American Journal of Emergency Medicine 95 (2025) 107–114

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Norepinephrine versus epinephrine after cardiac arrest: A systematic review and meta-analysis

Caitlin A. Williams, MD MS [a,*], Ali Pourmand, MD MPH [a], Trager Hintze, PharmD [b], Jennifer A. Walker, MD [c,d], Madison Moran [e], Khai Dinh [e], Anna Shaw [e], Samantha Camp [f], Emily F. Gorman, MLIS [g], Quincy K. Tran, MD PhD [h,i,**]

[a] *Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States*
[b] *Department of Medical Education, Alice L. Walton School of Medicine, Bentonville, AR 72712, United States*
[c] *Department of Emergency Medicine, Baylor Scott and White All Saints Medical Center in Fort Worth, Fort Worth, TX 76104, United States*
[d] *Burnett School of Medicine at Texas Christian University, Fort Worth, TX 76104, United States*
[e] *Research Associate Program in Emergency Medicine & Critical Care, Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, United States*
[f] *School of Medicine, University of Maryland Baltimore, Baltimore, MD, United States*
[g] *Health Sciences and Human Services Library, University of Maryland, Baltimore, MD, United States*
[h] *Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, United States*
[i] *Program In Trauma, The R Adam Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD, United States*

ARTICLE INFO

Article history:
Received 17 March 2025
Received in revised form 16 May 2025
Accepted 21 May 2025

Keywords:
Norepinephrine
Epinephrine
Cardiac arrest
Return of spontaneous circulation
Hospital survival
Recurrent cardiac arrest
Unfavorable neurological outcome

ABSTRACT

Objectives: Patients who obtain return of spontaneous circulation (ROSC) after cardiac arrest often experience post-resuscitation hypotension, typically managed with epinephrine (EPI). However, recent research suggests that norepinephrine (NE) may improve patient outcomes. This systematic review and meta-analysis evaluates the effectiveness of EPI versus NE in managing post-resuscitative shock in patients who achieve ROSC.
Methods: A systematic literature search in PubMed, Medline, Scopus, EMBASE, and Cochrane CENTRAL was performed. Observational or randomized studies on adults comparing EPI to NE after cardiac arrest were included in analysis. Outcomes were analyzed via random-effects meta-analysis and included rate of re-arrest during hospital stay, survival to discharge, and functional neurological outcome at discharge.
Results: After screening 1217 studies, we analyzed 6 studies, which involved 3458 patients, with mean (+/− SD) age of 64 (+/− 3) years, and 2188 (63 %) were male. The NE group consisted of 1833 (53 %) patients and 287 (41 %) of the total 703 re-arrest. Patients receiving NE were associated with 63 % lower odds of having recurrent arrest (OR 0.47, 95 % CI 0.24–0.92, $P = 0.03$, $I^2 = 89$ %). There was no statistical difference for rates of hospital survival (OR 2.04, 95 % 0.93–4.47) or discharge with unfavorable neurological outcome (OR 1.72, 95 % CI 0.92–3.22).
Conclusions: Among a small number of studies, norepinephrine use in post-cardiac arrest patients was associated with lower odds of recurrent cardiac arrest. However, high study heterogeneity highlights the need for well-designed future research to validate these findings.

1. Introduction

Cardiac arrest is one of the leading causes of morbidity and mortality in the United States [1,2]. Patients who achieve return of spontaneous circulation (ROSC) after cardiac arrest frequently experience significant complications, including post-resuscitation hypotension, also known as post-resuscitative shock [3]. Post-resuscitative shock leads to decreased perfusion of major organs and can lead to multi-organ failure, including myocardial dysfunction, renal failure, and liver injury [4]. Research suggests that the incidence of post-resuscitative shock ranges between 50 and 70 %, with in-hospital mortality rates ranging from 20 to 25 % [4].

* Corresponding author at: 2120 L St NW, Suite 610, Washington, DC 20037, United States.
** Corresponding author at: 22 South Greene Street, Suite T3n45, Baltimore, MD 21201, United States.
E-mail addresses: cawilliams@gwu.edu (C.A. Williams), pourmand@gwu.edu (A. Pourmand), trager.hintze@alwmed.org (T. Hintze), jennifer.walker@bswhealth.org (J.A. Walker), mmoran14@terpmail.umd.edu (M. Moran), samantha.camp@som.umaryland.edu (S. Camp), efgorman@hshsl.umaryland.edu (E.F. Gorman), qtran@som.umaryland.edu (Q.K. Tran).

https://doi.org/10.1016/j.ajem.2025.05.038
0735-6757/

The management of post-resuscitative shock primarily involves the use of vasopressors and inotropes for hemodynamic support, although the optimal agent is often debated. Epinephrine (EPI), which acts on both alpha- and beta-adrenergic receptors, is widely used during advanced cardiac life support (ACLS) and is routinely the medication of choice for post-resuscitative shock, however, norepinephrine (NE) is another common medication used and may have some advantages [5].

