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Simulation and education

Cost-effectiveness of extracorporeal cardiopulmonary resuscitation after in-hospital cardiac arrest: A Markov decision model

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Abstract

Background: This study aimed to estimate the cost-effectiveness of extracorporeal cardiopulmonary resuscitation (ECPR) for in-hospital cardiac arrest treatment.

Methods: A decision tree and Markov model were constructed based on current literature. The model was conditional on age, Charlson Comorbidity Index (CCI) and sex. Three treatment strategies were considered: ECPR for patients with an Age-Combined Charlson Comorbidity Index (ACCI) below different thresholds (2–4), ECPR for everyone (EALL), and ECPR for no one (NE). Cost-effectiveness was assessed with costs per quality-of-life adjusted life years (QALY).

Measurements and main results: Treating eligible patients with an ACCI below 2 points costs 8394 (95% CI: 4922–14,911) euro per extra QALY per IHCA patient; treating eligible patients with an ACCI below 3 costs 8825 (95% CI: 5192–15,777) euro per extra QALY per IHCA patient; treating eligible patients with an ACCI below 4 costs 9311 (95% CI: 5478–16,690) euro per extra QALY per IHCA patient; treating every eligible patient with ECPR costs 10,818 (95% CI: 6357–19,400) euro per extra QALY per IHCA patient. For WTP thresholds of 0–9500 euro, NE has the highest probability of being the most cost-effective strategy. For WTP thresholds between 9500 and 12,500, treating eligible patients with an ACCI below 4 has the highest probability of being the most cost-effective strategy. For WTP thresholds of 12,500 or higher, EALL was found to have the highest probability of being the most cost-effective strategy.

Conclusions: Given that conventional WTP thresholds in Europe and North-America lie between 50,000–100,000 euro or U.S. dollars, ECPR can be considered a cost-effective treatment after in-hospital cardiac arrest from a healthcare perspective. More research is necessary to validate the effectiveness of ECPR, with a focus on the long-term effects of complications of ECPR.

Keywords: Extracorporeal membrane oxygenation, Extracorporeal life support, In-hospital cardiac arrest, Cost-effectiveness, Decision model, Intensive care

Introduction

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Cardiac arrest, cardiopulmonary arrest, or circulatory arrest is the loss of effective blood circulation, which inevitably leads to death if cardiopulmonary resuscitation (CPR) is not started. Cardiac arrest is usually divided based on location into out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). OHCA is described to occur around 19–104 times per 100,000 population per year and results in 10% survival at hospital discharge.[1] The incidence of IHCA is 1–6 events per 1000 hospital admissions[2–4] and recent meta-analyses showed a pooled survival to discharge of 15% (ranging from 3% to 40%) and a one-year survival of 13% (ranging from 4% to 69%).[5,6] Patient-specific factors associated with survival are age,[7,8] comorbidities[9–12] and presence of shockable rhythm.[13]

A possible advantage for patients suffering IHCA versus OHCA is that hospitals are equipped with advanced life support teams, who could employ extracorporeal cardiopulmonary resuscitation (ECPR) using veno-arterial extracorporeal membrane oxygenation (VA-ECMO). This technique has seen an increase in use over the last decades.[14,15] By taking over cardiac and respiratory function, VA-ECMO ensures oxygenation and circulation.[16] Although evidence from randomized controlled trials is lacking,[17] observational studies have repeatedly shown an increase in survival after ECPR compared to conventional CPR.[18–20] Furthermore, the American Heart association recommends the in-hospital use of ECPR in patients with a reversible cause of CA (e.g.: acute coronary syndrome).

When assessing whether or not to implement ECPR, cost-effectiveness should be taken into account. Ethical and economic considerations are of increasing importance in decision making pertaining to intensive care allocation.[21] Financial resources are limited and health care should be focused more on therapies that do not only extend life, but rather offer a reasonable health-related quality of life (HRQoL). This study was designed to provide cost-effectiveness evidence for international comparison and to provide an overview of current knowledge of the economic aspects of ECPR.

