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An LDAR-Based Nomogram for Early Prediction of 28-Day Mortality in Heatstroke: A Multicenter Retrospective Cohort Study

Running title: LDAR-Based Nomogram for Heatstroke Mortality

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Conflict of interest

The authors declare that they have no conflict of interest.

Abstract

Background Early risk stratification is important in heatstroke. This study aimed to evaluate the association between the lactate–D-dimer product-to-albumin ratio (LDAR) and 28-day all-cause mortality and to develop an LDAR-integrated risk prediction model.

Methods This multicenter retrospective cohort study enrolled 230 adults with heatstroke presenting within 24 h of onset to the emergency departments (EDs) of eight centers in Sichuan, China. Multivariable logistic regression evaluated the association between LDAR and 28-day all-cause mortality. An LDAR-integrated nomogram was developed and assessed using receiver operating characteristic analysis, calibration, bootstrap resampling, and decision curve analysis.

Results Among 230 patients, 80 (34.8%) died within 28 days. After adjustment for age, sex, temperature at ED presentation, and Sequential Organ Failure Assessment (SOFA) score, LDAR remained independently associated with mortality (adjusted odds ratio, 1.344; 95% confidence interval [CI], 1.104–1.636; P = 0.003). The nomogram incorporating LDAR, age, temperature at ED presentation, and SOFA score achieved an area under the curve (AUC) of 0.832 (95% CI, 0.778–0.885), higher than that of SOFA alone (0.774; P = 0.011) but not significantly different from that of LDAR alone (0.794; P = 0.242). Bootstrap internal validation yielded a mean AUC of 0.825 and a mean absolute calibration error of 0.0271. At the optimal probability threshold of 0.308, sensitivity and specificity were 80.0% and 74.0%, respectively, and decision curve analysis suggested potential clinical net benefit. No statistically significant difference in discrimination was observed between classic and exertional heatstroke (AUC, 0.842 vs 0.817; P = 0.666). When the onset-to-presentation window was extended to ≤48 and ≤72 h, the corresponding AUCs were 0.793 and 0.788, respectively.

Conclusion LDAR was independently associated with 28-day mortality and may complement SOFA-based risk assessment. The LDAR-integrated nomogram showed good internal performance and may support early risk stratification, but requires external validation.

Keywords: Heatstroke; lactate–D-dimer product-to-albumin ratio; nomogram; risk prediction.

Background

With global warming, the incidence of heat-related illnesses and their associated morbidity and mortality continue to rise [1–3]. Heatstroke, the most severe form, is characterized by hyperthermia and central nervous system dysfunction and can rapidly progress to multiorgan dysfunction and death [4,5]. Mortality rates of up to 26.5% and 63.2% have been reported for exertional and classic heatstroke, respectively, in intensive care settings [4]. Early identification of patients at high risk of death is therefore essential to guide clinical monitoring, organ support, and treatment decisions.

The Sequential Organ Failure Assessment (SOFA) score is widely used to quantify organ dysfunction in critically ill patients and has demonstrated prognostic value in heatstroke [6]. However, heatstroke involves not only organ dysfunction but also direct thermal injury, tissue hypoperfusion, metabolic derangements, coagulation activation, microcirculatory dysfunction, endothelial injury, and capillary leakage [4,7–9]. Conventional severity scores or individual biomarkers may therefore inadequately capture the overall burden of systemic injury. Previous evidence indicates that lactate independently predicts mortality in severe heatstroke and that combining lactate with SOFA improves mortality prediction over SOFA alone, supporting the potential value of incorporating additional biomarkers into conventional organ dysfunction scores [10,11].

Lactate, D-dimer, and albumin may reflect hypoperfusion, coagulation activation, and inflammation-related capillary leakage, respectively [4,7–13]. Accordingly, the lactate–D-dimer product-to-albumin ratio (LDAR) was constructed as a composite index integrating hypoperfusion, coagulation activation, and hypoalbuminemia, with the aim of complementing SOFA-based prognostic assessment. As the prognostic value of LDAR in heatstroke remains unclear, this multicenter retrospective cohort study evaluated its independent association with 28-day all-cause mortality and developed an LDAR-integrated nomogram to assess its potential utility for early risk stratification.

Methods

Study design

This multicenter retrospective cohort study was approved by the Biomedical Ethics Review Committee of West China Hospital, Sichuan University (No. 2022-1478), and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective study design.

Study population

Patients with heatstroke presenting to the emergency departments of eight medical centers in Sichuan Province, China, between July 1, 2022, and October 31, 2024, were consecutively screened. Data were collected using a standardized case report form and entered into a centralized database. For patients with multiple eligible presentations during the study period, only the first presentation was included.

Heatstroke diagnosis

Heatstroke was diagnosed according to the Chinese expert consensus [14]. Diagnosis was based on a history of exposure to a hot and humid environment or strenuous physical exertion and at least one of the following clinical manifestations: central nervous system dysfunction, core temperature greater than 40°C, dysfunction of two or more organs, or severe coagulopathy or disseminated intravascular coagulation, in the absence of an alternative explanation.

Inclusion and exclusion criteria

Patients were eligible if they (1) were aged ⩾18 years; (2) presented to a participating ED within 24 h of heatstroke onset; (3) had lactate, D-dimer, and albumin measured and the SOFA score calculated within 2 h of presentation; (4) had complete data on all variables required for the primary analysis; and (5) had documented 28-day vital status.

Exclusion criteria were (1) advanced or progressive malignancy; (2) active or severe hematologic disease; (3) end-stage liver disease; (4) end-stage kidney disease requiring maintenance dialysis; (5) end-stage heart disease, defined as New York Heart Association class IV functional status; or (6) end-stage pulmonary disease requiring

long-term oxygen therapy or involving chronic respiratory failure.

Data collection

Trained investigators collected data from medical records, laboratory databases, follow-up records, and telephone interviews when required, using a standardized case report form. Data included (1) demographic and clinical characteristics: age, sex, occupation, personal history, and comorbidities; (2) heatstroke presentation: setting, precipitating factors, symptoms, time from onset to presentation, and heatstroke subtype; (3) status at emergency department presentation: core temperature, heart rate, blood pressure, respiratory rate, peripheral oxygen saturation, level of consciousness, shock, mechanical ventilation, and SOFA score; (4) laboratory findings: hematologic and biochemical parameters, cardiac biomarkers, coagulation indices, disseminated intravascular coagulation status, and blood gas measurements; and (5) outcome: vital status within 28 days of onset.

