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Advances in esophageal cancer surgery with neoadjuvant therapies

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Advances in esophageal cancer surgery with neoadjuvant therapies

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Table of contents

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Editorial: Frontiers' research topic "advances in esophageal cancer surgery with neoadjuvant therapies"

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neoadjuvant therapy, esophageal cancer, prognosis factors, risk factors, nomogram model

Editorial on the Research Topic
Advances in esophageal cancer surgery with neoadjuvant therapies

Introduction

Esophageal cancer is considered one of the most common cancers globally, characterized by high regional incidence, mortality, and poor prognosis. Locally advanced esophageal cancer accounts for the majority of deaths. Conventional radical resection alone provides insufficient outcomes for these patients. There is now increasing adoption of neoadjuvant therapies followed by surgery. However, neither neoadjuvant chemotherapy nor chemoradiotherapy has yielded promising results for esophageal cancer patients. Thus, there remains an urgent need to identify optimized treatment regimens, multimodality therapies, and immunotherapy combinations to augment the effects of neoadjuvant treatment. Therefore, the topic titled "Advances in Esophageal Cancer Surgery with Neoadjuvant Therapies" was proposed and has collated 12 contributions from experts dedicating in exploring the potential predictive models with clinical significance or prognostic predictors in terms of esophageal cancer patients received the neoadjuvant therapy.

Development of individualized treatment for patients with locally advanced esophageal cancer

Individualized treatment requires examination methods and tailored therapeutic schemes. Jin et al. found that for esophageal squamous cell carcinoma patients, preoperative radiotherapy (RT) improved overall survival of cT3-4N0M0 patients but not cT1-2N0M0 patients (Jin et al.). Though immunotherapy combined with chemotherapy is proven effective in advanced esophageal cancer, the optimal regimen remains unclear. Zhang et al. found that Sintilimab combined with paclitaxel liposome and carboplatin had

a relatively high partial response rate (22.2%) and safety profile, warranting further study (Zhang et al.). Li et al. integrated 15 trials on immunotherapy in neoadjuvant esophageal cancer. R0 resection rates ranged from 80.5% to 100.0%. When neoadjuvant immunotherapy was combined with chemotherapy, pathological complete response ranged from 16.7% to 50.0% and major pathological response ranged from 41.7% to 72.2% (Li et al.). Radiomics involves extracting quantitative imaging features and analyzing related clinical data. Though playing an active role in cancer research, it has little impact on predicting and managing esophageal cancer patients undergoing neoadjuvant therapy. Guo et al. reviewed radiomics' application in this setting. They found that based on CT, PET/CT and MRI radiomics models, pathological complete response after neoadjuvant therapy can be well predicted (Guo et al.). Combining radiomics features with biomarkers like CD44 and SHH further improves accuracy. Radiomics can also perfectly predict recurrence and survival after neoadjuvant therapy.

Decision of identifying prognostic predictors

Several studies focused on identifying prognostic factors for esophageal cancer patients after neoadjuvant therapy. Reported prognostic predictors include gender, the modified Ryan pathological grading, regional lymph node recurrence, cell senescence-related gene expression signature, and systemic inflammatory markers.

Wang et al.'s study demonstrated that males with locally advanced esophageal cancer had significantly decreased cancer-specific survival after neoadjuvant chemoradiation ($p < 0.05$). Zhang et al. found that the modified Ryan score score was significantly correlated with smoking history, lymphovascular invasion (LVI) and/or peripheral nerve invasion (PNI), however, it's not confirmed as the independent prognostic factors (Wang et al.).

Dai et al. observed that regional lymph node recurrence within 1 year after surgery was the main factor for failure and inferior survival. Irrespective of neoadjuvant therapy, patients with 1-year lymph node recurrence had significantly decreased survival (HR = 11.331, 95% CI 6.870–16.688, $P < 0.001$) with upper thoracic location and N2-3 stage as independent risk factors (Zhang et al.).

Zhang et al. demonstrated that senescence-related genes play a critical role in immune checkpoint regulation. They established that an esophageal cancer senescence-related gene expression signature was negatively correlated with survival (HR = 1.83, 95% CI 1.28–2.59, $p = 0.004$) (Dai et al.).

Han et al.'s meta-analysis indicated that high systemic inflammation levels (SII > 921.80) and early clinical stage were significantly associated with pathological complete response after neoadjuvant induction chemotherapy (OR = 5.32, 95% CI 3.12–9.07, $p < 0.001$), suggesting the feasibility of SII as a predictive tool (Zheng et al.).

Predictive model construction

Nomograms combine risk factors with predictive factors to assess individual risk and are widely used to aid clinical decision-making. Among the 12 studies, nomogram construction mainly predicted outcomes after neoadjuvant treatment.

For predicting complications after neoadjuvant therapy, Chen et al. established a nomogram to evaluate preoperative anastomotic leakage risk in esophageal cancer patients (Chen et al.). They found that aortic calcification, heart disease, obesity and low FEV1 conferred higher risk. The nomogram's AUC was 0.67, better predicting postoperative leakage. Fang et al. identified preoperative Alb ≤ 41.2 g/L, LA diameter >32.9 mm, Hb > 149 g/L and EF > 67.61% as post-esophagectomy atrial fibrillation (POAF) risk factors. The nomogram (AUC = 0.77) assessed POAF risk to guide individualized treatment (Fang et al.).

For predicting prognosis after neoadjuvant therapy, 7 studies established nomogram models. Wang et al. identified sex, T stage, N stage and M stage as independent cancer-specific survival factors in locally advanced esophageal cancer patients after neoadjuvant chemoradiation (Wang et al.). The nomogram predicted 3-, 5- and 7-year survival (AUC 0.612–0.638). Zhang et al.'s nomogram based on the modified Ryan score had a C-index of 0.702. Similarly, Yang and He determined independent prognostic factors to construct a nomogram for 3-year overall survival (AUC 0.624) in esophageal cancer patients after neo-chemotherapy (Yang and He.). For CSRS and SII studies, the 5-year AUCs of nomograms predicting patient outcomes were 0.946 and 0.62, respectively, both well predicting prognosis and pathological complete response after neoadjuvant therapy.

Summary

Esophageal cancer has a high morbidity and mortality rate in East Asia, and more than half of the new cases of esophageal cancer all over the world are diagnosed in China. Most patients have suffered from locally advanced disease at the time of diagnosis. At present, surgery is still the basis for the treatment of esophageal cancer. For the treatment of resectable locally advanced esophageal cancer, neoadjuvant therapy combined with surgery may well reduce the volume of tumor and lymph nodes, increase the rate of R0 resection, and prolong survival. With the release of the results of the CROSS trial and the NEOCRTEC5010 trial, preoperative NCRT is the standard treatment for patients with resectable locally advanced esophageal cancer currently. Furthermore, with the FDA's approval of pembrolizumab for the treatment of patients with advanced esophageal cancer in 2019, the era of immunotherapy in esophageal cancer treatment began. However, not all patients with EC will benefit from the neoadjuvant therapy.

How to accurately identify and predict the treatment effect and prognosis of patients who have received neoadjuvant therapy, find

out the predictive factors that affect pCR and prognosis, and build a risk prediction model, so as to achieve the goal of individualized treatment. Undoubtedly, in this topic, we have collected a number of studies related to the prognosis of neoadjuvant therapy and pCR results, as well as a review of the current advanced neoadjuvant therapeutic schemes, including immunotherapy. Further, studies are needed in terms of the fields of Esophageal Cancer Surgery with Neoadjuvant Therapies Research.

Author contributions

Q-XS and Z-NH writed the manuscript. L-QC and M-QK revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sex differences in cancer-specific survival for locally advanced esophageal cancer after neoadjuvant chemoradiotherapy: A population-based analysis

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Objective: Neoadjuvant chemoradiotherapy (nCRT) is the recommended standard treatment for locally advanced esophageal cancer (LA-EC). This study aimed to determine whether sex makes a difference in cancer-specific survival (CSS) and construct a novel nomogram model to predict CSS for LA-EC after nCRT based on the SEER database.

Methods: Patients coded by 04–15 were identified from the SEER database. Patients with systemic treatment and radiotherapy before surgery were defined as nCRT. We further divided this population into a training group and a verification group at a ratio of 7:3. Univariate and multivariate cox analyses were applied to determine the prognostic risk factors based on the training cohort, and then the Nomogram model was established. The area under the curve (AUC) was used to evaluate the predictive ability of the model. We used the calibration curve to evaluate the consistency between the predicted status and actual status and decision curve analysis (DCA) to evaluate the clinical value. We used X-tile software to determine the best cut-off value of nomogram scores and divided the population into low-risk, medium-risk, and high-risk groups, and Kaplan-Meier analysis was applied to compare the CSS.

Results: A total of 2096 LA-EC patients were included for further analysis, with 1,540 in the training cohort and 656 in the validation group. Male (HR: 1.29, 95% CI, 1.04 –1.58), T stage, N stage, and M stage were identified as independent risk factors of CSS based on the training cohort. A Nomogram model was constructed to predict the 3-, 5- and 7-years CSS. ROC curve and AUC confirmed that this nomogram has median discrimination ability. The calibration curve showed good agreement between predicted status and actual status. The DCA curves confirmed the clinical value. Kaplan-Meier analysis indicated that patients in the high-risk subgroup had poorer CSS in both the training cohort and validation cohort ($P < 0.001$).

Conclusion: Male patients had poorer CSS in LA-EC patients after nCRT. A nomogram model composed of sex, T stage, N stage, and M stage was constructed to identify the high-risk population and provide a personalized follow-up plan.

KEYWORDS

neoadjuvant chemoradiotherapy, cancer-specific survival, SEER database, esophageal cancer, nomogram model, male, sex difference

Introduction

Esophageal cancer is a highly aggressive malignancy, with a 5-year overall survival (OS) of only 10% to 20% in patients with advanced-stage (1). Compared with the surgery alone group, neoadjuvant chemoradiotherapy (nCRT) could significantly improve overall survival (OS) (100.1 months vs. 66.5 months) and disease-free survival (100.1 months vs. 41.7 months) for locally advanced esophageal cancer (LA-EC) (2). The 10-year OS of the CROSS trial indicated that the absolute benefit of nCRT was 13% (38% vs. 25%) (3). Based on current evidence, nCRT is still the first choice of treatment for LA-EC. Sex is reported to be a clinicopathological feature that could affect long-term survival (4, 5). However, at present, whether sex could affect the survival of LA-EC receiving nCRT is still unclear.

The Union for International Cancer Control tumor/node/Metastasis (TNM) staging system is widely used to predict long-term survival and guide adjuvant therapy, but its identification ability is limited. Sometimes, patients diagnosed with EC have different survival, even with the same TNM stage (4, 5). Nomograms are widely used to effectively predict survival in patients with all types of cancer-based on clinicopathological features (6). Nomogram is a new visualization tool that combines risk factors with other predictors to assess the absolute risk of an individual patient and is widely used to help doctors make decisions. The sample size is an important factor in constructing a reliable

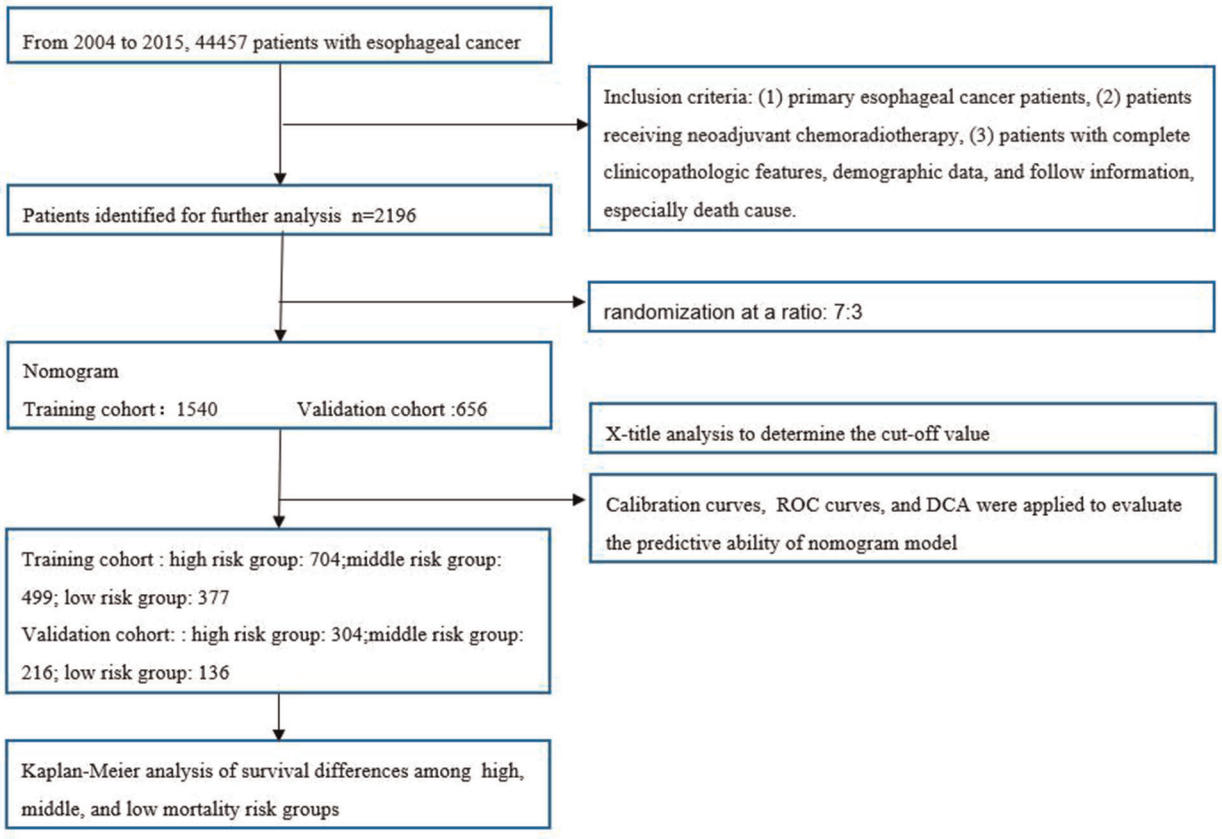

FIGURE 1
The flow chart of patient selection and data analysis.

TABLE 1 Comparisons of baseline characteristics between training cohort and validation cohort.

Contents	Training cohort	Validation cohort	*P*-value
Number	1540	656	
Race			0.1
Black	75	38	
Other	59	22	
White	1406	596	
Age			0.4
<50	162	61	
50–65	825	371	
>65	553	224	
Sex			0.84
Female	233	97	
Male	1307	559	
Marital status			0.96
Married	1088	464	
Unmarried	452	192	
Tumor size			0.64
< 51 mm	1016	419	
51–76 mm	322	145	
>76 mm	202	92	
T stage			0.5
T1-2	418	169	
T3-4	1122	487	
N stage			0.51
N0	515	229	
N1	1025	427	
M stage			0.66
M0	1402	590	
M1	138	66	
Grade			0.44
Grade I	75	33	
Grade II	675	275	
Grade III	765	341	
Grade IV	21	7	
Histology			0.59
Adenocarcinoma	1110	454	
Squamous cell carcinoma	261	130	
Others	169	72	
Primary site			0.75
Upper	16	6	
Middle	156	72	
Lower	1246	518	
Other	122	60	
Radiotherapy after surgery			0.64
With	58	22	
Without	1482	634	
Chemotherapy after surgery			0.8
With	139	57	
Without	1401	599	

(*continued*)

nomogram model. Surveillance, Epidemiology, and End Results (SEER) database population is a public population, which contains approximately 35% population of Americans, and could provide enough sample size for model development.

This study aimed to determine whether sex makes a difference in cancer-specific survival (CSS) and construct a novel nomogram model to predict CSS for LA-EC receiving nCRT based on the SEER database population, which could help in risk stratification and provide individualized therapy.

Methods

We downloaded data from SEER * stat software (version 8.3.6). The study included EC patients who underwent nCRT after esophagectomy between 2004 and 2015. Inclusion criteria: (1) primary EC, (2) preoperative nCRT, (3) sufficient clinicopathological features, demographic data, cause of death, and follow-up information. Exclusion criteria: (1) lack of basic clinical information such as age, sex, and marital status; (2) Lack of pathological information, T stage, N stage, pathological type, histological grade, and cause of death.

The demographic characteristics (age, sex, race, insurance status, and marital status), disease characteristics (histology, primary location, tumor size, grade, t, N, M stage), treatment methods (radiotherapy, chemotherapy), survival time and living status of patients were analyzed. We divided patients into three groups according to tumor size (<51, 51–76, and >76 mm). We divided the patients into three groups (>65 years old, 50 −65 years old, <50 years old). The primary site was defined according to the international classification of tumor diseases Code: lower esophagus 1 / 3 (15.5), middle esophagus 1 / 3 (15.4), upper esophagus 1 / 3 (15.3), and others. The histological types included adenocarcinoma, squamous cell carcinoma, and others. Tumor differentiation was divided into four groups: grade I, grade II, grade III, and grade IV. The population included in this study was staged by the 7th edition TNM stage system.

Statistical analysis

Univariate and multivariate Cox proportional hazards regression analyses were used to identify independent prognostic factors of CSS. Variables with $P < 0.05$ in univariate analysis

were included in multivariate Cox regression for further analysis.We used backward likelihood ratio to select variables in the multivariate Cox regression analysis. The Nomogram model was constructed based on the identified independent risk factors. We used the area under the curve (AUC) to evaluate the predictive ability. Calibration curves were drawn for the prediction of 3-,5-, and 7-year CSS, respectively, and decision curve analysis (DCA) curves were drawn to evaluate the clinical value. Based on the nomogram score, patients were divided into low-, medium-, and high-risk groups in X-tile software. The nomogram model was constructed based on the training cohort and evaluated in both the training cohort and validation cohort. We conducted analysis in R software (version 3.6.1). A two-sided P value < 0.05 was defined as statistically significant. The primary endpoint of the study was CSS, defined as the time between the date of diagnosis and the date of cancer death or the date of the last follow-up.

Results

Baseline characteristics in the training cohort and validation group

A total of 2,096 patients were identified from the SEER database using SEER*Stat Version 8.3.6 software. The details of patient selection were summarized in Figure 1. The total population was divided into a training cohort of 1,540 patients and a validation cohort of 656 patients. The training group and validation group were comparable in baseline characteristics ($P > 0.05$). The comparisons are summarized in Table 1.

Development and validation of nomogram model

We used the training cohort to find prognostic risk factors. Univariate analysis indicated that tumor size, M stage, N stage, T stage, grade, and sex were prognostic factors. Multivariate COX analysis determined that M stage (HR = 1.41, 95% CI, 1.14–1.75, $P = 0.002$), N stage (HR = 1.62, 95% CI, 1.39–1.89, $P < 0.001$), T stage (HR = 1.25, 1.06–1.46, $P = 0.01$), and sex (HR = 1.29, 95% CI, 1.04–1.58, $P = 0.02$) were independent prognostic factors. The details of univariate and multivariate Cox analysis were summarized in Table 2.

A Nomogram model was developed to predict 3-, 5-, and 7-years CSS (Figure 2). The AUC for 3-,5-, and 7-years CSS was 0.612,0.638, and 0.628 respectively in the training cohort, and 0.597,0.60, and 0.602 respectively in the validation cohort. Time-dependent ROCs noted that this model performed well in predicting CSS in both the training cohort and validation cohort (Figure 3) and also had a higher prediction accuracy

TABLE 2 Univariate and multivariate Cox analysis of cancer-specific survival for esophageal cancer patients receiving neoadjuvant chemoradiotherapy in the training cohort.

Characteristics	Univariate Cox analysis		Multivariate Cox analysis	
	HR 95% CI	*P*	HR 95% CI	*P*
Age				
<50	reference			
50–65	1.08 (0.87–1.35)	0.48		
>65	1.09 (0.86–1.37)	0.48		
Sex				
Female	reference			
Male	1.36 (1.12–1.67)	0.002	1.29 (1.04–1.58)	0.02
Race				
Black	reference	1.00		
Other	0.86 (0.53–1.37)	0.52		
White	0.99 (0.73–1.34)	0.94		
Martial				
Married	reference			
Marital_Unmarried	1.04 (0.9–1.21)	0.59		
Grade				
Grade I				
Grade II	1.11 (0.79–1.55)	0.56	1.09 (0.77–1.53)	0.63
Grade III	1.45 (1.04–2.02)	0.03	1.37 (0.98–1.92)	0.06
Grade IV	1.94 (1.03–3.66)	0.04	1.69 (0.9–3.18)	0.11
Histology				
Adenocarcinoma	reference			
Squamous cell carcinoma	0.78 (0.65–0.95)	0.01	0.91 (0.75–1.11)	0.36
Other	1.06 (0.86–1.31)	0.58	0.99 (0.8–1.22)	0.91
M stage				
M0	reference			
M1	1.44 (1.16–1.78)	0.001	1.41 (1.14–1.75)	0.002
N stage				
N0	reference			
N1	1.71 (1.47–1.99)	<0.001	1.62 (1.39–1.89)	<0.001
Primary site				
Upper	reference			
Middle	1.46 (0.64–3.34)	0.37		
Lower	1.58 (0.71–3.52)	0.27		
Other	2.1 (0.91–4.81)	0.08		
T stage				
T 1-2	reference			
T 3-4	1.38 (1.18–1.61)	<0.01	1.25 (1.06–1.46)	0.01
Tumor size				
<51 mm	reference			
51–76 mm	1.24 (1.05–1.46)	0.01	1.1 (0.93–1.3)	0.27
>76 mm	1.3 (1.07–1.58)	0.008	1.21 (1–1.48)	0.05
Radiotherapy after surgery				
without	reference			
with	1.15 (0.82–1.61)	0.41		
Chemotherapy after surgery				
without	reference			
with	0.83 (0.67–1.03)	0.09		

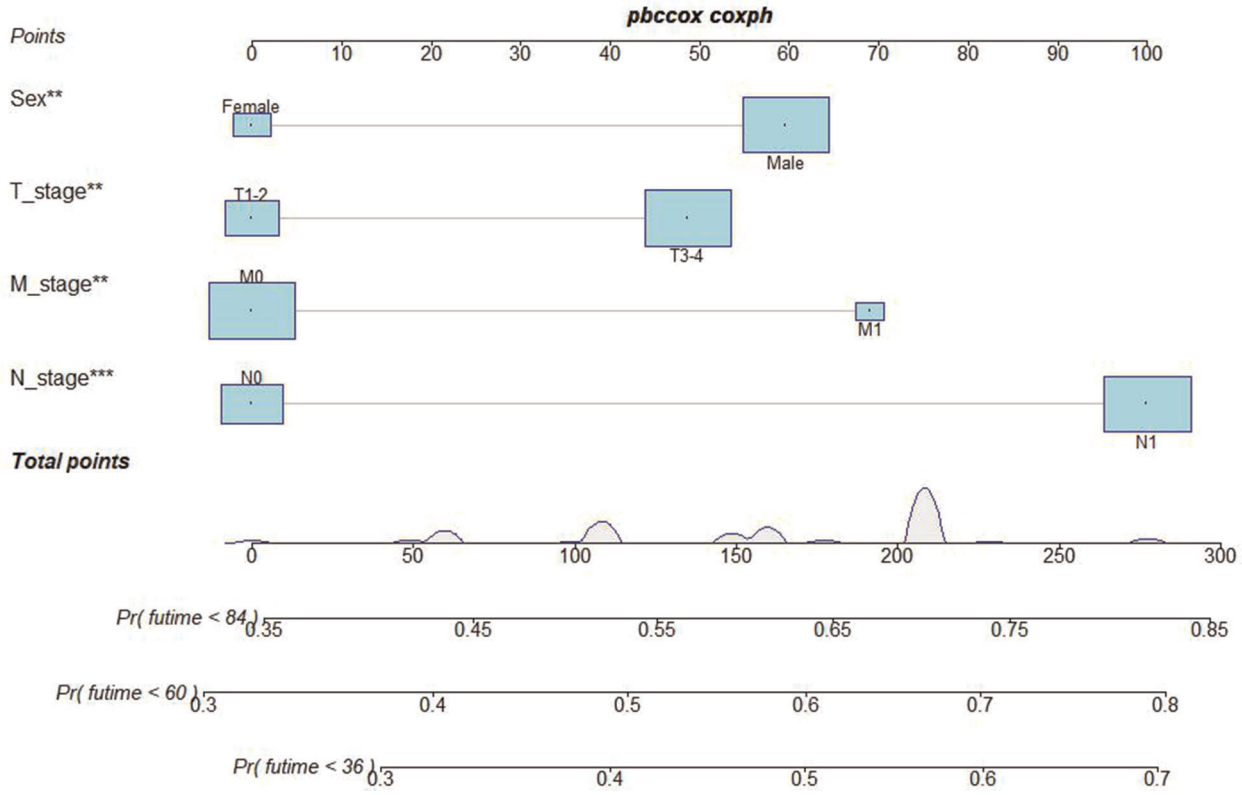

FIGURE 2
Nomogram model to predict the cancer-specific survival (CSS) at 3-,5-, and 7- years in patients receiving neoadjuvant chemoradiotherapy.

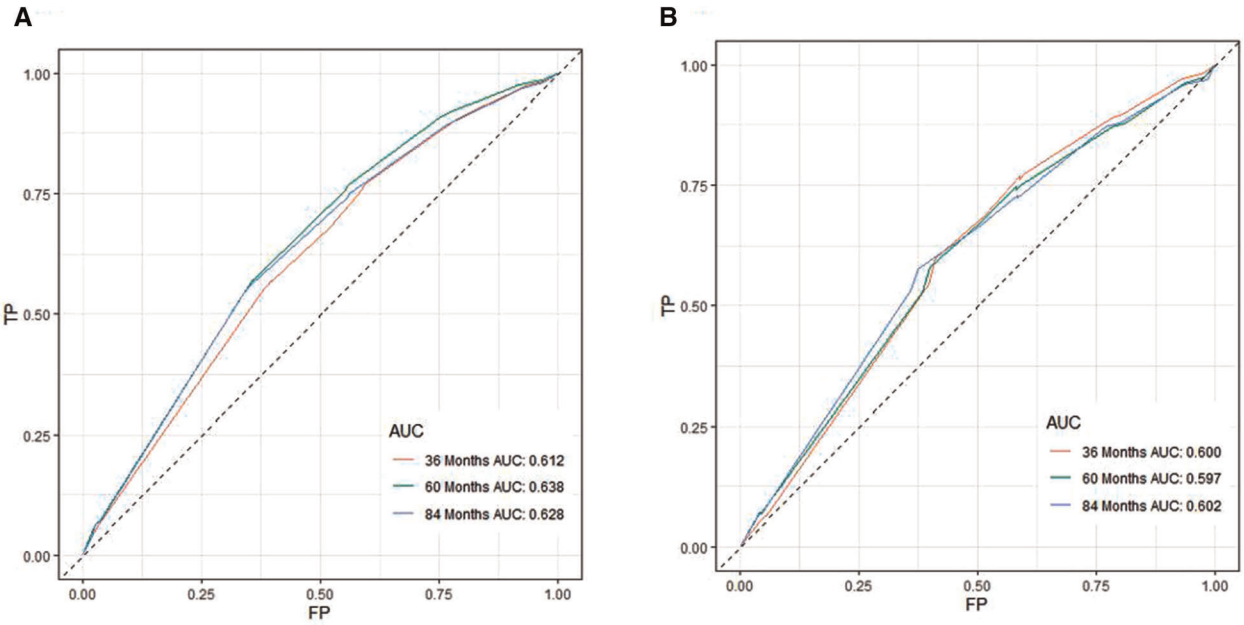

FIGURE 3
ROC curves for CSS prediction of patients receiving neoadjuvant chmoradiotherapy. (A) ROC curves of 3-, 5-, and 7-years in the training cohort, (B) ROC curves of 3-, 5-, and 7-years in the validation cohort. TP, True positive rate; FP, false positive rate; ROC, Receiver operating characteristic; CSS, cancer-specific survival.

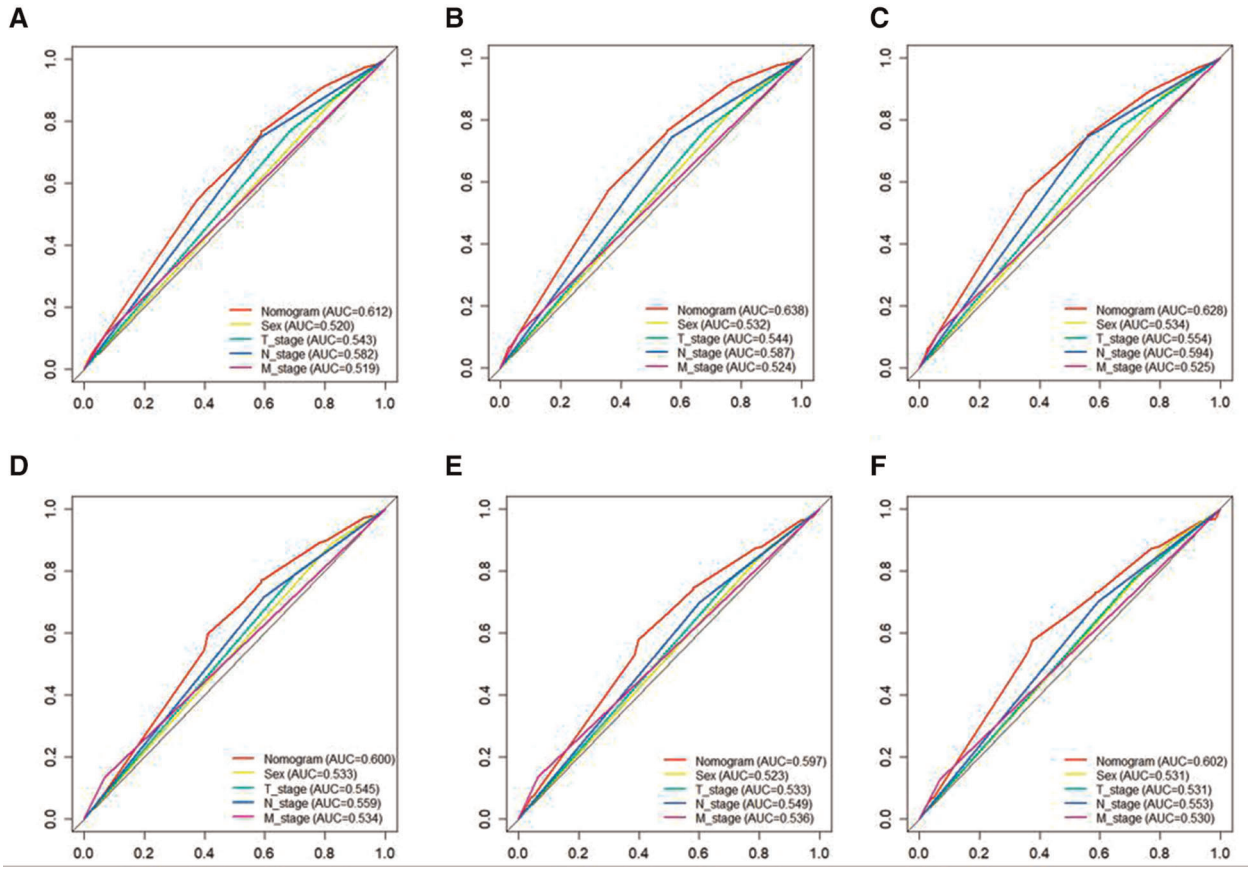

FIGURE 4
The ROC curves for CSS, including the nomogram model and all independent predictors at 3- (A), 5- (B), and 7-years (C) in the training cohort and at 3- (D), 5- (E), and 7-years (F) in the validation cohort. ROC, Receiver operating characteristic; CSS, cancer specific survival.

than individual prognostic factors included in the model (Figure 4). The calibration curves indicated that the predicted survival status was highly consistent with the actual status in both training and validation cohort (Figure 5). DCA indicated that this nomogram model had strong clinical applicability (Figure 6).

Kaplan-Meier analysis and risk stratification

Using X-tile software, patients were divided into low-risk, medium-risk subgroups, and high-risk subgroups according to nomogram scores. Nomogram scores of 0–5 are defined as a low-risk group, 6–10 as a medium-risk group, and 11–14 as a high-risk group. Compared with the low-risk group, the relative risk of the medium-risk group and high-risk group were 1.28 and 1.51, respectively. In the validation cohort and training cohort, patients in the low-risk group had significantly better CSS ($P < 0.001$) (Figure 7).

Discussion

To our knowledge, there is significant heterogeneity in the individual survival rate of EC, and the prediction of cancer-specific survival rate using the AJCC staging system alone seems to be inaccurate and inadequate. Although the AJCC staging system is the most widely used system for prognostic assessment and clinical treatment of cancer patients (7). However, due to a lack of demographic information, the AJCC system is not a perfect predictor of CSS in EC patients. Previous studies have confirmed that age at diagnosis, gender, race, marital status, and occupation are significantly associated with cancer survival (8–10). In the establishment of prognostic models for patients with EC, the prognostic value is limited due to the relatively limited sample size (11, 12). We found that sex also played an important role in CSS of EC patients receiving nCRT, and we further developed a richer and more accurate prognostic model (including T stage, N stage, M stage, and sex) to predict CSS. The nomogram could be used to calculate individual CSS predictions and

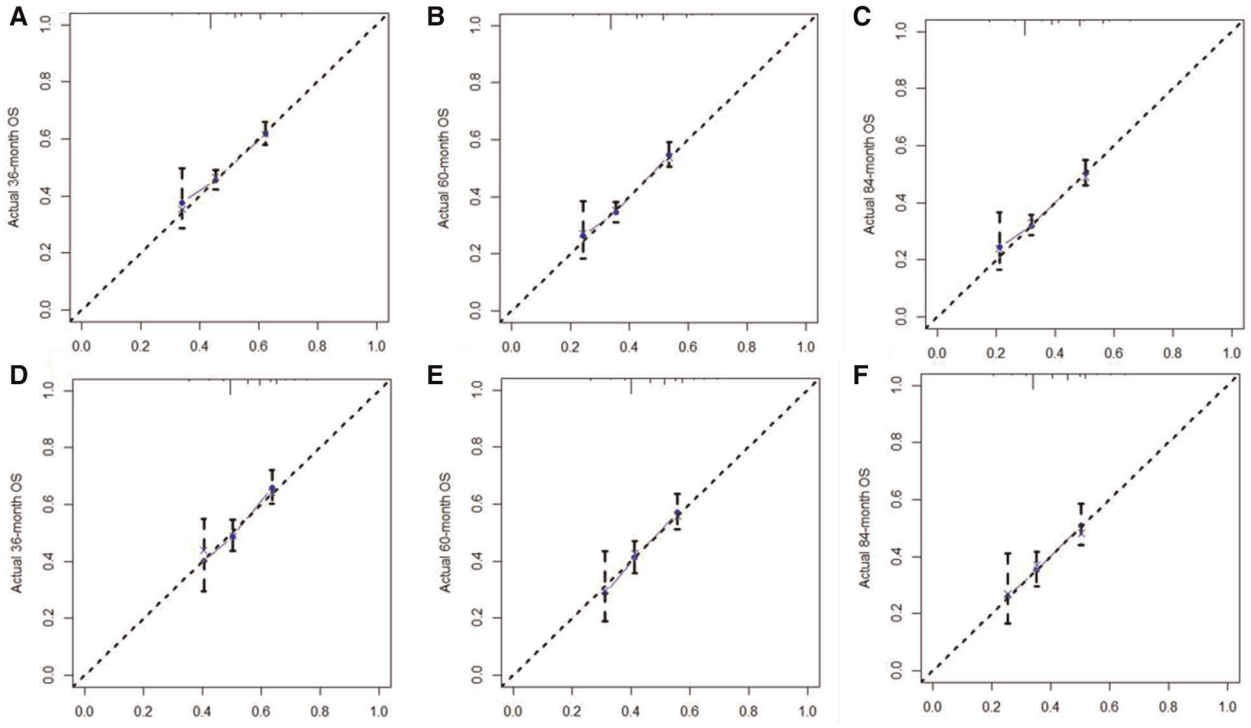

FIGURE 5
The calibration curve for predicting CSS at (A) 3-years, (B) 5-years, (C) 7-years in the training cohort, and at (D) 3-years, (E) 5-years, (F) 7-years in validation cohort. The nomogram-predicted probability of CSS is plotted on the X-axis, and the actual CSS is plotted on the Y-axis. CSS: cancer-specific survival.

provide better treatment allocation. Based on the nomogram, we could divide patients into low-, medium-, and high-risk, and a personalized follow-up plan could be conducted.

Male was an independent risk factor for poor CSS in EC receiving nCRT. Whether there is a sex difference in survival is still conflicting. Nobel TB et al. reported that postoperative mortality and overall survival (OS) were similar between sexes. In patients with clinical stage II/III, females received neoadjuvant therapy less frequently than males and had worse survival (13). Recently, Ji Zhang et al. found that women had a lower excess mortality rate ratio of 0.76 in EAC subtypes and 0.52 in ESCC based on 1,301 patients from Sweden nationwide. In patients with neoadjuvant therapy, the sex difference benefits still persisted (14). Kauppila JH et al. found that the women had better long-term survival than men in the ESCC subtype but not in the EAC subtype (15). Rowse PG et al. found that after induction chemoradiotherapy, the male sex had an 80% increased risk of recurrence (hazard ratio 1.80, $P = 0.008$) (16). Estrogen receptors (ERs) are highly expressed in ESCC, and estrogens were reported to inhibit squamous cell tumor growth (17, 18). However, age-stratified studies did not show better survival in younger women with higher sex hormone levels. Other key prognostic factors for EC involve alcohol consumption, smoking consumption, obesity, lifestyle, and oncogenic types of HPV (19). The female sex could respond better to induction chemoradiotherapy. The response difference may be due to sex-related differences in pharmacokinetics and pharmacodynamics (20). The mechanism is still unclear and should be further explored.

Based on the 7th AJCC staging system, differentiation grade is a staging factor for EC. He W et al. also reported that although patients with poorly differentiated EC respond better to nCRT than those with well-differentiated or moderately differentiated EC, however, resulted in poorer survival (21). For EC patients with the same pathological stage, a worse pathological grade often indicates a worse prognosis and a higher postoperative recurrence rate (22). However, we found that pathological grade wasn't an independent risk factor of CSS for EC receiving nCRT, which was consistent with the 8th AJCC staging system. One possible reason is that the cell redistribution or loss of original morphology after neoadjuvant therapy affects the judgment of pathological grade, which would reduce the value of pathological grade in predicting survival.

At present, the number of population-based EC patients after NCRT is still relatively limited. This study clarified the value of gender differences in CSS for EC patients after nCRT and established a new model to predict the CSS of EC patients after nCRT at 3, 5, and 7 years. However, this study had the following three limitations: first, this study is based on the SEER database. Due to the differences in demographic

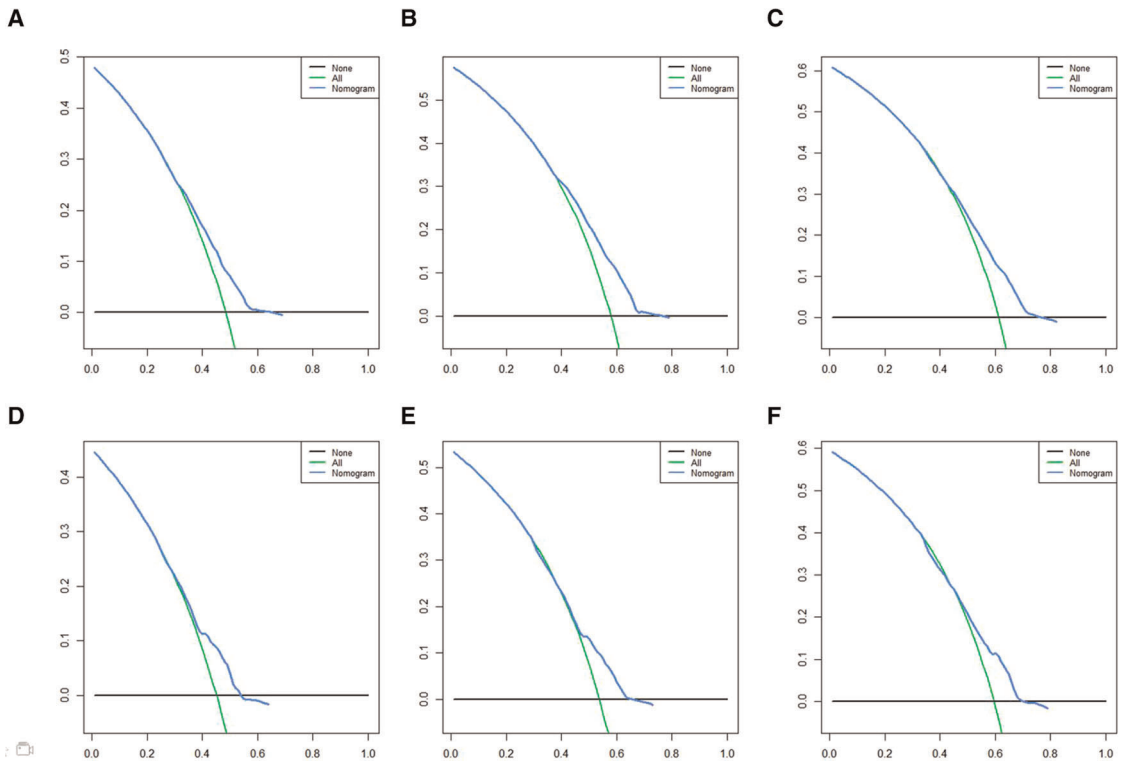

FIGURE 6
DCA for CSS prediction. (A) DCA of 3-years CSS in the training cohort, (B) DCA of 5-years CSS in the training cohort, (C) DCA of 7-years CSS in the training cohort, (D) DCA of 3-years CSS in the validation cohort, (E) DCA of 5-years CSS in the validation cohort, (F) DCA of 7-years CSS in the validation cohort. DCA, Decision curve analysis; CSS, cancer-specific survival.

