

CT Radiomics for Predicting Thoracic Vertebral Compression Fractures After Radiotherapy in Esophageal Squamous Cell Carcinoma: A Two-Center Retrospective Study

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Abstract

Background

Vertebral compression fractures (VCFs) are clinically significant skeletal complications that may occur after radiotherapy in patients with esophageal squamous cell carcinoma (ESCC). This study evaluated the predictive performance of computed tomography (CT) radiomics for newly developed post-radiotherapy thoracic VCFs and determined whether radiomics can provide additional value for individualized risk stratification.

Methods

This retrospective two-center study included 551 patients with pathologically confirmed ESCC who underwent radiotherapy. Patients from institution 1 were randomly assigned to a training cohort ($n = 321$) or an internal validation cohort ($n = 138$), whereas patients from institution 2 were included in an external validation cohort ($n = 92$). Vertebral CT attenuation and radiomics features were extracted from pretreatment CT images of irradiated thoracic vertebrae. Candidate predictors were identified using univariable Cox regression, followed by Akaike information criterion-based Cox model selection in the training cohort. Six prediction models were developed: vertebral CT attenuation, radiomics, radiotherapy, clinical–radiotherapy, clinical–radiotherapy–CT attenuation, and radiomics-integrated models. Model performance was evaluated using the concordance index (C-index), time-dependent area under the receiver operating characteristic curve (time-dependent AUC), calibration curves, decision curve analysis, net reclassification improvement, and integrated discrimination improvement.

Results

During a median follow-up of 0.92 years (interquartile range, 0.58–1.50 years), 77 of the included patients developed post-radiotherapy thoracic VCFs. Age, alcohol consumption, total radiotherapy dose, vertebral CT attenuation, and Radscore were retained in the final radiomics-integrated model. The radiomics-integrated model demonstrated the best overall performance, with C-index values of 0.878, 0.825, and 0.759 and 24-month AUCs of 0.895, 0.724, and 0.802 in the training and internal and external validation cohorts, respectively. Calibration and decision curve analyses demonstrated good calibration and clinical utility of the model.

Conclusion

CT radiomics demonstrated favorable predictive performance for post-radiotherapy VCFs in patients with ESCC and provided additional value for individualized risk stratification. The radiomics-integrated model may aid in identifying patients who require closer imaging surveillance and preventive management.

1 Background

Esophageal cancer is a major malignancy worldwide, with China accounting for a substantial proportion of the global burden(1–3). Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype in China, accounting for more than 80% of cases(4). Radiotherapy is used in definitive, neoadjuvant, adjuvant, and palliative ESCC treatment(5–7), making treatment-related skeletal complications an important clinical concern.

Vertebral compression fracture (VCF) is a clinically relevant skeletal complication after radiotherapy for esophageal cancer(8–10). VCF may cause persistent pain, impaired mobility, reduced pulmonary function, and increased

mortality(11). Its development is multifactorial, involving baseline skeletal vulnerability and radiotherapy-related factors such as dose and fractionation(12, 13). Radiation may disrupt bone remodeling and microvascular integrity, leading to progressive bone loss and reduced structural strength(14–16). Therefore, the accurate identification of patients at high risk of post-radiotherapy thoracic VCF may facilitate individualized surveillance and timely preventive management.

Dual-energy X-ray absorptiometry (DEXA) remains the reference standard for assessing bone mineral density and osteoporosis-related fracture risk(17, 18). Chest computed tomography (CT) is routinely performed during baseline evaluation and follow-up of patients with ESCC, enabling opportunistic assessment of vertebral bone status without additional imaging. Vertebral CT attenuation is associated with bone mineral density and fracture risk(19–21); However, CT attenuation primarily reflects the average density of the vertebral body and may not adequately capture intravertebral heterogeneity, trabecular texture, or microarchitectural changes associated with vertebral fragility.

Radiomics enables the high-throughput extraction of quantitative imaging features that characterize intensity distribution, texture, and spatial heterogeneity beyond conventional CT attenuation or visual assessment(22, 23). Previous studies have suggested that CT radiomics improves osteoporosis assessment and vertebral fracture prediction, including VCF prediction after spinal stereotactic body radiotherapy(24–26). However, it remains unclear whether vertebral radiomics can predict post-radiotherapy VCF in patients with ESCC and provide clinically meaningful risk information. Therefore, this study aimed to evaluate the predictive performance of CT radiomics for newly developed thoracic VCFs after radiotherapy in patients with ESCC and to determine whether radiomics provides any additional value for individualized risk stratification.

2 Methods

2.1 Population

This two-center retrospective study was conducted with approval from the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No. 2026ER325-1). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The requirement for written informed consent was waived by the Ethics Committee due to the retrospective nature of the study, which involved the analysis of anonymized clinical and imaging data without direct patient contact or intervention. Consecutive patients with pathologically confirmed ESCC who underwent radiotherapy between January 2016 and April 2025 were screened. Patients with complete clinical and radiotherapy records, pretreatment chest CT scans suitable for vertebral CT attenuation and radiomics analyses, and at least one post-radiotherapy chest CT scan were eligible for inclusion. Patients with poor-quality images, other primary malignancy, metastatic or tumor-invaded vertebral fracture, or insufficient follow-up information were excluded.

A total of 459 eligible patients from institution 1 were randomly assigned to a training cohort ($n = 321$) and an internal validation cohort ($n = 138$) at a 7:3 ratio. An independent cohort of 92 eligible patients from institution 2 served as the external validation cohort. The patient selection process, exclusion criteria, and cohort allocation are illustrated in Fig. 1. After radiotherapy, follow-up chest CT examinations were generally performed at approximately 3-month intervals during the first year and every 6 months thereafter, according to institutional practice and clinical requirements. Owing to the retrospective study design, the timing, frequency, and duration of follow-up CT examinations varied among patients. All included patients underwent at least one post-radiotherapy chest CT examination to assess newly developed thoracic VCFs. All available follow-up CT images were reviewed and compared with the pretreatment CT images to identify newly developed thoracic VCFs within the irradiation field. VCF was defined as a newly developed reduction of at least 20% in vertebral body height or at least 10% in vertebral body area on sagittal CT images during follow-up(27, 28). Representative sagittal CT images of newly developed thoracic VCFs are shown in Fig. 2. The primary outcome was the first occurrence of a newly developed thoracic VCF within the irradiation field after radiotherapy. For

patients without a newly developed thoracic VCF in the irradiation field, the date of the last available chest CT examination was considered as the last follow-up. For patients with multiple newly developed thoracic VCFs within the irradiation field, the date of the first detected VCF was used as the event time. The final follow-up date was April 30, 2025.

