ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Intravascular Targeted Temperature Management after Cardiac Arrest in England

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Abstract

Background Targeted temperature management (TTM) has been shown to improve neurological outcomes and survival in patients resuscitated from cardiac arrest; however, the cost effectiveness of multiple TTM methods is not well studied.

Objective This study aimed to evaluate the cost effectiveness of intravascular temperature management (IVTM) using Thermogard XP compared with surface cooling methods after cardiac arrest in the England from the perspectives of the UK national health service and Personal Social Services.

Methods We developed a multi-state Markov model that evaluated IVTM (Thermogard XP) compared with surface cooling using two different devices (Blanketrol III and Arctic Sun 5000) over a short-term and lifetime time horizon. Model input parameters were obtained from the literature and local databases. We assumed a hypothetical cohort of 1000 patients who required TTM after cardiac arrest per year in the England. The outcomes were costs (in £, year 2019 values) and quality-adjusted life-years (QALYs), discounted at 3.5% annually. Deterministic and probabilistic sensitivity analyses were undertaken to examine the effect of alternative assumptions and uncertainty in model parameters on the results.

Results The cost-effectiveness analysis determined that Thermogard XP resulted in direct cost savings of £2339 and £2925 (per patient) compared with Blanketrol III and Arctic Sun 5000, respectively, and a gain of 0.98 QALYs over the patient lifetime. The probabilistic sensitivity analysis demonstrated that the probability of Thermogard XP being cost saving would be 69.2% and 65.3% versus the Arctic Sun 5000 and Blanketrol III, respectively.

Conclusion Implementation of IVTM using Thermogard XP can lead to cost savings and improved patient quality of life versus surface cooling methods.

1 Introduction

Sudden cardiac arrest (SCA) is the third leading cause of death in Europe. Overall, less than 8% of patients experiencing out-of-hospital cardiac arrest (OHCA) survive to

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hospital discharge in England [1], an average that is also seen across Europe [2]. When cardiac arrest occurs in hospital (IHCA), higher survival rates of 15–34% across Europe are observed [2]. Independent of the setting of the event (OHCA or IHCA), SCA leads to loss of consciousness and death unless emergency resuscitation is given and the heart can be restarted [3]. Severe neurological injury has been considered to be the main consequence of SCA following successful resuscitation [4]. Irreversible brain injury is the most common cause of death in the post-cardiac arrest phase [5]. The limited available evidence also suggests that the health system costs associated with SCA in England and beyond are significant [6–9].

According to the literature, targeted temperature management (TTM) following cardiac arrest improves neurological and survival outcomes [10]. Leading medical societies recommend temperature management as part of the standard of care for patients with cardiac arrest [11]. In England,

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Key Points for Decision Makers

Intravascular temperature management (IVTM) is associated with better neurological outcomes and survival rates than are surface cooling methods over hospital discharge duration.

IVTM led to lower costs in the long term and was associated with better quality of life than surface cooling methods.

Using IVTM in patients with cardiac arrest can be considered a cost-saving strategy.

OHCA affects 30,000 people each year, corresponding to an incidence of 53 per 100,000 inhabitants [1]. Of these, approximately one-quarter can be hospitalised with a return of spontaneous circulation (ROSC) for post-resuscitation therapy [1]. Around 84% of these patients remain unconscious/comatose and are therefore indicated to receive TTM [12].

Multiple methods of TTM are in clinical use [13]. Different cooling methods have specific capabilities of extracting heat, which translate to varying rates of achieving the intended target temperature and varying abilities to accurately and precisely maintain a target temperature and control the rewarming phase after the TTM protocol [14]. TTM induced by surface cooling systems (SCS), intravascular temperature management (IVTM), and a combination of cooling methods has become standard therapy following cardiac arrest and is recommended by the UK National Institute for Health and Care Excellence (NICE) [3].

SCS works by circulating cold fluid or cold air through blankets or pads that are wrapped around the patient [14]. Conversely, IVTM (Thermogard XP®) controls a patient's body temperature through central venous heat exchange [13]. It can be used to induce and maintain TTM in critically ill patients after cardiac arrest [15]. IVTM uses central venous catheters placed in the subclavian, internal jugular, or femoral veins. Temperature control is achieved by circulating cool or warm saline in a closed loop through the catheter's balloon [15].

The objective of this study was to estimate the costs and effectiveness of IVTM using Thermogard XP versus SCS as standard of care among a hypothetical cohort of 1000 patients who need TTM after cardiac arrest per year in the UK national health service (NHS).

2 Methods

2.1 Model Overview

We developed a de novo economic model based on the current pathway for TTM following cardiac arrest. The population was a hypothetical cohort of 1000 patients (aged ≥ 18 years) with ROSC after cardiac arrest who were admitted to critical care with cardiac arrest as a primary or secondary diagnosis, as documented with the code 'I460 Cardiac arrest with successful resuscitation' from the International Classification of Diseases and Related Health Problems, Tenth Revision [16].

The outcomes of interest in the analysis included improved neurological outcomes at hospital discharge and over a lifetime time horizon, long-term survival rates, reduced adverse events (AEs), total costs for each strategy, and incremental cost per quality-adjusted life-year (QALY) as a measure of the value of health outcomes gained. For each treatment arm, costs and outcomes were aggregated based on a series of decisions and events that were represented in the model structure. The structure of the model was the same for the two treatment strategies. The recommended discount rate in the UK of 3.5% per annum for both costs and benefits was applied [17]. As per NICE guidelines [18], the base-case model considered all costs and health effects from the perspective of the UK NHS and Personal Social Services. To fully capture the costs and benefits of Thermogard XP and the comparator(s), a lifetime time horizon was applied in the base-case analysis.

