Prognostic value of nutritional and inflammatory biomarkers in patients with non-small cell lung cancer and bone metastasis: A retrospective study

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Abstract. To evaluate the prognostic significance of nutritional-inflammatory biomarkers in non-small cell lung cancer (NSCLC) patients with bone metastases. The present study constructed prognostic models using machine learning methods and assessed their performance, aiming to develop a clinically practical nomogram. A retrospective analysis of 233 patients with NSCLC and confirmed bone metastasis (BM) was conducted. The present study analyzed clinical and laboratory data, including 10 nutritional-inflammatory indicators. The present study used univariate and multivariate Cox regression, Least Absolute Shrinkage and Selection Operator (LASSO), Random Forest and extreme gradient boosting to select variables and construct Cox models. Performance was assessed via C-index, time-dependent area under the curve, Brier score, calibration curve and Akaike information criterion (AIC). A nomogram was developed based on the best-performing model. Multivariate Cox regression identified history of primary tumor surgery [hazard ratio (HR)=0.35; P<0.001], hemoglobin (HR=0.99; P=0.02), prognostic nutritional index (HR=0.98; P=0.002), CYFRA21-1 (HR=1.01; P<0.001), neuron-specific enolase (NSE; HR=1.03; P<0.001) and total cholesterol (HR=1.05; P=0.006) as independent prognostic factors. Individual nutritional-inflammatory biomarkers demonstrated limited discrimination (C-index range: 0.48-0.58). By contrast, integrated models incorporating these markers markedly improved predictive performance. The LASSO_yes model achieved the highest C-index (0.74; 95% CI: 0.70-0.77), with a 24-month area under the curve of 0.79 and the lowest Akaike information criterion (AIC; 1684.6). Based on the best-performing model, a prognostic nomogram was constructed to estimate individualized survival probabilities. Nutritional-inflammatory biomarkers provide incremental prognostic value when incorporated into integrated models. The LASSO-based nomogram may provide a potentially practical tool for individualized survival prediction in patients with NSCLC with BM, although external validation is still required before broader clinical application.

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most prevalent and deadly cancers globally, with distant metastasis being a major cause of mortality (1). Among metastatic sites, bone is the most common, occurring in 30-40% of patients with NSCLC and up to 60% present with bone metastases (BM) at initial diagnosis (2). BM markedly worsens prognosis, with a median survival time often <6 months, especially when accompanied by other metastases such as to the brain or liver (3). Skeletal-related events (SREs), including pain, pathological fractures, spinal cord compression and hypercalcemia, are frequent complications that further impair quality of life and survival (4,5). Despite advances in systemic therapy and bone-targeted agents such as bisphosphonates and denosumab, outcomes remain poor (6,7).

Chronic inflammation has been recognized as a hallmark of cancer, promoting tumor progression and metastasis through its effects on the tumor microenvironment (8). Tumor-associated neutrophils, for example, correlate with

poor prognosis in several cancers, including NSCLC (9). The duration and extent of inflammation are crucial; acute inflammation may be protective, while chronic inflammation is tumor-promoting (10,11). A review supports the role of inflammation in the development and progression of cancers such as lung and breast cancer (12). Nutritional status is another critical determinant of cancer outcomes. Hypoalbuminemia and cancer-related malnutrition are common in NSCLC and are associated with reduced treatment tolerance, impaired quality of life and shorter overall survival (OS) (13). Inflammation also contributes to cancer cachexia and sarcopenia, further exacerbating prognosis (14). Certain pathological features, such as squamous histology or poor differentiation, may intensify inflammation-driven nutritional decline (13). Recent studies have focused on composite inflammation and nutrition-based biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet-to-lymphocyte Ratio (PLR), systemic immune-inflammation index (SII), C-reactive protein-to-albumin ratio (CAR) and advanced lung cancer inflammation index (ALI), which can reflect the systemic inflammatory status and nutritional reserve of patients (15-17). These markers have shown prognostic value across various cancers, including NSCLC. Particularly in patients with NSCLC with BM, poor performance status, multiple bone lesions, elevated alkaline phosphatase (ALP)/lactate dehydrogenase (LDH), low albumin, and SREs have been linked to shorter overall survival (16,18). Furthermore, early inflammatory markers such as NLR and C-reactive protein (CRP) may predict response to immune checkpoint inhibitors (ICIs) (19).

However, studies specifically evaluating the prognostic value of these biomarkers in patients with NSCLC with BM are limited. Moreover, integrated models combining inflammatory and nutritional indices with clinical features remain lacking. Therefore, the present study aimed to develop and validate a prognostic model for patients with NSCLC with BM, incorporating routinely available serological and clinical parameters to improve prognostic stratification and guide personalized treatment strategies.

Materials and methods

Study design and patients. This retrospective cohort study included patients diagnosed with NSCLC and BM at Yunnan Cancer Hospital (Yunnan, China) between January 2017 and December 2019. Eligible patients met the following inclusion criteria: i) Pathologically confirmed NSCLC; ii) radiologically confirmed BM based on bone scintigraphy, computed tomography, or magnetic resonance imaging; iii) no history of other primary malignancies; and iv) availability of complete clinical and laboratory data at the time of BM diagnosis. Patients with small cell lung cancer, unclear primary tumor origin, severe chronic inflammatory or autoimmune diseases, active infections, liver cirrhosis, or incomplete data were excluded (Fig. 1).

According to the predefined inclusion criteria, a total of 233 patients who were newly diagnosed with NSCLC with BM at our institution were retrospectively enrolled. All cases were pathologically confirmed primary NSCLC. The cohort consisted of 141 males (60.5%) and 92 females (39.5%), with a median age of 59 years (range: 50-66 years). The median OS was 16 months (range: 6.0-50.0 months). A total of 160 patients (68.6%) were younger than 65 years, whereas 73 patients (31.3%) were aged 65 years or older.

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yunnan Cancer Hospital (approval no. KYLX2023-038). All patients signed a written informed consent form, which included consent to participate in the present study, use of their medical data for research purposes and the publication of anonymized findings.

Data collection. Medical records were accessed between January 2025 and March 2025 for the purpose of data collection and analysis. Clinical data were obtained from the hospital information system and included demographic characteristics, smoking history, Karnofsky Performance Status (KPS), pathological type, TNM stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system (20) treatment history before and after BM diagnosis and occurrence of skeletal-related events. Due to the retrospective nature of the study and changes in treatment strategies during the study period, detailed information regarding post-BM systemic therapies, including immunotherapy and targeted therapy regimens, was not consistently available for all patients.

Laboratory parameters collected at the time of BM diagnosis included complete blood counts, serum biochemistry, inflammatory markers, lipid profiles and tumor markers. Based on these data, 10 nutritional-inflammation indicators were calculated using established formulas: PLR, NLR, SII, PNI, CAR, C-reactive protein-to-lymphocyte ratio (CLR), ALI, body mass index (BMI), NLDA and HALP.

Outcome and follow-up. OS was defined as the interval from the diagnosis of BM to mortality from any cause or last follow-up. Survival status was obtained through medical records and telephone follow-up. Patients alive at the last follow-up were censored.

