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Review

Extracorporeal cardiopulmonary resuscitation for cardiac arrest: An updated systematic review

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Abstract

Objectives: To provide an updated systematic review on the use of extracorporeal cardiopulmonary resuscitation (ECPR) compared with manual or mechanical cardiopulmonary resuscitation during cardiac arrest.

Methods: This was an update of a systematic review published in 2018. OVID Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched for randomized trials and observational studies between January 1, 2018, and June 21, 2022. The population included adults and children with out-of-hospital or in-hospital cardiac arrest. Two investigators reviewed studies for relevance, extracted data, and assessed bias. The certainty of evidence was evaluated using GRADE.

Results: The search identified 3 trials, 27 observational studies, and 6 cost-effectiveness studies. All trials included adults with out-of-hospital cardiac arrest and were terminated before enrolling the intended number of subjects. One trial found a benefit of ECPR in survival and favorable neurological status, whereas two trials found no statistically significant differences in outcomes. There were 23 observational studies in adults with out-of-hospital cardiac arrest or in combination with in-hospital cardiac arrest, and 4 observational studies in children with in-hospital cardiac arrest. Results of individual studies were inconsistent, although many studies favored ECPR. The risk of bias was intermediate for trials and critical for observational studies. The certainty of evidence was very low to low. Study heterogeneity precluded meta-analyses. The cost-effectiveness varied depending on the setting and the analysis assumptions.

Conclusions: Recent randomized trials suggest potential benefit of ECPR, but the certainty of evidence remains low. It is unclear which patients might benefit from ECPR.

Keywords: Extracorporeal Cardiopulmonary Resuscitation, Extracorporeal Membrane Oxygenation, Cardiopulmonary Bypass, Cardiopulmonary Resuscitation, Cardiac Arrest

Introduction

Out-of-hospital cardiac arrest (OHCA) affects over 350,000 individuals in the United States[1] and 275,000 individuals in Europe[2,3] each year. In-hospital cardiac arrest (IHCA) occurs in an estimated 290,000 patients in the United States per year.[4] Cardiac arrest is associated with high mortality and morbidity, with approximately 10% of individuals with OHCA and 30% of patients with IHCA surviving to hospital discharge.[5]

Extracorporeal cardiopulmonary resuscitation (ECPR) is an advanced rescue therapy recognized by both the American Heart Association (AHA)[6,7] and the European Resuscitation Council (ERC)[8,9] to support circulation in selected patients with refractory cardiac arrest. Although ECPR may extend the time in which reversible causes of cardiac arrest can be treated, the benefit of applying ECPR as well as the optimal patient selection and timing of the procedure remain uncertain.

The previous systematic review on the use of ECPR for cardiac arrest, published by the International Liaison Committee on Resuscitation (ILCOR) in 2018, stated that the evidence was inconclusive.[10] Twenty-five observational studies (22 in adults and 3 in children) and no randomized trials were identified at the time of the previous

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https://doi.org/10.1016/j.resuscitation.2022.12.003

Received 2 November 2022; Received in Revised form 5 December 2022; Accepted 6 December 2022

review. With evidence from three randomized trials becoming available, an updated systematic review of the literature is needed.[11–13]

The aim of this study was to perform an updated systematic review on the use of ECPR compared with manual or mechanical cardiopulmonary resuscitation (CPR) during cardiac arrest to inform the international guidelines.

Methods

Protocol and registration

The protocol was prospectively submitted to the International Prospective register of Systematic Reviews (PROSPERO) (CRD42022341077) on June 21, 2022. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The PROSPERO protocol and PRISMA checklist are provided in the Supplementary Content.

Eligibility criteria and outcomes

This was an update of a systematic review addressing the same topic in 2018.[10] The specific study question was framed using the PICO (Population, Intervention, Comparison, Outcome) format: in adults (≥18 years) and children (<18 years) with cardiac arrest in any setting (out-of-hospital or in-hospital), does ECPR including extracorporeal membrane oxygenation or cardiopulmonary bypass during cardiac arrest, compared to manual or mechanical CPR, change clinical outcomes.

Relevant outcomes were selected for the review based on the data reported in the literature, including survival and favorable neurological outcome. Outcomes with similar time frames were combined into single categories (mid-term: intensive care unit discharge, hospital discharge, 30-days, and 1-month; long-term: 3-months, 6-months, and 1-year). Long-term survival reported as hazard ratios were also considered irrespective of the length of follow-up. Descriptive data were obtained from randomized trials on cannulation success, loss of limb and amputations, brain death, and organ donations.

