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Original Article

Construction and validation of a prognostic prediction model for critically ill lung cancer patients based on respiratory functional reserve and systemic inflammatory characteristics

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Abstract: Critically ill lung cancer (LC) patients are often admitted to the Department of Respiratory and Critical Care Medicine (RCCM), the Intensive Care Unit (ICU), or the Emergency Intensive Care Unit (EICU), where early risk stratification is essential because of their high short-term mortality. Despite close monitoring, their short-term mortality remains high, and general scoring systems fail to account for tumor-specific pathology. A total of 541 patients with pathologically or cytologically confirmed LC hospitalized in the RCCM, ICU, or EICU were enrolled. They were randomly divided into a training set (n=379) and a validation set (n=162) at a 7:3 ratio. The least absolute shrinkage and selection operator (LASSO) Cox regression with 10-fold cross-validation was used for variable selection. Restricted cubic spline analysis examined nonlinearity, and the Schoenfeld residual test verified the proportional hazards assumption. Multivariable Cox regression identified five independent predictors of 28-day mortality: pulse oxygen saturation (SpO_2), baseline ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2), C-reactive protein (CRP) level, hemoglobin level, and bone metastasis (the latter possibly due to its association with pneumonia). These were incorporated into a nomogram. In the training set, the area under the curve (AUC) for 14-day and 28-day mortality was 0.871 and 0.947, respectively, with a concordance index (C-index) of 0.874. In the validation set, the AUCs were 0.870 and 0.946, with a C-index of 0.852. Calibration curves and Brier scores demonstrated good agreement between predicted and observed outcomes. Decision curve analysis demonstrated net clinical benefit across a wide range of threshold probabilities. The 28-day survival rates for low-, intermediate-, and high-risk groups were 98.9%, 82.0%, and 13.8%, respectively (P<0.001). DeLong testing indicated that our model outperformed Acute Physiology and Chronic Health Evaluation II (APACHE II) in both datasets (all P<0.05). This nomogram, based on five routine clinical variables, offers good discrimination, calibration, and risk stratification, serving as a practical tool for early risk assessment and clinical decision-making in critically ill LC patients.

Keywords: Lung cancer, critical care, mortality prediction, nomogram, oxygenation index, systemic inflammation, prognostic model

Introduction

Lung cancer is one of the leading causes of cancer-related death globally and consistently ranks highest in both incidence and mortality among malignancies [1]. Advances in imaging, molecular profiling, targeted therapy, immunotherapy, and perioperative management have improved overall survival to some degree in recent years. Even so, a substantial number of patients still require admission to the Department of Respiratory and Critical Care Medicine (RCCM), Intensive Care Unit (ICU), or Emergency Intensive Care Unit (EICU) due to disease progression, treatment-related complications, or acute critical illness [2]. This is particularly relevant when patients experience respiratory failure, severe infection, sepsis, massive hemoptysis, or postoperative complications. Critical illness in lung cancer is a rapidly evolving condition associated with high short-term mortality, representing an essential

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oncologic critical care problem [3]. Early identification of high-risk patients, prognostication of their short-term outcome, and assistance in clinical management decisions at the time of admission to the RCCM, ICU, or EICU are of enormous practical value.

Prognostic factors in critically ill lung cancer patients are much more complex than those in the general ICU population. Beyond acute physiological derangements and organ dysfunction, outcomes are also influenced by tumor burden, metastatic status, prior antitumor therapy, baseline performance status, and nutritional reserve [4]. Lung cancer typically causes varying degrees of destruction of lung parenchyma, compression or obstruction of the airway, pleural effusion, infection, and tumor-associated inflammatory reactions. A patient with advanced lung cancer who deteriorates despite treatment is very likely to develop oxygenation failure and respiratory decompensation [5]. Consequently, decreased respiratory functional reserve is a frequent cause of ICU admission and is likely one of the primary mechanisms of short-term death. The development of malignancy, infectious complications, immune dysregulation, and multi-organ damage is also closely linked to systemic inflammatory responses. The higher the inflammatory burden, the greater the severity and the faster the deterioration [6, 7]. Ultimately, the combined impact of respiratory functional reserve, systemic inflammation, and tumor-related characteristics drives short-term outcomes in critically ill lung cancer patients.

Scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores are frequently used for disease evaluation and prognosis in the ICU [8]. These tools reasonably detect acute physiological abnormalities and organ dysfunction, which has value in critical care. However, traditional general-purpose scores have limitations for critically ill patients with lung cancer, a group characterized by high disease heterogeneity. Since these scores were derived from fairly general critical care populations, they insufficiently integrate tumor-specific factors, notably metastatic burden, baseline performance status, and tumor-related inflammation [9]. Previous studies have shown that the prognosis of lung cancer is also closely related to oxygenation status, respiratory reserve, and inflammatory dysregulation, yet these dimensions are poorly captured by existing scores [10]. In practice, patients with identical severity scores can have vastly different short-term outcomes, highlighting the need for a more tailored tool.

Outcomes research in critically ill cancer patients has focused mainly on general oncologic ICU cohorts, with limited lung cancer-specific research [11, 12]. Some studies have examined single indicators, such as inflammatory markers, lactate, or oxygenation parameters, in isolation - a univariate approach that rarely captures the complex pathophysiology of critically ill lung cancer patients [13]. Few existing models combine respiratory functional reserve and systemic inflammatory characteristics while remaining clinically usable, interpretable, and capable of short-term risk stratification. Clinicians in the intensive care unit would benefit from a tool that generates personalized estimates of 14-day or 28-day mortality risk, built on routinely available data to inform decisions regarding treatment intensity, resource allocation, and communication with patients and families.

In view of this, the present study aimed to identify key predictors of short-term mortality in critically ill lung cancer patients by integrating respiratory functional reserve, systemic inflammatory parameters, tumor metastatic status, and baseline physiological parameters. We sought to develop and validate a model for predicting 28-day mortality risk, presented as a nomogram, to enable personalized prediction. Additionally, the model's discrimination, calibration, net clinical benefit, and risk stratification capacity were systematically assessed, and its performance was benchmarked against APACHE II and SOFA scores to demonstrate its practical value for short-term prognostic assessment in this population. The overall goal was to create a simple, robust, and clinically meaningful prognostic tool to assist with early risk assessment and precision management of critically ill lung cancer patients.

Materials and methods

Study population

We conducted a retrospective single-center cohort study enrolling patients with a patholo-

gical or cytological diagnosis of lung cancer admitted to the RCCM, ICU, or EICU between January 2017 and January 2022. All records were obtained from the hospital's electronic medical record system, laboratory information system, and picture archiving and communication system. Only the first admission was considered for patients with multiple admissions. A total of 541 patients were ultimately enrolled. The study was approved by the Ethics Committee of the Affiliated Hospital of Shaoxing University, and informed consent was waived due to the retrospective observational nature.

Sample size estimation

Sample size estimation was based on the 28-day mortality rate and the value of key determinants in a Cox regression model. A large cohort study of 1,242 ICU patients with lung cancer reported a 28-day mortality of 30.6% [14]. Assumptions included a two-sided α of 0.05, power (1-β) of 0.80, and a minimum hazard ratio (HR) of 1.6. This HR value is consistent with independent risk factors such as metastatic status or SOFA score in similar populations [14] and represents a clinically significant increased risk. The required number of events (D) according to the Schoenfeld formula for Cox regression is:

$$D = \frac{(Z1 - \alpha/2 + Z1 - \beta)2}{p(1 - p)(\ln HR)2}$$

where D is the required number of events, and p is the proportion of patients exposed to the main predictor (estimated as 0.4 based on the reported prevalence of metastatic disease). The required number of events was calculated to be 148. Dividing this by the 28-day mortality rate of 30.6% yielded a total sample size requirement of 484. Allowing for a 10% missing data or exclusions rate, we aimed for enrollment of 538. The final cohort of 541 patients satisfied this requirement.

Inclusion and exclusion criteria

Inclusion criteria were: (1) Age ≥18 years; (2) Pathologically or cytologically confirmed lung cancer; (3) Admission to the RCCM, ICU, or EICU due to critical illness; (4) Complete baseline clinical data, vital signs, key laboratory results, and outcome data; and (5) Expected survival >3 days to ensure adequate acquisition of baseline clinical assessment and early physiological data.

Exclusion criteria were: (1) Age <18 years; (2) Repeated ICU admissions (only the first admission retained); (3) Diagnosis of another primary malignancy; (4) Missing key variable or outcome data; and (5) Unconfirmed pathological diagnosis or unverifiable clinical records; (6) Absence of arterial blood gas data at the 48-hour timepoint, as 48-hour oxygenation indices were used.

Clinical data collection

All clinical data were independently extracted from the electronic medical record system by two investigators using a standardized data extraction form. Variables included age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), pathological type, tumor stage, brain metastasis, bone metastasis, prior chemotherapy, prior targeted or immunotherapy, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic heart failure, chronic renal insufficiency, cerebrovascular disease, primary reason for admission to the RCCM/ICU/EICU, invasive mechanical ventilation, vasoactive agent use, continuous renal replacement therapy (CRRT), and antibiotic use.

Tumor stage, brain metastasis, and bone metastasis were determined by integrating pathological findings, imaging reports, and discharge diagnoses. Brain metastasis was confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) of the head. Bone metastasis was determined based on imaging evidence, including bone scintigraphy, positron emission tomography (PET)/CT, CT, or MRI. Radiological findings suggestive of metastatic involvement - such as osteolytic or osteoblastic lesions, abnormal radionuclide uptake, or metabolically active bone lesions - were interpreted according to formal radiology reports issued by experienced radiologists. The diagnosis was further confirmed by integrating imaging reports, discharge diagnoses, and corresponding clinical documentation. In cases of ambiguity, consistency across multiple sources of evidence was required to establish the presence of bone metastasis.

Vital signs and illness severity parameters recorded within 24 hours of RCCM, ICU, or EICU admission included heart rate, respiratory rate, mean arterial pressure, body temperature, APACHE II score, and SOFA score. Both scores were retrospectively calculated from the worst physiological and laboratory values during the first 24 hours.

Respiratory functional reserve parameters included pulse oxygen saturation (SpO_2), partial pressure of arterial oxygen (PaO_2), fraction of inspired oxygen (FiO_2), baseline oxygenation index (PaO_2/FiO_2), as well as PaO_2, FiO_2, and PaO_2/FiO_2 at 48 hours, and Delta PaO_2/FiO_2. Baseline values were obtained from the first arterial blood gas within 24 hours of admission. The 48-hour values were derived from the blood gas result closest to the 48-hour mark. Delta PaO_2/FiO_2 was calculated as the 48-hour PaO_2/FiO_2 minus the baseline PaO_2/FiO_2.

Laboratory variables included arterial lactate, arterial pH, partial pressure of arterial carbon dioxide ($PaCO_2$), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), C-reactive protein (CRP), albumin, procalcitonin (PCT), white blood cell count, hemoglobin, platelet count, creatinine, total bilirubin, alanine aminotransferase (ALT), D-dimer, and blood glucose. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. SII was calculated as platelet count × neutrophil count/lymphocyte count. Except for the 48-hour oxygenation indices, all laboratory values were obtained from the first measurement within 24 hours of admission to the RCCM, ICU, or EICU.

Measurement methods

Arterial blood gas analysis was performed using an ABL800 FLEX analyzer (Radiometer, Denmark); lactate, PaO_2, $PaCO_2$, and pH were measured according to the manufacturer's standardized protocol. Complete blood count parameters were analyzed using a BC-6800-Plus automated hematology analyzer (Mindray, China). Biochemical parameters (albumin, creatinine, total bilirubin, ALT, and blood glucose) were measured using an AU5800 automated biochemical analyzer (Beckman Coulter). CRP was measured by immunoturbidimetry on a Roche cobas c 702 platform; PCT was measured by electrochemiluminescence immunoassay (ECLIA) on a Roche cobas e 411. D-dimer was quantified by immunoturbidimetry on a Sysmex CS-5100. All specimens were processed by the hospital's clinical laboratory under unified quality control standards.

Outcome measures

The primary outcome was 28-day all-cause mortality after admission to the RCCM, ICU, or EICU; the secondary outcome was 14-day all-cause mortality. Survival time was defined as the interval from admission to death. Patients who remained alive at 28 days were censored. The vital status of patients who died within 28 days after hospital discharge was ascertained from inpatient records, follow-up data, or in-hospital death registries.

Statistical analysis

All analyses were conducted using R (4.5.3) and SPSS (27.0). Patients with missing data on key variables or outcome measures were excluded; thus, all variables included in the final analysis were complete and did not require imputation. Using a computer-generated random sampling plan in R with a fixed random seed, all patients were allocated into training and validation sets at a 7:3 ratio. The authors conducted repeated random sampling and settled on the final split when the main model-related variables showed adequate balance between the two sets based on *P* values and standardized mean differences (SMDs).

Continuous variables were expressed as mean ± standard deviation or median [interquartile range] according to their distribution; categorical variables were presented as counts (percentages). Normally distributed continuous variables were compared using the independent t-test, while the Mann-Whitney U test was used for non-normally distributed variables. The χ^2 test or Fisher's exact test was used for comparing categorical variables. We also calculated standardized mean differences (SMDs) between the training and validation sets to assess balance.

The variance inflation factor (VIF) was used to assess multicollinearity among candidate variables before modeling, and Spearman rank correlation was used to assess pairwise asso-

ciations. Least absolute shrinkage and selection operator (LASSO) Cox regression with 10-fold cross-validation was applied to the training set to identify variables with non-zero coefficients for subsequent analysis, using the λ.1se criterion. Restricted cubic spline (RCS) analysis was applied to continuous variables selected by LASSO to test for nonlinearity with mortality. The proportional hazards assumption was assessed using Schoenfeld residuals; variables that exhibited strong nonlinear effects or violated the proportional hazards assumption (where inclusion in the extended model produced parameter instability) were excluded from the final model for reasons of parsimony, robustness, and interpretability.

Univariable Cox regression was performed with 28-day mortality as the outcome of interest. Subsequently, multivariable Cox regression was performed using the candidate variables selected by LASSO. RCS modeling was applied to any nonlinear continuous variables among the candidates. A nomogram was created based on factors independently associated with 28-day mortality. Discriminative ability was evaluated using time-dependent receiver operating characteristic (ROC) curve analysis, as reflected by the area under the curve (AUC) and concordance index (C-index). Calibration curves and the Brier score were used to assess calibration. Decision curve analysis (DCA) was used to evaluate clinical utility.

Patients were divided into three risk groups based on the linear predictor from the training set using tertile cutoffs. Kaplan-Meier curves were drawn to compare survival across strata, and log-rank tests were performed for comparison. The DeLong test was applied to compare the discriminative ability of our model for 14-day and 28-day mortality with that of the APACHE II and SOFA scores. All tests were two-sided, and a *P* value <0.05 was considered statistically significant.

