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SYSTEMATIC REVIEW

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Refractory out-of-hospital cardiac arrest and extracorporeal cardiopulmonary resuscitation: A meta-analysis of randomized trials

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Abstract

Background: In adults with refractory out-of-hospital cardiac arrest, when conventional cardiopulmonary resuscitation (CPR) alone does not achieve return of spontaneous circulation, extracorporeal CPR is attempted to restore perfusion and improve outcomes. Considering the contrasting findings of recent studies, we conducted a meta-analysis of randomized controlled trials to ascertain the effect of extracorporeal CPR on survival and neurological outcome.

Methods: Pubmed via MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched up to February 3, 2023, for randomized controlled trials comparing extracorporeal CPR versus conventional CPR in adults with refractory out-of-hospital cardiac arrest. Survival with a favorable neurological outcome at the longest follow-up available was the primary outcome.

Results: Among four randomized controlled trials included, extracorporeal CPR compared with conventional CPR increased survival with favorable neurological outcome at the longest follow-up available for all rhythms (59/220 [27%] vs. 39/213 [18%]; OR = 1.72; 95% CI, 1.09–2.70; $p = 0.02$; $I^2 = 26\%$; number needed to treat of 9), for initial shockable rhythms only (55/164 [34%] vs. 38/165 [23%]; OR = 1.90; 95% CI, 1.16–3.13; $p = 0.01$; $I^2 = 23\%$; number needed to treat of 7), and at hospital discharge or 30 days (55/220 [25%] vs. 34/212 [16%]; OR = 1.82; 95% CI, 1.13–2.92; $p = 0.01$; $I^2 = 0.0\%$). Overall survival at the longest follow-up available was similar (61/220 [25%] vs. 34/212 [16%]; OR = 1.82; 95% CI, 1.13–2.92; $p = 0.59$; $I^2 = 58\%$).

Conclusions: Extracorporeal CPR compared with conventional CPR increased survival with favorable neurological outcome in adults with refractory out-of-hospital cardiac arrest, especially when the initial rhythm was shockable.

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KEYWORDS

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

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death and disability worldwide.[1,2] Despite significant improvements in resuscitation, the overall prognosis after OHCA remains poor, and many survivors are discharged with permanent neurological damage.[3] Refractory OHCA, defined as the failure to achieve return of spontaneous circulation (ROSC) despite high-quality advanced life support, is associated with an even worse prognosis. Survival rate drops quickly after 10 min of conventional cardiopulmonary resuscitation (CPR).[4,5] After 35 min of resuscitation, less than 1% of OHCA patients survive without neurological impairments.[5]

In patients with refractory OHCA, the implantation during ongoing CPR of veno-arterial extracorporeal membrane oxygenation (VA-ECMO), known as extracorporeal CPR, can restore and maintain organ perfusion to identify and treat the underlying etiology of the cardiac arrest while limiting brain injury. There is growing evidence that this approach might improve the chance of survival and neurological outcome.[6–10] After decades of evidence deriving from observational studies,[11–17] three single-center randomized controlled trials (RCT) investigated the effect of extracorporeal CPR compared to conventional CPR.[8,9,18] The ARREST single-center RCT demonstrated for the first time a survival benefit of extracorporeal CPR in 30 patients with refractory OHCA with an initial shockable rhythm.[8] A small RCT, the EROCA trial, failed to meet the feasibility goal of transporting patients to an extracorporeal CPR-capable emergency department within 30 min from OHCA,[18] confirming the challenges of providing extracorporeal CPR and of conducting RCTs in this field. Finally, the Prague single-center RCT, published in 2022, demonstrated that among 264 patients with refractory OHCA with any initial rhythm, extracorporeal CPR improved survival with a favorable neurological outcome at 30 days but not at 6 months.[9]

In 2023, the first multi-center RCT, the INCEPTION trial, was published and showed no major differences in survival with a favorable neurologic outcome in patients treated with extracorporeal CPR. This result contrasted with previous studies and expert opinions and generated intense debate on the effectiveness of extracorporeal CPR. Therefore, to ascertain the effect of extracorporeal CPR compared to conventional CPR on survival with good neurological outcome in adults with refractory OHCA, we updated our previous systematic review and meta-analysis,[10] focusing on RCTs only.

