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Prediction and risk stratification of survival in accidental hypothermia requiring extracorporeal life support: An individual patient data meta-analysis

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ABSTRACT

Background: Extra-corporeal life support (ECLS) is a life-saving intervention for patients with hypothermia induced cardiac arrest or severe cardiovascular instability. However, its application is highly variable due to a paucity of data in the literature to guide practice. Current guidelines and recommendations are based on expert opinion, single case reports, and small case series. Combining all of the published data in a patient-level analysis can provide a robust assessment of the influence of patient characteristics on survival with ECLS.

Objective: To develop a prediction model of survival with good neurologic outcome for accidental hypothermia treated with ECLS.

Methods: Electronic searches of PubMed, EMBASE, CINAHL were conducted with a hand search of reference lists and major surgical and critical care conference abstracts. Studies had to report the use of ECLS configured with a circuit, blood pump and oxygenator with an integrated heat exchanger. Randomized and observational studies were eligible for inclusion. Non-human, non-English and review manuscripts were deemed ineligible. Study authors were requested to submit patient level data when aggregate or incomplete individual patient data was provided in a study. Survival with good neurologic outcome was categorized for patients to last follow-up based on the reported scores on the Cerebral Performance Category (1 or 2), Glasgow Outcome Scale (4 or 5) and Pediatric Overall Performance Category (1 or 2). A one-stage, individual patient data meta-analysis was performed with a mixed-effects multi-level logistic regression model reporting odds ratio (OR) with a 95% confidence interval (CI).

Results: Data from 44 observational studies and 40 case reports (n = 658) were combined and analyzed to identify independent predictors of survival with good neurologic outcome. The survival rate with good neurologic outcome of the entire cohort was 40.3% (265 of 658). ECLS rewarming rate (OR: 0.93; 95% CI: 0.88, 0.98; $p = .007$), female gender (OR: 2.78; 95% CI: 1.69, 4.58; $p < 0.001$), asphyxiation (OR: 0.19; 95% CI: 0.11, 0.35; $p < 0.001$) and serum potassium (OR: 0.62; 95% CI: 0.53, 0.73; $p < 0.001$) were associated with survival with a good neurologic outcome. The logistic regression model demonstrated excellent discrimination (c-statistic: 0.849; 95% CI: 0.823, 0.875).

Conclusions: The use of extracorporeal life support in the treatment of hypothermic cardiac arrest provides a favourable chance of survival with good neurologic outcome. When used in a weighted scoring system, asphyxiation, serum potassium and gender can help clinicians prognosticate the benefit of resuscitating hypothermic patients with ECLS.

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Introduction

The use of extracorporeal life support (ECLS) to treat hypothermic cardiac arrest is associated with a 10–50% improvement in survival [1] over the baseline rate of 10–37% [2–4], yielding a number needed to treat of approximately 2–5 to save one life. Some 400–1500 persons die annually from hypothermia in the United States [5–8] yet most pre-hospital care systems and community hospitals do not have a protocol to identify and transfer appropriate hypothermic cardiac arrest patients to an ECLS center. With the increased use and availability of ECLS in the United States for treating cardiac arrest in the Emergency Department, this therapy has become increasingly accessible, making the appropriate triage of hypothermic patients particularly timely.

Clinical decision making regarding appropriate ECLS application can be challenging in situations where difficulty exists distinguishing between cardiac arrest victims who arrest and subsequently become hypothermic and those who cool prior to suffering cardiac arrest secondary to hypothermia. Indiscriminate use of ECLS in the resuscitation of all cardiac arrest patients who are cold would be costly and result in low survival rates. However overly restrictive ECLS criteria would result in patients with a reasonable probability of survival being denied a potentially lifesaving intervention. A reliable prognostication tool is currently lacking to assist in the appropriate allocation of ECLS therapy for hypothermic patients. Although poorly studied, this likely results in significant site-specific variability in hospital transfer policies and the application of this modality.

The primary purpose of this study was to identify factors independently associated with survival with good neurologic outcome in patients treated with ECLS for hypothermic cardiac arrest. Secondarily, if such factors could be identified, we sought to develop a scoring tool, using standard historical and/or clinical factors, to predict the probability of survival with good neurological outcome.