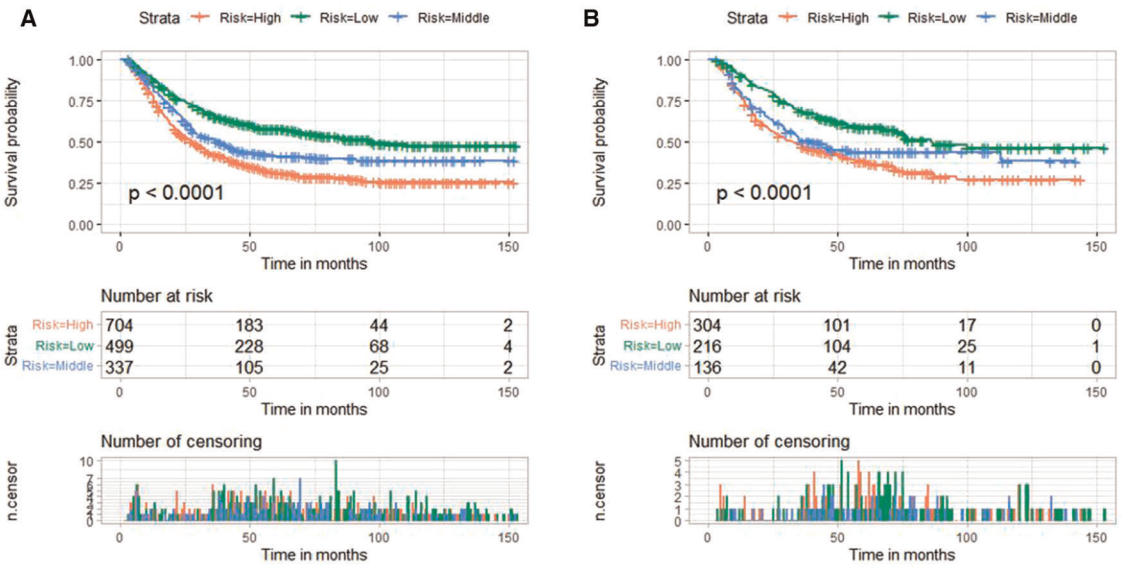

FIGURE 7
Risk stratification based on nomogram score and Kaplan-Meier curves for cancer-specific survival in training cohort (A) and validation cohort (B).

characteristics and pathological subtypes, it was uncertain whether the conclusions of this study are applicable to the Asian population. Secondly, there was no record of a chemoradiotherapy regimen in the SEER database. The radiotherapy or chemotherapy dose described in SEER data was yes or no/unknown. We defined a combination of preoperative systemic therapy and preoperative radiotherapy as nCRT. There weren't surgical method, R0 removal rate, and number of lymph nodes removed in the SEER database. Third, this novel model was only verified internally, not externally. The findings of this study should be further verified in later research.

Conclusions

Male patients had poorer CSS in LA-EC patients after nCRT. A nomogram model composed of sex, T stage, N stage, and M stage was constructed to identify the high-risk population and provide a personalized follow-up plan.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

JW and ZC conceived the concept and coordinated the design. JW and CY drafted the manuscript. All authors revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Neoadjuvant sintilimab and chemotherapy in patients with resectable esophageal squamous cell carcinoma: A prospective, single-arm, phase 2 trial

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Background: Immunotherapy (Programmed cell death 1 blockade) has entered the ranks of advanced esophageal cancer first-line treatment; however, little is known about the efficacy of PD-1 inhibitor as neoadjuvant therapy in resectable esophageal squamous cell carcinoma (ESCC). We aim to evaluate the activity and safety of the neoadjuvant sintilimab combined with chemotherapy in the treatment of resectable thoracic ESCC.

Methods: The enrolled patients with resectable (clinical stage II to IVA) ESCC received neoadjuvant sintilimab injection (200 mg/time, day 1), paclitaxel liposomes (135 mg/m^2, day 1), and carboplatin (area under curve of 5 mg/mL/min, day 1) every 21 days for 2 cycles, and esophagectomy was performed within 3-6 weeks after the 2 cycles of treatment. The primary endpoint of the study was the pathological complete response (PCR) rate.

Results: From July 2019 to March 2021, a total of 47 patients were enrolled, of which 33 patients (70.2%) had clinical stage III disease. All patients completed the full two-cycle treatment and forty-five patients received radical surgery, including 44 (97.8%) R0 resections. Ten (22.2%) of 45 patients had a PCR, and the major pathological response (MPR) rate was 44.4% (20/45). The grade 3–4 treatment-related adverse events (TRAEs) were mainly neutropenia (6 of 47,12.8%) and leucopenia (8 of 47,17.0%). One (2.1%) patient occurred

postoperative immune-associated encephalitis. No delays in surgery were observed.

Conclusions: sintilimab combined with paclitaxel liposome and carboplatin, as demonstrated in this phase II trial to exhibit a relatively high PCR rate and acceptable safety, warrants additional investigation in resectable ESCC.

Trial Registration: http://www.chictr.org.cn/, ChiCTR1900026593.

KEYWORDS

neoadjuvant, sintilimab and chemotherapy, resectable, esophageal squamous cell carcinoma, prospective

Introduction

Worldwide, the number of new cases of esophageal cancer (EC) reached 572,000, and the number of deaths was 509,000 in 2018 (1). In 2015, 246,000 new cases of esophageal cancer were reported in China, making it one of the top 10 common causes of cancer death (2). Esophageal squamous cell carcinoma (ESCC) in China accounts for approximately 90% of esophageal cancer cases (3). Surgery is still the cornerstone of treatment for potentially resectable ESCC. However, among patients with locally advanced EC, the R0 resection rate is low (around 50%), resulting in early recurrence after surgery (4, 5). Preoperative chemotherapy combined surgery was recommended as the standard regimen in Japan (6). Although a moderately high incidence of pathological response after neoadjuvant chemoradiotherapy is reported, the long-term clinical benefit is still suboptimal and unsatisfactory (7–9), which is associated with more postoperative complications and higher postoperative mortality. Preoperative chemotherapy provides the advantages of fewer side effects, ease of tolerance, as well as being easier to administer at general treatment centers. However, compared with preoperative chemoradiotherapy, its effective rate and PCR rate are lower.

The clinical research results of Keynote-590 (10) (enrolled 70% squamous cell carcinoma), CheckMate-648 (11) (enrolled 100% squamous cell carcinoma), and ESCORT-1st (12) (enrolled 100% squamous cell carcinoma) established the important role of immunotherapy combined with chemotherapy in the first-line treatment of advanced esophageal cancer. Sintilimab combined chemotherapy for ESCC significantly prolonged OS and reduced the risk of death by 37.2%, according to the preliminary results of the Research ORIENT-15 (NCT03748134) (13). However, to date, there has been no conclusive evidence to support the effectiveness of neoadjuvant immunotherapy in patients with ESCC.

There is no consensus on the optimal neoadjuvant chemotherapy treatment for patients with resectable locally advanced ESCC. Patients with advanced or locally progressed ESCC have been treated with paclitaxel plus platinum (14, 15), especially in China. Due to the limitation of poor water solubility of paclitaxel, researches on enhancing the tumor targeting of paclitaxel has been carried out continuously (16, 17). When compared to taxol, putting paclitaxel in liposomes results in a higher maximum tolerated dose, better paclitaxel transport into tumor cells, and fewer side effects (18, 19). In China, liposomal paclitaxel was first approved by the State Food and Drug Administration (national medicine permission number: H20030357) in 2003, and its combination with platinum has been utilized to treat advanced ESCC (20–22).

The study mainly observed the efficacy and safety/feasibility of using the combination of neoadjuvant PD-1 blockade with chemotherapy in patients with resectable ESCC, expecting to explore a more effective and less toxic neoadjuvant treatment regimen to improve the clinical outcomes of patients with ESCC.

Methods

Study design and participants

This trial was a single-center single-arm, phase II clinical trial performed at the Affiliated Cancer Hospital of Nanjing Medical University. The main eligibility criteria of this study were histologically confirmed, previously untreated esophageal thoracic squamous cell carcinoma, clinical stage II to IVA disease (defined by the eighth edition Union for International Cancer Control) (23), age 18 to 75 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Moreover, there was no disease progression before enrollment. Patients were excluded if they had esophageal perforation or hematemesis, prior history of autoimmune disease, severe cardiovascular disease, or other concomitant cancers. PD-L1 biomarker expression did not need to be considered in all enrolled patients.

All patients provided written informed consent before enrollment. The study protocol was approved by the clinical research ethics committee of Jiangsu Cancer Hospital. All patients enrolled in this experiment are Chinese.

Procedures

All patients had tumor clinical assessment, including diagnostic biopsy, esophagography, endoscopic ultrasonography, and boost brain-neck-thorax-abdomen computed tomography and/or positron emission tomography-CT. A routine electrocardiogram, echocardiography, and hematology index-related test were also carried out.

Patients received the following drugs intravenously before undergoing surgical resection (see Research Schematic 1 in Supplementary File): sintilimab (200 mg) on day 1 of each 21-day cycle, paclitaxel liposomes (135 mg/m^2) on day 1, and carboplatin (area under the curve [AUC] of 5 mg/mL per min) on day 1. To prevent possible anaphylaxis with paclitaxel liposomes, pretreatments were given 30 min before paclitaxel liposome treatment with intravenous dexamethasone, intramuscular injection with a promazine needle, and intravenous drip of cimetidine injection. It should be noted that the interval between dosing should not be less than 20 days and that sintilimab precedes paclitaxel and carboplatin. After two cycles of neoadjuvant immunotherapy combined with chemotherapy, enhanced CT of the neck, chest, and upper abdomen, ultrasound endoscopy, and esophagography were carried out. Two senior radiologists evaluated lymph node response according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (24), and esophageal lesion response was assessed by esophagography before and after treatment. (For specific evaluation details, see Supplemental File 1)

Surgery was scheduled for 21–42 days after the first day of the second treatment cycle. Patients completed radical surgery through the right chest and abdominal incision (Ivor-Lewis method) (25) and underwent two-field lymphadenectomy (the lymph nodes in the middle and lower mediastinum, upper abdomen, and the cervicothoracic junction of patients were selected for dissection). The following pathological evaluation after neoadjuvant therapy referred to the criterion of the College of American Pathologists (CAP)/National Comprehensive Cancer Network (NCCN) (26): All HE slides of patients enrolled in our trial were graded as 0 (PCR, no evidence of vital residual tumor cells), 1 (MPR, 10% or less vital residual tumor cells), 2 (residual cancer foci with interstitial fibrosis), and 3 (few or no tumor cell regression) under the microscope by pathologists.

Toxic effects were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) (27), version 5.0. The specific principles of dosing reduction during treatment are detailed in Supplemental File 2.

Outcomes

The primary endpoints of this study were efficacy (PCR rate as a short-term efficacy surrogate endpoint) and safety/feasibility. Toxicity profiles were assessed according to the NCI-CTCAE (version 5.0) guidelines. The secondary endpoints included disease control rate (DCR), disease-free survival (DFS, calculated from the date of enrollment), CAP/NCCN pathological tumor regression grade (TRG), and overall survival (OS).

Exploratory analysis

The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been used to predict therapeutic response in different tumors (28–30). However, few studies have evaluated its efficacy in patients with ESCC who received anti-PD-1 combined with neoadjuvant chemotherapy (31). In this study, the baseline inflammatory indicators of patients were analyzed to observe whether they have certain guiding significance in predicting the pathological efficacy of anti-PD-1 combined with neoadjuvant chemotherapy in the treatment of ESCC.

Statistical analysis

According to historical literature (32), the pathological complete response rate of neoadjuvant chemotherapy is 6.4%, and 19.2% is expected in our experimental group. The necessary sample size to guarantee an improvement in the PCR rate, with a global alpha risk of 5%, power of 80%, an accrual period of 18 months, and 10% patient loss, was calculated. Results for the primary endpoint were expressed as frequencies and percentages, and the exact two-sided 95% CIs were calculated by use of the Clopper-Pearson method. Survival probabilities were estimated by use of the Kaplan-Meier method. Associations between pathological response to anti-PD-1 plus neoadjuvant chemotherapy and NLR, LMR, PLR, and SII at baseline and post-treatment and their cutoff values were determined by ROC (receiver operating characteristic curve) analysis. SPSS 25.0 and GraphPad Prism 9.1 were used for data analyses.

Results

Baseline

From July 2019 to March 2021, 47 patients with esophageal squamous cell carcinoma were enrolled in Jiangsu Tumor

Hospital affiliated with Nanjing Medical University, and 45 patients underwent surgery (Figure 1). The population included 36 men (76.6%) and 11 women (23.4%). The median age was 66 (IQR, 64-70) years. A total of 38 patients (80.9%) had clinical stage III or IVA disease, and 24 (51.1%) had a tumor length greater than or equal to 5 cm. Nineteen (40.4%) of 47 patients had mid-thoracic esophageal cancer, 25 (53.2%) had lower-thoracic esophageal cancer, and 18 (38.3%) had diabetes, hypertension, or other basic diseases. Other baseline characteristics of the enrolled patients are detailed in Table 1.

Treatment exposure and safety

All 47 enrolled patients completed two cycles of neoadjuvant therapy, and no events of chemotherapy suspension or dose reduction due to physical reasons occurred. TRAEs are summarized in Table 2. The most frequently occurring TRAEs of grade 1-2 was anemia, which occurred in 25 (53.2%) of the 47 patients. Leukopenia (20 of 47, 42.6%), hair loss (16 of 47, 34.0%), thrombocytopenia (15 of 47,31.9%), neutropenia (13 of 47, 27.7%), and loss of appetite (12 of 47,25.5%) were also common among the patients. The treatment-related hematological adverse events of grade 3-4 were neutropenia (6 [12.8%]), leucopenia (8[17.0%]), anemia (1[2.1%]) and thrombocytopenia (4[8.5%]). One patient developed massive esophageal hemorrhage 3 weeks before surgery but received surgery successfully after positive symptomatic treatment. Immune-related AEs observed during neoadjuvant therapy were all grade 1-2, including rash (4.3%), increased liver transaminases (10.6%), abnormal thyroid function (6.4%), and increased brain natriuretic peptide (14.9%), none of which led to discontinuation of treatment, dose reduction, or surgical delay. In addition, one case of third-degree immune-related encephalitis attributable to neoadjuvant treatment was observed on the 14th postoperative day. The patient suffered from a sudden loss of consciousness and secondary seizures during the postoperative hospital stay. After a comprehensive multidisciplinary discussion, immune-related encephalitis was considered, and glucocorticoid anti-inflammatory therapy and antiepileptic drug therapy were given. As of the last follow-up, the patient's general condition was stable.

Surgery outcomes

There were no treatment-related surgical delays, but 2 patients gave up for personal reasons, one of whom chose concurrent chemoradiotherapy. The median interval between the last administration of systemic chemotherapy and surgery was 29 days (IQR, 26.5-35 days). Minimally invasive esophagectomy (Ivor-Lewis) was received by 45 patients, of which 44 (97.8%) had a successful R0 resection. The intraoperative blood loss and operative time were 175.0 ± 20.7 mL (mean ± SD) and 228.6 ± 31.1 min, respectively. Surgical complications are reported in Table 3. One patient died of hypovolemic shock within 24 hours after surgery. There were three (6.7%) cases of pulmonary infection, one (2.2%) case of anastomotic leakage, and one (2.2%) case of incisional hernia. The median Intensive care unit (ICU) stay was 1 day (range, 0–16) and the median postoperative hospital stay was 13 days (range, 7–52).

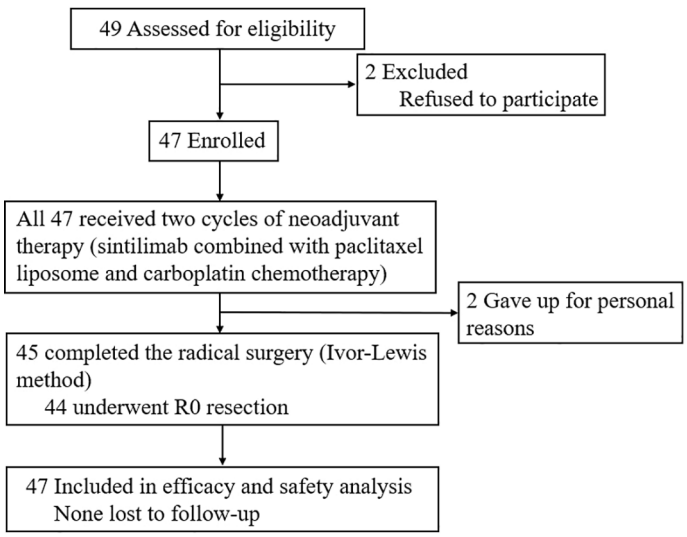

FIGURE 1
Study flow chart.

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TABLE 1 Baseline characteristics of enrolled patients (N=47 cases).

Variable	n (%)
Age(y)	Median 66 (IQR,64-70)
<70	35 (74.5)
≥70	12 (25.5)
Sex	
Male	36 (76.6)
Female	11 (23.4)
ECOG performance status	
0	38 (80.9)
1	9 (19.1)
Tumor location	
Middle thoracic	19 (40.4)
Lower thoracic	25 (53.2)
Both	3 (6.4)
Clinical stage(N)	
cN1	28 (59.6)
cN2	19 (40.6)
Clinical stage (UICC, 8th)	
II	9 (19.1)
III	33 (70.2)
IVA	5 (10.7)
Tumor length, cm	
<5	23 (48.9)
≥5	24 (51.1)
Smoking history	
Yes	28 (59.6)
No	19 (40.4)
Drinking history	
Yes	28 (59.6)
No	19 (40.4)
Medical disease	
Yes	18 (38.3)
No	29 (61.7)
Family history of cancer	
Yes	9 (19.1)
No	38 (80.9)

UICC, Union for International Cancer Control; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Efficacy

Ten (22.2%) of 45 patients who underwent successful surgical resection achieved a pathological complete response, and a major pathological response was observed in 20 (44.4%) patients. We also assessed the relationship between patient baseline characteristics and tumor pathological response in a *post hoc* analysis (Supplemental File 3). Of 18 patients with mid-thoracic esophageal squamous cell carcinoma who underwent successful surgical resection, 11 (61.1%) patients had a major pathological response, including 6 (33.3%) patients with pathological complete response. (Figure 2) In contrast, of 24 patients with lower-thoracic esophageal squamous cell carcinoma who underwent successful surgical resection, 6 (25.0%) patients had a major pathological response, and 2 (8.3%) had a pathological complete response (p=0.02). The distribution of the pathological response of primary tumor can be seen more visually through the waterfall plot (Figure 3). The median number of lymph nodes resected was 16 (IQR, 13-21). Among all patients who received surgery, 39 (86.7%) patients achieved pathological downstaging of clinical N stage, including 34 (75.6%) patients with decreased postoperative lymph node staging to pN0 and 5 (11.1%) patients with decreased postoperative lymph node staging to pN1. Lymph node staging remained unchanged in 4 (8.9%) patients, and lymph node progression occurred in 2 (4.4%) patients (both from cN1 to pN3). Of the 32 patients with pathologically confirmed N1/2 stage disease at baseline, 20 (62.5%) had nodal clearing after neoadjuvant treatment (downstaging from cN1/2 to pN0).

According to the comprehensive evaluation, after two cycles of neoadjuvant immunotherapy combined with chemotherapy, 12 (25.5%) patients were assessed as having a partial response, 33 (70.2%) patients achieved stable condition, and 2 (4.3%) patients had disease progression (no distant metastasis occurred). All patients were evaluated and deemed eligible for surgical treatment.

Follow-up

At the time of analysis (November 2021), the surviving patients had a median follow-up of 14.6 months (IQR, 11.3-24.0 months). No patient was lost to follow-up. A total of 4 (8.5%) patients died, three (6.4%) died of tumor cause and the other one (2.1%) died of postoperative hypovolemic shock. A total of 15 (31.9%) patients suffered recurrence. Nine (19.1%) had regional recurrence only and there were 6 patients (12.8%) with distant metastasis only, consisting of 2 (4.3%) patients with liver metastasis, 1 (2.1%) patient with abdominal metastasis, 1 (2.1%) patient with kidney metastasis, 1 (2.1%) patient with lung metastasis, and 1 (2.1%) patient with brain metastasis.

In the entire patient cohort, the median disease-free survival (DFS) and the median overall survival (OS) were not reached (Figures 4A, B). The 1-year OS was 90.8%, and the 1-year DFS was 68.3%. In *post hoc* analyses of survival, we found that patients who achieved MPR had significantly improved DFS (P=0.050; HR=0.35, 95%CI=0.13-0.92) and OS (P=0.066; HR=0.16, 95%CI=0.02-1.13), compared with those who did not. (Figures 4C, D)

Exploratory analysis

When the therapeutic efficacy of patients with anti-PD-1 plus chemotherapy was divided into CAP/NCCN pathological tumor regression grade 0 (PCR) and grade 1, 2, 3 (non-PCR), our results seemed to show baseline NLR、LMR、PLR、SII could not better predict the pathological tumor regression grade

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TABLE 2 Adverse Events (N=47 cases).

Adverse event	Grade1-2 (%)	Grade3 (%)	Grade4 (%)
Anemia	25 (53.2)	1 (2.1)	0
Leukopenia	20 (42.6)	6 (12.8)	2 (4.3)
Neutropenia	13 (27.7)	5 (10.6)	1 (2.1)
Thrombocytopenia	15 (31.9)	2 (4.3)	2 (4.3)
Loss of appetite	12 (25.5)	0	0
Nausea	3 (6.4)	0	0
Vomiting	2 (4.3)	0	0
Constipation	3 (6.4)	0	0
Fever	0	0	0
Fatigue	8 (17.0)	0	0
Hair loss	16 (34.0)	0	0
Rash	2 (4.3)	0	0
Increased BNP	7 (14.9)	0	0
Increased ALT	4 (8.5)	0	0
Increased AST	1 (2.1)	0	0
Dizziness	1 (2.1)	0	0
Cardiac toxicity&	1(2.1)	0	0
Hyperthyroidism	3 (6.4)	0	0
Encephalitis	0	1 (2.1)	0

BNP, type B natriuretic peptide; ALT, alanine aminotransferase concentrations; AST, aspartate aminotransferase concentrations; &:Increased myocardial enzymes.

by ROC curve analysis. When the therapeutic efficacy was categorized into pathological tumor regression grades 0, 1, and 2 (response) and grade 3 (no response or poor response), ROC curve analysis showed that NLR at baseline (cutoff=3.29, AUC=0.729, 95% CI 0.554–0.903, P= 0.020, sensitivity=0.50, specificity=0.91, Figure 5A), LMR at baseline (cutoff=3.57, AUC= 0.793, 95% CI 0.655–0.931, P=0.003, sensitivity=0.64, specificity=0.92, Figure 5B), PLR at baseline (cutoff=143.23, AUC=0.684, 95% CI 0.484–0.885, P=0.061, sensitivity=0.75, specificity=0.73, Figure 5C) and SII at baseline (cutoff=815.50, AUC=0.699, 95% CI 0.514–0.885, P=0.043, sensitivity=0.50, specificity=0.91, Figure 5D) could be used to predict pathological tumor regression grade. Besides, our results indicated a good predictive performance for MPR involving LMR at baseline (Supplemental File 4).

Discussion

This study prospectively observed the efficacy and safety of radical surgery after neoadjuvant PD1 (sintilimab) combined with chemotherapy in operable esophageal squamous cell carcinoma. To our knowledge, there is no relevant large-sample prospective study at home or abroad, so this trial can explore a new model for the clinical treatment of potentially resectable esophageal squamous cell carcinoma.

Based on the findings of several landmark studies (CROSS study, NEOCRTEC5010, and CheckMate-577 trial) (33–35), neoadjuvant chemoradiotherapy (NCRT) plus surgery has become a recommended treatment option for locally advanced ESCC, especially in most western countries. However, the improved PCR rate in NCRT failed to provide a more significant long-term survival benefit than in NCT (7–9). In addition, the clinical application of NCRT is restricted due to the superimposed toxicity of chemotherapy and radiotherapy. Dose reduction of chemoradiotherapy due to high toxicity weakens the patients' treatment adherence to a certain extent. In addition, NCRT may further add to the difficulty of surgical procedures (e.g., tissue adhesion and oedema) and increase perioperative complications (e.g., respiratory failure caused by radiation pneumonitis), which undesirably counteracts the survival benefits expected from NCRT.

In terms of toxicity, the incidence of the treatment-related hematological adverse events of grade 3-4 in this study was 40.4%, which was lower than that reported in the NEOCRTEC5010 neoadjuvant chemoradiotherapy group (54.3%) (33). Except for one case of immune-related encephalitis, all immune-related AEs were grade 1. In terms of surgical safety, the neoadjuvant therapy in this study did not delay surgery and the R0 resection rate reached 98%, while in previous studies the reported R0 resection rates with neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy were 60% and 98% (5, 33). The mean number of lymph nodes resected (16.0) and that reported in the CROSS (15.0) study was similar (35). These results suggest that this neoadjuvant therapy can result in high R0 resection rates, greatly reducing the difficulty for surgeons to completely remove the primary tumor or lymph nodes. In the aspect of postoperative

TABLE 3 Surgical outcomes (N=45 cases).

Characteristics	n/N (%) or mean ± SD or median (range)
Margins	
Negative	44/45 (97.8%)
Positive	1/45 (2.2%)
Changes in lymph node staging status	
Downstaging	39/45 (86.7%)
Unchanged staging	4/45 (8.9%)
Upstaging	2/45 (4.4%)
Blood loss (mL)	175.0 ± 20.7
Cumulative operative time	228.6 ± 31.1
(min)	13 (7–52)
Postoperative hospital stay	1 (0–16)
(day)	
ICU stay (day)	
Surgical complications	
Anastomotic leakage	1/45 (2.2%)
Pulmonary infection	3/45 (6.7%)
incisional hernia	1/45 (2.2%)
In- hospital mortality$	1/45 (2.2%)
30- day mortality	0
90- day mortality	0

Only patients who had undergone surgical treatment were counted; ICU, intensive care unit; $ One patient died of hypovolemic shock within 24 hours after surgery.

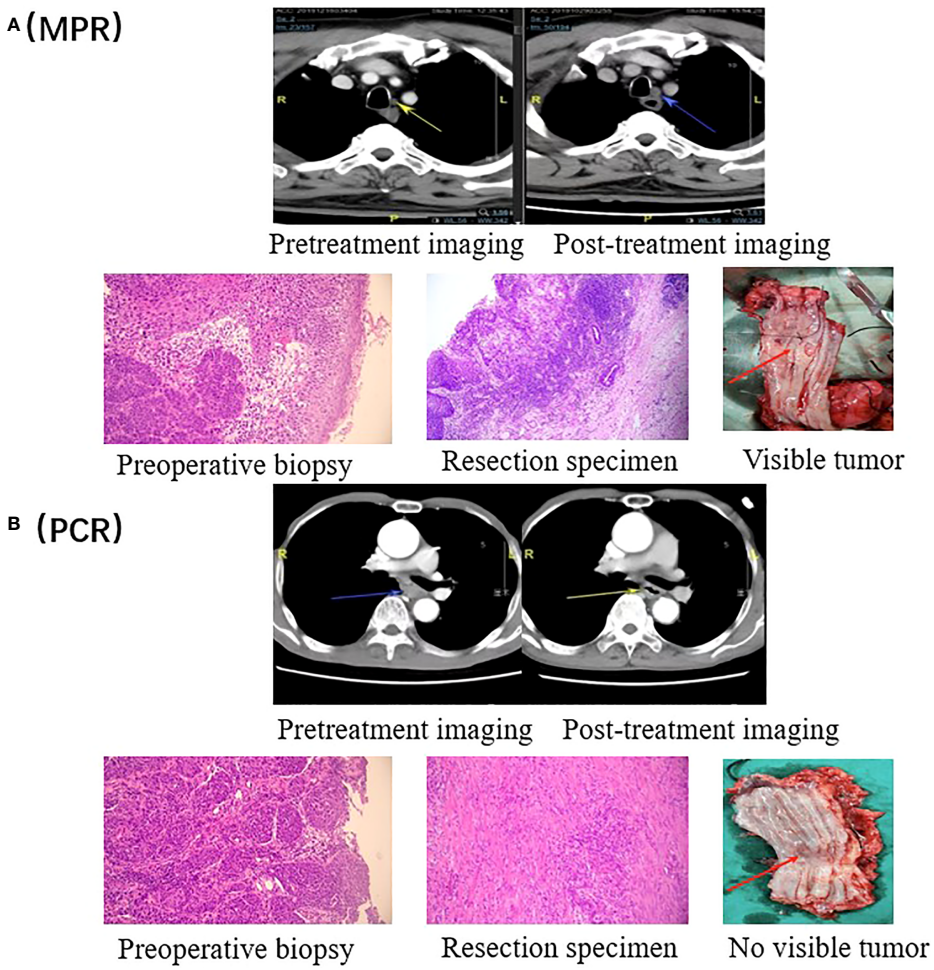

FIGURE 2
Radiographic and pathological responses. **(A)** Pretreatment and post- treatment CT and H&E images of a representative patient with a pathological response of MPR. The tumor is visible in the resected esophagus. **(B)** Pretreatment and post- treatment CT and H&E images of a representative patient with a PCR. There is no tumor visible in the resected esophagus.

complications, the incidence of anastomotic fistula in our study was 2.2%, which was lower than that previously reported in the CROSS study (22%) (35). Although there was one perioperative death, it was deemed unrelated to neoadjuvant therapy. In general, neoadjuvant chemotherapy combined with immunotherapy was well tolerated and safe.

Encouragingly, in this study, the PCR rate of neoadjuvant therapy with sintilimab combined with carboplatin and paclitaxel liposome reached 22.2%, which was higher than that of previously reported neoadjuvant chemotherapy (6.4%) (32) and similar to the two previous studies of neoadjuvant PD-1 blockade combined with chemotherapy (33%, 25%) (36, 37). We were pleasantly surprised to find that ESCC patients located in the mid-thoracic segment were associated with a more significant pathological response rate, which may be related to the shorter lesion length and lower lymph node stage at baseline in these patients compared with lower segment ESCC patients.We mainly consider the following reasons for the difference in PCR rate between this study and the CROSS study: 1), the addition of radiotherapy in the CROSS study brought better local control; 2), the patients enrolled in the CROSS study had a relatively early tumor stage (stage II or III), meanwhile, 11% of stage IVA patients were included in our study. It was also found in our study that obtaining MPR after neoadjuvant therapy was associated with better survival outcomes. However, whether this could translate into long-term survival benefits requires further research.

In ESCC studies, meta-analysis showed that clinical indicators such as NLR, PLR, LMR, and SII had moderate predictive value for prognosis (38), yet their potential prediction ability of therapeutic efficacy, especially in connection to immunotherapy, remains rarely documented. In our *post hoc* exploratory analysis, we found that

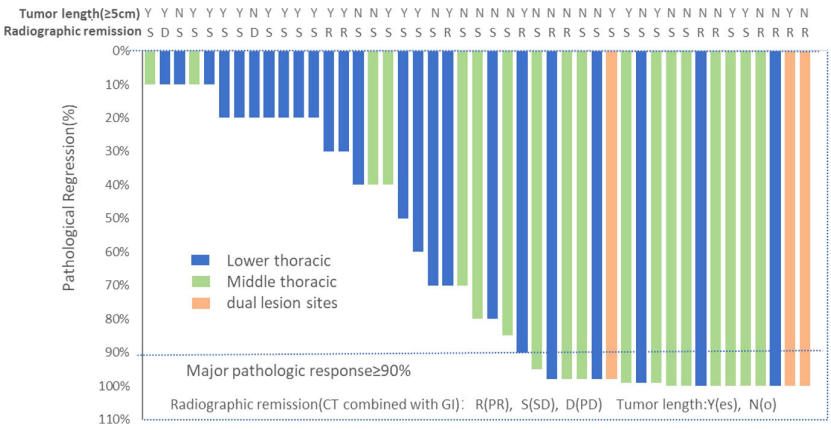

FIGURE 3
Waterfall plot of pathological tumor regression in the population (N=45). Each bar represents one patient. The upper column shows clinical characteristics and radiological responses.

serum inflammatory indexes at baseline in patients appeared to be predictors of pathological response. The model we constructed is easily applicable for clinical practice at no additional cost. Further verification is required to assess whether combining these inflammatory markers results in better predictive performance.

The significance of PD-L1 expression level in tumor immunotherapy has always been a research hotspot. According to the newly published ORIENT-15 study results (13), regardless of the level of PD-L1 expression, sintilimab combined with chemotherapy has benefits in the whole population, including the population with negative PD-L1 expression, so PD-L1 detection is considered non-essential. In addition, according to previous studies on the use of PD1 inhibitors in neoadjuvant therapy for esophageal squamous cell carcinoma, there was no significant correlation between PD-L1 expression and pathological response (39, 40), so the determination of PD-L1 level in tumor tissue was not mandatory in our study design. However, the guiding value of PD-L1 expression level in immunotherapy has always been recognized, and it is worthy of further exploration in subsequent large-sample studies.

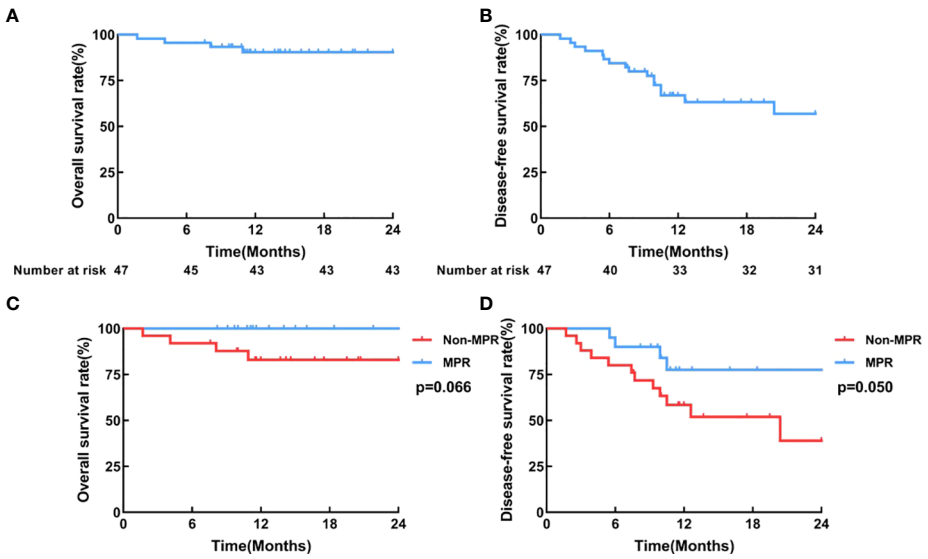

FIGURE 4
Survival curves. **(A)** Overall survival, **(B)** Disease-free survival curve of all patients who received surgery (N=45); **(C)** Overall survival, **(D)** Disease-free survival curves of the MPR group (n=20) and the non-MPR group (n=25).

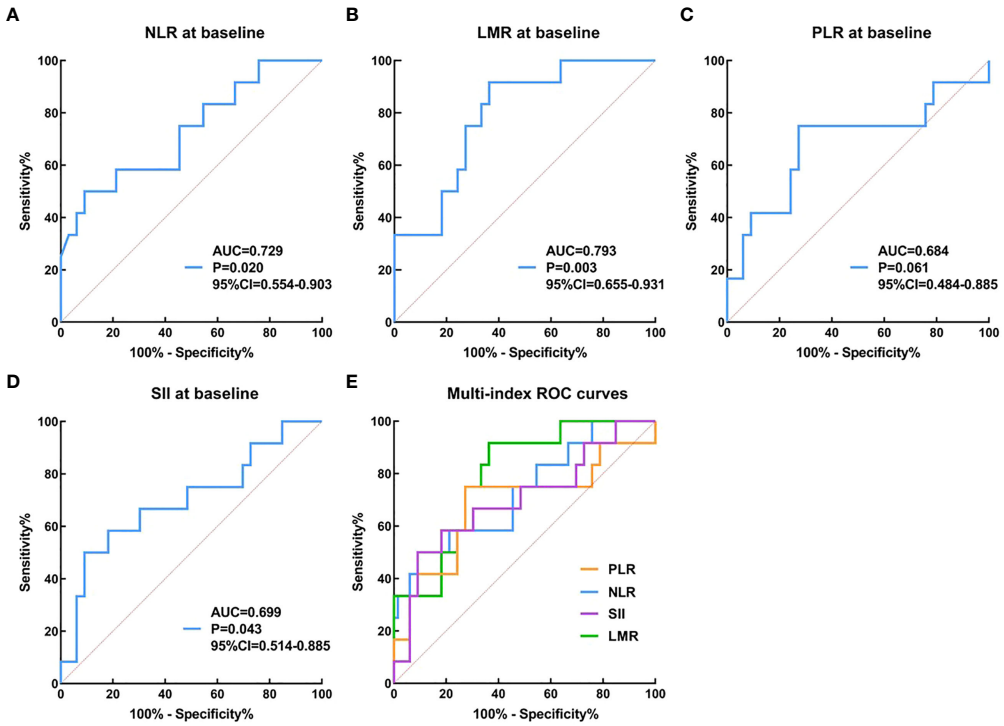

FIGURE 5
The prediction ability of serum inflammation indexes to distinguish pathological efficacy. **(A–E)**: the therapeutic efficacy was categorized into pathological tumor regression grades 0, 1, and 2 (response) and grade 3 (no response or poor response).

Limitations

There are some limitations to this study. First, because of this study being an exploratory pilot study, the number of enrolled patients was small and Interfering factors have a significant impact. Therefore, our findings and the survival data need to be interpreted with caution. Second, the follow-up time was short and longer follow-ups are needed to assess whether neoadjuvant immunochemotherapy can provide long-term survival benefits for patients. Third, indeed, as a taxane drug, paclitaxel liposome has its advantages, but due to its limited availability, the application of the results derived from this study to other parts of the world requires caution. Further investigation into the optimal duration of treatment and predictor of pathological response should be given more attention.

Conclusions

In general, for patients with operable esophageal squamous cell carcinoma, neoadjuvant sintilimab combined with chemotherapy followed by radical surgery is feasible and safe. With a high proportion of patients obtaining a pathological complete response, this regimen has favorable antitumor efficacy and is worthy of further test in a large sample prospective study.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Jiangsu Cancer Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GZ, KZ, ZZ, JY, and HL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JY, ZZ, GZ, and KZ. Acquisition, analysis, or interpretation of data: HL, JY, DA. Drafting of the manuscript: HL, JY, ZZ. Critical revision of the manuscript for important intellectual content: JY, ZZ, HL, GZ, KZ, DG, MD, DA, WC, YF, XX, CB. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1031171/full#supplementary-material

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Neoadjuvant immunotherapy for resectable esophageal cancer: A review

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Esophageal cancer (EC) is one of the most common cancers worldwide, especially in China. Despite therapeutic advances, the 5-year survival rate of EC is still dismal. For patients with resectable disease, neoadjuvant chemoradiotherapy (nCRT) in combination with esophagectomy is the mainstay of treatment. However, the pathological complete response (pCR) rate to nCRT of 29.2% to 43.2% is not satisfactory, and approximately half of the patients will develop either a locoregional recurrence or distant metastasis. It is, therefore, necessary to explore novel and effective treatment strategies to improve the clinical efficacy of treatment. Immunotherapy utilizing immune checkpoint inhibitors (ICIs) has significantly changed the treatment paradigm for a wide variety of advanced cancers, including EC. More recently, increasing clinical evidence has demonstrated that neoadjuvant immunotherapy can potentially improve the survival of patients with resectable cancers. Furthermore, accumulating findings support the idea that chemotherapy and/or radiotherapy can activate the immune system through a variety of mechanisms, so a combination of chemotherapy and/or radiotherapy with immunotherapy can have a synergistic antitumor effect. Therefore, it is reasonable to evaluate the role of neoadjuvant immunotherapy for patients with surgically resectable EC. In this review, we discuss the rationale for neoadjuvant immunotherapy in patients with EC, summarize the current results of utilizing this strategy, review the planned and ongoing studies, and highlight the challenges and future research needs.