Statistical analysis. Continuous variables were assessed for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables were summarized as frequencies and percentages. Group comparisons were performed using the Student's t-test, Mann-Whitney U test, χ^2 test, or Fisher's exact test.

Univariate Cox proportional hazards regression was used to identify potential prognostic factors for OS. Variables with $P<0.05$ in univariate analysis were further evaluated using multivariate Cox regression with stepwise selection based on the Akaike information criterion. Optimal cut-off values for continuous variables were determined using maximally selected rank statistics, and Kaplan-Meier survival curves were generated with log-rank tests.

Lasso regression, Random Forest survival models, and extreme gradient boosting (XGBoost) were applied for variable selection. Based on selected variables, Cox regression models were constructed using bootstrap resampling to enhance robustness. Model performance was evaluated using the concordance index (C-index), time-dependent area under

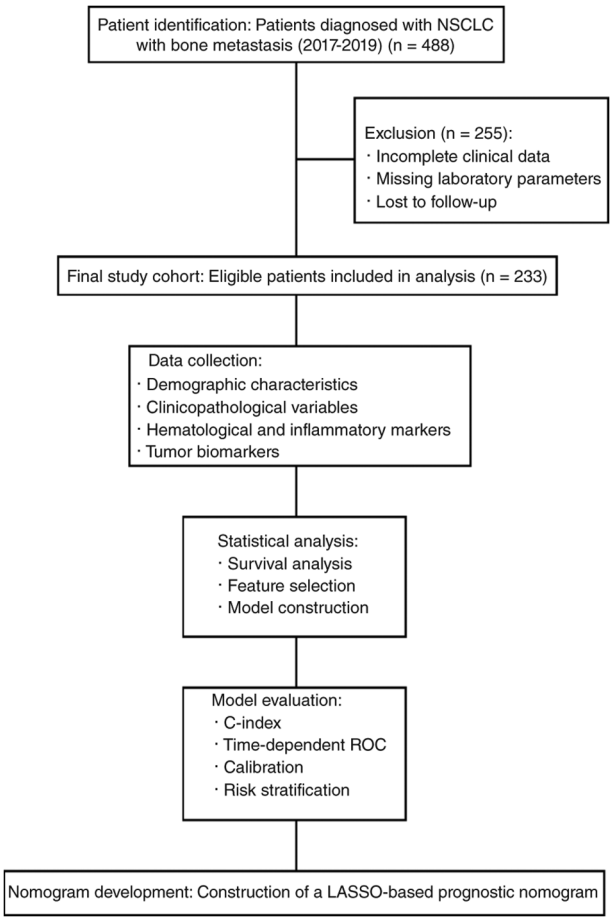

Figure 1. Study flow diagram. Overview of patient selection, data collection, statistical analysis and model development procedures. NSCLC, non-small cell lung cancer; LASSO, Least Absolute Shrinkage and Selection Operator.

the curve (AUC), Brier score, calibration curves, and AIC. Statistical analyses were performed using R software (version 4.3.1) and a two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of the study cohort. Comparative analysis of baseline characteristics between survival groups demonstrated significant differences in age, presence of intrapulmonary metastasis, bisphosphonate treatment after BM, prior surgical history, ALP, LDH, CLR and several tumor markers (all P<0.05). The proportion of elderly patients, males, squamous cell carcinoma, and both intrathoracic and extrathoracic metastases was higher in the deceased group compared with the surviving group. Detailed baseline characteristics are summarized in Tables I and SI.

Univariate and multivariate cox regression analyses of prognostic factors in patients with NSCLC and BM. Univariate Cox proportional hazards analysis identified multiple variables markedly associated with OS, including age, histological subtype, bisphosphonate treatment, history of primary tumor surgery, erythrocyte sedimentation rate, white blood cell count, hemoglobin (Hb), CA199, CYFRA21-1, NSE, D-dimer, fibrinogen, LDH, ALP, total cholesterol (TC), NLR, SII, PNI, CAR, CLR and CRP (all P<0.05).

After adjustment for potential confounders, multivariate Cox regression analysis demonstrated that history of primary tumor surgery was independently associated with improved OS (HR=0.35; 95% CI: 0.23-0.55; P<0.001). Higher Hb levels were also protective (HR=0.99; 95% CI: 0.986-0.999; P=0.02), as was higher PNI (HR=0.98; 95% CI: 0.97-0.99; P=0.002). By contrast, elevated CYFRA21-1 (HR=1.01; 95% CI: 1.00-1.01; P<0.001), NSE (HR=1.03; 95% CI: 1.02-1.05; P<0.001) and TC (HR=1.05; 95% CI: 1.01-1.08; P=0.006) were independently associated with increased mortality risk. Although several inflammatory markers, including NLR, SII, ALI, CAR, CLR, HALP, NLDA, PLR and BMI, were significant in univariate analysis, they did not retain statistical significance in the multivariate model. Detailed results are shown in Table SII and Fig. 2.

Survival impact and predictive performance of prognostic indicators. To further evaluate the prognostic relevance of the identified factors, optimal cutoff values for continuous variables were determined using the surv_cutpoint function (Fig. S1). Kaplan-Meier survival analyses demonstrated that patients with a history of primary tumor surgery had markedly prolonged OS compared with those without surgery (P<0.001). Higher Hb and PNI levels were associated with improved OS (P=0.004 and P=0.018, respectively), whereas elevated CYFRA21-1 and NSE levels were markedly associated with poorer survival (both P<0.001). No significant survival difference was observed between high and low TC groups (P=0.15; Fig. 3).

The discriminative ability of individual nutritional-inflammatory biomarkers was subsequently assessed using Harrell's concordance index (C-index). All single-marker models yielded C-index values below 0.60, ranging from 0.48-0.58 (mean: 0.54), indicating limited prognostic discrimination and performance only slightly above random prediction (Fig. S2A). Subgroup analyses revealed heterogeneity in predictive performance across clinical strata. Relatively higher C-index values were observed in patients with SREs (C=0.64), in those without surgery (C=0.59), and in male patients (C=0.60); however, these values remained below the threshold generally considered indicative of moderate predictive accuracy (C>0.70; Fig. S2B).

Time-dependent receiver operating characteristic (ROC) analysis was further performed to evaluate dynamic predictive performance. The AUC values of individual inflammatory indicator models demonstrated temporal variability (Fig. S2C). The predictive performance of PLR, NLR and CLR gradually improved over time. The SII model maintained relatively stable and comparatively higher AUC values at 12 and 24 months. By contrast, models such as ALI and BMI showed fluctuating performance across different time points. The AUC of PNI declined at 12 months and subsequently recovered at 24 months, indicating temporal variation in its prognostic sensitivity. Despite these dynamic changes, most individual biomarkers consistently exhibited relatively low AUC values across time points, suggesting limited standalone prognostic utility. An integrated prognostic model incorporating clinical and inflammatory variables was constructed.

Table I. Baseline clinicalcharacteristics of patients with non-small cell lung cancer and bone metastasis (n=233).

