

A Clinical and Biomarker-Based Model for Predicting in-Hospital Mortality in Patients Undergoing Extracorporeal Membrane Oxygenation: A Machine Learning-Based Nomogram Study

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Purpose: A nomogram was constructed for predicting in-hospital mortality in patients receiving extracorporeal membrane oxygenation (ECMO) using clinical indicators, to provide a reference for clinical risk stratification.

Patients and Methods: A retrospective cohort of 122 ECMO patients (81 survivors, 41 non-survivors) from Taizhou Hospital of Zhejiang Province (January 2022–December 2024) was used for model development, with 22 patients from the MIMIC-IV database serving as the external validation cohort. A two-step Boruta-LASSO feature selection strategy was applied to identify key predictors, followed by construction of five machine learning models; the best-performing model was used to develop a nomogram, validated internally and externally via ROC analysis, calibration curves, decision curve analysis, and SHAP interpretability analysis.

Results: Four key predictors were identified: malignant tumor, Lactic Acid, monocyte-to-white blood cell ratio (MWR), and activated partial thromboplastin time-to-albumin ratio (AAR). The logistic regression model exhibited the best and most stable predictive performance, with a cross-validated AUC of 0.765 (95% CI: 0.667–0.863) in the primary cohort. External validation in the MIMIC-IV cohort (n=22) yielded an AUC of 0.838 (95% CI: 0.655–1.000), suggesting preliminary external validation with acceptable generalizability.

Conclusion: Malignant tumor, elevated Lactic Acid, decreased MWR, and elevated AAR are key predictive factors for in-hospital mortality in ECMO patients. The nomogram model demonstrated satisfactory discriminatory ability, acceptable calibration, and potential clinical utility, serving as a valuable exploratory tool for bedside risk stratification in ECMO patients. Further validation in larger, multicenter, prospective cohorts is warranted before clinical implementation.

Keywords: ECMO, in-hospital mortality, nomogram, LASSO Regression, machine learning, Boruta algorithm, SHAP analysis

Introduction

Extracorporeal membrane oxygenation (ECMO) is a core life-support technology in critical care, simulating cardiopulmonary function to provide gas exchange and circulatory support.¹ It is widely used in reversible cardiopulmonary failure caused by severe pneumonia, acute respiratory distress syndrome, and cardiogenic shock.² Despite technological advancements, in-hospital mortality remains high (40%–60%),³ highlighting the need for early identification of high-risk patients and personalized intervention strategies.⁴

Most existing scoring systems target specific populations and may not cover the full spectrum of modern ECMO indications.⁵ Single lab markers or empirical clinical judgment fail to integrate multiple risk dimensions.⁶ General ICU

scores lack ECMO-specific features and depend on pre-intubation parameters.⁷ These gaps highlight the need for a systematic ECMO-tailored framework. Previous studies have identified age,⁸ prior CPR, and low initial platelet count⁹ as independent risk factors for in-hospital mortality in ECMO patients. Elevated pre-ECMO lactate¹⁰ and comorbidities¹¹ are also associated with poor outcomes.

To address these limitations, current studies on factors influencing the prognosis of patients treated with ECMO are mostly focused on single-center, small-sample analyses, with a lack of unified risk prediction models and external validation data.^{10,12} This study conducted a retrospective analysis of clinical data from ECMO patients, adopted a two-step feature screening strategy combining Boruta algorithm and LASSO regression to identify core predictive factors, and constructed multiple machine learning prediction models. A risk prediction nomogram was developed based on the optimal model, and SHAP analysis was used to realize the multi-dimensional interpretability of the model from population to individual. The model’s performance was validated using an external cohort from the MIMIC-IV database. It aims to provide clinicians with a standardized, interpretable and generalizable tool for assessing the mortality risk of ECMO patients, and assist critical care teams in optimizing diagnosis and treatment decisions.

Materials and Methods

Patients and Study Design

We retrospectively enrolled consecutive ECMO patients from Taizhou Hospital (Jan 2022–Dec 2024). Inclusion criteria: (1) age ≥ 18 years; (2) ECMO support duration ≥ 24 hours; and (3) availability of complete clinical and laboratory data within 24 hours before ECMO initiation. Exclusion criteria: brain death, treatment withdrawal before ECMO, incomplete data. The primary cohort (n=122) was split 8:2 into training (n=98) and test (n=24) sets.

For patient identification in the MIMIC-IV database (2008–2022), we queried ICD-10-PCS procedure code 5A15223 and ICD-9-CM procedure code 3965 to capture ECMO-related records across different data periods. The total number of identified ECMO-related records was 56. Patients were screened using the same inclusion criteria as the primary cohort. A total of 22 patients were ultimately included for validation, comprising 13 survivors and 9 non-survivors (Figure 1). Patient deduplication was performed using unique subject IDs, and data were extracted from the first 24 hours of ECMO support.

Samples and Laboratory Measurements

Peripheral venous blood samples were collected from all participants in the study cohort within 24 hours before ECMO initiation. Hematological parameters (WBC, neutrophil, monocyte, lymphocyte, Hb, PLT) were measured using a Mindray BC series automated hematology analyzer (Mindray, Shenzhen, China). Routine coagulation function tests (fibrinogen, APTT, PT,

