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Clinical paper

# Cost-effectiveness of extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: A modelling study

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## Abstract

**Background**: Extracorporeal cardiopulmonary resuscitation (E-CPR) is a method of CPR that passes the patient's blood through an extracorporeal membrane oxygenation (ECMO) device to provide mechanical haemodynamic and oxygenation support in cardiac arrest patients who are not responsive to conventional CPR (C-CPR). E-CPR is being adopted rapidly worldwide despite the absence of high quality trial data and its substantial cost. Published cost-effectiveness data for E-CPR are scarce.

**Methods**: We developed a mathematical model to estimate the cost-effectiveness of E-CPR relative to C-CPR in adult patients with refractory out-of-hospital cardiac arrest (OHCA). The model was a combination of a decision tree for the acute treatment phase and a Markov model for long-term periods. Cost-effectiveness was evaluated from the Australian health system perspective over lifetime. Cost-effectiveness was expressed as Australian dollars (AUD, 2021 value) per quality-adjusted life year (QALY) gained. Variables were parameterised using published data. Probabilistic and univariate sensitivity analyses were performed.

**Results**: The incremental cost-effectiveness ratio (ICER) of E-CPR was estimated to be AUD 45,716 per QALY gained over lifetime (95% uncertainty range 22,102–292,904). The cost-effectiveness of E-CPR was most sensitive to the outcome of the therapy.

**Conclusion**: E-CPR has median ICER that is below common accepted willingness-to-pay thresholds. Local factors within the health care system need to be considered to determine the feasibility of implementing an effective E-CPR program.

**Keywords**: Cost-effectiveness, ECMO, E-CPR, Out-of-hospital cardiac arrest

## Introduction

Extracorporeal cardiopulmonary resuscitation (E-CPR) is an emerging resuscitative therapy for cardiac arrest patients who are refractory (not responsive) to conventional CPR (C-CPR). This method uses extracorporeal membrane oxygenation (ECMO) to provide mechanical haemodynamic and oxygenation support whilst awaiting definitive treatment and recovery of effective cardiac output. Although there are inconsistencies in the reported effectiveness of E-CPR, there is emerging evidence of improved outcomes in carefully selected patients for E-CPR. To date, Belohlavek et al.[1] and Yannopoulos et al.[2] are the only randomised controlled trials on E-CPR (both are single centre, open-label). Belohlavek et al.[1] included a total of 256 out-of-hospital cardiac arrest (OHCA) patients and found that E-CPR did not significantly improve favourable neurological outcome at 180 days compared to C-CPR. In contrast, Yannopoulos et al.[2] included a total of 36 OHCA patients and reported higher rates of survival to hospital discharge among those receiving E-CPR than C-CPR (43 versus 7%). Furthermore, a number of small observational studies on E-CPR reported improved survival and neurological outcomes in both OHCA and in-hospital cardiac arrest (IHCA).[3–9].

International guidelines recommend that E-CPR may be considered as a rescue therapy for selected cardiac arrest patients for whom the suspected cause of the arrest is potentially reversible when C-CPR is failing (weak recommendation, very low certainty of evidence).[10,11] Despite limited evidence and the absence of high quality trial data, the adoption of E-CPR has increased rapidly. Annual E-CPR episodes among adult patients increased over 10-fold, from 35 in 2003 to over 400 in 2014 worldwide.[12] During the same period, the number of healthcare

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centres that performed E-CPR increased 12-fold, from 8 to 98 centres globally.[12].

Most healthcare systems around the world operate in resource constrained environments. E-CPR is resource-intensive; accordingly, quantifying its cost-effectiveness and identifying circumstances in which it provides the most value for money is essential. Data on the cost-effectiveness of E-CPR are scarce despite the rapid adoption of this technology. A limited number of studies in Japan,[13] Canada,[14] the United States,[15] the Netherlands,[16] and Australia[17] found that E-CPR is cost-effective in both OHCA and IHCA. These studies are subject to a number of limitations including incorporation of only resource use during the acute in-hospital phase, assumption of no survivor in C-CPR patients, no consideration of changes in neurological status after discharge, not including data from the Yannopoulos et al.[2] and Belohlavek et al.[1] trials, and short time horizon. Owing to these limitations and the pressing need for further evidence, we performed a cost-effectiveness analysis of E-CPR versus C-CPR in refractory OHCA patients from the perspective of the Australian healthcare system. We adopted a lifetime horizon and included costs and outcomes of both acute in-hospital and long-term periods.

