Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

Cost-effectiveness of extracorporeal cardiopulmonary resuscitation for adult out-of-hospital cardiac arrest: A systematic review

Danielle Addison[a], *Evan Cheng*[b], *Paul Forrest*[b,c], *Ann Livingstone*[a,1], *Rachael L. Morton*[a,1], *Mark Dennis*[b,*]

Abstract

Objective: The use of extracorporeal cardiopulmonary resuscitation (ECPR) for out-of-hospital cardiac arrests (OHCA) has increased dramatically over the past decade. ECPR is resource intensive and costly, presenting challenges for policymakers. We sought to review the cost-effectiveness of ECPR compared with conventional cardiopulmonary resuscitation (CCPR) in OHCA.

Methods: We searched Medline, Embase, Tufts CEA registry and NHS EED databases from database inception to 2021 or 2015 for NHS EED. Cochrane Covidence was used to screen and assess studies. Data on costs, effects and cost-effectiveness of included studies were extracted by two independent reviewers. Costs were converted to USD using purchasing power parities (OECD, 2022).[1] The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al., 2022)[2] was used for reporting quality and completeness of cost-effectiveness studies; the review was registered on PROSPERO, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Four studies met the inclusion criteria; three cost-effectiveness studies reported an incremental cost-effectiveness ratio (ICER) for OHCA compared with conventional care, and one reported the mean operating cost of ECPR. ECPR was more costly, accrued more life years (LY) and quality-adjusted life years (QALYs) than CCPR and was more cost-effective when compared with CCPR and other standard therapies. Overall study quality was rated as moderate.

Conclusion: Few studies have examined the cost-effectiveness of ECPR for OHCA. Of those, ECPR for OHCA was cost-effective. Further studies are required to validate findings and assess the cost-effectiveness of establishing a new ECPR service or alternate ECPR delivery models.

Keywords: Extracorporeal membrane oxygenation, ECMO, Cardiac Arrest, Out-of-hospital, Cost-effectiveness, Systematic Review

Introduction

Extracorporeal membrane oxygenation (ECMO) use during cardiopulmonary resuscitation (CPR) is increasingly being used to support patients who have suffered refractory cardiac arrest.[3] Recent randomised control trials have reported efficacy over conventional cardiopulmonary resuscitation (CCPR) in selected refractory out-of-hospital cardiac arrest (OHCA) patients,[4] and international guidelines recommend consideration of ECPR in patients who are refractory to CCPR.[5]

However, ECPR is technically challenging, resource intensive and significant concerns regarding its cost effectiveness remain[6] and further evaluation of the cost-effectiveness and resource allocation of ECPR in resuscitation is recommended.[7] To date, there exists no review of available data on the cost-effectiveness of ECPR compared with CCPR. The objective of this review was to assess the available cost-effectiveness data pertaining to ECPR in OHCA.

* Corresponding author.
E-mail address: mark.dennis@sydney.edu.au (M. Dennis).

[1] These authors contributed equally.

https://doi.org/10.1016/j.resuscitation.2022.07.010
Received 20 May 2022; Received in Revised form 30 June 2022; Accepted 6 July 2022

Methods

The review protocol was prospectively registered in PROSPERO (registration number: CRD42021284506); in December 2021. The literature review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The online systematic review management software, Covidence, was used to screen and assess eligible studies. A narative approach was used to summarise findings and study characteristics were described (Tables 1 and 2).

Inclusion and exclusion criteria

Studies were included if they assessed cost-effectiveness of ECPR for OHCA in adults; or completed full economic evaluations (e.g. cost-effectiveness analysis and cost-utility analysis) reporting outcomes in incremental benefits (e.g. life-years (LY) saved, quality-adjusted life years (QALYs) gained); or reported one or more of the following survival, health system resource or patient out-of-pocket costs. We excluded paediatric, animal or in-vitro assessments, in-hospital cardiac arrests (IHCA); non-primary studies (e.g. review articles, commentaries, letters, editorials, protocols, laboratory studies, conference abstracts and technical reports).

