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Original Article

Development and validation of a nomogram for predicting 90-day mortality in patients with advanced lung cancer based on inflammatory and nutritional biomarkers

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Abstract: This retrospective study of 455 stage III/IV non-small cell lung cancer patients treated at Sanmen People's Hospital from January 2022 to January 2025 aimed to identify prognostic factors for short-term mortality and develop a validated nomogram for risk assessment. Patients were divided into training (n = 318) and validation (n = 137) cohorts, with clinical and laboratory variables - age, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, chronic obstructive pulmonary disease (COPD), C-reactive protein (CRP), interleukin-6 (IL-6), serum albumin (ALB), and lactate dehydrogenase (LDH) - analyzed using Kolmogorov-Smirnov tests for data distribution, and t-tests, Mann-Whitney U tests, and chi-square tests for comparisons. Logistic regression identified CRP ≥ 24.42 mg/L (odds ratio = 6.285, P = 0.002), IL-6 ≥ 28.705 pg/mL (odds ratio = 38.364, P < 0.001), and LDH ≥ 357 U/L (odds ratio = 10.132, P < 0.001) as predictors of increased mortality risk, while ALB ≥ 32.65 g/L (odds ratio = 0.073, P < 0.001) and ECOG score = 0 (odds ratio = 0.214, P = 0.040) were associated with reduced risk. Cox regression confirmed CRP, IL-6, ALB, LDH, and COPD as significant predictors. A nomogram constructed from these factors showed strong performance, with area under the curve values of 0.932, 0.930, and 0.962 for 30-, 60-, and 90-day mortality in the training cohort, and 0.894, 0.916, and 0.925 in the validation cohort, respectively, alongside concordance indices of 0.922 (training) and 0.877 (validation). Decision curve analysis and calibration plots confirmed robust clinical applicability and prognostic precision, establishing the nomogram as a reliable tool for personalized risk stratification in advanced lung cancer.

Keywords: Advanced lung cancer, short-term mortality, nomogram, inflammatory biomarkers, nutritional status, risk prediction

Introduction

Advanced lung cancer (aLC), classified as stages III-IV, represents a significant global health burden and is a leading cause of cancer-related mortality worldwide [1]. aLC typically exhibits aggressive progression and is associated with a poor prognosis. Many patients experience rapid health deterioration, with substantial mortality occurring within the first few months after diagnosis [2]. Therefore, predicting short-term mortality risk is crucial for personalized treatment planning, facilitating shared decision-making, and optimizing healthcare resource allocation. This also helps patients and their families set realistic expectations, thereby improving quality of life [3]. However, existing aLC mortality prediction models have notable limitations, including complex structures, difficulties in generalizing across diverse populations, and limited clinical applicability [4]. As a result, identifying key prognostic factors for the development of effective, validated prediction models is imperative.

Outcomes in aLC are influenced by a multitude of influenced by a multitude of factors, including individual patient characteristics, comorbidities, prior treatments, and biomarker profiles [5]. Recent studies have underscored the pivotal role of systemic inflammation and nutritional status in determining clinical prognosis. Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are closely

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associated with the tumor microenvironment and cancer progression [6, 7]. Elevated CRP, a hallmark of systemic inflammation, has been linked to accelerated tumor growth. IL-6, a key cytokine involved in immune and inflammatory responses, enhances oncogenic pathways and is correlated with poor clinical outcomes in aLC and other malignancies [7]. In contrast, nutritional biomarkers such as serum albumin (ALB), an indicator of overall nutritional status, hold clinical relevance, as hypoalbuminemia correlates with reduced treatment tolerance and increased mortality risk [8]. Similarly, elevated lactate dehydrogenase (LDH), indicative of tissue breakdown and metabolic dysregulation, reflects advanced disease burden and predicts shorter survival in patients with aLC [9]. While the prognostic significance of these biomarkers has been supported by previous research, further are warranted to assess their independent predictive value and potential interactions, with the goal of elucidating their combined impact on patient prognosis.

While biomarkers provide valuable prognostic information, factors such as the Eastern Cooperative Oncology Group (ECOG) performance status and chronic conditions, including chronic obstructive pulmonary disease (COPD), are equally essential for assessing short-term mortality risk. COPD, a prevalent comorbidity in aLC patients, contributes to the amplification of systemic inflammation and deterioration of lung function, thereby accelerating disease progression and resulting in poorer survival outcomes [10]. Therefore, the integrated analysis of these clinical factors alongside biomarkers may enhance the precision of mortality risk stratification.

In modern oncology, the development of reliable predictive models is pivotal for enhancing prognostic evaluation. Nomograms are particularly valuable clinical tools due to their ability to incorporate multiple prognostic variables into an intuitive visual model, which facilitates straightforward interpretation by healthcare providers [10]. These visual tools quantify the contribution of each factor to the overall risk, enabling the formulation of personalized treatment strategies. The clinical utility of nomograms in lung cancer prognosis has been well established. For instance, Zhang et al. [11] applied machine learning algorithms, such as least absolute shrinkage and selection operator regression, to a cohort of 1,084 non-small cell lung cancer (NSCLC) cases, yielding a nomogram with high predictive accuracy for postoperative pulmonary infection risk (concordance index [C-index] = 0.935). Similarly, Rakaee et al. [12] utilized deep learning techniques to predict treatment outcomes for immune checkpoint inhibitors in advanced NSCLC. Their approach demonstrated improved prediction reliability when integrating tumor biomarkers like programmed death-ligand 1.

However, most existing short-term mortality prediction models for aLC have not undergone rigorous external validation, limiting their utility in predicting clinically meaningful endpoints at 30, 60, and 90 days. To address this gap, the present study systematically explores key determinants of short-term mortality in aLC, specifically CRP, IL-6, ALB, and LDH, and integrates them into a novel nomogram. Using time-dependent receiver operating characteristic (ROC) analysis, decision curve analysis (DCA), and calibration curves, we evaluate the predictive performance of the model in both training and independent validation cohorts. The ultimate goal is to provide a clinically actionable tool for risk stratification, thereby supporting individualized treatment planning and optimizing healthcare resource allocation.

Methods and materials

Statistical power analysis for sample size

To determine the required sample size for assessing the 90-day mortality rate in patients with aLC, we employed the standard formula for estimating proportions: $N = (Z^2 \times P \times (1\text{-}P))/E^2$. In this equation, P represents the expected proportion based on prior literature, specifically the 90-day mortality rate of 22.3% reported by Jeryczynski et al. in 2024 [13]. The Z-value of 1.96 corresponds to a 95% confidence level, and E denotes the allowable margin of error, which was set at 0.05. Using these parameters, the calculated minimum sample size was 267, ensuring sufficient statistical power and robustness for subsequent analyses.

Study population

This retrospective cohort study enrolled 455 NSCLC patients who received treatment at