Two small observational studies (US and Australia) have shown indications of cost-effectiveness of ECPR for both OHCA and IHCA.[22,23] There are however several caveats. Because of low sample size and estimates pertaining to local situations these studies are not likely to be generalizable to all settings. Furthermore, for the in-hospital and out-of-hospital setting, effectiveness should be assessed separately.

The primary aim of this study was therefore to assess the cost-effectiveness of ECPR treatment after IHCA based on current literature. By using all available evidence, this modelling approach would ensure a high generalizability of our results. For this purpose, a decision tree and Markov model were developed. Both models are frequently used in health-economic evaluations, because they are able to calculate quality of life adjusted life years (QALY).[24,25] The secondary aim was to assess in which patient group ECPR is most likely to be cost-effective.

Methods

This cost-effectiveness evaluation is reported according to the CHEERS reporting guidelines.[26] We searched PubMed for relevant studies to inform on all parameters used for the models. We used the search terms “in-hospital cardiac arrest” and “extracorporeal cardiopulmonary resuscitation” in combination with the specific parameter of interest. Furthermore, we found literature using the reference list of already found studies.

Decision tree

A three-strategy decision tree was created, which encompasses the in-hospital phase. This type of model uses known absolute and relative risks to calculate the probability of an outcome. The decision tree calculates the probability of dying before discharge. The strategies considered were ECPR for no one (NE), ECPR for every eligible patient (EALL) and ECPR for eligible patients with an Age-Combined Charlson Comorbidity Index (ACCI) score below a certain threshold (EACCI_lo). The thresholds for the ACCI analysed ranged from two to four: patients with an ACCI above the threshold did not receive ECPR. The ACCI thresholds have been based on best available ECPR guidelines to exclude patients with a terminal illness, comorbidities that form a contraindication for ICU admission or for intravascular cannulation.[27] Furthermore patients >75 years of age are generally not considered eligible. The ACCI score is described in Table 1, Supplement 1.

The ACCI threshold can be illustrated by the following example: a patient of 50 years old with moderate renal disease (GFR<40 mL/min/1.73 m^2) will have an ACCI of 3. If the patient would suffer a myocardial infarction the score will rise to 4.

The decision tree consists of multiple nodes with probability estimates found in literature (Fig. 1 and Table 1). The first node represents patients with a Do-Not-Resuscitate (DNR) status. This is

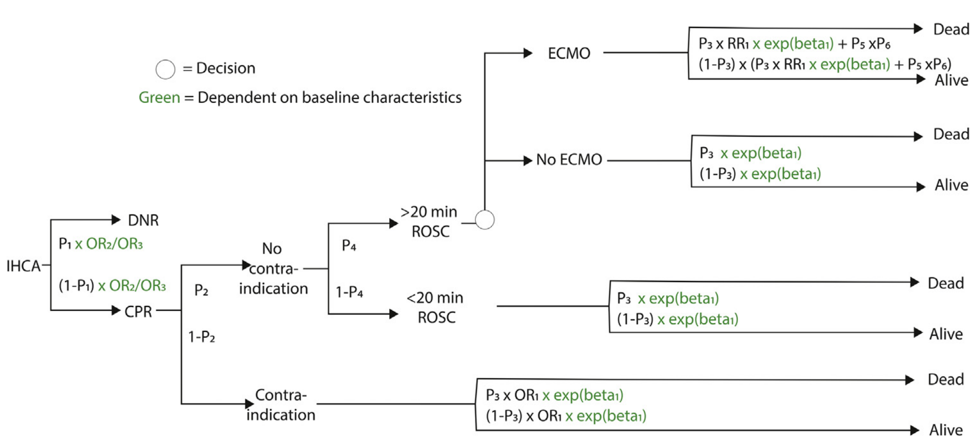

Fig. 1 – Decision tree of the in-hospital phase of the model. For the assumed probabilities (P), odds ratio’s (OR), relative risks (RR), and betas, see Table 1. DNR = do-not-resuscitate; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.

Table 1 – Assumed estimates and their distributions for the decision tree in the probabilistic sensitivity analysis.

