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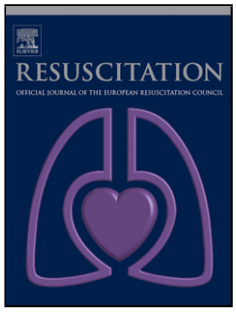

Title: Hypothermia outcome prediction after extracorporeal life support for hypothermic cardiac arrest patients: An external validation of the HOPE score

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Original Paper

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

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ABSTRACT

Aims: The HOPE score, based on covariates available at hospital admission, predicts the probability of in-hospital survival after extracorporeal life support (ECLS) rewarming of a given hypothermic cardiac arrest patient with accidental hypothermia. Our goal was to externally validate the HOPE score.

Methods: We included consecutive hypothermic arrested patients who underwent rewarming with ECLS. The sample comprised 122 patients. The six independent predictors of survival included in the HOPE score were collected for each patient: age, sex, mechanism of hypothermia, core temperature at admission, serum

potassium level at admission and duration of CPR. The primary outcome parameter was survival to hospital discharge.

Results: Overall, 51 of the 122 included patients survived, resulting in an empirical (global) probability of survival of 42% (95% CI=[33-51%]). This was close to the average HOPE survival probability of 38% calculated for patients from the validation cohort, while the Hosmer-Lemeshow test comparing empirical and HOPE (i.e. estimated) probabilities of survival was not significant (p=0.08), suggesting good calibration. The corresponding area under the receiver operating characteristic curve was 0.825 (95% CI=[0.753-0.897]), confirming the excellent discrimination of the model. The negative predictive value of a HOPE score cut-off of <0.10 was excellent (97%).

Conclusions: This study provides the first external validation of the HOPE score reaching good calibration and excellent discrimination. Clinically, the prediction of the HOPE score remains accurate in the validation sample. The HOPE score may replace serum potassium in the future as the triage tool when considering ECLS rewarming of a hypothermic cardiac arrest victim.

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

INTRODUCTION

Hypothermia is one of the reversible causes of cardiac arrest (CA).[1, 2] Patients who are successfully resuscitated with extracorporeal life support (ECLS) rewarming often have an excellent neurological outcome.[3] We previously developed a new score (Hypothermia Outcome Prediction after ECLS- HOPE) to better predict the probability of in-hospital survival of a given CA patient with accidental hypothermia after ECLS, based on covariates available at hospital admission.[4] The HOPE score was derived from a retrospective cohort of 286 patients using a multiple logistic regression model.[4] The score uses six variables available at hospital admission to predict survival with ECLS rewarming in hypothermic CA patients: age, sex, presence of asphyxia, potassium, cardio-pulmonary resuscitation (CPR) duration and temperature (online calculator at: www.hypothermiascore.org).[4] In this large retrospective study we found that the HOPE score was superior to the historical dichotomous triage based on serum potassium level in assessing which hypothermic patients

in CA would benefit from ECLS.[4] As our model has not been validated on an independent external data set, our aim was to externally validate the HOPE score.

METHODS

Study population

We included hypothermic CA victims who underwent rewarming with ECLS. Only consecutive ECLS patients from retrospective cohort studies or hospital data in one determined time frame were included. We excluded patients who were not in CA when ECLS was started and those for whom no individual data were available. Patients were identified and selected through a literature review and unpublished hospital data were added. First, the authors of the publications of potentially eligible studies identified by our original systematic review[4] not included in the original publication were asked to participate in the validation cohort.[5-9] Then we updated the research of the original article[4] by exploring Pubmed, Embase, and Cochrane from January 1st 2017 to August 1st 2018 using the following keywords: "Extracorporeal Membrane Oxygenation OR ECMO OR Extra-Corporeal Assisted Rewarming OR Cardiopulmonary Bypass AND Hypothermia". The last search was performed on August 1st 2018. In a case series with aggregated data, we contacted authors of the publications via e-mail to have access to individual data. We excluded cases used in the derivation cohort. Finally, retrospective unpublished data from additional hospitals were added (Bern, Poland, Grenoble). The data collection was approved by the institutional review board (N°2018-00779).

