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Development and validation a radiomics combined clinical model predicts treatment response for esophageal squamous cell carcinoma patients

Xiaoyan Yin[1†], Yongbin Cui[1†], Tonghai Liu[1], Zhenjiang Li[1], Huiling Liu[2], Xingmin Ma[1], Xue Sha[2], Changsheng Ma[1], Dali Han[1] and Yong Yin[1*]

Abstract

Purpose This study is aimed to develop and validate a machine learning model, which combined radiomics and clinical characteristics to predicting the definitive chemoradiotherapy (dCRT) treatment response in esophageal squamous cell carcinoma (ESCC) patients. Methods: 204 advanced ESCC patients were included who underwent dCRT at our hospital. Patients were randomly divided into training cohort and validation cohort with a ratio of 7:3. The radiomics features were selected by LASSO algorithm. The clinical features were selected by multivariate logistics analysis ($p < 0.05$). Subsequently, a combined radiomics and clinical model was established and validated to predict the treatment response in ESCC patients by logistic regression model. The performance of the model was evaluated by receiver operating characteristic (ROC) curve, decision curve analysis (DCA), nomogram, and calibration curve. Results: Total of 944 radiomics features were extracted from the pre-treatment contrasted enhanced CT images (CECT). After feature selection, 3 radiomics features and 3 clinical features were identified as the most predictive variables. The combined model shows better prediction performance among radiomics model or clinical model. The radiomics model's AUC values in training and validation cohort are 0.71,0.69. As for clinical model the AUC values were 0.74,0.75 in training and validation cohort. However, the AUC values in combined model are 0.79, 0.78 in training cohort and validation cohort, respectively. DCA and calibration curve also demonstrated good performance for the combined model. Conclusion: The radiomics combined clinical features model demonstrates superior treatment response prediction ability for ESCC patients received dCRT. This model has the potential to assist clinicians in identifying non-responsive patients before treatment and guide individualized therapy for advanced ESCC patients.

Keywords Radiomics, Treatment response, Definitive chemoradiotherapy, Esophageal squamous cell carcinoma

†Xiaoyan Yin and Yongbin Cui contributed equally for this work.

XiaoyanYin, Yongbin Cui co-first author.

*Correspondence:
Yong Yin
yinyongsd@126.com

[1]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences, Jinan, China
[2]Department of Radiation Oncology, Affiliated Cancer Hospital, The Third Affiliated Teaching Hospital of Xinjiang Medical University, Urumuqi, China

Introduction

Esophageal squamous cell carcinoma is the most common type of esophageal cancer in China [1]. Unfortunately, it is often detected at an advanced stage, leading to poor prognosis. The five-year survival rate for advanced ESCC is less than 20% [2]. Radiotherapy combined with chemotherapy has emerged as one of the primary treatment modalities for ESCC patients who are not eligible for surgery or have inoperable tumors. According to different physical conditions of patients, the treatment modes of chemoradiotherapy mainly contains concurrent radiotherapy and chemotherapy after induction(I-CCRT), concurrent radiotherapy and chemotherapy followed by consolidation (CCRT-C), induction and concurrent radiotherapy and chemotherapy after consolidation (I-CCRT-C) and sequential chemotherapy and radiotherapy (SCRT) [3, 4]. However, it is important to note that not all patients benefit from chemoradiotherapy due to the heterogeneity of the tumor [5].

At present, the treatment response is evaluated by Response Evaluation Criteria in Solid Tumors 1.1 version (RECIST 1.1). For the non-surgery advanced ESCC patients who received chemoradiotherapy, treatment response could be regarded as an early substitution for long term outcomes. Therefore, predicting the treatment response of patients with esophageal cancer before treatment might be helpful to assist clinicians to adjust the treatment plan and prolong the survival of patients.

Radiomics is a non-invasive method that allows for the extraction of high-throughput information from medical images [6]. This technology has shown promise in characterizing tumor heterogeneity and predicting prognosis, making it a potential tool in the field. Studies have found that radiomics features, particularly texture features, can predict the response of esophageal squamous cell carcinoma (ESCC) patients [7–9]. Additionally, a nomogram developed by Luo et al. has been validated for predicting complete response (CR) status in ESCC patients after dCRT [10]. But most of current studies are focused on the ESCC patients after dCRT, not involving other chemoradiotherapy models, which limits the models' generalization ability. To address this limitation, it is necessary to develop a machine learning model that combines radiomics and clinical features to predict treatment response in ESCC patients undergoing different chemoradiotherapy models, such as I-CCRT, CCRT-C, I-CCRT-C, and SCRT.