Abbr.	Parameter	Median (IQR)	Distribution	Source
Decision tree				
P_1	Probability of having DNR status if <75 years	0.05 (0.02–0.10)	Beta(5,95)	Clinical insight
P_2	Probability of ECPR contraindication	0.19 (0.11–0.32)	Beta(10,40)	Clinical insight
P_3	The probability of dying after CPR	0.85 (0.83–0.87)	Beta(850,150)	Zhu and Zhang[5]
P_4	The probability of having ROSC within 20 min	0.38 (0.35–0.41)	Beta(338,556)	Khan et al.[29]
P_5	Probability of complication	0.38 (0.29–0.47)	Beta(38,62)	Sheu et al., Muller et al. and Sakamoto et al.[30–32]
P_6	Probability of dying because of complication	0.2 (0.1–0.32)	Beta(10,40)	Clinical insight
RR_1	The relative risk of dying, ECPR vs non ECPR	0.43 (0.3–0.62)	Lognormal(−0.85, 0.19)	Chen et al.[18]
OR_1	OR of dying when contraindication for ECPR	2.00 (1.40–2.93)	Lognormal(0.69, 0.2)	Clinical insight
OR_2	OR of having DNR status if 75 - 84 years, compared to <75 years	1.71 (1.23–2.32)	Lognormal(0.53, 0.16)	Cook et al.[28]
OR_3	OR of having DNR status if >85 years, compared to <75 years	2.98 (2.38–3.75)	Lognormal(1.09, 0.12)	Cook et al.[28]
$Beta_1$	The log odds increase in dying per ACCI increase	0.09 (0.03–0.14)	Log-Lognormal (0.09, 0.03)	Hirlekar et al.[9]
Costs and utilities				
	In-hospital incremental cost of ECPR after cardiac arrest	51756.66 (31377.83–73978.21)	Normal(51997, 10767)	Oude Lansink-Hartgring et al.[37]
	Utility score for men	0.79 (0.69–0.87)	Triangle(a = 0.66, b = 0.89, c = 0.82)	Israelsson et al.[36]
	Utility score for women	0.74 (0.62–0.81)	Triangle(a = 0.58, b = 0.82, c = 0.81)	Israelsson et al.[36]

ECPR = extracorporeal cardiopulmonary resuscitation; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; ACCI = Age-Combined Charlson Comorbidity Index; DNR = do not resuscitate.

an agreement between a patient and a health care professional not to attempt cardiopulmonary resuscitation in case of cardiac arrest. Since a DNR status is more often agreed upon by patients with higher age,[28] we assumed higher probabilities for higher aged patients. We assumed that for patients who suffered cardiac arrest with a DNR status, no CPR would be attempted and death is certain. When patients did not have a DNR status, CPR would be attempted. The next node represents the probability of having a contra-indication for ECPR. Having a contra-indication, e.g. refractory cardiac disease or metastatic cancer, was assumed to increase the risk of dying after CPR. If CPR was started and no contra-indication was present, the next node represents the probability of having return of spontaneous circulation (ROSC) within 20 min after cardiac arrest.[29] If ROSC would not be achieved within 20 min, ECPR could be started and could increase the remaining survival probability.[18] The probability of having a complication of ECPR and the probability of subsequent death are also taken into account.[30–32] These probabilities were calculated from the ELSO database.[33] The extra probability of mortality, given that the patient had a complication was: the mortality rate of patients with a complication minus the overall mortality rate. Finally, the mortality rate after CPR increases with increasing Age-Combined Charlson Comorbidity Index (ACCI).[9,10]

The prevalence of DNR status below 75 years was assumed to be around 5% (range 2–10%), based on experience in our hospital: the Erasmus Medical Center, Rotterdam. The probability of having a contra-indication for ECPR was also based on experience in our hospital, where we implemented ECPR in 2016. We assumed that 20% (range 10–30%) of the patients have the contra-indications described by Makdisi et al. Since the described contra-indications (e.g. refractory cardiac disease or metastatic cancer) are severe conditions, the risk of dying was assumed to double (OR: 2.0, with a minimum of 1.4, and a maximum 2.9).