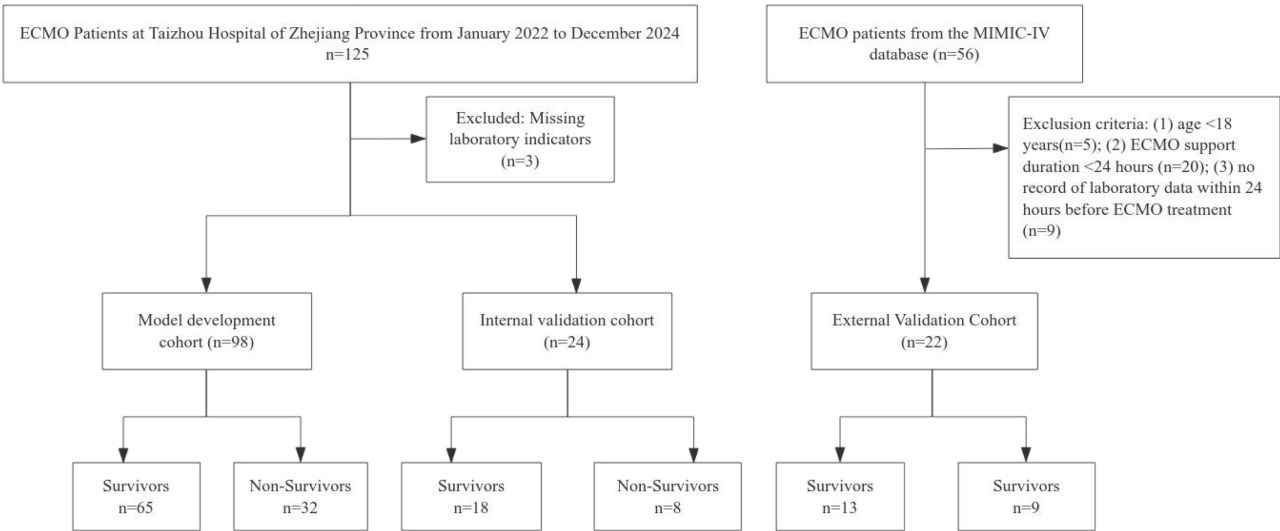


Figure 1 Flowchart of patient inclusion and exclusion.

INR) were performed using a Stago STR-Max automated coagulation analyzer (Stago, Cedex, France). Blood gas parameters (Lactic Acid, pH value) and oxygenation index were analyzed using a Siemens Rapid 500 automated blood gas analyzer (Siemens, Munich, Germany). Biochemical indicators (ALT, AST, TP, Alb, ALP, urea, creatinine, eGFR, glucose, total bilirubin) were assayed with a Beckman Coulter AU5800 automated biochemistry analyzer (Beckman Coulter, Brea, California, USA). All measurements were performed per standard protocols. Derived ratios were defined as: MWR (monocyte to WBC ratio), AHR (APTT to HGB ratio), AAR (APTT to Alb ratio), LAR (lactate to Alb ratio). All ratio calculations and feature engineering were conducted on the full dataset prior to train-test splitting.

Collection of Clinical Data and Outcome

Longitudinal clinical indicators were systematically collected from medical records in this study, including demographic data, underlying diseases, comorbidities (eg, cardiac disease, hypertension), organ dysfunction, and in-hospital outcomes (survival/non-survival). Outcome (in-hospital mortality) was defined as all-cause death during the index hospitalization, identified via discharge status codes in both the local electronic medical record system and MIMIC-IV database. Comorbidities including malignant tumor, hypertension, and diabetes were defined using ICD-10 diagnosis codes consistent with prior epidemiological studies of ECMO populations.

Statistical Methods

Data cleaning removed duplicates and implausible values; Missing values were not imputed given the complete case design, and all variables included in the final analysis had <5% missing data. We considered multiple imputation (MICE) as a sensitivity analysis, but given the low missing rate (<5%) and the small sample size, complete-case analysis was chosen to avoid introducing imputation bias. Sample size was pre-calculated (G*Power 3.1, power ≥ 0.70). The final model achieved an events-per-variable (EPV) of 10.25. Non-normal continuous variables were expressed as median (IQR) and compared via Wilcoxon test; categorical variables used chi-square test. Significance: $P < 0.05$.

Feature Selection

Collinearity among candidate variables was first assessed using the variance inflation factor (VIF), and variables with $VIF > 5$ were excluded. A two-step feature selection approach was then applied: (1) the Boruta algorithm was used for initial screening, identifying all relevant features by comparing their importance against random shadow variables, thereby reducing dimensionality; (2) LASSO regression with 10-fold cross-validation was subsequently applied to further shrink coefficients and select the most parsimonious set of predictors, minimizing overfitting.

Machine Learning Model Construction and Evaluation

Five models (Logistic regression, LASSO, Random Forest, LightGBM, XGBoost) were built on training data using default hyperparameters. In this cohort, logistic regression outperformed more complex tree-based and boosting models (Random Forest, LightGBM, XGBoost). This is likely attributable to the limited sample size ($n=122$) and small predictor set: complex models tend to overfit training-set noise in such settings, whereas logistic regression's lower complexity yields more stable generalization. The approximately linear feature–outcome relationships further favored logistic regression, which was therefore selected as the final model. The area under the receiver operating characteristic curve (AUC) was the primary metric; Calibration plots (1000 bootstrap) and repeated 10-fold cross-validation were performed. All statistical analyses were conducted in R (version 4.4.2), including glmnet (LASSO regression), randomForest (random forest), lightgbm (LightGBM), xgboost (XGBoost), pROC (ROC curves), rms (nomogram and calibration), dca (decision curve analysis), Boruta (feature selection), and shapviz (SHAP analysis). Repeated 10-fold cross-validation was performed to eliminate optimism bias.

Model Interpretability Analysis

The SHAP (SHapley Additive exPlanations) analysis was applied to all five models to quantify individual feature contributions and enable consistent cross-model comparison. For the logistic regression model, SHAP serves a supplementary interpretability role alongside standardized coefficients.

Nomogram Development and Validation

The best-performing model was used to build a nomogram (R, rms package). Clinical utility was assessed via decision curve analysis (DCA). Internal validation used ROC curves; external validation used the MIMIC-IV cohort, with AUC comparisons via Z-test.

Results

Baseline Clinical and Laboratory Characteristics of the Primary Cohort

A total of 122 ECMO patients were included in the primary cohort, with a male proportion of 64.75% (79/122) and a median age of 59.00 [46.00;70.00] years. Of these, 93 (76.23%) received VA-ECMO and 29 (23.77%) received VV-ECMO. The median ECMO duration was 3.00 [1.25;7.00] hours, and the overall in-hospital mortality rate was 33.61% (41/122) (Table S1). VA-ECMO and VV-ECMO patients differ in etiology, immune status, metabolism, and coagulation, reflecting their distinct indications (cardiac vs. respiratory support), yet survival rates are similar. There were no statistically significant differences between the survival and non-survival groups in terms of gender, age, and the incidence of underlying diseases including hypertension, diabetes mellitus, hepatic insufficiency and renal insufficiency (all $P>0.05$). However, the proportion of Malignant Tumor in the non-survival group was significantly higher than that in the survival group (12.2% vs 2.47%, $p=0.042$).

