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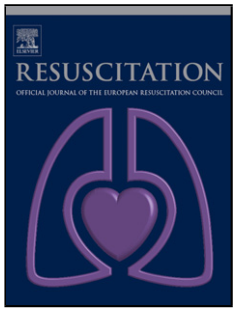

Title: Hypothermia outcome prediction after extracorporeal life support for hypothermic cardiac arrest patients: The HOPE score

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Original Paper

Hypothermia Outcome Prediction after Extracorporeal Life Support for Hypothermic Cardiac Arrest Patients: the HOPE Score.

PROSPERO registry (CRD42016052882).

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ABSTRACT

Aims: Currently, the decision to initiate extracorporeal life support for patients who suffer cardiac arrest due to accidental hypothermia is essentially based on serum potassium level. Our goal was to build a prediction score in order to determine the probability of survival following rewarming of hypothermic arrested patients based on several covariates available at admission.

Methods: We included consecutive hypothermic arrested patients who underwent rewarming with extracorporeal life support. The sample comprised 237 patients identified through the literature from 18 studies, and 49 additional patients obtained from hospital data collection. We considered nine potential predictors of survival: age; sex; core temperature; serum potassium level; mechanism of hypothermia; cardiac rhythm at admission; witnessed cardiac arrest, rewarming method and cardiopulmonary resuscitation duration prior to the initiation of extracorporeal life support. The primary outcome parameter was survival to hospital discharge.

Results: Overall, 106 of the 286 included patients survived (37%; 95% CI: 32-43%), most (84%) with a good neurological outcome. The final score included the following variables: age, sex, core temperature at admission, serum potassium level, mechanism of cooling, and cardiopulmonary resuscitation duration. The corresponding area under the receiver operating characteristic curve was 0.895 (95% CI: 0.859-0.931) compared to 0.774 (95% CI: 0.720-0.828) when based on serum potassium level alone.

Conclusions: In this large retrospective study we found that our score was superior to dichotomous triage based on serum potassium level in assessing which hypothermic patients in cardiac arrest would benefit from extracorporeal life support. External validation of our findings is required.

Keywords : Cardiac arrest; ECMO; ECPR; Hypothermia, Accidental; Potassium; Resuscitation; Triage

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INTRODUCTION

Accidental hypothermic cardiac arrest (CA) is often caused by homelessness or substance abuse, mountaineering accidents, or suicide attempts. In the United States alone, accidental hypothermia causes almost 1,500 deaths annually [1] and rates of hypothermia-related deaths have been increasing [2]. However, patients who are successfully reanimated with extracorporeal life support (ECLS) rewarming often have an excellent neurological outcome [3]. ECLS is, however, clinically invasive and resource intensive, and the critical therapeutic decision to initiate rewarming of a CA patient undergoing cardiopulmonary resuscitation (CPR) often has to be made rapidly based on a very limited amount of information and ancillary examination.

This decision has been based on serum potassium levels since landmark articles on the management of accidental hypothermia demonstrated nearly three decades ago that a high serum potassium value was associated with poor outcomes [4, 5]. However, the authors suggested at that time that multiple independent variables, thus far unaccounted for, probably also affected outcome. Although their conclusions regarding the practical implications of their findings were nuanced, current guidelines for CA patients experiencing accidental hypothermia or avalanche burial to date, suggest that a low serum potassium may indicate a potentially favorable prognosis [6-8] for which ECLS is indicated, while a markedly elevated level (>12mmol/L for accidental hypothermia and >8mmol/L for hypothermia due to avalanche burial) is considered an indicator of brain and heart hypoxia, secondary cell lysis, and a poor outcome [1,4,6,9,10].

However, the evidence supporting serum potassium-based triage is weak, and is based mainly on case reports and series and expert opinion. By analogy with out-of-hospital cardiac arrest or other survival prediction scores, we postulated that the outcome and success of ECLS rewarming would depend on several additional factors [5]: for example, the mechanism and speed of induction of hypothermia and CA [12], the type of cardiac arrhythmia [12], whether the CA was witnessed [13], core temperature, and the rewarming method used [14].

Our goal was to identify and analyze the predictors of survival following ECLS rewarming among hypothermic CA patients and to develop a score in order to better predict the probability of survival of a given CA patient with accidental hypothermia based on easily available covariates.

