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Establishment and Verification of a Prediction Model for Symptomatic Radiation Pneumonitis in Patients with Esophageal Cancer Receiving Radiotherapy

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Background: This study aimed to determine the value of the significant index in predicting symptomatic radiation pneumonitis (RP) in esophageal cancer patients, establish a nomogram prediction model, and verify the model.


Material/Methods: The patients enrolled were divided into 2 groups: a model group and a validation group. According to the logistic regression analysis, the independent predictors for symptomatic RP were obtained, and the nomogram prediction model was established according to these independent predictors. The consistency index (C-index) and calibration curve were used to evaluate the accuracy of the model, and the prediction ability of the model was verified in the validation group. Recursive partitioning analysis (RPA) was used for the risk stratification analysis.

Results: The ratio of change regarding the pre-albumin at the end of treatment ($P=0.001$), platelet-to-lymphocyte ratio during treatment ($P=0.027$), and neutrophil-to-lymphocyte ratio at the end of treatment ($P=0.001$) were the independent predictors for symptomatic RP. The C-index of the nomogram model was 0.811. According to the risk stratification of RPA, the whole group was divided into 3 groups: a low-risk group, a medium-risk group, and a high-risk group. The incidence of symptomatic RP was 0%, 16.9%, and 57.6%, respectively. The receiver operating characteristic curve also revealed that the nomogram model has good accuracy in the validation group.

Conclusions: The developed nomogram and corresponding risk classification system have superior prediction ability for symptomatic RP and can predict the occurrence of RP in the early stage.

Keywords: **Anti-Inflammatory Agents • Esophageal Neoplasms • Nomograms • Nutrition Assessment • Radiation Pneumonitis**

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Background

Esophageal cancer (EC) is one of the most common digestive system cancers, and the number of cases has been increasing year by year. In 2018, EC was ranked as the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related death worldwide [1]. Since most patients have EC too far advanced for radical resection when diagnosed, radiotherapy (RT) remains one of the main treatment methods, especially for local advanced EC. Several studies have suggested that the effect of concurrent chemo-RT is equivalent to surgical treatment [2-4].

However, the sensitivity of normal lung tissue to radiation limits the use of RT in thoracic tumors. Radiation-induced lung injury is the most common complication of EC patients after RT, which manifests as radiation pneumonia in the acute stage and radiation-induced pulmonary fibrosis in the chronic stage. This causes dry cough, dyspnea, and shortness of breath after activity, which affects the quality of life of patients, and even threatens life. Symptomatic radiation pneumonitis (RP) is of grade ≥ 2 , with obvious clinical symptoms, which affects the quality of life and requires clinical intervention. Most of these patients can recover after active treatment. However, this still has a certain impact on the life of the patients. It is of great significance for patients to determine the occurrence of symptomatic RP as early as possible, allowing the corresponding positive measures to be performed as soon as possible, thereby improving the quality of life.

In the past, the prediction of RP focused on dosimetry. From the results of previous studies, we know that there is a very close relationship between RP and radiation dosage in the lungs. The recognized dose constraints were defined for total lungs as follows: V5 <60%, V20 <30%, V30 <20%, mean lung dose (MLD) <20 Gy. Once the radiation dose to the lungs exceeds the threshold, the incidence of RP will increase significantly. The radiation dose to the lungs in our study was strictly controlled. However, more studies reported that even though the lung dose was strictly controlled, these patients still presented with radiation-induced lung injury, indicating that non-dosimetry factors play a considerable role in the development of radiation-induced pneumonia. Furthermore, the present data on RP are mostly from lung cancer, and the results of different studies vary. The present study aimed to evaluate the significant index before and during RT in predicting symptomatic RP in EC patients, establish a nomogram prediction model according to independent prediction factors, and verify the established model, hoping to predict the occurrence of symptomatic RP effectively at the earliest time.

Material and Methods

Patients

Inclusion criteria were: (1) newly diagnosed and pathologically confirmed EC; (2) receipt of ≥ 56 Gy of RT for a curative aim; (3) availability of clinicopathologic, dosimetric, and laboratory data; (4) complete pulmonary imaging within 6 months after RT; (5) no obvious signs of infection before treatment. Exclusion criteria were: (1) previous history of thoracic RT; (2) pregnant and lactating women; (3) patients with acute infectious disease.

Methods

The patients enrolled were divided into 2 groups: a model group and a validation group. Four types of data were collected as follows: (1) clinicopathologic characteristics of patients, such as age, smoking, drinking, height, weight, basic lung diseases, pathologic type, and tumor location; (2) dosimetry factors, such as radiation dose and lung exposure; (3) treatment technology and scheme, such as RT technology, chemotherapy scheme, and cycle; (4) hematologic index, such as neutrophil count, lymphocyte count, platelet count, monocyte count, albumin, and pre-albumin. According to the logistic regression analysis, the independent predictors for symptomatic RP were obtained, and the nomogram prediction model was established according to these independent predictors. The consistency index (C-index) and calibration curve were used to evaluate the accuracy of the model, and the prediction ability of the model was verified in the validation group. Recursive partitioning analysis (RPA) was used for the risk stratification analysis.

