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Predictive model for acute radiation esophagitis in esophageal carcinoma based on prognostic nutritional index and systemic inflammatory index and its application

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Abstract. Acute radiation esophagitis (ARE) is a common complication in patients with esophageal cancer undergoing radiotherapy. Therefore, it is important to construct an effective ARE risk-prediction model for clinical treatment. The present study performed a retrospective analysis of 225 patients with esophageal cancer who received radiotherapy at the First Affiliated Hospital of Anhui Medical University (Hefei, China) from January 2018 to December 2022. Univariate and logistic regression analyses were performed to screen patients with esophageal cancer after radiotherapy. The results revealed that 147 patients developed radiation esophagitis. Logistic regression analysis results demonstrated that the prognostic nutritional index [odds ratio (OR), 0.864; 95% confidence interval (CI), 0.809-0.924], neutrophil to lymphocyte ratio (OR, 1.795; 95% CI, 1.209-2.667) and platelet to lymphocyte ratio (OR, 1.011; 95% CI, 1.000-1.022) were independent predictors of ARE in patients receiving intensity-modulated conformal radiotherapy for esophagus cancer ($P<0.05$). A nomogram model for predicting the occurrence of ARE was established based on the three risk factors. The decision curve suggested a high net benefit value when the threshold probability was within 0.25-1.0. External verification confirmed the reproducibility and generalizability of the nomogram model. In general, the calibration curve of this model was close to the ideal curve and had excellent prediction accuracy. Therefore, it may be used as a new tool for early prediction of the ARE risk.

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Introduction

Esophageal cancer is a malignant tumor with one of the highest incidences and mortality rates globally. According to the Global Cancer Statistics Report 2022, esophageal cancer has the seventh-highest incidence rate and the sixth-highest total mortality rate worldwide (1). Notably, China alone accounts for >50% of esophageal cancer cases globally (2,3). Therefore, studying the treatment and recovery methods has clinical significance.

Although advanced therapies such as targeted therapy and immunotherapy have seen rapid development, radiotherapy (a traditional treatment) is still widely used for esophageal cancer owing to its considerable efficacy. However, radiotherapy damages adjacent normal tissues, resulting in radiation-related side effects such as radiation-induced lung and esophageal injuries, threatening the quality of life of patients (4,5). Notably, the probability of radiation esophagitis in the irradiated field, including the esophagus, is as high as 100% (6). It has been suggested that intensity-modulated conformal radiotherapy (IMCRT) can greatly reduce the damage to normal tissues and key organs. It can also decrease the incidence of radiation esophagitis (7). However, IMCRT may lead to acute radiation esophagitis (ARE), one of the most common radiotherapy-related complications. ARE can cause dysphagia, pain and esophageal perforation and may even lead to the termination of the treatment. Hence, ARE poses a serious threat to the quality of life and health of patients (8). Therefore, it is essential to perform early prevention and timely intervention for ARE in these patients.

Esophageal cancer has the highest incidence of malnutrition among all tumor types. A previous study has also reported that malnutrition is associated with the occurrence of ARE in patients with esophageal cancer (9). Due to large variations in case selection, previous studies have employed diverse nutritional indicators to assess the nutritional status of patients. However, this has led to significant heterogeneity among conclusions, making it challenging to suggest a common effective treatment method (10). Notably, the metabolic process in patients with esophageal cancer can cause malnutrition too, further inducing the systemic inflammatory response (11-13). Therefore, malnutrition and systemic inflammatory response may interact and serve an important role in tumor progression and treatment. In spite of their importance, the association between nutritional indicators and systemic inflammatory indicators in the development of ARE in patients with esophageal cancer has not yet been elucidated.

The present study retrospectively analyzed the factors associated with radiation esophagitis in patients with esophageal cancer. Specifically, the present study aimed to develop a risk-prediction model for ARE using prognostic nutritional index (PNI) along with neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR). Furthermore, the target of the present work was to develop methods for early detection of people at high risk of ARE and to propose targeted preventive interventions to reduce the incidence of radiation esophagitis in such patients.