Rationale and definition of LDAR

LDAR was constructed a priori as a mechanism-based exploratory composite index of complementary pathophysiological abnormalities in heatstroke, with lactate and D-dimer as positive components and albumin as an inverse component. It was calculated using the first measurements obtained within 2 h of ED presentation as follows:

$$\mathbf{LDAR} = \frac{\mathbf{Lactate \times D\text{-}dimer}}{\mathbf{Albumin}}$$

Lactate, D-dimer, and albumin were expressed in mmol/L, mg/L fibrinogen-equivalent units (FEU), and g/L, respectively.

Primary outcome

The primary outcome was 28-day all-cause mortality after heatstroke onset. Vital status was ascertained from medical and follow-up records or, when necessary, by telephone follow-up.

Nomogram development and validation

Candidate predictors were selected a priori based on clinical relevance and the study objective. The multivariable logistic regression model included age, sex, temperature at ED presentation, SOFA score, and LDAR. Individual LDAR components and variables already represented in SOFA were excluded to reduce collinearity. Predictors with $P < 0.05$ were retained in the final model, which included age, temperature at ED presentation, SOFA score, and LDAR and was presented as a nomogram. Discrimination, calibration, and potential clinical utility were assessed using receiver operating characteristic curves, calibration curves, and decision curve analysis, respectively. Internal validation used 1,000 bootstrap resamples.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables are reported as mean (standard deviation) or median (interquartile range) and were compared using the independent-samples t test or Mann–Whitney U test, as appropriate. Categorical variables are reported as number (percentage) and were compared using Pearson's χ^2 test or Fisher's exact test. Associations with 28-day all-cause mortality were examined using univariable and multivariable logistic regression, with candidate covariates prespecified based on clinical relevance and the study objective. Discrimination was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC). DeLong's test was used to compare the nomogram AUC with those of LDAR and SOFA and to compare nomogram AUCs between classic and exertional heatstroke. Optimal thresholds were determined using the Youden index. Model fit was assessed using the Hosmer–Lemeshow test. All tests were two-sided, with $P < 0.05$ indicating statistical significance. Analyses were performed using SPSS 21.0 and R 4.2.2.

Sensitivity analysis

To assess robustness across broader onset-to-presentation windows, nomogram discrimination was evaluated in the ≤48 h and ≤72 h cohorts. Because both cohorts included the primary ≤24 h cohort, these analyses were considered sensitivity analyses

rather than independent validation.

Results

Study selection and baseline characteristics

A total of 333 patients with heatstroke were screened. After excluding 24 patients with missing key clinical data and 79 who presented more than 24 h after onset, 230 patients were included in the primary analysis. At 28 days, 150 (65.2%) were alive and 80 (34.8%) had died. The study flowchart is shown in Figure 1.

Baseline characteristics are presented in Table 1. Compared with survivors, nonsurvivors were more frequently male, more likely to have a maximum preadmission temperature >40°C, and more likely to have a history of alcohol use (all $P < 0.05$). Age, heatstroke subtype, onset-to-presentation interval, location of onset, occupation, other medical history, and prehospital management did not differ significantly between groups.

At ED presentation, nonsurvivors had higher body temperature, heart rate, quick SOFA (qSOFA) score, and SOFA score and lower blood pressure, peripheral oxygen saturation, and Glasgow Coma Scale (GCS) score (all $P < 0.05$). They also exhibited greater hepatic and renal dysfunction, hypoperfusion, muscle injury, and coagulation abnormalities, as reflected by higher lactate, creatinine, blood urea nitrogen, aminotransferase, myoglobin, and D-dimer levels and lower platelet count, albumin, pH, and ratio of arterial oxygen partial pressure to inspired oxygen fraction (PaO_2/FiO_2) (all $P < 0.05$). LDAR was substantially higher in nonsurvivors than in survivors [1.03 (0.31–2.61) vs 0.18 (0.05–0.45); $P < 0.001$].

Multivariable association between LDAR and 28-day all-cause mortality

Multivariable logistic regression showed that LDAR remained independently associated with 28-day all-cause mortality after adjustment for age, sex, temperature at ED presentation, and SOFA score (Table 2). Each one-unit increase in LDAR was associated with a 34.4% increase in the odds of death (adjusted odds ratio [OR], 1.344;

95% confidence interval [CI], 1.104–1.636; P = 0.003). Age, temperature at ED presentation, and SOFA score were also independently associated with mortality (all P < 0.05), whereas sex was not statistically significant (P = 0.069).

Nomogram development and visualization

A nomogram incorporating age, temperature at ED presentation, LDAR, and SOFA score was developed to estimate the probability of 28-day all-cause mortality (Figure 2). The nomogram achieved an AUC of 0.832 (95% CI, 0.778–0.885) in the primary cohort. Internal validation using 1,000 bootstrap resamples yielded a mean AUC of 0.825 (95% CI, 0.802–0.841; Supplementary Figure S1).

Nomogram discrimination and comparative performance

ROC analysis was used to compare the discrimination of the nomogram, LDAR, and SOFA score for 28-day all-cause mortality (Figure 3). The AUC was 0.832 (95% CI, 0.778–0.885) for the nomogram, 0.794 (95% CI, 0.736–0.853) for LDAR, and 0.774 (95% CI, 0.712–0.837) for SOFA. DeLong's test showed that the nomogram had a significantly higher AUC than SOFA (P = 0.011), whereas no significant difference in AUC was observed between the nomogram and LDAR (P = 0.242; Table 3).

Youden index–derived optimal thresholds and corresponding predictive performance are presented in Table 4. At a predicted probability threshold of 0.308, the nomogram yielded 80.0% sensitivity and 74.0% specificity. The optimal thresholds for LDAR and SOFA were 0.665 and 5.5, yielding sensitivities of 62.5% and 80.0% and specificities of 83.3% and 66.0%, respectively.

Nomogram calibration

Calibration was assessed by comparing predicted and observed probabilities of 28-day all-cause mortality using a calibration curve (Figure 4). The bias-corrected mean absolute calibration error was 0.0271. The Hosmer–Lemeshow test showed no evidence of lack of fit (χ^2 = 10.953; P = 0.204).

Potential clinical utility of the nomogram

Decision curve analysis was used to assess the clinical net benefit of the nomogram (Figure 5). The nomogram provided greater net benefit than either the treat-all or treat-none strategy across threshold probabilities of 0.0135–0.6000. At the ROC-derived optimal threshold of 0.308, its net benefit was 0.203, compared with 0.058 for the treat-all strategy and 0 for the treat-none strategy.

Nomogram discrimination across heatstroke subtypes

The nomogram achieved AUCs of 0.842 (95% CI, 0.777–0.906) in classic heatstroke and 0.817 (95% CI, 0.723–0.910) in exertional heatstroke, with no statistically significant difference between subtypes (DeLong's test, P = 0.666; Supplementary Figure S2).