The six independent predictors of survival included in the HOPE score[4] were collected for each patient: age, sex, mechanism of hypothermia, core temperature at admission (if not available, the prehospital temperature was used), serum potassium level at admission, and duration of CPR (defined as the time elapsed from initiation of external CPR to the start of ECLS). 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 (e.g. submersion, avalanche with burial of the head under the snow).[10] Neurological outcome at hospital discharge was assessed for the survivors by the cerebral performance category (CPC) [11]. A CPC of 1 or 2 was considered as a "favourable neurological outcome" [12, 13]. As in the original study, the primary outcome parameter was survival to hospital discharge.

Statistical analysis

We assessed the validity of the HOPE score by calculating this score for the new patients who did not participate in the original (or derivation) study where the corresponding model was developed. The external validity of the HOPE model was assessed following a methodological framework close to that proposed in Debray et al.[14] We first compared the validation cohort with the derivation cohort to evaluate their case-mix differences. To summarize these differences, we fitted a logistic regression model to predict cohort membership (validation vs derivation) using individual data on survival and its six predictors above, and calculated the area under the corresponding ROC curve (AUC). A value close to 0.5 indicates similar case-mix, while higher values indicate different case-mix. In addition, we compared the means and the standard deviations of the HOPE scores (calculated according to the equation above) in both cohorts. In case of good discrimination and good calibration, a model is then said to be "reproducible" in case of a similar case-mix and "transportable" in case of a different case-mix, although no clear-cut criterion is available to decide what means similar and what means different.

Discrimination was assessed using the AUC criterion[15] to discriminate survivors from non-survivors based on the HOPE score in the validation cohort. Calibration of the model was assessed by comparing empirical and estimated probabilities of survival via a Hosmer-Lemeshow test.[16] In addition, a logistic regression model to predict survival using the HOPE score was fitted, where we could test whether the intercept was significantly different from zero and the slope significantly different from one.

The missing values for predictors used in the HOPE score were handled through multiple imputations using a multivariate imputation by chained equations (MICE) algorithm.[17] We used m=100 imputed data sets and 50 iterations of the algorithm such that the scores obtained were ultimately averaged over the m=100 imputed data sets. The mice package (version 2.25) from the R statistical software was used.[17] Analyses were performed using the statistical software R, version 3.1.2 (R Foundation for Statistical Computing). P values <0.05 were considered as statistically significant. We followed the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines (https://www.tripod-statement.org).[18]

RESULTS

The research strategy allowed the collection of 122 new patients to enter the validation cohort (**Figure 1, eTable 1**). Patient's characteristics in the derivation (n=286) and the validation (n=122) cohort are presented in **Table 1**. The validation cohort was older compared to the derivation cohort (median of 50 vs 35 years, respectively; p<0.001) with less asphyxia-linked CA mechanism (38% vs 51%, respectively; p=0.01). When predicting the cohort membership (validation vs derivation) using the characteristics summarized in **Table 1** (including survival), only the age remained significant (p<0.001). The AUC of the corresponding ROC curve (also known as c-statistic) summarizing case-mix differences between the two cohorts was 0.646 (95%CI: 0.592-0.699). Nineteen out of the 122 patients had one or two missing value(s) in some predictor(s) used to calculate the HOPE score: 8 for duration, 6 for potassium, 5 for mechanism and 1 for age. A total of 51 patients out of the 122 survived, resulting in an empirical (global) probability of survival of 42% (95%CI: 33-51%). The CPC was ≤2 for 37 of the 49 (76%) survivors for whom this information was available.