2.2 Intervention and Comparator

The intervention in this study was IVTM using Thermogard XP, applied in a hospital setting to control a patient's body temperature through central venous heat exchange. The current European Resuscitation Council and European Society of Intensive Care Medicine guidelines on post-resuscitation care recommend TTM for adults after either OHCA or IHCA with any initial rhythm who remain unresponsive after ROSC [11]. Body temperature is to be maintained at a constant value between 32 and 36 °C for at least 24 h. As comparators, to address heterogeneity in device costs, we considered Arctic Sun 5000 and Blanketrol III as two different devices that may be used as part of the surface cooling technique. Surface cooling is considered standard care in the NHS, based on the interventional procedure guidelines of TTM following cardiac arrest developed by NICE [3].
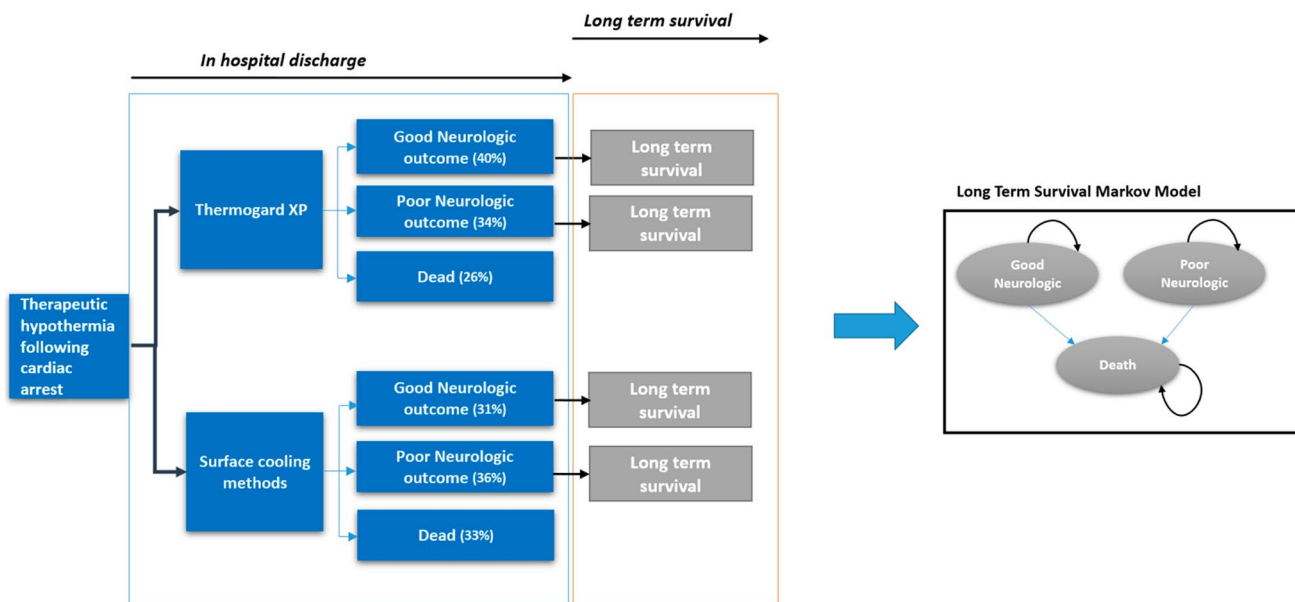
2.3 Model Structure

The economic model was developed in Microsoft Excel. A two-part economic model was developed, consisting of a short-term decision tree and a long-term Markov model. The decision tree has a short time horizon that estimates costs and effectiveness up until hospital discharge, and the Markov model is used to follow individual patients with good and poor neurological outcomes over the analysis' lifetime time horizon, in annual cycles. The Markov model comprises three health states used for survivors: good neurological outcome, poor neurological outcome, and death. The neurological outcome is defined based on cerebral performance category (CPC), which is a validated scoring system for early stratification of neurological outcomes after cardiac arrest [19]. Based on this tool, CPC 1 and CPC 2 were considered good neurological outcomes, and CPC 3 and CPC 4 were considered poor neurological outcomes [19]. The probabilities of incurring different neurological outcomes in the decision tree component of the model were determined at hospital discharge following the cardiac arrest event and were presumed to remain constant thereafter. All patients experiencing different levels of neurological outcomes entered the long-term survival Markov model, where they remained until they died according to long-term mortality based on their assigned level of neurological outcome. The model structure is illustrated in Fig. 1.

2.4 Model Inputs

2.4.1 Clinical Efficacy

We conducted a subgroup meta-analysis based on data from studies included in two recent reviews and meta-analyses [13, 20] to estimate the pooled probability of unfavourable neurological outcomes and mortality over the hospital admittance duration (short-term decision tree). Since these two recent, larger meta-analyses did not categorise studies in terms of time or duration of admittance, with all included studies with different time horizons pooled together, their output was not suitable for direct inclusion in our own analysis. Therefore, to increase the reliability of our model and to ensure consistency with our short-term horizon (at hospital discharge), we used data from the included studies and conducted a separate re-pooled analysis to estimate neurological outcome and mortality probabilities over the initial hospital discharge period (see the electronic supplementary material [ESM] SI-I).

We estimated the pooled probability of a neurological outcome with IVTM versus SCS. As evidence was lacking, we assumed the same clinical efficacy for two different surface cooling devices (Blanketrol III and Arctic Sun 5000). Finally, we calculated the percentage of patients in each health state in our decision tree model over a short-term time horizon according to results of the pooled estimate of clinical efficacy.

Fig. 1 Economic model structure. Percentage of good neurological outcome = (1 − probability of poor neurological outcome derived from meta-analysis) (see Table 1); percentage of poor neurological outcome = (1 − mortality rate in each arm derived from meta-analysis). Percentage of mortality = mortality rate in each arm derived from meta-analysis. The probability of a poor neurological outcome was derived from the meta-analysis (see Table 1)

To estimate long-term mortality based on the level of neurological outcome, we digitalised data from published Kaplan–Meier estimates for survival according to CPC score [21] and used them to estimate the parameters for parametric survival curves based on the methodology provided by Hoyle and Henley [22]. Parametric survival models were fitted to the overall survival data to extrapolate survival beyond the period of observation seen during the studies. Transition probabilities between health states for the Markov model were determined from these parametric survival functions. All estimated parametric survival functions are presented in the ESM (SI-II). All model input parameters are presented in Table 1.

2.4.2 Quality of Life

To estimate the total QALYs gained in the Markov model, survival time was adjusted by health-related quality of life. The utility values/quality-of-life inputs included utilities associated with health states and the disutility associated with treatment-related AEs.

Utility weights were sourced from multiple studies. In the base case, we used results from a UK-based study [23]; however, we also applied data from other relevant studies to estimate the range of utility weights. Detailed information regarding sources of utility value are presented in the ESM (SI-III).

Health-related quality of life associated with cardiac arrest survival based on patient's CPCs was derived from relevant published literature and previous economic evaluation studies in this area and are presented in Table 1 [24]. Following the literature, we assumed a constant utility following survival after cardiac arrest [9].

2.4.3 Adverse Events

The most common AEs associated with IVTM and SCS included shivering, temperature overcooling, local or skin injury, deep venous thrombosis (DVT), serious bleeding requiring transfusion, arrhythmias, pneumonia, and sepsis. We derived the risk difference in AEs in IVTM versus SCS groups based on the results of a recent random-effects meta-analysis study [13]. The risk difference in occurrence of AEs, along with the disutility of each event, are presented in Table 1. Utility decrements or disutilities associated with AEs are equivalent to the annual reduction in utility due to an AE that was derived from previous economic evaluations or studies [25–28].

