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Clinical paper

Factors predicting mortality in the cardiac ICU during the early phase of targeted temperature management in the treatment of post-cardiac arrest syndrome – The RAPID score

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Abstract

Introduction: Survival rates after out-of-hospital cardiac arrest (OHCA) remain low, and early prognostication is challenging. While numerous intensive care unit scoring systems exist, their utility in the early hours following hospital admission, specifically in the targeted temperature management (TTM) population, is questionable. Our aim was to create a score system that may accurately estimate outcome within the first 12 h after admission in patients receiving TTM.

Methods: We analyzed data from 103 OHCA patients who subsequently underwent TTM between 2016 and 2022. Patient demographic data, prehospital characteristics, clinical and laboratory parameters were already available in the first 12 h after admission were collected. Following a bootstrap-based predictor selection, we constructed a nonlinear logistic regression model. Internal validation was performed using bootstrap resampling. Discrimination was described using the c-statistic, whereas calibration was characterized by the intercept and slope.

Results: According to the Akaike Information Criterion (AIC) heart rate (AIC = 9.24, $p = 0.0013$), age (AIC = 4.39, $p = 0.0115$), pH (AIC = 3.68, $p = 0.0171$), initial rhythm (AIC = 4.76, $p = 0.0093$) and right ventricular end-diastolic diameter (AIC = 2.49, $p = 0.0342$) were associated with 30-day mortality and were used to build our predictive model and nomogram. The area under the receiver-operating characteristics curve for the model was 0.84. The model achieved a C-statistic of 0.7974, with internally validated acceptable calibration (intercept: −0.0190, slope: 0.7772) and low error rates (mean absolute error: 0.040).

Conclusion: The model we have developed may be suitable for early risk assessment of patients receiving TTM as part of primary post-resuscitation care. The calculator needed for scoring can be accessed at the following link: https://www.rapidscore.eu/.

Keywords: Sudden Cardiac Arrest, Out-of-Hospital Cardiac Arrest, Cardiopulmonary Resuscitation, Targeted Temperature Management, Prediction of Mortality

Abbreviations: AIC, Akaike Information Criterion, AUC, area under curve, APACHE II, acute physiology and chronic health evaluation II, CAHP, cardiac arrest hospital prognosis, BMI, body mass index, CABG, coronary artery bypass graft, CI, confidence interval, CV, cardiovascular, ICU, intensive care unit, IQR, interquartile range, NSTEMI, non-ST-elevation myocardial infarction, OHCA, out-of-hospital cardiac arrest, PAD, peripheral arterial disease, PCAS, post cardiac arrest syndrome, rCAST, revised cardiac arrest survival test, ROC, receiver operating characteristic, ROSC, return of spontaneous circulation, RVEDD, right ventricle end-diastolic diameter, RVFAC, right ventricular fractional area change, SAPS II, simplified acute physiology score II, SCA, sudden cardiac arrest, STEMI, ST-elevation myocardial infarction, SOFA, sequential organ failure assessment, TAPSE, tricuspid annular plane systolic excursion, TIA, transient ischemic attack, TTM, targeted temperature management

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Background

In developed countries, sudden cardiac arrest (SCA) remains a leading cause of cardiovascular death, with the incidence of out-of-hospital cardiac arrest (OHCA) in Europe ranging from 53 to 139 per 100,000 population.[1–3] Post-cardiac arrest brain injury is the main cause of mortality in patients who achieve return of spontaneous circulation.[4] Thus, post-resuscitation therapy aims to prevent secondary brain damage through appropriate neuroprotective measures. Although targeted temperature management (TTM), which involves lowering core body temperature to 32–36 °C, has been widely used for this purpose, recent large randomized controlled trials, including TTM and TTM2, have questioned its efficacy in preventing hypoxic brain injury.[5,6] Our study has two primary objectives. Its first goal is to pinpoint specific parameters or factors that can reliably predict early mortality within the initial 12 h of admission in post-cardiac arrest patients who undergo TTM. The second aim of this study is to develop a predictive model that can accurately predict the probability of 30-day mortality, with a particular focus on the ability to make these predictions within the first 12 h of admission, independently of the TTM method and level of targeted temperature.

Methods

Study population

A single-center retrospective non-interventional analysis was conducted at the Semmelweis University Heart and Vascular Center between 1 January 2016 and 31 December 2022. Patients included in the study were adult patients (≥18 years) who suffered OHCA and remained comatose after the return of spontaneous circulation (ROSC), admitted to the cardiac intensive care unit, where an early TTM was initiated. At our institution, we selected patients for temperature control based on specific criteria. Specifically, patients who suffered cardiac arrest, were comatose, or sedated and mechanically ventilated due to long duration of cardiac arrest to ROSC, aged over 18 years, with a maximum interval of 5–15 min from cardiac arrest to the initiation of full medical care, successful cardiopulmonary resuscitation (CPR) within 30 min, and an initial body temperature above 30 °C. Until 2022, we targeted a temperature of 33 °C for all such patients, adhering to our domestic protocol. According to our protocol, we excluded patients based on the following criteria: pregnant women, individuals under 18 years of age, terminal illness, previously diagnosed coagulopathy or cryoglobulinemia, relative has denied consent for retrospective data analysis, coma not related to cardiac arrest (e.g., intoxication, electrolyte imbalance, trauma, cerebrovascular accident, status epilepticus), active bleeding (known International Normalized Ratio > 3.0, spontaneous Partial Thromboplastin Time > 3 times the normal, platelet count < 50,000), mean arterial pressure < 60 mmHg for more than 30 min requiring more than 2 vasopressors (e.g., norepinephrine and adrenaline or vasopressin/terlipressin), prolonged hypoxemia (O_2 saturation < 85% for more than 20 min), and unstable arrhythmia that cannot be stabilized. Additionally, exclusion criteria included missing clinical data concerning the circumstances of cardiac arrest and first response or interruption of TTM within the first 24 h. Only data from those who met all our eligibility criteria were analyzed. Among a series of 135 consecutive patients selected for TTM, 27 were excluded from analyses due to data loss exceeding 10%, 2 were excluded from the study because of age, and 3 were excluded due to death from cardiogenic shock during the first 12 h of cooling. Otherwise, all patients meeting the inclusion criteria remained in the study. The study protocol was reviewed and approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval number: 194/2020) and was in accordance with the Declaration of Helsinki. All the data of patients were handled according to the actual General Data Protection Regulation. Informed consent was obtained from all subjects and/or their legal guardian(s).

