



Cost-Effectiveness Analysis of Out-Of-Hospital versus In-Hospital Extracorporeal Cardiopulmonary Resuscitation for Out-Hospital Refractory Cardiac Arrest

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Abstract: It has been speculated that out-of-hospital cardiac arrest (OHCA) patients' survival might be improved by implementing extracorporeal cardiopulmonary resuscitation (ECPR) before arrival to hospital. Therefore, we sought to assess the cost-effectiveness of OH-ECPR versus in-hospital (IH)-ECPR in OHCA patients in Qatar. From the hospital perspective, a conventional decision-analytic model was constructed to follow up the clinical and economic consequences of OH-ECPR versus IH-ECPR in a simulated OHCA population over one year. The primary outcome was the survival at discharge after arrest as well as the overall direct healthcare costs of managing OHCA patients. The robustness of this model was evaluated via sensitivity analyses. The OH-ECPR yielded 16% survival at discharge after arrest compared to 7% with IH-ECPR, [risk ratio (RR)=0.91; 95% CI 0.79 to 1.06; $P = 0.26$]. Incorporating the uncertainty associated with this survival rate, and based on the estimated willingness to pay threshold in Qatar, the

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OH-ECPR was cost-effective with an incremental cost-effectiveness ratio of QAR 464,589 (USD 127,634). Sensitivity and uncertainty analyses confirmed the robustness of the study outcome. This is the first cost-effectiveness evaluation of OH-ECPR versus IH-ECPR in OHCA patients. OH-ECPR is potentially an economically acceptable resuscitative strategy in Qatar. (Curr Probl Cardiol 2022;47:101387.)

Introduction

Cardiac arrest is the sudden loss of effective blood flow, which inevitably leads to death if cardiopulmonary resuscitation (CPR) is not initiated.^{1,2} The overall survival rate at hospital discharge among patients with out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) resuscitated with conventional CPR ranges from 2%-15% and 15%-22%, respectively.³⁻⁵ Also, considerable morbidity occurs in patients who have survived prolonged cardiac arrests, such as severe neurological deficits in up to 30%-60% of OHCA survivors and 10%-20% of IHCA survivors.⁵

For OHCA patients, who are refractory to conventional CPR, and in whom the cause of the OHCA is potentially reversible, extracorporeal cardiopulmonary resuscitation (ECPR) may serve as a potential bridge for recovery.⁶ Although there are discrepancies with regards to the benefits of ECPR among patients with OHCA, evidence has shown promisingly high survival rates with ECPR, with up to 10 folds increase in use within the last 10 years.⁷⁻¹¹

As evidence emerged regarding the success of ECPR over conventional CPR for IHCA, some practices are attempting to use ECPR in very highly selected patients who developed OHCA.¹²⁻¹⁴ One major factor contributing to the likelihood of survival in OHCA patients receiving ECPR is the duration of CPR prior to cannulation. Therefore, it has been speculated that the outcomes for OHCA patients might be improved by cannulation before arrival to the hospital, consequently reducing the period of inadequate circulation.¹⁴ However, there are numerous barriers to pre-hospital ECPR implementation.¹³ To date, the only study of the clinical effectiveness of ECPR for OHCA patients, by Bougouin et al., showed that pre-hospital ECPR led to higher survival (15% vs 7%) and favorable neurological outcomes compared to when patients received ECPR in hospital.¹²

As ECPR is resource-demanding and has been shown to be associated with a high economic burden, scrutinizing the clinical effectiveness of the ECPR will need to be evaluated against the significant value of the health care resources that it consumes.¹⁵⁻¹⁷ Hence, for whether to implement ECPR for OHCA patients, determining the value of cost-effectiveness is critical to curtailing costs. To date, some studies have examined the cost-effectiveness of ECPR in OHCA versus IHCA.^{6,18} What has never been evaluated, however, is the cost-effectiveness of the out-of-hospital initiation of ECPR (OH-ECPR) compared to initiating it in-hospital (IH-ECPR) for the OHCA patients. The purpose of this study, therefore, is to evaluate the cost-effectiveness of OH-ECPR versus IH-ECPR in OHCA patients.

