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Clinical paper

Cost effectiveness and quality of life analysis of extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest

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Abstract

Background: The use of extracorporeal membrane oxygenation (ECMO) in refractory cardiac arrest (ECPR) has increased exponentially. ECPR is a resource intensive service and its cost effectiveness has yet to be demonstrated. We sought to complete a cost analysis with modelling of cost effectiveness and quality of life outcomes. We sought to complete a cost analysis with modelling of cost effectiveness and quality of life outcomes of patients who have undergone ECPR.

Methods: Using data on all extracorporeal cardiopulmonary resuscitation (ECPR) patients at two ECMO centres in Sydney, Australia; we completed a costing analysis of ECPR patients. A Markov model of cost, quality of life and survival outcomes was developed to examine cost per QALY estimates and incremental cost effectiveness ratios (ICERs). Probabilistic sensitivity analysis (PSA) was completed to assess the probability of cost effectiveness for base case and variations.

Results: Sixty-two consecutive ECPR patients were analysed; mean age of 51.9 ± 13.6 years, 38 (61%) were in hospital cardiac arrests (IHCA). Twenty-five patients (40%) survived to hospital discharge; all with a cerebral performance category (CPC) of 1 or 2. The mean cost per ECPR patient was AUD 75,165 (€50,535; ±AUD 75,737). Over 10 years ECPR was estimated to add a mean gain of 3.0 Quality Adjusted Life Years (QALYs) per patient with an incremental cost effectiveness ratio (ICER) of AUD 25,212 (€16,890) per QALY, increasing to 4.0 QALYs and an ICER of AUD 18,829 (€12,614) over a 15-year survival scenario. Mean cost per QALY did not differ significantly by OHCA or IHCA.

Conclusions: ECMO support for refractory cardiac arrests is cost effective and compares favourably to accepted cost effectiveness thresholds.

Keywords: Extracorporeal membrane oxygenation, Cardiac arrest, Cost, Markov, Quality of life, ECMO

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Introduction

Cardiac arrest continues to be a leading cause of death in otherwise healthy adults. Despite much effort, overall survival rates are reported at 2–15% for out of hospital cardiac arrest (OHCA)[1,2] and 22–34% for in-hospital cardiac arrests (IHCA),[3,4] with significant neurological deficits in survivors. Extracorporeal membrane oxygenation (ECMO) enables end organ perfusion support whilst awaiting definitive treatment and cardiac recovery. A number of small non-randomised studies using ECMO in refractory cardiac arrest (ECPR) have reported promising survival rates and improved neurological outcomes.[5] Despite the lack of high quality trial data, the use of ECPR has increased exponentially.[6]

The provision of an ECMO service is resource intensive requiring specialised expertise and equipment. Concerns exist over its cost effectiveness and health related quality of life (HRQoL) outcomes.[7] We sought to a conduct a costing analysis to establish average cost per ECPR patient in New South Wales (NSW), Australia and integrate survival outcomes with quality of life metrics of patients who have survived cardiac arrest with ECPR.

Methods

Analysis participants and design

All patients treated with ECPR for refractory cardiac arrest at Royal Prince Alfred Hospital (RPAH) and St Vincent's Hospital (SVH) in Sydney, Australia between September 2009 and October 2018 were included for analysis. A retrospective study group to February 2016 (n = 37) had no set inclusion criteria for ECPR support and has previously been reported.[8] In February 2016 the inclusion criteria for ECPR were changed and included a criterion of age <70 years, witnessed cardiac arrest, shockable initial rhythm, 10 min of arrest without return of spontaneous circulation (ROSC) and use of the LUCAS2™ mechanical CPR device (Stryker Medical, Sydney, Australia). Data collected for both cohorts were consolidated for the total study group (n = 62). Institutional ethics committee approval was completed as per Sydney Local Health District (SLHD) Research Ethics and Governance Office - Protocol X14-0337.