## Methods

### *Model description*

We developed a model in TreeAge Pro (version 2020; TreeAge Software Inc., Williamstown, MA, USA) to estimate and compare the costs, health outcomes (quality-adjusted life years, QALYs) and cost-effectiveness of E-CPR versus C-CPR. We considered a hypothetical cohort of adult OHCA patients who were aged between 18 and 75 years,[7,18] refractory to C-CPR, eligible for E-CPR and transported to an ECMO-capable hospital. Fig. 1 shows a schematic presentation of the model. The model structures and health states are the same for both E-CPR and C-CPR; however, epidemiological and clinical input values are unique to each group. Input values for the model were derived from published literature and are presented in Table 1.

The model is a combination of a decision tree for the acute in-hospital phase following the cardiac arrest event and for a short-term period (3 months after hospital discharge), and a Markov model for long-term follow-up (3 months after discharge to 10 years, and after 10 years). We modelled the acute in-hospital phase in which each patient was assigned to either E-CPR or C-CPR, and discharged into one of the four cerebral performance category (CPC) scores (CPC-1, CPC-2, CPC-3, CPC-4) or death.[19] We accounted for changes (improvement or worsening) of CPC scores within the first 3 months after discharge as demonstrated in both clinical trials[1,2] and observational studies.[7,19] This was done by allowing patients to move up or down from their initial CPC score at discharge to other CPC scores, with the probabilities of such changes derived from the literature (Table 1). We assumed that patients stayed in their same CPC score after 3 months from discharge.[2,20] While undergoing E-CPR, patients had a probability of developing significant complications associated with the procedure and, as a consequence, experienced additional risk of death and incurred additional costs.[4,7,14,16,21] The potential long-term impact of E-CPR complications on mortality and costs was not considered in our model.

We divided the long-term period into two sub-periods: from 3 months after discharge until 10 years, and after 10 years until death. During each Markov cycle of 1 year, patients were either alive and stayed in the same CPC score[2,20] or died. The probability of death specific to each CPC score for the first sub-period (from 3 months after discharge until 10 years) was derived from the literature that followed up OHCA patients for 10 years following the index event.[22] For the second sub-period (after 10 years), we assumed no excess mortality (i.e. OHCA had no effect on survival after 10 years),[14] and used age and sex-specific annual probability of death from the Australian Life Tables (Supplementary Table S1).[23] We assumed that the type of resuscitative therapy received during cardiac arrest treatment (E-CPR or C-CPR) would not affect longer-term outcomes.[14] Subsequent successfully-resuscitated cardiac arrest, if any, during the lifetime in the same patient was not considered. We did not consider destination therapies after E-CPR (e.g. long-term ventricular assist device, heart transplant). We conducted the analysis from the perspective of the Australian healthcare system.

Cost inputs were derived from Australian studies that adopted the healthcare system perspective, and were presented in 2021 AUD (Table 1). Conversion of cost data from past years to year 2021 value was done using the following formula: Cost in 2021 value = (Cost in past year value) × (Consumer price index 2021/ Consumer price index past year). Cost of E-CPR during acute treatment was estimated to be AUD 60,197 and included all elements attributed to the patient's episode of care from time of cardiac arrest to hospital discharge or death as described in Dennis et al.[17] Complications due to E-CPR were assumed to incur an additional cost of AUD 3,645.[17] Due to the lack of data specific for cardiac arrest and as per previous studies,[20] annual long-term cost of CPC-1 and CPC-2 survivors was assumed to be the same as that estimated from Australian patients with ischaemic heart disease, at AUD 4,965.[24] Like previous studies,[20] annual ongoing cost of CPC-3 and CPC-4 survivors was assumed to be the same as first-ever ischaemic stroke patients in Australia, estimated to be AUD 5,928.[25] We defined incremental cost-effectiveness ratios (ICERs) as additional cost per QALY gained from E-CPR relative to C-CPR. Given that Australia does not mandate a willingness-to-pay (WTP) threshold, we did not adopt one in our study. Rather, we presented numerical results of the ICERs so that determination of the cost-effectiveness of E-CPR can be made against any nominal WTP value.