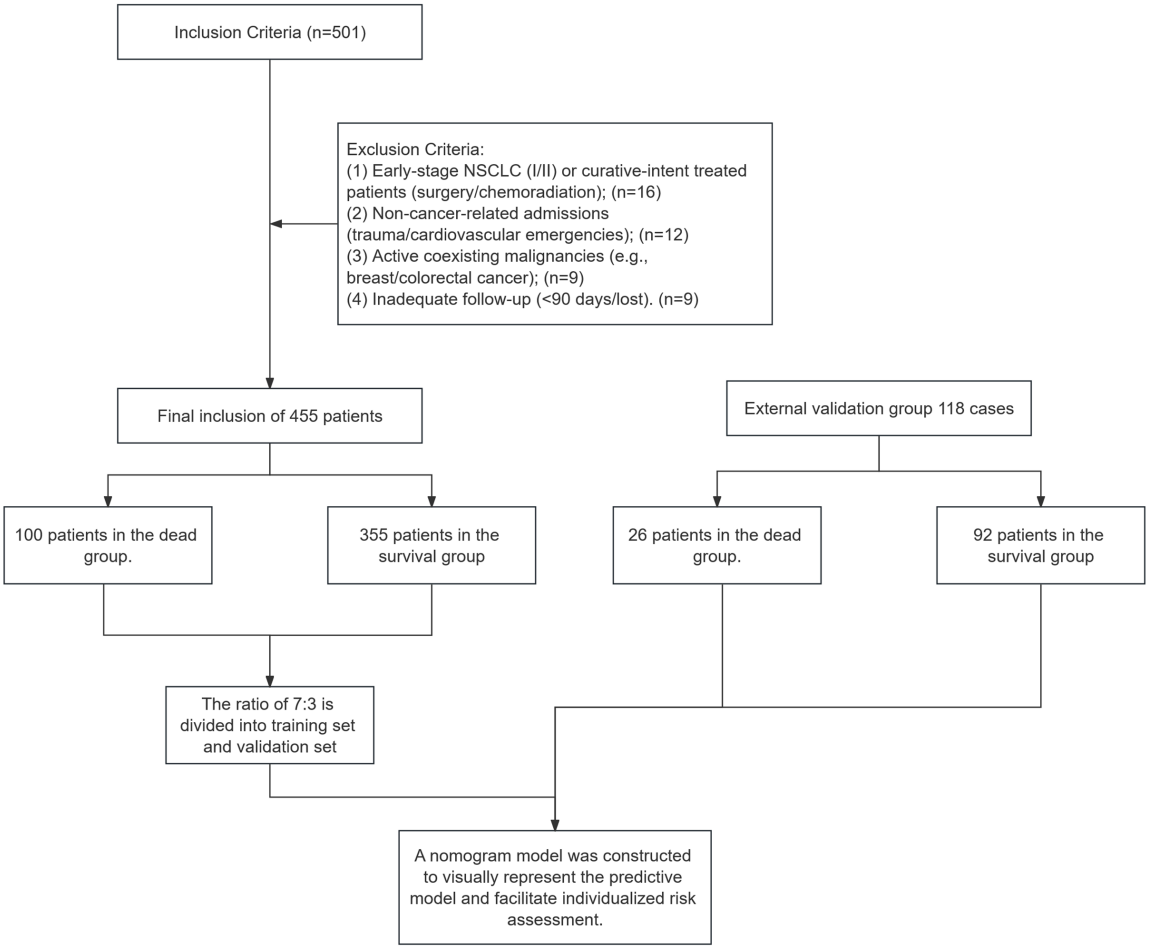

Figure 1. Flow diagram of patient selection, grouping, and model development. Note: NSCLC, non-small cell lung cancer.

Sanmen People's Hospital between January 2022 and January 2025. The study protocol was reviewed and approved by the Institutional Review Board of Sanmen People's Hospital prior to data collection. In addition, an external validation cohort comprising 118 aLC patients, treated at the same institution between January 2020 and December 2021, was incorporated for model validation. The study flow diagram is shown in **Figure 1**.

Patient selection criteria

Inclusion criteria: (1) Confirmed diagnosis: Histologically or cytologically confirmed NSCLC, classified as stage III or IV according to the tumor, node, metastasis (TNM) staging system (advanced disease) [14]. (2) Data availability: Complete clinical and laboratory data available for analysis. (3) Follow-up status: Documented 90-day survival outcome (survived or deceased) for mortality outcomes. (4) Age requirement: Aged 18 years or older at the time of diagnosis to ensure an adult study population representative of advanced NSCLC.

Exclusion criteria: (1) Early-stage disease or curative treatment: Diagnosis of stage I/II NSCLC or receipt of curative-intent therapy (e.g., surgical resection or definitive chemoradiation). (2) Non-oncologic admissions: Hospitalizations primarily for non-cancer-related acute conditions (e.g., trauma, cardiovascular emergencies). (3) Concurrent malignancies: Presence of active secondary malignancies (e.g., breast or colorectal cancer), to reduce confounding prognostic factors. (4) Incomplete follow-up: Less than 90 days of follow-up or loss to follow-up, precluding definitive mortality determination.

Clinical data collection

We performed a retrospective analysis of medical records and hospital databases from aLC patients to collect comprehensive clinical data and laboratory indicators. These data were subsequently utilized to develop and validate a short-term mortality risk prediction model. The clinical data encompassed several key categories: (1) demographic information, including age, gender, and ethnicity; (2) anthropometric variables such as body mass index (BMI); (3) lifestyle factors like smoking history and alcohol consumption; (4) comorbidities, including COPD, diabetes, and cardiovascular disease history; (5) performance status, assessed using the ECOG performance score [15]; (6) treatment history, covering chemotherapy and radiotherapy; (7) disease characteristics, such as TNM stage, pathological subtype, differentiation degree, and epidermal growth factor receptor (EGFR) mutation status; and (8) specific cancer treatments, including EGFR tyrosine kinase inhibitors and anti-vascular endothelial growth factor (VEGF) therapies. Additionally, we collected laboratory indicators, which consisted of hematological parameters (e.g., white blood cell count [WBC], hemoglobin [Hb], and platelet count [PLT]), inflammatory markers (e.g., CRP and IL-6), nutritional indicators (e.g., ALB), tumor biomarkers (e.g., carcinoembryonic antigen and cytokeratin 19 fragment antigen 21-1 [CYFRA21-1]), and metabolic enzymes (e.g., LDH). All data were obtained from patients' initial examinations upon hospital admission.

Outcome measures

Primary outcomes: (1) Model development and performance: Logistic and Cox regression analyses were performed to identify predictors of 90-day mortality. A nomogram was developed to represent the predictive model. Time-dependent ROC curves and C-index were used to evaluate model performance. (2) Validation: The model was validated both internally and externally using training and validation cohorts. Clinical utility was assessed through DCA and calibration curves.

Secondary outcomes: (1) Baseline characteristics: Baseline characteristics were compared between groups using appropriate statistical tests, including chi-square tests for categorical variables and t-tests for continuous variables. (2) Survival analysis: Kaplan-Meier survival analysis with log-rank testing was conducted to compare survival distributions across different subgroups.

Statistical analysis

Statistical analyses were conducted with SPSS 26.0 (IBM Corp., USA) and R 4.3.3 (R Foundation, Austria). All statistical tests were two-tailed, with statistical significance set at $P < 0.05$. Data distribution was first assessed using the Kolmogorov-Smirnov test. For normally distributed continuous variables, results were expressed as mean ± standard deviation ($\bar{x} \pm s$), and group differences were assessed using independent samples t-tests. For non-normally distributed data, the median [interquartile range] was reported, and comparisons were made using the Mann-Whitney U test. Categorical variables were shown as counts (percentages) and compared through chi-square tests. Multicollinearity was assessed by calculating variance inflation factors, with values below 10 considered indicative of no significant collinearity. Potential predictors of 90-day mortality were identified through both univariate and multivariate logistic regression analyses, with outcomes expressed as odds ratios (ORs) and 95% confidence intervals (CIs). For survival analysis, Cox proportional hazards (PH) regression was applied. The PH assumption was tested before model construction, and variables that violated this assumption (e.g., IL-6) were categorized based on predefined cutoff values to ensure model robustness. Key prognostic factors were further validated through multivariate Cox PH analysis, with hazard ratios (HRs) and 95% confidence intervals provided. A nomogram was developed based on significant predictors, and individual risk scores were calculated. The model's predictive performance was evaluated using time-dependent ROC curves, with area under the curve (AUC) values calculated for mortality prediction at 30, 60, and 90 days. DCA was conducted to assess the clinical net benefit, and model calibration was verified by comparing predicted probabilities with actual outcomes. The C-index was calculated to quantify the overall predictive accuracy of the model.

