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SYSTEMATIC REVIEW

Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A systematic review and meta-analysis of randomized and propensity score-matched studies

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Abstract

Background: In selected patients with refractory out-of-hospital cardiac arrest, extracorporeal cardiopulmonary resuscitation represents a promising approach when conventional cardiopulmonary resuscitation fails to achieve return of spontaneous circulation. This systematic review and meta-analysis aimed to compare extracorporeal cardiopulmonary resuscitation to conventional cardiopulmonary resuscitation.

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials up to November 28, 2021, for randomized trials and observational studies reporting propensity score-matched data and comparing adults with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation with those treated with conventional cardiopulmonary resuscitation. The primary outcome was survival with favorable neurological outcome at the longest follow-up available. Secondary outcomes were survival at the longest follow-up available and survival at hospital discharge/30 days.

Results: We included six studies, two randomized and four propensity score-matched studies. Patients treated with extracorporeal cardiopulmonary resuscitation had higher rates of survival with favorable neurological outcome (81/584 [14%] vs. 46/593 [7.8%]; OR = 2.11; 95% CI, 1.41–3.15; $p < 0.001$, number needed to treat 16) and of survival (131/584 [22%] vs. 102/593 [17%]; OR = 1.40; 95% CI, 1.05–1.87; $p = 0.02$) at the longest follow-up available compared with conventional cardiopulmonary resuscitation. Survival at hospital discharge/30 days was similar between the two groups (142/584 [24%] vs. 122/593 [21%]; OR = 1.26; 95% CI, 0.95–1.66; $p = 0.10$).

Conclusions: Evidence from randomized trials and propensity score-matched studies suggests increased survival and favorable neurological outcome in patients with refractory out-of-hospital cardiac arrest treated with extracorporeal

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cardiopulmonary resuscitation. Large, multicentre randomized studies are still ongoing to confirm these findings.

KEYWORDS

extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, neurological outcome, out-of-hospital cardiac arrest

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of global mortality and disability.[1,2] Despite advances in the field of resuscitation, rates of survival in patients treated with conventional cardiopulmonary resuscitation (C-CPR) remain low and many survivors have persistent neurological damage.[3] Chances of survival after OHCA start to decline rapidly after 10 min of C-CPR.[4] After 35 min, less than 1% of patients achieve return of spontaneous circulation (ROSC) and survive with a favorable neurological outcome.[5] In selected patients with refractory OHCA due to a potentially reversible cause, latest guidelines recommend considering extracorporeal cardiopulmonary resuscitation (E-CPR).[6,7]

The use of extracorporeal circulation for patients in refractory cardiac arrest was first suggested in 1976.[8] Only in recent years, the rapid deployment of veno-arterial extracorporeal membrane oxygenation (ECMO) during ongoing CPR, termed E-CPR, has been increasingly adopted for refractory OHCA. Although E-CPR is a promising approach for OHCA patients who do not achieve ROSC with C-CPR, its role has not been clearly elucidated yet. Premature E-CPR may unnecessarily expose patients who may potentially achieve ROSC with C-CPR to a highly invasive and expensive procedure with significant additional risks. On the contrary, delaying E-CPR may reduce its potential benefit and increase the risk of brain and multiorgan injury. In addition, it is still unknown if the growing use of E-CPR[9] is increasing the number of survivors with neurological impairments.

Observational studies reported that E-CPR may improve survival and neurological outcomes in patients with OHCA when compared to C-CPR.[9–13] However, other studies showed small or no effect on survival and systematic reviews conducted on the topic yielded contrasting results.[14,15] Such discordant results probably reflect the high heterogeneity of the included studies and different selection criteria leading to highly variable survival rates between 15% and 50%. More recently, two small, single-center, randomized trials were presented with encouraging results.[16,17] Therefore, we conducted this systematic review and meta-analysis of randomized trials and propensity score-matched studies to evaluate the effect of E-CPR, compared with C-CPR, on survival and neurological outcome in OHCA adult patients.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[18] and the protocol was registered in PROSPERO (CRD42021286205). The review question was designed with the PICO (Population, Intervention, Comparison, Outcome) framework: among adult patients with OHCA (P), does the treatment with E-CPR (I), compared to C-CPR (C), increase survival with favorable neurological outcome (O)?

2.1 | Search strategy and study selection

We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to November 28, 2021. In addition, we searched for abstracts and presentation from congresses. We included studies comparing adult OHCA patients treated with E-CPR with patients treated with C-CPR (i.e., basic and advanced life-support maneuvers). We considered eligible randomized trials and observational studies reporting propensity score-matched data. We excluded feasibility studies, studies enrolling less than 20 patients, and studies not reporting the primary outcome of survival with favorable neurological outcome. After the removal of duplicates, an eligibility assessment at the title/abstract level was performed by two investigators. The final selection of included articles was based on complete manuscripts with disagreements resolved under the supervision of one investigator.