Markov model

For the calculation of long-term outcomes, a Markov model was used. A Markov model uses states and transition probabilities to calculate long-term outcomes.[24] We propose a model consisting of two states: an alive state (with decreased HRQoL) and a dead state (the absorbing state). Markov models can be used to calculate the time spent in each state. Therefore, QALYs can be calculated, making this type of model useful for cost-effectiveness analysis.[25] Each individual probability of dying at the end of the decision tree described above is used as input in the subsequent Markov model. The model simulated 20 years of follow-up and the model cycles were one year long. The data on age and sex specific mortality rates were provided by Statistics Netherlands (CBS).[34] We did not assume a lasting effect of IHCA on long-term survival.[35] The amount of life-years were then multiplied by the sex-specific utility score after IHCA to obtain QALYs for men and women[36] (Table 1).

As an example, consider a patient with a 100% chance of surviving the in-hospital phase: the Markov model will calculate the amount of life years this patient will spend after discharge. For a patient with 0%

chance of surviving the in-hospital phase, the Markov model will estimate 0 life years after discharge. For chances between 0% and 100%, the model calculates the average life years that patients with the same characteristics will spend after discharge.

Cost-effectiveness analysis

The total costs of ECPR were calculated based on how many patients received ECPR following the decision tree outcomes: a patient received ECPR according to the treatment strategy if they did not have a DNR status, no contra-indication, and no ROSC within 20 min (Fig. 1 and Table 1).

Only direct additional costs of ECPR treatment were taken into account, taking a health care's perspective. The average additional costs of ECPR described in the literature were used in the model. A detailed description of the items included in the total costs has been described by Lansink-Hartgring et al.[37] A discount rate of 4% was applied, the appropriate rate for cost-effectiveness analyses in the Netherlands.[38] To assess cost-effectiveness of the strategies, incremental cost-effectiveness ratios (ICER) were calculated, where NE serves as the reference category. The ICER informs about how many extra euro per QALY a strategy costs, compared to NE. The incremental costs and QALYs were plotted and the cost-effectiveness acceptability curves were calculated and drawn to obtain the most cost-effective strategy.

Important to take into account is that the calculated costs for ECPR are notably lower than the costs of ECMO. This is due to the model structure, in which costs are calculated for an average patient who suffers IHCA, thereby including also patients who do not receive ECPR.

Probabilistic sensitivity analysis

To take the uncertainty of our model parameters into account, a probabilistic sensitivity analysis (PSA) was performed. A PSA repeats the model a large number of times with different (but probable) parameters. The type of distributions that were used were beta distributions for probabilities, log-normal distributions for the odds ratios and relative risks, and log–log-normal distribution for the log-odds increase in mortality for an ACCI point increase. The characteristics of the distributions were adjusted so that the median and interquartile range were identical to the estimate and 95% confidence interval. The type and characteristics of the distributions of the parameters are described in Table 1. From these distributions, 1000 random samples were drawn, resulting in 1000 replicates of the model. Additionally, a representative cohort of 1000 patients was randomly sampled (Table 2).[10,39] After running the 1000 replicates of the model in this cohort, outcomes were calculated 1000 times. We calculated the QALYs and costs per strategy. The median was taken as the most probable estimate of the model. The 2.5th and 97.5th percentile were calculated, which indicated the borders of the 95% credibility interval.

To estimate whether the conclusions were affected by the parameters that were not found in literature, linear regression was performed. As the dependent variable, the ICER of the EALL strategy per iteration was used. As predictors, the standardized parameter values were used. The coefficients of the model could therefore be interpreted as "with one standard deviation (SD) increase in the parameter, the ICER for the EALL strategy increases with x".

All analyses were performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). For the Markov model, the "dampack" package was used.[40] The code of the model is online available in Appendix 2, for transparency and reproducibility.[41]

Table 2 – Patient characteristics of the simulated cohort, based on literature.[10,39]

Characteristic	N = 1000
Age (mean (sd))	65.49 (15.71)
Male (%)	578 (57.80)
CCI (%)	
0	373 (37.30)
1	230 (23.00)
2	183 (18.30)
3	107 (10.70)
4	43 (4.30)
5	40 (4.00)
6	15 (1.50)
7	4 (0.40)
8	5 (0.50)

CCI = Charlson Comorbidity Index.