Methods

An individual patient data (IPD) meta-analysis with a multivariable prediction model component was performed using methods described in Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-IPD) (Checklist, online Supplementary Data) and the Transparent Reporting of a Multivariate Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [9,10].

Data sources and article selection

Pubmed (1966 to November 25, 2017), EmBase (1980 to November 25, 2017) and CINAHL (1980 to November 25, 2017) were searched by one author (RSS) to identify all studies employing extracorporeal life support (ECLS) assisted rewarming in the setting of accidental hypothermia (AH). The search strategy used structured keywords combined with Boolean operators in the following format: [(accidental hypothermia) AND (extracorporeal life support)] OR (extracorporeal circulation) OR (extracorporeal rewarming). Subheading restriction excluded non-human and non-English language manuscripts. Due to the variability in terminology in the literature, ECLS was defined as the use of an extracorporeal circuit with an integrated blood pump, oxygenator and heat exchanger. In order to be eligible for inclusion articles had to report the use of ECLS in an observational or randomized cohort, or case report. An article was deemed ineligible when it reported ECLS use for non-human subjects, non-English manuscripts, or topic review. A reference list review was performed on included studies. Grey literature search included conference abstracts from the Society of Thoracic Surgeons, American Association of Thoracic Surgery, European Association of Cardiothoracic Surgery, and the Society of Critical Care Medicine. Centres reporting duplicate cohorts had one study selected based on data comprehensiveness.

Data collection and analysis

Data extraction

A standardized data extraction form was developed, and data were electronically captured using Stata 14/IC (Stata Corporation, College Station, TX, USA). One reviewer (RS) transcribed data and a second reviewer (CS) verified data accuracy. Any data discrepancies were resolved through consensus discussion. Inter-annotator data agreement was assessed with the Cohen's Kappa statistic for each variable. All included studies had extraction of IPD or aggregate data for: study year, number of patients, age, gender, initial core temperature, type of ECLS (extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass pump (CPB)), cannulation site (peripheral or central), initial cardiac rhythm (asystole, pulseless electrical activity (PEA), ventricular fibrillation (VF), spontaneous rhythm (SR)), cooling mechanism (air, water, snow), asphyxiation, CPR to ECLS time, rewarming rate (calculated by dividing the initial core temperature, or if reported, the core temperature at initiation of ECLS, by the time taken to rewarm to 36 °C or ECLS discontinuation as degrees Celsius per hour), initial blood chemistry values (potassium, pH, lactate), neurologic outcome and survival. The term asphyxiation, frequently encountered in this literature, was considered to be a proxy for presumed hypoxia, and was defined as the absence of an air pocket in snow burial and water submersion. Neurologic outcomes were dichotomized according to the score on the Cerebral Performance Category (CPC), Glasgow Outcome Scale (GOS) and Pediatric Overall Performance Category (POPC). Good neurologic outcome was defined as CPC 1–2, or GOS 4–5, or POPC 1–2, while CPC 3–5, GOS 1–3 or POPC 3–6 was categorized as poor neurologic outcome. Patients in studies not utilizing a neurologic outcome score but reporting disability severity were categorized according to description.

Missing data

To capture any missing data the first author was contacted through email or ground mail with an invitation to submit data as part of the International Accidental Hypothermia Extracorporeal Life Support (ICE) Collaborators. This request occurred when a study had missing data fields or reported aggregate data. In the latter circumstance, the author was requested to submit complete IPD. No attempt was made to contact authors with studies published prior to 1999, due to the unlikelihood of locating the author. After all requests for data were submitted the remaining missing data were considered missing-at-random and underwent multiple imputation using a Markov chain Monte Carlo algorithm (*mi impute mvn*) in Stata, version 14/IC [11].

Study quality

Risk of bias was assessed for each study with the Down's and Black quality score [12]. The Down's and Black quality score has been validated for both randomized and observational studies. The score ranges between 0 and 32, where a higher point allocation is awarded to a study with enhanced methodological attributes.