2.2 | Data collection and risk of bias assessment

Two authors independently extracted data using a standardized form. Disagreements were resolved by discussion

involving a third reviewer. Extracted data included first author, publication year, country, study period, age, sex, bystander CPR, shockable rhythm, survival with favorable neurological outcome at the longest follow-up available, survival at hospital discharge or at 30 days.

Risk of bias was assessed with the recommended version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2)[19] and with the Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I) for non-randomized studies.[20] The overall certainty of the evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and classified as very low, low, moderate, or high.[21] The GRADEpro software prepared the GRADE evidence profile tables. The presence of publication bias was investigated by visual estimation of the funnel plot. In case of funnel plot asymmetry, effect size was adjusted with Duval and Tweedie's trim and fill method.[22]

2.3 | Outcomes

The pre-specified primary outcome was survival with favorable neurological outcome measured at the longest follow-up available. Pre-specified secondary outcomes included survival at the longest follow-up available, survival at hospital discharge/30 days,[23] and rate of neurological impairments.

2.4 | Statistical analysis

We calculated pooled odds ratios (ORs) and 95% confidence intervals (CI) using the Mantel–Haenszel method for binary outcomes. Statistical heterogeneity hypothesis was tested with Cochrane Q statistic and I^2 value. I^2 value greater than 50% was considered heterogeneous, and the random effect model was used for analyses. A two-tailed p-value <0.05 was considered statistically significant for hypothesis testing of effect. We conducted a subgroup analysis for study design (randomized or observational studies), and the difference between subgroups estimates was considered significant for $p_{\text{interaction}} < 0.10$. The number needed to treat (NNT) was calculated using the pooled results. All data analyses were performed with R version 4.1.2.

3 | RESULTS

3.1 | Study characteristics

Our search strategy performed by two independent investigators in electronic databases yielded 1751 records.

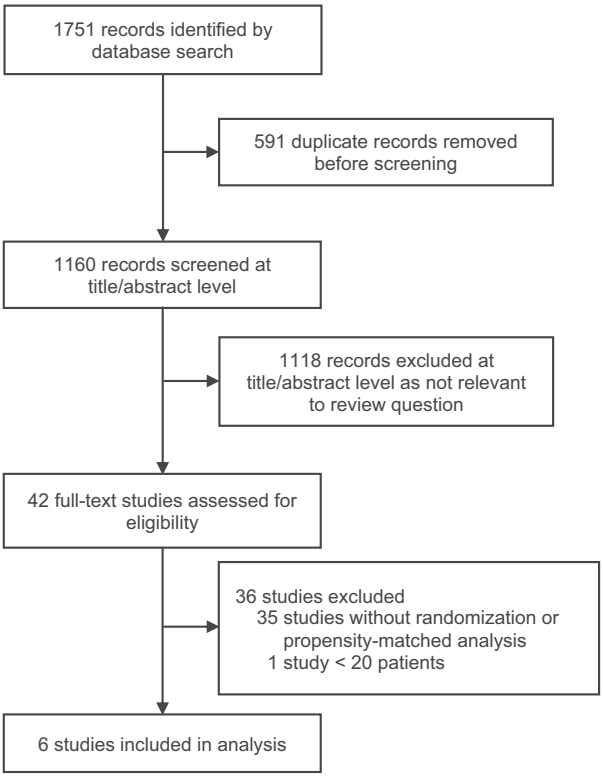


FIGURE 1 Flowchart of the literature search

After screening, six studies were finally included in the meta-analysis (Figure 1). Details of major exclusions are displayed in Table S1. All included studies were published between 2013 and 2021. Three studies were conducted in Asia,[24–26] two in Europe,[17,27] and one in the US.[16] All included studies initiated E-CPR after hospital arrival. The two randomized trials[16,17] were assessed to have a low risk of bias, whereas the remaining four propensity score-matched studies[24–27] were considered to have a moderate risk of bias primarily due to the study design and risk of confounding. The characteristics of included studies are reported in Table 1.

3.2 | Neurological outcome and survival

We found that OHCA patients treated with E-CPR compared with C-CPR had higher rate of survival with favorable neurological outcome at the longest follow-up available (Figure 2; 81/584 [14%] vs. 46/593 [7.8%]; OR = 2.11; 95% CI, 1.41–3.15; $p < 0.001$; $I^2 = 21\%$). Length of follow-up ranged from hospital discharge to 6 months. In addition, we calculated the NNT and found that 16 patients with refractory OHCA should be treated with E-CPR to achieve one additional survivor with favorable neurological outcome (NNT 16).

