Short paper

Clinician miscalibration of survival estimate in hypothermic cardiac arrest: HOPE-estimated survival probabilities in extreme cases

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Abstract

Aim: Patients with hypothermic cardiac arrest may survive with an excellent outcome after extracorporeal life support rewarming (ECLSR). The HOPE (Hypothermia Outcome Prediction after ECLS) score is recommended to guide the in-hospital decision on whether or not to initiate ECLSR in patients in cardiac arrest following accidental hypothermia. We aimed to assess the HOPE-estimated survival probabilities for a set of survivors of hypothermic cardiac arrest who had extreme values for the variables included in the HOPE score.

Methods: Survivors were identified and selected through a systematic literature review including case reports. We calculated the HOPE score for each patient who presented extraordinary clinical parameters.

Results: We identified 12 such survivors. The HOPE-estimated survival probability was ≥10% for all (n = 11) patients for whom we were able to calculate the HOPE score.

Conclusion: Our study confirms the robustness of the HOPE score for outliers and thus further confirms its external validity. These cases also confirm that hypothermic cardiac arrest is a fundamentally different entity than normothermic cardiac arrest. Using HOPE for extreme cases may support the proper calibration of a clinician's prognosis and therapeutic decision based on the survival chances of patients with accidental hypothermic cardiac arrest.

Keywords: Hypothermia, Cardiac arrest, Extracorporeal life support rewarming, Triage

Introduction

Patients with hypothermic cardiac arrest (CA) may survive with an excellent outcome after extracorporeal life support rewarming (ECLSR).[1] The Hypothermia Outcome Prediction after ECLS (HOPE) score is a specific prognostic tool developed to guide the in-hospital decision on whether or not to initiate ECLSR in patients in CA following accidental hypothermia.[2] This calculator underwent external validation, which confirmed its excellent discrimination and good calibration.[3]

To minimise the publication bias, researchers who reported HOPE score derivation and validation studies included consecutive ECLS

patients from retrospective cohort studies or hospital data over one specific period.[2,3] We hypothesised that the HOPE score would also work well for outliers and would thus further confirm its external validity.

Methods

A systematic literature review was conducted. We included survivors of CA secondary to accidental hypothermia with extreme values of variables included in the HOPE score. We considered the most extreme accidental hypothermia cases found in the literature and not included in HOPE score development and validation studies.[2,3]

Search strategy

The literature search covered an unlimited period to 1 January 2021. Pubmed, Embase, and Cochrane databases were explored using the following keywords: "Extracorporeal Life Support" OR "ECLS" OR "Extracorporeal Circulation" OR "Extracorporeal Membrane Oxygenation" OR "ECMO" OR "Cardiopulmonary Bypass" OR "CPB" OR "Heart-Lung Machine" AND "accidental hypothermia" OR "rewarming" OR "hypothermic cardiac arrest".

Studies were also sought by reviewing the bibliographies of included studies and those known to the researchers of the present study. We limited the search to studies in the English language. At stage 1, two reviewers (TD and PP) ruled out clearly irrelevant titles and abstracts and screened the remaining titles and abstracts. At stage 2, full papers categorised as potentially eligible for inclusion were screened by a consensus meeting of two reviewers (TD and SK) and disagreements were resolved in real time by consensus.

Data analysis

Data were extracted using a standardised data extraction form. The six variables of the HOPE score were collected for each patient: age, sex, mechanism of hypothermia (asphyxia-related or not), core temperature on admission, first serum potassium level at hospital, and duration of cardiopulmonary resuscitation (CPR).[2] We aimed to determine the HOPE survival probability for each survivor.[2] In case of missing data for potassium, we calculated the highest potassium value that the patient would have in order to have a HOPE-estimated survival probability of 10%. A HOPE survival probability of $\geq$10% was considered indicative of adequate performance of HOPE in detecting and qualifying patients for ECLSR.