Results

Baseline clinical and laboratory characteristics

The whole cohort consisted of 541 patients, including 191 deaths and 350 survivors. The primary reasons for admission to the RCCM, ICU, or EICU differed significantly between the two groups (all P<0.001). Deceased patients were more often admitted for acute respiratory failure, whereas postoperative monitoring was more common among survivors. ECOG PS differed significantly between groups (P<0.001). The death group had a generally worse functional status, with more patients scoring 3-4. In terms of tumor characteristics, tumor stage (P=0.002), cerebral metastasis (P<0.001), and osseous metastasis (P<0.001) were all significantly distinct, reflecting a more advanced tumor burden and distant metastasis in the death group. Patients who died required more organ support and were more severely ill, as indicated by higher use of invasive mechanical ventilation (P<0.001), vasoactive agents (P<0.001), and CRRT (P<0.001) (**Table 1**).

Patients who died were older than survivors. As shown in **Table 1**, they had faster heart rates (P<0.001), higher respiratory rates (P<0.001), lower mean arterial pressure (P<0.001) and higher body temperatures (P<0.001), reflecting greater physiological derangement and cardiorespiratory stress. Regarding respiratory parameters, the death group had significantly lower SpO_2 (P<0.001) and PaO_2 (P<0.001) values and higher FiO_2 values (P<0.001). After 48 hours, PaO_2 remained lower (P<0.001) and FiO_2 remained higher (P<0.001). The death group had lower baseline PaO_2/FiO_2 (P<0.001), 48-hour PaO_2/FiO_2 (P<0.001), and Delta PaO_2/FiO_2 (P<0.001), indicating worse initial oxygenation and little short-term improvement in respiratory function (**Table 1**).

The death group had significantly higher levels of arterial lactate (P<0.001), $PaCO_2$ (P<0.001), NLR (P<0.001), SII (P<0.001), CRP (P<0.001), PCT (P<0.001), white blood cell count (P< 0.001), creatinine (P<0.001), total bilirubin (P<0.001), ALT (P<0.001), D-dimer (P<0.001), and blood glucose (P<0.001), while pH (P< 0.001), albumin (P<0.001), hemoglobin (P< 0.001), and platelet count (P=0.012) were lower. These findings point to more pronounced systemic inflammatory activation, more severe acid-base disturbance, and greater multi-organ dysfunction in the death group (**Table 1**). Sex, smoking history, pathological type, prior chemotherapy, prior targeted or immunotherapy, hypertension, diabetes mellitus, COPD, chronic heart failure, chronic renal insufficiency, cerebrovascular disease, and antibiotic use did not differ between groups (all P>0.05) (**Table 1**).

Table 1. Comparison of baseline clinical characteristics, respiratory functional reserve, systemic inflammatory markers, and treatment-related variables between the non-survival group and survival group (N=541)

Variable	Total (N=541)	Survival group (n=350)	Non-survival group (n=191)	Statistic	*P* value
Primary reason for admission to RCCM/ICU/EICU				19.96	<0.001
Acute respiratory failure	222 (41.04%)	124 (35.43%)	98 (51.31%)		
Sepsis/Infection	128 (23.66%)	82 (23.43%)	46 (24.08%)		
Massive hemoptysis	70 (12.94%)	52 (14.86%)	18 (9.42%)		
Postoperative monitoring	68 (12.57%)	56 (16.00%)	12 (6.28%)		
Other	53 (9.80%)	36 (10.29%)	17 (8.90%)		
Sex				0.731	0.393
Male	354 (65.43%)	224 (64.00%)	130 (68.06%)		
Female	187 (34.57%)	126 (36.00%)	61 (31.94%)		
Smoking history				2.434	0.119
Yes	320 (59.15%)	198 (56.57%)	122 (63.87%)		
No	221 (40.85%)	152 (43.43%)	69 (36.13%)		
ECOG PS				34.89	<0.001
Score 0-1	180 (33.27%)	143 (40.86%)	37 (19.37%)		
Score 2	210 (38.82%)	134 (38.29%)	76 (39.79%)		
Score 3-4	151 (27.91%)	73 (20.86%)	78 (40.84%)		
Pathological type				0.95	0.813
Adenocarcinoma	243 (44.92%)	161 (46.00%)	82 (42.93%)		
Squamous cell carcinoma	156 (28.84%)	98 (28.00%)	58 (30.37%)		
Small cell carcinoma	84 (15.53%)	52 (14.86%)	32 (16.75%)		
Other	58 (10.72%)	39 (11.14%)	19 (9.95%)		
Tumor stage				9.46	0.002
Stage III	137 (25.32%)	104 (29.71%)	33 (17.28%)		
Stage IV	404 (74.68%)	246 (70.29%)	158 (82.72%)		
Brain metastasis				54.637	<0.001
Present	166 (30.68%)	69 (19.71%)	97 (50.79%)		
Absent	375 (69.32%)	281 (80.29%)	94 (49.21%)		
Bone metastasis				93.908	<0.001
Present	190 (35.12%)	71 (20.29%)	119 (62.30%)		
Absent	351 (64.88%)	279 (79.71%)	72 (37.70%)		
Prior chemotherapy				1.056	0.304
Yes	260 (48.06%)	162 (46.29%)	98 (51.31%)		
No	281 (51.94%)	188 (53.71%)	93 (48.69%)		

Prior targeted/immunotherapy				0.522	0.470
Yes	136 (25.14%)	84 (24.00%)	52 (27.23%)		
No	405 (74.86%)	266 (76.00%)	139 (72.77%)		
Hypertension				0.239	0.625
Yes	212 (39.19%)	134 (38.29%)	78 (40.84%)		
No	329 (60.81%)	216 (61.71%)	113 (59.16%)		
Diabetes mellitus				0.355	0.551
Yes	110 (20.33%)	68 (19.43%)	42 (21.99%)		
No	431 (79.67%)	282 (80.57%)	149 (78.01%)		
COPD				0.522	0.470
Yes	136 (25.14%)	84 (24.00%)	52 (27.23%)		
No	405 (74.86%)	266 (76.00%)	139 (72.77%)		
Chronic heart failure				0.596	0.440
Yes	86 (15.90%)	52 (14.86%)	34 (17.80%)		
No	455 (84.10%)	298 (85.14%)	157 (82.20%)		
Chronic renal insufficiency				0.558	0.455
Yes	70 (12.94%)	42 (12.00%)	28 (14.66%)		
No	471 (87.06%)	308 (88.00%)	163 (85.34%)		
Cerebrovascular disease				0.089	0.766
Yes	58 (10.72%)	36 (10.29%)	22 (11.52%)		
No	483 (89.28%)	314 (89.71%)	169 (88.48%)		
Invasive mechanical ventilation				69.573	<0.001
Yes	213 (39.37%)	92 (26.29%)	121 (63.35%)		
No	328 (60.63%)	258 (73.71%)	70 (36.65%)		
Vasoactive agent use				62.682	<0.001
Yes	196 (36.23%)	84 (24.00%)	112 (58.64%)		
No	345 (63.77%)	266 (76.00%)	79 (41.36%)		
CRRT				23.814	<0.001
Yes	80 (14.79%)	32 (9.14%)	48 (25.13%)		
No	461 (85.21%)	318 (90.86%)	143 (74.87%)		
Antibiotic use				0.748	0.387
Yes	406 (75.05%)	258 (73.71%)	148 (77.49%)		
No	135 (24.95%)	92 (26.29%)	43 (22.51%)		
Age (years)	65.06±9.52	64.15±9.50	66.73±9.35	-3.038	0.002
APACHE II score	20.00 [16.00, 25.00]	18.00 [14.00, 22.00]	24.00 [21.00, 28.00]	10.898	<0.001

SOFA score	6.00 [5.00, 8.00]	5.00 [4.00, 7.00]	8.00 [6.00, 11.00]	11.085	<0.001
Heart rate (beats/min)	92.28±17.55	86.49±13.92	102.88±18.56	-11.593	<0.001
Respiratory rate (breaths/min)	22.00 [19.00, 27.00]	21.00 [17.00, 24.00]	27.00 [23.00, 31.00]	10.85	<0.001
Mean arterial pressure (mmHg)	74.00 [66.00, 83.00]	78.00 [70.00, 85.00]	67.00 [59.00, 74.50]	9.361	<0.001
Body temperature (°C)	37.40 [36.80, 38.00]	37.20 [36.70, 37.70]	37.90 [37.20, 38.60]	8.442	<0.001
SpO_2 (%)	93.00 [89.00, 96.00]	94.00 [91.00, 97.00]	89.00 [85.00, 93.00]	9.981	<0.001
PaO_2 (mmHg)	85.90 [70.30, 102.30]	95.55 [80.85, 106.80]	70.60 [57.85, 84.35]	10.994	<0.001
FiO_2 (%)	49.00 [38.00, 62.00]	43.50 [34.00, 52.00]	62.00 [50.00, 73.00]	11.398	<0.001
PaO_2 at 48 h (mmHg)	86.00 [69.00, 104.00]	95.00 [82.25, 111.00]	65.00 [55.00, 78.50]	13.969	<0.001
FiO_2 at 48 h (%)	43.00 [34.00, 55.00]	39.00 [30.00, 46.00]	59.00 [48.00, 69.00]	12.982	<0.001
Baseline PaO_2/FiO_2	179.53 [124.92, 244.75]	217.87 [167.12, 281.60]	114.80 [89.85, 150.36]	14.002	<0.001
PaO_2/FiO_2 at 48 h	202.50 [133.33, 281.58]	257.14 [198.01, 322.95]	114.71 [87.97, 152.51]	16.2	<0.001
Delta PaO_2/FiO_2	14.76 [-48.68, 87.57]	37.75 [-59.50, 120.55]	3.35 [-35.60, 38.99]	3.439	<0.001
Arterial lactate (mmol/L)	2.40 [1.36, 3.79]	2.02 [1.16, 2.75]	4.02 [2.48, 5.71]	11.449	<0.001
$PaCO_2$ (mmHg)	43.00 [35.50, 49.70]	39.90 [34.00, 46.50]	48.20 [41.55, 55.70]	8.338	<0.001
Arterial pH	7.37±0.08	7.40±0.06	7.32±0.08	14.703	<0.001
NLR	8.55 [5.24, 12.54]	6.81 [4.20, 9.56]	13.29 [9.29, 17.84]	12.94	<0.001
SII	1030.50 [675.60, 1391.80]	889.05 [550.50, 1128.98]	1508.90 [1088.20, 1932.20]	11.491	<0.001
CRP (mg/L)	56.50 [33.80, 83.10]	45.05 [24.85, 68.18]	84.20 [57.35, 108.10]	11.062	<0.001
Albumin (g/L)	31.60 [28.10, 35.10]	32.80 [29.55, 36.60]	29.30 [25.40, 32.50]	8.326	<0.001
Procalcitonin (ng/mL)	2.03 [1.00, 3.56]	1.56 [0.77, 2.33]	4.06 [2.32, 6.47]	11.862	<0.001
White blood cell count ($\times 10^9$/L)	9.62 [7.04, 12.67]	9.02 [6.54, 11.36]	12.29 [8.21, 15.11]	7.067	<0.001
Hemoglobin (g/L)	105.00 [94.00, 117.00]	110.00 [99.00, 122.00]	95.00 [84.00, 107.00]	9.242	<0.001
Platelet count ($\times 10^9$/L)	200.00 [127.00, 265.00]	205.50 [139.25, 266.00]	189.00 [104.00, 243.50]	2.501	0.012
Creatinine (μmol/L)	98.00 [62.00, 129.00]	88.00 [58.00, 118.00]	114.00 [79.50, 147.50]	5.774	<0.001
Total bilirubin (μmol/L)	18.90 [12.00, 25.30]	16.65 [10.95, 22.65]	22.90 [14.20, 32.10]	6.288	<0.001
ALT (U/L)	35.00 [22.00, 48.00]	32.00 [21.00, 44.00]	39.00 [24.00, 62.00]	4.275	<0.001
D-dimer (mg/L)	2.27 [1.20, 3.78]	1.74 [0.93, 2.60]	4.98 [2.48, 7.09]	12.246	<0.001
Blood glucose (mmol/L)	7.60 [5.70, 9.80]	6.95 [5.32, 8.90]	9.40 [7.00, 12.40]	7.329	<0.001

Note: RCCM, Department of Respiratory and Critical Care Medicine; ICU, intensive care unit; EICU, emergency intensive care unit; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; CRP, C-reactive protein; ALT, alanine aminotransferase.

Table 2. Comparison of baseline clinical characteristics and laboratory parameters between the training cohort and validation cohort (N=541)

Variable	Total (N=541)	Training cohort (n=379)	Validation cohort (n=162)	Statistic	*P* value
Primary reason for admission to RCCM/ICU/EICU				2.653	0.618
Acute respiratory failure	222 (41.04%)	163 (43.01%)	59 (36.42%)		
Sepsis/Infection	128 (23.66%)	85 (22.43%)	43 (26.54%)		
Massive hemoptysis	70 (12.94%)	46 (12.14%)	24 (14.81%)		
Postoperative monitoring	68 (12.57%)	48 (12.66%)	20 (12.35%)		
Other	53 (9.80%)	37 (9.76%)	16 (9.88%)		
Sex				0.088	0.767
Male	354 (65.43%)	250 (65.96%)	104 (64.20%)		
Female	187 (34.57%)	129 (34.04%)	58 (35.80%)		
Smoking history				0.064	0.801
Yes	320 (59.15%)	226 (59.63%)	94 (58.02%)		
No	221 (40.85%)	153 (40.37%)	68 (41.98%)		
ECOG PS				1.026	0.599
Score 0-1	180 (33.27%)	129 (34.04%)	51 (31.48%)		
Score 2	210 (38.82%)	149 (39.31%)	61 (37.65%)		
Score 3-4	151 (27.91%)	101 (26.65%)	50 (30.86%)		
Pathological type				0.170	0.982
Adenocarcinoma	243 (44.92%)	171 (45.12%)	72 (44.44%)		
Squamous cell carcinoma	156 (28.84%)	108 (28.50%)	48 (29.63%)		
Small cell carcinoma	84 (15.53%)	60 (15.83%)	24 (14.81%)		
Other	58 (10.72%)	40 (10.55%)	18 (11.11%)		
Tumor stage				0.286	0.593
Stage III	137 (25.32%)	93 (24.54%)	44 (27.16%)		
Stage IV	404 (74.68%)	286 (75.46%)	118 (72.84%)		
Brain metastasis				0.951	0.329
Present	166 (30.68%)	111 (29.29%)	55 (33.95%)		
Absent	375 (69.32%)	268 (70.71%)	107 (66.05%)		
Bone metastasis				0.446	0.504
Present	190 (35.12%)	137 (36.15%)	53 (32.72%)		
Absent	351 (64.88%)	242 (63.85%)	109 (67.28%)		
Prior chemotherapy				0.398	0.528
Yes	260 (48.06%)	186 (49.08%)	74 (45.68%)		
No	281 (51.94%)	193 (50.92%)	88 (54.32%)		