2 | MATERIALS AND METHODS

The present systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] This is an update of a previously published meta-analysis on the same topic where also non-RCTs were included.[10] The protocol was pre-registered in the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42023396482. The review question, developed according to the PICO (Population, Intervention, Comparison, Outcome) framework, was as follows: in adults with refractory OHCA (P), does extracorporeal CPR (I), compared to conventional CPR (C), increase the proportion of patients surviving with favorable neurological outcome (O)?

2.1 | Search strategy and study selection

A systematic search of PubMed via MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted up to February 3, 2023. The complete search strategy is reported in the Supplement.

RCTs enrolling adults with refractory OHCA randomized to receive extracorporeal CPR or conventional CPR alone (basic life support and advanced life support with manual or mechanical chest compressions) were considered eligible. Exclusion criteria were the observational design of the study, studies conducted on in-hospital cardiac arrests, and studies not reporting the outcome of survival with favorable neurological outcome.

After the removal of duplicates, eligibility was assessed at title/abstract level independently by two investigators using the pre-defined inclusion and exclusion criteria. Two investigators performed the final selection of included articles independently and based on full-text manuscripts. Disagreements on inclusion or exclusion of articles were resolved under the supervision of another investigator.

2.2 | Data collection and risk of bias assessment

Two authors independently extracted data from selected RCTs using a standardized form. Disagreements on extracted data were solved by discussion involving another investigator. Collected data included: first author, publication year, country, study period, number of centers, the proportion of patients with an initial shockable rhythm, location of VA-ECMO cannulation, proportion of patients that received ECMO in the treatment and control (indicating cross-over) groups, time from cardiac arrest to ECMO flow, and outcomes data.

Two authors independently assessed the risk of bias of the included RCTs with the recommended version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[20] The risk of bias in each domain (randomization process, intervention assignment, missing outcome data, measurement of outcome, selection of the reported result, other bias) and the overall bias were judged as low, with some concerns, or high. The publication bias for the primary outcome was investigated through visual estimation of the funnel plot.

The overall certainty of the evidence was assessed independently by two authors with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology and rated as very low, low, moderate, or high.[21]

2.3 | Primary and secondary outcomes

The primary outcome was survival with favorable neurological outcome at the longest follow-up available. Among secondary outcomes, we evaluated survival with favorable neurological outcome measured at hospital discharge or 30 days, overall survival at the longest follow-up available and at hospital discharge or 30 days, and rate of survival with poor neurological outcomes at the longest follow-up available. Favorable neurological outcome was defined as 1 or 2 in the Cerebral Performance Category (CPC) score or 1, 2, or 3 in the modified Rankin Scale (mRS).[22] A poor neurological outcome was defined as a CPC score of 3 or 4 or an mRS score of 4 or 5.[22]

2.4 | Statistical analysis

We calculated pooled odds ratios (ORs) and 95% confidence intervals (CI) using the Mantel–Haenszel method for dichotomous 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 instead of the fixed effect model for analyses. A two-tailed p-value <0.05 was considered statistically significant for hypothesis testing of effect.

We performed a fixed effect model trial sequential analysis according to an overall type I error of 5% and power of 80%. A 15% relative risk reduction and a 10% survival with favorable neurological outcome in the control arm were hypothesized. The meta-analysis monitoring boundaries, the required information size, the diversity-adjusted information size (D^2), and adjusted 95% confidence intervals were calculated.

We conducted a separate analysis for patients with initial shockable rhythm and a subgroup analysis for study design (single-center or multi-center) for the primary outcome. The difference between subgroup estimates was considered significant for $P_{interaction}$<0.10. The number needed to treat (NNT) with 95% CI was calculated from the meta-analytic results for the primary outcome for all rhythms and for initial shockable rhythms only.

All data analyses were performed with R version 4.1.2, except trial sequential analysis using TSA software version 0.9.5.10.[23]