Characteristic	Total (n=233)	Survival (n=51)	Death (n=182)	P-value
Age, years	59.0 (50.0;66.0)	52.0 (47.0;59.5)	60.0 (52.0;67.0)	<0.001
Sex				1.00
Female, n (%)	92 (39.5)	20 (39.2)	72 (39.6)	
Male, n (%)	141 (60.5)	31 (60.8)	110 (60.4)	
T stage, n (%)				0.75
T1	102 (43.8)	22 (43.1)	80 (44.0)	
T2	92 (39.5)	20 (39.2)	72 (39.6)	
T3	20 (8.58)	3 (5.88)	17 (9.34)	
T4	8 (3.43)	2 (3.92)	6 (3.30)	
Tx	11 (4.72)	4 (7.84)	7 (3.85)	
N stage, n (%)				0.42
N1	44 (18.9)	5 (9.80)	39 (21.4)	
N2	78 (33.5)	20 (39.2)	58 (31.9)	
N3	34 (14.6)	8 (15.7)	26 (14.3)	
N0	66 (28.3)	16 (31.4)	50 (27.5)	
Nx	11 (4.72)	2 (3.92)	9 (4.95)	
Pathological type, n (%)				0.08
Adenocarcinoma	199 (85.4)	48 (94.1)	151 (83.0)	
Squamous cell carcinoma	34 (14.6)	3 (5.88)	31 (17.0)	
Lung metastasis, n (%)				<0.01
No	136 (58.4)	21 (41.2)	115 (63.2)	
Yes	97 (41.6)	30 (58.8)	67 (36.8)	
Extrathoracic metastasis, n (%)				0.44
Renal	6 (2.58)	1 (1.96)	5 (2.75)	
Brain	18 (7.73)	6 (11.8)	12 (6.59)	
Liver	16 (6.87)	2 (3.92)	14 (7.69)	
Lymph node	4 (1.72)	0 (0.00)	4 (2.20)	
Other	14 (6.01)	1 (1.96)	13 (7.14)	
None	175 (75.1)	41 (80.4)	134 (73.6)	
SREs, n (%)				0.71
No	108 (46.4)	21 (41.2)	87 (47.8)	
Yes	125 (53.6)	30 (58.8)	95 (52.2)	
KPS score, n (%)	90.0 (80.0;100)	90.0 (80.0;100)	90.0 (80.0;100)	0.19
89Sr therapy, n (%)				0.46
No	222 (95.3)	50 (98.0)	172 (94.5)	
Yes	11 (4.72)	1 (1.96)	10 (5.49)	
Bisphosphonates therapy, n (%)				0.03
No	191 (82.0)	36 (70.6)	155 (85.2)	
Yes	42 (18.0)	15 (29.4)	27 (14.8)	
Combined therapy, n (%)				1.00
No	229 (98.3)	50 (98.0)	179 (98.4)	
Yes	4 (1.72)	1 (1.96)	3 (1.65)	
Primary surgery, n (%)				<0.01
No	189 (81.1)	33 (64.7)	156 (85.7)	
Yes	44 (18.9)	18 (35.3)	26 (14.3)	
Chemotherapy, n (%)				0.83
No	183 (78.5)	39 (76.5)	144 (79.1)	
Yes	50 (21.5)	12 (23.5)	38 (20.9)	

Table I. Continued.

Characteristic	Total (n=233)	Survival (n=51)	Death (n=182)	P-value
Radiotherapy, n (%)				1.00
No	222 (95.3)	49 (96.1)	173 (95.1)	
Yes	11 (4.72)	2 (3.92)	9 (4.95)	
Targeted therapy, n (%)				0.26
No	214 (91.8)	49 (96.1)	165 (90.7)	
Yes	19 (8.15)	2 (3.92)	17 (9.34)	
Immunotherapy, n (%)				1.00
No	233 (100)	51 (100)	182 (100)	
Smoking history, n (%)				0.86
No	169 (72.5)	36 (70.6)	133 (73.1)	
Yes	64 (27.5)	15 (29.4)	49 (26.9)	

Continuous variables are presented as median (interquartile range, IQR), expressed as median (P25; P75). SREs, skeletal-related events; KPS, Karnofsky performance status.

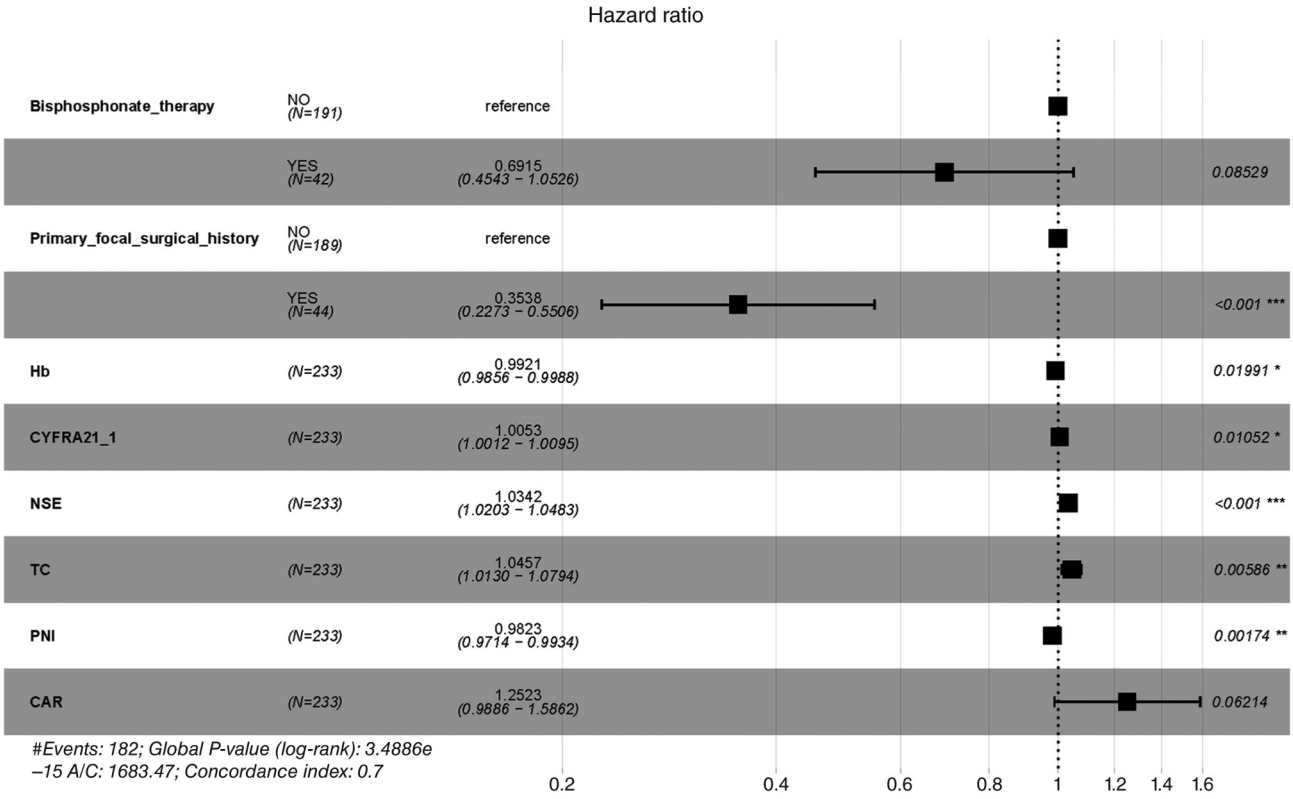

Figure 2. Forest plot of multivariable Cox regression analysis for overall survival in patients with NSCLC with bone metastasis. *P<0.05; **P<0.01; ***P<0.001. NSCLC, non-small cell lung cancer; AIC, Akaike information criterion.