Prior targeted/immunotherapy				3.167	0.075
Yes	136 (25.14%)	104 (27.44%)	32 (19.75%)		
No	405 (74.86%)	275 (72.56%)	130 (80.25%)		
Hypertension				1.821	0.177
Yes	212 (39.19%)	141 (37.20%)	71 (43.83%)		
No	329 (60.81%)	238 (62.80%)	91 (56.17%)		
Diabetes mellitus				0.000	1.000
Yes	110 (20.33%)	77 (20.32%)	33 (20.37%)		
No	431 (79.67%)	302 (79.68%)	129 (79.63%)		
COPD				1.278	0.258
Yes	136 (25.14%)	101 (26.65%)	35 (21.60%)		
No	405 (74.86%)	278 (73.35%)	127 (78.40%)		
Chronic heart failure				0.004	0.948
Yes	86 (15.90%)	61 (16.09%)	25 (15.43%)		
No	455 (84.10%)	318 (83.91%)	137 (84.57%)		
Chronic renal insufficiency				0.504	0.478
Yes	70 (12.94%)	46 (12.14%)	24 (14.81%)		
No	471 (87.06%)	333 (87.86%)	138 (85.19%)		
Cerebrovascular disease				0.069	0.792
Yes	58 (10.72%)	42 (11.08%)	16 (9.88%)		
No	483 (89.28%)	337 (88.92%)	146 (90.12%)		
Invasive mechanical ventilation				0.273	0.602
Yes	213 (39.37%)	146 (38.52%)	67 (41.36%)		
No	328 (60.63%)	233 (61.48%)	95 (58.64%)		
Vasoactive agent use				0.882	0.348
Yes	196 (36.23%)	132 (34.83%)	64 (39.51%)		
No	345 (63.77%)	247 (65.17%)	98 (60.49%)		
CRRT				0.000	1.000
Yes	80 (14.79%)	56 (14.78%)	24 (14.81%)		
No	461 (85.21%)	323 (85.22%)	138 (85.19%)		
Antibiotic use				0.403	0.526
Yes	406 (75.05%)	281 (74.14%)	125 (77.16%)		
No	135 (24.95%)	98 (25.86%)	37 (22.84%)		
Age (years)	65.00 [58.00, 72.00]	66.00 [58.50, 72.00]	65.00 [58.25, 71.00]	0.586	0.558
APACHE II score	20.00 [16.00, 25.00]	20.00 [16.00, 24.50]	21.00 [17.00, 25.00]	0.698	0.485

SOFA score	6.00 [5.00, 8.00]	6.00 [5.00, 8.00]	6.00 [5.00, 8.00]	0.083	0.934
Heart rate (beats/min)	91.00 [80.00, 103.00]	90.00 [80.00, 102.50]	92.00 [81.00, 104.00]	0.489	0.625
Respiratory rate (breaths/min)	22.00 [19.00, 27.00]	22.00 [19.00, 27.00]	23.00 [19.00, 28.00]	1.111	0.267
Mean arterial pressure (mmHg)	74.12±12.63	74.36±12.70	73.57±12.47	0.665	0.507
Body temperature (°C)	37.40 [36.80, 38.00]	37.40 [36.90, 38.05]	37.30 [36.80, 37.90]	1.493	0.135
SpO_2 (%)	93.00 [89.00, 96.00]	93.00 [89.00, 96.00]	92.00 [89.00, 96.00]	0.613	0.540
PaO_2 (mmHg)	85.90 [70.30, 102.30]	85.90 [69.10, 102.60]	85.50 [70.85, 99.60]	0.278	0.781
FiO_2 (%)	49.00 [38.00, 62.00]	49.00 [38.00, 61.00]	49.50 [40.00, 62.00]	0.632	0.527
PaO_2 at 48 h (mmHg)	86.00 [69.00, 104.00]	86.00 [70.00, 104.00]	83.00 [68.25, 102.00]	1.280	0.201
FiO_2 at 48 h (%)	43.00 [34.00, 55.00]	43.00 [34.00, 55.50]	42.00 [34.00, 55.00]	0.077	0.938
Baseline PaO_2/FiO_2	179.53 [124.92, 244.75]	181.35 [125.42, 244.94]	173.33 [120.18, 243.53]	0.472	0.637
PaO_2/FiO_2 at 48 h	202.50 [133.33, 281.58]	206.98 [135.10, 284.24]	200.00 [127.95, 266.28]	0.864	0.388
Delta PaO_2/FiO_2	14.76 [-48.68, 87.57]	14.51 [-47.18, 88.00]	16.86 [-53.43, 83.65]	0.222	0.824
Arterial lactate (mmol/L)	2.40 [1.36, 3.79]	2.31 [1.33, 3.83]	2.62 [1.52, 3.57]	0.395	0.693
$PaCO_2$ (mmHg)	43.00 [35.50, 49.70]	42.60 [35.05, 49.45]	43.55 [35.92, 50.77]	1.200	0.230
Arterial pH	7.38 [7.32, 7.43]	7.38 [7.32, 7.42]	7.39 [7.33, 7.44]	1.647	0.100
NLR	8.55 [5.24, 12.54]	8.66 [5.18, 12.15]	8.14 [5.48, 12.63]	0.416	0.678
SII	1030.50 [675.60, 1391.80]	1025.80 [703.20, 1418.85]	1030.90 [641.68, 1326.35]	0.571	0.568
CRP (mg/L)	56.50 [33.80, 83.10]	56.00 [34.70, 82.90]	58.15 [31.32, 82.70]	0.299	0.765
Albumin (g/L)	31.60 [28.10, 35.10]	31.40 [28.15, 35.10]	31.90 [28.02, 34.98]	0.253	0.800
Procalcitonin (ng/mL)	2.03 [1.00, 3.56]	2.11 [1.11, 3.64]	1.92 [0.91, 3.42]	1.158	0.247
White blood cell count ($\times 10^9$/L)	9.62 [7.04, 12.67]	9.49 [6.71, 12.67]	10.04 [7.36, 12.67]	0.964	0.335
Hemoglobin (g/L)	105.00 [94.00, 117.00]	106.00 [94.00, 117.00]	103.00 [94.00, 116.00]	0.413	0.680
Platelet count ($\times 10^9$/L)	200.00 [127.00, 265.00]	203.00 [140.00, 267.00]	188.50 [113.00, 251.75]	1.704	0.088
Creatinine (μmol/L)	98.00 [62.00, 129.00]	97.00 [59.50, 129.00]	98.50 [70.25, 131.00]	0.930	0.353
Total bilirubin (μmol/L)	18.90 [12.00, 25.30]	19.00 [11.45, 24.90]	17.50 [12.22, 26.87]	0.473	0.636
ALT (U/L)	35.00 [22.00, 48.00]	36.00 [23.00, 48.50]	31.00 [20.00, 46.00]	1.652	0.099
D-dimer (mg/L)	2.27 [1.20, 3.78]	2.23 [1.20, 3.76]	2.35 [1.20, 3.81]	0.411	0.681
Blood glucose (mmol/L)	7.60 [5.70, 9.80]	7.50 [5.60, 9.60]	8.00 [5.90, 10.35]	1.569	0.117

Note: RCCM, Department of Respiratory and Critical Care Medicine; ICU, intensive care unit; EICU, emergency intensive care unit; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; CRP, C-reactive protein; ALT, alanine aminotransferase.

Comparison of baseline characteristics between training and validation sets

The training and validation sets showed no significant differences in primary reason for admission to the RCCM/ICU/EICU, sex, smoking history, ECOG PS, pathological type, tumor stage, brain metastasis, bone metastasis, prior chemotherapy, prior targeted or immunotherapy, comorbidities, invasive mechanical ventilation, vasoactive agent use, CRRT, or antibiotic use (all P>0.05). Continuous parameters including age, APACHE II score, SOFA score, vital signs, all oxygenation indices, and laboratory variables were likewise comparable between the two sets (all P>0.05), confirming adequate balance for subsequent analysis (**Table 2**).

Baseline characteristics of deceased and surviving patients in the training set

In the training set, the primary reason for RCCM, ICU, or EICU admission differed significantly between the death and survival groups (P=0.014). ECOG PS (P<0.001), tumor stage (P=0.011), brain metastasis (P<0.001), and bone metastasis (P<0.001) all showed statistically significant differences. Invasive mechanical ventilation (P<0.001), vasoactive agent use (P<0.001), and CRRT (P=0.004) also differed between groups (**Table 3**).

Age (P=0.001), APACHE II score (P<0.001), SOFA score (P<0.001), heart rate (P<0.001), respiratory rate (P<0.001), mean arterial pressure (P<0.001), and body temperature (P< 0.001) all differed significantly. SpO_2, PaO_2, FiO_2, and all oxygenation indices at baseline and 48 hours (all P<0.001), along with Delta PaO_2/FiO_2 (P=0.015), were significantly lower in the death group, reflecting markedly poorer respiratory reserve and less oxygenation recovery (**Table 3**).

Arterial lactate, $PaCO_2$, pH, NLR, SII, CRP, albumin, PCT, white blood cell count, hemoglobin, creatinine, total bilirubin, ALT, D-dimer, and blood glucose all differed significantly between groups (all P<0.001); platelet count did not (P=0.114). Sex, smoking history, pathological type, prior therapy, comorbidities, and antibiotic use showed no significant differences (all P>0.05) (**Table 3**).

Multicollinearity diagnostics and correlation analysis

According to VIF analysis, multicollinearity among candidate variables was not severe, as no VIF value exceeded 5, indicating no linear dependency among candidate variables. The multicollinearity levels for different indicators - such as respiratory reserve, systemic inflammation, organ function, and baseline characteristics - were all acceptable when stratified by variable category. **Figure 1A** showed that the VIF values for baseline P/F ratio and Delta P/F ratio were relatively high, but still did not reach the warning threshold.

Spearman correlation analysis revealed mostly weak to moderate pairwise correlations, with no strong redundancies. Pairs of variables with higher correlation included Delta P/F ratio versus baseline P/F ratio (P<0.001), pH versus NLR (P<0.001), arterial lactate versus baseline P/F ratio (P<0.001), baseline P/F ratio versus D-dimer (P<0.001), baseline P/F ratio versus NLR (P<0.001), arterial lactate versus D-dimer (P<0.001), arterial lactate versus NLR (P<0.001), and procalcitonin versus D-dimer (P<0.001). Overall, markers of impaired respiratory function were consistently correlated with indicators of tissue inflammatory burden, hypoperfusion, and organ dysfunction. Inflammatory markers were also internally coherent with one another (**Figure 1B**). These associations, while modest in size, further substantiate a biological relationship between decreased respiratory reserve, heightened systemic inflammation, and organ dysfunction, without hindering subsequent variable selection or model construction.

LASSO regression for selection of prognostic features

LASSO Cox regression was applied to the training set to reduce the number of variables and select prognostic factors. According to the cross-validation analysis, as the penalty parameter increased, the partial likelihood deviance stabilized. The λ.1se criterion was chosen as the optimal penalty because it balances model parsimony and stability. This method retained 12 variables with non-zero coefficients, as shown in **Figure 2A**. The retained variables included pH, arterial lactate, D-dimer,

Table 3. Comparison of baseline clinical characteristics, respiratory functional reserve, and laboratory parameters between the non-survival group and survival group in the training cohort (N=379)

Variable	Total (N=379)	Survival group (n=250)	Non-survival group (n=129)	Statistic	*P* value
Primary reason for admission to RCCM/ICU/EICU				12.447	0.014
Acute respiratory failure	163 (43.01%)	97 (38.80%)	66 (51.16%)		
Sepsis/Infection	85 (22.43%)	52 (20.80%)	33 (25.58%)		
Massive hemoptysis	46 (12.14%)	34 (13.60%)	12 (9.30%)		
Postoperative monitoring	48 (12.66%)	40 (16.00%)	8 (6.20%)		
Other	37 (9.76%)	27 (10.80%)	10 (7.75%)		
Sex				1.017	0.313
Male	250 (65.96%)	160 (64.00%)	90 (69.77%)		
Female	129 (34.04%)	90 (36.00%)	39 (30.23%)		
Smoking history				1.518	0.218
Yes	226 (59.63%)	143 (57.20%)	83 (64.34%)		
No	153 (40.37%)	107 (42.80%)	46 (35.66%)		
ECOG PS				27.639	<0.001
Score 0-1	129 (34.04%)	104 (41.60%)	25 (19.38%)		
Score 2	149 (39.31%)	98 (39.20%)	51 (39.53%)		
Score 3-4	101 (26.65%)	48 (19.20%)	53 (41.09%)		
Pathological type				0.400	0.940
Adenocarcinoma	171 (45.12%)	115 (46.00%)	56 (43.41%)		
Squamous cell carcinoma	108 (28.50%)	69 (27.60%)	39 (30.23%)		
Small cell carcinoma	60 (15.83%)	39 (15.60%)	21 (16.28%)		
Other	40 (10.55%)	27 (10.80%)	13 (10.08%)		
Tumor stage				6.544	0.011
Stage III	93 (24.54%)	72 (28.80%)	21 (16.28%)		
Stage IV	286 (75.46%)	178 (71.20%)	108 (83.72%)		
Brain metastasis				43.600	<0.001
Present	111 (29.29%)	45 (18.00%)	66 (51.16%)		
Absent	268 (70.71%)	205 (82.00%)	63 (48.84%)		
Bone metastasis				65.509	<0.001
Present	137 (36.15%)	54 (21.60%)	83 (64.34%)		
Absent	242 (63.85%)	196 (78.40%)	46 (35.66%)		
Prior chemotherapy				0.002	0.967
Yes	186 (49.08%)	122 (48.80%)	64 (49.61%)		
No	193 (50.92%)	128 (51.20%)	65 (50.39%)		

Prior targeted/immunotherapy				0.993	0.319
Yes	104 (27.44%)	64 (25.60%)	40 (31.01%)		
No	275 (72.56%)	186 (74.40%)	89 (68.99%)		
Hypertension				0.316	0.574
Yes	141 (37.20%)	90 (36.00%)	51 (39.53%)		
No	238 (62.80%)	160 (64.00%)	78 (60.47%)		
Diabetes mellitus				0.786	0.375
Yes	77 (20.32%)	47 (18.80%)	30 (23.26%)		
No	302 (79.68%)	203 (81.20%)	99 (76.74%)		
COPD				1.022	0.312
Yes	101 (26.65%)	62 (24.80%)	39 (30.23%)		
No	278 (73.35%)	188 (75.20%)	90 (69.77%)		
Chronic heart failure				2.865	0.091
Yes	61 (16.09%)	34 (13.60%)	27 (20.93%)		
No	318 (83.91%)	216 (86.40%)	102 (79.07%)		
Chronic renal insufficiency				0.078	0.780
Yes	46 (12.14%)	29 (11.60%)	17 (13.18%)		
No	333 (87.86%)	221 (88.40%)	112 (86.82%)		
Cerebrovascular disease				0.173	0.677
Yes	42 (11.08%)	26 (10.40%)	16 (12.40%)		
No	337 (88.92%)	224 (89.60%)	113 (87.60%)		
Invasive mechanical ventilation				44.085	<0.001
Yes	146 (38.52%)	66 (26.40%)	80 (62.02%)		
No	233 (61.48%)	184 (73.60%)	49 (37.98%)		
Vasoactive agent use				45.275	<0.001
Yes	132 (34.83%)	57 (22.80%)	75 (58.14%)		
No	247 (65.17%)	193 (77.20%)	54 (41.86%)		
CRRT				8.315	0.004
Yes	56 (14.78%)	27 (10.80%)	29 (22.48%)		
No	323 (85.22%)	223 (89.20%)	100 (77.52%)		
Antibiotic use				0.211	0.646
Yes	281 (74.14%)	183 (73.20%)	98 (75.97%)		
No	98 (25.86%)	67 (26.80%)	31 (24.03%)		
Age (years)	65.21±9.54	64.07±9.48	67.40±9.32	-3.260	0.001
APACHE II score	20.00 [16.00, 24.50]	18.00 [15.00, 22.00]	24.00 [21.00, 28.00]	9.093	<0.001