2.2 CT Acquisition

Pretreatment chest CT examinations were performed using multidetector CT scanners at both institutions. At institution 1, pretreatment chest CT examinations were performed using a Siemens SOMATOM Force, GE LightSpeed VCT, or Philips Brilliance multidetector CT scanner. The main acquisition parameters were 120 kVp, approximately 100 mA, a pitch of 0.984:1, and a rotation time of 0.5 s. Images were reconstructed using a standard soft-tissue kernel with a 512×512 matrix, a slice thickness of 5 mm, and an interval of 5 mm. At institution 2, CT examinations were performed using a GE Revolution CT or United Imaging uCT 530 scanner. The GE Revolution CT protocol used 120 kVp, automatic tube-current modulation (Smart mA, 200–500 mA), a noise index of 10, a pitch of 0.992:1, and a rotation time of 0.5 s. The uCT 530 protocol used 120 kVp, 140 mAs, a pitch of 0.925, and a rotation time of 0.6 s.

Axial images reconstructed with a slice thickness of 5 mm were used for vertebral CT attenuation measurement and radiomics analysis. Sagittal reformatted images with a slice thickness and reconstruction interval of 1.0 mm were used to evaluate vertebral morphology and identify VCFs.

Whenever feasible, follow-up CT used the same scanner and acquisition protocol as the pretreatment examination. Images were retrieved from the picture archiving and communication system and transferred to a post-processing workstation.

2.3 Vertebral CT Attenuation Measurement and Radiomics Analysis

One index irradiated thoracic vertebra was analyzed for each patient. In patients with VCF, the vertebra that fractured earliest during follow-up was selected. In patients without VCF, one eligible nonfractured vertebra was selected from the irradiated thoracic vertebrae by simple random sampling using a prespecified random seed. This strategy ensured that each patient contributed only one observation and avoided within-patient clustering resulting from the inclusion of multiple vertebrae. Vertebral CT attenuation was measured by placing three ROIs within the cancellous bone at the upper, middle, and lower portions of the vertebral body on axial CT images, and the mean Hounsfield unit value was calculated.

Radiomics analysis was performed using the same index vertebra. The cancellous portion of the vertebral body was manually segmented using 3D Slicer, excluding the cortical bone, endplates, focal lesions, blood vessels, and imaging artifacts. Images were resampled to a voxel size of $1 \times 1 \times 1$ mm³. First-order, shape, and texture features were extracted from the original, Laplacian-of-Gaussian-filtered, and wavelet-transformed images using PyRadiomics. Segmentation reproducibility was evaluated in 30 randomly selected patients from the training cohort using intraobserver and interobserver intraclass correlation coefficients. Only features with both ICCs ≥ 0.70 were retained.

All preprocessing and feature selection procedures were conducted in the training cohort. Radiomics features were normalized using Z-score normalization, highly correlated features were removed, and LASSO-Cox regression was used to select radiomics features and calculate the Radscore. The same normalization parameters and fixed model coefficients were subsequently applied to the validation cohorts.

2.4 Model Development and Validation

All predictor selection and model development procedures were performed exclusively in the training cohort. Candidate predictors were initially identified using univariable Cox proportional hazards regression, and variables with a p-value <

0.05 were considered eligible for subsequent Akaike information criterion (AIC)-based model selection. Multicollinearity among candidate predictors was evaluated using variance inflation factors and pairwise correlation analysis. Because total radiotherapy dose and the number of radiotherapy fractions were highly correlated, they were not included simultaneously in the same Cox model. Instead, two parallel AIC-based Cox model selection procedures were performed: one including total radiotherapy dose and the other including number of radiotherapy fractions, together with the remaining candidate predictors identified in the univariable analysis. The dose-based candidate model produced a lower AIC than the fraction-based candidate model and was therefore selected as the final model framework. The final model retained age, alcohol consumption, total radiotherapy dose, vertebral CT attenuation, and Radscore as the final predictors. These AIC-selected variables were used to construct the prediction model, and their adjusted associations with post-radiotherapy thoracic VCF were evaluated using multivariable Cox regression. Six models were developed and evaluated: M1, vertebral CT attenuation; M2, Radscore; M3, total radiotherapy dose; M4, clinical-radiotherapy model (age, alcohol consumption, and total dose); M5, clinical-radiotherapy-CT attenuation model (M4 plus vertebral CT attenuation); and M6, radiomics-integrated model (M5 plus Radscore). Model discrimination was assessed using Harrell's concordance index (C-index) and time-dependent area under the receiver operating characteristic curve (time-dependent AUC). Model performance was further evaluated using calibration, decision curve analysis, net reclassification improvement (NRI), integrated discrimination improvement (IDI), Kaplan–Meier analysis, and a sensitivity analysis excluding patients without VCF who had follow-up periods shorter than 12 months.

2.5 Statistical Analyses

Statistical analyses were performed using SPSS version 27.0 and R. Continuous variables are expressed as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as frequencies and percentages. Cohorts were compared using one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Time-to-event analyses were performed using Cox proportional hazards regression, with the time origin defined as the initiation of radiotherapy. Patients who did not develop new thoracic VCF within the irradiation field were censored at the date of their last available follow-up CT. For ease of interpretation, hazard ratios for Radscore were reported per 0.1-unit increase. For prediction model development, variables retained through the AIC-based selection were included in the final model. Model discrimination was evaluated using Harrell's C-index and time-dependent receiver operating characteristic curve analysis. The 24-month time point was prespecified as the primary prediction horizon, and time-dependent AUCs at 12, 24, and 36 months were also reported to characterize model performance across clinically relevant follow-up intervals. Calibration curves were used to assess the agreement between the predicted and observed fracture risks. Decision curve analysis was performed to evaluate clinical net benefit across a range of threshold probabilities. The overall workflow for vertebral CT attenuation measurement, radiomics feature extraction, model construction, and model evaluation is illustrated in Fig. 3.

3 Results

3.1 Patient Characteristics and Follow-up Outcomes

A total of 551 patients with ESCC were included, comprising 321 patients in the training cohort, 138 in the internal validation cohort, and 92 in the external validation cohort. Newly developed thoracic VCFs within the irradiation field occurred in 47 patients (14.6%) in the training cohort, 21 (15.2%) in the internal validation cohort, and 9 (9.8%) in the external validation cohort. During a median follow-up of 0.92 years (interquartile range, 0.58–1.50 years), 77 patients (14.0%) developed post-radiotherapy thoracic VCFs, corresponding to an annual incidence rate of 11.4 per 100 person-years (95% CI, 9.0–14.3). Among patients, 62 sustained a single vertebral fracture, whereas 15 had multiple vertebral fractures, including 12 patients with two fractured vertebrae and 3 patients with three fractured vertebrae. Twenty

patients (26.0%) with fractures received radiotherapy alone, whereas 57 (74.0%) received chemoradiotherapy. The annual fracture did not differ significantly between the chemoradiotherapy and radiotherapy-alone groups (incidence rate ratio = 0.73, 95% CI: 0.43–1.28, $p = 0.260$).

