Does extracorporeal cardiopulmonary resuscitation improve survival with favorable neurological outcome in out-of-hospital cardiac arrest? A systematic review and meta-analysis

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ABSTRACT

Purpose: Extracorporeal cardiopulmonary resuscitation (*E*-CPR) may improve survival with favorable neurological outcome in patients with refractory out-of-hospital cardiac arrest (OHCA). Unfortunately, recent results from randomized controlled trials were inconclusive. We performed a meta-analysis to investigate the impact of *E*-CPR on neurological outcome compared to conventional cardiopulmonary resuscitation (C-CPR).
Methods: A systematic research for articles assessing outcomes of adult patients with OHCA either treated with *E*-CPR or C-CPR up to April 27, 2023 was performed. Primary outcome was survival with favorable neurological outcome at discharge or 30 days. Overall survival was also assessed.
Results: Eighteen studies were included. *E*-CPR was associated with better survival with favorable neurological status at discharge or 30 days (14% vs 7%, OR 2.35, 95% CI 1.61–3.43, $I^2 = 80\%$, $p < 0.001$, NNT = 17) than C-CPR. Results were consistent if the analysis was restricted to RCTs. Overall survival to discharge or 30 days was also positively affected by treatment with *E*-CPR (OR = 1.71, 95% CI = 1.18–2.46, $I^2 = 81\%$, $p = 0.004$, NNT = 11).
Conclusions: In this meta-analysis, E-CPR had a positive effect on survival with favorable neurological outcome and, to a smaller extent, on overall mortality in patients with refractory OHCA.

1. Introduction

Mortality after out-of-hospital cardiac arrest (OHCA) remains high and the neurological outcome poor, with more recent studies reporting a survival to hospital discharge with Cerebral Performance Category (CPC) of 1 or 2 around 8% [1]. Prompt initiation of high-quality cardiopulmonary resuscitation (CPR) is key to improve OHCA survival. In this setting, extracorporeal CPR (*E*-CPR), by providing adequate perfusion to vital organs until the return of spontaneous circulation (ROSC), may improve survival and preserve neurological functions, especially in patients without immediate ROSC (i.e refractory OHCA). One phase 2b and two phase 3 randomized clinical trials (RCTs) have recently investigated the benefit of *E*-CPR compared to conventional CPR (C-CPR) with conflicting results and, in two cases, premature termination [2-4]. This is in contrast with the large part of former observational studies, which have largely supported the potential of *E*-CPR for the management of refractory OHCA, confirming the limitations of non-randomized studies [5-9]. Some metanalyses exploring the benefit of *E*-CPR across all the available RCTs have been published lately [10-14]. However, they are hindered by small sample size, focus on long-term outcome alone or

Abbreviations: C-CPR, conventional CPR; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; *E*-CPR, extracorporeal CPR; NNT, number needed to treat; OHCA, out-of-hospital cardiac arrest; RCTs, randomized clinical trials; ROSC, return of spontaneous circulation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

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inclusion of both in and out of hospital cardiac arrest. Thus, we performed an updated systematic review and meta-analysis of all studies, observational and RCTs, comparing the effect of *E*-CPR vs C-CPR on survival with favorable neurological outcome in refractory OHCA.

2. Methods

This systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the protocol was registered in PROSPERO (CRD 42023412490). The review question was formulated following the PICO (population, intervention, comparison, outcome) framework: among adult people (age $\geq$ 18 years) with OHCA (P), does *E*-CPR (I), compared to C-CPR (C), improve survival with good neurological outcome at discharge or 30 days (O)?

2.1. Search strategy

We systematically searched Medline and the Cochrane Central Register of Controlled Trials (CENTRAL) up to April 27, 2023. Additional studies were identified by review of the reference lists of relevant articles. Detailed information on search strategy are reported in Supplementary material.

2.2. Data collection

Data from the included studies were extracted into a standardized Excel spreadsheet (Microsoft Corp). If propensity score matching (PSM) was made, then matched data were extracted.

The following variables were extracted from the studies: general study information (first author, publication year, journal of publication, country, study design, study period), demographics (number of patients enrolled in each arm of treatment, age, sex), resuscitation parameters (cardiac arrest secondary to acute coronary syndrome, bystander CPR, CPR duration, initial shockable rhythm, rate of ROSC), outcomes (survival and favorable neurological outcome).

The primary outcome was survival with favorable neurological outcome at discharge or 30 days, whichever outcome measure was available. No studies reported both the outcomes. Secondary outcomes were overall survival to hospital discharge or at 30 days and survival with favorable neurological outcome at 180 days. Survival with favorable neurological outcome at discharge and at 30 days were also assessed separately. Favorable neurological status was defined across all studies as score 1 or 2 of the Glasgow-Pittsburgh CPC. Two studies used modified Rankin Scale (mRS) score of 0 to 3 to express good functional status.

We used the recommended version 2 of the Cochrane risk-of-bias (RoB2) tool for RCTs and the Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I) for observational studies to assess the risk of bias within studies. The certainty of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Funnel plot was performed to evaluate publication bias.

2.3. Statistical analysis

Odds ratios (ORs) with 95% confidence interval (CI) were calculated for dichotomous outcomes. The outcomes of interest were pooled with the DerSimonian-Laird random-effects model. Number needed to treat (NNT) was calculated as the inverse of the absolute risk difference and the Wald method was used to calculated the relative 95% CI. Heterogeneity was reported by Cochrane's Q statistic and I^2 statistic. Meta-regression and subgroup analyses were performed to further assess heterogeneity, searching for possible interaction between the main outcome and potential confounders, such as study design (randomized vs observational studies), area of the studies (European and USA vs Asian countries) and rhythm at presentation (shockable vs non-shockable). To assess consistency of results, 10% fixed I2 and "leave-one-out" random-effects metanalyses were run. A *p*-value <0.05 was considered statistically significant. All the statistical analyses were performed by Stata 17.0 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Study characteristics

Among 780 articles initially screened from the databases research, 18 studies (3 RCTs [2-4] and 15 observational studies [5-9,15-24], of which 6 with a PSM design [15-20,22]) were finally included in the meta-analysis. Detailed flow diagram of literature search and studies selection is presented in Fig. 1.

Overall 21,877 patients were included in the meta-analysis, of which 3129 in the *E*-CPR group. The first study was published in 2013 and the last in 2023. Eleven studies were held in Asia [5-9,15-20], three in U.S. [2,21,24] and four in Europe [3,4,22,23]. Table 1 shows the main characteristics of the included studies. Quality assessment of the studies is reported in **Supplementary Table 1**. Funnel plot for the primary outcome is shown in **Supplementary Fig. 1,** suggesting a bias of publication.

In Table 2 we summarized the main demographic details and resuscitation parameters of the patients included in the 18 studies according to the arm of treatment. Among patients treated with *E*-CPR, 83% were men, 57% received a bystander CPR and 61% presented with shockable rhythm.

3.2. Primary outcome

The primary outcome was reported in 14 studies (7 reported discharge assessment and 8 reported 30-days assessment). Survival with favorable neurological outcome at discharge or 30 days was higher in patients treated with *E*-CPR compared to C-CPR (14% vs 7%, OR = 2.35, 95% CI = 1.61–3.43, I2 = 80%, $p < 0.001$; number needed to treat – NNT = 17, 95% CI = 14–21) (Fig. 2).

