Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with cardiac arrest: a comparative meta-analysis and trial sequential analysis

Christopher Jer Wei Low, Kollengode Ramanathan*, Ryan Ruiyang Ling, Maxz Jian Chen Ho, Ying Chen, Roberto Lorusso, Graeme MacLaren, Kiran Shekar, Daniel Brodie*

Summary

Background Although outcomes of patients after cardiac arrest remain poor, studies have suggested that extracorporeal cardiopulmonary resuscitation (ECPR) might improve survival and neurological outcomes. We aimed to investigate any potential benefits of using ECPR over conventional cardiopulmonary resuscitation (CCPR) in patients with out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA).

Methods In this systematic review and meta-analysis, we searched MEDLINE via PubMed, Embase, and Scopus from Jan 1, 2000, to April 1, 2023, for randomised controlled trials and propensity-score matched studies. We included studies comparing ECPR with CCPR in adults (aged ≥18 years) with OHCA and IHCA. We extracted data from published reports using a prespecified data extraction form. We did random-effects (Mantel-Haenszel) meta-analyses and rated the certainty of evidence using the Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE) approach. We rated the risk of bias of randomised controlled trials using the Cochrane risk-of-bias 2.0 tool, and that of observational studies using the Newcastle–Ottawa Scale. The primary outcome was in-hospital mortality. Secondary outcomes included complications during extracorporeal membrane oxygenation, short-term (from hospital discharge to 30 days after cardiac arrest) and long-term (≥90 days after cardiac arrest) survival with favourable neurological outcomes (defined as cerebral performance category scores 1 or 2), and survival at 30 days, 3 months, 6 months, and 1 year after cardiac arrest. We also did trial sequential analyses to evaluate the required information sizes in the meta-analyses to detect clinically relevant reductions in mortality.

Findings We included 11 studies (4595 patients receiving ECPR and 4597 patients receiving CCPR) in the meta-analysis. ECPR was associated with a significant reduction in overall in-hospital mortality (OR 0·67, 95% CI 0·51–0·87; p=0·0034; high certainty), without evidence of publication bias (p_{egger}=0·19); the trial sequential analysis was concordant with the meta-analysis. When considering IHCA only, in-hospital mortality was lower in patients receiving ECPR than in those receiving CCPR (0·42, 0·25–0·70; p=0·0009), whereas when considering OHCA only, no differences were found (0·76, 0·54–1·07; p=0·12). Centre volume (ie, the number of ECPR runs done per year in each centre) was associated with reductions in odds of mortality (regression coefficient per doubling of centre volume –0·17, 95% CI –0·32 to –0·017; p=0·030). ECPR was also associated with an increased rate of short-term (OR 1·65, 95% CI 1·02–2·68; p=0·042; moderate certainty) and long-term (2·04, 1·41–2·94; p=0·0001; high certainty) survival with favourable neurological outcomes. Additionally, patients receiving ECPR had increased survival at 30-day (OR 1·45, 95% CI 1·08–1·96; p=0·015), 3-month (3·98, 1·12–14·16; p=0·033), 6-month (1·87, 1·36–2·57; p=0·0001), and 1-year (1·72, 1·52–1·95; p<0·0001) follow-ups.

Interpretation Compared with CCPR, ECPR reduced in-hospital mortality and improved long-term neurological outcomes and post-arrest survival, particularly in patients with IHCA. These findings suggest that ECPR could be considered for eligible patients with IHCA, although further research into patients with OHCA is warranted.

Funding None.

Lancet Respir Med 2023

Published **Online** May 22, 2023 https://doi.org/10.1016/S2213-2600(23)00137-6

See **Online/Comment** https://doi.org/10.1016/S2213-2600(23)00150-9

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Introduction

Despite advances in resuscitation and critical care, very few patients with cardiac arrests survive to discharge.[1] Survival ranges between 2% and 11% for people with out-of-hospital cardiac arrest (OHCA),[2–4] and between 15% and 25% for people with in-hospital cardiac arrest (IHCA).[4–6] Thus, there is a crucial need to identify measures that can improve patient outcomes. Cardiac arrest is typically managed by conventional cardiopulmonary resuscitation (CCPR), with survival being dependent on no-flow time (time from cardiac arrest to CCPR) and low-flow time (duration of CCPR).

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Research in context

Evidence before this study

Extracorporeal cardiopulmonary resuscitation (ECPR) in patients who have had a cardiac arrest has received considerable scrutiny in the past 3 years. Three randomised controlled trials have been published since 2019—namely, the Advanced Reperfusion Strategies for Patients with Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation (ARREST), the Prague Out-of-Hospital Cardiac Arrest (Prague OHCA), and the Early Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest (INCEPTION) trials. Although ECPR improved patients' survival in the ARREST trial compared with conventional CPR (CCPR), no differences in survival were found in the Prague OHCA and INCEPTION trials. We did a systematic review and meta-analysis because of the lack of definitive evidence of ECPR use for cardiac arrest. We searched MEDLINE via PubMed, Embase, and Scopus between Jan 1, 2000, and April 1, 2023, for randomised controlled trials or propensity-score matched studies investigating the effects of ECPR in adults (aged ≥18 years) with cardiac arrest using the keywords "extracorporeal membrane oxygenation", "cardiac arrest", and "cardiopulmonary resuscitation", without language restrictions. Of 2165 retrieved studies, 11 studies adhered to our eligibility criteria. As part of the search, we also found seven systematic reviews published between 2016 and 2023, which found that ECPR was associated with reduced mortality and improved neurological outcomes. However, these seven systematic reviews had several limitations, such as including observational studies with concerns of bias due to no propensity-score adjustments, not including the latest data from the INCEPTION trial, not assessing differences in OHCA and in-hospital cardiac arrest (IHCA), or not doing a trial sequential analysis.