Treatment

Pretreatment Assessment

The clinicopathologic information, imaging data, and laboratory test results were all acquired from medical records. The clinicopathologic parameters included age, sex, smoking, drinking, smoking index, pulmonary bulla, pathologic diagnosis, tumor location and length, tumor-lymph node-metastasis stage [5], radiation dose, and chemotherapy.

Radiotherapy

All of the patients were treated with intensity-modulated RT (IMRT). The delineation of target volumes and organs at risk (OARs) referred to the Radiotherapy and Oncology Group (RTOG) guidelines. All RT plans were delivered with 6 MV of photon beams. The prescribed doses of RT were 56.00-69.96 Gy at 1.8-2.2 Gy per fraction, once daily, and 5 fractions per week. The plans were normalized to 95% of the planning tumor volume (PTV) received at 100% of the prescribed dose. The dose

constraints were defined for OARs as follows: total lungs: V5 <60%, V20 <30%, V30 <20%, MLD <20 Gy; maximum point dose of the spinal cord <45 Gy; heart: V30 <40%, V40 <30%.

Chemotherapy

A total of 113 patients received chemotherapy among the 131 cases in the model group, and 38 patients received chemotherapy among the 43 cases in the validation group. The chemotherapy plan was based on platinum. The chemotherapy plans were as follows: platinum+5-fluorouracil; taxus+platinum; etoposide+cisplatin. During the treatment, the corresponding symptomatic treatment was taken when the patient presented with adverse reactions. When the patient could not tolerate the follow-up chemotherapy, the chemotherapy was suspended.

Collection of Hematologic Index

The hematologic index was obtained at 3 different time points: pretreatment, at 3 to 4 weeks during RT, and at the end of RT. The platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and systemic immune inflammation index (SII) were calculated as follows: $PLR=P/L$; $NLR=N/L$; $LMR=L/M$; $SII=P \times N/L$ (neutrophil count [N], lymphocyte count [L], platelet count [P], and monocyte count [M]).

Measurement of Body Mass Index (BMI)

The height and weight of each patient were measured before and at the end of the RT. The BMI was obtained using the formula: $BMI = \text{weight (kg)} / \text{square of height (m}^2\text{)}$.

Follow-up

Patients were followed up at 1 month and 3 months after completion of the RT, and subsequently every 3 months for the first year for the evaluation of RP. If the patient had obvious cough, expectoration, shortness of breath, dyspnea, and other discomforts after or during the RT, chest computed tomography was performed for further diagnosis. The endpoint of the present study was symptomatic RP defined as grade ≥ 2 RP occurring within 6 months after RT.

Statistical Analysis

All data were analyzed using SPSS 24.0 and R 3.4.2. The characteristics of patients were calculated as the proportion for categorical variables, or mean \pm standard deviation for continuous variables. The differences between variables were evaluated by chi-square test, *t* test, or Mann-Whitney *U* test. The optimal cutoff values of the dosimetric and inflammatory indicators were calculated using receiver operating characteristic

(ROC) curves. According to the results of the univariate analysis, factors with $P < 0.05$ were further included in the multivariate logistic regression model to determine the independent prognostic factors. The nomogram model was established using the RMS package of the R software and on the basis of the results of the multivariate analysis. The prediction accuracy of nomograms was evaluated using the C-index and calibration curve. RPA was used for the risk stratification analysis.

Results

Patient Characteristics

A total of 174 cases of EC, which was confirmed by pathology, were enrolled in the present study. Among these, 131 cases in April 2013 to December 2018 were assigned to the modeling group and 43 cases in January 2019 to August 2020 were assigned to the validation group. The detailed characteristics of the enrolled population are listed in **Table 1**.

Incidence of RP

RP was graded in accordance with the classification criteria of the American RTOG and the European tumor treatment research cooperative group. The incidence of symptomatic RP was 23.7% and 18.6% in the primary and validation cohort, respectively (**Figure 1, Table 2**).

Predictive Factors of Symptomatic RP in the Modeling Group

The factors significantly correlated with symptomatic RP were MLD ($P=0.021$), V5 ($P=0.011$), V10 ($P=0.007$), V15 ($P=0.028$), and V20 ($P=0.028$) before RT, whereas during the RT, albumin ($P < 0.001$), and pre-albumin ($P < 0.001$) at the end of the RT; the ratio of change regarding the pre-albumin at the end of treatment (the pre/end ratio of albumin, $P < 0.001$), the pre-albumin, PLR, LMR, and SII during the RT, and the NLR, PLR, LMR, SII, and D-dimer at the end of RT were also closely correlated with symptomatic RP. The further multivariate analysis indicated that the pre/end ratio of pre-albumin, PLR during the RT, and NLR at the end of RT were independent predictors of symptomatic RP (**Tables 3-5**).

Establishment of the Nomogram Model

According to the multivariate analysis results, the RMS software package of r3.4.2 was used to establish the nomogram prognosis model (**Figure 2**). According to internal validation, the C-index of the nomogram model was 0.811 (95% confidence interval [CI]: 0.723-0.900, Akaike information criterion=115.5), which was higher than any other predictors. The area under

Table 1. Baseline characteristics of all patients.