Data collection

Data were collected from hospital medical records, intensive care unit charts, and the Hungarian National Ambulance Service report sheets. Demographic information, including age, gender, and body mass index were collected. In addition, our study analyzed the etiology of cardiac arrest, durations of pre- and in-hospital treatments, imaging and laboratory test results measured at hospital admission, and therapeutic interventions. We analyzed only data from all the recorded parameters when data loss did not exceed 10%. In total, we were able to identify fourty eligible clinical parameters. Standard blood gas parameters such as partial arterial pressure of carbon dioxide, partial arterial pressure of oxygen, pH, oxygen saturation, oxyhemoglobin, carboxyhemoglobin, base excess, and bicarbonate measured at hospital admission were collected. In the echocardiographic assessment, we recorded ejection fraction, tricuspid annular plane systolic excursion (TAPSE), presence of pericardial effusion, and the right ventricle end-diastolic diameter (RVEDD).

Among the basic metabolic panel and complete blood cell counts measured at hospital admission, we collected the white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, thrombocyte count, international normalized ratio, sodium level, potassium, blood urea nitrogen, creatinine, estimated glomerular filtration rate, urea, blood glucose level, C-reactive protein, glutamic pyruvic transaminase, and gamma-glutamyl transferase.

Additionally, we recorded clinical parameters such as initial heart rhythm, heart rate, systolic and diastolic blood pressure, need of intensive circulatory support within the first 24 h: dosage of intravenous noradrenaline and dobutamine. We defined the initial rhythm as the first recorded rhythm by the first response team upon ROSC, according to national protocol.

On average, there was a 51-minute interval between the initiation of targeted temperature management and the blood gas analysis. The baseline laboratory values were collected an average of 10.02 min from the start of TTM. The first laboratory results were available 1.03 h (61.8 min) average after the start of TTM. Heart rate and blood pressure parameters were recorded hourly for 72 h following the initiation of cooling. At our institution, echocardiograms are performed on all patients according to protocol. On average, 3 ± 1 h elapsed between hospital admission and the echocardiogram.

Outcome measures

The primary outcome was defined as the 30-day mortality. The focus of the study was to identify parameters that could potentially impact the 30-day mortality rate. The National Health Insurance Fund of Hungary database was used to determine the time of death. In cases

where death did not occur at our center or a pathological report was not available in the National e-Health Infrastructure system, social insurance ID inactivation was used as an endpoint.

Cooling method

All patients underwent TTM using a surface temperature-management device known as Blanketrol® (Cincinnati SubZero Medical Division, Cincinnati, Ohio, USA), aiming to achieve and maintain a target temperature of 33 °C. Upon hospital arrival, we immediately initiated cooling in the intensive care unit. We achieved the target temperature of 32–33 °C within 5 h, as part of the induction phase, where our goal was to reduce the core temperature as quickly as possible. During the maintenance phase, we consistently maintained the target temperature of 32–34 °C. Subsequently, rewarming was performed gradually with a rate of 0.25 °C per hour.

Statistical analyses

Contingency analysis in 2 × 2 tables was conducted using Fisher's exact test. Comparison of continuous variables was performed using the Mann-Whitney test after checking for normality with the Shapiro-Wilk test. Consequently, continuous variables were represented using medians and interquartile ranges, whereas categorical variables were presented as absolute numbers and percentages. Missing data (2.79%) were handled by single imputation. We used nonlinear logistic regression analysis for model construction. The presence of nonlinear relationships of the continuous candidate predictors to log odds of 30-day mortality was explored using restricted cubic splines, which were evaluated graphically and by Wald testing for linearity. To determine the most relevant predictors, backward stepwise logistic regression was combined with bootstrap resampling using the Akaike's information criterion (AIC) as a stopping rule.[7] Variables selected in at least 40% of the 10,000 resamples were included in the final model. The independence of the predictors (lack of collinearity) was evaluated by the variance inflation factor using a cut-off value of five. The likelihood ratio statistics was used as an overall test of association for each predictor in the analysis of variance. The prognostic importance of individual variables in the model was assessed by the Akaike's information criterion. Discrimination

Table 1 – Basic characteristics of patients.