Patient costs

Patient "costs" were defined as the sum of money attributed to the patient's episode of care. All elements attributed to the patients care from time of cardiac arrest to hospital discharge or death were assessed. This included, but was not limited to: ambulance, medical, nursing and allied health staffing costs, pharmacological therapy, diagnostic and therapeutic procedures, renal replacement therapy, consumables, ECMO circuits, clinical complications, blood and blood products and hospital overheads including critical care and ward management. Unit costs were sourced from the ECMO Australian Refined Diagnosis Related Group (ARDRG), NSW cost of care standards, the Australian Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) consistent with standards for health economic evaluation in Australia.[8,9] For details of unit cost sources see Online Table 1. The cost analysis process integrated ECMO DRG figures adjusted for mean ECMO run and ICU and ward costs based on length of stays (LOS). Other costs not identified in the DRG e.g. clinical procedures, surgery and complications were individually reviewed for each patient to ensure only costs incurred at or after time of arrest were included. Ongoing costs post hospital discharge were not assessed. All costs are presented in 2016 Australian dollars, EURO 1 = 1.493 AUD as at June 2016.

ECMO diagnosis related groups (DRG)

ECMO DRG figures were cross validated with disaggregated individual component costs to ensure accuracy of ECMO DRG cost weights. The analysis examined 3 available years (2012–13–2014–15, n = 723) to assess annual cost stability. The ECMO DRG was only applied for the time spent on the ECMO circuit. Author MD reviewed individual patient encounters to ensure validity against supplied DRG costings.

ICU and ward costs

Daily ICU costs for ECPR were calculated from multiple sources including the critical care component of the ECMO DRG and segmented ICU support costs across staffing, clinical support services (radiology and pathology) and consumables (medications, clinical and nonclinical supplies). ECPR ICU costs were also compared with established estimates of average ICU cost per day referenced in Australian health economic guidelines.[10] Hospital ward care costs were based on NSW cost of care standards.

CPC and health-related quality of life (HRQoL)

All patients had cerebral performance category (CPC) scores documented at discharge. CPC scores have been validated against HRQoL for the classification of patient's quality of life[11]; and were used to provide an estimate of Quality Adjusted Life Years (QALYs). ECPR QALY estimates were examined in context of life expectancy based on mean age of survivors, NSW life tables and related Australian HR-QoL population norms,[12,13] and documented HRQoL results for ECPR patients.[7]

Outcomes

The primary outcome was cost per ECPR patient. Secondary outcomes included cost per survivor, QALY gained and incremental cost effectiveness ratio (ICER). Additional modelling scenarios were completed as per section below.

Statistical analysis

Categorical variables were summarised using number and percentages and continuous variables using the summary statistics n, mean and standard deviation (SD). Cost and related LOS data were examined for normality using the Shapiro–Wilk test confirming data for survivors and non-survivors were non-parametrically right skewed, as commonly the case for healthcare data. Non-parametric data were assessed using the Wilcoxon rank-sum (Mann–Whitney) test. A value of 0.05 was considered significant. All tests were completed with Microsoft Excel 2016 and STATA v 13.1 (StataCorp LP, College Station, Texas, USA).

Modelling

A Markov model was developed combining the costing analysis results with patient outcomes to examine ECPR effectiveness over an extended 10-year timeframe. Within the ECPR cohort, patient pathways were established for OHCA and IHCA episodes with subsequent ICU and hospital costs and outcomes defined within each branch — Fig. 1. The model framework integrated costing figures with patient survival rates and estimated patient QALYs based on survivor CPC scores. A CPC of 1 is highly probable to equate to a health utility index above 0.8.[11] CPC scores of 2 were not separately estimated and were conservatively ascribed the lowest index for the range of 0.4. Formulation of a base case model assumed a mean utility of 0.85 with a standard deviation of 0.05 to provide an approximate spread above the expected minimum of 0.8.

Sensitivity and scenario analysis

A 10-year base case horizon was developed using the mean survival age of the ECPR study group and reported levels of QoL for cardiac arrest survivors discharged without significant neurological deficits.[14] Additional scenarios undertaken including a reduced 5 year survival case, extending the timeframe from 10 to 15 years and survival rates increasing and decreasing by 10%.