Hence in, the objective of this study is to establish a comprehensive machine learning model that integrates radiomics features and clinical features to accurately predict the treatment response of chemoradiotherapy ESCC patients. The model will be used to guide clinicians' pre-treatment decision-making, which is expected to facilitate the precise individual treatment and improve the survival.

Materials and methods

Patients

This study enrolled 246 ESCC patients who treated with chemoradiotherapy in our hospital from February 2012 to December 2018. The inclusion criteria were as follows: [1] Age > 18; [2] No history of anti-tumor treatment prior to admission; [3] Received chemotherapy in combination with radiotherapy after admission.; [4] Confirmed diagnosis squamous cell carcinoma based on pathological biopsy. The exclusion criteria were as follows: [1] Poor quality CT images; [2] Treatment was interrupted for other reasons unrelated to the study; [3] Presence of primary tumors in other sites; [4] Changed chemoradiotherapy regimes during treatment. The research protocol was approved by the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital accordance with the principles of Declaration of Helsinki. Due to the research was a retrospective study, the informed consents were waived off.

CT images acquisition and ROI delineation

Philips CT (Phillips Medical Systems, 96 Highland Heights, OH) was used to perform the imaging on all enrolled ESCC patients at our hospital. The scanning parameters were as follows: tube voltage of 120KvP, tube current from 53 to 400 mA, a scanning period around 2.8 and an interval time of 1.8 s. 512 × 512 image matrix and a voxel size of 0.9766 mm×0.9766 mm×3 mm was used to reconstructed the CT images. The image thickness was set at 3 mm. Following the scanning, contrast medium was injected using a high-pressure automatic injector at a flow rate of 3.0 ml/s.

One oncologist with more than ten years of experience delineated the Region of Interesting (ROI) on CECT images according to the guide of National Comprehensive Cancer Network (NCCN). The ROI referred as the gross tumor volume (GTV), which contains the visible primary tumor (GTVp) and positive lymph nodes (GTVnd) detected by CECT. To enhance accuracy, the barium esophagogram, endoscopic examination or PET imaging were suppled to reference for target delineation. After delineation, another senior oncologist reviewed the targets. If there were any conflicts, two oncologists discussed and driven a consensus conclusion.

Clinical variables collection and treatment response evaluation

The pre-treatment clinical variables were summarized, which mainly including: age, gender, tumor location, TNM stage, differentiation, Eastern cooperative oncology group performance status (ECOG PS), therapeutic

model, radiotherapy technology, radiotherapy dose, chemotherapy plan, chemotherapy cycles, carcinoembryonic antigen (CEA), Cyfra21. Tumor location was divided into four parts: cervical, upper thoracic, middle thoracic, lower thoracic. These variables were analyzed to assess their impact on the treatment response and to develop a predictive model for treatment outcomes in ESCC patients undergoing chemoradiotherapy.

The treatment response of ESCC patients after CRT were evaluated by the RECIST1.1. Two experienced oncologists, each with more than 10 years of experience in oncology, assessed the treatment response independently. All of the patients were stratified into two groups: objective response (OR)and non-OR group. In this study, ESCC patients who achieved complete remission (CR) or partial remission (PR) were regarded as ORs. On the other hand, patients who had stable disease (SD) or progressive disease (PD) were categorized as non-ORs.

Radiomics feature extraction

Radiomics features were extracted from the pre-treatment CT images using Py-Radiomics based on 3D slicer. Total of 944 features were extracted, which contain 14 shape features, 180 first-order features and 750 texture features. The voxel sizes of the images were resampled to a standardized size of $3 \times 3 \times 3$ mm^3 to ensure slice thickness and the bin width was set as 15 [11]. The radiomics features were generated from the original, wavelet-filtered, and Laplacian of Gaussian (LoG)-filtered images. The Log-kernel size was set as 3×3. Texture features were consisted by Gray Level Cooccurrence Matrix (GLCM), Gray Level Dependence Matrix (GLDM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM) and Neighborhood Gray-tone Difference Matrix (NGTDM).

Feature selection and model Building

The total ESCC patients were randomly divided into training cohort and validation cohort as the proportion of 7:3. All of the features were normalized by Z-Score. According to the training cohort, all extraction radiomics features were selected by the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm, which adapted L1 regularization. The LASSO algorithm was applied with 10-fold cross-validation based on the training cohort to determine the optimal set of radiomics features that were most predictive of treatment response. The search space was: C = [0.01, 0.1, 1, 10, 100]. The iteration time was set as 1000 times. Based on the selected radiomics features, a radiomics model with good prediction performance for treatment response was developed by logistic regression algorithm. Additionally, clinical features were selected by multivariate logistics regression analysis ($p < 0.05$). The selected clinical features were used to established the clinical model for prediction of response.

