Zhao *et al. BMC Cancer* (2025) 25:484
https://doi.org/10.1186/s12885-025-13884-9

BMC Cancer

RESEARCH

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Predicting anastomotic leak in patients with esophageal squamous cell cancer treated with neoadjuvant chemoradiotherapy using a nomogram based on CT radiomic and clinicopathologic factors

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Abstract

Background Anastomotic leak (AL) is a common complication in patients with operable esophageal squamous cell carcinoma (ESCC) treated with neoadjuvant chemoradiotherapy (NCRT) and radical esophagectomy. Therefore, this study aimed to establish and validate a nomogram to predict the occurrence of AL.

Methods Between March 2016 and December 2022, ESCC patients undergoing NCRT and radical esophagectomy were retrospectively collected in China. Clinicopathologic and radiomics characteristics were included in the univariate logistic regression analysis, and statistically significant factors were enrolled to develop the nomogram, which was evaluated by the area under the curve (AUC) of the receiver operating characteristic curve, calibration curve, and decision curve analysis (DCA).

Results 231 eligible patients were divided into training ($n = 159$) and validation cohorts ($n = 72$). Univariate and multivariate analyses revealed that dose at the anastomosis ≥ 24 Gy, gross tumor volume ≥ 60 cm3, postoperative albumin < 35 g/L, comorbidities, duration of surgery ≥ 270 min, and computed tomography-based radiomics characteristics were independent predictors of AL. The nomogram AUC in the training and validation cohorts was 0.845 (95% confidence interval [CI]: 0.770–0.920) and 0.839 (95% CI: 0.718–0.960), respectively, indicating good discriminatory ability. The calibration curves showed good agreement between the predicted and actual AL occurrence and the DCA demonstrated favorable clinical outcomes.

Conclusions We developed and validated a nomogram based on radiomics and clinicopathologic characteristics. This predictive model could be a powerful tool to predict AL occurrence in patients with ESCC treated with NCRT.

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Keywords Esophageal squamous cell carcinoma, Anastomotic leak, Neoadjuvant, Chemoradiotherapy, Nomogram

Background

Esophageal cancer is a common malignancy of the digestive tract. According to the current global cancer statistics, it has the seventh and sixth highest incidence and mortality rates, respectively [1]. Based on the CROSS and NEOCRTEC5010 studies, neoadjuvant chemoradiotherapy (NCRT) and radical esophagectomy is the current standard treatment for operable locally advanced esophageal squamous cell carcinoma (ESCC) [2, 3]. However, ESCC has a high risk of anastomotic leak (AL) after NCRT and radical esophagectomy [4]. The incidence of AL after NCRT and surgery was as high as 22.4% in the CROSS study, and 22% in the Koëter et al. study [2, 5], representing one of the major limitations of this treatment modality. AL is mainly affected by factors such as poor anastomosis and local blood supply, resulting in anastomotic tissue tearing, which induces infection, prolongs hospitalization, decreases the quality of life, and increases mortality [6–10]. Furthermore, AL after radical esophagectomy seriously affects patient safety. Therefore, promptly identifying high-risk patients for AL and actively implementing preventive measures is crucial. Radiomics is a tool for converting medical images into mineable data through high-throughput extraction of quantitative features and holds great promise for cancer diagnosis, prognosis, and treatment response predictions [11–13]. Several studies have analyzed the risk factors for AL which include chronic wasting diseases (such as diabetes), malnutrition manifestations (such as hypoalbuminemia), prolonged surgery, and postoperative pulmonary infections [14, 15]. However, most of these studies focused on high-risk factors for the development of AL only after radical esophagectomy and did not analyze patients that were treated with NCRT and surgery. The effect of factors such as dose at the anastomosis and extent of irradiation at neoadjuvant radiotherapy on AL is unknown. Consequently, for the first time, we aimed to establish and validate, a non-invasive and personalized predictive tool for the occurrence of AL after NCRT and esophagectomy using basic clinical, computed tomography (CT)-based radiomics, and radiotherapy data from patients with ESCC.

Methods

Patients

We retrospectively analyzed 231 patients with locally advanced ESCC who underwent NCRT and esophagectomy at the Cancer Hospital of Shandong First Medical University between March 2016 and December 2022. All methods adhered to the relevant guidelines and regulations. Patient staging was based on the eighth edition of the American Joint Committee on Cancer (AJCC) TNM classification. The inclusion criteria were pathologically confirmed ESCC; receiving NCRT and surgery; and CT scanning before the operation. The exclusion criteria were pathologic types other than esophageal squamous cell carcinoma; administration of other neoadjuvant therapy (including targeted therapy and immunotherapy); absence of preoperative CT scanning, and the dose of radiotherapy was not in the 40–50.4 Gy range (Fig. 1). AL was defined by the Esophageal Complications Consensus Group as "a total gastrointestinal defect involving the esophagus, anastomosis, sutures, or catheter regardless of the presentation or method of recognition" [16]. A minimum of two experienced radiation oncologists and imaging physicians diagnosed AL based on clinical symptoms and imaging examinations. This study was approved by the Ethics Committee of Cancer Hospital Affiliated to Shandong First Medical University, which waived the need for informed consent because of the retrospective nature of the study. We declare that patients information was kept confidential and that we adhered to the principles of the Declaration of Helsinki.