Search strategy

We searched MEDLINE and Embase (via OvidSP), Tufts CEA registry and NHS Economic Evaluation Database (EED) from inception to September 2021, or for NHS EED until March 2015. Databases were searched for medical subject headings (MeSH) and keywords, combining terms related to cardiac arrest (such as 'cardi* or heart', 'arrest* or stoppage*', 'sudden cardiac death*) with terms aligning with the intervention (such as 'extra corp*', 'cardiopulm* adj2 resuscit*, CPR, ECMO or E-CMO or ECLS or E-CLS, ECPR or E-CPR or ECCO, 'extracorporeal circulation', extracorporeal membrane oxygenation', 'assisted circulation' and 'cardiopulmonary resuscitation'). Economic evaluation terms were searched simultaneously and included broader cost and benefit information (such as 'costs and cost analysis', quality-adjusted life year, cost benefit analysis, ICER, QALY, health care costs, economics, economics hospital, fees and charges) (A1). Included article reference lists were reviewed for additional articles.

Study selection and data extraction

Two reviewers (E.C, A.L) independently screened article titles and abstracts using pre-defined screening criteria. Any disagreement was resolved via discussion between the reviewers and a third reviewer (M.D or R.L.M) as needed. Duplicates were removed.

Variables extracted from the four studies include author and year published, country, study methodology, economic evaluation type, reference year and currency, sources of funding and conflicts, inclusion and exclusion criteria, target population, sample size, setting (OHCA, IHCA, or both), intervention, comparator, total costs, total health benefits, cost-effectiveness, cost categories, healthcare resource use, utility measures, data sources and sensitivity analyses.

Quality assessment and completeness of reporting

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (2) was used by two authors (D.A. and E.C) to rate the overall methodologic quality and completeness of reporting for included cost-effectiveness studies.

Table 1 – Included study characteristics.

First author	Year of publication	Country	Type of Study	Study design	Setting and/or population	Source of funding
Bharmal M.	2019	United States	Economic evaluation	Single-centre retrospective review; cost utility analysis; within trial	US (N = 32; 15 IHCA, 17 OHCA)	Sources of funding not reported.
Dennis M.	2019	Australia	Economic evaluation	Retrospective study; cost effectiveness analysis; Markov model; modelled	Australia (N = 62, 38 IHCA and 24 OHCA)	An independent grant from Stryker Australia Pty ltd (manufacturers of the LUCAS2TM mechanical CPR device), was provided to Sydney Local Health District (LHD) to undertake the ECPR economic analysis project.
Matsuoka Y.	2020	Japan	Economic evaluation	Multi-centre prospective cohort study; cost effectiveness analysis; decision tree analysis modelled	Japan (N = 454, across 46 hospitals)	A grant from the Japanese Ministry of Health, Labour, and Welfare.
St-Onge M.	2015	Canada	Economic evaluation	Retrospective review; cost effectiveness analysis; decisions tree analysis; modelled	Canada (N = 62; approx.0.14 cardiac arrest and 48 severe shock; calculated)	The authors have no financial disclosure.

Table 2 – Summary of methods and results from included economic evaluations.

Economic evaluation (setting)	Intervention, comparator, indication	Perspective	Time horizon (years)	Reference year for costs or currency	Discount rate (%/ year)	Incremental cost	Incremental QALYs	ICER (Cost per QALY; cost per LY; original currency)	Sensitivity analysis conducted	Threshold
Bharmal (US)	ECPR; VA-ECMO, All other health interventions, IHCA and OHCA	Not reported	Not reported	2018 United States dollars	Not reported	Incremental costs for OHCA patients alone are not reported. Mean operating costs for OHCA compared with IHCA are $69,731 and $176,703, respectively	Not reported separately for OHCA	ICER of $56,156/ QALY saved for ECPR in this population (OHCA and IHCA patients combined)	Probabilistic sensitivity analysis	The cost-utility analysis within the threshold considered cost-effective in the US (<$150,000/ QALY gained)
Dennis (Australia)	ECPR; VA-ECMO, CCPR, refractory cardiac arrest	Australian Health system	Lifetime horizon	2015–2016 Australian dollars; results reported in EUROs and AUD currency; conversion rate (EURO 1 = 1.493 AUD)	3.5	OHCA and IHCA; $59,389 and $85,943, respectively	OHCA had a mean effectiveness of 2.4 QALYs vs 3.3 QALY for IHCA	ICER of $24,794 per QALY gained for OHCA and $25,256 per QALY gained for IHCA	Scenario probabilistic sensitivity analysis	Australia does not mandate a cost effectiveness threshold for medical interventions. However, t his is based against a threshold of €20,000-€25,000 in the Spanish National Health service and 20,000–30,000 GBP in the National Institute for Health and Care Excellence (NICE) (approximately 35,000–53,000 AUD) per QALY gained
Matsuoka (Japan)	ECPR; VA-ECMOP, CCPR, refractory ventricular fibrillation/ pulseless ventricular tachycardia (VF/ pVT)	Healthcare payers	Lifetime horizon	2010 Japanese Yen; (1 Euro = 116.49 Yen)	2	OHCA ECPR and OHCA CCPR; ¥5,435,128 and ¥1,913,939, respectively	OHCA ECPR group had an estimated effectiveness of 1.71 QALYs vs 0.37 QALY for OHCA CCPR group. ECPR led to an incremental effectiveness of 1.34 QALYs	ICER of ¥2,619,692 (22,489) per QALY gained for ECPR compared with CCPR	One-way deterministic sensitivity and probability sensitivity analysis	The willingness to pay threshold is set at ¥5,000,000 per QALY gained