The HOPE survival probabilities calculated for the patients from this validation cohort ranged from 0 to 94%, averaging 38%, close to the empirical 42% above and compatible with a good calibration. The HOPE scores calculated in the validation cohort compared to the derivation cohort differed neither with respect to the mean (-1.02 vs -1.24, respectively; p=0.43) nor with respect to the standard deviation (2.27 vs 2.62, respectively; p=0.06). Boxplots of HOPE survival probabilities for the survivors and non-survivors from the validation cohort are presented in **Figure 2**, together with the corresponding ROC curve. The AUC for this ROC curve was 0.825 (95%CI:0.753-0.897), which was compatible with the estimated AUC corrected for the excess of optimism of 0.866 previously published from the derivation cohort,[4] providing therefore a similar good discrimination of the HOPE model.

Figure 3 shows the empirical vs the averaged HOPE probabilities of survival for 10 groups of 12 or 13 patients with similar values of HOPE survival probabilities. The close cropping along the identity line suggests that the model is well calibrated. The only exception was the fourth group, where 6 patients died and 6 patients survived, resulting in an empirical probability of survival of 6/12 (50%), whereas the average of the HOPE probabilities was only 16% in this group. In line with these results, in a logistic regression model to predict survival using the HOPE score, the intercept was not different from 0 (p=0.45) and the slope was not different

from one (p=0.09), indicating again a good calibration of the HOPE model. We also refitted the logistic regression model to the new 122 patients. Each predictor included in the original model had the same signs for the coefficients, and a similar magnitude, apart for gender. The Spearman correlation between the HOPE score and the refitted score for the new patients (n=122) was high (0.92).

The sensitivities, specificities, positive and negative predictive values (PPV and NPV, respectively), as well as the percentage of false positive and negative (FP and FN, respectively) obtained when using a HOPE survival probability ≥0.10 to predict survival are provided in **Table 2.** These were all similar in the patients from the derivation and validation cohort despite the fact that we had one false erroneous prediction of non survival in the validation, but none in the derivation cohort.

DISCUSSION

This study provides the first external validation of the HOPE score. Our new sample of 122 patients included 46% of cases from three new hospitals, collected over different periods. As such, we provide a geographical and temporal validation.[22] Our study confirms the good calibration and excellent discrimination of the score. The validation AUC at 0. 825 was slightly lower than the derivation AUC at 0.866; however, the original AUC was still within the validation of 95% CI interval (upper limit of 0.897). The validation AUC was also greater than 0.8 which is suggested as a cut-off providing excellent discrimination.[16] The calibration was also good, with a mean observed survival probability only 3.7% higher than predicted. One of the group of 12 hypothermic patients with similar values of HOPE survival probabilities had a higher survival of 50% for a prediction of 16%. This difference, although large, is neither statistically (via the Hosmer-Lemeshow test) nor clinically relevant (since the group had a predicted survival greater than 0.1, the threshold above which ECLS rewarming is recommended). Interestingly, the neurological outcome was favorable in only 2 of the 6 survivors of this group (40%), which was less than the proportion of favorable neurological outcome in the other groups (35 out of/43, 81%; p=0.026). Finally, the Spearman correlation between the calculated scores via the derivation equation and the refitted equation of the logistic regression model to the new 122 patients was 0.92, illustrating the closeness of the calculated and refitted scores. This high correlation suggests that one would get a similar score by fitting the original HOPE score to another sample of similar patients.

Clinically, the prediction of the HOPE score remains accurate in the validation sample. Specifically, the negative predictive value (NPV) of a HOPE score cut-off of <0.10 was excellent (97%). This is especially important in the situation of hypothermic CA patients for whom under-treatment (i.e. denying access to ECLS rewarming to a patient with potential for survival) would signify the death of the patient. The initial HOPE score had a NPV of 100%. This 3% difference is the consequence of the survival of one out of 35 patients with a HOPE score <10%. This patient was a 7 years-old boy submerged in a river who survived to hospital discharge with a CPC of 1. His HOPE survival probability was 4% (potassium 6.6 mmol/L, core temperature 27.5°C and CPR duration 71 minutes), which is below the HOPE suggested cut-off of 10%. Young children have been noticed to survive cold water submersion with hypoxia and rapid cooling, as they may rapidly become hypothermic prior to hypoxia and to have potential for neurologically intact survival after submersion.[23-28] Given this case, clinicians should exercise caution when using the HOPE score with the proposed threshold of 10% to predict children outcome. Besides this single false-negative case, the lowest HOPE score values of the survivors were 11, 13, 16 and 19%.