Development and validation of integrated prognostic models

Feature selection. To construct a comprehensive prognostic model for patients with NSCLC with BM, multiple clinical and laboratory variables were considered, including demographic characteristics, routine hematological parameters, tumor biomarkers and nutritional-inflammatory indicators. Feature selection was performed using three machine learning approaches, LASSO, Random Forest (RF) and XGBoost. Multicollinearity among selected variables was assessed using variance inflation factor (VIF), with VIF <10 indicating no significant collinearity. The variables selected by each method are shown in Fig. S3. Based on the selected features, two categories of multivariable Cox regression models were developed to evaluate the incremental prognostic value of nutritional-inflammatory indicators. One set of models incorporated these indicators (Lasso_yes, RF_yes, XGBoost_yes), whereas the other excluded them (Lasso_no, RF_no, XGBoost_no).

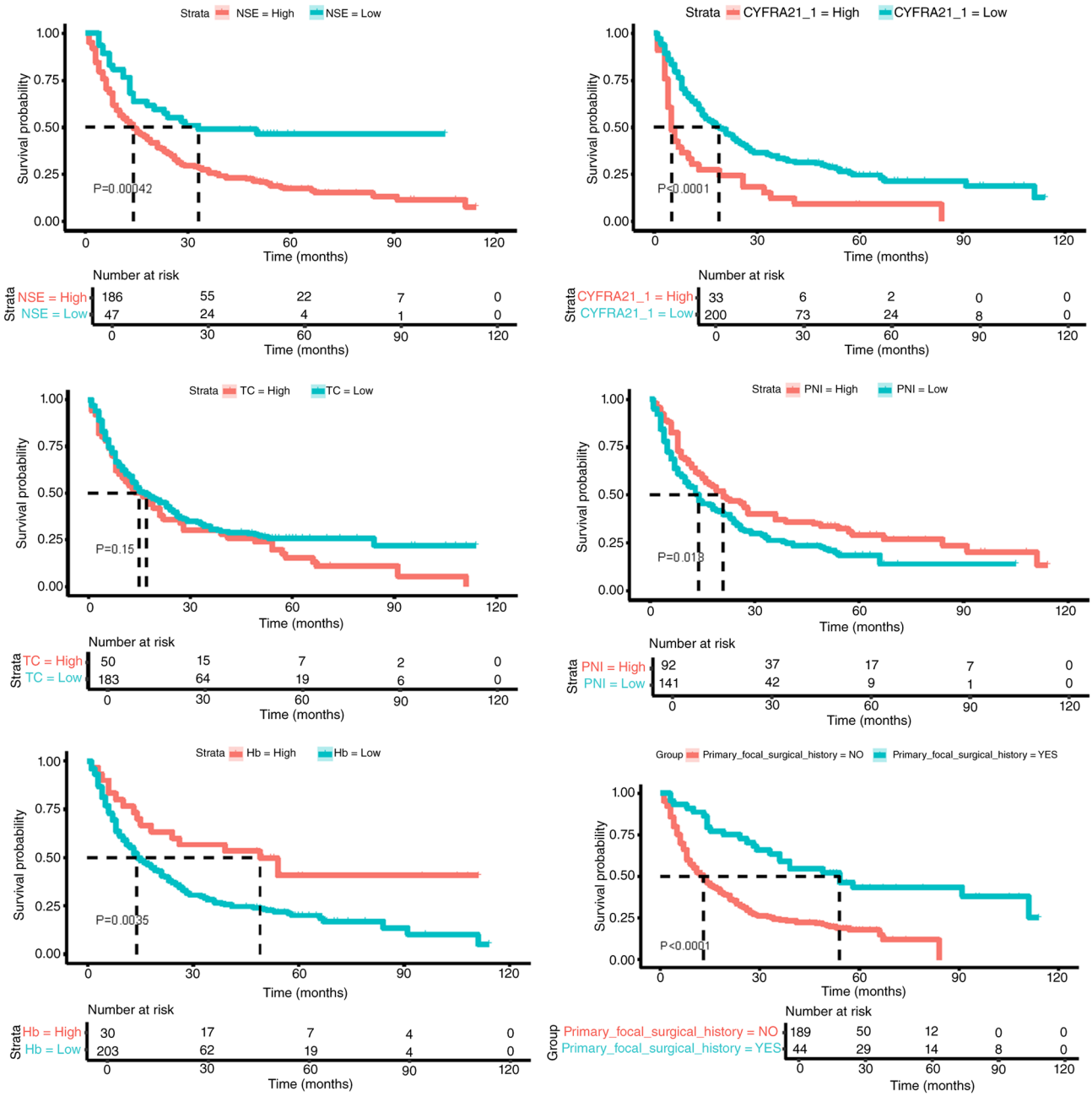

Figure 3. Kaplan-Meier survival curves for overall survival according to independent prognostic factors, including NSE, CYFRA21-1, TC, PNI, Hb, and primary focal surgical history in patients with NSCLC with bone metastasis. NSE, neuron-specific enolase; TC, total cholesterol; PNI, prognostic nutritional index; Hb, hemoglobin; NSCLC, non-small cell lung cancer.

Model performance comparison. The predictive performance of the six models was comprehensively evaluated using C-index, time-dependent AUC, Brier score, calibration analysis, risk stratification and AIC. The C-index analysis demonstrated that models incorporating nutritional-inflammatory indicators consistently outperformed those without these variables. The Lasso_yes model achieved the highest discriminative ability (C-index=0.74; 95% CI: 0.70-0.77), followed by XGBoost_yes (0.72; 95% CI: 0.68-0.76) and RF_yes (0.68; 95% CI: 0.62-0.72). All corresponding models without nutritional-inflammatory indicators showed significantly lower C-index values (all P<0.05; Fig. 4). Time-dependent ROC analysis further confirmed the superior performance of models incorporating nutritional-inflammatory factors. At 24 months, the Lasso_yes model achieved the highest AUC (0.79; 95% CI: 0.75-0.87), followed by XGBoost_yes (0.77; 95% CI: 0.73-0.85; Fig. 5). Models without nutritional-inflammatory indicators demonstrated consistently lower AUC values across all time points. Risk score and its association with survival time are shown in Fig. S4. Brier score analysis showed that models including nutritional-inflammatory indicators generally yielded lower prediction error, particularly in mid- and long-term survival prediction (Table SIII; Fig. S5). Calibration plots demonstrated good agreement between predicted and observed survival probabilities, with Lasso_yes exhibiting the most favorable calibration performance (Table SIV; Fig. 6). The numbers of patients at risk at 1, 3 and 5 years were 138 (59.2%), 74 (31.8%), and 26 (11.2%),