(continued on next page)

Table 2 (continued)

Economic evaluation (setting)	Intervention, comparator, indication	Perspective	Time horizon (years)	Reference year for costs or currency	Discount rate (%/year)	Incremental cost	Incremental QALYs	ICER (Cost per QALY; cost per LY; original currency)	Sensitivity analysis conducted	Threshold
St-Onge (Canada)	ECPR; VA-ECMO, Standard therapies (e.g. high dose insulin, calcium, and vasopressors), cardiac arrest and sever shock due to cardiotoxicants	Societal perspective	Lifetime horizon	2013 Canadian dollars; results reported in Canadian and US currency; conversion rate ($1.00 Canadian = $0.9562 US dollars)	Not reported	OHCA VA-ECMO and OHCA non-ECMO; $145,931 and $88,450, respectively	OHCA VA_ECMO group had an estimated effectiveness of 18 LY vs 10LY in the OHCA non-ECMO group	ICER of $7185/LY for OHCA VA-ECMO; $5155/LY if treating only patients in cardiac arrest	Probabilistic sensitivity analysis	The acceptable threshold for LY is unclear

*OHCA = out-of-hospital cardiac arrest.
*IHCA = in-hospital cardiac arrest.
*ICER = incremental cost-effectiveness ratio.

Results

Four studies were identified from Australia, Japan, Canada and the US and are summarised in the PRISMA flow chart (Fig. 1 and Table 1). Three studies presented details on costs, life years and QALYs and calculated incremental cost-effectiveness ratios (ICERs) for ECPR compared with CCPR or standard therapies (e.g. highdose insulin, calcium, and vasopressors). All economic evaluations described existing hospital-based ECPR services for OHCA.

Study design(s)

Characteristics of included studies are reported in Table 1. Three studies were modelled evaluations using lifetime horizons and reported the perspective of the economic evaluation; (i.e. Dennis et al. adopted a health system perspective,[8] Matsouka et al. adopted a healthcare payer perspective[9] and St-Onge et al. adopted a societal perspective.[10] All studies considered ECPR in the intervention arm compared with CCPR or other standard therapies.

Resource use and costs

Healthcare resource utilisation and cost data was sourced from both primary and secondary sources in cost-effectiveness studies, and primary data alone in the cost-utility analysis. Primary hospital utilisation data was collected in Bharmal et al.[11] and Dennis et al.[8] In the two other studies, healthcare resource use data was identified from independent sources reporting patient-level claims data and clinical event probabilities. Cost estimates were obtained either directly from hospital expense data, other clinical trials, or through a range of sources such as the Japanese national fee schedule. Direct medical costs were included but were not limited to: all chargeable items, type of ECPR pump, non-physician personnel time, physician charges, intensive care units (ICU) support, hospital ward and anaesthesia. Direct non-medical costs such as patient transport or carparking to attend appointments, and indirect costs such as productivity losses, were not reported.