Uncertainty in model variables was assessed using non-parametric bootstrapping methods of Probabilistic sensitivity analysis (PSA). Estimated cost effectiveness was plotted as cost effectiveness acceptability curves to display the probability that ECPR is cost effective in context of the health system's willingness to pay. The cost of implementing ECPR was derived from the health system perspective with all costs and health outcomes discounted at 3.5% per annum and cost figures adjusted to 2015–16 Australian dollars (AUD); conversion rate of one EURO = 1.493 AUD as at June 2016. The Markov Model was developed using TreeAge Pro 2018 r2.1.

Role of the funding source

The sponsors of the study had no input in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for decision to submit for publication.

Results

Baseline characteristics

Sixty-two patients (mean age of 51.9 ± 13.6 years); were analysed with baseline characteristics in Table 1. Thirty-eight (61.3%) were IHCAs and 24 (38.7%) OHCAs — Fig. 2. Twenty-five patients (40.3%) survived to hospital discharge, 17/38 (45%) IHCA cases and 8/24 (33%) OHCA cases. Twenty-three (92%) survivors recorded a CPC score of 1, the remaining 2 cases had a CPC of 2.

Cost analysis

Cost analysis by survivor status is shown in Table 2. The mean cost per ECPR patient was AUD 75,165 ± 75,737 and per survivor AUD 118,664 ± 72,216. The mean ECMO related costs for survivors and non-survivors was AUD 21,758 ± 23,059 and AUD 22,031 ± 25,938 respectively. Survivors had a mean ICU LOS of 11.6 ± 8.9 days at a mean cost of AUD 53,506 ± 40,990 versus 1.9 ± 8.0 at AUD 8614 ± 36,812 for non-survivors. Following ICU discharge; survivors had a mean LOS in hospital of 24.2 ± 24.0 days in hospital at an estimated cost AUD 27,892 ± 28,165). There was no significant difference in cost per ECPR patient between the retrospective and prospective cohorts, AUD 73,090 ± 72,376 vs. AUD 78,238 ± 81,885; p = 0.80.

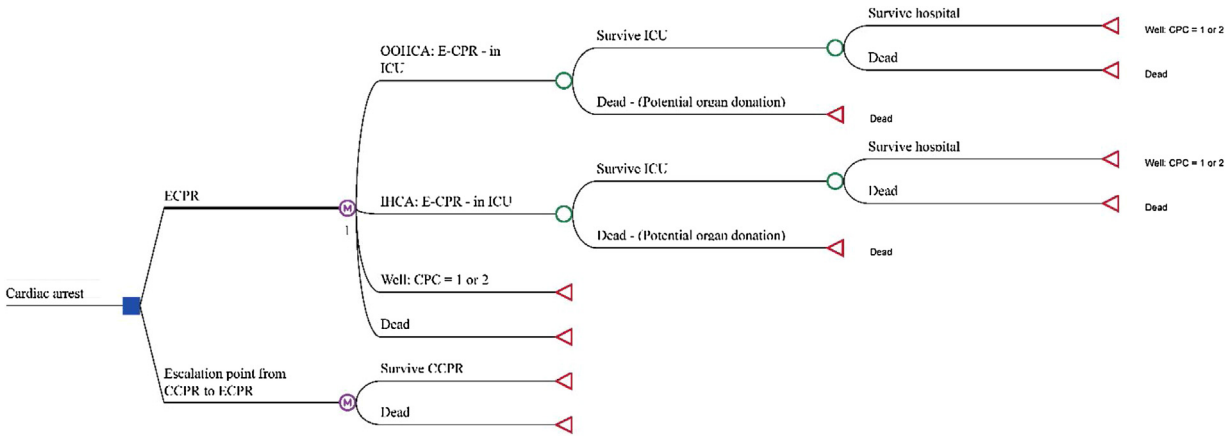

Fig. 1 – ECPR Markov model structure.
IHCA — in-hospital cardiac arrest, ECPR — ECMO cardiopulmonary resuscitation, CCPR — conventional cardiopulmonary resuscitation, OOHCA — out of hospital cardiac arrest, CPC — cerebral performance category, ICU — intensive care unit.