### *Uncertainty and sensitivity analysis*

Uncertainty analysis was performed with Monte Carlo simulation (10,000 iterations) to randomly sample parameters from their distributions (Table 1). We reported 95% uncertainty ranges around projected point estimates. Univariate sensitivity analysis was also carried out to understand the key ICER drivers. The variables that were considered in the univariate sensitivity analysis were E-CPR cost, cost of E-CPR complications, annual long-term cost of survivors, probability of death due to E-CPR complications, probability of E-CPR patients discharged with CPC-1, assumption of E-CPR and C-CPR having the same probabilities of changes in CPC scores within 3 months after discharge, and discount rate.

## Results

Table 2 shows the projected costs and health outcomes of the two therapies. The ICER of E-CPR relative to C-CPR was AUD 45,716

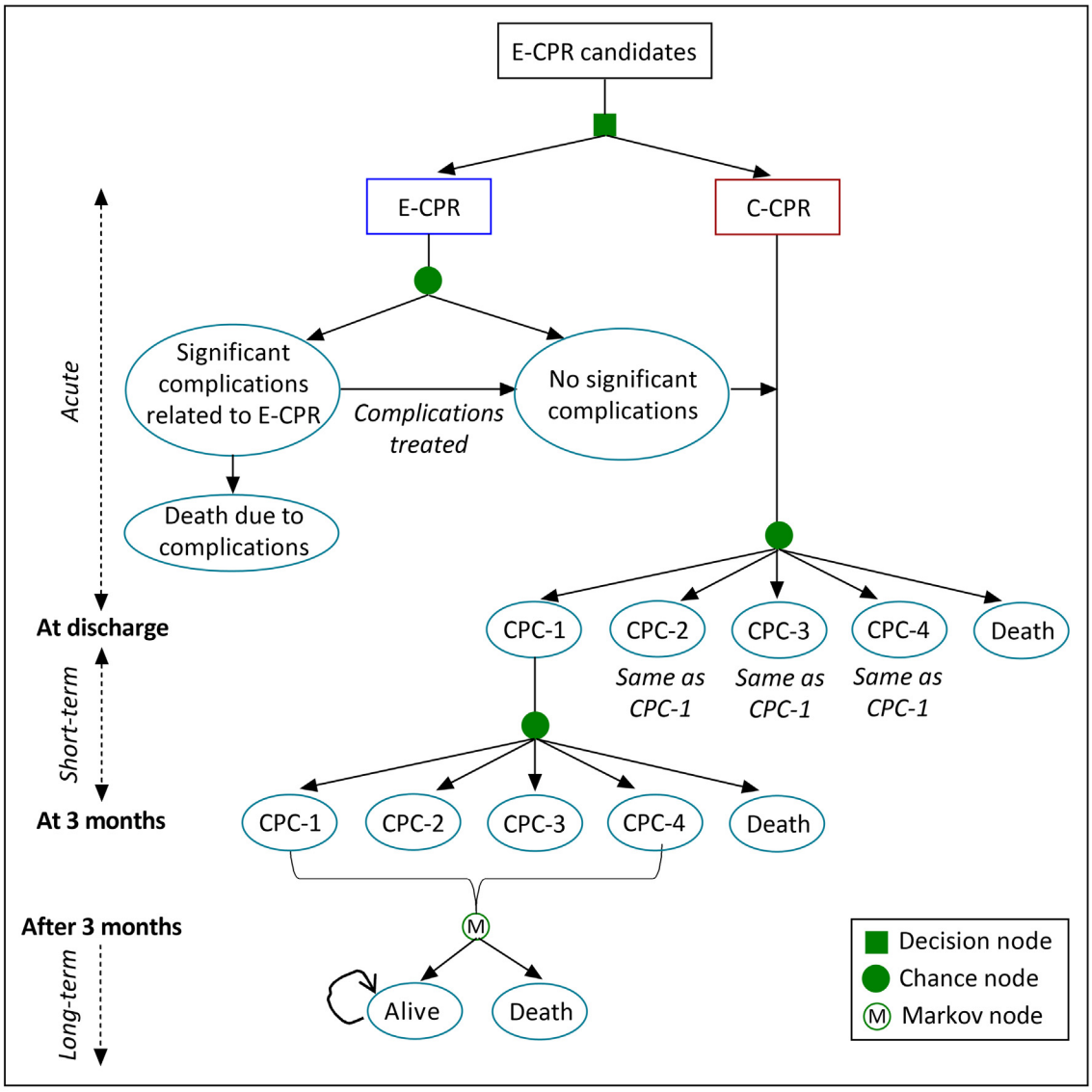


**Fig. 1 – Schematic presentation of the model. C-CPR, conventional cardiopulmonary resuscitation; CPC, cerebral performance category; E-CPR, extracorporeal cardiopulmonary resuscitation.**