Materials and methods

Study design. In the training cohort, 225 patients with esophageal cancer received radiotherapy at the First Affiliated Hospital of Anhui Medical University (Hefei, China) from January 2018 to December 2022. In the validation cohort, 169 patients with esophageal cancer received radiotherapy at Gaoxin Hospital, the First Affiliated Hospital of Anhui Medical University from January 2023 to April 2024. Esophageal cancer was segmented according to the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging system (14). Both squamous cell carcinoma and adenocarcinoma were adopted in this study.

The following inclusion criteria were used: i) Pathologically-confirmed esophageal cancer; ii) suitability for radiotherapy (in doses of 45-60 Gy) along with chemotherapy; and iii) complete clinical and follow-up data. Furthermore, the following exclusion criteria were used: i) Recurrent esophageal cancer; ii) other primary malignant tumors; and iii) missing baseline information, such as routine blood and blood biochemistry results before radiotherapy.

External verification. External verification was performed using 169 patients with esophageal cancer who received radiotherapy at Gaoxin Hospital, the First Affiliated Hospital of Anhui Medical University. The model was evaluated based on two aspects: Discrimination and calibration. The receiver operating characteristic (ROC) curve was used for discrimination evaluation, and the calibration curve was used for calibration evaluation.

Treatment procedure. All patients received IMCRT using a 6MVX linear accelerator pedal. After reviewing radiological (X-ray barium meal, CT and/or PET/CT scanning) images and endoscopic or endoscopic ultrasonographical manifestation of the patients, the tumor target area was outlined using a Philips Pinnacle 3 workstation (Phillips Healthcare), a treatment planning system. It required a 95% planning target volume to reach the prescribed dose. In the whole group, the radiotherapy dosage was applied in fractions of 1.8-2.2 Gy five times a week, up to total doses of 45-60 Gy.

Evaluation criteria. The following evaluation criteria were used: i) Parameter information was collected using follow-up data and the hospital information system, specifically regarding sex, age, alcohol consumption, smoking, comorbidities, tumor-node-metastasis (TNM) stage (14), concurrent chemotherapy and pathological type; ii) all patients had routine blood and blood biochemistry laboratory indexes assessed 1 week before radiotherapy, including neutrophil counts, lymphocyte counts, platelet counts and albumin levels. PNI [serum albumin (g/l) + 5x total number of lymphocytes in peripheral blood (x10^9/l)], NLR (neutrophil count/peripheral blood lymphocyte count), and PLR (peripheral blood platelet count/peripheral blood lymphocyte count) were calculated; iii) before performing radiotherapy on the patients, the age-adjusted Charlson Comorbidity Index (ACCI) (15) was calculated using a scoring system based on patient comorbidities. All comorbidity and age scores were added up to obtain the ACCI score. The higher the score, the higher the number of comorbidities, and the worse the basal status; and iv) ARE was evaluated according to the toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC) (16), the primary study endpoint was the occurrence of ARE. Follow-up was performed ≤3 months after the end of radiotherapy.

Statistical analysis. SPSS 28.0 software (IBM Corp.) was used to analyze the data. Continuous variables that conformed to normal distribution are expressed as mean ± standard deviation and were analyzed using an independent sample t-test. Data that did not conform to normal distribution are expressed as the median (interquartile range) and were assessed using the Mann-Whitney U test. Categorical variables are expressed as n (%) and were assessed using the Pearson χ^2 or Fisher's exact test. The Youden index (sensitivity + specificity -1) was calculated using the ROC curve to determine the optimal threshold of PNI before radiotherapy (the maximum point of the Youden index corresponds to the PNI value). All patients included in the present study were categorized into either high-PNI (H-PNI; >48.2) or low-PNI (L-PNI; ≤48.2) groups. The relationship between pre-radiotherapy PNI and the incidence and severity of ARE in patients with esophageal cancer was assessed using the χ^2 test and Spearman's correlation analysis. A multifactorial logistic regression model was used to evaluate the independent risk factors for the occurrence of ARE in patients with esophageal cancer. A column-line graphical model was produced by using the R (R3.5.3) software package (The R Foundation). The predictive efficacy of the model was assessed using calibration curves and decision curves. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of patients. In the training cohort, 60 (26.7%) patients were women and 165 (73.3%) were men, with a median age of 63 years (interquartile range, 61-69 years). A total of 84 patients (37.3%) were smokers and 54 (24.0%) consumed alcohol. In the validation cohort, 43 (25.4%) patients were women and 126 (74.6%) were men, with a median age of 61 years (interquartile range, 60-68 years). A total of 56 patients (33.1%) were smokers and 39 (23.1%) consumed alcohol. Comparing the general

Table I. Baseline characteristics of all patients in the training and validation cohorts.