Baseline characteristics	Total	Non-survivors	Survivors	*p*-value
Parameters				
Patients (*n*)	103	45	58	–
Female, *n* (%)	33 (32.1)	12 (26.7)	21 (36.2)	0.395
Age year (IQR)	57.9 (50.5–65)	62 (55–69)	54.8 (45.3–63.8)	0.007
BMI kg/m^2 (IQR)	28.8 (25.9–31.1)	28.9 (26.1–31.1)	28.7 (25.4–31.2)	0.727
Known CV disease, *n* (%)	38 (36.9)	16 (35.6)	22 (37.9)	0.839
Hypertension, *n* (%)	49 (47.6)	23 (51.1)	26 (44.8)	0.554
Diabetes mellitus, *n* (%)	23 (22.3)	13 (28.9)	10 (17.2)	0.233
Hyperlipidemia, *n* (%)	14 (13.6)	9 (20.0)	5 (8.6)	0.146
Prior myocardial infarction, *n* (%)	14 (13.6)	7 (15.6)	7 (12.1)	0.773
PAD, *n* (%)	8 (2.0)	6 (13.3)	2 (3.4)	0.077
Prior CABG, *n* (%)	4 (7.8)	2 (4.4)	2 (3.4)	1.000
Prior stroke, *n* (%)	3 (2.9)	2 (4.4)	1 (1.7)	0.579
Right ventricular end-diastolic diameter mm (IQR)	32.8 (29–35.3)	34.2 (28.5–38.8)	31.8 (29–35)	0.020
Left ventricular end-diastolic diameter mm (IQR)	49.9 (44–56)	50.3 (45–58)	49.6 (43–54.3)	0.670
Left ventricle ejection fraction % (IQR)	36.5 (28–45)	35.4 (28–45)	37.2 (29.3–45)	0.428
pH (IQR)	7.29 (7.25–7.36)	7.25 (7.18–7.35)	7.31 (7.26–7.38)	0.008
Etiology				
Cardiac origin of cardiac arrest, *n* (%)	98 (95.1)	41 (91.1)	57 (98.2)	0.165
STEMI, *n* (%)	72 (69.9)	29 (64.4)	43 (74.1)	0.387
NSTEMI, *n* (%)	3 (2.9)	1 (2.2)	2 (3.4)	1.000
Acute decompensation of heart failure, *n* (%)	9 (8.7)	3 (6.6)	6 (10.3)	0.728
Cardiomyopathy, *n* (%)	9 (8.7)	6 (13.3)	3 (5.2)	0.174
Valvular disease, *n* (%)	3 (2.9)	0	3 (5.4)	0.255
Other, *n* (%)	2 (1.9)	2 (4.4)	0	0.188
Non-cardiac origin, *n* (%)	5 (4.9)	4 (8.9)	1 (1.7)	0.165
Initial rhythm				
Shockable rhythm				
VT/VF (%)	84 (81.5)	31 (68.9)	53 (91.4)	0.03
Non-shockable rhythm				
Asystole (%)	10 (9.7)	6 (13.3)	4 (6.9)	0.297
Pulseless electric activity (%)	5 (4.9)	4 (8.9)	1 (1.7)	0.127
Bradycardia (%)	1 (1)	1 (2.2)	0	0.323
No available data	3 (2.9)	3 (6.7)	0	0.083

The "survivor" group (S) comprises participants who survived the observed period, such as the 30-day monitoring period. The "non-survivor" group (NS) consists of participants who did not survive this period. Tests for significance were conducted using Mann-Whitney tests for continuous variables and Pearson's chi-square for categorical variables. Two-tailed *p*-values smaller than 0.05 were considered significant.

BMI: body mass index, CABG: coronary artery bypass graft, CV: cardiovascular, IQR: interquartile range, n: number, NSTEMI: non-ST-elevation myocardial infarction, PAD: peripheral arterial disease, STEMI: ST-elevation myocardial infarction, TIA: transient ischemic attack, VF: ventricular fibrillation, VT: ventricular tachycardia.

and calibration were characterized by receiver operating characteristic (ROC) curve analysis / c statistic (with bootstrapped confidence intervals) and the calibration intercept/slope, respectively.[8] Since the performance of a model in the derivation data set may overestimate the true performance, we conducted internal validation by bootstrapping using 10,000 replicates.[9] Statistical analyses and graphical interpretation of the results were performed with R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) using the rms 6.7-1, Hmisc 5.1-1, pROC 1.18.5, ggplot2 3.4.4, wesanderson 0.3.7 packages. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Prehospital characteristics

The study population comprised 103 patients (32.1% women; median age 57.9 years). The "survivor" group (S) includes those who survived the 30-day mortality period, while the "non-survivor" group (NS) comprises those who did not. The baseline characteristics of the population are presented in Table 1.

Most of our patients died from cardiogenic shock, followed by multi-organ failure. Recurrent cardiac arrest was the third most common cause of death, with progression of the underlying disease being the least frequent. While active or passive WLST significantly contributes to mortality, it is not legally permitted in Hungary, limiting our study's ability to address it.

Predictors of 30-day mortality

Admission heart rate as a nonlinear variable appears to be the strongest predictor, according to the Akaike Information Criterion (AIC = 9.24) with a p-value of 0.0013. Other factors such as initial rhythm (AIC = 4.76, $p = 0.0093$), age (AIC = 4.39, $p = 0.0115$), pH (AIC = 3.68, $p = 0.0171$), and right ventricular end-diastolic diameter (RVEDD) (AIC = 2.49, $p = 0.0342$) also significantly predict 30-day mortality. The best prognostic markers selected for the model can be seen in Fig. 1.

A detailed analysis of the predictors is shown in Fig. 2. The plots indicate a non-linear relationship, with an initial decrease in mortality probability as heart rate increases, followed by an increase at higher heart rates. Furthermore, patients with a shockable initial rhythm have a lower probability of 30-day mortality compared to those with a non-shockable rhythm. The plot also suggests an inverse relationship; higher pH (non-acidic state) values correlate with a lower probability of 30-day mortality. Finally, a linear association can be seen between RVEDD and the log odds of 30-day mortality.

The model's area under the curve (AUC) value is 0.8352, with a bootstrapped 95% confidence interval ranging from 0.7548 to