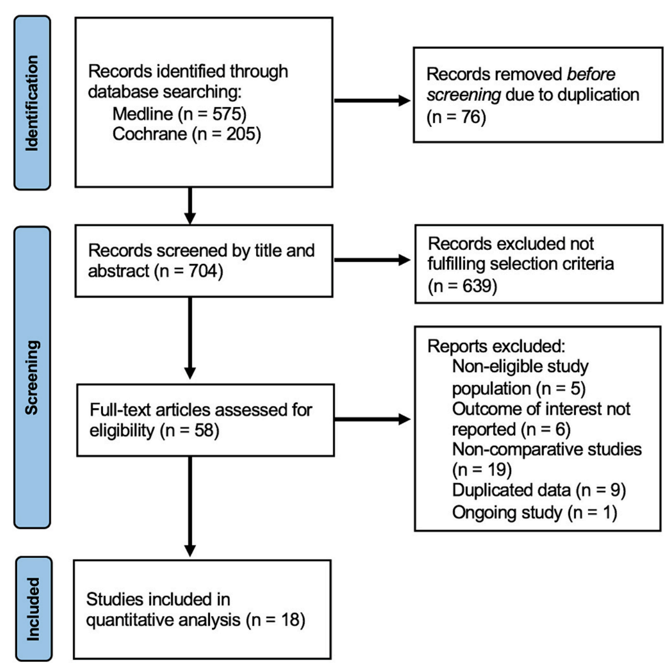

Fig. 1. Flow diagram of literature search and studies selection.
Number of records identified through database searching, screened for eligibility and finally included in the meta-analysis are reported at each stage of the study selection process. Reasons for studies exclusion are also stated.

Table 1
Characteristics of studies comparing E-CPR vs C-CPR for OHCA, ordered by first author's name.

First author	Publication year	Journal	Country	Enrollment period	Study type	Population (E-CPR)*	Population (C-CPR)*	Outcomes
Bartos	2020	Circulation	USA	2011–2018	Retrospective	160	654	Survival with favorable neurologic status (CPC $\leq$ 2 or mRS $\leq$ 3) at hospital discharge.
Belohavek	2022	JAMA	Czech Republic	2013–2020	Randomized clinical trial	124	132	180-day survival with favorable neurologic status (CPC $\leq$ 2). 30-day survival with cardiac recovery (no need for pharmacological or mechanical cardiac support for 24 h); neurologic recovery (CPC $\leq$ 2) at any point within the first 30 days after cardiac arrest; 180-day survival.
Bougouin	2019	EHJ	France	2011–2018	Retrospective (PSM)	525 (429)	12,666 (429)	Survival to hospital discharge. Favorable neurological outcome (CPC $\leq$ 2) at hospital discharge.
Choi	2015	Resuscitation	Korea	2009–2013	Retrospective (PSM)	320 (320)	36,277 (320)	Neurologically favorable survival (CPC $\leq$ 2) at hospital discharge. Survival to hospital discharge
Choi	2016	Clin Exp Emerg Med	Korea	2011–2015	Retrospective	10	50	Good neurologic state (CPC $\leq$ 2) at 1 month after cardiac arrest. Survival at 1 month after cardiac arrest.
Choi	2023	Critical Care	Korea	2013–2020	Retrospective (PSM)	484 (458)	117,907 (1832)	Survival with good neurological recovery (CPC 1–2) at discharge. Survival to discharge.
Jeong	2022	Shock	Korea	2015–2020	Retrospective (PSM)	272 (271)	11,734 (271)	30 day-survival with good neurologic outcome (CPC $\leq$ 2)
Kim	2014	Critical Care	Korea	2006–2013	Retrospective (PSM)	55 (52)	444 (52)	Good neurological outcome (CPC $\leq$ 2) at 3 months post cardiac arrest. 24-h survival rate; survival to discharge; survival rate at 3 months post cardiac arrest.
Kitada	2020	J Intensive Care	Japan	2014–2017	Retrospective	307	2278	Favorable neurological outcome (CPC $\leq$ 2) at 1 month.
Maekava	2013	Critical Care Medicine	Japan	2000–2004	Prospective observational, post hoc analysis (PSM)	53 (24)	109 (24)	Favorable neurologic status (CPC $\leq$ 2) at 3 months after cardiac arrest. Survival at hospital discharge.
Matsuoka	2019	Resuscitation	Japan	2010–2017	Register-based prospective cohort study	188	330	1-month favorable neurological outcome (CPC $\leq$ 2) after cardiac arrest. 1-month survival.
Nakashima	2019	Circ J	Japan	2008–2011	Prospective observational	250	157	Favorable neurological outcome (CPC $\leq$ 2) at 6 months.
Sakamoto	2014	Resuscitation	Japan	2008–2011	Prospective observational	260	194	Favorable neurologic status (CPC $\leq$ 2) at 1 month and 6 months after cardiac arrest
Schober	2017	Emerg Med J	Austria	2002–2012	Retrospective	7	232	180-days favorable neurological outcome (CPC $\leq$ 2).
Suverein	2023	NEJM	Netherlands	2017–2021	Randomized clinical trial	70	64	30-day survival with a favorable neurologic outcome (CPC $\leq$ 2). 30-day and 6-month survival
Yannopoulos	2017	JACC	USA	2015–2016	Prospective	62	170	Survival to hospital discharge with favorable neurological status (CPC $\leq$ 2). 3-month survival with favorable neurological status (CPC $\leq$ 2).
Yannopoulos	2020	Lancet	USA	2019–2020	Randomized clinical trial	15	15	Survival to hospital discharge. Survival at 3 and 6 months. Functionally favorable status (modified Rankin score $\leq$ 3 and CPC $\leq$ 2) at hospital discharge and at 3 and 6 months after hospital discharge
Yoshida	2020	J Emerg Med	Japan	2012–2013	Retrospective	38	493	Survival at 1 and 3 months. Favorable neurological outcome (CPC $\leq$ 2) at 1 and 3 months.

Abbreviations: C-CPR = conventional cardiopulmonary resuscitation, CPC = Cerebral Performance Category, *E*-CPR = extracorporeal cardiopulmonary resuscitation, mRS = modified Rankin Scale, PSM = propensity score matching.
* matched population reported in brackets.

Interestingly, subgroup analysis by study design did not show significant differences between RCTs and observational studies ($p = 0.348$); the OR for the primary outcome when only RCTs were considered was 1.83 (95% CI 1.13–2.96). Overall heterogeneity was high ($I^2 = 80\%$), but was mainly driven by observational studies ($I^2 = 84\%$ vs $I^2 = 0\%$ among RCTs). Meta-regression was concordant, indicating that study design did not account for heterogeneity ($p = 0.637$) (**Supplementary Table 2**). Similarly, subgroup analyses according to the rhythm at presentation ($p = 0.410$) and the study area ($p = 0.153$) did not explain the heterogeneity among studies investigating the primary outcome (**Supplementary Fig. 2).** These data were confirmed by meta-regressions ($p = 0.373$ and $p = 0.219$ for rhythm at presentation and the study area, respectively) (**Supplementary Table 2**). Sensitivity meta-analysis exploring the impact of 10% fixed I^2 on the results was consistent with

Table 2
Demographic details and resuscitation parameters for all the included studies.