Clinicopathological characteristic	Training cohort (n=225)	Validation cohort (n=169)	P-value
Age, years	63 (61-69)	61 (60-68)	0.356
Sex			
Male	165 (73.3)	126 (74.6)	0.817
Female	60 (26.7)	43 (25.4)	
Smoker			
Yes	84 (37.3)	56 (33.1)	0.397
No	141 (62.7)	113 (66.9)	
Alcohol consumption			
Yes	54 (24.0)	39 (23.1)	0.905
No	171 (76.0)	130 (76.9)	
ACCI score			
1-2	63 (28.0)	45 (26.6)	0.873
3-4	121 (53.8)	90 (53.3)	
5-7	41 (18.2)	34 (20.1)	
Chemotherapy			
Yes	96 (42.7)	72 (42.6)	0.990
No	129 (57.3)	97 (57.4)	
TNM stage			
≥III	66 (29.3)	50 (29.6)	0.957
<III	159 (70.7)	119 (70.4)	
Histological type			
Adenocarcinoma	55 (24.4)	41 (24.3)	0.966
Squamous cell carcinoma	170 (75.6)	128 (75.7)	
PNI	46.3±5.1	45.9±4.4	0.911
NLR	2.8±1.7	2.6±1.9	0.937
PLR	119.6±47.8	117.2±53.3	0.985

Data are presented as n (%), median (interquartile range) or mean ± standard deviation. ACCI, Charlson Comorbidity Index; TNM, tumor-node-metastasis; PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

clinicopathological characteristics, there were no statistically significant differences between the two groups in terms of sex, age, smoking and alcohol consumption, ACCI, chemotherapy status, TNM stage, histological type, PNI, NLR and PLR (P>0.05; Table I).

Relationship between pre-radiotherapy PNI and ARE in patients with esophageal cancer. The optimal cutoff value of PNI before radiotherapy was 48.2 with an AUC of 0.677, a sensitivity of 66%, and a specificity of 69%. The maximum value of the Youden index was determined as 0.35 by plotting the ROC curve of PNI (Fig. 1). The patients were divided into the following groups based on their PNI cutoff value before radiotherapy: Well-nourished group (H-PNI group; n=108; PNI >48.2) and the malnourished group (L-PNI group; n=117; PNI ≤48.2). The χ^2 test results revealed that pre-radiotherapy PNI was significantly associated with the occurrence of ARE in patients with esophageal cancer, the incidence of ARE in H-PNI group was lower than that in L-PNI group (52.8% vs. 76.9%; χ^2=14.46; P<0.001; Table II). In addition, Spearman's correlation analysis demonstrated the negative correlation of pre-radiotherapy PNI with the grade of ARE after radiotherapy, with higher PNI indicating a lower grade of ARE (P<0.001; Table III).

Table II. Relation between prognostic nutritional index and the incidence of acute radiation esophagitis.

ARE	n	H-PNI (n=108)	L-PNI (n=117)	χ^2 value	P-value
Yes	147	57	90	14.46	<0.001
No	78	51	27		

ARE, acute radiation esophagitis; PNI, prognostic nutritional index; H-PNI, high-PNI (PNI >48.2); L-PNI, low-PNI (PNI ≤48.2).

Analysis of factors affecting ARE in patients with esophageal cancer. A univariate analysis was performed on all 225 patients based on clinicopathological parameters. The results revealed that PNI, NLR and PLR are major risk

Table III. Spearman's correlation analysis between prognostic nutritional index and acute radiation esophagitis grades.