Sensitivity analysis across presentation time windows

The onset-to-presentation window was extended to ≤48 h (n = 248) and ≤72 h (n = 263) to assess the robustness of nomogram discrimination. The corresponding AUCs were 0.793 (95% CI, 0.734–0.853) and 0.788 (95% CI, 0.729–0.847), respectively (Supplementary Figure S3). Although slightly lower than the primary-analysis AUC, these estimates indicated that discrimination remained acceptable. Because the cohorts overlapped, these analyses were considered sensitivity analyses rather than independent validation.

Discussion

The prognosis of heatstroke is shaped by multiple interrelated pathophysiological processes, including tissue hypoperfusion, coagulation dysfunction, and multiorgan injury, that may not be adequately reflected by individual biomarkers or conventional organ dysfunction scores. In this study, LDAR, which integrates lactate, D-dimer, and albumin, was independently associated with 28-day all-cause mortality. After adjustment for age, sex, temperature at ED presentation, and SOFA score, each one-unit increase in LDAR was associated with 34.4% higher odds of death. A nomogram incorporating LDAR, age, temperature at ED presentation, and SOFA score

demonstrated good discrimination and calibration, with potential clinical net benefit. Its AUC was numerically higher than those of LDAR and SOFA alone and was significantly higher than that of SOFA. These findings suggest that LDAR may capture prognostically relevant pathophysiological information complementary to SOFA and support its potential use in early risk stratification after heatstroke.

LDAR is calculated as the product of lactate and D-dimer divided by albumin, thereby integrating three routinely available emergency laboratory measures. Lactate reflects tissue perfusion and systemic metabolic status; elevated levels may result from impaired perfusion, an imbalance between oxygen supply and demand, accelerated stress-induced glycolysis, or reduced clearance [15,16]. In heatstroke, lactate levels are higher in nonsurvivors and have been associated with multiorgan dysfunction and mortality [10,17,18]. D-dimer, a specific degradation product of cross-linked fibrin, reflects coagulation activation and secondary fibrinolysis [19]. Sustained coagulation activation promotes microthrombosis, impairs microcirculatory perfusion, and aggravates organ dysfunction, thereby contributing to the development of multiple organ dysfunction syndrome (MODS) in heatstroke [8]. D-dimer levels increase with the severity of coagulopathy and are closely associated with heatstroke-induced coagulopathy and disseminated intravascular coagulation (DIC); patients with DIC have higher rates of MODS and mortality [20–22]. Albumin is essential for maintaining plasma oncotic pressure and vascular barrier integrity. Hypoalbuminemia may reflect systemic inflammation, capillary leakage, impaired hepatic synthesis, and increased catabolism [23–25]. Albumin extravasation further reduces intravascular oncotic pressure and promotes tissue edema, whereas its interaction with the endothelial glycocalyx contributes to vascular barrier and microcirculatory homeostasis [24]. In heatstroke, hypoalbuminemia may result from the combined effects of inflammation, endothelial injury, and hepatic dysfunction and has been associated with DIC and adverse outcomes [22]. Collectively, lactate, D-dimer, and albumin capture distinct but interconnected aspects of hypoperfusion and metabolic stress, coagulation–fibrinolysis activation, systemic inflammation, and endothelial barrier dysfunction. LDAR may therefore

provide a more integrated measure of the combined burden of hypoperfusion, coagulopathy, and hypoalbuminemia, which may explain its independent association with mortality.

Whereas SOFA primarily quantifies organ dysfunction, LDAR, derived from early laboratory measurements, may additionally capture metabolic, microcirculatory, and coagulation abnormalities. LDAR achieved an AUC of 0.794 for predicting 28-day all-cause mortality. At the optimal cutoff of 0.665, LDAR had a specificity of 83.3% but a sensitivity of 62.5%, suggesting that it may be more useful for identifying high-risk patients than for ruling out mortality risk when used alone. The nomogram incorporating age, temperature at ED presentation, LDAR, and SOFA score yielded a more balanced sensitivity–specificity profile, with a sensitivity of 80.0% and a specificity of 74.0% at an optimal predicted probability threshold of 0.308. Thus, LDAR may serve as a readily available early risk marker, whereas the nomogram may enable more comprehensive individualized risk estimation.

LDAR is clinically accessible because it is derived from routinely available emergency laboratory measurements and requires no specialized testing. It may support prompt identification of patients requiring additional evaluation and intensified monitoring, particularly in resource-constrained settings. The nomogram showed no statistically significant difference in discrimination between heatstroke subtypes and retained acceptable discrimination in sensitivity analyses using extended onset-to-presentation windows, providing preliminary support for its robustness.

Strengths and limitations

LDAR combines three routinely available laboratory measures without requiring specialized testing and achieved an AUC similar in magnitude to that of SOFA. In this cohort, the nomogram incorporating LDAR, age, temperature at ED presentation, and SOFA showed significantly better discrimination than SOFA alone, suggesting potential value for early risk stratification.

This study has several limitations. First, its retrospective design may have introduced selection and information bias and residual confounding, precluding causal inference. Second, LDAR was based on the first measurements of its components obtained within 2 h of ED presentation; temporal changes and the effects of early interventions were not assessed. Third, the nomogram underwent only bootstrap internal validation, as the subgroup and overlapping-cohort sensitivity analyses did not constitute external validation. Fourth, LDAR is a newly constructed, unit-dependent exploratory index; therefore, its formula, prognostic performance, and cutoff require validation using consistent measurement units. Prospective, geographically diverse external cohorts are needed to confirm the generalizability and clinical utility of LDAR and the nomogram.

Conclusions

LDAR was independently associated with 28-day all-cause mortality and may provide prognostic information complementary to the SOFA score. The LDAR-integrated nomogram demonstrated good internal predictive performance and potential clinical utility for early risk stratification. Independent external validation is required before clinical implementation.