Materials and Methods

Model structure

A conventional type of decision-tree model was developed to follow up the clinical pathways undertaken by hypothetical OHCA patients with refractory ventricular fibrillation or pulseless ventricular tachycardia who received OH-ECPR vs IH-ECPR. OHCA patients receiving OH- or IH-ECPR were initially differentiated based on survival or death at discharge. Those who survived at discharge were followed up until further differentiated based on survival or death 3-6 months after arrest. Surviving 3-6 months after an arrest can be differentiated based on whether patients have good versus poor neurological outcomes. The decision-analytic model is presented in Supplementary Material Figure S1. The duration of the model follow up was until death at discharge, death after 3-6 months after arrest, or for a one-year after discharge with poor neurological outcomes. A case of success in the current model was defined as survival at discharge after arrest. We assumed that all the success cases are transferred to a rehabilitation setting to ensure the overall well-being of the patients.¹⁹

OHCA patients were those who had sudden loss of cardiac mechanical contractility with the absence of signs of circulation outside hospital settings.²⁰ The OH-ECPR is defined as the implementation of ECPR before arrival to hospital within an average of 45 minutes after cardiac arrest,¹⁴ and IH-ECPR is defined as implementation of in-hospital ECPR with the arrival to hospital. For survival at 3-6 months after arrest, with good or poor neurological outcomes, or the 1 year after discharge, with poor neurological outcomes, rehabilitation care was received to ensure the overall

well-being of the patients. A good neurological outcome is defined as a case that had Cerebral Performance Category (CPC) scores of 1 or 2, while a poor neurological outcome is defined as a case that had CPC scores of 3, 4, or 5.⁹

Considering the real-life interactions among different concurrent inherent uncertainties in the literature-based model input data, the base-case of the model was analyzed based on multivariate uncertainty analysis of the model event probabilities. Based on 1000 iterations to simulate a hypothetical cohort population of 1000 people, a multivariate uncertainty analysis was performed to include variations in all clinical probabilities, based on 95% confidence interval (CI) uncertainty ranges and a triangular type of distribution. This uncertainty analysis was performed using Monte Carlo simulation via @Risk-7.6 (Palisade Corporation, NY, US). The Monte Carlo simulation enables the incremental cost-effectiveness ratio (ICER) acceptability curves and cost-effectiveness planes (CEPs), and a tornado analysis of clinical outcomes as per their impact on the economic outcome.

Clinical inputs

Clinical model event rates were primarily based on registry and meta-analysis studies, by Bougouin et al. and Kim et al., respectively.^{9,12} The Bougouin et al. study is a population-based registry of OHCA patients resuscitated with IH-ECPR, which included all cases of sudden OHCA occurring in the Paris region. The Kim et al. study is a meta-analysis of OHCA versus IHCA patients, managed with IH-ECPR. The probability of survival at discharge with IH-ECPR after OHCA was obtained from the Bougouin et al. study. For the probability of survival with the OH-ECPR after OHCA, however, this is not available in any literature study. Nevertheless, the probability of survival at discharge is available for the IH-ECPR patients after IHCA in the study by Kim et al.⁹ Here, for the purpose of the study, the survival with IH-ECPR patients after IHCA, where the ECPR takes place at the same site of the arrest, was utilized to estimate the survival with OH-ECPR after OHCA, where the ECPR also takes place at the site of the arrest. Considering the added risk associated with the OH-ECPR, the probability of survival at discharge with OH-ECPR after OHCA was calculated to be equal to that for IH-ECPR patients after IHCA, reduced by 10%. After survival at discharge, the probability of the survival versus death at 3-6 months after arrest and the probability of good versus poor neurological outcomes the 3-6 months after arrest time point were obtained from the Kim et al study.⁹ The

model event probability inputs and their uncertainties can be seen in [Table 1](#).