ARE grade	n	H-PNI (n=108)	L-PNI (n=117)	Spearman's correlation index	P-value
0	78	51	27	-0.352	<0.001
I	42	27	15		
II	42	15	27		
III	63	15	48		
IV	0	0	0		

ARE, acute radiation esophagitis; PNI, prognostic nutritional index; H-PNI, high-PNI, (PNI >48.2); L-PNI, low-PNI (PNI ≤48.2).

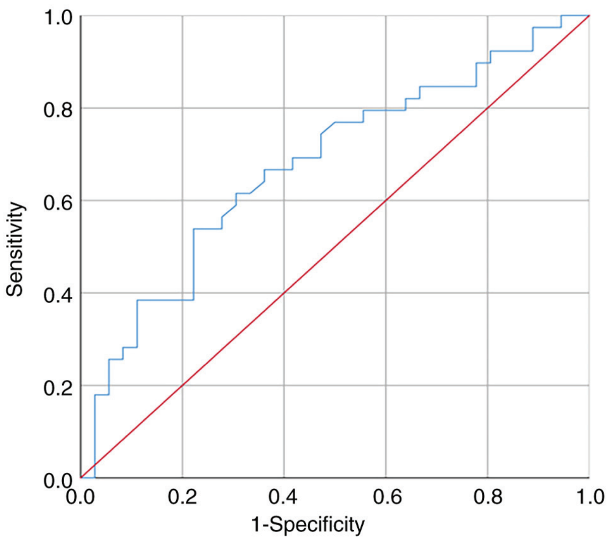

Figure 1. Cutoff value of the prognostic nutritional index before radiotherapy, calculated by plotting a receiver operating characteristic curve.

factors for ARE in patients undergoing intensity-modulated radiotherapy for esophageal cancer (Table IV). Multifactorial logistic regression analysis demonstrated that PNI, NLR and PLR are independent risk factors affecting ARE in patients treated with radiotherapy for esophageal cancer (Table IV).

Modeling and evaluation for predicting ARE in patients treated with IMCRT for esophageal cancer. The risk of ARE in patients undergoing IMCRT for esophageal cancer was modeled as a histogram based on three independent predictors (Fig. 2), with a total score of 254 points in three columns. The calibration curve tended to be close to the ideal curve, indicating that the predicted values were in good agreement with the actual values and that the predictive accuracy of the model was good (Fig. 3). The clinical decision curve demonstrated that when the risk threshold was between 0.25 and 1.0, the net benefit was >0, which is clinically significant (Fig. 4). The smaller the risk threshold, the larger the net benefit of the model, and the better the clinical application effect. Therefore, this column diagram indicated good clinical value for predicting the occurrence of ARE in patients undergoing IMCRT for esophageal cancer.

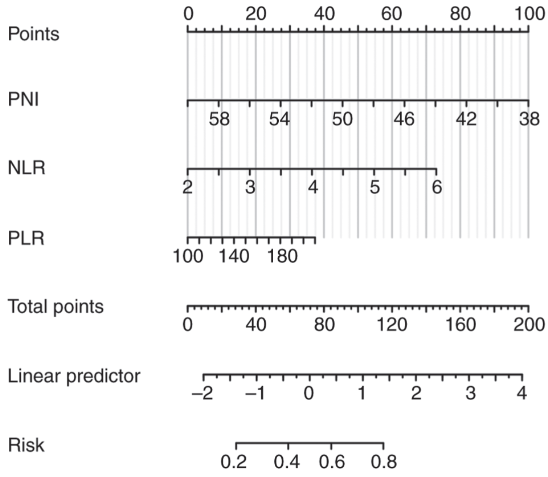

Figure 2. Nomogram for predicting acute radiation esophagitis in patients undergoing IMCRT. PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