The baseline characteristics of the three cohorts are summarized in Table 1. Most clinical, radiotherapy-related, and imaging variables were well balanced. Age differed significantly ($p = 0.024$), with the external cohort being slightly younger, and the proportion undergoing primary tumor resection also differed ($p = 0.030$), with a higher rate in the external cohort. All fractured vertebral segments were located within the corresponding radiation field (Supplementary Table 1), with substantial overall agreement ($\kappa = 0.792$, $p < 0.001$).

Table 1
Baseline characteristics of the study cohorts

Feature	Training (n = 321)	Internal validation (n = 138)	External validation (n = 92)	P value
Baseline characteristics				
Female, n (%)	115 (35.8)	44 (31.9)	26 (28.3)	0.355
Age(years)	65.97 ± 8.59	65.47 ± 6.67	63.34 ± 8.49	0.024
BMI(Kg/m ²)	21.33 ± 2.60	21.22 ± 2.89	21.79 ± 2.80	0.262
TNM stage, n (%)				0.657
I	7 (2.2)	3 (2.2)	1 (1.1)	
II	124 (38.6)	50 (36.2)	45 (48.9)	
III	117 (36.4)	54 (39.1)	29 (31.5)	
IV	73 (22.7)	31 (22.5)	17 (18.5)	
Tumor location,n (%)				0.109
Upper thoracic	75 (23.4)	41 (29.7)	15 (16.3)	
Middle thoracic	187 (58.3)	69 (50.0)	53 (57.6)	
Lower thoracic	59 (18.4)	28 (20.3)	24 (26.1)	
History of smoking, n (%)	120 (37.4)	56 (40.6)	37 (40.2)	0.767
History of drinking, n (%)	96 (29.9)	42 (30.4)	31 (33.7)	0.784
Radiotherapy technique, n (%)				0.223
3D-CRT	15 (4.7)	5 (3.6)	0 (0.0)	
IMRT	233 (72.6)	105 (76.1)	73 (79.3)	
VMAT	73 (22.7)	28 (20.3)	19 (20.7)	
Total Dose(Gy)	58.42 ± 8.67	58.01 ± 7.46	58.96 ± 5.69	0.676
Radiotherapy fraction	29.96 ± 4.41	29.50 ± 3.43	30.12 ± 2.58	0.411
Dose per fraction(Gy)	1.94 ± 0.16	1.96 ± 0.18	1.95 ± 0.16	0.489
Vertebral CT attenuation	141.47 ± 41.41	138.26 ± 38.82	150.37 ± 37.63	0.074
Resection of primary esophageal tumor, n (%)	219 (68.2)	89 (64.5)	74 (80.4)	0.030
Chemotherapy, n (%)	240 (74.8)	106 (76.8)	78 (84.8)	0.132

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. BMI, body mass index; TNM, tumor–node–metastasis; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy; CT, computed tomography. Vertebral CT attenuation was measured in Hounsfield units. Continuous variables were compared using Welch one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test, as appropriate.

3.2 Predictor Selection

In the training cohort, univariable Cox regression identified age, alcohol consumption, total dose, fraction number, vertebral CT attenuation, and Radscore as significant predictors. AIC-based multivariable selection retained age, alcohol consumption, total dose, vertebral CT attenuation, and Radscore. These variables were included in the primary multivariable analysis, and Radscore remained significantly associated with fracture risk when modeled per 0.1-unit increase (Table 2).

Table 2
Univariable and multivariable Cox regression analyses based on the training cohort

Feature	Univariable		P value	Multivariable		P value
	HR	95% CI		HR	95% CI	
Sex(Female)	1.615	0.910–2.868	0.102	-		-
Age	1.069	1.032–1.109	< 0.001	1.042	1.003–1.083	0.036
BMI	0.948	0.849–1.058	0.335	-		-
TNM stage						
I	Reference		0.082	-		-
II	0.559	0.158–1.977	0.367	-		-
III	1.031	0.301–3.534	0.962	-		-
IV	1.547	0.429–5.575	0.505	-		-
Tumor location						
Upper thoracic	Reference		0.211	-		-
Middle thoracic	1.088	0.564–2.099	0.801	-		-
Low thoracic	0.469	0.153–1.441	0.186	-		-
Smoking history	1.028	0.562–1.881	0.929	-		-
Alcohol consumption	2.313	1.293–4.139	0.005	2.940	1.550–5.577	< 0.001
Radiotherapy technique						
3D-CRT/VMAT	Reference		0.418	-		-
IMRT	0.778	0.428–1.416	0.412	-		-
Total radiation dose	1.042	1.017–1.068	0.004	1.032	1.004–1.060	0.026
Radiotherapy fraction	1.108	1.050–1.169	0.001	-		-

Notes: HR, hazard ratio; CI, confidence interval; BMI, body mass index; TNM, tumor–node–metastasis; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiotherapy; CT, computed tomography. Vertebral CT attenuation was measured in Hounsfield units. The HR for the Radscore was calculated per 0.1-unit increase; For Cox regression analysis, radiotherapy technique was dichotomized into IMRT and 3D-CRT/VMAT, with 3D-CRT/VMAT used as the reference category, because of the limited number of patients treated with 3D-CRT.

Feature	Univariable		P value	Multivariable		P value
	HR	95% CI		HR	95% CI	
Dose per fraction	1.291	0.286–5.824	0.744	-		-
Vertebral CT attenuation	0.973	0.964–0.982	< 0.001	0.986	0.976–0.996	0.007
Radscore, per 0.1 increase	1.408	1.284–1.544	< 0.001	1.322	1.181–1.480	< 0.001
Resection of primary esophageal tumor	0.861	0.470–1.577	0.628	-		-
Chemotherapy	0.886	0.440–1.786	0.736	-		-

Notes: HR, hazard ratio; CI, confidence interval; BMI, body mass index; TNM, tumor–node–metastasis; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiotherapy; CT, computed tomography. Vertebral CT attenuation was measured in Hounsfield units. The HR for the Radscore was calculated per 0.1-unit increase; For Cox regression analysis, radiotherapy technique was dichotomized into IMRT and 3D-CRT/VMAT, with 3D-CRT/VMAT used as the reference category, because of the limited number of patients treated with 3D-CRT.

3.3 Radiomics Signature

A total of 1,316 radiomics features were initially extracted from each selected index vertebra. Following reproducibility assessment and redundancy reduction, LASSO-Cox regression identified four radiomics features for constructing the radiomics signature. These included three first-order features and one texture feature derived from the gray-level run-length matrix (GLRLM).