Characteristics	Primary cohort No. (%)	Validation cohort No. (%)
Sex		
Male/Female	120/11	39/4
Age (years)		
<57/≥57	65/66	20/23
Smoking		
Yes/no	92/39	22/21
Smoking index		
<400/≥400	54/77	29/14
Drinking		
Yes/no	99/32	31/12
Location		
Cervical/upper/middle/lower/multifocal	15/39/56/16/5	4/12/16/8/3
T stage		
T1-T2/T3-T4	14/117	4/39
N stage		
N0-N1/N2-N3	81/50	21/22
M stage		
M0/M1	119/12	35/8
Clinical stages		
I-II/III-IV	34/97	6/37
Chemotherapy		
Platinum-fluorouracil regimen/taxus-platinum regimen/other/none	57/55/1/18	19/19/0/5
Chemotherapy cycle		
<4/≥4	99/32	28/15
Pulmonary bulla		
0/1/2/3	110/15/4/2	39/3/1/0

the curve (AUC) values of the pre/end ratio of pre-albumin, PLR during the RT, and NLR at the end of RT alone were 0.689 (95% CI: 0.602-0.768), 0.645 (95% CI: 0.556-0.727), and 0.678 (95% CI: 0.591-0.757), respectively. The AUC of the nomogram model was 0.811 (95% CI: 0.733-0.874), evidently improving the prediction ability (Figure 3, Table 6). The calibration curve revealed that the nomogram model has good accuracy in predicting the occurrence of symptomatic pneumonia (Figure 4). The nomogram model could be used to differentiate the patients that have RP grade ≥ 2 with 74.19% sensitivity, 76.77% specificity, and 76.15% accuracy. According to the nomogram

model, the scores of each variable were as follows: when the pre/end ratio of pre-albumin was 0-7, the scores were 0-100, respectively; when the PLR was 0 and 1, the scores were 0 and 18, respectively; when the NLR was 0 and 1, the scores were 0 and 23, respectively. The sum of the scores of all variables of each patient was the total points. According to the risk probability corresponding to the nomogram, the probability of symptomatic RP can be predicted.