Results

Comparison of baseline characteristics

The baseline characteristics of aLC patients were compared between the training and validation groups (all P > 0.05; **Table 1**). No statistically significant differences were observed across multiple parameters, including age, gender, ethnicity, BMI, smoking history, alcohol consumption, and comorbidities such as COPD, diabetes, and cardiovascular disease. Performance status, assessed via the ECOG score, and prior treatment history (chemotherapy and radiotherapy) were also comparable. Tumor-related characteristics, including TNM stage, pathological subtype, degree of differentiation, and EGFR mutation status, showed no significant variation. Treatment-related factors, such as EGFR-tyrosine kinase inhibitor therapy and anti-VEGF treatment, were similarly distributed. Laboratory parameters, including complete blood counts (WBC, Hb, PLT), inflammatory markers (CRP and IL-6), biochemical indicators (ALB and LDH), and tumor biomarkers (carcinoembryonic antigen, CYFRA21-1), were balanced between the groups. Additionally, no significant differences were detected in CRP, IL-6, ALB, or LDH levels across the derivation, internal validation, and external validation cohorts (all P > 0.05; Table S1).

Comparison of baseline characteristics stratified by survival status

Significant differences were observed between surviving and deceased aLC patients in both the training and validation cohorts (**Table 2**). In the training cohort, key factors associated with 90-day mortality included BMI (P = 0.002), comorbid COPD (P < 0.001), ECOG performance status (P < 0.001), history of chemotherapy (P < 0.001), TNM stage (P < 0.001), and blood biomarkers (CRP, IL-6, ALB, LDH; all P < 0.001). No significant differences were found in age, gender, ethnicity, smoking history, alcohol consumption, or other comorbidities (all P > 0.05). A similar pattern was observed in the validation cohort, where BMI, COPD, ECOG status, chemotherapy history, TNM stage, and blood biomarkers (CRP, IL-6, ALB, LDH) (all P < 0.05) were significant, while other factors showed no notable differences (all P > 0.05). These findings suggest that BMI, COPD, ECOG score, chemotherapy history, TNM stage, and specific blood biomarkers are potential predictors of short-term mortality risk in aLC patients.

Logistic regression analysis of short-term mortality risk

Univariate and multivariate logistic regression analyses were conducted to identify factors associated with short-term mortality risk in aLC patients (**Table 3**). Univariate analysis revealed significant associations with mortality. Key risk factors included BMI (23-25 kg/m^2: P = 0.004, OR = 2.500; > 25 kg/m^2: P = 0.002, OR = 3.551), presence of COPD (P < 0.001, OR = 2.751), ECOG score of 0 (P = 0.001, OR = 0.254), absence of chemotherapy history (P < 0.001, OR = 0.208), and TNM stage III (P < 0.001, OR = 0.254). Elevated biomarkers were also associated with increased risk: CRP (≥ 24.42 mg/L, P < 0.001, OR = 5.443), IL-6 (≥ 28.705 pg/mL, P < 0.001, OR = 45.214), LDH (≥ 357 U/L, P < 0.001, OR = 11.565), and ALB (≥ 32.65 g/L, P < 0.001, OR = 0.045).

Multivariate analysis confirmed independent predictors of increased mortality risk: CRP (≥ 24.42 mg/L, P = 0.002, OR = 6.285), IL-6 (≥ 28.705 pg/mL, P < 0.001, OR = 38.364), and LDH (≥ 357 U/L, P < 0.001, OR = 10.132). In contrast, higher ALB levels (≥ 32.65 g/L, P < 0.001, OR = 0.073) and ECOG score of 0 (P = 0.040, OR = 0.214) were associated with reduced mortality risk. BMI, COPD, chemotherapy history, and TNM stage were not significant in the multivariate model (all P > 0.05), suggesting that their effects may be confounded by systemic inflammation, nutritional status, or functional performance.

PH assumption testing and variable categorization

The PH assumption was tested prior to Cox regression modeling. Initial testing revealed a violation of the assumption (P < 0.001), with IL-6 showing significant non-proportionality (P < 0.05; **Figure 2**). To address this, continuous variables were categorized using the surv_cutpoint() function in R, which identified optimal cutoff values that maximized survival discrimination. Binary variables were then generated based on these cutoffs (**Table 4**). Reassessment of the PH assumption following categorization confirmed model validity (P > 0.05; **Figure 3**), supporting the use of Cox regression analysis.

Table 1. Comparison of baseline characteristics between training and validation groups

Variable	Total	Training group (n = 318)	Validation group (n = 137)	Statistic	P
Age (< 60/60-70/> 70)	130/257/68	94/179/45	36/78/23	0.814	0.666
Gender (male/female)	317/138	225/93	92/45	0.588	0.443
Ethnicity (Han/others)	420/35	295/23	125/12	0.314	0.575
BMI (< 23/23-25/> 25)	99/240/116	69/162/87	30/78/29	2.093	0.351
Smoking history (yes/no)	348/107	247/71	101/36	0.831	0.362
Alcohol consumption history (yes/no)	76/379	51/267	25/112	0.336	0.562
Comorbid COPD (yes/no)	203/252	142/176	61/76	0.001	0.980
Diabetes history (yes/no)	96/359	64/254	32/105	0.601	0.438
Cardiovascular disease history (yes/no)	163/292	112/206	51/86	0.168	0.682
ECOG score (0/1-3)	125/330	86/232	39/98	0.097	0.755
History of chemotherapy (yes/no)	304/151	215/103	89/48	0.302	0.582
History of radiotherapy (yes/no)	172/283	114/204	58/79	1.714	0.191
TNM stage (III/IV)	277/178	192/126	85/52	0.112	0.738
Pathological subtype (squamous cell carcinoma/adenocarcinoma)	177/278	128/190	49/88	0.810	0.368
Differentiation degree (low differentiation/others)	226/229	151/167	75/62	2.019	0.155
EGFR mutation (yes/no)	122/333	82/236	40/97	0.568	0.451
EGFR-TKI (yes/no)	128/327	93/225	35/102	0.648	0.421
Anti-VEGF therapy (yes/no)	196/259	144/174	52/85	2.096	0.148
WBC (10^9/L)	11.76±2.93	11.74±2.96	11.80±2.86	0.194	0.846
Hb (g/L)	111.84±17.48	111.48±17.21	112.67±18.10	0.666	0.506
PLT (10^9/L)	216.00 [165.50, 269.00]	221.50 [166.00, 272.50]	211.00 [165.00, 254.00]	1.222	0.222
CRP (mg/L)	18.40 [12.84, 24.37]	18.43 [13.24, 24.31]	17.86 [12.49, 24.82]	0.202	0.840
IL-6 (pg/mL)	22.05 [15.87, 30.77]	21.89 [14.62, 30.62]	23.46 [17.59, 32.29]	1.276	0.202
ALB (g/L)	36.40 [33.80, 39.40]	36.30 [33.52, 39.68]	36.60 [34.20, 38.90]	0.021	0.983
LDH (U/L)	309.00 [259.20, 369.35]	308.60 [263.60, 369.85]	309.00 [248.20, 367.50]	0.705	0.481
CEA (ng/mL)	85.09±5.32	85.08±5.39	85.12±5.18	0.080	0.936
CYFRA21-1 (ng/mL)	30.98±9.05	31.07±9.16	30.76±8.81	-0.337	0.736

Note: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; WBC, white blood cell count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1.