Methodologically, we have also assessed external validation following guidelines suggested by Debray et al.[14] As we achieved a similar discrimination and good calibration with a case-mix that was not significantly different in the validation and derivation samples except for age, this validation study suggests that the HOPE score is reproducible more than transportable. It should therefore be used in similar patients until additional validations assess its transportability in a more diverse population.

The use of the HOPE score may have several important clinical implications. The first is that using the HOPE score with the proposed cutoff of 10% instead of the serum potassium would prevent many futile ECLS rewarming attempts.[4] Combining our derivation and validation studies, 109 (27%) patients would not have been subjected to futile ECLS if this therapeutic decision had been based on HOPE with the proposed cutoff of 10% instead of a serum potassium ≤12 mmol/L. Reducing futile care is an important goal in emergency medicine, and the HOPE score provides a survival prognosis that may help physicians or relatives to decide on the better course of action.[29] Of note, one is of course free to use a different cut-off than the proposed threshold of 10% for different subgroups of the population (e.g. for children). This is actually the interest of having a survival probability rather than just a 0/1 decision which allows to apply a differential decision for

different subgroups of the population. The HOPE score may also help in the triage decisions if more victims than available ECLS are present at a given hospital, or if transporting a victim to an ECLS-able hospital would be logistically very challenging or risky for emergency medical services personnel. Another beneficial consequence of an accurate survival prediction score may be to prompt clinicians to initiate ECLS rewarming. The provision of a reliable estimate of the survival probabilities to hospital discharge is an essential piece of information that physicians need when they consider ECLS as a treatment option. Based on our experience, many emergency physicians are not familiar with the management of accidental hypothermia. They may underestimate the good overall survival, and specifically the potential for good neurological outcome of hypothermic CA patients compared to normothermic CA patients.[12, 30] Consideration of neurological outcome has emerged as a key patient-centred outcome that must weigh heavily in the resuscitation decision.[31] Failure to provide a life-saving intervention is not an option, especially given the excellent potential neurological outcome: 76% in the present study and 84% in the derivation sample.[4]

The better prognostic performance of the HOPE score compared to potassium alone is not its only advantage in clinical practice. The HOPE score uses six different variables independently predicting survival instead of one single biological parameter (e.g. serum potassium). The use of potassium as a triage criterion is not only based on little evidence from older studies,[32, 33] but its dosage may not always be accurate.[34] False-positive elevations due to numerous underlying medical conditions, including medications may leads to an inaccurate prognosis and a deadly therapeutic abstention.[35] The use of a multivariable score may therefore mitigate this risk. The multivariable HOPE score helps to avoid futile ECLS rewarming attempts. The validity of serum potassium for clinical decision-making may be considered limited, and may need revision.[24]

Limitations

Our study suffers from some limitations. The first is the potential of selection bias owing to the retrospective study design. Published cases may arise from centers with specific characteristics (notably high volumes) and outcome and therefore not represent the reality of other settings. It is in fact the essence of ECLS to be available in large centers. A significant proportion of cases were also unpublished, and came from hospital registries. Moreover, the inclusion of consecutive cases was intended to lower this bias. Finally, no “center effect” was found in the derivation study study.[4] Albeit prospective validation would have been the ideal

