

Integration of Delta-Radiomics Features and Inflammatory Biomarkers for Neoadjuvant Chemo-Immunotherapy Efficacy in Locally Advanced Esophageal Squamous Cell Carcinoma

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Purpose: Neoadjuvant chemo-immunotherapy (NACI) significantly increases the pathological complete response (pCR) rate in locally advanced esophageal squamous cell carcinoma (LA-ESCC). However, not all patients benefit from this approach. This study aims to construct a multi-omics model for predicting the efficacy of NACI in LA-ESCC patients by integrating delta-radiomics features (delta-RFs) and the dynamic changes in inflammatory biomarkers.

Patients and Methods: Our study was the first to develop a multi-omics model based on dynamic CT imaging features and inflammatory indices in patients with LA-ESCC. A total of 217 patients were divided into training (n = 152) and validation (n = 65) cohorts. Following the completion of the data standardization process, delta-RFs were extracted using the PyRadiomics, representing the relative imaging changes between pre- and post-treatment. The algorithm known as the least absolute shrinkage and selection operator (LASSO) was selected to pinpoint the most significant RFs for predicting pCR. The imaging signatures and clinical characteristics were integrated by the logistic regression analysis. Finally, a nomogram was constructed based on the identified independent predictors.

Results: The pCR rates were approximately 30% among the enrolled patients. A total of 1834 delta-RFs were extracted. The 12 delta-RFs signature was determined by the optimal regularization parameter using the LASSO algorithm. Furthermore, multivariate regression analyses confirmed that tumor length, delta-RFs signature, and delta-systemic immune-inflammation index (SII) served as independent predictors for pCR prediction. Finally, a nomogram was constructed and the multi-omics model exhibited impressive predictive performance, with area under curve (AUC) values of 0.853 and 0.796 for the training and validation cohorts, respectively. This method aims to support informed treatment decisions and facilitate the development of personalized treatment strategies.

Conclusion: The multi-omics model, which is based on the delta-RFs signature and delta-SII indicators prior to surgery, effectively predicts the NACI treatment response in patients with LA-ESCC.

Keywords: locally advanced esophageal squamous cell carcinoma, neoadjuvant chemo-immunotherapy, delta-radiomics features, systemic immune-inflammation index, Pathological complete response

Introduction

Globally, more than half of all new cases of esophageal squamous cell carcinoma (ESCC) occur in China each year, making it a major contributor to the country's cancer burden.¹ Due to its aggressive nature, ESCC is often diagnosed at an advanced local stage. Neoadjuvant therapy aims to downstage the tumor prior to surgery and improve patient

outcomes. Clinical studies have shown that neoadjuvant chemo-immunotherapy (NACI) significantly increases the pathological complete response (pCR) rate in locally advanced ESCC (LA-ESCC).^{2,3} The recent Phase III ESCORT-NEO/NCCES01 trial demonstrated that NACI substantially improved the pCR rate compared to neoadjuvant chemotherapy alone (28.0% vs 4.7%).⁴ However, not all patients benefit from this approach, highlighting the urgent need to identify predictive biomarkers for treatment efficacy.^{5,6}

The spatial heterogeneity of solid tumors significantly limits the predictive performance of biomarkers derived from invasive biopsies. Commonly used biomarkers, such as tumor mutation burden (TMB) and PD-1/PD-L1 expression, have yet to demonstrate consistent and reliable predictive value for the efficacy of NACI in LA-ESCC.⁷ With advances in imaging technologies, the non-invasive advantages of radiomics have become increasingly prominent in tumor research.^{8,9} CT, a widely used imaging modality, plays an important role in the diagnosis and evaluation of tumor activity in ESCC. Previous studies have demonstrated that radiomics offers strong predictive performance in the diagnosis, prognosis, and treatment response assessment of ESCC.^{10–13} However, models based on single-phase imaging data fail to account for temporal changes during treatment, thereby limiting their predictive accuracy. As a result, delta-radiomics, an approach that analyzes changes in radiomics features (RFs) over the course of treatment, has attracted growing interest. The delta-RFs have shown promising results in predicting treatment response and clinical prognosis across various tumor types.^{14–17}

Single radiomics models often lack clinical interpretability. Currently, multi-omics models that integrate imaging and clinical data are emerging as the trend in tumor model construction. This study primarily focuses on the development of a NACI response prediction model. Recent studies have indicated that cancer-related inflammatory responses are closely associated with tumorigenesis, progression, prognosis, and treatment response.^{18,19} In clinical practice, peripheral blood inflammatory indexes are commonly used to reflect systemic inflammatory status. Given these insights, this study constructed a predictive model for the efficacy of NACI in LA-ESCC, for the first time, by integrating dynamic CT RFs and changes in inflammatory biomarkers throughout the treatment process. The successful establishment of this model will effectively guide neoadjuvant therapy for LA-ESCC patients and promote the further adoption of personalized clinical treatment strategies.

Materials and Methods

Patient Selection

Approval from the appropriate ethics committees at Harbin Medical University Cancer Hospital was secured. All patients signed informed consent forms.