Statistical analysis

A one-stage, patient level pooled analysis was used for model development. Treatment effects were modeled with mixed-effects multilevel logistic regression in order to preserve clustering of patients within trials. In situations where only aggregate data were available for a study, the data structure was preserved in the analysis [13]. Continuous variables were entered as linear functions unless univariable graphical display of survival with good neurologic outcome partitioned into deciles demonstrated a non-linear relationship. Candidate variable selection for the full model was based on the Wald test ($p < 0.25$). The full model was reduced through stepwise backward covariate elimination. Treatment effect modifiers (interaction terms) were assessed prior to model determination. Internal validation was performed with

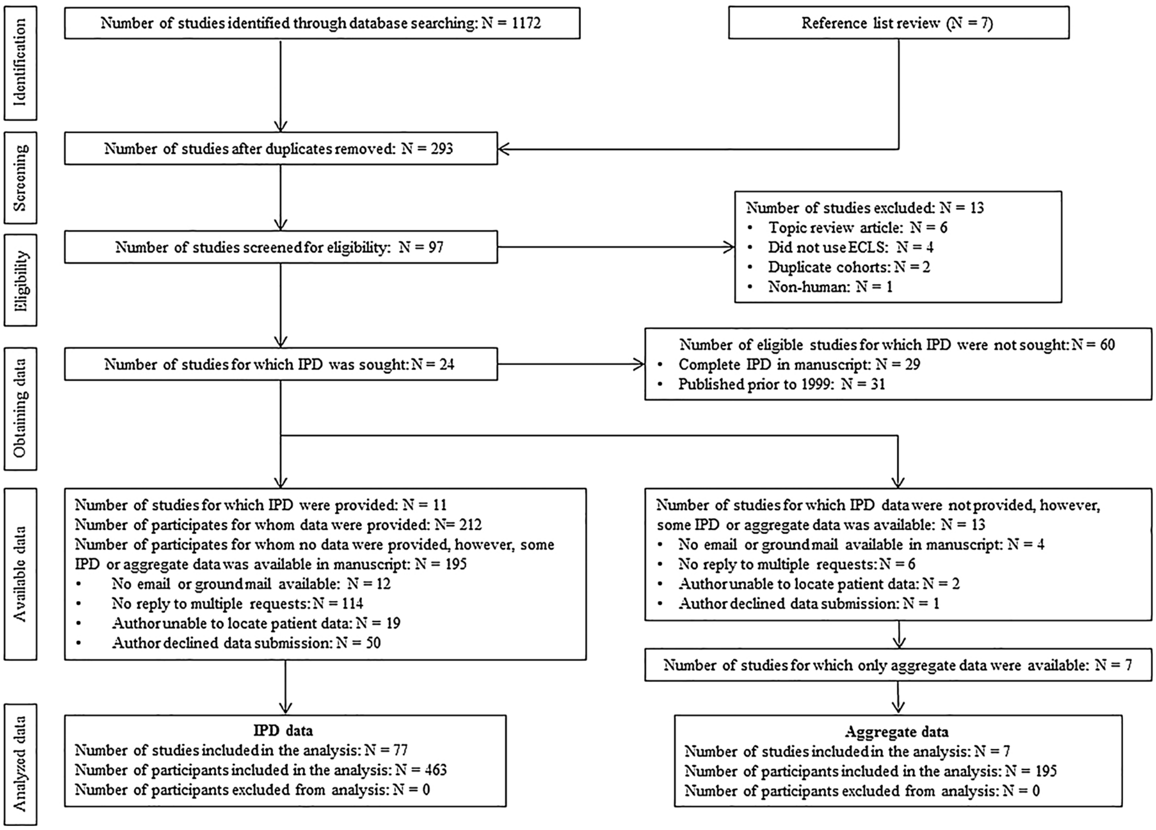

Fig. 1. PRISMA Flow chart.
Abbreviations: IPD = individual patient data.

bootstrap samples (n = 1000) with replacement. A linear shrinkage factor was applied to recalibrate predictor coefficients to mitigate model optimism [14]. Calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test and a calibration plot. The C-statistic assessed model discrimination. The final main effects model independent predictors were expressed as odds ratio (OR) with 95% confidence interval (CI). The β-coefficients from the final model were used to derive a survival score [15]. Statistical significance was present with 2-side tests at a $p < 0.05$. Stata, version 14/IC (Stata Corporation, College Station, TX, USA) was used for quantitative analysis.