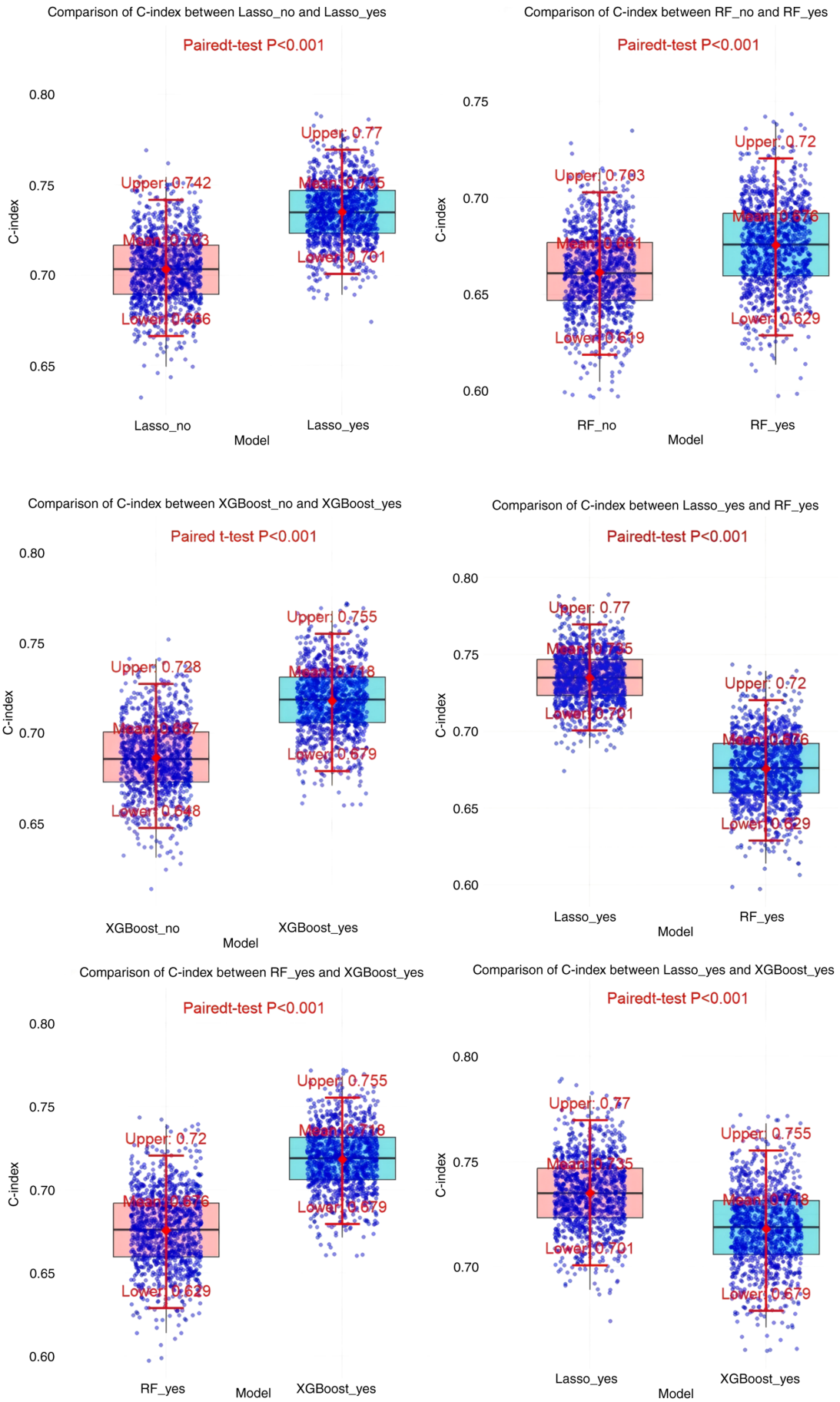

Figure 4. Pairwise comparison of C-index values among prognostic models with and without nutritional-inflammatory markers for predicting overall survival in patients with NSCLC with bone metastasis. Statistical significance was assessed using paired t-tests. C-index, concordance index; NSCLC, non-small cell lung cancer; RF, Random Forest; XGBoost, extreme gradient boosting.