Magnitude and direction of the primary outcome were confirmed in a subgroup analysis by study design

TABLE 1 Characteristics of studies comparing extracorporeal versus conventional cardiopulmonary resuscitation ordered by publication year

Study	Journal	Year	Country	Study design	Risk of bias[a]
Maekawa et al.	Crit Care Med	2013	Japan	Propensity score-matched	Moderate
Kim et al.	Crit Care	2014	South Korea	Propensity score-matched	Moderate
Choi et al.	Resuscitation	2016	South Korea	Propensity score-matched	Moderate
Patricio et al.	Crit Care	2019	France	Propensity score-matched	Moderate
Yannopoulos et al.	Lancet	2020	USA	Randomized	Low
Belohlavek et al.	Abstract	2021	Czech Republic	Randomized	Low

[a]Detailed risk of bias assessment is available in Table S2.

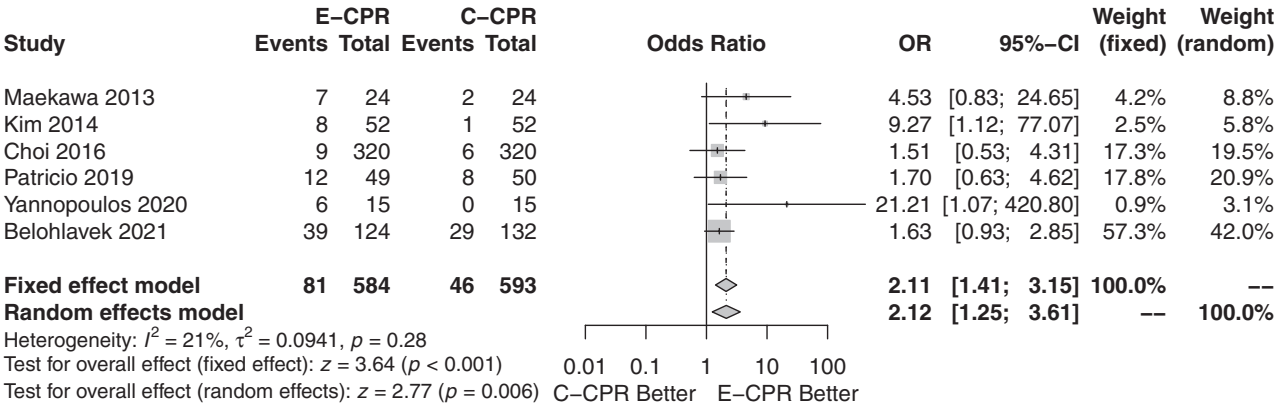


FIGURE 2 Forest plot for survival with favorable neurological outcome at the longest follow-up available

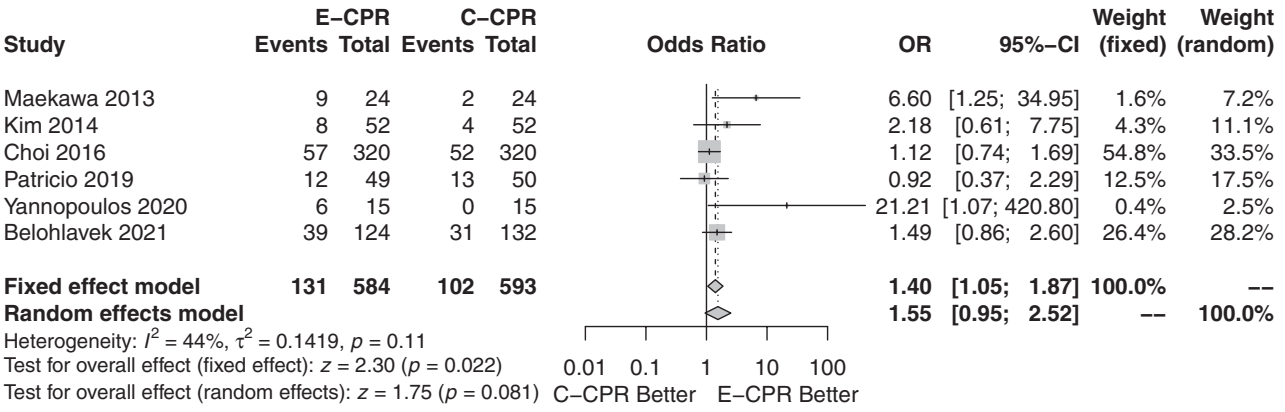


FIGURE 3 Forest plot for survival at the longest follow-up available

(randomized or paired-matched studies) (Figure S1). At visual inspection of funnel plot, we detected an asymmetry arising from publication bias (Figure S2A). Therefore, we applied the "trim and fill" method (Figure S2B) producing a bias-adjusted OR of 1.73 (95% CI, 1.16–2.59; $p = 0.008$; $I^2 = 40\%$).