Added value of this study

Our meta-analysis investigated whether ECPR improves outcomes in people with cardiac arrest. Compared with CCPR (4597 patients), ECPR (4595 patients) was associated with reduced mortality (odds ratio 0·67, 95% CI 0·51–0·87; p=0·0034). Importantly, we found that ECPR reduced mortality in studies reporting on IHCA (0·42, 0·25–0·70; p=0·0009), whereas no difference in mortality was noted in studies reporting on OHCA (0·76, 0·54–1·07; p=0·12). We also found that increasing centre volumes (ie, the number of ECPR runs done per year in each centre) was associated with reductions in odds of mortality. ECPR was associated with higher odds of survival and odds of survival with favourable neurological outcomes in the long term (≥90 days after cardiac arrest), but not in the short term (from hospital discharge to 30 days after cardiac arrest). Our meta-analyses were also concordant with trial sequential analyses, which provided new insight as to whether the required information sizes were reached to identify clinically significant benefits. A meaningful benefit was found for all outcomes except for short-term neurological outcomes and for mortality when considering randomised controlled trials only or studies reporting on patients with OHCA only.

Implications of all the available evidence

ECPR appears to be associated with improved outcomes in people with IHCA, but not in people with OHCA, for whom the time to cannulation for extracorporeal membrane oxygenation (ECMO) would presumably be longer. Various factors such as time to ECMO cannulation and centre experience could affect survival, and adequate training and experience are crucial to ensure a feasible ECPR programme. These findings might be of interest to policy makers in formulating protocols to respond to cardiac arrests, with special consideration given to the location of cardiac arrest (in-hospital or out-of-hospital) and to the capabilities of individual centres.

However, during CCPR, cardiac output is lower than the normal range, with optimal CPR delivering only 20–30% of normal cardiac output,[7] and a longer low-flow time results in worsening hypoperfusion of vital organs.[8] As such, prolonged CCPR is inadequate in people with refractory cardiac arrest, and return of spontaneous circulation becomes less probable with increases in the low-flow time.[9]

In patients with refractory cardiac arrest, extracorporeal CPR (ECPR) could be considered. Yet, whether ECPR is beneficial remains unclear. Although several studies found improvements in neurological outcomes and survival,[9–11] other studies showed no significant survival benefit.[12,13] Data from meta-analyses are also inconclusive, with findings for survival benefit varying among studies.[14–20] Additionally, previous systematic reviews included observational studies with risk of bias,[14,15] did not include the latest trial evidence (eg, the Early Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest [INCEPTION] trial[21]),[16–18,20] or did not do a trial sequential analysis (TSA).[16,17,19] Three randomised controlled trials investigating ECPR for OHCA were also published: although the Advanced Reperfusion Strategies for Patients with Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation (ARREST) trial[22] found significant benefits with ECPR, the Prague Out-of-Hospital Cardiac Arrest (Prague OHCA)[23] and the INCEPTION[21] trials showed no effect on mortality. Separate studies suggested that estimates from propensity-score matched studies might be similar to, and as robust as, randomised controlled trials.[24–26] Taken together, an updated systematic review focusing on high-quality propensity-score matched studies and randomised controlled trials and incorporating the latest evidence could provide more insight on the efficacy of ECPR for cardiac arrest. The aim of this systematic review and

meta-analysis of propensity-score matched studies and randomised controlled trials is to investigate the benefits of ECPR over CCPR in adults with cardiac arrest.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was done in adherence with the PRISMA guidelines (appendix pp 5–6),[27] and the protocol was prospectively registered with PROSPERO (CRD42022332623). We searched MEDLINE via PubMed, Embase, and Scopus for articles published in English from Jan 1, 2000, to April 1, 2023, using the following terms and their variations: "extracorporeal membrane oxygenation", "cardiopulmonary resuscitation" or "cardiac arrest", and "randomised controlled trial" or "propensity" (appendix pp 7–8). We also reviewed the studies in the reference lists of the identified articles. We included randomised controlled trials and propensity-score matched studies comparing ECPR with CCPR in adults with cardiac arrest. We excluded studies reporting on patients younger than 18 years, non-human studies, and observational studies that did not undertake propensity-score matching. CJWL, RRL, and MJCH screened the studies (independently and in duplicate), collected the data, and assessed the risk of bias; conflicts over inclusion were resolved by KR. If data were missing, we contacted the corresponding authors of each study to obtain additional data for analysis.

Data analysis

We collected data using a prespecified data extraction form (appendix p 9). In the case of overlapping patient data, we included the largest study and excluded any other overlapping studies. We assessed risk of bias in the included studies using the Cochrane risk-of-bias 2.0 tool (RoB 2.0) for randomised controlled trials and the Newcastle–Ottawa Scale (NOS) for observational studies. We assessed certainty of evidence using the Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE) approach, which ranks the certainty of evidence from high (we are confident that the true effect lies close to that of the estimate of the effect) to very low (we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect).[28,29]

The primary outcome was in-hospital mortality. Secondary outcomes were complications during extracorporeal membrane oxygenation (ECMO; classified in broad groups described by the Extracorporeal Life Support Organization [ELSO],[30] and assessed as part of our data extraction analysis), short-term (from hospital discharge to 30 days after cardiac arrest) and long-term (≥90 days after cardiac arrest) survival with favourable neurological outcomes (defined as cerebral performance category scores 1 or 2), and post-arrest survival (measured as survival during follow-up at 30 days, 3 months, 6 months, and 1 year). We did random-effects meta-analyses (Mantel-Haenszel method) for binary outcomes using the DerSimonian-Laird model,[31–33] and conventional inverse-variance weighted meta-analyses for continuous outcomes.[34] We present binary outcomes as pooled odds ratios (ORs), and continuous outcomes as mean differences, each with their corresponding 95% CIs. We assessed statistical heterogeneity (inconsistency) as part of the GRADE approach, quantitatively using I^2, τ^2, and p-values from the Cochran's Q test, and qualitatively via visual inspection of forest plots.[35] Assessment of publication bias was done qualitatively with visual inspection of funnel plots when less than ten studies were included in the meta-analysis, and quantitatively with Egger's regression test when ten or more studies were included. We corrected for small-study effects using the random-effects trim-and-fill (R_0 estimator) procedure. We did a sensitivity analysis after excluding studies with high risk of bias (defined as Cochrane RoB 2.0 high risk or NOS score <7).