per QALY gained (95% uncertainty range 22,102–292,904). The cost-effectiveness plane for the ICERs is presented in Fig. 2, highlighting the uncertainty around the results due to simultaneous variations in input values. The cost-effectiveness acceptability curve (Fig. 3) represents the probability of E-CPR being cost-effective relative to C-CPR over a range of WTP thresholds. The curve shows that E-CPR was more likely to be cost-effective than C-CPR at any WTP threshold that was above AUD 46,700 per QALY gained. Univariate sensitivity analysis is shown in Fig. 4. The cost-effectiveness of E-CPR was most sensitive to the outcome of the therapy, modelled through the proportion of patients discharged with CPC-1. There was an inverse relationship between the cost-effectiveness of E-CPR and its outcome. Threshold analysis in Supplementary Fig. S1 shows the ICER corresponding to each of the simulated values of the probability of E-CPR patients discharged with CPC-1. For example, the ICER would exceed AUD 100,000 per QALY gained when the probability of CPC-1 is below 6.0%.

## Discussion

We found that E-CPR has an estimated ICER (AUD 45,716 per QALY gained) that is below current accepted WTP thresholds internationally (Supplementary Table S2).[13,14,20,26–28] Whilst Australia does not have an explicit WTP threshold, it requires evidence that a new medical technology represents value for money before it is considered for government subsidies, and a number of countries mandate a WTP threshold (Supplementary Table S2).[13,14,20,26–28] The World Health Organization's Choosing Interventions that are Cost–Effective (WHO-CHOICE) suggests that an intervention that costs less than three times the national annual gross domestic product (GDP) per capita is considered cost-effective, and less than one GDP per capita highly cost-effective.[29] In 2021, GDP per capita in Australia was AUD 82,599.[30] Our estimated ICER (AUD 45,716 per QALY gained) is below all of the aforementioned thresholds. For comparison, our ICER for E-CPR is lower than that for some

**Table 1 – Model input values.**

| Variable | Base-case value | Uncertainty range | Distribution | Reference for base-case | Reference for range |
|---|---|---|---|---|---|
| Age of cohort at start | 18–75 years | | Triangular | 7,18 | |
| Male | 79% | 70–90% | Triangular | 7 | 3,12 |
| Probability of significant E-CPR complications | 8.6% | 0–32% | Triangular | 7 | 4,6,34 |
| Probability of death due to E-CPR complications | 6.9% | 4.1–11.2% | Triangular | 35 | 35 |
| CPC score at discharge | | | | | |
| E-CPR | | | | | |
| CPC-1 | 13.5% | 9.8–30.6% | Triangular | 19 | 1,7,20 |
| CPC-2 | 1.9% | 0–3.8% | Triangular | 19 | 3,20 |
| CPC-3 | 0% | 0–3.8% | Triangular | 19 | 3 |
| CPC-4 | 1.9% | 0–11.5% | Triangular | 19 | 3 |
| Death | 82.7% (complement) | | | | |
| C-CPR | | | | | |
| CPC-1 | 1.9% | 0.6–18.2% | Triangular | 19 | 1,3,20 |
| CPC-2 | 0% | 0–1.3% | Triangular | 19 | 3,20 |
| CPC-3 | 3.8% | 1.9–4.2% | Triangular | 19 | 3 |
| CPC-4 | 15.4% | 6.7% – 16.9% | Triangular | 19 | 2,19 |
| Death | 78.9% (complement) | | | | |
| CPC score at 3 months | | | | | |
| E-CPR | | | | | |
| CPC-1 → CPC-1 | 100% | | | 7,19 | |
| CPC-2 → CPC-1 | 53.8% | 53.8–100% | Triangular | 7 | 2,7 |
| CPC-2 → CPC-2 | 46.2% | Complement | | 7 | |
| CPC-3 → CPC-1 | 66.7% | | | 2 | |
| CPC-3 → CPC-2 | 33.3% | | | 2 | |
| CPC-3 → CPC-3 | 0% | | | | |
| CPC-4 → CPC-4 | 100% | 0% | | 2 | 19 |
| CPC-4 → Death | 0% (complement) | Complement | | | 19 |
| C-CPR | | | | | |
| CPC-1 → CPC-1 | 100% | | | 19 | |
| CPC-2 → CPC-1 | 0% | | | 19 | |
| CPC-2 → CPC-2 | 100% | | | 19 | |
| CPC-3 → CPC-1 | 0% | | | 19 | |
| CPC-3 → CPC-2 | 0% | | | 19 | |
| CPC-3 → CPC-3 | 100% | | | 19 | |
| CPC-4 → CPC-4 | 12.5% | Complement | | 19 | |
| CPC-4 → Death | 87.5% | 87.5–100% | | 19 | 2 |
| CPC score after 3 months | Same as CPC score at 3 months | | | 2,20 | |
| Annual probability of background death | Refer to Supplementary Table S1 | | | 23 | |
| Utility scores | | | | | |
| CPC-1 | 0.85 | 0.75–0.95 | Triangular | 36 | 20,37 |
| CPC-2 | 0.85 | 0.75–0.86 | Triangular | 36 | 20,37 |
| CPC-3 | 0.47 | 0.20–0.58 | Triangular | 36 | 20,37 |
| CPC-4 | 0.33 | 0.10–0.47 | Triangular | 37 | 20,36 |
| Death | 0 | | | | |
| Time horizon | Lifetime | | | | |
| Discount rate | 3% | 2–5% | Univariate sensitivity analysis only | | |
| Costs | | | | | |
| Cost of E-CPR during acute treatment | AUD 60,197 | ±10% | Gamma (402.6; 0.007) | 17 | Assumed |
| Cost of complications related to E-CPR | AUD 3,645 | ±10% | Gamma (590.5; 0.162) | 17 | Assumed |
| Cost of C-CPR during acute treatment | AUD 17,159 | ±10% | Gamma (363.5; 0.021) | 17 | Assumed |
| Annual long-term cost, CPC 1–2 | AUD 4,965 | ±10% | Gamma (293.1; 0.059) | Assumed to be the same as ischaemic heart disease[24] | Assumed |
| Annual long-term cost, CPC 3–4 | AUD 5,928 | ±10% | Gamma (390.5; 0.066) | Assumed to be the same as first-ever ischemic stroke[25] | Assumed |