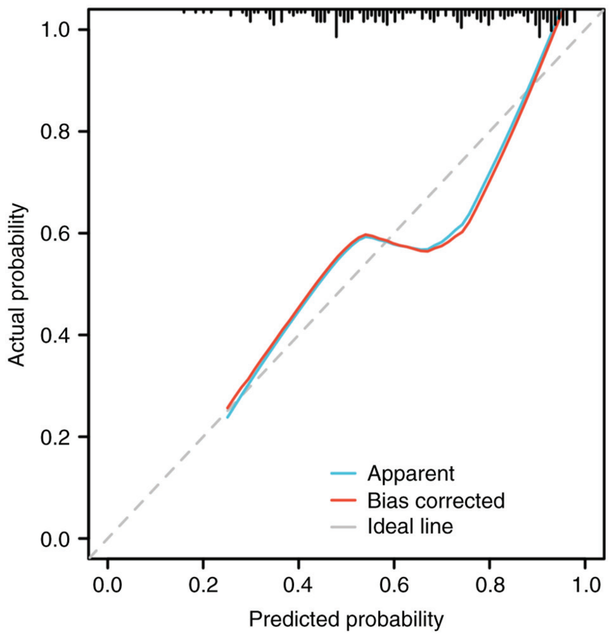

Figure 3. Calibration curve indicates good predictive accuracy of the model.

External validation of the ARE model for patients treated with IMCRT for esophageal cancer. A total of 169 patients with esophageal cancer were enrolled from Gaoxin Hospital, the First Affiliated Hospital of Anhui Medical University, who underwent IMCRT as the external validation set of the model. The C-statistic was 0.768, indicating a high degree of discrimination (Fig. 5A) and the calibration curve was close to the ideal curve (Fig. 5B), indicating good predictive accuracy of the model.

Discussion

Generally, ~21% of patients with esophageal cancer discontinue radiotherapy due to severe ARE (17). A previous study reported that the occurrence of ARE is associated with the radiotherapy dose (18). However, the risk of ARE is not the

Table IV. Logistic analysis of factors affecting acute radiation esophagitis in patients with esophageal cancer.

		Univariate analysis		Multivariate analysis	
Characteristic	n	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	225	0.993 (0.959-1.029)	0.705		
Sex					
Male	165	Reference			
Female	60	1.201 (0.640-2.256)	0.569		
Smoker					
Yes	84	Reference			
No	141	0.910 (0.515-1.609)	0.746		
Alcohol consumption					
Yes	54	Reference			
No	171	1.565 (0.835-2.931)	0.162		
ACCI score					
1-2	63	Reference			
3-4	121	1.397 (0.738-2.646)	0.305		
5-7	41	0.869 (0.389-1.939)	0.731		
Chemotherapy					
Yes	96	Reference			
No	129	0.978 (0.561-1.704)	0.937		
TNM stage					
≥III	66	Reference			
<III	159	1.337 (0.738-2.424)	0.338		
Histological type					
Adenocarcinoma	55	Reference			
Squamous cell carcinoma	170	1.503 (0.805-2.807)	0.201		
PNI	225	0.839 (0.789-0.893)	<0.001[a]	0.864 (0.809-0.924)	<0.001[a]
NLR	225	1.952 (1.371-2.779)	<0.001[a]	1.795 (1.209-2.667)	0.004[a]
PLR	225	1.019 (1.010-1.029)	<0.001[a]	1.011 (1.000-1.022)	0.046[a]

[a]P<0.05. CI, confidence interval. ACCI, Charlson Comorbidity Index; TNM, tumor-node-metastasis; PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

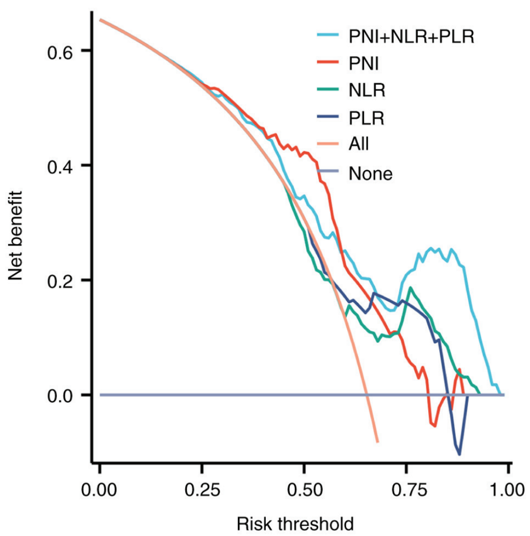

Figure 4. Clinical decision curve analysis of the nomogram. PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