Neoadjuvant treatment regimens

All patients received NCRT before radical esophagectomy with a total dose of 40–50.4 Gy, at 1.8–2 Gy per fraction, 5 days per week. Intensity-modulated radiotherapy techniques were employed. Large-aperture CT scans were performed and CT localization images were imported into the Varian Eclipse program system. The target area was dominated by the area involved in the lesion. The gross tumor volume (GTV) included the primary tumor volume and prechemotherapy positive lymph node regions. Positive lymph nodes were defined as lymph nodes with a positive pathological biopsy, with a short axis ≥ 1 cm in the mediastinum, or clusters of small lymph nodes with a short axis < 1 cm within a region. Clinical target volume (CTV) was defined using the CTV of the primary tumor obtained from 3.0 cm of upward and downward GTV of the primary tumor expansion, 0.5 cm of margin expansion, and the CTV of the pathological lymph nodes obtained by 0.5 cm of margin expansion of the GTV from the pathological lymph nodes and edited according to anatomy as involved field irradiation. However, in this study, 53 patients with elective nodal irradiation remained, which included high-risk lymph nodal regions. The planning target volume (PTV) was defined by further expanding the CTV with a 0.5 cm margin. The preoperative chemotherapy regimen mainly comprised platinum-based drugs (nedaplatin at 75 mg/m2, carboplatin at an area under the curve (AUC) of 5,

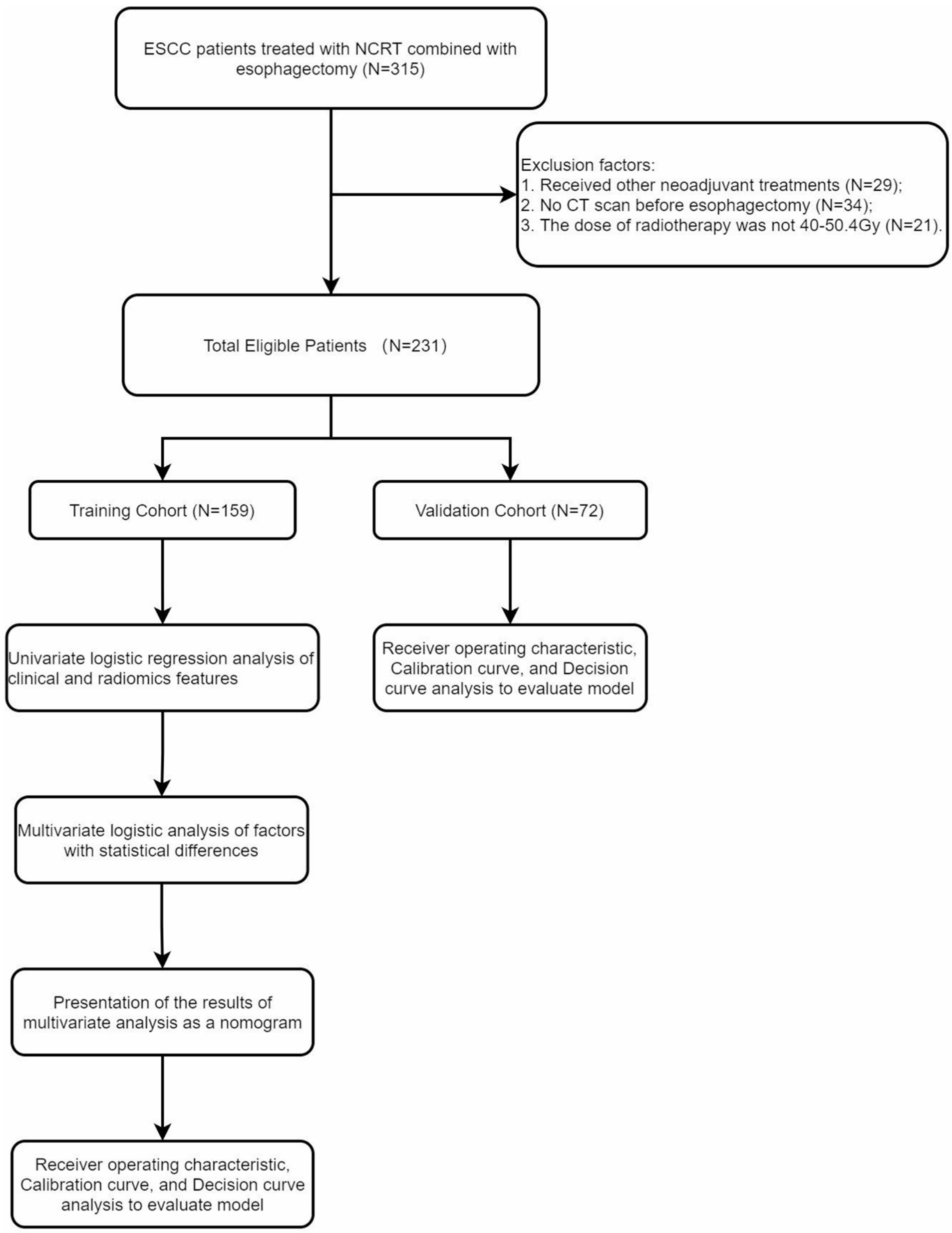

Fig. 1 Flow chart of the study design. Abbreviations: ESCC, esophageal squamous cell carcinoma; NCRT, neoadjuvant chemoradiotherapy; CT, computed tomography

or cisplatin at 25 mg/m2 on days 1–3) along with fluorouracil at 50 mg/m2 on days 1–5 (PF regimen), or platinum-based drugs and paclitaxel at 135–175 mg/m2 and albumin-paclitaxel at 260 mg/m2 (TP regimen) via intravenous injection. Patients received 1–3 preoperative chemotherapies (PF or TP regimen) every 3 weeks, with an average of 2 treatment cycles.

Surgical treatment

Patients enrolled in this study were clinically evaluated for ESCC suitability for radical esophagectomy. Most patients underwent esophagectomy and mediastinal lymph node dissection under general anesthesia 4–8 weeks after the last neoadjuvant therapy. However, 34 patients were > 8 weeks while 11 patients were < 4 weeks. Surgery was performed using open or thoracic laparoscopy, with two- and three-incision surgical incisions and dual-field lymph node dissection as standard treatments. Standard three-field lymph node dissection was performed in patients with suspected cervical lymph node enlargement.