The Radscore was calculated as follows:

$$\text{Radscore} = 0.201128885 \times (\log.\text{sigma}.2.0.\text{mm}.3\text{Dfirstorder}10\text{Percentile}) + 0.105936651 \times (\log.\text{sigma}.2.0.\text{mm}.3\text{DfirstorderMean}) + 0.135638396 \times (\log.\text{sigma}.4.0.\text{mm}.3\text{DfirstorderMedian}) + 0.018167759 \times (\text{wavelet.LLHglrlmLongRunLowGrayLevelEmphasis})$$

The selected radiomics features captured complementary aspects of vertebral image characteristics(29). The first-order features quantified gray-level intensity distribution, whereas the GLRLM feature characterized long runs of low-gray-level voxels, reflecting spatial texture beyond conventional CT attenuation. These feature classes have been used in radiomics studies of vertebral disease(30–32). Radscore was incorporated as a continuous variable in Cox regression and model evaluation; coefficients are summarized in Table 3.

Table 3
LASSO-Cox regression coefficients

Feature type	Feature name	Coefficient (β)
First-order	log.sigma.2.0.mm.3Dfirstorder10Percentile	0.201128885
First-order	log.sigma.2.0.mm.3DfirstorderMean	0.105936651
First-order	log.sigma.4.0.mm.3DfirstorderMedian	0.135638396
Texture	wavelet.LLHglrlmLongRunLowGrayLevelEmphasis	0.018167759

3.4 Model Performance and Incremental Value

The predictive performance of the six models is summarized in Table 4. Among single-predictor models, the radiomics model demonstrated the best overall discrimination, with C-index values of 0.835, 0.791, and 0.734 in the training, internal validation, and external validation cohorts, respectively. The time-dependent ROC curves at 24 months are shown in Fig. 4.

Table 4
Performances of different models across cohorts

	Training Cohort				Internal Validation Cohort				External Validation Cohort			
	1 year-AUC	2 year-AUC	3 year-AUC	C index	1 year-AUC	2 year-AUC	3 year-AUC	C index	1 year-AUC	2 year-AUC	3 year-AUC	C index
Model1	0.789	0.755	0.728	0.780	0.832	0.476	0.563	0.695	0.603	0.649	0.641	0.670
Model2	0.846	0.857	0.964	0.835	0.905	0.762	0.784	0.791	0.602	0.818	0.975	0.734
Model3	0.698	0.645	0.655	0.609	0.530	0.655	0.719	0.667	0.259	0.328	0.500	0.414
Model4	0.806	0.804	0.745	0.760	0.350	0.641	0.761	0.669	0.821	0.612	0.723	0.646
Model5	0.900	0.841	0.783	0.843	0.682	0.620	0.792	0.767	0.739	0.596	0.675	0.682
Model6	0.900	0.895	0.955	0.878	0.832	0.724	0.849	0.825	0.739	0.802	0.968	0.759
Notes: Model 1 = Vertebral CT attenuation; Model 2 = Radscore; Model 3 = radiotherapy dose; Model 4 = age + alcohol consumption + radiotherapy dose; Model 5 = age + alcohol consumption + radiotherapy dose + vertebral CT attenuation; Model 6 = age + alcohol consumption + radiotherapy dose + vertebral CT attenuation + Radscore												

After integration of Radscore with clinical factors, total dose, and vertebral CT attenuation, the radiomics-integrated model exhibited the best overall performance, with C-index values of 0.878, 0.825, and 0.759 and 24-month AUCs of 0.895, 0.724, and 0.802 in the three cohorts, respectively. The relatively high 3-year AUC in the external cohort should be interpreted cautiously because of the limited number of events.

Sequential incorporation of vertebral CT attenuation and Radscore progressively improved the clinical-radiotherapy model. In the training cohort, the radiomics-integrated model significantly improved risk reclassification and discrimination, yielding an NRI of 1.074 (95% CI, 0.499–1.451; $p < 0.001$) and an IDI of 0.221 (95% CI, 0.086–0.338; $p < 0.001$). In the internal and external validation cohorts, NRI and IDI showed positive but non-significant trends. Detailed analyses are provided in Supplementary Tables 3–5.

At the 24-month prediction horizon, the radiomics-integrated model demonstrated variable threshold-based classification performance, with lower sensitivity in the external cohort (Supplementary Table 2). Decision curve analysis indicated potential clinical net benefit, calibration curves showed acceptable agreement, and Kaplan–Meier analysis demonstrated higher cumulative VCF incidence in the high-risk group (Figs. 5–7). In sensitivity analysis excluding non-VCF patients with follow-up < 12 months, model performance remained generally consistent. C-index values were 0.869, 0.817, and 0.802 and 24-month AUCs were 0.897, 0.728, and 0.788 in the three cohorts, respectively (Supplementary Tables 6–7).

4 Discussion

In this two-center retrospective study, we developed and externally validated a CT radiomics-integrated model for predicting newly developed thoracic VCFs after radiotherapy in patients with ESCC. Vertebral radiomics provided complementary predictive information beyond conventional CT attenuation and radiotherapy dose. The best-performing

model integrated age, alcohol consumption, total dose, vertebral CT attenuation, and Radscore, supporting the potential role of CT radiomics as an adjunctive imaging biomarker for post-radiotherapy VCF risk.

Post-radiotherapy thoracic VCF is an increasingly recognized skeletal complication in patients with esophageal cancer. Previous studies have revealed that vertebral fractures after radiotherapy for esophageal cancer frequently occur within or adjacent to the irradiation field, suggesting a potential association between radiation exposure and vertebral fragility(8–10). Moreover, radiation-related insufficiency fractures have been reported in patients with other malignancies, including gastric, cervical, rectal, and gynecologic cancers, suggesting that radiation-induced skeletal injury is a broad treatment-related complication and not just a disease-specific phenomenon(13, 15, 33). In our study, all fractured segments were within the radiation field, with substantial agreement between field involvement and fracture location. Radiation may disrupt bone remodeling through damage to bone cells and the osseous microvasculature(15, 16, 34), while older age and alcohol consumption may reflect baseline skeletal vulnerability(35–37). Taken together, these findings suggest that post-radiotherapy thoracic VCFs in patients with ESCC develop because of the combined effects of baseline skeletal vulnerability and radiotherapy-related vertebral injury.