Results

Initial search of Pubmed, EMBASE and CINAHL identified 1172 potential studies. After exclusions, 84 manuscripts were selected for analysis (Fig. 1). No randomized studies were identified. All of the studies were observational designs comprised of 44 retrospective cohort studies and 40 individual case descriptions (Table 2, online Supplementary Data). The Cohen's Kappa statistic for inter-annotator agreement was 0.993 (95% CI: 0.987, 0.999) and 0.987 (95% CI: 0.978, 0.996) for survival and neurologic outcome, respectively. Seven studies reported only aggregate data in the published manuscript [16–22]. Missing data in the studies required the contact of primary authors (n = 24). Eleven authors agreed to submit data [16,20,23–31]. After receipt of author submissions, missing data was reduced for cannulation site (3.8%, 25 of 658), initial cardiac rhythm (0.6%, 4 of 658), cooling mechanism (0.2%, 1 of 658), asphyxiation (0.6%, 4 of 658), CPR to ECLS time (17.6%, 116 of 658), rewarming rate (5%, 33 of 658), serum potassium (14.7%, 97 of 658), pH (23.6%, 155 of 658), and lactate (15%, 99 of 658). The remaining missing data underwent multiple imputation, thereby constructing complete data fields for every patient.

The final dataset resulted in a pooled study population of 658 patients requiring ECLS for AH. The majority of the cohort was classified as Swiss stage III/IV hypothermia (98.6%, 650 of 658) with the remaining as stage II (1.4%, 9 of 658) [32]. Stage III/IV patients presented with cardiovascular collapse or severe instability requiring the institution of ECLS. The Stage II patients were electively placed on ECLS due to insufficient response to rewarming techniques used to increase core temperature. The key patient characteristics and neurologic outcomes are summarized in Table 1. A history of presumed hypoxia secondary to asphyxiation was present in 42.4% (279 of 658) of cases. Of these 12.8% (34 of 265) survived with a good neurologic outcome – 91.2% (31 of 34) with a history of water submersion and 8.8% (3 of 34) with snow burial.

The mean survival rate of the entire study cohort was 46% (303 of 658) with 40.3% (265 of 658) surviving having a good neurologic outcome. Among patients who survived and were successfully weaned from ECLS, a good neurologic outcome was found in 87.5% (265 of 303) of cases.

Univariable analysis of candidate predictors identified several variables associated with survival with good neurologic outcome (Table 2). However, after multivariable-adjustment the four statistically significant independent predictors identified were: ECLS rewarming rate, female gender, asphyxiation and serum potassium (Table 2). To assess the stability of the model estimates, the cohort dataset was divided between studies reporting IPD and those reporting aggregate data. A repeat multi-level logistic regression analysis was undertaken for studies for which only IPD were reported. The results were similar to the initial final dataset analysis and identified the same independent predictors of rewarming rate (OR: 0.92; 95% CI: 0.87, 0.97; $p = .006$), female gender (OR: 3.58; 95% CI: 1.99, 6.45; $p < 0.001$), asphyxiation (OR: 0.17; 95% CI: 0.07, 0.32; $p < 0.001$), and serum potassium (OR: 0.76, 95% CI: 0.65, 0.87; $p < 0.001$). The Hosmer-Lemeshow test ($p = 77.9$) and calibration plot (Fig. 2A) demonstrated good model

Table 1
Patient Characteristics and Neurological Outcome.

