American Journal of Emergency Medicine 81 (2024) 69–74

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Development and validation of a clinico-biological score to predict outcomes in patients with drowning-associated cardiac arrest

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ARTICLE INFO

Article history:
Received 9 October 2023
Received in revised form 12 March 2024
Accepted 16 April 2024

Keywords:
Drowning-associated cardiac arrest-ICU-prognosis score

ABSTRACT

Background: While several scoring systems have been developed to predict short-term outcome in out-of-hospital cardiac arrest patients, there is currently no dedicated prognostic tool for drowning-associated cardiac arrest (DACA) patients.
Methods: Patients experiencing DACA from two retrospective multicenter cohorts of drowning patients were included in the present study. Among the patients from the development cohort, risk-factors for day-28 mortality were assessed by logistic regression. A prediction score was conceived and assessed in patients from the validation cohort.
Results: Among the 103 included patients from the development cohort, the day-28 mortality rate reached 51% (53/103). Identified independent early risk-factors for day-28 mortality included cardiopulmonary resuscitation duration longer than 20 min (OR 6.40 [95% CI 1.88–23.32]; $p = 0.003$), temperature at Intensive Care Unit admission <34 °C (OR 8.84 [95% CI 2.66–32.92]; $p < 0.001$), need for invasive mechanical ventilation (OR 6.83 [95% CI 1.47–40.87]; $p = 0.02$) and lactate concentration > 7 mmol/L (OR 3.56 [95% CI 1.01–13.07]; $p = 0.04$). The Area Under the ROC Curve (AUC) of the developed score based on those variables reached 0.91 (95% CI, 0.86–0.97). The optimal cut-off for predicting poor outcomes was 4 points with a sensitivity of 92% (95% CI, 82–98%), a specificity of 82% (95% CI, 67–91%), a positive predictive value (PPV) of 84% (95% CI, 72–95%) and a negative predictive value (NPV) of 91% (95% CI, 79–96%). The assessment of this score on the validation cohort of 81 patients exhibited an AUC of 0.82. Using the same 4 points threshold, sensitivity, specificity, PPV and NPV values of the validation cohort were: 81%, 67%, 72% and 77%, respectively.
Conclusion: In patients suffering from drowning induced initial cardiac arrest admitted to ICU with a DACA score ≥ 4, the likelihood of survival at day-28 is significantly lower. Prospective validation of the DACA score and assessment of its usefulness are warranted in the future.

1. Introduction

Despite advances in the prevention and management of drowning patients [1], drowning remains a global public health concern resulting in >372,000 deaths worldwide [2]. Critically ill drowning patients may experience Drowning-Associated Cardiac Arrest (DACA) due to hypoxia caused by inhalation of water into the lungs [3]. The occurrence of DACA

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https://doi.org/10.1016/j.ajem.2024.04.032
0735-6757/

has been described as having a major influence on prognosis with survival rates ranging from 43% to 54% [4,5]. The uncertain prognosis of these patients is mainly promoted by brain hypoxic injury and ischaemia-reperfusion phenomenon. Management of DACA is standardized and mainly based on symptomatic measures including by-standers' cardiopulmonary resuscitation [6]. However, beyond the initial management of these patients, outcomes may vary depending on several factors such as the duration as well as the circumstances of the drowning process [7-9].

Although early accurate assessment of prognosis to identify patients that would benefit from intensive care is necessary, prognostication tools for survival of DACA patients remain poorly explored. Therefore, we sought to develop a clinico-biological score to predict poor outcomes in patients admitted to intensive care units (ICUs) after the occurrence of a DACA.

2. Methods

2.1. Setting and patients

For the development cohort, we performed an ancillary analysis of a 7-year retrospective multicenter study conducted in 14 ICUs, including drowned adult patients (≥18 years old) [10]. Only patients with initial DACA were included in the present study.

The multicenter validation cohort was composed of patients that suffered from initial DACA among the study population of a multicenter retrospective study including critically ill drowning patients from June 2010 to September 2013 [11]. There was no data overlap between the development and the validation samples.