SOFA score	6.00 [5.00, 8.00]	6.00 [4.00, 7.00]	9.00 [6.00, 11.00]	9.885	<0.001
Heart rate (beats/min)	92.13±17.85	86.27±13.54	103.50±19.68	-9.999	<0.001
Respiratory rate (breaths/min)	22.68±5.95	20.71±4.69	26.50±6.28	-10.109	<0.001
Mean arterial pressure (mmHg)	74.36±12.70	77.95±11.26	67.40±12.49	8.326	<0.001
Body temperature (°C)	37.48±0.88	37.22±0.68	37.99±0.98	-8.972	<0.001
SpO_2 (%)	93.00 [89.00, 96.00]	94.00 [91.00, 97.00]	89.00 [85.00, 93.00]	8.126	<0.001
PaO_2 (mmHg)	85.90 [69.10, 102.60]	97.05 [80.85, 107.17]	69.00 [57.30, 81.50]	9.230	<0.001
FiO_2 (%)	49.00 [38.00, 61.00]	43.00 [34.00, 52.00]	62.00 [50.00, 73.00]	9.545	<0.001
PaO_2 at 48 h (mmHg)	86.00 [70.00, 104.00]	95.00 [83.00, 112.00]	65.00 [55.00, 79.00]	11.391	<0.001
FiO_2 at 48 h (%)	43.00 [34.00, 55.50]	39.00 [30.00, 46.00]	58.00 [48.00, 69.00]	10.571	<0.001
Baseline PaO_2/FiO_2	181.35 [125.42, 244.94]	221.33 [169.88, 279.02]	116.17 [87.12, 149.82]	11.984	<0.001
PaO_2/FiO_2 at 48 h	206.98 [135.10, 284.24]	261.81 [197.52, 323.08]	114.71 [89.47, 155.00]	13.252	<0.001
Delta PaO_2/FiO_2	14.51 [-47.18, 88.00]	34.53 [-57.04, 122.56]	8.51 [-29.45, 38.69]	2.433	0.015
Arterial lactate (mmol/L)	2.31 [1.33, 3.83]	1.96 [1.12, 2.58]	4.22 [2.82, 5.74]	10.247	<0.001
$PaCO_2$ (mmHg)	42.82±10.59	40.01±8.96	48.27±11.38	-7.732	<0.001
Arterial pH	7.37±0.08	7.40±0.06	7.31±0.07	12.988	<0.001
NLR	8.66 [5.18, 12.15]	6.82 [4.19, 9.56]	13.40 [9.17, 17.78]	10.820	<0.001
SII	1025.80 [703.20, 1418.85]	893.05 [585.02, 1141.18]	1510.30 [1083.60, 1884.20]	9.515	<0.001
CRP (mg/L)	56.00 [34.70, 82.90]	46.40 [27.10, 68.95]	83.10 [54.30, 109.80]	8.756	<0.001
Albumin (g/L)	31.40 [28.15, 35.10]	32.75 [29.55, 36.60]	29.00 [25.00, 31.90]	7.374	<0.001
Procalcitonin (ng/mL)	2.11 [1.11, 3.64]	1.62 [0.82, 2.36]	4.06 [2.37, 6.52]	10.257	<0.001
White blood cell count ($\times 10^9$/L)	9.49 [6.71, 12.67]	8.82 [6.46, 11.36]	12.31 [8.05, 14.93]	5.523	<0.001
Hemoglobin (g/L)	106.00 [94.00, 117.00]	110.00 [99.25, 123.00]	95.00 [84.00, 107.00]	7.871	<0.001
Platelet count ($\times 10^9$/L)	203.00 [140.00, 267.00]	207.50 [147.50, 269.75]	191.00 [119.00, 252.00]	1.582	0.114
Creatinine (μmol/L)	97.00 [59.50, 129.00]	85.00 [56.25, 117.00]	114.00 [84.00, 150.00]	5.210	<0.001
Total bilirubin (μmol/L)	19.00 [11.45, 24.90]	16.95 [10.75, 22.80]	22.40 [15.10, 30.60]	5.041	<0.001
ALT (U/L)	36.00 [23.00, 48.50]	34.00 [22.25, 45.00]	40.00 [25.00, 61.00]	3.319	<0.001
D-dimer (mg/L)	2.23 [1.20, 3.76]	1.69 [0.93, 2.66]	5.01 [2.49, 6.92]	10.264	<0.001
Blood glucose (mmol/L)	7.50 [5.60, 9.60]	7.05 [5.40, 8.90]	9.00 [6.20, 12.40]	4.973	<0.001

Note: RCCM, Department of Respiratory and Critical Care Medicine; ICU, intensive care unit; EICU, emergency intensive care unit; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oxygen saturation; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; CRP, C-reactive protein; ALT, alanine aminotransferase.

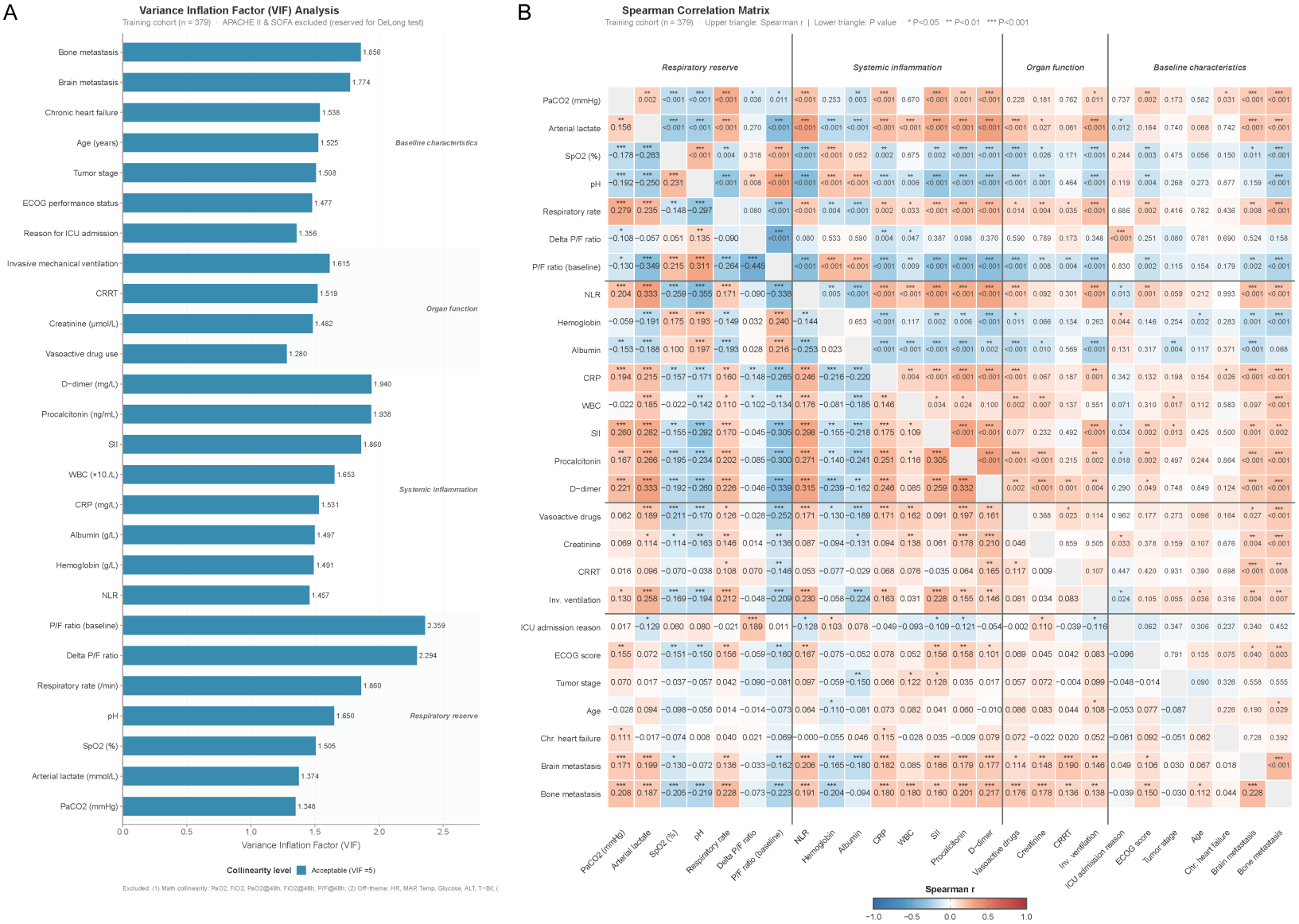


Figure 1. Collinearity diagnosis and Spearman correlation analysis of candidate predictors. A. Variance inflation factor analysis of candidate predictors. B. Spearman correlation matrix among candidate predictors. Note: VIF, variance inflation factor; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; $PaCO_2$, partial pressure of arterial carbon dioxide; SII, systemic immune-inflammation index; WBC, white blood cell count; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; CRRT, continuous renal replacement therapy; ICU, intensive care unit; ECOG PS, Eastern Cooperative Oncology Group performance status.

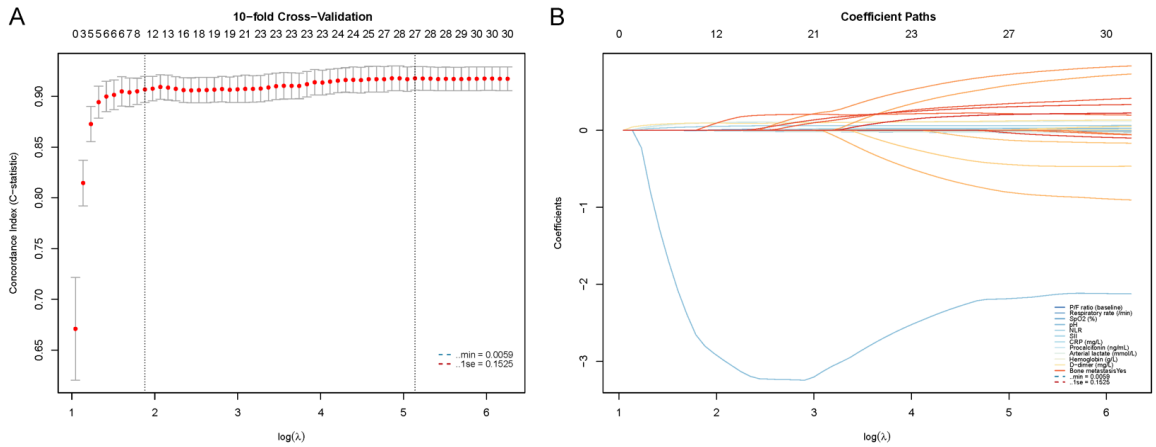


Figure 2. Feature selection of prognostic variables using LASSO Cox regression in the training cohort. A. Ten-fold cross-validation plot for selection of the optimal tuning parameter in the LASSO Cox regression model. B. Coefficient profiles of candidate variables in the LASSO Cox regression model. Note: LASSO, least absolute shrinkage and selection operator; CV, cross-validation; SE, standard error; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

procalcitonin, NLR (neutrophil-to-lymphocyte ratio), bone metastasis, SpO_2, respiratory rate, baseline P/F (PaO_2/FiO_2) ratio, CRP, hemoglobin, and SII (systemic immune-inflammation index). Among these, pH, SpO_2, baseline P/F ratio, and hemoglobin had negative regression coefficients, suggesting a potential protective role, while arterial lactate, D-dimer, procalcitonin, NLR, bone metastasis, respiratory rate, and CRP had positive coefficients, indicating increased risk of adverse outcomes. SII's coefficient was retained under λ.1se but was shrunk almost to zero (**Figure 2B**). The selected covariates - reflecting respiratory functional reserve, systemic inflammatory response, tumor metastatic characteristics, and baseline physiological state - were all consistent with a multisystem prognostic model in critically ill patients with lung cancer.

Nonlinear effect analysis of LASSO-selected continuous variables

RCS analysis examined the dose-response relationships between LASSO-selected continuous variables and mortality risk. All included variables had statistically significant overall effects (all P<0.001). pH (P for nonlinear =0.016), arterial lactate (P for nonlinear <0.001), D-dimer (P for nonlinear <0.001), procalcitonin (P for nonlinear <0.001), NLR (P for nonlinear =0.007), respiratory rate (P for nonlinear =0.041), and SII (P for nonlinear <0.001) all showed significant nonlinear associations, favoring their inclusion as spline terms in subsequent modeling (**Figure 3**). In contrast, SpO_2 (P for nonlinear =0.181), baseline P/F ratio (P for nonlinear =0.839), CRP (P for nonlinear =0.246), and hemoglobin (P for nonlinear =0.996) showed no significant nonlinear effects and could reasonably be modeled as linear terms (**Figure 3**).

Higher pH, SpO_2, baseline P/F ratio, and hemoglobin were associated with lower mortality risk, while higher arterial lactate, D-dimer, procalcitonin, NLR, respiratory rate, CRP, and SII corresponded to increased risk. For several inflammatory and metabolic markers, risk appeared relatively stable at lower values but escalated more steeply above a certain range, consistent with threshold-dependent and nonlinear risk dynamics in this patient population (**Figure 3**).