3 | RESULTS

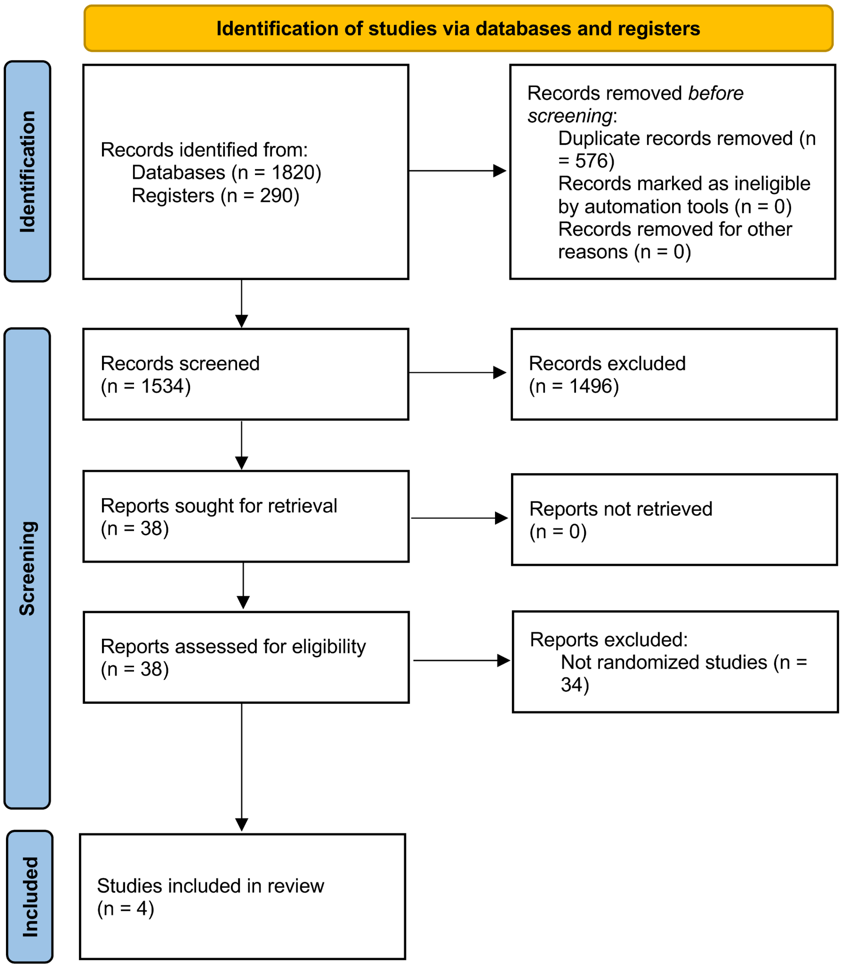
3.1 | Search strategy

Our search strategy yielded 2110 records. After completing the screening process, four randomized studies enrolling 433 patients[8,9,18,24] were included in the present systematic review and meta-analysis (Figure 1). The list of major exclusions is reported in Table S1.

3.2 | Characteristics of included trials

All included studies were published between 2020 and 2023.[8,9,18,24] Two studies were conducted in the United States[8,18] and two in Europe.[9,24] Three studies were single-center RCTs[8,9,18] and one study was a multi-center, single-nation RCT.[24] Two studies enrolled only patients with an initial shockable rhythm,[8,24] while in the other two approximately half of patients had pulseless electrical activity or asystole as the first rhythm.[9,18] Other baseline characteristics of patients enrolled were comparable between included RCTs. All studies adopted a load-and-go approach and performed extracorporeal CPR at hospital arrival. The proportion of patients receiving VA-ECMO in the intervention arm ranged from 42% to 80%, and the median time from OHCA to ECMO ranged between 59 and 74 min (Table 1).

FIGURE 1 Study selection process flowchart. [Color figure can be viewed at wileyonlinelibrary.com]



All studies were assessed to have an intermediate risk of bias (Table S2) due to the absence of blinding of the treating team in all studies and unblinded assessors of neurological outcome in one study.[18]

3.3 | Survival with favorable neurological outcome

In this meta-analysis of four RCTs, adult OHCA patients treated with extracorporeal CPR compared with conventional CPR had a higher rate of survival with favorable neurological outcome at the longest follow-up available (Figure 2A; 59/220 [27%] vs. 39/213 [18%]; OR = 1.72; 95% CI, 1.09–2.70; $p = 0.02$; $I^2 = 26\%$). The length of follow-up was 6 months for three studies and 3 months for one study. The NNT was 9 (95% CI, 5–66). In the trial sequential analysis (Figure S1), the cumulative Z-curve crossed the traditional boundary and the trial sequential monitoring boundary for benefit, confirming the significant beneficial effect of extracorporeal CPR (trial sequential analysis-adjusted 95% CI, 1.03–2.87). However, the sample size included in the meta-analysis did not reach the required information size (n = 520). Visual inspection of the funnel plot did not suggest publication bias (Figure S2).