2.4.4 Costs

The following costs were included in the model: annual capital cost and consumable cost of Thermogard XP and of each SCS, the cost associated with a stay in the intensive care unit (ICU) and hospital ward, and costs associated with the treatment of AEs. All cost input parameters are reported in Table 1. The cost of Thermogard XP was extracted from the Medtech innovation briefing developed by NICE and NHS supply chain [15], and the costs of the SCS devices were derived from different Medtech innovation briefings developed by NICE [29]. Healthcare resource utilisation costs associated with particular neurological outcomes, including length of stay, were derived from a UK single-centre cost study that estimated the hospital costs of patients with OHCA treated in ICUs, evaluated using the national tariff-based system [9]. The long-term cost of poor and good neurological outcomes were sourced from a US-based study [30]. We converted international cost-effectiveness data to UK prices [31] and used gross domestic product per capita in purchasing power standards to convert US-based costs to UK-specific costs.

AE costs were obtained from NHS reference costs [32] and were adjusted by the rate of each AE in the two arms. Costs were measured in UK pound sterling (£), year 2019 values.

2.5 Analysis

The cumulative estimates of costs and effectiveness were reported for each treatment arm. The incremental cost per life-year and incremental cost per QALY gained were reported. Deterministic sensitivity analyses (DSAs) were conducted to investigate the impact of key assumptions and parameter values used in the base-case analysis using the hypothetical increases or decreases of 25%. The results were reported using tornado diagrams and supporting tables. The model also allows for probabilistic sensitivity analysis (PSA) using Monte Carlo simulation to be performed. This form of analysis is used to estimate parameter uncertainty. To conduct the PSA, probabilistic distributions were assigned to each input in the model and used to randomly select new plausible values. Each new sampled value applied in the model and the new results of the model were recorded. This process was repeated for a large number of iterations (10,000) to produce a distribution of results from the model. The outcomes were reported using cost-effectiveness scatter plots and cost-effectiveness acceptability curves (CEACs).

Table 1 Input parameters

Parameter	Value	Distribution	Source
Mortality rate (hospital discharge)			
Mortality rate (Thermogard XP)	0.43	Beta (4271, 566.1)	Calculated using the pooled estimate reported in two recent meta-analyses [13, 20]
Mortality rate (surface cooling)	0.48	Beta (2643.2, 2863.5)	Calculated using the pooled estimate reported in two recent meta-analyses [13, 20]
Probability of poor neurological outcome			
Thermogard XP	0.60	Beta (76.6, 51.0)	Calculated using the pooled estimate reported in two recent meta-analyses [13, 20]
Surface cooling	0.69	Beta (157.5, 70.8)	Calculated using the pooled estimate reported in two recent meta-analyses [13, 20]
Long-term survival (years)			
CPC1	25.70	Weibull (0.08, 0.76)	Phelps et al. [21]
CPC2	8.11	Weibull (0.10, 0.86)	Phelps et al. [21]
CPC3	2.74	Weibull (0.19, 0.72)	Phelps et al. [21]
CPC4	0.61	Weibull (0.53, 0.59)	Phelps et al. [21]
Health utility[a]			
Good neurological outcome	0.79	Beta (8860.2, 2355.2)	Stiell et al. [33], Hurdus et al. [23], Fryback et al. [34]
Poor neurological outcome	0.39	Beta (103.2, 161.4)	Gage et al. [35], Raina et al. [36]
In hospital	0.74	Beta (8260.1, 2842.2)	Hurdus et al. [23]
Adverse event disutility			
Temperature overshoot	−0.03	Fixed	Hoek et al. [28]
Shivering	−0.03	Fixed	Hoek et al. [28]
Serious bleeding	−0.20	Fixed	Preblick et al. [25]
Deep venous thrombosis	−0.19	Fixed	Preblick et al. [25]
Arrhythmia	−0.02	Fixed	Wehler et al. [26]
Pneumonia	−0.22	Fixed	Stein et al. [27]
Adverse event rates			
Thermogard XP			
Temperature overshoot	0.15	Beta (4.70, 26.65)	Bartlett et al. [13]
Shivering	0.25	Beta (73.67, 217.05)	Gillies et al. [37], Tømte et al. [38], Deye et al. [39], Glover et al. [40]
Serious bleeding	0.12	Beta (1.90, 13.95)	Bartlett et al. [13]
Deep venous thrombosis	0.02	Beta (15.06, 737.89)	Bartlett et al. [13]
Arrhythmia	0.15	Beta (2.87, 16.26)	Bartlett et al. [13]
Pneumonia	0.56	Beta (9.20, 7.23)	Bartlett et al. [13]
Surface cooling			
Temperature overshoot	0.33	Beta (1.94, 3.94)	Bartlett et al. [13]
Shivering	0.28	Beta (53.35, 151.91)	Gillies et al. [37], Tømte et al. [38], Deye et al. [39], Glover et al. [40]
Serious bleeding	0.07	Beta (4.86, 64.61)	Bartlett et al. [13]
Deep venous thrombosis	0.05	Beta (22.81, 433.38)	Bartlett et al. [13]
Arrhythmia	0.19	Beta (6.16, 26.28)	Bartlett et al. [13]
Pneumonia	0.48	Beta (4.63, 4.72)	Bartlett et al. [13]
Costs (device and consumable) (£)			
Device cost (Thermogard XP)	34,648	Fixed	NHS supply chain [41]
Annual cost (Thermogard XP)	4717.87	Fixed	Calculated[b]
Intravascular catheters (Cool Line)	505.48	Fixed	NHS supply chain [41], Icy £794.95, Quattro £822.0
Start-up kit (model CG-500D)	363.70	Fixed	NHS supply chain [41]
Foley temperature probe	10.0	Fixed	Medtech innovation briefing (MIB37) [15]
Temperature probe interface cable	11.13	Fixed	Medtech innovation briefing (MIB37) [15]
Device cost (surface cooling: Blanketrol III)	9495.0	Fixed	Medtech innovation briefing (MIB112) [29]

Table 1 (continued)