	Population, n (%)		Age (years)[a]		Sex (male), n (%)		ACS, n (%)	
	E-CPR	*C-CPR*	*E-CPR*	*C-CPR*	*E-CPR*	*C-CPR*	*E-CPR*	*C-CPR*
Bartos 2020	160	654	57 ± 1	59 ± 0,4	126 (79)	528 (81)	NR	NR
Belohavek 2022	124	132	59 (48–66)	57 (47–65)	102 (82)	110 (83)	64 (52)	63 (48)
Bougouin 2019	525	12,666	50 ± 13	66 ± 16	442 (84)	8480 (67)	196 (37)	1082 [9]
Choi 2015[b]	320	320	56 (45–68)	58 (47–68)	258 (81)	259 (81)	NR	NR
Choi 2016	10	50	58 ± 6	59 ± 12	7 (70)	38 (76)	5 (56)[c]	2 (13)[c]
Choi 2023[b]	458	1832	56 ± 14	56 ± 16	374 (82)	1474 (80)	NR	NR
Jeong 2022[b]	271	271	58 (49–67)	57 (47–71)	211 (78)	206 (76)	NR	NR
Kim 2014[b]	52	52	54 (41–69)	54 (42–68)	40 (77)	38 (73)	44 (85)	46 (89)
Kitada 2020	296[d]	1362[d]	61 (48–70)	77 (66–85)	257 (84)	1457 (64)	NR	NR
Maekava 2013[b]	24	24	57 (48–63)	57 (50–68)	19 (79)	19 (79)	5 (21)[c]	6 (25)[c]
Matsuoka 2019	188	330	66 (57–75)	69 (59–78)	147 (78)	261 (79)	NR	NR
Nakashima 2019	250	157	59 (48–64)	60 (51–68)	227 (91)	139 (89)	163 (65)	82 (52)
Sakamoto 2014	260	194	56	58	235 (90)	172 (89)	165 (64)	115 (59)
Schober 2017	7	232	46 (31–59)	60 (50–70)	5 (71)	178 (74)	2 (28)[c]	11 (5)[c]
Suverein 2023	70	64	54 ± 12	57 ± 10	63 (90)	57 (89)	51 (73)	52 (81)
Yannopoulos 2017	62	170	58 ± 10	56 ± 7	44 (71)	124 (73)	46 (84)[c]	NR
Yannopoulos 2020	15	15	59 ± 10	58 ± 10	14 (93)	11 (73)	NR	NR
Yoshida 2020	38	493	61 ± 16	72 ± 16	27 (71)	307 (62)	8 (21)	21 (4)

	Bystander CPR, n (%)		CPR duration (min)[a]		Shockable rhythm, n (%)		ROSC, n (%)	
	E-CPR	*C-CPR*	*E-CPR*	*C-CPR*	*E-CPR*	*C-CPR*	*E-CPR*	*C-CPR*
Bartos 2020	105 (66)	376 (57)	60 ± 1	35 ± 1	160 (100)	654 (100)	NR	NR
Belohavek 2022	123 (99)	129 (98)	58 (43–70)	46 (33–68)	72 (58)	84 (64)	34 (27)	58 (44)
Bougouin 2019	424 (81)	5952 (49)	NR	NR	358 (69)	2996 (25)	134 (26)	4789 (38)
Choi 2015[b]	95 (30)	102 (32)	35 (19–55)	28 (15–37)	93 (29)	88 (28)	NR	NR
Choi 2016	8 (80)	41 (82)	NR	NR	3 (30)	13 (26)	9 (90)	15 (30)
Choi 2023[b]	248 (54)	1025 (56)	NR	NR	271 (59)	1052 (57)	NR	NR
Jeong 2022[b]	148 (55)	144 (53)	NR	NR	162 (60)	157 (58)	260 (96)	257 (95)
Kim 2014[b]	22 (42)	22 (42)	63 (49–88)	61 (40–84)	31 (60)	29 (56)	16 (31)	17 (33)
Kitada 2020	156 (51)	991 (44)	NR	NR	216 (70)	463 (20)	307 (100)	2278 (100)
Maekava 2013[b]	13 (54)	14 (58)	49 (43–66)	52 (43–65)	13 (54)	14 (58)	NR	NR
Matsuoka 2019	91 (48)	147 (45)	NR	NR	188 (100)	330 (100)	NR	NR
Nakashima 2019	112 (46)	64 (43)	NR	NR	127 (51)	56 (36)	189 (76)	48 (30)
Sakamoto 2014	127 (49)	90 (46)	NR	NR	70 (100)	281 (100)	NR	NR
Schober 2017	2 (28)	71 (31)	97 (79–147)	77 (58–95)	4 (57)	134 (58)	4 (57)	89 (38)
Suverein 2023	69 (99)	61 (95)	NR	NR	69 (99)	63 (98)	18 (26)	20 (31)
Yannopoulos 2017	52 (84)	127 (75)	NR	NR	62 (100)	170 (100)	47 (76)	63 (37)
Yannopoulos 2020	13 (87)	12 (80)	59 ± 28	83 ± 9	15 (100)	15 (100)	12 (80)	2 (13)
Yoshida 2020	NR	NR	NR	NR	0 (0)	0 (0)	NR	NR

Abbreviations: ACS = acute coronary syndrome, CPR = cardiopulmonary resuscitation, C-CPR = conventional cardiopulmonary resuscitation, E-CPR = extracorporeal cardiopulmonary resuscitation, n = number, NR = not reported, ROSC = return of spontaneous circulation.
[a] Data are reported as mean ± standard deviation or median (interquartile range) according to available data.
[b] Studies with propensity matched analysis; the data herein shown refers to the matched cohorts.
[c] When rate of ACS was not available, we reported rate of percutaneous coronary intervention performed as a surrogate.
[d] number of patients per group included in the outcome analysis for reporting an interval from witnessed OHCA to start of reperfusion (start of extracorporeal membrane oxygenation for ECPR or return of spontaneous circulation for CCPR) > 30 min.

the primary meta-analysis (OR 1.77, 95% CI 1.50–2.09, $p < 0.001$) (**Supplementary Table 3**). Leave-one-out analysis is reported in **Supplementary Fig. 3**.

3.3. *Secondary outcome*

When survival with favorable neurological outcome was assessed separately at discharge (7 available studies) and at 30-days (8 available studies) results were consistent with the primary outcome analysis (OR for *E*-CPR vs C-CPR at discharge 1.77, 95% CI = 1.15–2.73, $I^2 = 73\%$, $p = 0.009$; OR at 30 days 3.04, 95% CI = 1.59–5.80, $I^2 = 83\%$, $p < 0.001$) (Fig. 3). Survival with favorable neurological outcome was also better at 180 days in patients treated with *E*-CPR compared with C-CPR (6 studies included, OR = 2.72, 95% CI = 1.47–5.04, $I^2 = 47\%$, $p = 0.002$; NNT 12, 95% CI = 9–19) (Fig. 3).