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METHODS

Patients were identified and selected through a systematic literature review, and unpublished hospital data were added. We included consecutive primarily hypothermic CA victims who underwent rewarming with ECLS. To minimize the risk of inclusion bias, only consecutive ECLS patients from retrospective cohort studies or hospital data in one determined time frame were *a priori* included. Published cases in convenience samples or single case reports were excluded, as they were considered at risk of bias. We also excluded patients who were not in CA when ECLS was started and those for whom no individual data were available.

Literature search

We used a mixed literature research strategy. Firstly, the patients from one recent systematic review were assessed for eligibility [12]. Secondly, we updated this research with the same methodology by exploring Pubmed, Embase, and Cochrane from January 1st 2013 to December 31st 2016 using the following keywords: "Extracorporeal Membrane Oxygenation OR ECMO OR Extra-Corporeal Assisted Rewarming OR Cardiopulmonary Bypass AND Hypothermia". We also searched Pubmed for cases series using the following keywords: "Extracorporeal Membrane Oxygenation OR Cardiopulmonary Bypass AND hypothermia". We limited the research to case reports from January 1st 1987 to December 31st 2016. The last search was performed on January 5th 2017. Finally, references of retrieved papers were searched for additional patients, as were all the authors' personal libraries.

One author (MP) performed the literature search and built the database. Authors were asked for provision of individual or missing data as required, as well as for the provision of data from additional eligible unpublished patients (for details see eTable 1 *only for Reviewers information*). Duplicate patients were excluded.

Published studies were independently and blindly assessed for potential bias by two of the authors (MP, TD). Possible disagreements were given to a third author (VR) to solve. Data from a random sample of 5% (n=14) of all included patients were randomly selected and blindly checked by one author (TD) to estimate the quality of data transcription of the main variables (n=14), representing 168 single data points [15]. This resulted in 0% of discordant data between the two authors.

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Hospital data collection

The data collection was approved by the institutional review board (N° 2016-01267) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Beside the addition of eligible unpublished patients provided by the authors of the retrieved studies, retrospective data from two additional hospitals were added (University Hospital, Lausanne 2000-2016 and Hospital of Sion 2004-2016, both in Switzerland).

The following data were collected for each patient: age; sex; mechanism of hypothermia; core temperature at admission (if not available, the out-of-hospital temperature was used); serum potassium level at admission; whether CA had been witnessed by rescuers or not; duration of CPR (defined from initiation of external CPR until start of ECLS); modality of ECLS rewarming (cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO)); and CA initial rhythm at hospital admission (i.e. asystole, ventricular fibrillation or pulseless electrical activity (PEA)). In the case of CA developing after admission, the CA rhythm when starting ECLS was registered. The mechanisms for hypothermia were further classified as non-asphyxia-related (e.g. immersion, outdoor or indoor exposure to cold) or asphyxia-related (i.e., submersion, avalanche with burial of the head under the snow) [9].

All variables mentioned above were considered as potential predictors in our model. The primary outcome parameter was survival to hospital discharge [16]. A secondary outcome was the neurological outcome at hospital discharge assessed by the Cerebral Performance Category (CPC) [16]. A CPC of 1 or 2 was considered as a "favorable neurological outcome" [17,18].

We termed the study design mixed, because we performed a literature search at first; and then, a data analysis complying as closely as possible with the PRISMA and TRIPOD guidelines (http://www.prisma-statement.org and https://www.tripod-statement.org); and finally, we also added unpublished patients. This study was registered in the PROSPERO registry (CRD42016052882).

Statistical analysis

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Univariate associations between predictors and survival were assessed using chi-square tests to compare proportions for the categorical predictors, and using a Mann-Whitney test, together with logistic regression including a quadratic term for the continuous predictors. P values <0.05 were considered as statistically significant.