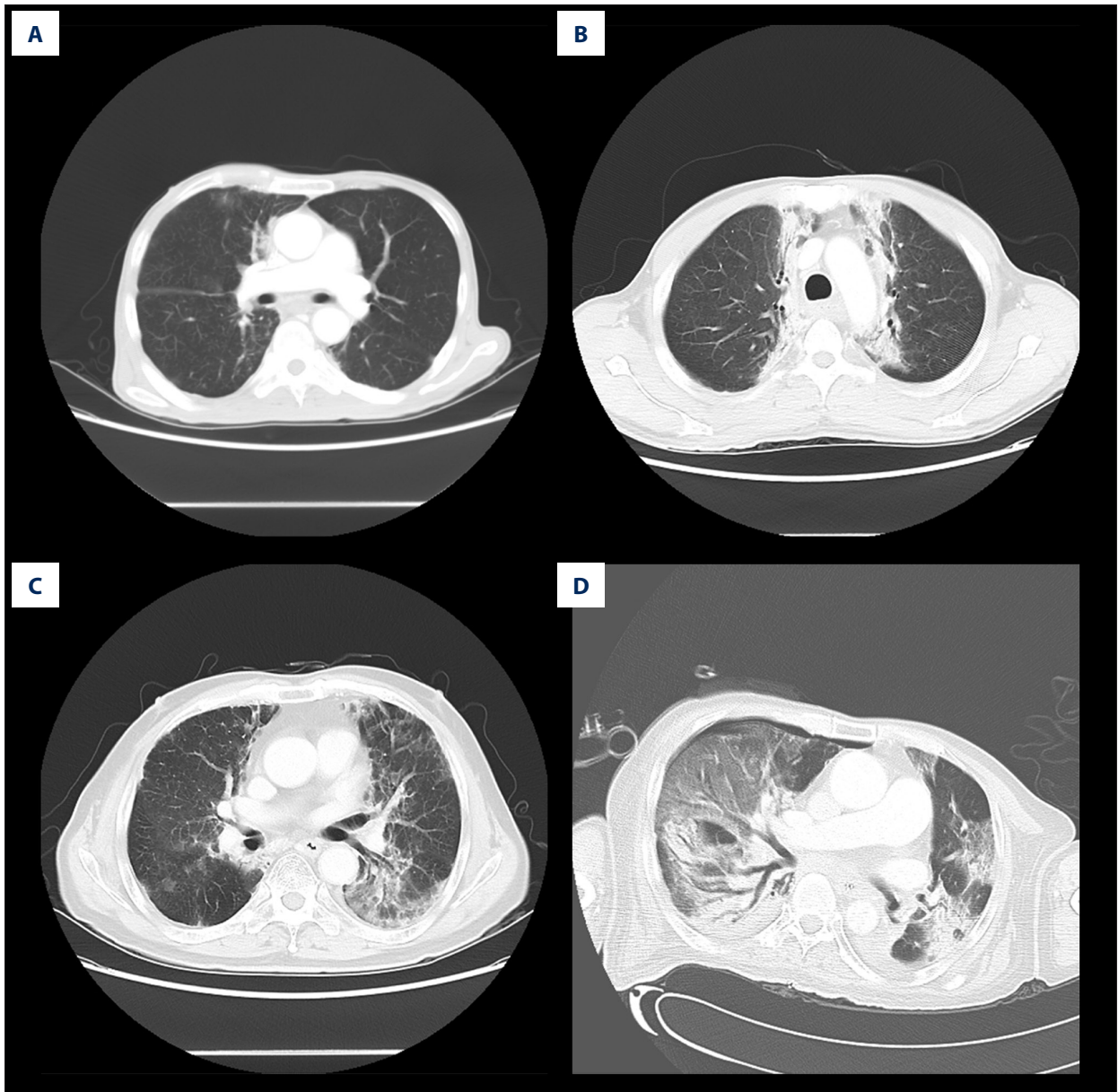


Figure 1. Computed tomography (CT) manifestations of radiation pneumonitis (RP). (A) CT manifestations of grade 1 RP. (B) CT manifestations of grade 2 RP. (C) CT manifestations of grade 3 RP. (D) CT manifestations of grade 4 RP.

Table 2. Occurrence of radiation pneumonia in esophageal cancer.

	Primary cohort		Validation cohort	
	No.	(%)	No.	(%)
Grade 0	36/131	27.5%	18/43	41.9%
Grade 1	64/131	48.9%	17/43	40.0%
Grade 2	18/131	13.7%	6/43	14.0%
Grade 3	7/131	5.3%	1/43	2.3%
Grade 4	6/131	4.6%	1/43	2.3%

Table 3. Univariate analysis of clinicopathologic, dosimetric, and inflammatory parameters in predicting symptomatic radiation pneumonitis.

Parameters	χ^2	P
Sex (Male vs Female)	0.087	1.000
Age (≤ 60 vs >60 ; years)	0.065	0.799
Smoking (yes vs no)	0.120	0.729
Smoking index (<400 vs ≥ 400)	0.009	0.926
Drinking (yes vs no)	0.042	0.838
Location (Cervical/upper/middle/lower/multifocal)	3.843	0.428
T stage (T1-T2 vs T3-T4)	2.369	0.228
N stage (N0-N1 vs N2-N3)	0.244	0.621
M stage (M0 vs M1)	1.719	0.340
Clinical stages (I-II vs III-IV)	0.358	0.809
Chemotherapy (PF regimen vs TP regimen)	2.797	0.094
Chemotherapy cycle (<4 vs ≥ 4)	1.515	0.218
Pulmonary bulla (0/1/2/3)	2.281	0.516
Fractional dose (<2.13 Gy vs ≥ 2.13 cGy)	0.357	0.770
MLD (<1575.4 cGy vs ≥ 1575.4 cGy)	5.336	0.021
V5 ($<86.5\%$ vs $\geq 86.5\%$)	6.471	0.011
V10 ($<64.5\%$ vs $\geq 64.5\%$)	7.262	0.007
V15 ($<45.5\%$ vs $\geq 45.5\%$)	4.811	0.028
V20 ($<28.5\%$ vs $\geq 28.5\%$)	4.813	0.028
V25 ($<22.5\%$ vs $\geq 22.5\%$)	1.66	0.198
V30 ($<18.5\%$ vs $\geq 18.5\%$)	1.594	0.207
V35 ($<12.5\%$ vs $\geq 12.5\%$)	1.432	0.231
V40 ($<9.5\%$ vs $\geq 9.5\%$)	1.378	0.240
NLR during RT (<8.14 vs ≥ 8.14)	3.824	0.051
PLR during RT (<523.78 vs ≥ 523.78)	6.504	0.004
LMR during RT (<0.75 vs ≥ 0.75)	5.017	0.025
SII during RT (<1554.23 vs ≥ 1554.23)	4.477	0.034
NLR at the end of RT (<7.98 vs ≥ 7.98)	11.728	0.001
PLR at the end of RT (<616.32 vs ≥ 616.32)	6.370	0.012
LMR at the end of RT (<0.685 vs ≥ 0.685)	9.266	0.002
SII at the end of RT (<1912.09 vs ≥ 1912.09)	6.346	0.012

PF – platinum-fluorouracil; TP – taxus-platinum; MLD – mean lung dose; NLR – neutrophil-to-lymphocyte ratio; RT – radiation therapy; PLR – platelet-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio; SII – systemic immune inflammation index.

Nomogram Model and Risk Stratification

In the present study, the nomogram model had a better prediction ability for symptomatic RP. According to the nomogram model, RPA was carried out for the total score of the prediction of symptomatic RP in the modeling group, and the risk of patients was stratified. All patients were divided into

3 risk groups: low (score <23), medium ($23 \leq$ score <55), and high (score ≥ 55). It can be observed from the table that there was a significant difference in the incidence of symptomatic RP in the different risk stratification groups ($P < 0.001$). The incidence was 0% in the low-risk group, 17.14% in the medium-risk group, and 57.58% in the high-risk group (Table 7). It was found that the incidence of symptomatic RP in the high-risk

Table 4. Univariate analysis of nutritional parameters and coagulation function in predicting symptomatic radiation pneumonitis.