Finally, overall survival to discharge or at 30 days was higher among *E*-CPR compared to C-CPR treated patients (OR = 1.71, 95% CI = 1.18–2.46, $I^2 = 81\%$, p 0.004; NNT 11, 95% CI = 9–13), effect mainly driven by observational studies and by the better 30-day survival (Fig. 4). In Table 3 we summarized all the outcomes' measures.

4. Discussion

The main findings of this meta-analysis are that: 1) *E*-CPR for the treatment of refractory OHCA demonstrated to improve survival with favorable neurological outcome at discharge/30 days compared with C-CPR with a NNT of 17; 2) the superiority of *E*-CPR on C-CPR persisted at 180 days outcome analysis; 3) *E*-CPR also showed to significantly improve survival at discharge/30 days, regardless of the neurological status, but with a lesser extent compared with the primary endpoint analysis and not significantly in the RCTs subgroup analysis.

4.1. *Heterogeneity of definitions and results across literature*

The in-hospital mortality of patients with OHCA remains unacceptably high. In this meta-analysis overall survival to discharge was 9.5%, which is in line with rates reported in literature [1]. The possibility to deliver *E*-CPR as a rescue treatment for patients with refractory OHCA created the premise for a potentially life-saving strategy. However, *E*-CPR is highly demanding in terms of economic, human and logistical resources. Moreover, long-term management of patients surviving to

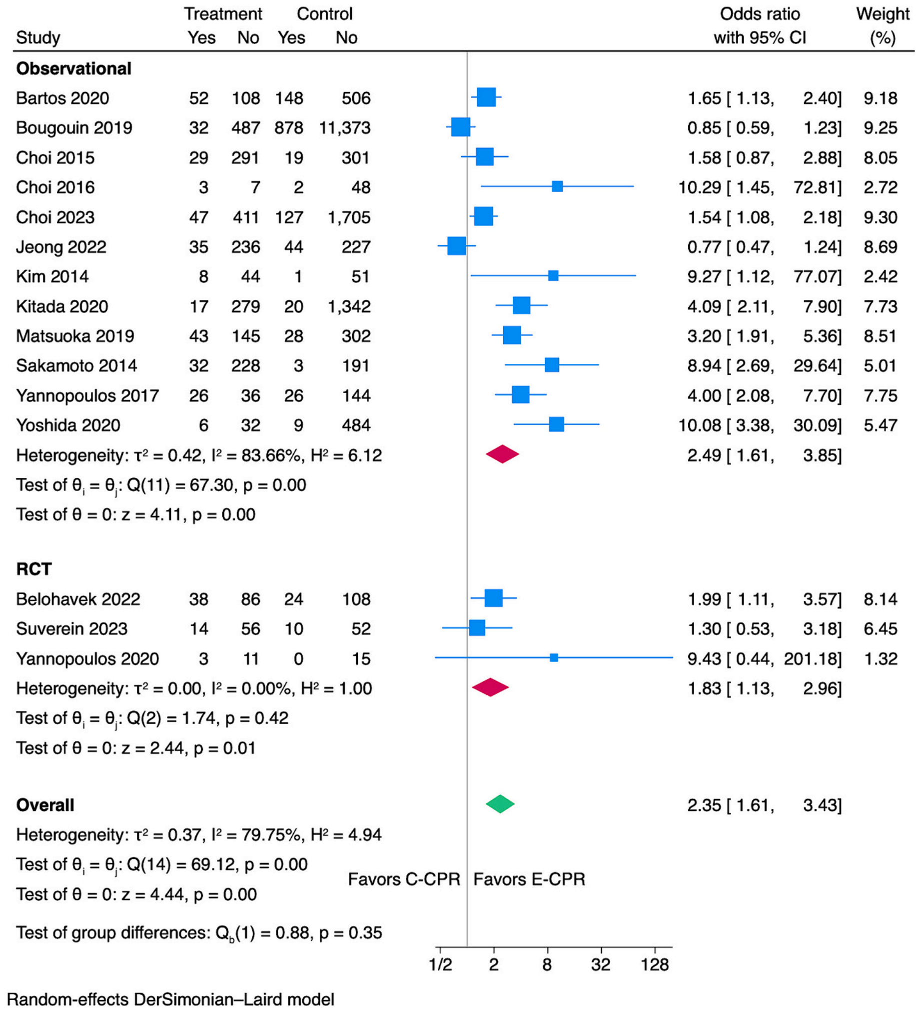

Fig. 2. Forest plot of studies reporting the primary outcome.
Favorable neurological outcome either at discharge or at 30 days is reported according to study design (observational studies vs RCT). Results are expressed in odds ratio with 95% CI and weigh of each study is displayed as percentage. Overall and subgroups heterogeneity as well as *P* value for the test of group differences are also described. The model used for meta-analysis is reported at the bottom of the fig. CI = confidence interval; RCT = randomized clinical trial.

discharge with permanent neurological sequelae generates serious ethical and economic implications for the health-care systems and for the society. Therefore, the definition of the efficacy and sustainability of *E*-CPR in the emergency care is critical. Former observational studies supported the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for *E*-CPR, but they were extremely heterogeneous with, for instance, reported survival rates to discharge ranging between 1718% [15,17] and 38% [18].

Recently, one phase 2 [2] and two phase 3 [3,4] RCTs were published assessing the use of VA-ECMO for supporting E-CPR in refractory OHCA with conflicting results and several limitations which included the heterogeneity in inclusion/exclusion criteria, treatment strategies and outcome definition, the limited power related to the small sample size and, for two of them [2,3], the single center design. The ARREST trial was a phase 2 single center open-label RCT which assessed survival to hospital discharge as the primary endpoint and was prematurely stopped for the excess of benefit observed for *E*-CPR vs C-CPR. Survival to hospital discharge with good neurological status was assessed as a secondary endpoint and was also superior for the *E*-CPR group compared with C-CPR, although not significant due to the very small sample size [2]. The two phase 3 RCTs enrolled larger populations and both were neutral for the primary endpoint [3,4]. Indeed, in the Prague OHCA study, which was prematurely stopped as criteria for futility were met, an invasive strategy of care including *E*-CPR was not superior to conventional care for the primary outcome survival with good neurological outcome at 180 days. However, results at 30 days reported a better outcome for patients randomized in the invasive strategy arm [3]. In the INCEPTION trial, which was the first multicenter RCT on *E*-CPR and enrolled 160 patients, *E*-CPR had similar effects on 30-days survival with favorable neurological outcome compared to C-CPR [4].