Table 2. Comparison of baseline characteristics stratified by survival status

Variable	Training group (n = 318)		P	Validation group (n = 137)		P
	Surviving patients (n = 251)	Deceased patients (n = 67)		Surviving patients (n = 104)	Deceased patients (n = 33)	
Age (< 60/60-70/> 70)	73/144/34	21/35/11	0.724	30/58/16	6/20/7	0.429
Gender (male/female)	181/70	44/23	0.303	71/33	21/12	0.622
Ethnicity (Han/others)	235/16	60/7	0.380*	95/9	30/3	1.000*
BMI (< 23/23-25/> 25)	44/132/75	25/30/12	0.002	17/61/26	13/17/3	0.010
Smoking history (yes/no)	198/53	49/18	0.315	75/29	26/7	0.448
Alcohol consumption history (yes/no)	43/208	8/59	0.304	21/83	4/29	0.296
Comorbid COPD (yes/no)	99/152	43/24	< 0.001	35/69	26/7	< 0.001
Diabetes history (yes/no)	51/200	13/54	0.868	27/77	5/28	0.201
Cardiovascular disease history (yes/no)	91/160	21/46	0.455	40/64	11/22	0.595
ECOG score (0/1-3)	79/172	7/60	< 0.001	36/68	3/30	0.005
History of chemotherapy (yes/no)	189/62	26/41	< 0.001	78/26	11/22	< 0.001
History of radiotherapy (yes/no)	92/159	22/45	0.563	46/58	12/21	0.425
TNM stage (III/IV)	169/82	23/44	< 0.001	75/29	10/23	< 0.001
Pathological subtype (squamous cell carcinoma/adenocarcinoma)	98/153	30/37	0.395	37/67	12/21	0.935
Differentiation degree (low differentiation/others)	125/126	26/41	0.109	56/48	19/14	0.708
EGFR mutation (yes/no)	66/185	16/51	0.688	33/71	7/26	0.247
EGFR-TKI (yes/no)	76/175	17/50	0.433	27/77	8/25	0.844
Anti-VEGF therapy (yes/no)	114/137	30/37	0.925	42/62	10/23	0.298
WBC (10^9/L)	11.79±2.90	11.53±3.21	0.515	11.86±2.79	11.60±3.10	0.658
Hb (g/L)	111.43±17.73	111.69±15.25	0.913	113.74±18.90	109.30±15.11	0.221
PLT (10^9/L)	222.75±76.77	220.94±85.31	0.867	215.54±69.89	202.24±70.25	0.343
CRP (mg/L)	17.39±7.46	23.87±7.41	< 0.001	15.62 [11.66, 21.16]	26.19 [22.63, 31.96]	< 0.001
IL-6 (pg/mL)	19.15 [12.54, 25.49]	38.23 [31.33, 43.61]	< 0.001	21.58±8.54	33.89±11.06	< 0.001
ALB (g/L)	37.42±3.55	31.08±5.57	< 0.001	37.53±3.02	31.82±4.68	< 0.001
LDH (U/L)	292.35±69.27	399.55±82.02	< 0.001	284.22±69.88	395.86±89.74	< 0.001
CEA (ng/mL)	84.89±5.34	85.76±5.55	0.242	85.43±5.36	84.15±4.51	0.218
CYFRA21-1 (ng/mL)	30.94±8.94	31.56±10.00	0.623	31.07±8.81	29.78±8.90	0.464

Note: *Denotes the application of continuous calibration testing. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; WBC, white blood cell count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1.

Table 3. Logistic regression analysis of short-term mortality risk

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
CRP (mg/L)				
< 24.42	Reference		Reference	
≥ 24.42	5.443 (3.039-9.748)	< 0.001	6.285 (1.925-20.522)	0.002
IL-6 (pg/mL)				
< 28.705	Reference		Reference	
≥ 28.705	45.214 (19.274-106.068)	< 0.001	38.364 (10.822-135.996)	< 0.001
ALB (g/L)				
< 32.65	Reference		Reference	
≥ 32.65	0.045 (0.023-0.089)	< 0.001	0.073 (0.024-0.227)	< 0.001
LDH (U/L)				
< 357	Reference		Reference	
≥ 357	11.565 (6.212-21.530)	< 0.001	10.132 (3.317-30.947)	< 0.001
BMI				
< 23	Reference		Reference	
23-25	2.500 (1.330-4.699)	0.004	3.080 (0.840-11.295)	0.090
> 25	3.551 (1.624-7.766)	0.002	2.701 (0.612-11.924)	0.190
Comorbid COPD				
No	Reference		Reference	
Yes	2.751 (1.571-4.815)	< 0.001	1.876 (0.664-5.304)	0.235
ECOG score				
1-3	Reference		Reference	
0	0.254 (0.111-0.581)	0.001	0.214 (0.049-0.934)	0.040
History of chemotherapy				
Yes	Reference		Reference	
No	0.208 (0.118-0.367)	< 0.001	0.538 (0.177-1.633)	0.273
TNM stage				
IV	Reference		Reference	
III	0.254 (0.144-0.448)	< 0.001	0.503 (0.171-1.484)	0.214

Note: CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis; OR, odds ratio; CI, confidence interval.

Cox regression analysis of short-term mortality risk

Univariate and multivariate Cox regression analyses were conducted to identify factors associated with short-term mortality risk in aLC patients (**Table 5**). Univariate Cox regression analysis identified significant associations with mortality: CRP (≥ 24.42 mg/L, P < 0.001, HR = 4.367), IL-6 (≥ 28.705 pg/mL, P < 0.001, HR = 27.631), LDH (≥ 357 U/L, P < 0.001, HR = 8.395), COPD (P < 0.001, HR = 2.511), ECOG score 1-3 (P = 0.001, HR = 0.280), absence of chemotherapy history (P < 0.001, HR = 0.250), and TNM stage III (P < 0.001, HR = 0.286). Higher ALB (≥ 32.65 g/L, P < 0.001, HR = 0.084) and BMI (23-25 kg/m^2: P = 0.003, HR = 0.446; > 25 kg/m^2: P < 0.001, HR = 0.311) were associated with reduced mortality risk.

Multivariate Cox regression confirmed independent predictors of increased mortality risk: CRP (≥ 24.42 mg/L, P < 0.001, HR = 2.495), IL-6 (≥ 28.705 pg/mL, P < 0.001, HR = 12.627), LDH (≥ 357 U/L, P < 0.001, HR = 3.307), and COPD (P = 0.035, HR = 1.800). ALB remained an independent protective factor (≥ 32.65 g/L, P < 0.001, HR = 0.283). BMI, ECOG score, chemotherapy history, and TNM stage did not retain significance (all P > 0.05). Kaplan-Meier sur-