Radiomics

The CT scans obtained before surgical treatment were analyzed. All tumor target areas were manually depicted layer-by-layer using the medical image processing and navigation software 3D Slicer (version 5.2.1) by an author specializing in radiation oncology. Subsequently, the region of interest was confirmed by another radiologist with 10 years of experience in chest CT analysis. Z-score normalization was performed on all data as a preprocessing step to reduce the variation between different patient images. Moreover, feature selection was performed in two steps to reduce any bias or overfitting caused by several features. First, the intra-class correlation coefficient (ICC) index was calculated to filter out features with high repeatability and stability. In this study, ICC > 0.9 was used as the criterion to filter features. Features with high repeatability were initially filtered, downscaled, and filtered for key features using Least Absolute Shrinkage and Selection Operator regression [17, 18]. Finally, the radiomics score (Rad score) of each patient was determined by a linear combination of the selected characteristics, with their respective coefficients being used as weights [19].

Model construction and evaluation

Based on previous AL studies, we retrospectively analyzed basic information (such as age), radiotherapy information (such as GTV and dose at the anastomosis), and radiomics information. First, univariate logistic regression models were used in the training cohort to evaluate the predictive ability of the clinical and radiomics characteristics for AL. Second, multivariate logistic regression analysis was performed to assess factors with $P < 0.05$ in the univariate analysis. Third, a nomogram was constructed using factors with significant predictive values from the multivariate analysis. The discriminatory ability of the nomogram was then assessed using receiver operating characteristic (ROC) curves in the training and validation cohorts, calibration curves to assess the agreement between predicted AL and actual observations, and decision curve analysis (DCA) to validate the nomogram by quantifying the net benefit of the nomogram at different threshold probabilities to illustrate its clinical utility.

Statistical analysis

All data analyses and graphing were performed using R software version 4.0.3. The independent sample t-test and rank-sum test were employed to contrast continuous variables. The chi-square and Fisher's exact tests were used to compare category variables. All tests were two-sided, and $P < 0.05$ indicated statistical significance.

Results

Patients' baseline characteristics

Ultimately, 231 patients with locally advanced ESCC who underwent NCRT and esophagectomy were included in this study, 48 (20.8%) of whom were diagnosed with AL (baseline characteristics are shown in Table 1). The patients were randomly assigned to the training ($n = 159$) and validation ($n = 72$) cohorts in a 7:3 ratio (Fig. 1). In the training and validation cohorts, AL occurred in 36 (22.6%) and 12 (16.7%) patients, respectively, and 119 (74.8%) and 59 (82.0%) patients received radiotherapy with involved-field irradiation, respectively.

Univariate and multivariate analysis

Regarding the univariate analysis in the training cohort, we observed five high-risk factors for AL as follows: dose at the anastomosis ≥ 24 Gy (25.0% vs. 10.6%, $P = 0.027$), GTV ≥ 60 cm3 (44.4% vs. 25.2%, $P = 0.026$), postoperative albumin < 35 g/L (27.8% vs. 9.8%, $P = 0.006$), comorbidities (58.3% vs. 20.3%, $P < 0.001$), and duration of surgery ≥ 270 min (41.7% vs. 22.0%, $P = 0.018$) (Table 2). The eight radiomics characteristics that were most valuable in predicting AL were selected (Fig. 2), and the calculated Rad scores were (1.76 ± 1.41 vs. 0.57 ± 1.58, $P < 0.001$) in patients who developed AL and in those who did not.

Multivariate logistic regression analysis was performed on the six factors with $P < 0.05$ in the univariate analysis, including dose at the anastomosis ≥ 24 Gy (odds ratio [OR]: 4.572, 95% confidence interval [CI]: 1.329–16.689, $P = 0.017$), GTV ≥ 60 cm3 (OR: 4.165, 95% CI: 1.555–11.903, $P = 0.006$), postoperative albumin < 35 g/L (OR: 6.035, 95% CI: 1.790–21.769, $P = 0.004$), comorbidities (OR: 4.377, 95% CI: 1.729–11.912, $P = 0.002$), duration of surgery ≥ 270 min (OR: 2.850, 95% CI: 1.053–7.888, $P = 0.040$), and Rad score (OR: 1.671, 95% CI: 1.229–2.353, $P = 0.002$). These six factors were independent predictors of AL (Table 2).

Modeling and validation

Based on the multivariate logistic regression analysis, the prediction model was visualized as a nomogram (Fig. 3). The ROC curve shows that the AUC of the model was 0.845 (95% CI: 0.770–0.920) in the training cohort, which was higher than the AUC of each factor (dose at the anastomosis ≥ 24 Gy, AUC: 0.572; GTV ≥ 60 cm3, AUC: 0.596; postoperative albumin < 35 g/L, AUC: 0.590; comorbidities, AUC: 0.671; duration of surgery ≥ 270 min, AUC: 0.599; Rad score, AUC: 0.716) (Fig. 4a) (Table 3). Thus, the nomogram showed high predictive efficiency (Table 4).