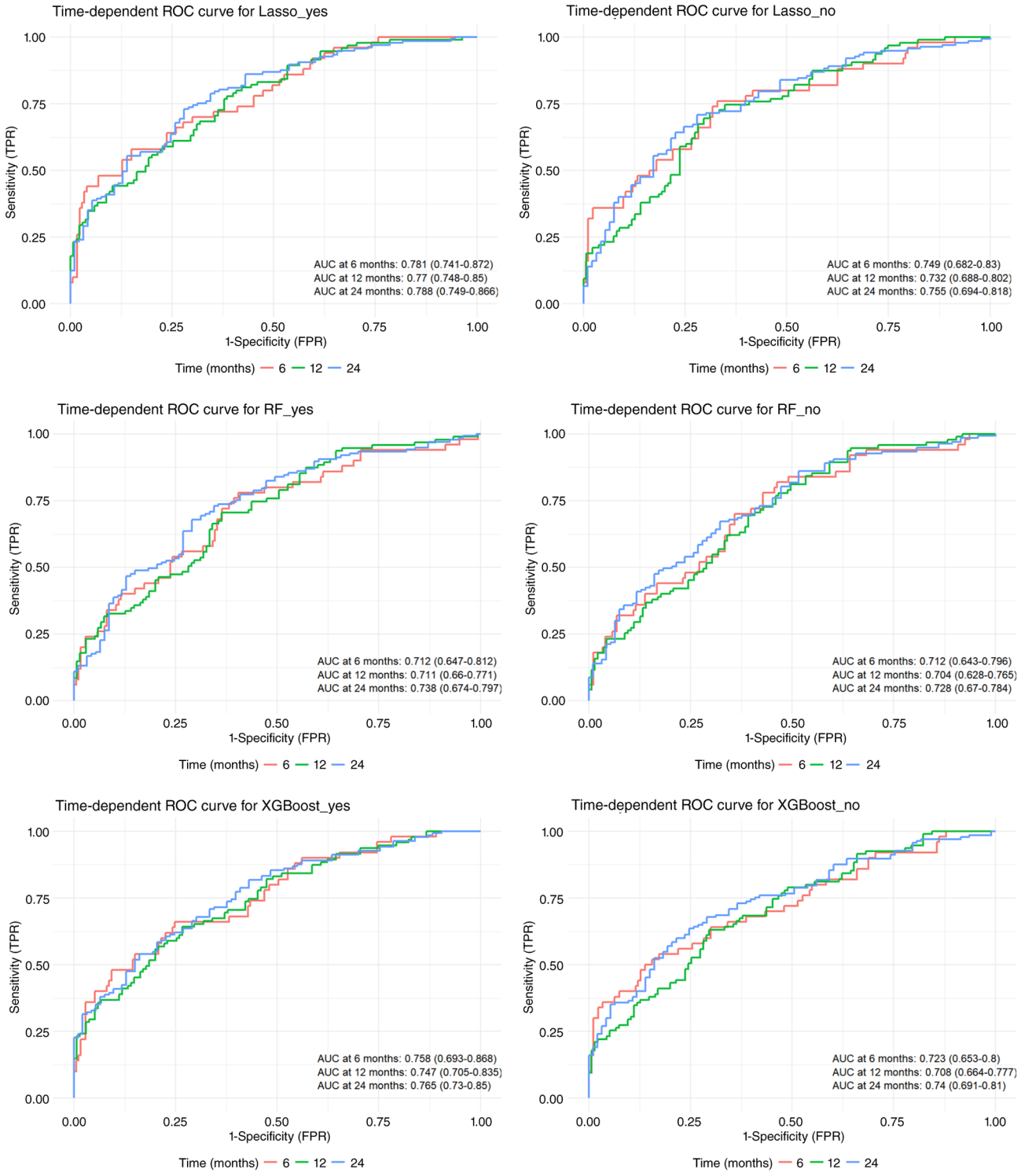

Figure 5. Time-dependent ROC curves of prognostic models with and without nutritional-inflammatory markers for predicting overall survival at 6, 12, and 24 months in patients with NSCLC with bone metastasis. ROC, receiver operating characteristic; NSCLC, non-small cell lung cancer; LASSO, Least Absolute Shrinkage and Selection Operator; RF, Random Forest; XGBoost, extreme gradient boosting.

respectively. As only 26 patients (11.2%) remained at risk at 5 years, long-term survival predictions should be interpreted with caution. Risk stratification analysis revealed that all models markedly distinguished high-risk from low-risk patients (log-rank P<0.05). However, models incorporating nutritional-inflammatory indicators demonstrated more pronounced separation of Kaplan-Meier survival curves, particularly the Lasso_yes model (Fig. 7). Among all models, the Lasso_yes model achieved the lowest AIC value (1,684.6), indicating superior goodness-of-fit (Fig. S6).

Nomogram development. Based on the superior overall performance of the Lasso_yes model, a final prognostic nomogram was developed to predict overall survival in patients with NSCLC with BM. The nomogram integrated selected clinical and laboratory variables into a quantitative scoring system,

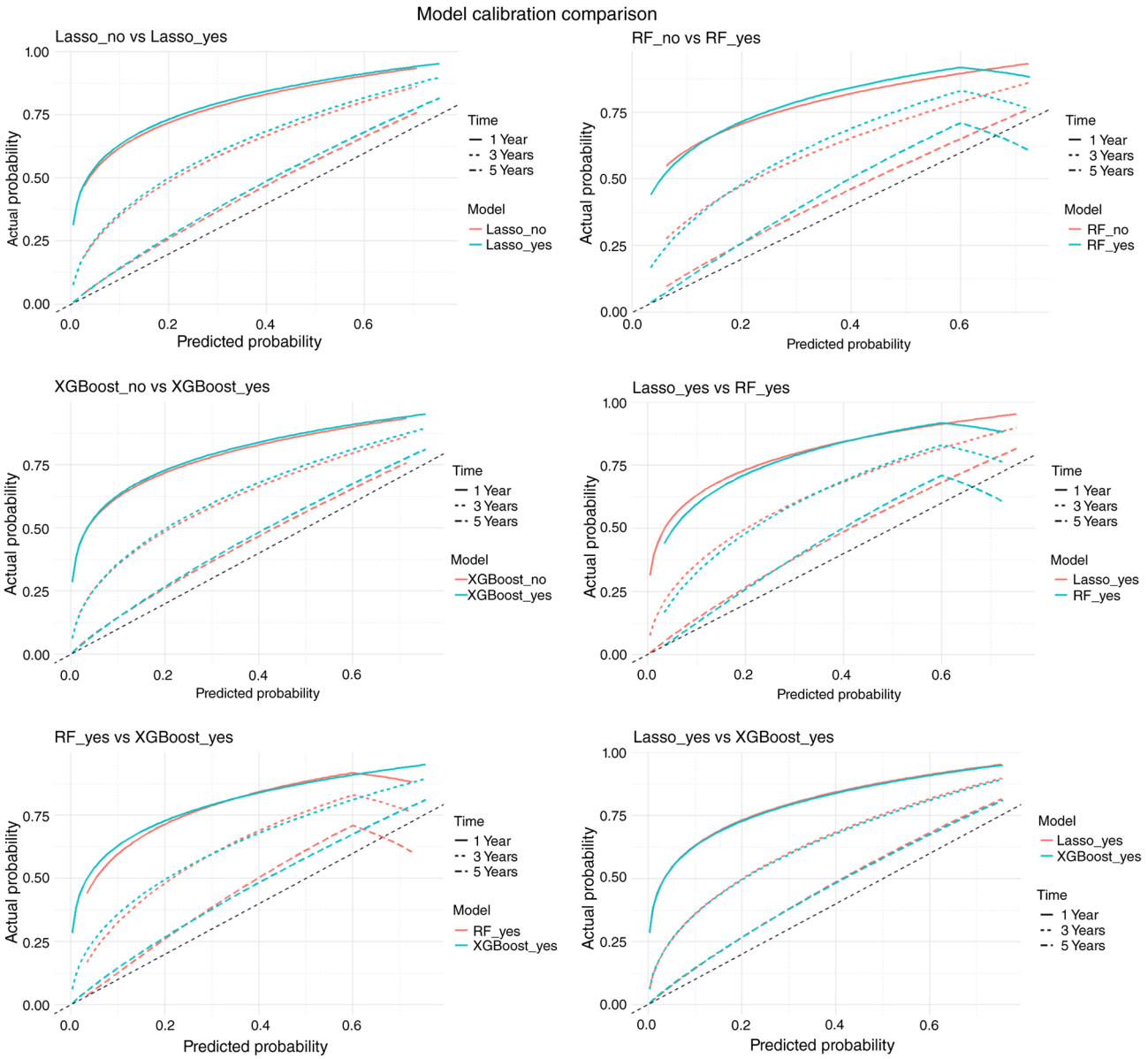

Figure 6. Comparison of calibration curves for predicting overall survival at 1, 3, and 5 years between models with and without nutritional-inflammatory markers in patients with NSCLC and bone metastasis. NSCLC, non-small cell lung cancer; LASSO, Least Absolute Shrinkage and Selection Operator; RF, Random Forest; XGBoost, extreme gradient boosting.

providing individualized survival probability estimates for clinical application (Fig. 8).

Discussion

Principal findings. The present study systematically evaluated the prognostic value of nutritional-inflammatory biomarkers in patients with NSCLC with BM and developed integrated prognostic models incorporating clinical and laboratory variables. The findings can be summarized as follows: i) Several nutritional-inflammatory markers were markedly associated with OS, although most lacked independent predictive value when analyzed individually; ii) the prognostic performance of single inflammatory markers was limited and varied across time points and clinical subgroups; iii) integrated models incorporating nutritional-inflammatory indicators markedly improved predictive performance compared with models excluding these markers; and iv) a LASSO-based Cox model demonstrated the best overall discrimination and calibration and was used to construct a prognostic nomogram.