4.2. Gaps in evidence and the potential role of the meta-analysis

Previously published meta-analyses concluded for the positive impact of *E*-CPR and proposed criteria for the definition of who has the highest expected probability to benefit from *E*-CPR [26-30]. New meta-analysis incorporating all the available RCTs partially agreed with historical results: the favorable effect of *E*-CPR on short/mid-term neurological outcome was confirmed, while overall survival was not affected (Table 4) [10-14]. However, updated meta-analysis suffered from small sample size and effect measures of the treatment were in general lacking. Therefore, there was a residual gap of evidence which led our group to perform this meta-analysis. Globally, in our meta-analysis, *E*-CPR was effective, increasing the probability of survival with good neurological status at discharge or 30 days with an OR of 2.35 and a NNT of 17. When only the RCTs were considered, results were consistent with the overall analysis and can be considered as confirmatory of the most recent meta-analyses [10-12,14]. The decision to combine the discharge and 30-day

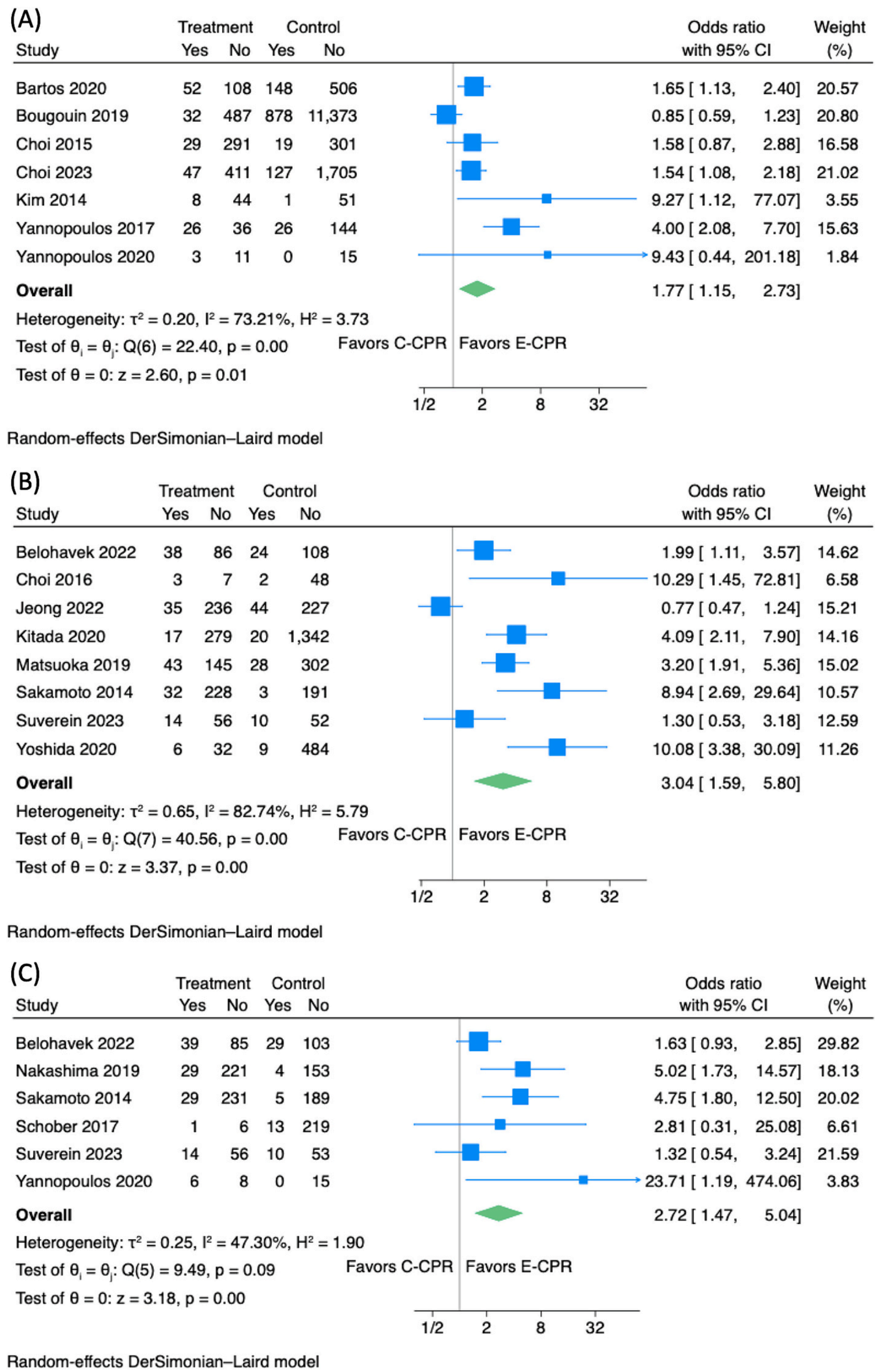

Fig. 3. Forest plots of studies reporting neurological outcome at different follow-up times.
Favorable neurological outcome at discharge (A), at 30 days (B) and at 180 days (C) are shown from top down. Significance of the benefit derived from *E*-CPR in OHCA is preserved through the three different follow-up periods. CI = confidence interval; E-CPR = extracorporeal-cardiopulmonary resuscitation; OHCA = out-of-hospital cardiac arrest.

timeline for outcome assessment was taken in order to expand the pooled population as the studies reported only one of the two measures of outcome. However, results were consistent when survival with good neurological status was assessed separately at discharge and at 30 days. Overall heterogeneity was relatively high, but it was largely determined by observational studies, whereas it was absent in RCTs. Subgroup and meta-regressions analyses according to the rhythm at presentation (shockable vs non-shockable) and to the study area (Asian vs European/US countries) were consistent with the primary analysis and thus, they did not justify the heterogeneity between studies. Consistency also emerged from the sensitivity meta-analyses (10% fixed I2 and leave-one-out).

Observational and RCTs data were also assessed separately, confirming the efficacy of *E*-CPR in the population derived from RCTs, even though of a lesser extent compared with observational studies. Since two of the three RCTs are considered as neutral, this result is very important as it confirms the potential of *E*-CPR for the treatment of refractory OHCA and should be interpreted as a claim for additional, larger and

