

Supplementary material

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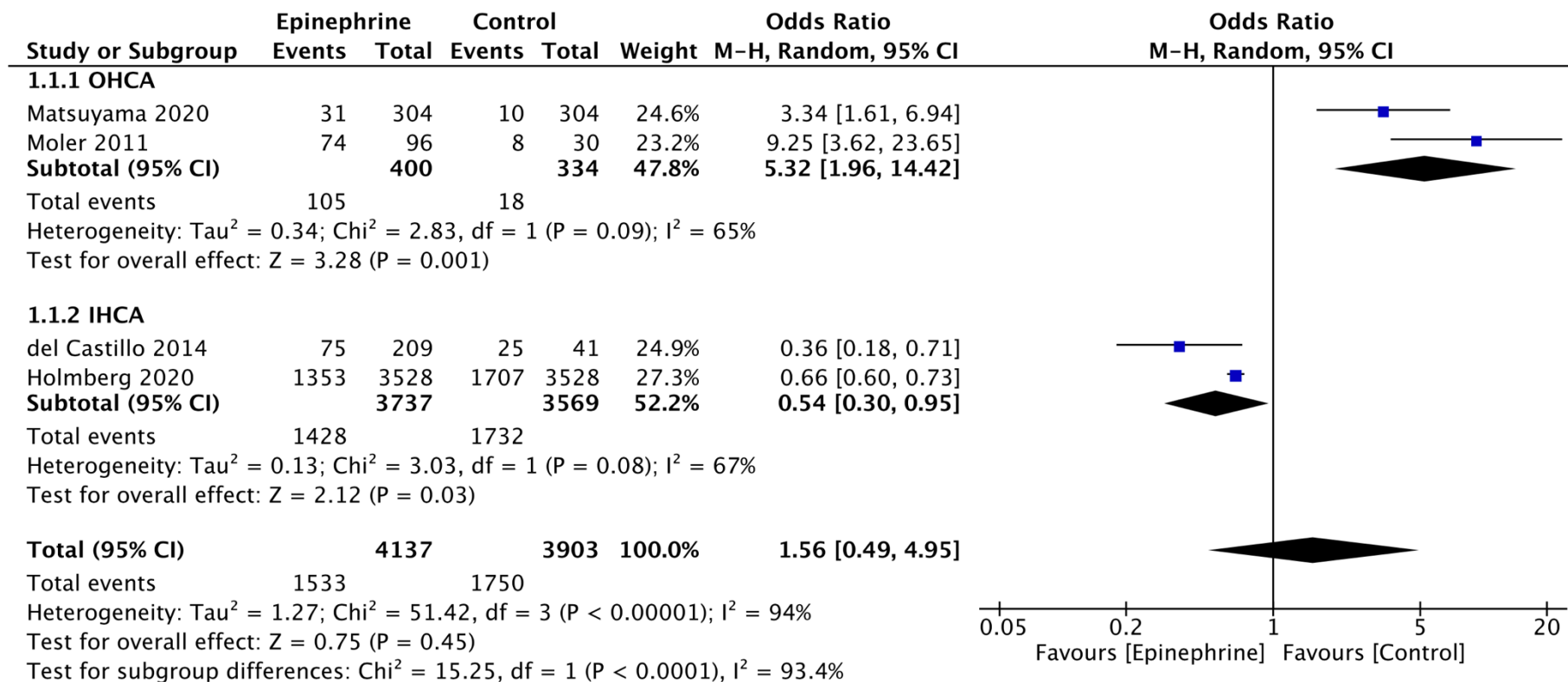
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Supplementary Figure S1. Forest plot of survival to hospital discharge rate while using epinephrine in out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for 95% CI. The diamonds represent pooled results

Supplementary Table S1. Characteristics of the included studies

Study	Country	Study design	Cardiac arrest setting	Number of patients		Gender, male		Survival to hospital discharge/1-month	
				Epinephrine	Control	Epinephrine	Control	Unmatched RR (95% CI)	Matched RR (95% CI)
Del Castillo et al. 2014	Spain/Italy Portugal/ Argentina	Prospective multicenter study	IHCA	209	41	NS	NS	0.36 (0.18, 0.71)	–
Holmberg et al. 2020	USA	Retrospective study	IHCA	3528	3528	1944	1916	0.40 (–0.47, 0.51)	0.79 (0.74, 0.85)
Matsuyama et al. 2020	Japan	Nationwide population-based observational study	OHCA	306	3655	232	2304	1.14 (0.80, 1.62)	1.13 (0.67, 1.93)
Meert et al. 2018	USA	Secondary analysis of RCT data	IHCA	313	15	NS	NS	–	–
Moler et al. 2011	USA	Retrospective cohort	OHCA	108	30	NS	NS	2.89 (1.58, 5.28)	–

Legend: IHCA = in-hospital cardiac arrest; NS = not specified; OHCA = out-of-hospital cardiac arrest; RCT = randomized clinical trial.