KEYWORDS

esophageal cancer (EC), immune checkpoint inhibitor (ICI), immunotherapy, neoadjuvant therapy, chemotherapy, radiotherapy

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality worldwide, with approximately 544,000 deaths from EC in 2020 (1). In contrast to Western countries, esophageal squamous cell carcinoma (ESCC) accounts for approximately 90% of EC cases in East Asia (1, 2). Surgery remains the mainstay for

the treatment of early-stage EC. However, most patients with EC are already in a locally advanced stage at the time of diagnosis, and surgery alone has a limited effect, with a 5-year survival rate of only 25% (3). For resectable locally advanced EC, neoadjuvant chemoradiotherapy (nCRT) could improve survival compared to surgery alone (4, 5). Therefore, preoperative nCRT followed by surgery has become the standard of care for these patients (6). However, nearly half of patients still develop local recurrence or distant metastases after surgery (4). It is therefore necessary to explore novel and effective treatments to improve survival.

In recent years, immune checkpoint inhibitors (ICIs) have made significant advances in a variety of tumors (7, 8). In EC, the KEYNOTE-181 study showed that compared with chemotherapy, pembrolizumab demonstrated a longer overall survival (OS, 6.7 vs. 9.3 months), a higher objective response rate (ORR, 7.4% vs. 16.7%) and a lower incidence of grade 3-5 adverse events (AEs, 40.9% vs. 18.2%) as 2nd-line treatment (9). In addition, the RATIONALE-302 (10), ATTRACTION-3 (11) and ESCORT studies (12) all showed positive results in similar populations. The latest results from the JUPITER-06 (13), CheckMate 648 (14), ORIENT-15 (15), ESCORT-1st (16) and KEYNOTE-590 (17) studies showed that treatment of patients with advanced EC with programmed death 1 (PD-1) inhibitors plus chemotherapy as 1st-line therapy resulted in significantly longer OS and progression-free survival (PFS) than chemotherapy alone. These results suggest that ICIs have promising prospects for EC treatment.

Currently, ICI neoadjuvant therapy has been tried in a variety of tumors, such as lung cancer (18, 19), melanoma (20–23), bladder cancer (24), colon cancer (25) and glioblastoma (26, 27). ICI neoadjuvant therapy for EC is also being actively explored. In this review, we will describe the rationale for ICI neoadjuvant therapy in EC, the reported outcomes, the planned and ongoing studies, the unresolved issues, and the directions for future research.

Rationale of neoadjuvant therapy

Biological basis of EC

Antitumor immune responses can be driven by mutation-associated neoantigens that are recognized as nonself-foreigners by T cells that have escaped negative selection during T-cell development (28). Tumor mutational burden (TMB) is a prototype measure of tumor foreignness that reflects the diversity of neoantigens (28). Therefore, a high TMB is positively correlated with the efficacy of ICIs (29–32), and the US Food and Drug Administration approved TMB as a companion diagnostic biomarker as an indication for using the PD-1 inhibitor pembrolizumab to treat patients with unresectable or metastatic solid tumors. The genomic aberrations in EC have been comprehensively studied (33–38), and a high TMB occurs in most cases of EC (39, 40). In addition, programmed cell death-ligand 1 (PD-L1) is widely expressed in EC cells and is associated with a poor prognosis (41–43). In a pooled analysis, PD-L1 overexpression was found in 559/1,350 ESCC patients (41.4%) (42). For patients with ESCC, PD-L1 was negatively associated with a pathological complete response (pCR, 13% vs. 32%) after nCRT treatment (44, 45). Furthermore, PD-L1 expression also predicts a high postoperative recurrence rate and low survival rate in ESCC patients (46). Not surprisingly, anti-PD-1 antibodies show good clinical efficacy and safety for the treatment of advanced EC (9–17). It is also reasonable to evaluate the role of ICIs in preoperative treatment.

Actions of ICIs

Anti-PD-(L)1 antibodies block the inhibitory signals between tumor cells and T cells in the tumor microenvironment (TME), reversing the exhausted state of T cells (47–49). Dendritic cells (DCs) originating from primary tumors take up tumor antigens and traffic to tumor-draining lymph nodes, where they present antigens in an ineffective or tolerogenic manner to tumor-specific T cells. Anti-PD-(L)1 antibodies also increase antigen presentation by blocking the inhibitory signals between PD-L1-expressing DCs and T cells, resulting in the "in situ" expansion of tumor-specific T cells. These activated T cells enter the blood circulation or lymphatic vessels and then enter the primary tumor tissue or distant micrometastases to exert antitumor effects. The presence of a primary tumor allows the induction of a broader and stronger T-cell response (48, 49) (Figure 1). In addition, tumor-specific T cells in the blood circulation continue to clear residual tumor cells after surgery (49) (Figure 1). Moreover, preoperative immunotherapy can activate the patient's immune system to form immune memory cells (50), enabling the immune system to play an immune surveillance role (47–49) (Figure 1). Compared with adjuvant immunotherapy, neoadjuvant immunotherapy seems to be more advantageous (47–49). In 2016, researchers validated this idea in mouse models of spontaneously metastatic breast cancer where neoadjuvant therapy was superior to adjuvant immunotherapy in eradicating distant micrometastases (51). In human studies, neoadjuvant immunotherapy has been explored in a variety of tumors, such as lung cancer (18, 52), melanoma (20–23), and glioblastoma (26, 27).

Synergistic effect with radiotherapy

In addition to local effects, radiotherapy sometimes leads to tumor regression in unirradiated lesions, a phenomenon known as the abscopal effect (53–55). Demaria et al. (56) first attributed the abscopal effect to immune-mediated mechanisms, and others also confirmed that radiotherapy could activate the

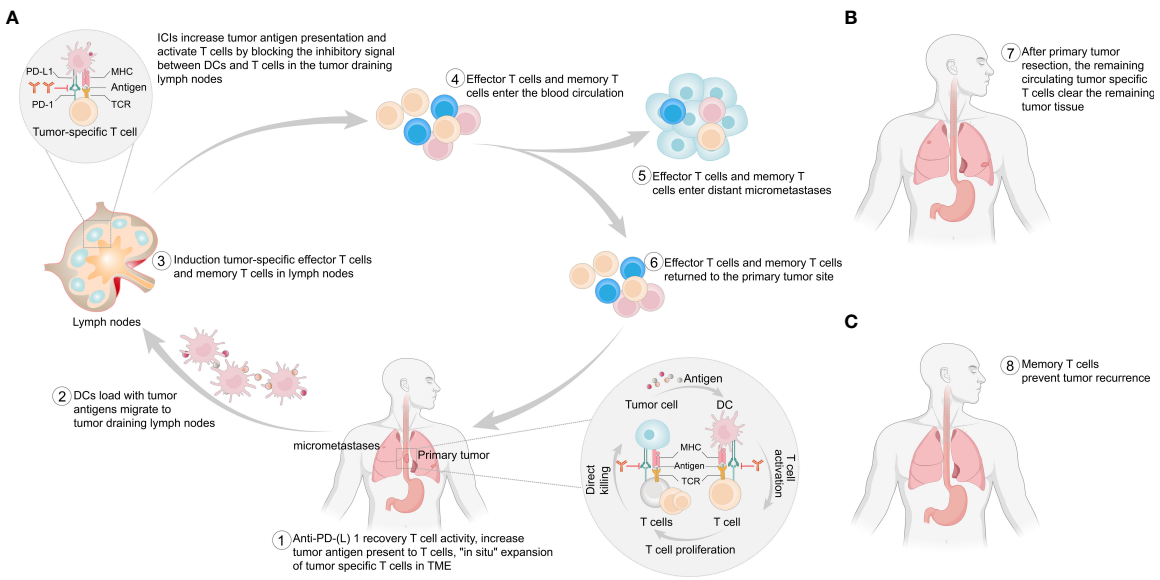

FIGURE 1
Potential mechanism of neoadjuvant immunotherapy. **(A)** This figure provides a stepwise overview of the potential mechanism of the antitumor effect of ICIs in the presence of a primary tumor. **(B)** After surgical removal of the primary tumor, T cells in the blood circulation can continue to exert antitumor effects to clear any remaining tumor cells. **(C)** After surgical removal of the primary tumor, immune memory cells prevent any postoperative recurrence and metastasis. PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; MHC, major histocompatibility complex; TCR, T-cell receptor; TME, tumor microenvironment; DCs, dendritic cells.

body's immune system (57, 58). ICIs block the inhibitory signals between immune cells and tumor cells, increasing the presentation of tumor antigens (47–49). Radiotherapy also modulates the immune system in multiple ways (Figure 2). Radiotherapy induces immunogenic cell death, upregulates chemokines or cytokines, and recruits immune cells to the TME (59–61). Radiotherapy activates the type I interferon response *via* the stimulator of interferon genes pathway. Type I interferon is a well-known mediator of DC recruitment and maturation (62–64). Importantly, radiation therapy serves as an *in situ* vaccine by increasing the release of tumor antigens and the uptake of antigens by DCs (65–67). Last but not least, radiotherapy increases the expression of PD-L1 (59, 68). Although the interactions between ICIs and radiotherapy are not well established, their combination enhances the antitumor effects (69–73), which has been confirmed in preclinical models (59, 73, 74). In patients with EC, this combination is now being actively considered as a first-line treatment (75, 76).

Synergistic effects with chemotherapy

Chemotherapy has dual modulatory effects on the immune system. In addition to its well-known immunosuppressive effects, chemotherapy has recently been found to have immune-activating properties (77, 78). Chemotherapy promotes immunogenic cell death and initiates antitumor immune responses (79, 80). Chemotherapy suppresses immunosuppressive cells, activates effector cells, and increases DC and T-cell infiltration (80–86). Chemotherapy kills tumor cells, which releases tumor antigens (87). Both preclinical and clinical studies found that commonly used chemotherapeutic agents, such as oxaliplatin, cisplatin, paclitaxel, and 5-fluorouracil, promote the upregulation of PD-L1 expression in EC and other cancers (86, 88–94). Therefore, chemotherapy is also synergistic with ICIs (Figure 2). In advanced EC, compared with chemotherapy alone, the combination of chemotherapy and ICIs shows clinical and statistical survival benefits (9–17), and this combination has been approved for the treatment of a variety of tumors (82).

In summary, ICIs exert antitumor effects by modulating the body's immune system instead of killing tumor cells directly. In accumulating studies, durable tumor control was achieved with better effects than traditional chemotherapy and/or radiotherapy (95–98). This unique mechanism provided the rationale for neoadjuvant immunotherapy, whereby long-term survival is expected. It is theoretically feasible to combine chemotherapy and/or radiotherapy with ICIs for neoadjuvant treatment of locally advanced resectable EC.

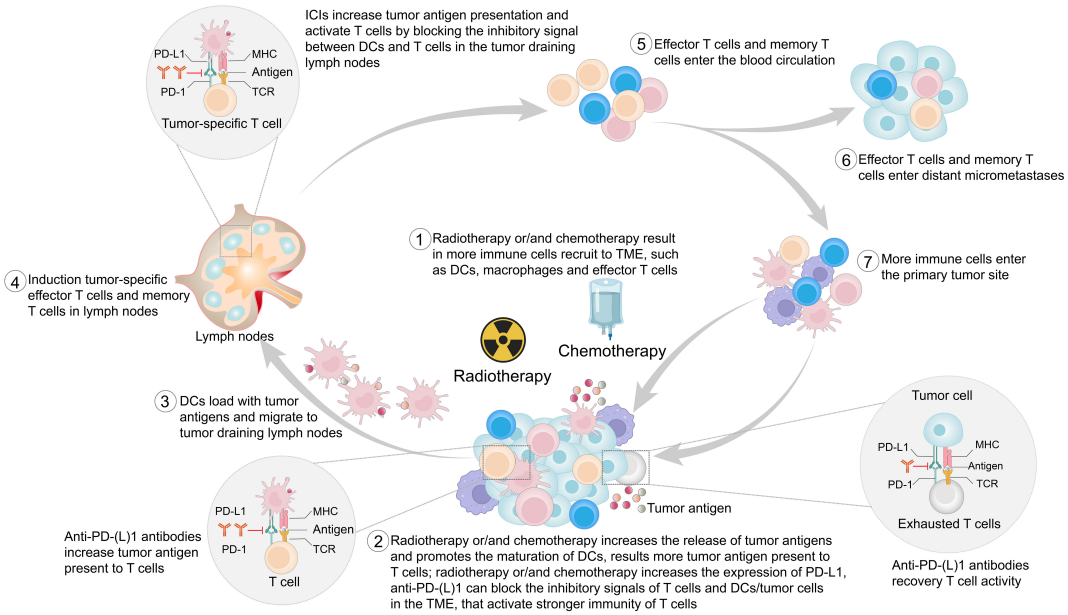

FIGURE 2
This figure provides a stepwise overview of the potential mechanism of the synergistic antitumor effect of immune checkpoint inhibitors (ICIs) combined with radiotherapy and/or chemotherapy. PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; MHC, major histocompatibility complex; TCR, T-cell receptor; TME, tumor microenvironment; DCs, dendritic cells.

Clinical studies

Reported clinical studies

Multiple clinical trials have explored the efficacy and safety of immunotherapy against resectable EC in the neoadjuvant setting (Table 1, Figure 3). Initially, clinical trials examined neoadjuvant immunotherapy plus chemoradiotherapy (CRT) (99, 100), and recent trials have evaluated neoadjuvant chemoimmunotherapy (101–112) and neoadjuvant immunotherapy plus antiangiogenic therapy (113). Current reported clinical trials on neoadjuvant immunotherapies are mainly single-arm studies with small samples. Most of them were conducted in China and were directed against ESCC.

Efficacy

The efficacy outcomes are graphically summarized in Figure 3. Among the 15 included studies, 13 evaluated the radiologic response with the Response Evaluation Criteria in Solid Tumors (RECIST) (99, 101–111), with the ORR fluctuating from 49.0% to 100% and the disease control rate (DCR) fluctuating from 87.5% to 100% (Figure 3). All of these studies reported R0 resection rates ranging from 80.5% to 100.0%.

The pCR rate was reported by all studies, and 10 of 15 reported the major pathological response (MPR) rate. Five studies did not report MPR (100, 101, 104, 105, 108). The addition of ICI to CRT led to pCR rates of 55.6% and 30.3%, respectively (99, 100), and led to an MPR rate of 89.0% (99) (Figure 3). When neoadjuvant ICI was combined with chemotherapy, different pCR and MPR rates were achieved, with the pCR ranging from 16.7% to 50.0% (101–112) and the MPR from 41.7% to 72.2% (102, 103, 106, 107, 109–112) (Figure 3). Combining chemotherapy with camrelizumab and apatinib led to a pCR rate of 24.1% and an MPR rate of 51.7% (113) (Figure 3). It is noteworthy that 11 of these 15 studies noted that a pCR was defined as the absence of residual tumor in both the primary tumor and lymph nodes (ypT0N0) (99–103, 106–110, 112), whereas the other 4 studies did not explicitly indicate ypT0N0 was required for a pCR (104, 105, 111, 113).

When compared with the classic CROSS (49%) (114) or NEOCRTEC5010 study (43.2%) (4), ICIs combined with chemotherapy showed no significant advantage in the pCR rate. In studies where ICIs were combined with CRT, such as the PALACE-1 study (99), a better pCR of 55.6% was reported. In another PERFECT study (100), a higher pCR in patients with EAC was also reported (30.3% vs. 23% for CRT). Notably, the results of these small-scale preliminary studies were unreliable, and additional large-scale studies are needed to confirm the efficacy of neoadjuvant immunotherapy in patients with locally advanced resectable EC.

TABLE 1 Reported clinical trials of neoadjuvant immunotherapy for the treatment of resectable esophageal cancer.

	PALACE-1	PERFECT	Shen et al.	ESONICT-1	SIN-ICE	Yang et al.	Xing et al.	Yang et al.	He et al.	NICE	ESONICT-2	NIC-ESCC2019	PEN-ICE	TD-NICE	Wang et al.
Study phase	Ib	II	II	II	Pilot study	Pilot study	II	Pilot study	II	II	II	II	II	II	Ib
Enrolled patients	20	40	28	30	23	16	30	23	20	60	20	56	18	45	30
Pathological type	ESCC	EAC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC
Clinical stage	II-IVA	II-IVA	II-IVA	III-IV	II-IVA	II-IVA	II-IVA	II–III	III-IVa	III-IVA	III-IVA	II-IVA	II–IVA	II-IVA	II-III
Immune drugs	Pembrolizumab	Atezolizumab	Nivolumab, pembrolizumab, camrelizumab	sintilima	sintilimab	Camrelizumab	Toripalimab	Camrelizumab	Toripalimab	Camrelizumab	Toripalimab	Camrelizumab	Pembrolizumab	Tislelizumab	Camrelizumab
Immune targets	PD-1	PD-L1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1
Chemotherapeutic drugs	carboplatin, paclitaxel	carboplatin, paclitaxel	nab-paclitaxel, carboplatin	albumin-bound paclitaxel, cisplati	Docetaxel/ albumin-bound paclitaxel, nedaplatin	Paclitaxel, carboplatin	Paclitaxe, cisplatin	nab-paclitaxel, carboplatin	Paclitaxel, carboplatin	nab-paclitaxel, carboplatin	Docetaxel, cisplatin	nab-paclitaxel, cisplatin	Platinum-based two-drug	nab-paclitaxel, carboplatin	nab-paclitaxel, nedaplatin, apatinib
Chemotherapy cycle	5, Q1W	5, Q1W	2, Q3W	2, Q3W	3, Q3W	2, Q3W	2, Q3W	2, Q3W	2, Q3W	2, Q3W	2, Q3W	2, Q3W	3, Q3W	3, Q3W	2-4, Q3W
Radiotherapy	23 fractions of 1.8 Gy	23 fractions of 1.8 Gy	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Time from neoadjuvant therapy to surgery	4-6 weeks	1-3 weeks	3-5 weeks	4-6 weeks	4-6 weeks	4 weeks	4-6 weeks	3-6 weeks	4-6 weeks	4-6 weeks	4-6 weeks	6 weeks	4-6 weeks	4-6 weeks	4-8 weeks
Primary endpoints	Safety	Feasibility	Safety, feasibility	pCR, AEs	pCR, safety	pCR	pCR	Safety, feasibility	Safety, feasibility, MPR	pCR	pCR, AEs	pCR	Safety, efficacy	MPR	Safety

ESCC, Esophageal squamous cell carcinoma; EC, Esophagus adenocarcinoma; NA, Not Applicable; pCR, Pathologic complete response; MPR, Major pathological response; AE, Adverse events.

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FIGURE 3
Published clinical studies on immune checkpoint inhibitor (ICI) neoadjuvant therapy in resectable esophageal cancer (EC). **(A)** The radiologic response. **(B)** The pathological response. **(C)** The safety results. ICIs, immune checkpoint inhibitors; CRT, chemoradiotherapy; ORR, objective response rate; DCR, disease control rate; pCR, pathologic complete response; MPR, major pathological response; AEs, adverse events; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; NA, not available.

Safety

The safety results are graphically summarized in Figure 3. The rates of failure to complete neoadjuvant therapy varied from 0% to 15.0%, mainly due to treatment-related AEs (TRAEs) (99, 100, 108), patient decisions (107, 110, 112) or disease progression (100). One study did not report the specific reason for 2 patients not proceeding to the planned neoadjuvant treatment (103). The rates of failure to undergo resection ranged from 0% to 40%. There were various reasons reported for not proceeding to resection: disease progression (99, 100, 102, 103, 105, 108, 111, 112), patient refusal (100–103, 105–112), death (99, 100, 108), TRAEs (105), compromised general condition (110) and dropped out (108). Notably, in the ESONICT-2 study, 8 of 20 patients failed to undergo surgery, 3 patients refused surgery due to symptom relief, and another 5 patients were not suitable for radical surgery, but no specific reasons were reported (109). Surgical delays were reported in 2 of the 15 included studies, and all were attributed to TRAEs (108). The rates of patients experiencing surgical delay were 15.7% (108) and 17.2% (113), respectively.

In the two studies that added ICI to CRT, the incidence of grade 3 and higher AEs was 65.0% and 42.5%, respectively (99, 100). Most of these AEs were lymphopenia or gastrointestinal related (i.e., anorexia or nausea) and occurred during the neoadjuvant treatment period (99, 100). During neoadjuvant treatment with ICI chemotherapy, reported rates of AEs ranged from 3.0% to 56.7%. Here, the most frequently reported AEs were hematological disorders (101–103, 105–112), followed by gastrointestinal-related (i.e., anorexia, vomiting, diarrhea) (103, 107, 110–112), and immune-related AEs (i.e., enteritis, hyperthyroidism, dermatitis) (105, 109, 110). Rash (101, 110), pneumonia (105, 108), alopecia (103, 111), fatigue (107, 111), fever (108) and blurred vision (108) have been reported in only a few studies. One study reported AEs associated with neoadjuvant therapy; however, these events were not reported in a graded manner (104). The combination of chemotherapy with ICI and apatinib led to 36.7% of patients experiencing grade 3 AEs. No grade 4 or 5 AEs were reported (113).

Registered clinical trials

More clinical trials can be found at ClinicalTrials.gov (Table 2). In most of them, either CRT or chemotherapy is

TABLE 2 Registered clinical trials in ClinicalTrials.gov investigating neoadjuvant immunotherapy for the treatment of resectable esophageal cancer.

Neoadjuvant treatment protocol	NCT Number	Pathological type	Phase	Intervention	Sample size	Primary endpoint	Status
ICIs+CRT	NCT05357846	ESCC	3	Tislelizumab/Paclitaxel/Cisplatin /Radiation	422	OS	Not yet recruiting
	NCT05323890	ESCC	2	Tislelizumab/ Albumin paclitaxel/Cisplatin/ Radiation	15	MPR, pCR	Recruiting
	NCT05043688	ESCC	2	SHR-1210/Albumin paclitaxel/Carboplatin/ Radiation	204	pCR	Not yet recruiting
	NCT04974047	ESCC	2	Tislelizumab/Paclitaxel/Cisplatin/Radiation	65	pCR	Recruiting
	NCT04973306	ESCC	2/3	Tislelizumab/Paclitaxel/Carboplatin/ Radiation	176	pCR, OS	Recruiting
	NCT04888403	ESCC	2	Toripalimab/Albumin paclitaxel/Nedaplatin/ Radiation	45	pCR	Not yet recruiting
	NCT04776590	EC	2	Tislelizumab/Albumin paclitaxel/Caboplatin/ Radiation	30	pCR	Recruiting
	NCT04644250	ESCC	2	Toripalimab/Paclitaxel liposome/ Carboplatin/Radiation	32	pCR	Recruiting
	NCT04568200	ESCC	2	Durvalumab/Paclitaxel/Carboplatin/ Radiation	60	Tumor and pathological response	Recruiting
	NCT04437212	ESCC	2	Toripalimab/Paclitaxel/Cisplatin/Radiation	20	MPR	Recruiting
	NCT04435197	ESCC	2	Pembrolizumab/Carboplatin/Paclitaxel/ Radiation	143	pCR	Recruiting
	NCT04177875	EC	2	Teripalimab/Docetaxel or albumin paclitaxel/Cisplatin/Radiation	44	MPR/ORR	Recruiting
	NCT03792347	ESCC	2	Pembrolizumab/Paclitaxel/Carboplatin/ Radiation	143	pCR	Recruiting
	NCT03544736	EC	1/2	Nivolumab/Paclitaxel/Carboplatin/Radiation	30	TEAE	Recruiting
	NCT03490292	EC/GEC	1/2	Avelumab/Paclitaxel/Carboplatin/Radiation	24	DLTs/pCR	Recruiting
	NCT03064490	EGC	2	Pembrolizumab/Paclitaxel/Carboplatin/ Radiation	38	pCR	Recruiting
	NCT03044613	EC/GC/EGC	1	Nivolumab/Relatlimab/Carboplatin/ Paclitaxel/Radiation	25	TRAE	Recruiting
	NCT02844075	ESCC	2	Pembrolizumab/Taxol/Carboplatin/ Radiation	18	pCR	Active, not recruiting
ICIs+Chemo	NCT05476380	ESCC	2	Camrelizumab/Paclitaxel/Cisplatin	39	pCR	Recruiting
	NCT05302011	ESCC	2	Pembrolizumab/Docetaxel/Carboplatin or Cisplatin	30	Tumor and pathological response	Recruiting
	NCT05281003	ESCC	2	Pembrolizumab/Paclitaxel/Cisplatin	128	pCR	Not yet recruiting
	NCT05244798	ESCC	3	Tislelizumab/Albumin paclitaxel/Cisplatin Tislelizumab/Albumin paclitaxel/Cisplatin/ Radiation	360	pCR	Not yet recruiting
	NCT05213312	ESCC	2/3	Nivolumab/Paclitaxel or 5Fluorouracil/ Cisplatin	90	pCR	Recruiting
	NCT05189730	ESCC	2	Tislelizumab/Paclitaxel/Cisplatin	80	pCR, AEs	Recruiting
	NCT05182944	ESCC	2	Camrelizumab/Albumin paclitaxel/Cisplatin	130	pCR, DFS	Recruiting
	NCT05174325	ESCC	2	Sintilimab/Albumin paclitaxel/Cisplatin	30	pCR	Recruiting
	NCT05050760	ESCC	NA	Camrelizumab/Oxaliplatin/Docetaxel/ Tegafur	55	Safety, Feasibility	Not yet recruiting
	NCT05028231	ESCC	NA	PD-1 or PD-L1/Chemotherapy	46	pCR	Recruiting
	NCT04937673	ESCC	2	Camrelizumab/Albumin paclitaxel or paclitaxel/Cisplatin	40	Biomarkers related to pCR	Not yet recruiting
	NCT04848753	ESCC	3	Toripalimab/Paclitaxel/Cisplatin	500	EFS	Recruiting
	NCT04844385	ESCC	2	Toripalimab/Albumin paclitaxel/Nedaplatin	83	2-year PFS rate	Recruiting

(Continued)

TABLE 2 Continued

Neoadjuvant treatment protocol	NCT Number	Pathological type	Phase	Intervention	Sample size	Primary endpoint	Status
	NCT04813523	GEJAC	2	Pembrolizumab/5Fluorouracil /Cisplatin/	30	MPR	Recruiting
	NCT04807673	ESCC	3	Pembrolizumab/Paclitaxel/Cisplatin	342	EFS	Recruiting
	NCT04804696	ESCC	2	Toripalimab/Paclitaxel/Cisplatin	53	pCR	Recruiting
	NCT04767295	ESCC	2	Camrelizumab/Albumin paclitaxel/ Carboplatin	28	ORR	Recruiting
	NCT04625543	ESCC	2	Sintilimab/Paclitaxel/Cisplatin	100	MPR	Not yet recruiting
	NCT04506138	ESCC	1/2	Camrelizumab/Albumin paclitaxel/ Carboplatin	46	pCR/MRP	Recruiting
	NCT04460066	EC	1/2	Anti-PD-L1 antibody/Albumin paclitaxel/ Cisplatin	70	MPR	Not yet recruiting
	NCT04389177	ESCC	2	Pembrolizumab/Carboplatin/Paclitaxel	50	MPR	Recruiting
	NCT04280822	EC	3	JS001/Paclitaxel/Cisplatin	400	3 years EFS/5 years EFS	Recruiting
	NCT04221555	GAC/GEJAC	2	Durvalumab/Docetaxel/Oxaliplatin/S-1	68	pCR	Recruiting
	NCT04006041	ESCC	2	Toripalimab/Paclitaxel/Cisplatin	44	pCR	Recruiting
	NCT03946969	ESCC	1/2	Sintilimab/Liposomal paclitaxel/Cisplatin/S-1	40	TEAE	Recruiting
	NCT03917966	ESCC	2	SHR-1210/Docetaxel/Nedaplatin	40	ORR/MPR	Recruiting
	NCT03914443	ESCC	1	Nivolumab/5Fluorouracil /Cisplatin/ Docetaxel	36	DLTs	Active, not recruiting
	NCT03448835	GC/GEJC	2	Atezolizumab/Capecitabine/Oxaliplatin/ Docetaxel	20	AE	Recruiting
ICIs alone	NCT04215471	ESCC	2	Anti-PD-L1 antibody SHR-1316	30	OR	Not yet recruiting
	NCT04196465	EC/GC/Liver Cancer	2	Anti-PD-L1 antibody IMC-001	48	MPR	Recruiting
	NCT03987815	ESCC	2	Nivolumab	20	MPR	Recruiting
	NCT02735239	EC	1/2	Durvalumab	75	AE/DLT	Active, not recruiting
ICIs+Radiation	NCT05176002	ESCC	1/2	Camrelizumab/Radiation	26	MPR, AEs	Recruiting
	NCT03200691	ESCC	2	Anti-PD-1 antibody SHR-1210/Radiation	21	pCR	Unknown status
ICIs+CRT+Multi-targeted inhibitor	NCT04929392	EC/GEC	2	Pembrolizumab/Paclitaxel/Carboplatin/ Radiation/Lenvatinib Mesylate	24	pCR, cCR	Recruiting
ICIs+Chemo+ Multi-targeted inhibitor	NCT04757363	EGC	2	Nivolumab/Regorafenib/Oxaliplatin/ Leucovorin/ 5-FU	35	6-month PFS	Recruiting
	NCT04666090	ESCC	2	Carillizumab/Albumin paclitaxel/ Nedaplatin/Apatinib	38	MPR	Recruiting
ICIs+CRT+anti-EGFR antibody	NCT05355168	ESCC	1/2	Camrelizumab/Nimotuzumab/ Chemoradiotherapy	57	pCR, MPR	Recruiting
Dual ICIs+CRT	NCT03776487	GC/GAC/GEJAC	1/2	Ipilimumab/Nivolumab/5Fluorouracil/ Oxaliplatin/Radiation	30	AE	Recruiting

AE, Adverse events; cCR, clinical complete response; DLT, Dose limiting toxicity; EC, Esophagus cancer; EGC, Esophagogastric cancer; EGFR, Epidermal growth factor receptor; EFS, Event free survival; ESCC, Esophageal squamous cell carcinoma; GAC, Gastric adenocarcinoma; GC, Gastric cancer; GEJAC, Gastroesophageal junction adenocarcinoma; MPR, Major pathological response; NA, Not Applicable; OR, Objective response; ORR, Objective remission rate; pCR, Pathologic complete response; PFS, Progression free survival; TEAE, Treatment emergent adverse events; TRAE, Treatment-related adverse events.

adopted in combination with ICI. In others, ICI is used alone (NCT04215471, NCT04196465, NCT03987815, NCT02735239), combined with radiotherapy (NCT05176002, NCT03200691), combined with both multitargeted small molecule inhibitors and CRT or chemotherapy (NCT04929392, NCT04757363, NCT04666090), combined with both CRT and anti-EGFR antibody (NCT05355168), or used in combination with another ICI and CRT (NCT03776487).

In addition to these phase 2 studies, several phase 3 studies deserve special attention. Hong et al. designed a randomized

controlled trial (RCT) to compare PD-1 inhibitors combined with preoperative CRT versus neoadjuvant CRT for locally advanced ESCC (NCT05357846). The KEYSTONE-002 study was designed to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy for preoperative neoadjuvant therapy and then the continued use of pembrolizumab as adjuvant therapy postoperatively compared with neoadjuvant CRT and surgery for locally advanced ESCC (NCT04807673). Two other studies are comparing the efficacy of neoadjuvant chemotherapy combined with immunotherapy versus neoadjuvant chemotherapy in resectable ESCC (NCT04848753, NCT04280822). Immunotherapy plus neoadjuvant chemotherapy versus immunotherapy plus neoadjuvant CRT is also being studied (NCT05244798).

In summary, neoadjuvant chemoradiotherapy remains the standard treatment for locally advanced esophageal cancer, and neoadjuvant immunotherapy is in the clinical trial stage. No indications for neoadjuvant immunotherapy are currently authorized.

The challenges

Neoadjuvant immunotherapy in EC is still in its infancy, and many unanswered questions remain. Here, we summarize the challenges and future directions (Figure 4).

AEs

ICIs might cause specific toxicity profiles, i.e., immune-related AEs, different from those of chemo- or radiotherapy (70, 115). In addition, when combination therapy is adopted, the type and severity of TRAEs might be more complex (70, 116). The PACIFIC study reported a higher incidence of treatment discontinuation due to AEs in the ICI plus CRT group than in the CRT alone group (15.4% vs. 9.8%) (117). In a meta-analysis including 3,144 patients, ICIs plus chemotherapy had a significantly higher incidence of AEs in non-small cell lung cancer (NSCLC) (118). Similarly, the CheckMate 648 study reported that patients with advanced

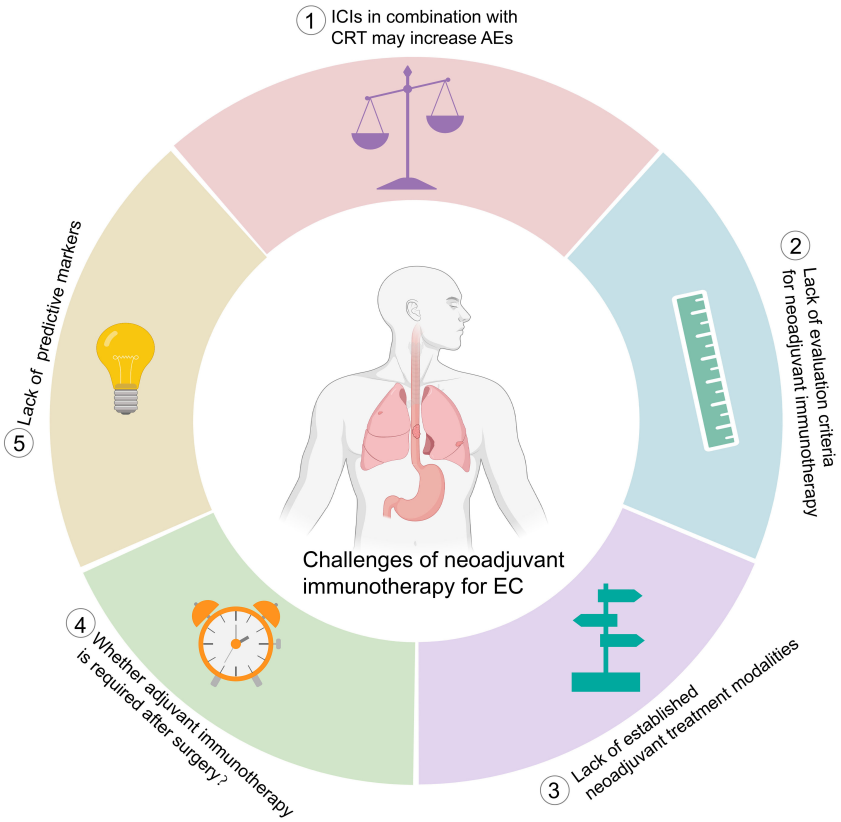

FIGURE 4
Challenges of neoadjuvant immunotherapy for esophageal cancer. ICIs, immune checkpoint inhibitors; CRT, chemoradiotherapy, AEs, adverse events; EC, esophageal cancer.

ESCC treated with nivolumab plus chemotherapy had a higher incidence of grade 3-4 TRAEs than those treated with chemotherapy alone (47% vs. 36%) (14).

In neoadjuvant immunotherapy for EC, a combination of CRT with ICIs increased the pCR rate, but the incidence of grade 3 or worse AEs was high, and deaths during treatment were reported (99, 119). In the PALACE-1 study, one patient died of esophageal hemorrhage while awaiting surgery (99). In another phase II clinical study (NCT02844075), among the 26 patients who underwent surgery after treatment with pembrolizumab and CRT, 2 patients died of acute lung injury after surgery (119). In radiation-free therapies, although the grade 3-4 AE rate was decreased (120), treatment-related surgical delay was reported (108). In the NICE study, surgery was delayed by a median of 19 days due to AEs (108).

The current available toxicity data were all collected from single-arm studies with limited numbers of patients. Large randomized controlled studies are warranted to establish the safety of ICI neoadjuvant treatment of EC. From the above reports, lung injury is a concern when CRT and ICIs are used concurrently. In clinical practice, the extent of cancer lesions or lymph node metastases and the dose of radiation delivered to the lungs should be clearly defined for patients receiving CRT in combination with ICIs. In addition, delayed toxicities remain elusive due to insufficient follow-up.

Response evaluation

Pathologic response is the most common surrogate endpoint for relapse-free survival and OS in cancer neoadjuvant therapy (48). pCR is defined as the absence of any viable tumor in the surgically resected specimens and all sampled lymph nodes (121). MPR, described as ≤10% of residual viable tumor (RVT) in a surgically resected specimen, has been proposed as an alternative parameter (122). To date, pCR and MPR are the most commonly used metrics for assessing the response to neoadjuvant immunotherapy. However, other criteria for pathological assessment have been used for EC. In the PERFECT study, the pathologic response was assessed according to Mandard's tumor regression grade score (100).

It is highly appreciated when the pathological response is reported in a uniform and reproducible manner to allow for valid cross-study comparisons. However, the pathological response criteria that were developed for chemotherapy and/or radiotherapy may not be suitable for neoadjuvant immunotherapy. In addition, OS was reported to be correlated with the response spectrum of RVT, implying that if assessments beyond pCR and MPR could be performed, prognostication could potentially be available for all patients (123, 124).

Recently, immune-related pathologic response criteria (irPRC) have been developed, that is, scoring 0 to 100% irRVT in 10% intervals (125). This approach, first described for neoadjuvant anti-PD-1 monotherapy in NSCLC (18), has been extended to other tumor types and combination treatment regimens (126). %irRVT =viable tumor area/total tumor bed area, whereby the total tumor bed=regression bed +RVT+ necrosis. The regression bed is defined as the area of immune-mediated tumor clearance characterized by tumor-infiltrating immune cells, tumor cell death with cholesterol clefts, and hallmarks of tissue repair, such as neovascularization and proliferative fibrosis (125). Currently, irPRC has not been adopted in EC, and more studies are needed to confirm the prognostic value of %irRVT.

Additionally, neoadjuvant immunotherapy may bring difficulties to radiological response evaluation since the tumor regression pattern seems different from what may happen during chemo- or radiotherapy. Radiographic responses such as pseudoprogression or a delayed response to immunotherapy have been frequently reported (127–129) and are expected during the neoadjuvant immunotherapy of EC. However, no such observations were reported in the 15 included studies. None of the studies reported any mismatch between the radiological and pathological responses. Whether this was due to the limited number of patients is unknown. We predict that as more studies related to neoadjuvant immunotherapy become available, such discrepancies in the radiological response between immunotherapy and chemotherapy and/or radiotherapy will be revealed. This will pose a challenge in the near future.

Treatment modalities

In neoadjuvant immune combination therapy, the chemotherapy regimens were mainly paclitaxel and platinum (99, 100, 111, 112) (Figure 3). Chemotherapy was administered weekly for 5 weeks in neoadjuvant therapy with CRT and ICIs (99, 100, 119, 130, 131). In neoadjuvant therapy using ICIs and chemotherapy, preoperative treatment was generally administered every 3 weeks for 2 cycles (101–110). However, a higher pCR and MPR were achieved in two studies that used 3 cycles of treatment (111, 112).

Theoretically, chemotherapy may induce lymphopenia and selectively deplete immunosuppressive cells (80), while ICI therapy may result in the proliferation of tumor-specific T cells (48). Therefore, ICI therapy applied after chemotherapy may allow for the proliferation of effector T cells and reduce the possibility of killing tumor-specific T cells with the chemotherapeutic drugs, producing better antitumor efficacy. In a retrospective study, ICIs used 1-10 days after chemotherapy was superior to ICIs used before or concurrent with chemotherapy in patients with refractory lung cancer (132). In addition, Xing et al. (105) showed that in neoadjuvant treatment of EC, sequential immunotherapy after chemotherapy was more effective than concurrent chemo-immunotherapy.

From these reported results, ICI combined with CRT achieved higher rates of pCR and MPR over chemotherapy (120). It should be kept in mind that the results from these small-scale preliminary studies are unstable and inconclusive. Whether pCR from variant treatment modalities could be translated into improved survival remains largely unknown. The most suitable treatment modality for neoadjuvant therapy has yet to be determined. It was interesting to see other treatment modalities such as ICI in combination with radiotherapy (NCT05176002, NCT03200691), kinase inhibitors (NCT04929392, NCT04757363, NCT04666090), or ICIs alone (NCT04215471, NCT04196465, NCT03987815, NCT02735239) are being evaluated in different trials, in addition to the mainstream CRT or chemotherapy combination (Table 1).