As the usefulness of a prognostic score for survival in patients with cardiac arrest might be considered greater for those requiring subsequent ICU hospitalization, the prognostic score was evaluated only in patients with DACA hospitalized in the ICUs.

The study protocol was approved by the ethical committee of the French Society of Intensive Care Medicine (CE SRLF 22–067).

2.2. Data collection

Collected data included pre-hospital demographic characteristics, comorbidities and drowning features (presumed etiology of drowning, water salinity, presence of a witness and Cardiopulmonary Resuscitation (CPR) duration). Clinical and biological parameters at ICU admission recorded comprised temperature, mean arterial pressure, PaO2/FIO2 ratio, PaCO2, arterial lactate levels, leukocyte count, severity score (SAPS II: Simplified Acute Physiology Score II [12] and SOFA: Sequential Organ Failure Assessment [13]) and need for invasive mechanical ventilation. Organ dysfunctions, treatments received and outcomes (day-28 mortality, length of stay, mechanical ventilation duration) were also collected. Neurological status at hospital discharge was assessed using the Cerebral Performance Category (CPC) scale [14].

2.3. Objectives

We first aimed to compare patients' characteristics according to day-28 survival status. Then, risk-factors for poor outcomes were assessed. Finally, we sought to develop a clinico-biological score to predict day-28 mortality among the study population. This prognosis score was assessed in a validation cohort.

2.4. Statistical analysis

Descriptive statistics were used to assess characteristics of the study population according to day-28 survival status. Continuous variables were reported as median (interquartile range) and compared between groups using the Mann-Whitney test. Categorical variables were described as number (percentages) and compared using the Fisher's exact or the Chi2 tests, as appropriate. Risk-factors for day-28 mortality were first assessed by performing a univariate logistic regression. Non-collinear variables achieving a p value <0.2 in the bivariable analysis were subjected to a multivariable analysis. A multiple backward stepwise procedure with an exit threshold set at $p = 0.05$ was performed to select variables of the final model. Results of logistic regression analysis were expressed as Odds Ratio (OR) with their 95% confidence intervals (95% CI). Finally, variables independently associated with day-28 morality were selected to develop a prediction score of poor prognoses, attributing weights according to the logistic regression β-coefficients. The discrimination performance of the developed prediction score was performed using the area under the receiver-operating characteristic (ROC) curve. We determined optimal cutoff using the Youden index. The prediction of mortality according to the different values of the score developed was determined by using the intercept term from the logistic regression of the survival status at day 28 according to the score (DACA score), and then by applying the following formula: predicted probability = 1 / (1 + e ^(−(DACA Score + intercept term))).

External validation of the developed score was assessed using data from the validation cohort. Using the "MICE" R package (R Foundation for Statistical Computing, Vienna, Austria) and assuming that missing data were randomly missing, multiple imputation using Monte Carlo Markov chained equations was used to generate 5 data sets without missing values. Overall, 30 and 75 missing values (in 29 and 54 patients) were imputed in the development and validation cohort, respectively.

A p value <0.05 was considered significant, and all p values were two-tailed. Statistical analyses were done using R software version 4.0.4 (https://www. rproject.org) and Easy Med Stat© (www.easy-med-stat.com).

The design of this study followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis (TRIPOD) checklist [15].

3. Results

3.1. Development cohort

Among the 270 identified ICU drowned patients, 103 experienced initial cardiac arrest and were included in the present study. Return of spontaneous circulation was achieved for all of them. Among those patients, the day-28 mortality rate reached 51% (53/103). Neurological sequelae assessment revealed that 55/103 patients (53.4%) had unfavorable neurological status (A CPC score > 2).