The patient characteristics of the simulated cohort are based on the eligibility criteria of Bougouin et al. study.¹²

Cost calculations

Based on the hospital perspective, only the direct medical cost of patient management was included in the analysis. Regardless of the OH-ECPR, the patient receives ECPR management in hospital once admitted. The cost of OH-ECPR, therefore, was the running cost of mobile ECPR plus the cost of IH-ECPR. The running cost of mobile ECPR and the cost of events as part of the IH-ECPR were obtained from the finance department of HMC. Mobile ECPR cost includes cost of personnel, driver, arterial blood gas analyzer, oxygenator, ambulance, ultrasound machine, extracorporeal membrane oxygenation (ECMO) machine, ECMO vehicle, and other ECMO equipment. The cost calculation of IH-ECPR was based on the daily cost of relevant events per patient, taking into consideration the duration of events. Costs of events included the costs of the different resource categories involved in patient management, calculated based on a micro-costing approach of involved direct medical resources. The medical resource cost categories constituted the medications, laboratory tests, diagnosis, mobile ECPR, and hospitalization categories. The cost of hospitalization until discharge included costs of ICU stay, ECPR stay, and general ward stay, with the estimated duration of each obtained from locally available HMC administrative report. Average durations of different settings during hospitalization for alive versus dead patients are presented in [Table 2](#). The cost of the 3-6 months survival after arrest outcomes was based on a mean duration of 4.5 months minus the duration of hospitalization until discharge. The cost of the 3-6 months was obtained from Weng et al.²¹, which involved cost of resources utilized during outpatient, emergency, and in-patient settings. The cost of patients with poor neurological outcome, defined as patients with a Glasgow Coma Scale score of below 6 points, was obtained from Graf et al.²² and included post-hospital and nursing home costs. All costs obtained from published literature were adjusted to its Qatari value using the health expenditure per capita and the Purchasing Power Parities for gross domestic product.²³ All costs were calculated in the 2022 year value of the Qatari Riyal (QAR), and were presented in United States Dollar (USD, USD1=QAR3.64). Due to the short duration of follow up, no cost discounting

TABLE 1. Base-case model inputs and their uncertainty ranges

Parameter	Point estimate	Variation range, 95%CI		Point estimate	Variation range, 95%CI		Distribution	Reference
	OHCA-E CPR	Lower	Upper	IHCA-E CPR	Lower	Upper		
Survival to discharge	0.16	0.07	0.29	0.07	0.02	0.19	Triangular	12
Death at discharge	0.84	0.71	0.93	0.93	0.83	0.99	Triangular	12
Survival at 3-6 months	0.26	0.15	0.40	0.22	0.12	0.36	Triangular	9
Death at 3-6 months	0.74	0.60	0.85	0.78	0.64	0.88	Triangular	9
Good neurological outcomes at 3-6 months	0.21	0.12	0.36	0.2	0.10	0.34	Triangular	9
Poor neurological outcomes at 3-6 months	0.79	0.64	0.88	0.80	0.66	0.90	Triangular	9

OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, ECPR: extracorporeal cardiopulmonary resuscitation, CI: confidence interval.

TABLE 2. Average durations with their associated costs at different settings during hospitalization

Parameter	Average stay (days)	Cost of each day of stay, QAR (USD)	Total cost per duration, QAR (USD)
ECMO duration	4.9	124,355 (34,154)	609,340 (167,355)
ICU duration	39.8	9,811 (2,695)	390,473 (107,243)
General ward duration	10.6	1,660 (456)	17,597 (4,833)

ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, 1 USD=3.64 QAR.

was performed. The resource cost inputs in the study model are listed in Supplementary Material Table S2.

Outcome measures

The trade-off between the added survival with OH-ECPR in HMC versus its cost was investigated and calculated via an ICER per case of success for OH-ECPR compared IH-ECPR. Here, success was defined as survival at discharge after arrest. In the current study, the willingness-to-pay (WTP) cost-effectiveness threshold is estimated to be QAR 546,000 (USD 150,000) per case of success.²⁴⁻²⁷

Study perspective

The hospital perspective of the economic model is that of the Hamad Medical Corporation (HMC), Qatar.²⁸ The research is based on literature and publicly accessible data, and did not require patient consent or institutional ethical approvals.