Patients with LA-ESCC were retrospectively recruited from Harbin Medical Cancer Hospital between February 2019 and December 2024. A total of 372 patients met the inclusion criteria, which were as follows: (1) biopsy-confirmed LA-ESCC (cT1b-2N+M0 or cT3-4a any N M0); (2) patients who received NACI and completed the NACI regimen; (3) CT examinations performed within two weeks before NACI initiation and surgery. Patients were excluded if they met any of the following criteria: (1) presence of distant metastases or other malignancies; (2) absence of CT images or clinical data before and after NACI; (3) administration of other anti-cancer treatments before NACI; (4) insufficient CT image quality. Finally, 217 patients remained eligible for the study. These eligible individuals were randomly assigned to a training cohort (n=152) and a validation cohort (n=65) in a 7:3 ratio for further analysis. To minimize bias and ensure balanced representation of responders and non-responders, we applied stratified randomization based on pCR status. The overall flowchart of this study was shown in [Figure 1](#).

NACI Administration

All patients received 2–4 cycles of NACI before undergoing radical esophagectomy with lymphadenectomy upon completion of the treatment regimen. This regimen includes immune checkpoint inhibitors (Camrelizumab or Tislelizumab) in combination with Paclitaxel for Injection (Albumin Bound) (260mg/m²) and Cisplatin (75mg/m²). Tumor response was assessed twice: after the second cycle of chemotherapy and again prior to surgery, following the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Further details on the treatment protocol are available in previous studies.³ Clinical characteristics were documented before the initiation of treatment and prior to surgical intervention.

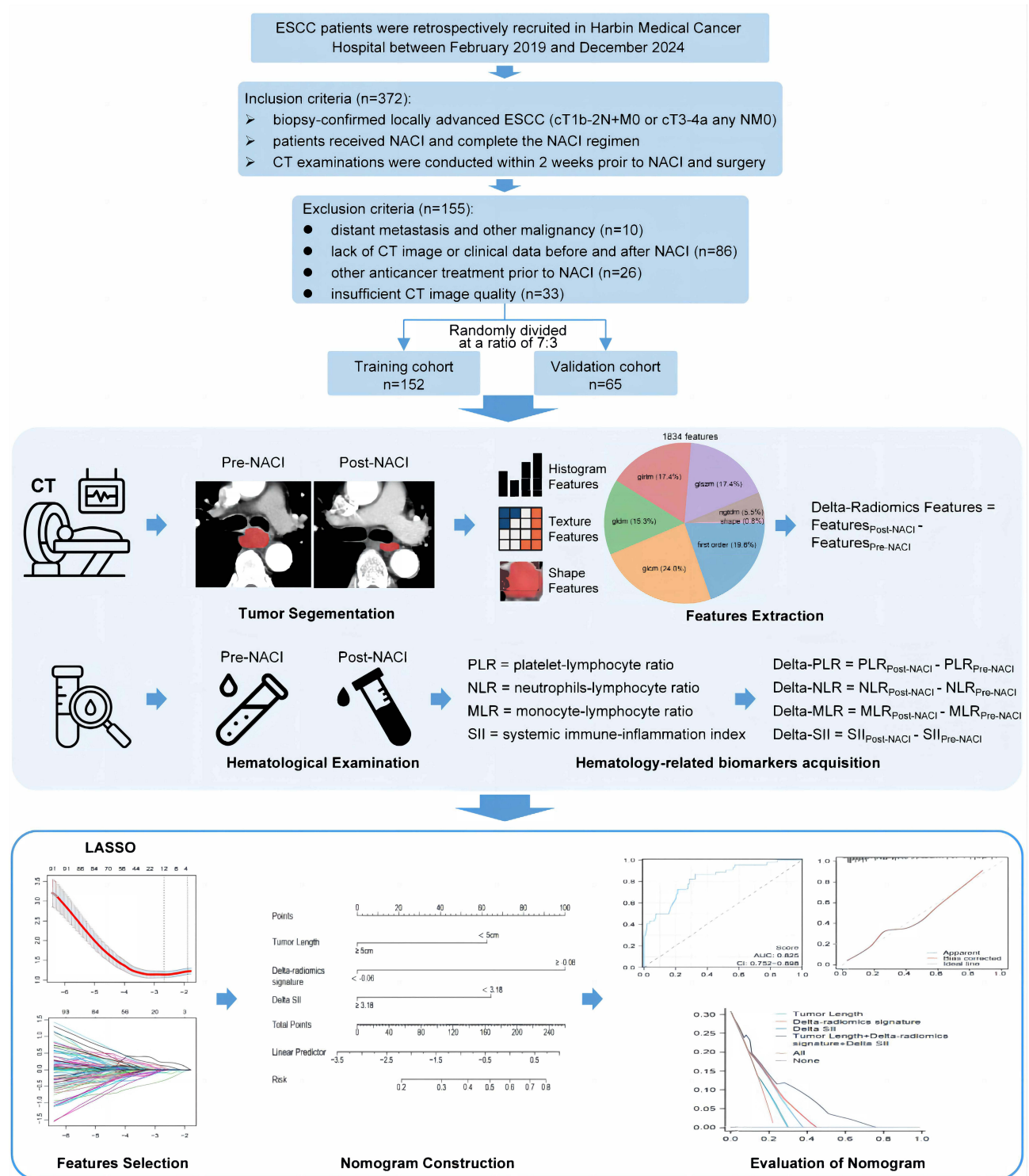


Figure 1 The study design.