Results

In the decision tree, survival rates between 9% and 13% were observed for the NE strategy, and between 30% and 35% for the EALL strategy (Fig. 1, Supplement 1). After applying a Markov model, expected life years after CPR per patient for the NE strategy ranged from 0.79 to 2.48 and for the EALL strategy from 2.57 to 6.55 years (Fig. 2, Supplement 1).

The expected costs per ICHA patient for treating eligible patients below an ACCI of 2 points with ECPR are 3975 (95% CI: 2418–5780) euro, and increased to 23,272 (95% CI: 14,159–33,838) euro for treating all eligible patients (Table 3). The associated QALYs for treating no patients with ECPR are 1.2 (95% CI: 1.0–1.5); for treating eligible patients below an ACCI of 2 points 1.7 (95% CI: 1.4–2.0); for treating eligible patients below an ACCI of 3 points 2.1 (95% CI: 1.7–2.6); for treating eligible patients below an ACCI of 4 points 2.6 (95% CI: 2.0–3.2); and for treating all eligible patients 3.4 (95% CI: 2.4–4.2).

Table 3 – The health economic evaluation for each strategy.

Strategy	Costs[a]	QALY	ICER[b]
NE	–	1.2 (1.0–1.5)	–
ACCI < 2	3975 (2418–5780)	1.7 (1.4–2.0)	8394 (4922–14,911)
ACCI < 3	8066 (4909–11,731)	2.1 (1.7–2.6)	8825 (5192–15,777)
ACCI < 4	12,942 (7881–18,829)	2.6 (2.0–3.2)	9311 (5478–16,690)
EALL	23,272 (14,159–33,838)	3.4 (2.4–4.2)	10,818 (6357–19,400)

The strategies are nobody ECPR (NE), treating everyone with an Age-Combined Charlson Comorbidity Index (ACCI) of 2, 3 or 4 or less, and treating everyone with ECPR (EALL). The ranges indicate 95% credibility intervals (CI).

[a] In Euro, only direct additional ECPR costs.

[b] The incremental cost-effectiveness ratio (ICER) is calculated with the most conservative method (NE: nobody ECPR) as the reference method. It represents the costs per extra QALY.

