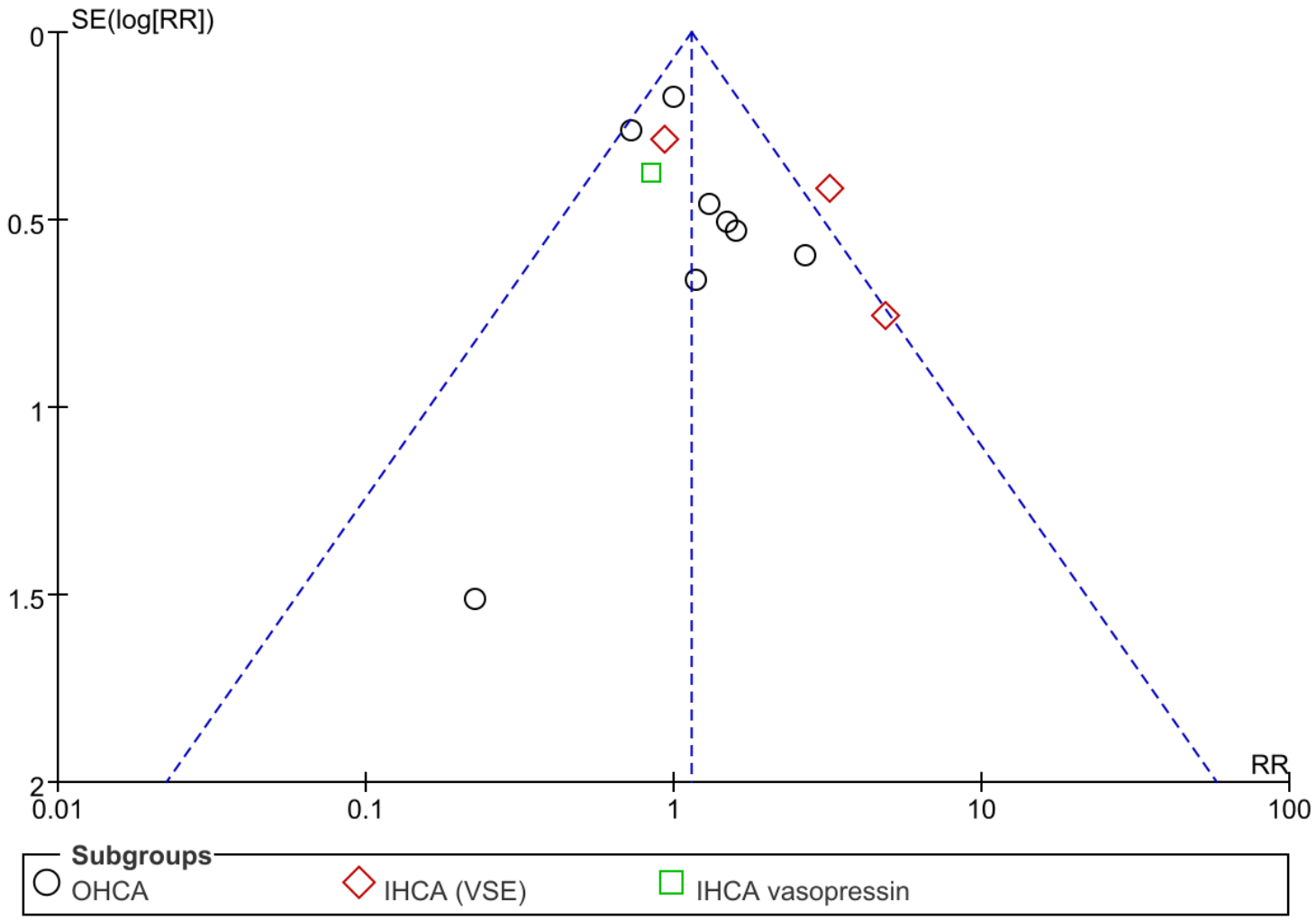

Figure 7

Funnel plot of mild-term survival

Legend section: OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; VSE: vasopressin, steroids and epinephrine.

Supplementary Files

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- additionalfile.docx