Abbreviations: CT, computed tomography; ESCC, esophageal squamous cell carcinoma; LASSO, least absolute shrinkage and selection operator; MLR, monocyte-lymphocyte ratio; NACI, neoadjuvant chemo-immunotherapy; NLR, neutrophils-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index.

Regions of Interest Segmentation and Feature Extraction

CT images were acquired using one of two multi-slice spiral CT scanners (SOMATOM Definition or Brilliance 64). Detailed information on CT parameters is provided in [Table S1](#). To avoid introducing temporal bias, it is advisable to utilize imaging data obtained from the same equipment both prior to and following patient treatment whenever feasible.

CT images were reconstructed with a slice thickness of 1.5 mm and an increment of 1.5 mm. All patients received an intravenous injection of nonionic iodine contrast agents. Tumor regions were delineated independently and blindly by two experienced radiologists using ITK-Snap software (version 3.6.0). To evaluate annotation consistency, regions of interest (ROIs) were re-evaluated after a two-month interval. Intraclass correlation coefficients (ICCs) were calculated to ensure the reliability of the segmentations.

Before extracting RFs, image preprocessing was performed in three steps. First, linear interpolation was applied for image resampling to a uniform voxel size of $1 \times 1 \times 1$ mm. Second, gray-level discretization was implemented to convert serial images into discrete integer values. Finally, mixed noise introduced during image digitization was reduced using logarithmic and wavelet filters, enabling the extraction of both high- and low-frequency features. RFs were extracted using the open-source package PyRadiomics (version 3.0.1, <https://pyradiomics.readthedocs.io/en/latest/>).²⁰ A total of 1834 RFs were derived separately from unenhanced, arterial, and venous phase images to quantify tumor heterogeneity.

Delta-RFs Selection and Delta-Radiomics Signature Construction

To ensure reproducibility and minimize operator bias, ROI segmentation was independently performed by two board-certified radiologists, each with over 10 years of experience in oncologic imaging. Both were blinded to all clinical characteristics, treatment regimens, and patient outcomes. Image datasets were randomly assigned for segmentation, and discrepancies were resolved by consensus during a joint review session. To further validate segmentation stability, a senior radiologist repeated ROI delineation on 30 randomly selected patients after a 2-month interval, and the ICC was calculated to assess test–retest reproducibility. Features with $ICC > 0.75$ were considered robust and retained for further analysis. Delta-RFs, representing the relative change in RFs between pre-treatment and post-treatment images, were calculated using the following formula: $\text{delta-RFs} = \text{Features}_{\text{Post-NACI}} - \text{Features}_{\text{Pre-NACI}}$. $\text{Features}_{\text{Pre-NACI}}$ and $\text{Features}_{\text{Post-NACI}}$ correspond to the radiomic feature values extracted from CT images before the initiation of NACI and after its completion, respectively. All feature values were extracted in their original units (eg, intensity-based features in Hounsfield units, texture features as dimensionless ratios), and delta-RFs were expressed in the same corresponding units.

To minimize redundancy and reduce computational complexity, the least absolute shrinkage and selection operator (LASSO) algorithm was applied to the training cohort to identify the most relevant delta-RFs for pCR prediction. To ensure reproducibility of feature selection, a fixed random seed ($\text{set.seed} = 1234$) was applied during cross-validation. The optimal regularization parameter (λ) was determined through 10-fold cross-validation, selecting the value that maximized the area under the receiver operating characteristic curve (AUC). With this optimal λ , the coefficients of most irrelevant delta-RFs were reduced to zero, while only the features with nonzero coefficients, which were strongly associated with pCR, were retained to construct the delta-radiomics signature.

A fitting formula for the delta-radiomics signature was developed using a linear combination of the selected features weighted by their corresponding nonzero coefficients. This formula was subsequently applied to compute the delta-radiomics signature for each patient in both the training and validation cohorts. The association between the delta-radiomics signature and pCR was initially assessed in the training cohort and then independently validated in the validation cohort to confirm its predictive value with the predictive ability of the AUC and calibration curves.

Hematology-Related Biomarkers Acquisition

Peripheral blood cell counts obtained within two weeks prior to the initiation of NACI and surgery were extracted from the hospitals' clinical data repositories. Absolute counts of neutrophils, monocytes, platelets, and lymphocytes were used to calculate hematology-related biomarkers, including the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and systemic immune-inflammation index (SII). $SII = (\text{platelet count} \times \text{neutrophil count}) / \text{lymphocyte count}$. Delta-PLR, delta-NLR, delta-MLR, and delta-SII represent the differences in PLR, NLR, MLR, and SII values measured before and after treatment, respectively.

Nomogram Construction and Validation

The logistic regression analyses were performed to evaluate the association of pCR with clinical characteristics, delta-RFs signature, delta-PLR, delta-NLR, delta-MLR, and delta-SII. Variables with a P-value of less than 0.05 in the

univariate logistic regression analysis were included in the multivariate logistic regression model to identify independent predictive factors. Based on the results of the multivariate analysis in the training cohort, nomograms were developed to provide an individualized estimation of pCR probability. These nomograms incorporated all independent predictive factors and served as visual predictive tools. The performance of the nomogram model was evaluated using the concordance index (C-index), AUC, calibration curves, and decision curve analysis (DCA).