AUD, Australian dollar; C-CPR, conventional cardiopulmonary resuscitation; CPC, cerebral performance category; E-CPR, extracorporeal cardiopulmonary resuscitation.

**Table 2 – Projected costs and health outcomes per patient over lifetime.**

| | Cost (AUD) | QALYs | ICER (AUD/QALY gained) |
|---|---|---|---|
| E-CPR | 65,008 (59,043–71,430) | 1.60 (1.06–2.45) | 45,716 (22,102–292,904) |
| C-CPR | 18,887 (16,716–21,507) | 0.60 (0.21–1.34) | |

AUD, Australian dollar; C-CPR conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

other expensive new medical technologies currently used in Australia such as pelvic exenteration (AUD 227,330 per QALY gained compared to without the intervention),[31] and nivolumab for the treatment of renal cell carcinoma (AUD 266,871 per QALY gained compared to everolimus).[32]

Our median ICER estimate supports findings of empirical studies that E-CPR for eligible refractory OHCA patients is cost-effective from a health system perspective. In Canada, E-CPR was found to be cost-effective at CAD 28,792 per life year gained (2019 value, ~ AUD 31,383), assuming a WTP threshold of CAD 50,000.[14] In Japan, the ICERs of E-CPR ranged from JPY 2,619,692 (2010 value, ~AUD 32,547)[20] to USD 16,246 (2016 value, ~AUD 21,864)[13] per QALY gained. The authors concluded that the treatment was cost-effective using a WTP threshold of JPY 5,000,000 – 6,000,000 (~AUD 59,000–70,000).[13,20] In the United States, Bharmal et al.[15] estimated that E-CPR cost USD 56,156 per QALY gained (2018 value, ~ AUD 75,234) for OHCA and IHCA combined, suggesting the therapy was cost-effective using a contemporary WTP threshold of USD 150,000.[15] To date, Dennis et al.[17] is the only published cost-effectiveness study in the Australian setting. The authors reported an ICER of AUD 25,212 per QALY gained for OHCA and IHCA combined (2016 value) and concluded that ICER was cost-effective against common accepted WTP thresholds. While the acute costs of E-CPR and C-CPR in our study were derived from this study, there are some noticeable differences between our analysis and Dennis et al.[17] Unlike Dennis et al.[17] which assumed no survivor among C-CPR patients, we allowed for the fact that C-CPR patients may survive cardiac arrest, even with favourable neurological outcomes, as demonstrated in the literature.[2,3,19,20] Furthermore, Dennis et al.[17] was limited to resource usage up to the point of hospital discharge whereas we accounted for long-term healthcare costs. Dennis et al.[17] did not allow for changes in neurological functions after discharge; whereas we accounted for such possibility.