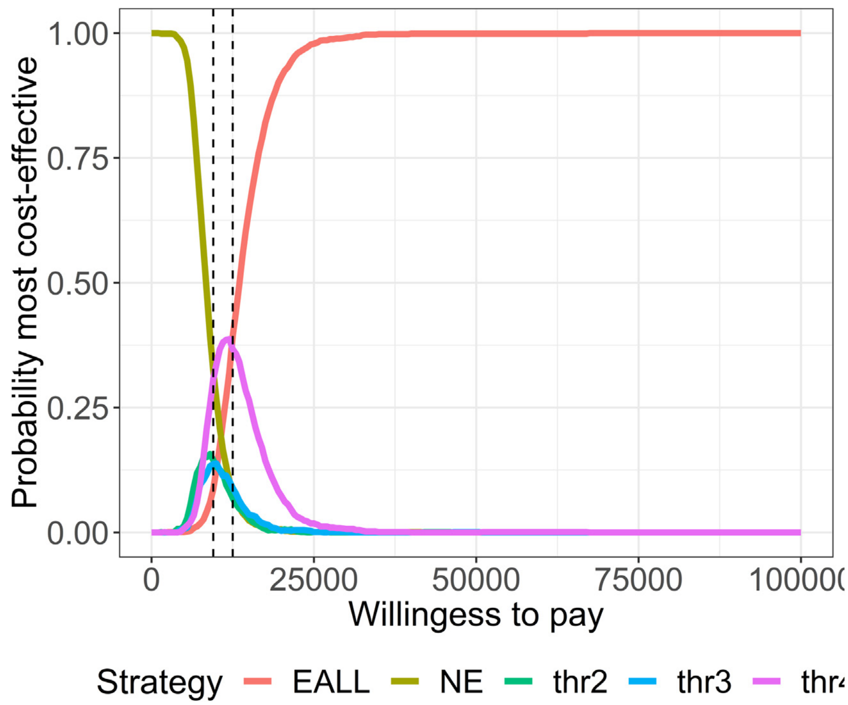

Fig. 2 – Cost-effectiveness acceptability curves. For given willingness to pay (WTP) thresholds, the probability of being the most cost-effective strategy is plotted. The strategies are nobody ECPR (NE), treating everyone with an Age-Combined Charlson Comorbidity Index (ACCI) of 2, 3 or 4 or less (thr2, thr3, thr4 respectively), and treating everyone with ECPR (EALL). The dotted lines indicates the WTP thresholds of 9500 and 12,500.

Compared to treating NE, the expected incremental costs per extra QALY (ICER) for treating eligible patients with an ACCI below 2 points is 8394 (95% CI: 4922–14,911) euro per extra QALY; for treating eligible patients with an ACCI below 3, the ICER is 8825 (95% CI: 5192–15,777) euro per extra QALY compared to NE; for treating eligible patients with an ACCI below 4, the ICER is 9311 (95% CI: 5478–16,690) euro per extra QALY; for treating all eligible patients, the ICER was 10,818 (95% CI: 6357–19,400) euro per extra QALY. Table 3 displays an overview of the economic evaluation. The considered strategies are comparable in terms of mean ICER, but the incremental costs and incremental QALYs vary significantly between the considered strategies (Fig. 3, Supplement 1).

The cost-effectiveness acceptability curves depicted in Fig. 2 show that for WTP thresholds of 0–9500 euro, NE has the highest probability of being the most cost-effective strategy. For WTP thresholds between 9500 and 12,500, treating eligible patients with an ACCI below 4 has the highest probability of being the most cost-effective strategy. For WTP thresholds of 12,500 or higher, EALL was found to have the highest probability of being the most cost-effective strategy.

The only parameter that was found to influence the cost-effectiveness significantly was the relative risk of dying of ECPR (effect of one unit increase of the parameter on the ICER was −255 (−481 to −28) euros per incremental QALY), see Table 2, Supplement 2.

Discussion

In this study we found that the expected costs per IHCA patient of treating each eligible IHCA patient with ECPR are approximately 23,000 euro. A patient was eligible when no contraindications was present, and in whom ROSC cannot be achieved within 20 min after cardiac arrest. Per QALY increase, the associated costs were around 15,000. The Willingess-To-Pay tresholds in Europe and North-America are between 50,000–100,000 euro per incremental QALY. Within this range, performing ECPR in every eligible IHCA patient, is likely to be costs-effective.

The use of ECMO has steadily increased from 2007 onwards.[14] Positive results from observational studies and increasing clinical applicability led to the inclusion of ECPR in the Advanced Life Support Guidelines by the European Resuscitation Counsil.[42] However, ECPR is costly and labour-intensive and careful economic evaluation was still lacking.

Because ECPR was found to be cost-effective, this study substantiates its increased implementation and inclusion as possible treatment in the guidelines. The allocation of intensive care treatments should be critically evaluated, especially when financial resources are limited.[21] The difference in survival probability after ECPR seems to be sufficient to render the therapy cost-effective. Because we performed an analysis taking all uncertainties of parameters into account, we believe that we reliably estimated the average cost per IHCA patient when every eligible patient is treated with ECPR: around 11,000 euro per extra QALY.

Our cost-effectiveness analysis based on literature supports findings of empirical studies. Firstly, our study confirms the results of a recent small retrospective study in the United States that suggested that ECPR after IHCA is cost-effective, considering only in-hospital costs.[22] This study suggested that the costs per extra QALY saved is around 56,000 U.S. dollars. This estimate is larger than our estimate of 11,000 euros, but health care expenditures in the United States tend to be higher than in Europe.[43] Nevertheless, it is reassuring that both studies conclude that ECPR after IHCA is cost-effective, since they both assess primarily in-hospital costs. Secondly, our study confirms the results of Dennis et al.