Table 1 – Baseline characteristics and intervention data.

	Demographics and baseline data				Intervention data		
	Patients (n)	Patients (%)	SD	Range		Patients (n)	Patients (%)
Total patients	62.0				RBC transfused	46	74.2%
Mean Age (years)	51.9		13.6	17–70	Angiogram	38	61.3%
Male (n)	43.0	69.4%			Bleeding	30	48.4%
Mean ECMO run (days)	3.8		4.0	0.5–19	LUCAS support	23	37.1%
Initial Rhythm					RRT	21	33.9%
VT/VF	34.0	54.8%			First stent	19	30.6%
PEA	14.0	22.6%			Ischaemic leg	14	22.6%
Asystole	3.0	4.8%			Vessel repair	11	17.7%
Witnessed	49.0	79.0%			Cannulation bleed	9	14.5%
Unwitnessed	5.0	8.1%			Thrombolysed	6	9.7%
Unknown if witnessed or not	8.0	12.9%			Second stent	6	9.7%
Bystander CPR					Backflow clot	6	9.7%
Yes	53.0	85.5%			CAGS	5	8.1%
No	1.0	1.6%			Blood infection	5	8.1%
Unknown	8.0	12.9%			IABP	4	6.5%
Arrest to CPR time					DVT	4	6.5%
<5min	42.0	67.7%			Stroke	3	4.8%
5–10 min	6.0	9.7%			PE	2	3.2%
>10min	3.0	4.8%			Amputation	1	1.6%
unknown	11.0	17.7%					
Location							
IHCA	38.0	61.3%					
OHCA	24.0	38.7%					

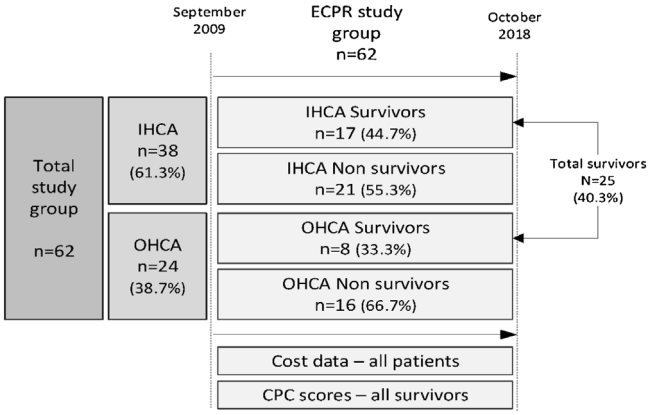

Fig. 2 – E-CPR study groups and sample sizes.
IHCA — in-hospital cardiac arrest, OHCA — out of hospital cardiac arrest.

IHCA vs. OHCA

Mean IHCA costs were AUD 85,779 ± 65,615 vs. AUD 58,360 ± 88,352 for OHCA cases – (Online Table 2). IHCA cases had significantly longer ECMO run compared to OHCA (4.9 ± 4.5 vs. 2 ± 2.3; p = 0.001), but not ICU LOS (5.6 ± 7.8 vs. 6.1 ± 12; p = 0.86) nor ward stay (14.8 ± 20.8 vs. 7.50 ± 23.1, p = 0.213).

Modelling

Base case analysis

The Markov model base case combined ECPR mean incremental cost following patient escalation point from conventional CPR (CCPR) (AUD 76,580) and an estimated increase of 3.0 QALYs– Fig. 3. The bootstrapped point estimates in the scatterplot reflect high variation in ECPR pathways, durations of care and complications with estimated 95% confidence interval ranging from a minimum of AUD 39,487 to a maximum of AUD 129,460 in complex cases.

Sensitivity analysis and cost effectiveness acceptability

The probability of ECPR being cost effective at given willingness to pay thresholds is shown as acceptability curves, Fig. 4. Cost effectiveness acceptability curves (CEACs) extend deterministic methods by combining the joint variation in all model parameters including survival, care pathways and related cost. The 10-year base case estimated ICER is AUD 25,212 per QALY. Under a 15-year survival scenario estimated mean QALYs increased from 3.0 to

Table 2 – ECPR resource use and cost summary.