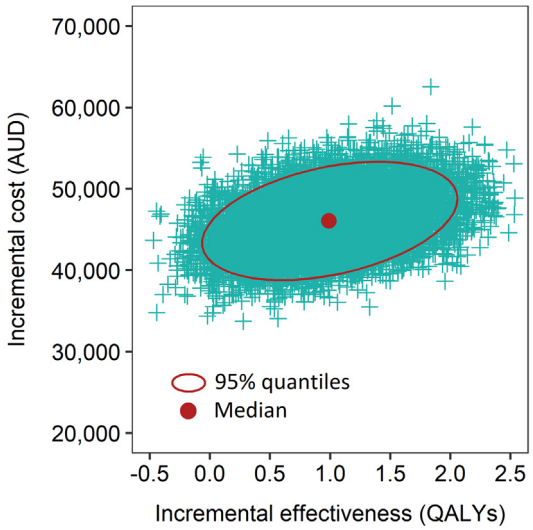


**Fig. 2 – Incremental cost and incremental effectiveness of E-CPR relative to C-CPR. The plus symbols represent 10,000 simulations across the range of parameters, with each plus symbol being the average result for a hypothetical cohort of 15,000 patients. AUD, Australian dollar; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; QALY, quality-adjusted life year.**

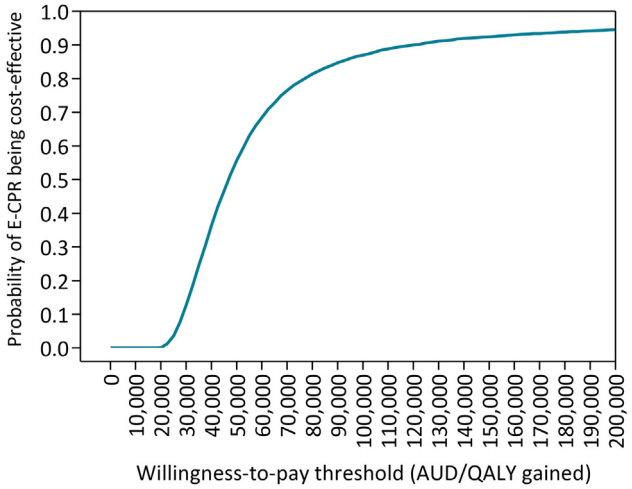


**Fig. 3 – Cost-effectiveness acceptability curve showing the probability of E-CPR being cost-effective relative to C-CPR across a range of willingness-to-pay thresholds. AUD, Australian dollar; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; QALY, quality-adjusted life year.**

To date, patient selection for E-CPR remains a contentious issue. Although variation exists, common criteria include adults (18 – up to 75 years), witnessed arrest with reversible causes, initial shockable rhythm, and estimated transfer time <30 minutes or total low-flow period <60 minutes.[2,7,33] Parameterisation for our base-case analysis was primarily based on Kim et al.,[19] which did not consider initial arrest rhythm or transfer/low-flow time in their selection of patients. Had Kim et al.[19] adopted more stringent criteria, the clinical outcomes would likely have been better, and our estimated cost-effectiveness would have been more favourable.

We found that the cost-effectiveness of E-CPR was most sensitive to the outcome of the therapy. Nevertheless, at the lower limit of the modelled effectiveness of E-CPR (proportion of patients discharged with CPC-1), the median ICER (AUD 63,225 per QALY gained) remained to be within the WTP thresholds adopted in international literature and well below GDP per capita for Australia (AUD 82,599). For the median ICER to exceed a hypothetical WTP threshold of one GDP per capita (AUD 82,599), the proportion of E-CPR