The collection of the data arising from the HOPE study was approved by the institutional review board (No. 2016−01267).[2]
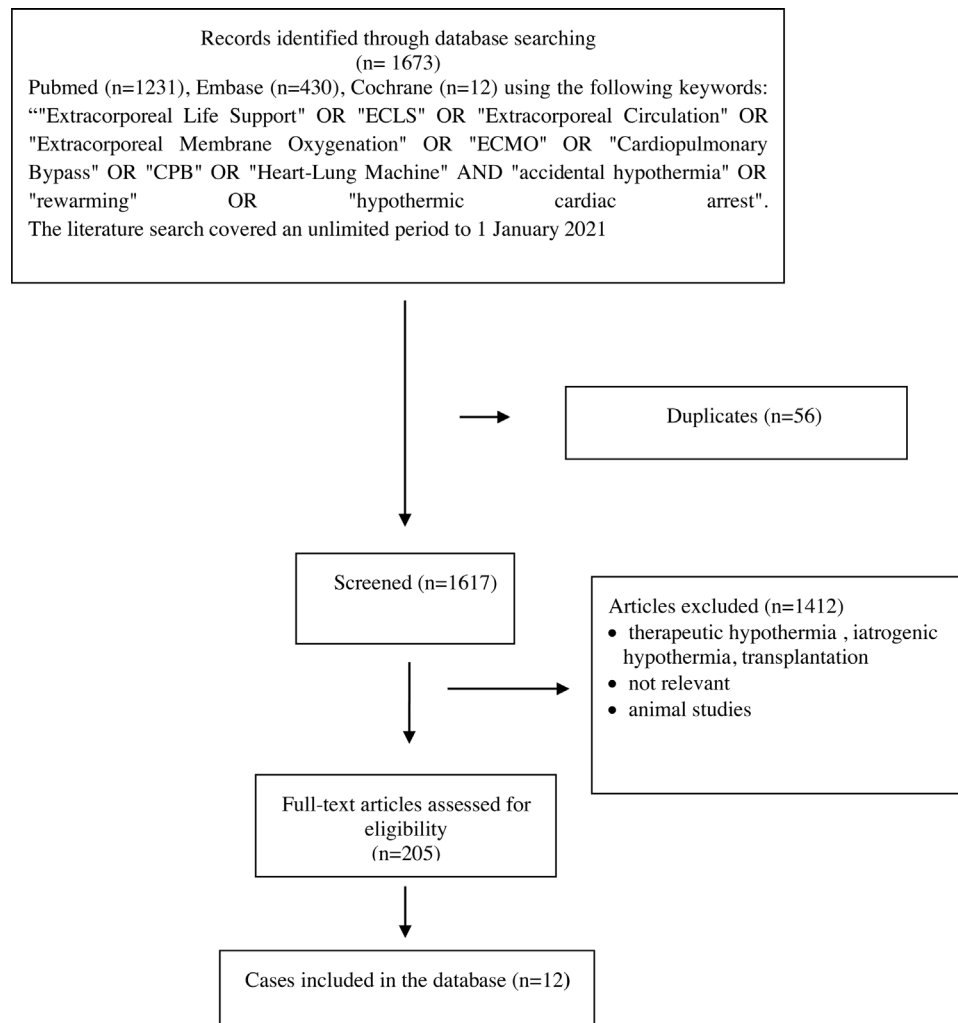
Fig. 1 – Flowchart of study patients.

Results

The literature search generated 1617 publications (Fig. 1). We identified 12 survivors of hypothermic CA who presented with extreme values included in the HOPE score. The neurological outcome was favourable for all 12 cases for whom this information was available. We were able to calculate the HOPE survival probabilities in 11 patients. The HOPE-estimated survival probability was ≥10% for all 11 patients Table 1.

The characteristics of the six independent survival predictors from HOPE in the survivors from the HOPE derivation and validation studies, who had the most extreme values of the HOPE continuous variables are presented in Table 2.

Discussion

The HOPE score was designed for in-hospital decision-making for the initiation of ECLSR. A cut-off of ≥10% was chosen to initiate ECLSR. This cut-off was evaluated in an external validation study, which included consecutive cases, in order to avoid selection bias.[3] The negative predictive value of a HOPE score of <10% was 97%, and the area under the receiver operating characteristic curve was of 0.8250, suggesting excellent discrimination.[3] Appropriate prognostication is important not only because patients may have an excellent outcome

after ECLSR, but also because of the burdens and costs of ECLSR.[1] The present study shows that using the 10% cut-off would have accurately detected and qualified for ECLSR those patients who presented with extreme values of the variables included in the HOPE score and who survived. Our findings confirm the robustness of the HOPE estimation of the survival probability in hypothermic CA. This finding deserves attention and discussion, notably regarding the very different extracorporeal CPR (ECPR) criteria for normothermic vs. hypothermic patients with refractory CA.