Finally, the selected radiomics features and clinical features were combined to develop a machine learning model for prediction treatment response in ESCC patients. What's more, the predictive ability of combined model was verified in the validation cohort ($n = 61$). The prediction ability of treatment response was evaluated by the Receiver Operator Characteristic (ROC) curve. The ROC curve provides a graphical representation of the sensitivity and specificity of the model at different thresholds and can be used to assess the discrimination ability of the model. Nomograms and calibration curve were built based on the combined model. Calibration curves were plotted to evaluate the consistency between the nomogram-predicted results and recorded treatment results. The decision curve analysis (DCA) was performed to assess the clinical usefulness of the prediction model.

Statistical analysis

Radiomics features was extracted by 3D Slicer (Version 4.11, https://www.slicer.org/). Statistical analyses and model establishment were conducted by R software (Version 3.4.0, https://www.r-project.org/). The Kruskal–Wall test was performed in SPSS (Version 25.0, https://www.ibm.com/cn-zh/spss/)was used to analyze the different groups. *P* values less than 0.05 were considered as statistically significant. All statistical tests were two-sided.

Results

Patient characteristics

Our study finally enrolled 204 ESCC patients who received dCRT. The patient characteristics details are shown in Table 1. There are no significances between training cohort and validation cohort.

Features selection and model development

944 radiomics features are extracted by Py-radiomics based on pre-treatment CT images. LASSO algorithm is used to reduce the redundancy of radiomics features and filter the optimal radiomics features in training cohort, as shown in the Fig. 1a, b.

Finally, as for radiomics features, original- ngtdm-Coarseness (ONC), wavelet-HHH- first order-Variance (WHFV) and wavelet-LLL-first order-Skewness (WLFS) are selected and the details information are displayed in the Table S1 (see Additional file 1). As for clinical features, ECOG PS, differentiation, and therapy model are also be screened to predict treatment response. The three clinical features are shown in the Table 2. All of the six features have statistically significant between the OR group and Non-OR group (Table S2, see Additional file1).

Table 1 Patient characteristics in training($n=143$) and validation cohorts($n=61$)

	Training Cohort	Validation Cohort	*P* values
Clinical characteristic			
Age (years, median-range)	61 (39 ~ 78)	61 (44 ~ 79)	0.903
Gender (Male/Female)	115/28	48/13	0.778
ECOG PS			0.625
PS = 0	71	28	
PS ≥ 1	72	33	
Tumor location			0.129
Cervical	16	12	
Upper	53	22	
Middle	54	22	
Lower	20	5	
Differentiation			0.482
Well	71	27	
Intermediate/ Poorly	72	34	
T stage			0.478
T1-T2	16	9	
T3-T4	127	52	
N stage			0.335
N0	24	7	
N+	119	54	
M stage			0.334
M0	111	51	
M1	32	10	
Therapeutic model			0.139
CCRT-C	33	17	
I-CCRT	11	8	
I-CCRT-C	26	12	
SCRT	73	24	
Radiotherapy technology			0.375
3D-CRT	47	24	
IMRT	96	37	
Radiotherapy dose (Gy)			0.838
< 60	49	20	
≥ 60	94	41	
Chemotherapy plan			0.991
DP	96	41	
PF	47	20	
Chemotherapy cycles			0.721
4–5	90	40	
6–8	53	21	
The hematology test results			
CEA (ng/ml)			0.195
< 3.4	119	46	
≥ 3.4	24	15	
Cyfra21(ng/ml)			0.489
< 3.3	106	48	
≥ 3.3	37	13	
Treatment response			0.301
OR	100	47	
Non-OR	43	14	

Continued Table 1. ECOG PS: Eastern cooperative oncology group performance status; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy; DP: cisplatin plus docetaxel; PF: cisplatin plus fluorouracil; OR: Objective response;