Liver function: total bilirubin was significantly lower in the non-survival group (7.90 [5.00; 11.50] vs 11.50 [7.80; 15.00] $\mu\text{mol/L}$, $P=0.004$); Metabolic indicators: Lactic Acid was markedly higher (11.00 [5.10; 15.40] vs 4.60 [2.50; 8.90] mmol/L , $P<0.001$) and pH value was lower (7.24 [7.04; 7.37] vs 7.32 [7.24; 7.42], $P=0.022$) in non-survivors; Coagulation indicators: APTT and INR were significantly higher in non-survivors (57.70 [37.40; 180.00] vs 44.00 [36.50; 62.40] seconds, $P=0.043$; 1.42 [1.12; 1.92] vs 1.16 [1.08; 1.49], $P=0.048$); Derived ratio indicators: MWR was significantly lower in non-survivors (0.03 [0.02; 0.05] vs 0.05 [0.03; 0.06], $P=0.006$), while LAR, AAR, and AHR were significantly higher (all $P<0.05$) (Table 1).

Table 1 Baseline Characteristics of ECMO Patients on the Day of Treatment (N=122)

Indicator	Overall (N=122)	Non-Survival (N=41)	Survival (N=81)	P
Male, n (%)	79 (64.75)	28 (68.29)	51 (62.96)	0.703
Age, years	59.00 [46.00;70.00]	59.00 [46.00;72.00]	59.00 [47.00;70.00]	0.795
Hypertension, n (%)	52 (42.62)	15 (36.59)	37 (45.68)	0.444
Diabetes Mellitus, n (%)	29 (23.77)	12 (29.27)	17 (20.99)	0.430
Hepatic Insufficiency, n (%)	39 (31.97)	15 (36.59)	24 (29.63)	0.567
Renal Insufficiency, n (%)	35 (28.69)	13 (31.71)	22 (27.16)	0.755
Malignant Tumor, n (%)	7 (5.74)	5 (12.20)	2 (2.47)	0.042
Blood routine test				
WBC ($10^9/\text{L}$)	11.78 [8.85;16.86]	11.78 [9.99;16.90]	11.56 [8.20;16.73]	0.612
Neutrophil ($10^9/\text{L}$)	8.96 [5.05;13.76]	8.99 [5.99;13.80]	8.90 [4.70;13.65]	0.780
Monocyte ($10^9/\text{L}$)	0.50 [0.30;0.70]	0.46 [0.23;0.60]	0.50 [0.35;0.80]	0.092
Lymphocyte ($10^9/\text{L}$)	1.75 [0.81;4.02]	2.20 [1.21;4.04]	1.35 [0.60;4.02]	0.093
Hb (g/L)	124.28 (28.27)	119.78 (28.88)	126.56 (27.86)	0.219
Myocardial enzyme				
hs-cTn (ng/mL)	0.20 [0.03;4.41]	0.20 [0.03;3.20]	0.20 [0.04;4.49]	0.702
Biochemistry Liver function				
ALT (U/L)	57.00 [27.00;130.50]	57.00 [25.00;208.00]	57.00 [29.00;121.00]	0.952
AST (U/L)	112.00 [33.50;346.50]	112.00 [33.00;497.00]	112.00 [35.00;228.00]	0.690
TP (g/L)	60.40 [52.82;65.72]	60.00 [50.80;62.70]	60.80 [53.50;65.80]	0.430

(Continued)

Table 1 (Continued).

Indicator	Overall (N=122)	Non-Survival (N=41)	Survival (N=81)	P
Alb (g/L)	33.40 (6.80)	32.34 (7.86)	33.94 (6.18)	0.259
ALP (U/L)	84.00 [67.00;105.00]	85.00 [72.00;108.00]	83.00 [58.00;103.00]	0.208
Total Bilirubin (μmol/L)	10.50 [6.73;14.68]	7.90 [5.00;11.50]	11.50 [7.80;15.00]	0.004
Renal function				
Creatinine (μmol/L)	106.00 [80.25;136.75]	108.00 [83.00;139.00]	104.00 [78.00;136.00]	0.453
eGFR	66.95 (28.66)	60.89 (25.84)	69.83 (29.68)	0.156
Metabolic index				
Glucose (mmol/L)	12.65 [9.06;15.44]	13.40 [8.80;17.20]	12.60 [9.20;14.74]	0.463
Lactic Acid (mmol/L)	6.10 [2.80;11.62]	11.00 [5.10;15.40]	4.60 [2.50;8.90]	0.001
pH Value	7.31 [7.13;7.41]	7.24 [7.04;7.37]	7.32 [7.24;7.42]	0.022
Oxygenation Index	208.50 [90.50;373.25]	224.00 [92.00;386.00]	195.00 [90.00;343.00]	0.478
Coagulation				
Fibrinogen (g/L)	3.10 [2.31;3.90]	2.69 [1.96;3.66]	3.15 [2.62;4.11]	0.068
APTT (s)	45.10 [36.70;120.97]	57.70 [37.40;180.00]	44.00 [36.50;62.40]	0.043
PT (s)	15.40 [14.00;18.20]	16.00 [14.20;20.60]	15.00 [13.90;17.70]	0.052
INR	1.23 [1.10;1.58]	1.42 [1.12;1.92]	1.16 [1.08;1.49]	0.048
Derived ratio indicators				
MWR	0.04 [0.03;0.06]	0.03 [0.02;0.05]	0.05 [0.03;0.06]	0.006
LAR	17.41 [8.12;34.29]	26.00 [17.01;43.50]	15.00 [7.17;25.21]	0.002
AAR	144.24 [100.97;302.45]	146.82 [121.32;521.74]	144.24 [97.25;187.68]	0.044
AHR	0.40 [0.28;0.99]	0.53 [0.30;1.41]	0.38 [0.28;0.54]	0.019
ECMO duration,(hour)	3.00 [1.25;7.00]	1.00 [1.00;4.00]	5.00 [2.00;8.00]	<0.001

Notes: Data was presented as median (P25-P75) or mean (SD). P value was obtained by Kruskal–Wallis H-test. $p < 0.05$ was considered as statistically significant.

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; Alb, Albumin; CK, Creatine Kinase; eGFR, Estimated Glomerular Filtration Rate; ALP, Alkaline Phosphatase; hs-cTn, High-Sensitivity Troponin; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; PT, Prothrombin Time; WBC, White Blood Cell; Hb, Hemoglobin; PLT, Platelet Count; MWR, Monocyte to White blood cell Ratio; LAR, Lactate to Alb Ratio; AAR, APTT to Alb Ratio; AHR, APTT to Hb Ratio.