same even when the radiotherapy dose is similar, suggesting that the occurrence of ARE may be related to other factors besides dose. Therefore, to avoid the effect of the radiotherapy dose, the present study chose a population with a relatively consistent dose as the study population. The clinical data of 225 patients with esophageal cancer from January 2018 to December 2022 were retrospectively analyzed and an operating characteristic PNI curve was generated for the patients. Based on the results obtained, the patients were categorized in two groups using a PNI value of 48.2 as the cutoff point: H-PNI group (n=108) and the L-PNI group (n=117). The incidence and severity of ARE were significantly lower in the H-PNI group (n=57) than they were in the L-PNI group (n=90). Further analysis of the correlation between PNI before radiotherapy and the incidence and severity of ARE revealed a statistically significant difference in the severity of ARE between the H-PNI and L-PNI groups.

Risk-prediction column-line diagrams have the characteristics of clear visualization, quantification and

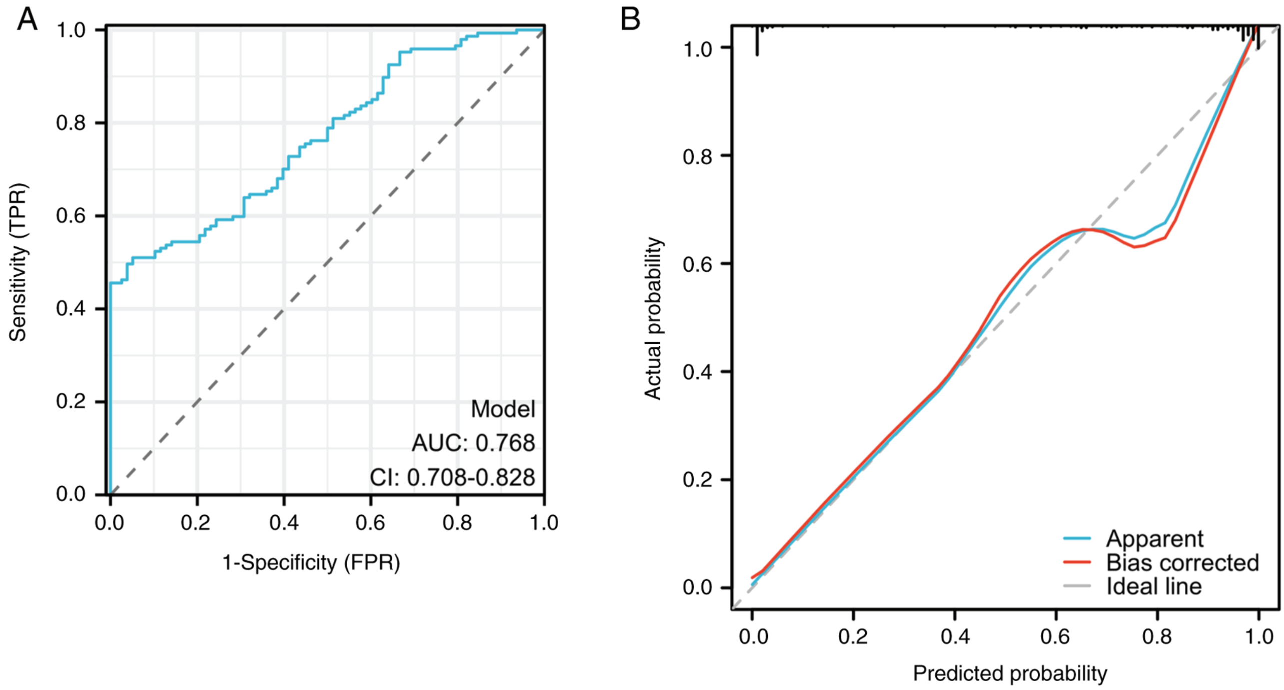

Figure 5. Validation of the nomogram. (A) Receiver operating characteristic and (B) calibration curves for the external validation set. AUC, area under the curve; CI, confidence interval. TPR, true positive rate. FPR, false positive rate.