Adjuvant immunotherapy

In the NADIM study, patients with resectable stage IIIA NSCLC received neoadjuvant treatment with platinum-based chemotherapy plus nivolumab before surgical resection, followed by adjuvant nivolumab monotherapy for 1 year. This study showed that the treatment regimen was well tolerated, and at 24 months, the PFS was 77% and the OS was 90% (19). Based on the results of the NADIM study, several ongoing phase III clinical studies of lung cancer (KEYNOTE 617, IMPOWER 030, AEGEAN) or breast cancer (KEYNOTE-522) are evaluating patients receiving ICIs neoadjuvant therapy followed by 1 year of ICIs after surgery. Similar studies are underway in the EC (NCT05213312, NCT05189730, NCT05182944, NCT04813523, NCT02844075, KEYSTONE-002). In a phase II clinical study (NCT02844075), ESCC patients received neoadjuvant immunotherapy, followed by surgery and immunotherapy for 2 years. The preliminary results of this study showed that at a median follow-up of 11.7 months, the median OS was not reached and the 6- and 12-month OS rates were 89.3% and 82.1%, respectively (119).

Theoretically, postoperative adjuvant ICI therapy is a reasonable option to prevent postoperative recurrence and metastasis. However, there are some issues that deserve our attention. As one example, in patients with HER2-positive early-stage breast cancer, neoadjuvant anti-HER2 therapy plus chemotherapy followed by surgery and adjuvant therapy with anti-HER2 therapy was beneficial only for patients without a pCR (133). These results prompted us to think that adjuvant therapy could be less relevant in selected populations, such as patients with a pCR (134). Among the ongoing clinical studies of neoadjuvant immunotherapy for EC, two studies are applying adjuvant treatment only for patients who have not achieved a pCR (NCT05213312, NCT05189730); in the KEYSTONE-002 study and the NCT04813523 study, postoperative adjuvant therapy is being administered to all patients; and in the NCT05182944 study, different adjuvant therapy is being used for patients with pCR and non-PCR. It remains unknown whether all patients should receive ICIs after surgery.

Additionally, prolonged use of ICIs may lead to increased AEs. In mouse tumor models, compared with mice given 2 doses of neoadjuvant immunotherapy, mice treated with 2 doses of neoadjuvant immunotherapy plus 4 adjuvant immunotherapy did not display any significant increase in OS but they did have an increase in immune-related AEs (135). Furthermore, the optimal treatment interval and duration of adjuvant ICIs related to treatment compliance and financial toxicity also represent significant challenges (134). The duration of adjuvant therapy in current clinical studies is very inconsistent. Of note, the half-life of most anti-PD-1 antibodies is 12-20 days regardless of the dose (136), suggesting a longer interval between adjuvant anti-PD1 doses might be optimal. All in all, the development of a postoperative adjuvant treatment strategy must be based on a comprehensive assessment of the survival benefit, treatment compliance, and the toxicities and side effects.

Predictive markers

PD-L1 expression could be used to predict the efficacy of pembrolizumab in advanced EC (9). However, for neoadjuvant therapy, the current data do not support PD-L1 expression as a biomarker in EC (99, 100, 103, 105–108, 110, 111, 113). Theoretically, the level of CD8+ T infiltration into the TME correlates with the efficacy of immunotherapy, since blocking the PD-1/PD-L1 interaction can restore the tumor-killing effect of exhausted CD8+ T cells (137). However, in neoadjuvant immunotherapy, recent studies showed no significant difference in CD8+ T cells between responders and nonresponders (99, 100, 106, 107). Recently, TCF-1+ CD8+ T cells were found to be precursor exhausted CD8+ T cells with stem cell-like properties, and TCF-1+CD8+ T cells were associated with immunotherapy efficacy (138, 139). The PALACE-1 study revealed that compared with nonpCR patients, there was an increased percentage of TCF-1+ cells in the samples from pCR patients (99). These findings are consistent with recent reports (139–141).

Genomic analysis showed that in some studies, TMB was higher in the pCR group compared to the nonpCR group (106, 108). However, He et al. (107) indicated TMB failed to distinguish the two groups. Beyond TMB, immune-related genes have received increasing attention. The PERFECT study found that those who responded to neoadjuvant immunotherapy had a significantly higher IFN-γ score at baseline, while those who did not respond to neoadjuvant immunotherapy had higher expression of ICI resistance-related genes in their tumor tissues despite the presence of cytotoxic T-lymphocyte infiltration (100). He et al. (107) also

found that responders had higher chemokine CXCL5 expression and lower chemokine CCL19 and UMODL1 expression compared with nonresponders.

In summary, TCF-1+ CD8+ T cells, TMB and immune-related genes deserve further exploration in larger-scale clinical studies for predicting the response to neoadjuvant immunotherapy for EC. Going forward, the identification of biomarkers reflecting complex tumor-immune system interactions and immune system-host interactions will help us to identify patients who will truly benefit from neoadjuvant immunotherapy. In addition, although traditional imaging techniques cannot accurately reflect the pathological changes of tumor tissue during neoadjuvant therapy, with advances in imaging technology, particularly positron emission tomography technology, we may be able to label specific immune cells, checkpoint molecules, or markers of metabolic processes associated with the neoadjuvant treatment response or resistance to guide or adjust clinical decision-making (142, 143).

Conclusion

Although the use of immunotherapy for preoperative neoadjuvant therapy versus adjuvant therapy may be theoretically more effective, and neoadjuvant immunotherapy has shown preliminary positive results in resectable EC in some clinical studies, further validation of the feasibility, safety, and efficacy of neoadjuvant immunotherapy in large randomized clinical studies is still needed. In addition, a number of unresolved issues must be addressed before neoadjuvant ICIs strategies can be widely adopted as the standard of care. Identifying predictive biomarkers will be key to selecting appropriate populations, and the role of adding adjuvant therapy must be fully understood. Furthermore, long-term follow-up is needed to determine the long-term outcomes and assess any delayed toxicity. We are confident that neoadjuvant immunotherapy will move forward into a new chapter.

Author contributions

ZD and QL contributed to the conception and design of the review. QL and TL prepared the manuscript draft. ZD revised it critically for important intellectual content and approved the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1051841/full#supplementary-material

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Predictive value of systemic immune-inflammation index for pathological complete response in patients receiving neoadjuvant immunochemotherapy for locally advanced esophageal cancer

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Objectives: Neoadjuvant immunochemotherapy (nICT) has been confirmed with promising pathological complete response (pCR) among locally advanced esophageal squamous cell carcinoma (ESCC). However, there were still no reliable and accurate predictors to predict the treatment response. This study aimed to explore the predictive value of inflammatory and nutritional parameters.
Methods: Patients with ESCC who underwent radical surgery after nICT between January 2020 and April 2022 were included in the study. First, the least absolute shrinkage and selection operator regression (LASSO) logistic regression analysis was used to screen independent inflammatory and nutritional parameters. Secondly, univariate and multivariate logistic regression were used to screen and predict independent risk factors for pCR. Thirdly, a nomogram was constructed based on the independent predictive factors, and 30% of the included population was randomly selected as the validation cohort. We used the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA) curve to evaluate the nomogram model.
Results: A total of 97 ESCC patients were screened for analysis, with 20 patients with pCR (20.32%). Only the systemic immune-inflammation index (SII) was screened after LASSO-logistic regression when λ was 0.06. The cut-off value of SII was 921.80 with an area under curve (AUC) value of 0.62. We defined SII > 921.80 as high SII and SII ≦ 921.80 as low SII. Further, the univariate and multivariate analysis further determined SII(OR = 3.94, 95%CI:1.26–12.42, P = 0.02) and clinical stage(OR = 0.35, 95%CI:0.12–0.98, P = 0.05) were independent predictive factors of pCR. One novel nomogram was established with an AUC value of 0.72 in the training cohort and 0.82 in the validation cohort. The Brier score of the calibration curve was 0.13. The calibration curve showed good agreement between the predicted results and the actual results in both the training cohort and the validation cohort. Compared with the clinical stage, the DCA confirmed a better clinical value of the nomogram model in both the training cohort and the validation cohort.

Conclusions: High pretreatment SII and early clinical stage were independently associated with pCR among ESCC receiving nICT. We further established and validated one novel nomogram model to effectively predict pCR among ESCC after nICT.

KEYWORDS

esophageal squamous cell carcinoma, pathological complete response, systemic immune-inflammatory index, neoadjuvant immunochemotherapy, nomogram model

Introduction

Esophageal cancer is one of the most severe malignant tumors in the digestive system. Its incidence rate and mortality rate rank seventh and sixth among all malignant tumors in the world, respectively (1). China is one of the regions with the highest risk of esophageal cancer. More than 90% of esophageal cancer is squamous cell carcinoma, and the overall 5-year survival rate is less than 30% (2). For patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC), the effect of simple surgical treatment is limited, and the incidence of postoperative recurrence and metastasis is high. Therefore, people put forward the concept of new adjuvant treatment to improve the survival rate of LA-ESCC patients (3).

In recent years, the application of immunotherapy has gradually matured, and many studies have confirmed the good therapeutic effect of neoadjuvant immunotherapy combined with chemotherapy (nICT) in LA-ESCC patients (4,5). Pathological complete remission (pCR) is one of the evaluation indicators of tumor neoadjuvant therapy, which can provide effective prognosis evaluation, postoperative follow-up, and individualized treatment guidance for patients. Preoperative CPS and TPS scores of PD-L1 could not effectively predict the degree of pathological reaction in patients receiving nICTin patients receiving nICT (6). The PALACE study indicated that the expression of PD-L1 wasn't obviously associated with the pathologic regression among patients receiving preoperative pembrolizumab combined with chemoradiotherapy (7). The NICE-2 study presented no significant correlation between PD-L1 expression and pathological response in ESCC patients receiving ocrelizumab and chemotherapy (8). Thus, it's of great significance to find simple and effective indicators to accurately predict the pathological response before treatment.

Previous studies have shown that inflammation plays a crucial role in the occurrence, development, and metastasis of tumors (9). Among many indicators reflecting host systemic inflammatory response, lymphocyte, neutrophil, and platelet counts in peripheral blood have been widely reported to be able to predict postoperative recurrence and long-term survival of patients with various malignant tumors and show a certain clinical application prospect (10–13). Recently, Feng J et al. showed that integrative inflammatory and nutritional score (IINS) before treatment was an independent predictor of pCR in patients with resectable LA-ESCC receiving nICT (14).

However, studies focused on predicting whether patients would achieve pCR were still limited. The purpose of this study was to explore the predictive value of inflammatory and nutritional parameters in the prediction of pCR among ESCC patients receiving nICT. Further, we also aimed to establish a novel nomogram model based on the independent predictive factor and hope to provide a reference for an individualized treatment plan.

Methods

Patient selection

This was a retrospective study based on prospectively collected data. This study was approved by the ethics committee of Fujian Medical University Union Hospital. The ethical approval number was 2022YK202. We conducted this analysis strictly adhering to the Declaration of Helsinki (1964). Consecutive patients who underwent nICT for ESCC after esophagectomy between January 2020 and April 2022 were identified.

Inclusion criteria included: pathological type was ESCC; cT3 + or cN + before treatment; ASA status ≤ III; without clinical signs of distant metastasis; undergoing radical esophagectomy. Exclusion criteria included: Patients who had unresectable tumors or metastases; Patients who received other induction therapy, such as neoadjuvant chemoradiotherapy or neoadjuvant immnochemoradiotherapy, or neoadjuvant chemotherapy.

Treatment protocols

The treatment regimen received by patients in the NICT group was intravenous PD-1 inhibitors (pembrolizumab at a dose of 200 mg, sintilimab at a dose of 200 mg, toripalimab at a dose of 240 mg, tirelizumab at a dose of 240 mg, and camrelizumab at a dose of 200 mg) every three weeks (1 day) in combination with platinum-based chemotherapy and paclitaxel/docetaxel (CF / DF group). Previously we have completed two phase II clinical trials, and the details of neoadjuvant regimens were listed in previously published

articles (15,16). For patients who completed two or three cycles of nICT, we clinically evaluated the patients again to determine whether the patients should undergo esophagectomy or continue the induction treatment. For patients suitable for radical esophagectomy, we conduct thoracoscopically assisted or robot-assisted McKeown minimally invasive esophagectomy (MIE) in 4–6 weeks after the last cycle of neoadjuvant therapy. We performed 2-field lymphadenectomy and used a 3.0–3.5 cm width tube stomach to replace the esophagus. When there were enlarged cervical lymph nodes, we conducted 3-field lymphadenectomy.

Outcome measures

The primary outcome was pathological complete response (pCR), which was defined as no residual tumor in both the primary tumor and lymph nodes. Tumor regression grade (TRG) (modified Ryan scheme) 0 was equal to pCR (17). All specimens were systematically evaluated by an experienced pathologist, and if necessary pathological slides would be evaluated by another pathologist. The 8th AJCC/UICC TNM staging system was applied in this analysis.

The value of inflammatory and nutritional parameters was collected from the medical record system. The Neutrophils (NEU), platelet (PLT), lymphocyte(LY), monocyte (MONO), albumin (ALB), body weight, hemoglobin (HB), and body mass index(BMI) were obtained within one week before nICT. The PLR, NLR, and LMR were defined as PLTs divided by LYs, NEUTs divided by LYs, and LYs divided by MONOs respectively. The hemoglobin albumin lymphocyte platelet (HALP) was calculated as follows: HALP = HB × ALB × LY/PLT. The systemic immune-inflammation index (SII) was calculated as follows: SII = PLT × NEUT/LY. The systemic inflammation response index (SIRI) was calculated as follows: SIRI = MONO × NEUT/LY. The prognostic nutritional index (PNI) was calculated as follows: PNI = ALB (g/L) + 5 × LY (10^9/L) (18).

Statistical analysis

First, the patients were divided into pCR group and non pCR group. We use mean ± standard deviation or median (interquartile distance) to represent continuous data and use numbers (percentage) to represent classified data. Baseline characteristics and postoperative information were compared. Student t-test or Mann Whitney U test was used for continuous variables, and the chi-square test or Fisher exact test was used for categorical variables. Continuous variables were converted into categorical variables according to the best cut-off value of the ROC or clinical experience of the subjects. Secondly, considering there were a total of 18 inflammation and nutrition indicators with potential collinearity of variables, we used the least absolute shrinkage and selection operator regression (LASSO) regression model to screen variables. The principle of LASSO regression screening variables is to compress the regression coefficients of each variable in the form of penalty increment (12). In addition, we also cross-verified the Lasso regression model. Thirdly, the inflammatory and nutritional factors screened by LASSO regression and the baseline clinical variable were analyzed by univariate analysis and multivariate analysis to determine the independent predictive factors. P value < 0.10 in the univariate analysis was put into the multivariate analysis. Fourth, we established one novel nomogram model based on the determined independent predictive factors. We evaluated the nomogram prediction ability through ROC and area under the curve (AUC). The consistency between the predicted results and the actual results was measured with the correction curve, and the clinical value of the Nomogram model was further evaluated with the decision curve analysis (DCA). A total of 30 cases were randomly selected to internally validate the nomogram model using ROC, calibration curve, and DCA curve. We use R software (version 3.6.3) and Python (version 3.7) for statistical analysis. Bilateral P value <0.05 is statistically significant in this study.

Results

Comparisons of baseline characteristics between the pCR group and the non-pCR group

A total of 97 patients were included for further analysis, with 20 (20.62%) patients in the pCR group and 77 (79.38%) patients in the non-pCR group. The clinical and demographic characteristics of the two groups were comparable, including sex, age, left ventricular ejection fraction (LVEF), American Society of Anesthesiologists (ASA) status, drinking history, smoking history, diabetes, hypertension, tumor location, forced expiratory volume in one second (FEV1), and tumor location ($P > 0.05$). The non-pCR group had a higher clinical stage, but the difference wasn't significant ($P = 0.06$). The neoadjuvant chemotherapy regiment, neoadjuvant cycle, and PD-1 drug type were similar in both groups. The time to surgery was 42 days and 41 days in the pCR group and non-pCR group, respectively. The comparisons of baseline characteristics are summarized in **Table 1**.

The details of comparisons of inflammatory and nutritional parameters between the pCR group and the non-pCR group were summarized in **Table 2**. Compared with the non-pCR group, the pCR group had a higher SII (median 871.72 vs. 614.71), but not significant. In addition, we summarized the ROC of the included inflammatory and nutritional parameters in **Figure 1**.

TABLE 1 Comparisons of baseline characteristic between the pCR group and non-pCR group.

Contents	Total	pCR group (*n* = 77)	non-pCR group (n = 20)	*p*
sex, *n* (%)				0.88
Female	23 (23.71)	18 (23.38)	5 (25.00)	
Male	74 (76.29)	59 (76.62)	15 (75.00)	
Age, mean (±SD)	60.35 ± 6.73	60.44 ± 6.38	60.00 ± 7.94	0.80
LVEF, mean (±SD)	67.21 ± 5.47	67.24 ± 5.83	67.09 ± 3.75	0.90
FEV1, mean (±SD)	2.58 ± 0.63	2.56 ± 0.62	2.69 ± 0.65	0.42
ASA status, *n* (%)				0.67
2	90 (92.78)	71 (92.21)	19 (95.00)	
3	7 (7.22)	6 (7.79)	1 (5.00)	
Smoking History, *n* (%)				0.86
No	42 (43.30)	33 (42.86)	9 (45.00)	
Yes	55 (56.70)	44 (57.14)	11 (55.00)	
Dringking History, *n* (%)				0.75
No	65 (67.01)	51 (66.23)	14 (70.00)	
Yes	32 (32.99)	26 (33.77)	6 (30.00)	
Hypertension, *n* (%)				0.41
No	79 (81.44)	64 (83.12)	15 (75.00)	
Yes	18 (18.56)	13 (16.88)	5 (25.00)	
Diabetes, *n* (%)				0.81
No	91 (93.81)	72 (93.51)	19 (95.00)	
Yes	6 (6.19)	5 (6.49)	1 (5.00)	
Tumorlocation, *n* (%)				0.87
Upper third	9 (9.28)	7 (9.09)	2 (10.00)	
Middle third	49 (50.52)	38 (49.35)	11 (55.00)	
Lower third	39 (40.21)	32 (41.56)	7 (35.00)	
Clinical stage, *n* (%)				0.06
≦2	40 (41.24)	28 (36.36)	12 (60.00)	
>2	57 (58.76)	49 (63.64)	8 (40.00)	
Drugs type, *n* (%)				0.98
Pembrolizumab	39 (40.21)	31 (40.26)	8 (40.00)	
Others	58 (59.79)	46 (59.74)	12 (60.00)	
Neoadjuvant cycles, *n* (%)				0.66
≦2	67 (69.07)	54 (70.13)	13 (65.00)	
>2	30 (30.93)	23 (29.87)	7 (35.00)	
Chemotherapy regimens, *n* (%)				0.38
TP regiment	87 (89.69)	68 (88.31)	19 (95.00)	
PF regiment	10 (10.31)	9 (11.69)	1 (5.00)	
Time to surgery, median[IQR]	41[33,50]	42[33,52]	41[34,44]	0.38

ASA, American Society of Anesthesiologists; FEV1, forced expiratory volume in one second; LVEF, left ventricular ejection fractions.

TABLE 2 Comparisons of preteratment inflammatory and nutritional indicators between the pCR group and non-pCR group.

Contents	Total	Non-pCR group ($n = 77$)	pCR group ($n = 20$)	p
Pretreatment HALP, median[IQR]	43.00[19.00,67.00]	43.00[19.00,68.00]	48.00[25.00,55.00]	0.66
Pretreatment SIRI, median[IQR]	0.98[0.65,1.41]	0.98[0.65,1.32]	1.19[0.69,1.98]	0.27
Pretreatment SII, median[IQR]	635.31[414.18,878.57]	614.71[414.18,844.79]	871.72[474.24,1127.46]	0.11
Pretreatment PNI, median[IQR]	50.30[47.25,54.15]	51.00[47.80,54.25]	49.10[45.60,52.30]	0.12
Pretreatment PLR, median[IQR]	152.35[111.96,200.69]	147.87[108.16,184.67]	201.52[140.31,210.35]	0.06
Pretreatment LMR, median[IQR]	4.25[3.46,5.61]	4.31[3.52,5.62]	3.96[3.46,4.90]	0.15
Pretreatment NLR, median[IQR]	2.45[1.79,3.35]	2.42[1.79,3.04]	3.59[1.98,3.90]	0.14
Pretreatment BMI, median[IQR]	20.83[19.53,22.43]	20.94[19.53,22.72]	20.58[19.53,22.21]	0.55
Preatment weight, median[IQR]	57.00[53.00,62.00]	57.00[53.00,62.00]	57.00[54.00,60.50]	0.95
Pretreatment PLT, mean (±SD)	257.90 ± 56.21	254.30 ± 55.81	271.75 ± 55.61	0.22
Preatment Hb, mean (±SD)	139.13 ± 15.21	139.81 ± 15.48	136.55 ± 13.82	0.40
Pretreatment MONO, median[IQR]	0.40[0.33,0.48]	0.40[0.33,0.48]	0.41[0.34,0.55]	0.46
Preatment LY, median[IQR]	1.70[1.37,2.08]	1.70[1.45,2.13]	1.48[1.22,1.96]	0.13
Preatment NEUT, median[IQR]	4.17[3.40,4.95]	4.17[3.41,4.82]	4.22[3.38,5.84]	0.50
Preatment WBC, median[IQR]	6.52[5.60,7.77]	6.52[5.60,7.74]	6.92[5.76,7.77]	0.62
Preatment cholesterol, median[IQR]	4.74[4.25,5.30]	4.74[4.23,5.20]	4.74[4.35,5.52]	0.41
Pretreatment albumin, median[IQR]	41.70[38.80,44.20]	41.70[39.10,44.30]	41.20[38.10,42.90]	0.23

Screening predictive inflammatory nutritional indicators using LASSO-logistic regression analysis

Considering the potential collinearity between inflammatory nutritional indicators, we used LASSO regression analysis (**Figure 2A**) and cross-validation (**Figure 2B**) for each predictive factor to screen the independent variables. A total of 17 potential factors were put into the LASSO analysis, including HALP, SIRI, SII, PNI, PLR, LMR, NLR, BMI, weight, PLT, Hb, MONO, LY, NEUT, WBC, cholesterol, and Alb. The smallest verification error (λ) was 0.06, and only one predictive factor (SII) was included in the regression model. The cut-off value of SII was 921.80, with an AUC value of 0.62. Further, we defined SII > 921.80 as high SII and SII ≦ 921.80 as low SII.

Univariate analysis and multivariate analysis of pCR predictive factors

To determine the independent factors of pCR, we conducted univariate and multivariate analyses to determine the independent predictive factors, and finally, two factors were screened. High SII (OR = 3.94, 95%CI:1.26–12.42, $P = 0.02$) and early clinical stage(OR = 0.35, 95%CI:0.12–0.98, $P = 0.05$) were determined as independent predictive factors of pCR. The analysis details are summarized in **Table 3**.

Establishment and validation of the nomogram model

We combined clinical stage and SII to establish a novel nomogram model to predict the pCR(**Figure 3**). The established nomogram model showed good discriminative ability in both the training cohort and validation cohort, with an AUC 0.72 (95% CI:0.61–0.84) and 0.82(95%CI: 0.66–0.98) (**Figure 4**). The Brier score of the calibration curve was 0.13, which was below 0.25. Thus, the calibration curve showed good agreement between the predicted results and the actual results in both the training cohort and the validation cohort (**Figure 5**). Compared with the clinical stage, the DCA confirmed a better clinical value of the nomogram model in both the training cohort and the validation cohort (**Figure 6**).

Discussion

The pCR is an important evaluation index of the short-term efficacy of neoadjuvant therapy for ESCC, which was closely also associated with improved long-term overall survival and decreased recurrence. The JCOG9907 trial showed that the

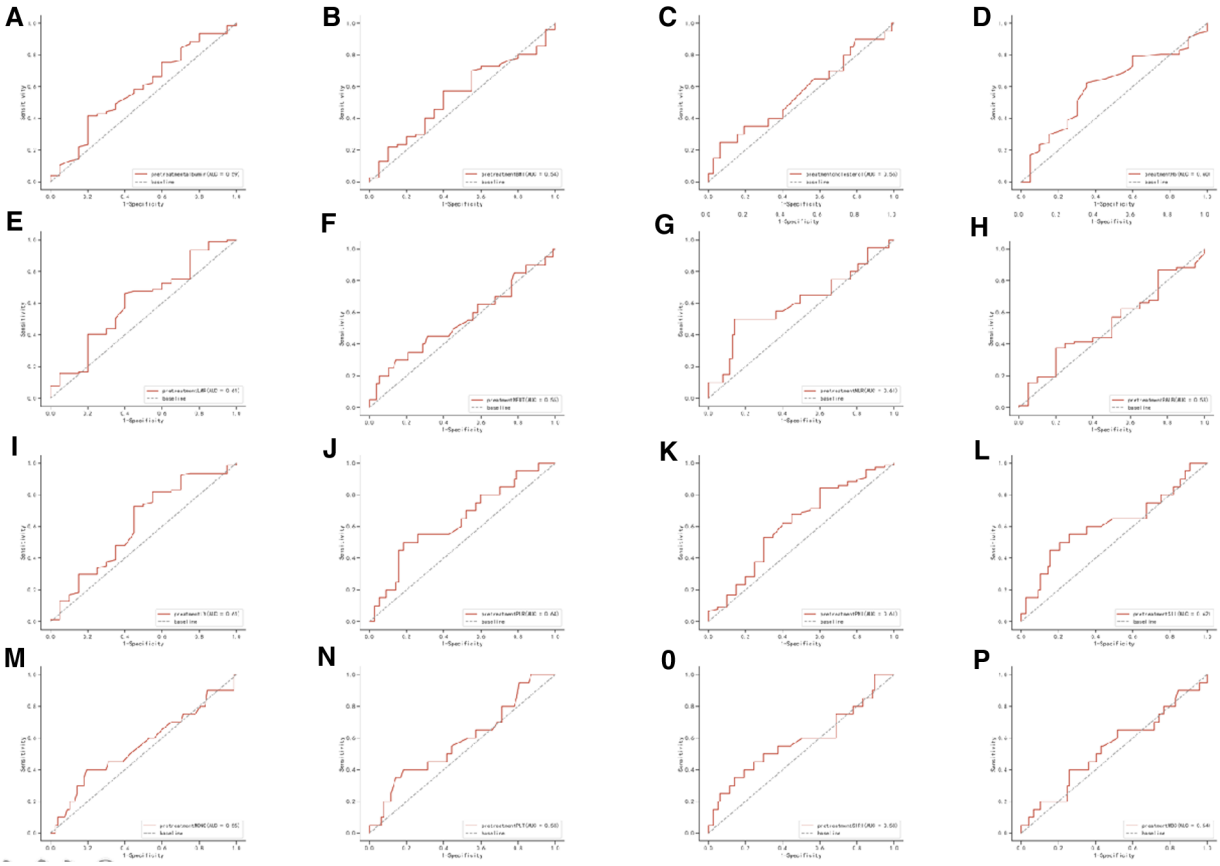

FIGURE 1
Receiver operating characteristic (ROC) of the following 16 predictive factors: HALP, SIRI, SII, PNI, PLR, LMR, NLR, BMI, PLT, Hb, MONO, LY, NEUT, WBC, cholesterol, and Alb.

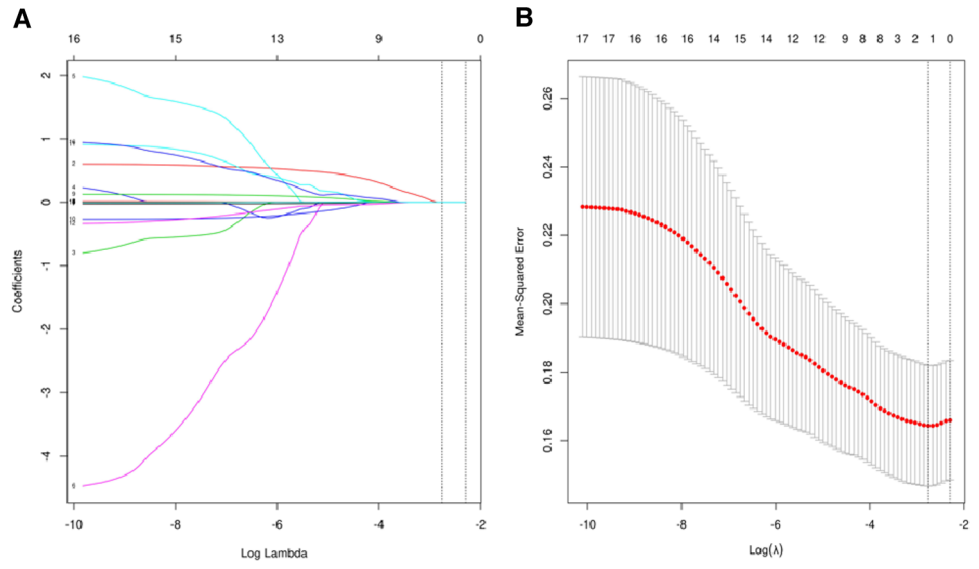

FIGURE 2
(A) regression analysis of influence factors based on Lasso for variable selection; (B) cross-validation of the regression model.

TABLE 3 Univariate analysis and multivariate analysis of pCR predictive factors.

Variables	N	OR	95%CI	*P*	OR	95%CI	*P*
Sex							
Female	23						
Male	74	0.92	[0.29,2.87]	0.88			
Age							
≦51	10						
>51	87	0.57	[0.13,2.42]	0.44			
PD-1 type, *n* (%)							
Pembrolizumab	58						
Others	39	0.99	[0.36,2.70]	0.98			
Neoadjuvant cycles, *n* (%)							
≦2	67						
>2	30	1.26	[0.45,3.58]	0.66			
Chemotherapy regiment							
TP regiment	87						
PF regiment	10	0.40	[0.047,3.34]	0.40			
Time to surgery							
≦45	65						
>45	32	0.44	[0.133,1.44]	0.17			
Pretreatment SII							
≦921.80	77						
>921.80	20	3.61	[1.22,10.70]	0.02	3.94	[1.26,12.42]	0.02
ASAstatus							
2	90						
3	7	0.62	[0.07,5.49]	0.67			
Smokinghistory							
No	42						
Yes	55	0.92	[0.34,2.47]	0.86			
Dringkinghistory							
No	65						
Yes	32	0.84	[0.29,2.44]	0.75			
Hypertension							
No	79						
Yes	18	1.64	[0.51,5.31]	0.41			
Diabetes							
No	91						
Yes	6	0.76	[0.08,6.88]	0.81			

(*continued*)

TABLE 3 Continued

Variables	N	OR	95%CI	*P*	OR	95%CI	*P*
FEV1202							
≦2.02	24						
>2.02	73	2.13	[0.56,8.00]	0.27			
LVEF							
≦70.5	70						
>70.5	27	0.39	[0.10,1.46]	0.16			
Tumorlocation							
Upper	9						
Middle third	49	1.01	[0.18,5.60]	0.99			
Lower third	39	0.77	[0.13,4.50]	0.77			
Clinical stage							
≦2	40						
>2	57	0.38	[0.14,1.04]	0.06	0.35	[0.12,0.98]	0.05

pCR rate among EC patients receiving neoadjuvant chemotherapy was only 2.4% (19). In this study, a total of 20 (20.62%) patients achieved pCR. Recently, a meta-analysis included 621 resectable esophageal cancer patients receiving neoadjuvant immunotherapy, and among them, 33.8% (95% CI: 29.6%-37.9%) patients achieved pCR (20). Based on present evidence, the efficacy of the nICT pattern is promising and has the potential to be the standard treatment of locally advanced esophageal cancer. Thus, the prediction of independent predictive factors for pCR and the establishment of accurate prediction models are of great importance for the formulation of individual neoadjuvant therapy. In this study, we identified early clinical stage and high SII as independent predictors of pCR and established a novel Normogram model for predicting pCR among patients receiving nICT. The model had a good discriminant ability, with an AUC of 0.72 in the training queue and 0.82 in the verification queue. Using the nomogram model, each predictive factor was quantified and visualized by the model to predict the probability of pCR. In addition, physicians could predict an individual's response to nICT and personalize neoadjuvant treatment plans.

The SII uses a simple calculation based on lymphocyte, neutrophil, and platelet counts in peripheral blood to evaluate patients' immune status objectively and is widely reported as a prognostic marker of multiple malignant tumors. Chen et al. retrospectively analyzed 1,383 patients undergoing radical surgery for colorectal cancer and found low SII was associated with longer overall survival and disease-free survival (21). Wang et al. found that high SII could be used as an independent predictor of poor prognosis in patients with stage I-III gastric cancer and was superior to NLR and PLR (22). Feng JF et al. confirmed that ESCC patients with SII $\leq$ 410 had a significantly better 5-year cancer-specific survival (51.9% vs. 24.0%) (23). The predictive value of SII among ESCC patients receiving nICT was rarely reported.

In this study, we found that high SII(OR = 3.94, 95% CI:1.26–12.42, $P = 0.02$) was associated with better treatment response. Recently, Xinke Z et al. combined NLR, LMR, PLR, and SII to predict the pathological effect of anti-PD-1 combined with neoadjuvant chemotherapy in ESCCpatients (24). In Xinke Z's analysis, patients with treatment response had high baseline SII, and the cut-off value of SII at baseline was 559.266 with an AUC value of 0.681 (14), which also indicated a positive correlation between the SII and pathological response. The PD-1 blockade is designed to inhibit the interaction between PD-1 and PD-L1to activate T cells, which helps in restoring the anti-cancer immune response. Despite the promising results of PD-1, drug resistance is considered a major problem in PD-1 treatment because a large proportion of patients couldn't respond to PD-1 at the beginning of treatment (25). Tumor-associated neutrophils have been reported to indirectly promote the antitumor function of CD8 + T cells by regulating interleukin (IL)-17 production (26). However, the mechanisms of high SII associated with a better treatment response among ESCC patients receiving nICT were unclear. At present, we are conducting single-cell sequencing analysis to examine the difference in cell distribution in patients with response to nICT and patients without response to nICT, and the study is still in the data collection stage. We would put SII as a

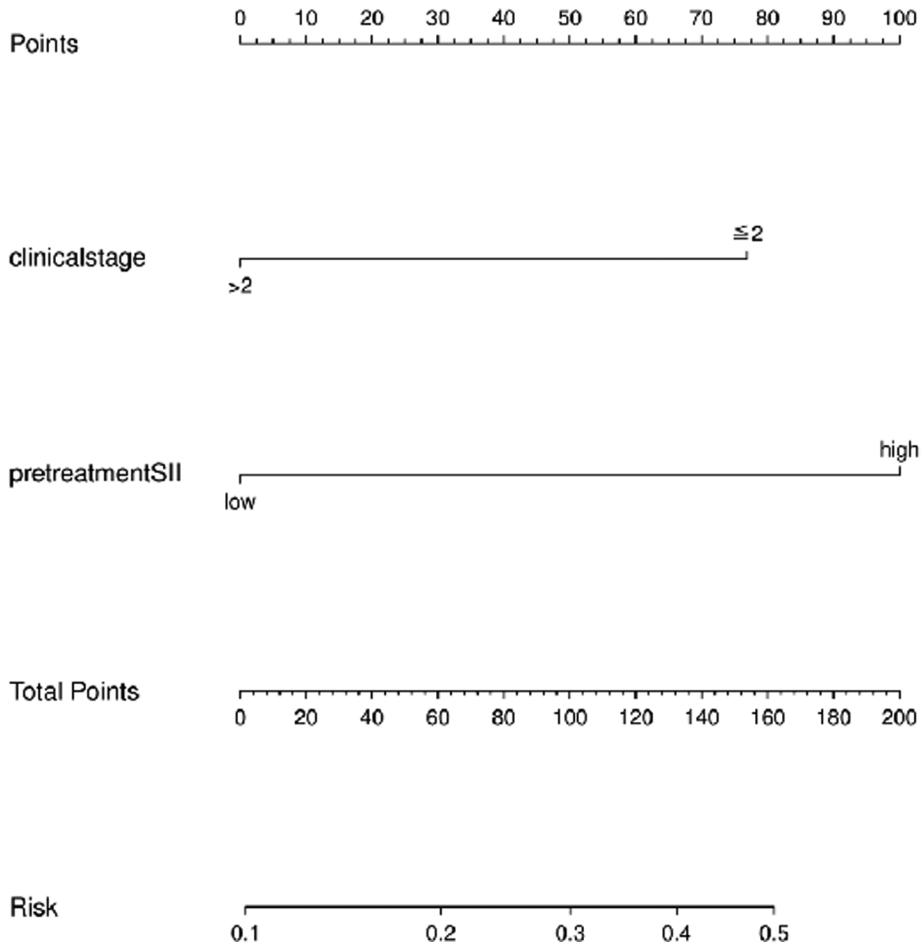

FIGURE 3
Nomogram model to predict pCR among ESCC patients receiving nICT.

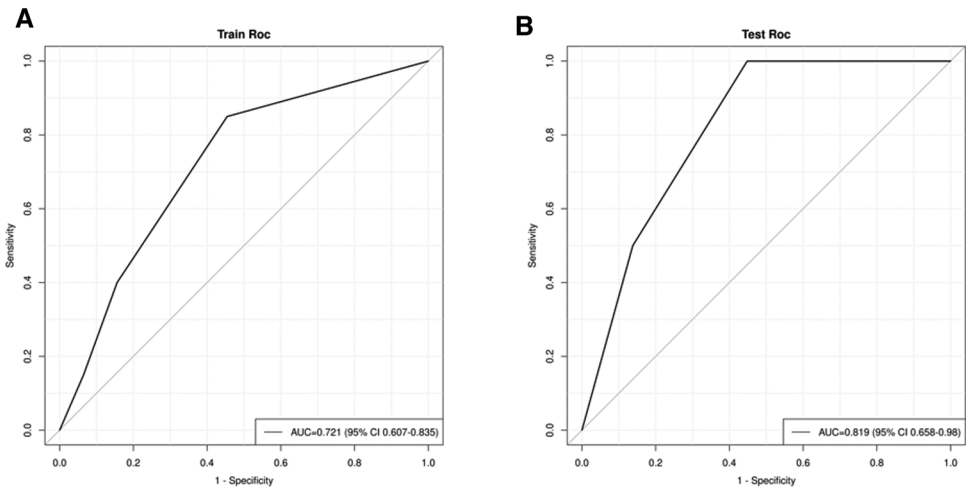

FIGURE 4
(A) receiver operating characteristic (ROC) in the training cohort; (B) ROC in the validation cohort.

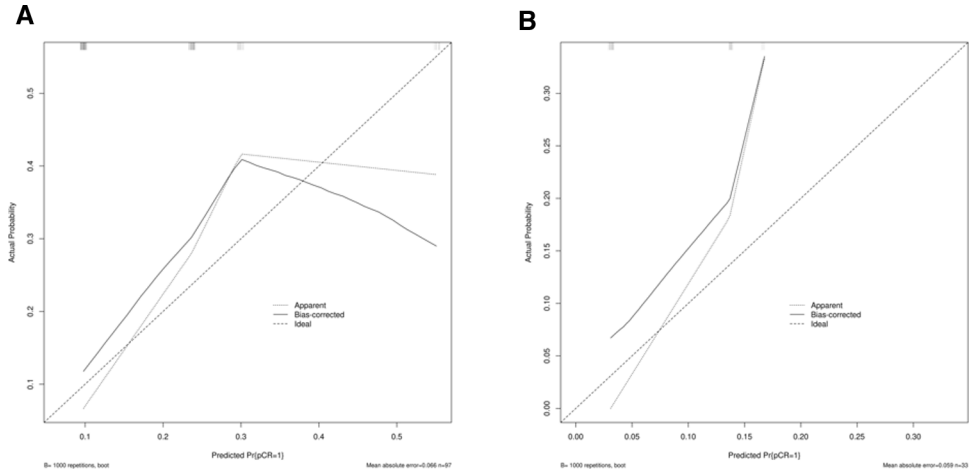

FIGURE 5
(A) Calibration curve in the training cohort; (B) calibration curve in the validation cohort.