design, the retrospective design was justified by the paucity of hypothermic CA patients, as acknowledged by other experts in this domain.[23] Furthermore, the prospective inclusion of a sufficient number of patients for a validation study would take several years. The development of an international high quality registry collecting data of hypothermic CA patients would however be welcome. Specifically, the prospective collection of decisional criteria used to initiate or to forego ECLS and patient outcome would be key to be able to compare which prediction scores, if any, are used, if the HOPE score may have missed important determinants of the decision-making process, and most of all, which has the best predictive characteristics. Another limitation is development and validation of the score by the same research group. This situation, however, is relatively frequent in the quarter of published prediction models that undergo external validation.[36] Furthermore, both the development[4] and the current validation studies have included cases from many different centers. Finally, given the relatively low proportion of avalanche victims in the current validation study, it would be wise to use the HOPE score cautiously in this specific group of patients.

CONCLUSIONS

This study provides the first external validation of the HOPE score reaching good calibration and excellent discrimination. Clinically, the prediction of the HOPE score remains accurate in the validation sample. The HOPE score may replace serum potassium in the future as the triage tool when considering ECLS rewarming of a hypothermic cardiac arrest victim.

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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

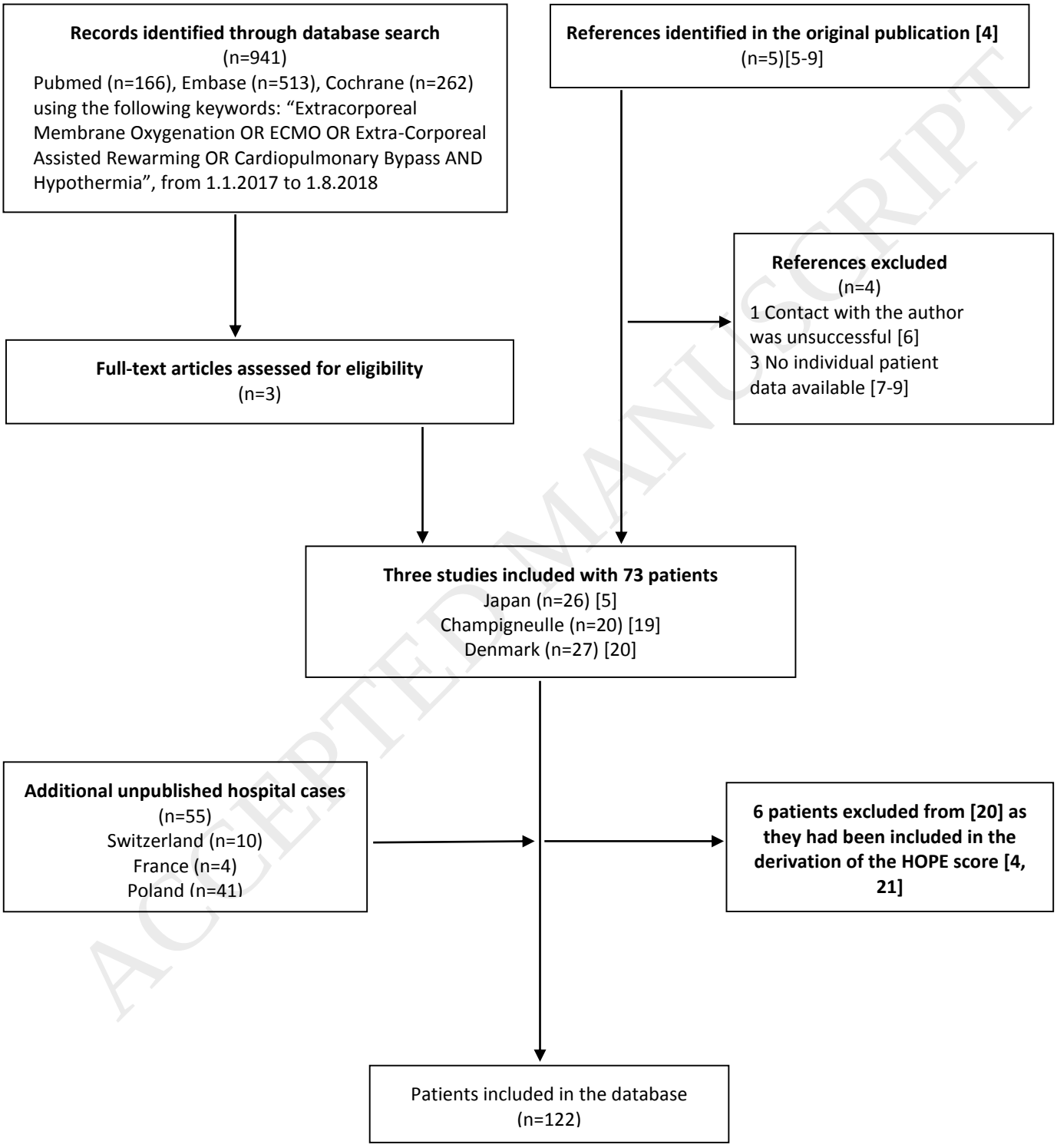

Fig. 2. Hypothermia outcome prediction after ECLS (HOPE) survival probabilities (left panel) and receiver operating characteristic curve of the survival probabilities (right panel) were estimated from 122 patients using HOPE model. AUC=area under the curve

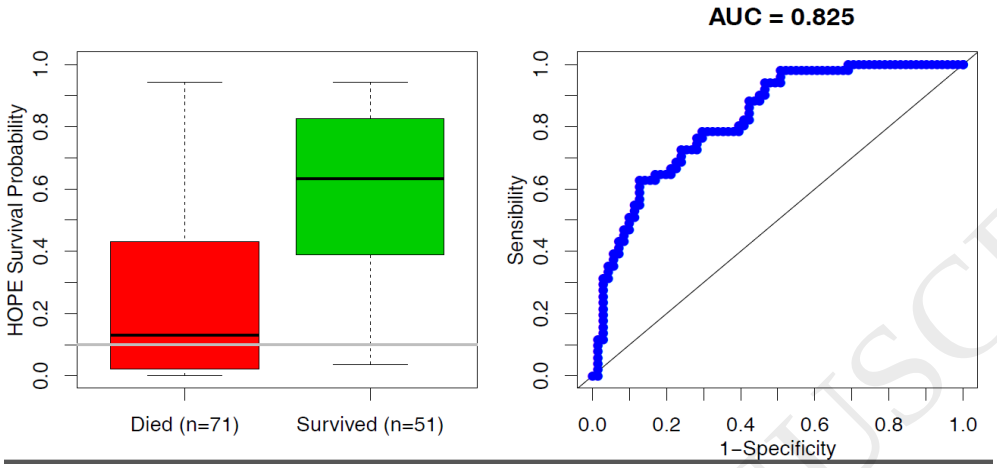

Fig. 3. Observed probability of survival according to the predicted survival rate in the validation sample (n=122). Each one of the red plots represent a decile of the predicted survival probabilities in the whole derivation sample. The Hosmer-Lemeshow (p=0.08) indicates that the differences between observed and predicted survival probabilities are not significant, indicating good calibration of the model