Demographic characteristics did not differ according to survival status (Table 1). Patients with worsened outcomes downed more frequently in freshwater (45.3% (24/53) versus 22% (12/50); $p = 0.04$) and had longer CPR duration (30 min (IQR 23–40) versus 5 min (IQR 2–14); $p < 0.001$). The presence of a witness during drowning was less frequent among patients who died within the first 28 days after ICU admission (49.1% (26/53) versus 72% (36/50); $p = 0.03$). Temperature at ICU admission as well as mean arterial pressure were lower among patients that died compared with survivors (respectively, 32.3 °C (30.5–33.6) versus 35.4 °C (34.2–36.6); $p < 0.001$ and 72 mmHg (59–88) versus 90 mmHg (78–102); p < 0.001). Patients who died had higher lactate blood concentration (10.20 mmol/L (7.6–13.7) versus 4.05 mmol/L (2.12–7.60); $p < 0.001$) and required invasive mechanical ventilation at ICU admission more frequently (100% (53/53) versus 50% (25/50); p < 0.001).

3.2. Predictors of outcome

Identified independent risk-factors for day-28 mortality included CPR duration longer than 20 min (OR 6.40 [95% CI 1.88–23.32]; $p = 0.003$), temperature at ICU admission <34 °C (OR 8.84 [95% CI 2.66–32.92]; p < 0.001), need for invasive mechanical ventilation (OR

Table 1
Characteristics of drowning patients according to day-28 survival status.

	All patients $n = 103$	Survivors $n = 50$	Dead $n = 53$	*p* value
Baseline characteristics				
Age (years)	62 (51–72)	62 (55–72)	60 (48–72)	0.212
Male sex	64 (62.1)	28 (56)	36 (68)	0.297
At least one psychiatric comorbidity	28 (27.2)	10 (20)	18 (34)	0.171
Obesity	15 (14.6)	6 (14)	9 (20.5)	0.604
Alcoholism	21 (20.4)	6 (12)	15 (28.3)	0.071
Cardiovascular disease	5 (4.8)	1 (2)	4 (7.5)	0.395
Etiology				
Drug or alcohol intoxication	18 (17.5)	7 (14)	11 (20.8)	0.520
Suicide attempt	9 (9)	2 (4)	7 (13.2)	0.192
Presumed cardiac	13 (12.6)	11 (22)	2 (3.8)	0.013
Presumed neurologic	8 (7.8)	5 (10)	3 (5.7)	0.650
Accident	55 (53.4)	25 (50)	30 (56.6)	0.636
Scene Information				
Type of water: freshwater	36 (34.9)	12 (24.0)	24 (45.3)	0.040
Event witnessed	62 (60.2)	36 (72.0)	26 (49.1)	0.030
Asystolia	85 (82.5)	40 (80.0)	45 (84.9)	0.692
CPR duration (minutes)	17 (5–30)	5 (2–14)	30 (23–40)	<0.001
Clinical and laboratory findings at ICU admission				
Temperature (°C)	34 (32–36)	35.4 (34.2–36.6)	32.3 (30.5–33.6)	<0.001
Mean arterial pressure (mmHg)	81 (67–95)	90 (78–102)	72 (59–88)	<0.001
Leukocyte count (109/L)	11.7 (8.3–17)	12.15 (8.3–16.1)	11.1 (8.4–18.3)	0.588
PaO2/FIO2 (mm Hg/%)	141 (83–239)	131 (92–188)	152 (72–270)	0.325
PaCO2 (mmHg)	48 (39–57)	48 (39.65–54.75)	49 (37–62)	0.524
Invasive MV at day 1	78 (75.7)	25 (50)	53 (100)	<0.001
Lactate (mmol/L)	7.6 (3.9–10.8)	4.05 (2.12–7.60)	10.20 (7.6–13.7)	<0.001
SAPS II at day 1	65 (41–82)	39 (26–58)	78 (70–91)	<0.001
SOFA at day 1	8 (4–12)	3.5 (1–8)	12 (9–15)	<0.001
Clinical course and ICU management				
Duration of mechanical ventilation (days)	3.5 (2–6)	4 (2–6)	3 (2–6)	0.808
Neuromuscular blockers	45 (43.7)	9 (18)	36 (67.9)	<0.001
Prone positioning ventilation	17 (16.5)	5 (10)	12 (22.6)	0.144
Need for vasopressors	61 (59.2)	13 (26.0)	48 (90.6)	<0.001
AKI	44 (42.7)	7 (14.0)	37 (69.8)	<0.001
RRT use	8 (7.8)	0 (0.0)	8 (15.1)	0.013
SOFA at day 3	6 (0−11)	3 (0–11)	8 (0−12)	0.375
CPC score > 2 at discharge	55 (53.4)	2 (4)	53 (100)	<0.001
ICU length of stay (days)	3 (2–7)	3 (2–6)	3 (2–7)	0.912