Missing Data Handling

Prior to statistical analysis, a comprehensive assessment of data completeness was conducted. Patients with missing key variables—such as pre- or post-treatment CT images, inflammatory biomarkers, or pathological outcomes—were excluded during eligibility screening. For remaining clinical variables with missing values less than 5%, single imputation using the mean (for normally distributed variables) or median (for non-normally distributed variables) was performed. No variable exhibited a missingness rate exceeding 5%. Sensitivity analyses demonstrated that imputation did not substantially alter the predictive performance of the multi-omics model.

Statistical Analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test, while continuous variables were compared using the Mann-Whitney U-test or independent t-test, depending on data distribution. The median value of continuous variables was used as the cutoff point. A two-sided P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R (version 4.2.1) and Python (version 3.7.0). To evaluate whether the sample size provided sufficient statistical power for the predictive modeling. Based on the observed pathological complete response rate (30%), the available sample size ensured >80% power to detect odds ratios of 2.0 or greater for independent predictors at a two-sided α level of 0.05. In addition to the AUC and calibration curves, the Brier score was calculated to quantify the overall accuracy of probabilistic predictions, with lower values indicating better model calibration. The optimal cutoff value for discriminating pCR from non-pCR was determined using the Youden index derived from the receiver operating characteristic (ROC) curve. Sensitivity and specificity corresponding to this cutoff were calculated for both the training and validation cohorts to evaluate the clinical applicability of the model.

Results

Patient Characteristics

The study included a total of 217 patients with LA-ESCC, who were stratified into a training cohort (n=152) and a validation cohort (n=65). A summary of baseline clinical characteristics for both cohorts is provided in [Table 1](#), which include age, gender, smoking and drinking status, clinical tumor, lymph node, and metastasis (TNM) stages, tumor location, tumor length, number of chemo-immunotherapy cycles, delta-PLR, delta-NLR, delta-MLR, and delta-SII (all $P > 0.05$). The pCR rates were 28.9% in the training cohort and 30.8% in the validation cohort.

Delta-RFs Selection and Signature Establishment

A total of 1834 RFs were extracted from the CT images. To capture dynamic changes during NACI, delta-RFs were computed to provide complementary predictive information. In the training cohort, the LASSO algorithm was used to determine the optimal regularization parameter ($\log [\lambda] = -2.722$), resulting in the selection of 12 delta-RFs for pCR stratification ([Figure 2A and B](#)). A delta-RFs signature was subsequently developed using a linearly weighted combination of these selected features and their corresponding nonzero coefficients, as detailed in [Table S2](#). The delta-RFs signature values were calculated for each patient in both the training and validation cohorts.

The delta-RFs signature demonstrated strong discriminative ability for differentiating pCR from non-pCR, with an AUC of 0.825 in the training cohort ([Figure 2C](#)). This performance was further validated in the independent validation cohort, achieving an AUC of 0.760 ([Figure 2D](#)). Moreover, calibration curves showed a high level of agreement between observed pCR outcomes and predicted probabilities in both cohorts ([Figure 2E and F](#)). These findings indicate that the delta-RFs signature is a promising imaging biomarker for predicting pCR in patients undergoing NACI.

Table 1 Baseline Clinical Characteristics of the Training and Validation Cohorts

Characteristics	Training Cohort (n = 152)	Validation Cohort (n = 65)	P-value
Age (years), n (%)			0.395
< 60	63 (41.4%)	31 (47.7%)	
≥ 60	89 (58.6%)	34 (52.3%)	
Gender, n (%)			0.935
Male	147 (96.7%)	63 (96.9%)	
Female	5 (3.3%)	2 (3.1%)	
Smoking, n (%)			0.315
Never	39 (25.7%)	21 (32.3%)	
Former or current	113 (74.3%)	44 (67.7%)	
Drinking, n (%)			0.089
Never	43 (28.3%)	26 (40%)	
Former or current	109 (71.7%)	39 (60%)	
cT stage, n (%)			0.261
T2	49 (32.2%)	16 (24.6%)	
T3	103 (67.8%)	49 (75.4%)	
cN stage, n (%)			0.651
N0	14 (9.2%)	5 (7.7%)	
N1	88 (57.9%)	42 (64.6%)	
N2	50 (32.9%)	18 (27.7%)	
cTNM stage, n (%)			0.307
II	24 (15.8%)	14 (21.5%)	
III	128 (84.2%)	51 (78.5%)	
Tumor Location, n (%)			0.416
Upper	7 (4.6%)	6 (9.2%)	
Middle	77 (50.7%)	32 (49.2%)	
Lower	68 (44.7%)	27 (41.5%)	
Tumor length (cm), n (%)			0.867
< 5	87 (57.2%)	38 (58.5%)	
≥ 5	65 (42.8%)	27 (41.5%)	
Cycles, n (%)			0.192
2–3	114 (75%)	54 (83.1%)	
4	38 (25%)	11 (16.9%)	
Delta-PLR, mean ± sd	2.158 ± 0.182	2.186 ± 0.167	0.106
Delta-NLR, mean ± sd	4.618 ± 0.582	4.656 ± 0.499	0.641
Delta-MLR, mean ± sd	0.515 ± 0.122	0.523 ± 0.118	0.661
Delta-SII, mean ± sd	3.190 ± 0.249	3.162 ± 0.233	0.434
pCR, n (%)			0.787
No	108 (71.1%)	45 (69.2%)	
Yes	44 (28.9%)	20 (30.8%)	

Abbreviations: Cycles, the number of chemo-immunotherapy cycles before surgery; cT, clinical tumor staging; cN, clinical lymph node staging; cM, clinical distance metastasis staging; MLR, mono-cyte-lymphocyte ratio; NLR, neutrophils-lymphocyte ratio; OR, odds ratio; pCR, pathological complete response; PLR, platelet-lymphocyte ratio; SD, standard deviation; SII, systemic immuneinflammation index.