Abbreviations

AUC: Area under the curve

CI: Confidence interval

DIC: Disseminated intravascular coagulation

ED: Emergency department

FEU: Fibrinogen-equivalent units

GCS: Glasgow Coma Scale

LDAR: Lactate – D-dimer product-to-albumin ratio

MODS: Multiple organ dysfunction syndrome

OR: Odds ratio

PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fraction of inspired oxygen

qSOFA: Quick Sequential Organ Failure Assessment

ROC: Receiver operating characteristic

SOFA: Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

This multicenter retrospective cohort study was approved by the Biomedical Ethics Review Committee of West China Hospital, Sichuan University (No. 2022-1478), and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective study design.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Conceptualization, Y.Q.X.; investigation, Y.Q.X. and X.L.; writing—original draft preparation, Y.Q.X., T.S.Z., and X.L.; writing—review and editing, Y.Q.X., F.J., and R.Y.; visualization, T.S.Z. and F.J.; supervision, R.Y.; funding acquisition, R.Y. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1. Baseline characteristics of heatstroke patients stratified by 28-day survival status

Variable	Overall (n=230)	Survivors (n=150)	Non-survivors (n=80)	P value
Demographic and clinical characteristics				
Age, years	69.00 (54.00–77.00)	66.00 (54.00–76.00)	73.00 (55.50–78.75)	0.071
Male sex, n (%)	114 (49.6)	67 (44.7)	47 (58.8)	0.042
Exertional heatstroke, n (%)	86 (37.4)	60 (40.0)	26 (32.5)	0.263
Onset-to-admission time, h	4.00 (2.00–9.25)	4.00 (1.00–10.00)	4.00 (2.00–7.00)	0.966
Indoor onset, n (%)	144 (62.6)	91 (60.7)	53 (66.3)	0.405
Pre-admission peak temperature > 40°C, n (%)	129 (56.1)	75 (50.0)	54 (67.5)	0.011
Outdoor or manual work, n (%)	106 (46.1)	69 (46.0)	37 (46.3)	0.971
Medical and lifestyle history				
Hypertension, n (%)	14 (6.1)	11 (7.3)	3 (3.8)	0.389
Diabetes mellitus, n (%)	11 (4.8)	5 (3.3)	6 (7.5)	0.197
Neuropsychiatric disease, n (%)	23 (10.0)	12 (8.0)	11 (13.8)	0.166
Cardiovascular disease, n (%)	26 (11.3)	14 (9.3)	12 (15.0)	0.196
Respiratory disease, n (%)	12 (5.2)	5 (3.3)	7 (8.8)	0.116
Smoking history, n (%)	18 (7.8)	10 (6.7)	8 (10.0)	0.370
Alcohol use history, n (%)	17 (7.4)	7 (4.7)	10 (12.5)	0.031
Prehospital management				
Prehospital tracheal intubation, n (%)	21 (9.1)	12 (8.0)	9 (11.3)	0.415
Prehospital cooling, n (%)	73 (31.7)	44 (29.3)	29 (36.3)	0.283
Prehospital vasoactive drug use, n (%)	26 (11.3)	17 (11.3)	9 (11.3)	0.985
Prehospital fluid resuscitation, n (%)	68 (29.6)	40 (26.7)	28 (35.0)	0.187
Vital signs and severity scores at admission				

Temperature at admission, °C	39.30 (37.50–40.80)	39.10 (37.40–40.50)	40.00 (37.63–41.00)	0.007
Heart rate, beats/min	118.20 ± 28.95	113.24 ± 29.12	127.50 ± 26.37	<0.001
Glasgow Coma Scale score	8.00 (3.00–13.00)	10.00 (5.00–13.25)	5.00 (3.00–10.00)	<0.001
Respiratory rate, breaths/min	24.00 (20.00–30.00)	23.00 (20.00–27.25)	24.00 (21.25–31.00)	0.090
Systolic blood pressure, mmHg	120.00 (100.00–140.25)	123.00 (106.75–141.25)	111.50 (90.00–136.50)	0.001
Diastolic blood pressure, mmHg	70.00 (58.75–81.00)	73.00 (63.00–82.00)	64.00 (52.00–76.75)	0.003
Mean arterial pressure, mmHg	88.00 (73.58–99.08)	90.33 (78.08–99.92)	80.50 (63.75–95.83)	0.004
SpO_2, %	96.00 (93.00–98.00)	96.00 (94.00–98.00)	95.00 (89.00–98.00)	0.045
qSOFA score	2.00 (1.00–2.00)	2.00 (1.00–2.00)	2.00 (2.00–3.00)	<0.001
SOFA score	5.50 (3.00–9.00)	4.00 (2.00–7.00)	8.50 (6.00–11.00)	<0.001
Laboratory parameters on admission				
Platelet count, $\times 10^9$/L	130.00 (86.75–178.50)	145.50 (92.50–190.75)	114.50 (73.00–148.75)	0.010
Red blood cell count, $\times 10^{12}$/L	4.15 ± 0.75	4.16 ± 0.74	4.13 ± 0.76	0.744
Hemoglobin, g/L	127.23 ± 21.72	127.25 ± 22.31	127.18 ± 20.70	0.981
Hematocrit, L/L	0.37 (0.34–0.41)	0.37 (0.33–0.41)	0.37 (0.34–0.42)	0.431
White blood cell count, $\times 10^9$/L	11.26 (8.48–15.45)	11.11 (8.61–15.05)	11.89 (7.79–16.23)	0.822
Neutrophil count, $\times 10^9$/L	8.87 (6.14–12.68)	9.06 (6.67–12.59)	8.66 (5.49–13.00)	0.297
Lymphocyte count, $\times 10^9$/L	1.32 (0.74–2.34)	1.07 (0.63–1.95)	1.67 (0.97–2.75)	<0.001
Monocyte count, $\times 10^9$/L	0.65 (0.37–1.10)	0.67 (0.40–1.00)	0.61 (0.32–1.23)	0.859
Total bilirubin, μmol/L	18.30 (12.61–26.00)	17.95 (12.08–25.94)	20.27 (13.30–27.90)	0.116
Direct bilirubin, μmol/L	7.00 (4.47–11.42)	6.39 (4.00–10.03)	8.25 (5.95–13.15)	0.001
ALT, U/L	39.50 (19.00–68.50)	33.50 (18.15–62.25)	52.00 (24.50–107.00)	0.004
AST, U/L	62.50 (34.00–140.50)	47.50 (32.00–95.75)	100.65 (40.75–285.50)	<0.001
Albumin, g/L	38.33 ± 6.10	39.44 ± 6.11	36.23 ± 5.56	<0.001
Glucose, mmol/L	9.83 (7.44–13.39)	9.54 (7.49–12.48)	10.66 (7.20–14.08)	0.204
Blood urea nitrogen, mmol/L	7.64 (5.66–10.20)	7.20 (5.04–9.13)	8.85 (6.62–11.61)	<0.001