Nutritional-inflammatory biomarkers and prognosis. Traditional laboratory parameters remain widely accessible and cost-effective tools in oncology practice. In contrast to molecular profiling, these biomarkers reflect systemic host responses, including inflammation, nutritional status, and immune function. However, data regarding their prognostic relevance in patients with NSCLC with BM remain limited.

PNI, which integrates serum albumin and lymphocyte count, reflects the interaction between nutritional status and immune competence. In the present study, higher PNI was independently associated with improved survival, consistent with previous reports in advanced NSCLC (21,22).

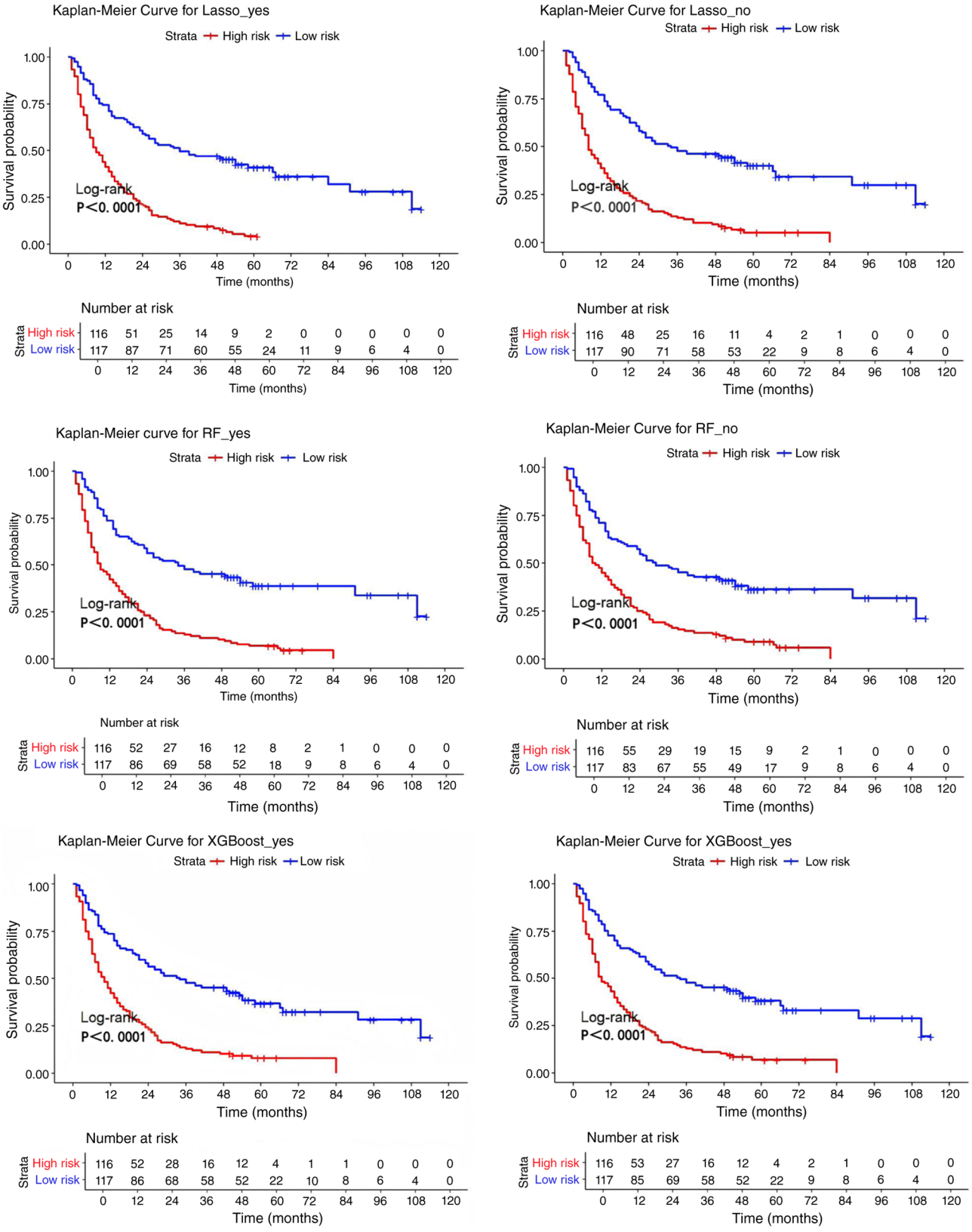

Figure 7. Kaplan-Meier survival curves for high- and low-risk groups stratified by six prognostic models, with statistical significance assessed using the log-rank test. LASSO, Least Absolute Shrinkage and Selection Operator; RF, Random Forest; XGBoost, extreme gradient boosting.

Hypoalbuminemia may indicate protein-energy malnutrition and systemic inflammation (14), whereas lymphopenia reflects impaired antitumor immune surveillance (23,24). These factors may collectively contribute to disease progression in metastatic settings. Hb, although not a classical inflammatory marker, also emerged as an independent prognostic factor (25). Cancer-related anemia is common in advanced lung cancer and may promote tumor progression