Assessment of the proportional hazards assumption

Schoenfeld residual tests were employed to assess the proportional hazards assumption. The global test illustrated that the model as a whole met the assumption (P=0.096) (**Figure 4**). Individual variables, including D-dimer (P=0.106) procalcitonin (P=0.123) NLR (P= 0.531), SII (P=0.962) SpO_2 (P=0.642) CRP (P=0.283) hemoglobin (P=0.340), also satisfied

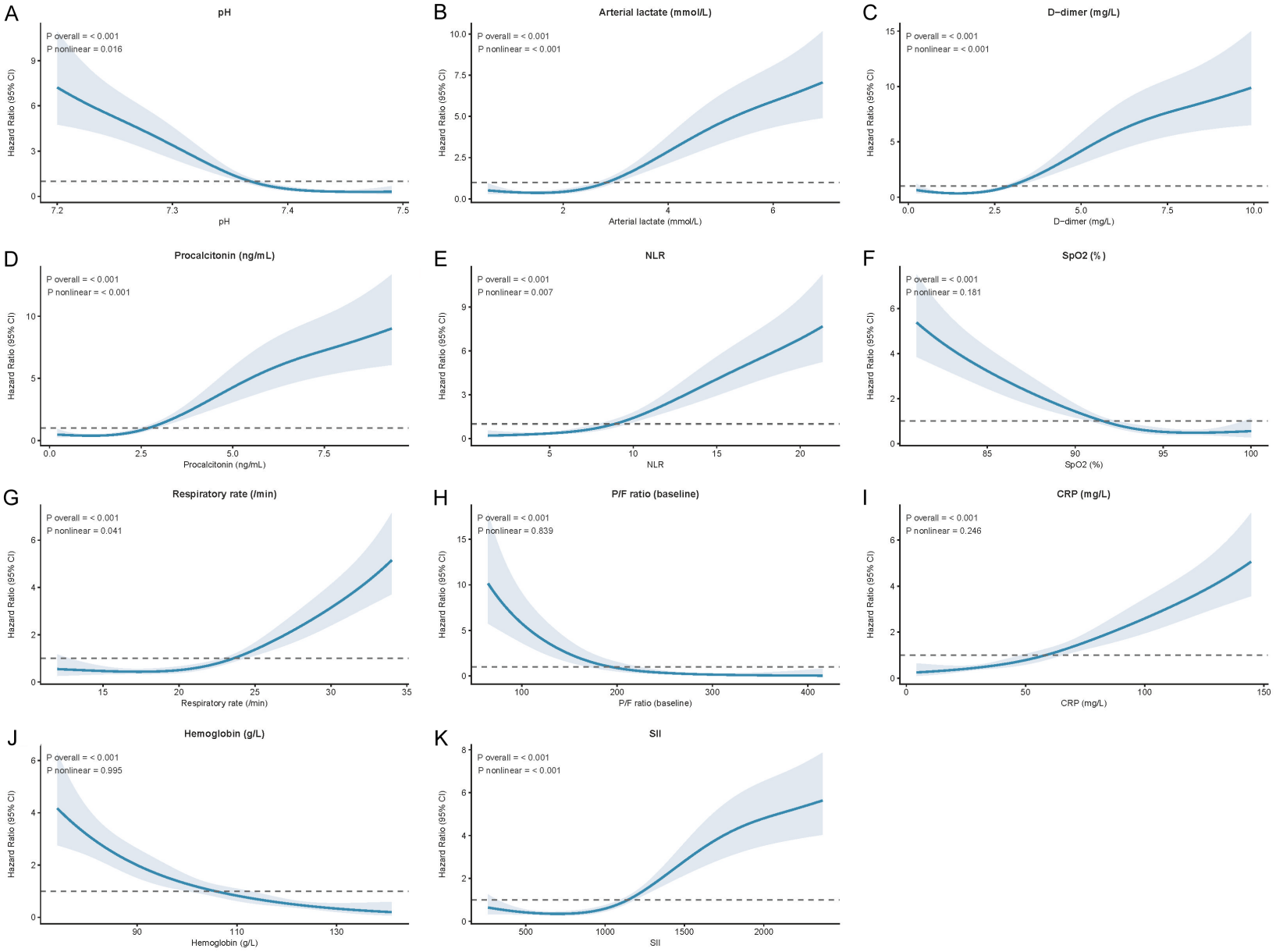
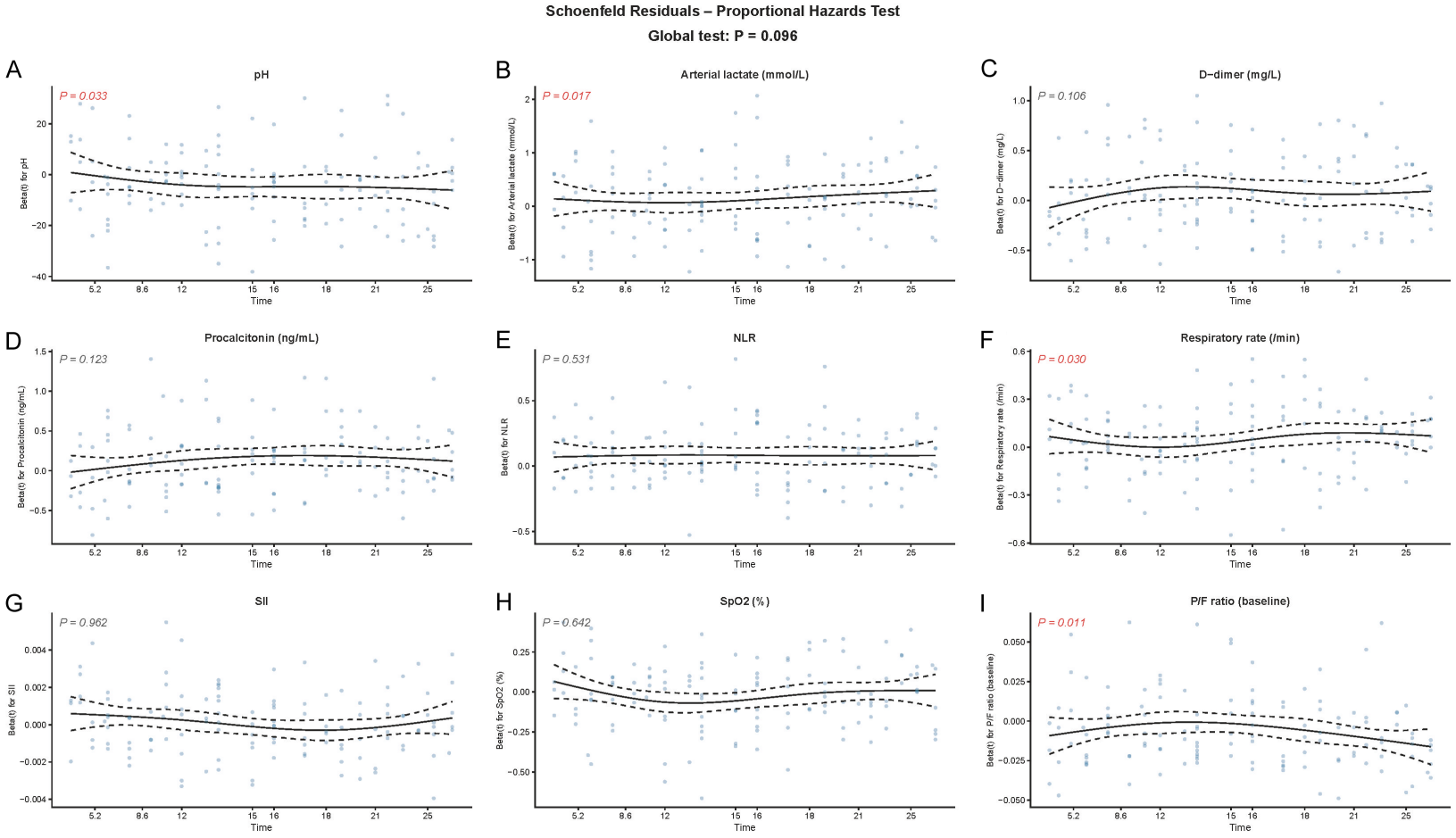

A
pH
P overall = < 0.001
P nonlinear = 0.016
Hazard Ratio (95% CI)
pH
B
Arterial lactate (mmol/L)
P overall = < 0.001
P nonlinear = < 0.001
Hazard Ratio (95% CI)
Arterial lactate (mmol/L)
C
D−dimer (mg/L)
P overall = < 0.001
P nonlinear = < 0.001
Hazard Ratio (95% CI)
D−dimer (mg/L)
D
Procalcitonin (ng/mL)
P overall = < 0.001
P nonlinear = < 0.001
Hazard Ratio (95% CI)
Procalcitonin (ng/mL)
E
NLR
P overall = < 0.001
P nonlinear = 0.007
Hazard Ratio (95% CI)
NLR
F
SpO2 (%)
P overall = < 0.001
P nonlinear = 0.181
Hazard Ratio (95% CI)
SpO2 (%)
G
Respiratory rate (/min)
P overall = < 0.001
P nonlinear = 0.041
Hazard Ratio (95% CI)
Respiratory rate (/min)
H
P/F ratio (baseline)
P overall = < 0.001
P nonlinear = 0.839
Hazard Ratio (95% CI)
P/F ratio (baseline)
I
CRP (mg/L)
P overall = < 0.001
P nonlinear = 0.246
Hazard Ratio (95% CI)
CRP (mg/L)
J
Hemoglobin (g/L)
P overall = < 0.001
P nonlinear = 0.995
Hazard Ratio (95% CI)
Hemoglobin (g/L)
K
SII
P overall = < 0.001
P nonlinear = < 0.001
Hazard Ratio (95% CI)
SII

Figure 3. Restricted cubic spline analyses for nonlinear associations between selected continuous variables and mortality risk. A. Nonlinear association between pH and mortality risk. B. Nonlinear association between arterial lactate and mortality risk. C. Nonlinear association between D-dimer and mortality risk. D. Nonlinear association between procalcitonin and mortality risk. E. Nonlinear association between NLR and mortality risk. F. Association between SpO_2 and mortality risk. G. Nonlinear association between respiratory rate and mortality risk. H. Association between baseline P/F ratio and mortality risk. I. Association between CRP and mortality risk. J. Association between hemoglobin and mortality risk. K. Nonlinear association between SII and mortality risk. Note: RCS, restricted cubic spline; HR, hazard ratio; CI, confidence interval; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.



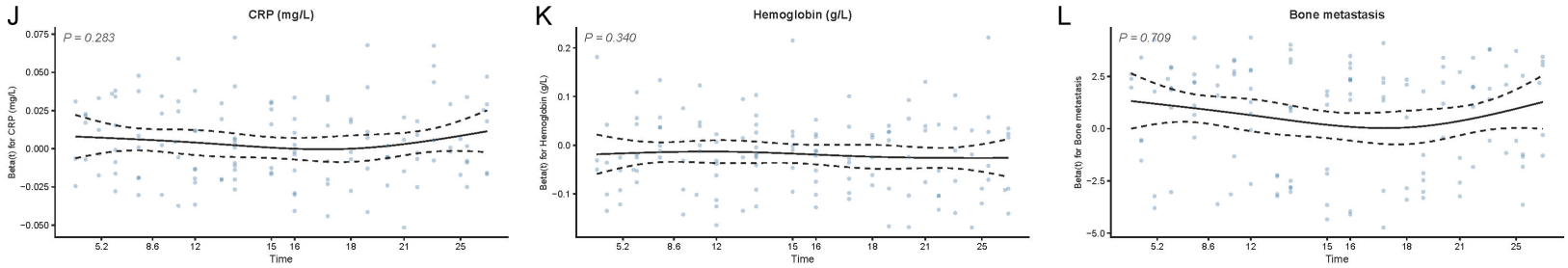


Figure 4. Schoenfeld residual-based assessment of the proportional hazards assumption for the Cox model. A. Schoenfeld residual plot for pH. B. Schoenfeld residual plot for arterial lactate. C. Schoenfeld residual plot for D-dimer. D. Schoenfeld residual plot for procalcitonin. E. Schoenfeld residual plot for NLR. F. Schoenfeld residual plot for respiratory rate. G. Schoenfeld residual plot for SII. H. Schoenfeld residual plot for SpO_2. I. Schoenfeld residual plot for baseline P/F ratio. J. Schoenfeld residual plot for CRP. K. Schoenfeld residual plot for hemoglobin. L. Schoenfeld residual plot for bone metastasis. Note: Cox model, Cox proportional hazards model; PH, proportional hazards; Schoenfeld residuals, PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

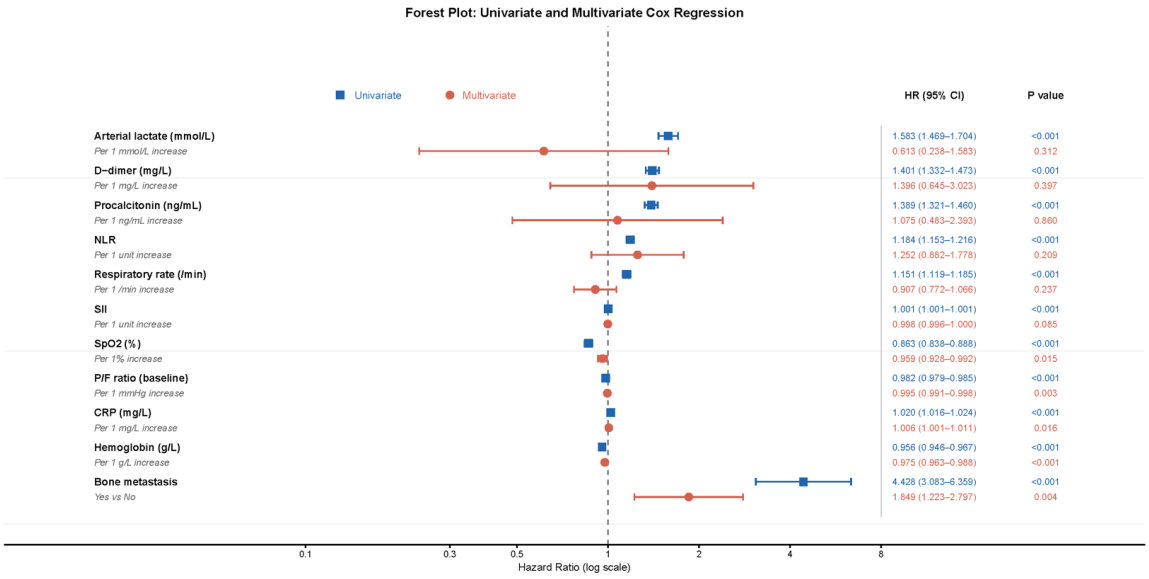


Figure 5. Forest plot of univariate and multivariable Cox regression analyses for mortality risk. Blue squares indicate hazard ratios and 95% confidence intervals of candidate predictors in univariable Cox regression analysis, and red circles indicate hazard ratios and 95% confidence intervals of candidate predictors in multivariable Cox regression analysis. Note: Cox regression, Cox proportional hazards regression; HR, hazard ratio; CI, confidence interval; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

the assumption. In contrast, pH (P=0.033), arterial lactate (P=0.017), respiratory rate (P=0.030) and baseline P/F ratio (P=0.011) did not, indicating time-varying effects for these variables (**Figure 4**). Despite these individual violations, the overall stability and interpretability of the model were supported by an acceptable overall test result. Future research could use time-interaction terms, stratification, or extended Cox models to address these violations (**Figure 4**). pH was removed from the final model despite being retained by LASSO and showing association with 28-day mortality in univariable analysis, due to its simultaneous nonlinear effects and violation of the proportional hazards assumption. Including it in multivariable Cox modeling led to unstable parameter estimates with very wide confidence intervals, compromising parsimony and robustness.