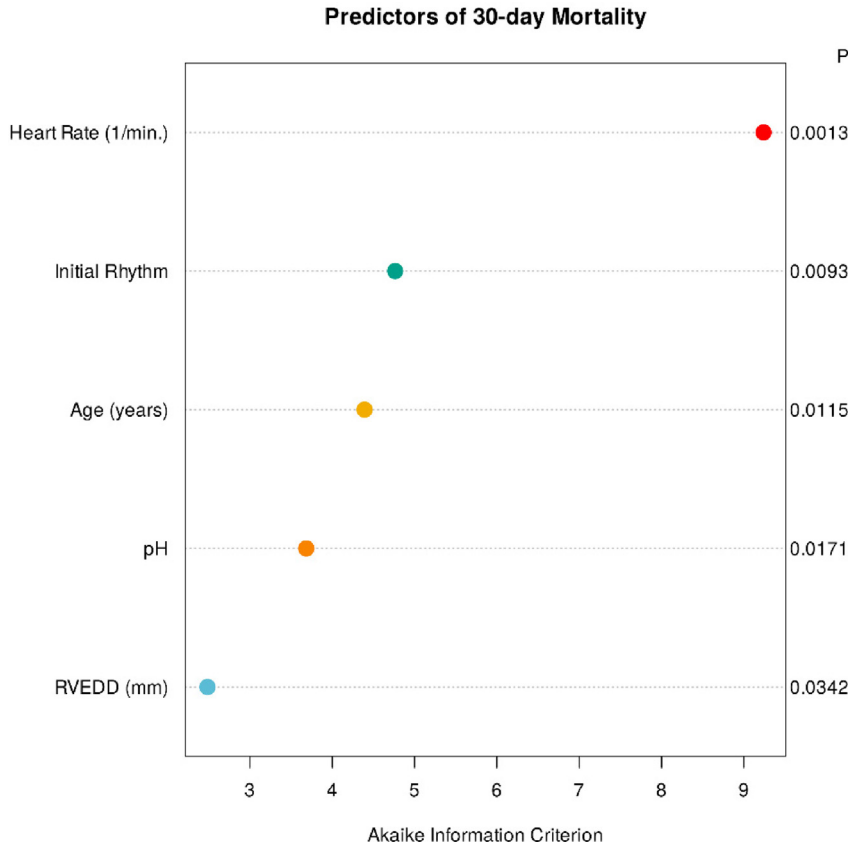

Fig. 1 – Prognostic importance of variables in the model. Dot charts depict the importance of each variable as measured by the Akaike Information. The p value denotes statistical significance according to analysis of variance using likelihood ratio chi-square tests. RVEDD: right ventricular end-diastolic diameter.

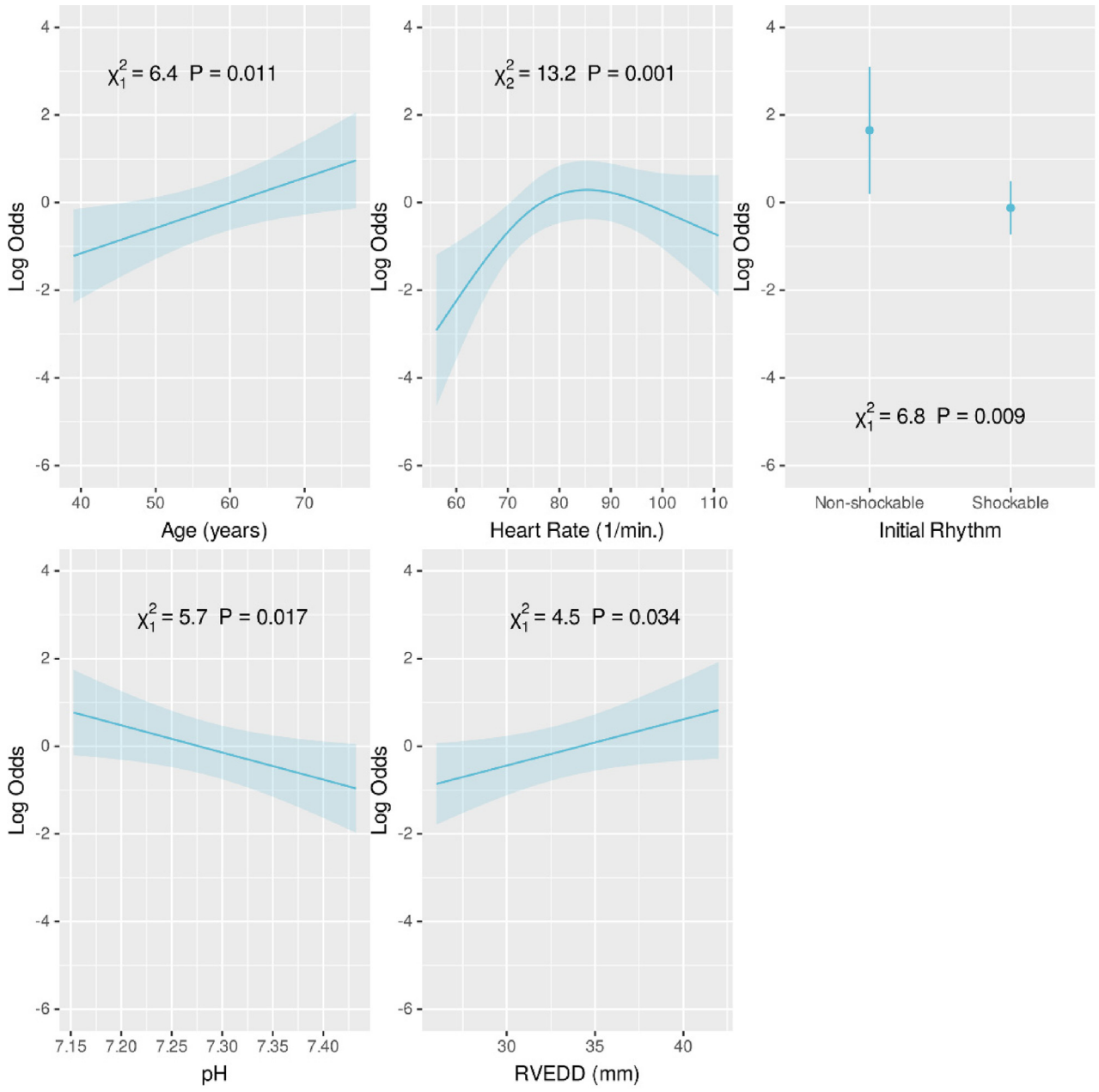

Fig. 2 – Relationship between various predictors and the log odds of 30-day mortality in the context of TTM after OHCA. Age vs. 30-day mortality, Heart Rate vs. 30-day mortality, initial rhythm vs. 30-day mortality, pH vs. 30-day mortality, RVEDD vs. 30-day mortality. In the plots, shaded areas represent the confidence intervals, the narrower the shaded area, the more precise the estimation is. RVEDD: right ventricular end-diastolic diameter.