Logistic Analysis Outcomes in the Training Cohort

Univariate and multivariate logistic analyses for pCR showed that tumor length (odds ratio [OR] = 0.364; 95% confidence interval [CI], 0.153–0.864; $P = 0.022$), delta-RFs signature (OR = 5.051; 95% CI, 2.131–11.978; $P < 0.001$), and delta-SII (OR = 0.353; 95% CI, 0.156–0.798; $P = 0.012$) served as the independent predictors (Table 2). The variance inflation factor for each included predictor (tumor length, delta-RFs signature, and delta-SII) were calculated to assess multicollinearity.

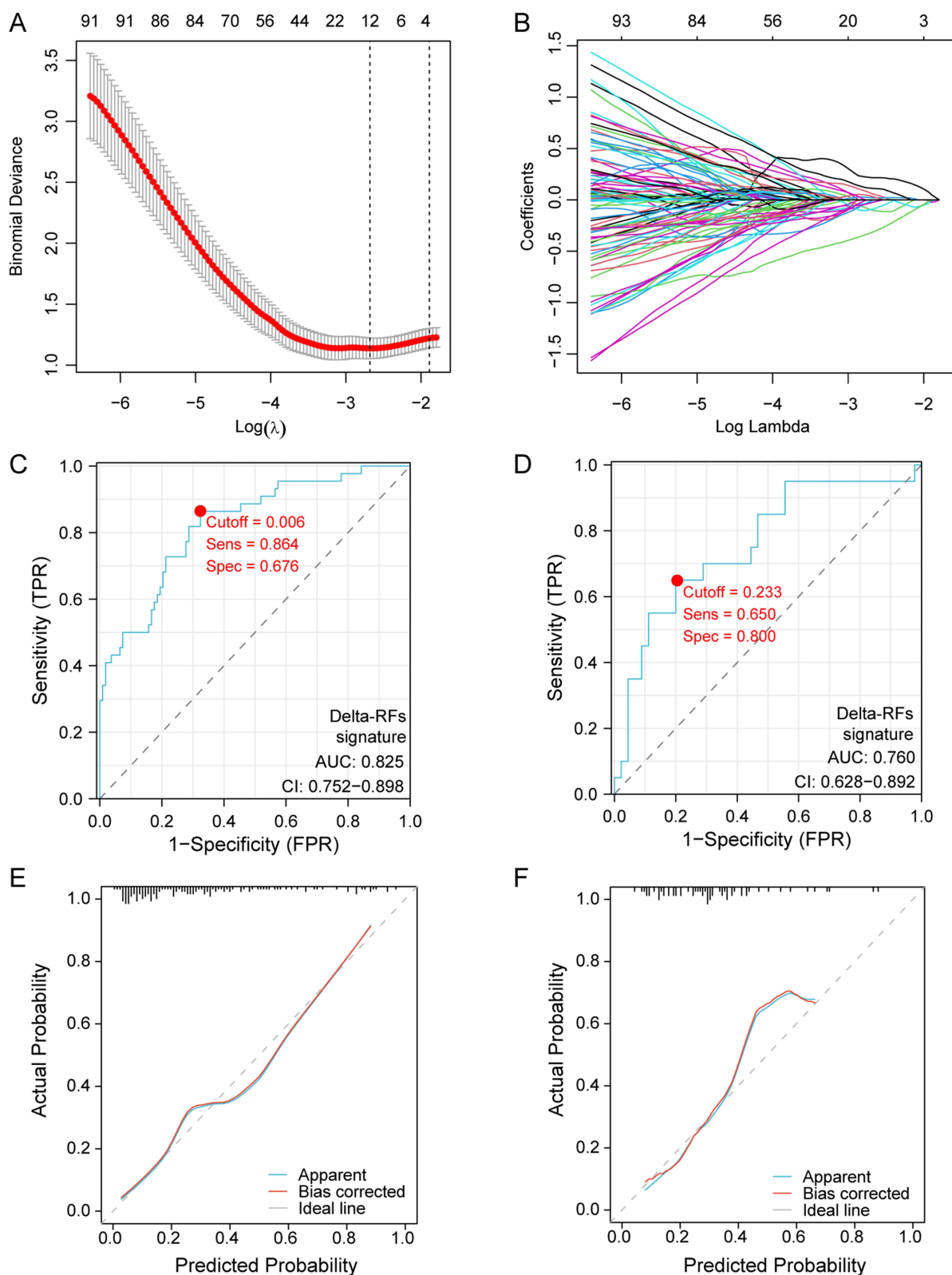


Figure 2 Features selection and delta-RFs signature construction. Least absolute shrinkage and selection operator (LASSO) logistic regression of delta-RFs (A) and the regularization parameter λ (B). Receiver operating characteristic curves for the prediction of pCR with delta-RFs signature in the training (C) and validation sets (D). Calibration curves of the delta-RFs signature in the training (E) and validation sets (F).