Parameter	Value	Distribution	Source
Annual cost (Blanketrol III)	1469.0	Fixed	Calculated[a]
Reusable connecting hose	79.0	Fixed	Medtech innovation briefing (MIB112) [29]
Patient temperature probe cable	40.0	Fixed	Medtech innovation briefing (MIB112) [29]
Lite patient vest	133.0	Fixed	Medtech innovation briefing (MIB112) [29]
Lite adult	129.0	Fixed	Medtech innovation briefing (MIB112) [29]
Kool Kit	347.0	Fixed	Medtech innovation briefing (MIB112) [29]
Device cost (surface cooling: Arctic Sun 5000)	20,600.0	Fixed	Medtech innovation briefing (MIB112) [29]
Annual cost (Arctic Sun 5000)	3187.2	Fixed	Calculated[a]
Temperature in cable	116.3	Fixed	Medtech innovation briefing (MIB112) [29]
Temperature out cable	93.09	Fixed	Medtech innovation briefing (MIB112) [29]
Fill tube	37.2	Fixed	Medtech innovation briefing (MIB112) [29]
Fluid delivery line	1394.4	Fixed	Medtech innovation briefing (MIB112) [29]
Drain tube	32.5	Fixed	Medtech innovation briefing (MIB112) [29]
Foley catheter temperature sensor	349.1	Fixed	Medtech innovation briefing (MIB112) [29]
Arctic gel pad kit	628.3	Fixed	Medtech innovation briefing (MIB112) [29]
Arctic gel pad	545.9	Fixed	Medtech innovation briefing (MIB112) [29]
Primary (Foley)	10.3	Fixed	Medtech innovation briefing (MIB112) [29]
Maintenance	2800.0	Fixed	Medtech innovation briefing (MIB112) [29]
Costs (healthcare utilisation) (£)			
ICU costs per patient per day	1414.5	Gamma (96, 14.7)	NHS reference costs [32]
Hospitalisation costs per patient per day	354.0	Gamma (96, 3.7)	NHS reference costs [32]
Long-term cost of CPC1	15,040.0	Gamma (96, 156.6)	Chan et al. [30]
Long-term cost of CPC2	23,993.0	Gamma (96, 249.8)	Chan et al. [30]
Long-term cost of CPC3	33,420.0	Gamma (96, 348)	Chan et al. [30]
Long-term cost of CPC4	24,587.0	Gamma (96, 256)	Chan et al. [30]
Costs (adverse events) (£)			
Temperature overshoot	194.0	Gamma (100, 1.9)	NHS reference costs [32]
Shivering	322.0	Gamma (100, 3.2)	NHS reference costs [32]
Serious bleeding	752.0	Gamma (100, 7.5)	NHS reference costs [32]
Deep venous thrombosis	862.0	Gamma (100, 8.6)	NHS reference costs [32]
Arrhythmia	734.0	Gamma (100, 7.3)	NHS reference costs [32]
Pneumonia	1405.0	Gamma (100, 14.1)	NHS reference costs [32]
Average LOS			
In ICU (days): good neurological	8.2	Gamma (12.9, 0.6)	Petrie et al. [9]
In a hospital ward (days): good neurological	20.5	Gamma (13.3, 1.5)	Petrie et al. [9]
In ICU (days): poor neurological	21.0	Gamma (67.8, 0.3)	Petrie et al. [9]
In a hospital ward (days): poor neurological	65.0	Gamma (19.3, 3.4)	Petrie et al. [9]
In ICU (days): non-survivor	6.2	Gamma (12.3, 0.5)	Petrie et al. [9]
In a hospital ward (days): non-survivor	9.0	Gamma (19.4, 0.5)	Petrie et al. [9]

CPC cerebral performance category, *ICU* intensive care unit, *LOS* length of stay, *NHS* national health service,

[a]Utility in hospital was assigned to patients within the duration of hospital discharge and adjusted based on the duration (we assumed 2 months based on expert opinion from a UK hospital). Utility of poor and good neurological outcomes was adjusted based on the average LOS in a hospital ward and ICU in terms of good and poor neurological outcome

[b]Annual cost of Thermogard XP calculated as the device cost divided by the annualisation factor (annualisation factor estimated by considering the lifetime of the device [10 years] and the discount rate [5%] for Thermogard XP and lifetime [8 years] of the surface cooling devices)
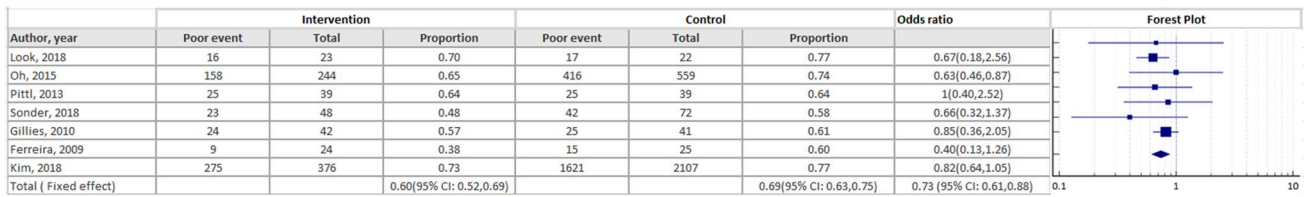
Author, year	Intervention			Control			Odds ratio	Forest Plot
	Poor event	Total	Proportion	Poor event	Total	Proportion		
Look, 2018	16	23	0.70	17	22	0.77	0.67(0.18,2.56)	
Oh, 2015	158	244	0.65	416	559	0.74	0.63(0.46,0.87)	
Pittl, 2013	25	39	0.64	25	39	0.64	1(0.40,2.52)	
Sonder, 2018	23	48	0.48	42	72	0.58	0.66(0.32,1.37)	
Gillies, 2010	24	42	0.57	25	41	0.61	0.85(0.36,2.05)	
Ferreira, 2009	9	24	0.38	15	25	0.60	0.40(0.13,1.26)	
Kim, 2018	275	376	0.73	1621	2107	0.77	0.82(0.64,1.05)	
Total (Fixed effect)			0.60(95% CI: 0.52,0.69)			0.69(95% CI: 0.63,0.75)	0.73 (95% CI: 0.61,0.88)	0.1 1 10

Fig. 2 Forest plot of poor neurological outcomes in hospital discharge duration: intravascular temperature management vs. surface methods

3 Results

3.1 Clinical Efficacy

The results of the subgroup meta-analysis on neurological outcome (Fig. 2) indicate that seven studies [37, 42–47] compared the neurological outcomes associated with IVTM versus a SCS over a hospital discharge duration. The meta-analysis showed that the pooled estimates of the probability of poor neurological outcomes with IVTM and SCS were 0.60 (95% CI: 0.52–0.69) and 0.69 (95% CI: 0.63–0.75), respectively. IVTM had a lower probability of unfavourable neurological outcomes than did SCS (odds ratio [OR] 0.73; 95% confidence interval [CI] 0.61–0.88). Figure 3 shows that 12 studies compared the mortality associated with IVTM versus SCS over a hospital discharge duration [37,42–49505152]. The meta-analysis showed that the pooled estimates of probability of mortality during hospital discharge in IVTM and SCS group were 0.43 (95% CI: 0.40–0.47) and 0.48 (95% CI: 0.47–0.50), respectively. IVTM was associated with a lower probability of mortality than surface methods (OR 0.87; 95% CI 0.75–1.02).