Creatinine, μmol/L	112.90 (79.00–160.75)	93.95 (72.00–134.25)	149.45 (114.00–207.55)	<0.001
Uric acid, μmol/L	387.50 (288.20–554.75)	337.00 (260.23–451.04)	495.50 (370.50–657.25)	<0.001
pH	7.43 (7.35–7.48)	7.43 (7.37–7.49)	7.39 (7.29–7.45)	<0.001
$PaCO_2$, mmHg	28.90 (22.90–32.68)	28.60 (22.60–33.43)	29.65 (23.55–32.33)	0.365
PaO_2/FiO_2 ratio, mmHg	325.28 (235.75–391.25)	356.00 (269.00–411.25)	272.00 (186.00–366.50)	<0.001
Lactate, mmol/L	2.85 (1.40–4.58)	2.10 (1.20–3.70)	4.20 (2.90–6.46)	<0.001
Myoglobin, ng/mL	810.68 (244.15–3000.00)	498.15 (161.88–1875.75)	3000.00 (691.93–3000.00)	<0.001
Creatine kinase, U/L	548.00 (252.00–1663.50)	476.20 (245.46–1092.49)	669.00 (331.03–2102.58)	0.015
CK-MB, ng/mL	5.70 (2.23–25.90)	4.78 (2.07–15.75)	8.11 (2.50–42.30)	0.033
Cardiac troponin T, ng/L	25.20 (1.96–163.48)	22.00 (5.55–126.00)	28.65 (1.06–305.33)	0.367
PT, s	12.80 (11.60–14.63)	12.40 (11.20–13.90)	14.05 (12.23–16.55)	<0.001
APTT, s	27.30 (24.20–30.83)	26.45 (23.80–29.33)	28.40 (24.88–37.40)	<0.001
TT, s	18.40 (17.10–20.13)	18.30 (16.90–19.70)	19.60 (17.60–22.60)	0.001
Fibrinogen, g/L	2.28 (1.77–3.00)	2.38 (1.83–3.09)	2.14 (1.64–2.69)	0.019
D-dimer, mg/L FEU	4.48 (1.44–10.98)	3.05 (1.19–6.88)	9.56 (4.37–25.59)	<0.001
LDAR	0.30 (0.09–1.11)	0.18 (0.05–0.45)	1.03 (0.31–2.61)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. P values were calculated using the independent-samples t test, Mann–Whitney U test, Pearson's chi-square test, or Fisher's exact test, as appropriate. Outdoor or manual work included farmers, manual workers, and firefighters. Lactate values >20 mmol/L and myoglobin values >3000 ng/mL were recorded as 20 mmol/L and 3000 ng/mL, respectively.

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; FEU, fibrinogen-equivalent units; FiO_2, fraction of inspired oxygen; LDAR, lactate–D-dimer product-to-albumin ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PT, prothrombin time; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment; SpO_2, peripheral oxygen saturation; TT, thrombin time.

Table 2. Multivariable logistic regression for 28-day mortality

Variable	β	Adjusted OR	95% CI	P value
Male sex	0.631	1.879	0.953–3.704	0.069
Age, years	0.028	1.028	1.006–1.051	0.011
Admission temperature, °C	0.277	1.319	1.094–1.591	0.004
LDAR	0.296	1.344	1.104–1.636	0.003
SOFA score	0.271	1.311	1.187–1.448	<0.001

Adjusted ORs were derived from a multivariable binary logistic regression model including sex, age, admission temperature, LDAR, and SOFA score. Female sex was used as the reference category.

Abbreviations: CI, confidence interval; LDAR, lactate–D-dimer product-to-albumin ratio; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

Table 3. Comparison of AUCs between models

Comparison	AUC_1	AUC_2	ΔAUC	95% CI	Z	P
Nomogram vs. LDAR	0.832	0.794	0.037	-0.025–0.100	1.17	0.242
Nomogram vs. SOFA	0.832	0.774	0.057	0.013–0.102	2.539	0.011
SOFA vs. LDAR	0.774	0.794	-0.020	-0.095–0.055	-0.524	0.600

P values were calculated using DeLong's test. $\Delta AUC = AUC_1 - AUC_2$. Bold indicates $P < 0.05$. The nomogram included age, admission temperature, LDAR, and SOFA score.

Abbreviations: AUC, area under the curve; CI, confidence interval; LDAR, lactate–D-dimer product-to-albumin ratio; SOFA, Sequential Organ Failure Assessment.

Table 4. Predictive performance of the nomogram, LDAR, and SOFA score for 28-day all-cause mortality

Predictor	AUC (95% CI)	Optimal cutoff	Sensitivity (%)	Specificity (%)	Youden index
Nomogram	0.832 (0.788–0.885)	0.308	80.0	74.0	0.540
LDAR	0.794 (0.736–0.853)	0.665	62.5	83.3	0.458
SOFA score	0.774 (0.712–0.837)	5.5	80.0	66.0	0.460

Optimal cutoff values were determined by maximizing the Youden index.

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; LDAR, lactate–D-dimer product-to-albumin ratio; SOFA, Sequential Organ Failure Assessment.