In addition, we did not find higher rates of survivors with neurological impairments (available in five studies) in the E-CPR group compared with C-CPR (Figure S3; 50/535 [9.3%] vs. 51/543 [9.4%]; OR = 0.98; 95% CI, 0.65–1.48; $p = 0.92$; $I^2 = 0\%$).

Survival at the longest follow-up available was higher among patients treated with E-CPR compared to C-CPR (Figure 3; 131/584 [22%] vs. 102/593 [17%]; OR = 1.40; 95% CI, 1.05–1.87; $p = 0.02$; $I^2 = 44\%$). Length of follow-up ranged from hospital discharge to 6 months. When survival

status was censored at hospital discharge/30 days, there was no differences between E-CPR and C-CPR (Figure S4; 142/584 [24%] vs. 122/593 [21%]; OR = 1.26; 95% CI, 0.95–1.66; $p = 0.10$; $I^2 = 33\%$).

A summary of main findings is reported in Table 2.

3.3 | Characteristics of patients

Baseline characteristics of patients were similar between groups (Figure S5). Specifically, age (56 vs. 57 years; MD = −0.96; 95% CI, −2.70–0.77; $p = 0.28$; $I^2 = 0\%$), male sex (234/295 [79%] vs. 227/303 [75%]; OR = 1.30; 95% CI, 0.88–1.91; $p = 0.18$; $I^2 = 0\%$), rate of bystander-initiated CPR (266/535 [50%] vs. 279/543 [51%]; OR = 0.95; 95% CI, 0.71–1.26; $p = 0.70$; $I^2 = 0\%$), proportion of shockable first monitored rhythm (248/615 [40%] vs. 253/623 [41%]; OR = 1.00; 95% CI, 0.78–1.27; $p = 0.99$; $I^2 = 0\%$), EMS response time (6.7 vs. 6.5 min; MD = −0.05; 95% CI, −0.36–0.26; $p = 0.75$; $I^2 = 0\%$) were all comparable between the two groups.

4 | DISCUSSION

In this systematic review and meta-analysis including only randomized trials and propensity score-matched studies, patients with OHCA treated with E-CPR had higher rates of survival, also with favorable neurological outcome, compared to C-CPR.

Brain injury following cardiac arrest is determined primarily by the duration of ischemia (no-flow time) and occurs within minutes.[3,28] Therefore, reducing the duration of no-flow time with bystander CPR is the most effective strategy to contain brain injury after cardiac arrest. Other advanced interventions like drugs and intra-arrest cooling were proven ineffective in improving neurological outcome.[29,30] In addition, secondary brain injury occurs during CPR in the low flow period and after reperfusion.[3,28] Our meta-analysis found higher rates of survival with favorable neurological outcome, further supporting that early initiation of E-CPR may be a promising strategy when initial resuscitation maneuvers with C-CPR are unsuccessful.

It is important to note that our meta-analysis also confirmed that C-CPR alone in this specific population of patients with OHCA has very poor outcome: only 7.8% survived with good neurological outcome compared to 14% in the E-CPR group. Among studies, survival rates of patients treated with E-CPR vary considerably mainly due to different criteria to identify patients eligible for E-CPR. The most common selection criteria adopted in the studies included in this meta-analysis were cardiac cause, witnessed cardiac arrest, bystander CPR, short no-flow time, and initial shockable rhythm. To achieve high rates of survival in a E-CPR program, accurate selection of patients eligibility, effective pre-hospital care and close cooperation with high volume cardiac arrest centers[31] are mandatory prerequisites. However, to date, there is no consensus on indications for E-CPR and rates of bystanders' interventions are still suboptimal in many countries.[32] It is imperative to remember that interventions to increase survival after OHCA should be focused initially in improving bystanders' interventions through community initiatives.[33,34] Without the timely initiation of CPR to reduce no-flow times and prevent irreversible brain injury, any further advanced intervention like E-CPR will have only little or no effect on survival.