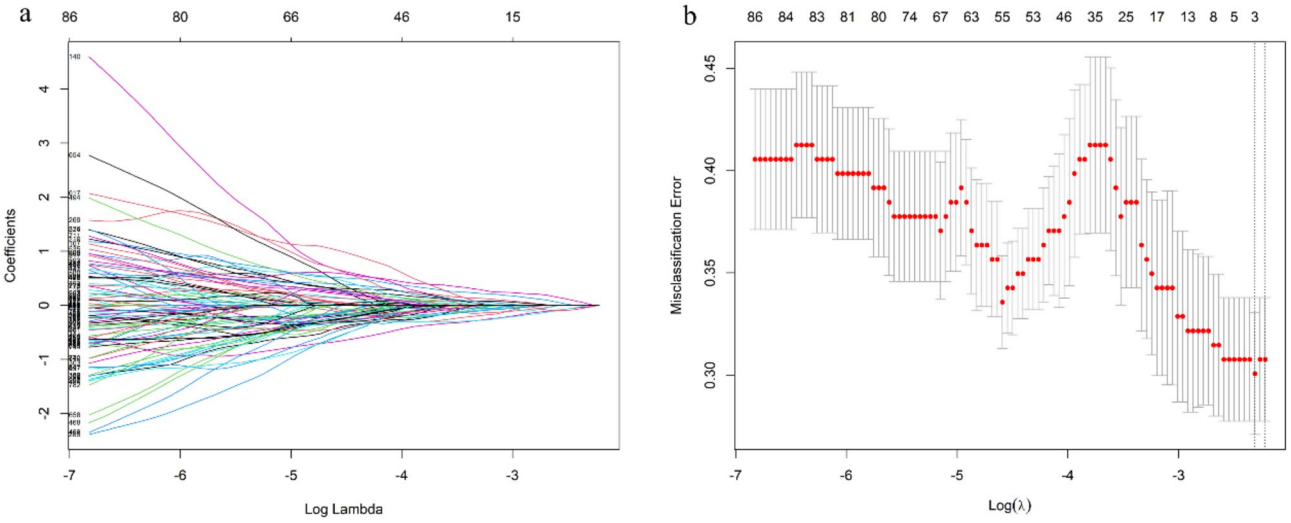

Fig. 1 Selected the radiomics features associated treatment response

Table 2 Clinical features selected by multivariate analysis ($n = 143$)

	Coefficient	Z values	*P* values
Clinical characteristic			
Age	-0.0214	-0.86	0.391
Gender	0.313	0.650	0.515
ECOG PS	-0.8653	-2.29	0.022
Tumor location	-0.202	-0.950	0.340
Differentiation	-0.865	-2.290	0.022
T stage	-1.205	-1.550	0.122
N stage	-0.303	-0.590	0.554
M stage	-0.614	-1.470	0.143
Therapeutic model	-0.585	-3.130	0.002
Radiotherapy technology	-0.020	-0.050	0.959
Radiotherapy dose	0.614	1.630	0.103
Chemotherapy plan	-0.130	-0.340	0.737
Chemotherapy cycles	-0.009	-0.020	0.981
Hematology test			
CEA	0.303	0.590	0.554
Cyfra21	-0.150	-0.360	0.716

ECOG PS: Eastern cooperative oncology group performance status;

The radiomics model is established based on the three radiomics features. The AUC values are 0.71,0.69 in training cohort and validation cohort, respectively (Fig. 2a and b).

Similarly, the clinical model is also established based on the three clinical features. The AUC values are 0.74,0.75 in training cohort and validation cohort, respectively (Fig. 2a and b). The radiomics features and clinical features are combined to develop the combined model for response prediction. The AUC values are 0.79,0.78 in training cohort and validation cohort, respectively (Fig. 2a and b). The Delong test has also been conducted between the three models. The results are displayed in the Table S3.

The nomogram combines radiomics and clinical features for the prediction of treatment response (Fig. 3). Nomograms are graphical representations that assign a numerical score to each predictor variable and provide a visual tool for predicting the probability of an event, in this case, treatment response. The calibration curve is also plotted to calibrate the model's performance, as shown in the Fig. 4. Furthermore, the Decision Curve Analysis (DCA) curve is also plotted to validate our model's capability in the Fig. 5.

Discussion

Chemoradiotherapy plays an important role for the advanced ESCC patients' treatment. However, due to the heterogeneity of tumors, not all of the patients will be benefit from chemoradiotherapy [12]. Several studies have explored the application of radiomics in predicting treatment response in ESCC patients [10, 13, 14]. For instance, Luo et al. [10] developed a nomogram for predicting the treatment response of patents. However, they only focused on the complete remission not including partial remission. Wang et al. [13] developed a machine learning model that incorporated clinical and radiomics features to predict pathological complete response. But the standard of pathological complete remission is diagnosed by invasive biopsy. So, our study establishes and validates a machine learning model for predicting the treatment response of advanced ESCC patients, which is aimed to help the clinician to identify the insensitive patients for chemoradiotherapy based on pre-treatment information.