Characteristic	All Patients (n = 658)	Neurologic Outcome Good (n = 265)	Neurologic Outcome Poor (n = 393)
Age, median (IQR)	36.0 (22.0–55.1)	44.5 (26.0–59.0)	28.0 (18.0–46.5)
Female, n (%)	190 (29%)	112 (42%)	78 (20%)
Initial core temperature, mean (SD), ˚C	23.9 (3.8)	24.0 (3.3)	23.9 (4.2)
Initial cardiac rhythm, n (%)			
Asystole	326 (50%)	88 (33%)	238 (61%)
PEA	35 (5%)	12 (4%)	23 (6%)
VF	186 (28%)	91 (35%)	95 (24%)
SR	111 (17%)	74 (28%)	37 (9%)
ECMO instead of CPB pump, n (%)	290 (44%)	144 (54%)	146 (37%)
Peripheral cannulation, n (%)	558 (85%)	245 (93%)	313 (79%)
Rewarming rate, mean (SD), ˚C/hr	7.0 (4.8)	6.0 (4.7)	7.8 (4.7)
CPR to ECLS time, mean (SD), min.	123.8 (81.1)	116.2 (82.5)	129.1 (79.8)
Cooling mechanism, n (%)			
Air	254 (39%)	159 (60%)	95 (24%)
Water	297 (45%)	81 (31%)	216 (55%)
Snow	107 (16%)	25 (9%)	82 (21%)
Asphyxiation, n (%)	279 (43%)	34 (13%)	245 (62%)
pH, mean (SD)	6.88 (0.28)	7.01 (0.28)	6.79 (0.25)
Initial lactate, mean (SD), mmol/liter	12.5 (6.3)	10.7 (5.9)	13.7 (6.2)
Initial potassium, mean (SD), mmol/liter	5.9 (3.4)	4.3 (1.8)	7.0 (3.8)
Down's and Black score, median (IQR)	21 (18–24)	21 (18–23)	21 (18–24)

Abbreviations: ˚C/hr = degrees Celsius per hour; PEA = pulseless electrical activity; VF = ventricular fibrillation; SR = spontaneous rhythm; ECMO = extracorporeal membrane oxygenation; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; ECLS = extracorporeal life support.

Table 2
Studied Variables and their Association with Survival with Good Neurologic Outcome.

Characteristic	β-Coefficient	OR (95% CI)	p-value
Univariable Associations			
Publication year	0.22	1.25 (0.79–1.95)	0.340
Age	0.01	1.01 (0.99–1.02)	0.052
Female	1.05	2.85 (1.83–4.43)	< 0.001
Initial core temperature, ˚C	-0.03	0.97 (0.91–1.03)	0.327
Initial cardiac rhythm			
Asystole	-1.14	0.33 (0.21–0.51)	< 0.001
PEA	-0.28	0.78 (0.34–1.81)	0.562
VF	0.78	2.21 (1.37–3.57)	0.001
SR	1·71	5.56 (2.32–13.34)	< 0.001
ECMO instead of CPB pump	1.18	3.23 (1.46–7.17)	0.004
Peripheral cannulation	1.17	3.18 (1.44–7.04)	0.004
Rewarming rate, ˚C/hr	-0.09	0.92 (0.87–0.97)	0.002
CPR to ECLS time, min.	-0.01	0.99 (0.99–1.00)	0.437
Cooling mechanism			
Air	0.78	2.17 (1.36–3.46)	< 0.001
Water	-0.55	0.57 (0.36–0.92)	0.021
Snow	-0.43	0.61 (0.29–1.26)	0.181
Asphyxiation	-2.12	0.12 (0.07–0.21)	< 0.001
pH	2.69	14.75 (5.09–36.83)	< 0.001
Initial lactate, mmol/liter	-0.07	0.93 (0.89–0.96)	< 0.001
Initial potassium, mmol/liter	-0.53	0.57 (0.49–0.66)	< 0.001
Down's & Black score.	-0.01	0.99 (0.98–1.00)	0.393
Multivariable Associations			
Rewarming rate, ˚C/hr	− 0.08	0.93 (0.88–0.98)	0.007
Female	1.02	2.78 (1.69–4.58)	< 0.001
Asphyxiation	− 1.64	0.19 (0.11–0.35)	< 0.001
Initial potassium, mmol/liter	− 0.48	0.62 (0.53–0.73)	< 0.001

Abbreviations: OR = odds ratio; CI = confidence interval; PEA = pulseless electrical activity; VF = ventricular fibrillation; SR = spontaneous rhythm; ˚C/hr = degrees Celsius per hour; ECMO = extracorporeal membrane oxygenation; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; ECLS = extracorporeal life support.

predictive performance. Model discrimination was classified as having excellent capability to discern survival as represented by the c-statistic (0.849; 95% CI: 0.823, 0.875) (Fig. 2B).