In the validation cohort, the AUC of the model was 0.839 (95% CI: 0.718–0.960), which was higher than the AUC of each factor (dose at the anastomosis ≥ 24 Gy AUC: 0.508; GTV ≥ 60 cm3 AUC: 0.558; postoperative

Table 1 Clinical characteristics of patients in the training and validation cohorts

Characteristic	Training (n = 159)	Validation (n = 72)	*P*-value
Sex			
Female	23 (14.5%)	6 (8.3%)	0.276
Male	136 (85.5%)	66 (91.7%)	
Age (years)			
≤ 60	68 (42.8%)	37 (51.4%)	0.224
> 60	91 (57.2%)	35 (48.6%)	
Height[1]	1.67 ± 0.07	1.68 ± 0.07	0.287
Weight[1]	63.15 ± 10.41	64.46 ± 10.36	0.378
Smoking			
No	64 (40.3%)	29 (40.3%)	1.000
Yes	95 (59.7%)	43 (59.7%)	
Drinking			
No	69 (43.4%)	35 (48.6%)	0.552
Yes	90 (56.6%)	37 (51.4%)	
Comorbidities			
No	95 (59.8%)	38 (52.8%)	0.321
Yes	64 (40.2%)	34 (47.2%)	
Tumor location			
Lower-thoracic	83 (52.2%)	34 (47.2%)	0.782
Middle-thoracic	64 (40.3%)	32 (44.4%)	
Upper-thoracic	12 (7.5%)	6 (8.3%)	
GTV (cm^3)			
< 60	112 (70.4%)	49 (68.1%)	0.715
≥ 60	47 (29.6%)	23 (31.9%)	
Dose at the anastomosis (Gy)			
< 24	137 (86.2%)	55 (76.4%)	0.066
≥ 24	22 (13.8%)	17 (23.6%)	
Chemotherapy regimen			
PF	21 (13.2%)	8 (11.1%)	0.817
TP	138 (86.8%)	64 (88.9%)	
Total protein (g/L)			
≤ 60	13 (8.2%)	4 (5.6%)	0.483
>60	146 (91.8%)	68 (94.4%)	
Postoperative albumin (g/L)			
< 35	22 (13.8%)	18 (25.0%)	0.038
≥ 35	137 (86.2%)	54 (75.0%)	
Triglycerides (mmol/L)			
≤ 1.7	117 (73.6%)	56 (77.8%)	0.497
>1.7	42 (26.4%)	16 (22.2%)	
Red cells (10^{12}/L)			
≤ 4.0	80 (50.3%)	30 (41.7%)	0.224
>4.0	79 (49.7%)	42 (58.3%)	
Lymphocytes (10^9/L)			
≤ 0.8	53 (33.3%)	20 (27.8%)	0.401
>0.8	106 (66.7%)	52 (72.2%)	
Neutrophils (10^9/L)			
≤ 2.0	17 (10.7%)	7 (9.7%)	0.823
>2.0	142 (89.3%)	65 (90.3%)	
Hemoglobin (g/L)			
≤ 110	22 (13.8%)	9 (12.5%)	0.783
>110	137 (86.2%)	63 (87.5%)	
Target Area			
IFI	119 (74.8%)	59 (82.0%)	0.327

Table 1 (continued)

Characteristic	Training (n = 159)	Validation (n = 72)	*P*-value
ENI	40 (25.2%)	13 (18.0%)	
Duration of surgery (mins)			
<270	117 (73.6%)	44 (61.1%)	0.056
≥ 270	42 (26.4%)	28 (38.9%)	
Type of surgery			
Lvor Lewis	30 (18.9%)	13 (18.0%)	0.834
McKeown	129 (81.1%)	59 (82.0%)	
Anastomotic method			
Mechanical sewn	56 (35.2%)	23 (31.9%)	0.546
Hand-sewn	103 (64.8%)	49 (68.1%)	

Abbreviations: GTV, gross tumor volume; 1, presented as mean ± standard deviation; TP, platinum-based drugs and paclitaxel/albumin paclitaxel; PF, platinum-based drugs and fluorouracil; IFI, involved field irradiation; ENI, elective nodal irradiation

albumin < 35 g/L AUC: 0.700; comorbidities AUC: 0.567; duration of surgery ≥ 270 min AUC: 0.658; Rad score AUC: 0.725) (Fig. 4b). Therefore, the nomogram also showed high predictive efficiency (Table 4). Additionally, the calibration curves for the training and validation cohorts showed good agreement between the predicted AL and actual observations (Fig. 5a and b). Moreover, the DCA showed that the nomogram had satisfactory net benefits for most threshold probabilities, indicating good potential clinical outcomes for the model (Fig. 5c and d).

Discussion

One of the most severe complications of esophagectomy is AL, affecting patient prognosis and increasing mortality [6–9]. The incidence of AL in this study was 20.8%, similar to the 22% reported by Koëter et al. [5] and 22.4% by the CROSS study [2]. Vande Walle et al. found that radiation dose to the fundus of the stomach was an independent predictor of anastomotic complications in patients who received NCRT and radical esophagectomy [20]. Similarly, Morita et al. found that the incidence of AL was significantly higher in patients treated with NCRT than in patients treated with surgery alone (28% vs. 16.5%) [21]. Although Koe¨ter et al. concluded that NCRT does not increase the incidence of AL, the 22% incidence is equally noteworthy [5]. To the best of our knowledge, this study is the first to develop and validate a predictive model for AL for patients undergoing NCRT and radical esophagectomy. Patients who develop an AL within 3 days after esophagectomy are usually caused mainly by intraoperative malpractice, such as instrument malfunction and tearing of the stomach of the lifting tube. Because our study was trying to discover which therapeutic factors or the patient's own factors have an impact on the occurrence of AL, we excluded patients who developed AL within 3 days. Regarding this study, the multivariate analysis identified dose at the anastomosis ≥ 24 Gy, GTV ≥ 60 cm3, postoperative albumin < 35 g/L, comorbidities, duration of surgery ≥ 270 min, and radiomics characteristics as independent risk factors for AL. The AUC values of the training and validation cohorts were 0.845 and 0.839, respectively, and the AUC of the nomogram in both cohorts was higher than that of each individual factor, proving that the nomogram had a high predictive value.