Figures

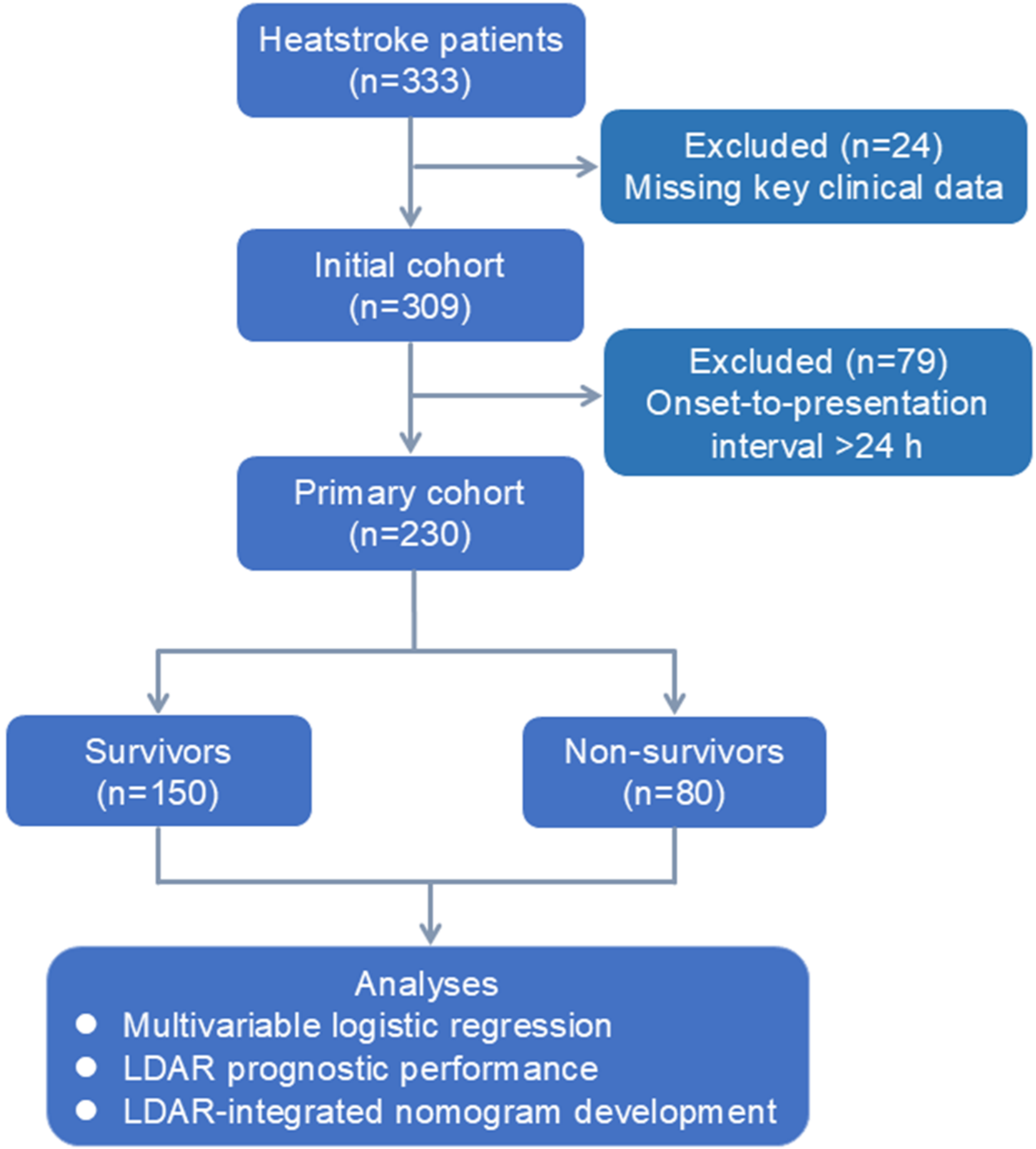
Figure 1. Flow diagram of patient selection and study analyses. LDAR, lactate–D-dimer product-to-albumin ratio.

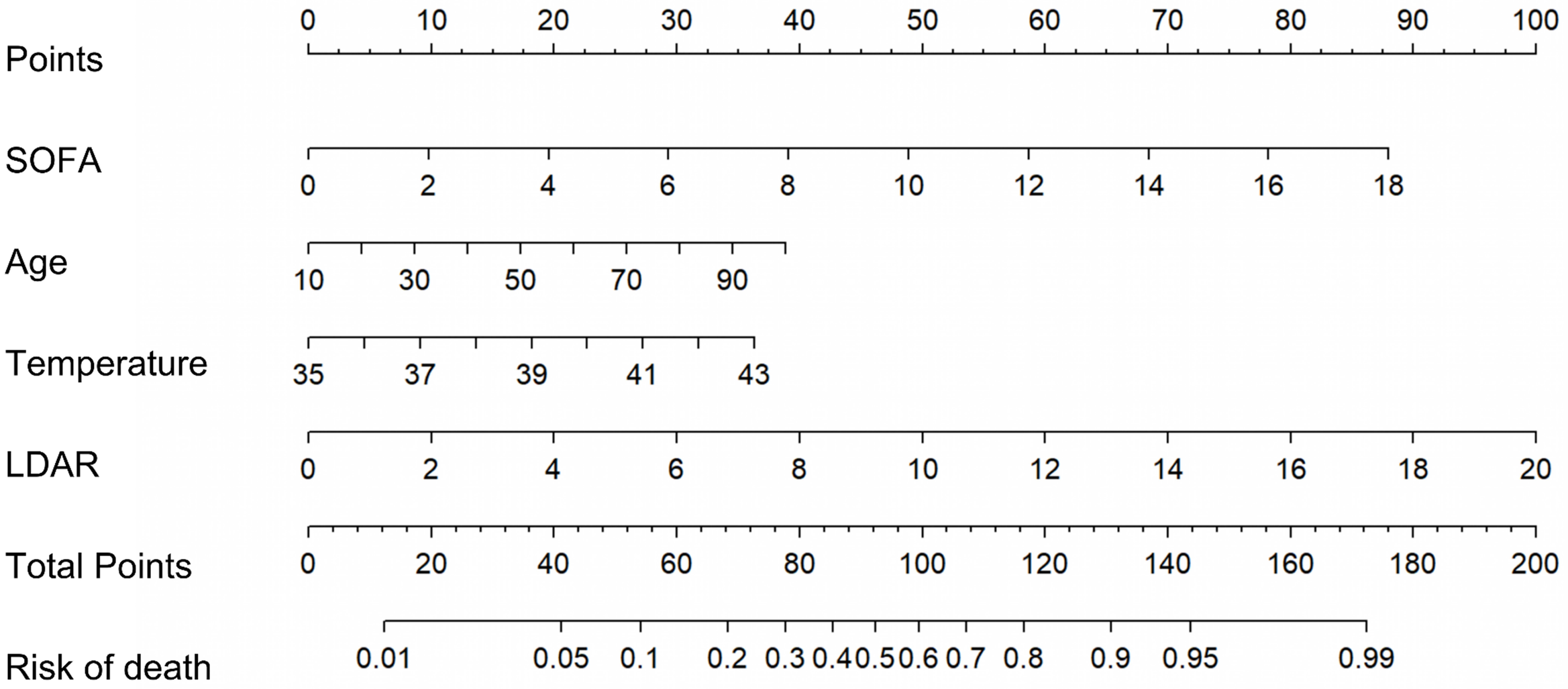
Figure 2. Nomogram for estimating the probability of 28-day all-cause mortality in patients with heatstroke. The points assigned to each predictor are summed and mapped to the corresponding predicted probability of 28-day all-cause mortality. LDAR, lactate–D-dimer product-to-albumin ratio; SOFA, Sequential Organ Failure Assessment.