When considering only patients with an initial shockable rhythm, extracorporeal CPR compared to conventional CPR increased the proportion of patients surviving with favorable neurological outcome at the longest follow-up available (Figure 2B; 55/164 [34%] vs. 38/165 [23%]; OR = 1.90; 95% CI, 1.16–3.13; $p = 0.01$; $I^2 = 23\%$) with an NNT of 7 (95% CI, 4–31). This benefit of extracorporeal CPR was also observed at hospital discharge or 30 days (Figure S3; 51/164 [31%] vs. 34/164 [21%]; OR = 1.93; 95% CI, 1.16–3.23; $p = 0.01$; $I^2 = 0.0\%$). When analyzing studies by design (single-center or multi-center), a statistically significant difference in survival with favorable neurological outcome at the longest follow-up available was confirmed among single-center studies (Figure S4; 45/150 [30%] vs. 29/150 [19%]; OR = 1.88; 95% CI, 1.11–3.19; $p = 0.02$; $I^2 = 48\%$).

At hospital discharge or 30 days, more patients were alive with favorable neurological outcomes when treated with extracorporeal CPR compared with conventional

CPR (Figure 3; 55/220 [25%] vs. 34/212 [16%]; OR = 1.82; 95% CI, 1.13–2.92; $p = 0.01$; $I^2 = 0.0\%$) (Table 2).

No difference in patients surviving with poor neurological outcomes at the longest follow-up available was observed in the extracorporeal CPR group compared with conventional CPR (Figure S5; 0/220 [0.0%] vs. 4/213 [1.9%]; OR = 0.24; 95% CI, 0.05–1.26; $p = 0.78$; $I^2 = 0.0\%$).

The certainty of evidence for survival with favorable neurological outcome at the longest follow-up available and at hospital discharge or 30 days, as assessed with the GRADE approach, was judged as low due to inconsistencies and wide confidence intervals in effect sizes (Table S3).

3.4 | Overall survival

Overall survival at the longest follow-up available was not statistically significantly different among patients treated with extracorporeal CPR and conventional CPR (Figure 4A; 61/220 [25%] vs. 34/212 [16%]; OR = 1.82; 95% CI, 1.13–2.92; $p = 0.59$; $I^2 = 58\%$). The length of follow-up ranged from 30 days to 6 months. Similarly, there were no statistically significant differences in the proportion of patients alive at hospital discharge or 30 days (Figure 4B; 72/220 [33%] vs. 58/214 [27%]; OR = 1.35; 95% CI, 0.55–3.29; $p = 0.51$; $I^2 = 55\%$).

The certainty of evidence for the outcomes of survival at the longest follow-up available and at hospital discharge or 30 days, as assessed with the GRADE approach, was judged as low due to inconsistencies and wide confidence intervals in effect sizes (Table S3).

4 | DISCUSSION

4.1 | Key findings

In this meta-analysis of RCTs, survival with a favorable neurological outcome at the longest follow-up available was higher in patients randomized to receive extracorporeal CPR compared to conventional CPR. The highest benefit was observed in patients with an initial shockable rhythm. Nine patients with all-rhythm refractory OHCA or seven with an initial shockable rhythm should be treated with extracorporeal CPR to achieve one additional survivor with a favorable neurological outcome. However, no difference in survival at hospital discharge or 30 days and at 3 or 6 months was found. These findings were derived from pooling four RCTs enrolling adults with refractory OHCA and favorable characteristics (young age, witnessed cardiac arrest with early bystander CPR and brief no-flow time).

TABLE 1 Characteristics of randomized controlled trials investigating extracorporeal conventional cardiopulmonary versus conventional cardiopulmonary resuscitation.

Study	Journal	Year	Country	Centers	Patients	Shockable	Cannulation location	Received ECMO in treatment and control groups	Time to ECMO
Yannopoulos et al.	*Lancet*	2020	USA	1	30	100%	In-hospital	80%–0%	59 min (SD, 28)
Hsu et al.	*Ann Emerg Med*	2021	USA	1	15	53%	In-hospital	42%–0%	66 min (SD, 17)
Belohlavek et al.	*JAMA*	2022	Czech Republic	1	264	61%	In-hospital	66%–8%	61 min (IQR, 55–70)
Suverein et al.	*N Engl J Med*	2023	The Netherlands	10	134	99%	In-hospital	66%–5%	74 min (IQR, 63–87)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; SD, standard deviation.