Univariable and multivariable cox regression for 28-day mortality

In univariable Cox regression, arterial lactate, D-dimer, procalcitonin, NLR, respiratory rate, SII, SpO_2, baseline P/F ratio, CRP, hemoglobin, and bone metastasis were all significantly associated with 28-day mortality risk (all P< 0.001) (**Figure 5**). The 11 LASSO-identified candidate variables were then entered into multivariable Cox regression, with RCS fitting applied to variables with significant nonlinear effects. SpO_2 (P=0.015), baseline P/F ratio (P=0.003), CRP (P=0.016), hemoglobin (P<0.001), and bone metastasis (P=0.004) retained independent associations with 28-day mortality (**Figure 5**). Higher SpO_2, baseline P/F ratio, and hemoglobin were associated with lower 28-day mortality risk, whereas higher CRP and the presence of bone metastasis were associated with increased risk. Arterial lactate (P=0.312), D-dimer (P=0.397), procalcitonin (P=0.860), NLR (P=0.209), respiratory rate (P=0.237), and SII (P=0.085) did not retain independent significance in multivariable analysis (**Figure 5**).

Construction of the 28-day mortality prediction nomogram

Based on the multivariable Cox regression, five variables - SpO_2, baseline P/F ratio, CRP, hemoglobin, and bone metastasis - were incorporated into a nomogram for short-term mortality risk prediction (**Figure 6**). Each predictor is assigned a score, and the total score is converted to individualized 14-day and 28-day mortality probabilities. Bone metastasis and

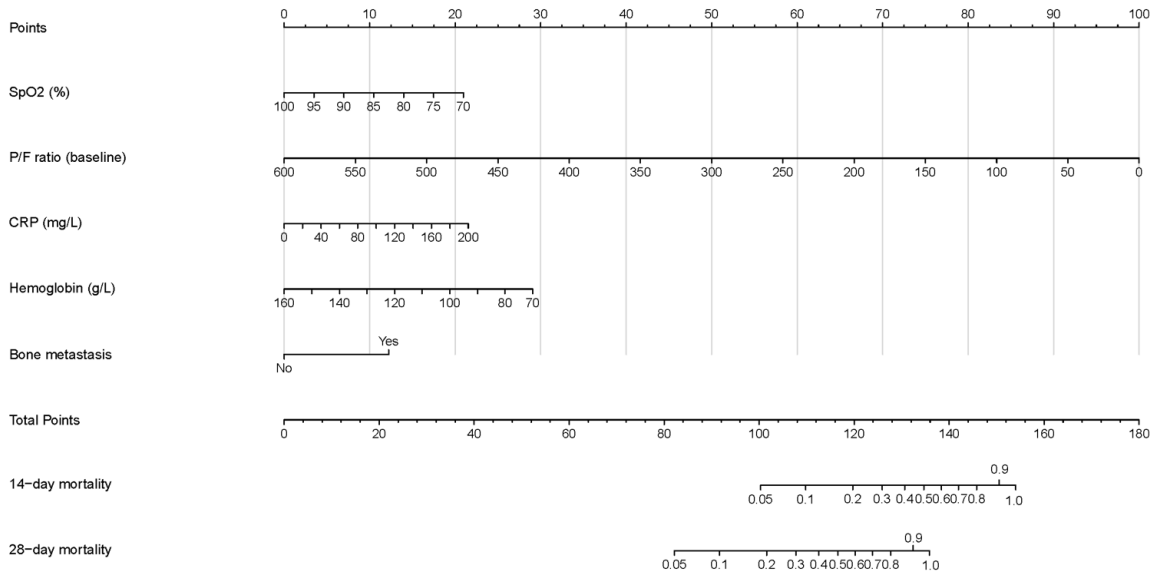


Figure 6. Nomogram for predicting 14-day and 28-day mortality in critically ill patients with lung cancer. Nomogram developed from the final Cox regression model incorporating SpO_2, baseline P/F ratio, CRP, hemoglobin, and bone metastasis. The total points derived from each predictor correspond to the estimated probability of 14-day mortality and 28-day mortality. Note: nomogram, PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SpO_2, pulse oxygen saturation; CRP, C-reactive protein.

elevated CRP levels predict poor outcomes, whereas high SpO_2, high baseline P/F ratio, and high hemoglobin predict better outcomes. By combining respiratory functional reserve, systemic inflammatory state, anemia status, and tumor metastatic characteristics, the nomogram enables estimation of short-term adverse outcome risk for individual patients. In the training set, the C-index of the model was 0.874, indicating good global discriminative ability (**Figure 6**).

Model discrimination, calibration, net clinical benefit, and risk stratification in the training set

The five-variable model displayed strong discriminative performance in the training set. Time-dependent ROC analysis showed that the AUC for 14-day mortality was 0.871 (95% CI: 0.831-0.912), and the AUC for 28-day mortality was 0.947 (95% CI: 0.927-0.968). The C-index was 0.874 (95% CI: 0.851-0.898) (**Figure 7A**). The optimal Youden-index threshold for 14-day mortality was a predicted probability cutoff of 0.092, yielding a sensitivity of 93.2% and specificity of 72.8% (Youden index: 0.660). For 28-day mortality, the optimal threshold was 0.241, yielding a sensitivity of 91.1%, specificity of 84.7%, and Youden index of 0.758. The predicted mortality probabilities from our model were consistent with actual rates. The Brier scores indicated that the model fitted the data well for short-term mortality prediction at 14 days (0.100) and 28 days (0.092) (**Figure 7B**). Although the Gronnesby-Borgan test showed a statistically significant deviation ($P<0.05$), which may be due to the moderate sample size making this test more sensitive, the calibration curves and Brier scores indicated acceptable overall agreement. DCA showed net benefit across threshold probabilities of 0.1 and above for both time-points, with the 28-day model demonstrating higher net benefit (**Figure 7C**). Kaplan-Meier survival curves revealed significant outcome differences by model-defined risk group ($P< 0.001$) (**Figure 7D**).

Model validation in the validation set

The model showed good discriminative ability in the validation set. Time-dependent ROC analysis revealed AUCs of 0.870 (95% CI: 0.816-0.923) for 14-day mortality and 0.946 (95% CI: 0.912-0.979) for 28-day mortality (**Figure 8A**). The C-index demonstrated substantial predictive capability. The optimal Youden-index th-

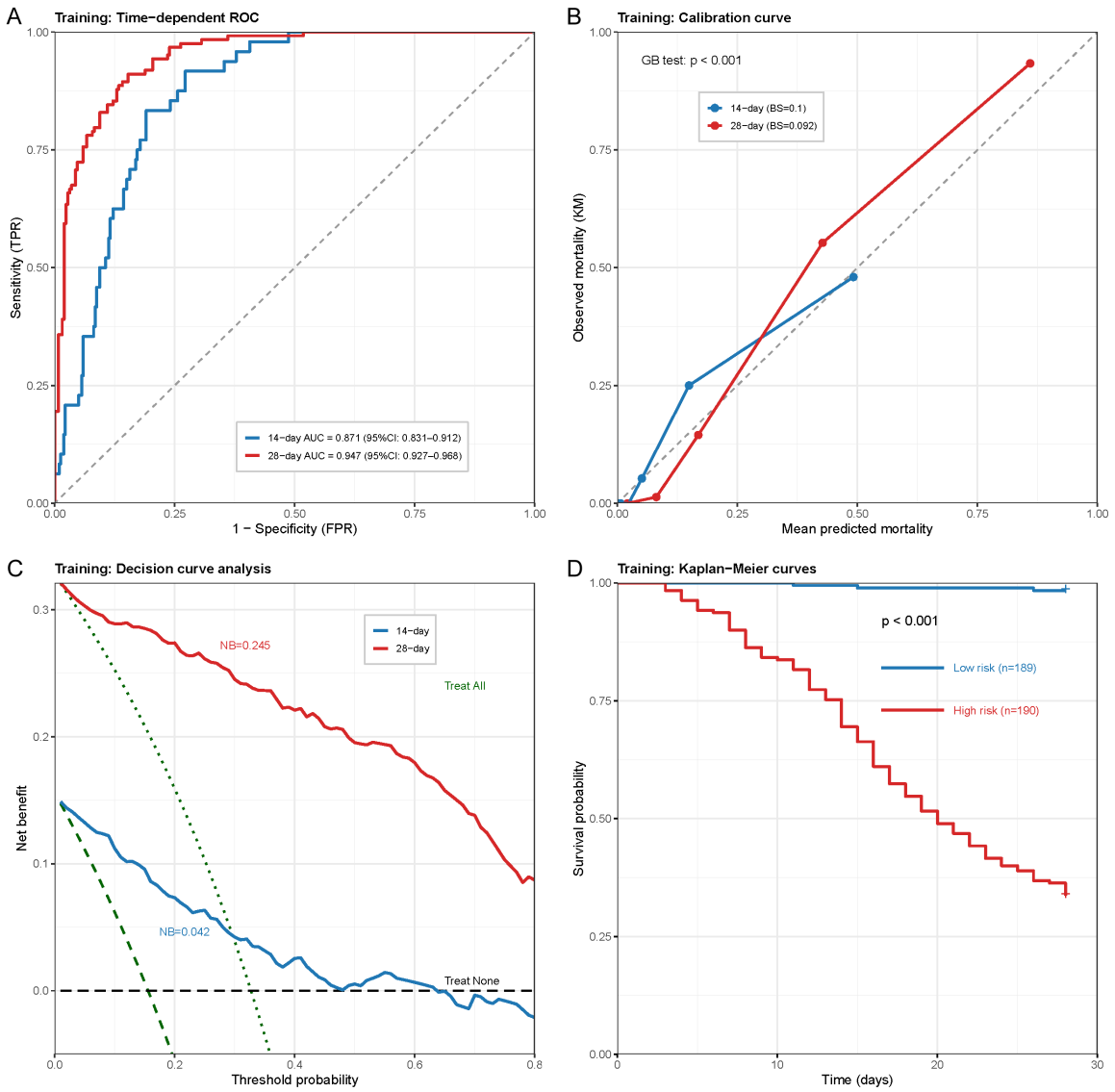


Figure 7. Performance of the final prognostic model in the training cohort. A. Time-dependent ROC curves of the final model for predicting 14-day and 28-day mortality in the training cohort. B. Calibration curves of the final model for 14-day and 28-day mortality in the training cohort. C. Decision curve analysis of the final model for 14-day and 28-day mortality in the training cohort. D. Kaplan-Meier survival curves of risk groups stratified by the final model in the training cohort. Note: ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; BS, Brier score; DCA, decision curve analysis; KM, Kaplan-Meier.

reshold for 14-day mortality was a predicted probability cutoff of 0.075, with a sensitivity of 97.3%, specificity of 72.8%, and Youden index of 0.701. For 28-day mortality, the cutoff was 0.290, with a sensitivity of 89.8%, specificity of 90.3%, and Youden index of 0.801. Calibration curves showed acceptable agreement. The Brier scores were 0.149 for 14-day and 0.103 for 28-day mortality; 28-day predictions were better calibrated than 14-day predictions (**Figure 8B**). Although the Gronnesby-Borgan test indicated potential minor miscalibration ($P<0.05$), graphical assessment and Brier scores demonstrated acceptable calibration performance. DCA confirmed that net benefit was stable across a wide range of thresholds, especially for 28-day mortality (**Figure 8C**). Kaplan-Meier survival curves showed that patients in different risk groups had significantly different outcomes ($P<0.001$), indicating the model's capacity for risk stratification and generalizability (**Figure 8D**).

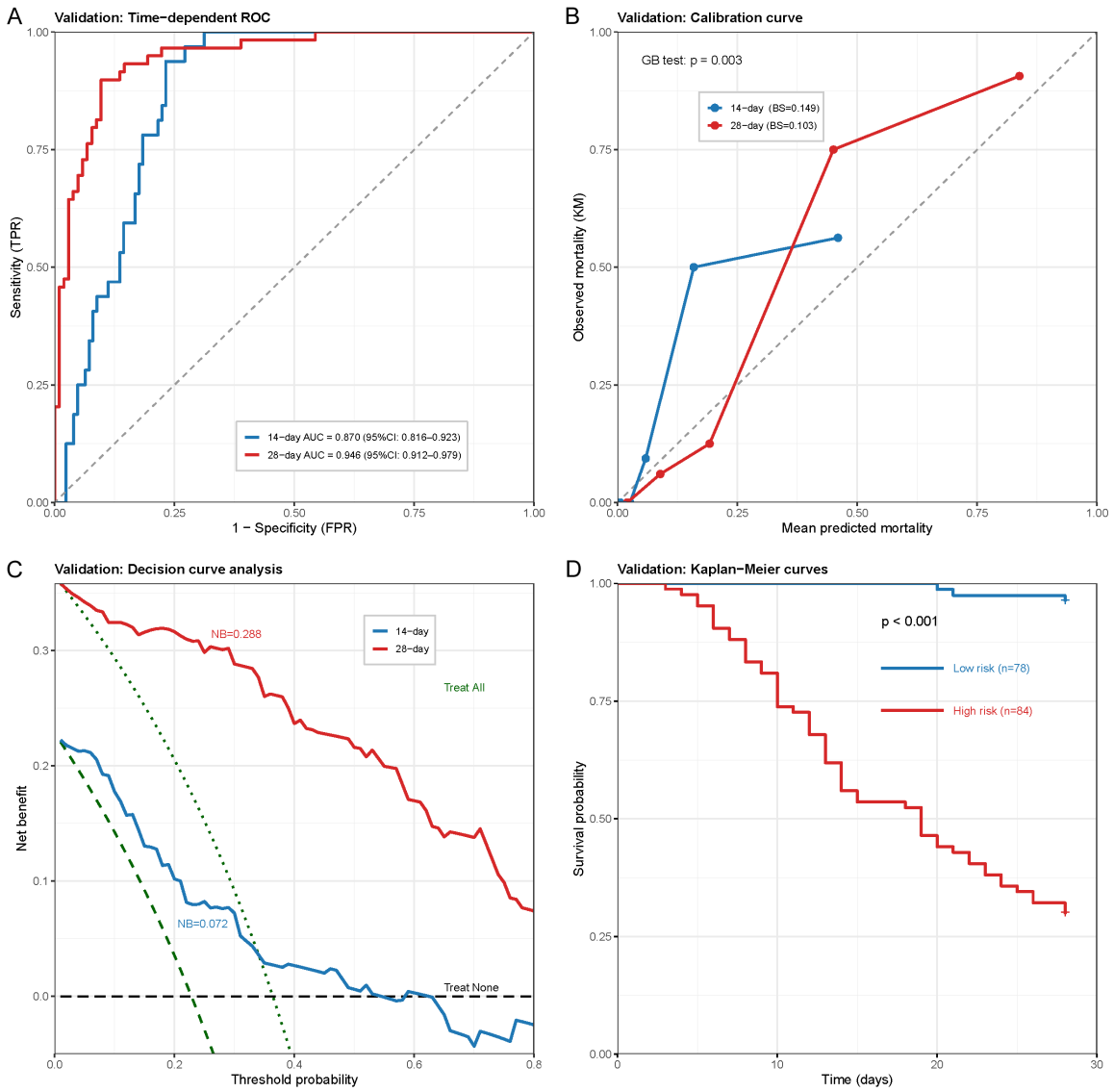


Figure 8. External validation performance of the final prognostic model in the validation cohort. A. Time-dependent ROC curves of the final model for predicting 14-day and 28-day mortality in the validation cohort. B. Calibration curves of the final model for 14-day and 28-day mortality in the validation cohort. C. Decision curve analysis of the final model for 14-day and 28-day mortality in the validation cohort. D. Kaplan-Meier survival curves of risk groups stratified by the final model in the validation cohort. Note: ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; BS, Brier score; DCA, decision curve analysis; KM, Kaplan-Meier.