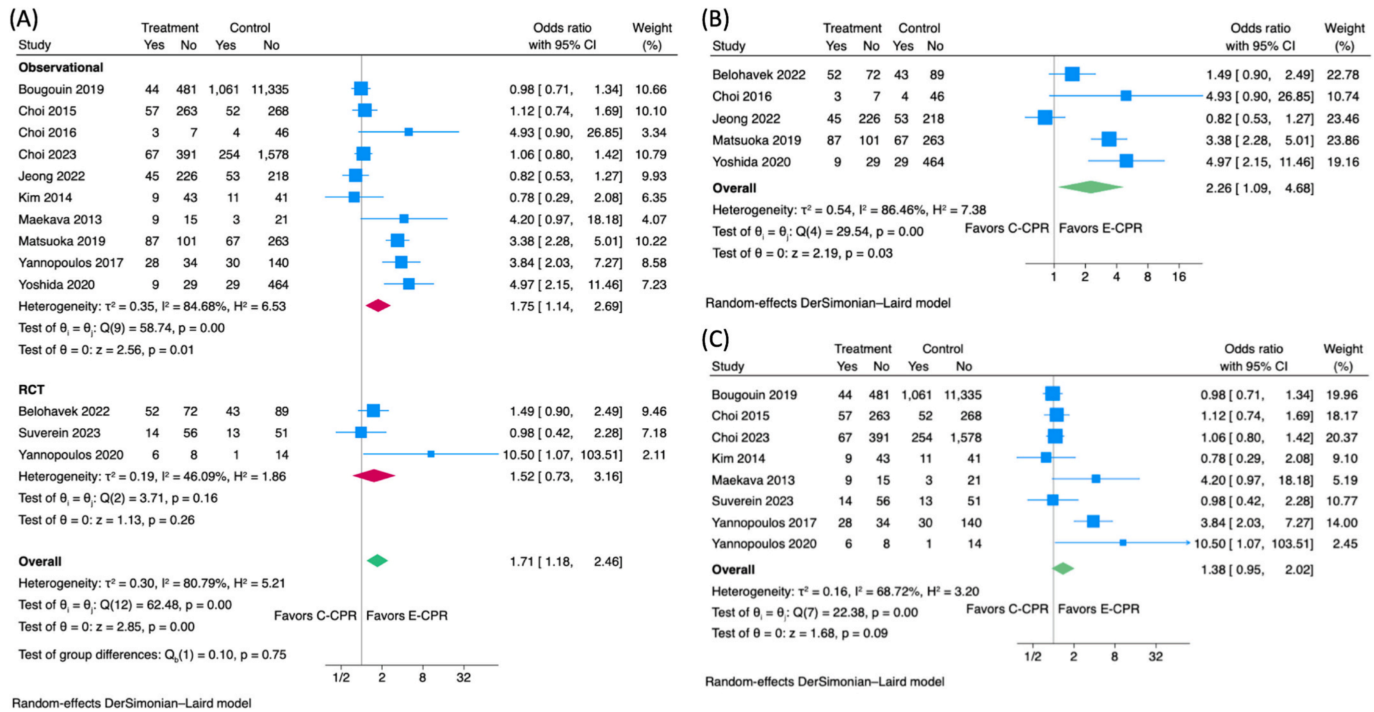

Fig. 4. Forest plot of studies reporting overall survival.
Survival to discharge or at 30 days, regardless of the neurological status, is herein reported according to study design (observational studies vs RCT) on the left. Overall survival at 30 days (A) and to discharge (B) and are shown on the right. CI = confidence interval; E-CPR = extracorporeal-cardiopulmonary resuscitation; RCT = randomized clinical trial.

Table 3
Summary of pooled analysis of studies comparing E-CPR vs C-CPR.

Outcomes	E-CPR	C-CPR	OR (95% CI)	p value	*I²*	*NNT*
		Primary outcome				
Discharge/30-day favorable neurological outcome	385/2842 (14%)	1339/18188 (7%)	2,35 (1,61–3,43)	< 0,0001	80%	17 (14–21)
		Secondary outcomes				
Favorable neurological outcome at discharge	197/1585 (13%)	1199/15294 (8%)	1,77 (1,15-2,73)	0,0094	73%	22 (16–35)
30-day favorable neurological outcome	188/1257 (15%)	140/2894 (5%)	3,04 (1,59–5,80)	0,0007	83%	10 (9–13)
180-day favorable neurological outcome	118/725 (16%)	61/793 (8%)	2,72 (1,47–5,04)	0,0015	47%	12 (9–19)
Discharge/30-day survival	430/2156 (20%)	1621/16149 (10%)	1,71 (1,18-2,46)	0,0044	81%	11 (9–13)
Survival to discharge	234/1126 (21%)	1425/13058 11%)	1,38 (0,95–2,02)	0,0936	69%	11 (9–14)
30-day survival	196/631 (31%)	196/1276 (15%)	2,26 (1,09-4,68)	0,0286	86%	7 (5–9)

Abbreviations: C-CPR = conventional cardiopulmonary resuscitation, CI = confidence interval, E-CPR = extracorporeal cardiopulmonary resuscitation, NNT = number needed to treat, OR = odd ratio.

well-designed RCTs on the topic. As previously mentioned, discrepancies in the results from RCTs are in part the consequence of the low numerosity; in the present meta-analysis, indeed, total patients from RCTs were only 446. Moreover, the lack of homogeneous definition of the appropriate endpoints for studies on mechanical circulatory supports is an additional concern in the interpretation of RCTs' results [31].

As a secondary outcome measure, we prolonged the timeline of observation assessing the effect of *E*-CPR on survival with good neurological outcome at 180 days. Although multiple competing events can alter the effect of *E*-CPR after the acute phase, it is relevant when a complete balancing that include efficacy, sustainability, resources requirement is needed. Moreover, this outcome was adopted as the primary endpoint in the Prague OHCA study. In our meta-analysis, the effect of *E*-CPR at 180 days decreased but was convincingly superior to C-CPR, even though the two larger RCTs did not significantly impact on this outcome [3,4].

4.3. *Challenges in outcome definition*

When overall survival at discharge or 30 days was explored in our meta-analysis, the benefit of *E*-CPR remained significant, attesting the potential of *E*-CPR strategy to reduce mortality in refractory OHCA. However, in the subgroup analysis by study design, survival did not significantly differ between *E*-CPR and C-CPR arms when only RCTs

Table 4
Endpoints across the latest published meta-analyses on E-CPR.

Meta-analysis	N° RCTs/obs	Overall survival/mortality	Survival with favorable neurological outcome
Scquizzato et al. 2024	4/0	Overall survival at the longest follow-up available was similar OR = 1.82 95% CI, 1.13–2.92 $I^2 = 58\%$; $p = 0.59$	Survival with favorable neurological outcome at the longest available follow-up OR = 1.72 95% CI, 1.09–2.70 $I^2 = 26\%$; $p = 0.02$
Cheema et al. 2023	4/0	Mid-term survival RR 1.21 95% CI 0.64–2.28 $I^2 = 48\%$; $p = 0.55$	Mid-term survival with favorable neurological outcome RR 1.59 95% CI 1.09–2.33 $I^2 = 0\%$; $p = 0.02$
Gomes et al. 2023	3/0	In-hospital mortality RR 0.89 95% CI 0.74–1.07 $p = 0.23$	Survival with favorable neurological outcome at the shortest follow-up RR 1.47 95% CI 0.91–2.40 $p = 0.12$
Kiyohara et al. 2023	4/0	Survival at 6 months OR 1.50 95% CI 0.67–3.36 $I^2 = 50\%$; p = ns	Short term survival with favorable neurological outcome OR 1.84 95% CI 1.14–2.99 $I^2 = 0\%$
Low et al. 2023	3/9	In-hospital mortality OR 0.67 95% CI 0.51–0.88 $I^2 = 74\%$; $p < 0{,}01$	Short-term favorable neurological outcome* OR 1.57 95% CI 1.14–2.15 $I^2 = 56\%$; $p = 0{,}02$

Abbreviations: C-CPR = conventional cardiopulmonary resuscitation, CI = confidence interval, E-CPR = extracorporeal cardiopulmonary resuscitation, RCTs = randomized clinical trials, obs = observational studies, OR = odd ratio.
* Including in-hospital cardiac arrest.