	RP of grade <2	RP of grade ≥2	P value
Albumin before RT	38.18±3.79	36.96±4.18	0.129
Albumin during RT	34.22±3.66	33.28±3.398	0.218
Albumin at the end of RT	34.62±4.31	30.92±4.94	0.000
Pre/end ratio of pre-albumin	1.11±0.15	1.22±0.20	0.009
Pre-albumin before RT	211.80±59.52	193.84±60.07	0.145
Pre-albumin during RT	183.63±65.78	158.77±64.35	0.076
Pre-albumin at the end of RT	182.07±70.03	123.53±61.39	0.000
Pre/end ratio of pre-albumin	1.31±0.54	2.04±1.36	0.007
BMI before RT	21.20±3.16	21.48±3.02	0.674
BMI at the end of RT	20.50±2.78	20.08±2.82	0.475
Pre/end BMI	1.04±0.10	1.07±0.10	0.134
D-Dimer before RT	0.82±2.16	0.77±0.94	0.898
D-Dimer at the end of RT	1.10±1.37	2.42±3.26	0.046
Fibrinogen before RT	4.01±1.28	3.83±1.02	0.487
Fibrinogen at the end of RT	3.94±1.37	4.28±1.72	0.278

RT – radiation therapy; BMI – body mass index.

Table 5. Multivariate analysis of potential parameters in predicting symptomatic radiation pneumonitis.

Parameters	P value	OR	95% CI
Pre/end ratio of pre-albumin	0.001	2.750	1.504-5.028
PLR during RT	0.027	3.408	1.146-10.135
NLR at the end of RT	0.001	5.322	1.940-14.600

OR – odds ratio; CI – confidence interval; PLR – platelet-to-lymphocyte ratio; RT – radiation therapy; NLR – neutrophil-to-lymphocyte ratio.

group was higher than that in the low-risk group and medium-risk group ($P<0.001$).

Verification of the Nomogram Model

The nomogram model was validated in the validation group. According to the nomogram model, the total score of each case in the validation group was calculated. According to external validation, the AUC of the nomogram model in the validation group was 0.854 (95% CI: 0.696-1.000), which was higher than any other predictors. The AUC values of the pre/end ratio of pre-albumin, PLR during the RT, and NLR at the end of RT alone was 0.718 (95% CI: 0.562-0.873), 0.698 (95% CI: 0.484-0.913), and 0.738 (95% CI: 0.562-0.913), respectively (Figure 5, Table 8). The ROC curve also revealed that the nomogram model had good accuracy in the validation group. According to the total score in the validation group, the incidence was 6.7% in the low-risk group, 11.1% in the medium-risk group, and 50% in

the high-risk group (Table 9). It was found that the incidence of symptomatic RP in the high-risk group was higher than that in low-risk group and medium-risk group ($P<0.05$).

Discussion

EC is one of the most common malignant tumors in the digestive system. Most of these patients cannot undergo an operation and therefore receive comprehensive RT treatment. However, the related adverse reactions caused by RT can seriously affect the quality of life of these patients, and can even lead to the interruption of RT, thereby affecting the efficacy. Radiation-induced lung injury is the most common complication in EC patients after RT. Once this occurs, it is difficult to reverse. The present study aimed to determine the correlation between the significant indexes and symptomatic RP in patients with EC before and during RT. Under the premise

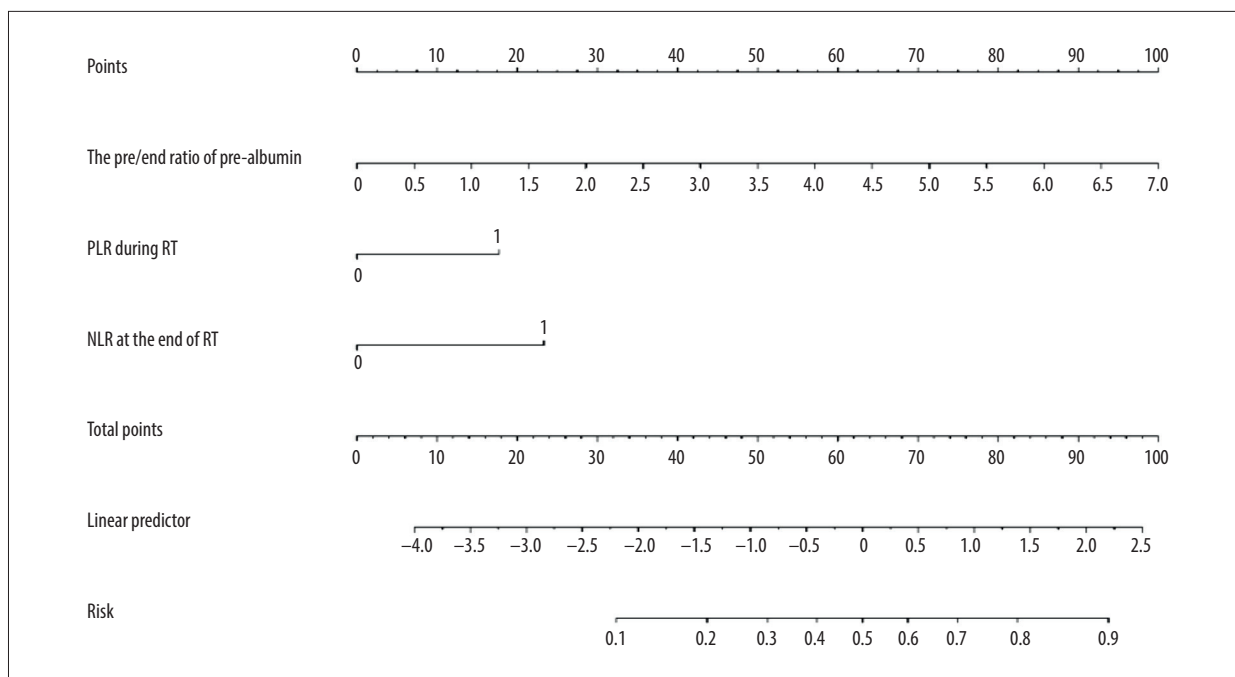


Figure 2. Nomogram predicting the development of symptomatic radiation pneumonitis for esophageal cancer.