0.9069. The red dot on the curve represents the optimal cut-off value of 0.4659 based on the maximum value of Youden index.[10] Using this cut-off, the test's sensitivity is 0.7778 and the specificity is 0.7586 (Fig. 3.).

Internal validation

Internal validation of the discrimination and calibration of the models was performed using bootstrap resampling with 10,000 replicates. The graphical assessment of the calibration of the apparent and optimism-corrected model is depicted in Fig. 4.

Nomogram

To provide a more precise prediction of the expected outcome for each selected parameter value, we have introduced a weighting system, as illustrated in Fig. 5. Each patient is assigned a total score based on specific criteria, and this score correlates with the likelihood of mortality within 30 days post-arrest.

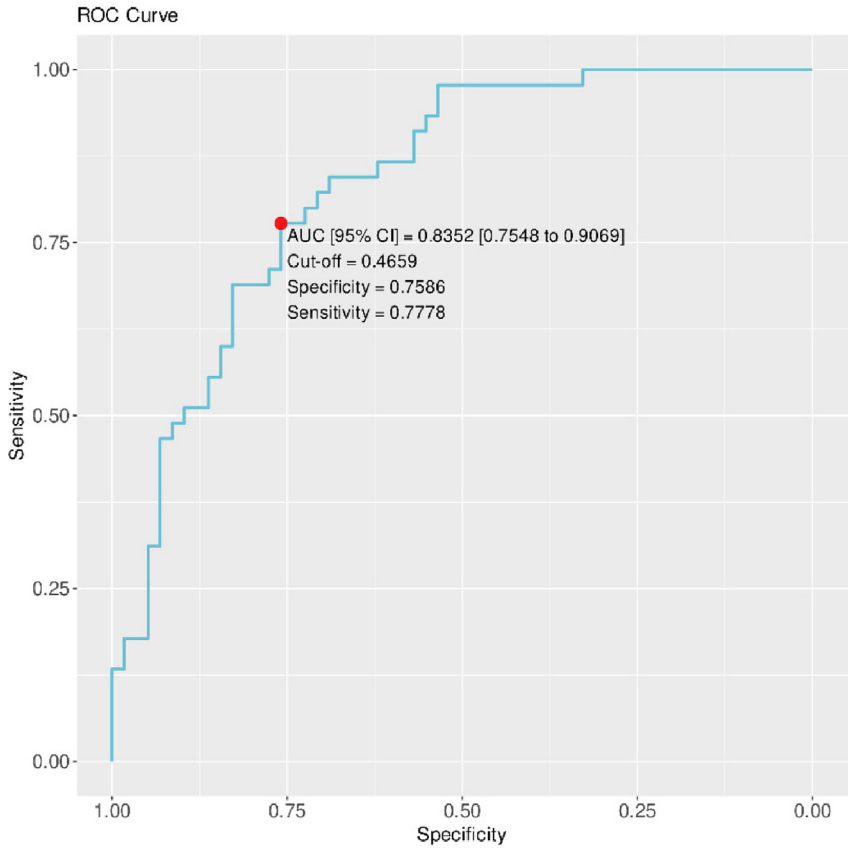

Fig. 3 – Receiver operating characteristic curve of the model for identifying 30-day mortality of patients treated with targeted temperature management after out-of-hospital cardiac arrest. AUC: area under curve, CI: confidence interval. Red dot represents the AUC value based on the best ratio of sensitivity and specificity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Discussion

Main findings

Our analysis has revealed crucial early predictors of 30-day mortality, particularly relevant for evaluating patients within 12 h of admission during therapy for post-cardiac arrest syndrome and targeted temperature management. These predictors include heart rate, age, blood pH, initial rhythm, and RVEDD.

The importance of our study is highlighted by the limitations of current predictive scoring systems within the targeted temperature management group post-resuscitation, especially within the initial 12 h. Despite these challenges, accurately predicting patient outcomes during this critical timeframe remains essential. Therefore, we crafted our model with a specific focus on these key variables.

Referencing preceding reports and the place of our model in clinical practice

The debate over the application of targeted temperature management after cardiac arrest remains a key point of discussion, especially among specific patient groups where its potential benefits are actively explored and researched.[11]

Table 2 summarizes the studies that examined different intensive care unit (ICU) scoring systems used in the TTM subpopulation. However, it is crucial to recognize scores specifically developed for OHCA patients undergoing TTM, such as CAST, rCAST, and OHCA scores, which perform similarly to our score.[12–14] We have also included additional OHCA-specific scores,[15–19] many of which have multiple external validations and examine long-term outcomes.[20,21] However, many of the existing scores include prehospital parameters such as absence of witness and time until return of spontaneous circulation, which can often be uncertain. In Hungary, high-quality basic life support is unfortunately performed infrequently, and the exact time of collapse is often unknown. Furthermore, the Glasgow Coma Scale motor score is less informative in patients who remain in poor condition, are comatose, ventilated, and sedated. Since neurological assessment is not feasible during TTM, we did not include parameters requiring neurological evaluation in the RAPID score system. Furthermore, the inclusion of RVEDD in the RAPID score highlights the importance of right ventricular function in predicting outcomes, which is a relatively underexplored area in early prognostic models. This parameter can provide additional information regarding right ventricular failure.