We sought to develop a score to aid clinicians in determining the probability of survival with good neurologic outcome. To do this only pre-ECLS covariates from the final multivariate model were used for the score development. Gender, serum potassium and asphyxiation are pre-ECLS observable parameters. In contrast, rewarming rate is a parameter that is controlled during the ECLS. As a result, a survival score was derived without the inclusion of rewarming rate. A point allocation scheme was developed based on gender, asphyxiation and serum potassium level. The summation of allocated points generates a survival score ranging from minus three to fifteen (Fig. 3A). The ICE survival score has the ability to discern survival with good neurologic outcome between the eight possible total score combinations. (Fig. 3B).

Discussion

The most important clinical outcome in hypothermic cardiac arrest resuscitation is survival with good neurologic outcome, typically viewed as a moderate or high level of cognition and independent functional status. Previously reported survival rates for hypothermic cardiac arrest treated with ECLS rewarming range from 10 to 100%. Our pooled data found a survival with good neurologic outcome rate of 40.3% and a relatively low proportion (5.6%) of survivors with a poor neurologic outcome.

After multivariate analysis, we identified four variables independently associated with survival with good neurologic outcome: asphyxiation, serum potassium level, gender, and rewarming rate. Interestingly, despite their significant univariate association: initial rhythm, air cooling, pH and lactate were not found to be independently associated with survival after multivariable modeling. Additionally, patient age, initial core temperature, and duration of CPR were not found to be associated with survival with good neurologic outcome. With respect to treatment, we found a slower rate of ECLS rewarming was independently associated with improved survival with good neurologic outcome.

Our results indicate a history of presumed hypoxia is highly associated with death or poor neurologic outcome. We defined presumed hypoxia as a history of submersion or avalanche burial without access to an air pocket. To our surprise 5.2% of this cohort survived with a good outcome. A proportion of these survivors were young children, who have been previously documented to survive cold water submersion with hypoxia and rapid cooling. In adults, cold water immersion with core temperature decrease prior to submersion/hypoxia likely accounted for the rest of the survivors.

Serum potassium has long been used in the assessment and triage of hypothermic cardiac arrest patients. The value above which resuscitative efforts are presumed futile has changed over time. Current guidelines advise that a serum potassium of > 12.0 mmol/L is not compatible with survival [1]. Our data support continuation of the practice of using serum potassium to assist with prognostication, but offers a more accurate prediction of the rate of survival with good neurologic outcome across various potassium levels. Isolating the effect of serum potassium in the clinical prediction model, a serum potassium level of < 5 mmol/L was associated with a range of survival with good neurologic outcome of approximately 35%–85%, in contrast to 10%–50% for levels of 5–10 mmol/L and 0%–20% for potassium levels greater than 10 mmol/L.