Baseline Characteristics of the Training and Baseline Characteristics of the Training and Test Groups

Patients were randomly divided into a training group ($n=98$) and a test group ($n=24$, comprising 16 survivors and 8 non-survivors, non-survivor proportion 33.3%, consistent with the overall cohort mortality rate of 33.6%). Most baseline characteristics, comorbidities, laboratory parameters, and derived ratio indicators were well balanced between groups (all $P>0.05$) (Table 2).

Table 2 Baseline Characteristics of ECMO Patients in the Training and Test Groups

Indicator	Training Group (N=98)	Test Group (N=24)	P
Survivors, n (%)	65 (66.3)	16 (66.7)	1
Male, n (%)	65 (66.3)	14 (58.3)	0.620
Age, years	59.00 [48.25;70.00]	57.50 [43.75;68.00]	0.650
Hypertension, n (%)	41 (41.8)	11 (45.8)	0.901
Diabetes Mellitus, n (%)	22 (22.4)	7 (29.2)	0.671

(Continued)

Table 2 (Continued).

Indicator	Training Group (N=98)	Test Group (N=24)	P
Hepatic Insufficiency, n (%)	34 (34.7)	5 (20.8)	0.289
Renal Insufficiency, n (%)	30 (30.6)	5 (20.8)	0.485
Malignant Tumor, n (%)	5 (5.1)	2 (8.3)	0.904
Blood routine test			
WBC (10 ⁹ /L)	11.69 [8.54,16.81]	12.12 [10.18,16.92]	0.499
Neutrophil (10 ⁹ /L)	8.96 [5.20,13.59]	9.17 [4.19,14.80]	0.870
Monocyte (10 ⁹ /L)	0.49 [0.30,0.60]	0.66 [0.45,0.77]	0.096
Lymphocyte (10 ⁹ /L)	2.65 [1.80,4.98]	2.65 [1.37,4.80]	0.059
Hb (g/L)	124.00 [106.25,143.75]	123.00 [111.75,144.25]	0.852
Myocardial enzyme			
hs-cTn (ng/mL)	0.20 [0.04,4.38]	0.12 [0.02,4.39]	0.316
Biochemistry Liver function			
ALT (U/L)	57.00 [27.25,175.75]	51.00 [26.25,109.75]	0.378
AST (U/L)	112.00 [35.25,422.25]	87.50 [33.00,187.75]	0.268
TP (g/L)	60.05 [50.80,65.60]	62.05 [59.92,65.62]	0.149
Alb (g/L)	34.10 [27.58,38.05]	34.65 [32.88,38.27]	0.285
ALP (U/L)	83.50 [67.00, 105.00]	87.00 [64.75, 102.00]	0.903
Total Bilirubin (μmol/L)	10.75 [6.73,15.00]	9.70 [7.23,11.75]	0.267
Renal function			
Creatinine (μmol/L)	108.50 [80.25,139.75]	101.00 [82.00,112.25]	0.297
eGFR	62.50 [44.25,88.50]	72.00 [61.00,85.00]	0.357
Metabolic index			
Glucose (mmol/L)	12.62 [8.85,15.31]	13.20 [10.14,15.35]	0.524
Lactic Acid (mmol/L)	6.00 [2.50, 11.78]	7.80 [3.67, 10.40]	0.600
pH Value	7.31 [7.13,7.42]	7.27 [7.17,7.37]	0.180
Oxygenation Index	212.00 [93.25,384.00]	114.00 [55.75,272.25]	0.058
Coagulation			
Fibrinogen (g/L)	3.10 [2.15,4.07]	3.12 [2.67,3.71]	0.569
APTT (s)	45.10 [37.82,151.07]	44.15 [31.57,78.40]	0.248
PT (s)	15.45 [14.05,18.77]	14.55 [13.78,15.55]	0.096
INR	1.27 [1.10,1.64]	1.14 [1.07,1.25]	0.124
Derived ratio indicators			
MWR	0.04 [0.02,0.06]	0.05 [0.04,0.07]	0.112
LAR	17.41 [7.50,35.21]	20.91 [13.56,28.66]	0.638
AAR	144.24 [107.14,338.52]	132.47 [88.09,207.25]	0.309
AHR	0.40 [0.28,1.09]	0.38 [0.26,0.58]	0.386

Notes: Data was presented as median (P25-P75) or mean (SD). P value was obtained by Kruskal–Wallis H-test. $p < 0.05$ was considered as statistically significant.

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TP, Total Protein; Alb, Albumin; ALP, Alkaline Phosphatase; WBC, White Blood Cell Count; Hb, Hemoglobin; PLT, Platelet; MWR, Monocyte to White blood cell Ratio; AHR, APTT to Hb Ratio; PAR, PT to Ib Ratio; AAR, APTT to Alb Ratio; LAR, Lactate to Alb Ratio.

Feature Selection Results

A two-step feature screening was performed using the Boruta algorithm and LASSO regression. The Boruta algorithm (Figure 2A) identified Lactic Acid and MWR as confirmed important features with significant discriminatory ability for survival outcomes, and malignant tumor as a tentative important feature, while AAR and other indicators were initially classified as shadow features without significant predictive value. The box plot of feature importance showed that Lactic Acid had the highest median importance (approximately 7.5), significantly higher than other indicators, indicating its core role in distinguishing survival outcomes, followed by MWR (approximately 5), and the importance of malignant tumor was slightly lower than that of MWR.