Abbreviations: RF, radiomics feature; pCR, pathological complete response.

Variance inflation factor values were 1.32 for tumor length, 1.47 for the delta-RFs signature, and 1.29 for delta-SII, indicating no evidence of multicollinearity.

Nomogram Development and Validation

Based on the results of the multivariate logistic regression analysis, a visually interpretable nomogram was developed by integrating tumor length, the delta-RFs signature, and delta-SII (Figure 3A). In the training cohort, the nomogram demonstrated

Table 2 Univariate and Multivariate Logistic Regression Analysis for pCR in the Training Cohort

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)				
< 60	Reference			
≥ 60	0.794 (0.391–1.611)	0.522		
Smoking				
Never	Reference			
Former or current	0.889 (0.402–1.966)	0.771		
Drinking				
Never	Reference			
Former or current	1.074 (0.49–2.35)	0.859		
cT stage				
T2	Reference			
T3	1.192 (0.557–2.553)	0.651		
cN stage				
N0	Reference			
N1	0.678 (0.378–1.217)	0.193		
N2	0.624 (0.127–1.365)	0.245		
cTNM stage				
II	Reference			
III	0.411 (0.168–1.015)	0.101		
Tumor Location				
Upper	Reference			
Middle	1.034 (0.562–1.901)	0.915		
Lower	1.318 (0.262–5.437)	0.771		
Tumor length (cm)				
< 5	Reference		Reference	
≥ 5	0.283 (0.127–0.631)	0.002	0.364 (0.153–0.864)	0.022
Cycles, n (%)				
2–3	Reference			
4	1.183 (0.533–2.624)	0.681		
Delta-RFs signature				
< −0.06	Reference		Reference	
≥ −0.06	6.355 (2.773–14.563)	< 0.001	5.051 (2.131–11.978)	< 0.001
Delta-PLR				
< 2.17	Reference			
≥ 2.17	0.881 (0.436–1.775)	0.721		
Delta-NLR				
< 4.57	Reference			
≥ 4.57	1.676 (0.824–3.408)	0.154		

(Continued)

Table 2 (Continued).

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Delta-MLR				
< 0.51	Reference			
≥ 0.51	0.768 (0.424–1.635)	0.689		
Delta-SII				
< 3.18	Reference		Reference	
≥ 3.18	0.301 (0.141–0.636)	0.002	0.353 (0.156–0.798)	0.012

Abbreviations: Cycles, the number of chemo-immunotherapy cycles before surgery; cT, clinical tumor staging; cN, clinical lymph node staging; cM, clinical distance metastasis staging; MLR, monocyte-lymphocyte ratio; NLR, neutrophils-lymphocyte ratio; OR, odds ratio; pCR, pathological complete response; PLR, platelet-lymphocyte ratio; RF, radiomics feature; SII, systemic immuneinflammation index.

excellent discrimination ability, with a C-index of 0.832 and an AUC of 0.853 (Figure 3B). Similarly, in the validation cohort, the model maintained strong predictive accuracy, achieving a C-index of 0.783 and an AUC of 0.796 (Figure 3C).

In the training cohort, the calibration curves demonstrated a high degree of agreement between the nomogram-predicted probability of pCR and the actual observed outcomes, confirming the model's reliability (Figure 4A). DCA further validated the clinical utility of the nomogram by exhibiting satisfactory positive net benefits across a range of