An age of >70 years usually contraindicates ECPR for normothermic refractory CA.[15,16] Despite the poorer outcome associated with increasing age,[2] older patients with hypothermic CA may nonetheless survive with a good outcome. In a recent case report, a 95-year-old man not only survived a hypothermic CA treated with ECPR, but he had no neurological sequalae.[13] His estimated probability of survival by HOPE was 36%. Age itself should therefore not be listed as an absolute contraindication to ECLSR in hypothermia but has to be interpreted within the whole clinical context, as well as for the expected survival probability according to HOPE.

Using the HOPE survival probability would also have correctly indicated ECLSR for the patient in hypothermic CA who survived with the lowest (12.6°C) core temperature at hospital admission.[9] His HOPE-estimated survival probability was 50%.

The univariate association between core temperature and survival was not linear in the HOPE derivation study, with lower estimated survival probabilities for both very low and very high temperatures.[2]

Table 1 – The HOPE survival probabilities of the survivors from most extreme accidental hypothermia cases with cardiac arrest.

No.	Record type	Sex	Age [years]	Asphyxia	Core T° C	Potassium [mmol/L]	CPR duration [min]	HOPE survival probability [%]	CPC[a]
	CPR duration								
1	307 min including 25 min intermittent[4]	F	57	No	16.9	5.8	307	54	1−2
2	288 min[5]	F	65	No	20.8	2.8	288	90	1−2
3	273 min[6]	M	41	No	25	5.9	273	14	1
4	222 min[7]	M	31	No	26.1	4.8	222	23	1
	Lowest survived core temperature								
5	Adult[8]	F	29	No	14.4[b]	4.3	131	87	1−2
6	Child[9]	M	2	No	12.6[c]	4.9	127	50	1
	Highest potassium								
7	Adult[10]	M	38	No	26.7	9.0	NA	NA (10% threshold would be reached with a CPR duration of 51 min)	1−2
8	Child[11]	F	2.6	No	14.2	11.8	120	35	1
9	Child[12]	F	7	Yes	13.8	11.3	64	11	1
	Age								
10	95 years old[13]	M	95	No	22.9	5.5	41	36	1
	Hypothermia with asphyxia								
11	Submersion 83 min[12] − (same case as no. 9)	F	7	Yes	13.8	11.3	64	11	1
12	Submersion 66 min[14]	F	2	Yes	22.4	"normal"	190	55[d]	1−2

Abbreviations
CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; F=female; M=male; NA=not available.
[a] CPC was considered to be 1 if it returned to baseline status.
[b] 14.4°C at admission to the operating room, and then 13.7°C rectal temperature 5 min after cardiopulmonary bypass.
[c] 12.6°C at admission to the operating room, and then 11.8°C rectal temperature 10 min after ECMO.
[d] Potassium level presumed to be 4.5 (described as "normal") to calculate the HOPE survival probabilities.

Table 2 – The HOPE survival probabilities of survivors from the most extreme accidental hypothermia cases with cardiac arrest in the HOPE derivation and validation studies.[2,3]

Record type	Sex	Age [years]	Asphyxia	Core T °C	Potassium [mmol/L]	CPR duration [min]	HOPE survival probability [%]	CPC[a]
Age								
Younger (male)	M	1.5	Yes	20.7	4.3	150	32	1
Younger (female)	F	2	Yes	28	2.6	117	63	1
Older (male)	M	86	NA	24	4.9	120	NA	4
Older (female)	F	73	No	26.1	3.2	20	94	1
Temperature								
Lowest (male)	M	15	No	16	4	178	70	3
Lowest (female)	F	16	No	15.5	4	241	89	1
Highest (male)	M	28	No	30.3	2.8	59	41	2
Highest (female, case no. 1)	F	2	Yes	28	2.6	117	63	1
Highest (female, case no. 2)	F	54	No	28	4.90	295	24	1
Potassium level								
Lowest (male)	M	51	No	23	2.1	150	89	2
Lowest (female)	F	38	No	25.4	2	107	97	1
Highest (male)	M	63	No	22.5	8.6	105	12	1
Highest (female)	F	34.4	No	20.4	7.9	90	68	1
CPR duration								
Longest (male)	M	41	No	26.1	5.5	300	11	3
Longest (female)	F	25	No	16.9	4.3	345	83	1

Abbreviations

CPC: cerebral performance category; CPR: cardiopulmonary resuscitation; F=female; M=male; NA=not available.

[a] CPC was considered to be 1 if it returned to baseline status.