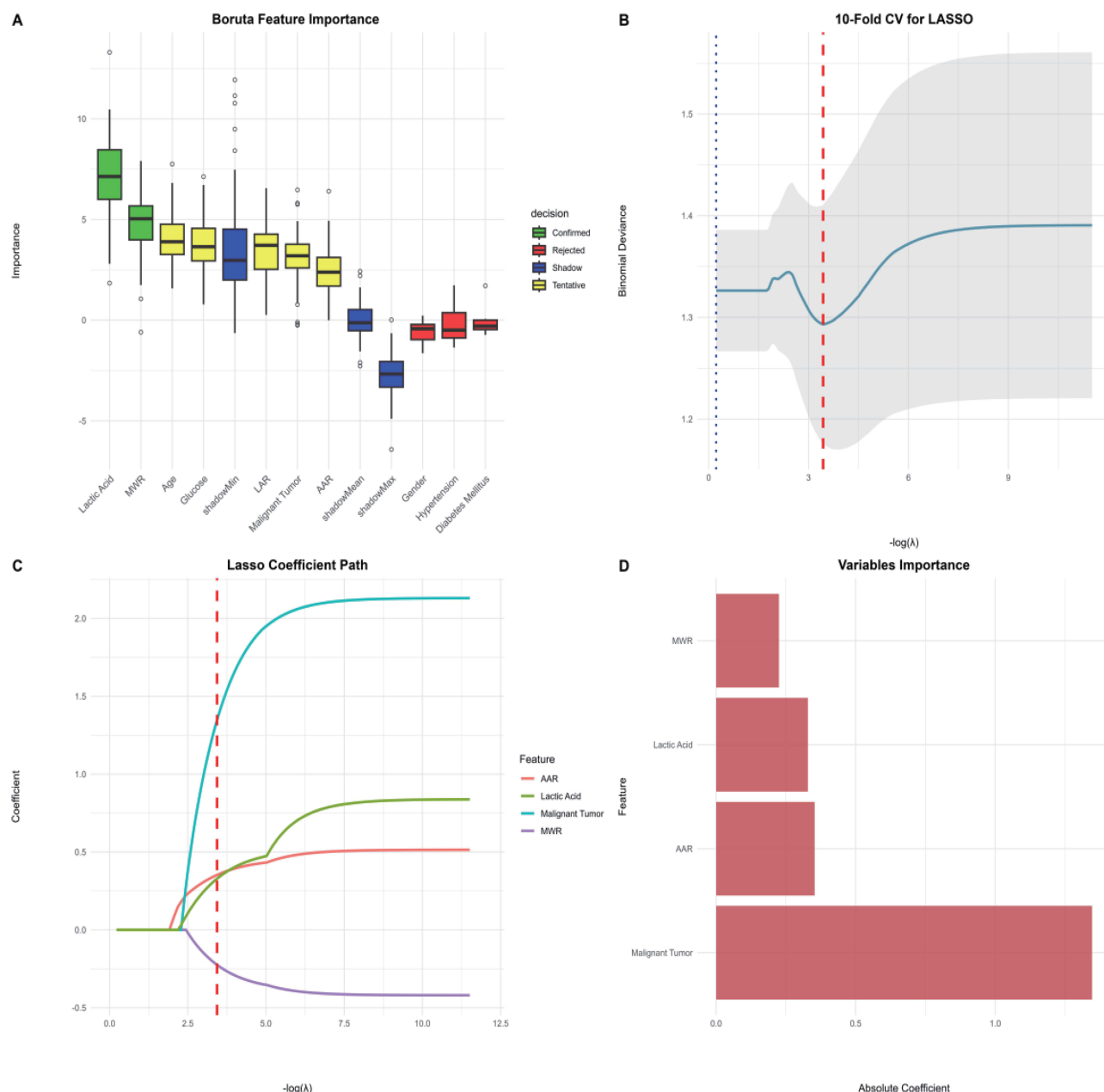


Figure 2 Boruta and LASSO feature selection and model evaluation for ECMO patient mortality prediction. **(A)** Boruta feature importance: Boxplot of feature importance classified into confirmed, shadow, and tentative groups. **(B)** 10-Fold CV for LASSO: Binomial deviance curve with $\lambda_{\min}$ and λ_{1se} markers for optimal regularization. **(C)** Lasso coefficient path: Trajectory of coefficients shrinking with increasing λ , with optimal λ marked. **(D)** Variables importance: Barplot of feature importance based on absolute LASSO coefficients.

Based on the results of preliminary screening, LASSO regression with 10-fold cross-validation (Figure 2B) selected the optimal λ value at $-\log(\lambda)=3.5$ (red dashed line) with the minimum binomial deviance, and finally retained four core features: malignant tumor, AAR, Lactic Acid and MWR. The coefficient path plot (Figure 2C) showed that with the decrease of λ (increase of model complexity), the regression coefficients of each feature gradually became non-zero: the coefficient of malignant tumor stabilized to a positive value at the earliest, followed by the increase of AAR and Lactic Acid coefficients, while the MWR coefficient was negative, suggesting that different features had distinct effect directions on in-hospital mortality. The variable importance plot (Figure 2D), measured by the absolute value of LASSO regression coefficients, showed that malignant tumor had the highest contribution ($|\beta| \approx 1.3$), followed by AAR ($|\beta| \approx 0.3$), Lactic Acid ($|\beta| \approx 0.3$) and MWR ($|\beta| \approx 0.2$). The results of Boruta algorithm and LASSO regression formed

a complementary effect, in which the former focused on the outcome discrimination ability of features, and the latter emphasized the predictive contribution of features in the model.

Construction and Evaluation of Machine Learning Models

Based on the two-step screened core indicators, five machine learning models were constructed in the training group, and their predictive performance was evaluated in the training set and test set with AUC, optimal cutoff value, sensitivity and specificity as evaluation indices (Table 3). The results showed that all models had good predictive performance ($AUC > 0.75$) in the training set, with XGBoost exhibiting the highest training set AUC (0.827, 95% CI: 0.739–0.915) and satisfactory sensitivity (0.758) and specificity (0.846). Logistic regression showed the best performance in the test set, with an AUC of 0.891 (95% CI: 0.761–1.000), optimal cutoff value of 0.408, sensitivity of 1.000, and specificity of 0.750. LASSO regression achieved a test AUC of 0.844 (95% CI: 0.675–1.000), with a sensitivity of 0.750 and specificity of 0.812. Random forest and LightGBM also showed favorable performance in the test set, with AUCs of 0.832 and 0.816, respectively; while XGBoost presented the lowest test set AUC (0.699, 95% CI: 0.486–0.913) and the lowest specificity (0.438), indicating obvious overfitting and poor generalizability. The cross-validated AUCs, which we now report as the primary performance metrics, are more stable and conservative: logistic regression (0.757 ± 0.097), LASSO regression (0.754 ± 0.096), Random Forest (0.623 ± 0.097), LightGBM (0.679 ± 0.080), and XGBoost (0.687 ± 0.092).