were considered. This, in conjunction with the lower magnitude of mortality benefit compared to the neurological recovery endpoints, and with the neutral impact when only mortality at discharge was assessed, might be interpreted as a reduced effect of *E*-CPR on early survival, due to the difficult selection of patients eligible for *E*-CPR. Indeed, pre-hospital prognostic stratification and awareness of the limits of *E*-CPR are crucial in clinical practice in order to reduce futility but also in research for the standardization of future RCTs' design. Several pre- and in-hospital factors may influence the outcome in patients treated with *E*-CPR, including witnessed cardiac arrest, rhythm at presentation, timing and quality of CPR, quality and type of the prehospital emergency medical system included expedited transport, volume of VA-ECMO implantation in the hub centers, quality of intensive care units, etc. [25,30,32-34]. These factors are hardly randomizable in a RCT setting and are an additional potential reason for the conflicting results of the three RCTs and for the very limited strength of the evidences reported by guidelines [35,36]. To appreciate the relevance of those factors in our meta-analysis, we run a qualitative evidence synthesis by reporting the demographic details and resuscitation parameters for all the included studies. An attempt to explore the feasibility of expedited transport to Emergency Department was performed by Hsu et al. in the EROCA trial; they showed that the majority of patients did not meet eligibility criteria for *E*-CPR with only 42% of patients in the expedited transport group reaching the Emergency Department in ≤30 min and 60% starting *E*-CPR in ≤30 min from arrival [37]. Clinical practice, outside rigorous protocols and with many variables unaccounted in RCTs, is expected to further distance from studies results. Moreover, considerable resources and new operating procedures and flow of patients are needed to fulfill these demanding timelines. However, our results contribute to preserve the potential of *E*-CPR as a life-saving treatment for refractory OHCA, until this gap in knowledge will be filled.

4.4. Limitations

This study has limitations. The chosen primary endpoint aimed to investigate the largest available population but might raise concern in terms of heterogeneity. However, results from the secondary analyses assessing discharge and 30-days outcomes separately were consistent. Variability in inclusion criteria and interventions across studies could have differently affected the outcome, accounting for part of the heterogeneity between studies. Observational studies are inherently susceptible to selection and observation biases, and PSM design reduces but not eliminates them. Nevertheless, meta-regression and subgroup analyses by study design (observational vs RCTs) were consistent with the primary analysis. Subgroup analyses with regard to pre- and in-hospital factors, even though crucial, could not be performed because of an aggregate data approach. This study included refractory OHCA, as in-hospital CA holds distinct presentation and management delay.

5. Conclusions

This meta-analysis including RCTs and observational studies supports the use of *E*-CPR in OHCA to improve survival with favorable neurological outcome at discharge or 30 days and at 180 days. At the same time, the smaller benefit observed in the overall survival analysis highlights the need of a correct selection of patients eligible for *E*-CPR in order to reduce futility and to correctly allocate resources. Standardization of future clinical trials remains critical for obtaining more solid evidences on the treatment of refractory OHCA.

Ethical approval and consent to participate

Not applicable.

Consent for participating

Not applicable.

Availability of data and materials

All data supporting the findings of this study are available within the paper and its Supplementary Information files.

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Authors' contributions

D.S. and E.F. contributed to the conception and design of the work; G.S. and E.M. provided administrative support and provision of study materials; L.P. and E.F. dealt with the acquisition and analysis of data; S. R. and M.G. contributed to assembly of data; D.S., E.F. and L.P. interpreted the data; L.P. drafted the work; D.S. and E.F. carefully reviewed the analyses and the draft; all authors reviewed the manuscript and approved the submitted version.

Disclosures

No relationships with industry to declare for any author in relation to the submitted work.

CRediT authorship contribution statement

Linda Pagura: Writing – original draft, Formal analysis. **Enrico Fabris:** Writing – review & editing, Conceptualization. **Serena Rakar:** Data curation. **Marco Gabrielli:** Data curation. **Enzo Mazzaro:** Resources, Project administration. **Gianfranco Sinagra:** Resources, Project administration. **Davide Stolfo:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

No competing interests to declared.

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Appendix A. Supplementary data

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References

[1] Dyson K, Brown SP, May S, et al. International variation in survival after out-of-hospital cardiac arrest: a validation study of the Utstein template. Resuscitation 2019;138:168–81. https://doi.org/10.1016/j.resuscitation.2019.03.018.

[2] Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single Centre, open-label, randomised controlled trial. Lancet 2020 Dec 5;396(10265):1807–16. https://doi.org/10.1016/S0140-6736(20)32338-2 (Epub 2020 Nov 13).

[3] Belohlavek J, Smalcova J, Rob D. Et al; Prague OHCA study group. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 2022 Feb 22;327(8):737–47. https://doi.org/10.1001/jama.2022.1025.

[4] Suverein MM, Delnoij TSR, Lorusso R, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. N. Engl. J. Med. 2023 Jan 26;388(4):299–309. https://doi.org/10.1056/NEJMoa2204511.

[5] Choi DH, Kim YJ, Ryoo SM, et al. Extracorporeal cardiopulmonary resuscitation among patients with out-of-hospital cardiac arrest. Clin Exp Emerg Med. 2016 Sep 30;3(3):132–8. https://doi.org/10.15441/ceem.16.145.

[6] Kitada M, Kaneko T, Yamada S, Harada M, Takahashi T. Extracorporeal cardiopulmonary resuscitation without target temperature management for out-of-hospital cardiac arrest patients prolongs the therapeutic time window: a retrospective analysis of a nationwide multicentre observational study in Japan. J. Intensive Care 2020 Aug;3(8):58. https://doi.org/10.1186/s40560-020-00478-9.

[7] Matsuoka Y, Ikenoue T, Hata N, et al. Hospitals' extracorporeal cardiopulmonary resuscitation capabilities and outcomes in out-of-hospital cardiac arrest: a population-based study. Resuscitation 2019 Mar;136:85–92. https://doi.org/10.1016/j.resuscitation.2019.01.013 (Epub 2019 Jan 19).

[8] Sakamoto T, Morimura N, Nagao K, SAVE-J Study Group, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. Resuscitation 2014 Jun;85(6):762–8. https://doi.org/10.1016/j.resuscitation.2014.01.031 (Epub 2014 Feb 12).

[9] Yoshida T, Fujitani S, Wakatake H, et al. Exploratory observational study of extracorporeal cardiopulmonary resuscitation for nonshockable out-of-hospital cardiac arrest occurring after an emergency medical services arrival: SOS-KANTO 2012 study report. J. Emerg. Med. 2020 Mar;58(3):375–84. https://doi.org/10.1016/j.jemermed.2019.12.004 (Epub 2020 Jan 28).

[10] Cheema HA, Shafiee A, Jafarabady K, Seighali N, Shahid A, Ahmad A, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a meta-analysis of randomized controlled trials. Pacing Clin. Electrophysiol. 2023 Oct;46(10):1246–50.

[11] Kiyohara Y, Kampaktsis PN, Briasoulis A, Kuno T. Extracorporeal membrane oxygenation-facilitated resuscitation in out-of-hospital cardiac arrest: a meta-analysis of randomized controlled trials. J. Cardiovasc. Med. (Hagerstown) 2023 Jul 1;24(7):414–9. https://doi.org/10.2459/JCM.0000000000001503. Epub 2023 May 17. doi: 10.1111/pace.14820. (Epub 2023 Sep 12).

[12] Low CJW, Ramanathan K, Ling RR, Ho MJC, Chen Y, Lorusso R, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with cardiac arrest: a comparative meta-analysis and trial sequential analysis. Lancet Respir. Med. 2023 Oct;11(10):883–93. https://doi.org/10.1016/S2213-2600(23)00137-6 (Epub 2023 May 22).