Cost item	Survivors						Non survivors						Total					
	n	Mean LOS	SD LOS	Mean Cost (AUD)	SD (AUD)	% Survivors	n	Mean LOS	SD LOS	Mean Cost (AUD)	SD (AUD)	% Non Survivors	n	Mean LOS	SD LOS	Mean Cost (AUD)	SD (AUD)	% Total
ECMO run	25	3.7	3.2	21,354	18,491	100%	37	3.8	4.5	22,031	25,938	100%	62	3.8	4.0	21,758	23,059	100%
ICU LOS	25	11.6	8.9	53,506	40,990	100%	6	1.9	8.0	8614	36,812	16%	31	5.8	9.6	26,716	44,201	50%
Hosp LOS	25	24.2	24.0	27,892	28,165	100%	3	3.7	15.8	4,435	18,749	8%	28	12.0	21.8	13,893	25,576	45%
Total ECMO and Hospital	25			102,753	62,036	100%	37			35,080	58,111	100%	62			62,367	68,023	100%
Care procedures				10,325	14,079					5,476	9,331					7,431	11,624	
Complications				5,586	3,584					5,219	5,857					5,367	5,033	
Total cost	25			118,664	72,216	100%	37			45,775	63,567	100%	62			75,165	75,737	100%

4.0 reducing the ICER to AUD 18,829. A conservative scenario based on 5-year survival reduced the mean QALY gain from 3.0 to 1.8 increasing the estimated ICER to AUD 42,584.

Assuming a 10% decrease in ECPR survival rates from our base case data reduced QALY gain from 3.0 to 2.4 and increased the estimated cost per QALY to AUD 29,530. With longer post arrest survival and/or increased rates of survival ECPR becomes significantly more cost effective. A decrease in favourable neurological outcomes was assessed by reduction of the assuming QoL utility of 0.5 resulting in an increased in ICER of AUD 40,437.

By arrest location, the mean cost for OHCA was AUD 59,389 with a mean effectiveness of 2.4 QALYs and ICER AUD 24,794 per QALY (95% CI: AUD 18,509 AUD 143,449) vs. mean cost for IHCA of AUD 85,943; mean effectiveness of 3.3 QALYs and ICER AUD 25,256 per QALY (95% CI: AUD 38,004 AUD 159,303).

Discussion

To our knowledge, this study is the largest and most comprehensive ECPR cost analysis and modelling to date. We found that ECPR is cost-effective by current accepted thresholds.

At present, Australia does not mandate a cost effectiveness threshold for medical interventions. However, a threshold of €20,000–€25,000 in the Spanish National Health service has been suggested[15] and the National Institute for Health and Care Excellence (NICE), United Kingdom, has an established cost effectiveness threshold for new medical treatments of 20,000–30,000 GBP (approximately 35,000–53,000 AUD) per QALY gained.[16] Further, the American Heart Association (AHA) with the American Cardiology Association (ACA) have proposed a tiered threshold level of intervention value.[17] Our base case has established a cost per QALY gained well below these thresholds.

Modelling estimates are sensitive to survival rates, length of ICU and hospital stay, length of survival post arrest and neurological outcomes. Our survival rates, (45% for IHCA and 33% for OHCA), are comparable to other studies.[18–21] We report that the cost per QALY and ICER were comparable between IHCA and OHCA where the higher mean cost per IHCA patient was offset by the increased mean QALYs resulting from a higher survival rate. Importantly, using sensitivity analysis with an assumed 10% decrease in ECPR survival rates from base case across both the IHCA and OHCA pathways, the provision of an ECPR service remains below the NICE cost effectiveness threshold[16] and within AHA/ACA guidelines.