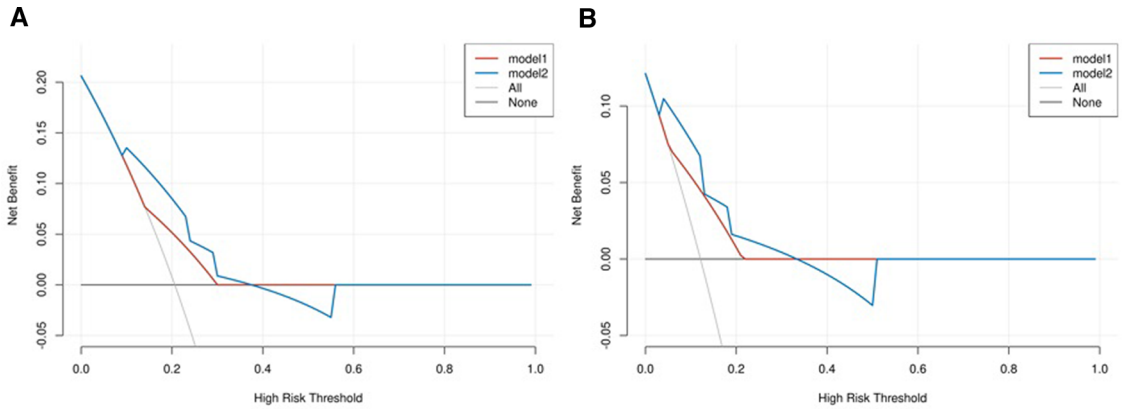

FIGURE 6
(A) Decision curve analysis (DCA) in the training cohort; (B) DCA in the validation cohort. The model 1 stands for clinical stage, and the model 2 stands for combination of clinical stage and SII.

subgroup factor in the following analysis and hope to give a clear explanation of this finding.

To our best knowledge, this study first investigated the predictive value of SII in the prediction of pCR and established one nomogram model to predict pCR among patients receiving nICT. However, this study has the following limitations: First, the analysis lacks data randomization, and the study may have a potential bias in patient selection and processing of missing values. Second, although the prediction model has good discriminative power, however, it only includes relatively limited cases whose pathological type is squamous cell carcinoma, and it has not been verified externally. Therefore, further external validation is necessary before applying the Nomogram model to patients in other centers. Third, the impact of SII on the long-term Four, it is unclear whether this nomogram will be suitable for patients with locally advanced esophageal cancer receiving other neoadjuvant therapy, such as neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy. Fifth, the mechanism should be further investigated using single-cell sequencing analysis.

Conclusions

High pretreatment SII and early clinical stage were independently associated with pCR among ESCC receiving nICT. Calculation of SII is based on routine preoperative hematologic indicators. We further established and validated one nomogram model to predict pCR among ESCC receiving nICT, which is easy to be applied in clinical decision-making,

and the evaluation process is simple and feasible. Considering the relatively limited case number from a single center, external validation, including more cases, are necessary to support our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

WH and ZH conceived the concept and coordinated the design. KW, ZH, and *PZ* drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Predictive nomogram for postoperative atrial fibrillation in locally advanced esophageal squamous carcinoma cell with neoadjuvant treatment

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Background: Neoadjuvant therapy following minimally invasive esophagectomy is recommended as the standard treatment for locally advanced esophageal squamous carcinoma cells (ESCC). Postoperative atrial fibrillation (POAF) after esophagectomy is common. We aimed to determine the risk factors and construct a nomogram model to predict the incidence of POAF among patients receiving neoadjuvant therapy.

Methods: We retrospectively included patients with ESCC receiving neoadjuvant chemotherapy (nCT), neoadjuvant chemoradiotherapy (nCRT), or neoadjuvant immunochemotherapy (nICT) following minimally invasive esophagectomy (MIE) for analysis. Patients without a history of AF who did not have any AF before surgery and who developed new AF after surgery, were defined as having POAF. We applied a LASSO regression analysis to avoid the collinearity of variables and screen the risk factors. We then applied a multivariate regression analysis to select independent risk factors and constructed a nomogram model to predict POAF. We used the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA) curve to evaluate the nomogram model.

Results: A total of 202 patients were included for analysis, with 35 patients receiving nCRT, 88 patients receiving nCT, and 79 patients receiving nICT. POAF occurred in 34 (16.83%) patients. There was no significant difference in the distribution of neoadjuvant types between the POAF group and the no POAF group. There was a significant increase in postoperative hospital stay ($p = 0.04$), hospital expenses ($p = 0.01$), and comprehensive complication index ($p < 0.001$). The LASSO analysis screened the following as risk factors: blood loss; ejection fraction (EF); forced expiratory volume in 1 s; preoperative albumin (Alb); postoperative hemoglobin (Hb); preoperative Hb; hypertension; time to surgery; age; and left atrial (LA) diameter. Further, preoperative Alb ≤41.2 g/L ($p < 0.001$), preoperative Hb >149 g/L ($p = 0.01$), EF >67.61% ($p = 0.008$), and LA diameter >32.9 mm ($p = 0.03$) were determined as independent risk factors of POAF in the multivariate logistic analysis. The nomogram had an area under the curve (AUC) of 0.77. The Briser score of the calibration curve was 0.12. The DCA confirmed good clinical value.

Conclusions: Preoperative Alb ≤41.2 g/L, LA diameter >32.9 mm, preoperative Hb >149 g/L, and EF >67.61% were determined as the risk factors for POAF among patients with ESCC. A novel and valuable nomogram was constructed and validated to help clinicians evaluate the risk of POAF and take personalized treatment plans.

KEYWORDS

esophageal squamous carcinoma cell, neoadjuvant treatment, postoperative atrial fibrillation, risk factors, nomogram model

Introduction

Esophageal squamous carcinoma cell (ESCC) is the primary subtype of esophageal cancer (EC) in Asia, especially in China (1). A combination of neoadjuvant therapy and surgery is recommended as the standard treatment for locally advanced ESCC. There is still no consensus on neoadjuvant therapy. Compared with surgery alone, both neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) have been confirmed to improve overall survival and disease-free survival (2, 3). The nCRT pattern is recommended as the first choice in the national comprehensive cancer network (NCCN) and Chinese society of clinical oncology (CSCO) guidelines. However, due to unpromising long-term survival and the high distant recurrence incidence, the exploration of novel treatment patterns is necessary. Phase II clinical trials showed that neoadjuvant immunochemotherapy (nICT) had a promising pathological response and manageable adverse events (4, 5).

With the development of minimally invasive esophagectomy (MIE), morbidity and mortality have reduced (6); however, complications (especially pneumonia, anastomotic leakage, and atrial fibrillation) after MIE are still high, and management is still challenging. Among patients with solid cancers, patients with EC had the highest risk of atrial fibrillation [adjusted sub-distribution hazard ratio (HR) 2.69; 95% confidence interval (CI) 2.45–2.95] (7). In patients who underwent esophagectomy, postoperative atrial fibrillation (POAF) was highly associated with postoperative infectious complications (8). A recent meta-analysis showed that the incidence of POAF was 16.5%, and patients with POAF had a higher risk of anastomotic leakage, pneumonia, death, and other adverse events (9). In addition, a 21-year follow-up cohort showed that POAF was associated with poorer long-term survival after esophagectomy (HR 2.99, 95% CI=1.37–6.53). Further, POAF increased the risk of stroke, cognitive decline, and depression, reduced the quality of life, and brought a great burden to patients and the medical system (10).

Previous reports indicated that the application of neoadjuvant treatment contributed to the occurrence of POAF (11). Considering the promotion of neoadjuvant treatment plus esophagectomy, it is of clinical importance to understand the risk factors of POAF among patients receiving neoadjuvant therapy (nCT, nCRT, or nICT). The aim of the present study was to determine the risk factors of POAF among patients receiving neoadjuvant therapy and construct a nomogram model to help clinicians evaluate the risk of POAF and take personalized treatment plans. Another concern was whether POAF was associated with the types of neoadjuvant treatment.

Materials and methods

Patient selection

This was a retrospective analysis based on a prospectively collected dataset. The inclusion criteria were as follows: (1) diagnosed with ESCC; (2) clinical stage in the range of II–IVA; (3) receiving nCT, nCRT, or nICT; (4) undergoing radical transthoracic MIE (including robotic-assisted and video-assisted); and (5) without AF before operation. The exclusion criteria were as follows: (1) a history of heart failure or preoperative AF; (2) severe liver and kidney dysfunction; (3) unresectable tumors or metastases during exploratory surgery; (4) cervical EC; and (5) laryngopharyngeal carcinoma-esophagectomy. This study was approved by the ethics committee at Fujian Medical University Union Hospital. In addition, this study was conducted in strict accordance with the Declaration of Helsinki (1964).

Data collection and definition of variables

The patients' demographic characteristics [sex, age, body mass index (BMI], smoking history, drinking history, preoperative complications, American society of anesthesiologists (ASA) status), preoperative examinations [preoperative albumin, preoperative hemoglobin (Hb), ejection fraction (EF), forced expiratory volume in 1 s (FEV1)], neoadjuvant treatment (types, time to surgery), tumor characteristics (tumor location, pathological grade, pathological T stage, pathological N stage, lymph nodes removed number), surgery (types, surgical time, blood loss), and postoperative information [comprehensive complication index (CCI), hospital stay, thoracic tube stay, hospital expenses] were collected for analysis.

POAF was the primary outcome of this study. Patients without a history of AF who did not have any type of AF before surgery and who developed new AF after surgery, were defined as POAF. The tumor location was divided into upper third, middle third, and lower third. The pathological TNM stage used in this study was the 8th AJCC staging system. Neoadjuvant treatment included nCT, nCRT, and nICT. The CCI was developed based on the Clavien–Dindo classification system to measure the severity of postoperative complications. The calculation was conducted at www.assessurgery.com.

Statistical analysis

First, we divided the patients into a POAF group and no POAF group. We expressed the continuous data as mean ± standard deviation or median (interquartile range) and the categorical data as numbers (percentages). The comparisons of baseline characteristics and postoperative information were compared. The Student's *t*-test or Mann–Whitney *U* test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. The continuous variables were converted into categorical variables according to the optimal cutoff value of the receiver operator characteristic (ROC) curve or clinical experience. Second, due to the relatively large number of variables and to avoid the collinearity of variables, we used the LASSO regression model to screen the variables. The principle of LASSO regression screening the variables is to compress the regression coefficients of each variable in the form of a penalty increase (12). Further, we also conducted cross-validation to verify the Lasso regression model. Third, the risk factors screened by the LASSO regression model were included in a multivariate logistic regression model to further determine the independent risk factors. Four, a nomogram model was constructed based on the screened independent risk factors. We evaluated the predictive ability of the nomogram by ROC and area under the curve (AUC) values. We measured the agreement between predicted and actual results by calibration curves. We further evaluated the clinical value of the nomogram model by decision curve analysis (DCA). We conducted the statistical analysis using R software (version 3.6.3) and Python (version 3.7). The two-sided $p < 0.05$ was considered statistically significant in this study.

Results

Comparisons of preoperative characteristics between the POAF and no POAF groups

A total of 202 patients were included for analysis. POAF occurred in 34 (16.83%) patients. There were 35 patients receiving nCRT, 88 patients receiving nCT, and 79 patients receiving nICT. There was a significant difference in age, preoperative ALB, preoperative Hb, EF, and FEV1 between the POAF and no POAF groups ($p < 0.05$). There were no statistically significant differences between the POAF and no POAF groups in BMI, smoking history, drinking history, ASA status, blood loss, surgical time, MIE type, lymph nodes moved number, tumor location, pathological grade, pathological T stage, pathological N stage, neoadjuvant type, left atrial (LA) diameter, and time to surgery ($p > 0.05$). The details of comparisons of baseline characteristics between the POAF and no POAF groups are presented in **Table 1**.

Compared with the no POAF group, the POAF group had an increase in postoperative hospital stay (median 11 days vs. 10 days), CCI (median 32.00 vs. 22.60), and hospital expenses (median 99707.22 yuan vs. 88916.27 yuan). There was no significant difference in total hospital stay and thoracic drainage tube stays ($p > 0.05$). The details of the comparisons of perioperative outcomes were summarized in **Table 2** and presented in **Figure 1**.

Screening predictive factors using LASSO logistic regression analysis

LASSO regression analysis (**Figure 2A**) and cross-validation (**Figure 2B**) were performed for each influencing factor, and the independent variables were further screened. The value with the smallest verification error ($\lambda = 0.12$) was selected to fit the regression model, and there were 10 variables of the model in total, including blood loss, EF, FEV1, preoperative Alb, postoperative D1 Hb, preoperative Hb, hypertension, time to surgery, age, and LA diameter. Further, multivariate logistic regression, including the above 10 predictive factors, was conducted to determine the independent risk factors. Preoperative Alb ≦41.2 g/L ($p < 0.001$), preoperative Hb >149 g/L ($p = 0.01$), EF >67.61% ($p = 0.008$), and LA diameter >32.9 mm ($p = 0.03$) were determined as the independent risk factors of POAF. The results of multivariate logistic regression are summarized in **Table 3**.

Development and validation of a nomogram model

We used the independent risk factors determined by the LASSO logistic regression strategy; we developed a nomogram model to predict POAF (**Figure 3**). The AUC of the established nomogram model was 0.76 (95% CI 0.69–0.86), which indicated the good discriminative ability of the model (**Figure 4A**). In addition, the AUC of the nomogram model was superior to each factor included in the model (**Figure 4B**). The Briser score of the calibration curve was

TABLE 1 Comparisons of demographic and clinicopathological characteristics between the POAF group and no POAF group.

Contents	Variables	Total ($n = 202$)	No POAF ($n = 168$)	POAF ($n = 34$)	*P*
Age (years)	≦62	113 (55.94)	102 (60.71)	11 (32.35)	0.002
	>62	89 (44.06)	66 (39.29)	23 (67.65)	
BMI	≦20.54	57 (28.22)	50 (29.76)	7 (20.59)	0.28
	>20.54	145 (71.78)	118 (70.24)	27 (79.41)	
Smoking history	No	87 (43.07)	71 (42.26)	16 (47.06)	0.61
	Yes	115 (56.93)	97 (57.74)	18 (52.94)	
Drinking history	No	147 (72.77)	122 (72.62)	25 (73.53)	0.91
	Yes	55 (27.28)	46 (27.38)	9 (26.47)	
Hypertension	No	166 (82.18)	144 (85.71)	22 (64.71)	0.004
	Yes	36 (17.82)	24 (14.29)	12 (35.29)	
Diabetes	No	191 (94.55)	160 (95.24)	31 (91.18)	0.34
	Yes	11 (5.45)	8 (4.76)	3 (8.82)	
Coronary heart disease	No	196 (97.03)	164 (97.62)	32 (94.12)	0.27
	Yes	6 (2.97)	4 (2.38)	2 (5.88)	
ASA status	≦2	175 (86.63)	145 (86.31)	30 (88.24)	0.76
	>2	27 (13.37)	23 (13.69)	4 (11.76)	
EF	≦67.6%	104 (51.49)	93 (55.36)	11 (32.35)	0.01
	>67.6%	98 (48.51)	75 (44.64)	23 (67.65)	
FEV1	≦2.38	76 (37.62)	57 (33.93)	19 (55.88)	0.02
	>2.38	126 (62.38)	111 (66.07)	15 (44.12)	
LA (mm)	≦32.9	141 (69.80)	120 (71.43)	21 (61.76)	0.04
	>32.9	61 (30.20)	48 (28.57)	13 (38.24)	
Preoperation alb (g/L)	≦41.2	119 (58.91)	90 (53.57)	29 (85.29)	<0.001
	>41.2	83 (41.09)	78 (46.43)	5 (14.71)	
Post D1 Alb (g/L)	≦31	46 (22.77)	35 (20.83)	11 (32.35)	0.14
	>31	156 (77.23)	133 (79.17)	23 (67.65)	
Preoperation Hb (g/L)	≦149	189 (93.56)	160 (95.24)	29 (85.29)	0.03
	>149	13 (6.44)	8 (4.76)	5 (14.71)	
Post D1 Hb (g/L)	≦138	176 (87.13)	149 (88.69)	27 (79.41)	0.14
	>138	26 (12.87)	19 (11.31)	7 (20.59)	
Time to surgery (day)	≦44	124 (61.39)	99 (58.93)	25 (73.53)	0.11
	>44	78 (38.61)	69 (41.07)	9 (26.47)	
Tumor location	Upper third	22 (10.89)	15 (8.93)	7 (20.59)	0.13
	Middle third	111 (54.95)	95 (56.55)	16 (47.06)	
	Lower third	69 (34.16)	58 (34.52)	11 (32.35)	
Neoadjuvant type	nCRT	35 (17.33)	31 (18.45)	4 (11.77)	0.09
	nCT	88 (43.56)	77 (45.83)	11 (32.35)	
	nICT	79 (39.11)	60 (35.71)	19 (55.88)	

(*continued*)

TABLE 1 Continued

Contents	Variables	Total ($n = 202$)	No POAF ($n = 168$)	POAF ($n = 34$)	P
Surgical time (min)	≦300	78 (38.61)	65 (38.69)	13 (38.24)	0.96
	>300	124 (61.39)	103 (61.31)	21 (61.76)	
Blood loss (ml)	≦150	173 (85.64)	147 (87.50)	26 (76.47)	0.09
	>150	29 (14.36)	21 (12.50)	8 (23.53)	
MIE type	Video-assisted	169 (83.66)	143 (85.12)	26 (76.47)	0.21
	Robotic-assisted	33 (16.34)	25 (14.88)	8 (23.53)	
ypG	G0	43 (21.29)	35 (20.83)	8 (23.53)	0.35
	G1	33 (16.34)	31 (18.45)	2 (5.88)	
	G2	47 (23.27)	38 (22.62)	9 (26.47)	
	G3	79 (39.11)	64 (38.10)	15 (44.12)	
ypT	T0	43 (21.29)	35 (20.83)	8 (23.53)	0.89
	T1–2	66 (32.67)	56 (33.33)	10 (29.41)	
	T3–4	93 (46.04)	77 (45.83)	16 (47.06)	
ypN	N0	110 (54.46)	90 (53.57)	20 (58.82)	0.58
	N+	92 (45.54)	78 (46.43)	14 (41.18)	
Lymph nodes moved number	≦38	138 (68.32)	118 (70.24)	20 (58.82)	0.19
	>38	64 (31.68)	50 (29.76)	14 (41.18)	

POAF, postoperative atrial fibrillation; BMI, body mass index; Hb, hemoglobin; Alb, albumin; FEV1, forced expiratory volume in one second; EF, ejection fraction; MIE, minimally invasive esophagectomy; LA, left atrial.

TABLE 2 Comparisons of perioperative outcomes between the POAF group and no POAF group.

Contents	Total ($n = 202$)	No POAF ($n = 168$)	POAF ($n = 34$)	P
Thoracic drainage tube stay (days)	10.90 ± 8.02	10.22 ± 6.51	14.33 ± 12.72	0.08
Postoperative hospital stay (days)	10[8,14]	10[8,13]	11[9,27]	0.04
Total hospital stay (days)	16[12,24]	16[12,24]	16[13,35]	0.16
CCI	24.20[8.70,32.00]	22.60[8.70,28.90]	32.00[25.70,44.30]	<0.001
Hospital expenses (RMB)	89,623.27[79,549.69,107,293.68]	88,916.27[79,113.85,103,342.57]	99,707.22[84,003.12,134,154.56]	0.01

POAF, postoperative atrial fibrillation; CCI, comprehensive complication index; RMB, ren min bi.

0.12, which indicated that the predicted results were highly consistent with the actual results (Figure 4C). The DCA indicated that this nomogram model had a high clinical application value (Figure 4D).

Discussion

POAF is a common complication after esophagectomy, and the overall incidence of POAF in this study was 16.83% (34/202). Compared with non-esophageal surgery, patients undergoing esophagectomy had a higher incidence of POAF (17.66% vs 7.63%) (13). There was a significant increase in postoperative hospital stay ($p = 0.04$), hospital expenses ($p = 0.01$), and CCI ($p < 0.001$). Therefore, the identification of independent risk factors and the development of an accurate predictive model for POAF are critical for optimal treatment planning in high-risk individuals with MIE after neoadjuvant therapy. Preoperative Alb ≦41.2 g/L, LA diameter >32.9 mm, preoperative Hb >149 g/L, and EF >67.61% were identified as the independent risk factors for POAF, and a novel nomogram model was constructed to predict POAF. The model not only showed the good discriminative ability but also had the best agreement between the predicted results and the observed results. Based on this nomogram model, each prognostic factor was quantified and visualized with a

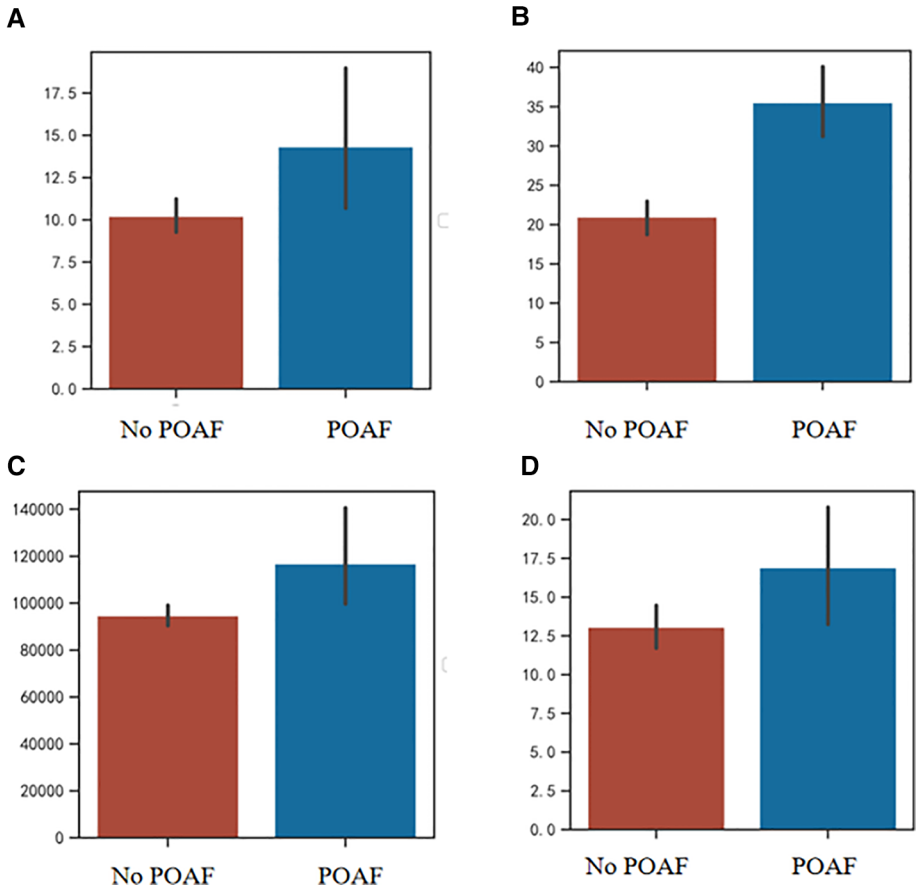

FIGURE 1
(A) Comparison of thoracic tube stay between POAF group and no POAF group; (B) Comparison of CCI between POAF group and no POAF group; (C) Comparison of hospital expenses between POAF group and no POAF group; (D) Comparison of postoperative hospital stay between POAF group and no POAF group. POAF, postoperative atrial fibrillation; CCI, comprehensive complication index.

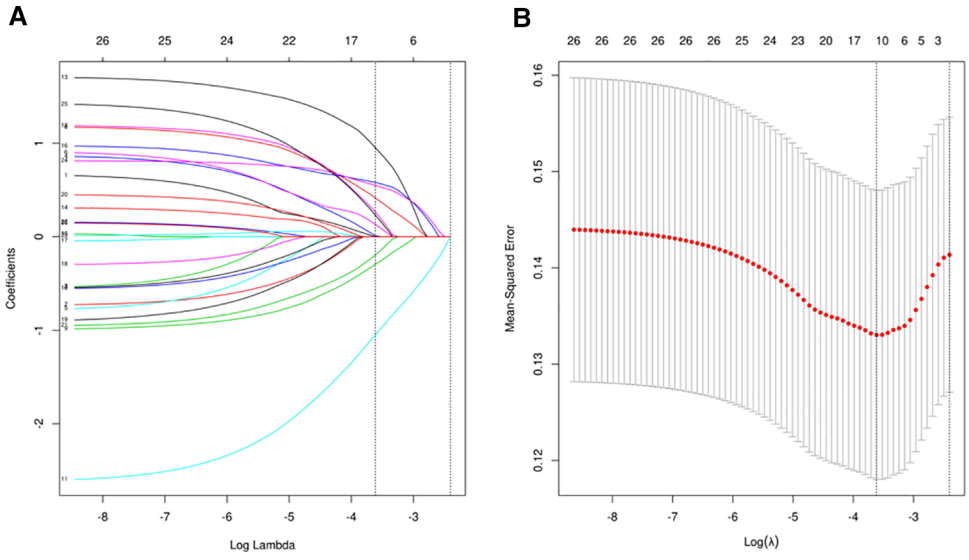

FIGURE 2
(A) The regression analysis of influence factors based on Lasso analysis for variable selection; (B) the cross-validation of the regression model.

TABLE 3 Multivariate logistic analysis of postoperative atrial fibrillation.

Predictor	Before selection				After selection			
	p	OR	Lower	Upper	*p*	Odds ratio	Lower	Upper
Blood loss ≦ 150 ml	Reference							
Blood loss > 150 ml	0.25	1.90	0.61	5.64				
FEV1 ≦ 2.38 L	Reference							
FEV1 > 2.38 L	0.10	0.45	0.17	1.16				
EF ≦ 67.61%	Reference							
EF > 67.61%	0.03	2.99	1.17	8.31	0.008	3.23	1.40	8.06
Preoperation Alb ≦ 41.2 g/L	Reference							
Preoperation Alb > 41.2 g/L	0.001	0.12	0.03	0.35	<0.001	0.14	0.04	0.37
Postoperation D1 Hb ≦ 138 g/L	Reference							
Postoperation D1 Hb > 138 g/L	0.06	3.55	0.94	13.39				
Preoperation Hb ≦ 149 g/L	Reference							
Preoperation Hb > 149 g/L	0.02	6.46	1.27	33.99	0.01	5.82	1.40	24.23
Hypertension no	Reference							
Hypertension yes	0.10	2.30	0.84	6.25				
Time to surgery ≦ 44 days	Reference							
Time to surgery > 44 days	0.07	0.39	0.13	1.03				
Age ≦ 62 years	Reference							
Age > 62 years	0.08	2.35	0.91	6.39				
LA diameter ≦ 32.9 mm	Reference							
LA diameter > 32.9 mm	0.02	3.33	1.21	9.59	0.03	2.67	1.09	6.64

OR, odds ratio; Hb, hemoglobin; Alb, albumin; FEV1, forced expiratory volume in one second; EF, ejection fraction; LA, left atrial.

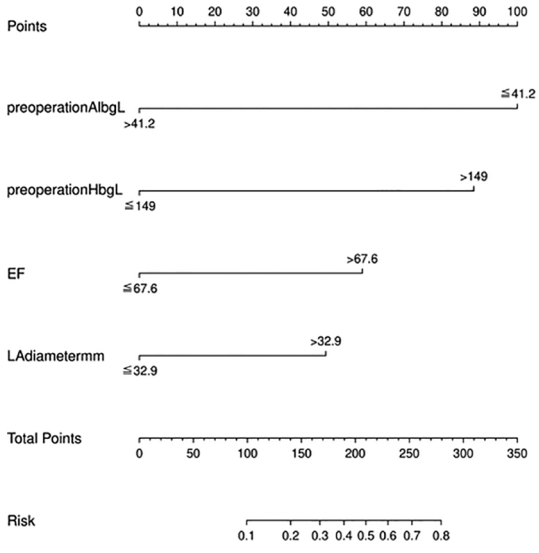

FIGURE 3
The nomogram model to predict postoperative atrial fibrillation among patients receiving neoadjuvant therapy and minimally invasive esophagectomy.

nomogram model to predict the probability of POAF. By using this predictive nomogram, physicians could judge individual risk, predict outcomes, personalize treatment, and take preventive measures for patients at high risk.

In this study, we determined LA diameter ≥32.9 mm as an independent risk factor of POAF. Nagatsuka et al. investigated 200 patients undergoing esophagectomy for EC and determined a LA diameter ≥36.0 mm [odds ratio (OR) 2.47, 95% CI 1.06–5.71] as an independent risk factor ($p = 0.035$) (14). A relationship between LA diameter and AF has been proposed in the general population. One hypothesized direct underlying cause of AF is the result of organic changes in the "remodeling" of the left atrium to maintain a normal sinus rhythm. Increased left ventricular diastolic blood pressure during diastolic dysfunction is associated with increased left ventricular diastolic blood pressure. With the increase of left atrial pressure, atrial wall extension increases and atrial remodeling occurs (15). Interestingly, we also found that left ventricular EF >67.61% was an independent risk factor of POAF. This finding seemed to be inconsistent with previous reports. Zacharias et al. enrolled a total of 8,051 consecutive

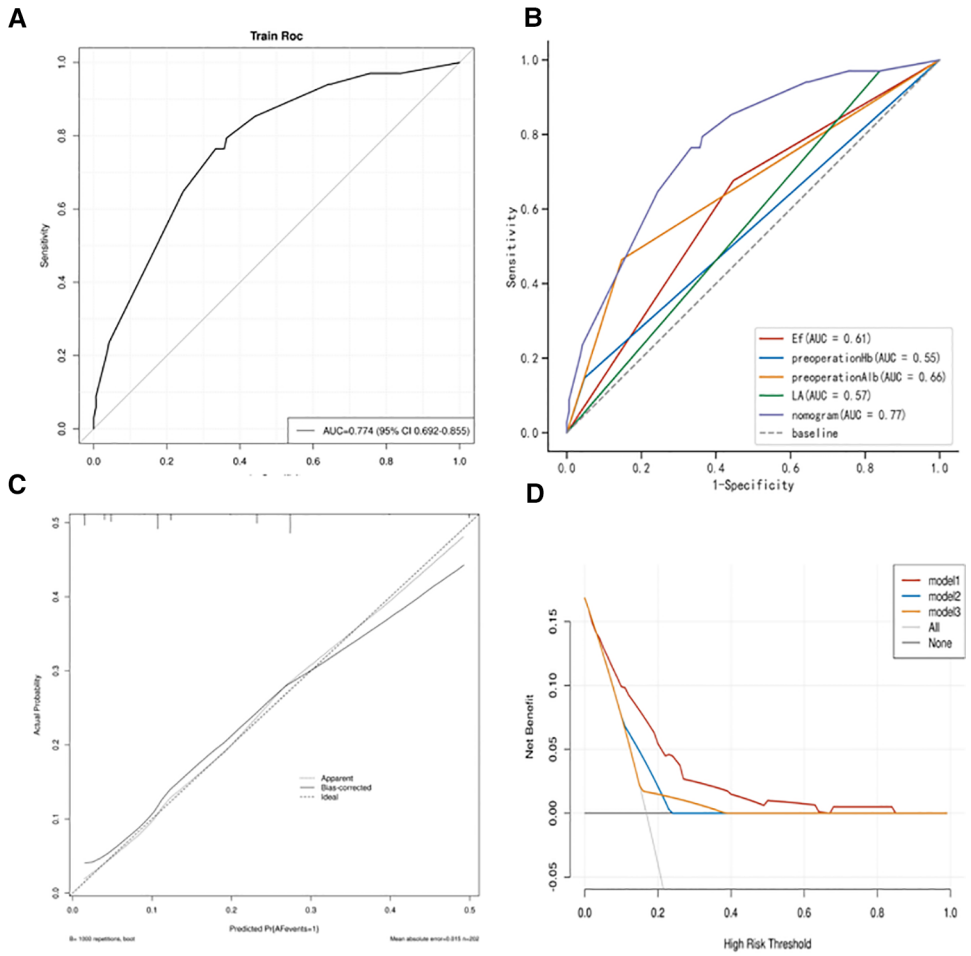

FIGURE 4
(A) Receiver operating characteristic (ROC) curves of the established nomogram model; (B) Comparison of ROC curves between the established nomogram model and the constructed factors; (C) Calibration curve of the established nomogram model; (D) Decision curve analysis of the established nomogram model.

cardiac surgery patients and found that EF <40% (OR 1.16, 95% CI 1.03–1.31) was an independent risk factor of POAF (16). However, a large cohort study (203,135 patients from Pennsylvania and 35,976 patients from New Zealand) investigated the relationship between left ventricular ejection fraction (LVEF) and mortality, and they found an HR of 1.71 (95% CI 1.64–1.77) at LVEF of ≥70% and an HR of 1.73 (95% CI 1.66–1.80) at LVEF of 35%–40%, which indicated a U curve relation between LVEF and mortality (17). Another analysis of 2,867 ICU patients (including 324 patients with EF >70%) showed that the presence of EF >70% increased 28-day mortality (OR 1.39, 95% CI 1.04–1.84) (18). This finding first suggested the association between the high LVEF and the POAF. Further studies are necessary to explore the mechanisms.

There are still limited studies focusing on the relationship between preoperative serum Alb and POAF among patients undergoing esophagectomy. Zhong et al. explored the association between serum Alb and paroxysmal AF based on a Chinese cohort of 305 patients with AF and 610 patients without AF and found that low Alb in male patients is a risk factor for paroxysmal AF (19). Liao et al. conducted a large-scale epidemiological and Mendelian randomization (MR) study and found that the serum Alb level was negatively correlated with the incidence of AF, but the causal relationship between serum Alb level and AF was not clarified (20). In this study, we found that preoperative Alb ≦41.2 g/L was associated with a higher incidence of POAF. This finding supports that low Alb contributed to the occurrence of POAF. Serum Alb plays important roles in anti-inflammatory, antioxidant, anticoagulant, antiplatelet aggregation, and colloid osmotic effects. One recent dose–response analysis showed that for each increase of 10 g/L in serum Alb, the risk of AF would decrease by 36% (21). Present evidence supports that hypoalbuminemia is a modifiable risk factor associated with cardiovascular events (22). In future studies, it would be interesting to explore the relationship between preoperative

nutrition and the incidence of POAF among patients with ESCC. Similarly, there are still no reports investigating the relationship between high Hb and POAF among patients with ESCC. Recently, Nakatani et al. found that high Hb is an independent risk factor of new-onset AF among patients with heart failure with preserved EF (23). Commonly, patients with paroxysmal AF often have elevated Hb in clinical practice (24). One explanation was that polyuria induced by the excess secretion of atrial natriuretic peptide contributed to the high Hb in patients with AF.

At present, there are different opinions on whether to take preventive treatment for POAF (25). Rao et al. held the opinion that the simple prevention of POAF, including using prophylactic drugs, was unlikely to improve long-term survival and unlikely to be cost-effective (11). However, the model including age and neoadjuvant therapy established by Rao et al. only had a moderate c-statistic (0.62). Compared with previous models, the nomogram model in this study had an AUC of 0.76, which indicated a better discriminative ability. Therefore, we suggest taking measures to prevent the occurrence of POAF when the nomogram model suggests a high possibility of POAF. Although AF can occur as an isolated event, it can occur in conjunction with other complications in a population predisposed to cardiopulmonary complications. The application of enhanced recovery after surgery is necessary to reduce overall mortality and morbidity.

To the best of our knowledge, this study was the first predictive nomogram model for POAF in patients with ESCC receiving neoadjuvant therapy. However, the study has the following limitations: first, the model was analyzed based on retrospective data, which may have a potential bias due to a lack of randomization, patient selection, and some missing values. Second, although nCRT is currently the first choice for patients with low events raised by the radiotherapy, relatively few patients received nCRT in this cohort. Further, we did not conduct a subgroup analysis to evaluate the effect of radiation dose on the incidence of POAF. Third, the prediction model has good discrimination, but it has not been verified externally. Further, the case number is relatively limited. External validation is necessary before applying the nomogram model to patients at other centers. Four, whether this nomogram is suitable in patients with locally advanced esophageal adenocarcinoma remains unclear.

Conclusions

In summary, we determined preoperative Alb ≦41.2 g/L, LA diameter >32.9 mm, preoperative Hb >149 g/L, and EF >67.61% to be the risk factors for POAF among patients with ESCC receiving neoadjuvant therapy and MIE. A novel and useful nomogram model was constructed and validated to help clinicians evaluate the risk of POAF and take personalized treatment plans. The predictive ability and clinical value of the nomogram model were promising. For additional external validation, generalization, and application of this prediction model, large prospective multicenter studies are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Fujian Medical University Union Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SC conceived the concept and coordinated the design. XD evaluated the clinical stage. MF, MC, and XD drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Risk factors for early local lymph node recurrence of thoracic ESCC after McKeown esophagectomy

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Objectives: Even underwent radical resection, some patients of thoracic esophageal squamous cell carcinoma (ESCC) are still exposed to local recurrence in a short time. To this end, the present study sought to differentiate patient subgroups by assessing risk factors for postoperative early (within one year) local lymph node recurrence (PELLNR).

Methods: ESCC patients were selected from a prospective database, and divided into high- and low-risk groups according to the time of their local lymphatic recurrence (within one year or later). Survival analysis was conducted by the Cox regression model to evaluate the overall survival (OS) between the two groups. The hazard ratio (HR) and 95% confidence interval (CI) of different variables were also calculated. Logistic regression analysis was used to explore the high-risk factors for PELLNR with the odds ratio (OR) and 95% CI calculated.

Results: A total of 432 cases were included. The survival of patients in the high-risk group ($n = 47$) was significantly inferior to the low-risk group ($n = 385$) (HR = 11.331, 95% CI: 6.870–16.688, $P < 0.001$). The 1-year, 3-year, and 5-year OS rate of the patients in high/low-risk groups were 74.5% vs. 100%, 17% vs. 88.8%, and 11.3% vs. 79.2%, respectively ($P < 0.001$). Risk factors for local lymph node recurrence within one year included upper thoracic location (OR = 4.071, 95% CI: 1.499–11.055, $P = 0.006$), advanced T staging (pT3–4, OR = 3.258, 95% CI: 1.547–6.861, $P = 0.002$), advanced N staging (pN2–3, OR = 5.195, 95% CI: 2.269–11.894, $P < 0.001$), and neoadjuvant treatment (OR = 3.609, 95% CI: 1.716–7.589, $P = 0.001$). In neoadjuvant therapy subgroup, high-risk group still had unfavorable survival (Log-rank $P < 0.001$). Multivariate analysis demonstrated that upper thoracic location (OR = 5.064, 95% CI: 1.485–17.261, $P = 0.010$) and advanced N staging (pN2–3) (OR = 5.999, 95% CI: 1.986–18.115, $P = 0.001$) were independent risk factors for early local lymphatic recurrence. However, the cT downstaging (OR = 0.862, 95% CI: 0.241–3.086, $P = 0.819$) and cN downstaging (OR = 0.937, 95% CI: 0.372–2.360, $P = 0.890$) for patients in the neoadjuvant subgroup failed to lower PELLNR. The predominant recurrence field type was single-field.

Abbreviations

CI, confidence interval; CT, computed tomography; cT, clinical tumor stage; cN, clinical node stage; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; PET, positron emission tomography; HR, hazard ratio; OR, odds ratio; OS, overall survival; pN, pathologic node stage; pT, pathologic tumor stage; TNM, tumor-node-metastasis; VATS, video-assisted thoracoscopic surgery.

Conclusions: Thoracic ESCC patients with lymph node recurrence within one year delivered poor outcomes, with advanced stages (pT3–4/pN2–3) and upper thoracic location considered risk factors for early recurrence.

KEYWORDS

early local lymph node recurrence, mckeown esophagectomy, risk factors, esophageal squamous cell carcinoma, prognosis of esophageal cancer

Introduction

Esophageal squamous cell carcinoma (ESCC) is the most common esophageal malignancy, featuring an Asian lineage and a thoracic location as the most common circumstances (1, 2). Multidisciplinary treatment is the generally accepted treatment strategy for locally advanced ESCC, with surgery considered a key component of a comprehensive treatment framework (3, 4). However, even after radical resection, some patients still face local recurrence in a short period (5, 6). Particularly, early local lymphatic recurrence within one year after surgery is the main reason for postoperative failure and poor prognosis for long-term survival (7). In addition, early recurrence raises questions among doctors and patients about the role of surgery in comprehensive treatment of ESCC. However, the clinical factors affecting early postoperative local lymphatic recurrence are inconclusive, thereby resulting in the lack of support for adjuvant treatment of patients undergoing R0 resection in clinical guidelines, including *The National Comprehensive Cancer Network* (8). It is hereby hypothesized that distinct clinicopathological characteristics determine the likelihood of early local lymphatic recurrence within one year after radical resection. Two subgroups of patients are speculated to require different diagnosis and treatment programs. Thus, a retrospective review was hereby conducted upon the prospective database of the Thoracic Surgery Department I of Peking University Cancer Hospital, taking thoracic ESCC patients having undergone radical esophagectomy as subjects. Clinicopathological factors and follow-up information were reviewed to assess risk factors for early local lymphatic recurrence, and long-term prognostic characteristics were examined to clarify the early-recurrence subgroup of patients.