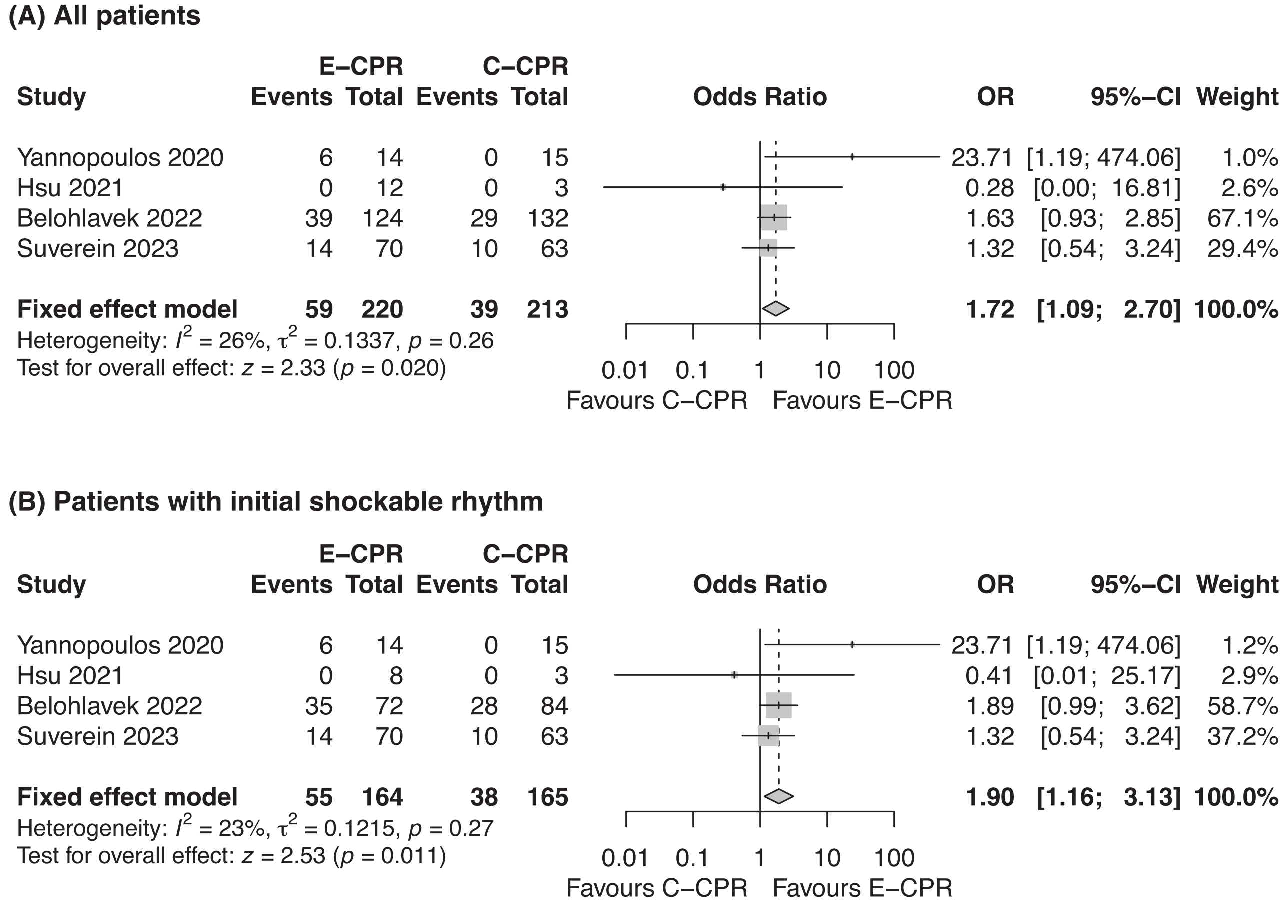


FIGURE 2 Forest plot for survival with a favorable neurological outcome at the longest follow-up available among (A) all-rhythm patients (shockable and nonshockable initial rhythm) OHCA patients and (B) patients with an initial shockable rhythm only. Abbreviations: C-CPR, conventional cardiopulmonary resuscitation; CI, confidence interval; E-CPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio.