3.2 Cost-Effectiveness Analysis

The results of the base-case cost analysis over a lifetime time horizon demonstrated that the average device cost per patient (annual cost of equipment along with consumable cost) of Thermogard XP was £932.91 per patient compared with £503.40 for Blanketrol III and £1075.30 for Arctic Sun 5000. Additionally, the cost of an ICU stay associated

with treatment with Thermogard XP was £17,108 per patient compared with £17,204 with SCS. Considering the costs of hospital ward stay, AE treatments, and long-term costs, the total average discounted cost for the intervention was £82,846. In comparison, the average discounted cost for Blanketrol III and Arctic Sun 5000 was £85,185 and £85,771, respectively. Thermogard XP resulted in direct cost savings of £2339 and £2925 (per patient) compared with Blanketrol III and Arctic Sun 5000. Treatment with Thermogard XP led to an increase of 0.98 discounted QALYs relative to Blanketrol III and Arctic Sun 5000 over a lifetime time horizon (Table 2). The estimated incremental cost-effectiveness ratio (ICER) was dominant for Thermogard XP versus Arctic Sun 5000 and Blanketrol III over a lifetime horizon, i.e., the intervention was less costly and more effective than the comparator(s).

The results of the PSA are presented as a cost-effectiveness plane and a CEAC plot, respectively, for IVTM compared with SCS (Figs. 4, 5). The results of the cost-effectiveness plane demonstrated that, in the majority of cases, the ICER was located in the south-east quadrant, i.e., the intervention was less costly and more effective. The probability of the intervention being cost saving was 69.2% and 65.3% versus the Arctic Sun 5000 and Blanketrol III, respectively, based on the CEAC plot (Figs. 4, 5). In the DSA, key cost and outcome parameters were subject to hypothetical increases or decreases of 25% to determine the key drivers of the model results. Results from the one-way sensitivity analyses generally supported the base-case findings, and findings from the different scenario analyses are shown in Fig. 6a and b in terms of change in incremental cost versus
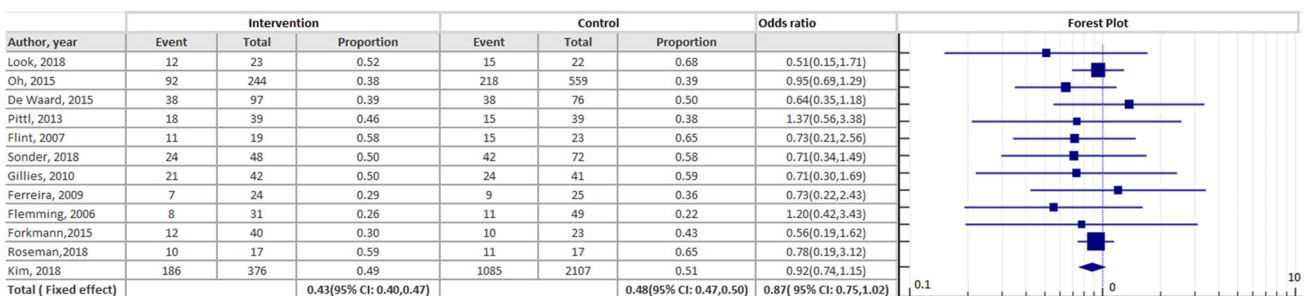
Author, year	Intervention			Control			Odds ratio	Forest Plot
	Event	Total	Proportion	Event	Total	Proportion		
Look, 2018	12	23	0.52	15	22	0.68	0.51(0.15,1.71)	
Oh, 2015	92	244	0.38	218	559	0.39	0.95(0.69,1.29)	
De Waard, 2015	38	97	0.39	38	76	0.50	0.64(0.35,1.18)	
Pittl, 2013	18	39	0.46	15	39	0.38	1.37(0.56,3.38)	
Flint, 2007	11	19	0.58	15	23	0.65	0.73(0.21,2.56)	
Sonder, 2018	24	48	0.50	42	72	0.58	0.71(0.34,1.49)	
Gillies, 2010	21	42	0.50	24	41	0.59	0.71(0.30,1.69)	
Ferreira, 2009	7	24	0.29	9	25	0.36	0.73(0.22,2.43)	
Flemming, 2006	8	31	0.26	11	49	0.22	1.20(0.42,3.43)	
Forkmann,2015	12	40	0.30	10	23	0.43	0.56(0.19,1.62)	
Roseman,2018	10	17	0.59	11	17	0.65	0.78(0.19,3.12)	
Kim, 2018	186	376	0.49	1085	2107	0.51	0.92(0.74,1.15)	
Total (Fixed effect)			0.43(95% CI: 0.40,0.47)			0.48(95% CI: 0.47,0.50)	0.87(95% CI: 0.75,1.02)	0.1 0 10

Fig. 3 Forest plot of mortality in hospital discharge duration: intravascular temperature management vs. surface methods

Table 2 Results of cost-effectiveness analysis over lifetime time horizon

Cost and effectiveness	Thermogard XP	Surface cooling	Incremental[a]
Cost			
Average cost per patient vs. Blanketrol III	£82,846	£85,185	(£2339)
Average cost per patient vs. Arctic Sun 5000	£82,846	£85,771	(£2925)
Effectiveness			
Total life-years lived per patient	9.09	10.22	1.13
Total QALYs lived per patient	6.38	5.40	0.98
ICER Thermogard XP vs. Blanketrol III	Dominant		
ICER Thermogard XP vs. Arctic Sun 5000	Dominant		
NMB vs. Blanketrol III[b]	£21,929		
NMB vs. Arctic Sun 5000[b]	£22,515		
Probability of being cost saving vs. Blanketrol III	65.3%		
Probability of being cost saving vs. Arctic Sun 5000	69.2%		

ICER incremental cost-effectiveness ratio, *NMB* net monetary benefit, *QALYs* quality-adjusted life-years

[a]Incremental (cost and effectiveness of Thermogard XP − cost and effectiveness of surface cooling method)