Total of six radiomics and clinical features are selected to build the model. As for the clinical features, ECOG PS, differentiation and therapeutic model are chosen to predict OR. ECOG PS is a measure of a patient's functional

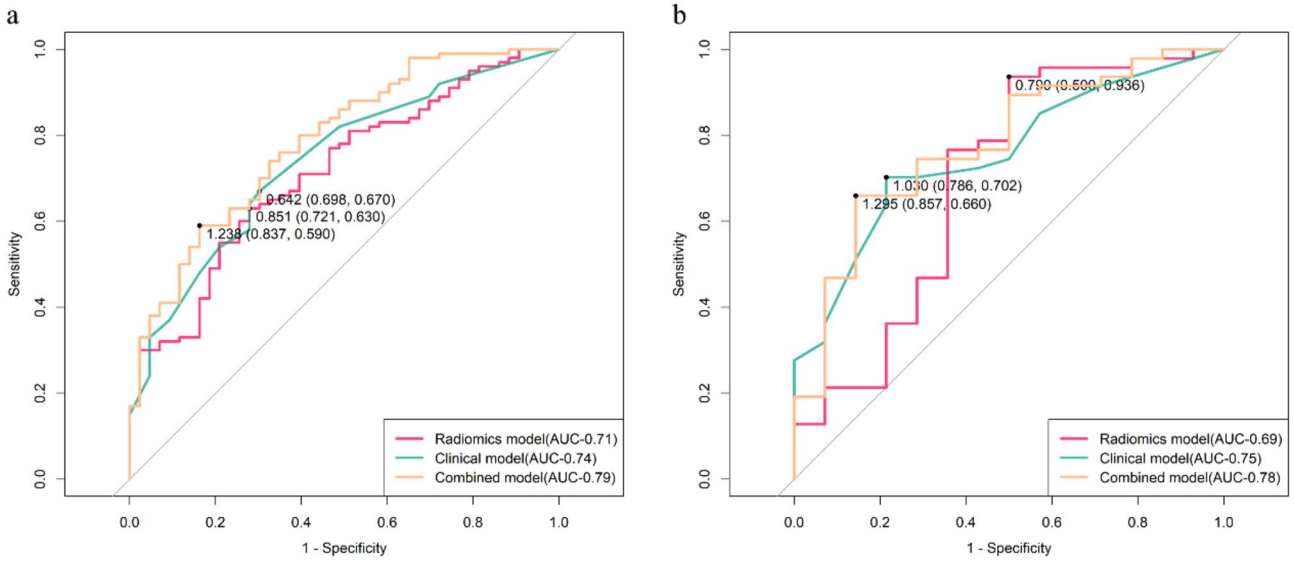

Fig. 2 The ROC curves of prediction model. **a**: ROC curve in training cohort; **b**: ROC curve in validation cohort. AUC: Area under the curve