[13] Gomes DA, Presume J, Ferreira J, Oliveira AF, Miranda T, Brízido C, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: a systematic review and meta-analysis of randomized clinical trials. Intern. Emerg. Med. 2023 Oct;18(7):2113–20. https://doi.org/10.1007/s11739-023-03357-x (Epub 2023 Jun 30).

[14] Scquizzato T, Bonaccorso A, Swol J, Gamberini L, Scandroglio AM, Landoni G, et al. Refractory out-of-hospital cardiac arrest and extracorporeal cardiopulmonary resuscitation: a meta-analysis of randomized trials. Artif. Organs 2023 May;47(5):806–16. https://doi.org/10.1111/aor.14516 (Epub 2023 Mar 16).

[15] Choi DS, Kim T, Ro YS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: a propensity score-matched analysis. Resuscitation 2016 Feb;99:26–32. https://doi.org/10.1016/j.resuscitation.2015.11.013 (Epub 2015 Dec 10).

[16] Jeong D, Lee GT, Park JE, et al. Extracorporeal life-support for out-of-hospital cardiac arrest: a Nationwide multicenter study. Shock 2022 May 1;57(5):680–6. https://doi.org/10.1097/SHK.0000000000001924 (Epub 2022 Mar 10).

[17] Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit. Care 2014 Sep 26;18(5):535. https://doi.org/10.1186/s13054-014-0535-8.

[18] Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit. Care Med. 2013 May;41(5):1186–96. https://doi.org/10.1097/CCM.0b013e31827ca4c8.

[19] Nakashima T, Noguchi T, Tahara Y. Et al; SAVE-J group. Patients with refractory out-of-cardiac arrest and sustained ventricular fibrillation as candidates for extracorporeal cardiopulmonary resuscitation - prospective multi-center observational study. Circ. J. 2019 Apr 25;83(5):1011–8. https://doi.org/10.1253/circj.CJ-18-1257 (Epub 2019 Mar 20).

[20] Choi Y, Park JH, Jeong J, Kim YJ, Song KJ, Shin SD. Extracorporeal cardiopulmonary resuscitation for adult out-of-hospital cardiac arrest patients: time-dependent propensity score-sequential matching analysis from a nationwide population-based registry. Crit. Care 2023 Mar 6;27(1):87. https://doi.org/10.1186/s13054-023-04384-y.

[21] Bartos JA, Grunau B, Carlson C, et al. Improved survival with extracorporeal cardiopulmonary resuscitation despite progressive metabolic derangement associated with prolonged resuscitation. Circulation 2020 Mar 17;141(11):877–86. https://doi.org/10.1161/CIRCULATIONAHA.119.042173 (Epub 2020 Jan 3).

[22] Bougouin W, Dumas F, Lamhaut L, et al. Sudden death expertise center investigators. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. Eur. Heart J. 2020 Jun 1;41(21):1961–71. https://doi.org/10.1093/eurheartj/ehz753.

[23] Schober A, Sterz F, Herkner H, Wallmueller C, Weiser C, Hubner P, et al. Emergency extracorporeal life support and ongoing resuscitation: a retrospective comparison for refractory out-of-hospital cardiac arrest. Emerg. Med. J. 2017 May;34(5):277–81. https://doi.org/10.1136/emermed-2015-205232 (Epub 2017 Feb 17).

[24] Yannopoulos D, Bartos JA, Raveendran G, et al. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. J. Am. Coll. Cardiol. 2017 Aug 29;70(9):1109–17. https://doi.org/10.1016/j.jacc.2017.06.059.

[25] Yamaguchi Y, Woodin JA, Gibo K, Zive DM, Daya MR. Improvements in out-of-hospital cardiac arrest survival from 1998 to 2013. Prehosp. Emerg. Care 2017 Sep-Oct;21(5):616–27. https://doi.org/10.1080/10903127.2017.1308604 (Epub 2017 Apr 20).

[26] Chen Z, Liu C, Huang J, et al. Clinical efficacy of extracorporeal cardiopulmonary resuscitation for adults with cardiac arrest: Meta-analysis with trial sequential analysis. Biomed. Res. Int. 2019 Jul;9(2019):6414673. https://doi.org/10.1155/2019/6414673.

[27] Alfalasi R, Downing J, Cardona S, et al. A comparison between conventional and extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a systematic review and Meta-analysis. Healthcare 2022;10(3):591. https://doi.org/10.3390/healthcare10030591.

[28] Scquizzato T, Bonaccorso A, Consonni M, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a systematic review and meta-analysis of randomized and propensity score-matched studies. Artif. Organs 2022 May;46(5):755–62. https://doi.org/10.1111/aor.14205 (Epub 2022 Feb 23).

[29] Kim SJ, Kim HJ, Lee HY, Ahn HS, Lee SW. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: a meta-analysis. Resuscitation 2016 Jun;103:106–16. https://doi.org/10.1016/j.resuscitation.2016.01.019 (Epub 2016 Feb 2).

[30] Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017 Mar;112:1–10. https://doi.org/10.1016/j.resuscitation.2016.12.011 (Epub 2016 Dec 19).

[31] Dalzell JR. Issues with the Design of Randomized Trials of temporary mechanical circulatory support for cardiogenic shock. Circulation 2023 May 16;147(20):1489–91. https://doi.org/10.1161/CIRCULATIONAHA.122.063616 (Epub 2023 May 15).

[32] Poppe M, Weiser C, Holzer M, et al. The incidence of "load&go" out-of-hospital cardiac arrest candidates for emergency department utilization of emergency extracorporeal life support: a one-year review. Resuscitation 2015;91:131–6. https://doi.org/10.1016/j.resuscitation.2015.03.003.

[33] Alm-Kruse K, Sørensen G, Osbakk SA, et al. Outcome in refractory out-of-hospital cardiac arrest before and after implementation of an ECPR protocol. Resuscitation 2021;162:35–42. https://doi.org/10.1016/j.resuscitation.2021.01.038.

[34] Karve S, Lahood D, Diehl A, et al. The impact of selection criteria and study design on reported survival outcomes in extracorporeal oxygenation cardiopulmonary resuscitation (ECPR): a systematic review and meta-analysis. Scand. J. Trauma Resusc. Emerg. Med. 2021 Sep 26;29(1):142. https://doi.org/10.1186/s13049-021-00956-5.

[35] Panchal AR, Bartos JA, Cabañas JG, et al. Adult basic and advanced life support writing group. Part 3: adult basic and advanced life support: 2020 American Heart

Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020 Oct 20;142(16_suppl_2):S366–468. https://doi.org/10.1161/CIR.0000000000000916 (Epub 2020 Oct 21).
[36] Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation 2021 Apr;161:115–51. https://doi.org/10.1016/j.resuscitation.2021.02.010. Epub 2021 Mar 24. Erratum in: Resuscitation. 2021 Oct;167:105–106.
[37] Hsu CH, Meurer WJ, Domeier R, Fowler J, Whitmore SP, Bassin BS, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest (EROCA): results of a randomized feasibility trial of expedited out-of-hospital transport. Ann. Emerg. Med. 2021 Jul;78(1):92–101. https://doi.org/10.1016/j.annemergmed.2020.11.011 (Epub 2021 Feb 1).