Furhermore, these scoring systems can also pose greater challenges and exhibit lower predictive value in the TTM subpopulation. That is because during TTM, numerous physiological changes occur, including bradycardia, tachycardia, tachypnea, increased diuresis, heightened metabolic rate, hyperglycemia, changing hematocrit, decreased platelet, and leukocyte counts.[22]

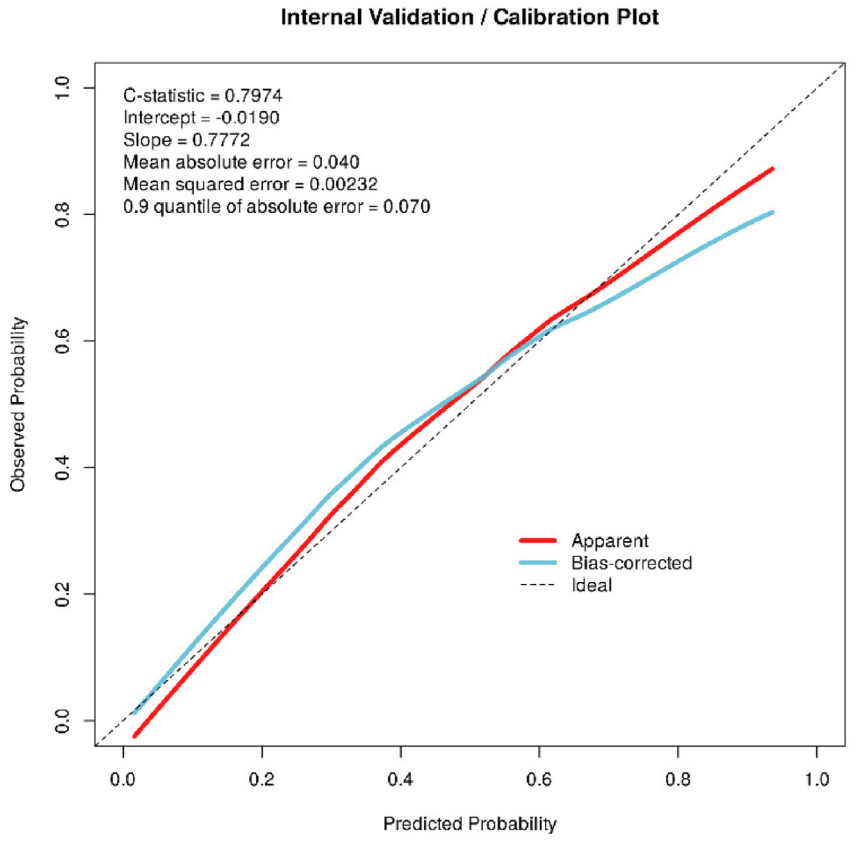

Fig. 4 – Calibration plot showing evaluation of the performance of the created predictive model.

Variants based on the RAPID scoring system

R: Heart **R**ate: A meta-analysis of 681 comatose post-cardiac arrest patients undergoing TTM found that sinus bradycardia (<50 bpm) significantly reduced 180-day mortality.[27] Oksanen et al.'s study of 504 patients showed lower mean heart rates and heart rates below 60, 80, and 100 bpm were linked to better one-year neurological outcomes.[28] Additionally, a large multicenter cohort confirmed bradycardia (<50 bpm) during TTM at 33 °C is associated with lower 180-day mortality and better neurological outcomes.[29] In our study lower heart rate is also associated with favorable survival ($p = 0.0013$). However, it is important to highlight that as shown in Fig. 2. Heart rate follows an inverted J-shaped curve, meaning above 70 beats per minute, the mortality risk is minimally 30%, at 75 beats per minute it rises to 50%, and interestingly, beyond 110 beats per minute, it starts to decrease again to 30–35%. It may refer to a compensatory mechanism to maintain physiologic circulation. Furthermore, the wide confidence interval indicates greater variability and uncertainty in the estimate at these higher heart rate values, which can be attributed to the smaller sample size within this range. While our data clearly suggest that lower heart rate is associated with better outcomes, the influence of high heart rate may indeed be limited by the relatively small number of cases in this category.

A: Age: It is known that with increasing age, there is a higher risk of mortality in the OHCA population.[30–32] Our study also confirmed that patients with advanced age experience significantly higher mortality rates ($p = 0.007$).

P: pH: Severe metabolic acidosis increases the mortality risk in this patient population especially, as proven by extensive research.[33–35] In our study the average time between taking the blood gas sample and the initiation of cooling was 0.9 ± 1.3 h. The pH value was also an effective predictor of 30-day mortality. Additionally, as tissue hypoperfusion rate and duration increases, metabolism shifts towards the anaerobic pathway, leading to an increased lactate production and profound metabolic acidosis, which can be further worsened by respiratory acidosis due to ventilation difficulties during and after resuscitation.[22] Our study revealed an inverse relationship: lower pH values were associated with an increased likelihood of 30-day mortality ($p = 0.0171$).

I: Initial rhythm: Shockable initial rhythms correlate with better survival rates in OHCA patients. While data from the Swedish Cardiac Arrest Registry show higher survival rates for ventricular fibrillation cases,[36] a study by Lee et al. found no significant difference in survival between initial shockable rhythms and turn-to-shockable rhythms during TTM.[37] In our study, shockable rhythm was detected in 84% of the cases, which met the ratio presented in the TTM2 trial but not representing the EURECA II numbers.[2,6] This may be related to the fact that our clinic has a select group of patients with SCA: more than 90% of cases are of cardiac origin, for which a higher prevalence of shockable rhythm is well known.[38] Non-shockable rhythm predicts the presence of heart failure or other non-cardiac comorbidities e.g., hypoxic/metabolic e.g. acut kidney injury with hyperkalemic insult that may result in a higher mortality rate.[39] The non-shockable initial rhythm was identified as a predictor of 30-day mortality, demonstrating poorer survival compared to shockable rhythms ($p = 0.0093$) in our study.