Comparing the pharmacology of EPI and NE, there are some key differences to note, particularly in the setting of their varying activity levels on alpha- and beta-adrenergic receptors. In the setting of post-resuscitative shock, the primary action of EPI is alpha-1 agonism [6]. Since alpha-1 receptors are primarily found in smooth muscle cells of blood vessels, this activation leads to peripheral arterial and venous vasoconstriction ultimately increasing blood pressure and increasing perfusion to vital organs [6]. EPI also activates beta-1 and beta-2 receptors, which have an 80 % and 20 % distribution in cardiac tissue, respectively [6]. Compared to NE, EPI demonstrates significantly more beta-1 activity, effectively increasing inotropic and chronotropic activity in the heart. On the other hand, EPI also stimulates beta-2 receptors, which are predominant in the smooth muscle cells of the bronchi. When activated they relax these smooth muscles and lead to bronchodilation, which is why EPI is so useful in cases of anaphylactic shock. Beta-2 receptors are also located in the peripheral vasculature and have a vasodilatory effect when they are activated [6]. This is the opposite effect of the vasoconstriction that occurs when alpha-1 receptors are activated in the peripheral vasculature. At low doses, EPI may readily stimulate beta-2 receptors more than alpha-1 receptors, which could potentially induce hypotension [6].

NE is another commonly used vasopressor in the post-resuscitation phase of care. Like EPI, NE primarily acts on alpha-1 receptors. As it stimulates these receptors it has effectively the same action of vasoconstriction, with dose-dependent increases in vascular tone [6]. Differing from EPI, NE has significantly lower effects on beta-1 receptors, and effectively no effect on beta-2 receptors. This means that NE has less positive inotropic and chronotropic effects, which stands in contrast to EPI [6].

Recent research suggests that NE may be at least as effective as EPI in managing post-resuscitative shock, with some evidence suggesting potential advantages. Particularly, some studies have shown improvement in mortality [7-9], re-arrest rates [7,8,10], and neurological outcomes [8] in patients given primarily NE infusions compared to EPI after ROSC. However, recent research suggests that there is possibly no difference in outcomes between EPI and NE after ROSC [11,12]. The varying evidence highlights the need for a meta-analysis to determine whether one vasopressor provides better patient outcomes post-ROSC. This systematic review and meta-analysis aims to compare the efficacy of EPI and NE in treating post-resuscitative shock in patients who achieve ROSC, with a particular focus on recurrent cardiac arrest, hospital survival, and neurological outcomes.

2. Methods

2.1. Search strategy and selection criteria

This systematic review and meta-analysis is being reported in compliance with the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [13]. Once the PICO framework (population, intervention, comparison, outcome) was identified, the databases MEDLINE (Ovid interface), EMBASE (Elsevier interface), Scopus (Elsevier interface), and Cochrane Register of Controlled Trials (Wiley interface) were searched from their beginning to June 2024, using the search terms listed in Appendix 1. An updated search was run on January 21, 2025 in all databases.

The patient population was any adult patient having any medical cardiac arrest. The intervention was NE infusion after patients had ROSC. The control group included patients who received EPI infusion after ROSC. The outcome measure was the rate of recurrent arrest at any time point during hospitalization, as defined by the studies' authors. All experimental, quasi-experimental, and observational (prospective or retrospective) studies involving adult patients (18 years of age or older) that compared NE versus EPI were eligible. Studies that were not published in full text (abstracts, conference reports), or in English language were excluded. We also excluded case reports or case series, studies involving traumatic cardiac arrest, as these patients may undergo different treatment (i.e., thoracotomy) than patients suffering medical cardiac arrest.

Two investigators independently screened titles and abstracts for determination of full text inclusion. A third investigator served as an arbitrator when discrepancies occurred. A similar process was utilized for the full text screening step. We used Covidence (www.covidence.org, Melbourne, Australia) for management of the literature search results. We also reviewed the references of included studies for additional references, but we did not contact the authors of the included studies for additional data. This study was registered with the PROSPERO database (CRD42024522012), and there was no change from the submitted protocol.

2.2. Outcome measure

We considered the rate of recurrent arrest as the primary outcome. This outcome measure was reported in all of the included studies, and it is most relevant to the efficacy of NE and EPI infusion for patients who achieved ROSC, which is to prevent further shock. The first secondary outcome included hospital survival. Another secondary outcome was the rate of unfavorable neurological outcomes, as defined by the studies' authors. Although this is a patient-centered outcome, it was reported by only a few studies.

2.3. Quality assessment and heterogeneity

We assessed the quality of observational studies using the Newcastle-Ottawa Scale (NOS) and the Cochrane's Risk of Bias 2 (RoB 2) tool for randomized trials [14,15]. For each observational study, the NOS assesses three domains of quality: selection of cohort, comparability of groups, and quality of outcomes, and assigns a maximum score of 9. A score from 7 to 9 is high, 4–6 is medium, and a score ≤ 3 is low. The RoB2 tool assesses RCTs for potential bias in 4 domains: patient randomization, protocol deviations, measurement and reporting of outcomes, and treatment of missing data. The overall study is rated in concordance to the highest level of bias assigned to any domain.

Two investigators independently assessed each study's quality and risk of bias. They first attempted to solve any discrepancies by discussion, but a third investigator would adjudicate any unsolved discrepancies. We reported heterogeneity of the studies using both Cochran Q-statistic and the I^2 values. These two types of heterogeneity assess different aspects of heterogeneity, but they complement each other.