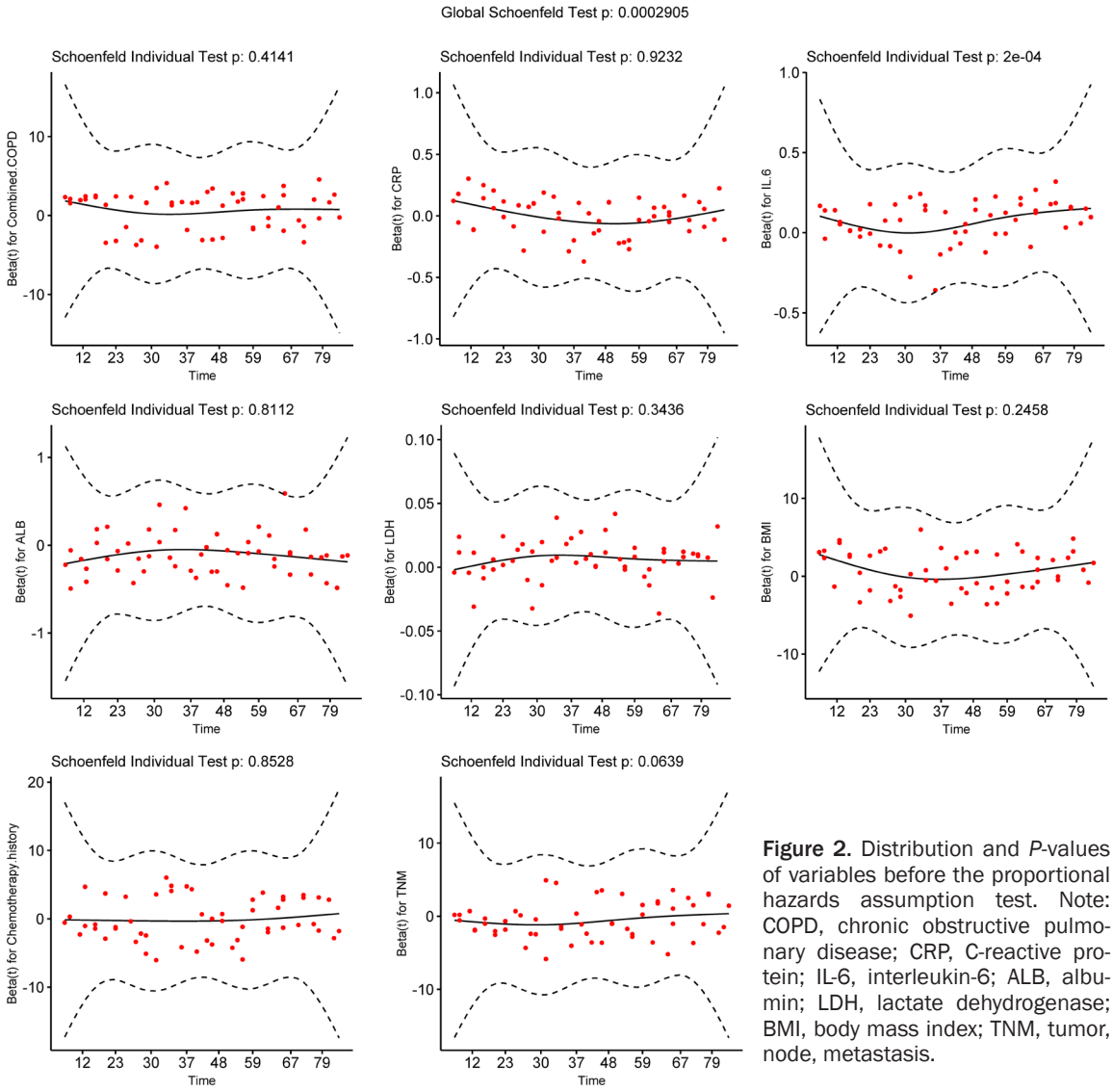

Figure 2. Distribution and *P*-values of variables before the proportional hazards assumption test. Note: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; BMI, body mass index; TNM, tumor, node, metastasis.

Table 4. Variable assignment criteria for the short-term mortality risk prediction model

Variable	Assignment content	VIF
CRP (mg/L)	≥ 24.42 = 1, < 24.42 = 0	1.1123
IL-6 (pg/mL)	≥ 28.705 = 1, < 28.705 = 0	1.0682
ALB (g/L)	≥ 32.65 = 1, < 32.65 = 0	1.3798
LDH (U/L)	≥ 357 = 1, < 357 = 0	1.1120
BMI	< 23 = 0, 23-25 = 1, > 25 = 2	1.5667
Comorbid COPD	Yes = 1, no = 0	1.1758
ECOG score	1-3 = 1, 0 = 0	1.1123
History of chemotherapy	Yes = 1, no = 0	1.4965
TNM stage	IV = 1, III = 0	1.2847

Note: CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis; VIF, variance inflation factor.

vival analysis with log-rank tests confirmed significant survival differences across these prognostic factors (all $P < 0.05$; **Figure 4**). These results establish CRP, IL-6, ALB, LDH, and COPD as robust and clinically relevant predictors for short-term mortality risk in aLC patients, supporting their integration into risk stratification models.

Development and validation of the nomogram for predicting short-term mortality risk

The study developed a nomogram integrating significant predictors -

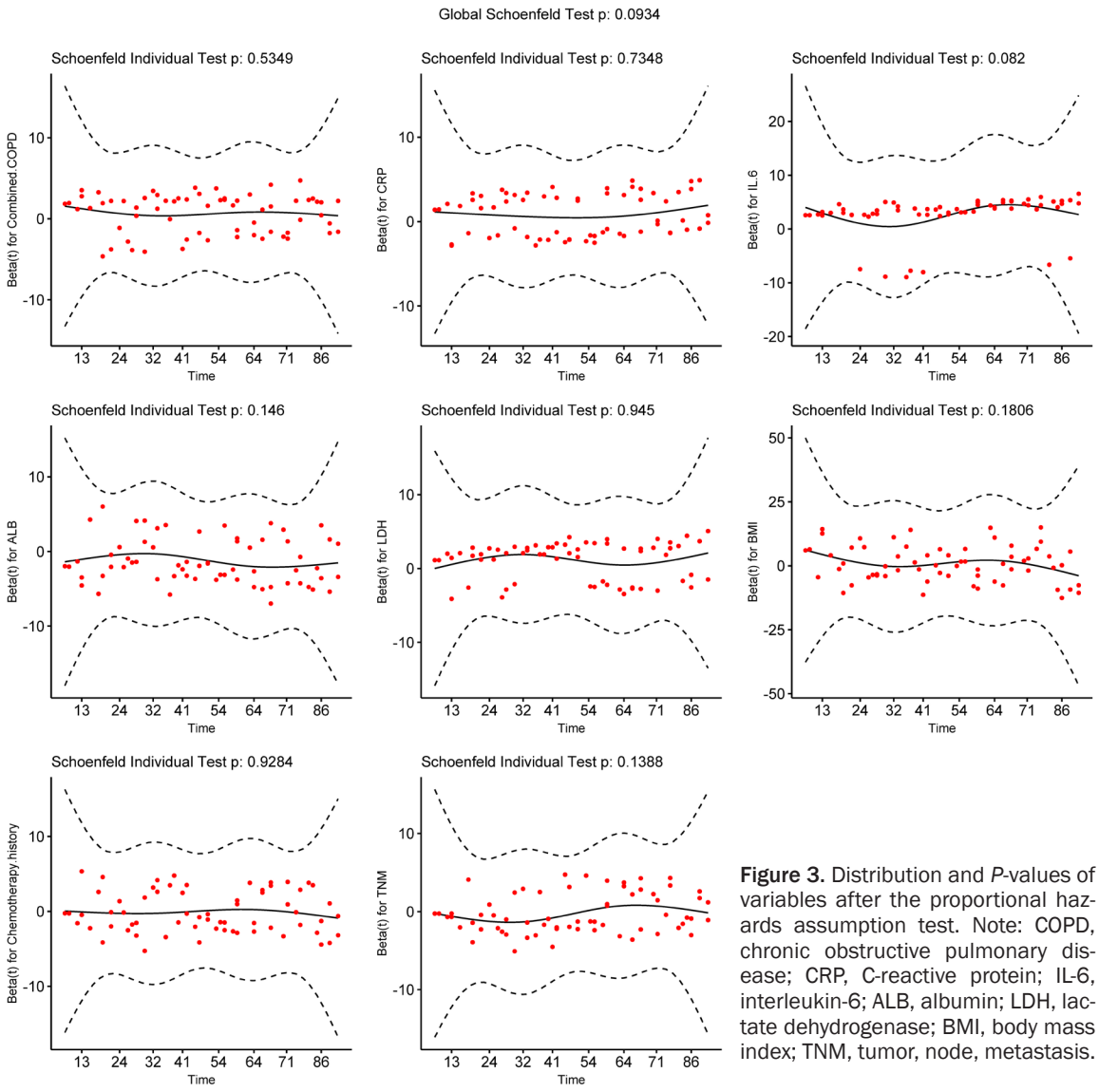

Figure 3. Distribution and *P*-values of variables after the proportional hazards assumption test. Note: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; BMI, body mass index; TNM, tumor, node, metastasis.

CRP ≥ 24.42 mg/L, IL-6 ≥ 28.705 pg/mL, ALB ≥ 32.65 g/L, and LDH ≥ 357 U/L - to estimate 30-, 60-, and 90-day survival probabilities in advanced lung cancer patients. Each variable contributes points proportionally based on its relative impact on short-term mortality, and total points are used to project survival probability. The nomogram demonstrates that elevated CRP, IL-6, and LDH levels are associated with increased mortality risk, while higher ALB levels predict improved survival. According to the nomogram (**Figure 5**), 30-day survival probability ranges from approximately 0.9 to 0.2, 60-day from 0.8 to 0.2, and 90-day from 0.8 to 0.2 across the point spectrum (**Figure 5**).