Longitudinal follow up of cardiac arrest patients report median survival above 5 years for both OHCA and IHCA.[22] We established a 10 years base case model given the comparably lower mean age of our ECPR group but also included a 5-year horizon scenario that confirmed ECPR as a cost effective intervention at this time interval. Most current ECPR trial inclusion criteria include patients below 70 years of age which is associated with better outcomes in ECPR patients.[23] Expansion inclusion criteria above the age of 70 will likely be at the expense of significant cost effectiveness.

A majority of the cost associated with ECPR is determined by the length of intensive care and hospital stay and the duration of ECMO support. Our data is consistent with the existing ECPR literature,[19,24] with ECPR patient pathways being characterised by a rapidly declining survival curve. Non-survivors typically do not survive the initial days of ECMO support, (have shorter ICU and ward LOS and therefore reduced costs), whereas survivors are rapidly weaned from

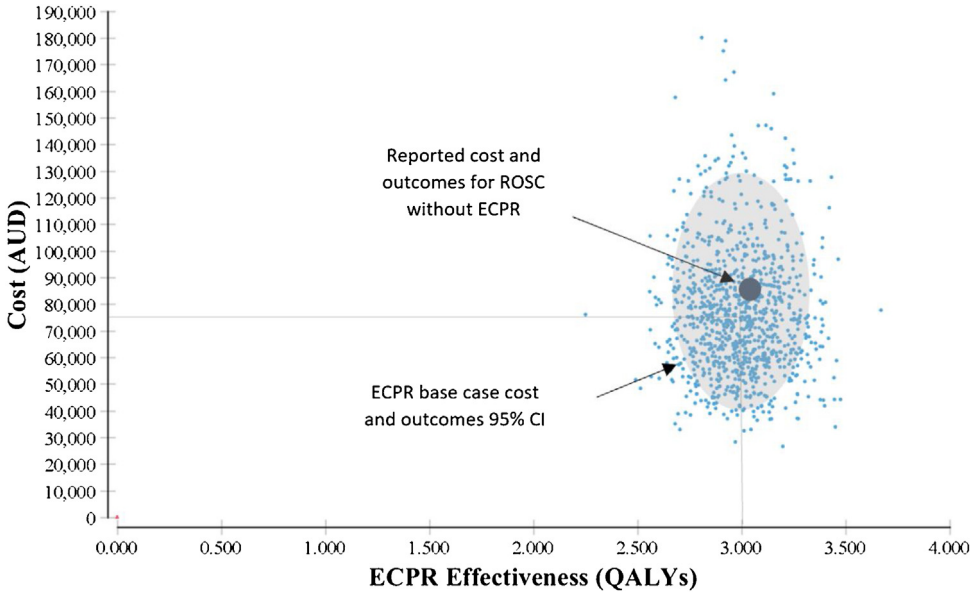

Fig. 3 – ECPR base case estimated cost effectiveness.

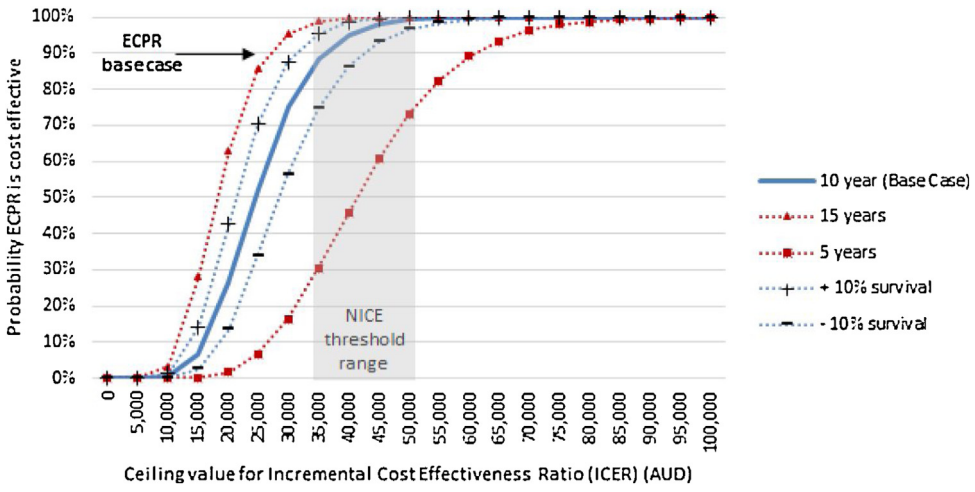

Fig. 4 – ECPR cost effectiveness acceptability curves.