Supplementary Table S2. Inclusion and exclusion criteria

Study	Inclusion criteria	Exclusion criteria	Primary outcomes	Secondary outcomes	Findings
Del Castillo et al. 2014	Children aged from 1 month to 18 years with in-PICU cardiac arrest	NS	Survival to hospital discharge	Neurological outcome at hospital discharge	Survival with good neurological outcome of cardiac arrest in PICU is improving. The most important prognostic indicator is the duration of resuscitation
Holmberg et al. 2020	Pediatric patients (≤ 18 years of age) with an in-hospital non-pulseless cardiac arrest	Patients with a non-index event, patients receiving < 2 min of chest compressions, events in the delivery room, and hospital visitors	Survival to hospital discharge	Sustained return of adequate circulation (ROSC), survival to 24 h, favorable neurological outcome at hospital discharge, and progression to pulseless cardiac arrest at any time during the event	In children receiving CPR for bradycardia with poor perfusion, epinephrine was associated with worse outcomes, although the study does not eliminate the potential for confounding
Matsuyama et al. 2020	Pediatric patients with OHCA (age 8–17 years) resuscitated by bystanders	(1) OHCA without ELST involvement; (2) EMS-witnessed cardiac arrest; (3) OHCA with	1-month survival	1-month survival with favorable neurological outcome, defined as the	Pre-hospital epinephrine administration was associated with ROSC, whereas there were no

	and/or EMS personnel and subsequently transported to medical institutions	unknown first documented rhythm; (4) OHCA with unknown or inappropriate time-dependent variables (e.g., time from initiation of EMS CPR to epinephrine administration, time from initiation of EMS CPR to first shock delivery, time from initiation of EMS CPR to pre-hospital ROSC, time from emergency call to initiation of EMS CPR, and time from initiation of EMS CPR to hospital arrival); (5) OHCA with an interval between emergency call and initiation of EMS CPR \geq 30 min		Glasgow-Pittsburgh CPC scale of 1 or 2, and pre-hospital ROSC	significant differences in 1-month survival or favorable neurological outcome between those with and without epinephrine
Meert et al. 2018	Patient > 48 h and < 18 years of age who had a	Inability to be randomized within 6 h of return of circulation,	12-month survival	12-month survival with VABS-II decreased by \leq 15	Cardiac arrest and resuscitation factors are associated with long-term

	cardiac arrest that began in a hospital, received chest compressions for ≥ 2 min, and required mechanical ventilation after return of circulation	Glasgow Coma Scale motor score of 5 or 6, and a decision to withhold aggressive treatment		points from baseline, and 12-month survival with VABS-II ≥ 70	survival and neurobehavioral function among children who are comatose after in-hospital arrest
Moler et al. 2011	Patients between 24 h and 18 years of age (inclusive) who experienced an OHCA, defined as receiving chest compression for ≥ 1 min, and had a ROSC for ≥ 20 min	Patients who received < 1 min of chest compressions, whether or not epinephrine or defibrillation was administered	Survival to hospital discharge	NS	Multiple factors were identified to be associated with survival after pediatric OHCA with ROSC