Return of spontaneous circulation (ROSC) was not included as an outcome given that ROSC is difficult to meaningfully define in this population. A favorable neurological outcome was generally defined as a modified Rankin Scale score of 0–3 or a Cerebral Performance Category score of 1–2 indicating that the patient does not need assistance with activities of daily living.

New randomized controlled trials, non-randomized controlled trials, and observational studies (cohort studies and case-control studies) with a control group (patients not receiving ECPR) were included. Ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, and unpublished studies were not included. Studies assessing cost-effectiveness were included for a descriptive overview. All languages were considered if there was an English abstract or an English full-text article.

Studies exclusively assessing the use of extracorporeal membrane oxygenation (ECMO) for cardiac or respiratory failure after sustained ROSC were not included. Studies assessing ECMO for deep hypothermia (or other conditions) were only included if cardiac arrest was documented.

Information sources and search strategy

The following electronic databases were searched between January 1, 2018, and June 21, 2022: OVID Medline, Embase, and the Cochrane Central Register of Controlled Trials. The bibliographies of included articles were reviewed for potential additional articles. The search strategy for each database is provided in the protocol. To identify ongoing or unpublished randomized trials, the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.Gov were searched on October 5, 2022. Additional details are provided in the Supplementary Methods.

Study selection

Pairs of two reviewers independently screened all titles and abstracts retrieved from the systematic search. Any disagreement regarding inclusion or exclusion were resolved via discussion between the reviewers and with a third reviewer as needed. The Kappa-values for inter-observer variance was calculated. A third reviewer reviewed all excluded titles and abstracts to ensure optimized sensitivity given that the Kappa-value between the initial pairs of reviewers was below 0.60. Two reviewers then independently reviewed all the full-text reports of the publications passing the first level of screening. Any disagreement regarding eligibility was resolved via discussion.

Data collection and data items

Two reviewers extracted data from individual manuscripts using a predefined standardized data extraction form. Any discrepancies in the extracted data were identified and resolved via discussion. Missing statistical parameters and variance measures of importance (odds ratios and confidence intervals) were calculated if the data permitted.

Risk of bias in individual studies

Two reviewers independently assessed the risk of bias for the included studies. Risk of bias was assessed using version 2 of the Cochrane Risk of Bias tool for randomized trials[15] and using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool for observational studies[16]. Any disagreement was resolved via discussion. Risk of bias was assessed for each outcome within studies. If the bias was different for outcomes this was noted. Additional considerations regarding bias assessments are provided in the Supplementary Methods.

Data synthesis

Studies were assessed for clinical (participants, interventions, and outcomes), methodological (study design or risk of bias), and statistical (forest plots, Chi-squared statistics, and I^2 statistics) heterogeneity. Separate meta-analyses for randomized trials and observational studies were planned as described in the protocol.

Confidence in cumulative evidence

The certainty in the overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[17] based on studies identified in the previous[10] and present systematic review. GRADEpro (McMaster University, 2022) was used for drafting of the GRADE tables.

Results

Overview

The search identified 5573 unique records of which 84 full-text manuscripts were assessed for eligibility (Fig. 1). A total of 35 articles were identified, including 3 trials, 27 observational studies, and 6

cost-effectiveness studies (one was also an observational study).[11–13,18–49] No additional studies were identified after reviewing the references of included studies. The search for ongoing or unpublished randomized trials identified 4 records (Table 1).

Study heterogeneity precluded any meaningful meta-analyses for both randomized trials and observational studies. A descriptive overview of the studies is provided below. Additional study characteristics, patient characteristics, and results of individual studies are provided in the data extraction sheets in the Supplementary Content.