This study showed that for IHCA, 15,000 euros (25,000 AUD) per extra QALY was expected, which is similar to our estimate.[23]

The results of our study are also similar to results of the cost-effectiveness of a mobile ECPR team.[44] This team is able to treat patients with ECPR in multiple centres, and its application was found to be potentially cost-effective. The application could benefit centres that do not have the resources for ECPR or lack experience with its application. Centres that often use ECPR rely on perfusionists for aid in initiation and maintenance of treatment, which enhances the costs. Therefore, it could well be that ECPR is mostly cost-effective when there is no need for these extra costs. This hypothesis, however, warrants further investigation.

The range of costs of ECMO found in the literature is large.[45] Mostly because studies inconsistently report their results, there are no factors described that explain this variation. We used a structured Dutch study as input for our cost-effectiveness analysis, since it describes clearly the incremental costs for ECPR.[37] This study found that the majority of the costs are composed of nursing days. Being able to shorten the length of ICU stay would therefore enhance cost-effectiveness of ECPR after IHCA.

We did not find that treating a subgroup of IHCA patients with ECPR based on Age-Combined Charlson Comorbidity Index affected cost-effectiveness. Since others described that cost-effectiveness depends on patient characteristics,[44] we consider this to be attributed to two factors. First, the effect of comorbidity on survival of CPR is uncertain.[10,46] More research into this relationship is necessary. Second, if there is an effect of comorbidity, this effect is more likely to be significant in a cohort with a high prevalence of comorbidities. The prevalence in our representative cohort, however, was low.[10,39]

This study has several limitations. Unfortunately, not all information needed for the model could be found in the literature. The lack of evidence had two consequences. First, it was necessary to base some of the parameters on clinical knowledge; e.g., for the probability of having a contraindication for ECPR. However, a sensitivity analysis showed that these parameters were not likely to influence the overall cost-effectiveness of ECPR. Second, cost-effectiveness might be somewhat overestimated. Evidence from randomized controlled trials was unfortunately absent at this moment.[17] Observational studies could have overestimated the effect of ECPR on survival because of confounding bias.[18,19] An overestimated effect of ECPR would result in an overestimated cost-effectiveness. Additionally, we were not able to model long-term effects of complications of ECPR: the extra health care costs and lower quality of life after major complications of ECPR (stroke, acute kidney injury) could decrease overall cost-effectiveness.

Although we did not take non-direct costs of ECPR into account, we still believe this study provides a valid economic evaluation. Other identifiable costs are costs of rehabilitation, future health care costs and non-medical costs such as loss of participation in working life. However, these costs are more interesting from a societal perspective than a health care perspective. Other costs that are not taken into account are the costs of implementation. These expenses are large and could explain the stagnating increase in the use of ECPR.[47,48] Therefore, we believe that our findings are most applicable to large hospitals in western countries, which often do have access to these resources to overcome the first barrier to an apparent cost-effective therapy.

We believe future studies should have three goals. First, to identify patients who could benefit most from ECPR. Second, randomized controlled trials are necessary, as indicated in the advanced life support guidelines.[42] Fortunately, five ongoing randomized controlled trials will hopefully fill this knowledge gap in the upcoming years.[20] Third, the long-term effects of complications of ECPR should be investigated, since they could decrease the cost-effectiveness of the intervention. The knowledge gained from further research could improve implementation and cost-effectiveness of this costly and labour-intensive intervention.

Conclusion

For in-hospital cardiac arrest patients, extracorporeal cardiopulmonary was demonstrated to be cost-effective from a healthcare perspective given that conventional WTP thresholds lie between 50,000–100,000 euro or U.S. dollars. More research is necessary to validate the effectiveness of ECPR, with a focus on the long-term effects of complications of ECPR.

Conflict of interest

DRM received speaking fees from Xenios GmbH. The authors declare that they did not receive any other financial support for this study and that the Xenios GmbH had no role in the commencement, development, interpretation, or reporting of this cost-effectiveness analysis.

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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.2019.08.024.

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