In order to build our score, we started by considering a multiple logistic regression model to predict survival, which included the nine potential predictors (Additional file 2: Statistics**)**. Since our goal was to identify the best model for prediction, we used the Akaike Information Criterion (AIC) as a model selection criterion [19]. All p-values for the predictors included in the best model according to AIC should be < 0.157 [20]. Thus, at each step of a backward elimination procedure, the least significant predictor was removed and the procedure stopped when all the p-values associated with the remaining predictors in the model were < 0.157 [20]. Five of the nine predictors had a few missing values, which were imputed using a MICE algorithm (Multivariate Imputation by Chained Equations) implemented in the "MICE" package (version 2.25) [21] from the R statistical software program [22]; this generated m=100 imputed data sets after 50 iterations of the algorithm, where the eight remaining predictors and our response variable (survival) were all used circularly to impute the missing data for a given predictor. Therefore, each of our multiple logistic regression models were run 100 times (with the 100 different imputed data sets) while the results were aggregated using Rubin's rules [23]. Bootstrap method was used for internal validation (for details see eStatistics) [24].

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RESULTS

The literature search generated 1,881 publications. Eighteen studies were included, for a total of 237 patients. The hospital data collection resulted in 49 additional patients (Fig. 1, eTable 1 and eTable 2). Out of the 286 included patients, 106 survived and 180 died, resulting in an overall survival of 37% (95% CI: 32-43%), with a CPC of 1 or 2 for 84 (84%) of the 100 survivors for whom this information was available.

Univariate associations between the nine predictors and survival are summarized for both the categorical (Table 1) and the continuous predictors (Table 1, eFig. 1). The backward model selection procedure (eTable 3 and eStatistics) resulted in a final model including six predictors and eight parameters yielding the following score: **score=2.44** $\mathbf{-1.55\times male - 1.95\times(asphyxia\text{-}related\ mechanism) - 0.0191\times age - 2.07\times \log_2 potassium - 0.573\times \log_2(CPR\ duration) + 0.937\times temperature - 0.0247\times temperature^2}$**.** It should be noted that this score is expressed on the logit scale. The Hypothermia Outcome Prediction after ECLS (HOPE) survival probability score can then be simply obtained from the score by calculating: **HOPE survival probability=exp(score)/(1+exp(score))**. An example of a HOPE survival probability score is provided as a supplementary file (eExample). A dedicated calculator of the HOPE survival probability score, together with a 95% confidence interval, is available online at www.hypothermiascore.org.

The boxplots of HOPE survival probabilities estimated for our 286 patients are presented in Fig. 2. The area under the corresponding receiver operating characteristic curve (AUC) was 0.895 (95% CI: 0.859-0.931) compared to 0.774 (95% CI: 0.720-0.828) when based on serum potassium level alone. Using our internal validation procedure (Additional file 2: Statistics**)**, we estimated an excess of optimism of 0.029, such that our corrected estimation of AUC would be of 0.866. Of note, the year of data collection (p=0.665), and whether data had been published (p=0.514), were not statistically significant when added into our final analysis. Further, introducing the hospital as an additional factor in our final model did not improve the AIC (AIC=240.8 for our final model when averaged over the 100 imputed data sets), whether treated as a fixed effect (AIC=246.0) or as a random effect (AIC=242.3).

The sensitivities and specificities based on the traditional triage criteria and those estimated from our data are provided in Table 2. While the sensitivity of temperature or potassium criteria was high (99-100% for any criterion),

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the specificity was at most 23% (for potassium >8 mmol/L) and was only 8% (95% CI: 5-13%) for the commonly applied criterion potassium>12 mmol/L. These results were improved using the HOPE survival probability score, the specificity reaching 51% (95% CI: 45-60%) if using criterion HOPE<0.1 as a criterion for a poor prognosis (Table 2, Fig. 2). Calculated over the entire sample of patients and using the same cutoff of 0.1 for the HOPE criterion, the proportion of patients estimated to survive but who died (false positives) was 31% (95% CI: 25-36%) compared to 58% (95% CI: 52-63%) using potassium≤12 mmol/L as a rewarming criterion (Fig. 3). The proportion of patients estimated to die but who survived (false negatives) was estimated to be 0% (95% CI: 0-1.7% for HOPE, 0-1.4% for potassium) in both situations.