Randomized trials

Three trials comparing an ECPR strategy to local standard care were identified.[11–13] All trials included adult patients with OHCA. There was some heterogeneity in the patient populations and interventions between the trials (Tables 2 and 3 and Table S1). Yannopoulos et al. included 30 cardiac arrests with a shockable rhythm, randomized patients upon arrival to the Emergency Department, and found a benefit of ECPR in survival and favorable neurological status.[11] Hsu et al. included 15 cardiac arrests[12] and Belohlavek et al. included 264 cardiac arrests[13] with any rhythm, randomized patients in the prehospital setting, and found no statistically significant differences in outcomes, although there was a strong signal towards benefit in the larger trial.[13] The intervention group obtained immediate access to a catheterization laboratory in the trials by Yannopoulos et al. and Belohlavek et al.[11,13] All trials were terminated prior to enrolling the intended number of subjects. Effect measures could not be estimated for all outcomes in all trials due to a limited number of events. ECPR was initiated in 42% to 80% of patients in the treatment groups. The mean time from cardiac arrest to ECPR ranged from 59 to 66 minutes. The risk of bias was assessed as intermediate for trials due to the lack of blinding (Table S2).

Observational studies in adults

There were 23 observational studies in adults.[18–40] Fourteen studies included patients with OHCA,[18–31] 6 studies included patients with either OHCA or IHCA,[32–37] and in 3 studies the setting of cardiac arrest was unclear.[38–40] Years of patient inclusion ranged from 2004 to 2022. ECPR was assessed in the prehospital setting in 1 study[22] and in the in-hospital setting in the remaining studies. The setting of ECPR was unclear in 4 studies.[29–32] The number of patients analyzed ranged from 25 to 253,806, the number of exposed patients receiving ECPR ranged from 7 to 5612, and the proportion of exposed patients receiving ECPR ranged from 2% to 66%. The median age of exposed patients ranged from 31 to 72 years. Twelve studies reported the number of patients receiving targeted temperature management or coronary procedures. Results of individual studies were inconsistent, although many studies favored ECPR (Fig. S1). This risk of bias was assessed as critical for all observa-

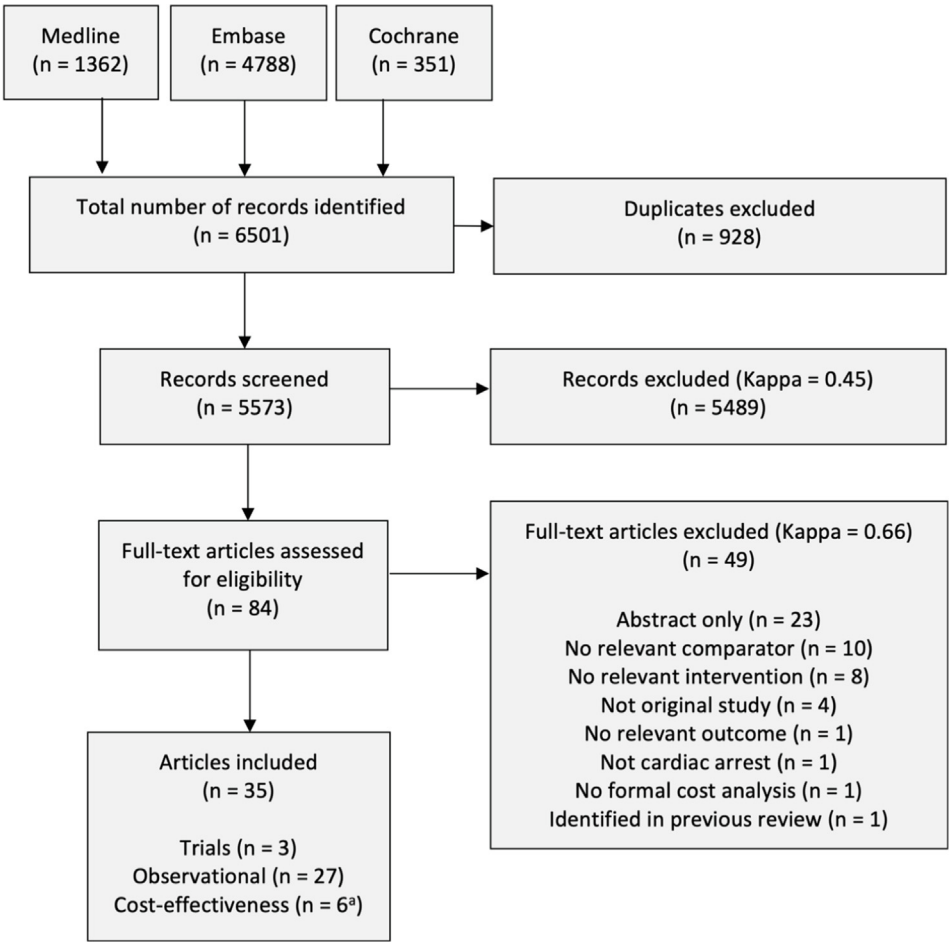

Fig. 1 – PRISMA diagram. Chart illustrating the flow of articles. Of 5573 titles and abstracts, 84 full-text articles were assessed for eligibility, and 35 articles were included in the review. [a] Including one of the observational studies