In case of refractory OHCA, E-CPR is part of a bundle of treatments that begin in the pre-hospital setting, continue during transport, and is completed in the hospital. In the pre-hospital setting, it is of paramount importance to ensure that bystanders immediately initiate high-quality CPR and pre-hospital on-scene time are reduced. When a potential E-CPR candidate is identified, advanced life support should be initiated in a timely fashion. The

TABLE 2 Pooled analysis of studies comparing extracorporeal versus conventional cardiopulmonary resuscitation

Outcomes	E-CPR	C-CPR	Odds ratio (95% CI)	*p*-value	I^2 (%)
Primary outcome					
Survival with good neurological outcome at the longest follow-up available, *n* (%)	81/584 (14%)	46/593 (7.8%)	2.11 (1.41–3.15)	<0.001	21%
Secondary outcomes					
Survival at the longest follow-up available, *n* (%)	131/584 (22%)	102/593 (17%)	1.40 (1.05–1.87)	0.02	44%
Survival at hospital discharge or 30 days, *n* (%)	142/584 (24%)	122/593 (21%)	1.26 (0.95–1.66)	0.10	33%
Survival with unfavorable neurological outcome, *n* (%)	50/535 (9.3%)	51/543 (9.4%)	0.98 (0.65–1.48)	0.41	0%

Abbreviations: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation.

patient should be prepared for transport to a cardiac arrest center capable of E-CPR, mechanical CPR should be initiated, a valid vascular access obtained, and a definitive airway placed. At hospital arrival, E-CPR must be initiated immediately and followed by post-cardiac arrest care that include temperature control, advanced ventilatory, and circulatory support, and definitive treatment (e.g., coronary angioplasty). In the post-cardiac arrest phase, a comprehensive approach to mechanical circulatory support should be available, including intra-aortic balloon pump and left ventricular assist devices.

Differently from previous systematic reviews published on the topic,[14,35–37] our meta-analysis included only randomized trials and propensity score-matched studies in the setting of OHCA, thus excluding in-hospital cardiac arrests. Observational unmatched studies are at high risk of confounding by indication, in particular in the context of E-CPR. Clinicians' decision to initiate E-CPR is based on factors such as comorbidities of the patients and prehospital cardiac arrest variables which in turn impact on the outcome. The choice to include only randomized and propensity score-matched data allowed us to minimize differences between groups and potential confounders. Despite propensity score-matched studies mimic the setting of a randomized study, residual confounders from unmeasured variables may remain in the pooled estimates.

Moreover, compared to previous systematic reviews, two randomized trials investigating E-CPR versus C-CPR[16,17] were evaluated for the first time in our meta-analysis. The ARREST trial was the first to demonstrate in a randomized fashion that ECMO-facilitated resuscitation improves survival.[16] The results of the Prague OHCA study, presented at the congress of the American College of Cardiology and still unpublished, similarly demonstrated that a hyperinvasive approach improves outcomes.[17] However, both trials were prematurely stopped because of the significant survival benefit observed with E-CPR. Therefore, it was deemed unethical to preclude some patients the possibility to receive E-CPR.[16,17] Large, multicentre randomized trials are still needed to confirm our results and we were able to identify four randomized trials comparing E-CPR with C-CPR for patients with OHCA are currently ongoing (Table S3).

Despite the numerous strengths of this new meta-analysis, there are two major limitations that should be addressed. First, due to the strict selection criteria and study availability, our meta-analysis had a small sample size that can reduce the power of detecting beneficial effects. Second, different inclusion criteria and methods of intervention were adopted among studies with possible biases in the estimate of survival outcomes. In fact, selection criteria and interventions following E-CPR (e.g., temperature control, advanced ventilatory and circulatory support, prognostication, and early withdrawal of life-support therapy) could affect the survival and neurological outcome of patients.

5 | CONCLUSIONS

Evidence from randomized trials and propensity score-matched studies suggests that treating refractory OHCA patients with E-CPR increases survival, also with favorable neurological outcome. However, it is important to identify which patients are most likely to benefit from E-CPR. Large, multicentre randomized studies are needed to confirm these findings.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Design of the study: Tommaso Scquizzato, Alessandra Bonaccorso, Michela Consonni, Anna Mara Scandroglio, Justyna Swol, Giovanni Landoni, Alberto Zangrillo; Data collection: Tommaso Scquizzato, Alessandra Bonaccorso, Michela Consonni, Anna Mara Scandroglio, Justyna Swol, Giovanni Landoni, Alberto Zangrillo; Statistical analysis: Tommaso Scquizzato, Alessandra Bonaccorso, Michela Consonni, Giovanni Landoni; Manuscript draft and critical review: Tommaso Scquizzato, Alessandra Bonaccorso, Michela Consonni, Anna Mara Scandroglio, Justyna Swol, Giovanni Landoni, Alberto Zangrillo; Administrative support: Giovanni Landoni, Alberto Zangrillo.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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