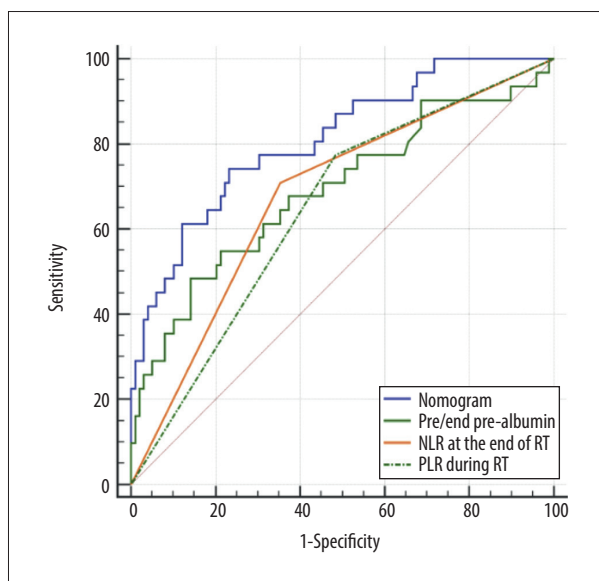


Figure 3. Receiver operating characteristic curve based on the sensitivity and specificity of the pre/end ratio of pre-albumin, platelet-to-lymphocyte ratio during radiation therapy (RT), neutrophil-to-lymphocyte ratio at the end of RT, and nomogram model in the model group.

that the lung dose is effectively controlled, the present study revealed that the pre/end ratio of pre-albumin, PLR during RT, and NLR at the end of RT were independent predictors of symptomatic RP. On the basis of this, a prediction tool that is convenient for clinical use was developed to facilitate clinicians in RT, the early prediction of the risk of symptomatic

Table 6. Areas under the receiver operating characteristic (ROC) curve for the independent predictors and nomogram model in the modeling group.

	Areas under the ROC curve	95% CI
Pre/end pre-albumin	0.689	0.602-0.768
PLR during RT	0.645	0.556-0.727
NLR at the end of RT	0.678	0.591-0.757
Nomogram model	0.811	0.733-0.874

CI – confidence interval; PLR – platelet-to-lymphocyte ratio; RT – radiation therapy; NLR – neutrophil-to-lymphocyte ratio.

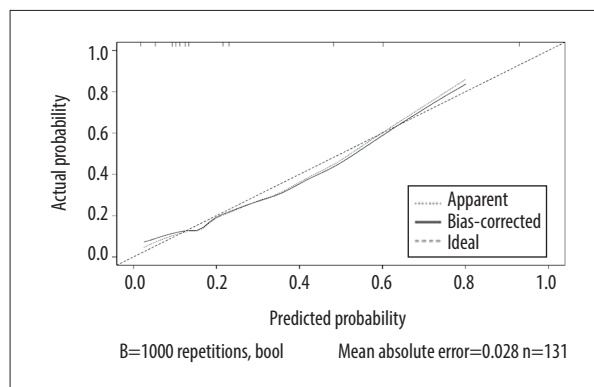


Figure 4. Calibration curves of the nomogram predicting symptomatic radiation pneumonitis in the primary cohort.

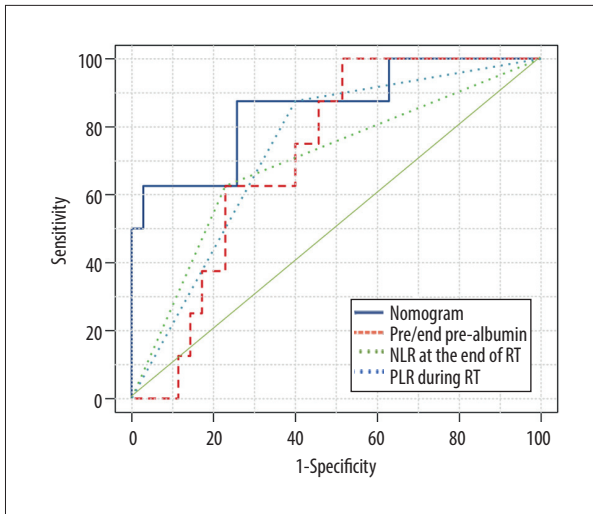


Figure 5. Receiver operating characteristic curve based on the sensitivity and specificity of the pre/end ratio of pre-albumin, platelet-to-lymphocyte ratio during radiation therapy (RT), neutrophil-to-lymphocyte ratio at the end of RT, and nomogram model in the validation group.