See Online for appendix

We did prespecified subgroup analyses based on the location of cardiac arrest (in-hospital or out-of-hospital), type of study (propensity-score matched study or randomised controlled trial), study quality, and geographical region (Asia, Europe, or North America). We did random-effects, inverse variance,[36] univariable meta-regression when at least six data points were reported, to explore potential sources of heterogeneity, or prognostically relevant prespecified study-level covariates (centre volume [ie, the number of ECPR runs done per year in each centre; per doubling of centre volume], age [per year], proportion of male patients, BMI [per 1 kg/m^2], duration of CPR [per min], and proportion of patients presenting with ventricular fibrillation or tachycardia). We estimated the centre volume in propensity-score matched studies and randomised controlled trials separately: for observational studies we divided the number of patients who received ECPR by the number of centres and by the number of years comprising the study period. For randomised controlled trials, we used the number of patients who were eligible for ECPR. Similar methods for calculating centre volume have been reported in previous reviews of the ELSO registry.[37,38]

We did TSAs using TSA (version 0.9.5.10), assessing efficacy on the basis of the O'Brien-Fleming α-spending function, and futility on the basis of the O'Brien-Fleming β-spending function. TSA combines a cumulative meta-analysis with a sample size calculation to evaluate a cumulative pooled effect after an additional trial is included based on the information size thus obtained. The principles of TSA are similar to those of group sequential monitoring boundaries in randomised controlled trials during interim analyses (appendix pp 3–4).[39] We estimated the required information size and cumulative Z scores using the relative risk reduction and baseline estimates of the CCPR group based on the results of our meta-analyses. We estimated the variance of the

For more on the **TSA software** see https://ctu.dk/tsa

pooled estimates and heterogeneity using the TSA software. We assumed a type I error of 5% and a power of 80%. For continuous variables, we pooled the means from the aggregate data presented in each study as per Wan and colleagues.[40] We added trials to the cumulative meta-analyses according to the year they were published

In post-hoc analyses, we pooled the adjusted ORs and hazards ratios (HRs) reported by the individual studies to adjust for potential factors that might confound the association between mortality and ECPR. Additionally, we pooled the HRs for mortality for potential prognostic factors, including age (per year), duration of CPR (per min), and initial presenting rhythm (shockable *vs* unshockable) to better understand some of the prognostic factors that might affect mortality. We also did post-hoc sensitivity analyses after excluding any studies that individually contributed substantial weight to mortality outcomes due to their large sample sizes. We did an additional post-hoc analysis including all observational studies that did not undertake propensity-score matching. We used p values less than 0·05 as the threshold for statistical significance. We did all statistical analyses using R (version 4.0.5).

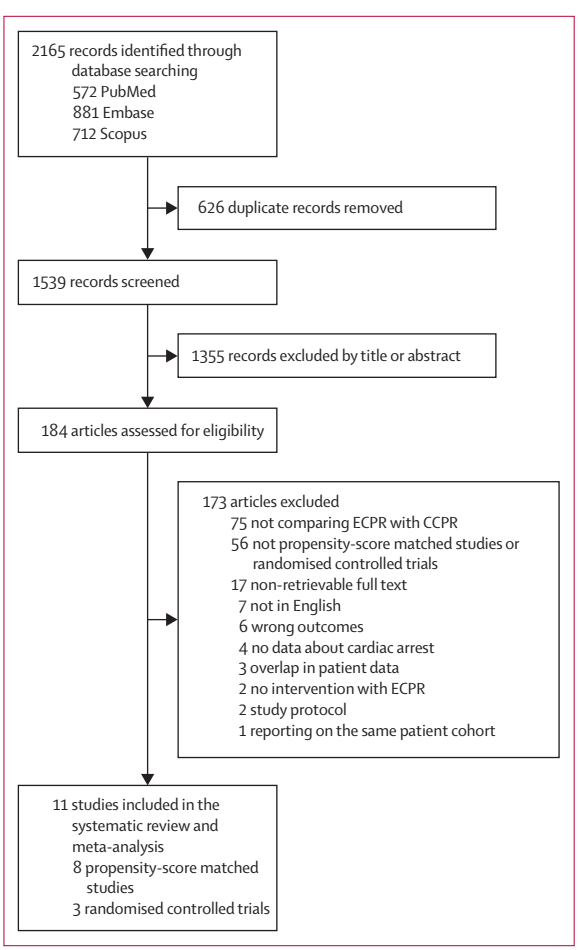

Figure 1: **Study selection**
CCPR=conventional cardiopulmonary resuscitation. ECPR=extracorporeal cardiopulmonary resuscitation.

Role of the funding source
There was no funding source for this study.

Results

The literature search identified 2165 records (figure 1). After removing 626 duplicates and excluding 1539 articles in the title and abstract screening, we assessed 184 full-text articles for eligibility. 12 papers were initially identified for inclusion; however, data from two studies were combined because they reported on the same patient cohort.[41,42] We included 11 studies (4595 patients received ECPR and 4597 patients received CCPR) in our systematic review and meta-analysis, of which eight were propensity-score matched studies and three were randomised controlled trials (figure 1).[9,10,12,21–23,41–46] Patients' characteristics across all studies are summarised in the appendix (pp 10–12). The proportion of male patients was similar between the groups (75·3% [95% CI 69·0–80·6] in the ECPR group *vs* 78·3% [69·3–85·2] in the CCPR group); pooled mean age was also similar (59·0 years [95% CI 57·3–60·7] *vs* 59·3 years [56·3–62·4]; appendix p 12). Six studies assessed only OHCA,[21–23,44–46] four assessed only IHCA,[10,12,41,43] and one study assessed patients in both IHCA and OHCA settings.[9] The most common cause of cardiac arrest was acute coronary syndrome (six studies[10,12,21,23,41,43]) and ranged from 32·7% to 76·8% of all cardiac arrests (appendix pp 13–16). Other causes of cardiac arrest are shown in the appendix (appendix pp 13–16). Shockable rhythms (nine studies[9,10,12,21–23,41,43,46]) accounted for 56·8% (95% CI 21·4–86·4) and 59·5% (25·1–86·6) of initial presenting rhythms in patients of ECPR and CCPR groups, respectively (appendix pp 13–16). The no-flow time (two studies[23,46]) ranged from 0 min to 5 min, and the time to ECPR (three studies[21–23]) ranged from 51 min to 73 min (appendix pp 13–16). The low-flow times for ECPR (47·8 min [95% CI 40·2–55·3]) and CCPR (43·9 min [38·4–49·5]) were similar. Targeted temperature management after cardiac arrest (six studies[9,22,23,43,45,46]) was used in 45·3% (95% CI 17·8–76·1%) of patients receiving ECPR, and in 15·3% (6·3–32·8) of patients receiving CCPR (appendix pp 17–18). Other types of therapies are detailed in the appendix (pp 17–18). In six studies,[9,21–23,44,46] patients with OHCA were transported to emergency centres, with initial CCPR at the site of cardiac arrest followed by ECPR initiation at the hospital (ie, scoop-and-run [rapid transport to definitive care] approach). One study did not specify whether patients with OHCA were transported to emergency centres before initiating ECPR, or whether they were administered ECMO at the site of cardiac arrest (ie, stay-and-play [on-scene resuscitation] approach).[45]