Methods

Characteristics of the database

Eligible patients were screened from the prospective ESCC database of our department. In accordance with the Institutional Review Board, the informed consent requirement was waived for this study. The database was established in 2000, and is provided with the following characteristics:

1) It featured a high-level standardization. Data collection was designed as a pull-down menu of standardized items, which avoided varying physician descriptions.
2) Baseline data must be entered before initial treatment, and the pre-operative data including the re-staging information must be entered before surgery. The intraoperative findings (operation notes) must be completed before the patient leaves the operating room, and discharge notes must be entered before the patient leaves the hospital. Outpatient follow-up information must be entered in real-time.
3) The pre-treatment/pre-operation examinations included gastroscopy with tumor biopsy and pathological diagnosis. The staging and quantitative examinations included gastroscopy bronchoscopy (middle or upper thoracic ESCC), chest/abdominal contrast CT scan, abdominal ultrasound, and cervical-supraclavicular ultrasound, and upper gastrointestinal barium meal. Since its establishment in 2012, whole-body PET/CT and ultrasound endoscopy have been performed routinely.
4) Patients were staged according to *The 7th Edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM* staging system for esophageal cancer (9).
5) Locally advanced patients (cT3~4a or cN+) received neoadjuvant treatment, predominantly induction chemotherapy; the regimens were dual drug combinations based on platinum, 95% of which were paclitaxel combined with cisplatin. All patients underwent surgery 4~6 weeks after neoadjuvant chemotherapy.
6) Follow-up was defined as outpatient visit with standard examinations. Follow-up evaluation consisted of interviews at 3-month intervals for 2 years, then at 6-month intervals for 3 years, and finally at 12-month intervals until death. Outpatient follow-up visits included records of symptoms and findings of physical examinations. Objective examinations included chest CT scan, barium upper esophagography, abdominal and cervical ultrasound, and gastroscopy, if necessary. Since 2010, some subjects have undergone positron emission tomography-computed tomography (PET/CT) examinations.
7) Local lymph node recurrence was defined as regional lymph nodes within the surgical field, while lymph node-recurrent regions were classified as cervical-supraclavicular lymph node, mediastinal lymph node, and abdominal lymph

node according to locations of the lymph nodes. The standard for recurrence was newly found enlarged lymph nodes (minimal diameter > 10 mm) on the follow-up cervical-supraclavicular region by physical examination/ultrasound/CT, chest by CT, and abdominal by CT/ultrasound, which was hypermetabolic on PET/CT.

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients having received surgery between January 1 2010 and April 30 2017; 2) Treatment naïve patients before visiting us; 3) Pathologically confirmed squamous cell carcinoma; and 4) Patients having undergone the McKeown (open/minimal invasive) procedure and R0 resection (en-bloc) with at least two-field lymph node dissection.

Exclusion criteria:1) Patients with cervical esophageal cancer; 2) Patients with distant metastases or local recurrence plus distant metastases as the first recurrence; 3) Patients exposed to anastomotic recurrence; 4) Patients subject to perioperative death (died within 90 days after surgery); 5) Patients having died from reasons other than cancer; 6) Patients having received adjuvant radiotherapy after surgery; or 7) Patients presenting other malignancies at the time of ESCC.

Herein, a total of 432 cases were ultimately surveyed. Based on the observation of the lymph node recurrence risk of esophageal cancer in this center, it was found that one year after surgery was the highest risk of recurrence, which was thus divided into a high-risk group (local lymphatic recurrence within one year) and a low-risk group (local lymphatic recurrence after one year) (**Supplementary Appendix S1**).

TABLE 1 Multivariate COX regression overall survival analysis.

Item	Multivariate		
	OR	95% CI	*P*
Sex (Male vs. Female)	1.177	0.700–1.981	0.539
Age (>60 year vs. ≤ 60 year)	0.844	0.549–1.298	0.441
Location			0.771
L1 vs. L3	1.064	0.607–1.867	0.828
L2 vs. L3	0.879	0.459–1.683	0.697
Neoadjuvant therapy (Yes vs. No)	1.189	0.732–1.931	0.485
Lvi (Yes vs. No)	0.880	0.496–1.561	0.662
pT (T3-4 vs. T1-2)	2.493	1.562–3.980	0.000
pN (N2-3 vs. N0-1)	2.223	1.241–3.982	0.007
Lymph nodes dissected (>20 vs. ≤ 20)	1.392	0.905–2.141	0.132
High-risk vs. low-risk group	11.331	6.870–18.688	0.000

OR, odds ratio; CI, confidence interval; L1, upper thoracic location; L2, middle thoracic location; L3, lower thoracic location; Lvi, lymph-vascular invasion.

Statistics

SPSS 25.0 software (IBM Corp, Armonk, NY) was used for statistical analysis; the chi-square test or Fisher's exact probability method was used for numerical data comparisons, and the rank sum test was used for ranked data comparison. The correlation between different parameters was analyzed using Pearson correlation analysis, and the Kaplan-Meier curve was used to analyze the survival of patients. Intergroup survival analysis was completed using the Log-Rank method. Multivariate survival analysis was conducted based on the Cox regression model. The hazard ratio (HR) and 95% confidence interval (CI) of different variables were also calculated. A logistic regression model was used to evaluate risk factors for recurrence within one year with the odds ratio (OR) and 95% CI calculated. The *P* value less than 0.05 was defined as statistical significance.

Results

General characteristics of the patients

A total of 432 cases were selected for this study, of which, 327 (78.2%) were male and 105 (21.8%) were female, with a median age of 60 (range: 39–80). Besides, 216 patients (50%) received neoadjuvant therapy, and 17 (8%) obtained pCR as confirmed by postoperative pathological examination. The numbers of cases with Stage I, II, and III were 122 (28.2%),

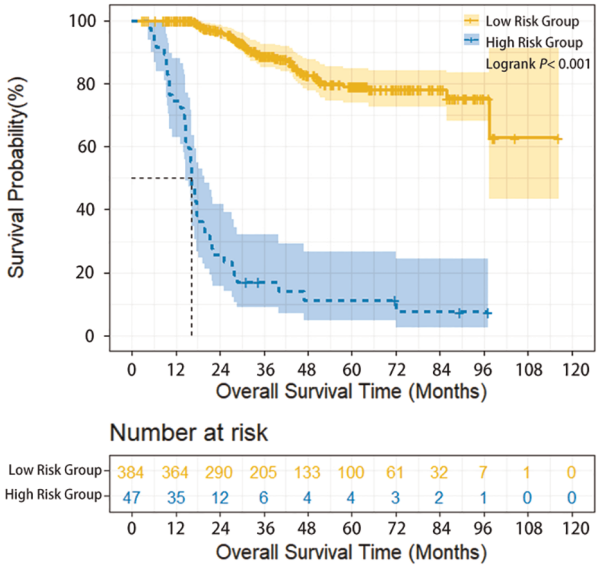

FIGURE 1
Overall survival of ESCC patients with different lymphatic recurrence risk in whole group. Overall survival of high-risk patients was significantly worse compared with low-risk patients in the whole group ($P < 0.001$).

186 (43.1%), and 107 (24.8%), respectively. The follow-up rate was 91.2%, with 38 cases lost to follow-up. The median follow-up time was 41.9 months (3.2 months to 116.5 months). At the last follow-up, 114 cases (26.4%) had local recurrence, and 93 (49.2%) died. Upon recurrence, 76 cases (66.7%) received chemo/chemoradiotherapy, and 38 (33.3%) received supportive treatment only. The general clinicopathological data of the high-risk group vs. the low-risk group and the neoadjuvant treatment group vs. the direct surgery group are shown in **Supplementary Appendices S2, S3**.

Survival analysis

The survival of high-risk patients (47 cases, 10.9%) was significantly worse than that of low-risk patients (385 cases, 90.1%) (HR = 11.331, 95% CI: 6.870–16.688, $P < 0.001$) (**Table 1**). The 1-year, 3-year, and 5-year overall survival (OS) of high-risk and low-risk patients was 74.5% vs. 100%,17% vs. 88.8%, and 11.3% vs. 79.2% ($P < 0.001$), respectively (**Figure 1**).

Analysis for risk factors of PELLNR within one year

Upper thoracic location (OR = 4.071, 95% CI: 1.499–11.055, $P = 0.006$), advanced T staging (pT3–4) (OR = 3.258, 95% CI: 1.547–6.861, $P = 0.002$), advanced N staging (pN2–3) (OR = 5.195, 95% CI: 2.269–11.894, $P < 0.001$), and neoadjuvant therapy (OR = 3.609, 95% CI: 1.716–7.589, $P = 0.001$) were found independent risk factors for early local lymphatic recurrence *via* multivariate analysis (**Table 2**).

Subgroup analysis for patients with neoadjuvant therapy

Herein, 206 (95.37%) of 216 patients with neoadjuvant chemotherapy were treated with TP regimen (paclitaxel/nab-paclitaxel+cisplatin) and 22 (10.19%), 169 (78.24%), 17 (7.87%) and 8 (3.70%) patients underwent 1, 2, 3 and 4 cycles of preoperative treatment, respectively. Compared with patients having undergone directly surgery, patients who received neoadjuvant therapy had more advanced stages, and the proportion of cN+cases in the two subgroups was 16.2% and 64.8%, respectively. In addition, for neoadjuvant therapy cases, high-risk group (35 cases, 16.2%) had poorer survival compared with low-risk group (181 cases, 83.8%) (HR = 7.991, 95% CI: 4.482–14.248, $P < 0.001$). The 1-year, 3-year, and 5-year OS of high-risk and low-risk patients were 80% vs. 100%, 15.2% vs. 82.6%, and 10.2% vs. 75.2%, respectively ($P < 0.001$) (**Figure 2**). Multivariate analysis demonstrated that upper thoracic location (OR = 5.064, 95% CI: 1.485–17.261, $P = 0.010$) and advanced N staging (pN2–3) (OR = 5.999, 95% CI: 1.986–18.115, $P = 0.001$) were independent risk factors for early local lymphatic recurrence. However, after neoadjuvant therapy, cT downstaging (OR = 0.862, 95% CI: 0.241–3.086, $P = 0.819$) or cN downstaging (OR = 0.937, 95% CI: 0.372–2.360, $P = 0.890$) failed to lower the risk for early lymphatic recurrence (**Table 3**).

Lymph node dissection site and common sites for local lymphatic recurrence

All the patients in the study had two- or three-field lymph node dissection. Patients who had mediastinal lymph node

TABLE 2 Results of univariate and multivariate analyses of risk factors for PELLNR in ESCC patients with radical esophagectomy.

Item	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (Female vs. Male)	1.218	0.616–2.405	0.571			
Age (>60 year vs. ≤ 60 year)	0.624	0.338–1150	0.131			
Smoker (Yes vs. No)	1.107	0.585–2.096	0.755			
Location (L1 vs. L2+L3)	3.32	1.319–8.359	0.11	4.071	1.499–11.055	0.006
Multiple primary tumor (Yes vs. No)	1.644	0.599–4.509	0.334			
Neoadjuvant therapy (Yes vs. No)	3.287	1.656–6.525	0.001	3.609	1.716–7.589	0.001
Approach (VATS vs. Open)	0.741	0.378–1.453	0.383			
Lymph nodes dissected (>20 vs. ≤ 20)	1.125	0.613–2.064	0.704			
Lvi (Yes vs. No)	2.168	1.097–4.284	0.026	1.262	0.557–2.857	0.577
pT (T3-4 vs. T1-2)	4.423	2.226–8.788	<0.001	3.258	1.547–6.861	0.002
pN (N2-3 vs. N0-1)	7.127	3.459–14.682	<0.001	5.195	2.269–11.894	<0.001
Serious complication (Yes vs. No)	1.518	0.556–4.142	0.415			
Postoperative adjuvant therapy (Yes vs. No)	1.444	0.783–2.663	0.239			

HR, hazard ratio; CI, confidence interval; L1, upper thoracic location; L2, middle thoracic location; L3, lower thoracic location; VATS, video-assisted thoracoscopic surgery; Lvi, lymph-vascular invasion.

dissection mainly included 304 cases (70.37%) with left and right recurrent laryngeal nerve lymph nodes, 419 cases (96.99%) with subcarinal lymph nodes, 432 cases (100%) with paraesophageal lymph nodes, and 323 cases (74.77%) of superior phrenic lymph nodes; patients who had abdominal lymph node dissection mainly included 422 (97.69%) with right cardiac lymph nodes, 422 patients (97.69%) with left cardiac lymph nodes, 422 patients (97.69%) with gastric lesser curvature lymph nodes, 422 patients (97.69%) with left gastric periarterial lymph nodes; 19 patients (4.39%) underwent cervical lymph node dissection. The most common sites for local lymphatic recurrence were mediastinal lymph nodes (74 cases, 17.1%), cervical lymph nodes (44 cases, 10.2%), and abdominal lymph nodes (19 cases, 4.4%), successively. The predominant field type for recurrence was single-field, with 92 (21.3%) cases found to have a single-field recurrence, and 22 (5.1%), multiple-field recurrence.

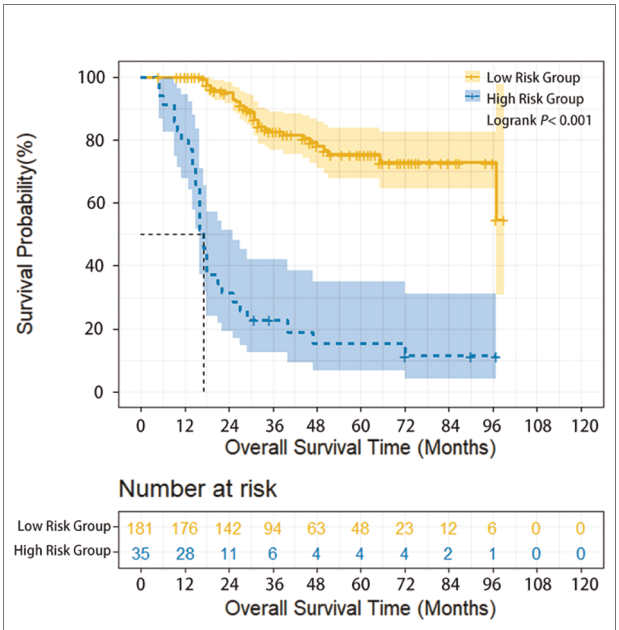

FIGURE 2
Overall survival of ESCC patients with different lymphatic recurrence risk in neoadjuvant treatment subgroup. Overall survival of high-risk patients was significantly worse compared with low-risk patients in the neoadjuvant treatment subgroup ($P < 0.001$).

Comment

A high-quality prospective database is important for a reliable retrospective study, and standardized terms, prospective maintenance, and formatted content are the sole requirements for data quality. Herein, the original data (including image series) were traceable for each patient in our study. In order to avoid the interference of different lymph node dissection ranges of different procedures, the inclusion/exclusion criteria were hereby designed to avoid possible ambiguous factors to affect the survival. For example, only patients having undergone the McKeown (open/minimally invasive) procedure and en-bloc resection were included (10). All patients had at least two-field (chest and abdomen) lymph node dissection and R0 resection (11). Patients with cervical esophageal cancer and those who either had simultaneous distant metastases as the first

TABLE 3 Results of univariate and multivariate analyses of risk factors for PELLNR in ESCC patients with neoadjuvant therapy.

Item	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (Female vs. Male)	0.881	0.358–2.167	0.783			
Age (>60 year vs. ≤ 60 year)	0.547	0.260–1.152	0.112			
Smoker (Yes vs. No)	1.127	0.751–1.692	0.563			
Location (L1 vs. L2+L3)	4.435	1.424–13.812	0.01	5.064	1.485–12.261	0.01
Multiple primary tumor (Yes vs. No)	1.118	0.304–4.116	0.866			
Approach (VATS vs. Open)	0.827	0.373–1.834	0.64			
Lymph nodes dissected (>20 vs. ≤ 20)	1.017	0.492–2.103	0.964			
Lvi (Yes vs. No)	3.312	1.428–7.684	0.005	2.117	0.777–5.768	0.142
pT (T3-4 vs. T1-2)	3.301	1.498–7.275	0.003	2.73	0.760–9.807	0.124
pN (N2-3 vs. N0-1)	8.922	3.466–22.963	<0.001	5.999	1.986–18.115	0.001
cT down staging	0.413	0.188–0.910	0.028	0.862	0.241–3.086	0.819
cN down staging	0.516	0.234–1.138	0.101	0.937	0.372–2.360	0.89
Serious complication (Yes vs. No)	1.212	0.327–4.495	0.774			
Postoperative adjuvant therapy (Yes vs. No)	1.1	0.514–2.354	0.806			

HR, hazard ratio; CI, confidence interval; L1, upper thoracic location; L2, middle thoracic location; L3, lower thoracic location; VATS, video-assisted thoracoscopic surgery; Lvi, lymph-vascular invasion.

recurrence, anastomotic recurrence or underwent postoperative supplementary radiation, were excluded (12, 13). Even though, 10.9% of PELLNR cases were still observed. Although 87% of the patients received radiotherapy/chemotherapy upon the detection of recurrence, the long-term prognosis was still far worse than that of the low-risk group. In this case, it was thought that the long-term survival of ESCC patients could be improved by strengthening local control measures to control regional lymph node recurrence better.

Upper thoracic location, advanced T/N staging, and preoperative therapy were found independent risk factors for early local recurrence *via* multivariate analysis, and such a finding is provided with the following clinical implications:

1. Cervical lymph node dissection should be emphasized for upper thoracic ESCC. Japanese surgeons believe that cervical lymph node dissection should be routinely performed to reduce the local recurrence rate of ESCC in the upper thorax (14, 15). However, in this study, cervical lymph node dissection was only performed for those with clinical suspicious lymph node metastases (only 19 cases), which might be one of the reasons for the higher risk of ESCC in the upper thorax.
2. Staging of esophageal cancer is hindered by the low coincidence rate between clinical and postoperative pathological staging, and methods from multiple perspectives are thus required for more accurate staging. Compared with other solid malignancies such as lung cancer, various preoperative staging methods for esophageal cancer are subject to certain limitations, thereby affecting the accuracy of clinical staging, also the differentiation of the postoperative curative effect (16, 17). For this reason, the pathological staging was still hereby used to reflect the malignant degree of the tumor. According to multivariate analysis, patients with more advanced stages (pT3–4/pN2–3) presented higher infiltration and metastatic ability of the tumor and were more likely to have PELLNR.
3. The importance of re-staging after induction therapy needs to be emphasized. Neoadjuvant chemotherapy could reduce the tumor size, eliminate potential metastases, and downstage the tumor, thus reducing postoperative recurrence and metastasis, and improving the long-term survival of the patients (3). In order to minimize the impact of selection bias on the results, subgroup analysis was performed for patients with neoadjuvant therapy. The results showed that upper thoracic location and pN2–3 were still risk factors for PELLNR. However, the responses to neoadjuvant therapy (cT downstaging and cN downstaging) were not independent risk factors for PELLNR. The potential reasons were: first, the small sample size limited the influence of different tumor responses on the risk of PELLNR; second, the accuracy of clinical evaluation for the efficacy of neoadjuvant therapy was still unsatisfactory.
4. Efforts should be made to introspect the survival benefits of chemotherapy alone and provide more evidence for the effect of induction chemotherapy alone and induction chemoradiotherapy. In the current study, those having received neoadjuvant therapy were more likely to have PELLNR. Although further analysis showed that the proportion of cN +was higher in the neoadjuvant therapy group (64.8%) compared with that in the upfront surgery group (16.2%), the benefit of neoadjuvant therapy could not counteract the influence of the advanced stage. Additional research should focus on the differences in the clinical benefit of curative chemoradiotherapy or surgery for the patients who failed to get downstaging after induction chemotherapy, and finally provide a reference for clinicians to establish the corresponding treatment strategies for different patient subgroups (8, 9).

Limitations of the study

First, the retrospective nature of the study determined the inevitable selection bias. For example, most patients who had received neoadjuvant therapy due to an advanced disease still had an early recurrence. Second, although the type of esophagectomy was limited to the McKeown procedure, and the resection pattern and dissection range of lymph nodes were strictly controlled, the influence of surgical quality on the recurrence could not be assessed. Third, the sample size was rather limited, and the single-center nature of the hereby selected data might have biased the interpretation of the results.

In summary, the results showed that patients with PELLNR had poorer survival and that upper thoracic location and advanced T/N staging (pT3–4/pN2–3) were the risk factors for PELLNR. For patients having received induction therapy due to advanced disease at the baseline, re-staging after neoadjuvant treatment should be reinforced to distinguish those who could oncologically benefit from surgery and those with only technically resectable tumors.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

K-NC: putting forward research ideas and designing research programs, LD: Conducting research and writing paper; Y-BY, Y-YW, W-PY, Z-MW: collecting data. HF: analyzing data. YL: translating literature. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1043755/full#supplementary-material.

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Prognostic significance of tumor regression grade in esophageal squamous cell carcinoma after neoadjuvant chemoradiation

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Backgrounds: Trimodal therapy (neoadjuvant chemoradiotherapy followed by esophagectomy) for locally advanced esophageal squamous cell carcinoma (ESCC) is associated with a significant survival benefit. Modified Ryan score is an effective tool to evaluated the tumor regression grade (TRG) after neoadjuvant therapy. The aim of this study was to evaluate the prognostic value of TRG for overall survival (OS) and disease-free survival (DFS) in ESCC patients undergoing neoadjuvant chemoradiation.

Methods: The study retrospectively reviewed 523 ESCC patients who underwent neoadjuvant chemoradiotherapy and radical esophagectomy at Jinling Hospital from January 2014 to July 2020. Kaplan–Meier curves with log-rank test and Cox regression model were used to evaluate the prognostic factor of TRG based on modified Ryan scoring system on OS and DFS.

Results: After application of inclusion and exclusion criteria, 494 patients with ESCC following neoadjuvant chemoradiotherapy and radical esophagectomy were available for analysis. The TRG scores are significantly associated with smoke history ($p = 0.02$), lymphovascular invasion (LVI) and/or peripheral nerve invasion (PNI) ($p < 0.01$), and postoperative adjuvant therapy ($p < 0.01$). Meanwhile, tumor characteristics including tumor length ($p < 0.01$) and tumor differentiation grade ($p < 0.01$) are also significantly associated with TRG score. The results of multivariable Cox regression modal showed that TRG is not an independently prognostic factor for OS ($p = 0.922$) or DFS ($p = 0.526$) but tumor length is an independently prognostic factor for DFS ($p = 0.046$).

Conclusions: This study evaluated the prognostic value of modified Ryan scoring system for ESCC after trimodal therapy and concluded that modified Ryan scoring system can predict survival and recurrence rates but is not an independently prognostic factor for OS and DFS.

KEYWORDS

esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy, esophagectomy, tumor regression grade, modified ryan scoring system

Introduction

Esophageal cancer (EC) is now the sixth leading cause of cancer deaths worldwide and the second deadliest gastrointestinal cancer after gastric carcinoma (1). The morbidity of EC varies extremely from areas and countries. Literatures reported that about 200,000 people die of EC annually worldwide and most cases of EC are diagnosed at an advanced stage (2). Esophageal squamous cell carcinoma (ESCC) is the most common EC in China. Although tremendous improvement of therapeutic modalities has been seen recently, the ESCC patient's quality of life remains poor and the 5-year survival rate rarely exceeds 40% (1). Currently, the standard treatment for clinical stages I/II/III (except for T4) ESCC is based on a combination of esophagectomy with/without adjuvant with/without neoadjuvant chemotherapy or chemoradiotherapy (3). Relative to surgery alone, multimodality therapy for locally advanced disease is associated with a significant survival benefit. It has been reported that EC patients could benefit from neoadjuvant therapy, and thus the standard treatment for these patients is neoadjuvant therapy followed by surgery (4).

The long-term survival after esophagectomy with neoadjuvant chemoradiotherapy is primarily based on the neoadjuvant treated TNM (ypTNM) staging according to the eighth American Joint Committee on Cancer (AJCC) staging system for esophageal cancer (5). However, the tumor characteristics generally are not used for prognosis. Neither tumor characteristics, such as tumor length, tumor histology, or tumor differentiation grade, nor tumor regression grade (TRG) are incorporated in the 8th AJCC ypTNM staging (6). The number of ESCC patients undergoing neoadjuvant chemoradiotherapy followed by surgery has been increasing, and it is necessary to explore which pathological factors in addition to ypTNM might be associated with an overall survival (OS) and disease-free survival (DFS).

The influence of the tumor length and tumor differentiation of EC on survival has been assessed in ESCC or mixed cohorts with ESCC and esophageal adenocarcinoma (EAC) (7, 8). Generally, patients with a shorter tumor length and a favorable tumor differentiation grade have a better long-term survival than patients with adverse tumor characteristics. A number of TRG scoring systems are used to assess the effectiveness of neoadjuvant therapy (9). One of these is the Ryan scoring system, based on the ratio of residual cancer cells to the amount of fibrosis (10). The Ryan scoring system ranges from 1 (complete or near-complete response) to 3 (poor or not response to neoadjuvant therapy). The reproducibility and prognostic value of Ryan scoring system were extensively studied in a variety of cancers, in which Ryan scoring system has been proved to be a reliable instrument to classify the tumor regression (9, 11). Modified Ryan scoring system was subsequently introduced to divide score 1 into two group: score 0 (complete response) and score 1 (near-complete response), which was more precise to stratify the patients undergoing neoadjuvant therapy compared with Ryan scoring system (11).

Accordingly, the 8th AJCC considers TRG an additional prognostic factor for rectal cancers after neoadjuvant therapy but failed to add this into the staging system (12, 13). However, whether TRG graded based on modified Ryan scoring system could be considered as a prognostic factor in addition to ypTNM in patients undergoing neoadjuvant chemoradiotherapy and esophagectomy remains controversial. Therefore, we performed this large-scale retrospective study to evaluate the independent relationship of post-treatment pathologic regression with OS and DFS in ESCC.

Methods

Patients

The study retrospectively reviewed 523 ESCC patients who underwent neoadjuvant chemoradiotherapy and radical esophagectomy at Jinling Hospital from January 2014 to July 2020. This study was approved by Jinling Hospital institutional review board. All the patients were informed concerning the risks of the neoadjuvant/adjuvant therapy and esophagectomy.

The inclusion criteria are listed as follows: (1) patients pathologically were diagnosed as ESCC before treatment; (2) patients received neoadjuvant chemoradiotherapy and esophagectomy; (3) patients were staged according to the American Joint Committee on Cancer (AJCC) 8th edition (5) (5); detailed data on the pathological information and tumor regression grade were collected (6); patients were assessed as negative surgical margin pathologically after radical esophagectomy with R0 resection. Patients were excluded if they: had missing data of pathological information, had unknown tumor regression grade, or had pathologic M1 disease. The CONSORT diagram (**Figure 1**) shows the inclusion and exclusion criteria of our study.

Tumor regression grade

We referred to the modified Ryan scoring system to score tumor regression grades (TRGs) (10). The TRG 0–3 are defined as follows: TRG 0: no viable cancer cells (complete response); TRG 1: single cell or rare small groups of cancer cells (near complete response); TRG 2: residual cancer with evident tumor regression but more than single cell or rare small groups of cancer cells (partial response); TRG 3:

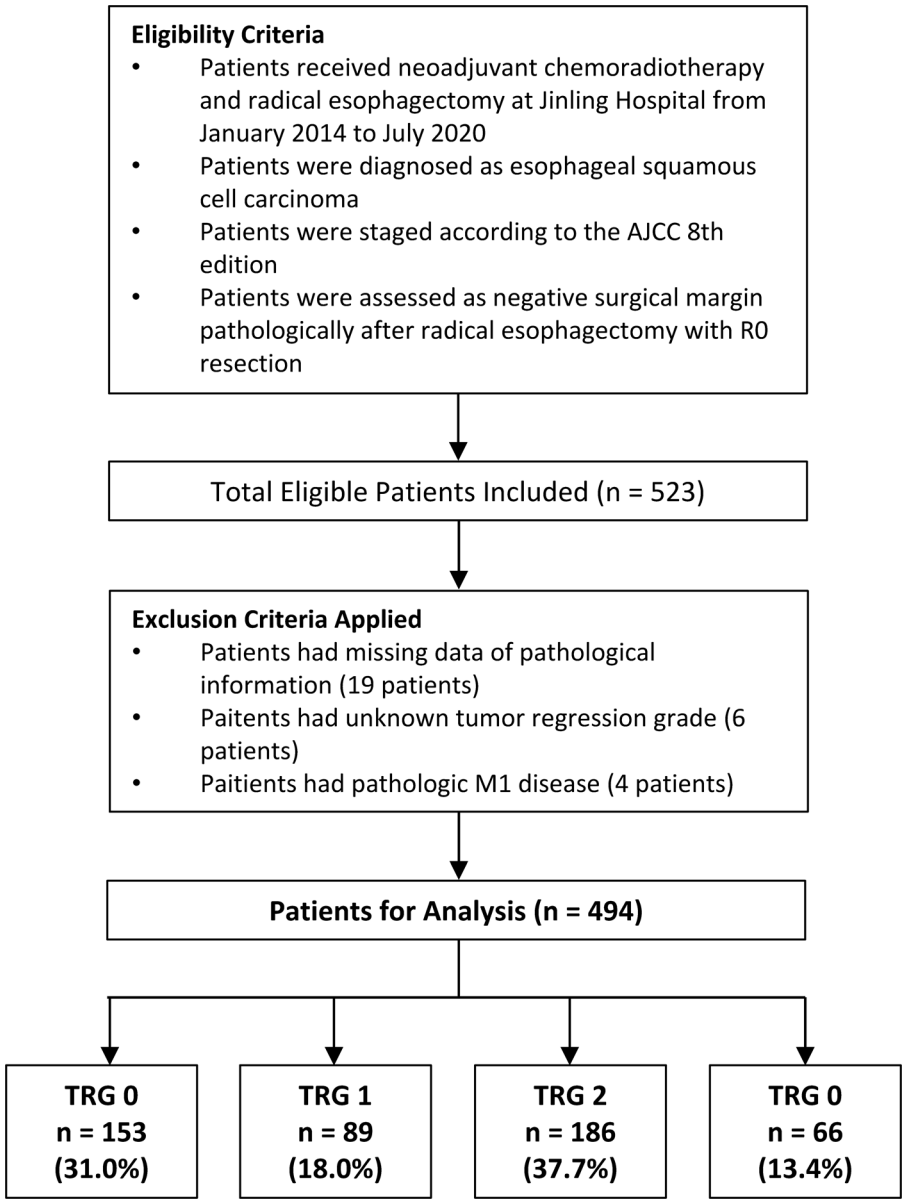

FIGURE 1
CONSORT diagram.

extensive residual cancer with no evident tumor regression (poor or not response). Three pathologists reexamined the results of the pathological sections, and the final TRG had to be agreed upon by two or more pathologists.

Patients were divided into "TRG 0', "TRG 1", "TRG 2" or "TRG 3" groups for log-rank test, Kaplan–Meier analysis, and Cox regression analysis. Meanwhile, patients were further divided in to two groups (TRG 0–1 and TRG 2–3) for subgroup analysis stratified by patients' characteristics. Demographic characteristics, operative data, postoperative complications, and pathological information were collected on all patients.

Follow-up

Patients were followed up every 3 months for the first 2 years, and then every 6 months thereafter. Neck and abdominal ultrasound, chest CT, gastroscopy, and blood test were performed on the basis of patient's symptoms during follow-up. The patient status (including death and survival), and the tumor status (including tumor recurrence and metastasis), and the patient loss of follow-up were all documented. Our follow-ups were implemented *via* telephone or outpatient department visit. The last follow-up was conducted in April 1, 2022.

Neoadjuvant therapy

The selection of neoadjuvant therapy depended on preoperative clinical stage of EC patients. Neoadjuvant chemoradiotherapy was routinely administered for patients with cN1–3 and/or cT4a-b. Neoadjuvant chemoradiotherapy included 2 cycles of chemotherapy with sequential or concurrent radiotherapy. The neoadjuvant chemoradiotherapy treatment cycle was 3 weeks (treatment during weeks 1 and 4). Pacilitaxel in a dose of 175 mg/m^2 (day 1) or carboplatin in a dose of AUC 5 (day 1), with a combination of cisplatin in the amount of 75 mg/m^2/24 h (days 1–2 or days 1–3), was given intravenously. Patients received concurrent radiation to a total dose of 50 gray (Gy), delivered in 2.0 Gy per fractions, starting at day 1 of the first chemotherapy cycle (week 1) and ending at the completion of the second chemotherapy cycle (week 4). Sequential radiation to the same doses was arranged after end of the second chemotherapy cycle. Intensity-modulated radiotherapy technique was used to perform radiotherapy in all patients.

Surgical procedure and pathology

The surgical options depended on preoperative examinations of the patients and their general condition. McKeown esophagectomy with cervical anastomoses or Ivor-Lewis esophagectomy with thoracic anastomoses combining with radical lymph node dissection were performed in a standardized manner. Meanwhile, the gastric conduit was the means of reconstruction during esophagectomy. Surgeons then separated the dissected lymph nodes from the resected esophagus and peri-esophagus tissues. Two experienced pathologists fixed the dissected specimens, then embedded and stained them with diaminobenzidine chromogen counterstain solution and hematoxylin to routinely assess resected specimens histologically and pathologically. The status of lymphovascular invasion (LVI) and peripheral nerve invasion (PNI) were also evaluated.

Adjuvant therapy

In our institution, adjuvant therapy selection was determined by a multidisciplinary team or by patients' preference. Generally, cisplatin, taxane and/or 5-fluorouracil were included in the chemotherapy regimen. External beam radiation with a total dose of 45 to 50.4 Gy (1.8–2.0 Gy/d) was utilized to administer radiotherapy by using three-dimensional conformal radiation. Chemoradiotherapy was the radiotherapy conducted from the first day of the first chemotherapy cycle. Keytruda or Opdivo combined with radiotherapy was administrated for patients undergoing adjuvant immnoradiotherapy. Usually, adjuvant therapy started 4 to 6 weeks after surgery.

Statistical analysis

Pearson's Chi-square tests or Fisher exact test was used to compare categorical variables expressing as frequencies. The independent-sample Student's *t*-test or the Mann-Whitney non-parametric U-test was used to compare continuous variables expressed as mean±standard deviation. Kaplan-Meier curves were used to analyze overall survival (OS) and disease-free survival (DFS), and the log-rank test was employed to determine statistical significance between groups. Cox regression model was used to determine pathologic variables independently associated with OS and DFS. Variables were selected for multivariate Cox-regression model entry if $p < 0.05$ on univariate analysis. In addition, factors with a *p*-Value < 0.05 in univariate analysis were further analyzed in a multivariate Cox proportional hazards model using a backwards model selection procedure (elimination criterion: $p < 0.10$). Finally, factors that were included in the final model were used to build the nomogram and risk classification system. All tests were two-sided, and $p < 0.05$ was considered as statistical significance. All statistical analysis was implemented with R (version 3.5.3).

Results

Patient characteristics

After application of inclusion and exclusion criteria, 494 patients with ESCC following neoadjuvant chemoradiotherapy and radical esophagectomy were available for analysis. Demographic characteristics, comorbidities, operative data, postoperative complications, and pathological information of included patients are displayed in **Table 1**. Complete response (TRG 0) was reported in 153 (31.0%) patients, near complete response (TRG 1) in 89 (18.0%) patients, partial response (TRG 2) in 186 (37.7%) patients, and poor or not response (TRG 3) in 66 (13.4%) patients. Adjuvant therapy was documented for in 159 (32.2%) patients. The tumors were graded as well and moderately differentiated ($n = 133$, 24.7%), or poorly differentiated ($n = 161$, 32.6%). For 200 patients (40.5%), the grade could not be determined (Gx). The median of tumor length was 3 cm, which was used as the cut-off value of tumor length. There were 186 (37.7%) patients having a tumor length more than 3 cm and the remaining 308 (62.3%) patients had a tumor length less than or equal to 3 cm.

TABLE 1 Patient characteristics.

Variable	All cohort No. (%) ($n = 494$)
Gender	
Male	404 (81.8%)
Female	90 (19.2%)
Missing	0 (0.0%)
Age (year)	
≤ 70	425 (86.0%)
> 70	69 (14.0%)
Missing	0 (0.0%)
Smoke	
Yes	252 (51.0%)
No	240 (48.6%)
Missing	2 (0.4%)
Tumor site	
Upper	61 (12.3%)
Middle	228 (46.2%)
Lower	205 (41.5%)
Missing	0 (0.0%)
Tumor length (cm)	
≤ 3 cm	308 (62.3%)
> 3 cm	186 (37.7%)
Missing	0 (0.0%)
ypTNM	
I	233 (47.2%)
II	75 (15.2%)
IIIA	55 (11.1%)
IIIB	116 (23.5%)
IVA	15 (3.0%)
Missing	0 (0.0%)
ypT	
T0	167 (33.8%)
T1	70 (14.2%)
T2	72 (14.6%)
T3	185 (37.4%)
Missing	0 (0.0%)
ypN	
N0	308 (62.3%)
N1	122 (24.7%)
N2	49 (9.9%)
N3	15 (3.0%)
Missing	0 (0.0%)
ypM	
M0	494 (100%)
M1	0 (0.0%)
Missing	0 (0.0%)
Tumor differentiation	
G1-2	133 (24.7%)
G3	161 (32.6%)
Gx	200 (40.5%)
Missing	0 (0.0%)
LVI and/or PNI	
Yes	121 (24.5%)
No	373 (75.5%)
Missing	0 (0.0%)
Complications (Clavien-Dindo)	
Grade I	78 (15.8)
Grade II	156 (31.6%)
Grade III	30 (6.1%)
Grade IV	7 (1.4%)
Missing	0 (0.0%)
Postoperative Adjuvant Therapy	
Yes	159 (32.2%)
No	335 (67.8%)
Missing	0 (0.0%)
Tumor regression grade	
TRG 0	153 (31.0%)
TRG 1	89 (18.0%)
TRG 2	186 (37.7%)
TRG 3	66 (13.4%)
Missing	0 (0.0%)

LVI, lymphovascular invasion; PNI, peripheral nerve invasion; TRG, tumor regression grade.

Characteristics associated with TRG

Patients were divided in to two groups (TRG 0–1 and TRG 2–3) for comparison. The analysis of characteristics associated with TRG was showed in Table 2. The TRG score is significantly associated with smoke history ($p = 0.02$), LVI and/or PNI ($p < 0.01$), and postoperative adjuvant therapy ($p < 0.01$). Meanwhile, tumor characteristics including tumor length ($p < 0.01$) and tumor differentiation grade ($p < 0.01$) are also significantly associated with TRG scores. Patients with poor response to neoadjuvant chemoradiotherapy (TRG2–3) were more likely to have: smoke history, longer tumor length, poorer tumor differentiation grade, poorer tumor stage, more positive lymph nodes, advanced stage, lymphovascular and peripheral nerve invasion.

Survival analysis

The median follow-up was 13.6 months (interquartile range 6.9–24.7 months) for the overall cohort. In all cohort, the OS rate was 81.8% (95% CI: 78.1–85.5%) after 1 year, 58.7% (51.8–65.6%) after 3 years, and 54.8% (45.0–64.6%) after 5

TABLE 2 Patient characteristics associated with tumor regression grade.

Variables	TRG 0–1 ($n = 242$) No. (%)	TRG 2–3 ($n = 252$) No. (%)	p-Value
Gender			0.13
Male	191 (78.9%)	213 (84.5%)	
Female	51 (21.1%)	39 (15.5%)	
Missing	0 (0.0%)	0 (0.0%)	
Age (year)			0.12
≤ 70	202 (83.5%)	223 (88.5%)	
> 70	40 (16.5%)	29 (11.5%)	
Missing	0 (0.0%)	0 (0.0%)	
Smoke			0.02
Yes	111 (45.9%)	141 (56.0%)	
No	131 (54.1%)	109 (43.3%)	
Missing	0 (0.0%)	2 (0.8%)	
Tumor site			0.18
Upper	24 (9.9%)	37 (14.7%)	
Middle	110 (45.5%)	118 (46.8%)	
Lower	108 (44.6%)	97 (38.5%)	
Missing	0 (0.0%)	0 (0.0%)	
Tumor length (cm)			0.00
≤ 3 cm	187 (77.3%)	121 (48.0%)	
> 3 cm	55 (22.7%)	131 (52.0%)	
Missing	0 (0.0%)	0 (0.0%)	
ypTNM			0.00
I	194 (80.2%)	39 (15.5%)	
II	6 (2.5%)	69 (27.4%)	
IIIA	30 (12.4%)	25 (9.9%)	
IIIB	8 (3.3%)	108 (42.9%)	
IVA	4 (1.7%)	9 (3.6%)	
Missing	0 (0.0%)	0 (0.0%)	
ypT			0.00
T0	161 (66.5%)	6 (2.4%)	
T1	47 (19.4%)	23 (9.1%)	
T2	24 (9.9%)	48 (19.0%)	
T3	10 (4.1%)	175 (69.4%)	
Missing	0 (0.0%)	0 (0.0%)	
ypN			0.00
N0	199 (82.2%)	109 (43.3%)	
N1	34 (14.0%)	88 (34.9%)	
N2	5 (2.1%)	44 (17.5%)	
N3	4 (1.7%)	9 (3.6%)	
Missing	0 (0.0%)	0 (0.0%)	
Tumor differentiation			0.00
G1-2	32 (13.2%)	101 (40.1%)	
G3	28 (11.6%)	133 (52.8%)	
Gx	182 (75.2%)	18 (7.1%)	
Missing	0 (0.0%)	0 (0.0%)	
LVI and/or PNI			0.00
Yes	10 (4.1%)	111 (44.0%)	
No	232 (95.9%)	141 (56.0%)	
Missing	0 (0.0%)	0 (0.0%)	
Postoperative adjuvant therapy			0.00
Yes	55 (22.7%)	104 (41.3%)	
No	187 (77.3%)	148 (58.7%)	
Missing	0 (0.0%)	0 (0.0%)	

TRG, tumor regression grade; LVI, lymphovascular invasion; PNI, peripheral nerve invasion.

years. Meanwhile, the DFS rate was 75.8% (71.7–80.0%) after 1 year, 53.4% (46.9–59.9%) after 3 years, and 54.8% (39.5–70.1%) after 5 years. When comparing patients with different TRG, patients with poorer response had a significantly shorter post-resection OS and DFS compared with those with better response (Log-Rank, OS: $p < 0.01$; DFS: $p < 0.01$, Figure 2). Patients were then divided in to two groups (TRG 0–1 and TRG 2–3) for comparison. The OS and DFS of patients with poor response (TRG 2–3) were significantly shorter than those with complete response (TRG 0–1) (Figure 3).