Nomogram Development and Validation

A nomogram model integrating the four core predictive features (malignant tumor, Lactic Acid, MWR, AAR) was developed based on the optimal Logistic regression model (Figure 3A). Internal validation showed that the calibration curve of the nomogram with 1000 bootstrap resamples had a good agreement between predicted and observed probabilities of death (Figure 3B), indicating acceptable calibration of the model. DCA demonstrated that the nomogram model had a positive clinical net benefit across a range of high-risk thresholds (Figure 3C), which was significantly higher than the all-treat and no-treat strategies, suggesting potential clinical utility across a range of threshold probabilities. ROC curve analysis showed that the nomogram model had good discriminatory ability in the training set ($AUC = 0.765$), test set ($AUC = 0.891$) (Figure 3D).

SHAP Model Interpretability Analysis

SHAP analysis confirmed Lactic Acid as the dominant predictor across all models (mean $|SHAP| \approx 0.10$ for logistic regression; Figure 4A and B). Dependence and waterfall plots further illustrated individual-level risk contributions (Figure 4C and D).

External Validation of the Prediction Model

External validation was conducted in the MIMIC-IV cohort ($n = 22$). Lactic Acid were significantly higher in the non-survival group (both $P < 0.05$), consistent with the primary cohort. No significant differences were observed for AAR, MWR or malignant tumor (both $P > 0.05$), likely due to the small external sample size (Table 4). The model maintained good discrimination in external validation, with an AUC of 0.838 (0.655–1.000), indicating preliminary external validation with acceptable generalizability (Figure 3D).

Discussion

This study employed a two-step Boruta-LASSO approach for feature screening and four machine learning algorithms for model development to identify key predictors of in-hospital mortality in patients ECMO. A parsimonious prediction model with favorable discrimination and generalizability was subsequently established.

In this cohort, logistic regression outperformed more complex tree-based and boosting models (Random Forest, LightGBM, XGBoost). This is likely attributable to the limited sample size ($n = 122$) and small predictor set: complex models tend to overfit training-set noise in such settings, whereas logistic regression's lower complexity yields more stable generalization. The approximately linear feature–outcome relationships further favored logistic regression, which was therefore selected as the final model.

Table 3 Model Performance in Training and Test Sets for ECMO Mortality Prediction

Model	Train AUC CI	Train Cutoff	Train Sensitivity	Train Specificity	Test AUC CI	Test Cutoff	Test Sensitivity	Test Specificity	Repeated 10 Fold CV AUC
Logistic Regression	0.765 (0.667–0.863)	0.5	0.758	0.738	0.891 (0.761–1)	0.408	1	0.75	0.757 ± 0.097
LASSO Regression	0.772 (0.675–0.868)	0.499	0.727	0.769	0.844 (0.675–1)	0.454	0.75	0.812	0.754 ± 0.096
Random Forest	0.901 (0.839–0.962)	0.595	0.727	0.923	0.832 (0.669–0.996)	0.295	1	0.625	0.623 ± 0.097
LightGBM	0.757 (0.658–0.857)	0.345	0.545	0.846	0.816 (0.647–0.986)	0.326	1	0.625	0.679 ± 0.08
XGBoost	0.827 (0.739–0.915)	0.37	0.758	0.846	0.699 (0.486–0.913)	0.176	1	0.438	0.687 ± 0.092

Abbreviations: AUC, area under the curve; CI, confidence interval; Cut-off, optimal threshold.