Table 1 – Overview of registered randomized trials

Title	Country	Estimated completion	Treatment	Control	Patients	Status[a]
Emergency Cardiopulmonary Bypass for Cardiac Arrest (ECPB4OHCA)	Austria	December 2020	Emergency CPB	Standard treatment	40	Terminated early due to low enrollment
A Comparative Study Between a Pre-Hospital and an In-Hospital Circulatory Support Strategy in Refractory Cardiac Arrest (APACAR2)[57]	France	July 2020	Prehospital ECMO	In-hospital ECMO	65	Completed
Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest (INCEPTION)[58]	Netherlands	February 2022	ECPR upon ED arrival	Standard treatment	134	Completed
On-Scene Initiation of Extracorporeal Cardiopulmonary Resuscitation During Refractory Out-of-Hospital Cardiac Arrest (ON-SCENE)[59]	Netherlands	January 2026	Prehospital ECPR	Standard treatment	390	Recruiting

CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; ED: emergency department
[a] Status obtained through correspondence with the principal investigators

tional studies, primarily due to the risk of confounding and selection bias (Table S3 and the Supplementary Methods).

Observational studies in children

There were 4 observational studies in children.[41–44] All studies included patients with IHCA. Years of inclusion ranged from 2000 to 2017. ECPR was assessed in the in-hospital setting in all studies. The number of patients analyzed ranged from 17 to 20,654, the number of exposed patients receiving ECPR ranged from 6 to 1670, and the proportion of exposed patients receiving ECPR ranged from 8% to 55%. The median age was only reported in 1 study as 2.5 years. Three studies reported the number of patients receiving targeted temperature management or coronary procedures. Studies generally favored no ECPR although the confidence intervals were wide (Fig. S2). The risk of bias was assessed as critical for all observational studies, primarily due to the risk of confounding and selection bias (Table S4 and the Supplementary Methods).

Cost-effectiveness studies

Six cost-effectiveness studies were identified[45–49] including 1 observational study that performed a cost analysis.[40] The number of patients analyzed ranged from 32 to 796. The perspective, time horizon, assumed costs, effect of ECPR, and utility varied considerably between the studies. The reported incremental cost-effectiveness ratios of ECPR were converted to euros (EUR) and accounted for inflation until 2022. The calculated incremental cost-effectiveness ratios ranged from 12,254 to 155,739 EUR per quality-adjusted life year in individual studies (Table S5).

Certainty in the overall evidence

The certainty in the evidence was assessed as low for adults with OHCA (Table 4) and as very low for adults with IHCA (Table S6) based on the randomized trials. The certainty in the evidence was assessed as very low for children with OHCA (Table S7) and children with IHCA (Table S8) based on the observational studies in the previous[10] and present systematic review. Observational studies in adults were not used to assess the certainty in the evidence given that new evidence from randomized trials was available.

Discussion

This systematic review provides an update on the use of ECPR compared with manual or mechanical CPR during cardiac arrest. The search identified 3 trials, 27 observational studies (23 in adults and 4 in children), and 6 cost-effectiveness studies published between 2018 and 2022. This review adds to the previous systematic review which identified 25 observational studies prior to 2018.[10]

The purpose of ECPR is to provide circulatory and respiratory support in cardiac arrest, thereby extending the time for recovery, diagnostics, and treatment of potentially reversible causes. Although the application of ECPR appears to have increased over the past decade, data on the potential benefit in cardiac arrest has until recently been limited to observational studies and case series.[50] The paucity of randomized trials, the very-low certainty in the available evidence, and the substantial resources associated with the procedure led to a weak recommendation in the previous cardiac arrest guidelines by ILCOR.[51]

No meta-analyses were conducted of the 3 trials included in this review due to heterogeneity in the included patient populations and interventions, as well as a very low number of events for many outcomes. Yannopoulos et al. included cardiac arrests with an initial shockable rhythm refractory to defibrillation attempts, randomized patients after arrival at the hospital, and found a substantial benefit of ECPR in survival and favorable neurological status.[11] Hsu et al. and Belohlavek et al. included cardiac arrests with any initial rhythm, randomized patients during ongoing resuscitation in the prehospital setting, and found no significant differences in outcomes.[12,13] The

Table 2 – Characteristics of randomized trials.