Cox regression analysis

The results of univariate and multivariate Cox regression were showed in Tables 3, 4. The ypTNM stage and 3 tumor characteristics including tumor length, tumor differentiation grade and TRG were included for univariate Cox regression. The results showed that the ypTNM stage and 3 tumor characteristics were all significantly associated with OS and DFS. Patients with worse OS and DFS were more likely to have: longer tumor length, poorer tumor differentiation grade, poorer TRGs, and more advanced ypTNM stage. These four variables were selected for multivariate Cox regression model entry due to $p < 0.05$ on univariate analysis. The results of Cox regression analysis on OS shows that only ypTNM stage are independently prognostic factor for OS in patients undergoing trimodal therapy. The results of Cox regression analysis on DFS shows that both ypTNM stage and tumor length were independently prognostic factors for DFS. However, TRG is not an independently prognostic factor for OS ($p = 0.922$) or DFS ($p = 0.526$).

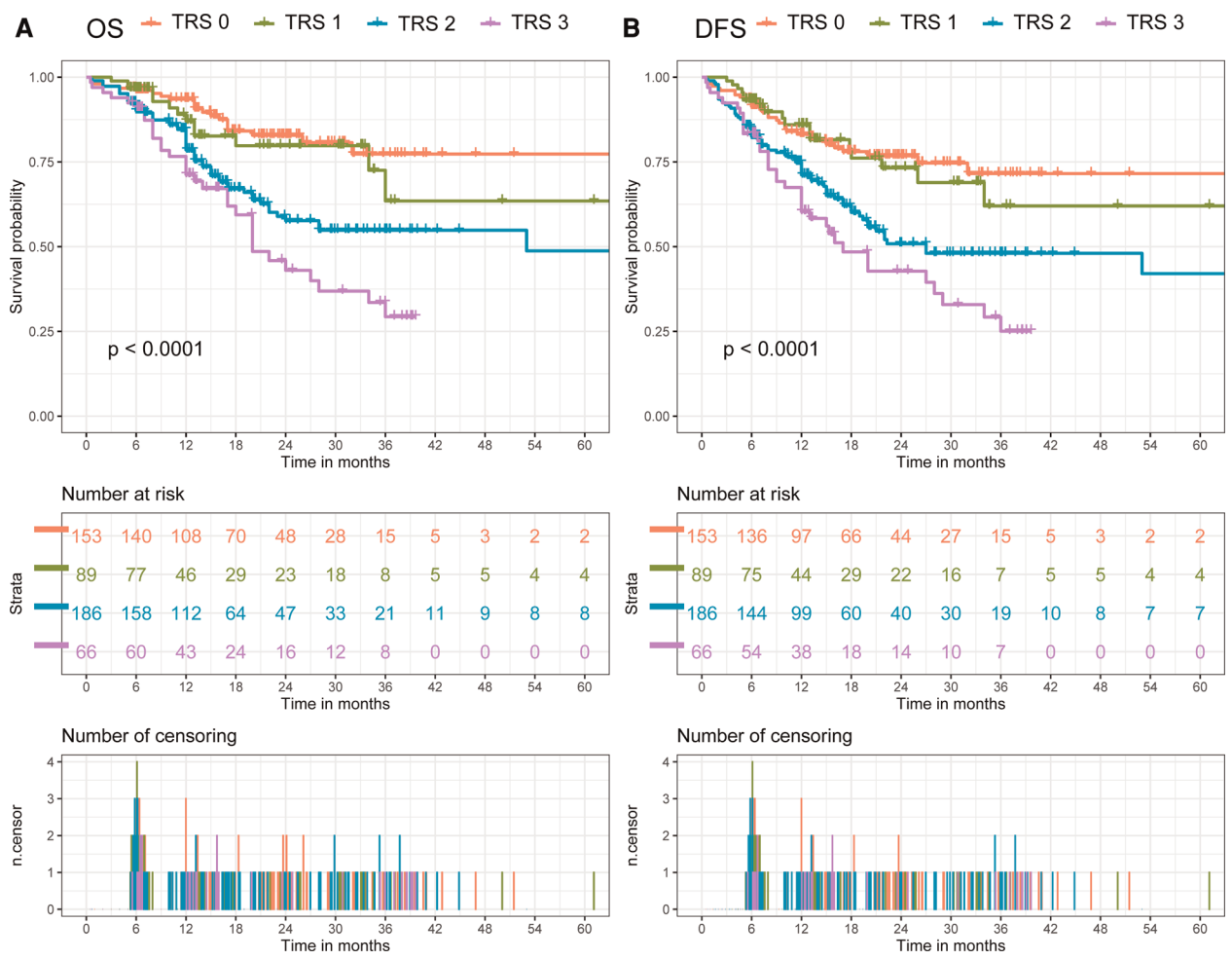

FIGURE 2
Comparison of overall survival (OS) and disease-free survival (DFS) in all cohort. (A) Comparison of OS between patients with different tumor regression grade. (B) Comparison of DFS between patients with different tumor regression grade.

Building and validating the novel nomogram

Multivariate Cox proportional hazards model by using a backwards model selection procedure was utilized to analyze the factors with a *P*-value < 0.05 in univariate analysis. Finally, factors including ypTNM stage and tumor length were identified as independent predictors of DFS and were included in the predictive model (**Supplementary Table S1**). The predictive model was virtually presented in the form of a nomogram (**Supplementary Figure S1**). The C-index of the novel nomogram was 0.702, reflecting the good discrimination ability of the model.

Discussion

Esophagectomy with radical lymphadenectomy is the primary treatment for localized ESCC. Recently, preoperative chemoradiation has become the standard treatment among most patients with potentially curable ESCC, since the CROSS Group reported good results of neoadjuvant therapy (14, 15). Therefore, concurrent neoadjuvant chemoradiotherapy followed by surgery has been considered as a preferred treatment strategy for these patients diagnosed as ESCC in China. Many systematic reviews concluded that preoperative chemoradiation could be an effective treatment for locally advanced esophageal cancer, since it reduces margin-positive resections and improves survival rates (16). Recently, tumor regression grade has been introduced to evaluate the efficacy of neoadjuvant therapy (9). Complete pathologic response to neoadjuvant therapy has been proved to be associated with higher survival rates and lower recurrence rates and is, therefore, a vital prognostic factor.

Many scoring systems have been proposed to evaluate pathologic response. Mandard et al. (17) first reported a five-tier system for assessing TRG in esophageal carcinoma in

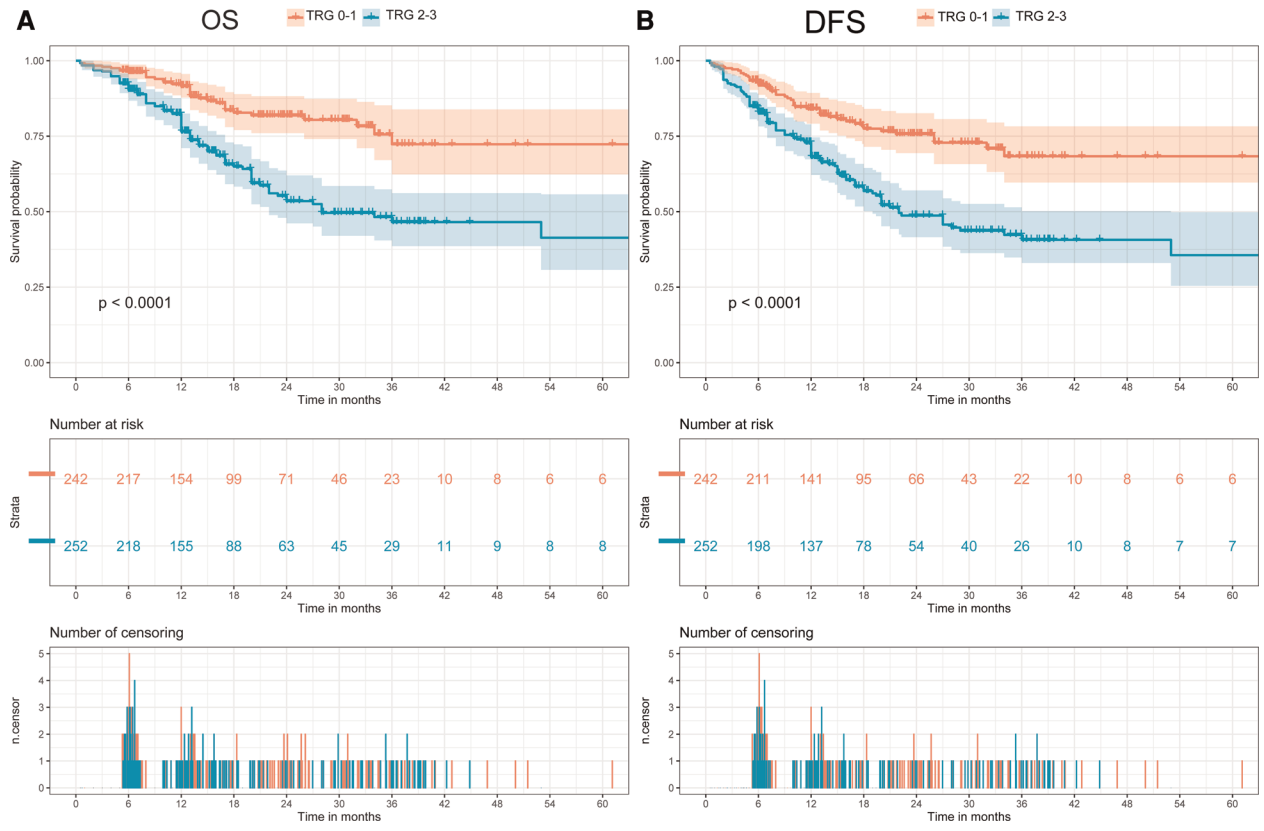

FIGURE 3
Comparison of overall survival (OS) and disease-free survival (DFS) between two groups (TRG 0-1 vs. TRG 2-3). (A) Comparison of OS between two groups (TRG 0-1 vs. TRG 2-3). (B) Comparison of DFS between two groups (TRG 0-1 vs. TRG 2-3).

1994. Subsequent studies validated its efficacy of predicting long-term survival. Afterwards, Chirieac et al. (18) introduced a three-tier system in 2005 and Schneider et al. (19) published a four-tier system that considers lymph node involvement. Each one of these systems emphasizes determinate histological features, evaluating the presence/absence of residual cancer cells differently. In the same year, Ryan et al. (10) reported a practical three-point system to assess TRG of patients with locally advanced rectal adenocarcinoma who underwent neoadjuvant therapy. Compared with other systems, it is associated with better reproducibility and more concordance between pathologists. The use of Ryan scoring system for ESCC and its correlation with OS, DFS, and recurrence of disease is currently unprecedented (11). Ryan scoring system enables easier and more clear-cut scoring than other scoring systems and can predict long-term survival and recurrence.

Takeda et al. (11) in 2019 first introduced Ryan scoring system to evaluate the efficacy of neoadjuvant therapy and explore its correlation with survival outcomes. They used a three-tier system, in which score 1 was defined as complete response (no viable cancer cells) or near-complete response (single cells or rare small groups of cancer cells). Their study concluded that Ryan score predicts survival and recurrence rates. However, several limitations existed in their study. Three-tier system could not precisely stratify the EC patients undergoing trimodal therapy. Therefore, in our study the modified Ryan scoring system (a four-tier system) was evaluated for prognosis. In this system, the Score 1 was divided into two scores: TRG 0 (complete response) and TRG 1 (near complete response). On the other hand, the study by Takeda et al. (11) only used univariable Cox regression modal to evaluate the prognostic value of Ryan scoring system. Therefore, whether Ryan scoring system could be an independently prognostic factor for EC patients remains unclear. The results of our study showed that modified Ryan scoring system is not an independently prognostic factor for OS or DFS in ESCC patients undergoing trimodal therapy. Furthermore, only ESCC patients were included in our study, which is different from the study by Takeda et al. in which ESCC and EAC patients were both included.

The primary purpose of this study was to evaluate the prognostic impact of TRG after preoperative chemoradiotherapy on OS and DFS in ESCC patients. The

TABLE 3 Impact of treatment outcome and prognostic relevance on overall survival and disease-free survival.

Univariate analyses	3-year OS % (95% CI)	Overall survival		3-year DFS % (95% CI)	Disease-free survival	
Variables		HR (95% CI)	*p*-Value		HR (95% CI)	*p*-Value
ypTNM stage			0.000			0.000
I	79.9 (70.5–89.3)	1 (ref)		74.4 (66.2–82.6)	1 (ref)	
II	67.0 (52.5–81.5)	2.193 (1.184–4.064)		62.7 (48.4–77.0)	1.730 (1.017–2.941)	
IIIA	56.5 (37.9–75.1)	3.343 (1.802–6.202)		52.2 (32.4–72.0)	2.143 (1.224–3.750)	
IIIB	28.6 (16.8–40.4)	5.285 (3.300–8.466)		21.7 (11.1–32.3)	4.266 (2.874–6.333)	
IVA	0.0 (0.0–0.0)	15.708 (7.592–32.499)		0.0 (0.0–0.0)	13.676 (7.034–26.592)	
Tumor length (cm)			0.000			0.000
≤ 3	68.2 (58.6–77.8)	1 (ref)		63.5 (54.9–72.1)	1 (ref)	
> 3	47.1 (37.7–56.5)	2.246 (1.572–3.210)		41.0 (31.8–50.2)	2.152 (1.567–2.955)	
Tumor differentiation			0.000			0.000
G1-2	56.6 (43.5–69.7)	1 (ref)		50.2 (63.1–63.1)	1 (ref)	
G3	43.9 (32.7–55.1)	1.703 (1.119–2.592)		37.5 (26.7–48.3)	1.595 (1.095–2.324)	
Gx	73.4 (64.8–82.0)	0.605 (0.375–0.979)		72.7 (64.1–81.3)	0.590 (0.386–0.902)	
Tumor regression grade			0.000			0.000
TRG 0	95.2 (91.7–98.7)	1 (ref)		71.4 (60.8–82.0)	1 (ref)	
TRG 1	63.5 (41.2–85.8)	1.259 (0.640–2.476)		62.0 (43.8–80.2)	1.058 (0.591–1.894)	
TRG 2	54.9 (45.3–64.5)	2.432 (1.488–3.975)		48.0 (38.6–57.4)	2.045 (1.345–3.107)	
TRG 3	29.3 (14.0–44.6)	3.790 (2.201–6.527)		25.1 (10.4–39.8)	3.042 (1.888–4.902)	

OS, overall survival; DFS, disease-free survival; TRG, tumor regression grade.

TABLE 4 The multivariate analysis of overall survival and disease-free survival.

Multivariate analyses	Overall survival			Disease-free survival		
Variables	HR	95% CI of HR	*p*-Value	HR	95% CI of HR	*p*-Value
ypTNM stage			0.000			0.000
II vs. I	2.074	0.957–2.120		1.586	0.786–3.200	
IIIA vs. I	3.139	1.588–6.204		2.014	1.086–3.735	
IIIB vs. I	5.222	2.709–10.066		4.097	2.234–7.516	
IVA vs. I	11.804	4.803–29.010		15.708	7.592–32.499	
Tumor length (cm)			0.067			0.025
> 3 vs. ≤ 3	1.439	0.976–2.120		1.485	1.051–2.099	
Tumor differentiation			0.149			0.114
G3 vs. G1-2	1.535	0.996–2.365		1.416	0.963–2.082	
Gx vs. G1-2	1.264	0.672–2.378		0.913	0.494–1.687	
Tumor regression grade			0.922			0.526
TRG1 vs. TRG0	0.763	0.355–1.643		0.610	0.308–1.207	
TRG2 vs. TRG0	0.845	0.354–2.017		0.670	0.312–1.439	
TRG3 vs. TRG0	0.829	0.324–2.124		0.605	0.262–1.396	

TRG, tumor regression grade.

secondary aim of this study was to assess the prognostic impact of tumor characteristics including tumor length and tumor differentiation on OS and DFS. To our knowledge, this is the first study based on 8th AJCC ypTNM staging and modified Ryan scoring system to investigate the prognostic impact of tumor characteristics including tumor length, tumor differentiation, and TRG on OS and DFS in ESCC patients undergoing trimodal therapy.

The results of the present study showed that smoke status and tumor length of patients could influence the pathologic response to neoadjuvant chemoradiotherapy. Patients who had smoke history were more likely to have poor response to neoadjuvant therapy. When the tumor length of patients was more than 3 cm, the risk of poor response also increased. Hollis et al. (8) conducted a retrospective analysis including 358 patients and found that tumor size is associated with tumor grade, pathological T and N stages, and prognosis. Several previous studies on gastric cancer have also shown that tumor size is related to TRG and prognosis (20–22), but the mechanism has not been investigated. Meanwhile, the results showed that TRG was not only correlated with the tumor invasion status after neoadjuvant CRT, but also associated with lymph node metastasis. The proportion of ypN+patients in TRG 2–3 group were significantly higher than that in TRG 0–1 group. This result indicated that neoadjuvant chemoradiotherapy could concurrently improve the status of lymph node metastasis in patients with complete or near complete response. Remarkably, in patients undergoing neoadjuvant chemoradiotherapy, TRG was significantly correlated with incidence of LVI and/or PNI. Numerous reports have demonstrated that LVI and PNI are poor prognostic factors for patients with ESCC who have undergone surgery. The present study indicated that patients with complete response were less likely to have LVI and PNI, which implied that neoadjuvant chemoradiotherapy could also be an effective treatment to reduce the LVI and PNI of ESCC patients. In general, the purpose of neoadjuvant chemoradiotherapy is not only to shrink the primary tumor, but also to prevent the early spread of systemic disease.

The results of our study showed that TRG at the primary site were significantly correlated with systemic therapeutic effects, including a better survival outcome and a reduction in recurrence. Better long-term survival was observed in patients with complete or near complete response. Meanwhile, the univariable Cox regression analysis indicated that TRG could be a prognostic factor for OS and DFS. However, this prognostic effect was eliminated by the ypTNM stage in multivariable Cox regression analysis, which indicated that TRG was strongly associated with ypTNM stage. Therefore, TRG is not an independently prognostic factor for OS and DFS in ESCC patients undergoing trimodal therapy.

Tumor length was the only independently prognostic factor for DFS in tumor characteristics. Patients with tumor length > 3 cm had a 40% increased risk of death and recurrence compared with patients with tumor length ≤ 3 cm (HR: 1.413, 95% CI: 1.006–1.985, $p = 0.046$). The results implied that the extent of tumor invasion is also an important prognostic factor in addition to ypT stage, which may also be included in the ypTNM staging system. The C-index of the novel nomogram was 0.702, reflecting the good discrimination ability of the model.

In addition to tumor characteristics, perioperative complications are also an important factor affecting the postoperative prognosis of patients with esophageal cancer (23, 24). Multidisciplinary management of perioperative complications remains an important way to improve the long-term prognosis of patients.

There are several limitations inherent to the retrospective and observational nature of this study design to be considered. Meanwhile, this study is a single-center research, which may lead to selection bias. Therefore, controlled prospective studies, with multi-center samples are warranted to validate modified Ryan scoring system and evaluate its concordance for ESCC. Furthermore, future studies should evaluate different radiation field setting and different neoadjuvant regimens other than taxane and platinum based.

Conclusions

This study evaluated the prognostic value of modified Ryan scoring system for ESCC after trimodal therapy and concluded that modified Ryan scoring system can predict survival and recurrence rates but is not an independently prognostic factor for OS and DFS. The smoke status, tumor length, status of LVI and PNI, and ypN stage are significantly correlated with TRG score. Tumor length is an independently prognostic factor for DFS in ESCC patients undergoing neoadjuvant chemoradiation.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Jinling Hospital institutional review board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZC and SY wrote the main manuscript text. WQ, XF, HLW and CZZ prepared **Tables 1–4** and **Supplementary Table S1**. ZZ, LC, QBM and QY prepared **Figures 1–3** and **Supplementary Figure S1**. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1029575/full#supplementary-material.

SUPPLEMENTARY FIGURE S1
Nomogram predicting the disease-free survival (DFS) for patients undergoing neoadjuvant chemoradiotherapy and esophagectomy. For every patient, 2 lines are drawn upward to determine the points received from the 2 predictors in the nomogram. The sum of these points is located on the 'Total Points' axis. In addition, a line is drawn downward to determine the possibility of 12-, 24-, 48-, and 60-month DFS, and the median DFS for patients with the same total score.

SUPPLEMENTARY TABLE S1
Multivariate Cox regression model using a backwards model selection procedure.

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Construction and validation of a nomogram model to predict the overall survival rate of esophageal cancer patients receiving neoadjuvant chemotherapy: A population-based study

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Introduction: The development of neoadjuvant chemotherapy(nCT) improves the overall survival (OS) of patients with esophageal cancer(EC). The aim of this study was to determine the independent prognostic factors of EC patients receiving nCT, and to construct a nomogram model for predicting OS.
Method: This retrospective analysis was conducted from the National Cancer Institute's Surveillance Epidemiology and End Results, Clinicopathological data of patients with EC who received nCT from 2004 to 2015. The included patients were randomly divided into the training cohort and the validation cohort. Univariate and multivariate Cox proportional hazards models were used to analyze the patients in the training cohort to determine the independent prognostic factors. Based on the independent prognostic variables, nomogram models for 1-year, 2-year and 3-year OS were constructed. The receiver operating characteristic (ROC) and area under curve (AUC) were used to evaluate the discriminative ability. The calibration curves, decision curve analysis (DCA) and Kaplan-Meier (K-M) survival analysis were used to evaluate the predictive accuracy and clinical application value.
Results: A total of 2,493 patients were enrolled, with 1,748 patients in the training cohort and 745 patients in the validation cohort. Gender, marital status, tumor pathological grade, T stage, N stage, and M stage were identified as independent prognostic factor ($P < 0.05$). A novel nomogram model was constructed. ROC curve analysis revealed that the model had moderate predictive performance, which was better than that of the AJCC TNM staging system.The calibration curves showed a high agreement between the actual observed values and the predicted values. The DCA suggested that the newly constructed prediction model had good clinical application value. K-M survival analysis showed that the model was helpful to accurately distinguish the prognosis of patients with different risk levels.
Conclusions: Gender, tumor pathological grade, marital status, T stage, N stage and M stage were identified as independent prognostic factors for overall survival of patients with esophageal cancer who received neoadjuvant

chemotherapy. A nomogram prediction model was established, which was helpful to accurately and reliably predict the overall survival rate of patients with esophageal cancer who received neoadjuvant chemotherapy at 1, 2 and 3 years.

KEYWORDS

neoadjuvant chemotherapy, esophageal cancer, nomogram model, overall survival, clinical research

Introduction

Esophageal cancer (EC) is a common gastrointestinal malignancy, ranking the 7th among the most common cancers in the world, and the 6th among cancer-related deaths (1, 2). Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two main pathological types of EC.The detection rate and accuracy of imaging examinations for EC are limited due to the occult early symptoms and relatively limited lesion scope.At the same time, the EC clinical tumor markers (cytokeratin 19 fragment, squamous cell carcinoma antigen and carcinoembryonic antigen) in the detection and lack of ideal sensitivity and specific degrees (3, 4). Most patients with EC are at an locally advanced stage at the time of initial diagnosis, and the five-year survival rate after esophageal surgery alone is less than 25% (5).

In recent years, the multidisciplinary combination of neoadjuvant therapy has been continuously discussed in the clinical management of patients with EC, among which neoadjuvant chemotherapy(nCT) has been recommended as the first-line treatment option for locally advanced EC by NCCN guidelines (6). The purpose of nCT is to reduce the tumor lesion, reduce the pathological stage, improve the surgical resection rate and thus help to prolong the long-term survival. At present, the commonly used nCT is platinum combined with fluorouracil or paclitaxel (7). Ando N et al. reported that the nCT regimen of cisplatin plus fluorouracil could prolong the disease-free survival of EC patients (8). In addition to initiating neoadjuvant chemotherapy, determining prognostic factors and prognostic assessment are also important components of clinical management of EC patients. The TNM staging system proposed by the American Joint Committee on Cancer (AJCC) has been regarded by clinicians as the main basis for disease progression and prognosis evaluation of cancer patients. The primary tumor stage(T), lymph node involvement(N) and distant organ metastasis (M) are the three dimensions to evaluate the tumor stage. Although the AJCC staging system has been widely used, and its prognostic value and role in tumor patient stratification have been consistently confirmed in clinical practice. However, recent studies have consistently found that in addition to AJCC staging system, other clinical factors are also significantly associated with the prognosis of esophageal cancer patients. Qian et al. found that in addition to AJCC stage, patients' age, gender, race, and tumor grade were independently related to the prognosis of esophageal adenosquamous carcinoma (9). In addition, Huang et al. conducted prognostic analysis and constructed a survival prediction model for osteosarcoma patients who received nCT (10). Unfortunately, there was still limited studies focusing on constructing a nomogram model to predict the survival of EC patients receiving nCT.

Therefore, this study aimed to determine the independent prognostic factors for overall survival(OS), and to establish a nomogram model for predicting the 1-year, 2-year and 3-year OS of EC patients who received nCT. The representative cohort was from the Surveillance, Epidemiology and End Results (SEER) database from 2004 to 2015.

Methods

Study design

This study utilizes SEER*Stat version 8.3.9 (https://SEer.cancer.gov/) access the SEER database (covering 18 registries) established by the National cancer Institute of the United States. This publicly available database records the clinical data, pathological data and follow-up information of a large number of patients with malignant tumors in the United States, which is an important tool for the study of cancer epidemiology and prognosis of cancer patients. We retrospectively collected basic demographic information, clinicopathological data, treatment information, survival status and follow-up data of patients diagnosed with EC from 2004 to 2015 in the SEER database. Patients diagnosed with EC were staged according to the American Joint Committee on Cancer (AJCC) TNM staging system. Considering thta SEER database does not publish personally identifiable information of patients, the analysis of data in this study was exempt from medical ethical review, and informed consent was not required. All procedures performed in studies involving human participants comply with the 1,964 Declaration of Helsinki and its subsequent amendments or similar ethical standards.

Inclusions and exclusions

The inclusion criteria were as follows: (1) Patients with histologically diagnosed EC between 2004 and 2015; (2) Patients whose primary site of malignant tumor was esophagus (tumor location coded C15.0-C15.9); (3) Patients with EC as primary tumor; (4) patients receiving nCT. The exclusion criteria were as follows: (1) Patients who died during follow-up but whose cause of death was unknown; (2) patients with unknown demographic information; (3) patients with missing or unknown clinicopathological data, including the specific primary location of the tumor, pathological grade of the tumor, AJCC TNM stage of the tumor and tumor size information; (4) Patients with unknown treatment information, including primary site surgery, radiotherapy and chemotherapy.

Variable extraction and definition

Based on patient-specific information from the SEER database, 13 study variables were extracted for further analysis, including age, sex, race, marital status, primary tumor location, pathological differentiation grade, tumor size, T stage, N stage, M stage, radiation and chemotherapy information.

The primary tumor site was defined according to the International Classification of Neoplastic Diseases (ICD-O) anatomic code. (ICD-O) Codes: Upper third (C15.3), middle third (C15.4), lower third (C15.5) and other sites. Regarding marital status, we excluded misleading data on unmarried or cohabiting couples, and then included "unmarried," "separated," "single," and "widowed" all in the unmarried group. Race includes white, black or other races. To facilitate data processing, patients were divided into three age groups: ≤60 years old and >60 years old. The tumor size was divided into three groups: <5 cm, 5–10 cm, and >10 cm. Overall survival (OS), defined as the interval from the date of diagnosis to the last follow-up or death from any cause, was selected as the primary outcome of this study.

Statistical analysis

Firstly, all included patients were randomly divided into training cohort and validation cohort according to the ratio of 7:3. Chi-square test and Fisher's exact test or independent sample t-test were used to compare the differences between groups. In the prognostic analysis, the univariate Cox proportional hazards regression model was used to determine the prognostic factors of esophageal cancer patients receiving neoadjuvant chemotherapy, and the statistically significant variables in the univariate Cox proportional hazards regression model analysis ($P < 0.05$) were further included in the multivariate analysis. Variables that remained statistically significant in multivariate Cox proportional hazards regression models were identified as independent prognostic factors for OS in patients with esophageal cancer who received neoadjuvant chemotherapy. Subsequently, we constructed a novel nomogram to predict OS in patients with esophageal cancer receiving neoadjuvant chemotherapy using the "rms" and "regplot" packages, respectively, using identified independent prognostic factors. The differentiation, calibration and clinical value of nomogram were evaluated by multi-dimensional index. The sensitivity and specificity of the model were evaluated by Receiver operator characteristic (ROC) curve and Area under curve (AUC). A calibration curve and 1,000 Bootstrap resampling were used to visually compare the survival probabilities predicted by the nomogram with the actual survival conditions, thus internally and externally evaluating the agreement between the predicted and actual probabilities. Decision analysis curve (DCA) was used to analyze the clinical practicability of the model. Finally, all patients were divided into three risk subgroups: high, medium, and low, according to the optimal cut-off value of the total score determined by X-Tile software. Kaplan-Meier survival analysis and log-rank test were used to compare the survival differences among subgroups.

In this study, all statistical tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analysis of this study was conducted in IBM SPSS Statistics 25.0. The nomogram construction and validation are carried out in R software (version: 3.6.1).

Results

Baseline characteristics

A total of 2,493 eligible patients with EC who received nCT were enrolled in this tudy according to a rigorous screening procedure with inclusion and exclusion criteria. According to the ratio of 7:3, all patients were divided into the training cohort and the validation cohort, of which 1,748 patients were assigned to the training cohort and 745 patients were assigned to the validation cohort. Among inluded patients, 2,122 cases (85.11%) were male and 371 cases (14.88%) were female, and the racial distribution was predominantly white (2,265 cases, 90.85%). There were 1,198 cases (48.05%) with tumor size less than 5 cm, 674 cases (27.04%) with T1–2 stage, 844 cases (33.85%) with N0 stage, and 2,235 cases (89.65%) with M0 stage. Most of the patients were married (70.60%). The detailed basic information of EC patients receiving nCT is summarized in **Table 1**.

Determination of independent prognostic factors of OS

In this study, univariate Cox proportional hazards regression model analysis showed that gender, tumor

TABLE 1 The demographic and clinicopathological information of esophageal cancer patients receiving neoadjuvant chemotherapy.

Variables		Total cohort (*n*, %) *n* = 2493	Training cohort (*n*, %) *n* = 1748	Validation cohort (*n*, %) *n* = 745	*p*
Age	≤60 years	1,068 (42.84)	755 (43.19)	313 (42.01)	0.62
	>60 years	1,425 (57.16)	993 (56.81)	432 (57.99)	
Marital status	Married	1,760 (70.60)	1,236 (70.71)	524 (70.34)	0.89
	Unmarried	733 (29.40)	512 (29.29)	221 (29.66)	
	Black	129 (5.17)	88 (5.03)	41 (5.50)	0.41
Race	Other	99 (3.97)	64 (3.66)	35 (4.70)	
	White	2,265 (90.85)	1,596 (91.30)	669 (89.80)	
Sex	Female	371 (14.88)	261 (14.93)	110 (14.77)	0.96
	Male	2,122 (85.12)	1,487 (85.07)	635 (85.23)	
Primary site	Lower third	2,011 (80.67)	1,430 (81.81)	581 (77.99)	0.10
	Middle third	245 (9.83)	164 (9.38)	81 (10.87)	
	Upper third	25 (1.00)	14 (0.80)	11 (1.48)	
	Other	212 (8.50)	140 (8.01)	72 (9.66)	
Histology	Adenocarcinoma	1,800 (72.20)	1,284 (73.46)	516 (69.26)	0.09
	SCC	437 (17.53)	296 (16.93)	141 (18.93)	
	Other	256 (10.27)	168 (9.61)	88 (11.81)	
Grade	Grade I	122 (4.89)	85 (4.86)	37 (4.97)	0.64
	Grade II	1,074 (43.08)	764 (43.71)	310 (41.61)	
	Grade III	1,265 (50.74)	879 (50.29)	386 (51.81)	
	Grade IV	32 (1.28)	20 (1.14)	12 (1.61)	
T stage	T1–2	674 (27.04)	473 (27.06)	201 (26.98)	1.00
	T3–4	1,819 (72.96)	1,275 (72.94)	544 (73.02)	
N stage	N0	844 (33.85)	593 (33.92)	251 (33.69)	0.95
	N1	1,649 (66.15)	1,155 (66.08)	494 (66.31)	
M stage	_M0	2,235 (89.65)	1,563 (89.42)	672 (90.20)	0.61
	_M1	258 (10.35)	185 (10.58)	73 (9.80)	
Radiation	No	191 (7.66)	135 (7.72)	56 (7.52)	0.92
	Yes	2,302 (92.34)	1,613 (92.28)	689 (92.48)	
Chemotherapy	Without post	2,228 (89.37)	1,559 (89.19)	669 (89.80)	0.70
	With post	265 (10.63)	189 (10.81)	76 (10.20)	
Tumor size	<5 cm	1,327 (53.23)	901 (51.54)	426 (57.18)	0.01
	5–10 cm	1,095 (43.92)	801 (45.82)	294 (39.46)	
	>10 cm	71 (2.85)	46 (2.63)	25 (3.36)	

pathological grade, T stage, N stage, M stage, marital status, and primary tumor site were significantly correlated with OS of EC patients receiving nCT ($P < 0.05$). The above variables were further included in multivariate Cox proportional hazards regression model analysis, and the results of multivariate analysis indicated that gender, tumor pathological grade, T stage, N stage, M stage and marital status were independent prognostic factors for OS in EC patients receiving nCT (Table 2).

Consrtuction and validation of a nomogram model

Based on the results of multivariate Cox regression, six prognostic factors independently associated with OS were included to construct the nomogram for predicting the 1-year, 2-year, and 3-year OS of EC patients receiving neoadjuvant chemotherapy (Figure 1). To facilitate the use of the model, we created an on-line nomogram (https://shubei11.shinyapps.io/nomogramforos/). In the nomogram model, the individual score of each variable could be obtained according to the variable situation of each patient, and the total score of the patient can be obtained by accumulating each individual score. A vertical line was drawn down from the total score to obtain the estimated OS at 1, 2, and 3 years for this patient. In the training cohort, the area under the ROC curve (AUC) of the 1-year, 2-year and 3-year OS nomogram were 0.598, 0.619 and 0.624, respectively, while in the validation cohort, the AUC of the 1-year, 2-year and 3-year OS nomogram were 0.632, 0.642 and 0.626, respectively (Figures 2A,B). In general, the constructed nomogram had moderate predictive ability. In addition, the time correlation ROC curve indicated that the establised nomogram constructed was better than the traditional TNM staging system in predicting OS at almost all time points (Figures 2C,D). Calibration curve analysis revealed a high degree of agreement between the 1-year, 2-year, and 3-year OS predicted by the nomogram and the

TABLE 2 Univariate and multivariate cox analysis of overall survival in EC patients with neoadjuvant chemotherapy.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age				
≤60	Reference			
>60	1.01 (0.9–1.14)	0.83		
Race				
Black	Reference			
Other	0.99 (0.67–1.47)	0.97		
White	0.9 (0.69–1.16)	0.40		
Sex				
Female	Reference		Reference	
Male	1.29 (1.09–1.53)	0.003	1.35 (1.14–1.61)	<0.001
Marital status				
Married	Reference		Reference	
Unmarried	1.16 (1.02–1.31)	0.02	1.2 (1.06–1.36)	0.004
T stage				
T1–2	Reference		Reference	
T3–4	1.31 (1.15–1.5)	<0.001	1.22 (1.06–1.39)	0.005
N stage				
N0	Reference		Reference	
N1	1.47 (1.3–1.67)	<0.001	1.42 (1.25–1.61)	<0.001
M stage				
M0	Reference		Reference	
M1	1.48 (1.24–1.76)	<0.001	1.44 (1.21–1.71)	<0.001
Tumor size				
<5 cm	Reference			
5–10 cm	1.01 (0.9–1.13)	0.89		
>10 cm	1.01 (0.7–1.45)	0.96		
Primary site				
Lower third	Reference			
Middle third	1.03 (0.85–1.26)	0.76	1.21 (0.99–1.48)	0.0673
Upper third	0.88 (0.44–1.77)	0.72	0.8 (0.4–1.62)	0.5423
Other	1.38 (1.13–1.69)	0.002	1.37 (1.12–1.68)	0.0523
Histology				
Adenocarcinoma	Reference			
SCC	0.96 (0.82–1.12)	0.60		
Other	1.17 (0.97–1.42)	0.10		
Grade				
Grade I	Reference		Reference	
Grade II	1.27 (0.95–1.7)	0.11	1.2 (0.9–1.62)	0.22
Grade III	1.54 (1.15–2.05)	0.004	1.46 (1.09–1.95)	0.01
Grade_Grade IV	1.83 (1.01–3.32)	0.045	1.73 (0.96–3.14)	0.07
Radiotherapy				
No	Reference			
Yes	1.04 (0.84–1.28)	0.74		
Chemotherapy				
Withoutpost	Reference			
Withpost	1.01 (0.85–1.21)	0.89		

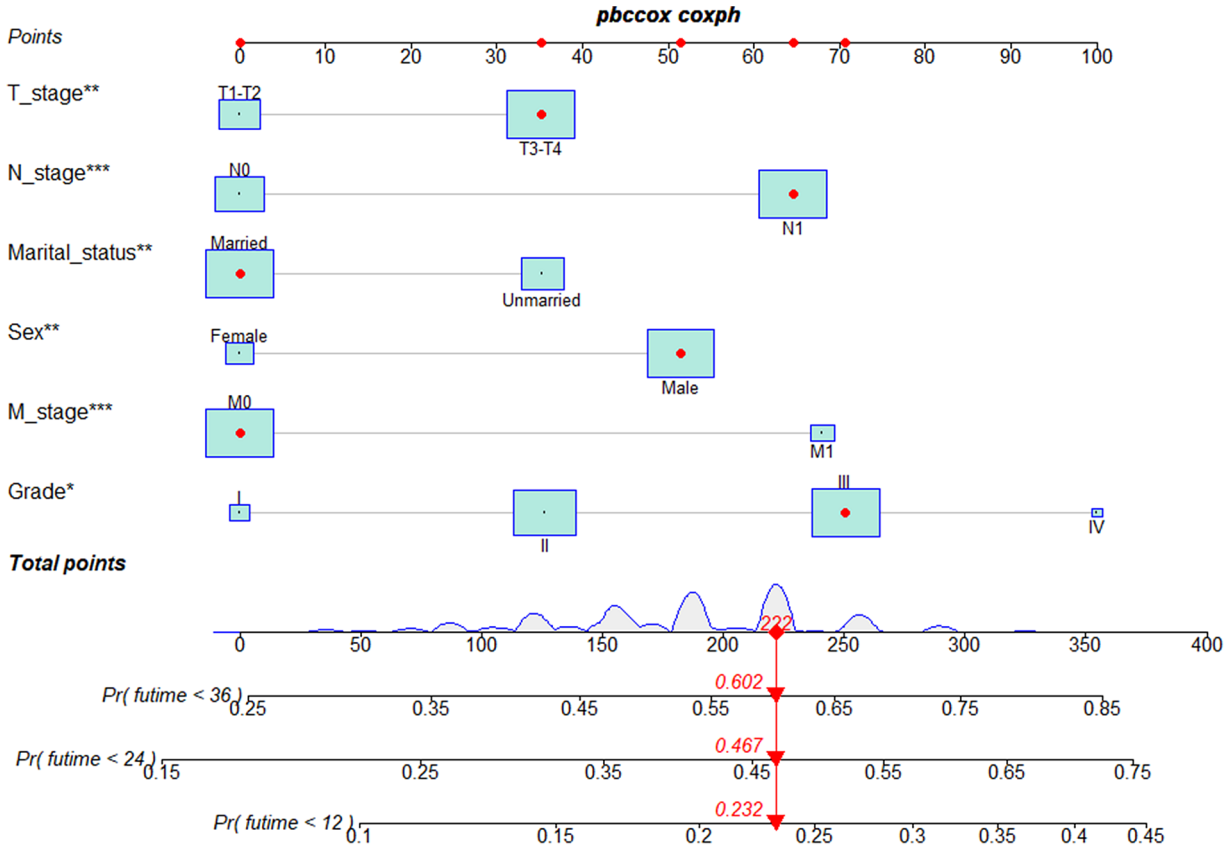

FIGURE 1
Nomogram predictive models for 1 -, 2 -, and 3-year overall survival in patients with esophageal cancer receiving neoadjuvant chemotherapy.

actual prognostic outcomes in both the training cohort and the validation cohort(**Figure 3**). The results of DCA showed that the nomogram established in this study had excellent clinical practical application efficacy in predicting the 1-year, 2-year and 3-year OS of esophageal cancer patients receiving neoadjuvant chemotherapy (**Figure 4**).