Tertile-based risk stratification analysis

Using tertile cutoffs of the linear predictor from the training set, patients were divided into low-, intermediate-, and high-risk groups. The 28-day survival curves were significantly different across the three groups in the training set (**Figure 9A**), validation set (**Figure 9B**), and entire cohort (**Figure 9C**) (all P<0.001). The 28-day survival rates in the training set were 99.2%, 83.3%, and 15.1% for the low-, intermediate-, and high-risk groups, respectively. In the validation set, these rates were 98.0%, 78.9%, and 10.9%. For the overall cohort, the rates were 98.9%, 82.0%, and 13.8%. Survival decreased progressively with increasing risk level. When comparing the high- and low-risk groups, the hazard ratios were 234.910 (P< 0.001) in the training set, 105.853 (P<0.001) in the validation set, and 171.805 (P<0.001) in the overall cohort. The model reliably identified patients at high risk of short-term death, as shown by the nearly identical risk stratification in both datasets (**Figure 9C**).

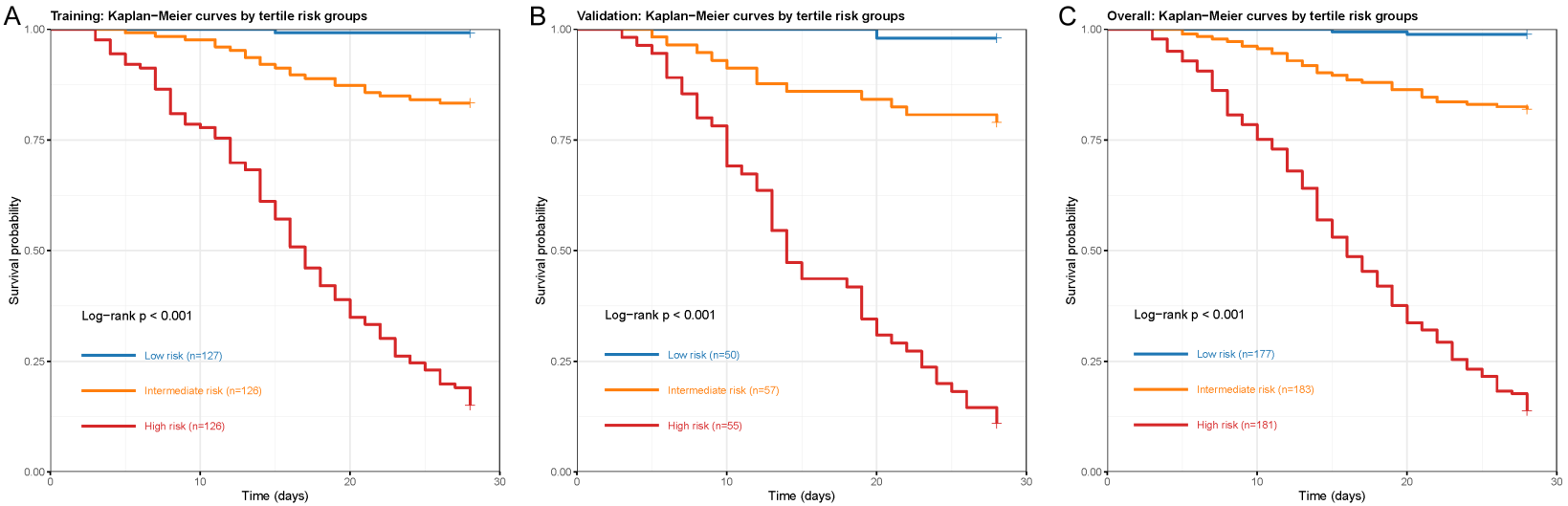


Figure 9. Kaplan-Meier survival curves according to tertile-based risk stratification in the training, validation, and overall cohort. A. Kaplan-Meier survival curves of low-, intermediate-, and high-risk groups in the training cohort. B. Kaplan-Meier survival curves of low-, intermediate-, and high-risk groups in the validation cohort. C. Kaplan-Meier survival curves of low-, intermediate-, and high-risk groups in the overall cohort. Note: KM, Kaplan-Meier; HR, hazard ratio; CI, confidence interval.

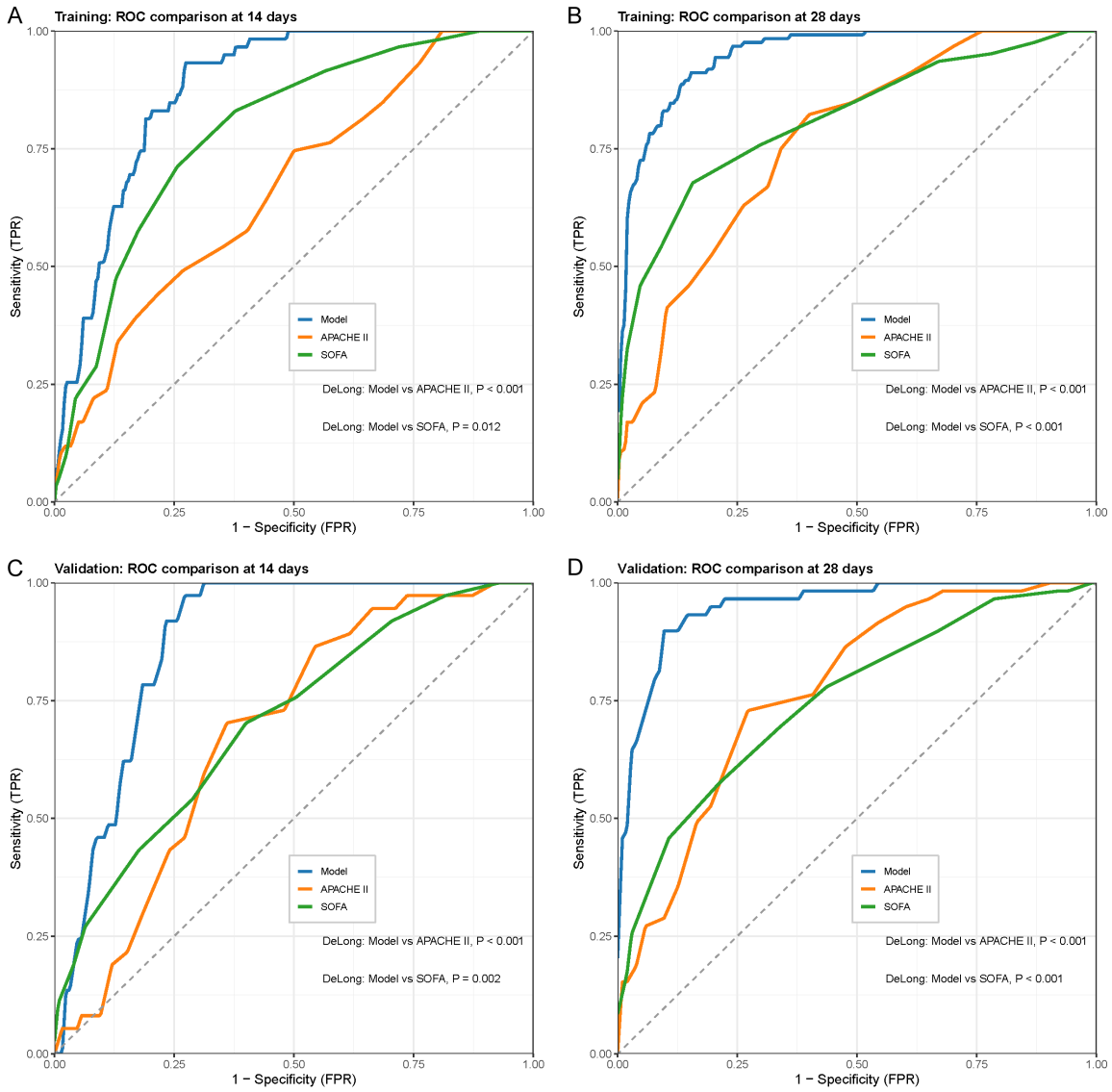


Figure 10. Comparison of discriminatory performance between the final model and conventional severity scores for short-term mortality prediction. A. ROC comparison among the final model, APACHE II score, and SOFA score for 14-day mortality in the training cohort. B. ROC comparison among the final model, APACHE II score, and SOFA score for 28-day mortality in the training cohort. C. ROC comparison among the final model, APACHE II score, and SOFA score for 14-day mortality in the validation cohort. D. ROC comparison among the final model, APACHE II score, and SOFA score for 28-day mortality in the validation cohort. Note: ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

Comparison of model discrimination against APACHE II and SOFA scores

Our prediction model outperformed the traditional scoring systems in the training set. For 14-day mortality, the model achieved an AUC of 0.875, compared with 0.667 for APACHE II and 0.788 for SOFA. DeLong testing showed significant improvement (vs. APACHE II: P<0.001; vs. SOFA: P=0.012). For 28-day mortality, our model was also statistically superior to both APACHE II and SOFA (both P<0.001) (**Figure 10A**, **10B**).

In the validation set, the model again showed superior discrimination. For 14-day mortality, the AUC was 0.872 versus 0.683 for APACHE II and 0.706 for SOFA (vs. APACHE II: P<0.001;

Table 4. Comparison of AUCs between the final model, APACHE II score, and SOFA score for prediction of 14-day and 28-day mortality

Dataset	Horizon	Method	AUC (95% CI)	DeLong comparison	*P* value
Training	14-day	Model	0.875 (0.838-0.913)	Model vs. APACHE II	<0.001
	14-day	APACHE II	0.667 (0.594-0.740)	Model vs. SOFA	0.012
	14-day	SOFA	0.788 (0.730-0.846)	APACHE II vs. SOFA	0.01
	28-day	Model	0.948 (0.927-0.968)	Model vs. APACHE II	<0.001
	28-day	APACHE II	0.766 (0.718-0.814)	Model vs. SOFA	<0.001
	28-day	SOFA	0.812 (0.764-0.861)	APACHE II vs. SOFA	0.200
Validation	14-day	Model	0.872 (0.819-0.924)	Model vs. APACHE II	<0.001
	14-day	APACHE II	0.683 (0.596-0.771)	Model vs. SOFA	0.002
	14-day	SOFA	0.706 (0.612-0.799)	APACHE II vs. SOFA	0.711
	28-day	Model	0.946 (0.912-0.979)	Model vs. APACHE II	<0.001
	28-day	APACHE II	0.773 (0.701-0.845)	Model vs. SOFA	<0.001
	28-day	SOFA	0.753 (0.675-0.831)	APACHE II vs. SOFA	0.708

Note: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic curve; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

vs. SOFA: P=0.002). For 28-day mortality, the AUC was 0.946 versus 0.773 for APACHE II and 0.753 for SOFA (both P<0.001) (**Figure 10C**, **10D**). APACHE II and SOFA scores differed significantly from each other only for 14-day mortality in the training set (P=0.010); no significant differences were found for 28-day prediction in the training set (P=0.200), 14-day prediction in the validation set (P=0.711), or 28-day prediction in the validation set (P=0.708) (**Table 4**).

At the optimal Youden-index threshold, the prediction model consistently outperformed both scoring systems in discriminative efficiency. For 28-day mortality in the training set, the model achieved a Youden index of 0.758 (sensitivity 91.1%, specificity 84.7%) at a predicted probability cutoff of 0.241, compared with a Youden index of 0.423 for APACHE II (cutoff ≥19.5, sensitivity 82.3%, specificity 60.0%) and 0.521 for SOFA (cutoff ≥7.5, sensitivity 67.7%, specificity 84.3%). In the validation set, the model's Youden index for 28-day mortality was 0.801 (sensitivity 89.8%, specificity 90.3%, cutoff 0.290), versus 0.457 for APACHE II (cutoff ≥21.5, sensitivity 72.9%, specificity 72.8%) and 0.363 for SOFA (cutoff ≥7.5, sensitivity 57.6%, specificity 78.6%). A similar pattern was observed for 14-day mortality prediction across both datasets. These findings indicate that the model not only achieves a higher AUC but also yields more balanced and clinically meaningful sensitivity-specificity trade-offs compared with conventional scoring systems.

Discussion

In this single-center retrospective cohort study, we enrolled 541 critically ill patients with lung cancer. We developed a 28-day mortality prediction model based on SpO_2, baseline PaO_2/FiO_2, CRP, hemoglobin, and bone metastasis that integrates respiratory functional reserve, systemic inflammatory state, and tumor characteristics. The model exhibited robust discrimination, calibration, and risk stratification capability in both the training and validation cohorts and demonstrated significantly superior performance compared with traditional APACHE II and SOFA scores. A multicenter cross-sectional study by Liu et al. [15] that included data from 37 oncology-specialized hospitals in China found that lung cancer patients had the highest ICU admission rate among all cancer patients, as well as the worst overall survival. This underlines the urgency of this issue in oncologic critical care. The clinical relevance and mechanisms of the independent predictors, the interpretation and benchmarking of model performance, and the study's limitations are discussed below.