graphical presentation. Hence, they are widely used in the diagnosis, treatment, and prognostic assessment of several diseases (19-21). The present study performed univariate and multivariate logistic regression analyses to comprehensively evaluate the risk factors associated with ARE in patients with esophageal cancer. The results identified the nutrition-related index, PNI, and the systemic inflammation-related indexes, NLR and PLR, as independent risk factors for the incidence of ARE in patients that had undergone IMCRT. Subsequently, a column-line prediction model was constructed. When the calibration curve was used to evaluate the predictive power of the nomogram, it approached the ideal curve, indicating that the predicted value was in good agreement with the actual value, and that the predictive accuracy of this model was good. In addition, external verification confirmed that this model exhibited a high degree of discrimination and calibration. Therefore, the results indicate that this nomogram model can be employed to predict the occurrence of ARE in patients undergoing IMCRT for esophageal cancer. In clinical practice, according to the predicted probability of the model, patients with a high incidence of ARE can be prophylactically treated with agents such as antibiotics and radioprotectants. In addition, nursing care can be strengthened to minimize the incidence of ARE. In certain patients with esophageal stenosis, gastrostomy and gastroenteritis tubes can be considered before performing radiotherapy to ensure adequate nutritional supply during radiotherapy. Patients were closely monitored during their radiotherapy treatments, assessed weekly, and promptly managed based on the results.

The nutritional status of patients with esophageal cancer gradually deteriorates during radiotherapy. Consequently, the risk of malnutrition gradually increases, which in turn can further trigger the onset of ARE (7). Therefore, the relationship between ARE and malnutrition deserves an in-depth investigation. However, there are differences in the current findings. Wang *et al* (22) identified malnutrition as a major risk factor for the development of radiation esophagitis in patients undergoing radiotherapy for esophageal cancer. However, no measurement tool for malnutrition was mentioned. Cao *et al* (23) used the Patient Subjective Global Assessment for assessing the nutritional status and reported that malnutrition increased the incidence of radiation esophagitis. However, Wang *et al* (22) used the same tool and reported that malnutrition had no significant association with acute side effects or the short-term efficacy of radiotherapy in patients (9). PNI, which now finds wide applications in the evaluation of several solid tumors, can comprehensively reflect the nutritional status of the body, is noninvasive, and is easily obtained (24-26). However, the application of PNI in ARE in esophageal cancer is still in its infancy.

Esophageal cancer is often associated with a systemic inflammatory state. This affects metabolic processes, leading to malnutrition, which further induces a systemic inflammatory response, forming a vicious circle (27,28). NLR and PLR are among the most commonly used indicators to assess the systemic inflammatory status of patients with cancer (29,30). Several studies have reported a strong association between poor prognosis and NLR/PLR in patients with esophageal cancer (31,32). Both PNI, a nutritional index, and NLR/PLR, a systemic inflammatory index, impact patients with esophageal cancer. However, no study has yet confirmed the association between ARE and the nutritional index along with systemic inflammatory index in patients with esophageal cancer, to the best of our knowledge.

The present study has certain limitations: i) It is a retrospective study resulting in an inevitable selection bias; ii) the present study had limited inclusion of factors and there may be certain confounding factors that were not included; and iii) the present study aimed to collect laboratory indicators before radiotherapy in patients and construct a risk prediction model for the occurrence of ARE. It provides a certain reference basis for the early detection of individuals with a high risk of ARE and for reducing the occurrence of ARE. In the future, the indicators will be tested weekly during radiotherapy to assess the occurrence of ARE and provide timely management to ensure the smooth progress of radiotherapy. Furthermore, under the premise of ensuring the authenticity and objectivity of the data, the sample size is still limited. A prospective study with a larger sample size in multiple centers should be performed to clarify the value of the model for predicting ARE in this group of patients, exploring additional risk factors, and providing interventions to mitigate the occurrence of ARE.

In summary, PNI, NLR and PLR are independent risk factors affecting ARE in patients undergoing IMCRT. In the present study, the risk-predicting nomogram model based on the risk factors had a high clinical application value and could accurately and intuitively predict the risk degree of ARE in patients with esophageal cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW, WL and SL conceived and designed the study. LW, XM, MY and YW collected and analyzed the data. LW, MY, YW and SL wrote the manuscript. LW and SL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in the present study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of Anhui Medical University (Hefei, China; approval no. 82240081, 2024-07-31). Due to the retrospective nature of the present study, informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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