By analyzing the radiotherapy dose curves of each patient, we found that the dose received at the anastomosis after radical resection for esophageal cancer was strongly associated with AL occurrence. We analyzed the position of the anastomosis in each patient's postoperative CT and the isodose profile in the radiotherapy plan. When the dose at the anastomosis was ≥ 60% of the total dose (the lowest total dose included in this study was 40 Gy, therefore, the cutoff value for the dose at the anastomosis was 24 Gy), a significant increase in AL incidence was observed; in some patients, the anastomosis even remained within the PTV. If the anastomosis was exposed to a large radiation dose, subsequent anastomotic surgery and perioperative safety were affected. A similar conclusion was reached in the study by Klevebro et al. wherein the anastomosis radiation dose was strongly correlated with the severity of postoperative anastomosis complications [22]. Therefore, for patients receiving NCRT, the anastomosis should not be in the irradiation field, and a safe distance should be set aside for the anastomosis to limit the radiation dose received at the anastomosis; the use of intensity-modulated radiotherapy is routinely recommended. Moreover, if conditions permit, proton irradiation may be used in units where it is available. This is consistent with Wang et al.'s view that reducing the dose to normal tissues by using complex techniques such as intensity-modulated radiation therapy or proton beam therapy can reduce pulmonary and gastrointestinal complications [23]. However, Koëter et al. showed no significant correlation between the radiation dose and AL development at an average radiation dose of 24.2 Gy in the region of the future anastomosis [5]. Therefore, larger

Table 2 Univariate and multivariate analysis of clinical and radiomics characteristics for AL prediction

Univariate analysis				Multivariate analysis		
Characteristics	**AL (*n* = 36)**	**No AL (*n* = 123)**	***P*-value**	**Regression coefficient**	**OR (95% CI)**	***P*-value**
Sex						
Female	8 (22.2%)	15 (12.2%)	0.217			
Male	28 (77.8%)	108 (87.8%)				
Age (years)						
≤ 60	16 (44.4%)	58 (47.2%)	0.774			
> 60	20 (55.6%)	65 (52.8%)				
Smoking						
No	14 (38.9%)	50 (40.7%)	1.000			
Yes	22 (61.1%)	73 (59.3%)				
Dose at the anastomosis (Gy)						
≥ 24	9 (25.0%)	13 (10.6%)	0.027	1.520	4.572 (1.329,16.689)	0.017
< 24	27 (75.0%)	110 (89.4%)	Ref	Ref		
GTV (cm^3)						
≥ 60	16 (44.4%)	31 (25.2%)	0.026	1.427	4.165 (1.555, 11.903)	0.006
< 60	20 (55.6%)	92 (74.8%)	Ref	Ref		
Postoperative albumin (g/L)						
< 35	10 (27.8%)	12 (9.8%)	0.006	1.798	6.035 (1.790, 21.769)	0.004
≥ 35	26 (72.2%)	111 (90.2%)	Ref	Ref		
Tumor location						
Lower-thoracic	19 (52.8%)	64 (52.0%)	0.611			
Middle-thoracic	13 (36.1%)	51 (41.5%)				
Upper-thoracic	4 (11.1%)	8 (6.5%)				
Comorbidities						
Yes	24 (66.7%)	40 (32.5%)	< 0.001	1.476	4.377 (1.729, 11.912)	0.002
No	12 (33.3%)	83 (67.5%)	Ref	Ref		
Chemotherapy regimen						
PF	4 (11.1%)	17 (13.8%)	0.887			
TP	32 (88.9%)	106 (86.2%)				
Total protein (g/L)						
≤ 60	2 (5.6%)	11 (8.9%)	0.518			
> 60	34 (94.4%)	112 (91.1%)				
Red cells (10^{12}/L)						
≤ 4.0	21 (58.3%)	59 (48.0%)	0.912			
> 4.0	15 (41.7%)	64 (52.0%)				
Hemoglobin (g/L)						
≤ 110	7 (19.4%)	15 (12.2%)	0.272			
> 110	29 (80.6%)	108 (87.8%)				
Rad score[1]	1.76 ± 1.41	0.57 ± 1.58	<0.001	0.513	1.671 (1.229,2.353)	0.002
Duration of surgery (mins)						
≥ 270	15 (41.7%)	27 (22.0%)	0.018	1.047	2.850 (1.053,7.888)	0.040
<270	21 (58.3%)	96 (78.0%)	Ref	Ref		
Surgical approach						
Thoracotomy	19 (52.8%)	52 (42.3%)	0.267			
MIE	17 (47.2%)	71 (57.7%)				
Intraoperative bleeding (ml)						
≤ 100	25 (69.4%)	102 (82.9%)	0.080			
> 100	11 (30.6%)	21 (17.1%)				
Target Area						
IFI	26 (72.2%)	93 (75.6%)	0.501			
ENI	10 (27.8%)	30 (24.4%)				
Type of surgery						

Table 2 (continued)

Univariate analysis				**Multivariate analysis**		
Characteristics	**AL** ***(n = 36)***	**No AL** ***(n = 123)***	***P*-value**	**Regression coefficient**	**OR (95% CI)**	***P*-value**
Lvor Lewis	8 (22.2%)	22 (17.9%)	0.517			
McKeown	28 (77.8%)	101 (82.1%)				
Anastomotic method						
Mechanical sewn	12 (33.3%)	44 (35.8%)	0.963			
Hand-sewn	24 (66.7%)	79 (64.2%)				

Abbreviations: AL, anastomotic leak; OR, odds ratio; 95% CI, 95% confidence interval; GTV, Gross Tumor Volume; TP, platinum-based drugs and paclitaxel/albumin paclitaxel; PF, platinum-based drugs and fluorouracil; Rad score, radiomics score; 1, Presented as mean ± standard deviation; MIE, minimally invasive esophagectomy; IFI, involved field irradiation; ENI, elective nodal irradiation