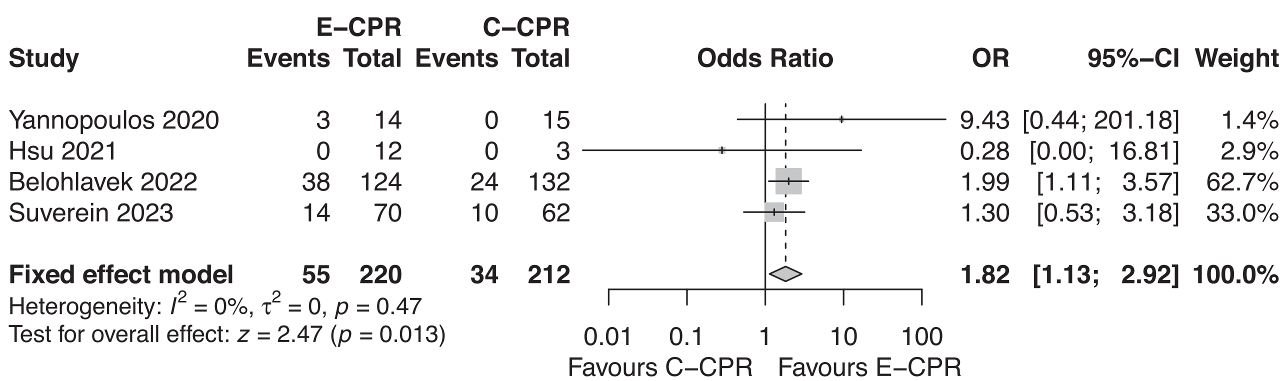


FIGURE 3 Forest plot for survival with a favorable neurological outcome at hospital discharge or 30 days. Abbreviations: C-CPR, conventional cardiopulmonary resuscitation; CI, confidence interval; E-CPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio.

4.2 | Relationship to previous studies

In the last decade, several observational studies, mainly retrospective, investigated the effect of extracorporeal CPR. Most studies described the potential of extracorporeal CPR to improve survival and neurological outcomes.[11–15] However, others revealed a minor or no effect on survival.[17,25] Such conflicting results probably arose from the heterogeneity in the strength of the chain of survival, patient selection criteria, adopted strategy, logistical organization, center experience, and post-resuscitation care practice (e.g., advanced circulatory and ventilatory

TABLE 2 Summary of major findings on the effect of extracorporeal conventional cardiopulmonary versus conventional cardiopulmonary resuscitation.

Outcomes	Extracorporeal CPR	Conventional CPR	Odds ratio (95% CI)	P for effect	I^2 (%)
Primary outcome					
Survival with good neurological outcome (longest follow-up available), *n* (%)	59/220 (27%)	39/213 (18%)	1.72 (1.09–2.70)	0.020	26
Among patients with initial shockable rhythm	55/164 (34%)	38/165 (23%)	1.90 (1.16–3.13)	0.011	23
Secondary outcomes					
Survival with good neurological outcome (hospital discharge or 30 days), *n* (%)	55/220 (25%)	34/212 (16%)	1.82 (1.13–2.92)	0.013	0.0
Among patients with initial shockable rhythm	51/164 (31%)	34/164 (21%)	1.93 (1.16–3.23)	0.012	0.0
Survival (longest follow-up available), *n* (%)	61/220 (28%)	47/214 (22%)	1.31 (0.49–3.49)	0.592	58
Survival (hospital discharge or 30 days), *n* (%)	72/220 (33%)	58/214 (27%)	1.35 (0.55–3.29)	0.514	55
Survival with unfavorable neurological outcome, *n* (%)	0/220 (0.0%)	4/213 (1.9%)	0.24 (0.05–1.26)	0.780	0.0

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation.