Time-dependent ROC analysis of short-term mortality risk

The predictive performance of the short-term mortality risk model was evaluated using time-dependent ROC curve analysis across three cohorts: the training cohort, validation cohort, and external validation cohort. In the training cohort, the model demonstrated high discriminative ability, with AUC values of 0.932, 0.930, and 0.962 at 30, 60, and 90 days, respectively, with optimal performance at the 90 days (**Figure 6A**). In the internal validation cohort, the model exhibited yielded AUCs of 0.894, 0.916, and 0.925 across the same time points, again peaking at 90 days (**Figure 6B**). The exter-

Table 5. Cox regression analysis of short-term mortality risk

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
CRP (mg/L)				
< 24.42	Reference		Reference	
≥ 24.42	4.367 (2.701-7.060)	< 0.001	2.495 (1.476-4.219)	< 0.001
IL-6 (pg/mL)				
< 28.705	Reference		Reference	
≥ 28.705	27.631 (12.600-60.593)	< 0.001	12.627 (5.506-28.960)	< 0.001
ALB (g/L)				
< 32.65	Reference		Reference	
≥ 32.65	0.084 (0.050-0.140)	< 0.001	0.283 (0.153-0.525)	< 0.001
LDH (U/L)				
< 357	Reference		Reference	
≥ 357	8.395 (4.926-14.305)	< 0.001	3.307 (1.856-5.891)	< 0.001
BMI				
< 23	Reference		Reference	
23-25	0.446 (0.262-0.758)	0.003	0.900 (0.490-1.654)	0.735
> 25	0.311 (0.156-0.620)	< 0.001	0.642 (0.296-1.395)	0.263
Comorbid COPD				
No	Reference		Reference	
Yes	2.511 (1.524-4.139)	< 0.001	1.800 (1.042-3.111)	0.035
ECOG score				
1-3	Reference		Reference	
0	0.280 (0.128-0.612)	0.001	0.438 (0.191-1.004)	0.051
History of chemotherapy				
Yes	Reference		Reference	
No	0.250 (0.153-0.409)	< 0.001	0.936 (0.506-1.731)	0.834
TNM stage				
IV	Reference		Reference	
III	0.286 (0.173-0.474)	< 0.001	0.759 (0.425-1.357)	0.353

Note: CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis; HR, hazard ratio.

nal validation cohort confirmed the model's robustness, with AUCs of 0.931, 0.884, and 0.950, respectively (**Figure 6C**). Across all three cohorts and time points, AUC values consistently exceeded 0.89, underscoring the model's strong predictive accuracy and generalizability. These findings support the model's utility in reliably stratifying short-term mortality risk in aLC patients and highlight its potential value in clinical decision-making.

DCA of short-term mortality risk

The clinical utility of the short-term mortality risk model was assessed using DCA across three cohorts: the training, validation, and external validation cohorts. In the training cohort (n = 318), the DCA curve for the risk score, derived from the Cox model (β = 1, HR = 2.718), demonstrated strong net benefit across a clinically relevant range of risk thresholds. The model exhibited excellent discriminative performance, with a C-index of 0.922 (95% CI: 0.907-0.937). Global tests further confirmed high statistical significance and robust predictive performance (likelihood ratio test: 211.87, $P < 2 \times 10^{-16}$; Wald test: 134.71, $P < 2 \times 10^{-16}$; Score test: 264.79, $P < 2 \times 10^{-16}$) (**Figure 7A**). Similarly, in the validation cohort (n = 137), the DCA curve for the risk predictor (β = -0.73293) showed favorable net benefit. The model maintained high discrimination, with a C-index of

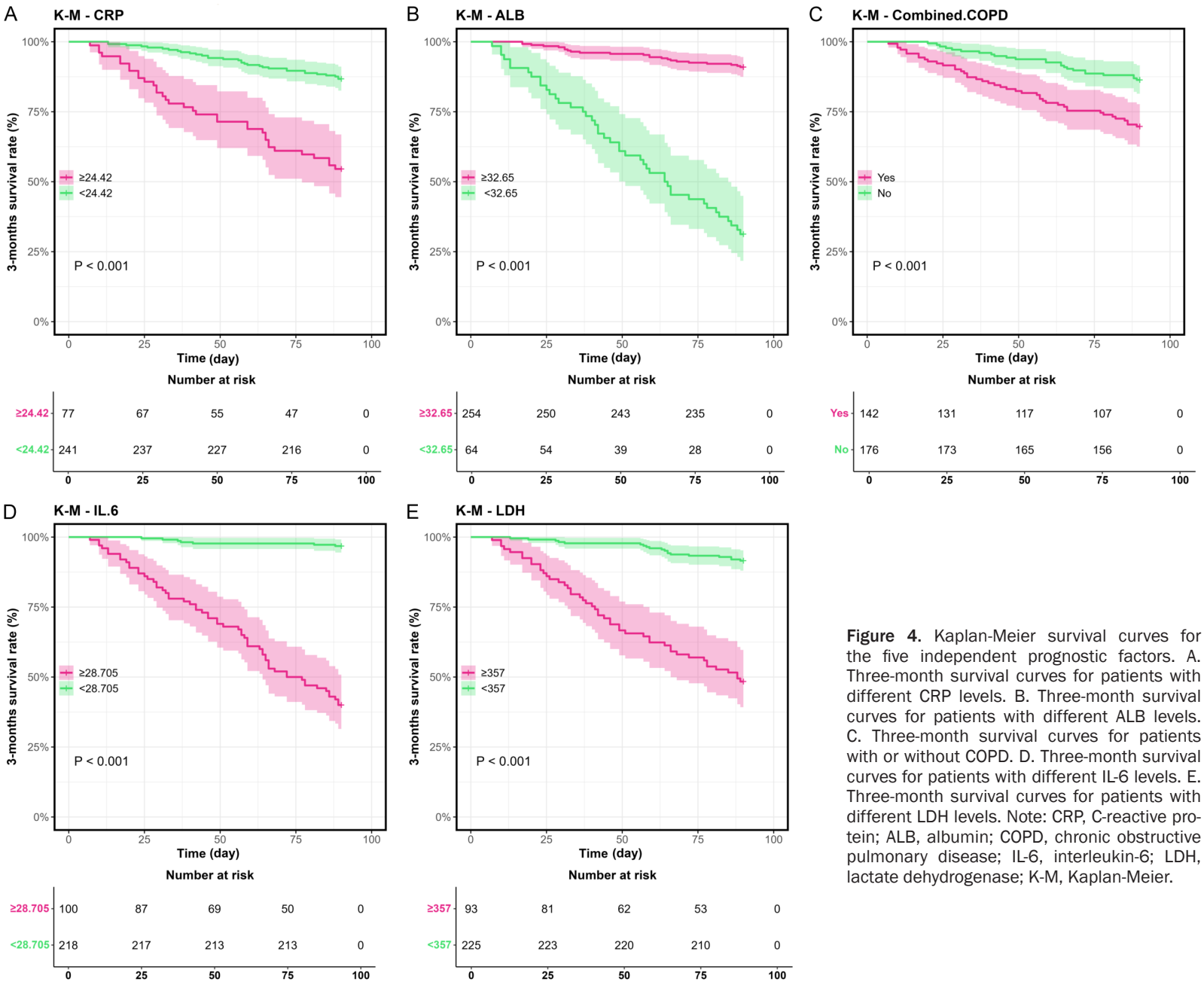

Figure 4. Kaplan-Meier survival curves for the five independent prognostic factors. A. Three-month survival curves for patients with different CRP levels. B. Three-month survival curves for patients with different ALB levels. C. Three-month survival curves for patients with or without COPD. D. Three-month survival curves for patients with different IL-6 levels. E. Three-month survival curves for patients with different LDH levels. Note: CRP, C-reactive protein; ALB, albumin; COPD, chronic obstructive pulmonary disease; IL-6, interleukin-6; LDH, lactate dehydrogenase; K-M, Kaplan-Meier.