Table 3 AUC (95% CI) for predictors of AL in the training and validation cohorts

Characteristic	**Training AUC (95% CI)**	**Validation AUC (95% CI)**
Nomogram	0.845 (0.770, 0.920)	0.839 (0.718, 0.960)
Dose at the anastomosis (≥ 24 Gy)	0.572 (0.495, 0.649)	0.508 (0.370, 0.647)
GTV (≥ 60cm^3)	0.596 (0.505, 0.687)	0.558 (0.401, 0.715)
Postoperative albumin (< 35 g/L)	0.590 (0.511, 0.669)	0.700 (0.546, 0.854)
Comorbidities (YES)	0.671 (0.582, 0.759)	0.567 (0.408, 0.726)
Duration of surgery (≥ 270 min)	0.599 (0.509, 0.688)	0.658 (0.407, 0.727)
Rad score	0.716 (0.629, 0.804)	0.725 (0.601, 0.849)

Abbreviations: AUC, area under the curve; GTV, gross tumor volume; 95% CI, 95% confidence interval; Rad score, radiomics score

clinical studies are required to determine the maximum dose range at the anastomosis.

In addition, we found that GTV was an independent risk factor for AL. The larger the GTV, the larger the corresponding increase in irradiated normal tissues and resulting increase of the effect on the blood supply, which predisposes patients to AL. When the cutoff value of GTV was 60 cm3, differentiating between patients with and without AL was possible. Radiotherapy may lead to an increase in vascular fragility, thus making postoperative anastomosis more difficult. Additionally, radiotherapy may also damage the vascular endothelium, leading to fibrous tissue proliferation, which may cause vascular occlusion and blood and fluid leakage from the surgical area, affecting the prognosis of the anastomosis, similar to the view of a previous study [4]. Therefore, we suggest that for patients with large tumor volumes, NCRT should be carefully administered to avoid AL.

Malnutrition has been reported in approximately 40–60% of patients with ESCC at diagnosis [24]. In this study, we observed that a postoperative albumin level < 35 g/L was an independent risk factor for AL, similar to the results of Choudhuri et al. [25]. This is because low albumin levels affect postoperative wound and anastomotic healing, increasing AL risk. Fergus et al. established a scoring system wherein serum albumin levels affected the incidence of AL after esophagectomy and postoperative mortality [26]. Therefore, clinicians are advised to promptly assess patient's nutritional status after surgical treatment and provide enteral or parenteral nutrition promptly when serum albumin levels are < 35 g/L [24, 27]. The study also found that comorbidities were independent risk factors for the development of postoperative AL. The comorbidities in this study

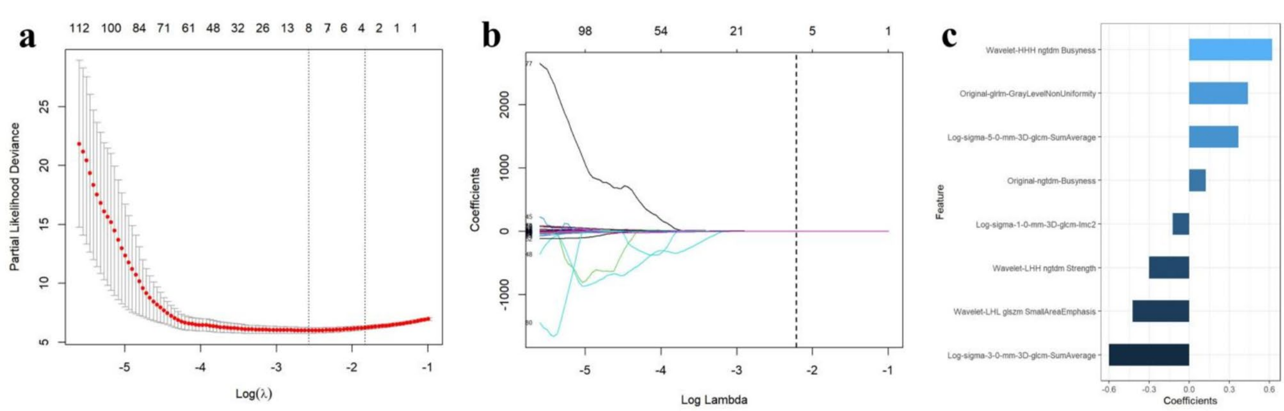

Fig. 2 Radiomics feature selection using the LASSO method. (**a**) The LASSO regression model identified radiomics features with non-zero coefficients predicting. (**b**) Distribution of LASSO regression coefficients for radiomics characteristics. (**c**) The optimal combination of radiomic features and their correlation coefficients. Abbreviations: LASSO, the least absolute shrinkage and selection operator

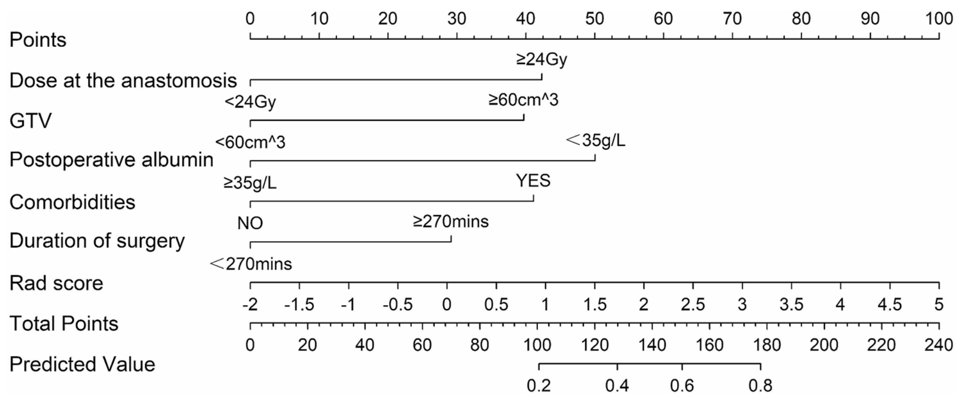

Fig. 3 Nomogram for predicting anastomotic leak (AL). Abbreviations: GTV, gross tumor volume; Rad score, radiomics score