A: Calibration Plot

B: Receiver Operating Curve

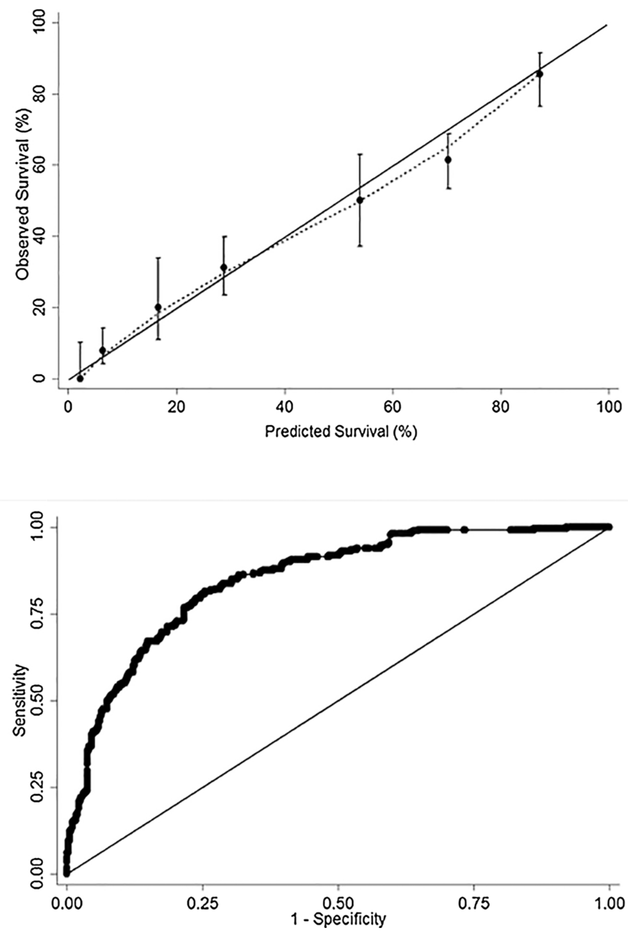

Fig. 2. Measures of Model Performance.
A: Calibration plot: The calibration plot compares observed survival with good neurologic outcome to the predicted survival with good neurologic outcome for each of the possible 8 ICE Survival Scores. ICE Survival Score 12 and 15 were collapsed into one observation as there were no survivors for either of these total scores. The circles are the point estimate (95% CI). The dotted line is the Lowess smoothing line. The solid line represents perfect agreement between observed and predicted survival with good neurologic outcome.
B: **Receiver Operating Curve**: The area under the receiver operating curve is equivalent to the c-statistic (0.849; 95%CI: 0.823, 0.875).

Female gender has been found to be associated with better neurologic outcome following cardiac arrest [33–35]. Our results indicate that female gender is associated with approximately 10%–25% increase in the probability of survival with good neurologic outcome. The reasons for improved survival from cardiac arrest in women remain unknown, however there is a growing body of evidence that suggests that estrogen and progesterone may confer a neuroprotective effects in cardiac arrest [36,37].

We also identified rate of rewarming to have a small independent association with survival with good neurologic outcome. This provides additional support to existing evidence and cardiac surgery guidelines suggesting that good neurologic outcome of hypothermic patients is inversely related to the rewarming rate [38,39]. It is postulated that this may be due to a cerebral temperature overshoot that can occur when larger temperature gradients are required by a more rapid ECLS rewarming. However, the ideal rate of rewarming of hypothermic ECLS patients remains unknown and requires further investigation.

A number of variables were not found not to be independently associated with survival with good neurologic outcome. Some, such as patient age, initial core temperature, pH, lactate, cardiac rhythm and duration of CPR, may seem surprising as they contrast with their presumed or proven utility in predicting survival in other etiologies of cardiac arrest. This information should help clinicians avoid the pitfall of inappropriately using such data when making ECLS allocation decisions. When faced with a cold patient in cardiac arrest, clinicians must integrate all available historical and laboratory information in order to decide whether to initiate ECLS either locally or by diversion to an ECLS center. In an effort to assist clinical decision making, we derived a clinical prediction model to estimate the probability of survival of hypothermic patients treated with ECLS rewarming. To our knowledge, the model we developed is the most robust tool available to estimate the probability of survival with good neurologic outcome in severe hypothermia treated with ECLS. Used correctly this could allow for improved prehospital triage, targeted ECLS rewarming and improved patient outcomes. In order to be successful applied, site and region specific multi-disciplinary determination of futility and agreement on patients appropriate for ECLS rewarming is required.