[b]Using £20,000 willingness to pay
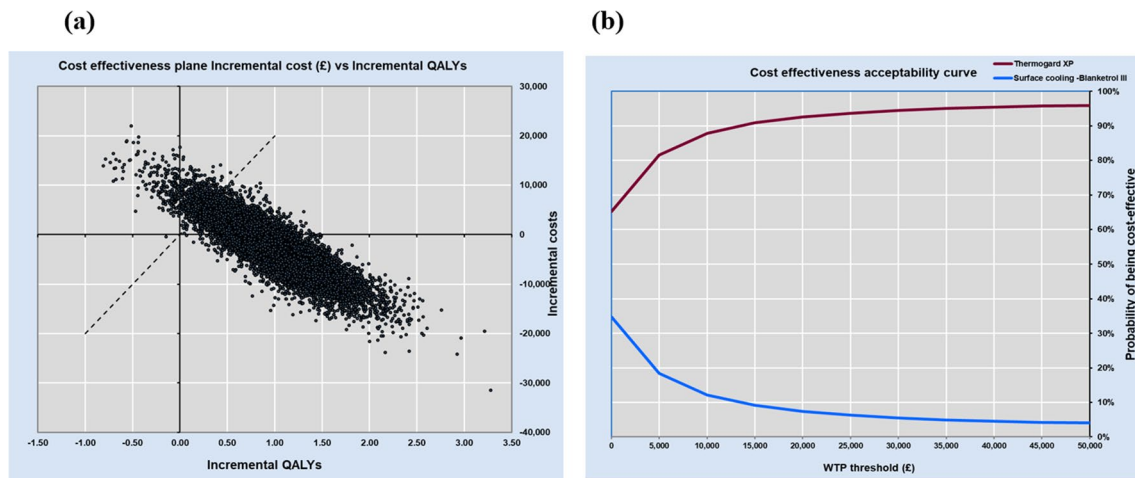
Fig. 4 Cost-effectiveness plane (**a**) and cost-effectiveness acceptability curve plot (**b**) for Thermogard XP versus Blanketrol III

Blanketrol III and Arctic Sun 5000, respectively. Regarding the results of DSA, the probability of neurological outcome (i.e., the neurological outcome health state that patients entered in the short term) had the most significant effect on the base-case results. In addition, in the base-case analysis, we assumed a cool line was used for intravascular catheters; however, considering different catheters for IVTM, such as Icy and Quattro, did not change the cost-effectiveness analysis results. The results of the base-case analysis over the hospital discharge time horizon are presented in the ESM (SI-IV).

4 Discussion

We performed a cost-effectiveness analysis to explore the impact of treating patients with IVTM using Thermogard XP compared with the SCS by Blanketrol III or Arctic Sun 5000, following a cardiac arrest. Results of the cost-effectiveness analysis over a lifetime time horizon indicated that this intervention was dominant compared with the SCS. To the best of our knowledge, this is the first cost-effectiveness analysis to evaluate IVTM using a Markov model.

According to the literature, TTM following cardiac arrest improves neurological and survival outcomes. Although different temperature management procedures to control cardiac arrest survival are cost effective [24, 53], identifying the

(a)

(b)
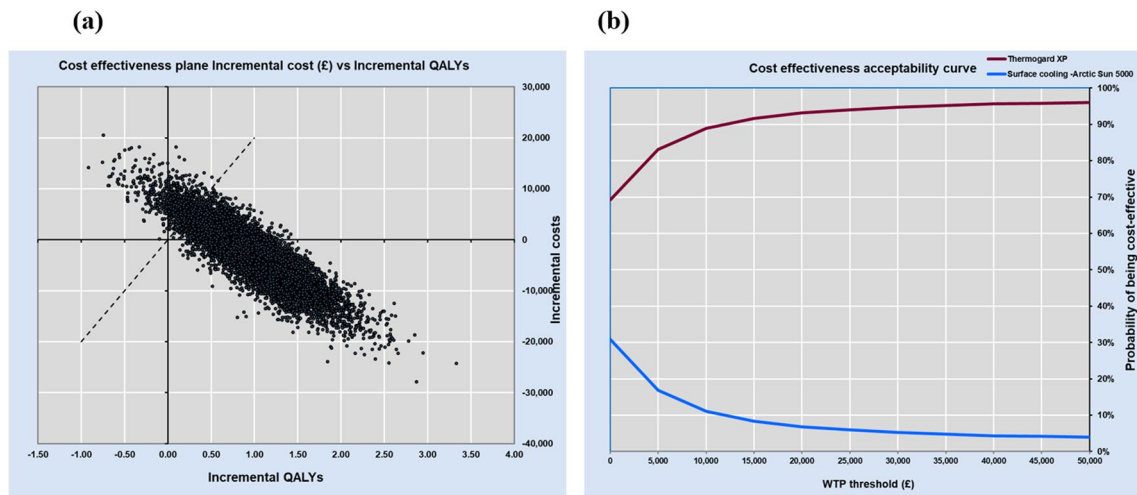
Fig. 5 Cost-effectiveness plane (**a**) and cost-effectiveness acceptability curve plot (**b**) for Thermogard XP versus Arctic Sun 5000

most cost-effective cooling procedure is an area that needs to be explored.