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Pre/end pre-albumin	0.718	0.562-0.873
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Nomogram model	0.854	0.696-1.000

CI – confidence interval; PLR – platelet-to-lymphocyte ratio; RT – radiation therapy; NLR – neutrophil-to-lymphocyte ratio.

Table 7. Incidence of symptomatic radiation pneumonitis (RP) in the modeling group.

	Grade <2 RP	Grade ≥2 RP	χ^2	P value	P value of pairwise comparison
Low-risk group	27 (100.0%)	0 (0.0%)	31.176	<0.001	Low-medium-risk group: 0.053
Medium-risk group	59 (83.1%)	12 (16.9%)			Low-high-risk group: <0.001
High-risk group	14 (42.4%)	19 (57.6%)			Medium-high-risk group: <0.001

Table 9. Incidence of symptomatic radiation pneumonitis (RP) in the validation group.

	Grade <2 RP	Grade ≥2 RP	χ^2	P value	P value of pairwise comparison
Low-risk group	14 (93.3%)	1 (6.7%)	8.588	0.023	Low-medium-risk group: 0.570
Medium-risk group	16 (88.9%)	2 (11.1%)			Low-high-risk group: 0.023
High-risk group	5 (50.0%)	5 (50.0%)			Medium-high-risk group: 0.036

RP, and timely intervention, which could maximize the benefits of the treatment.

In recent decades, many researchers have devoted themselves to investigating factors that can predict the occurrence and severity of RP. The research results mainly included the following 4 aspects: (1) clinical characteristics of patients, such as age [6-10], smoking [11-15], lung function [16-18], and basic lung diseases [19, 20]; (2) dosimetry factors, such as radiation dose [21,22] and lung exposure [7,23]; (3) treatment technology and scheme, such as RT technology [24-26] and chemotherapy scheme [27]; (4) individual genetic sensitivity, such as tumor transforming growth factor- β 1(TGF- β 1) gene

polymorphism [28]. However, different studies still show great differences in these results. With the development of RT technology and the popularization of IMRT, the dose for lungs in EC has been well controlled, which was basically controlled within the limited range. However, the incidence of radiation-induced lung injury remains high. In clinical practice, patients with the same stage received almost the same dose in both lungs, but the occurrence and severity of radiation-induced lung injury may be completely different, revealing that to a certain extent, when predicting the radiation-induced lung injury, in addition to considering conventional factors, some new independent prediction factors also need to be given increasing attention.

In a strict sense, RP is a kind of aseptic inflammation and an inflammatory response to radiation injury. Therefore, it can be assumed that the inflammatory index is correlated with RP to some extent. Some inflammatory markers, such as C-reactive protein and lactate dehydrogenase, have been reported to be associated with radiation-induced pneumonia [29], whereas some cytokines, such as TGF- β 1, interleukin-1 α (IL-1 α), IL-6, and IL-10, have also been shown to be associated with radiation-induced pneumonia [30-32]. However, some of these indicators have not been widely used in clinics, or the cost was a little high. Therefore, these could not be routinely used in clinics. Whole blood cell count is a routine, cheap, and simple detection method that can provide information on blood components. Among these, the NLR has been proven to be an important marker of inflammation. Some studies have reported that NLR is a marker of the severity and deterioration of lung diseases (such as pneumonia [33] and chronic obstructive pulmonary disease [COPD] [34]). A study on COPD patients revealed that the NLR of patients with acute exacerbation is significantly higher than that of patients with a stable stage, and is the most sensitive of all inflammatory serum markers [34]. There have been few reports on the relationship between RP and inflammatory indexes. In the study conducted by Lee et al [35], NLR was used to predict RP. It was found that the NLR value of patients with symptomatic pneumonia was significantly higher than that of patients without symptoms, when imaging changes occurred (4.99 vs 2.90, respectively). These were the independent predictors of symptoms of RT. However, when RP occurred, it was no longer significant to measure NLR. In the study conducted by Shaverdian et al [36], it was considered that patients with high NLR before RT had a lower incidence of symptomatic radiation-induced pneumonia. Platelets release proinflammatory mediators such as chemokines and cytokines [37] to mediate the inflammatory response. Therefore, PLR was also considered as an inflammatory marker that can be used to predict inflammation and mortality in many diseases [38]. In addition to NLR, the investigators attempted to describe the dynamic changes of PLR, LMR, and SII in the course of RT to determine whether these have more predictive significance for RP. In the present study, it was found that NLR, PLR, and SII gradually increased in the course of the RT, but decreased near the end of the RT, and that these were ultimately higher than the level before RT. The increase in inflammatory index in the symptomatic radiation pneumonitis group was higher than that in the nonsymptomatic group, whereas the change trend of LMR was just the opposite. The further multivariate analysis revealed that PLR during RT and NLR at the end of RT were independent predictors of symptomatic RP.