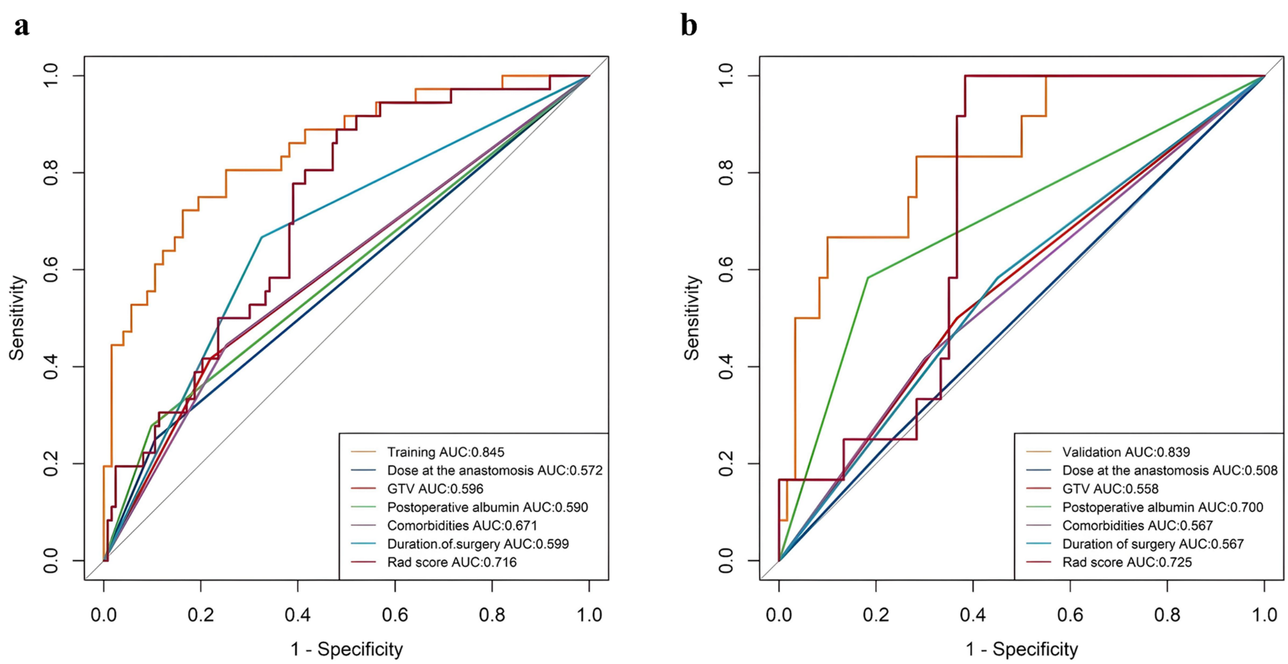

Fig. 4 ROC for training and validation cohorts. (**a**) ROC curves for each predictor and nomogram in the training cohort. (**b**) ROC curves for each predictor and nomogram in the validation cohort. Abbreviations: ROC, receiver operating characteristic; AL, anastomotic leak; GTV, gross tumor volume; AUC, area under the curve; Rad score, radiomics score

Table 4 Prediction performance of nomogram in training and validation cohorts

Parameters	Training	Validation
AUC (95% *CI*)	0.845 (0.770, 0.920)	0.839 (0.718, 0.960)
ACC	0.811	0.861
Sen	0.722	0.667
Spe	0.837	0.900
PPV	0.565	0.571
NPV	0.912	0.931

Abbreviations: AUC, area under the curve; ACC, accuracy; Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value

included hypertension, diabetes, and chronic obstructive pulmonary disease (COPD), which were consistent with the results of Gooszen et al. for COPD (17.7% vs. 12.8%), hypertension (36.4% vs. 31.6%), and diabetes (20.1% vs. 14.5%). Thus, the patient's condition is an important factor in postoperative AL that should not be ignored, and a comprehensive preoperative evaluation should be performed to identify these risk factors as early as possible and actively manage them promptly [28].

Similar to previous studies that have shown intraoperative factors such as surgical methods are also high-risk factors for AL [29–33], in the present study, duration of surgery ≥ 270 min was significantly associated with the occurrence of AL. The increased number of surgical operations such as repeated squeezing and lifting of