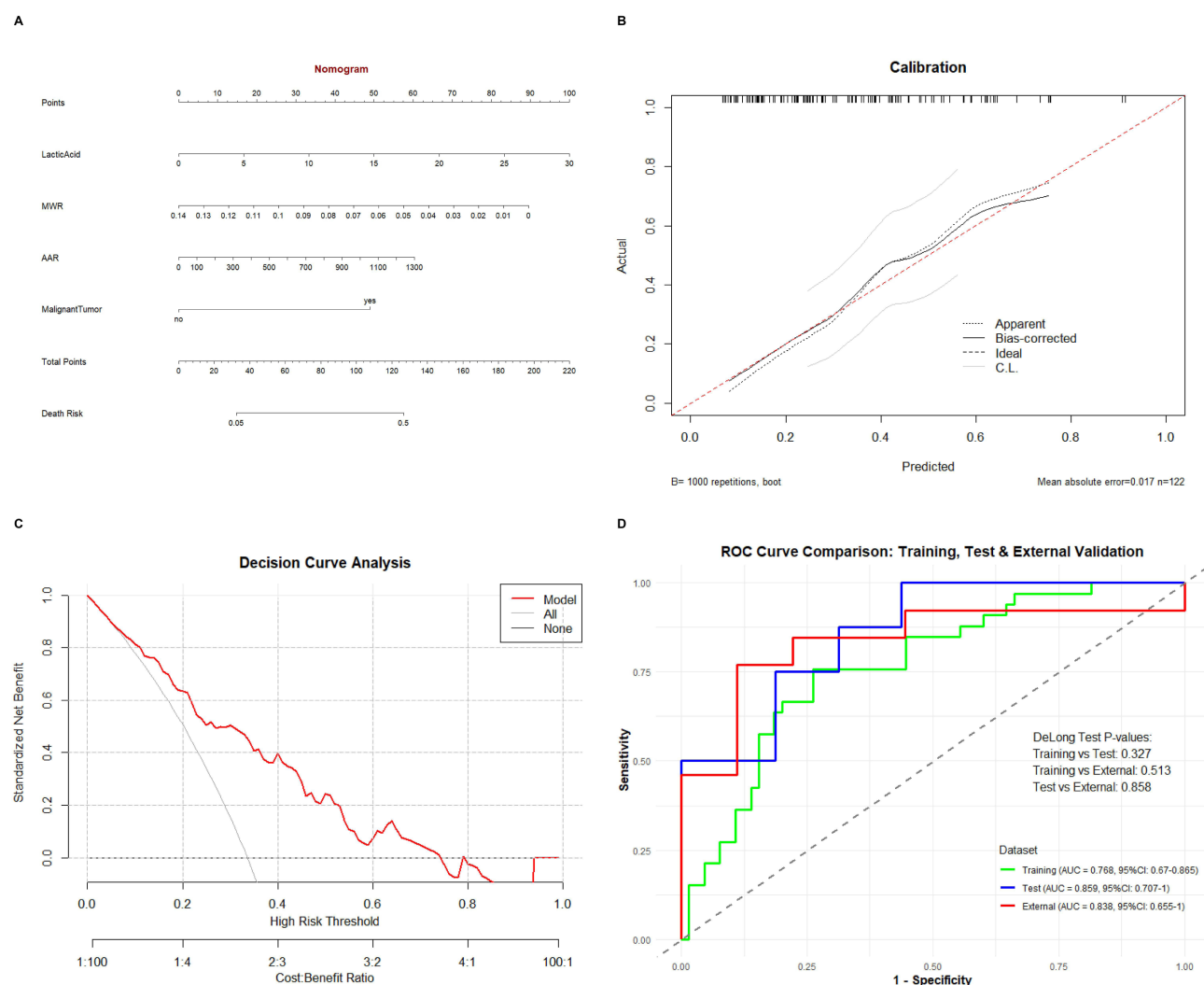


Figure 3 Development and validation of the nomogram for predicting in-hospital mortality in ECMO patients. **(A)** Nomogram integrating four key predictors (Lactic Acid, MWR, AAR, and Malignant Tumor) to estimate individual mortality risk. **(B)** Calibration curve of the nomogram with 1000 bootstrap resamples, showing reasonable agreement between predicted and observed probabilities of death. **(C)** Decision curve analysis (DCA) demonstrating the clinical net benefit of the prediction model across a range of high-risk thresholds. **(D)** Receiver operating characteristic (ROC) curves of the nomogram in the training, test, and external validation cohorts, with corresponding area under the curve (AUC) values.

Malignant Tumor was an independent risk factor, likely due to the poor functional status, immune impairment, and advanced organ dysfunction often present in these patients. The invasive nature of ECMO may further exacerbate systemic stress and inflammatory responses.

Lactic Acid emerged as the most powerful predictor of in-hospital mortality in this cohort. The persistent elevation of lactate despite ECMO may further suggest ongoing microcirculatory dysfunction, irreversible cellular injury, or sepsis-related metabolic disturbances, all of which are associated with higher mortality in critically ill patients^{13,14} As a direct marker of tissue hypoperfusion and hypoxia, elevated lactate levels, which were more than double in non-survivors compared to survivors, strongly indicate unfavorable outcomes during ECMO support.¹⁵

The AAR (APTT-to-Albumin Ratio), a novel composite indicator, integrates and reflects concurrent coagulation dysfunction (prolonged APTT) and nutritional/metabolic compromise (hypoalbuminemia). Notably, APTT has long been recognized as a key indicator for anticoagulation monitoring during ECMO support, as it directly assesses the integrity of the intrinsic coagulation pathway and the efficacy of anticoagulant agents such as heparin¹⁶ When combined with hypoalbuminemia—a marker of nutritional depletion, systemic inflammation, and impaired synthesis—the elevated AAR synergistically integrates two independent adverse prognostic factors. In the context of ECMO, hypoalbuminemia can

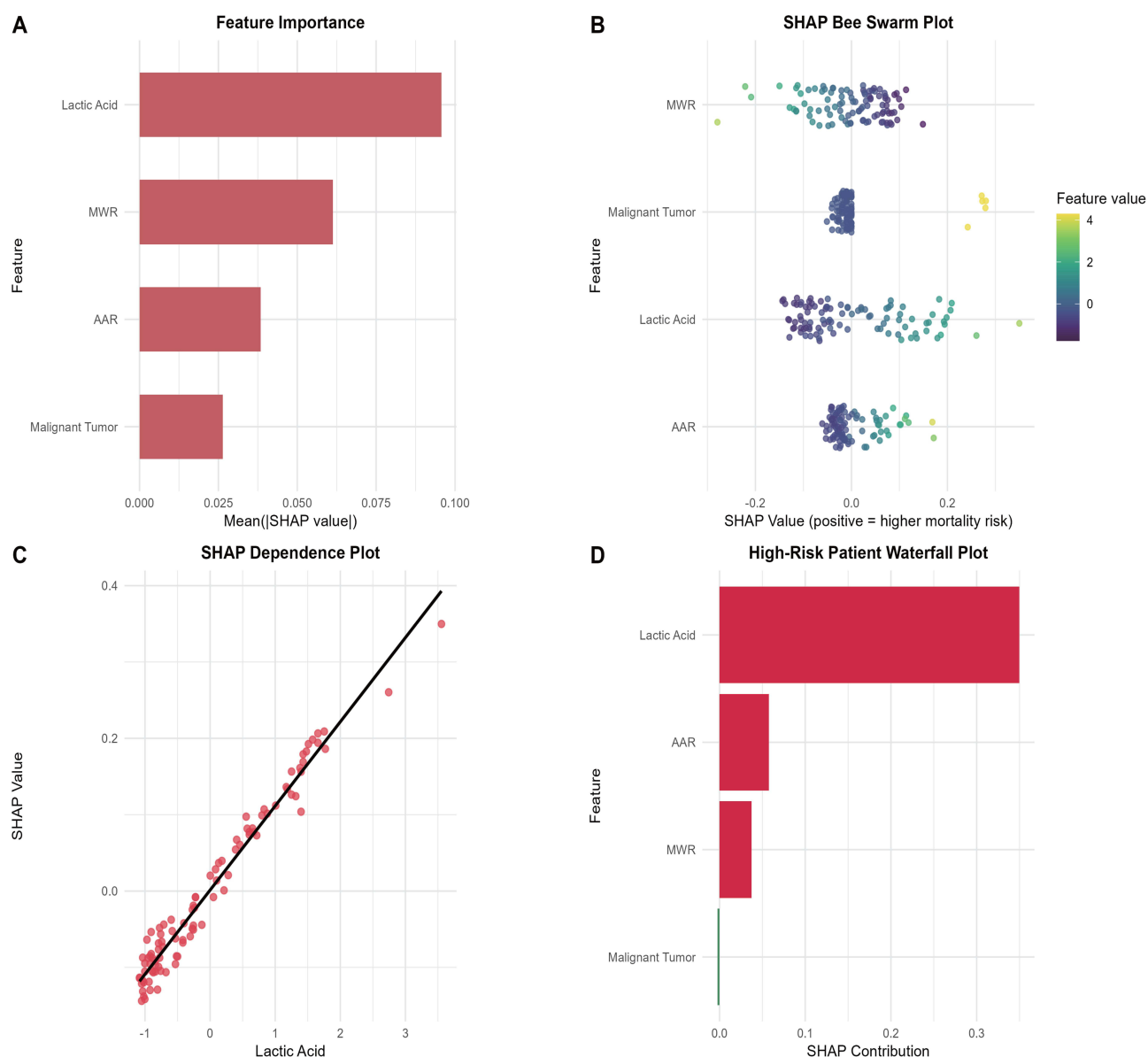


Figure 4 SHAP analysis of the logistic regression model for ECMO patient mortality prediction. **(A)** Global feature importance: Ranked by mean absolute SHAP values. **(B)** SHAP bee swarm plot: Distribution of SHAP values showing feature impact direction and magnitude. **(C)** SHAP dependence plot: Linear association between Lactic Acid and its SHAP values. **(D)** High-risk waterfall plot: SHAP contribution decomposition for a representative high-mortality patient.