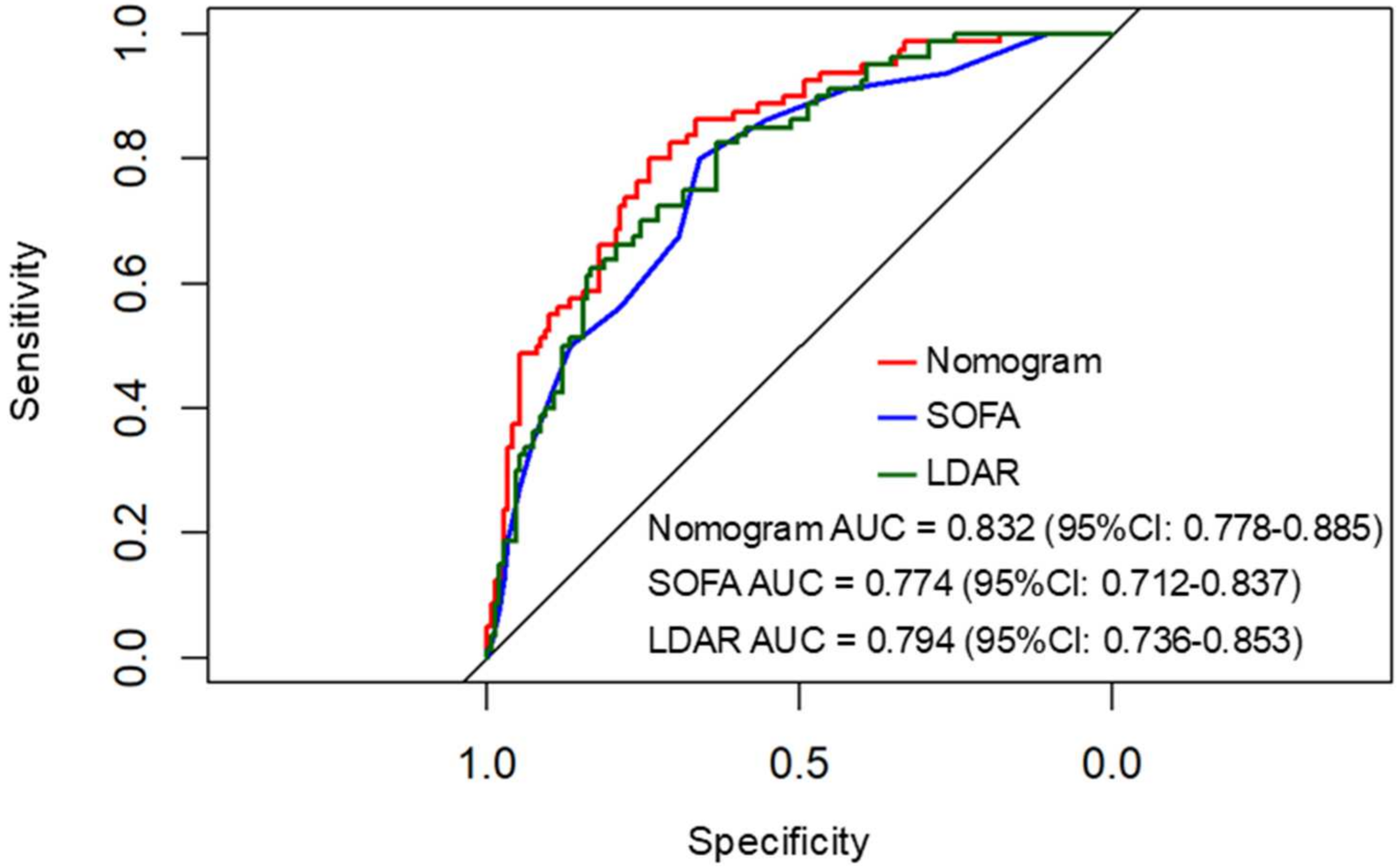
Figure 3. Receiver operating characteristic curves comparing the nomogram, LDAR, and SOFA score for 28-day all-cause mortality in patients with heatstroke. The diagonal line represents the no-discrimination reference line. AUC, area under the curve; CI, confidence interval; LDAR, lactate–D-dimer product-to-albumin ratio; SOFA, Sequential Organ Failure Assessment.

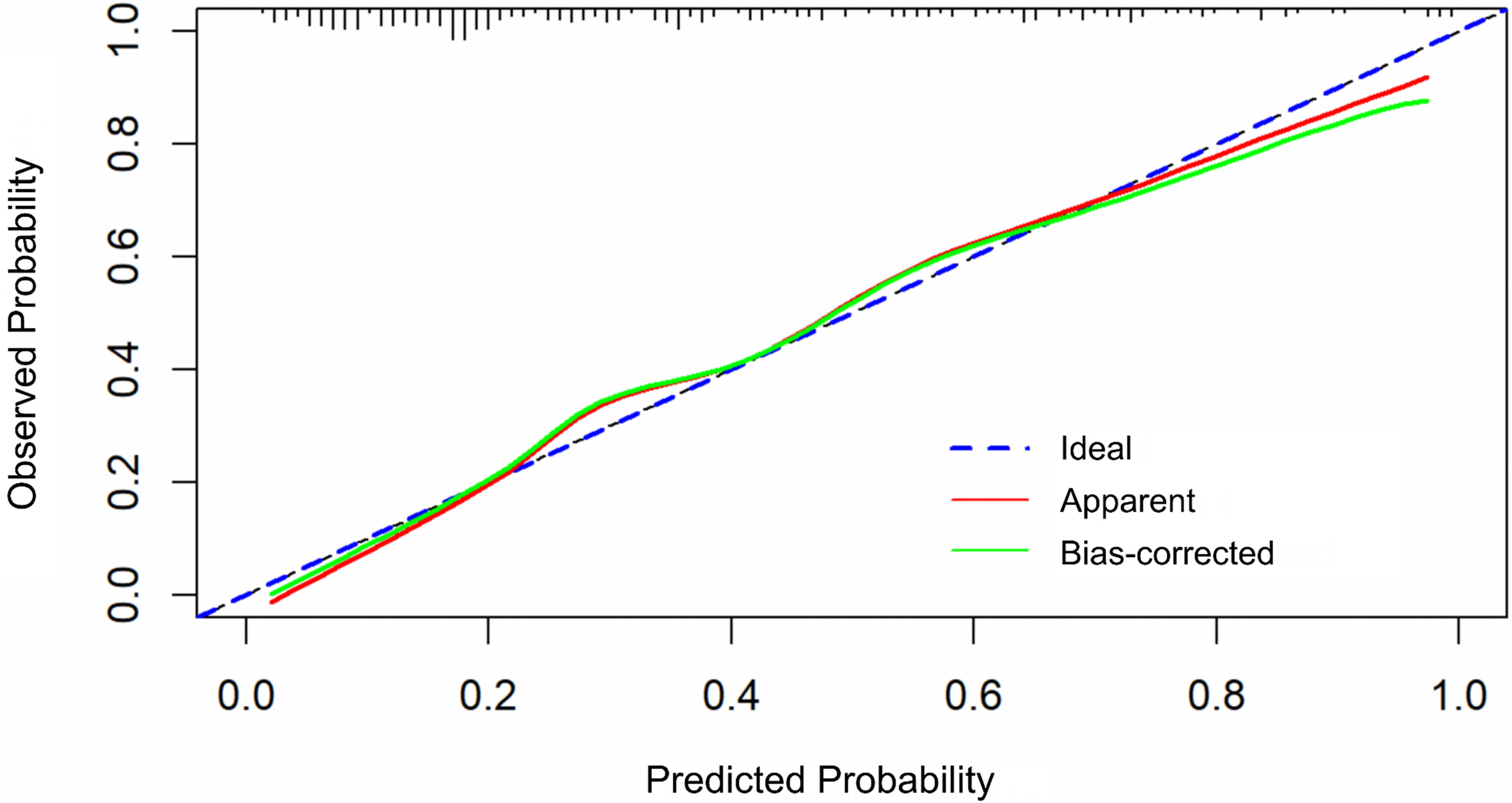
Figure 4. Calibration curve of the nomogram for estimating the probability of 28-day all-cause mortality in patients with heatstroke. The dashed line represents perfect agreement between predicted and observed probabilities. The red line represents the apparent calibration of the nomogram in the primary cohort, and the green line represents the bootstrap-corrected calibration obtained from 1,000 bootstrap resamples. The mean absolute calibration error was 0.0271.