Study	Country	Centers	Time of inclusion	Main inclusion criteria	Location of randomization	ECPR location	ECMO in treatment group	Location of cannulation	Physician performing cannulation	Time to ECMO
Yannopoulos, 2020[11]	USA	1	2019–2020	Age 18–75, initial shockable rhythm, no ROSC after 3 shocks, transfer time to ED < 30 min	ED	In-hospital	80%	Femoral	Cardiologist	59 min (SD: 28)
Hsu, 2021[12]	USA	1	2017–2020	Age 18–70, initial shockable rhythm or witnessed, persistent cardiac arrest after rhythm analysis and shock if indicated, transfer time to ED < 30 min	Prehospital	In-hospital	42%	Femoral	Emergency physician	66 min (SD: 17)
Belohlavek, 2022[13]	Czech Republic	1	2013–2020	Age 18–65, witnessed, cardiac cause, at least 5 min of ACLS, time to cath. lab < 60 min	Prehospital	In-hospital	66%	Femoral	Cardiologist	61 min (IQR: 55, 70)

ECMO: extracorporeal membrane oxygenation; ROSC: return of spontaneous circulation; ED: emergency department; Cath. Lab.: catheterization laboratory; ECPR: extracorporeal cardiopulmonary resuscitation; ACLS: advanced cardiac life support.

Table 3 – Main results of randomized trials

Study	Patients	Treatment	Control	Mid-term survival[a]		Mid-term favorable neurological outcome[a]		Long-term survival[b]		Long-term favorable neurological outcome[b]	
				Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Yannopoulos, 2020[11]	30	Access to cath. lab and ECPR upon hospital arrival	Standard ACLS in the ED	6/14 (43%)	1/15	3/14	0/15 (0%)	6/14 (43%)	0/15 (0%)	6/14 (43%)	0/15 (0%)
Hsu, 2021[12]	15	Expedited transport to ECPR capable ED	Standard ACLS on site	0/12 (0%)	1/3 (33%)	0/12	0/3 (0%)	0/12 (0%)	1/3 (33%)	0/12 (0%)	0/3 (0%)
Belohlavek, 2022[13]	264	Intra-arrest transport to cardiac center for ECPR	Standard ACLS on site	52/124 (42%)	43/132 (33%)	38/124 (31%)	24/132 (18%)	41/124 (33%)	33/132 (25%)	39/124 (32%)	29/132 (22%)

ECPR: extracorporeal cardiopulmonary resuscitation; ED: emergency department; ACLS: advanced cardiac life support

[a] Mid-term defined as hospital discharge or 30 days

[b] Long-term defined as 3 months or 6 months

Table 4 – Certainty of evidence for randomized trials in adults with out-of-hospital cardiac arrest.

Outcomes	Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other[a]	Overall
Survival to hospital discharge or 30 days	3 studies[11–13]	Not serious	Serious[b]	Not serious	Serious[c]	None	Low
Survival to 3 months or 6 months	3 studies[11–13]	Not serious	Serious[b]	Not serious	Serious[c]	None	Low
Favorable neurological outcome at hospital discharge or 30 days	3 studies[11–13]	Not serious	Serious[b]	Not serious	Serious[c]	None	Low
Favorable neurological outcome at 3 months or 6 months	3 studies[11–13]	Not serious	Serious[b]	Not serious	Serious[c]	None	Low

[a] Includes assessment of publication bias and magnitude of the effect

[b] Some inconsistencies in effect sizes

[c] Although no pooled estimate was calculated, the small sample sizes led to wide confidence intervals

primary outcomes were defined as survival to hospital discharge in the trial by Yannopoulos et al., time to Emergency Department arrival or ECPR initiation in the trial by Hsu et al., and favorable neurological status at 180 days in the trial by Belohlavek et al.