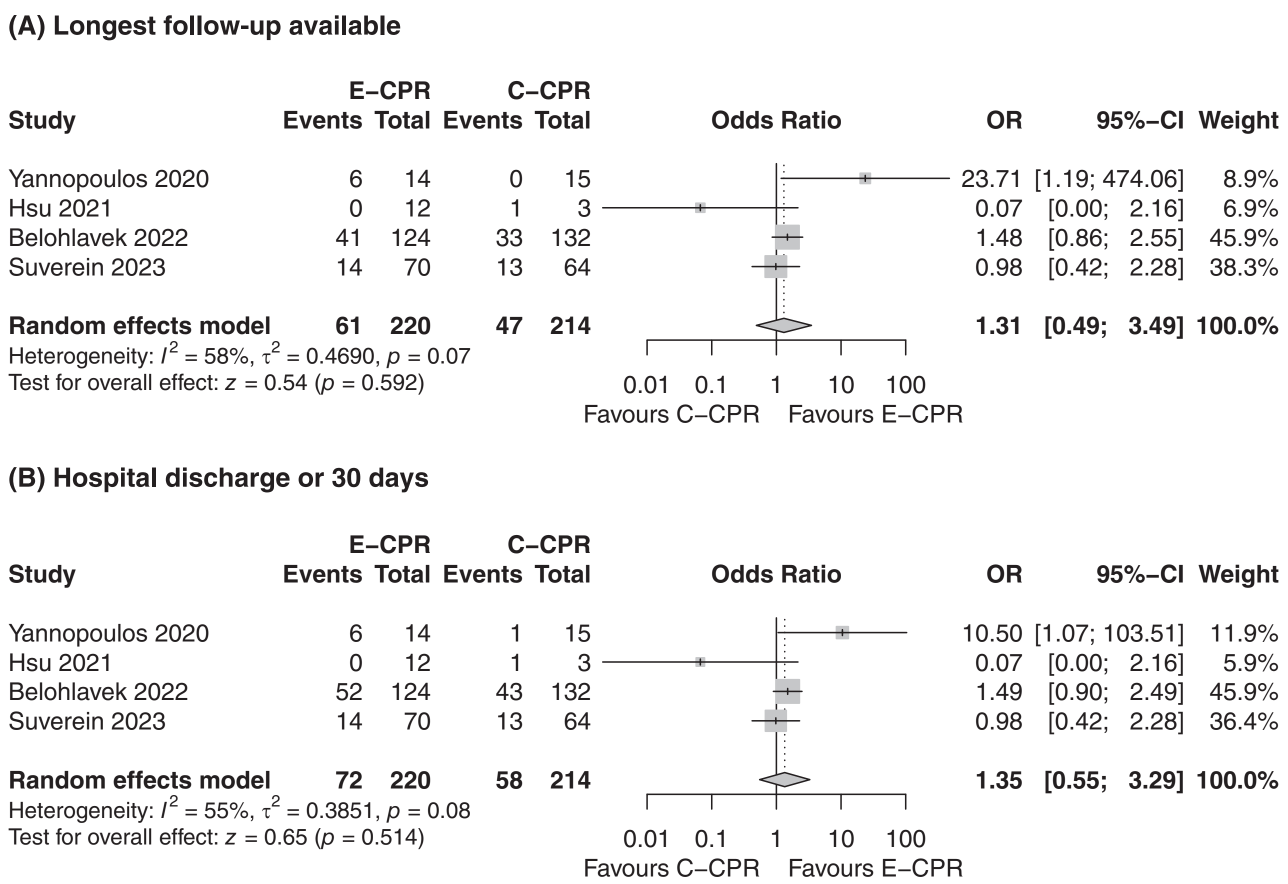


FIGURE 4 Forest plot for survival (A) at the longest follow-up available and (B) at hospital discharge or 30 days. Abbreviations: C-CPR, conventional cardiopulmonary resuscitation; CI, confidence interval; E-CPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio.

support, temperature management, and prognostication/withdrawal of life-support therapy), leading to highly variable survival rates.[26]

After decades of evidence in support for extracorporeal CPR limited to observational studies, three single-center RCTs,[8,9,18] of which one pilot trial,[18] and one multi-center, single-nation RCT[24] were published between 2020 and 2023. These four long-awaited RCTs[8,9,18,24] were pooled together for the first time in this meta-analysis. In previous systematic reviews or meta-analyses,[16,27–30] RCTs were not available yet, and thus not included, or were not pooled together. Observational studies are at high risk of bias, especially with extracorporeal CPR, where the decision to treat is based on clinicians' evaluation and comorbidities and prognostic factors with a strong impact on the outcome. Focusing on RCTs only minimizes between-group differences and confounding factors and provides the most unbiased possible estimate of the effect of extracorporeal CPR.

Compared to our previous meta-analysis of propensity-score matched and randomized studies,[10] in the present meta-analysis, we excluded observational studies, focusing only on RCTs, and added two additional RCTs,[18,24] including the recently published multi-center INCEPTION RCT.[24] Overall, we confirmed the beneficial effect of extracorporeal CPR in increasing survival with favorable neurological outcomes, both at the longest follow-up available and at hospital discharge or 30 days. All included RCTs, except the pilot EROCA trial,[18] reported a consistent direction of the effect of this outcome, with the ARREST trial and the Prague OHCA study reporting a statistically significant difference in favor of extracorporeal CPR up to 180 days and at 30 days only, respectively.[8,9]