Sensitivity analysis

Sensitivity analyses were performed to test the robustness of the model to input uncertainty and to increase the generalizability of results.

A deterministic one-way sensitivity analysis was conducted by assigning a $\pm 10\%$ uncertainty range to the mobile ECPR running cost, a $\pm 20\%$ uncertainty range to the annual poor neurological cost per patient, and cost of follow-up at 4.5 months per person using the triangular distribution.

A probabilistic sensitivity analysis was conducted by introducing uncertainty to the main base-case cost inputs. A $\pm 10\%$ uncertainty range of the base-case value was applied to costs of ICU stay, general ward stay, and ECMO using a triangular distribution.

As with the base-case, sensitivity analyses were performed using the Monte Carlo simulation by @Risk 7.6 (@Risk Software, Palisade Corporation, NY, USA), with 1000 iterations.

Results

Base-case analysis

OHCA patients who received OH-ECPR achieved 16% survival at discharge compared to 7% with OHCA who received IH-ECPR, [risk ratio (RR)=0.91; 95% CI 0.79 to 1.06; $P=0.26$], with an ICER of QAR 464,589 (USD 127,634), in favor of OH-ECPR. Patient outcomes probabilities, their costs, and the overall costs of OH-ECPR versus IH-ECPR are illustrated in [Table 3](#).

Based on the WTP of QAR 546,000 (USD 150,000), the CEP indicated that 89.16% of simulated OH-ECPR cases were within the WTP threshold, 2% of cases were dominated (ie, lower success with increased cost), and 8.84% of cases were not cost effective, [Figure 1](#).

At the base-case, as per a regression tornado analysis of the strength (size) of the impact of the model clinical outcomes on the ICER for success at discharge, the most influential model inputs were the probabilities of survival and death at discharge with OH-ECPR, followed by death at discharge with IH-ECPR. Death at 3-6 months and the poor neurological outcomes rate with IH-ECPR were the least influential factors. The rank of the main model input events as per the size of their relationship with the ICER is presented in [Figure 2](#).

Sensitivity analysis

One-way sensitivity analysis. The base-case probability of cost-effectiveness associated with OH-ECPR was not sensitive to the one-way uncertainty assigned to model inputs. The one-way sensitivity analysis inputs and results are in [Table 4](#).

Probabilistic sensitivity analysis. Adding the event cost uncertainty to the base-case probability uncertainty did not reverse the advantage of OH-ECPR, with 82.9% of cases are between dominant (ie, higher success with cost savings) and cost effective. The CEP showed that initiating OH-ECPR in OHCA patients was dominant in 35.3% of simulated cases, cost-effective in 47.6% of simulated cases, dominated in 9% of cases,

and not cost effective in 8.1% of the cases (Supplementary Material Figure S3). Event costs and their uncertainty ranges are presented in Table 4.

According to the regression tornado analysis (Supplementary Material Figure S4), the cost of ECMO, and the probability of survival in OH-ECPR, were the most influential factors, while the probability of good neurological outcomes at 3-6 months with OH-ECPR and probability of survival at 3-6 months with IH-ECPR were the least influential factors.

Discussion

This study is the first cost-effectiveness evaluation in the literature that investigates the economic consequences of OH-ECPR versus IH-ECPR among OHCA patients, which is from the perspective of HMC, using clinical data inputs from registry and meta-analysis studies, by Bougouin et al. and Kim et al. respectively. Our model predicted that initiating OH-ECPR before arrival to hospital achieved 16% survival at discharge compared to 7% with OHCA who received IH-ECPR, with an ICER of QAR 464,589 (USD 127,634) in favor of OH-ECPR. The cost effectiveness of the OH-ECPR in OHCA was achieved in 89.16% of simulated cases, where the ICER was within the WTP threshold in the study.