There is a possibility that the trials were underpowered to detect a clinical important difference for some outcomes as all trials were terminated early leading to wide confidence intervals. Moreover, the different trial settings and healthcare systems make the results difficult to generalize and the findings should be interpreted cautiously in the context of the logistical and geographical constraints within each trial. For example, the trial by Belohlavek et al. may better reflect settings where resuscitation for those not receiving ECPR is continued on-scene, which has been associated with improved outcomes compared to intra-cardiac arrest transport in observational studies.[52] Similarly, the trial by Yannopoulos et al. may better reflect settings where all patients are equally likely to be transported to the hospital during ongoing resuscitation. The patients included in the 3 trials were highly selected with only 6–10% of all screened patients being eligible for enrollment and randomization. The study populations may, therefore, reflect variations in ECPR eligibility criteria and patient selection within each trial. Ongoing trials are pending to assess the effect of initiating ECPR on-scene which will be informative for settings where this is possible.

The included observational studies were all assessed to have a critical risk of bias, mainly due to confounding and selection bias for similar reasons as described in the previous ILCOR systematic review.[10] This is further illustrated by the wide range of effect estimates obtained from observational studies in adults with odds ratios ranging from 0.24 (95%CI: 0.13, 0.46) to 43.1 (95%CI: 10.0, 185) for survival and from 0.33 (95%CI: 0.14, 0.76) to 70.4 (95%CI: 9.38, 528) for favorable neurological status. Many studies provided only unadjusted results, did not adjust adequately for potential confounding factors which increases the risk for residual confounding, or adjusted for post-cardiac arrest characteristics which cannot be direct confounders of the relationship between ECPR and outcomes.[53] For some studies, patient selection was strongly related to the intervention and outcome, thereby, introducing collider bias.[54] Very few studies adequately controlled for the timing of ECPR, may have led to resuscitation time bias – a bias occurring when patients with short duration of resuscitation (potentially due to ROSC) cannot receive the intervention.[55] Resuscitation time bias was considered an issue of confounding in the previous ILCOR systematic review but determined to be more related to selection bias in this review. Although many studies attempted to control for this bias by including the duration of resuscitation in the statistical model, this is problematic as time is also a mediator on the causal pathway between ECPR and outcomes. The above issues illustrate some of the limitations in addressing this question using observational data and the need for additional randomized trials.

ECPR is a resource intensive and costly procedure that is only available in selected settings. Despite the well-known costs, there have until recently been no formal analysis to assess the cost-effectiveness of the intervention. The cost-effectiveness studies included in this review were all conducted prior to publication of any randomized trial, meaning that many of the assumptions used for the analyses (such as the effect size of the intervention) were either based on expert opinion, theoretical models, or observational data. As illustrated by the results of the individual studies, these assumptions have led to very wide incremental cost-effectiveness ratios (the difference in the cost divided by the difference in the effect

between ECPR and no ECPR) ranging from 12,254 to 155,739 EUR per quality-adjusted life year, which makes the trade-offs between costs and benefits difficult to assess. More rigorous cost-effectiveness studies using data from the recently published trials are needed to inform the appropriate application of ECPR in different settings.

This systematic review should be interpreted in the context of some limitations. First, the interrater reliability for review of the literature was low (Kappa = 0.45) reflecting the difficulty in identifying relevant studies. However, we did not identify any additional studies through our subsequent review of excluded records, review of references of included studies, and discussion with content experts. Second, the decisions related to the risk of bias assessments were, at least in part, subjective and dependent on the reviewer. Third, we did not evaluate the optimal patient selection, indication, timing, and prognostication related to ECPR. Whether patient selection criteria should be more narrow or wider than those reported in the 3 randomized trials remains unknown, although a consensus statement have been published by the Extracorporeal Life Support Organization in an attempt to guide clinicians.[56] Lastly, we had originally planned to conduct meta-analyses, but determined that this was not feasible due to heterogeneity, a low number of events for many outcomes, and methodological challenges with few trials included.

Conclusions

Recent randomized trials suggest potential benefit of ECPR, but the certainty of evidence remains low. It is unclear which patients might benefit from ECPR.

Conflicts of Interest

Cindy H. Hsu was the lead investigator of the EROCA trial and was, therefore, not involved in the bias assessment of that study.[12] None of the remaining authors have any conflicts of interest to report.

Acknowledgments

The authors would like to thank Katherine M. Berg and Ian Drennan for reviewing the manuscript. Mathias J. Holmberg, Asger Granfeldt, Anne-Marie Guerguerian, Claudio Sandroni, Cindy H. Hsu, and Lars W. Andersen are task force members of the International Liaison Committee on Resuscitation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.12.003.

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