ECMO and do not have extended ICU admissions.[18,19] This decreases costs relative to other forms of ECMO support. The mean cost per ECMO treated patient during the CESAR trial[25] for respiratory failure, (median critical care LOS 24 days) was estimated at 73,979 GBP giving an ICER per QALY almost double that seen in our study.

Importantly, ECPR survival does not appear to be at the expense of neurological disability with excellent neurological outcomes in survivors reported in a number of studies.[18,19,26] Although not a sensitive measure of QoL, a CPC = 1 is highly probable to equate to high health utility.[11] Additional modelling assuming a reduction in assumed QoL utility did not result an ICER outside above cost-effective thresholds.

Meaningful cost and QoL comparison between ECPR and conventional CPR (CCPR) outcomes are difficult. Conventional CPR cost analysis and quality of life studies vary substantially in costs included and costing methodologies. Reported cost per survivor range from AUD 78,000 to AUD 138,000.[14,27–29] Our comparative analysis (Fig. 3) indicates that the care pathway and related costs of ECPR survivors is likely to be similar to CCPR. Moreover, should ECPR survivors be proven to have better neurological outcomes than CCPR survivors the cost per QALY will be inherently lower.

Of the 37 ECPR patients who did not survive only one case proceeded to organ donation. The prevalence of brain death is higher in ECPR than in CCPR.[30] In some selected centres organ donation has occurred in up to 50% of ECPR patients.[31] Whilst not included in our analysis, increased organ donation has the potential to significantly shift the cost effectiveness of ECPR albeit with careful consideration of ethical and moral issues that involved.

The provision of an ECPR service for refractory cardiac arrest cases is cost effective when compared to current accepted

effectiveness thresholds. Further research as to the benefit of ECPR over CCPR with longer quality of life follow up is required.

Limitations

The perspective is limited to the NSW health system and does not incorporate wider societal costs and benefits. The study is limited to the point of hospital discharge subsequent health service usage costs related to the patient's original cardiac arrest were not able to be assessed.

Secondly, the use of CPC scores to estimate HRQoL is based on broad functional outcome categories and may not be as sensitive to high end incremental scores as formally administered HRQoL instruments with long term follow up.

We did not perform a complete "bottom up approach" to costing the ECPR patients hence some costs incurred in the provision of the service may have been missed or inaccurate. However, the ECMO DRGs used in Australia are based on a comprehensive bottom up approach to ECMO costs. Furthermore, we undertook additional disaggregated analysis to ensure no major "outlier" costs were missed or inappropriately included.

We assumed that all patients in our study group would not have survived without ECPR. Whilst it is possible that a small number of our patients with refractory cardiac arrest may have survived with conventional our analysis indicated that even in this event the ECPR care pathway and related cost is likely to be similar to ECPR.

Inclusion criteria for activation for ECPR for cardiac arrests changed during the study period. However, there was no significant difference in ECPR costs before and after inclusion this change. Finally, whilst the study group size is limited it is comparable to many other published cohorts,[21,32] and reflects the relative infrequency of ECPR cases.

Conclusion

This ECPR study provides the first detailed costing analysis for ECPR in refractory cardiac arrest. Using conservative assumptions, ECPR compares favourably to established cost effectiveness thresholds.

Conflict of interest

Stryker Pty Ltd. provided funding to Sydney Local Health District (LHD) to undertake the ECPR economic analysis project. Sydney LDH separately engaged an independent health economics consultant — Mr Fredrick Zmudzki for completion of the study. Stryker had no role or influence in the study concept, design, collection, results or preparation and publication of the manuscript.

Acknowledgement

This work was supported by an independent grant from Stryker Australia Pty Ltd, Sydney, Australia. The study sponsor had no role in study design, data collection interpretation nor presentation of work completed.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.03.021.

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