Three studies reported the mean or median cost of OHCA ECPR and two studies reported the total cost of ECPR (OHCA and IHCA combined). Dennis et al.[6] reported a mean cost of ECPR OHCA patients $58,360 AUD ($41,564 USD) and healthcare cost per ECPR patient of $75,165 AUD ($53,533 USD). The estimated cost of OHCA ECPR in Matsouka[9] was ¥5,435,128 ($41,605 USD). Bhamal et al.[11] reported a median cost of OHCA ERCP at $69,731 USD and mean cost of ECPR at $156,263 USD.

Health outcomes

Three studies reported improved neurological outcomes resulting from improved Quality of Life (QoL) utility based on Cerebral Performance Categories (CPC) scores. Dennis et al.[8] notes numeous studies report exellect neurological outcomes in survivors where suvival of ECPR patients is not always directly linked to neuological disability.

QALYs gained were calculated in Dennis et al.[6] and Matsuoka et al.[9] by mapping CPC scores to Health Utilities Index Mark 3 (HUI-3) and EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) indexes, respectively. St-Onge et al.[10] calculated life years by determining the age-matched mean life expectancy of hospital survivors stratified by sex using data from Masson et al.[12] Bharmal et al.[11] adopted the Health Utilities Index Mark II (HUI-2) questionnaire to evaluate quality of life and make direct comparisons between

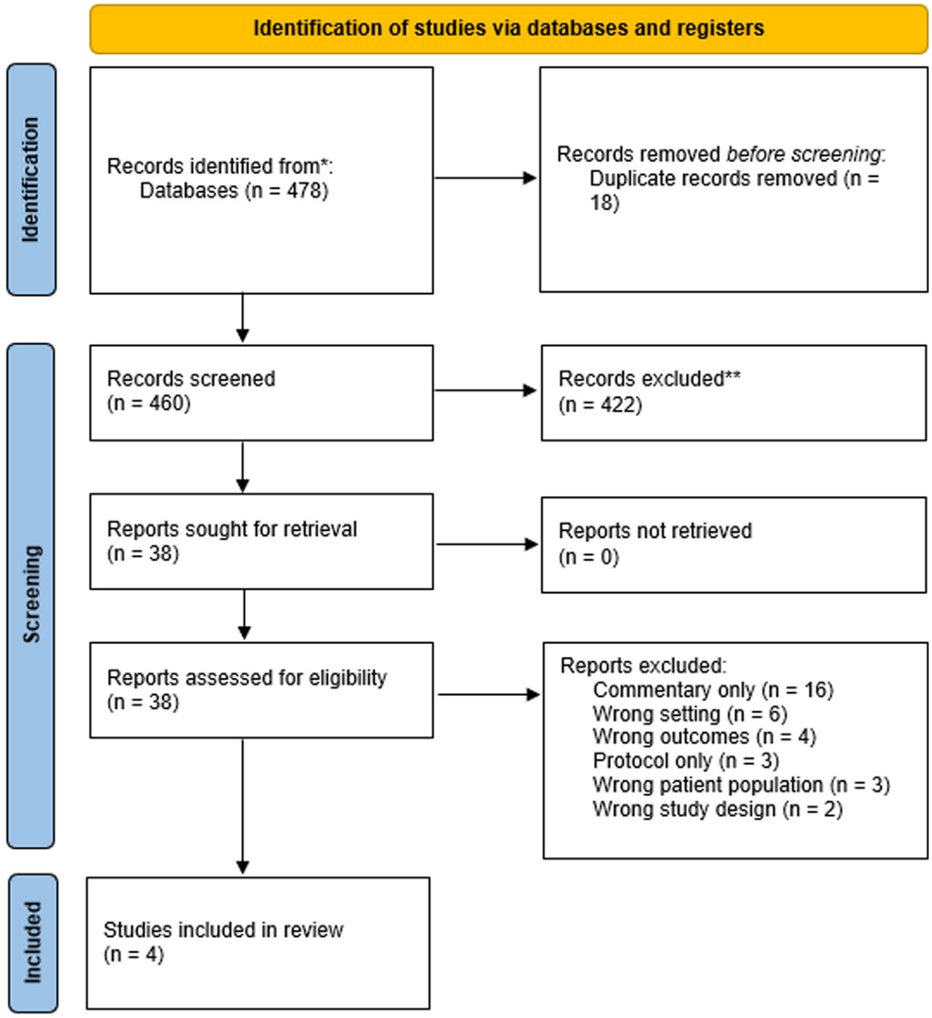

Fig. 1 – Modified PRISMA flowchart of included studies.