Vertebral CT attenuation is an opportunistic imaging marker of bone status and offers practical advantages for patients with ESCC who routinely undergo chest CT for pretreatment evaluation and for post-treatment follow-up. In the present study, lower vertebral CT attenuation was associated with a fracture risk in the univariable analysis and was retained in the final AIC-selected radiomics-integrated model, although it did not reach conventional statistical significance after multivariable adjustment. Previous studies have demonstrated that lower vertebral CT attenuation is associated with reduced bone mineral density and an increased risk of vertebral or insufficiency fractures after radiotherapy(8, 10, 13, 19, 38). These findings support the potential utility of CT attenuation as an easily accessible marker for fracture risk assessment. However, CT attenuation primarily reflects the average density of the selected vertebral body and provides limited information regarding trabecular architecture, intravertebral texture, and spatial heterogeneity. This limitation may partly explain why the CT attenuation model alone demonstrated only moderate predictive performance and why additional imaging biomarkers, such as radiomics, may further improve risk stratification.

Radiomics may complement vertebral CT attenuation by characterizing intravertebral heterogeneity that cannot be fully captured by mean density measurement. In the present study, the radiomics model demonstrated the highest overall discriminatory performance among the single-predictor models, suggesting that Radscore provides additional information regarding vertebral vulnerability beyond conventional CT attenuation or radiotherapy dose alone. The radiomics signature comprised three LoG-based first-order features and one wavelet-based GLRLM feature. These features quantify gray-level intensity distribution and spatial run-length patterns from complementary perspectives, suggesting that multiscale image filtering and texture analysis may enhance the detection of subtle vertebral structural alterations before overt fracture develops(29–32, 39). Previous studies have shown that CT radiomics improves osteoporosis assessment and vertebral fracture prediction, including the prediction of radiation-induced VCF following spinal stereotactic body radiotherapy(24). Our findings extend this evidence to patients with ESCC receiving radiotherapy and suggest that vertebral CT radiomics may serve as a valuable adjunctive imaging biomarker for individualized prediction of post-radiotherapy thoracic VCFs.

The highest overall predictive performance was achieved by integrating Radscore with clinical factors, total radiotherapy dose, and vertebral CT attenuation. This finding supports the concept that the risk of post-radiotherapy thoracic VCFs is multifactorial and may be more accurately characterized by combining patient-related, treatment-related, and imaging-derived factors rather than relying on a single predictor. Age and alcohol consumption may reflect baseline skeletal vulnerability(35–37), total radiotherapy dose represents treatment exposure, vertebral CT attenuation provides an accessible marker of vertebral bone density, and Radscore captures quantitative image heterogeneity beyond mean CT attenuation. The complementary nature of these predictors may explain the superior performance of the radiomics-

integrated model. Importantly, the incremental value of the radiomics-integrated model over the clinical-radiotherapy model was statistically significant in the training cohort, whereas the validation cohorts demonstrated positive but non-significant trends. Therefore, although the present findings support the added value of radiomics, its incremental benefit should be interpreted cautiously and confirmed in larger independent cohorts. The validation findings also suggest that apparent performance gains may be sensitive to cohort size and event distribution. Accordingly, radiomics should complement, rather than replace, clinical assessment and established approaches to bone health in routine clinical practice and follow-up. This cautious interpretation is important for future implementation.

Clinically, the proposed model may identify patients at increased risk who require closer imaging surveillance and comprehensive bone-health assessment. Because chest CT is routinely performed during ESCC care, CT attenuation and radiomics could potentially be incorporated into existing workflows without additional dedicated examinations. The model should be considered a risk-stratification tool rather than a definitive clinical decision-making instrument until prospective studies determine whether model-guided surveillance or preventive management reduces fracture-related morbidity.

5 Limitation

Several limitations should be acknowledged. First, the retrospective design may have introduced selection bias, and the limited number of fracture events, particularly in the external cohort and during longer follow-up, may have reduced estimate precision. Second, follow-up CT timing was not standardized; asymptomatic fractures after the final CT may have been missed, while fractures between scans were dated by first radiologic detection. Third, DEXA data and information on osteoporosis treatment, calcium or vitamin D supplementation, glucocorticoid exposure, and other bone-metabolism factors were not consistently available. Fourth, radiotherapy exposure was represented by total dose rather than vertebra-specific dosimetric parameters. Fifth, analysis of a single index vertebra may not capture heterogeneity among irradiated vertebrae. Finally, radiomic features may vary with CT acquisition, reconstruction, slice thickness, segmentation, and scanner type. Larger prospective multicenter studies with standardized imaging and follow-up, comprehensive dosimetry, and independent validation are needed.

6 Conclusion

In this two-center retrospective study, CT radiomics demonstrated favorable performance in predicting newly developed thoracic VCFs after radiotherapy in patients with ESCC. This radiomics-integrated model incorporated clinical factors, total radiotherapy dose, vertebral CT attenuation, and the Radscore and exhibited the best overall predictive performance and may provide additional value for individualized fracture risk stratification. Further prospective multicenter studies with standardized imaging protocols and detailed vertebra-specific dosimetric information are warranted to validate the clinical utility of this model.

Abbreviations

AIC Akaike information criterion

DEXA Dual-energy X-ray absorptiometry

ESCC Esophageal squamous cell carcinoma

GLRLM Gray-level run-length matrix

IDI Integrated discrimination improvement

NRI Net reclassification improvement

VCF Vertebral compression fracture

Declarations

Ethics approval and consent to participate

This two-center retrospective study was conducted with approval from the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Approval No. 2026ER325-1). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The requirement for written informed consent was waived by the Ethics Committee due to the retrospective nature of the study, which involved the analysis of anonymized clinical and imaging data without direct patient contact or intervention.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because of institutional privacy restrictions but are available from the corresponding author upon reasonable request and with permission from the relevant institutions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CP, LW contributed to the study design, data collection, image analysis, statistical analysis, and manuscript drafting. YT contributed to data collection, image analysis, statistical analysis, and manuscript revision. SJ, KS, YX, JH and YZ contributed to data collection and image analysis. ZY contributed to external validation data collection and clinical interpretation. RL and GD conceived and supervised the study, interpreted the results, and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