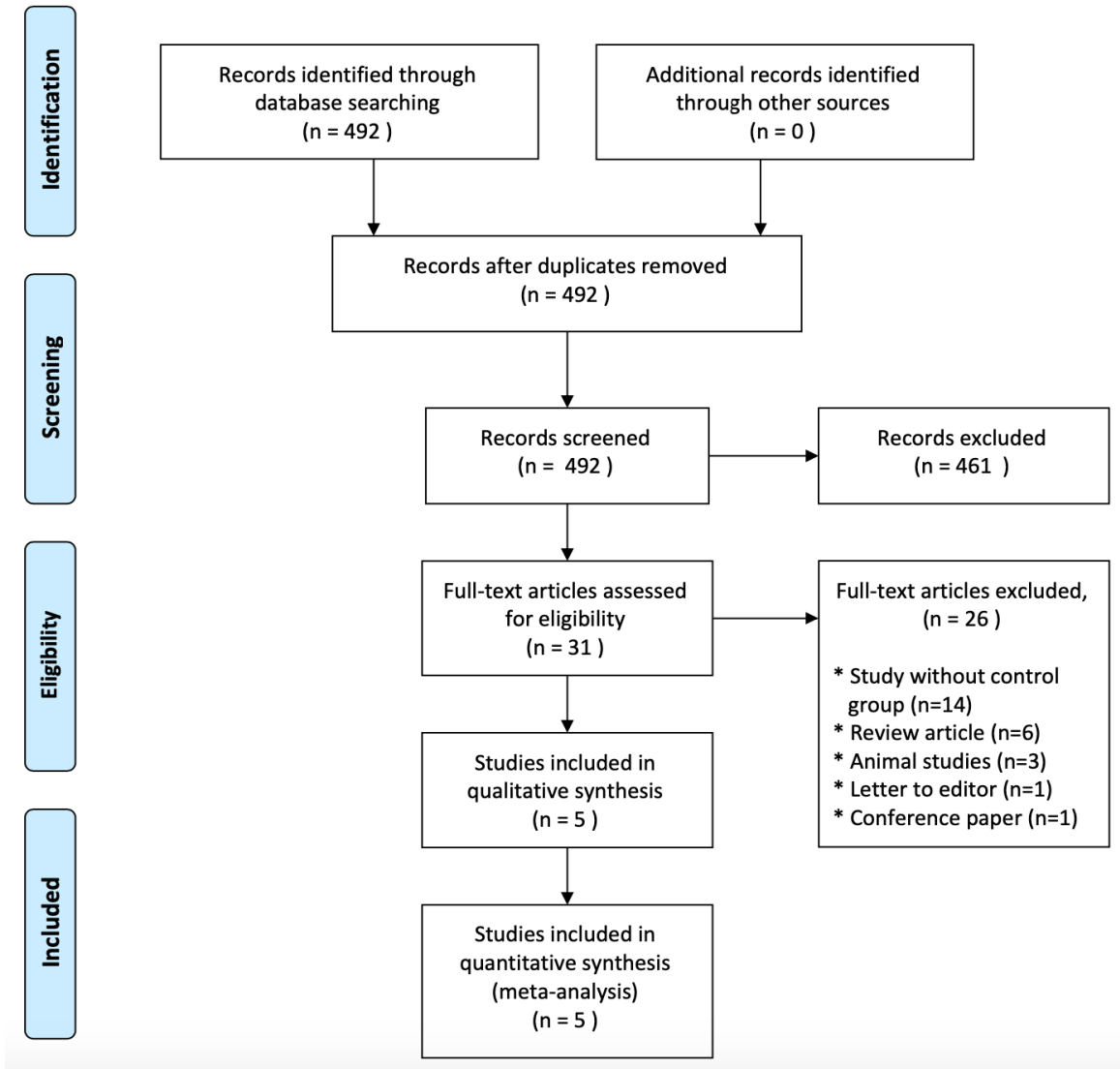
Legend: CPC = cerebral performance category; CPR = cardiopulmonary resuscitation; ELST = emergency life-saving technician; EMS = emergency medical service; NS = not specified; OHCA = out-of-hospital cardiac arrest; PICU = pediatric intensive care unit; ROSC = return of spontaneous circulation; VABS-II = Vineland Adaptive Behavior Scales, second edition.

Supplementary Table S3. Additional outcomes

Parameter	Cardiac arrest	Number of studies	Number of events		OR (95% CI)	P value	I ² statistic
			Epinephrine	Control			
Return of spontaneous circulation	OHCA	1	31/304	23/304	1.39 (0.79, 2.44)	0.26	NA
	IHCA	1	2357/3031	2609/3147	0.72 (0.64, 0.82)	< 0.001	NA
	Total	2	2388/3335	2632/3451	0.94 (0.50, 1.77)	0.85	80%
Survival to 24 h	IHCA	1	2083/3528	2441/3528	0.64 (0.58, 0.71)	< 0.001	NA
Survival to hospital discharge	OHCA	2	1428/3737	1732/3569	0.54 (0.30, 0.95)	0.03	67%
	IHCA	2	105/400	18/334	5.32 (1.96, 14.42)	0.001	65%
	Total	4	1533/4137	1750/3903	0.04 (-0.12, 0.21)	0.61	97%
Favorable neurological outcome at discharge*	OHCA	1	11/304	8/304	1.39 (0.55, 3.50)	0.49	NA
	IHCA	1	642/2974	822/2880	1.39 (0.55, 3.50)	< 0.001	NA
	Total	2	653/3278	830/3184	0.84 (0.45, 1.55)	0.57	54%
Progression to cardiac arrest	IHCA	1	1067/3528	914/3528	1.24 (1.12, 1.38)	< 0.001	NA
Survival to 12 months	OHCA	1	144/312	11/15	0.31 (0.10, 1.00)	0.05	NA
Survival to 12 months with VABS-II ≥ 70	OHCA	1	88/245	8/12	0.28 (0.08, 0.96)	0.04	NA
VABS-II decreased by ≤ 15 points	OHCA	1	84/303	9/14	0.21 (0.07, 0.650)	0.007	NA

Legend: IHCA = in-hospital cardiac arrest; NA = not applicable; OHCA = out-of-hospital cardiac arrest; VABS-II = Vineland Adaptive Behavior Scales, second edition.

* Defined as a Pediatric Cerebral Performance Category (PCPC) of 1 (normal or no cerebral disability) or 2 (mild cerebral disability) in accordance with the Pediatric Utstein criteria.



Supplementary Figure S2. Randomization flow chart