2.4. Data extraction

Two investigators independently extracted the same data into an Excel spreadsheet (Microsoft Corp, Redmond, Washington, USA), then the data was compared between the investigators. Disagreements were first solved by discussion between the investigators, or a third investigator if necessary. The consensus of the investigators was reported as the final results. We collected each study's demographic data (author, year of publication, countries of studies, study settings, study designs) and patients' clinical data (age, sex, initial rhythm, witnessed arrest, initial systolic blood pressure, rates of Targeted Temperature Management). Utilizing imputation of missing data, patients discharged to a facility with assistance were implied to have a poor neurological outcome in studies that did not explicitly disclose the neurological status at discharge.

2.5. Statistical analysis

We used descriptive analyses to report the data: mean (+/− Standard Deviation [SD]) or median (interquartile Range [IQR]) for continuous variables, and percentages for categorical variables. We performed random effects meta-analysis when any 3 studies reported the same outcome of interest. The results from the meta-analysis were expressed as Odd Ratios (OR) and 95 % Confidence Interval (95 % CI). Sensitivity analysis was performed with the one-study-removed random effects meta-analysis. Publication bias was performed with Egger's and Begg's tests. For the Egger's and Begg's test, p-value >0.05 indicated low likelihood of publication bias. Funnel plot analysis was only performed when investigating the rate of recurrent arrest during hospitalization, which was the primary outcome. For the secondary outcomes, the number of included studies was small and funnel plot analysis could not be performed.

We anticipated high heterogeneity from the included studies, so we performed moderator analyses, using categorical variables from the studies' demographic information. These moderator analyses were able to identify sources of heterogeneity and to compare effect sizes between different groups.

To further assess the association between clinical variables and the outcomes of interest, we performed exploratory univariable meta-regressions, using the continuous clinical variables as the independent variables, and the odd ratios of the outcomes of interest as the dependent variable. We expressed the results from the meta-regressions as the correlation coefficient (Corr. Coeff.) and its 95 % CI.

The statistical analyses, random-effects meta-analysis, sensitivity analysis, moderator analyses, and meta-regressions were performed with the software Comprehensive Meta-Analysis (CMA) version 4 (www.meta-analysis.com, Englewood, NJ). All statistical analysis with p-value <0.05 was considered significant.

3. Results

3.1. Study selection

The electronic search identified 1217 studies, after excluding duplicates. After reviewing 12 full-text articles, 6 studies [7-12] were included for data extraction and analysis (Fig. 1). Of the 6 studies, 1 study [11] was a randomized control trial, while the 5 other studies were retrospective observational [7-10,12] (Table 1).

3.2. Study quality

The quality and risk of bias in the studies are reported in Table 1. The 5 retrospective observational studies [7-10,12] were reported as having high quality, whereas the 1 randomized control trial by Pansiritanachot et al. [11] was reported as having some concerns for risk of bias.

3.3. Summary of studies

The included 6 studies involved a total 3458 patients, with mean (+/− SD) age of 64 (+/− 3) years, and 2188 (63 %) were male. There were 1833 (53 %) patients in the NE and 1625 (47 %) patients in the EPI group, respectively. Two studies were conducted outside of the United States; the study by Bougouin et al. [8] was conducted in France, while the study by Pansiritanachot et al. [11] was done in Thailand. Two studies by Wender et al. [10] and Smida et al. [12] involved only cardiac arrest in the pre-hospital settings. While most