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DISCUSSION

As far as we are aware, our study is the largest to date that assesses outcome of hypothermic arrested patients with ECLS rewarming and the first to predict survival with ECLS in arrested patients using a multivariable model. Based on our results, the prediction of survival probability to hospital discharge was both statistically and clinically significantly improved if estimated with our score instead of a traditional dichotomous potassium-based triage decision. Our mixed method of retrospective data collection from different sources circumvented the major limitation of all studies reporting survival after hypothermic CA, namely their small sample size, ranging from case reports to case series with patient numbers in low double digits [3,13,31,32]. The prospective inclusion of sufficient patients for a study of this nature would take years, even if several international centers cooperated to conduct a multivariable analysis comparable to our study. With nearly 300 patients from different centers worldwide, which is to our knowledge the largest sample size by far for arrested hypothermic patients, our study allowed us to test for predictors potentially associated with survival, using an approach designed to minimize the risk of inclusion bias by including consecutive patients.

There are several key features to this study. First, we confirm the association of six independent predictors of survival that had proven controversial in previous studies: sex; asphyxia-related mechanism of CA; age; potassium level; CPR duration; and temperature [9,14,27,29,33,34]. On the other hand, the significant univariate association between CA (witnessed vs. unwitnessed), described in several recent studies [13,35,36], was not retained as a predictive variable once entered in our multivariable analysis.

A second key feature is that our results support a paradigm shift from a dichotomous potassium triage [1,6,7] to a more comprehensive decision-making tool for patients arrested due to accidental hypothermia. Hyperkaliemia has long been known to be associated with poor prognosis in severe hypothermia [5]. The dichotomous potassium approach was proposed in 1990, when a key study found that serum potassium levels on admission in non-survivors were extremely high (14.5 mmol/L; range, 6.8-24.5 mmol/L) compared to survivors (3.5 mmol/L; range, 2.7-5.3 mmol/L) [4]. The same year, another group of investigators proposed ECLS rewarming as a promising therapeutic tool to treat hypothermic arrested patients. Five of eleven patients who had received CPB rewarming survived with good neurological outcome [37].

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Subsequently, attempts have been made to refine the potassium triage in accidentally hypothermic CA patients, including hypothermic avalanche patients in CA [38]. Instead of using a specific cutoff, our model uses the prognostic information provided by particular potassium levels. In one scenario (Additional file 3: Example) a potassium of 3.5 mmol/L is associated with a probability of survival of nearly 70%. This decreases to 59% with a potassium of 4 mmol/L and to 30% with a potassium of 6mmol/L, all other parameters remaining equal. Thus, our score is in accordance with studies where normal or even low serum potassium levels are observed at the onset of hypothermia [39]. A normal or low potassium level may be a marker of a short duration of CA indicative of better prognosis, even if it is still associated with a 30% risk of death in our example. Also, hypothermic patients may present with hypokalemia owing to several pathophysiological mechanisms, such as temperature-induced reduction of physiological processes, intracellular shift of potassium due to change in pH or β2-adrenergic receptor stimulation, or finally a hypothermia-membrane-stabilizing effect [40,41]. If serum potassium level is a parameter influenced by several factors beside heart or brain cell death, it seems unwise to base a life-or-death decision on this parameter alone.

The third and most important key feature is that estimates of survival probability using our new score are more accurate than those based on the present serum potassium-based triage and may provide better guidance for decision-making. An accurate prediction of survival is important to avoid both over- or undertreatment. Based on anecdotal reports and expert opinions, clinicians who are not familiar with hypothermic arrest may not start ECLS rewarming as they may underestimate the true patient's survival probability. Their judgment may be miscalibrated if based on the dismal survival of out-of-hospital cardiac arrest of normothermic patients.

Avoiding undertreatment is especially important, because the neurological outcome of survivors are significantly better than the neurologic outcomes of patients who survived ECLS after normothermic cardiac arrest [17]. On the other side, use of our score instead of the potassium threshold over the entire sample would have reclassified 27% of patients, avoiding one in four futile ECLS rewarming attempts, without losing a single additional life. Our model helps to direct limited resources of financially strained health care systems to those patients with a better chance to benefit, especially when a reliable triage of multiple patients is necessary.

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Finally, this study provides a practical software tool, which enables an estimate of the survival chances of a person in hypothermic CA. This tool can be easily accessed via the internet as a web application, and allows a rapid assessment of survival chances. A more accurate estimate of prognosis may also improve informed discussion with relatives pertaining to the initiation and outcome of ECLS rewarming.