As robust as our prediction tool appears to be, we believe limitations to its application should be recognized. If the history clearly indicates a hypoxic arrest in an adult prior to cooling and no signs of life are noted during resuscitation, then the prognostication tool should not be used as further resuscitation and ECLS rewarming would almost certainly be futile. However, in cases where the history suggests the possibility of significant cooling prior to hypoxia (eg: clinging to an object, prolonged swimming, or avalanche burial with large air pocket/partial access to surface air) or the patient is a young child, then application of the prognostication tool would be appropriate and ECLS rewarming may be indicated.

Limitations

To our knowledge this is the most methodologically rigorous analysis of the accidental hypothermia patients treated with ECLS. However, a number of limitations of our study should be considered, the most important of which is potential publication bias. It is highly likely that cases successfully resuscitated with ECLS are reported and published more often than those that are unsuccessful, potentially leading to distortion of our estimates. Also, there are a number of clinical variables that are scarcely reported in the studies reviewed and not available as IPD. It is not possible to assess the statistical utility of absent data such as, time from accident identification to ECLS support, mode of chest compressions (manual vs. device), and drugs

A: ICE Survival Score Point Allocation

Characteristic	Points
Gender	
male	0
female	-3
Asphyxiation	
no	0
yes	5
Serum Potassium (mmol/liter)	
<5	0
5–10	5
>10	10
Total point range	-3 to 15

B: Survival with Good Neurologic Outcome

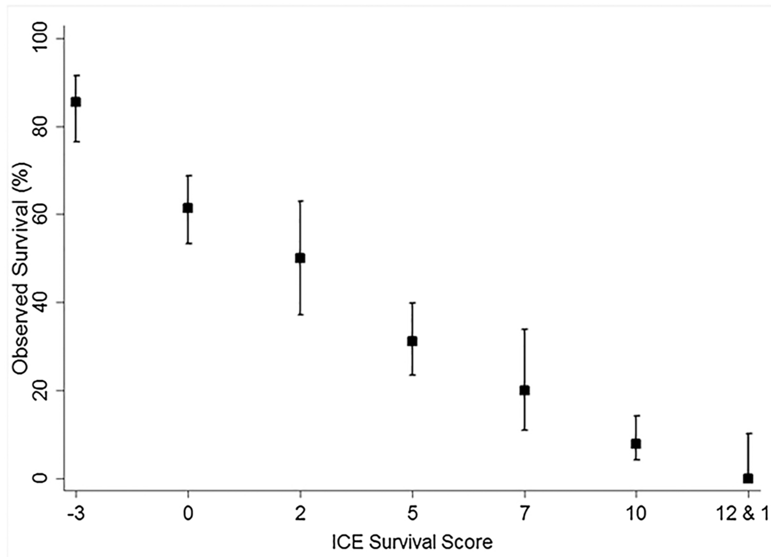

Fig. 3. The ICE Survival Score.
A: **ICE Survival Score Point Allocation**: The total point score is calculated by summing the points allocated for each of three presenting patient characteristics.
B: **Survival with Good Neurologic Outcome**: ICE survival scores of 12 and 15 were collapsed into one category as there were no survivors for either score.

administered during CPR. The inability to enter these data into our model may lead to variations in our estimates. Another limitation is the lack of external validation of our findings. We desired to externally validate our model; however were unable to identify a repository of data appropriate for doing. Given the limited sample size of our dataset we chose not to validate using a split sample technique, and instead used all cases to develop a precise a model as possible. Both the aforementioned limitations underscore the need for registries of hypothermic patients to allow for high quality inclusive prospective data collection and validation of our model.

Conclusion

This meta-analysis is the largest and most comprehensive dataset of its kind; it pools individual patient data from all the published reports where ECLS was used to rewarm AH patients with cardiovascular collapse or severe cardiac instability. Given the low incidence of severe AH, the inability to ethically perform a randomized trial and the lack of a large registry, this data represents the most robust evidence available at this time.

The analysis shows a favourable survival with good neurologic outcome in patients with severe AH treated with ECLS. ECLS rewarming rate, female gender, asphyxiation and serum potassium level are independent variables associated with survival with good neurologic outcome. The ICE survival score is a weighted risk stratification tool, when used in the appropriate clinical scenario, can assist clinicians in the prognostication of patients with severe hypothermia.

Conflict of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.03.028.

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