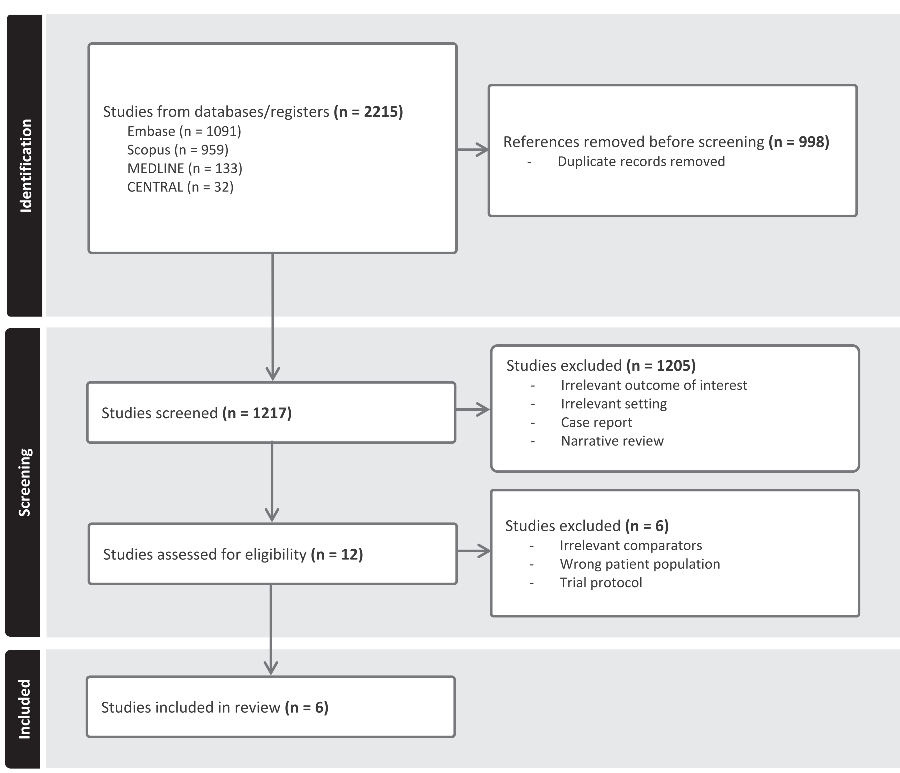


Fig. 1. PRISMA flow diagram.

Table 1
Study characteristics and study quality.

Author, year	Country of Study	Study Design	Multicenter	Clinical Setting	Type of Cardiac Arrest[a]	Timing of Recurrent Cardiac Arrest	Total Patients, N	Epinephrine Patients, N	Norepinephrine Patients, N	Study Quality[b]
Weiss, 2021	United States	Retrospective Observational	No	Hospital	OHCA & IHCA	During Hospital Stay	87	42	45	7
Bougouin, 2022	France	Retrospective Observational	Yes	Hospital	OHCA	During Hospital Stay	766	285	481	7
Normand, 2023	United States	Retrospective Observational	Yes	Hospital	OHCA	During Hospital Stay	221	70	151	7
Wender, 2023	United States	Retrospective Observational	No	Pre-Hospital	OHCA	Any Time Pre-Hospital	451	198	253	7
Pansiritanachot, 2024	Thailand	Randomized Control Trial	No	Hospital	OHCA & IHCA	Within 3 Hours of Initial Arrest	40	20	20	Some concerns
Smida, 2024	United States	Retrospective Observational	Yes	Pre-Hospital	OHCA	Any Time Pre-Hospital	1893	1010	883	8

[a] OHCA = outside hospital cardiac arrest, IHCA = in-hospital cardiac arrest.
[b] Newcastle-Ottawa Score (NOS) for retrospective observational studies and Risk of Bias (RoB2) for randomized control trials, as determined by study investigators.

studies involved only OHCA, two studies by Weiss et al. [9] and Pansiritanachot et al. [11] reported both OHCA and IHCA.

While the initial shockable rhythm was reported by all 6 studies, the initial unshockable rhythm was not reported by 2 studies [8,10]. Many important characteristics for outcomes of patients with cardiac arrest were missing. For example, only 3 studies reported witnessed arrest status [8,11,12]. Only two studies reported the duration of cardiopulmonary resuscitation (CPR) [7,9]. Two studies did not report the number of patients undergoing Targeted Temperature Management (TTM) [9,12].

3.4. Primary outcome: rate of recurrent arrest during hospitalization

All six studies reported the rate of recurrent arrest during hospitalization. Pansiritanachot et al. [11] reported recurrent arrest within 3 h, which was the shortest duration considered among the included studies, followed by Weiss et al. [9] at 6 h. The cumulative number of patients experiencing recurrent arrest was 703 (20 %). Overall, there were 287 (41 %) patients receiving NE compared with 416 (59 %) patients in the EPI group. Patients receiving NE were associated with statistically significant lower odds of having recurrent arrest (OR 0.47, 95 % CI 0.24–0.92, $P = 0.03$) (Fig. 2).

The Q-statistic was <0.001 and the I^2 value was 89 %, which indicated a high level of heterogeneity between the studies being included.

The sensitivity analysis with one-study-removed random effects meta-analysis a range of odds ratio of 0.38 to 0.59 (Fig. 3). Without one of the studies by Bougouin et al. [8], Normand et al. [7], or Wender et al. [10], the odd ratios were higher at 0.51–0.59 and the overall effect sizes were not statistically significant (Fig. 3).

3.4.1. Publication bias

The funnel plot (Fig. 4) demonstrated the same number of studies on both sides of the midline. Further analysis by Egger's test ($P = 0.54$), and Begg's test ($P = 0.71$) indicated low likelihood of publication bias in this meta-analysis.

3.4.2. Moderator analysis and meta-regression

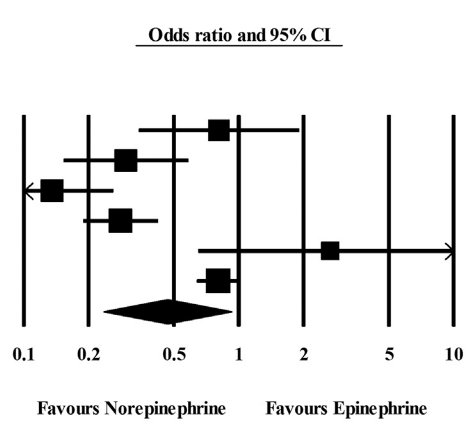
Moderator analyses using categorical variables from study characteristics showed that high heterogeneity existed in almost all subgroups, except for the studies with sample size >250 patients ($I^2 = 3$ %) (Table 2). Studies involving patients with OHCA only reported NE was associated with statistically lower odds of recurrent arrest (OR 0.32, 95 % CI 0.13–0.72, $P = 0.006$) compared with studies with mixture of OHCA/IHCA, in which there was no association between vasopressor choice and odds of re-arrest (OR 1.3, 95 % CI 0.4–3.9, $P = 0.67$) (Table 2).