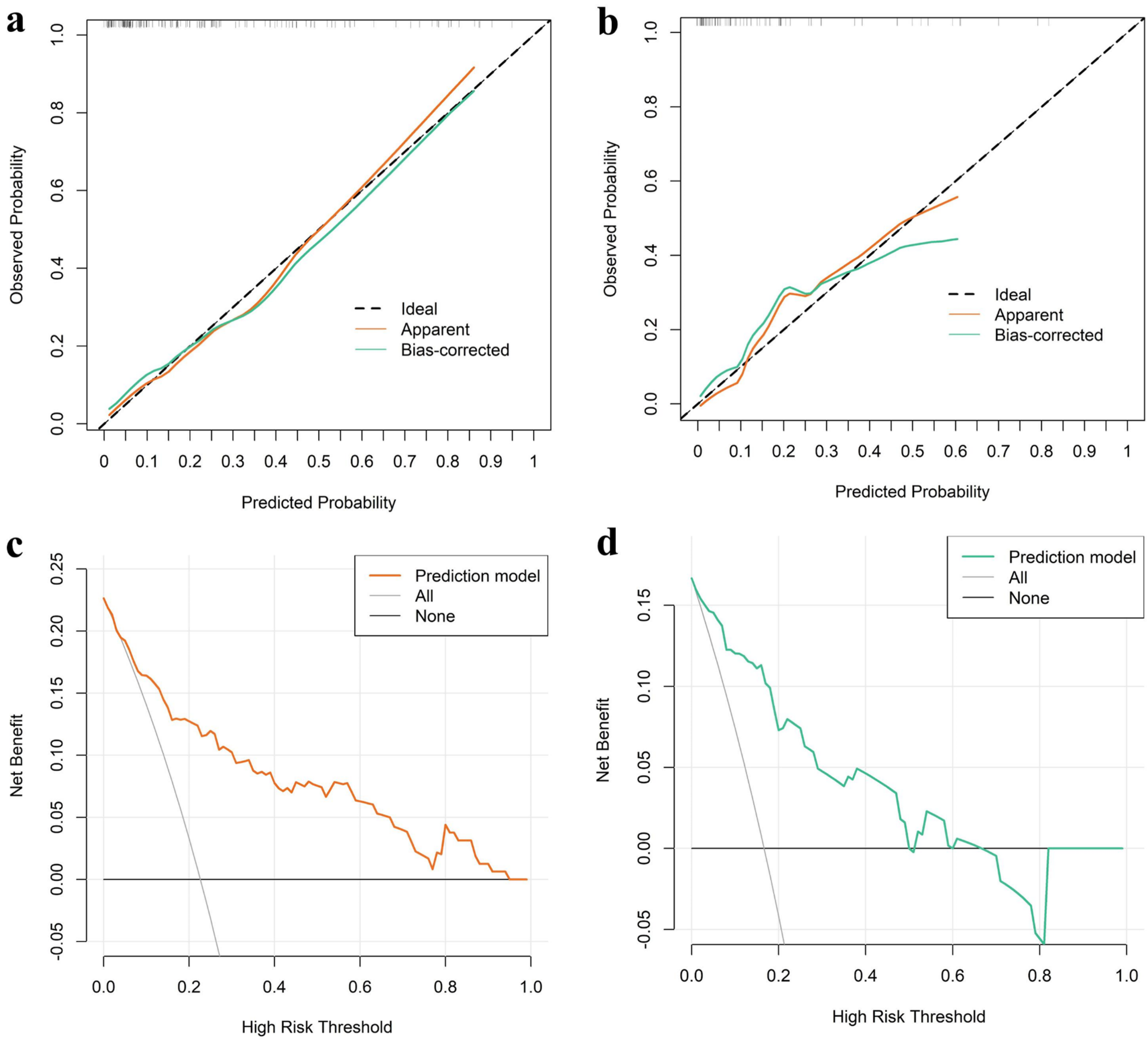

Fig. 5 Calibration curves and Decision curves for training and validation cohorts. (**a**) Calibration curves of the nomogram used to predict the occurrence of AL in the training cohort. (**b**) Calibration curves of the nomogram used to predict the occurrence of AL in the validation cohort. (**c**) Decision curves of the nomogram predicting the occurrence of AL in the training cohort. (**d**) Decision curves of the nomogram predicting the occurrence of AL in the validation cohort. Abbreviations: AL, anastomotic leak

the stomach causes lack of blood supply to the patient's postoperative esophageal and gastric tissue edema, thus affecting anastomotic healing.

Owing to the continuous development of imaging technologies and big data, radiomics has attracted considerable attention. Artificial intelligence is extensively utilized for extracting tumor information and establishing machine models for the prediction of tumor lymph node metastasis, tumor clinicopathological grading, and T-staging [10]. This study considered nine valuable imaging features in predicting AL and weighed them with their respective coefficients. Additionally, Rad scores were obtained and exhibited differences in univariate and multivariate analyses. This suggests the potential of radiomics to predict AL after esophagectomy. We internally validated the accuracy of our prediction model. The ROC, DCA, and calibration curves indicated that our model had a good potential clinical effect, implying that it could be replicated. Moreover, for patients predicted to have an elevated risk for AL by this nomogram, we suggest that clinicians perform regular esophagography scans and examinations to detect them promptly and provide symptomatic treatment, to reduce the impact of high-risk factors for AL.

Nonetheless, our study had some limitations. First, due to the retrospective nature of the study, selection bias was unavoidable; therefore, more prospective studies on AL are required. Second, this was a single-center study. Although internal validation indicated that the current prediction model has a relatively superior AUC of 0.839, the results will be more convincing with external validation. Finally, the quality of surgery has an equally important effect on the incidence of AL, which varies between operators, but this factor could not be controlled for due to the limitations of our retrospective study.

Conclusions

In conclusion, we developed and validated a nomogram based on both radiomics and clinicopathologic characteristics. This predictive model can be used as a powerful tool to predict the occurrence of AL in patients with ESCC treated with NCRT and surgery.

Acknowledgements
We thank the patients for allowing the use of their clinicopathological data for this study.

Author contributions
JZ and GY designed the study, analyzed and interpreted the data, and drafted the manuscript. YL, SL, HL, and DH analyzed and interpreted the data. QC and BL conceptualized and designed the study and revised the manuscript. The authors read and approved the final manuscript. All authors reviewed the manuscript.

Funding
This work was supported by the Clinical Medical Research Center of Shandong Province (2021LCZX04), Academic Promotion Program of Shandong First Medical University (2019LJ004), and Major Basic Research Project of Shandong Provincial Natural Science Foundation (ZR2022ZD31).

Data availability
The datasets used and/or analysed during the current 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 Cancer Hospital Affiliated to Shandong First Medical University, which waived the need for informed consent because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 11 March 2024 / Accepted: 7 March 2025
Published online: 15 March 2025

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