EC patients are often accompanied by light or heavy malnutrition before, during, and after treatment. For patients undergoing RT, malnutrition can also reduce the sensitivity of tumor

cells to RT, increase the positioning error of RT, reduce the tolerance to RT, and thereby increase the adverse reactions after RT. In the study conducted by Wen et al [39], it was found that human hemoglobin was significantly correlated with acute radiation esophagitis, and that the total lymphocyte count was significantly correlated with the acute adverse reactions in the blood system. The study conducted by Hill et al [40] revealed that 75.5% of patients have different degrees of weight loss through the RT treatment for gastrointestinal cancer. Weight loss was more serious in patients with unplanned RT interruption and failure to complete the planned chemotherapy cycle. Radiotoxicity was closely correlated with the patient-generated subjective global assessment score ($P < 0.01$). There were few reports on the relationship between malnutrition and RP. However, some studies have revealed that malnutrition is correlated with the severity of pneumonia [41-44]. Akuzawa and Naito [41] reported that the BMI of pneumonia patients was low, almost reaching the lower limit of normal values (18.5 kg/m²). Lee et al [42] significantly reduced the incidence of pneumonia by providing nutrition for patients in multiple approaches and improving their nutritional status. From previous studies it was found that RP is correlated with many cytokines in its occurrence and development, such as IL-1, IL-6, tumor necrosis factor- α (TNF- α), TNF- β , and interferon- γ (IFN- γ). These cytokines also play a pivotal role in the main pathologic factors of cancer malnutrition and may be correlated with the metabolic changes related to cancer emaciation. These can directly pass through the gastrointestinal tract or through the brain, changing the outgoing signals that regulate the satiety that regulates gastric movement and emptying, thereby inducing anorexia. Cytokines such as IL-1 and TNF- α may decrease food intake by increasing the level of corticotropin-releasing hormone and inhibiting the emission of neurotransmitters and glucose-sensitive neurons in the central nervous system, leading to anorexia-related cancer [45,46]. IL-6 is generally considered to be a key factor in the development of the tumor microenvironment. It can promote tumor growth and metastasis by acting as a bridge between chronic inflammation and cancer tissue and induce skeletal muscle atrophy and protein decomposition. Previous studies have shown that IL-6 is involved in the wasting process of colon cancer-bearing mice. However, Strassmann et al [47] reported that anti-IL-6 antibody treatment can reverse the malnutrition of colon cancer-bearing mice. Enomoto et al [48] also reported the effectiveness of a new nonpeptide IL-6 receptor antagonist in the treatment of C26 colorectal cancer cachexia. Another cytokine correlated with cachexia is IFN, which is produced by activated T and natural killer cells, and has biological activity overlapping with TNF. Matthys et al [49] used monoclonal antibodies against IFN to reverse the wasting syndrome related to lung cancer growth in mice, suggesting that IFN can be produced in tumor-bearing mice to cause metabolic changes in cancer malnutrition.

Therefore, it was speculated that RP and malnutrition are correlated with the same cytokines in the process of occurrence and development. Patients with malnutrition are more likely to develop RP, and similar conclusions have been reached in the present study. However, can nutritional support therapy be used to improve the nutritional status of patients, and reduce the incidence of radiation-induced pneumonia in patients with chest RT? Feijó et al [43] conducted a nutritional intervention on gastric cancer patients, and found that the level of IL-6 in the nutritional intervention group was significantly lower. That is, patients without nutritional intervention were significantly more prone to inflammation than patients with nutritional intervention. In the study conducted by Fabian et al [50], TNF- α and IL-6 in the serum of breast cancer patients decreased after 5 months of eicosapentaenoic acid/docosahexaenoic acid nutrition supplementation. However, this still requires a large number of prospective, randomized studies to confirm.

We were able to find a few recent studies on the prediction model of RP [51-53]. Yu et al [51] combined IL8 and chemokine (C-C motif) ligand 2 at baseline level and 2 clinical variables to construct a nomogram. The model achieved good predictability (AUC=0.863, accuracy=80.0%, sensitivity=100%, specificity=76.5%). Du et al [53] combined genetic and nongenetic factors to establish a multiple linear regression model for the assessment of grade ≥ 2 RP risk. This model can successfully distinguish the RP ≥ 2 population with 92.0% sensitivity and 100% specificity. However, the above prediction models were based on lung cancer. Moreover, inflammatory cytokines and single-nucleotide polymorphism sites have not been routinely detected in clinical studies. In our study, the nomogram model also achieved good predictability (AUC=0.811, accuracy=76.15%, sensitivity=74.19%, specificity=76.77%). In addition, the 3 factors included were obtained by conventional, cheap, and simple detection methods. Therefore, our model is more convenient for clinical use.

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The predictive model of symptomatic RP for patients with EC receiving RT established in the present study has good predictability. However, there are still limitations: (1) the present study was a single-center retrospective study with a small number of cases; (2) the relationship between continuous variables and symptomatic RP was linearly processed, which may have led to bias; (3) the validation of the nomogram was limited to cases in our research center, and the validation of external data was not strictly performed. However, under the premise that the lung dose is effectively controlled, this study shifted the focus of RP from dosimetry to inflammation and nutritional status, which also suggests to us whether reducing the inflammatory reaction or improving the nutritional status of patients during RT can reduce the incidence risk of pneumonia. Multicenter prospective studies are needed to confirm whether this model can be widely used for the prediction of symptomatic RP after RT for EC.

Conclusions

Under the premise that the lung dose is effectively controlled, the pre/end ratio of pre-albumin, PLR during RT, and NLR at the end of RT were the independent predictors of symptomatic RP. The nomogram chart based on these predictors has a better predictability for symptomatic RP, but it still needs more multicenter prospective studies to verify it.

Conflict of Interest

None.

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