Data are presented as median (IQR: interquartiles), n (%). P values comparing patients are tested by Mann-Whitney (continuous variables) and Chi2 or Fisher tests (categorical variables). Abbreviations: AKI: Acute Kidney Injury; CPC: Cerebral Performance Category; CPR: Cardiopulmonary resuscitation; FiO2: Fraction of inspired Oxygen; ICU: Intensive Care Unit; PaO2: arterial oxygen tension; PaCO2: Carbon dioxide tension; RRT: Renal Replacement Therapy; SAPS II: Simplified Acute Physiology Score II SOFA: Sequential Organ Failure Assessment.

6.83 [95% CI 1.47–40.87]; $p = 0.02$) and lactate concentration > 7 mmol/L (OR 3.56 [95% CI 1.01–13.07]; $p = 0.04$) (Table 2). From the model's result, a scoring system was developed (Table 3). The ROC curve was used to assess the discriminatory capacity of the DACA score (Fig. 1). The AUC of the ROC curve reached 0.91 (95% CI, 0.86–0.97). The optimal cut-off for predicting poor outcomes was 4 points with a sensitivity of 92% (95% CI, 82–98%), a specificity of 82% (95% CI, 67–91%), a positive predictive value of 84% (95% CI, 72–95%) and a negative predictive value of 91% (95% CI, 79–96%). The density of mortality within 28 days observed in the study population according to the value of the score developed is shown in Supplementary Fig. 1. Predicted probabilities of death according to the DACA score are displayed in Table 4.

3.3. Validation cohort

The validation cohort was composed of 81 patients that experienced drowning-associated cardiac arrest. The main characteristics of those patients are displayed in the Supplementary Table 1. Of them, 42 died within the first 28 days after ICU admission (51.8%). In this cohort, the AUC of the ROC curve for the DACA score was 0.82 (95% CI 0.74–0.91), the sensitivity and the specificity for a cut-off of 4 points were 81% and 67%, respectively. Finally, positive predictive value and negative predictive values were 72% and 77%, respectively (Fig. 2).

3.4. Sensitivity analysis

When analyzing only patients that received initial mechanical ventilation of the development cohort ($n = 78$), similar baselines characteristics differences according to ICU survival status were observed (Supplementary Table 2). In addition, CPR duration >20 min and body temperature < 34 °C remained independently associated with higher ICU mortality rates (OR 11.64 [95% CI 3.43–47.22]; $p = 0.002$ and OR 8.12 [95% CI 2.40–31.92]; $p = 0.001$, respectively) (Supplementary Table 3).

4. Discussion

In the present study, performed in patients experiencing drowning-associated cardiac arrest admitted to ICUs, we developed and validated a predictive model designed from easy to assess variables, to estimate the probability of mortality at day-28 after ICU admission.

Overall, mortality rate reached 51% in the development cohort and nearly 52% in the validation cohort. Despite a hypoxic origin, this mortality rate appears particularly low as compared with previous studies that focused on cardiac arrest with non-shockable rhythm [16]. Such a good prognosis emphasizes the need for prolonged CPR and the development of prognostication scores. Furthermore, in the development cohort, a quarter of DACA patients did not require mechanical ventilation.

Table 2
Univariate and Multivariate analysis of factors associated with day-28 mortality.