D: Right ventricular end-diastolic **D**iameter: Currently, we have limited information regarding the prognostic role of echocardiographic parameters. Recent studies indicate that reduced TAPSE,

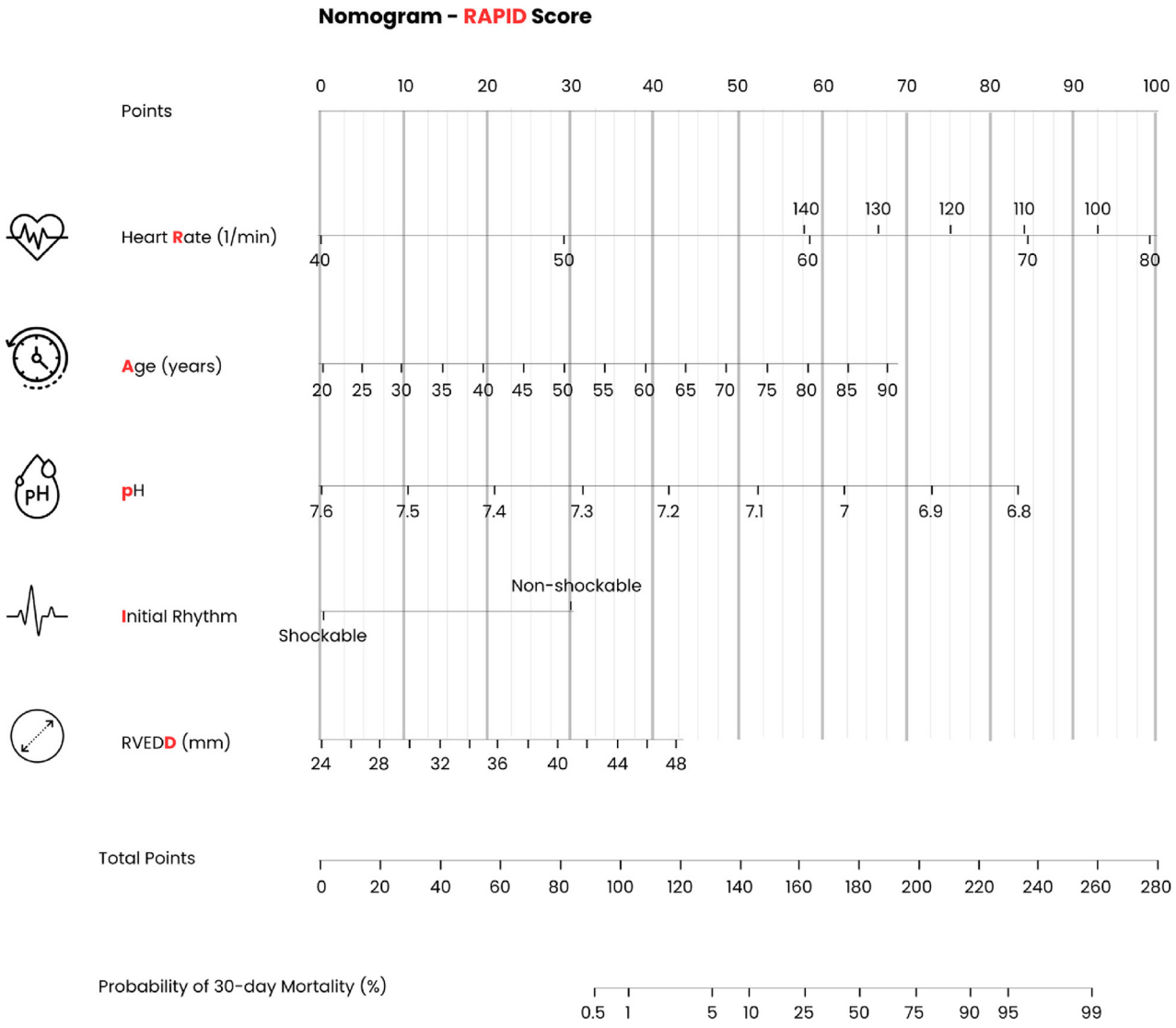

Fig. 5 – The RAPID score nomogram is a tool used to estimate the mortality risk for out-of-hospital cardiac arrest patients undergoing TTM. Points are assigned for each variable by drawing a line upward from the corresponding variable to the points line. The sum of points plotted on the total points line corresponds with the probability of 30-day mortality in TTM population. Users' instructions: Locate the patient's heart rate on the nomogram. Follow the line upward from the heart rate to find the predicted RAPID score for that heart rate. Repeat this process for each of the other four variables: age, pH, initial rhythm and RVEDD. Find where each variable's line intersects the predicted RAPID score axis. By considering the values associated with these intersections for all five variables, determine the overall predicted RAPID score for the patient. Alternatively, the online calculator may be used via https://www.rapidscore.eu/.

indicating right ventricular dysfunction, predicts early mortality in ICU patients. However, a 2021 study by Jansen et al. on 99 patients post-OHCA found that early TAPSE did not predict outcomes.[40] Additionally, in a study of 350 subjects, for right ventricular fractional area change independently predicted sudden cardiac death, with increased risk when combined with low left ventricular ejection fraction.[41] Our study has also pointed out that during the first 12 h of cooling, the right ventricular end-diastolic diameter can effectively predict 30-day mortality in patients undergoing TTM ($p = 0.0342$). RVEDD is a crucial measure of right ventricular size and preload. An increased RVEDD may indicate right ventricular dilation, which can be a result of volume overload, high intrathoracic pressures, or poor right ventricular compliance. In the setting of temperature control, maintaining optimal hemodynamics is essential, and variations in RVEDD can significantly influence the management and outcomes of TTM. An enlarged RVEDD also reflects the right ventricle's struggle to cope with increased afterload, emphasizing the need for careful monitoring and management. That is because TTM induces an increase in systemic vascular resistance, leading to a decrease in left and right ventricular cardiac output (a forward failure). Consequently, backward left ventricular failure during TTM may elevate the workload of the right ventricle, causing myocardial stretching (strain) and reducing the outward displacement of the right ventricular cavity, reflected in parameters such as the impaired TAPSE and right ven-

Table 2 – Comparison of different scoring systems and models for prognostication in patients with PCAS undergoing TTM.