Figure 5. Decision curve analysis of the nomogram for 28-day all-cause mortality in patients with heatstroke. The red line labeled “Nomogram (Validation)” represents the net benefit of the nomogram, and the shaded area represents the corresponding 95% confidence interval. The gray dashed line labeled “All” and the black dotted line labeled “None” represent the treat-all and treat-none strategies, respectively. CI, confidence interval.

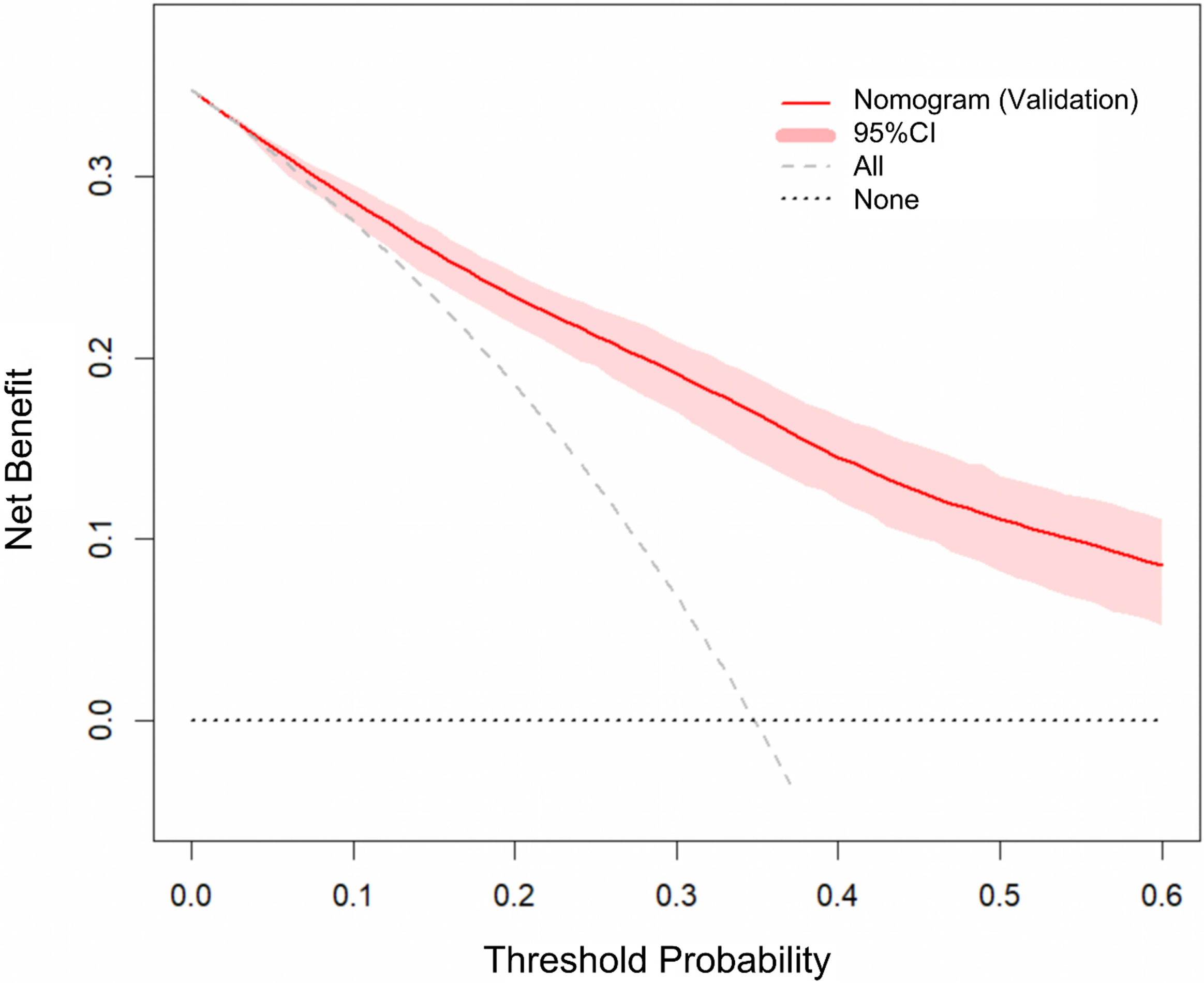

Heatstroke patients
(n=333)
Excluded (n=24)
Missing key clinical data
Initial cohort
(n=309)
Excluded (n=79)
Onset-to-presentation
interval >24 h
Primary cohort
(n=230)
Survivors
(n=150)
Non-survivors
(n=80)
Analyses
Multivariable logistic regression
LDAR prognostic performance
LDAR-integrated nomogram development


Points
0 10 20 30 40 50 60 70 80 90 100
SOFA
0 2 4 6 8 10 12 14 16 18
Age
10 30 50 70 90
Temperature
35 37 39 41 43
LDAR
0 2 4 6 8 10 12 14 16 18 20
Total Points
0 20 40 60 80 100 120 140 160 180 200
Risk of death
0.01 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95 0.99


Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1.0
0.5
0.0
Specificity
Nomogram
SOFA
LDAR
Nomogram AUC = 0.832 (95%CI: 0.778-0.885)
SOFA AUC = 0.774 (95%CI: 0.712-0.837)
LDAR AUC = 0.794 (95%CI: 0.736-0.853)



Bootstrap validation: B = 1,000; mean absolute calibration error = 0.0271; n = 230.


Nomogram (Validation)
95%CI
All
None
Net Benefit
0.0
0.1
0.2
0.3
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Threshold Probability

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx