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Original Article

Prognostic value of the lactate dehydrogenase-to-albumin ratio (LAR) combined with clinicopathological indicators for predicting outcomes in locally advanced cervical cancer undergoing concurrent chemoradiotherapy: a retrospective cohort study and nomogram development

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Abstract: This two-center retrospective study aimed to evaluate the prognostic value of the lactate dehydrogenase-to-albumin ratio (LAR) combined with clinicopathological variables for predicting short-term therapeutic response and overall survival (OS) in patients with locally advanced cervical cancer (LACC) undergoing concurrent chemoradiotherapy (CCRT), and to develop and validate dual nomogram models. A total of 622 patients treated with standard CCRT between January 2018 and June 2022 were enrolled. Patients from the Third Affiliated Hospital of Guangzhou Medical University were randomly divided into a training cohort (n = 373) and an internal validation cohort (n = 124) at a ratio of 0.75:0.25, while an external validation cohort (n = 125) was obtained from Jinshazhou Hospital of Guangzhou University of Chinese Medicine during the same period. Optimal cutoff values for squamous cell carcinoma antigen (SCCA), albumin (ALB), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin-to-fibrinogen ratio (AFR), and LAR were determined using the surv_cutpoint function in the training cohort and uniformly applied to the validation cohorts. Logistic regression was used to identify predictors of treatment response, and Cox proportional hazards regression was applied to construct nomograms predicting 1-, 2-, and 3-year OS. Model performance was assessed using receiver operating characteristic (ROC) curves, concordance index (C-index), Hosmer-Lemeshow test, calibration curves, and decision curve analysis (DCA), with internal validation performed by bootstrap resampling. Baseline clinicopathological characteristics were well balanced across the three cohorts (all $P > 0.05$), and the overall complete response rate was 81.99% (510/622). Multivariate logistic regression identified tumor stage, histological differentiation, depth of stromal invasion, NLR, and PLR as independent predictors of therapeutic response (all $P < 0.05$). Multivariate Cox regression analysis demonstrated that age ≥ 60 years, FIGO stage III-IV, poor differentiation, deep stromal invasion (≥ 1/2), SCCA ≥ 13.2 ng/mL, LAR ≥ 4.015, and negative HPV status were independent predictors of poor OS (all $P < 0.05$). The OS nomogram achieved C-index values of 0.792, 0.928, and 0.918 in the training, internal validation, and external validation cohorts, respectively, showing good calibration and consistent net clinical benefit across a wide range of threshold probabilities. Stratified survival analysis revealed a significantly lower 3-year OS rate in patients with high LAR compared with those with low LAR ($P < 0.001$). Furthermore, the area under the curve (AUC) of the nomogram-derived risk score was significantly

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higher than that of FIGO staging and LAR alone in the training cohort (0.853 vs. 0.708 and 0.706, respectively; all $P < 0.001$). These findings indicate that LAR combined with clinicopathological characteristics is a reliable predictor of both short-term treatment response and long-term survival in LACC patients receiving CCRT, and that the proposed nomograms provide a low-cost, non-invasive, and clinically useful tool for risk stratification, individualized treatment, and follow-up management.

Keywords: Cervical cancer, locally advanced, lactate dehydrogenase-to-albumin ratio, LAR, nomogram

Introduction

Cervical cancer still presents one of the most common malignant tumors in females. According to the World Health Organization (WHO) GLOBOCAN 2020 statistics, 604,000 new cases and 342,000 deaths occur annually, with approximately 18%-20% of global disease burden originating from China [1, 2]. Locally advanced cervical cancer (LACC), defined as FIGO stage IB3-IVA, accounts for nearly 50%-60% of all cervical cancer cases, representing the major contributor to the disease-related morbidity and mortality [2].

Concurrent chemoradiotherapy (CCRT) is currently recognized as the standard treatment for LACC, yielding a 5-year overall survival (OS) rate of 60%-70% and a complete response (CR) rate ranging form 50% to 85% [3]. However, prognosis among LACC patients varies greatly. Some patietns experience poor poor outcomes due to tumor recurrence, metastasis, or resistance to treatment [4]. The absence of reliable and convenient tools for predicting CCRT efficacy and long-term survival poses clinical challenges. Without accurate risk stratification, high-risk patients may miss the timewindow for enhanced intervention, while low-risk patients may be exposed to unnecessary treatment-related toxicity. As a result, there is an urgent need to develop non-invasive and easily accessible prognostic assessment methods to optimize the personalized treatment and follow-up strategies for LACC patients.

Prognostication in cervical cancer has conventionally relied mainly on FIGO staging, imaging-based tumor volume estimation, and performance status (PS) scoring [5]. This clearly indicates that although FIGO stage is the most powerful clinical prognostic indicator, it fails to capture the biological heterogeneity of tumors, including inflammatory status and metabolic alterations [6]. Imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET/CT) can evaluate tumour burden and lymph node metastasis, but are limited by high cost and technique dependence [7].

Histopathological parameters, such as tumor differentiation and depth of stromal invasion, have also been associated with prognosis. Howerver, these parameters are derived from surgical or biopsy specimens, and their invasive nature limits their routine application in LACC who are primarily treated with radiotherapy [8]. In recent years, systemic inflammatory parameters, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have attracted increasing attention. Several meta-analyses have reported hazard ratios (HR) ranging from 1.5 to 2.0 for these markers across various solid tumors, indicating a positive association with poor survival outcomes [9, 10].

Squamous cell carcinoma antigen (SCCA) is a relatively specific biomarker for LACC and correlates with tumor burden and radiotherapy response. However, its prognostic accuracy as a standalone biomarker remains suboptimal, as no individual biomarker can fully reflect the complex biological behavior of tumors [11]. Therefore, integrating clinicopathological and laboratory parameters is essential for improving prognostication. The lactate dehydrogenase-to-albumin ratio (LAR) has emerged as a promising composite biomarker, incorporating information on lactate dehydrogenase (LDH) and serum albumin (ALB) levels [10]. Elevated LDH indicates enhanced Warburg effect (aerobic glycolysis), which supports tumor proliferation and invasion, whereas reduced ALB levels indicate chronic inflammation and nutrition deprivation, and an immunosuppressive microenvironment [13].

Previous studies in colorectal, lung, and pancreatic cancers have demonstrated that elevated LAR is significantly associated with poor survival outcomes [14, 15]. In cervical cancer, several small-sample studies have suggested

that elevated LAR may be correlated with CCRT resistance and shorter survival, yet its prognostic significance in large-scale LACC cohorts remains insufficiently explored. Compared with NLR, PLR, and SCCA, LAR offers several advantages, including derivation from routine laboratory tests, low cost, widely accessible, and the potential to capture distinctive metabolic reprogramming features.

This study aimed to develop an integrated prognostic strategy that combines LAR with FIGO stage, histological differentiation, depth of stromal invasion, and other inflammatory or tumor-related markers (e.g., NLR, PLR, SCCA) to predict outcomes in LACC patients treated with CCRT. We hypothesize that nomograms based on logistic regression for short-term therapeutic efficacy prediction and Cox proportional hazards regression for OS prediction could provide accurate risk stratification across different time horizons. This retrospective cohort study integrates readily available clinicopathological and laboratory parameters to develop and validate dual nomogram models for predicting CR/NCR status and 1-3 year OS. Nomograms designed as inexpensive, non-invasive predictive tools may facilitate personalized therapeutic modifications, such as radiotherapy intensification, optimized nutritional support, or immunomodulatory interventions, and improve follow-up strategies compared with conventional single-indicator or imaging-based assessments.

Methods

Sample size calculation

The required sample size was calculated according to the principle of events-per-variable (EPV) for Cox proportional hazards regression models. Using the method reported by Yan et al. [16] for LACC prognostication, a 3-year mortality rate of about 30% was assumed. Considering the planned inclusion of 8-10 candidate predictors and the commonly accepted criterion of EPV ≥ 15, the required minimum sample size was estimated to be approximately 500 patients.

A total of 622 patients were finally included, yielding an estimated 187 outcome events, and an EPV of 18.7, thus fulfilling the statistical requirement for model development [17]. To maximize statistical power for model construction and evaluation, the whole cohort was randomly allocated into training, validation, and testing sets. This study was approved by the Ethics Committee of Jinshazhou Hospital of Guangzhou University of Chinese Medicine.

Study design and setting

In this two-center retrospective cohort study, consecutive LACC patients who received standard CCRT at the Third Affiliated Hospital of Guangzhou Medical University (Center 1) were included for model development and internal validation. An independent external validation cohort (testing set) was enrolled from Jinshazhou Hospital of Guangzhou University of Chinese Medicine (Center 2) during the same study period.

Grouping protocol

Data from Center 1 were randomly split into a training setand a validation set at a ratio of 0.75:0.25. The training set comprised 373 patients (305 complete responses [CR], 81.77%; 68 non-complete responses [NCR], 18.23%), and the validation set included 124 patients (101 CR, 81.45%; 23 NCR, 18.55%). Randomization was performed using the *set.seed()* and *sample()* functions in R software (version 4.3.3) to ensure reproducibility. The testing set (external validation cohort) comprised patients treated at Center 2 during the same period (n = 125; 104 CR, 83.20%; 21 NCR, 16.80%). The flow chart of study sample screening is illustrated in **Figure 1**.

Eligibility criteria

Inclusion criteria: age ≥ 18 years; a histopathologic diagnosis of LACC, staged as IB3, II, III, or IVA according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification [18]; completion of standard CCRT involving external beam radiotherapy combined with cisplatin-based chemotherapy; complete availability of baseline clinical, laboratory, and imaging data; and histological subtype limited to squamous cell carcinoma or adenocarcinoma.

Exclusion criteria: distant metastases (FIGO stage IVB) or a concurrent second malignancy; incomplete CCRT or use of non-standardized

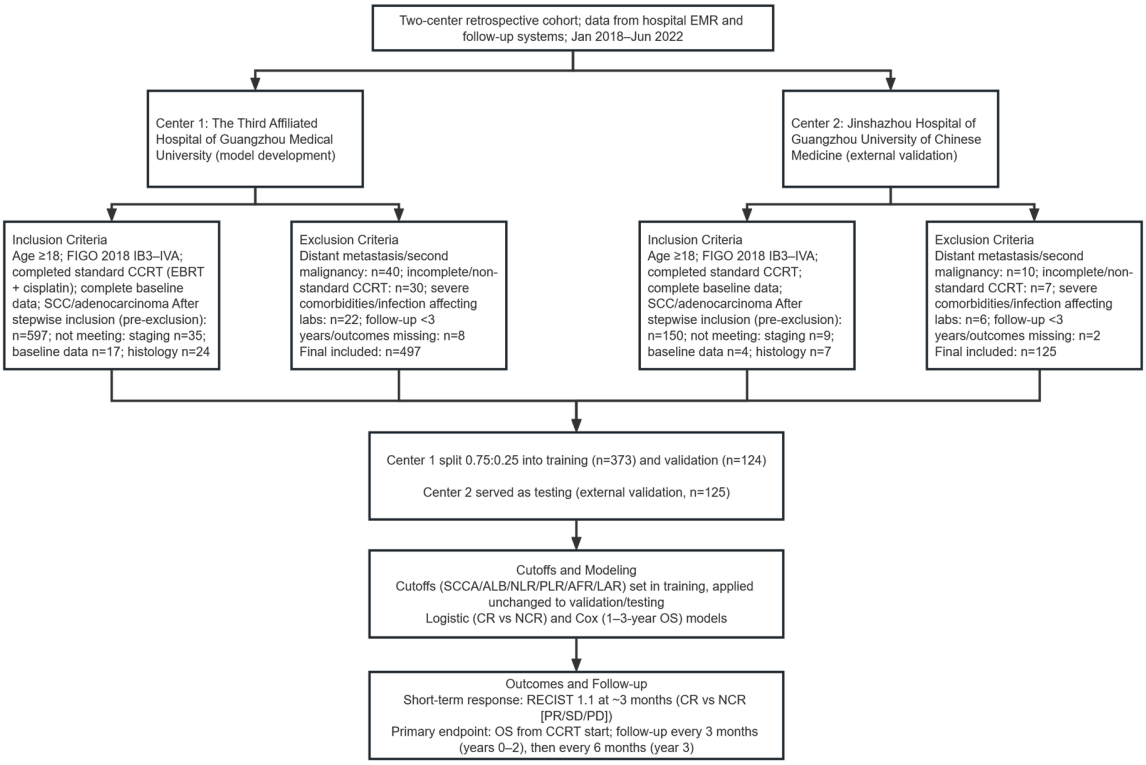

Figure 1. Flow chart of case inclusion.

regimens; severe comorbidities such as hepatic or renal failure or active infections that could potentially influence laboratory results; or incomplete baseline data or follow-up duration of less than three years.

Clinical data collection

Data acquisition encompassed general characteristics (age [< 60 vs. ≥ 60 years], body mass index [BMI; < 25 vs. ≥ 25 kg/m^2], menopausal status [premenopausal vs. postmenopausal], histories of hypertension, diabetes, smoking, and human papillomavirus [HPV] infection); tumor-related variables (FIGO stage, histological subtype [squamous cell carcinoma vs. adenocarcinoma], tumor differentiation [well/moderate vs. poorly differentiated], depth of stromal invasion [< 1/2 vs. ≥ 1/2 of cervical wall thickness], and vascular invasion [present vs. absent]); laboratory indicators (SCCA, ALB, NLR, PLR, albumin-to-fibrinogen ratio [AFR], and LAR); and treatment-related variables (total radiotherapy duration, < 8 vs. ≥ 8 weeks). All baseline laboratory measurements were obtained within one week prior to initiation of CCRT to ensure data consistency.

Measurement methods

Laboratory analyses were carried out using standardized platforms at both centers. SCCA was measured using chemiluminescent immunoassay on a Cobas e 601 analyzer (Roche Diagnostics, Switzerland). ALB was measured by bromocresol green method, and lactate dehydrogenase (LDH) activity was measured using enzymatic kinetic assay on an AU5800 chemistry analyzer (Beckman Coulter, USA). Complete blood counts required for the calculation of NLR and PLR were obtained using an XN-1000 (Sysmex, Japan) hematology analyzer. Fibrinogen levels required for calculation of AFR were measured using the coagulation method.

Both centers implemented stringent quality control protocols. Internal quality control (IQC) was performed twice daily (pre- and post-batch) using control material provided by the manufacturer, and assay performance was evaluated according to Westgard multirule criteria. Calibration of the Cobas e 601 and AU5800 analyzers was performed on a monthly basis or whenever there's a change of

reagent lot numbers. The XN-1000 hematology analyzer was calibrated weekly or upon reagent replacement. Both laboratories took part in the external quality assessment (EQA) programs organized by the China National Center for Clinical Laboratories (NCCL), with proficiency testing performed 2-4 times annually. Harmonized analytical protocols were applied at both centers to ensure inter-laboratory comparability.

HPV status assessment: Baseline HPV status was determined using cervical exfoliated cervical cell specimens collected before initiation of CCRT. At our institutions, high-risk HPV detection and genotyping were routinely performed using qPCR according to the manufacturer's instructions. PCR amplification and fluorescence detection were carried out on a standard real-time PCR platform (e.g., Applied Biosystems 7500/7500 Fast Real-Time PCR System, Thermo Fisher Scientific, USA). Detection of any high-risk HPV type was defined as HPV-positive, and absence of detectable high-risk HPV DNA was defined as HPV-negative. Due to the retrospective real-world design, some patients had undergone HPV testing at external institutions prior to referral, for whom only qualitative HPV results (positive/negative) were available in medical records. To ensure data completeness and consistency across the whole cohort and avoid selection bias, HPV status was analyzed as a binary variable (positive vs. negative), and genotype-specific information was not included in the final analysis.

FIGO stage was determined based on pelvic MRI and/or CT. Stromal invasion depth was assessed on MRI as the proportion of cervical wall thickness involved. Histologic type and tumor differentiation were determined from pre-treatment cervical biopsy specimens according to the WHO classification. Total radiotherapy duration was calculated as the time interval (weeks) from the start to the completion of external beam radiotherapy.

Follow-up

Post-treatment follow-up was conducted through outpatient visits, imaging assessments, and telephone interviews. Follow-up assessments were scheduled every three months in the first two years and every six months during in third year. The primary endpoint was OS, defined as the time from CCRT initiation to death from any cause or the last recorded follow-up.

Outcome measures

The primary outcome measure was CCRT efficacy, classified as CR or NCR; CR was defined as complete disappearance of all target lesions on MRI or CT, with no evidence of new disease within three months after treatment. NCR encompassed partial response, stable disease, and progressive disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [19]. The secondary outcome measure was the 3-year OS rate.

Statistical analysis

Statistical analyses were performed using R software (version 4.3.3) and SPSS (version 26.0). Continuous variables were described as mean ± standard deviation or median with interquartile range, while categorical variables were summarized as frequency and percentage. Optimal cut-off values for SCCA, ALB, NLR, PLR, AFR, and LAR were determined using the *surv_cutpoint* function of the "survminer" R package.

Baseline characteristics across the three datasets were compared using chi-square test or Fisher's exact test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Multicollinearity among candidate predictors was evaluated using variance inflation factor (VIF) analysis, with a VIF < 5 indicating acceptable independence. Predictors of treatment response were identified using univariate and multivariate logistic regression, expressed as odds ratios (OR) with 95% confidence intervals (CI). Predictors of OS were examined using univariate and multivariate Cox proportional hazards regression models, expressed as HR with 95% CI.

Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The proportional hazards assumption was tested using Schoenfeld residuals. Nomogram models were constructed based on variables identified as independent predictors. Model discrimination was evaluated

via receiver operating characteristic (ROC) curves and C-index estimation; calibration was assessed using Hosmer-Lemeshow goodness-of-fit test and visualized with calibration plots; and clinical net benefit was analyzed using decision curve analysis (DCA). Internal validation was performed using 1,000 bootstrap resampling. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients

A total of 622 patients with LACC were included, of whom 510 (81.99%) achieved CR and 112 (18.01%) were classified as NCR. The majority of patients were younger than 60 years (n = 407, 65.43%). BMI was < 25 kg/m^2 in 422 patients (67.85%) and ≥ 25 kg/m^2 in 200 (32.15%). A total of 376 patients (60.45%) were postmenopausal and 246 (39.55%) were premenopausal. History of hypertension was present in 114 patients (18.33%) and diabetes in 77 patients (12.38%). There were 223 smokers (35.85%) and 399 non-smokers (64.15%).

Regarding tumor stage, 82 patients (13.18%) were classified as FIGO stage IB3, 218 (35.05%) as stage II, 298 (47.91%) as stage III, and 24 (3.86%) as stage IVA. Histologically, squamous cell carcinoma constituted the predominant subtype (n = 561, 90.19%), with adenocarcinoma observed in 61 cases (9.81%). Well or moderately differentiated tumors were observed in 352 patients (56.59%), and poorly differentiated tumors in 270 (43.41%). Stromal invasion depth was < 1/2 of cervical wall thickness in 483 cases (77.65%) and ≥ 1/2 in 139 cases (22.35%); lymphovascular space invasion (LVSI) was present in 88 patients (14.15%).

Regarding laboratory parameters, 426 patients (68.49%) had SCCA < 13.2 ng/mL, while 196 (31.51%) had SCCA ≥ 13.2 ng/mL. 543 patients (87.30%) had serum ALB level < 30 g/L and 79 patients (12.70%) had ALB level ≥ 30 g/L. NLR was < 2.785 in 429 patients (68.97%) and ≥ 2.785 in 193 patients (31.03%); PLR was < 181 in 471 patients (75.72%) and ≥ 181 in 151 patients (24.28%); AFR was < 12.9 in 64 patients (10.29%) and ≥ 12.9 in 558 patients (89.71%); LAR was < 4.015 in 477 patients (76.69%) and ≥ 4.015 in 145 patients (23.31%). Total radiotherapy duration was < 8 weeks in 363 patients (58.36%) and ≥ 8 weeks in 259 (41.64%). Regarding HPV status, 559 patients (89.87%) were HPV-positive and 63 patients (10.13%) were HPV-negative. The detailed distribution of clinical and laboratory characteristics is presented (**Table 1**).

Optimal cut-off values of key clinical and laboratory indices

The optimal cut-off values for key clinical and laboratory indices, including SCCA, ALB, NLR, PLR, AFR and LAR, were determined using the *surv_cutpoint* function of the *survminer* R package. Distinct optimal thresholds were identified, reflecting heterogeneous distribution patterns across the cohort. These cut-off values are shown in **Figure 2** and were then used for patient stratification and prognostic evaluation.

Impact of clinical and laboratory variables on treatment response

Several clinical characteristics, including age, BMI, menopausal status, history of hypertension and diabetes, smoking history, histologic type, serum ALB level, AFR, total radiotherapy duration and HPV status showed no significant association with therapeutic response (all $P > 0.05$). In contrast, tumor characteristics such as tumor stage ($P < 0.001$), histological differentiation ($P < 0.001$), depth of stromal invasion ($P < 0.001$) and LVSI ($P = 0.032$) were significantly associated with treatment response. Among laboratory indicators, SCCA, NLR, PLR, and LAR were significantly correlated with therapeutic efficacy (all $P < 0.001$) (**Table 2**).

Comparison of baseline features among the training, validation, and testing sets

Baseline demographic, clinicopathologic, and laboratory variables did not differ significantly among the training, validation, and testing sets (all $P > 0.05$), indicating successful randomization and well-balanced baseline characteristics across the three groups (**Table 3**).

Comparison of clinical features between CR and NCR groups in the training set

Within the training set, age ($P = 0.783$), BMI ($P = 0.966$), menopausal status ($P = 0.660$), his-

Table 1. Baseline characteristics of patients

Variable	Total
Treatment Response	
CR	510 (81.99%)
NCR	112 (18.01%)
Age	
< 60	407 (65.43%)
≥ 60	215 (34.57%)
BMI	
< 25	422 (67.85%)
≥ 25	200 (32.15%)
Menopausal status	
No	246 (39.55%)
Yes	376 (60.45%)
History of hypertension	
No	508 (81.67%)
Yes	114 (18.33%)
History of diabetes	
No	545 (87.62%)
Yes	77 (12.38%)
History of smoking	
No	399 (64.15%)
Yes	223 (35.85%)
Tumor stage	
IB3	82 (13.18%)
II	218 (35.05%)
III	298 (47.91%)
IVA	24 (3.86%)
Histologic type	
Adenocarcinoma	61 (9.81%)
Squamous cell carcinoma	561 (90.19%)
Differentiation	
Moderate/high	352 (56.59%)
Poor	270 (43.41%)
Depth of invasion	
< 1/2	483 (77.65%)
≥ 1/2	139 (22.35%)
Vascular invasion	
No	534 (85.85%)
Yes	88 (14.15%)
SCCA (ng/mL)	
< 13.2	426 (68.49%)
≥ 13.2	196 (31.51%)
ALB (g/L)	
< 30	543 (87.30%)
≥ 30	79 (12.70%)
NLR	
< 2.785	429 (68.97%)
≥ 2.785	193 (31.03%)
PLR	
< 181	471 (75.72%)
≥ 181	151 (24.28%)
AFR	
< 12.9	64 (10.29%)
≥ 12.9	558 (89.71%)
LAR	
< 4.015	477 (76.69%)
≥ 4.015	145 (23.31%)
Total radiotherapy duration (weeks)	
< 8	363 (58.36%)
≥ 8	259 (41.64%)
HPV	
Positive	559 (89.87%)
Negative	63 (10.13%)

Note: SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV: Human papillomavirus.

tory of hypertension (P = 0.475), history of diabetes (P = 0.368), smoking history (P = 0.776), histologic type (P = 0.798), LVSI (P = 0.295), albumin level (P = 0.839), AFR (P = 0.696), total radiotherapy duration (P = 0.216), and HPV status (P = 0.434) showed no statistical difference between the CR and NCR subgroups. Conversely, significant differences were observed in tumor-related parameters, including tumor stage (P = 0.002), histologic differentiation (P = 0.003), and stromal invasion depth (P = 0.002). In addition, laboratory indices including SCCA (P = 0.010), NLR (P = 0.017), PLR (P = 0.010), and LAR (P = 0.032) also differed significantly between the CR and NCR groups (**Table 4**).

Multicollinearity assessment and variable coding

VIF analysis of all clinical and laboratory indicators confirmed that all variables exhibited VIF values close to 1, indicating no multicollinearity among these variables. Variables were subsequently dichotomized or categorized as needed for regression model construction (**Table 5**).

Logistic regression analysis for predictors of treatment response

In univariate logistic regression analysis, tumor stage (OR = 2.030, 95% CI: 1.367-3.015, P <

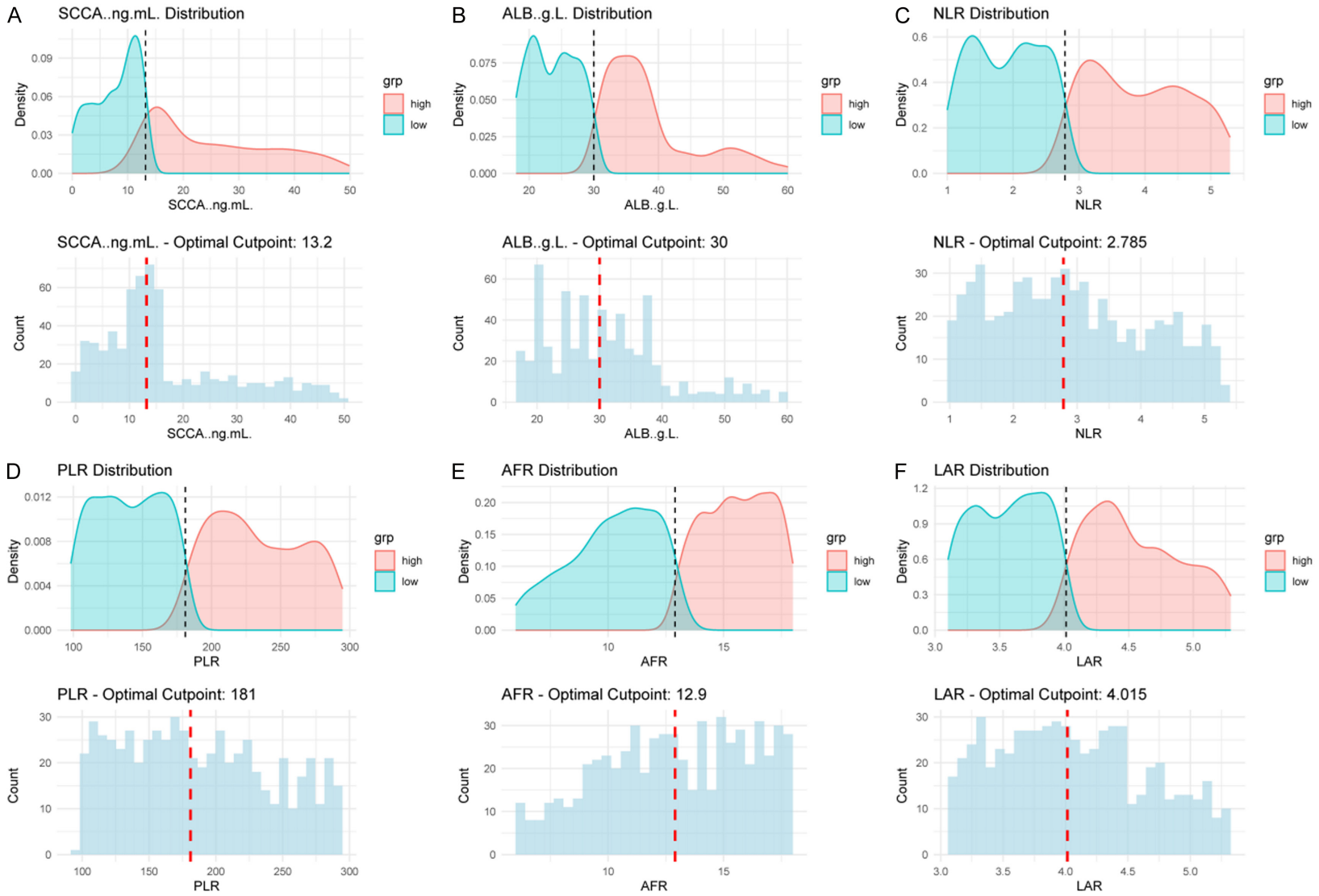

Figure 2. Optimal cut-off values and distributions for key clinical and laboratory parameters. A. SCCA; B. ALB; C. NLR; D. PLR; E. AFR; F. LAR. Note: SCCA, squamous cell carcinoma antigen; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AFR, albumin-to-fibrinogen ratio; LAR, lactate dehydrogenase-to-albumin ratio.

Table 2. Association between clinical/laboratory variables and treatment response

Variable	Total, n (%)	CR, n (%)	NCR, n (%)	X^2	*P*-value
Age				0.141	0.707
< 60	407 (65.43%)	332 (65.10%)	75 (66.96%)		
≥ 60	215 (34.57%)	178 (34.90%)	37 (33.04%)		
BMI				0.804	0.370
< 25	422 (67.85%)	342 (67.06%)	80 (71.43%)		
≥ 25	200 (32.15%)	168 (32.94%)	32 (28.57%)		
Menopausal status				0.240	0.624
No	246 (39.55%)	204 (40.00%)	42 (37.50%)		
Yes	376 (60.45%)	306 (60.00%)	70 (62.50%)		
History of hypertension				0.158	0.691
No	508 (81.67%)	418 (81.96%)	90 (80.36%)		
Yes	114 (18.33%)	92 (18.04%)	22 (19.64%)		
History of diabetes				0.458	0.499
No	545 (87.62%)	449 (88.04%)	96 (85.71%)		
Yes	77 (12.38%)	61 (11.96%)	16 (14.29%)		
History of smoking				1.112	0.292
No	399 (64.15%)	332 (65.10%)	67 (59.82%)		
Yes	223 (35.85%)	178 (34.90%)	45 (40.18%)		
Tumor stage				43.140	<0.001
IB3	82 (13.18%)	76 (14.90%)	6 (5.36%)		
II	218 (35.05%)	193 (37.84%)	25 (22.32%)		
III	298 (47.91%)	231 (45.29%)	67 (59.82%)		
IVA	24 (3.86%)	10 (1.96%)	14 (12.50%)		
Histologic type				0.119	0.730
Adenocarcinoma	61 (9.81%)	51 (10.00%)	10 (8.93%)		
Squamous cell carcinoma	561 (90.19%)	459 (90.00%)	102 (91.07%)		
Differentiation				20.267	< 0.001
Moderate/high	352 (56.59%)	310 (60.78%)	42 (37.50%)		
Poor	270 (43.41%)	200 (39.22%)	70 (62.50%)		
Depth of invasion				20.266	< 0.001
< 1/2	483 (77.65%)	414 (81.18%)	69 (61.61%)		
≥ 1/2	139 (22.35%)	96 (18.82%)	43 (38.39%)		
Vascular invasion				4.589	0.032
No	534 (85.85%)	445 (87.25%)	89 (79.46%)		
Yes	88 (14.15%)	65 (12.75%)	23 (20.54%)		
SCCA (ng/mL)				23.776	< 0.001
< 13.2	426 (68.49%)	371 (72.75%)	55 (49.11%)		
≥ 13.2	196 (31.51%)	139 (27.25%)	57 (50.89%)		
ALB (g/L)				1.399	0.237
< 30	543 (87.30%)	449 (88.04%)	94 (83.93%)		
≥ 30	79 (12.70%)	61 (11.96%)	18 (16.07%)		
NLR				11.830	< 0.001
< 2.785	429 (68.97%)	367 (71.96%)	62 (55.36%)		
≥ 2.785	193 (31.03%)	143 (28.04%)	50 (44.64%)		
PLR				20.959	< 0.001
< 181	471 (75.72%)	405 (79.41%)	66 (58.93%)		
≥ 181	151 (24.28%)	105 (20.59%)	46 (41.07%)		

AFR				0.257	0.612
< 12.9	64 (10.29%)	51 (10.00%)	13 (11.61%)		
≥ 12.9	558 (89.71%)	459 (90.00%)	99 (88.39%)		
LAR				21.737	< 0.001
< 4.015	477 (76.69%)	410 (80.39%)	67 (59.82%)		
≥ 4.015	145 (23.31%)	100 (19.61%)	45 (40.18%)		
Total radiotherapy duration (weeks)				1.974	0.160
< 8	363 (58.36%)	291 (57.06%)	72 (64.29%)		
≥ 8	259 (41.64%)	219 (42.94%)	40 (35.71%)		
HPV				0.051	0.821
Negative	63 (10.13%)	51 (10.00%)	12 (10.71%)		
Positive	559 (89.87%)	459 (90.00%)	100 (89.29%)		

Note: SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV: Human papillomavirus.

Table 3. Comparison of baseline characteristics among training, testing, and validation sets

Variable	Training set (n = 373)	Testing set (n = 124)	Validation set (n = 125)	X^2	*P*-value
Age				0.161	0.923
< 60	305 (81.77%)	101 (81.45%)	104 (83.20%)		
≥ 60	68 (18.23%)	23 (18.55%)	21 (16.80%)		
BMI				0.764	0.682
< 25	247 (66.22%)	77 (62.10%)	83 (66.40%)		
≥ 25	126 (33.78%)	47 (37.90%)	42 (33.60%)		
Menopausal status				4.992	0.082
No	257 (68.90%)	90 (72.58%)	75 (60.00%)		
Yes	116 (31.10%)	34 (27.42%)	50 (40.00%)		
History of hypertension				3.988	0.136
No	157 (42.09%)	49 (39.52%)	40 (32.00%)		
Yes	216 (57.91%)	75 (60.48%)	85 (68.00%)		
History of diabetes				3.625	0.163
No	297 (79.62%)	102 (82.26%)	109 (87.20%)		
Yes	76 (20.38%)	22 (17.74%)	16 (12.80%)		
History of smoking				1.960	0.375
No	325 (87.13%)	113 (91.13%)	107 (85.60%)		
Yes	48 (12.87%)	11 (8.87%)	18 (14.40%)		
Histologic type				0.870	0.647
Adenocarcinoma	236 (63.27%)	84 (67.74%)	79 (63.20%)		
Squamous cell carcinoma	137 (36.73%)	40 (32.26%)	46 (36.80%)		
Tumor stage				5.447	0.488
IB3	47 (12.60%)	14 (11.29%)	21 (16.80%)		
II	139 (37.27%)	37 (29.84%)	42 (33.60%)		
III	174 (46.65%)	66 (53.23%)	58 (46.40%)		
IVA	13 (3.49%)	7 (5.65%)	4 (3.20%)		
Differentiation				1.115	0.573
Moderate/high	36 (9.65%)	10 (8.06%)	15 (12.00%)		
Poor	337 (90.35%)	114 (91.94%)	110 (88.00%)		
Depth of invasion				1.338	0.512
< 1/2	218 (58.45%)	66 (53.23%)	68 (54.40%)		
≥ 1/2	155 (41.55%)	58 (46.77%)	57 (45.60%)		

Vascular invasion				0.448	0.799
No	293 (78.55%)	95 (76.61%)	95 (76.00%)		
Yes	80 (21.45%)	29 (23.39%)	30 (24.00%)		
SCCA (ng/mL)				0.690	0.708
< 13.2	317 (84.99%)	109 (87.90%)	108 (86.40%)		
≥ 13.2	56 (15.01%)	15 (12.10%)	17 (13.60%)		
ALB (g/L)				0.381	0.826
< 30	252 (67.56%)	87 (70.16%)	87 (69.60%)		
≥ 30	121 (32.44%)	37 (29.84%)	38 (30.40%)		
NLR				3.079	0.214
< 2.785	332 (89.01%)	103 (83.06%)	108 (86.40%)		
≥ 2.785	41 (10.99%)	21 (16.94%)	17 (13.60%)		
PLR				0.506	0.776
< 181	259 (69.44%)	87 (70.16%)	83 (66.40%)		
≥ 181	114 (30.56%)	37 (29.84%)	42 (33.60%)		
AFR				0.855	0.652
< 12.9	286 (76.68%)	90 (72.58%)	95 (76.00%)		
≥ 12.9	87 (23.32%)	34 (27.42%)	30 (24.00%)		
LAR				5.389	0.068
< 4.015	39 (10.46%)	18 (14.52%)	7 (5.60%)		
≥ 4.015	334 (89.54%)	106 (85.48%)	118 (94.40%)		
Total radiotherapy duration (weeks)				2.049	0.359
< 8	289 (77.48%)	98 (79.03%)	90 (72.00%)		
≥ 8	84 (22.52%)	26 (20.97%)	35 (28.00%)		
Age				0.517	0.772
< 60	222 (59.52%)	70 (56.45%)	71 (56.80%)		
≥ 60	151 (40.48%)	54 (43.55%)	54 (43.20%)		
HPV				0.045	0.978
Negative	37 (9.92%)	13 (10.48%)	13 (10.40%)		
Positive	336 (90.08%)	111 (89.52%)	112 (89.60%)		

Note: SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV: Human papillomavirus.

Table 4. Comparison of clinical characteristics between CR and NCR groups in the training set

Variable	Total, n (%)	CR, n (%)	NCR, n (%)	X^2	*P*-value
Age				0.076	0.783
≥ 60 years	126 (33.78%)	104 (34.10%)	22 (32.35%)		
< 60 years	247 (66.22%)	201 (65.90%)	46 (67.65%)		
BMI (kg/m^2)				0.002	0.966
≥ 25	116 (31.10%)	95 (31.15%)	21 (30.88%)		
< 25	257 (68.90%)	210 (68.85%)	47 (69.12%)		
Menopausal status				0.194	0.66
Yes	216 (57.91%)	175 (57.38%)	41 (60.29%)		
No	157 (42.09%)	130 (42.62%)	27 (39.71%)		
History of hypertension				0.51	0.475
Yes	76 (20.38%)	60 (19.67%)	16 (23.53%)		
No	297 (79.62%)	245 (80.33%)	52 (76.47%)		
History of diabetes				0.812	0.368
Yes	48 (12.87%)	37 (12.13%)	11 (16.18%)		
No	325 (87.13%)	268 (87.87%)	57 (83.82%)		

Smoking history				0.081	0.776
Yes	137 (36.73%)	111 (36.39%)	26 (38.24%)		
No	236 (63.27%)	194 (63.61%)	42 (61.76%)		
Tumor stage (FIGO 2018)				15.021	0.002
IB3	47 (12.60%)	43 (14.10%)	4 (5.88%)		
II	139 (37.27%)	121 (39.67%)	18 (26.47%)		
III	174 (46.65%)	134 (43.93%)	40 (58.82%)		
IVA	13 (3.49%)	7 (2.30%)	6 (8.82%)		
Histologic type				0.065	0.798
Squamous cell carcinoma	337 (90.35%)	275 (90.16%)	62 (91.18%)		
Adenocarcinoma	36 (9.65%)	30 (9.84%)	6 (8.82%)		
Degree of differentiation				8.546	0.003
Poor	155 (41.55%)	116 (38.03%)	39 (57.35%)		
Moderate/high	218 (58.45%)	189 (61.97%)	29 (42.65%)		
Depth of stromal invasion				9.463	0.002
≥ 1/2	80 (21.45%)	56 (18.36%)	24 (35.29%)		
< 1/2	293 (78.55%)	249 (81.64%)	44 (64.71%)		
Vascular invasion				1.098	0.295
Yes	56 (15.01%)	43 (14.10%)	13 (19.12%)		
No	317 (84.99%)	262 (85.90%)	55 (80.88%)		
SCCA (ng/mL)				6.56	0.01
≥ 13.2	121 (32.44%)	90 (29.51%)	31 (45.59%)		
< 13.2	252 (67.56%)	215 (70.49%)	37 (54.41%)		
ALB (g/L)				0.041	0.839
≥ 30	41 (10.99%)	34 (11.15%)	7 (10.29%)		
< 30	332 (89.01%)	271 (88.85%)	61 (89.71%)		
NLR				5.722	0.017
≥ 2.785	114 (30.56%)	85 (27.87%)	29 (42.65%)		
< 2.785	259 (69.44%)	220 (72.13%)	39 (57.35%)		
PLR				6.662	0.01
≥ 181	87 (23.32%)	63 (20.66%)	24 (35.29%)		
< 181	286 (76.68%)	242 (79.34%)	44 (64.71%)		
AFR				0.152	0.696
≥ 12.9	334 (89.54%)	274 (89.84%)	60 (88.24%)		
< 12.9	39 (10.46%)	31 (10.16%)	8 (11.76%)		
LAR				4.608	0.032
≥ 4.015	84 (22.52%)	62 (20.33%)	22 (32.35%)		
< 4.015	289 (77.48%)	243 (79.67%)	46 (67.65%)		
Total radiotherapy duration (weeks)				1.53	0.216
≥ 8	151 (40.48%)	128 (41.97%)	23 (33.82%)		
< 8	222 (59.52%)	177 (58.03%)	45 (66.18%)		
HPV				0.613	0.434
Negative	37 (9.92%)	32 (10.49%)	5 (7.35%)		
Positive	336 (90.08%)	273 (89.51%)	63 (92.65%)		

Note: CR: Complete response, NCR: Non-complete response, SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV: Human papillomavirus.

0.001), histologic differentiation (OR = 2.191, 95% CI: 1.285-3.735, P = 0.004), stromal invasion depth (OR = 2.425, 95% CI: 1.364-4.313, P = 0.003), SCCA (OR = 2.002, 95% CI: 1.170-

Table 5. Variance inflation factor (VIF) and variable coding scheme

Variable	VIF	Interpretation	Coding
Age	1.149	Low multicollinearity	≥ 60 = 1, < 60 = 0
BMI	1.038	Low multicollinearity	≥ 25 = 1, < 25 = 0
Menopausal status	1.118	Low multicollinearity	Yes = 1, No = 0
Hypertension	1.051	Low multicollinearity	Yes = 1, No = 0
Diabetes	1.086	Low multicollinearity	Yes = 1, No = 0
Smoking history	1.062	Low multicollinearity	Yes = 1, No = 0
Tumor stage	1.087	Low multicollinearity	IB3 = 1, II = 2, III = 3, IVA = 4
Histologic type	1.059	Low multicollinearity	Squamous carcinoma = 1, Adenocarcinoma = 0
Differentiation	1.081	Low multicollinearity	Poor = 1, Moderate/high = 0
Stromal invasion depth	1.148	Low multicollinearity	≥ 1/2 = 1, < 1/2 = 0
Vascular invasion	1.097	Low multicollinearity	Yes = 1, No = 0
SCCA (ng/mL)	1.05	Low multicollinearity	≥ 13.2 = 1, < 13.2 = 0
ALB (g/L)	1.068	Low multicollinearity	≥ 30 = 1, < 30 = 0
NLR	1.058	Low multicollinearity	≥ 2.785 = 1, < 2.785 = 0
PLR	1.074	Low multicollinearity	≥ 181 = 1, < 181 = 0
AFR	1.045	Low multicollinearity	≥ 12.9 = 1, < 12.9 = 0
LAR	1.096	Low multicollinearity	≥ 4.015 = 1, < 4.015 = 0
Total radiotherapy duration (weeks)	1.06	Low multicollinearity	≥ 8 = 1, < 8 = 0
HPV	1.089	Low multicollinearity	Negative = 1, Positive = 0

Note: VIF: Variance inflation factor, SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV: Human papillomavirus.

3.424, *P* = 0.011), NLR (OR = 1.925, 95% CI: 1.119-3.309, *P* = 0.018), PLR (OR = 2.095, 95% CI: 1.186-3.703, *P* = 0.011), and LAR (OR = 1.874, 95% CI: 1.050-3.346, *P* = 0.034) were significantly associated with treatment response. Multivariate logistic regression analysis further identified five independent risk factors for therapeutic efficacy: tumor stage (OR = 1.803, 95% CI: 1.210-2.761, *P* = 0.005), histologic differentiation (OR = 1.970, 95% CI: 1.116-3.506, *P* = 0.020), stromal invasion depth (OR = 2.053, 95% CI: 1.080-3.842, *P* = 0.026), NLR (OR = 2.027, 95% CI: 1.127-3.637, *P* = 0.018), and PLR (OR = 2.251, 95% CI: 1.201-4.183, *P* = 0.011) (**Table 6**).

Development of a nomogram for predicting treatment response based on logistic regression

A nomogram for predicting clinical therapeutic efficacy in LACC patients was constructed based on variables showing significant associations in univariate logistic regression analyses, including tumor stage, histologic differentiation, stromal invasion depth, SCCA, NLR, PLR, and LAR (**Figure 3**).

In this model, tumor stage contributed the greatest weight and emerged as the strongest predictor of treatment response. Other variables including histologic differentiation, stromal invasion depth, SCCA, NLR, PLR, and LAR provided moderate predictive contributions. By summing the individual scores corresponding to each variable, a total score can be obtained and further converted to the predicted probability of achieving a favorable response. The equation for the nomogram was defined as follows: linear_predictor = 0.417 + 0.302 × FIGO_stage2 + 1.013 × FIGO_stage3 + 1.559 × FIGO_stage4 - 0.690 × Differentiation_grade - 0.699 × Depth_of_invasion - 0.397 × SCCA - 0.719 × NLR - 0.817 × PLR - 0.587 × LAR.

Discrimination, calibration, and clinical net benefit assessment of the nomogram model

The model demonstrated good discrimination and stability across all three cohorts. Based on internal validation using the bootstrap method (B = 1000), the training set showed a Dxy of 0.5018 (optimism-corrected 0.5037), corresponding to a C-index of approximately 0.752; the validation set had a Dxy of 0.3375 (corrected 0.3355), corresponding to a C-index of approximately 0.668; the testing set showed a Dxy of 0.3622 (corrected 0.3633), corresponding to a C-index of approximately 0.682 (**Figure 4A-C**).

Table 6. Logistic regression analysis of risk factors associated with treatment response

Variable	Univariate			Multivariate		
	OR	*P*-value	95% CI	OR	*P*-value	95% CI
Age	0.924	0.783	0.528-1.619			
BMI (kg/m^2)	0.988	0.966	0.559-1.744			
Menopausal status	1.128	0.660	0.66-1.928			
Hypertension	1.256	0.476	0.671-2.353			
Diabetes	1.398	0.369	0.673-2.904			
Smoking history	1.082	0.776	0.629-1.86			
Tumor stage	2.03	< 0.001	1.367-3.015	1.803	0.005	1.21-2.761
Histologic type	1.127	0.798	0.45-2.825			
Differentiation	2.191	0.004	1.285-3.735	1.97	0.020	1.116-3.506
Depth of stromal invasion	2.425	0.003	1.364-4.313	2.053	0.026	1.08-3.842
Vascular invasion	1.623	0.158	0.829-3.179			
SCCA (ng/mL)	2.002	0.011	1.17-3.424	1.48	0.184	0.824-2.633
ALB (g/L)	0.915	0.839	0.387-2.161			
NLR	1.925	0.018	1.119-3.309	2.027	0.018	1.127-3.637
PLR	2.095	0.011	1.186-3.703	2.251	0.011	1.201-4.183
AFR	0.849	0.697	0.372-1.938			
LAR	1.874	0.034	1.05-3.346	1.783	0.073	0.937-3.332
Radiotherapy duration (weeks)	0.707	0.217	0.407-1.227			
HPV	0.677	0.436	0.254-1.807			

Note: OR: Odds ratio, CI: Confidence interval, SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LAR: Lactate dehydrogenase-to-albumin ratio, HPV, Human papillomavirus.

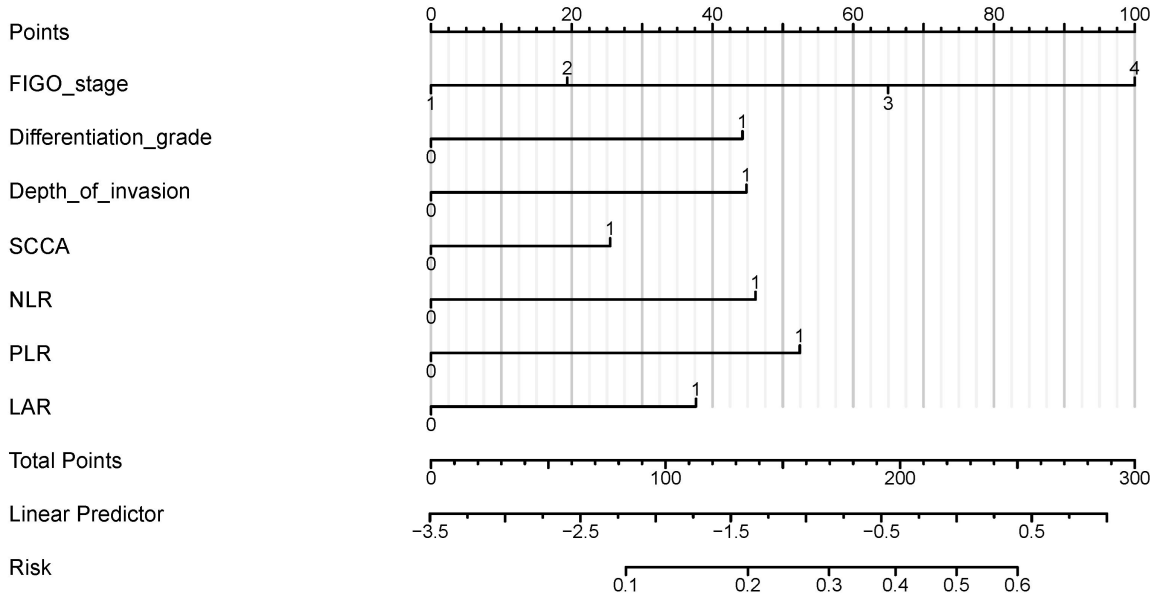

Figure 3. Nomogram predicting treatment efficacy based on logistic regression analysis. Note: SCCA, squamous cell carcinoma antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LAR, lactate dehydrogenase-to-albumin ratio; FIGO, International Federation of Gynecology and Obstetrics.

As shown in **Figure 4D-F**, Hosmer-Lemeshow goodness-of-fit tests indicated good model fit in all three cohorts, with no significant deviations observed in the training set (P = 0.874), valida-

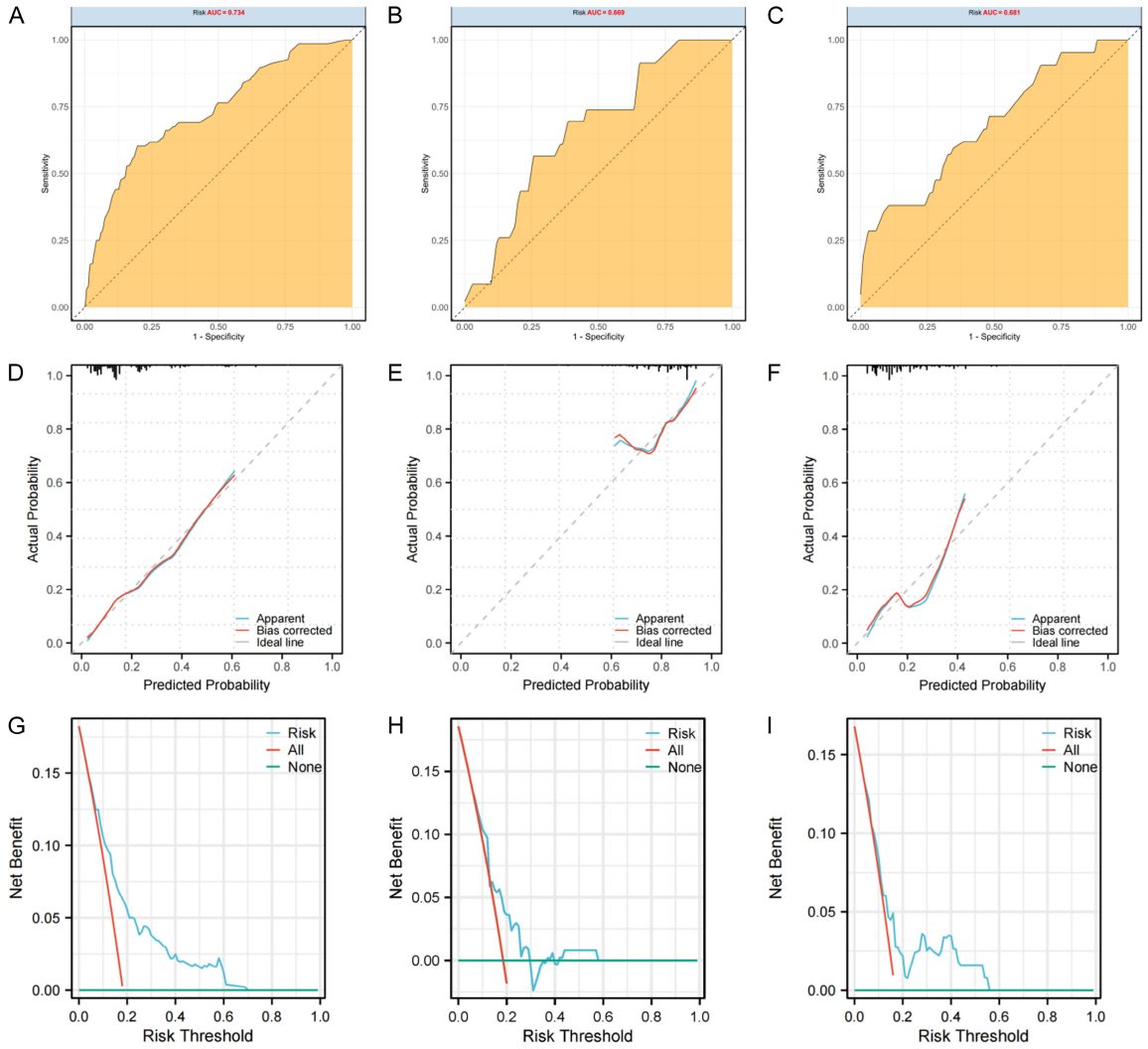

Figure 4. Nomogram performance evaluation. (A-C) ROC curves, (D-F) calibration curves, and (G-I) decision curve analyses, for the nomogram in the training, validation, and testing cohorts, respectively. Notes: ROC, receiver operating characteristic; DCA, decision curve analysis.

tion set (P = 0.565), or testing set (P = 0.302). Calibration curve analyses further supported good agreement between predicted and observed outcomes. The mean absolute prediction errors were 0.014, 0.020, and 0.037 in the training, validation, and testing sets, respectively. The 0.90 quantile absolute errors were 0.022, 0.041, and 0.086 across the three cohorts, respectively, indicating acceptable calibration performance.

DCA demonstrated that the nomogram provided a net benefit across a wide range of threshold probabilities ranging from 0% to 99% in the training cohort, peaking at around 18.23%. The validation set demonstrated net benefit between 0% and 43%, peaking at around 18.54%. The testing set demonstrated net benefit between 0% and 43%, peaking at around 16.80%. The details are shown in **Figure 4G-I**. The model showed good discrimination, reasonable calibration, and potential clinical utility in multiple datasets.

Survival analysis in the training cohort

During follow-up, a total of 50 deaths were reported among the 373 patients in the training cohort. Kaplan-Meier analysis demonstrated a relatively high OS rate with a gradual decline over time. The estimated 3-year OS rate was roughly 87%. Among those who died, the

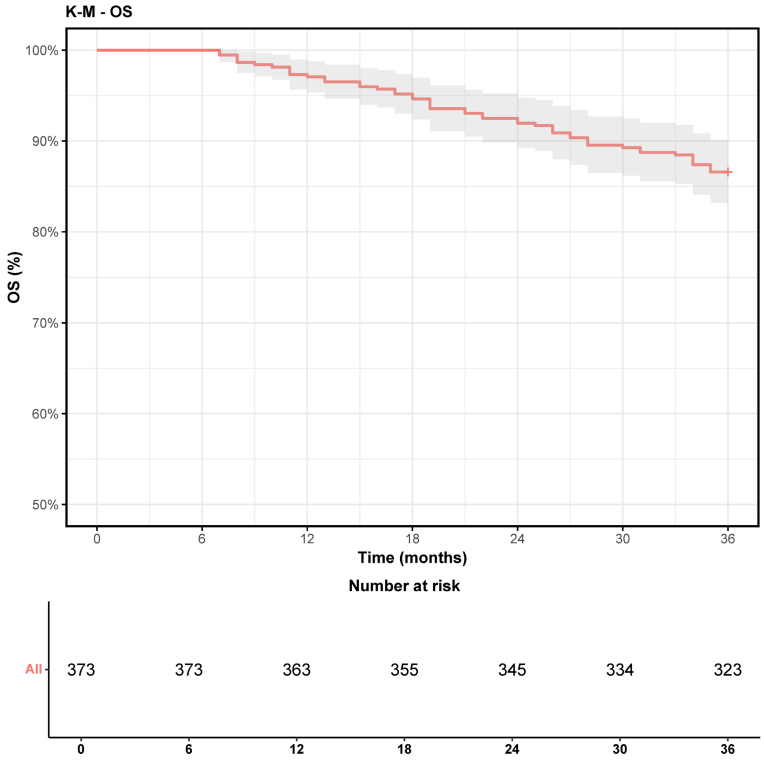

Figure 5. Kaplan-Meier curves for 3-year overall survival (OS) in the training cohort. Note: OS, overall survival.

Table 7. Proportional hazards assumption testing (Schoenfeld residuals) for Cox regression model

Variable	X^2	df	*P*-value
Age	0.717	1	0.397
Tumor stage	0.674	1	0.412
Differentiation	1.931	1	0.165
Depth of stromal invasion	1.679	1	0.195
Vascular invasion	0.005	1	0.941
SCCA (ng/mL)	3.931	1	0.047
LAR	0.011	1	0.918
HPV	1.039	1	0.308
GLOBAL	8.662	8	0.372

Note: PH: Proportional hazards, SCCA: Squamous cell carcinoma antigen, LAR: Lactate dehydrogenase-to-albumin ratio, HPV, Human papillomavirus.

mean time to death was 21.2 months, indicating that most patients achieved prolonged survival following treatment (**Figure 5**).

Proportional hazards assumption testing for cox regression

The Schoenfeld residual tests were applied to verify the proportional hazards assumption of the Cox regression model. The results showed that the proportional hazards assumption was satisfied for age (P = 0.397), tumor stage (P = 0.412), differentiation grade (P = 0.165), depth of stromal invasion (P = 0.195), LVSI (P = 0.941), SCCA (P = 0.047), LAR (P = 0.918), and HPV status (P = 0.308). The global Schoenfeld test further supported that the overall model satisfied the proportional hazards assumption (P = 0.372) (**Table 7**). It is noted that although Schoenfeld residual test for SCCA yielded a marginal *P* value of 0.047 (< 0.05), this variable was retained in the Cox regression analysis, given its well-established clinical relevance in cervical cancer prognosis.

Cox regression analysis for risk factors affecting patient OS

In univariate Cox regression analysis, age ≥ 60 years (HR = 2.298, 95% CI: 1.320-4.003, *P* = 0.003), tumor stage III-IV (HR = 2.774, 95% CI: 1.496-5.143, *P* = 0.001), poor differentiation (HR = 2.741, 95% CI: 1.539-4.884, *P* < 0.001), stromal invasion depth ≥ 1/2 of the cervical wall (HR = 4.364, 95% CI: 2.506-7.599, *P* < 0.001), LVSI (HR = 3.041, 95% CI: 1.678-5.511, *P* < 0.001), SCCA ≥ 13.2 ng/mL (HR = 2.509, 95% CI: 1.441-4.371, *P* = 0.001), LAR ≥ 4.015 (HR = 3.321, 95% CI: 1.904-5.793, *P* < 0.001), and negative HPV status (HR = 3.529, 95% CI: 1.843-6.758, *P* < 0.001) were all significantly associated with poor OS (**Table 8**). Kaplan-Meier stratified survival analysis further validated these findings, indicating that all these variables significantly affected 3-year OS (**Figure 6**). In multivariate Cox regression analysis, age ≥ 60 years (HR = 2.250, 95% CI: 1.281-3.954, *P* = 0.005), tumor stage III-IV (HR = 1.940, 95% CI: 1.004-3.751, *P* = 0.049), poor differentiation (HR = 2.491, 95% CI: 1.379-4.498, *P* = 0.002), stromal invasion depth ≥ 1/2 (HR = 3.703, 95% CI: 2.054-6.674, *P* < 0.001), SCCA ≥ 13.2 ng/mL (HR = 1.843, 95% CI: 1.038-3.273, *P* = 0.037), LAR ≥ 4.015 (HR = 3.178, 95% CI: 1.784-5.661, *P* < 0.001),

and negative HPV status (HR = 2.648, 95% CI: 1.310-5.355, *P* = 0.007) were independent risk factors affecting patient OS (**Table 8**).

Nomogram prediction model based on cox regression independent risk factors

Subsequently, a nomogram model was established to predict the 1-, 2-, and 3-year OS of LACC patients basd on the indepent prognostic factors. Each predictor was assigned a weighted score according to its regression coefficient, and the total score for an individual patient was calculated by summing the scores of all variables. This score then corresponded to estimated survival probabilities atr 12, 24 and 36 months. The nomogram provides a visualized and personalized risk evaluation tool that may serve as reference for clinical prognostic evaluation and clinical decision-making (**Figure 7**). The risk score was calculated using the following formula: Risk score = (0.782 × Age) + (0.720 × FIGO_stage) + (0.972 × Differentiation_grade) + (1.368 × Depth_of_invasion) + (0.615 × SCCA) + (1.213 × LAR) + (1.016 × HPV).

Validation and clinical utility assessment of the nomogram model

The nomogram model exhibited strong discrimination in the training cohort, with a C-index of 0.792 (95% CI: 0.758-0.827). Global model evaluation showed that the likelihood ratio test (χ^2 = 86.04, P < 0.001), Wald test (χ^2 = 92.21, P < 0.001), and log-rank test (χ^2 = 105.08, P < 0.001) were all highly significant, indicating good overall model performance.

In the validation cohort, the nomogram achieved an even higher C-index of 0.928 (95% CI: 0.897-0.959). The likelihood ratio test (χ^2 = 64.9, P < 0.001), Wald test (χ^2 = 43.9, P < 0.001) and log-rank test (χ^2 = 94.41, P < 0.001) consistently confirmed the stability and predictive accuracy of the model.

Similarly, in the testing cohort, the model C-index increased to 0.918 (95% CI = 0.889-0.947). Likelihood ratio test (χ^2 = 55.13, P < 0.001), Wald test (χ^2 = 34.23, P < 0.001), and log-rank test (χ^2 = 60.62, P < 0.001) further validated the robustness of this model in an independent cohorts.

Risk score-based Kaplan-Meier survival curves showed clear separation between high- and low-risk groups in the training, validation, and testing cohorts (**Figure 8A**, **8E**, **8I**), with significantly poorer survival observed in patients classified as high risk. At 3 years, the nomogram maintained good predictive performance, as demonstrated by time-dependent ROC analyses (**Figure 8B**, **8F**, **8J**). The predicted and observed values matched well (**Figure 8D**, **8H**, **8L**). The results of the DCA indicated that the training cohort demonstrated a positive net benefit in the threshold probability range of 0-82% (peak 12.5%). The validation cohort showed a positive net benefit in the range of 0-77% (peak 11.8%). The testing cohort exhibited a positive net benefit in the range of 0-78% (peak 11.7%) (**Figure 8C**, **8G**, **8K**). To sum up, the nomogram model provided excellent discrimination, good calibration and stable clinical utility in various cohorts (**Figure 8**).

ROC curve analysis and AUC comparison: FIGO stage, LAR, and risk score model

ROC curve analyses were performed using the pooled cohort comprising the training, validation, and testing datasets to compare the discriminative performance of FIGO stage, LAR, and the multivariable risk score model for predicting 3-year OS. In the training set, the ROC curve for FIGO stage demonstrated an AUC of 0.708, indicating a relatively limited ability to differentiate survival risk (**Figure 9A**). Similarly, LAR alone demonstrated an AUC value of 0.706, indicating modest prognostic performance (**Figure 9B**). Notably, the risk score model (**Figure 9C**) yielded substantially improved discriminative performance, with an AUC of 0.853, significantly higher than that of FIGO stage and LAR alone, reflecting a considerably stronger predictive ability. The AUC comparison in **Figure 9D** illustrated that the AUC values for risk score model were significantly higher than those of FIGO stage and LAR in training, validation and testing cohorts (all P < 0.001).

Discussion

This retrospective cohort study of 622 LACC patients systematically evaluated the prognostic value of LAR, both alone or in combination with clinicopathological variables. The results demonstrated that tumor stage, histological

Table 8. Cox regression analysis of prognostic factors affecting OS

Variable	Univariate			Multivariate		
	β	*P*-value	HR (95% CI)	β	*P*-value	HR (95% CI)
Age						
< 60 years						
≥ 60 years	0.832	0.003	2.298 (1.32-4.003)	0.811	0.005	2.25 (1.281-3.954)
BMI (kg/m^2)						
< 25						
≥ 25	-0.273	0.397	0.761 (0.404-1.431)			
Menopausal status						
No						
Yes	0.19	0.515	1.209 (0.683-2.14)			
Hypertension						
No						
Yes	0.118	0.729	1.126 (0.576-2.198)			
Diabetes						
No						
Yes	0.121	0.766	1.129 (0.508-2.51)			
Smoking history						
No						
Yes	-0.416	0.186	0.659 (0.356-1.223)			
Tumor stage (FIGO 2018)						
I + II						
III + IV	1.02	0.001	2.774 (1.496-5.143)	0.663	0.049	1.94 (1.004-3.751)
Histologic type						
Adenocarcinoma						
Squamous cell carcinoma	-0.036	0.938	0.964 (0.383-2.429)			
Differentiation						
Moderate/high						
Poor	1.008	< 0.001	2.741 (1.539-4.884)	0.913	0.002	2.491 (1.379-4.498)
Depth of stromal invasion						
< 1/2						
≥ 1/2	1.473	< 0.001	4.364 (2.506-7.599)	1.309	< 0.001	3.703 (2.054-6.674)
Vascular invasion						
No						
Yes	1.112	< 0.001	3.041 (1.678-5.511)	0.422	0.202	1.525 (0.797-2.916)
SCCA (ng/mL)						
< 13.2						
≥ 13.2	0.92	0.001	2.509 (1.441-4.371)	0.611	0.037	1.843 (1.038-3.273)
ALB (g/L)						
< 30						
≥ 30	-0.085	0.856	0.918 (0.364-2.313)			
NLR						
< 2.785						
≥ 2.785	0.244	0.408	1.276 (0.716-2.273)			
PLR						
< 181						
≥ 181	0.367	0.234	1.444 (0.789-2.644)			

AFR						
< 12.9						
≥ 12.9	0.049	0.916	1.051 (0.417-2.647)			
LAR						
< 4.015						
≥ 4.015	1.2	< 0.001	3.321 (1.904-5.793)	1.156	< 0.001	3.178 (1.784-5.661)
Radiotherapy duration (weeks)						
< 8						
≥ 8	0.437	0.122	1.548 (0.889-2.695)			
HPV						
Negative						
Positive	1.261	< 0.001	3.529 (1.843-6.758)	0.974	0.007	2.648 (1.31-5.355)

Note: HR: Hazard ratio, CI: Confidence interval, SCCA: Squamous cell carcinoma antigen, ALB: Albumin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, AFR: Albumin-to-fibrinogen ratio, LARP: Lactate dehydrogenase-to-albumin ratio, HPV, Human papillomavirus.

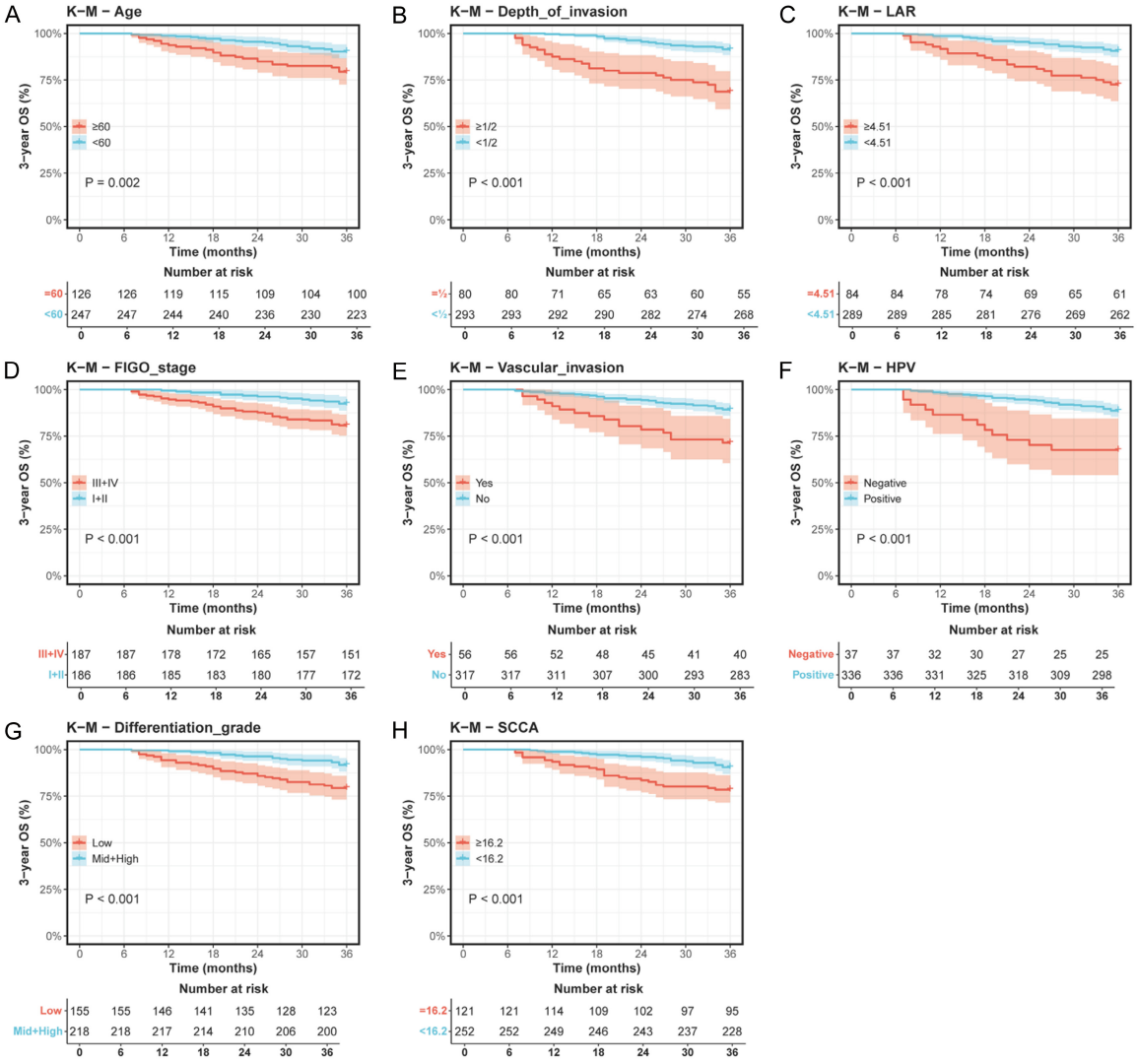

Figure 6. Stratified Kaplan-Meier survival curves. A. age (≥ 60 vs. < 60 years); B. stromal invasion (≥ 1/2 vs. < 1/2); C. LAR (≥ 4.015 vs. < 4.015); D. tumor stage (III + IV vs. I + II); E. vascular invasion (yes vs. no); F. HPV status (posi-

tive vs. negative); G. histologic differentiation (poor vs. moderate/high); H. SCCA (≥ 13.2 ng/mL vs. < 13.2 ng/mL). Notes: OS, overall survival; SCCA, squamous cell carcinoma antigen; LAR, lactate dehydrogenase-to-albumin ratio; HPV, Human papillomavirus.

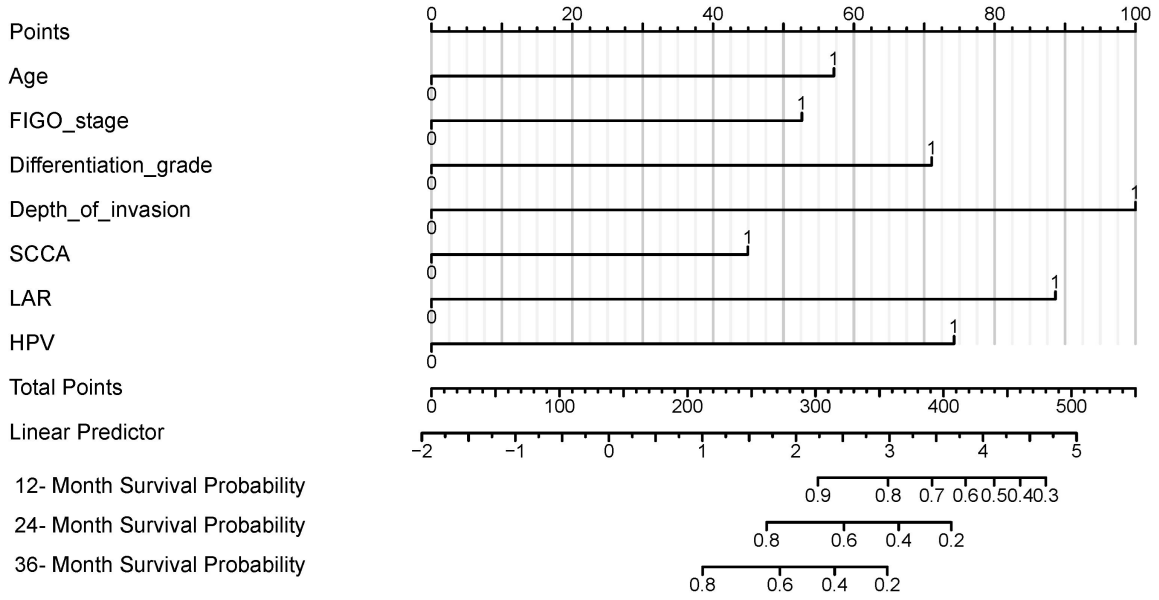

Figure 7. Nomogram for predicting 1-, 2-, and 3-year OS based on independent risk factors in the Cox regression model. Notes: OS, overall survival; SCCA, squamous cell carcinoma antigen; LAR, lactate dehydrogenase-to-albumin ratio; FIGO, International Federation of Gynecology and Obstetrics.

differentiation, depth of stromal invasion, NLR, and PLR were independent risk factors influencing the short-term efficacy of CCRT, with tumor stage showing the strongest predictive performance with OR = 1.803. Independent prognostic factors for OS included age ≥ 60 years, FIGO stage III-IV, poorl differentiation, stromal invasion ≥ 1/2 cervical wall, SCCA ≥ 13.2 ng/mL, and LAR ≥ 4.015. Among these variables, LAR showed the highest HR.

The dual nomogram models developed based on these factors demonstrated good discrimination and calibration in all three cohorts, with C-indices ranging from 0.668 to 0.941. DCA showed a positive net benefit over a wide range of threshold probabilities, supporting the clinical utility of these models. The performance of LAR in OS prediction was superior to SCCA, a traditional tumor marker, highlighting the unique value of LAR as a novel prognostic indicator. Further literature review has reinforced the prognostic role of LAR in multicenter studies, suggesting that the findings of the present study may have broader external validity [12]. FIGO stage, as the gold standard for prognostic assessment in cervical cancer, once again demonstrated a decisive role in survival prediction [18]. Other studies have also shown that a nomogram based on FIGO stage can accurately predict 3- to 5-year survival in cervical cancer patients [20]. A meta-analysis [21] indicated that high NLR is negatively associated with OS in cervical cancer; similarly, studies by Zhu et al. [22] and Cheng et al. [23] reported that elevated PLR and NLR were significantly associated with worse survival in metastatic cervical cancer.

Regarding LAR, previous research has mainly focused on solid tumors such as liver and lung cancers, reporting HR values generally ranging from 2 to 3. In our study, a higher HR (3.544) was observed in cervical cancer, which may be attributable to tumor-specific biological characteristics and differences in treatment modalities. Literature has indicated that elevated LAR is associated with adverse prognosis across multiple cancers [14]. Using a multifactorial predictive model incorporating multiple parameters, this study achieved a C-index of 0.796-0.941, which is significantly higher than the predictive accuracy reported in studies relying on single biomarkers (0.6-0.7). Additionally, this

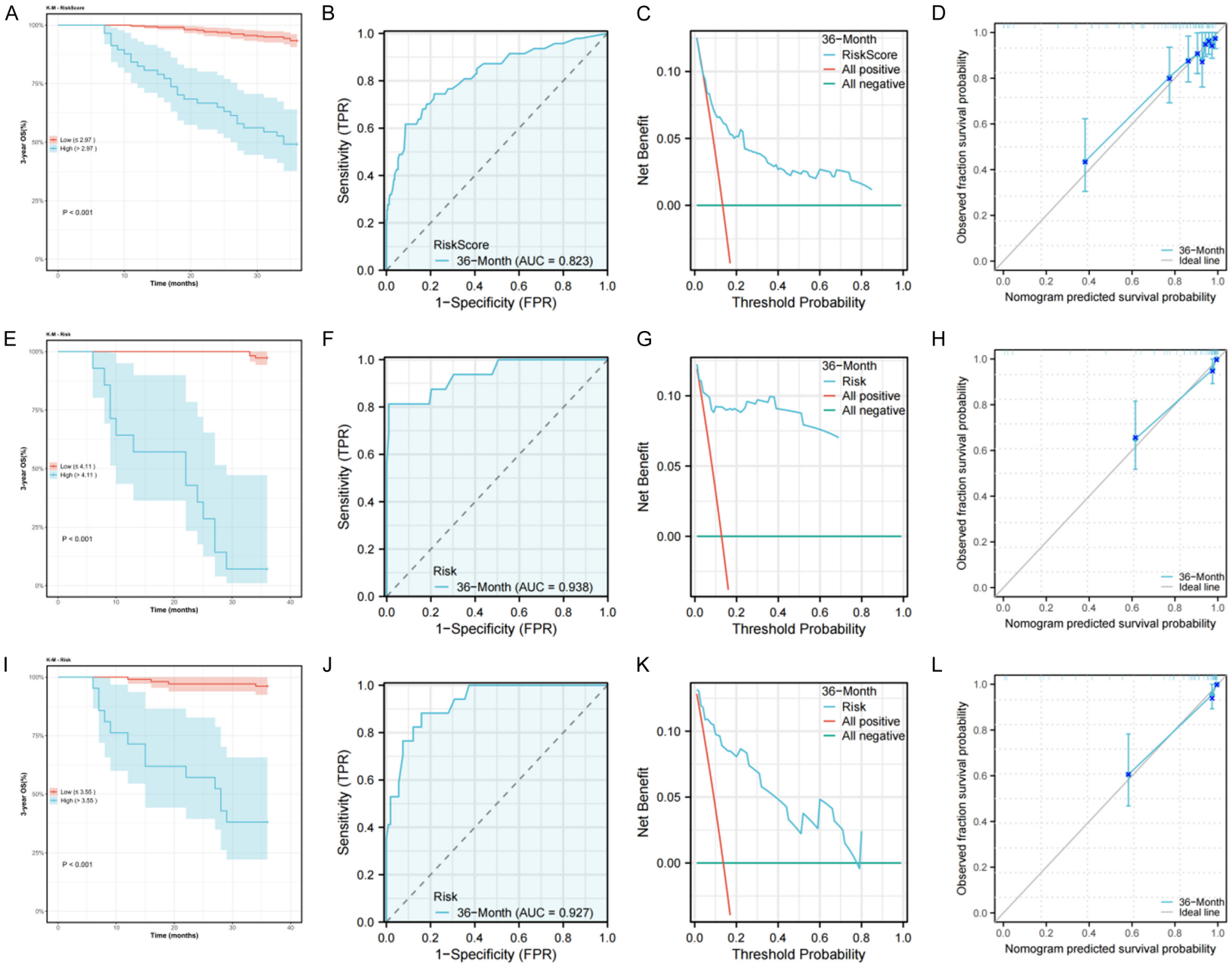
A
K-M - RiskScore
3-year OS(%)
Low (≤ 2.97)
High (> 2.97)
P < 0.001
Time (months)
B
Sensitivity (TPR)
RiskScore
36−Month (AUC = 0.823)
1−Specificity (FPR)
C
36−Month
RiskScore
All positive
All negative
Net Benefit
Threshold Probability
D
Observed fraction survival probability
36−Month
Ideal line
Nomogram predicted survival probability
E
K-M - Risk
3-year OS(%)
Low (≤ 4.11)
High (> 4.11)
P < 0.001
Time (months)
F
Sensitivity (TPR)
Risk
36−Month (AUC = 0.938)
1−Specificity (FPR)
G
36−Month
Risk
All positive
All negative
Net Benefit
Threshold Probability
H
Observed fraction survival probability
36−Month
Ideal line
Nomogram predicted survival probability
I
K-M - Risk
3-year OS(%)
Low (≤ 3.55)
High (> 3.55)
P < 0.001
Time (months)
J
Sensitivity (TPR)
Risk
36−Month (AUC = 0.927)
1−Specificity (FPR)
K
36−Month
Risk
All positive
All negative
Net Benefit
Threshold Probability
L
Observed fraction survival probability
36−Month
Ideal line
Nomogram predicted survival probability

Figure 8. Nomogram validation in the training, validation, and test sets. A, E, I. Kaplan-Meier survival curves stratified by risk scores; B, F, J. ROC curves for the nomogram in predicting 36-month OS; C, G, K. Decision curve analyses; D, H, L. Calibration plots. Notes: ROC, receiver operating characteristic; DCA, decision curve analysis; C-index, concordance index.

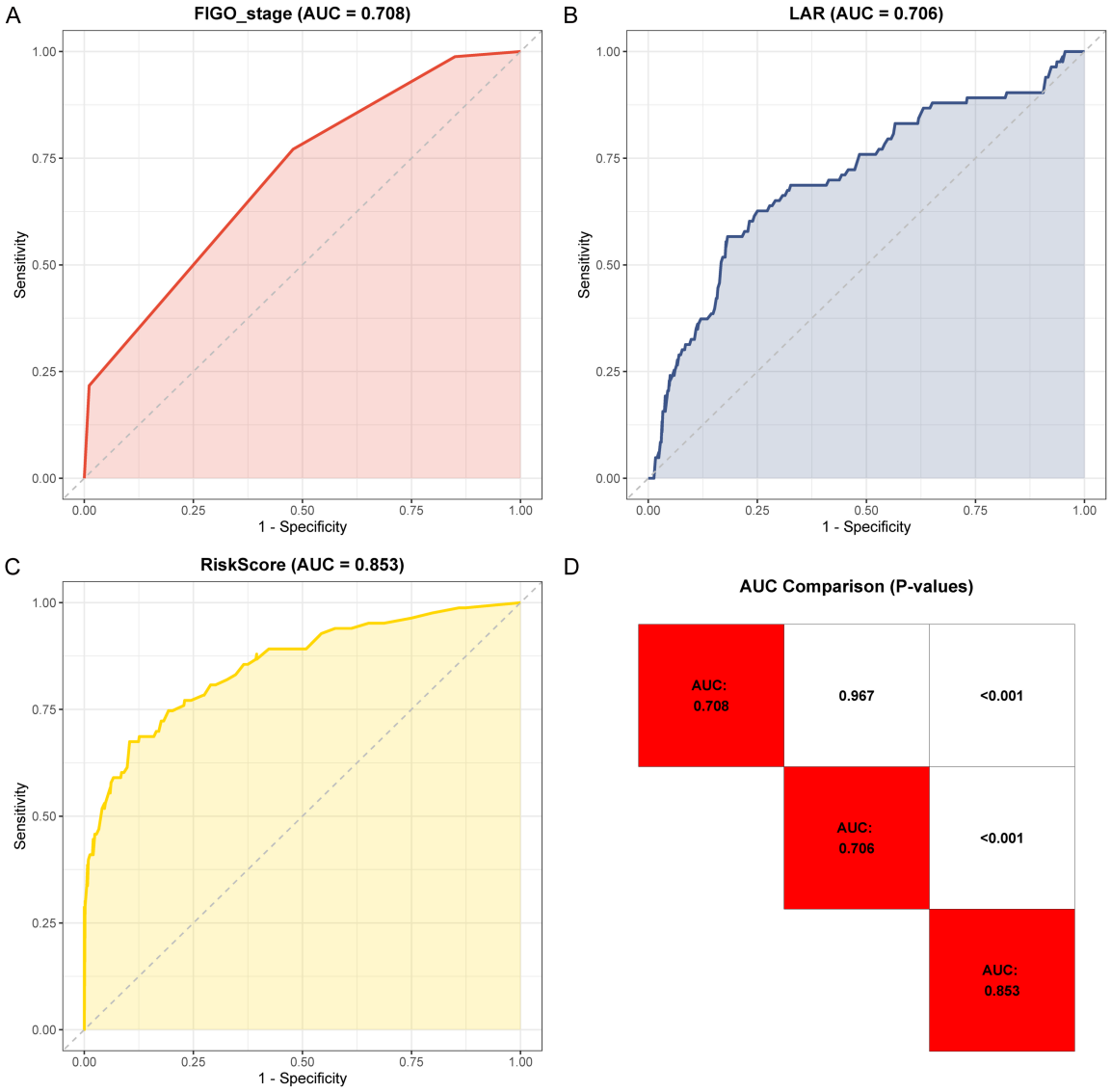

Figure 9. ROC curve analysis for predicting 3-year overall survival in the pooled cohort. A. ROC curve for the FIGO stage model (AUC = 0.708); B. ROC curve for the LAR model (AUC = 0.706); C. ROC curve for the multivariable risk score model (AUC = 0.853); D. AUC comparison matrix showing significant differences among the FIGO stage, LAR, and risk score models. Note: OS, overall survival; SCCA, squamous cell carcinoma antigen; LAR, lactate dehydrogenase-to-albumin ratio; HPV, human papillomavirus.

is the first large-cohort study to comprehensively evaluate LAR's prognostic value in LACC, addressing an important knowledge gap. Nonetheless, Wang et al. [24] report that in LACC, elevated levels of LDH and C-reactive protein (CRP) correlated with poorer OS. Given that LAR integrates metabolic and inflammatory components, it is biologically plausible that similar prognostic associations would be observed. Pooled HRs from similar studies (HR ≈ 1.8-2.5) further suggest that inflammation-metabolism-based biomarkers consistently predict prognosis across different ethnic groups and disease stages. However, the rela-

tively higher HRs observed in Asians may be partly due to differences in HPV subtype distribution and lifestyle-related factors [14].

LAR, defined as the ratio of LDH to ALB, integrates two critical dimensions of tumor-host interactions: tumor metabolic activity and host nutritional-immune status [12]. Elevated LDH reflects the Warburg effect, characterized by aerobic glycolysis in cancer cells even in the presence of oxygen. This metabolic reprogramming confers the biosynthesis and energy advantage to the cancer cells that fuel their proliferation and invasion. Further, excessive lactate accumulation in the tumor microenvironment induces acidosis, which restricts T-cell and natural killer (NK) cell function, thereby promoting immune escape [24-26]. Meanwhile, increased LDH levels usually reflect a higher tumor burden, enhanced invasiveness and CCRT-resistance. Kocianova et al. reported that the Warburg effect is regualted by p53 and hypoxia-inducible factor 1α (HIF-1α). In contrast, reduced ALB level signifies a condition of chronic inflammation and nutritional depletion, conditions that are closely associated with impaired antitumor immune responses. Tang et al. [27] and Gupta et al. [28] both reported in their studies that reduced ALB level serves an inflammatory marker and is negatively associated with cancer survival. Persistent HPV infection may amplify this effect in the case of cervical cancer as inflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α) can inhibit hepatic synthesis of ALB, thereby forming a vicious cycle.

An increased LAR, therefore, indicates both hyperactive tumor metabolism and compromised immune defense, resulting in a biological milieu favorable for tumor progression. Moreover, LAR may indirectly indicate the degree of tumor hypoxia and angiogenesis, both of which are associated with reduced radiosensitivity and poorer outcomes after CCRT. This finding is consistent with the findings of Liu et al. [29], who reported that Warburg effect contributes to chemoresistance mechanisms. Moreover, literature shows that targeting LDHA can reverse the Warburg effect, implying that LAR may also represent a potential therapeutic and stratification biomarker [30].

Prediction models incorporating LAR and clinicopathological variable may therefore have substantial clinical value. Patients with a high pre-treatment LAR (≥ 4.015) can be considered as a high-risk group dueing treatment planning. Clinician may consider more aggressive therapeutic strategies for these patients, including radiotherapy dose escalation, including chemotherapy cycles, and/or the addition of neoadjuvant therapy. In addition, these models may facilitate individualized follow-up strategies: high-risk patients may benefit from closer monitoring, while low-risk patients could undergo less intensive follow-up, thereby optimizing medical resources allocation. From a cost-effectiveness, perspective, LAR assessment relies on routine biochemical tests, with a cost of about 20-30 yuan, which is substantially lower than imaging or molecular biomarker detection, This affordability enhances its feasibility for widespread application, especially in primary and resource-limited facilities. In the era of precision medicine, such models offer a simple, economical, and efficient prognostic tool for patients with LACC, supporting truly individualized treatment.

Additionally, LAR levels could be monitored dynamically to act as a precursor outcome for therapeutic efficacy, with strong basing on a timely change. This corroborates the findings of Yang et al. [31]. who reported that nomogram models for LACC treated with CCRT could predict the 5-year survival rates and Chen et al. who used different parameters. A model like this could in clinical practice be combined with PET-CT to form an assessment framework that is multi-modal; for example, CCRT could be used in concert with immune checkpoint inhibitors in patients with high LAR to overcome resistance to treatment.

Several limitations in this study should be acknowledged. First, the single-center retrospective design may introduce selection bias, and the generalizability of these results needs external validation. Second, the median follow-up time was relatively short (approximately 3 years), limiting evaluation of the model's predictive value for long-term survival outcomes. Third, HPV genotyping, p16 expression, tumor mutation burden, and other molecular markers were not included, which may underestimate the influence of tumor biological heterogeneity

on prognosis. Fourth, the lack of data on dynamic changes in LAR during treatment precluded evaluation of its utility as a real-time monitoring indicator. Additionally, as the study population consisted mainly of Asian patients, the applicability of the findings to other ethnicities remains uncertain [32]. As noted in the literature [33], variations in nomogram and T-score predictive performance across different ethnic populations deserve further exploration in LACC.

Future work should validate the stability and generalizability of these models in multi-center prospective cohorts and explore the combination of LAR with molecular subtyping, radiomics, and other emerging technologies to build more precise multi-modal predictive models. Indeed, literature has suggested that incorporating artificial intelligence into long-term prognostic models can improve C-index performance [34]. Special attention should be paid to the predictive value of LAR in the immunotherapy and its correlation with immune microenvironment-related biomarkers, which may provide novel guidance for cervical cancer immunotherapy, such as predicting responses to PD-1 inhibitors in high-LAR patients. In addition, randomized controlled trials could be conducted to evaluate whether interventions stratified by LAR can improve OS, thereby strengthening the clinical translation of this model from an evidence-based medicine perspective.

Conclusion

The combination of LAR and clinicopathological features provides as an effective tool for predicting both short-term treatment response and long-term overall survival in LACC patients undergoing CCRT. The two nomogram models constructed herein demonstrated good discriminatory ability, calibration, and clinical applicability. As a low-cost, non-invasive, and readily generalizable evaluation method, this approach offers practical benefits for patient risk stratification, optimization of individualized treatment strategies, and follow-up management, thereby supporting the development of precision medicine for LACC.

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Disclosure of conflict of interest

None.

Ethics statement

This study adhered to the Declaration of Helsinki and was approved by the Ethics Committees of The Third Affiliated Hospital of Guangzhou Medical University ([2026] 004) and Jinshazhou Hospital of Guangzhou University of Chinese Medicine (JSZ-IEC-SL-KT-20251115(1)). Informed consent was obtained from participants at the former hospital, while it was waived at the latter due to the retrospective nature of the study.

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