Compared with CCPR, ECPR was associated with significant reduction in mortality (OR 0·67, 95% CI

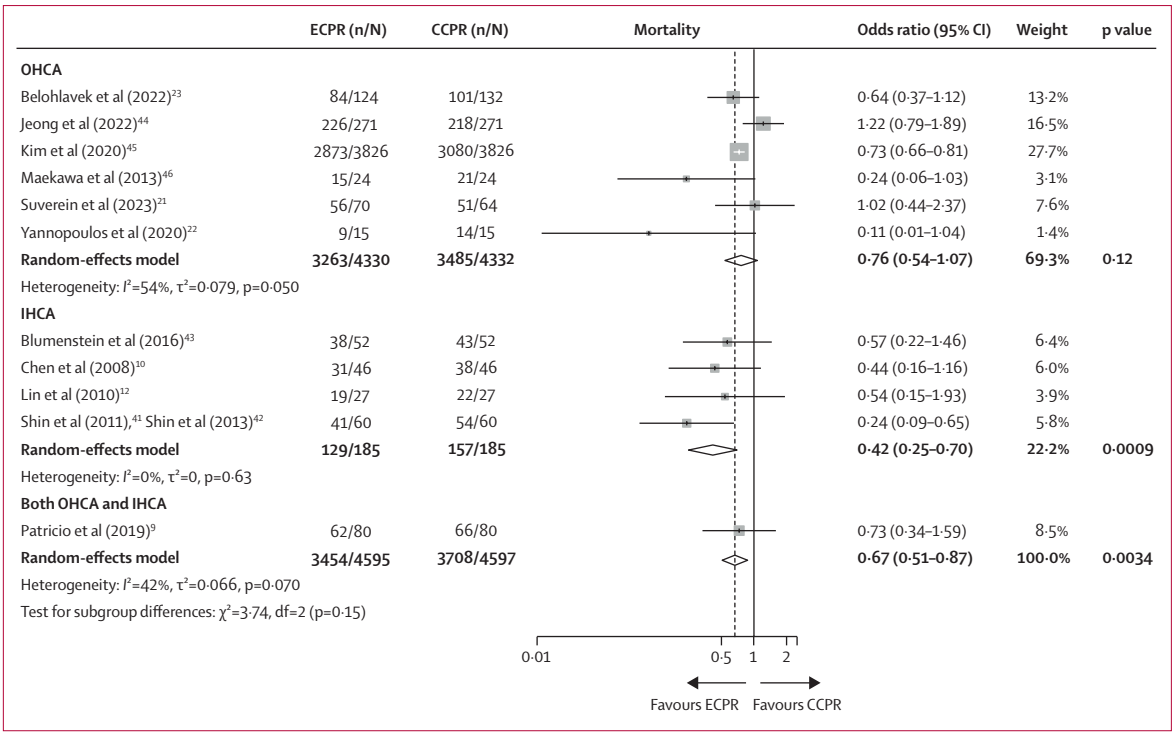

Figure 2: **Forest plot of the odds ratios for mortality in patients with cardiac arrest receiving ECPR or CCPR**
CCPR=conventional cardiopulmonary resuscitation. ECPR=extracorporeal cardiopulmonary resuscitation. IHCA=in-hospital cardiac arrest. OHCA=out-of-hospital cardiac arrest. n=cases of cardiac arrest. N=group size.

0·51–0·87; p=0·0034; figure 2, table; appendix pp 23–24), with high certainty based on GRADE (appendix p 20) and without evidence of publication bias (p_{egger}=0·19; appendix p 22). No studies were at high risk of bias (appendix p 19), and therefore we did not do the sensitivity analysis after excluding studies with high risk of bias. We did a post-hoc sensitivity analysis after excluding one study that contributed substantial weight, due to its large sample size,[45] to investigate the study's effect on the overall estimate (OR 0·60, 95% CI 0·41–0·89; p=0·010; table).

Subgroup analyses of the primary outcome—based on type of study, geographical region, location of cardiac arrest, and study quality—did not show significant differences in mortality ($p_{interaction}$>0·05; appendix p 25). Mortality was not significantly different between patients receiving ECPR and CCPR in randomised controlled trials (OR 0·65, 95% CI 0·32–1·34; p=0·24), but it was lower in patients in the ECPR group in propensity-score matched studies (0·65, 0·47–0·90; p=0·011; table). Additionally, when analysing OHCA studies and IHCA studies separately, ECPR had no significant effect on mortality in patients with OHCA (0·76, 0·54–1·07; p=0·12), whereas mortality was significantly reduced in patients with IHCA (0·42, 0·25–0·70; p=0·0009; table). The exclusion of the study by Kim and colleagues[45] (due to its weighing) from the analysis considering studies of patients with OHCA only did not significantly change the pooled estimates (0·71, 0·39–1·27; p=0·24).