		Crude OR				Adjusted OR		
	Beta	OR	95% CI	*p* value	Beta	OR	95% CI	*p* value
Baseline characteristics								
Age (years)	−0.01	0.98	0.96–1.00	0.15				
Male sex	0.51	1.66	0.75–3.75	0.21				
At least one psychiatric comorbidity	0.72	2.06	0.85–5.19	0.11				
Obesity	−0.43	0.65	0.14–2.31	0.54				
Alcoholism	1.06	2.89	1.06–8.80	0.045				
Cardiovascular disease	1.39	4	0.57–79.75	0.22				
Diabetes	−1.04	0.35	0.05–1.72	0.23				
Etiology								
Drug or alcohol intoxication	0.47	1.61	0.58–4.74	0.37				
Suicide attempt	1.29	3.65	0.83–25.3	0.12				
Presumed cardiac	−1.97	0.14	0.02–0.56	0.01				
Presumed neurologic	−0.62	0.54	0.11–2.33	0.42				
Accident	0.27	1.30	0.60–2.85	0.50				
Scene Information								
Type of water: Freshwater	0.96	2.62	1.14–6.25	0.02				
Event witnessed	−0.98	0.37	0.16–0.84	0.019				
Asystolia								
CPR duration >20 min	2.89	17.94	6.97–51.43	<0.001	1.86	6.40	1.88–23.32	0.003
Clinical and laboratory findings at ICU admission								
Temperature < 34 °C	2.94	18.90	7.22–55.89	<0.001	2.18	8.84	2.66–32.92	<0.001
PaO2/FIO2 (mm Hg/%)	0.00	1.00	1.00–1.01	0.08				
PaCO2 (mmHg)	0.01	1.01	0.99–1.03	0.18				
Invasive MV	3.05	21.21	6.64–95.46	<0.001	1.92	6.83	1.47–40.87	0.02
Lactate >7 mmol/L	1.97	7.18	3.08–17.71	<0.001	1.28	3.56	1.01–13.07	0.04

Abbreviations: CPR: Cardiopulmonary Resuscitation; FiO2: Fraction of inspired Oxygen; ICU: Intensive Care Unit; MV: Mechanical Ventilation; PaO2: arterial oxygen tension; PaCO2: Carbon dioxide tension.

Such a low proportion of patients placed on mechanical ventilation could reflect the reversibility of the DACA mechanism. Therefore, driving rapid improvement of the patient's general condition when cardiopulmonary resuscitation is initiated early enough.

Our scoring system offered an interesting tool for early and reliable prognostic assessment. In this study, the scoring system developed exhibited a good discrimination performance to predict survival at day-28. However, when the score was analyzed in the validation cohort, the prognostic performance was poorer (i.e., the AUC was 0.82). This might have been favored by the differences between the two populations. Although the two cohorts included patients suffering from DACA, patients from the validation cohort experienced drowning in freshwater less often whereas they were younger, less often suffering from obesity. Of them, a suicide attempt was also less frequently the presumed etiology of drowning. Furthermore, there are other possible reasons for this poorer performance, such as the geographical area in which patients were included, since all patients included in the validation cohort were hospitalized in hospitals in the south of France, whereas those in the development cohort were included in hospitals in western France. In addition, the inclusion period was different, since patients included in the development cohort were hospitalized between 2013 and 2020, whereas those in the validation cohort were admitted between 2010 and 2013.

In the present study, CPR duration >20 min appeared to be a predictor of worsened outcome. There are several possible reasons for this finding. Firstly, a longer CPR duration implies an increase in low-flow/low-oxygen time, which may favor the intensity of post-resuscitation syndrome and neurological sequelae. Secondly, longer CPR duration may also reflect initial severity, including immersion time and no-flow time.

Table 3
Equation of the DACA score.