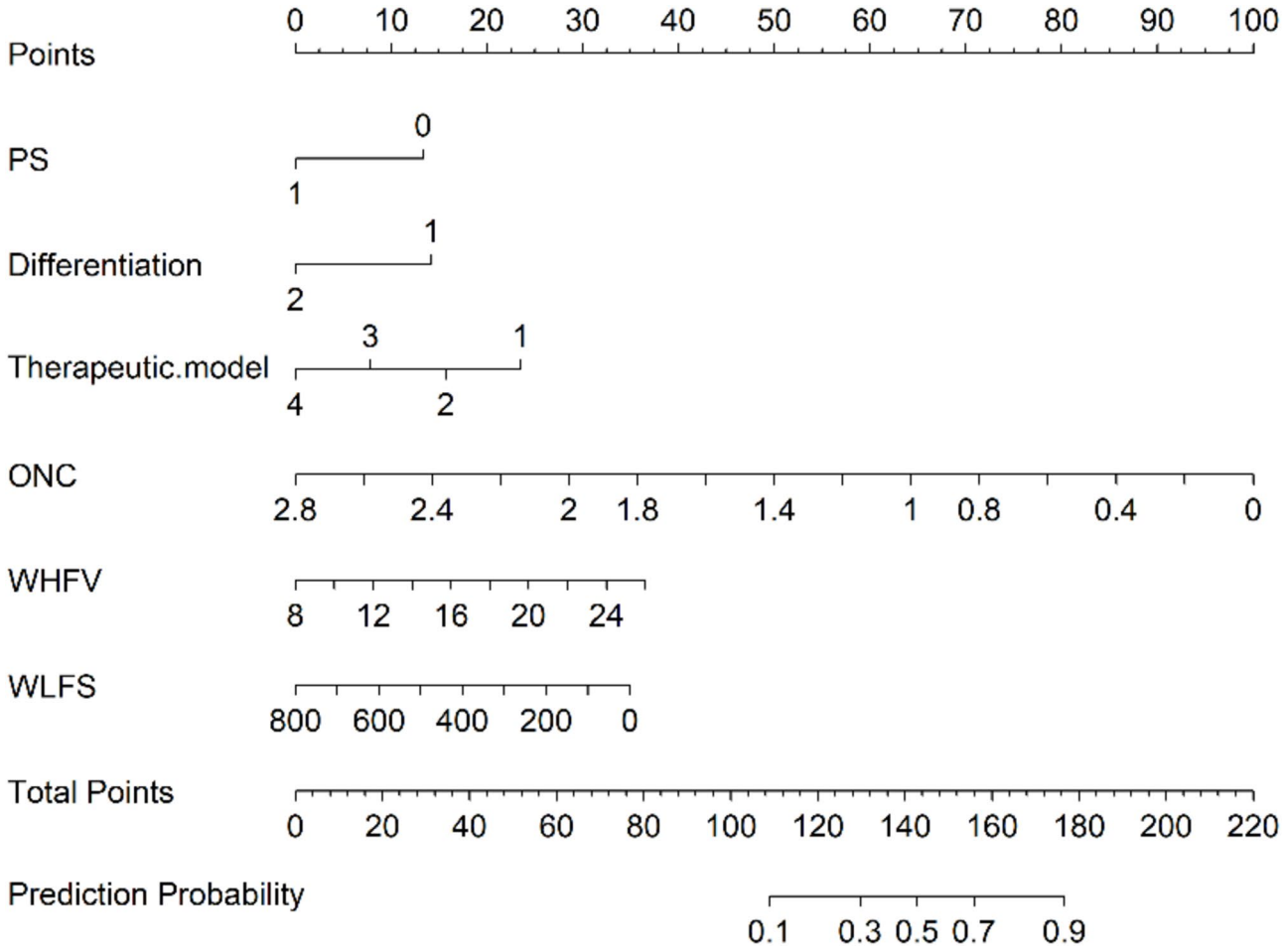

Fig. 3 The nomogram model for treatment response prediction. PS: 0 represents ECOG PS 0 grade, 1represents ECOG PS 1 and 2 grade; Therapeutic model: 1 represents I-CCRT, 2 represents CCRT-C, 3 represent I-CCRT-C,4 represents SCRT. ONC: original- ngtdm-Coarseness; WHFV: wavelet-HHH- first order-Variance; WLFS: wavelet-LLL- first order- Skewness