The exploratory univariable meta-regressions demonstrated that a higher percentage of patients with non-shockable rhythm in the NE group was positively correlated with the odds of recurrent arrest (Correlation Coefficient [Corr. Coeff.] 5.2, 95 % CI 1.9 to 8.4, $P = 0.002$) (Table 3).

3.5. Secondary outcome 1: rate of survival to hospital discharge

Five studies—all except Pansiritanachot et al. [11]—reported the number of patients who survived to hospital discharge. These 5 studies involved a cumulative population of 3418 patients, 1813 (53 %) in the NE group and 1605 (47 %) in the EPI group. The overall rate of survival to discharge was 494 (14 %). There were 346 (19 %) patients in the NE group who survived, compared with 148 (9 %) in the EPI group. Patients

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Norepinephrine (Recurrent Arrest / Total)	Epinephrine (Recurrent Arrest / Total)	Relative weight
2021 Weiss	0.81	0.34	1.91	0.63	17 / 45	18 / 42	15.48
2022 Bougouin	0.30	0.15	0.58	0.00	14 / 481	26 / 285	17.14
2023 Normand	0.14	0.07	0.26	0.00	22 / 151	39 / 70	17.26
2023 Wender	0.28	0.19	0.42	0.00	64 / 253	108 / 198	19.16
2024 Pansiritanachot	2.67	0.65	10.97	0.17	8 / 20	4 / 20	10.91
2024 Smida	0.80	0.64	1.01	0.06	162 / 883	221 / 1010	20.04
Pooled	0.47	0.24	0.92	0.03			



Test of heterogeneity

Q-value	D(f)	P	I^2
48	5	0.001	89%

Fig. 2. Forest plot comparing the rate of re-arrest among patients with cardiac arrest and receiving norepinephrine (NE) versus epinephrine (EPI).

Study name	Statistics with study removed			
	Point	Lower limit	Upper limit	p-Value
2021 Weiss	0.42	0.19	0.92	0.03
2022 Bougouin	0.51	0.23	1.13	0.10
2023 Normand	0.59	0.31	1.12	0.11
2023 Wender	0.53	0.23	1.22	0.14
2024 Pansiritanachot	0.38	0.19	0.76	0.01
2024 Smida	0.40	0.20	0.81	0.01
Pooled	0.47	0.24	0.92	0.03

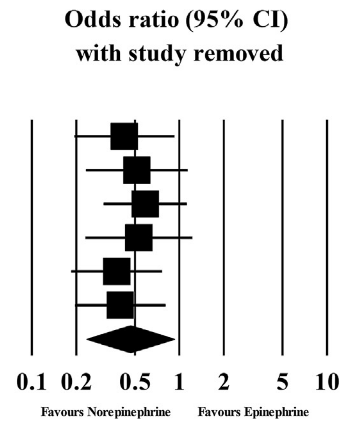


Fig. 3. Sensitivity analysis, using one-study-removed random effects meta-analysis, comparing the rate of re-arrest among patients with cardiac arrest and receiving norepinephrine (NE) versus epinephrine (EPI).

receiving NE were not associated with higher odds of survival, compared to patients receiving EPI (OR 2.04, 95 % CI 0.93–4.47, $P = 0.07$) (Fig. 5). There was a high level of heterogeneity among the five studies being included in this meta-analysis.

Funnel plot was not performed due to the small number of the included studies. However, results from the Egger's test ($P = 0.71$) and the Begg's test ($P = 1.00$) demonstrated low likelihood of publication bias for this outcome.

Moderator analysis revealed high heterogeneity among all subgroups, except among studies in the pre-hospital settings only ($I^2 = 0$ %) (Table 2). However, studies that involved cardiac arrest in hospital settings had significantly higher odds of survival to hospital discharge (OR 3.8, 95 % CI 2.2–6.8, $P = 0.001$) when compared to studies with pre-hospital settings only (OR 0.85, 95 % CI 0.61–1.2, $P = 0.32$) (Table 2).

Univariate meta-regression showed that a higher percentage of patients with shockable rhythm in the NE group was positively correlated with the odds of survival to hospital discharge (Corr. Coeff. 4.1 (95 % CI 1.2 to 7.0, $P = 0.005$) (Table 3).

3.6. Secondary outcome 2: rate of hospital discharge with unfavorable neurological outcome

Analysis was able to be completed on the rate of discharge with unfavorable neurological outcomes for four studies [7-10]. These four studies involved a total of 1525 patients, 930 (61 %) from the NE group and 595 (39 %) from the EPI group. The overall rate of discharge of patients who survived with unfavorable neurological outcome was 222 (15 %). Among these patients, 162 (73 %) patients were in the NE group, and 60 patients (27 %) in the EPI group.