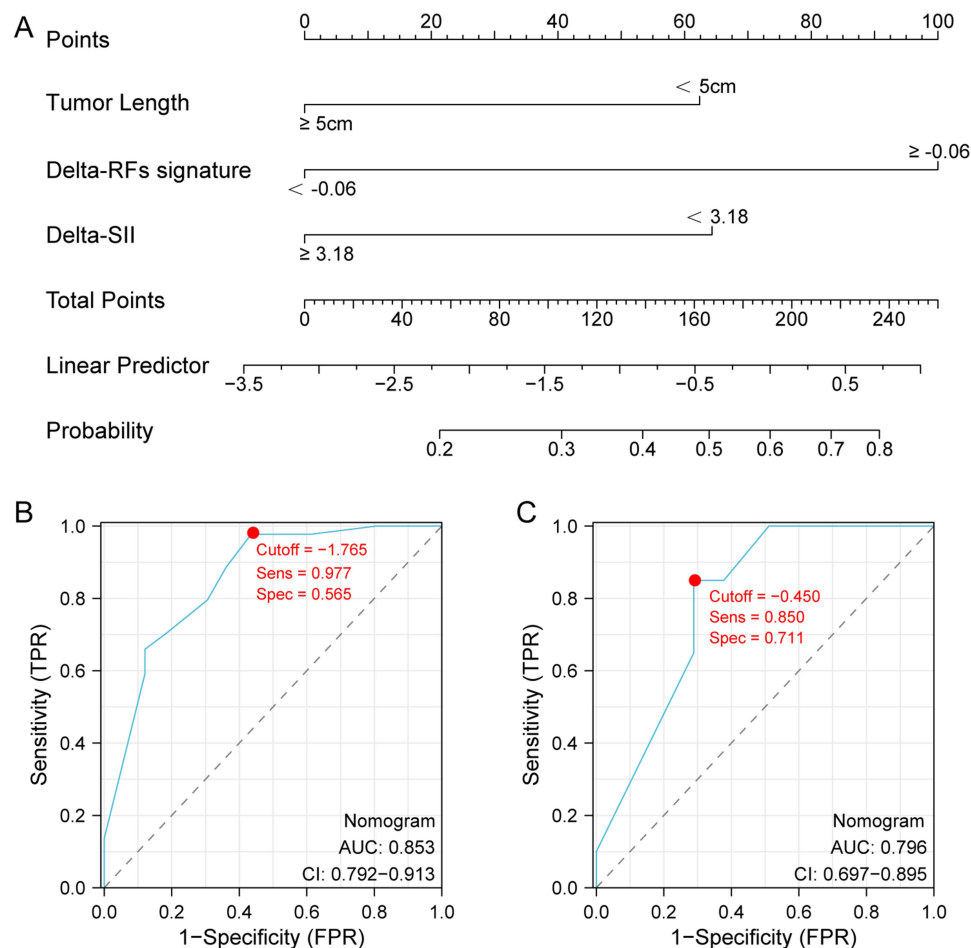


Figure 3 Nomogram development in the training set (A). Receiver operating characteristic curves for the prediction of pCR with nomogram in the training (B) and validation sets (C).

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; RF, radiomics feature; SII, systemic immune-inflammation index.

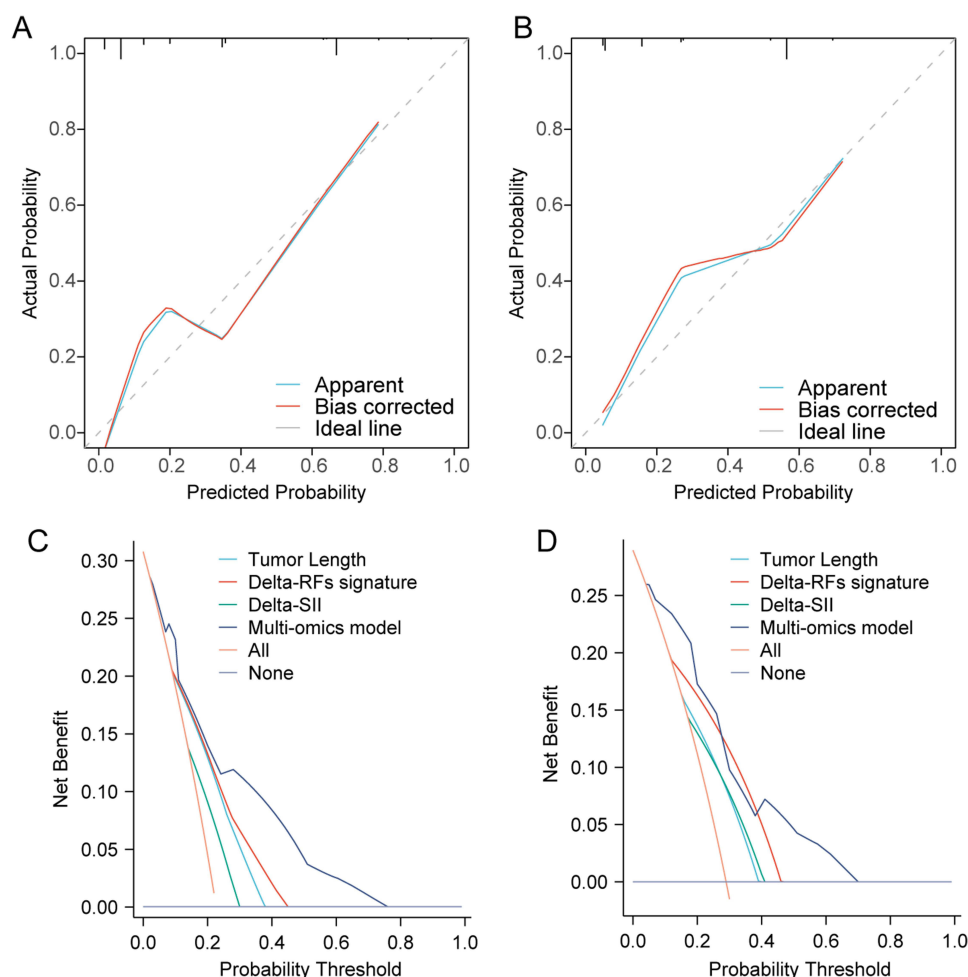


Figure 4 Calibration curves of the nomogram in the training (A) and validation sets (B). Decision curves of the four models in the training (C) and validation sets (D). **Abbreviations:** RF, radiomics feature; SII, systemic immune-inflammation index.

threshold probabilities (Figure 4B). Similarly, in the validation cohort, both calibration curves (Figure 4C) and DCA (Figure 4D) supported the feasibility and effectiveness of the nomogram, reinforcing its potential as a predictive tool for pCR assessment in patients undergoing NACI.