	Number of studies	Odds ratio (95% CI)	p value
Primary outcome			
All studies mortality	11	0·67 (0·51–0·87)	0·0034
Post-hoc mortality	10	0·60 (0·41–0·89)	0·010
OHCA mortality	6	0·76 (0·54–1·07)	0·12
IHCA mortality	4	0·42 (0·25–0·70)	0·0009
PSM mortality	8	0·65 (0·47–0·90)	0·011
RCT mortality	3	0·65 (0·32–1·34)	0·24
Secondary outcomes			
Overall short-term favourable neurological outcomes	7	1·65 (1·02–2·68)	0·042
Overall long-term favourable neurological outcomes	8	2·04 (1·41–2·94)	0·0001
OHCA short-term favourable neurological outcomes	3	1·24 (0·65–2·36)	0·51
OHCA long-term favourable neurological outcomes	4	1·96 (1·02–3·79)	0·045
IHCA short-term favourable neurological outcomes	4	2·37 (1·34–4·19)	0·0031
IHCA long-term favourable neurological outcomes	3	2·80 (1·31–6·00)	0·0080
30-day survival	7	1·45 (1·08–1·96)	0·015
3-month survival	3	3·98 (1·12–14·16)	0·033
6-month survival	6	1·87 (1·36–2·57)	0·0001
1-year survival	5	1·72 (1·52–1·95)	<0·0001
Bleeding	4	4·84 (1·91–12·24)	0·0009

IHCA=in-hospital cardiac arrest. OHCA=out-of-hospital cardiac arrest. PSM=propensity-score matched study. RCT=randomised controlled trial.

Table: **Summary of outcomes**

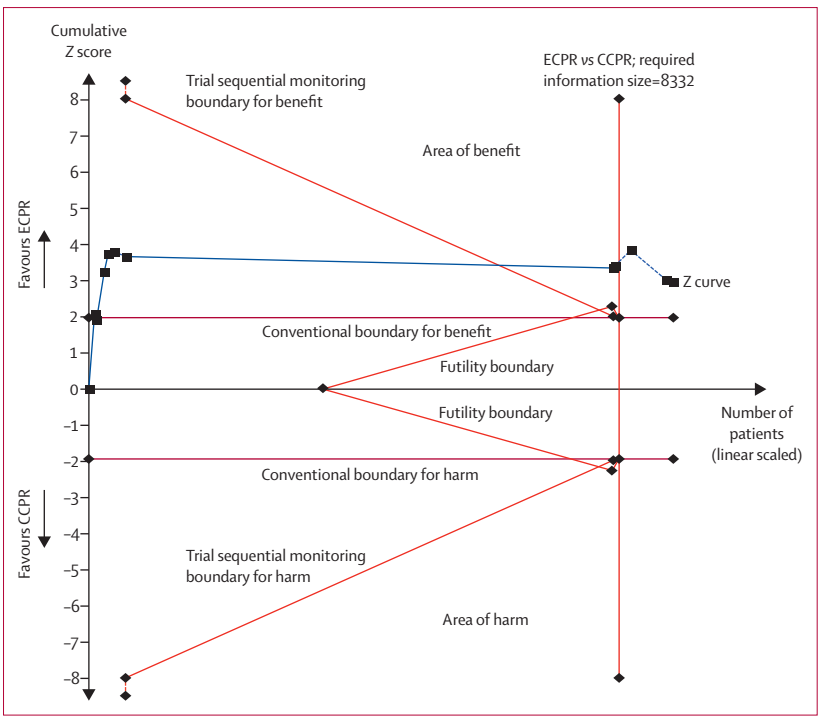

Figure 3: **TSA of 11 studies analysing in-hospital mortality in patients receiving either ECPR or CCPR**
Studies are shown as black-filled squares on the cumulative Z curve. For the conventional boundaries, p=0·05 and z=|1·96|. The TSA software only generates Z scores from –8 to +8. The cumulative Z curve crosses the required information size line at n=8332—ie, the required information size is achieved. The cumulative Z curve also crosses the conventional boundary for benefit and the TSA-adjusted monitoring boundary for benefit, showing that, compared with CCPR, ECPR has clinical benefit in reducing mortality. CCPR=conventional cardiopulmonary resuscitation. ECPR=extracorporeal cardiopulmonary resuscitation. TSA=trial sequential analysis.

Univariable meta-regression showed that centre volume was associated with a significant reduction in the odds of mortality in patients receiving ECPR (regression coefficient per doubling of centre volume –0·17, 95% CI –0·32 to –0·017; p=0·030). However, patients' characteristics (proportion of male patients, mean age, and other comorbidities), clinical factors (presenting rhythm), or procedural factors (duration of CPR) were not significant predictors of mortality (appendix pp 25–26).

We did TSA for in-hospital mortality in all studies (figure 3); we looked specifically at studies reporting on OHCA and IHCA, and at propensity-score matched studies and randomised controlled trials (appendix pp 27–30). The required information size was attained in all scenarios except for randomised controlled trials. We noted a clinically significant reduction in mortality in the primary analysis including all studies, studies on IHCA only, and propensity-score matched studies, but not for OHCA only or randomised controlled trials only. Boundaries for futility (ie, the lines delineating the area in which the addition of further studies probably does not change the no-effect results) were not noted in the TSA for studies on OHCA only, as the required information size was attained after cumulatively including only the study by Kim and colleagues.[45]

ECPR was associated with improved short-term (OR 1·65, 95% CI 1·02–2·68; p=0·042; moderate certainty) and long-term (2·04, 1·41–2·94; p=0·0001; high certainty; figure 4) survival with favourable neurological outcomes (table). Visual inspection of funnel plots did not indicate suspicions for publication bias (appendix p 22). After stratifying on the basis of the location of cardiac arrest, ECPR had variable effects on neurological outcomes in patients with OHCA (short-term OR 1·24, 95% CI 0·65–2·36; p=0·51; long-term 1·96, 1·02–3·79; p=0·045). However, ECPR had significantly better effects in patients with IHCA (short-term OR 2·37, 95% CI 1·34–4·19, p=0·0031; long-term 2·80, 1·31–6·00; p=0·0080; table). Survival outcomes after discharge were higher in patients receiving ECPR than in those receiving CCPR at 30-day (high certainty), 3-month (moderate certainty), 6-month (high certainty), and 1-year (high certainty) follow-ups (table; appendix p 20). Visual inspection of funnel plots for survival did not indicate suspicions for publication bias. The TSA was concordant with the meta-analysis of secondary outcomes. ECPR was associated with a clinically significant benefit for long-term neurological outcomes (figure 5), and with increased survival at 30-day, 3-month, 6-month, and 1-year follow-ups (appendix pp 32–35). For short-term neurological outcomes, the required information size was not met, and the cumulative Z curve did not cross the conventional boundary for benefit or the TSA-adjusted monitoring boundary for benefit, suggesting that more trials are needed to establish whether ECPR is associated with clinical benefits (appendix p 31).