A previous study determined that TTM with a cooling blanket among cardiac arrest survivors improves clinical outcomes and is a cost-effective intervention versus conventional care in the USA [24]. In this study, patients receiving TTM gained an average of 0.66 QALYs compared with conventional care, at an incremental cost of $US31,254. Another study evaluated different methods of temperature management, including blanket cooling, peritoneal lavage, and venovenous extracorporeal membrane oxygenation VV ECMO [53]. The results of this study showed that a cooling blanket was the most cost-effective intervention, with an ICER of $US58,329/QALY versus peritoneal lavage and VV ECMO.
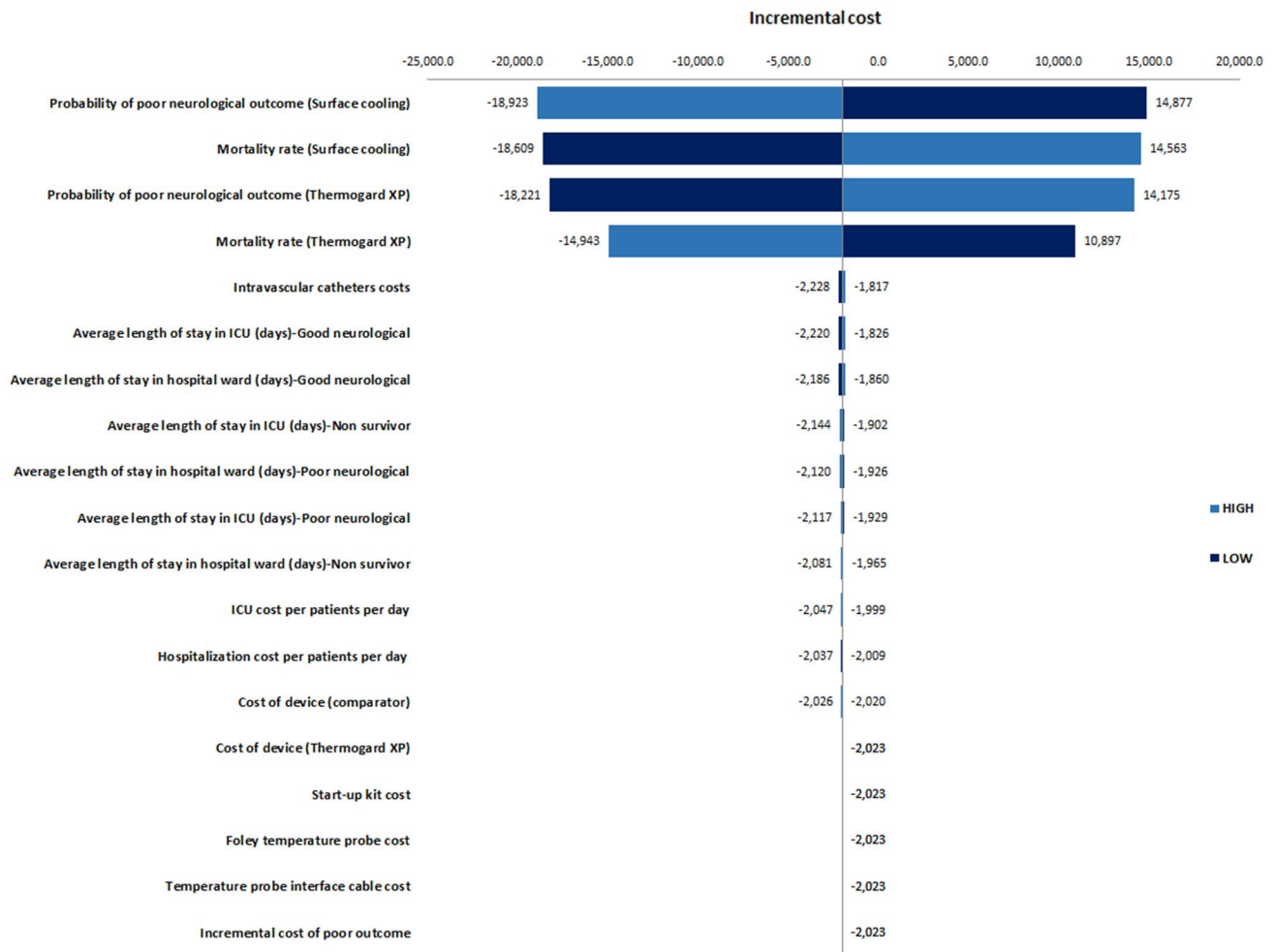
Since recent reviews [13] determined that IVTM was associated with improved neurological outcomes compared with SCS among survivors resuscitated following cardiac arrest, economic evaluation assessing the costs and outcomes of IVTM methods is important to help healthcare policymakers identify the optimal procedure. Besides improving neurological outcomes and survival rates, IVTM is associated with a reduced burden of significant AEs, including temperature overshoot, arrhythmia, deep venous thrombosis, and shivering [13]. These clinical challenges will complicate the treatment process and delay hospital discharge, which will impose more costs on the healthcare system. For instance, shivering is a common side effect in TTM and can lead to cerebral and metabolic stress [40, 54] that, in turn, can lead to additional usage of sedation treatments, prolonged length of stay, and increased healthcare utilisation. Recent findings show that IVTM is associated with a reduced rate of shivering (as low as 2.36%) compared

with SCS [37–40], which can be considered a positive clinical and economic impact of IVTM.

Furthermore, multiple studies [40, 45, 55, 56] have reported more rapid cooling and a more stable temperature profile (during both cooling and rewarming phases) with IVTM. This results in a faster time to reach target temperature and greater precision in maintaining the patient's temperature, two parameters that are repeatedly described as favourably impacting clinical outcomes following cardiac arrest [57–62]. The time- and cost-saving potential provided by this practical dimension was indirectly considered through the clinical outcome probabilities entered in the model presented.

In this study, we found that IVTM is likely to be the most cost-effective strategy among current temperature management procedures for delivering TTM after cardiac arrest. The probability of poor neurological outcomes was the main driver in this analysis, based on results from the DSA. There is a significant difference between the ICU and hospital ward length of stay associated with poor and good neurological outcomes in the UK healthcare system. As a result, the probability of neurological outcome parameters has a significant effect on costs, clinical outcomes, and economic evaluation results. One strength of our study is that we used multiple sources of high-level evidence to inform the probability of clinical outcomes in IVTM and SCS. Additionally, our incorporation of uncertainty in model inputs and assumptions in the results should provide reassurance that the overall findings are not materially affected by uncertain evidence.

The limitations of our study should also be acknowledged. Because UK-based studies on the cost estimation of long-term costs associated with cardiac arrest in terms of severity of neurological outcomes were lacking, we extracted data

Incremental cost

	-25,000.0	-20,000.0	-15,000.0	-10,000.0	-5,000.0	0.0	5,000.0	10,000.0	15,000.0	20,000.0

Probability of poor neurological outcome (Surface cooling) −18,923 | 14,877

Mortality rate (Surface cooling) −18,609 | 14,563

Probability of poor neurological outcome (Thermogard XP) −18,221 | 14,175

Mortality rate (Thermogard XP) −14,943 | 10,897

Intravascular catheters costs −2,228 | −1,817

Average length of stay in ICU (days)-Good neurological −2,220 | −1,826

Average length of stay in hospital ward (days)-Good neurological −2,186 | −1,860

Average length of stay in ICU (days)-Non survivor −2,144 | −1,902

Average length of stay in hospital ward (days)-Poor neurological −2,120 | −1,926

Average length of stay in ICU (days)-Poor neurological −2,117 | −1,929

Average length of stay in hospital ward (days)-Non survivor −2,081 | −1,965

ICU cost per patients per day −2,047 | −1,999

Hospitalization cost per patients per day −2,037 | −2,009

Cost of device (comparator) −2,026 | −2,020

Cost of device (Thermogard XP) −2,023

Start-up kit cost −2,023

Foley temperature probe cost −2,023

Temperature probe interface cable cost −2,023

Incremental cost of poor outcome −2,023

■ HIGH
■ LOW

Fig. 6 Tornado diagram for change in incremental cost vs. (**a**) Blanketrol III and (**b**) Arctic Sun 5000. *ICU* intensive care unit

from a US-based source and converted international cost-effectiveness data to UK values. We also assumed that the neurological outcome status of survivors of cardiac arrest was constant over a lifetime time horizon. We also combined CPC 1 and CPC 2 as good and CPC 3 and CPC 4 as poor neurological outcome status, which did not allow for variation in long-term care costs associated with each individual neurological state. To model this assumption, we derived the rate of each neurological status including CPC1, CPC2, CPC3, and CPC4 [21], and we then estimated the weighted average hazard ratio by adjusting the rate of CPC1 and CPC 2 for good and CPC3 and CPC 4 for poor neurological outcome. We also assigned the incremental cost of poor neurological outcomes among patients in this condition until death. Moreover, the main source of Kaplan–Meier

estimates for survival according to CPC category score and rate of each status was a US-based study [21], and we used the most recent UK national life table data to estimate age- and sex-adjusted hazard ratios for the final survival parameters in the model [63].