Promising findings from previous observational studies and increasing clinical applicability of ECPR resulted in incorporating ECPR in the Advanced Life Support Guidelines by the European Resuscitation Counsel.^{11,29} Bartos et al. found that the neurologically favorable survival was significantly higher in ECPR patients (33%) vs standard CPR patients (23%). However, the duration of CPR was significantly longer for ECPR patients (60 minutes) vs CPR patients (35 minutes), which is an important contributor towards enhanced survival.⁷ A recent systematic review of observational studies on ECPR demonstrated that the proportion of patients with good neurological outcome was 8.3%-41.6% in the ECPR group vs 1.5%-9.1% in the CPR group, respectively.³⁰ This was consistent with results from the SAVE-J study, reporting higher good neurological outcome with the ECPR group, 11.2% vs 2.6%.³¹

To date, there have been two economic analyses, by Bharmal et al. and Dennis et al., forecasting that ECPR would be a cost-effective resuscitation method for OHCA and IHCA patients.^{6,18} Important, unlike our current study, both of these studies targeted the economics of IH-ECPR, not the OH-ECPR. Furthermore, in their analysis, they assumed that all patients who did not receive ECPR would not survive. Therefore, the results of these studies may overestimate the cost-effectiveness of ECPR

TABLE 3. Model outcome probabilities and proportional costs, and total costs of OH-ECPR versus IH-ECPR

Therapy outcome	OH-ECPR			IH-ECPR		
	Probability, 95% CI	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)	Probability, 95% CI	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)
Survival at discharge	0.0517,0.1600,0.2911	858,017 (235,654)	137,283 (37,705)	0.0222,0.07,0.1923	532,425 (146,230)	37,270 (10,236)
Survival to discharge, survival at 3-6 month with good neurological outcome at 3-6 month	0.0001,0.0087, 0.0112	884,623 (242,962)	7,728 (2,122)	0.0001,0.0030,0.1109	559,030 (153,538)	1,722 (473)
Survival to discharge, survival at 3-6 month with poor neurological outcome at 3-6 month	0.0004, 0.0329,0.1240	1,015,974 (279,037)	33,389 (9,170)	0.0017,0.0121,0.329	698,816 (191,930)	8,609 (2,364)
Survival to discharge, death at 3-6 month	0.1153,0.1200,0.3596	480,019 (131,837)	56,834 (15,609)	0.0014,0.0501,0.2191	154,427 (42,413)	8,432 (2,316)
Death at discharge	0.7089,0.84,0.9283	471,585 (129,521)	396,132 (108,798)	0.8077,0.93,0.9778	145,993 (40,097)	135,773 (37,290)
Total cost per patient	QAR 631,366 (USD 173,405),95% CI QAR 478,584 to 855,749 (USD 131,443 to 235,031)			QAR 191,806 (USD 52,680), 95% CI QAR 142,829 to 287,530 (USD 39,228 to 78,970)		

OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, ECPR: extracorporeal cardiopulmonary resuscitation, QAR: Qatari Rial, USD: United States Dollar, CI: confidence interval, 1 USD=3.64 QAR.