ECPR and other health interventions. Bharmal et al.[11] identified patients from a ECPR patient registry and calculated the difference in operating costs between OHCA and IHCA using the costs of hospitalisation from ECMO initiation to hospital discharge.

Incremental cost-effectiveness

All studies determined ECPR to be cost-effective compared with CCPR or other standard therapies. Cost-effectiveness was primarily driven by higher survival rates for ECPR use in OHCA versus CCPR or standard therapies, weighed against higher treatment costs.

Bhamal et al.[11] reported an ICER of $56,156 USD per QALY for ECPR (OHCA and IHCA combined) compared with CCPR. St Onge et al.,[10] Dennis et al.[8] and Matsouka et al.[9] reported ICERs of $5,151 CAD ($4,026 USD) per LY, $24,794 AUD ($17,671 USD) per QALY and ¥2,619,692 ($20,053 USD) per QALY, respectively for OHCA ECPR compared with CCPR and standard therapies.

Uncertainty analyses

Three of the four studies identified the probability of survival as a major driver of the model by using scenario-based probabilistic sensitivity analysis and one-way deterministic sensitivity analysis. A decrease in survival rates results in a reduction in mean QALYs gained and therefore increases estimated ICERs. Contributors to total operating costs, including direct costs i.e. chargeable items and non-physician time, were reported in Bhamal et al.[11] as drivers of the economic model, which offset the impact of survival rates.

Quality appraisal of studies and completeness of reporting

Quality assessment and completeness of reporting was performed for the four identified studies using the 2022 revised CHEERS checklist (A2).[2] No study satisfied all 28 quality criteria, although three of the studies scored 25 or above and were of high quality. Risks of bias identified from the limited available evidence included small study samples sizes and different study locations. Both limited patient sample sizes and the geographical variation across studies produce a sampling bias as only a narrow spectrum of patient characteristics were analysed. The produced results therefore may not necessarily reflect similar outcomes for patients in different countries.

Discussion

Our systematic review investigating the cost-effectivenness of ECPR for OHCA versus CCPR found ECPR to be cost-effective in all four identified studies. There was substantial hetergeneity in study locations and health systems, however the quality and completeless of the economic evaluations were satisfactory overall. Additionally, recently Gravesteijn et. al. reported that ECPR was cost-effective from a healthcare perspective for IHCA patients by utilising a Markov decision model. While this study did not meet our review's inclusion criteria as a full economic evaluation, the data presented substantiates our findings.

Over recent years ECPR in cardiac arrest has increased eightfold.[3] Despite enthusiasm by clinicians, it is a resource intensive and a technically challenging intervention, and although recommended in international cardiac arrest guidelines for patients refractory to CCPR,[5] additional work on its cost-effectiveness is required and has been requested by industry organisations.[4] Governments and policymakers use cost-effectiveness thresholds to deem health interventions as cost-effective or not. These thresholds are not uniform and vary globally. The well-established guidelines by the National Institute for Health and Care Excellence (NICE), United Kingdom, stipulate an ICER of 20,000–30,000 GBP ($24,972-$37,458 USD calculated)[1] per QALY gained, or less to demonstrate cost-effectiveness. Compared with these standards, our systematic review finds that ECPR is a cost-effective intervention in the management of OHCA compared to CCPR.