The most quantitatively robust indicator of respiratory functional reserve included in this model is baseline PaO_2/FiO_2. The oxygenation index takes into account both the efficiency of ventilation-perfusion matching and oxygen delivery capacity. It is a core diagnostic criterion for acute respiratory distress syndrome per the Berlin Definition and a well-studied prog-

nostic marker in critical illness. Oxygenation failure in critically ill lung cancer patients may arise through several overlapping mechanisms. Tumor invasion of lung parenchyma, airway compression or obstruction, compressive atelectasis from pleural effusion, and tumor-associated pneumonia may impair gas exchange. Similarly, immunotherapy-related lung injury can also cause oxygenation failure. A prolonged smoking history, the presence of coexisting COPD, prior exposure to radiochemotherapy, and decreased pulmonary reserve all further reduce respiratory reserve. The combination of these factors can make patients highly prone to decompensation following any acute insult. The difference in baseline PaO_2/FiO_2 between the death and survival groups was statistically significant and retained independent predictive value in multivariable analysis. This has also been reported previously in ICU cancer and lung cancer studies. To identify independent predictors of 28-day mortality in lung cancer patients in the ICU, Qian et al. [14] used the MIMIC-III database. In their study, the 28-day mortality rate was 30.6%, and metastatic status and SOFA score were identified as independent predictors. Based on RCS analysis, PaO_2/FiO_2 showed a roughly linear negative association with mortality risk without a threshold effect. Research in invasively ventilated patients with sepsis-associated acute respiratory failure has further shown that early PaO_2/FiO_2 trajectories closely predict 28-day mortality; patients with persistently low oxygenation had the highest mortality, while those with initially low but subsequently improving trajectories fared much better [16]. This emphasizes the importance of monitoring dynamic oxygenation rather than relying on a single threshold measurement. In the current study, Delta PaO_2/FiO_2 differed significantly between groups in univariable analysis. However, it was not retained in the final multivariable model. This may be explained by its strong correlation with baseline PaO_2/FiO_2 and overlapping prognostic information. Furthermore, including Delta PaO_2/FiO_2 may decrease the timeliness and clinical applicability of early prediction models, as it requires data extending beyond 24 hours. A multicenter prospective study of 1,303 patients with moderate-to-severe ARDS confirmed that a PaO_2/FiO_2<150 mmHg at 24 hours was independently associated with significantly higher ICU mortality (HR 2.8, 95% CI 2.2-3.5) [17]. Thus, the oxygenation index is a central prognostic measure in critical illness.

Both SpO_2 and PaO_2/FiO_2 were included in the final model, demonstrating the added value of noninvasive versus invasive oxygenation monitoring. SpO_2 is a bedside measure that is noninvasive, continuous, and universally available. It showed independent predictive value alongside the oxygenation index, suggesting that it contains prognostic information not captured by PaO_2/FiO_2 alone. PaO_2/FiO_2 primarily reflects the efficiency of pulmonary gas exchange, whereas SpO_2 more directly reflects oxygen supply to peripheral tissues. SpO_2 can also be used in patients for whom arterial blood gas sampling is difficult, representing a practical extension of the model.

In this model, the primary marker of systemic inflammation is CRP. According to univariable analysis, NLR, SII, and PCT were significantly associated with 28-day mortality; however, in multivariable Cox regression analysis, only CRP retained an independent association. In a study involving 183 non-small cell lung cancer (NSCLC) patients, Liu et al. [18] found that both elevated NLR and elevated SII served as independent negative prognostic factors for 3-year survival; the AUC of the combined multi-indicator model was 0.906, which was superior to any individual marker. This indicates substantial information overlap among these inflammatory indices; when competing in multivariable analysis, only a few can simultaneously retain independent effects. The correlation analysis in this study demonstrated a moderate positive correlation between NLR and SII. Similarly, a correlation between PCT and NLR suggests some redundancy of information. Arterial lactate, D-dimer, and respiratory rate were significantly associated with 28-day mortality in univariable analysis but lost independent significance in multivariable Cox regression. This is likely due to their moderate correlations with the five retained predictors, as demonstrated in the Spearman correlation analyses, whereby their prognostic information was largely captured by SpO_2, baseline PaO_2/FiO_2, CRP, hemoglobin, and bone metastasis. Moreover, Schoenfeld residual testing showed that arterial lactate and respiratory rate violated the proportional hazards assumption, which limited their incorporation as stable indepen-

dent predictors in the final model. CRP is an acute-phase protein synthesized in the liver. It reflects both infectious and tumor-associated non-infectious inflammatory burden without being affected by differential white blood cell counts. Furthermore, CRP measurement is highly standardized and reproducible. It is one of the most widely used markers of inflammation. Chaftari et al. [19] developed a model to predict short-term mortality in cancer patients with suspected infection and identified CRP, PCT, and lactate as key predictors of 14-day mortality, achieving an AUC of 0.88 - further evidence of the independent prognostic value of CRP in critically ill cancer patients. Picod et al. [20], using data from 2,076 patients in the large prospective FROG-ICU cohort, confirmed that high CRP was independently associated with worse 90-day survival (HR 1.21) and greater use of vasopressors and renal replacement therapy. Thus, CRP is thought to reflect not only the intensity of the inflammatory response but also the degree of multi-organ dysfunction. Elevated CRP in critically ill lung cancer patients may occur in the setting of infections or sepsis. It may also result from activation of the tumor-associated inflammatory microenvironment, immune dysregulation secondary to immunotherapy, or multi-organ stress. The greater availability of CRP compared with PCT or NLR ensures wider clinical applicability of the model, as it can be routinely used even in community-level and county-level ICUs in China.

Hemoglobin is a common test included in assessments that integrate nutritional status, tumor burden, and oxygen delivery capacity. Anemia - a deficiency of healthy red blood cells to carry adequate oxygen to the body's tissues - is very common in critically ill lung cancer patients. It occurs through several overlapping mechanisms. It may result from tumor-related chronic inflammation, which ultimately suppresses erythropoietin synthesis and bone marrow function. Another cause is the myelosuppressive effects of chemotherapy, targeted therapy, or immunotherapy. Insufficient nutritional intake may lead to iron-deficiency anemia. Furthermore, bone marrow metastasis can occur due to direct depletion of the hematopoietic stem cell pool. Anemia exacerbates hypoxia in patients who are already hypoxic by reducing blood oxygen-carrying capacity. In multivariable analysis, hemoglobin was an independent predictor ($P<0.001$) [21]. The higher the hemoglobin level, the lower the risk of 28-day mortality. Anemia at ICU admission reflects the patient's baseline functional capacity and nutritional reserves. Anemia can also be considered an independent risk factor for short-term outcomes. Prior research has shown that composite nutritional-inflammatory indicators such as the red cell distribution width-to-albumin ratio independently predict 180-day mortality in ICU patients with lung cancer and are superior to SOFA score alone [10], indicating the role of the nutritional-inflammatory axis in prognostication. Future prospective studies are needed to assess whether active correction of anemia improves short-term outcomes in this population.

The only tumor-specific factor in the final model is bone metastasis. Among the variables retained by LASSO, both bone metastasis and brain metastasis were associated with prognosis, but only BM retained independent predictive value in multivariable analysis. Extensive bone metastasis indicates that the cancer has spread more widely throughout the body. The presence of bone marrow metastasis impairs blood cell production. Bone erosion can lead to hypercalcemia, causing cardiac rhythm disturbances, kidney damage, and altered mental status. Pain and immobility resulting from bone metastasis further reduce functional status and nutritional reserves. According to Wu et al. [21], bone metastasis in lung cancer is predominantly osteolytic. Furthermore, skeletal-related events (SREs) caused by osteolytic destruction are a major contributor to functional decline and decreased survival in these patients. Elkhapery et al. [9] performed a systematic review and meta-analysis of 33 studies comprising over 80,000 ICU lung cancer patients. They found that metastatic disease was an independent predictor of ICU mortality (RR 1.30, 95% CI 1.06-1.59), similar to the independent prognostic effect of bone metastasis found here [22]. The Chinese expert consensus states that approximately 50% of lung cancer patients with bone metastasis will experience SREs, which significantly shorten life expectancy. The care of patients with bone metastasis requires multidisciplinary management. According to Xue et al. [23], about 30-40% of patients with NSCLC ultimately develop bone metastasis. Although bone-tar-

geted agents are available, the overall prognosis remains poor. In a multicenter study involving advanced NSCLC patients undergoing immunotherapy, Du et al. [24] confirmed that bone metastasis was an independent negative predictor of durable response (HR 1.593). Bone metastasis status can be obtained from bone scans, PET/CT, or discharge diagnoses, which is easily accessible in retrospective studies and clinical practice. A graded prognostic assessment model for advanced NSCLC with bone-only metastasis was developed by Meng et al. [25]. Their findings showed that hypoalbuminemia and weight loss, together with bone metastasis, formed a multidimensional adverse prognostic profile. The final model in this study, on the other hand, included both hemoglobin and bone metastasis. This may suggest an intrinsic relationship between nutritional reserve and skeletal tumor burden in critically ill lung cancer patients.

The five-variable prediction model we developed showed excellent discrimination in both datasets, with 28-day mortality AUCs approaching 0.95 and C-indices of 0.874 and 0.852. This performance comfortably exceeds the high performance threshold typically considered for prognostic models in critical care. The calibration curves and Brier scores showed good agreement between predicted probabilities and observed outcomes. DCA demonstrated a positive net benefit across clinically relevant ranges of threshold probabilities, with strong net benefit for 28-day mortality. Research on predictive modeling using machine learning approaches has been conducted in critically ill cancer populations. For example, a large-scale model trained on multicenter ICU datasets showed strong discriminative performance for short-term mortality, with AUCs nearing 0.90 in derivation cohorts [26]. Although those models were constructed in heterogeneous cancer populations, they did not specifically address lung cancer, potentially missing some lung cancer-specific pathophysiological features relevant to disease modeling. The current model specifically targets lung cancer patients and achieves quite similar predictive performance using fewer and clinically relevant variables - not an insignificant detail.

A crucial finding is the comparison with conventional scoring systems. Both APACHE II and SOFA were intended for the general critical care population. However, they fail to capture tumor-specific data such as metastatic burden, baseline performance status, and tumor-related inflammation, which is an inherent limitation in critically ill lung cancer patients. Cabrera Losada et al. [27] conducted a systematic review analyzing seven frequently used ICU mortality prediction scores designed for cancer patients and found that existing scores generally underestimate mortality and lack adequate discrimination; the authors specifically called for the development of cancer-specific tools. In the present study, DeLong testing confirmed that our model significantly outperformed both APACHE II and SOFA for 14-day and 28-day mortality prediction. The results were consistent across training and validation sets. This advantage is obtained because the model captures lung cancer-related pathophysiology: it includes indicators of acute physiological state (SpO_2, PaO_2/FiO_2) and inflammation (CRP), as well as anemia (hemoglobin) and bone metastasis. Similarly, recent studies leveraging large ICU databases have demonstrated that incorporating multidimensional clinical features can enhance predictive accuracy in critically ill cancer patients [28]. However, those models generally used complex algorithms and a large number of variables, which may not be suitable for daily clinical use. In contrast, our model uses only five variables that are readily available, thus improving its practicality and making it feasible at the bedside without advanced computation.

The model's clinical translational value was enhanced by a tertile-based risk stratification. In the overall cohort, the 28-day survival rates were 98.9%, 82.0%, and 13.8% in the low-, intermediate-, and high-risk groups, respectively. Furthermore, the mortality hazard for high-risk patients was 171.8 times that of low-risk patients. This stratification pattern was replicated across both datasets. The model can continuously provide personalized risk probabilities and can also yield clinically meaningful patient classifications to help inform decisions regarding resource allocation, treatment intensity, and prognostic communication.

Most previous studies of critically ill cancer patients have been conducted in general oncologic ICU populations, with limited work spe-

cifically in lung cancer. Tang et al. [29] developed interpretable machine-learning models to predict ICU mortality in patients with sepsis combined with lung cancer, further supporting the feasibility of machine-learning-based risk stratification in critically ill lung cancer populations. The AUC of this model was 0.94. Furthermore, the CanICU model outperformed commonly used models such as APACHE and SOFA. Importantly, the objective of CanICU was similar to the performance target of the present study. Nevertheless, CanICU was built on a broadly defined cancer population and was not optimized for the pathophysiology of lung cancer specifically. Machine learning-based methods have also demonstrated efficacy in predicting in-hospital mortality among lung cancer patients admitted to the ICU, with SOFA score and albumin level proving to be important features across different model types [30] - consistent with the independent predictive roles of oxygenation and nutritional parameters found in this study. In a retrospective cohort study conducted in an oncology setting within the Mayo Clinic system, Koch and colleagues reported that advanced tumor stage and ECOG score >1 were independent predictors in the oncology-focused model. In contrast, age and SOFA score dominated the full physiological model (C-index 0.95), which aligns with the central roles of oxygenation and inflammatory markers in our model [8]. According to Park et al. [31], using a Korean nationwide database, tumor clinical stage and the need for mechanical ventilation were independent risk factors for ICU mortality in lung cancer patients, with an ICU mortality rate of 47.5% among non-surgical admissions. This study offers a novel disease-specific tool developed through systematic feature selection and multidimensional modeling of respiratory functional reserve, systemic inflammation, nutritional status, and tumor characteristics. The research employed LASSO dimensionality reduction, RCS testing for nonlinearity, Schoenfeld residual testing, and comparison of multiple performance metrics.

Several limitations warrant mention. Selection bias is an inherent limitation of a single-center retrospective design, and external generalizability must be validated through multicenter prospective studies. Standardization of laboratory results would depend on each hospital's quality control system, and inter-hospital variability may occur. Subgroup analyses by treatment type and pathological type were not performed, and the importance of tumor heterogeneity requires further analysis. The independent significance of dynamic oxygenation change (Delta PaO_2/FiO_2) did not persist and may be better assessed in future dynamic prediction models. Moreover, although several clinically important variables have established prognostic value (e.g., arterial lactate, D-dimer, procalcitonin, NLR, SII), they were not included in the final model owing to collinearity and shared prognostic information under strict modeling assumptions. While this improved model parsimony and stability, it may also limit comprehensiveness. The two-step variable selection strategy (LASSO followed by multivariable Cox regression), while useful for reducing dimensionality and enhancing interpretability, carries a risk of overfitting, especially in a retrospective setting. Furthermore, patients expected to die within 3 days were excluded to allow adequate collection of baseline data, which may limit the model's generalizability to patients with very early deterioration. The model also lacks external validation, and further confirmation of its generalizability across different settings is warranted.

In summary, the model was built using five routinely available clinical indicators and showed good discrimination and calibration. Moreover, it demonstrated good net clinical benefit, meaningful risk stratification, and predictive ability superior to that of APACHE II and SOFA scores. It shows potential to serve as a useful tool for early risk identification and precision management among lung cancer patients admitted to the RCCM, ICU, or EICU. Future studies should focus on multicenter prospective external validation of the model and on pathways for its integration into clinical decision support systems to translate research into practice.

Conclusion

With five routinely available clinical variables, namely SpO_2, baseline PaO_2/FiO_2, CRP, hemoglobin, and bone metastasis, an individualized nomogram for predicting 28-day short-term mortality risk was developed and validated in critically ill lung cancer patients admitted to the RCCM, ICU, or EICU. The model integrates

respiratory functional reserve, systemic inflammatory burden, nutritional and oxygen delivery status, and tumor metastatic characteristics. It showed excellent discrimination (28-day AUC approaching 0.95 and C-index >0.85 in both datasets), good calibration, clear net clinical benefit, and effective stratification into low-, intermediate-, and high-risk groups with significantly different 28-day survival. The model demonstrated significantly enhanced predictive ability compared with APACHE II and SOFA scores, thereby overcoming the limitations of traditional general-purpose scoring systems in integrating tumor-specific information.

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Disclosure of conflict of interest

None.

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