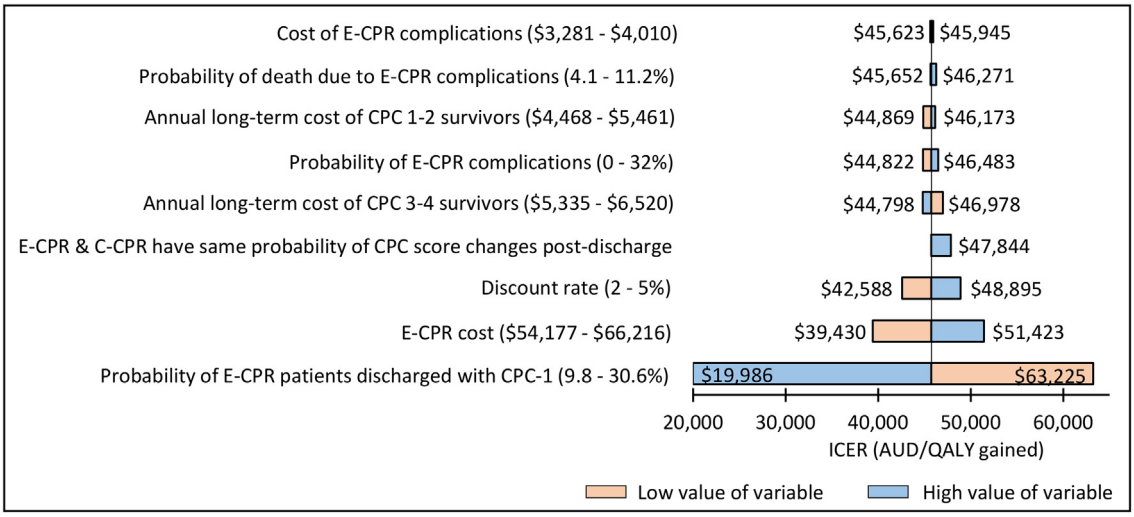


**Fig. 4 – Univariate sensitivity analysis of the ICER (AUD/QALY gained) of E-CPR versus C-CPR. Orange and blue bars show the ICERs corresponding to low and high values, respectively, of the variable in question, holding all other variables constant. The vertical line corresponds to the reference scenario (AUD 45,716/QALY gained). AUD, Australian dollar; C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.**

patients discharged with CPC-1 would need to be as low as 10%, which is lower than that reported in observational studies and clinical trials.[1,2,7,19,20] This suggests that more relaxed patient selection criteria may be feasible while still ensuring that the intervention is cost-effective. Nevertheless, such new criteria need to be evaluated prior to adoption.

This study is subject to a number of limitations. It was conducted from a health system perspective, and therefore did not incorporate indirect costs such as loss of productivity. Cost of destination therapies after E-CPR (e.g. long-term ventricular assist device, heart transplant) was not considered. Our study modelled E-CPR performed in the hospital setting, and did not cover rendezvous and pre-hospital E-CPR. Like other studies in this area, we did not incorporate costs associated with E-CPR training and maintenance due to the lack of data. We did not consider the potential gain in organ donation as an outcome associated with E-CPR. The inclusion of organ donation would further improve the cost-effectiveness of E-CPR. Although we used the best available and most relevant published data to parameterise our model, our results may not be generalisable to settings in which practices and costs are very different from those we used. In the absence of long-term cost data specific to OHCA survivors, we followed previous studies[20] and assumed that those costs were similar to ischaemic heart disease patients (for CPC-1 and CPC-2 survivors) and stroke survivors (for CPC-3 and CPC-4 survivors). Nevertheless, our results were not sensitive to such an assumption. Like most studies in this topic, we looked at the cost-effectiveness of E-CPR from a purely probabilistic and fiscal perspective. Regardless of how cost-effective the intervention appears to be from a theoretical standpoint, health facilities need to consider their own environment to determine whether it is feasible to deliver an effective E-CPR system in their context, dependent upon various factors such as the frequency of refractory OHCA cases and the capacity to deliver patients to hospital within eligible timeframes for ECMO. Furthermore, larger trials are needed and should include within-trial economic evaluation.

## Conclusions

E-CPR has median ICER that is below common accepted WTP thresholds. Larger trials and trial-based economic evaluations are needed. The feasibility to deliver an effective E-CPR program at a local level needs to be assessed, taking into account all relevant factors within the studied health care system.

## CRediT authorship contribution statement

**Tan N Doan:** Conceptualization, Data curation, Writing – original draft. **Stephen Rashford:** Conceptualization, Supervision, Writing – review & editing. **Jason Pincus:** . **Emma Bosley:** Conceptualization, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100309.

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