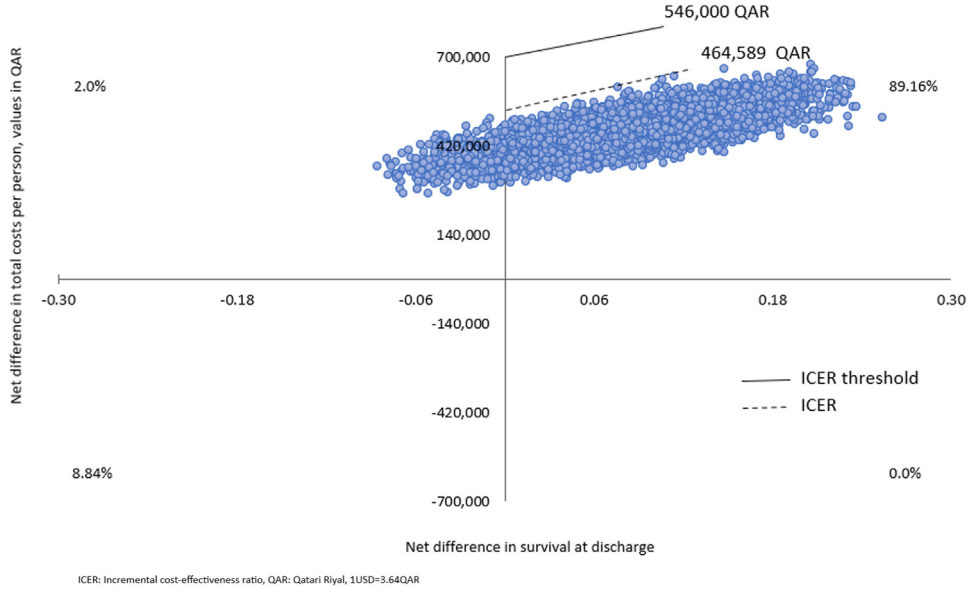


FIG 1. Scatter plot of incremental survival at discharge against incremental costs (base-case multivariate uncertainty analysis).

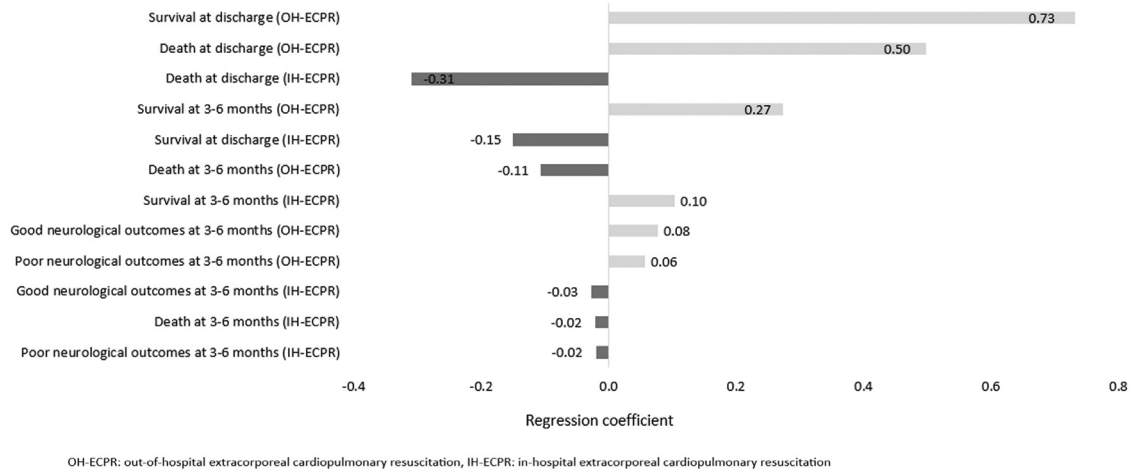


FIG 2. A tornado analysis of study clinical outcomes and their effects on incremental cost-effectiveness ratio (base-case multivariate uncertainty analysis).

TABLE 4. Sensitivity analysis results

Parameter	Point estimate/ Unit cost, QAR (USD)	Variation range, QAR (USD)	ICER, QAR (USD)
One-way sensitivity analysis results			
Mobile ECPR cost per patient	325,593 (89,424)	293,034 to 358,152 (80,482 to 98,366)	Mean 484,755 (133,174), 95% CI 435,120 to 549,001 (119,538 to 150,824)
Poor neurological follow-up resources cost (1 year)	131,352 (36,076)	105,082 to 157,622 (28,861 to 43,291)	Mean 470,853 (129,355), 95% CI 394,041 to 555,112 (108,253 to 152,503)
4.5 months follow-up cost for all patients regardless of neurological outcome	8,434 (2,311)	6,747 to 10,121 (1,853 to 2,780)	Mean 504,573 (138,618), 95% CI 421,201 to 600,787 (115,714 to 165,051)
Probabilistic sensitivity analysis (costs)			
ICU stay per day	9,811 (2,695)	8,830 to 10,792 (2,425 to 2,964)	Mean 497,404 (136,612), 95% CI (259,082 to 1,992,090 (71,157 to 547,127)
General ward stay per day	1,660 (456)	1,494 to 1,826 (410 to 502)	
ECMO per day	124,355 (34,154)	111,920 to 126,791 (30,739 to 34,823)	

OHCA: out-of-hospital cardiac arrest, IHCA: in-hospital cardiac arrest, ECPR: extracorporeal cardiopulmonary resuscitation, QAR: Qatari Rial, USD: United States Dollar, ICER: incremental cost-effectiveness ratio, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, CI: confidence interval, 1 USD=3.64 QAR.

for OHCA and IHCA patients. Further, both studies did not account for healthcare costs incurred after hospital discharge for survivors, such as outpatient follow-up costs and neurological follow-up costs.