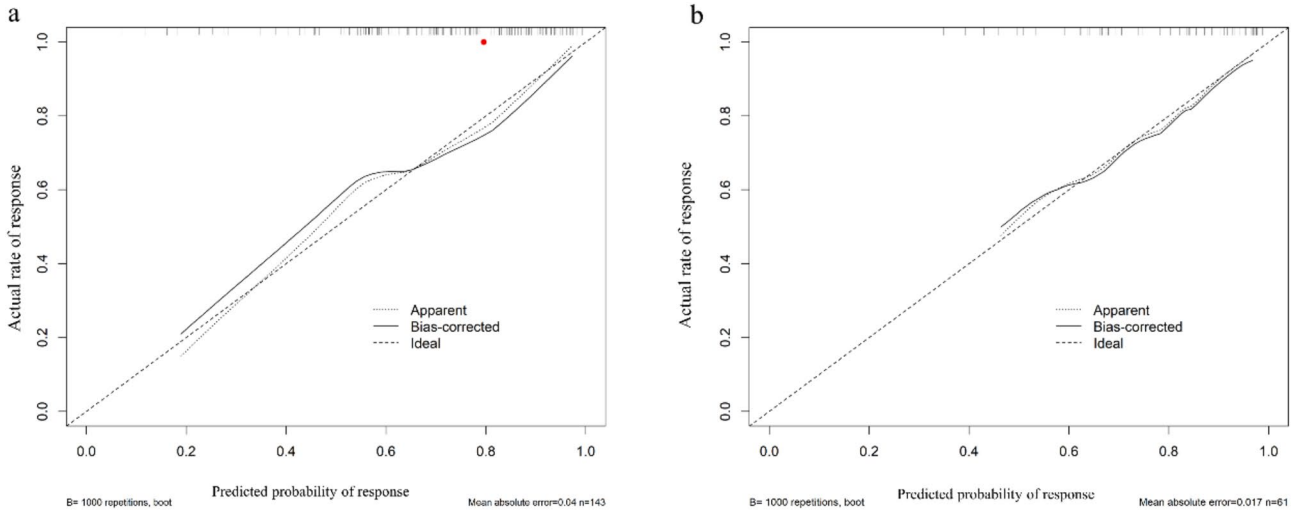

Fig. 4 The calibration curve in training cohort (Fig. 4a) and validation cohort (Fig. 4b)