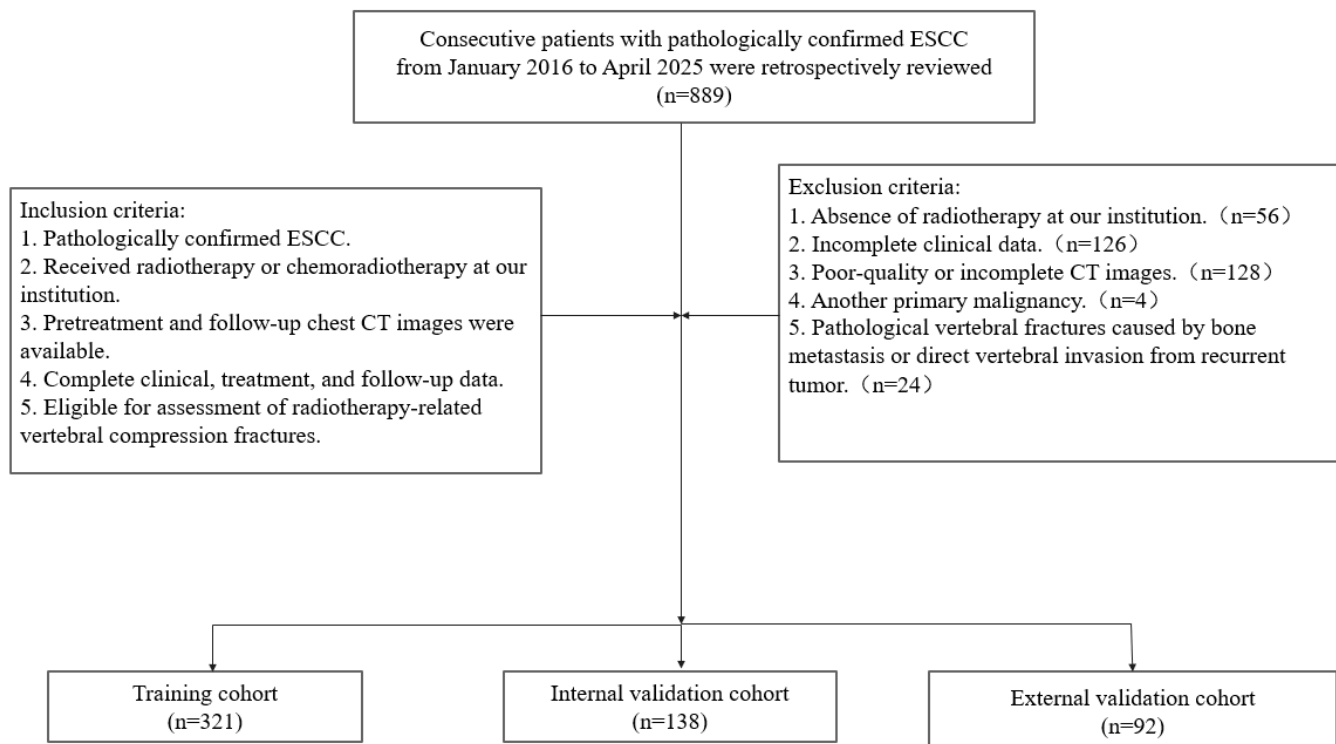


Figure 1

Flowchart illustrating the inclusion and exclusion criteria for the study population.

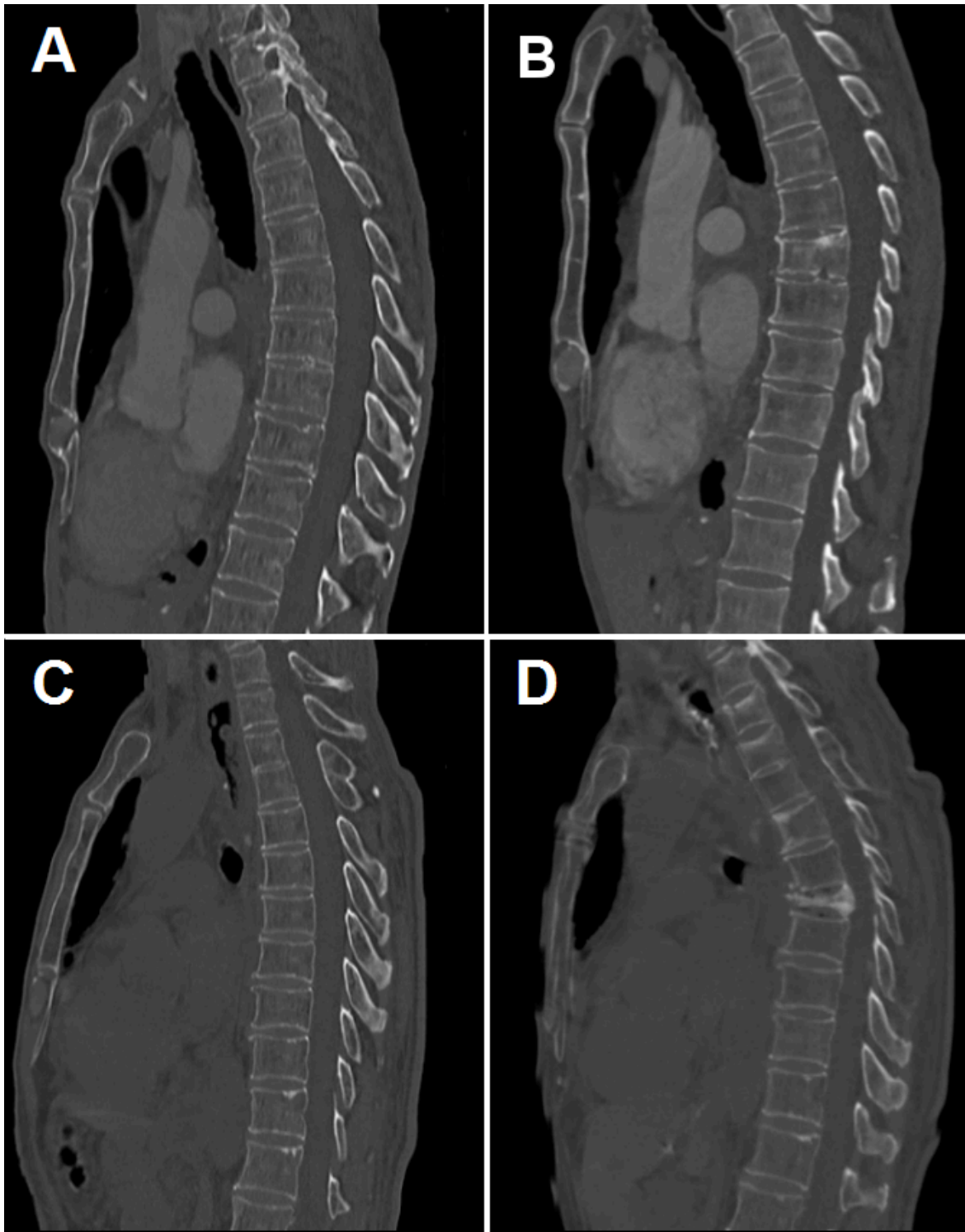


Figure 2

Representative sagittal CT images showing newly developed thoracic vertebral compression fractures after radiotherapy.

(A) Pretreatment sagittal CT image of a 66-year-old man showing no vertebral compression fracture. (B) Follow-up CT image obtained 24 months after radiotherapy showing a newly developed T7 vertebral compression fracture. (C) Pretreatment sagittal CT image of a 71-year-old man showing no vertebral compression fracture. (D) Follow-up CT image obtained 20 months after radiotherapy showing a newly developed T7 vertebral compression fracture.