5 Conclusion

Our findings show that using IVTM is associated with better neurological outcomes and survival rates over both short-term and long-term time horizons. In addition, IVTM improves life-year gains and reduces the total costs per patient over a lifetime time horizon versus surface cooling methods for managing patients' temperature after cardiac arrest.
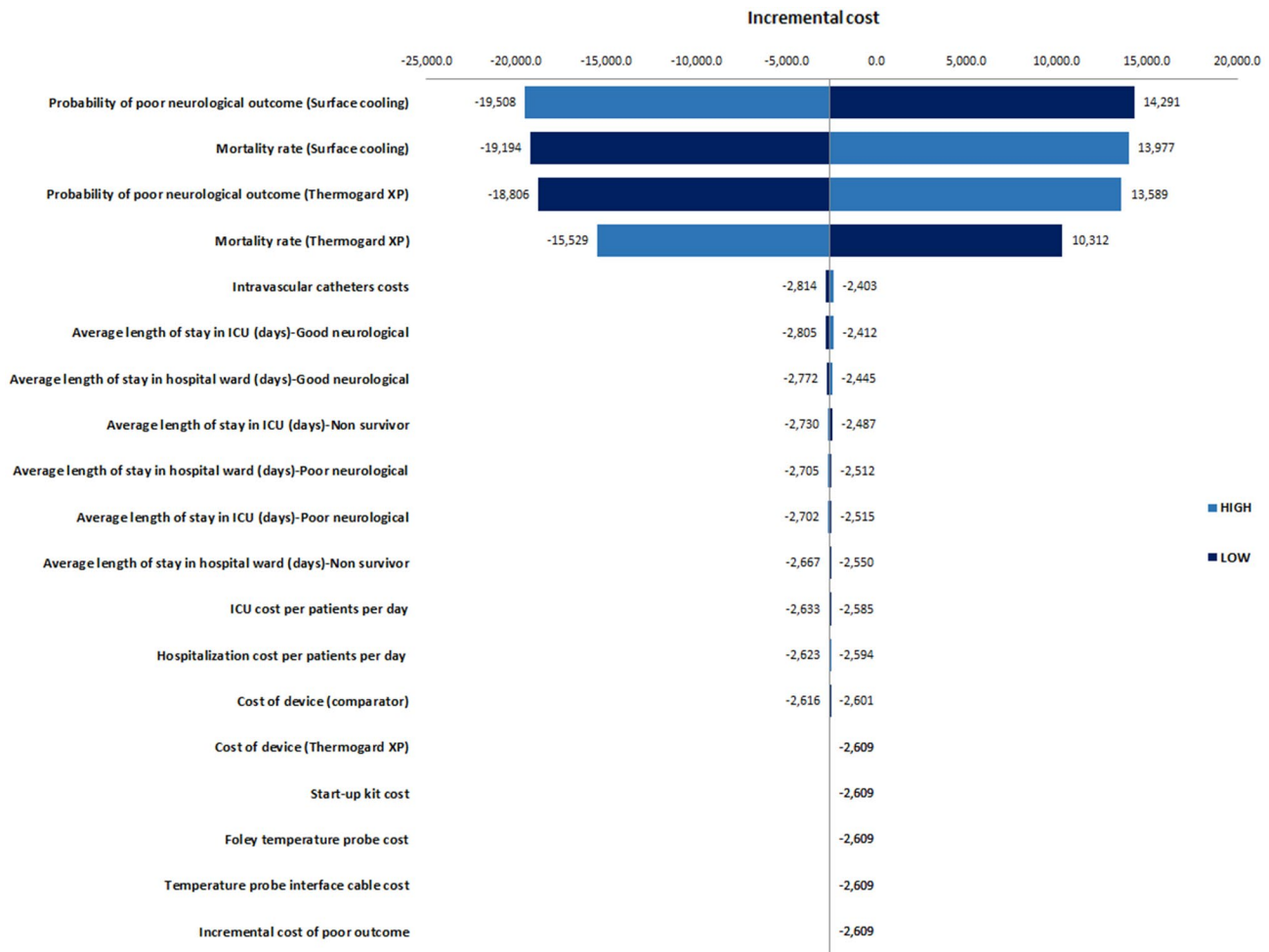
Incremental cost

Parameter	LOW	HIGH
Probability of poor neurological outcome (Surface cooling)	-19,508	14,291
Mortality rate (Surface cooling)	-19,194	13,977
Probability of poor neurological outcome (Thermogard XP)	-18,806	13,589
Mortality rate (Thermogard XP)	-15,529	10,312
Intravascular catheters costs	-2,814	-2,403
Average length of stay in ICU (days)-Good neurological	-2,805	-2,412
Average length of stay in hospital ward (days)-Good neurological	-2,772	-2,445
Average length of stay in ICU (days)-Non survivor	-2,730	-2,487
Average length of stay in hospital ward (days)-Poor neurological	-2,705	-2,512
Average length of stay in ICU (days)-Poor neurological	-2,702	-2,515
Average length of stay in hospital ward (days)-Non survivor	-2,667	-2,550
ICU cost per patients per day	-2,633	-2,585
Hospitalization cost per patients per day	-2,623	-2,594
Cost of device (comparator)	-2,616	-2,601
Cost of device (Thermogard XP)		-2,609
Start-up kit cost		-2,609
Foley temperature probe cost		-2,609
Temperature probe interface cable cost		-2,609
Incremental cost of poor outcome		-2,609

Fig. 6 (continued)

Declarations

Conflict of interest MJ and AM are employees of Optimax Access Ltd and MBH is an employee of Device Access Ltd. Both Optimax Access and Device Access Ltd received funds from ZOLL to conduct this study. TRK has received research funding from ZOLL. MY is an assistant professor at Mercer University, was employed by Optimax Access at the time of conducting the work, and received consulting fees for its contribution to this study. MRH is a freelance health economist and has no conflict of interest.

Author contributions MJ conceived the study question. MY, MJ, and MRH developed the analysis plan, conducted the economic model, and drafted the manuscript. All authors contributed to the study design, provided input on the model, and read and approved the final draft of the manuscript.

Availability of data and material The model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication All authors approve the manuscript and gave their consent for submission and publication.

Code availability Not applicable.

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