The typical core temperature at which hypothermic CA occurs is 24 °C.[17] There is to date no established temperature cut-off below which ECLSR would be contraindicated.

Using the potassium value as a single criterion for ECLSR may be hazardous, however, because of the risk of preanalytical errors (e.g. haemolysis), as well as the clinically relevant variability in potassium values between sampling sites, even in controlled conditions.[18] The use of a multivariable decision tool such as HOPE mitigates the risk that a single variable prone to measurement errors will disqualify a patient from a life-saving procedure such as ECLSR.[3]

An important exclusion criterion for ECPR in normothermic refractory cardiac arrest is the prolonged low flow time, a duration of more than 60−80 min being the threshold that usually contraidicates ECPR.[16] The CPR duration was also an independent predictor of poor outcome in the HOPE derivation study.[2] However, the median CPR duration was twice as long for survivors in the HOPE study than it was for normothermic CA (106 vs. 42 min), and survival has been reported despite prolonged CPR durations.[2,15] Unlike the case in normothermic CA, there is currently no low-flow time limit that contraindicates ECLSR in patients with hypothermic CA.

In some circumstances, it may be very difficult to categorize the victim as asphyxiated or not. In avalanche accidents, the patency of airway which are free of snow is usually used as a sign of non-asphyxia-related cardiac arrest. Drownings in an icy water are much more difficult to analyse because some patients may became severely hypothermic when floating with their airway above water surface. If they submerge due to the loss of consciousness or hypothermic cardiac arrest, their prognosis is quite good when compared to "warm" asphyxia.[1,8] The detailed anamnesis pertaining to accident settings may help clinicians to properly qualify such patients.

Beyond the confirmation of the robustness of the HOPE-based survival prognostication, our findings also confirm that hypothermic CA is a fundamentally different entity than normothermic CA. The survival of patients with extreme characteristics shows that in all cases analysed, the decision to initiate ECPR on the basis of clinical data was appropriate. However, publication bias is likely: the publication of these extreme cases relies first on the perception that they are extraordinary, and second on their positive outcome. Are these values truly extraordinary, or do they simply reflect clinicians' perception that they are extraordinary? This question is difficult to answer, as cases with similar extreme values may not have been published, either because of a fatal outcome despite ECLSR or because of withheld ECLSR. Such publication bias should be considered as a potential limitation of our findings.

From our results, we hypothesise that there may be a miscalibration in the prognostication of survival by clinicians in the specific case of hypothermic CA. Proper prognostic calibration is built on experience and defined by the observation of certain signals (signs and symptoms) and an outcome.[19] Clinicians have much more experience with normothermic than hypothermic CA, and for the former, factors such as an unwitnessed CA, duration of CPR, age, asystole as the initial rhythm, and dilated and fixed pupils are predictors of a poor prognosis, whereas they do not contraindicate ECLSR in hypothermic CA.[1] Prognostic miscalibration is further reinforced because withholding ECLSR leads to death—a self-fulfilling prophecy. The objective estimation of the survival probabilities provided by HOPE may help recalibrate clinical judgement. The overall survival rates of patients with hypothermic CA who received ECLSR in the HOPE derivation and validation studies were 37% and 42%, respectively, most with a favourable neurological outcome, as in the present study.[2,3] The survival rate after ECPR for out-of-hospital CA in normothermia is much lower.[16,20] The better survival rate in hypothermic CA is reassuring, but may also be the consequence of under-triage.

Conclusion

Our study confirms the robustness of the HOPE score for extreme cases and may support the proper calibration of a clinician's prognosis and therapeutic decision based on the survival chances of patients with CA from accidental hypothermia. This is especially important, as some evidence suggests that the clinician's estimation of survival for patients with hypothermic CA may be miscalibrated, with potential underestimation of the survival chances of these patients.

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Conflicts of interest

None.

CRediT authorship contribution statement

Tomasz Darocha: Conceptualization, Methodology, Formal analysis, Writing - original draft, Systematic review, Project administration. **Olivier Hugli:** Methodology, Formal analysis, Systematic review, Validation, Writing - review & editing. **Sylweriusz Kosiński:** Methodology, Formal analysis, Systematic review, Validation, Writing - review & editing. **Paweł Podsiadło:** Methodology, Formal analysis, Systematic review, Validation, Writing - review & editing. **David Caillet-Bois:** Methodology, Formal analysis, Systematic review, Validation, Writing - review & editing. **Mathieu Pasquier:** Methodology, Writing - review & editing, Supervision.

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