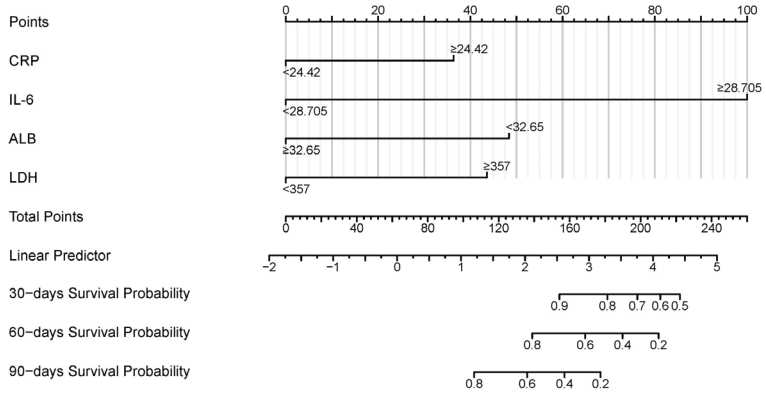

Figure 5. Nomogram for predicting short-term mortality risk. Note: CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase.

0.877 (95% CI: 0.852-0.902), and remained statistically significant across all global tests (likelihood ratio test: 72.29, $P < 2 \times 10^{-16}$; Wald test: 58.05, $P = 2.55 \times 10^{-14}$; Score test: 92.83, $P < 2 \times 10^{-16}$) (**Figure 7B**). When applied to the external validation cohort (n = 118), DCA revealed the model's clinical applicability. Discrimination remained robust, with a C-index of 0.88 (95% CI: 0.85-0.92), comparable to that observed in the other cohorts. The model's statistical significance was further validated (likelihood ratio test: 205.32, $P < 2 \times 10^{-16}$; Wald test: 128.47, $P < 2 \times 10^{-16}$; Score test: 251.64, $P < 2 \times 10^{-16}$) (**Figure 7C**).

Calibration curve analysis of short-term mortality risk

Model calibration was assessed across three independent cohorts: the training, validation, and external validation cohorts. In the training cohort, predicted and observed 30-, 60-, and 90-day survival probabilities showed strong agreement, with calibration curves closely aligned to the 45-degree reference line, indicating excellent calibration (**Figure 8A**). Similar concordance was observed in the validation and external validation cohorts, where predicted survival closely matched observed outcomes at all time points (**Figure 8B**, **8C**). This consistency across datasets supports the model's robustness and generalizability. The strong calibration performance demonstrates the model's reliability in estimating short-term mortality risk in aLC patients, reinforcing its potential utility in clinical decision-making.

Discussion

This study identified CRP, IL-6, ALB, LDH, and COPD as independent predictors of short-term mortality in aLC. Among inflammatory markers, both CRP and IL-6 play central roles in systemic inflammation in aLC [16]. CRP, an acute-phase reactant synthesized by hepatocytes in response to inflammatory stimuli, reflects the presence of a pro-inflammatory tumor microenvironment. Elevated CRP levels may accelerate disease progression by facilitating tumor proliferation, angiogenesis, and metastasis [17]. Recent studies have also highlighted the added prognostic value of inflammation-related biomarkers in predicting 30-day mortality [18]. Persistently high CRP levels are also closely associated with systemic organ failure and cancer-associated cachexia, both of which compromise treatment tolerance and survival capacity, thereby significantly elevating the 90-day mortality risk. In our nomogram model, elevated CRP was associated with an increased risk of short-term mortality. IL-6, a pleiotropic cytokine involved in inflammatory and immune regulatory pathways, has also been strongly linked to adverse clinical outcomes [19]. Liu et al. [20] demonstrated that elevated IL-6 levels significantly correlated with 30-day mortality in NSCLC patients undergoing palliative radiotherapy. In our model, elevated IL-6 was associated with tumor progression and systemic decline, underscoring its dominant role. Beyond its direct tumor-promoting effects, inflammation contributes to mortality indirectly by inducing organ dysfunction and reducing treatment responsiveness [21]. Collectively, CRP and IL-6 are reliable indicators of inflammatory burden and serve as important prognostic markers for early identification of short-term mortality in aLC patients.

In terms of nutrition, ALB, the primary protein synthesized by the liver, serves as a key biomarker of nutritional status and overall health [22]. Substantial evidence demonstrates that hypoalbuminemia is strongly associated with higher hospital readmission rates and elevated

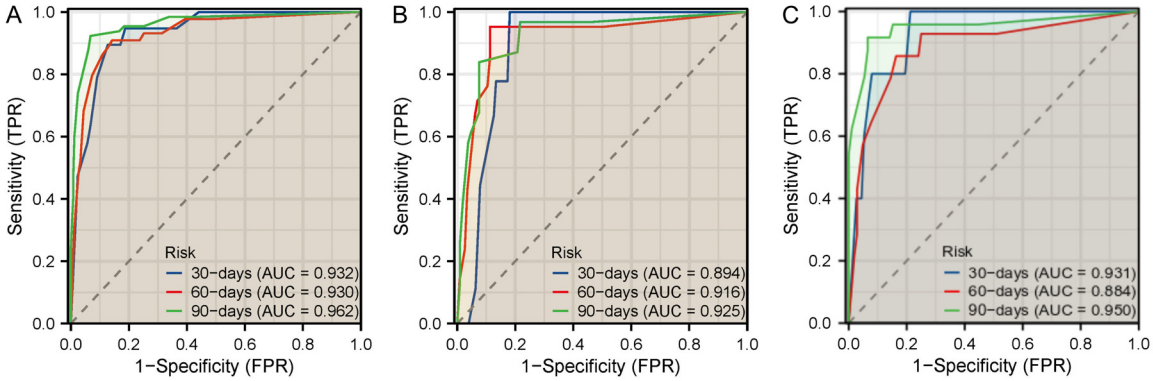

Figure 6. Time-dependent ROC curves of short-term mortality risk prediction. A. Time-dependent ROC curve for the training cohort. B. Time-dependent ROC curve for the validation cohort. C. Time-dependent ROC curve for the external validation cohort. Note: ROC, receiver operating characteristic; AUC, area under the curve; FPR, False Positive Rate.

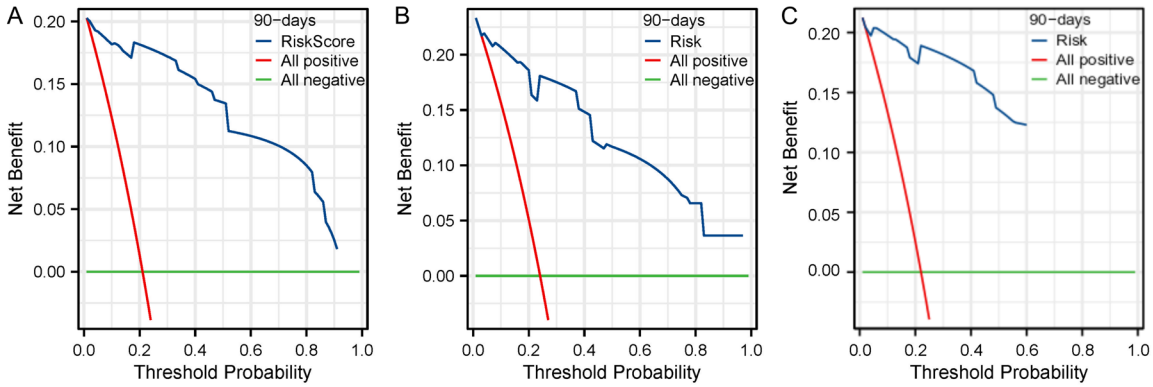

Figure 7. DCA of short-term mortality risk prediction. A. DCA curve for the training cohort. B. DCA curve for the validation cohort. C. DCA curve for the external validation cohort. Note: DCA, decision curve analysis.