Patients receiving NE were not associated with statistically significant higher odds of discharge with unfavorable neurological outcome (OR 1.72, 95 % 0.92–3.22, $P = 0.09$) (Fig. 6). The I^2 value was 54 %, which indicated high heterogeneity among the included studies.

Only Egger's and Begg's tests were performed for publication bias, as the funnel plot was not performed due to the very small number of studies. The results from the Egger's test ($P = 0.95$) and Begg's test ($P = 0.73$) indicated low likelihood of publication bias for this outcome.

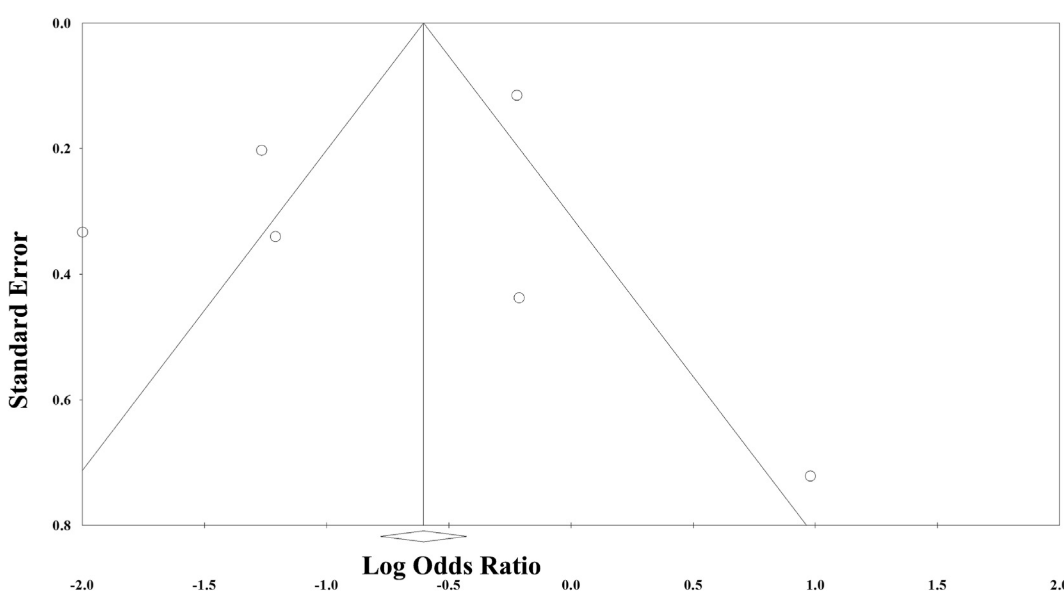


Fig. 4. Publication bias, using funnel plot, for the rate of recurrent arrest.

Table 2
Results from the moderator analyses using categorical variables from study characteristics.

Recurrent Cardiac Arrest										
		Meta-analysis				Heterogeneity				Between group comparison
Moderator Variables		Number of studies	Outcome	95 % CI	*P*	Q-value	D(f)	*P*	I^2	*P*
Country of study	Non-USA	2	0.81	0.10–6.90	0.85	8	1	0.006	86 %	0.54
	USA	4	0.4	0.17–0.91	0.03	40	3	0.001	92 %	
Study design	Prospective	1	2.7	0.65–10.9	0.17	NA	NA	NA	NA	0.02
	Retrospective	5	0.38	0.19–0.76	0.007	43	4	0.001	90 %	
Multicenter study	Yes	3	0.33	0.11–1.03	0.56	30	2	0.001	93 %	0.34
	No	3	0.73	0.22–2.4	0.6	12	2	0.002	84 %	
Clinical setting	Hospital	4	0.48	0.17–1.4	0.18	20	3	0.001	85 %	0.99
	Pre-hospital	2	0.48	0.1–1.3	0.16	20	1	0.001	95 %	
Type of cardiac arrest	OHCA & IHCA	2	1.3	0.4–3.9	0.67	2	1	0.16	49 %	0.05
	OHCA only	4	0.32	0.13–0.72	0.006	42	3	0.001	92 %	
Sample size	< 250 patients	2	1.28	0.41–3.9	0.67	2	1	0.16	49 %	0.05
	> 250 patients	4	0.32	0.14–0.72	0.006	42	3	0.01	3 %	
Survival to Hospital Discharge										
		Meta-analysis				Heterogeneity				Between group comparison
Moderator Variables		Number of studies	Outcome	95 % CI	*P*	Q-value	D(f)	*P*	I^2	*P*
Country of study	Non-USA	1	3.1	2.1–4.4	0.001	NA	NA	NA		0.31
	USA	4	1.83	0.72–4.6	0.21	25	3	0.001	88 %	
Study design	Prospective	0	NA	NA	NA	NA	NA	NA	NA	NA
	Retrospective	5	2	0.93–4.4	0.07	41	4	0.001	90 %	0.99
Multicenter study	Yes	3	2.6	0.9–7.8	0.09	31	2	0.001	94 %	0.45
	No	2	1.4	0.4–4.5	0.59	4	1	0.04	77 %	
Clinical setting	Hospital	3	3.8	2.2–6.8	0.001	4	2	0.14	49 %	0.001
	Pre-hospital	2	0.85	0.61–1.2	0.32	0.03	1	0.85	0 %	
Type of cardiac arrest	OHCA & IHCA	1	2.8	0.99–7.6	0.05	NA	NA	NA	NA	0.6
	OHCA only	4	1.9	0.79–4.7	0.15	40	3	0.001	92 %	
Sample size	< 250 patients	1	2.8	0.9–7.6	0.05	NA	NA	NA	NA	
	> 250 patients	4	1.9	0.79–4.7	0.15	40	3	0.001	92 %	0.61

We did not perform moderator analysis and meta-regression for this outcome because of the small number of included studies.