The patient age is an essential factor that influences the outcomes of ECPR, including the cost-effectiveness of it. Previous data found that there was a linear association between the patient age and ICER.³² While establishing an age limit for eligibility of ECPR remains controversial, some experts have advocated an age limit of 75 years.^{33,34}

Other important factors that influence the performance of the ECPR are the immediacy of ECPR implementation, pre-hospital resources, the speed with which ECPR may be initiated, local traffic congestion, and the distances between the site of OHCA patients and in-hospital resources, in addition to the experience of the team that will also mostly influence the rate of adverse events.

Considering the absence of local Qatari data sources to estimate long-term costs and patient outcomes for OHCA patients, it is appropriate for our economic analysis to be based on registry and meta-analysis studies by Bougouin et al. and Kim et al.,^{9,12} which are the main literature studies that provide data on OH-ECPR and IH-ECPR among OHCA patients. The registry study, by Bougouin et al., is a multi-center based, including a large sample size population. The meta-analysis, by Kim et al., included data about the neurological outcome consequences with the OH-ECPR versus IH-ECPR approaches.

There is no official approved WTP in Qatar.³⁵ Guiding decision in such cases, the WHO suggested that the value of the threshold in a country can be within 1-3 times the gross domestic product (GDP) per capita in the country. Qatar's GDP per capita has been one of the world's highest, and will calculate a WTP threshold range that is too large to be directly implemented. This study adapted a threshold value of USD 150,000,^{24,36} an increasingly accepted higher threshold value in the literature and, importantly, is also within the range suggested by the WHO for Qatar.

This study is not without limitations. First, due to the lack of head-to-head studies comparing OH-ECPR versus IH-ECPR among OHCA, calculating the survival in OHCA patients who received OH-ECPR beyond the Bougouin et al. and Kim et al. studies was based on assumptions. We assumed a reduction by 10% in the survival of OH-ECPR among OHCA at discharge that was obtained from Kim et al.,⁹ which may not be accurate. However, accommodating uncertainty, the base-case model analysis was based on a multivariate uncertainty, including the OH-ECPR survival at discharge probability, that is, 7%-29%. Also, a limitation is that cost

estimates, such as those for implementing that mobile ECPR program and for the long-term care, can differ between settings. Hence, results should be interpreted with caution before considered by other healthcare systems. Again, nonetheless, varying the cost inputs, as part of the one-way and multivariate sensitivity analyses, did not change the study conclusion. Furthermore, the long-term consequences of ECPR beyond one year were not considered in the model, whereby these can lead to extra healthcare costs and decreased quality of life. In addition, not considering the non-direct medical costs of ECPR in the study may influence the absolute monetary value of therapy. Finally, this analysis was partly performed based on data from the Bougouin et al. registry,¹² which is prone to selection bias, because the ECPR was not initiated as per protocol but rather at the discretion of physicians.

Conclusion

Based on the methods and assumptions in the current study, the OH-ECPR for OHCA patients, who are refractory to conventional CPR, is most likely a cost-effective approach relative to the IH-ECPR, supporting the increased utilization of the former as a potentially advantageous resuscitative approach in the OHCA patients.

Authors' contributions

DB conceived the study and its design. DA and DB developed the model, and analyzed and interpreted data, and wrote the manuscript. AA conceived the study question, contributed to the interpretation of data, and revised the manuscript. All authors read and approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.cpcardiol.2022.101387](https://doi.org/10.1016/j.cpcardiol.2022.101387).

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