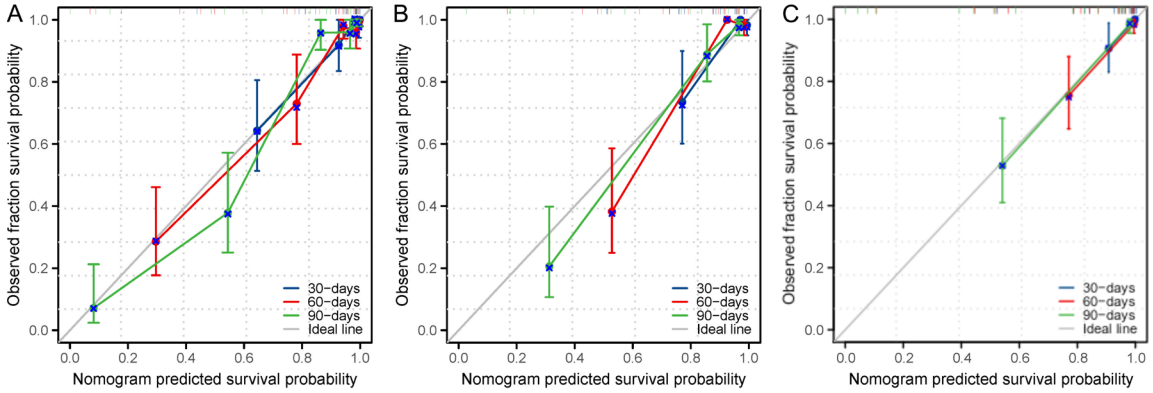

Figure 8. Calibration curves of short-term mortality risk prediction. A. Calibration curve for the training cohort. B. Calibration curve for the validation cohort. C. Calibration curve for the external validation cohort.

short-term mortality [23]. Reduced ALB levels not only signify malnutrition but may also indicate underlying systemic inflammation and hepatic dysfunction. This nutritional impairment is clinically relevant, as it contributes to cancer-associated cachexia, diminished treat-

ment tolerance, and heightened susceptibility to infections. In aLC patients, significant weight loss and anorexia frequently occur, and hypoalbuminemia further exacerbates immunosuppression and diminishes therapeutic response, ultimately resulting in poorer survival outcomes [24]. In our study, higher ALB levels were associated with a reduced risk of short-term mortality, indicating its protective role. This finding aligns with the systematic review by Ghanie et al., which established a significant association between nutritional status and 30-/90-day postoperative mortality in elderly patients undergoing hepatic resection [25]. These observations underscore the potential benefits of targeted nutritional support, including protein supplementation, in improving clinical condition, enhancing treatment tolerance, and ultimately prolonging survival.

In the context of cancer metabolism, LDH serves as a critical glycolytic enzyme, and elevated levels are strongly associated with increased cellular turnover, tissue damage, and high tumor burden [9]. Emerging evidence suggests that hepatic function parameters, particularly the aspartate aminotransferase to alanine aminotransferase ratio, hold prognostic value for short-term outcomes [26], underscoring the clinical importance of metabolic monitoring. Elevated LDH reflects both increased metabolic activity of malignant cells and the extent of necrosis, with progressively higher levels indicating greater tumor burden, larger lesion size, and more aggressive disease progression [27, 28]. Furthermore, increased LDH may signify a hypoxic tumor microenvironment and augmented glycolytic flux, both of which are established hallmarks of tumor aggressiveness. Clinical investigations have established [29] that preoperative and intraoperative metabolic parameters can effectively stratify 90-day mortality risk in patients with hepatocellular carcinoma. In our analysis, elevated LDH was associated with increased short-term mortality. Elevated LDH levels may substantially raise 90-day mortality risk by promoting accelerated tumor proliferation and contributing to systemic metabolic stress. As a robust biomarker of both tumor burden and metabolic dysregulation, LDH demonstrates considerable prognostic utility in predicting short-term mortality in oncological contexts.

COPD is a common comorbidity in patients with lung cancer, particularly those with smoking-related malignancies [30]. Beyond its detrimental effects on pulmonary function, COPD exacerbates lung cancer prognosis by amplifying systemic inflammation and elevating the risk of treatment-related complications [31]. Prior studies have demonstrated that comorbidities significantly influence short-term mortality outcomes in cancer patients [32]. The mechanisms through which COPD increases short-term mortality risk in aLC patients are multifactorial. COPD-induced airflow obstruction heightens the susceptibility to respiratory failure and pulmonary infections [33]. Chronic systemic inflammation, marked by elevated CRP and IL-6, may accelerate tumor progression and promote cancer-related cachexia [34]. Moreover, COPD is associated with higher risks of therapeutic complications, including radiation pneumonitis and chemotherapy-induced myelosuppression [35]. COPD frequently coexists with other comorbidities, collectively diminishing physiological reserve and treatment tolerance. Vesteghem et al. [36] demonstrated that incorporating comorbidities like COPD significantly enhances the accuracy of machine learning algorithms in predicting 30-day survival in aLC patients.

The proposed nomogram demonstrated superior predictive capability, with strong discrimination across all cohorts. AUC values ranged from 0.932 to 0.962 in the training cohort, 0.894 to 0.925 in the validation cohort, and 0.884 to 0.950 in the external validation cohort. The model also yielded high C-indices (0.922 and 0.877 for the training and validation cohorts, respectively). These findings align with findings from meta-analyses emphasizing the clinical importance of predictive accuracy [37], and are comparable to outcomes from multinational validation studies [38]. DCA revealed meaningful net clinical benefits across all cohorts, outperforming both “treat-all” and “treat-none” strategies. Calibration curves showed near-perfect alignment with the 45-degree reference line, confirming strong consistency between predicted and observed outcomes.

This study introduces an innovative approach to addressing the violation of the PH assumption by IL-6, through optimization of the Cox PH

model and construction of a multidimensional nomogram integrating inflammatory, nutritional, metabolic, and comorbidity-related factors. Clinically, this tool enables effective stratification of 90-day mortality risk, supporting early identification of high-risk patients and informing personalized interventions such as nutritional optimization, IL-6 targeted therapy, and comorbidity management, particularly in patients with COPD.

This study has several limitations. First, its single-center retrospective design may introduce selection bias and limit the representativeness of the findings. Second, the exclusion of emerging biomarkers such as circulating tumor DNA (ctDNA) may have restricted the model's comprehensiveness. Despite these constraints, the model demonstrated strong generalizabilit, as evidenced by its performance in external multicenter validation cohorts. Future prospective studies should aim to expand the scope of prognostic variables by incorporating novel biomarkers and dynamic monitoring indicators. Additionally, the development of user-friendly digital tools based on this model may further enhance its clinical applicability. Overall, the present findings establish a robust methodological foundation for precise risk stratification in aLC, supporting a potential shift from purely anti-tumor approaches to integrated, system-level therapeutic models.

Conclusion

This study identified CRP, IL-6, ALB, LDH, and COPD as independent predictors of 90-day mortality in aLC. The proposed nomogram demonstrated strong predictive performance across the training (AUC = 0.932-0.962), validation (AUC = 0.894-0.925), and external validation cohorts (AUC = 0.931-0.950), establishing its utility as a reliable tool for short-term risk stratification and individualized treatment planning. These findings provide a foundation for improving prognosis management in aLC within the framework of precision medicine.

Disclosure of conflict of interest

None.

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Table S1. Comparison of four characteristic variables among the training, verification, and external verification groups

Variable	Training group (n = 318)	Validation group (n = 137)	External validation group (n = 118)	Statistic	*p*_value
CRP (mg/L)	18.43 [13.24, 24.31]	17.86 [12.49, 24.82]	17.70 [13.32, 24.28]	0.201	0.904
IL-6 (pg/mL)	21.89 [14.62, 30.62]	23.46 [17.59, 32.29]	21.59 [13.14, 30.42]	2.054	0.358
ALB (g/L)	36.30 [33.52, 39.68]	36.60 [34.20, 38.90]	36.30 [34.02, 40.15]	0.473	0.789
LDH (U/L)	308.60 [263.60, 369.85]	309.00 [248.20, 367.50]	318.85 [266.82, 362.50]	0.667	0.716

Note: CRP, C-reactive protein; IL-6, interleukin-6; ALB, albumin; LDH, lactate dehydrogenase.