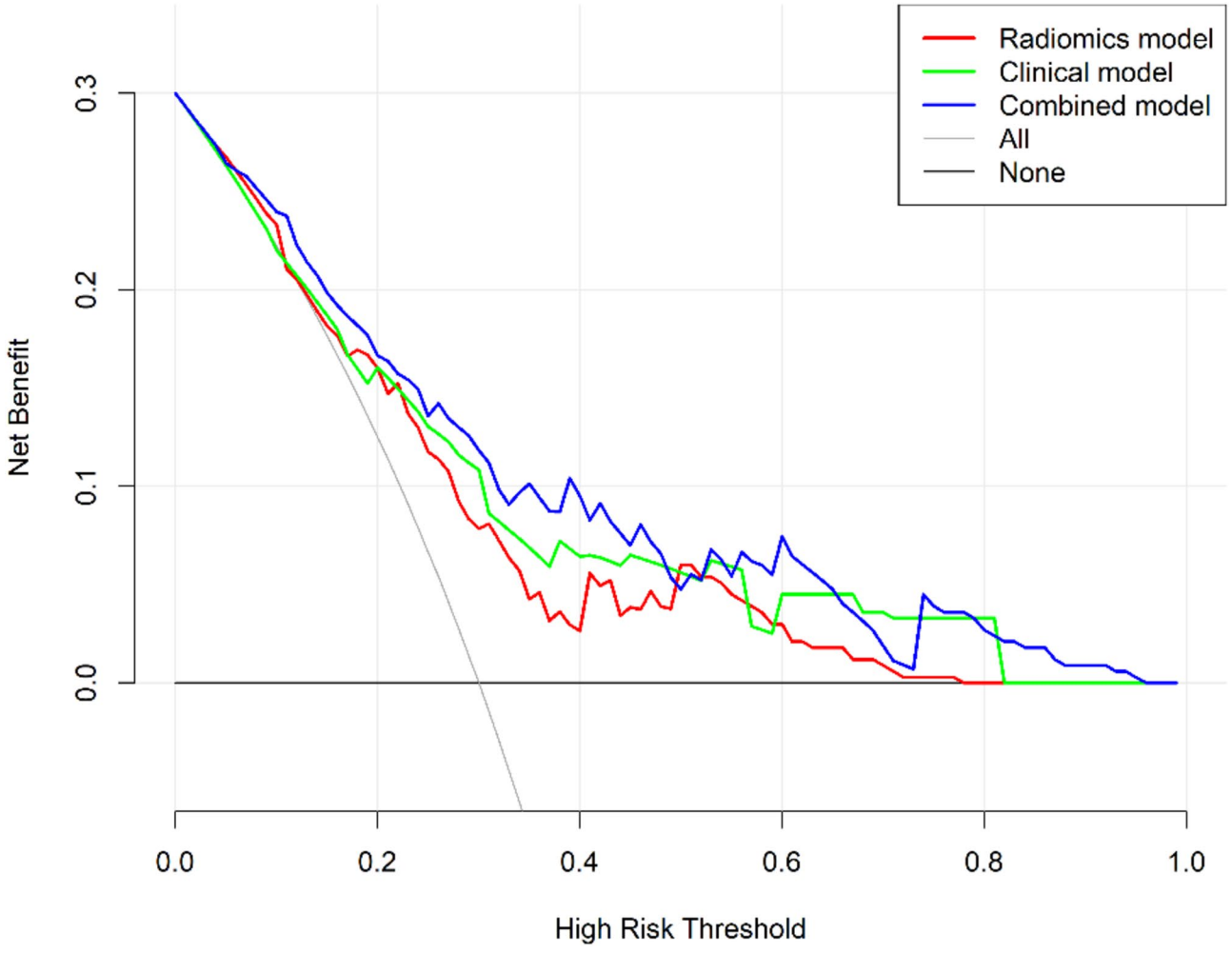

Fig. 5 Decision curve analysis for nomogram model

status and is determined by oncologists based on the patient's performance. This feature provides valuable information about the patient's overall health and ability to tolerate treatment. Differentiation, as suggested by Liu et al. [15], is a significant risk predictor of early recurrence for ESCC patients. In our study, we divided the pathological grade into two groups: well differentiation and intermediate/poorly differentiation, aligning with previous research findings. The therapeutic model, as highlighted by Gong et al. [16], has been identified as a prognostic factor for ESCC patients. Similarly, we considered the therapeutic model as a vital factor in our predictive model. This feature captures whether concurrent chemoradiotherapy was performed, which has implications for treatment outcomes. TNM stage was not included in our model building. This decision was based on the belief that ECOG PS, differentiation, and therapeutic model may play a more critical role in our specific research context [17]. Nonetheless, the exclusion of TNM stage does not diminish its importance in ESCC prognosis and overall patient management. All in all, the clinical information provides a reference for the decision marking of clinicians by the nomogram model before treatment.

ONC is the short name of original–Coarseness, which means a measure of average difference between the center voxel and its neighborhood in the original images [18]. This feature provides information about the spatial rate of change and a higher value indicates a lower spatial change rate and a locally more uniform texture. Song et al. [19] also approved ngtdm-Coarseness have the potential to predict the treatment outcomes based on pretreatment images. WHFV is defined as wavelet-HHH-first order-Variance, which is derived from first order features variance based on wavelet-filter transformed images. The variance represents the degree of difference in pixel gray-scale values of images [20]. The short name of wavelet-LLL- first order- Skewness is WLFS, which reflects the degree of asymmetry of the pixel gray value relative to the mean distribution in the wavelet-filter transformed images [21].Those three radiomics features contains two first order features and one texture features, which demonstrates the high-dimensional tumor characteristics of ESCC.

Actually, some researchers have made efforts for predicting the clinical treatment response by the non-invasive biomarker with ESCC patients [17, 22–25]. However, several critical challenges remain unresolved in current research. Jayaprakasam et al. [17] first used radiomics model to predict the PET responders to induction chemotherapy patients. However, their study had a relatively sample size of 74 patients, and the accuracy of their combined PET/CT model was only 70% in the test cohort. Li et al. [22] established an outperformance deep learning model for the clinical treatment response prediction of ESCC. But the working mechanism of deep learning algorithm is still like a black box, which limits interpretability of the model. Jin et al. [23] constructed a machine learning that combined radiomics features and dosimetric parameters to predict the response, but the model's AUC was 0.708 and 0.689 in the training and test set, respectively. Although Liu et al. [24] established a model for the treatment response successfully, their study only enrolled radiotherapy patients. An et al. [25] predicted treatment response in CCRT (concurrent chemoradiotherapy) patients using delta radiomics based on ADC (Apparent Diffusion Coefficient) maps. Notably, their investigation was conducted using MR images. Our study recruited 204 ESCC patients, who was treated with four different therapeutic models. And the pretreatment information, such as patients' characteristics, the hematology test results and treatment details, were thoroughly collected in our clinical variables. Therefore, our machine learning combined model has excellent interpretability, predictive performance, and generalization ability.

There are still some limitations in our study. Firstly, although the ROC curves, DCA and calibration curves showed good performance, it would be better if validated by an external validation group from another center. Then, our investigation only combines the radiomics and clinical features in the machine learning model. In the future, radiomics integrating pathomics, dosiomics, genomics and proteomics might improve the model's accuracy and bio- interpretability.

Conclusion

In a word, a noninvasive, comprehensive, interpretable and individualized chemoradiotherapy efficacy prediction model was established by pretreatment information of advanced ESCC patients based on machine learning algorithm. This model integrates radiomics features and clinical variables with good predictive accuracy, providing an efficient, convenient, and affordable method to guide the clinicians' treatment decision for ESCC patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03899-8.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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not applicable.

Author contributions
All authors contributed to the study conception and design. Conceptualization and data collection by TL, DH and CM. Data analysis were performed by YC, XY, HL and XM. The manuscript was written and reviewed by YC and YY. Software prepared by ZL and CM. YY and SX provide funding. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital according to the Declaration of Helsinki (Approval number: 2022006022). Due to the research was a retrospective study, the informed consents were waived off according to the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital.

Consent for publication
Not applicable.

Conflict of interest
All of the authors declare no conflict of interest.

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