Limitations

Our study suffers from some limitations. The first is the potential of selection bias owing to the retrospective nature of the study. We were unable to analyze patients for whom the clinicians decided against ECLS rewarming for whatever reason, nor patients declared dead at the scene. This selection bias may have led to an overestimation of the survival rate. Also, not having all the deaths in our sample may have induced some bias in some of our estimates such as specificities, which would actually be underestimated if those deaths would have achieved a low HOPE score. However, the retrospective design was necessary because of the relative rarity of hypothermic patients in CA. We tried to minimize the risk of inclusion bias by including only consecutive patients. Another potential limitation is the heterogeneity of caseload and experience of the centers we included. However, the lack of statistical evidence for a "center effect" in this study suggests potential good external validity, although independent validation is still necessary. Because of the difficulties linked to the prospective collection of sufficient amount of data, external validation would be best performed by using existing consecutive cases not included in this derivation cohort. The fact that the HOPE score cannot be calculated with missing values may also be considered as a limitation. Finally, our literature search was based on a previously published systematic literature review [12] whose quality and methodology was assumed to be good.

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Conclusions

In this large retrospective study we found that our multivariable model was superior to dichotomous triage based on serum potassium level in predicting which hypothermic patients in cardiac arrest would benefit from extracorporeal life support. This might be useful to improve the decision-making process when considering the rewarming of a hypothermic arrested patient. External validation of our findings is required.

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CONFLICT OF INTEREST

None to declare. We, all of the authors, have no financial or personal relationships with other people or organisations that could have inappropriately influenced our work.

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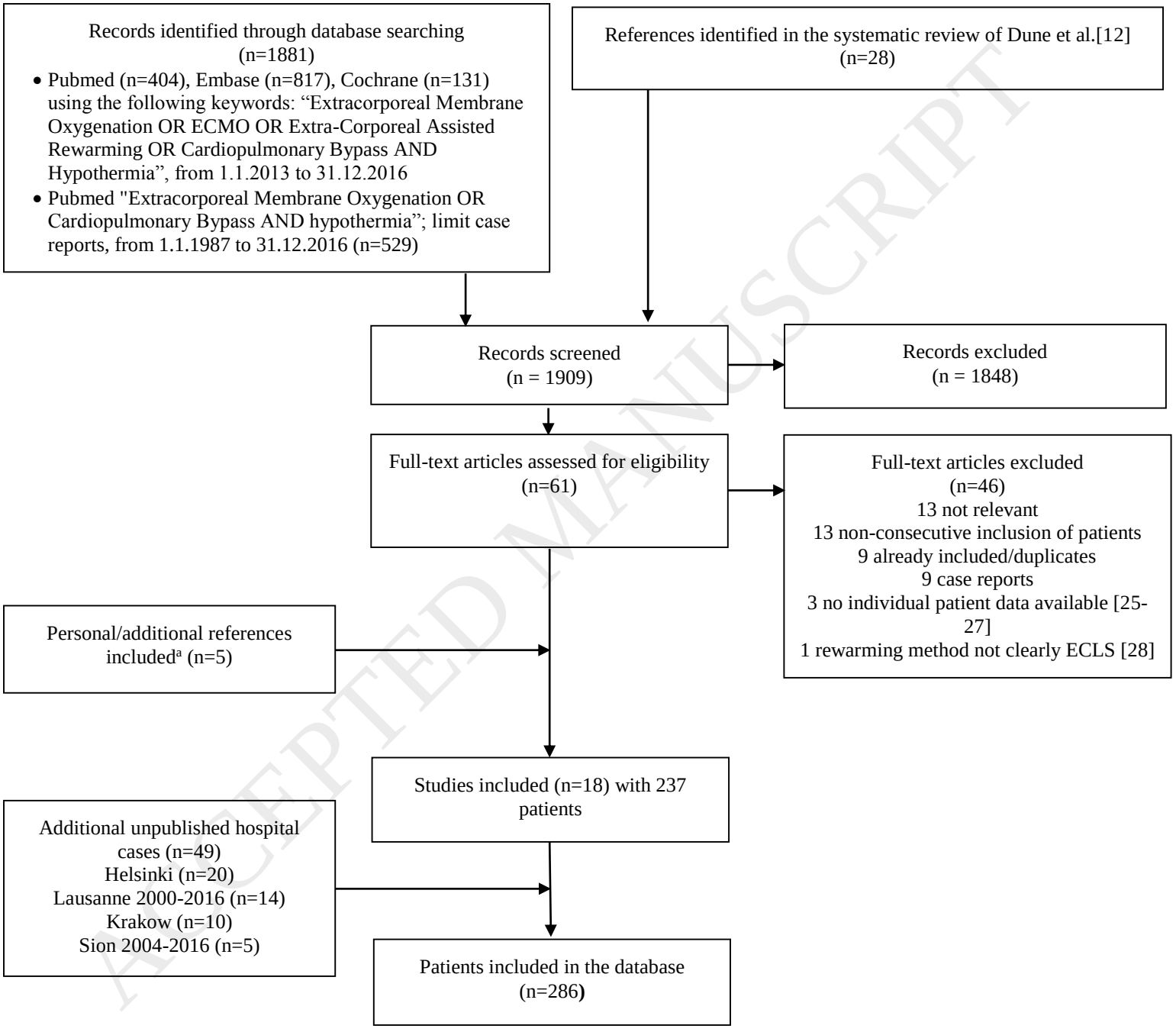
LEGENDS TO FIGURES.