The most common reported complication was bleeding (four studies[9,22,23,43]); patients receiving ECPR were more likely to have bleeding than were those receiving CCPR (OR 4·84, 95% CI 1·91–12·24; p=0·0009; high certainty). Other post-procedural outcomes are pooled qualitatively in view of heterogeneity, and are summarised in the appendix (pp 36–38).

As part of our post-hoc analyses, we pooled the adjusted HRs for mortality as reported by the individual studies to account for potential confounding factors (appendix p 39). ECPR was associated with reduced hazards for mortality at the time of longest follow-up, 6 months, and 1 year; however, results at 28-day follow-up were not significant. We also found that ECPR was associated with a significant increase in the odds of survival with favourable neurological outcomes, although time-to-event analysis did not show a significant increase in favourable neurological outcomes.

We also pooled the HRs for potential prognostic factors to investigate their effect on mortality (appendix p 39). The duration of CPR was associated with increased mortality (HR per min 1·01, 95% CI 1·00–1·01; p=0·0001), whereas an initial presentation with a shockable rhythm was associated with reduced mortality (HR 0·52, 95% CI 0·32–0·86; p=0·011). Age was not associated with mortality (HR per year 1·02, 95% CI 0·98–1·06; p=0·41).

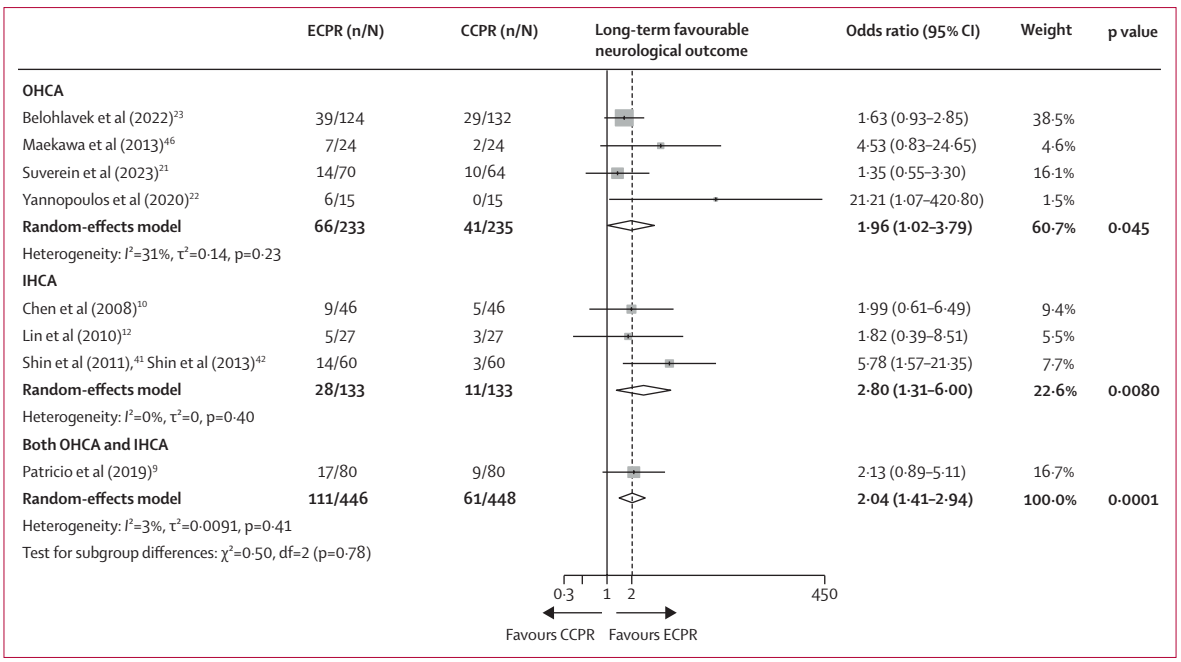

Figure 4: **Forest plot of the odds ratios for favourable long-term neurological outcomes in patients with cardiac arrest receiving ECPR or CCPR**
Favourable neurological outcomes were defined as cerebral performance category scores 1 or 2. Long term was defined as 90 days or more after cardiac arrest. CCPR=conventional cardiopulmonary resuscitation. ECPR=extracorporeal cardiopulmonary resuscitation. n=cases of cardiac arrest. N=group size.

In a separate post-hoc analysis, we included 12 additional observational studies without propensity-score matching, including 7007 patients receiving ECPR and 227 487 patients receiving CCPR.[11,13,47–56] In the analysis, we found that ECPR was associated with a reduction in mortality (OR 0·55, 95% CI 0·33–0·92; p=0·022; very low certainty). After stratifying the results on the basis of the location of cardiac arrest, ECPR was associated with reductions in mortality in both patients with IHCA (0·43, 0·27–0·69; p=0·0005) and patients with OHCA (0·50, 0·26–0·97; p=0·039; appendix p 40). When pooling the 12 observational studies alone, ECPR was not associated with a reduction in mortality (0·56, 0·26–1·21; p=0·14; very low certainty; appendix p 21, 41).

Discussion

Our meta-analysis found that ECPR was associated with improved short-term and long-term survival, with which the TSA analysis was concordant. We also found that ECPR was effective in improving survival in patients with IHCA. However, more studies are needed to establish whether ECPR improves survival in patients with OHCA, and whether it has clinical benefits for short-term neurological outcomes, ideally in different settings and jurisdictions.