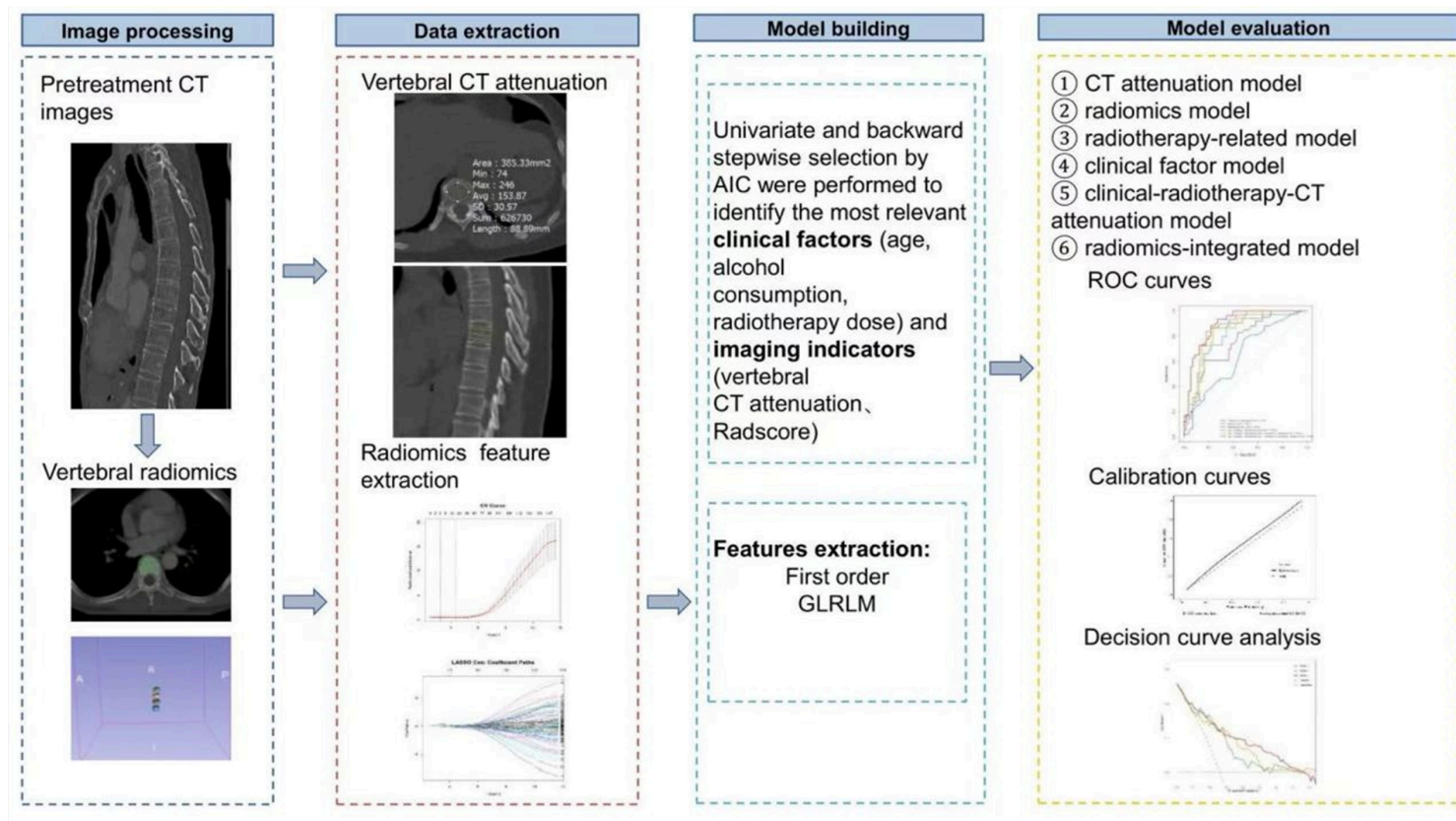


Figure 3

Workflow of vertebral CT attenuation measurement, radiomics feature extraction, model construction, and model evaluation.

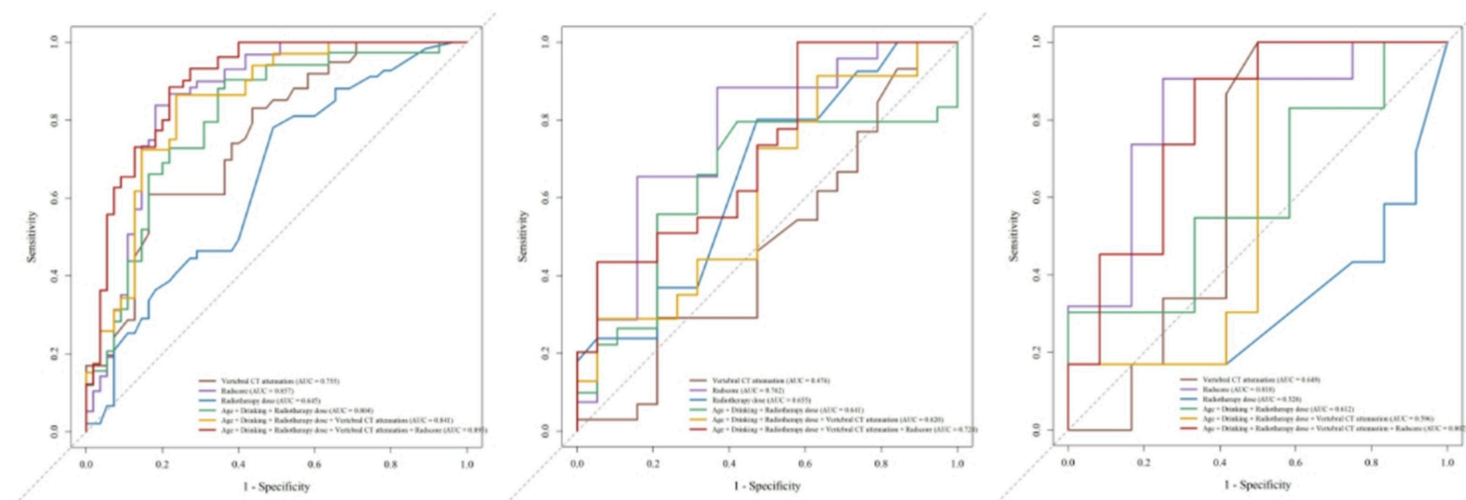


Figure 4

Time-dependent ROC curves of different models at 24 months in the training, internal validation, and external validation cohorts