4. Discussion

The studies included in this meta-analysis were associated with a high level of heterogeneity. We hypothesize that the heterogeneity between the studies could possibly be from different practice environments and different resource levels, as only a small number of studies reported the rate of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or extracorporeal cardiopulmonary resuscitation (ECPR) and the rates of patients undergoing TTM. Regardless of practice variability and resources, we observed that studies with relatively larger sample size were associated with lower heterogeneity, as these studies reported significantly lower odds of recurrent arrest among patients receiving NE. With a low rate of recurrent arrest among non-survivors to hospital discharge [16], it is intuitive that studies with larger sample size would capture more reliably the statistical difference in the rate of recurrent arrest among their patients.

The finding that patients receiving NE after ROSC have lower odds for recurrent cardiac arrest compared to those receiving EPI has significant implications for both patient outcomes and resource utilization. Although this meta-analysis did not find differences in neurological recovery between groups, recurrent cardiac arrest is associated with increased morbidity [17], including organ dysfunction and prolonged recovery, factors not specifically analyzed in this study. Additionally, resuscitation in cardiac arrest is a highly resource-intensive process, requiring significant staffing, equipment, medications, and time [18]. By reducing the rates of recurrent cardiac arrest, NE use post-ROSC may help alleviate the burden of re-arrest on emergency and critical care teams. Higher rates of recurrent cardiac arrest in patients receiving EPI are in line with its increased cardiac inotropic and chronotropic activity relative to NE, and therefore arrhythmias [6]. While dysrhythmias were reported by some studies, the cardiac rhythms on re-arrest were not reported.

Our moderator analyses observed that patients who had received NE after an OHCA had significantly lower odds of recurrent arrest. This is particularly important because it may help direct emergency medical systems (EMS) protocols on post-resuscitation care regarding which vasopressor to use post-cardiac arrest. Future research should focus on optimizing vasopressor strategies within EMS guidelines to enhance patient management.

Our study found that patients in cardiac arrest with a non-shockable cardiac rhythm have higher odds of recurrent cardiac arrest. While there is limited data on rates of re-arrest after ROSC, prior studies have shown conflicting results in terms of whether a shockable [19] or

Table 3
Exploratory meta-regressions using continuous variables to measure association between clinical variables and the odds ratio of recurrent arrest and survival to hospital discharge.

	Variables	Number of studies	Corr. Coeff. (95 % CI)	P
Primary outcome: recurrent arrest during hospitalization	Norepinephrine Percentage of Shockable rhythm	6	−3.2 (−6.9 to 0.5)	0.09
	Norepinephrine Percentage of Non-shockable rhythm	4	5.2 (1.9 to 8.4)	0.002
	Norepinephrine Percentage of Bystander CPR	4	−3.8 (2.5 to −8.7)	0.13
	Norepinephrine percentage of Targeted Temperature Management	4	−2.8 (−5.8 to 0.2)	0.07
Secondary outcome: survival to hospital discharge	Norepinephrine Percentage of Shockable rhythm	5	4.1 (1.2 to 7.0)	0.005
	Norepinephrine Percentage of Non-shockable rhythm	NA	NA	NA

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Hospital survival / Total: Norepinephrine	Hospital survival / Total: Epinephrine	Relative weight
2021 Weiss	2.76	1.00	7.62	0.05	16 / 45	7 / 42	16.73
2022 Bougouin	3.06	2.14	4.38	0.00	187 / 481	49 / 285	22.16
2023 Normand	7.57	3.26	17.61	0.00	69 / 151	7 / 70	18.31
2023 Wender	0.81	0.47	1.39	0.44	32 / 253	30 / 198	20.96
2024 Smida	0.87	0.57	1.31	0.50	42 / 883	55 / 1010	21.84
Pooled	2.04	0.93	4.47	0.07			

Test of heterogeneity

Q-value	D(f)	P	I^2
41	4	0.001	90%

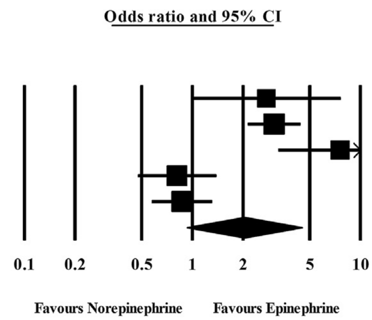


Fig. 5. Forest plot comparing the rate of hospital survival among patients with cardiac arrest and receiving norepinephrine (NE) versus epinephrine (EPI).