Fig. 1 Flowchart of study patients



[a] Among these two were further excluded because there was no individual data available [14,29] while one was excluded because the rewarming method was not clearly Extracorporeal Life Support [30].ECLS=Extracorporeal Life Support.

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Fig. 2. Hypothermia Outcome Prediction after ECLS (HOPE) survival probabilities (left panel) and receiver operating characteristic curve of the survival probabilities estimated from our 286 patients using Hypothermia Outcome Prediction after ECLS (HOPE) model or potassium (right panel). AUC=area under the curve

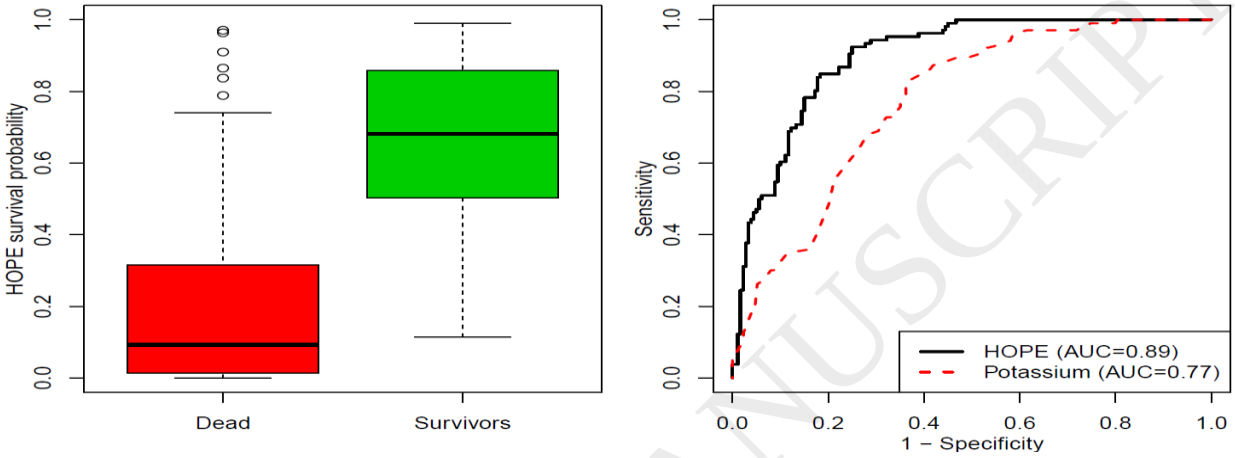
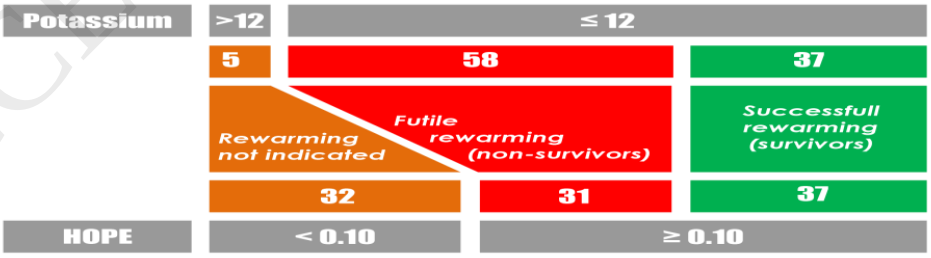