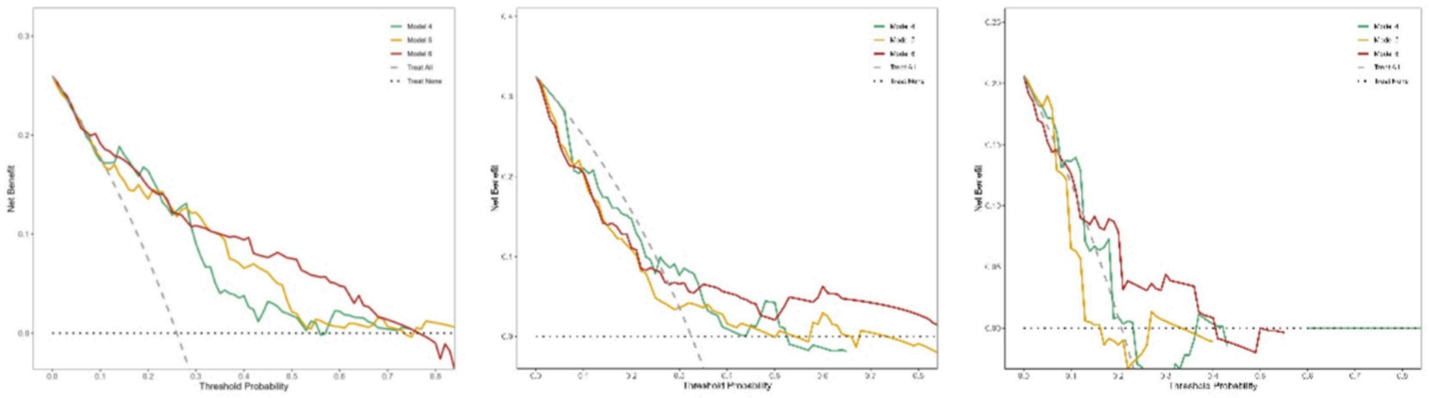


Figure 5

Decision curve analysis of the radiomics-integrated model in the training, internal validation, and external validation cohorts.

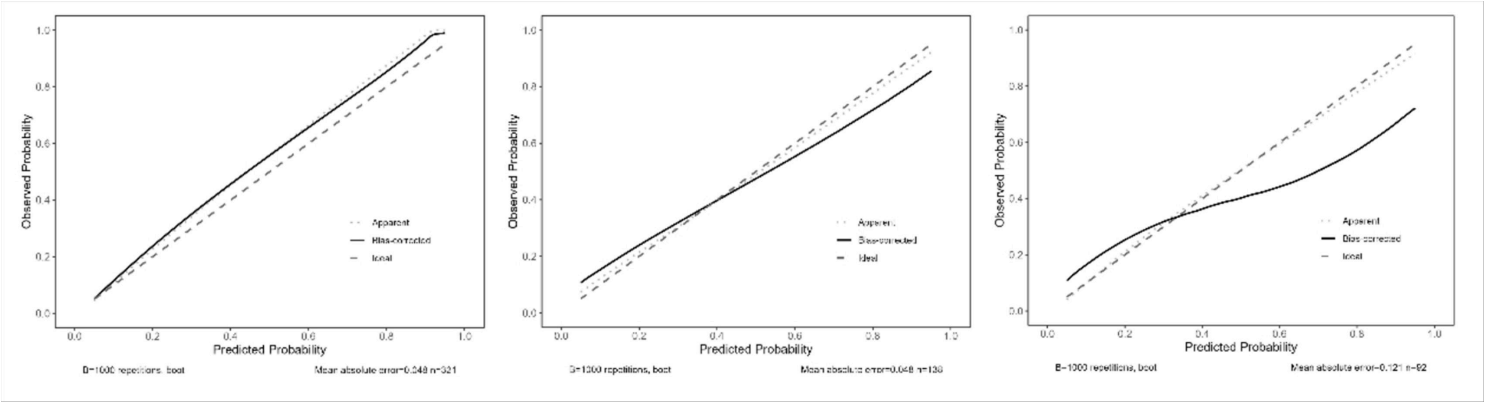


Figure 6

Calibration curve analysis of the radiomics-integrated model at 24 months in the training, internal validation, and external validation cohorts.

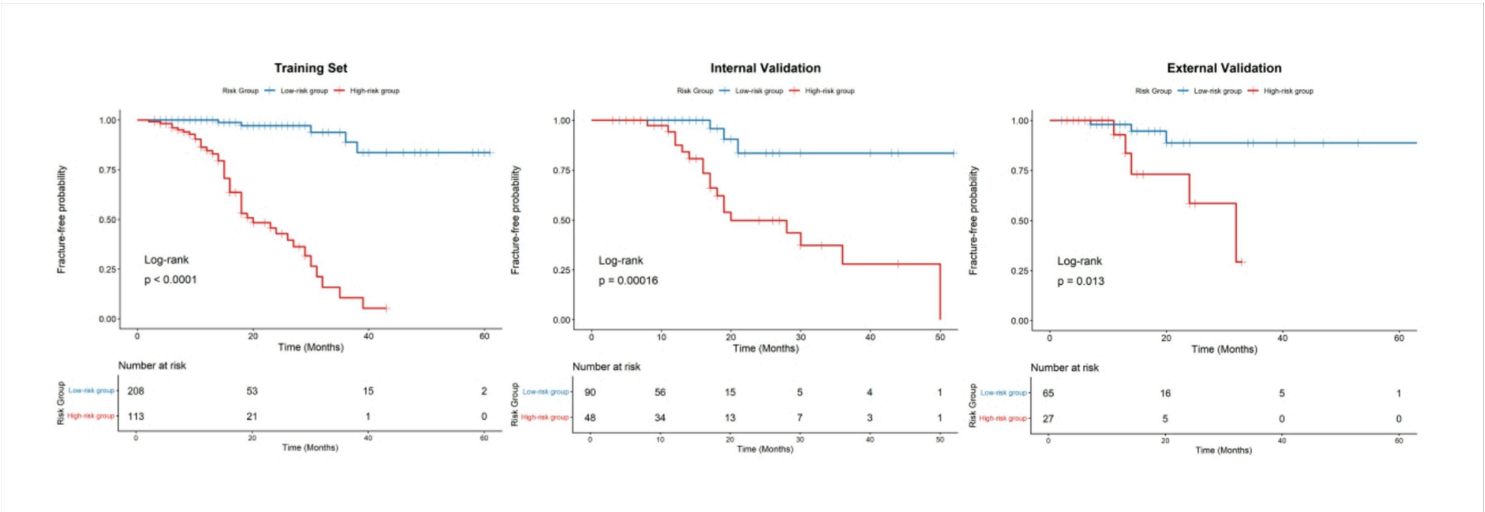


Figure 7

Kaplan-Meier curve analysis of the radiomics-integrated model at 24 months in the training, internal validation, and external validation cohorts. Patients were stratified into high- and low-risk groups according to the optimal cutoff value of the predicted risk score (0.1502), which was determined using the maximum Youden index in the training cohort. Tick marks indicate censored observations.

Supplementary Files

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