First author	Year	Study design		Study period	Country	No. of patients	PCAS after	No. of TTM patients (%)	Mortality outcome	Prediction model or score system	AUC
Chen[23]	2022	Retrospective cohort	Single center	2015–2021	Taiwan	108	OHCA or IHCA	108 (100)	28-day mortality	rCAST	0.794 (0.706–0.866)
Choi[12]	2018	Retrospective cohort	Single center	2010–2013	South Korea	173	OHCA	173 (100)	30-day mortality	APACHE II, SAPS II, OHCA	At 0 h: APACHE II: 0.715 (0.642–0.781); SAPS II: 0.686 (0.612–0.755); SOFA: 0.641 (0.564–0.712); OHCA: 0.740 (0.668–0.805)
Isenschmid[24]	2018	Prospective cohort	Single center	2012–2017	Switzerland	349	OHCA or unobserved IHCA	200 (57)	In-hospital and 30-day mortality	CAHP, OHCA, APACHE II, SAPS II	OHCA: 0.80 (0.75, 0.85); CHAP: 0.85 (0.80, 0.89); APACHE II: 0.80 (0.75, 0.84); SAPS II: 0.78 (0.73, 0.83)
Matsuda[25]	2020	Retrospective cohort	Single center	2015–2018	Japan	231	OHCA	144 (62)	30-day mortality	SOFA	0.852 (0.803–0.900)
Nishikimi[14]	2019	Prospective cohort	Multicenter	2014–2015	Japan	460	OHCA	460 (100)	30- and 90-day mortality	rCAST	0.832
Yoon[26]	2018	Retrospective cohort	Single center	2010–2015	South Korea	143	OHCA	143 (100)	28-day mortality	SOFA, APACHE II	At admission: SOFA: 0.634 (0.541–0.726); extracerebral SOFA: 0.619 (0.525–0.713); APACHE II: 0.637 (0.546–0.729)
Lim[16]	2022	Observational study	Multicenter	2016–2020	Korea	4712	OHCA	531 (11.3)	Favorable neurological outcome, survival to hospital discharge	ED-PLANN	Development cohort: 0.93 (95% CI, 0.92–0.94) Validation cohort: 0.94 (95% CI, 0.92–0.95)
Maupain[18]	2015	Prospective cohort	Multicenter	2011–2012	France	819	OHCA	NA	Neurological status at ICU discharge	CAHP	Development cohort: 0.93 Validation data sets: 0.91 and 0.85
Coppler[15]	2015	Prospective and retrospective cohort	Multicenter	2011–2013	United States	607	OHCA and IHCA	420 (69.2)	Survival to hospital discharge	PCAC	0.82
Pareek[19]	2020	Prospective cohort	Single center	2012–2017	United Kingdom	373	OHCA	NA	Poor neurological outcome	MIRACLE2	Development cohort: 0.90 Validation cohorts: 0.84/0.91
Martinell[17]	2017	Post hoc analysis	Multicenter	2010–2013	Europe and Australia	933	OHCA	939 (100)	6 months survival	Target temperature management risk score	0.842 (0.840–0.845)

APACHE II: acute physiology and chronic health evaluation II; CAHP: cardiac arrest hospital prognosis; OHCA: out-of-hospital cardiac arrest; PCAC: Pittsburgh Cardiac Arrest Category; rCAST: revised cardiac arrest survival test; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; TTM: targeted temperature management.

tricular end-diastolic diameter. This phenomenon can be also explained by the physiological changes occurring during TTM.

Conclusion

The RAPID score, designed for early and easy to use risk assessment in patients undergoing TTM after OHCA, incorporates heart rate, age, pH, initial rhythm, and right ventricular end-diastolic diameter. The model demonstrated robustness through ROC analysis and internal validation. However, the limited sample size, single-center nature necessitates further research. Additional external validation studies are warranted to confirm the model's predictive performance across diverse populations.

Limitation

While our model shows promise in early risk assessment for TTM patients after OHCA, several limitations must be acknowledged. The retrospective design introduces biases, preventing causal conclusions. Our study, focused on cardiac-origin SCA due to our cardiovascular institute affiliation, may not be applicable to other SCA etiologies. Additionally, 84% of our cases had shockable rhythms, likely due to our clinic's focus on cardiac-origin sudden death, leading to higher shockable rhythm incidence. Unaccounted confounding variables may also affect predictive accuracy. The small sample size from a single center limits generalizability, and the lack of application to different patient sets further restricts robustness. Additionally, there is a risk of self-fulfilling prophecies in predicting outcomes within a retrospective cohort. Our tool does not predict which patients will benefit more from specific treatments like temperature control or cardiac catheterization, highlighting areas for future research. Our score does not directly assess neurological outcomes. We focused exclusively on early mortality and did not analyze neurological outcomes, as our primary aim was to evaluate immediate survival predictors during TTM. Therefore, while our study is a step toward better early risk assessment, it requires external validation across diverse cohorts. Future studies should incorporate a wider range of predictive factors, including direct brain injury assessments.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval number: 194/2020) and was in accordance with the Declaration of Helsinki.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author (zima.endre@gmail.com) on reasonable request.

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CRediT authorship contribution statement

Bettina Nagy: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ádám Pál-Jakab:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gábor Orbán:** Writing – review & editing, Validation, Investigation. **Boldizsár Kiss:** Writing – review & editing, Visualization. **Alexa Fekete-Győr:** Writing – review & editing. **Gábor Koós:** Writing – review & editing, Validation, Investigation. **Béla Merkely:** Resources, Project administration, Funding acquisition. **István Hizoh:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Enikő Kovács:** Writing – review & editing, Validation. **Endre Zima:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100732.

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