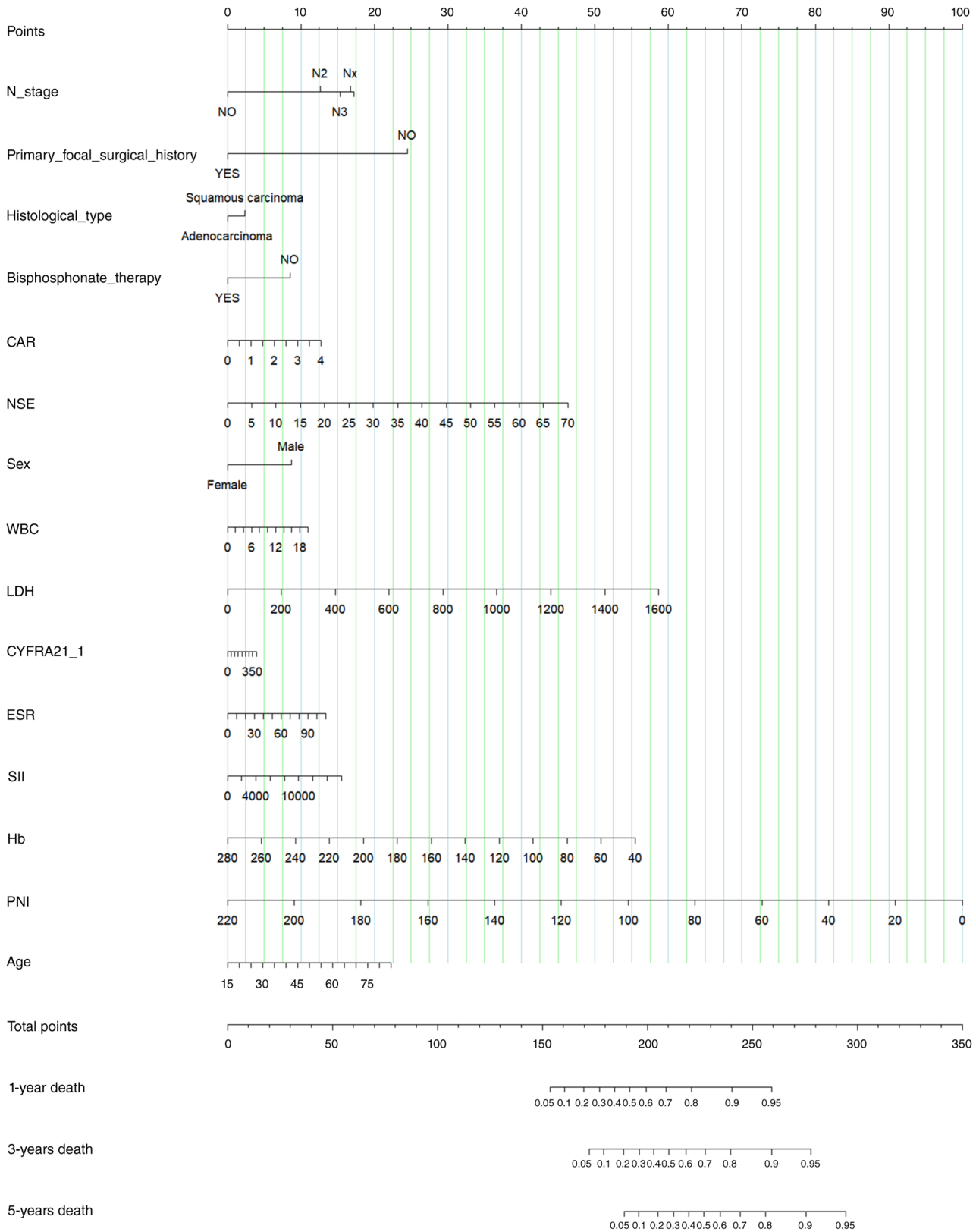

Figure 8. LASSO-based prognostic nomogram for predicting 1-, 3-, and 5-year death probability in patients with NSCLC with bone metastasis. The nomogram was developed based on the LASSO-selected multivariable Cox regression model. LASSO, Least Absolute Shrinkage and Selection Operator; NSCLC, non-small cell lung cancer; CAR, C-reactive protein-to-albumin ratio; NSE, neuron-specific enolase; WBC, white blood cell count; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; Hb, hemoglobin; PNI, prognostic nutritional index.

through hypoxia-related pathways (26,27). The findings of the present study extend previous evidence by demonstrating its prognostic significance specifically in patients with BM.

Several inflammatory indices, including SII and NLR, were markedly associated with OS in univariate analysis but did not retain independent significance in multivariable

models. This suggested that their prognostic contribution may be partially mediated through other clinical or laboratory factors. Importantly, markers such as CRP, CAR and CLR were also associated with survival, highlighting the relevance of systemic inflammation in this patient population.

Tumor biology and host metabolic integration. Traditional tumor biomarkers, including CYFRA21-1 and NSE, were independently associated with survival, emphasizing the importance of tumor burden-related biological activity. Additionally, metabolic indicators such as total cholesterol demonstrated independent prognostic relevance, suggesting that tumor biology and host metabolic status jointly influence survival outcomes in patients with NSCLC with BM. These findings support the concept that prognosis in metastatic lung cancer is determined not only by tumor characteristics but also by systemic host responses.

Temporal and subgroup heterogeneity of single markers. Time-dependent ROC analysis demonstrated dynamic changes in predictive performance over follow-up. Certain markers, such as PLR and CLR, showed gradual improvement in discrimination at later time points, whereas others exhibited fluctuating performance. Subgroup analyses revealed heterogeneity in predictive ability across clinical strata, including patients with SREs and those without prior surgery.

Although the absolute discrimination of individual markers remained modest, these findings suggest that the prognostic impact of inflammatory and nutritional parameters may vary according to disease stage, treatment history and host condition. However, the relatively low C-index values indicate that single biomarkers alone are insufficient for accurate risk stratification.

Incremental value of integrated modeling. To address the limited performance of individual markers, the present study constructed integrated prognostic models using LASSO, random forest, and XGBoost for feature selection. Models incorporating nutritional-inflammatory indicators consistently demonstrated superior discrimination, calibration, and overall performance compared with models excluding these variables.

Among all models, the LASSO-based Cox model achieved the highest C-index and lowest AIC, indicating optimal balance between predictive accuracy and model complexity. Based on this model, a prognostic nomogram was developed to facilitate individualized survival estimation in clinical practice.

These findings suggest that nutritional-inflammatory markers provide incremental prognostic information when integrated with tumor-related and clinical variables, rather than functioning as standalone predictors.

Strengths and limitations. The present study had several strengths, including comprehensive evaluation of multiple inflammatory markers, application of machine learning-based feature selection methods and systematic comparison of models with and without nutritional-inflammatory indicators.

However, several limitations should be acknowledged. First, this was a single-center retrospective study with a relatively limited sample size, which may restrict the generalizability of the findings and introduce potential selection bias. In addition, the proposed nomogram has not yet been externally validated in independent cohorts. Therefore, the current model should be considered a preliminary prognostic tool and further multicenter prospective validation is required before broader clinical application. Second, progression-free survival was not included as a formal endpoint because retrospective progression assessment was considered insufficiently reliable owing to irregular imaging follow-up and incomplete documentation. Therefore, only OS was analyzed in the present study. Third, treatment heterogeneity may have influenced survival outcomes. During the study period (2017-2019), the clinical use of targeted therapy and immunotherapy evolved substantially, but detailed treatment records after BM diagnosis were incomplete and therefore could not be fully adjusted for in the current analysis. Finally, certain bone metabolism-related biochemical markers were not included in the dataset.

In addition, although multiple machine learning-based feature selection methods and bootstrap resampling were applied to reduce overfitting risk, the relatively limited sample size compared with the number of candidate variables may still introduce model instability. Therefore, the predictive performance of the current models should be interpreted cautiously until validated in independent external cohorts.

Future studies integrating multicenter data, longitudinal biomarker monitoring and molecular profiling may further refine prognostic stratification and improve clinical applicability.

In conclusion, although individual nutritional-inflammatory markers demonstrate limited standalone predictive performance, they provide meaningful incremental value when incorporated into integrated prognostic models. A LASSO-based nomogram combining clinical, tumor-related, and host inflammatory parameters offers a practical tool for individualized survival prediction in patients with NSCLC with BM. Further external validation is warranted to confirm its clinical utility.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YC and LZ conceived and designed the present study. SW performed statistical analysis and machine learning modeling. HZ, YL and YB were responsible for data collection and preprocessing. ZD contributed to clinical data interpretation, methodological supervision and validation of the analytical framework. CL contributed to the methodology, validation of the analytical framework and interpretation of the data. SY contributed to study conception and overall supervision, secured funding support, and critically revised the manuscript. All authors contributed to manuscript revision. YC, LZ and SW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yunnan Cancer Hospital (approval number: KYLX2023-038). All patients signed a written informed consent form, which included consent to participate in the present study, use of their medical data for research purposes and the publication of anonymized findings.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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