By immediately maintaining organ perfusion, ECPR reduces low-flow time,[8] thus reducing multiorgan failure, cardiovascular instability, and brain injury after cardiac arrest, which account for most deaths occurring after cardiac arrest.[57] Long low-flow times during CCPR increase the risk of the aforementioned adverse outcomes.[57–59] Furthermore, because many patients have an ischaemic cause for their cardiac arrest, ECPR provides stable systemic perfusion and rapid access for definitive coronary angiography,[60] providing a bridge to treatment for underlying causes of cardiac arrest, possibly improving cardiac recovery and survival rates.[61,62]

Although we found significant differences in our primary meta-analysis, analysing studies reporting on IHCA and OHCA separately yielded different results; mortality reductions and neurological improvements were significant in patients with IHCA, but they were not significant in patients with OHCA. This finding was corroborated with our TSA. Although our sensitivity analysis including observational studies without propensity score matching found significant survival benefits in patients with OHCA, the certainty of the estimates for these studies was very low, probably due to the lack of adjustment of confounders, which potentially skews the analysis. The results of this sensitivity analysis should be interpreted with caution, and they were accordingly rated at a lower certainty. The non-significant results of the meta-analysis of patients with OHCA receiving ECPR might be due to increased low-flow time during transport to the hospital, increasing the likelihood of brain injury and organ failure and attenuating any benefits of ECPR. Variables such as varying robustness of responses of emergency medical services before hospital admission and stay-and-play or scoop-and-run approaches between emergency medical services could confound outcomes in patients with OHCA, resulting in different findings across different settings. Patients with IHCA are likely to have not

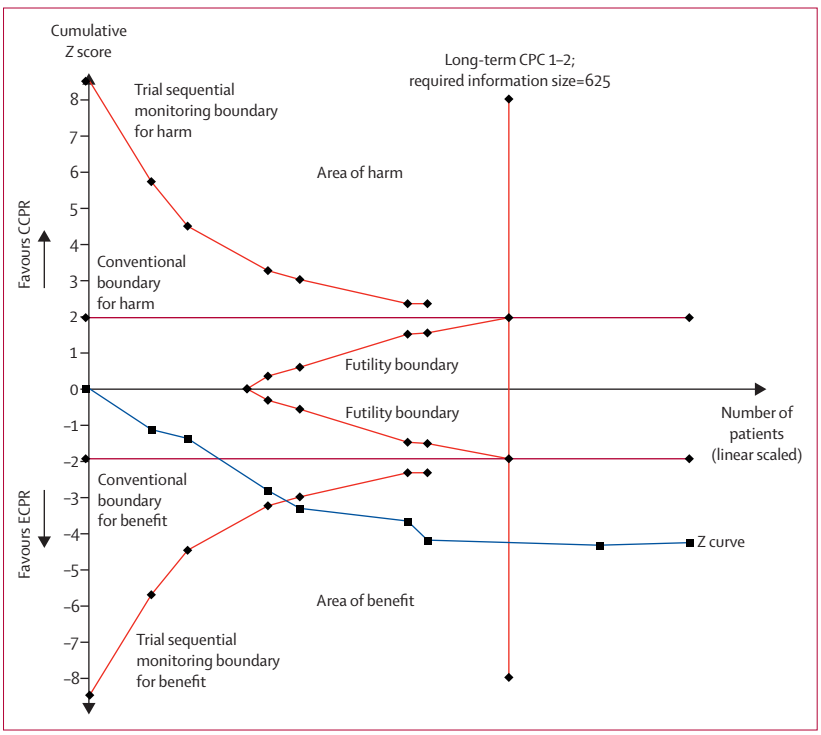

Figure 5: **TSA of eight studies analysing long-term favourable neurological outcomes in patients receiving either ECPR or CCPR**

Studies are shown as black-filled squares on the cumulative Z curve. For the conventional boundaries, p=0·05 and z=|1·96|. The TSA software only generates Z scores from −8 to +8. The cumulative Z curve crosses the required information size line at n=625—ie, the required information size is achieved. The cumulative Z curve also crosses the conventional boundary for benefit and the TSA-adjusted monitoring boundary for benefit, showing that, compared with CCPR, ECPR has clinical benefit, leading to favourable neurological outcomes. CCPR=conventional cardiopulmonary resuscitation. CPC=cerebral performance category. ECPR=extracorporeal cardiopulmonary resuscitation. TSA=trial sequential analysis.

only shorter low-flow times, but also higher rates of witnessed arrest and bystander CPR, reducing no-flow time as well.[63] Furthermore, as more information is known about patients with IHCA, they are likely to have a more refined patient selection for ECPR. Better outcomes for IHCA are concordant with findings from previous retrospective studies and systematic reviews.[64–66]

Our results are largely concordant with previous observational studies and systematic reviews.[9,16,17] Despite statistically significant benefits in short-term neurological outcomes, the required information size was not attained and, in the TSA graphs, the cumulative Z curve was between the conventional and the TSA-adjusted monitoring boundaries for benefit, suggesting that there is insufficient information to fully assess the clinical benefit of ECPR for this outcome. Existing literature also remains equivocal.[11,27,54,67] Although no adequate explanation has been suggested, the ability of ECPR to increase overall survival might also improve survival for patients with substantial neurological injury who would otherwise have died without ECPR, resulting in more patients with cerebral performance category scores of 3 or 4 in the short term. Improved long-term outcomes could then be attributed to recovery of some neurological function.