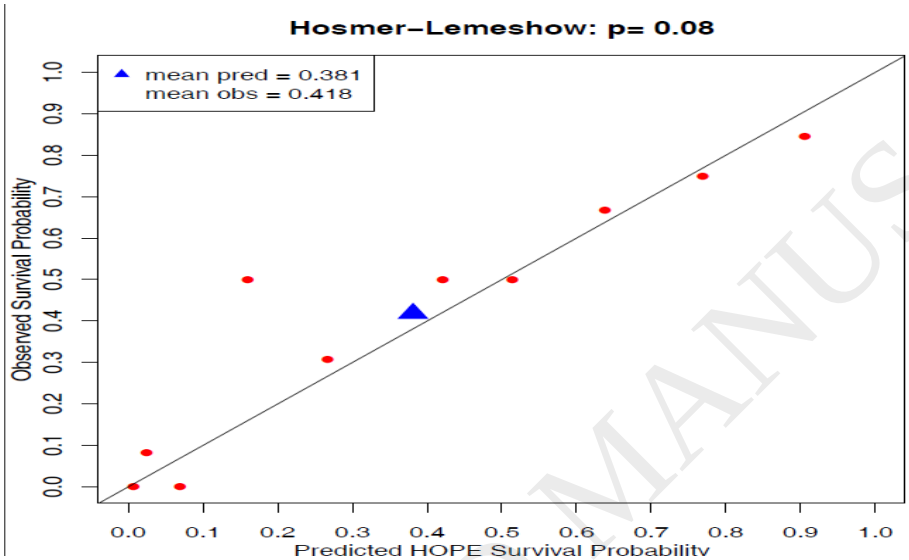

Table 1. Summary and comparison of baseline patient characteristics and outcomes in the derivation and validation groups.

	Derivation (n=286)	Validation[a] (n=122)	P value
Continuous candidate predictors, median (IQR[b])			
Age (years)	35 (16-55)	50 (34-59)	<0.001
Temperature (°C)	24 (22-27)	24 (22-27)	0.80
Potassium (mmol/L)	4.7 (3.6-6.6)	4.6 (3.7-6.1)	0.67
CPR[b] duration (min)	120 (85-169)	106.5 (68-150)	0.07
Categorical candidate predictors, n (%)			
Sex			0.45
Female	71/286=25%	26/122=21%	
Male	215/286=75%	96/122=79%	
Mechanism			<0.001
Exposure	98/283=35%	66/117=56%	
Immersion	40/283=14%	7/117=6%	
Submersion	94/283=33%	39/117=33%	
Avalanche	51/283=18%	5/117=4%	
Mechanism			0.01
Non-asphyxia-related	138/283=49%	73/117=62%	
Asphyxia-related	145/283=51%	44/117=38%	
Survival	106/286=37%	51/122=42%	0.37

[a] In the validation cohort, there were 8 missing values (1 survivor, 7 non-survivors) for CPR duration; 6 (2 survivors, 4 non-survivors) for potassium; 5 (4 survivors, 1 non-survivor) for the mechanism; and 1 (1 non-survivor) for the age.

[b] IQR and CPR denote interquartile range and cardiopulmonary resuscitation, respectively.

Table 2. Estimated sensitivity and specificity of a HOPE score ≥0.10 on predicting survival. HOPE denotes hypothermia outcome prediction after extracorporeal life support (ECLS).

	Sensitivity[a]	**Specificity[b]**	**PPV[c]**	**NPV[d]**	**FP[e]**	**FN[e]**
Derivation sample (n=286)						
HOPE ≥0.10 (95% CI)	106/106=100 % (97-100%)	92/180=51 % (44-58%)	106/194=55 % (48-61%)	92/92=100 % (96-100%)	88/286=31 % (26-36%)	0/286=0% (0-1%)
Validation sample (n=122)						
HOPE ≥0.10 (95% CI)	50/51=98% (90-100%)	34/71=48 % (37-59%)	50/87=57% (47-67%)	34/35=97 % (85-99%)	37/122=30 % (23-39%)	1/122=1% (0-4%)

[a] Sensitivity is defined as the probability that the criterion is fulfilled among the survivors.

[b] Specificity is defined as the probability that the criterion is not fulfilled among the non-survivors.

[c] The positive predictive value (PPV) is defined as the proportion of patients who survived among those fulfilling the criterion.

[d] The negative predictive value (NPV) is defined as the proportion of patients who died among those not fulfilling the criterion.

[e] FP denotes the percentage of false positive and FN the percentage of false negative (calculated over all the patients, whether positive or negative).