Covariates	No. of Points
CPR duration >20 min	2
Temperature < 34 °C	2
Invasive MV at ICU admission	2
Lactate >7 mmol/L	1

Abbreviations: CPR: Cardiopulmonary Resuscitation; MV: Mechanical Ventilation; ICU: Intensive Care Unit.

The challenge of prognostication of cardiac arrest patients is a global concern. Early identification of patients with expected poor outcomes may help physicians to adjust the management of these critical patients.

Several tools for risk prediction have been developed for patients experiencing out-of-hospital cardiac arrest (OHCA) [17,18]. However, the rates of patients with unfavorable neurologic outcomes observed along these studies were higher, ranging from 59.8% to 74%, as compared with 53.4% in our cohort. Such differences in outcomes emphasize the specificities of DACA [19].

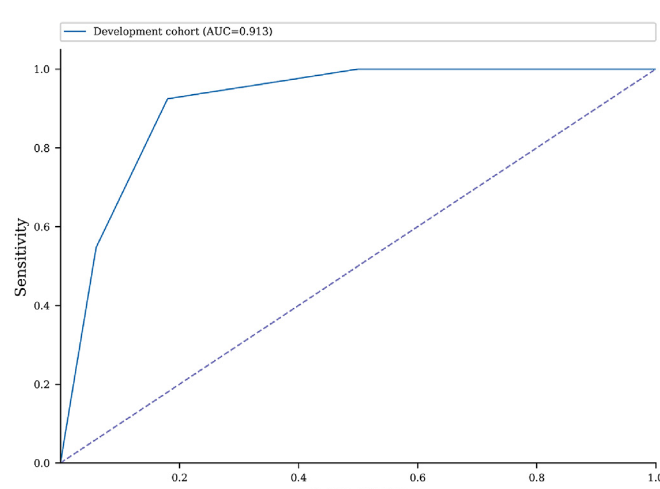

Fig. 1. Receiver operator characteristic curve for predictive model using the development cohort. The curve is based on a diagnosis-prediction model of poor prognosis at Day-28 after ICU admission incorporating 4 variables: Cardiopulmonary resuscitation >20 min, temperature < 34 °C, invasive mechanical ventilation at ICU admission and lactate>7 mM.

Table 4
Prediction of death within 28 days after ICU admission according to DACA score.

DACA score	Probability of death within 28 days after ICU admission
0	2.8%
1	7.2%
2	17.5%
3	36.6%
4	68.7%
5	82.5%
6	92.7%
7	97.2%

In addition, the relatively good performance of the prognostic score developed may reflect the homogeneous nature of the population studied, which is not always the case, especially in studies dedicated to all types of cardiac arrest. Only a few studies have examined outcome predictors following drowning associated cardiac arrest. Moreover, most of them were not focused on ICU patients and mainly used large population-based databases. Furthermore, to our knowledge, none of them aimed to generate an easy to assess prognostic score.

In the present study, hypothermia appeared to be associated with worsened outcomes. Although hypothermia may limit the neurological sequelae induced by cardiac arrest, in the setting of drowning, hypothermia may be assumed to reflect longer immersion and/or cardiac arrest, resulting in a higher mortality rate. Furthermore, although the developed score focuses on patients admitted to ICUs, prompting a question regarding the potential dissimilarities if the prognostic score were to be applied to patients in the emergency department. However, it may be considered that a scoring system to predict survival in patients with initial cardiac arrest is primarily useful for patients requiring further hospitalization after admission to the emergency department. Since it can be assumed that patients suffering from drowning associated cardiac arrest will either die quickly in the emergency department, require ICU admission (and may then either die or survive), or rapidly improve (rendering the survival score useless).