The three randomised controlled trials reporting on ECPR in patients with OHCA have discordant results. The INCEPTION[21] and the Prague OHCA[23] trials showed no effect on mortality, whereas the ARREST trial[22] found significant survival benefits. Differences in these results could be due to differences in some prognostic factors between studies. For example, time to cannulation differed among all trials (mean 59 min [SD 28] in the ARREST trial, 62 min [11] in the Prague OHCA trial, and 75 min [18] in the INCEPTION trial). These differences corroborate with our finding that the duration of CPR before ECMO was significantly associated with increased mortality (HR per min 1·01, 95% CI 1·00–1·01; p=0·0001). Furthermore, pre-hospital management factors such as rapid arrival of emergency medical services and rapid transport to hospital probably improve outcomes in patients with OHCA,[68,69] and although variably recorded, they could have affected the findings of the randomised controlled trials. We found that centre volume was an important prognostic factor for mortality, which is in line with previous studies.[70] In the three randomised controlled trials, centre volume varied, ranging from 2·82 cases per centre annually in the INCEPTION trial to 26·9 cases in the Prague OHCA trial and 36 cases in the ARREST trial. Ultimately, differing practices, experiences, and volumes between ECMO centres could account for discordant findings. Such confounding variables in post-cardiac arrest care are not limited to randomised controlled trials alone. Although poorly reported, we found substantial variation in the use of therapeutic temperature management, low-flow and cannulation times, and some aspects of both care in intensive care units after cardiac arrest and withdrawal of life support. These variations might contribute to differences in outcomes between centres, and between patients receiving ECPR and those receiving CCPR.

Although our study shows benefits to using ECPR, additional complications warrant consideration. The most commonly reported complication is bleeding,[61] affecting 32–70% of patients receiving ECPR,[71–73] although other notable complications include infection and leg ischaemia. Other considerations for potential prognostic factors include the low-flow time and presenting rhythm. Although our study did not find a significant association between age and survival, a previous study has shown that patients younger than 65 years had increased survival.[42] In addition to ECPR, immediate revascularisation where indicated will also be important in terms of survival.[42] Evaluation of institutional factors and systems of care available to each patient is another essential aspect to consider when assessing the overall benefit of ECPR. The preparedness of pre-hospital ECMO programmes and infrastructure for rapid referral of patients for early ECMO has an important role in determining outcomes. Optimisation of these factors will be essential to maximise prognostic benefits conferred by ECPR.

Our study has several notable strengths. Our systematic review included only high-quality propensity-score matched studies and randomised controlled trials, and it currently represents the highest level of evidence in support of ECPR. Previous reviews included observational studies without propensity-score adjustment, which can introduce confounding factors to the analysis, and they had overlaps in datasets.[8,14,74] Additionally, we used TSA to assess the efficacy and effectiveness of ECPR with respect to the required information size, and inform future research and clinical practice. The TSAs are particularly helpful because multiple meta-analyses and randomised controlled trials have been published, increasing the risk of type I errors. Furthermore, by pooling HRs, we provided a more robust picture of the efficacy of ECPR, which further augments our original analysis. We used a robust search strategy validated by a health services librarian, with comprehensive inclusion and exclusion criteria. Finally, we communicated our findings comprehensively and transparently using the GRADE approach.

Nevertheless, this study has limitations. First, there was variability in data for secondary outcomes, in relation to post-procedural complications, patient comorbidities, and cardiac arrest characteristics. Nonetheless, we accounted for some of the heterogeneity by restricting our inclusion criteria to high-quality studies and doing subgroup analyses and meta-regression. Second, residual confounding remains in propensity-score matched studies, and propensity score models were heterogenous between studies. Factors outside the propensity score model might not have been adjusted for, and potentially confound the analysis despite cohorts appearing well matched. For instance, the proportion of patients undergoing revascularisation varied and could be a confounder.[10,43] Third, the proportion of patients with IHCA was smaller than those with OHCA, which can lead to spurious findings and imprecise results. Nevertheless, our study made substantial distinctions between patients with IHCA and those with OHCA in our methodology and discussion, and results for both types of cardiac arrest were presented separately. Fourth, the calculation of centre volumes could not be cross-linked or validated to registries that include overall cardiac arrest volumes by centre, and therefore, it might not completely reflect the centre volumes in each study. Fifth, we did several post-hoc analyses, which should be considered as exploratory and interpreted with caution. Finally, data on quality of life after cardiac arrest and hospital discharge were scarce. Survival with favourable neurological outcomes does not measure other aspects associated with quality of life. Other psychological symptoms, such as depression and post-traumatic stress disorder are similarly important, because they affect more than 25% of patients with cardiac arrest.[75]

In conclusion, we found that ECPR was associated with a significant reduction in mortality for patients with IHCA, and a non-significant reduction for patients with OHCA, probably related to longer no-flow and low-flow times for ECPR. Compared with CCPR, ECPR also improves long-term neurological outcomes and post-arrest survival, whereas its effect on short-term neurological outcomes was not significant. Furthermore, ECPR was associated with procedural complications, especially bleeding. The non-significant results in patients with OHCA does not preclude the possibility that ECPR could be effective in the future, conditional on elucidating the appropriate patient population and timing of ECPR. Future research into this topic should focus on building sustainable systems to evaluate the number of patients eligible for ECPR to maximise patients' benefits, especially for patients with OHCA, and examine the potential cost-effectiveness of ECPR.

Contributors

KR, KS, and DB contributed to the study design. CJWL, KR, RRL, and MJCH were responsible for the search strategy and screening of the articles, the risk of bias assessment, and data collection, and had full access to and verified all the data. CJWL, KR, RRL, and YC analysed and interpretated the data. CJWL, RRL, and MJCH prepared the tables and figures. CJWL and KR wrote the draft of the manuscript. All authors critically revised the manuscript for intellectually important content. All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft. CJWL and KR had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

KR is the Co-Chair of the ELSO scientific oversight committee. KR has received honoraria from Xenios for educational lectures on ECMO. RL is a Consultant for LivaNova, Medtronic, Abiomed, and Getinge (all honoraria are paid to his university to support research activities), and a member of the medical advisory board of Eurosets, Xenios, and HemoCue. GM is the President of ELSO. KS is a member of the scientific committee of the International ECMO Network and is the Chair of the research working group of ELSO education taskforce—ELSOed. KS reports receiving honoraria in relation to educational lectures on ECMO from Getinge. DB receives research support from, and consults for, LivaNova. DB has been on the medical advisory boards for Abiomed, Xenios, Medtronic, Inspira, and Cellenkos. DB is the President-elect of ELSO and the Chair of the executive committee of the International ECMO Network. All other authors declare no competing interests.

Data sharing

All data generated or analysed in this study were extracted from published studies and their supplementary information files. Extracted data are available on request to the corresponding author.

Acknowledgments

We thank Suei Nee Wong for her assistance with the search strategy.

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