Fig. 3. Comparison of the outcome and proportion of patients for whom rewarming is indicated according to the HOPE vs potassium triage. In a situation where a phyisican would rewarm only those patients achieving a good prognosis, when facing 100 patients, 27 ECLS unsuccessful rewarming could be avoided without losing a single additional life using our score (with a cutoff at 0.10) rather than potassium alone (with a cutoff of 12 mmol/L) as a rewarming criterion



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Tables

Table 1 Univariate associations between potential predictors and survival. All predictors apart the rewarming method were significantly associated with survival

	Overall (n=286)	Survivors 106/286=37%	Non-survivors 180/286=63%	P value
Continuous potential predictors, median (IQR)				
Age (years)	35 (16-55)	40 (18-56)	29.5 (13-54)	0.035
Temperature (°C)	24 (22-27)	23 (21-25)	25 (22-28)	<0.001
Potassium (mmol/L)	4.7 (3.6-6.6)	3.8 (3.1-4.65)	5.8 (4.0-8.0)	<0.001
CPR duration (min)	120 (85-169)	106 (64-165)	120 (90-169)	0.013
Categorical potential predictors, n (%)				
Gender				p<0.001
Female	71/286=25%	43/71=61%	28/71=39%	
Male	215/286=75%	63/215=29%	152/215=71%	
Mechanism				p<0.001
Exposure	98/283=35%	56/98=57%	42/98=43%	
Immersion	40/283=14%	24/40=60%	16/40=40%	
Submersion	94/283=33%	18/94=19%	76/94=81%	
Avalanche	51/283=18%	6/51=12%	45/51=88%	
Cardiac rhythm				p<0.001
Asystole	139/256=54%	32/139=23%	107/139=77%	
Ventricular fibrillation	91/256=36%	49/91=54%	42/91=46%	
PEA	26/256=10%	18/26=69%	8/26=31%	
CA Circumstance				p<0.001
Unwitnessed CA	165/250=66%	44/165=27%	121/165=73%	
Witnessed CA	85/250=34%	48/85=56%	37/85=44%	
Type of ECLS				P=0.228

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CPB	201/286=70%	70/201=35%	131/201=65%	
ECMO	85/286=30%	36/85=42%	49/85=58%	

There were 9 missing values (3 for the survivors, 6 for the dead) for the potassium and 16 for CPR duration (5 for the survivors, 11 for the dead). CA denotes Cardiac Arrest, CPB Cardiopulmonary Bypass, CPR Cardiopulmonary Resuscitation, ECLS Extracorporeal Life Support ECMO Extracorporeal Membrane Oxygenation, PEA Pulseless Electrical Activity

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Table 2 Estimated sensitivity and specificity based on different criteria. HOPE denotes Hypothermia Outcome Prediction after ECLS

Criterion (good outcome)[a]	**Sensitivity[b]**	**Specificity[c]**	**PPV[d]**	**NPV[e]**	**FP[f]**	**FN[f]**
Potassium ≤12 mmol/L	103/103=100%	14/174=8%	39	100	58	0.0
Potassium ≤8 mmol/L	102/103=99%	40/174=23%	43	98	48	0.4
HOPE ≥0.05	106/106=100%	69/180=38%	49	100	39	0.0
HOPE ≥0.10	106/106=100%	92/180=51%	55	100	31	0.0
HOPE ≥0.20	101/106=95%	115/180=64%	61	96	23	1.7
HOPE ≥0.30	98/106 =92%	130/180=72%	66	94	17	2.8
HOPE ≥0.40	90/106=85%	147/180=82%	73	90	12	5.6
HOPE ≥0.50	81/106=76%	153/180=85%	75	86	9	8.7

[a] Nine values were missing for potassium. [b] The sensitivity is defined as the probability that the criterion is fullfilled among the survivors. [c] The specificity is defined as the probability that the criterion is not fullfilled among the non-survivors. [d] The Positive Predictive Value is defined as the proportion of patients who survive among those fulfilling the criterion. [e] The Negative Predictive Value is defined as the proportion of patients who dies among those not fulfilling the criterion. [f] FP denote the percentage of false positive and FN the percentage of false negative (calculated over all the patients, whether positive or negative).