Our study suffers from several limitations. Firstly, although sometimes useful for guiding the management of patients, the results of predictive scores are not absolute and must only be considered as supplementary information. Therapeutic strategies may consider their results but should not be only based on these scoring systems. Secondly, practices regarding discontinuation of care in patients with neurological sequelae induced by cardiac arrest may vary among centers and patients. This may have contributed to heterogeneity in timing and management of the end of life. Thirdly, the long study period of the development cohort (7 years) may have resulted in management differences over time. Notably, preventive antibiotic use [20] and targeted temperature management in patients with cardiac arrest [16,21] may have varied and could explain the improved survival observed in the present cohort as compared with previously observed. Fourthly, as our study focused on ICU patients, the development of a similar score for emergency department patients may have led to potential dissimilarities making the applicability of the score in different healthcare settings uncertain. Finally, the discriminatory abilities of the developed score appeared lower when assessed in the validation score, which may indicate a potential limitation in the generalizability of the prognostic score. Although the two populations had different baseline characteristics, and some residual confounding factors (such as geographic area of hospitalization, period of inclusion…) may have favored these differences in discriminatory abilities, a prospective evaluation of the developed prognostic score should be considered.

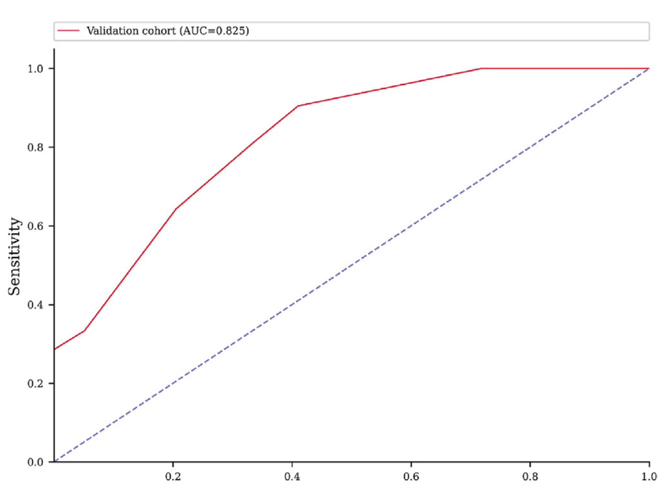

Fig. 2. Receiver operator characteristic curve for predictive model using the validation cohort.

To conclude, in two large multicenter retrospective cohorts of patients experiencing DACA, we generated an easy and reliable clinico-biological scoring system based on risk-factors for mortality. In patients suffering from drowning induced initial cardiac arrest admitted to ICU with a DACA score ≥ 4, the likelihood of survival at day-28 is significantly lower. Prospective validation of the DACA score and assessment of its usefulness are warranted in the future.

Ethics approval and consent to participate

This study conforms to the principles outlined in the Declaration of Helsinki and was approved by ethics committee of the French Society of Intensive Care Medicine (CE SRLF 22–067).

Funding

No funding was received for this work.

CRediT authorship contribution statement

Florian Reizine: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Agathe Delbove:** Writing – review & editing, Data curation, Conceptualization. **Guillaume Rieul:** Methodology, Formal analysis. **Laetitia Bodenes:** Investigation, Data curation. **Pierre Bouju:** Investigation, Data curation. **Pierre Fillâtre:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Aurélien Frérou:** Writing – review & editing, Investigation, Data curation. **Olivier Lesieur:** Writing – review & editing, Investigation, Data curation. **Thibaut Markarian:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Arnaud Gacouin:** Conceptualization, Data curation, Investigation, Writing – review & editing.

Data availability

The datasets from this study are available from the corresponding author on request.

Declaration of competing interest

The authors report no conflict of interest related to this work.

Acknowledgments

We thank the members DROWNAP Study group (to be searchable through their individual PubMed records). Guillaume Halley (Quimper), Alexandre Dos Santos (La Roche sur Yon), Patricia Courouble (Saint Nazaire), Florian Berteau (Morlaix), Jean Morin (Nantes), Flora

Delamaire (Rennes), Rémy Marnai (Le Mans) Anthony Le Meur (Cholet), Cécile Aubron (Brest), Jean Reignier (Nantes), Yannick Fedun (Vannes).

The authors also would like to thank Alison Mac Lean, Medical Librarian, Vannes Regional Hospital, for her help in drafting the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2024.04.032.

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