The multi-omics nomogram demonstrated strong discriminative and calibration performance, with Brier scores of 0.124 and 0.138 in the training and validation cohorts, respectively. The optimal cutoff values of the predicted probability for pCR, derived using the Youden index, were 0.42 (training) and 0.45 (validation), yielding sensitivities of 0.812 and 0.769 and specificities of 0.785 and 0.753, respectively. These results further confirm the robustness and clinical interpretability of the predictive model.

Discussion

NACI has the potential to significantly improve treatment outcomes for patients with LA-ESCC. However, there is currently deficiency of effective biomarkers. In this study, we developed a therapeutic response prediction model by collecting dynamic changes in RFs and clinical inflammatory indices. First, we included pre- and post-treatment CT data from 217 patients diagnosed with LA-ESCC. Following the completion of the data standardization process, we identified a total of 1834 imaging features. Feature selection was performed using the LASSO algorithm, which allowed us to construct a predictive model based on 12 delta-RFs. Subsequently, the logistic regression analyses were conducted to integrate the imaging model with clinical characteristics. Finally, a nomogram was constructed based on the results of the

multivariate regression analysis, and the multi-omics model exhibited impressive predictive performance with AUC values of 0.853 and 0.796 for the training and validation cohorts, respectively.

Accurately predicting the response to NACI is crucial for formulating personalized treatment strategies and minimizing preoperative treatment-related side effects. However, conventional biomarkers were limited by tumor heterogeneity, leading to suboptimal predictive performance.^{5,6} Radiomics, with its advantages of reproducibility and non-invasiveness, is increasingly gaining attention in this context.²¹ Currently, several retrospective radiomics analyses had been conducted to investigate predictive markers in LA-ESCC, yielding valuable insights. For instance, Zhu et al successfully constructed a prediction model for NACI efficacy using pre-treatment CT data of ESCC, which demonstrated commendable predictive performance.²² In 2025, Shi et al identified RFs of LA-ESCC through a deep learning algorithm to develop a NACI efficacy prediction mode.¹² However, the reliance on single-phase imaging data neglected the dynamic changes in imaging features, limiting the model's predictive performance.^{23–25} Ruan et al conducted a delta-RFs model aimed at predicting the response of LA-ESCC to NACI treatment, achieving an impressive AUC of 0.918.²⁶ Single radiomics models often lack clinical interpretability. To facilitate the clinical application, it is essential to integrate clinical pathological features with RFs to construct multi-omics models. A growing body of research has demonstrated that inflammatory and nutritional indices significantly influence the prognosis and treatment response in cancer patients.^{18,19} In 2024, A two-center retrospective study successfully predicted pCR after neoadjuvant chemoradiotherapy in LA-ESCC by integrating dynamic CT imaging features and clinical inflammatory indicators, demonstrating good consistency in both the training and validation cohorts with AUC values of 0.875 and 0.857, respectively.²⁷ Our study was the first to develop a multi-omics model based on delta-RFs and inflammatory indices in patients with LA-ESCC, effectively predicting pathological response following NACI treatment.

Immune-inflammation-response biomarkers have been established as prognostic indicators for various tumors.^{28–30} SII, a composite marker that integrated inflammatory and nutritional indices, was defined as the product of platelet count and NLR. In this study, delta-SII was identified as an independent predictor of pathological response. Researches had demonstrated that neutrophils can activate transcription factors, increase the synthesis of inflammatory mediators, and enable tumor cells to evade immune surveillance.^{31,32} Lymphocytes indirectly modulate tumor-associated angiogenesis by regulating the activation of myeloid cells, thus influencing the tumor immune microenvironment.³³ Additionally, activated platelets contain substantial amounts of proangiogenic substances, which promote tumor vascular growth and invasion.³⁴ In summary, the SII revealed a potential link between peripheral blood inflammatory status and the efficacy of immunotherapy. The incorporation of the delta-SII into multi-omics models can enhance the clinical applicability of model predictions while also promptly reflecting the patient's nutritional status. This allows for timely interventions and improvements, thereby aiding clinicians in the personalized management of patients with LA-ESCC.

Currently, we introduced a non-invasive preoperative method designed to predict pCR in patients with LA-ESCC undergoing NACI. However, this study has several limitations. Firstly, it is a single-center retrospective study, and the conclusions require further validation through prospective multicenter studies with larger sample sizes to confirm the generalizability of the multi-omics model. Secondly, the selection of the optimal cutoff value for the inflammatory indexes may be influenced by the size of the study population, potentially introducing biases that necessitate additional validation. Lastly, peripheral blood indicators can be influenced by various factors. To address certain limitations, this study plans to collect data from 100 cases across two additional hospitals over the course of one year to externally validate the model's predictive performance. Furthermore, we will collaborate with computer science experts to facilitate the integration of the model into the electronic medical record system for clinical implementation.

Conclusion

In conclusion, based on the changes in dynamic CT imaging features and SII indicators prior to surgery, the proposed multi-omics model effectively predicts the NACI treatment response in LA-ESCC, while accurately identifying the potential beneficiary patients. The conclusions drawn from this single-center study necessitate external validation through larger-scale multicenter samples. Nonetheless, our findings offer valuable insights for the development of personalized treatment strategies.

Data Sharing Statement

All clinical data collected in our study are available on request from the corresponding author, Haibo Lu.

Ethical Approval

This retrospective study was approved by Harbin Medical University Cancer Hospital ethics committee and conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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