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
2021 Weiss	3.25	0.82	12.96	0.09	14.46
2022 Bougouin	1.88	1.28	2.77	0.00	40.83
2023 Normand	2.83	1.04	7.70	0.04	21.72
2023 Wender	0.61	0.24	1.59	0.31	22.99
Pooled	1.72	0.92	3.22	0.09	

Test of heterogeneity

Q-value	D(f)	P	I^2
6	3	0.09	54%

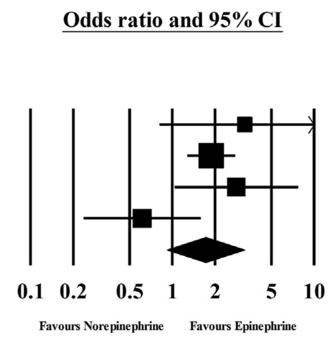


Fig. 6. Forest plot comparing the rate of hospital discharge with unfavorable neurological outcome among patients with cardiac arrest and receiving norepinephrine (NE) versus epinephrine (EPI).

non-shockable [20,21] rhythm is associated with higher rates of recurrent cardiac arrest. However, our finding that re-arrest occurs more commonly in non-shockable rhythms is in line with overall lower rates of ROSC and poor prognosis in cardiac arrest with non-shockable rhythms [22].

Overall, as previously mentioned, patients receiving NE did not have a statistically significant difference of surviving to hospital discharge or having a good neurological outcome compared to EPI. While NE may be beneficial to prevent re-arrest, it may not ultimately impact these final patient-centered outcomes, compared to EPI.

4.1. Limitations and future directions

Our study had several shortcomings. All but one of the included studies were observational, so they were at high risk for selection and reporting bias. Furthermore, most studies were performed in the United States, therefore the results might not be applicable to international clinical practice. Additionally, the sample sizes of each study varied significantly, with two studies having less than 100 patients. Additional studies should focus on larger sample sizes with varied patient populations for more generalizability.

Although a favorable neurological outcome is a patient-centered and preferred outcome [23] in studies with cardiac arrest, most of the included studies did not report this. Therefore, by utilizing imputation of missing data, patients discharged to a facility with assistance were implied to have a poor neurological outcome in studies who did not explicitly disclose the neurological status at discharge [7,9]. As a result, we reported unfavorable neurological outcomes among patients who survived to discharge, while acknowledging that favorable neurologic outcomes are often easier to contextualize. Additional studies should focus on favorable neurological outcomes in cardiac arrest for more meaningful analysis.

Many studies included in this meta-analysis did not include certain demographic information or patients' clinical data to perform more thorough subgroup analyses or meta-regressions. Specifically, most studies, due to their observational nature, did not report certain key factors for outcomes among patients with cardiac arrest: bystander CPR, CPR duration, medical history, important laboratory markers with prognostic values (e.g. serum lactate, pH), or dosing of EPI and NE (e.g. initial, median, or highest doses). We could not use those variables in our meta regression to further validate the association of NE and the outcomes. Future studies should collect these important variables to see what role they play in post-resuscitative shock.

5. Conclusions

Post-ROSC hypotension is a major cause of morbidity and mortality, highlighting the need for vasopressors and inotropes in patients with post-resuscitative shock. In our meta-analysis, we found no association between the use of NE post-ROSC and odds of survival to hospital discharge or functional neurological outcome when compared to EPI. However, the use of NE was associated with lower odds of recurrent cardiac arrest when compared to EPI, suggesting a potential benefit of preventing further hemodynamic decline. Future research should include randomized clinical trials that evaluate additional patient factors, resuscitation variables, and long-term prognostic data to determine which vasopressor is best for patient outcomes post-ROSC.

CRediT authorship contribution statement

Caitlin A. Williams: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Investigation. **Ali Pourmand:** Writing – review & editing, Writing – original draft, Conceptualization. **Trager Hintze:** Writing – review & editing, Writing

– original draft, Validation, Investigation. **Jennifer A. Walker:** Writing – review & editing, Writing – original draft, Investigation. **Madison Moran:** Visualization, Validation, Investigation, Data curation. **Khai Dinh:** Validation, Investigation, Data curation. **Anna Shaw:** Validation, Investigation, Data curation. **Samantha Camp:** Validation, Investigation, Data curation. **Emily F. Gorman:** Methodology, Investigation, Conceptualization. **Quincy K. Tran:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Presentation

Data from this manuscript was presented in part at the Society of Critical Care Medicine's Annual Congress in Orlando, Florida in February 2025.

This presentation was the recipient of the 2025 Society of Critical Care Medicine's Bronze Snapshot Award for abstracts among those with highest scores.

Funding

The authors did not receive any external or internal funding for the work of this manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A

Table A1
Study quality.

	Newcastle Ottawa Scale (NOS)					
Author, year	Total Score	Selection	Comparability	Outcome		
Weiss, 2021	7	4	1	2		
Bougouin, 2022	7	4	1	2		
Normand, 2023	7	4	1	2		
Wender, 2023	7	4	1	2		
Smida, 2024	8	4	1	3		
Risk of Bias 2 (RoB2)						
Author, year	Overall Risk	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5
Pansiritanachot, 2024	Some Concerns	Low	Some Concerns	Low	Low	Low

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