exacerbate endothelial dysfunction, alter drug pharmacokinetics (eg, of heparin),¹⁷ and reflect a severe systemic inflammatory state.¹⁸ An elevated AAR indicates a synergistic increase in mortality risk by reflecting the cumulative burdens of coagulation impairment and metabolic/inflammatory dysregulation in ECMO patients. The use of composite biomarkers like the HALP score (Hemoglobin, Albumin, Lymphocyte, Platelet), which integrates albumin as a marker of nutritional status and inflammation, is supported by evidence predicting adverse events after coronary bypass surgery.¹⁹ This growing body of literature underscores the clinical value of albumin-related composite indices in patients undergoing extracorporeal circulation support.

In our cohort, the MWR (Monocyte-to-White cell Ratio) was identified as a protective factor against in-hospital mortality. This finding aligns with emerging evidence highlighting the prognostic role of monocyte function in critical care settings. Specifically, a prospective study by Siegel et al demonstrated that monocyte dysfunction effectively predicts mortality in patients receiving VA-ECMO.²⁰ A low MWR may reflect a state of immune exhaustion, impaired monocyte function, and overwhelming systemic inflammation, all of which can hinder recovery in critically ill ECMO

Table 4 Comparison of Clinical Characteristics Between Survival and Non-Survival Patients in the External Validation Cohort

Indicator	Overall (n=22)	Survivors (n=13)	Non-Survivors (n=9)	P
Lactic Acid (mmol/L)	4.07 (1.90)	3.09 (1.46)	4.74 (1.91)	0.033
AAR	206.54 (97.75)	186.87 (66.99)	220.16 (115.06)	0.403
MWR	0.03 [0.02;0.06]	0.06 [0.04;0.07]	0.03 [0.02;0.03]	0.101
Malignant Tumor, n (%)	3 (13.64%)	0 (0.00%)	3 (23.08%)	0.240

Notes: Data was presented as median (P25–P75) or mean (SD). P value was obtained by Kruskal–Wallis H-test. $p < 0.05$ was considered as statistically significant.

Abbreviations: AAR, APTT to Alb Ratio; MWR, Monocyte to White Blood Cell Ratio.

patients.²¹ Thus, MWR serves not only as a simple hematologic index but also as an integrative marker of immune competence and inflammatory balance. Its identification as a protective factor underscores the importance of monitoring immune cell profiles in ECMO patients, potentially informing strategies aimed at modulating immune responses and improving outcomes in this high-risk population.

A nomogram was developed based on the logistic regression model for clinical application. Internal validation indicated good calibration, and decision-curve analysis demonstrated favorable clinical net benefit. External validation in the MIMIC-IV cohort (n=22) yielded an AUC of 0.838 (95% CI: 0.655–1.000), suggesting acceptable generalizability.

Existing ECMO mortality scores including SAVE and RESP were established for specific patient groups, so they do not apply to our heterogeneous cohort (76% VA-ECMO, 24% VV-ECMO).²² Direct AUC comparison would lead to spectrum bias and lack clinical value. Further studies with stratified, larger cohorts are required to compare our model with existing tools. Although individual predictors did not show statistically significant differences in the external cohort, the full model integrating all four indicators still demonstrated reasonable discriminative performance in external validation. This tool facilitates bedside risk assessment and supports individualized clinical decision-making.

This study has several limitations. The small retrospective single-center cohort (n=122, 41 in-hospital deaths) may cause inadequate statistical power and biases. Dynamic clinical parameters during ECMO, imaging and genetic markers were not included. External validation relied on a small MIMIC-IV subgroup (n=22), restricting model generalizability. Moreover, we did not compare our model with other prediction models. It should be seen as an exploratory tool, not a definitive clinical aid, until further model optimization through large multicenter studies with complete data and rigorous validation.

Conclusion

In this study, we identified Malignant Tumor, elevated Lactic Acid, AAR, and decreased MWR as potential predictors of in-hospital mortality in ECMO patients. A nomogram was built using two-step Boruta-LASSO feature selection and logistic regression, showing reasonable discrimination, acceptable calibration, and modest generalizability. SHAP analysis added clinical interpretability. This tool may help address a current gap in ECMO-specific risk assessment and support bedside mortality stratification and personalized decision-making. Larger external validation is still needed to confirm its reliability.

Statement

This study was conducted and reported in adherence to the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) reporting guidelines. All authors meet the journal’s authorship criteria. All authors have read and approved the final manuscript to be published, agreed on the target journal for submission, and take full responsibility for all aspects of this work.

Data Sharing Statement

The authors confirm that all data supporting the findings of this study are available from the corresponding author upon reasonable request. Prof. Zhu had full access to all data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. [Supplemental Materials](#), including the study protocol, programming code, and analysis scripts, are also available by contacting the corresponding author at [610608091@qq.com].

Ethics Approval and Informed Consent

This study involved a retrospective analysis of de-identified historical laboratory data from patients. Prior to admission, all patients were informed and provided written informed consent for the following: “To advance medical research and education, your medical records and residual biological specimens (including blood, body fluids, tissues, etc.) may be used for relevant research. During this process, your personal information will be strictly confidential”. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province (Approval No.: K20251042).

Author Contributions

Guangjun Zhu: Conceptualization, Methodology, Supervision, Project Administration, Funding Acquisition, Writing – Review & Editing;

Yunda Cai: Conceptualization, Investigation, Formal Analysis, Software, Writing – Original Draft, Visualization;

Li Lin: Resources, Validation, Formal Analysis, Data Curation, Writing – Review & Editing;

Chaochao Chen: Investigation, Data Curation, Software, Visualization, Writing–Review & Editing;

Xiaojie Bi: Investigation, Resources, Validation, Writing – Review & Editing.

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Disclosure

The authors declare no competing interests in this work.

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