However, several noteworthy limitations exist. First, substantial heterogeneity in the design of the evaluations. Two of the studies did not categorise their cardiac arrest population groups into OHCA or IHCA. Therefore, while these economic evaluations showed ECPR to be cost-effective when compared to CCPR, these results may be inaccurate when factoring in differences in OHCA and IHCA costs. Additionally, one of the studies reported that the mean operating cost of ECPR in OHCA is significantly lower than in IHCA patients likely due to improved survival rates.[10] Second, of the four studies only one study utilised a societal perspective with the remaining two evaluations using a healthcare system and payers perspective.[11] As such, these studies failed to consider both direct non-medical costs such as patient transport or carparking to attend appointments, and indirect costs such as productivity losses. Further, three of the four studies failed to report any adverse effects which might result in increased costs. Additionally, the authors did not provide any justification for this exclusion. ECPR, especially when compared with CCPR is both more invasive and physically demanding on patients and therefore further research into the costs of complications is required. Three of the four studies presented well-defined health economic evaluations stating their comparators, perspectives, and time horizons. Third, whilst the studies were all from different populations it is likely that the costs (and effectiveness) of an ECPR service vary substantially between health systems. Further, all studies were conducted in an existing ECPR service, the costs to develop ECMO capability and an ECPR system were not included in the analysis. Lastly, while there is clear support for the cost-effectiveness of ECPR, evidence from randomised controlled trials is lacking. This may result in a selection bias which may lead to lower mortality rates and therefore lower ICER and QALYs. Finally, while all studies identified were based on the provision of ECPR in an ECPR-capable hospital (hospital based ECPR), newer models of ECPR provision including rendezvous ECPR (whereby the ECPR team meets with emergency response personnel at the closest participating emergency department) and pre-hospital ECPR are being trialled.[13] Separate economic analyses of these models would be required.

Conclusions

Our review suggests hospital-based ECPR for OHCA is cost-effective when compared with CCPR but inferences are limited owing to heterogeneity in populations and health systems. Further, larger cost-effectiveness studies are required to validate these findings and assess new ECPR services and delivery models.

Conflicts of Interest

None of the authors have any conflicts of interest to report. Dr Dennis is supported by a National Heart Foundation Australia Post Doctoral Fellowship, Australia. Professor Morton is supported by a University of Sydney, Robinson Fellowship, Australia; and an NHMRC Investigator grant #1194703, Australia.

CRediT authorship contribution statement

Danielle Addison: Validation, Conceptualization, Methodology, Formal analysis, Writing – original draft. **Evan Cheng:** Validation, Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Paul Forrest:** Writing – review & editing, Supervision. **Ann Livingstone:** Conceptualization, Investigation, Writing – review & editing. **Rachael L. Morton:** Conceptualization, Writing – review & editing, Supervision. **Mark Dennis:** Conceptualization, Writing – review & editing, Supervision.

Author details

[a]NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia [b]Royal Prince Alfred Hospital, Camperdown, Australia [c]Faculty of Medicine and Health, The University of Sydney, Australia

REFERENCES

1. OECD (2022), Purchasing power parities (PPP) (indicator); 2022.
2. Husereau D, Drummond M, Augustovski F, et al. CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations.
3. Hadaya J, Dobaria V, Aguayo E, et al. National trends in utilization and outcomes of extracorporeal support for in- and out-of-hospital cardiac arrest. Resuscitation 2020.
4. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. Lancet 2020.
5. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation 2021;161:115–51. https://doi.org/10.1016/j.resuscitation.2021.02.010.
6. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020.

7. MacLaren G, Masoumi A, Brodie D. ECPR for out-of-hospital cardiac arrest: more evidence is needed. Crit Care 2020;24.
8. Dennis M, Zmudzki F, Burns B, et al. Cost effectiveness and quality of life analysis of extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest. Resuscitation 2019;139:49–56.
9. Matsuoka Y, Goto R, Atsumi T, et al. Cost-effectiveness of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A multi-centre prospective cohort study. Resuscitation 2020;157:32–8.
10. St-Onge M, Fan E, Mégarbane B, Hancock-Howard R, Coyte PC. Venoarterial extracorporeal membrane oxygenation for patients in shock or cardiac arrest secondary to cardiotoxicant poisoning: a cost-effectiveness analysis. J Crit Care 2015;30:437.
11. Bharmal MI, Venturini JM, Chua RFM, et al. Cost-utility of extracorporeal cardiopulmonary resuscitation in patients with cardiac arrest. Resuscitation 2019;136:126–30.
12. Masson R, Colas V, Parienti JJ, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation 2012;83:1413–7.
13. Singer B, Reynolds JC, Davies GE, et al. International ECMO Network (ECMONet). Sub30: Protocol for the Sub30 feasibility study of a pre-hospital Extracorporeal membrane oxygenation (ECMO) capable advanced resuscitation team at achieving blood flow within 30 min in patients with refractory out-of-hospital cardiac arrest. Resusc Plus 2020.