The recently published multi-center INCEPTION RCT enrolled 134 patients with refractory OHCA with initial shockable rhythm treated in 10 ECMO centers in the Netherlands between 2017 and 2021. This study demonstrated a similar effect of extracorporeal CPR and conventional CPR,[24] a contrasting result to previous single-center RCTs, and generated intense debate. It is common in critical care medicine that multi-center RCTs do not confirm the positive results of single-center RCTs.[31,32] This possibly reflects the complexity of translating the beneficial effect observed in RCTs conducted in single-center experiences[8,9] to different centers where extracorporeal CPR was not routine clinical practice or the level of expertise and logistical organization was not homogeneous. Other reasons include higher than expected survival in patients with refractory OHCA treated with conventional CPR and higher time from cardiac arrest to ECMO flow compared to previous single-center RCTs (Table 1), a factor strongly influencing survival and neurological outcome.[33,34]

4.3 | Implications of study findings for clinical practice

The effect of extracorporeal CPR in refractory OHCA is highly debated, mainly due to the considerable resources associated with the procedure and the complex required logistical organization. Our findings indicate that transporting with ongoing CPR selected patients with refractory OHCA to a cardiac arrest center for the treatment with extracorporeal CPR is supported by high-quality randomized evidence. However, we acknowledge that the beneficial effect of extracorporeal CPR observed in this meta-analysis is driven mainly by two single-center RCTs conducted in single, high-performing centers.

Extracorporeal CPR is complex and requires a well-organized system minimizing time to ECMO and a rigorous selection of patients' eligibility. Moreover, extracorporeal CPR should be provided as part of a bundle of treatments that involves different healthcare professionals in the pre-hospital setting (i.e., EMS dispatchers and ambulance team) and after hospital arrival (i.e., emergency department, catheterization laboratory, and intensive care unit clinicians). Close cooperation between EMS and high-volume ECMO-capable cardiac arrest centers[35] is mandatory.

Implementing extracorporeal CPR in different settings and healthcare systems might fail to reproduce the beneficial effect observed in this meta-analysis or single-center RCTs. Moreover, a strong relationship exists between center experience with extracorporeal CPR, estimated by the annual case volume, and outcomes.[26] In the process of implementing extracorporeal CPR, centers should critically assess their logistics and monitor the program's performance.

4.4 | Strengths and limitations

Differently from our previous meta-analysis[10] and other systematic reviews published on the topic,[16,27–30] the present meta-analysis provided for the first time a pooled estimate of the effect of extracorporeal CPR with data only from RCTs, including all the available RCTs in the field,[8,9,18] comprising the first multi-center RCT published in 2023.[24] Despite these important strengths, two limitations should be acknowledged. First, our meta-analysis still has a relatively small sample size (433 patients), also indicated by the trial sequential analysis that set the required information size at 520 patients. Consequently, the included RCTs and our meta-analysis may have been underpowered to detect clinically meaningful differences. Second, different inclusion criteria (e.g., any initial rhythm or shockable rhythm only) and different pre-hospital and in-hospital interventions were adopted among studies and could affect patients' survival and neurological outcome. However, in an attempt to reduce the bias originating from the different included populations, we analyzed patients with a shockable rhythm, finding an NNT as low as seven.

Finally, countries' differences in EMS systems and clinical practices in extracorporeal CPR and post-resuscitation management should be considered. An individual patient data meta-analysis could overcome some of these limits.

4.5 | Future directions and research

Large, international RCTs of extracorporeal CPR are still needed. However, in this context, such trials are difficult to conduct for two main reasons. First, high-volume cardiac arrest centers routinely providing extracorporeal CPR would consider it unethical to preclude this intervention for half of the enrolled patients.[36,37] Second, an extracorporeal CPR strategy that is high performing and effective in one center or system is not necessarily as effective and performant in another.

Future research should aim to identify the most effective strategy to provide extracorporeal CPR based on system-level characteristics, address logistical barriers of extracorporeal CPR, and improve patient selection. For example, many centers are already adopting pre-hospital initiation of extracorporeal CPR to reduce low-flow time, and others are starting.[38,39]

Finally, to improve outcomes after OHCA, the focus should be primarily on improving the early links of the chain of survival.[40,41] Without a timely initiation of bystanders' interventions (CPR and early defibrillation) to reduce or zero no-flow time and avoid irreversible brain injury, providing an advanced intervention such as extracorporeal CPR will achieve little or no effect.

5 | CONCLUSIONS

In this meta-analysis of RCTs, extracorporeal CPR compared to conventional CPR increased the proportion of patients surviving a refractory OHCA with favorable neurological outcome, especially in patients with an initial shockable rhythm.

AUTHOR CONTRIBUTIONS

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

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CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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