Risk stratification and Kaplan-Meier survival analysis based on nomogram score

We divided the included patients into three risk subgroups according to the cut-off point analysis of X-Tile procedure, including the low-risk group (<174 points), the medium-risk group (174–192 points), and the high-risk group (>192 points). Then K-M survival analysis was performed, and the results showed that patients in the high-risk group always had a worse prognosis than those in the low-risk group in both the training and validation cohorts (**Figure 5**). The risk classification system based on nomogram had significant predictive value for the prognosis of EC patients receiving nCT.

Discussion

With the promotion and application of nCT, the clinical management mode and OS of patients with EC are improved. In a randomized controlled trial conducted by Allum WH et al., the R0 excision rate, progression-free survival, and OS were significantly better in the nCT group than in the non-nCT group.The 5-year OS in nCT group and Non-nCT group were 23.00% and 17.10%, respectively ($P = 0.003$). Subgroup analysis showed that the 5-year overall survival rate of patients with ESCC (25.50% vs. 17.00%) and EAC (22.60% vs. 17.60%) in the nCT group were better than those in the non-nCT group. The efficacy of nCT is consistent in different histological types of EC (11). In addition, Ychou M et al. also concluded that receivingnCT is helpful to improve the radical resection rate, disease-free survival rate and OS of patients with EAC (12). Although the OS of patients with EC has been significantly improved by the development of nCT, the prognosis cann't be effectively evaluated by the present AJCC TNM staging system. In the prognostic studies of other common malignant tumors (13, 14), researchers have found that in addition to TNM stage, some other clinicopathological

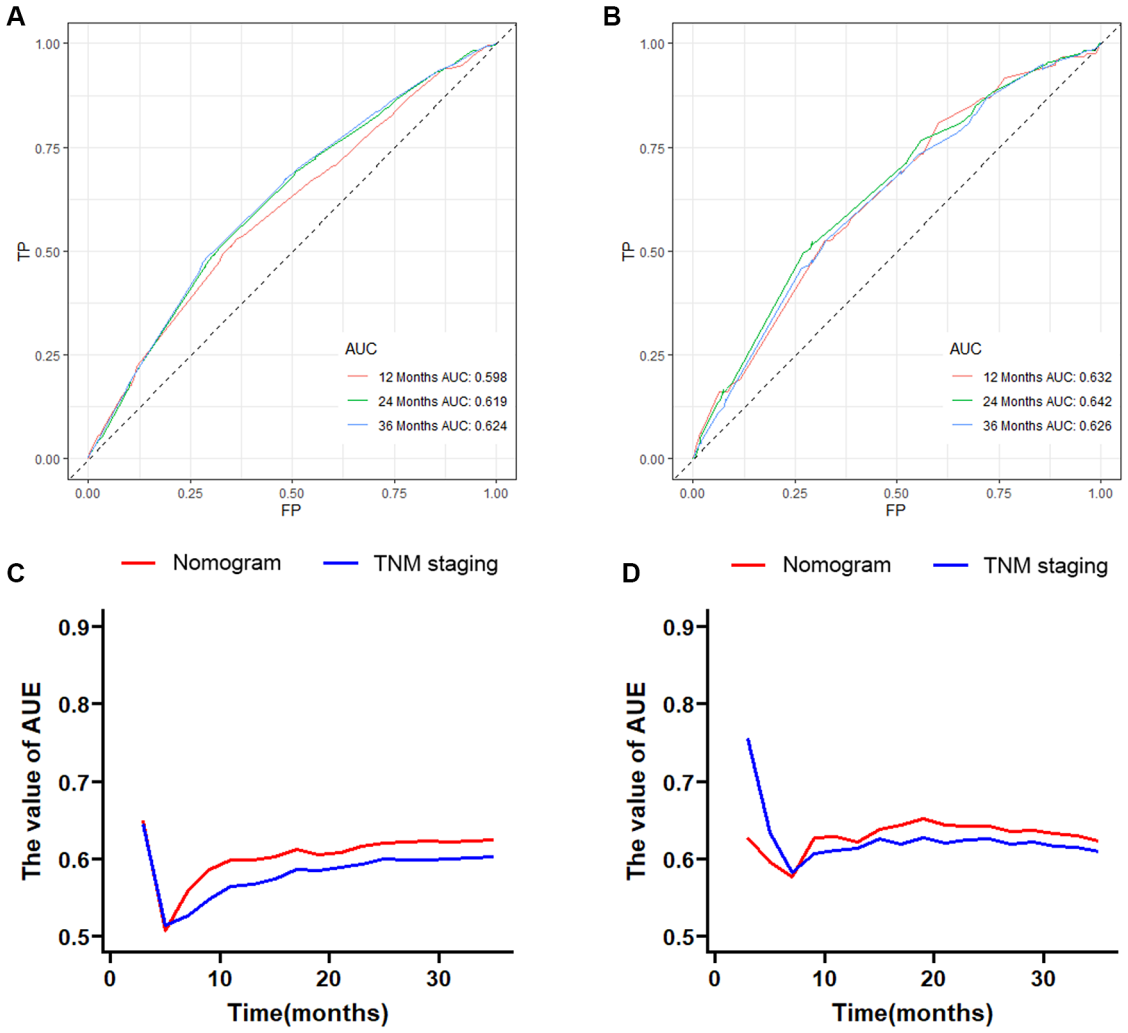

FIGURE 2
The 1-year, 2-year and 3-year ROC curves and area under the curve of the nomogram prediction model for predicting overall survival of esophageal cancer patients receiving neoadjuvant chemotherapy in the training cohort (A) and validation cohort (B); the time-dependent ROC curves in the training cohort (C) and validation cohort (D) were compared between the nomogram prediction model and traditional AJCC TNM staging.

factors are also closely related to the prognosis. Moreover, more importantly, these studies have established prediction models for predicting the prognosis of cancer patients based on independent prognostic risk factors, and demonstrated that the established model is better than the AJCC staging system.It is not accurate to judge the prognosis of tumor patients only by AJCC TNM staging system, and even patients in the same staging may have significantly different survival times. More importantly, TNM staging system cannot meet the growing demand of precision medicine, nor can it provide individual prognosis prediction at a specific time (15, 16). Recently, nomogram prediction models that comprehensively consider various independent prognostic factors have been widely investigated and developed (17, 18). Nomogram is one kind of prediction model based on statistical method and risk score formula to graphically show the survival rate of patients at a specific time. By summing the corresponding scores of all independent prognostic factors, the predicted survival rate for the corresponding years can be obtained by drawing a straight line downward. More importantly, previous studies have shown that the integration of multivariate nomogram is better than single variable in predicting the prognosis of patients, showing higher prediction accuracy.

In this study, we included and analyzed the clinical data of 2,493 patients with EC who received nCT to construct a nomogram model to predict the OS. Six independent prognostic factors were identified by univariate and multivariate COX regression analysis, including T stage, N stage, M stage, pathological grade, marital status and gender.

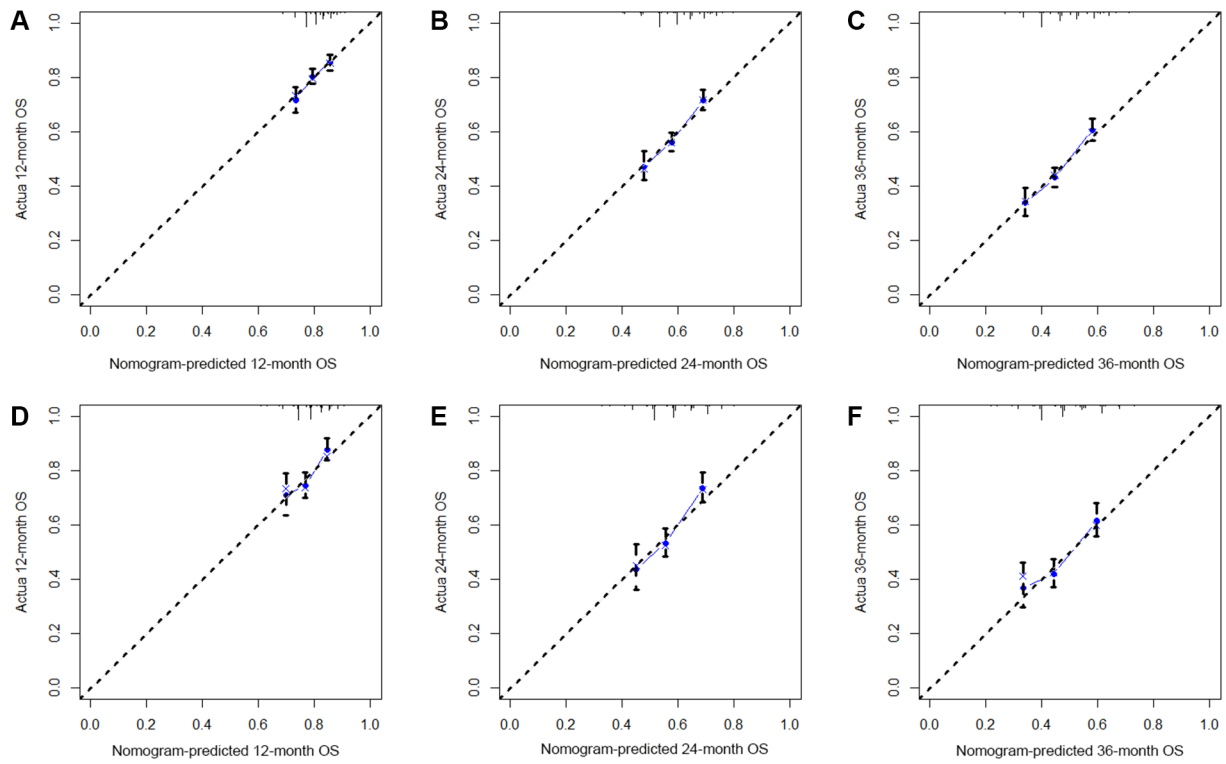

FIGURE 3
The 1-year (A), 2-year (B) and 3-year (C) calibration curves of the nomogram prediction model for predicting overall survival of esophageal cancer patients receiving neoadjuvant chemotherapy in the training cohort and the 1-year (D), 2-year (E) and 3-year (F) calibration curves in the validation cohort;.

A novel nomogram model to predict 1-year, 2-year, and 3-year OS was established. We confirmed that the model has good discriminative power and clinical application ability. In addition, the newly developed prediction model is superior to the traditional TNM staging system in predicting the OS. To the best of our knowledge, this is the first study to construct a prognostic nomogram model for EC patients receiving nCT based on a large population. This nomogram can help identify high-risk subgroups that may require more intensive treatment. In addition, for high-risk subgroups in the entire population identified by this nomogram, we should pay close attention and shorten the follow-up interval, and treatment could be adjusted timely. We should also provide patients in high-risk with more psychological or emotional support, if necessary.

Consistent with TNM staging system (19–21), this study found that patients with higher T, N and M stages had worse prognosis. The prognosis of patients with larger tumor size is worse, which may be related to the difficulty of surgical resection of local invasion of tumor. In clinical practice, larger tumors often indicate that it is more difficult to completely remove the tumor and obtain an R0 resection margin. At the same time, large tumors are usually accompanied by abundant neovascularization, which greatly increases the risk of blood-borne metastasis due to extrusion during surgery (22). The presence of lymph node involvement and metastasis to distant organs often indicates that the patient's primary tumor is more aggressive. Many studies have suggested that male and female cancer patients have different survival rates, and in a nationwide cohort study of 23,465 participants with lung adenocarcinoma, female lung adenocarcinoma patients had slightly higher tumor-specific survival rates than male patients (23). Meanwhile, female patients with tumor-specific survival may benefit more from the use of platinum-based chemicals (24). Similar to the findings in previous studies, female had a better OS in EC patients receiving nCT. Shi et al. found that tumor pathologic stage is an early death of patients with stage IV esophageal independent risk factors (25). This study indicated that EC patients receiving nCT with higher pathologic stage had a worse prognosis. We contributed this finding to that the high undifferentiated tumor differentiation tumor often lead to a more invasive condition. In addition, one of the surprising findings of this study was that marital status was also significantly associated with the outcome of EC patients receiving nCT. Married patients had better long-term OS. Married patients have stronger financial resources

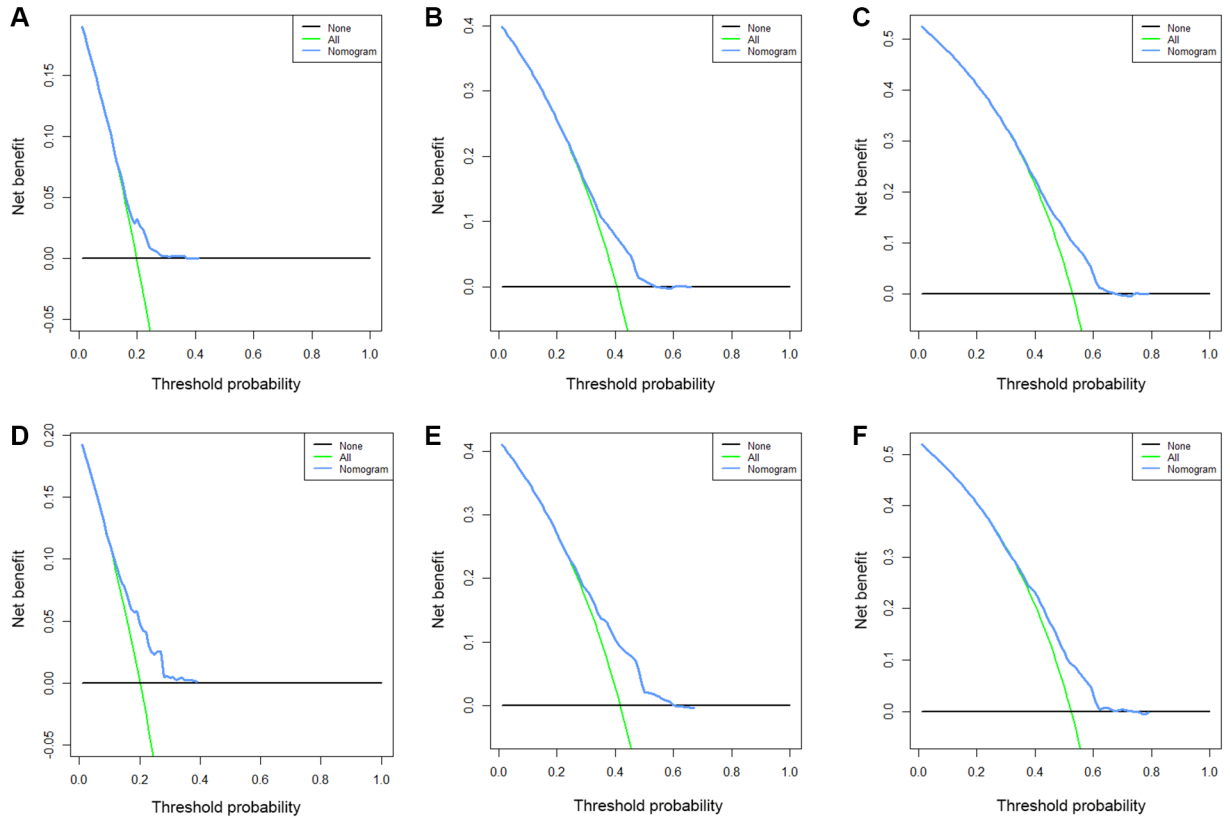

FIGURE 4
The 1-year (A), 2-year (B) and 3-year (C) DCA curves of the nomogram prediction model for predicting overall survival of esophageal cancer patients receiving neoadjuvant chemotherapy in the training cohort and the 1-year (D), 2-year (E) and 3-year (F) DCA curves in the validation cohort.

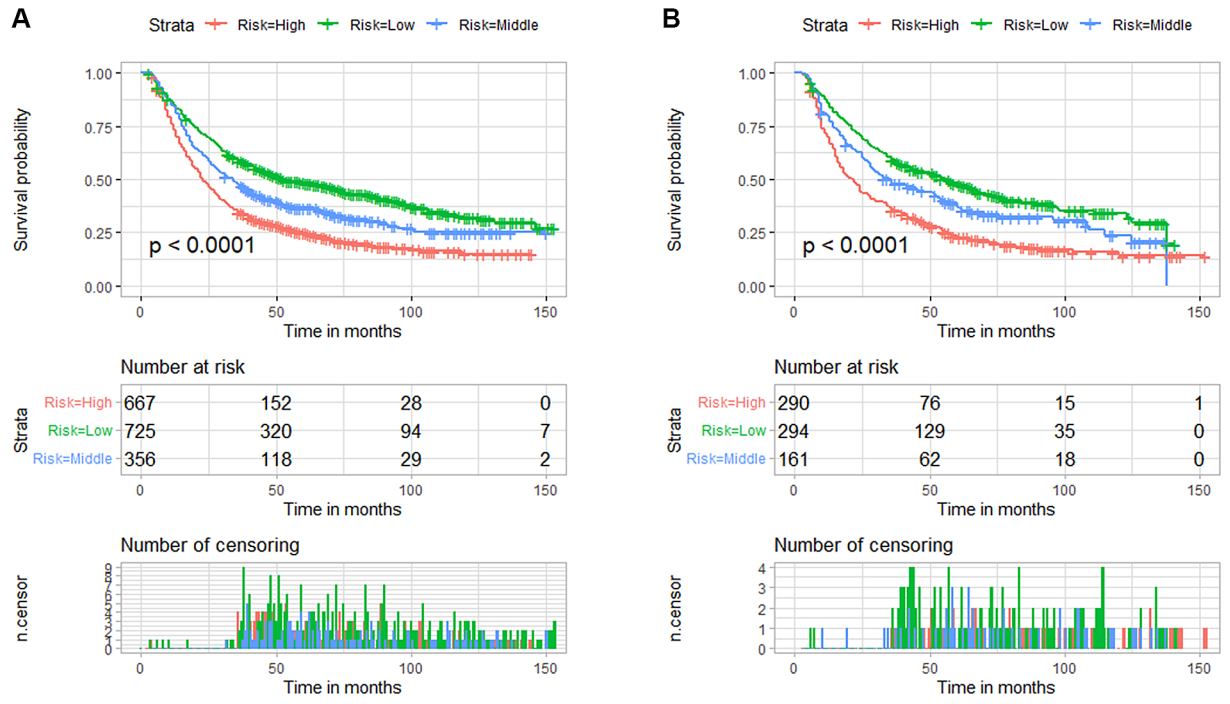

FIGURE 5
Kaplan-Meier survival curves for the three risk subgroups in the training cohort (A) and validation cohort (B) based on the nomogram prediction model for predicting overall survival in patients with esophageal cancer receiving neoadjuvant chemotherapy.

and are more able to afford expensive treatment to achieve a better prognosis (26). On the contrary, due to the lack of support from family members, unmarried patients may have a tendency to experience financial difficulties and decreased ability to pay (27). However, they have to pay almost the same amount, and the economic burden of the disease increases accordingly for them. Thus, the marital status would affect the overall prognosis of tumor patients to a certain extent.

This study still has some unavoidable limitations in study design, clinical data collection, and validation. Firstly, this is a retrospective study based on the SEER database, and the absence of some clinical variables inevitably leads to data bias. Secondly, although the SEER database has the advantage of large study samples from database sources, it also has a series of limitations in terms of data collection. For example, there is a lack of routinely available clinical data, such as specific patient underlying performance status, comorbidities, and laboratory tests. Thirdly, the absence of molecular biological information and specific chemotherapy/chemoradiotherapy protocols is also a drawback of the SEER database. Finally, the established nomogram still lacks external validation of the predictive power of the model from different regional study cohorts.

Conclusions

Gender, tumor pathological grade, marital status, T stage, N stage and M stage were identified as independent prognostic factors for overall survival of patients with esophageal cancer who received neoadjuvant chemotherapy. A nomogram prediction model was established, which was helpful to accurately and reliably predict the overall survival rate of patients with esophageal cancer who received neoadjuvant chemotherapy at 1, 2 and 3 years.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

YY and CH designed this study. YY drafted this manuscript. Both YY and CH revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic model construction and validation of esophageal cancer cellular senescence-related genes and correlation with immune infiltration

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Introduction: Cellular senescence is a cellular response to stress, including the activation of oncogenes, and is characterized by irreversible proliferation arrest. Restricted studies have provided a relationship between cellular senescence and immunotherapy for esophageal cancer.

Methods: In the present study, we obtained clinical sample of colon cancer from the TCGA database and cellular senescence-related genes from MSigDB and Genecard datasets. Cellular senescence-related prognostic genes were identified by WGCNA, COX, and lasso regression analysis, and a cellular senescence-related risk score (CSRS) was calculated. We constructed a prognostic model based on CSRS. Validation was performed with an independent cohort that GSE53625. Three scoring systems for immuno-infiltration analysis were performed, namely ssGSEA analysis, ESTIMATE scores and TIDE scores.

Result: Five cellular senescence-related genes, including H3C1, IGFBP1, MT1E, SOX5 and CDHR4 and used to calculate risk score. Multivariate regression analysis using cox regression model showed that cellular senescence-related risk scores (HR=2.440, 95% CI=1.154-5.159, p=0.019) and pathological stage (HR=2.423, 95% CI=1.119-5.249, p=0.025) were associated with overall survival (OS). The nomogram model predicts better clinical benefit than the American Joint Committee on Cancer (AJCC) staging for prognosis of patients with esophageal cancer with a five-year AUC of 0.946. Patients with high CSRS had a poor prognosis (HR=2.93, 95%CI=1.74-4.94, p<0.001). We observed differences in the distribution of CSRS in different pathological staging and therefore performed a subgroup survival analysis finding that assessment of prognosis by CSRS independent of pathological staging. Comprehensive immune infiltration analysis and functional enrichment analysis suggested that patients with high CSRS may develop immunotherapy resistance through mechanisms of deacetylation and methylation.

Discussion: In summary, our study suggested that CSRS is a prognostic risk factor for esophageal cancer. Patients with high CSRS may have worse immunotherapy outcomes.

KEYWORDS

cellular senescence, esophageal cancer, bioinformatics, immune infiltration, prognosis

Abbreviations

EC, esophageal cancer; CS, Cellular senescence; SASP, senescence-associated secretory phenotype; TCGA, The Cancer Genome Atlas; MSigDB, Molecular signatures database; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, Gene set enrichment analysis; CSRS, Cellular senescence-related risk score; DEG, Differentially expression gene; OS, Overall survival; AJCC, American Joint Committee on Cancer; DCA, decision curve analysis; KM, Kaplan-Meier; ROC curve, Receiver operating characteristic curve; EAC, Esophageal adenocarcinoma; ESCC, Esophageal squamous cell cancer; WGCNA, Weighted correlation network analysis; HDCA, Histone deacetylase; IGF, Insulin-like growth factor; EMT, Epithelial-mesenchymal transition.

Introduction

Esophageal cancer (EC) is the eighth most common cancer-related death worldwide disease (1–3). At present, clinical treatment of EC mainly includes surgery, chemotherapy, radiotherapy, targeted therapy and their combinations (4, 5). Approximately half of the patients have distant metastases when EC is diagnosed, surgery is no longer applicable (6). Unfortunately, radiotherapy, chemotherapy, and targeted therapy have made only limited progress in recent years in improving the generally disappointing outcome (6). Reaching the efficacy benefit of immunotherapy for EC remains challenging.

Cellular senescence (CS) is a stable cell cycle arrest that occurs in diploid cells and limits their proliferative life span, which induces a proliferative arrest in cells at risk of malignant transformation and is therefore widely considered as an anti-tumor mechanism (7, 8). The physiological role of the immune checkpoints is to prevent excessive immune response by termination immune system activation at appropriate time, which can be utilized by tumor to catalyze the auto-destruction of the immune responses (9, 10). Expression of the immune checkpoint PD-L1 was confirmed to be required for senescent cells to evade T-cell immunity, as well as for tumor cells (11).

Cellular senescence-based drugs are currently being explored and developed in two categories, senolytics and senomophics, including senescence-associated secretory phenotype (SASP) inhibitors (12, 13). Immunotherapy involving CS-based drugs seems to be a new therapeutic approach, but the role in the EC remains poorly defined. Thus, we hypothesized that CS-related genes promote EC progression by affecting immune regulation and constructed a prognostic model.

Materials and methods

Data acquisition

Transcriptomic data and clinical information of esophageal cancer (EC) derived from the TCGA-ESCA cohort as a training set (https://portal.gdc.cancer.gov/), involving 162 EC samples and 11 normal samples. Clinical information not available or ambiguous was removed. Independent cohort GSE53625 as validation set available from GEO database. Cellular senescence-related genes (CSRGs) were selected by the Molecular Signatures Database (MSigDB, http://www.gsea-msigdb.org/) and Genecards (https://www.genecards.org/) tools (**Supplementary Table S1**). The procedure detailed in this study is shown in **Figure 1**.

Identification of CS-related prognostic hub genes

Statistical analyses based on the TCGA database were performed with R. The differentially expressed genes (DEGs) in tumor and normal tissues of TCGA-ESCA cohort were screened by differential analysis. Combined with CS-related genes, CS-related DEGs in EC were initially screened by Venn analysis. The WGCNA weighting analysis of the distribution of correlation modules of these genes was performed, and CS-related prognostic genes were further obtained by univariate COX regression analysis. Finally, CS-related prognostic hub genes were identified by LASSO regression.

Construction and validation of CS-related risk scores prognostic models

Based on the coefficients of CS-related prognostic hub genes gained from Lasso regression analysis, the CS-related risk scores (CSRS) were constructed as follows.

$$\text{CS\_related risk scores(CSRS)} = \sum_{i=1}^{n} \text{expression}_{\text{gene\_}i} \times \text{lasso\_coeffieicent}_{\text{gene\_}i}$$

Independent prognostic factors were screened by univariate and multivariate COX regression analysis. These factors and CSRS were combined to construct a nomogram model for predicting survival in patients with EC. A preliminary assessment was performed with a calibration correction curve.

Data from the GSE53625 dataset was taken to validate the reliability of the model. The effectiveness of the nomogram model was demonstrated by the decision curve analysis (DCA) curve, Kaplan-Meier (KM) curve and receiver operating characteristic (ROC) curve.

Correlation between CSRS with clinical characteristics and survival

The Wilcoxon signed-rank sum test was used to compare the differences in clinical characteristics of patients in high- and low-CSRS groups. The prognostic value of CSRS for patients of different age groups, pathological staging, and pathological stages was performed by Kaplan-Meier.

Correlation between CSRS and immune cell infiltration

In the present study, three scoring systems for immuno-infiltration analysis were performed, namely ssGSEA analysis (14), ESTIMATE scores (15) and TIDE scores (16). Levels of infiltration of different immune cells in tumors were quantified by the ssGSEA algorithm through the GSVA package (17). The purity of tumor immune infiltration and abundance of stromal cells were calculated by ESTIMATE algorithm through the estimate package. The dysfunction score and exclusion scores from the TIDE scoring system were applied to predict the efficacy of immunotherapy in different CTL-related subgroups of patients.

Functional enrichment analysis

GO analysis and KEGG analysis for probing the potential biological functions of gene networks in different modules of the WGCNA with the clusterProfiler package and org.HS.eg.db package (18). The biological mechanisms leading to differences in high and low CSRS groups were explored *via* gene set enrichment analysis (GSEA) by the clusterProfiler package (17, 18).

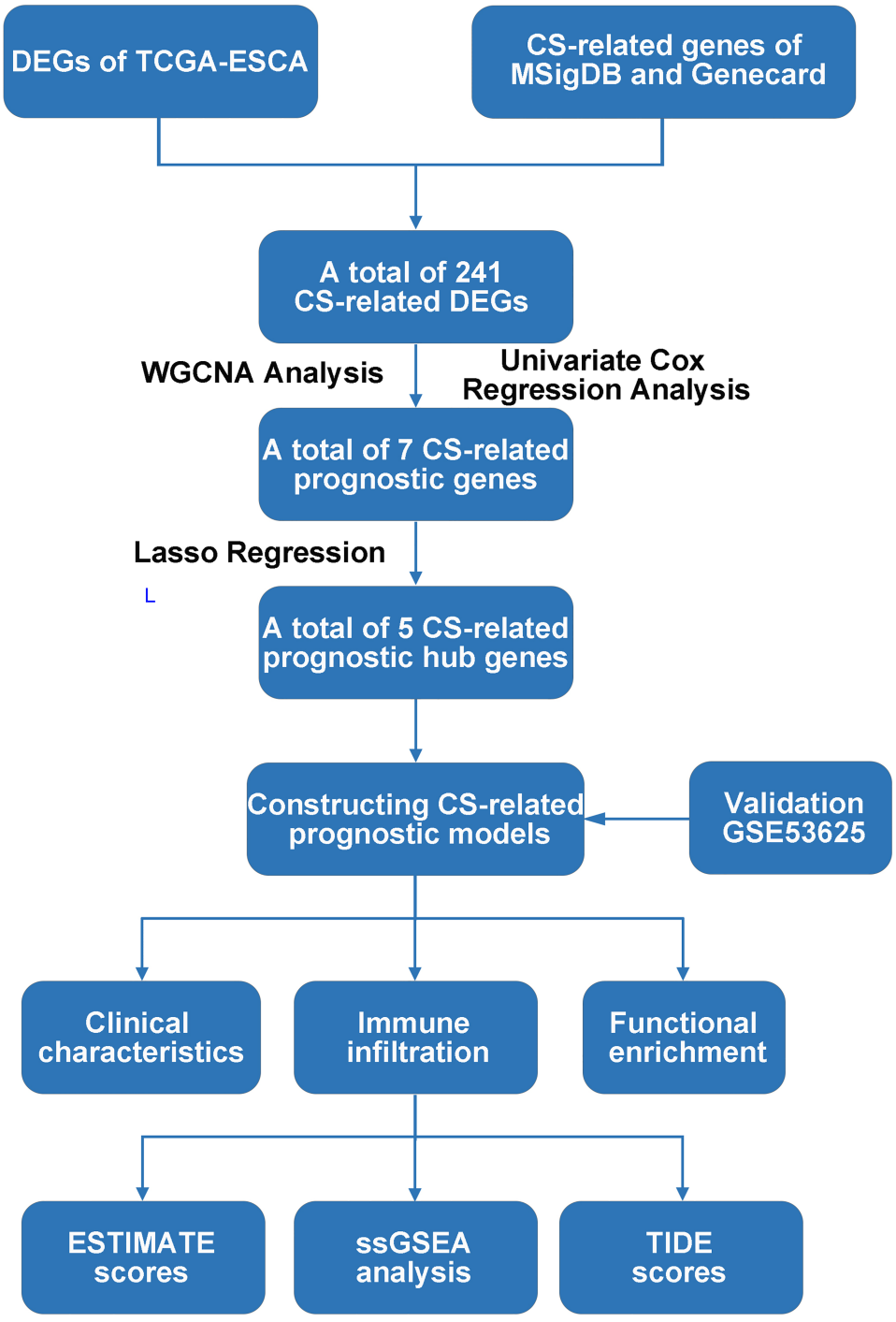

FIGURE 1
Flow chart of the present study. DEG: Differentially expression gene; TCGA, The Cancer Genome Atlas; CS, Cellular senescence; MSigDB, Molecular signatures database; DEGs, Differentially expressed genes; WGCNA, Weighted correlation network analysis; ESTIMATE, Estimation of STromal and Immune cells in MAlignant Tumours using Expression data; ssGSEA, Single sample gene set enrichment analysis; TIDE, Tumor Immune Dysfunction and Exclusion.

Result

Screening and identification of CS-related prognostic genes

A total of 1,153 CS-related genes were derived by MSigDB and Genecards tools (Supplementary Table S1), of which 241 genes (Figure 2A) were differentially expressed between EC and normal tissues (Figure 2B, $|\log_2 FC|>1$, $p<0.05$).

WGCNA analysis of TCGA-ESCA transcriptome data was performed to search for highly related gene modules. Based on the relationship between the soft threshold with the scale-free fit and the mean connectivity, a suitable soft threshold β was finally determined as 12 (Figure 2C). The network classified the

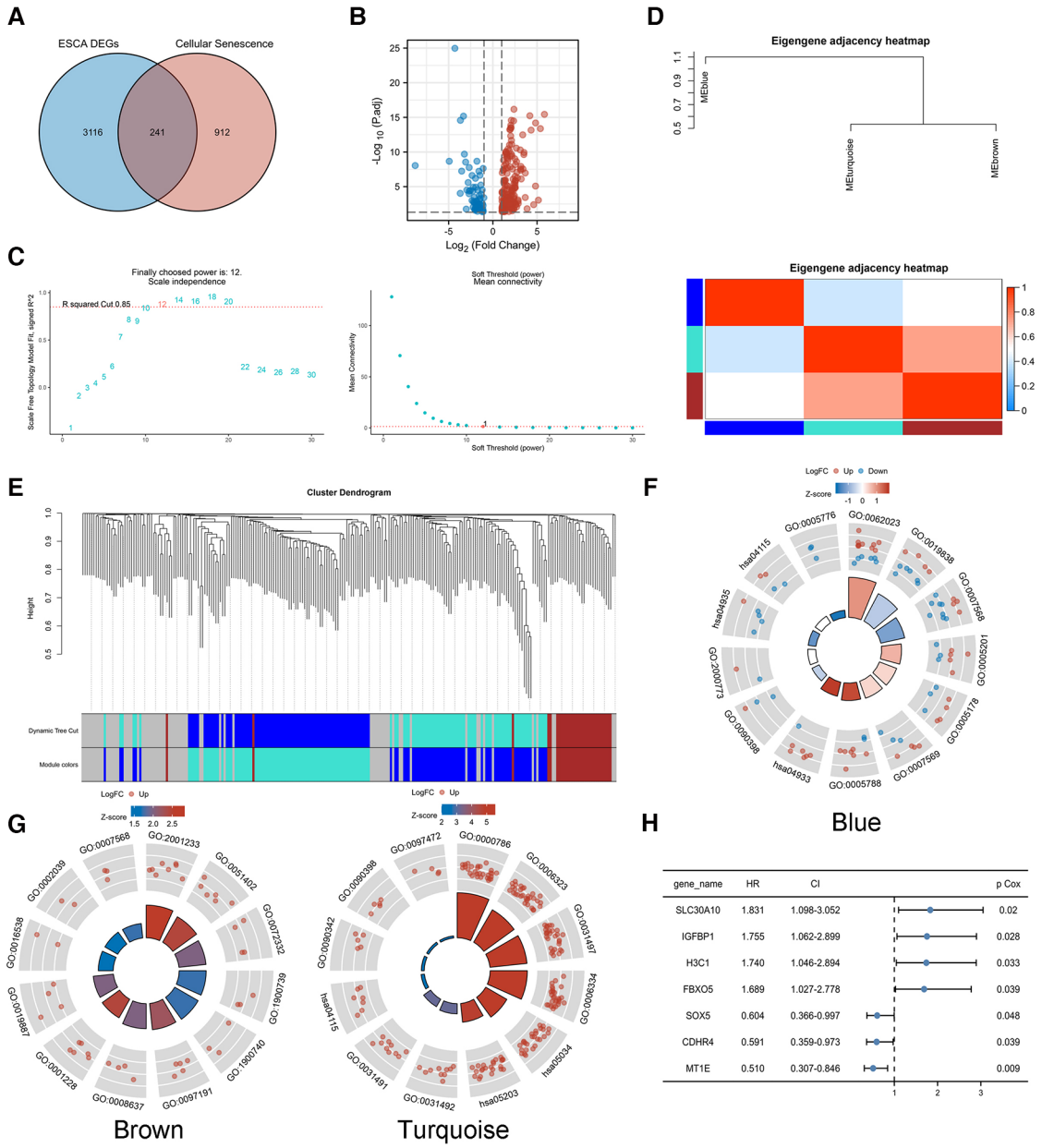

FIGURE 2
Identification of CS-related prognostic genes. (A,B) A total of 241 genes were differentially expressed between EC and normal tissues(|log2FC|>1, $p < 0.05$). (C) Soft threshold β of WGCNA was determined as 12 based on the scale-free fit and the mean connectivity. (D–E) WGCNA network classified the CS-related DEGs into three different modules, blue, brown and turquoise. GO/KEGG analysis was performed in module genes. (F) Blue module. (G) Brown and turquoise modules. (H) Univariate COX regression analysis of modular genes.

CS-related DEGs into three different modules, blue, brown and turquoise (Figures 2D,E), by using a dynamic tree cutting and clustering algorithm. The correlation between modules was presented by a heat map, which showed that the turquoise module was highly genetically correlated with the brown module.

GO/KEGG analysis was performed to probe the biological functions associated with each module gene. The genes of the blue module were mainly enriched in cellular senescence and aging (Figure 2F). The genes of the brown and turquoise modules (Figure 2G) might play a role in biological processes such as cellular senescence, as well as, apoptosis-related signaling pathways. The detailed GO/KEGG annotations are presented in Table 1.

Univariate COX regression analysis of the modular genes identified seven genes that were strongly associated with overall survival (OS), namely SLC30A10, IGFBP1, H3C1, FBXO5, SOX5, CDHR4 and MT1E (Figure 2H). The above genes were identified as CS-related prognostic genes.

TABLE 1 GO/KEGG analysis annotations of module genes.

ONTOLOGY	ID	Description
BP	GO:2000773	negative regulation of cellular senescence
BP	GO:0090398	cellular senescence
BP	GO:0007568	aging
BP	GO:0007569	cell aging
BP	GO:0007568	aging
BP	GO:2001233	regulation of apoptotic signaling pathway
BP	GO:1900739	regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
BP	GO:1900740	positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
BP	GO:0072332	intrinsic apoptotic signaling pathway by p53 class mediator
BP	GO:0051402	neuron apoptotic process
BP	GO:0008637	apoptotic mitochondrial changes
BP	GO:0097191	extrinsic apoptotic signaling pathway
BP	GO:0006323	DNA packaging
BP	GO:0031497	chromatin assembly
BP	GO:0006334	nucleosome assembly
BP	GO:0090342	regulation of cell aging
BP	GO:0090398	cellular senescence
CC	GO:0005776	autophagosome
CC	GO:0062023	collagen-containing extracellular matrix
CC	GO:0005788	endoplasmic reticulum lumen
CC	GO:0000786	nucleosome
MF	GO:0005178	integrin binding
MF	GO:0005201	extracellular matrix structural constituent
MF	GO:0019838	growth factor binding
MF	GO:0019887	protein kinase regulator activity
MF	GO:0002039	p53 binding
MF	GO:0001228	DNA-binding transcription activator activity, RNA polymerase II-specific
MF	GO:0016538	cyclin-dependent protein serine/threonine kinase regulator activity
MF	GO:0031492	nucleosomal DNA binding
MF	GO:0031491	nucleosome binding
MF	GO:0097472	cyclin-dependent protein kinase activity
KEGG	hsa04115	p53 signaling pathway
KEGG	hsa04935	growth hormone synthesis, secretion and action
KEGG	hsa04933	AGE-RAGE signaling pathway in diabetic complications
KEGG	hsa04115	p53 signaling pathway
KEGG	hsa05034	Alcoholism
KEGG	hsa05203	viral carcinogenesis

Development of CS-related risk scoring system and construction as well as validation of CSRS nomogram model

The regression coefficients (Table 2) of the above 7 CS-related prognostic genes were calculated by the Lasso algorithm (Figures 3A,B) using OS as an outcome indicator, with the

$$CSRS = 0.2901 \times H3C1 + 0.2158 * IGFBP1 - 0.7121 * CDHR4 - 0.1390 * MT1E - 0.1184 * SOX5$$

The prognostic DCA chart (Figure 3C) confirmed the utility of the CSRS scoring system in predicting survival outcomes in patients with EC.

We performed a COX regression analysis of the TCGA-ESCA cohort to uncover factors affecting the prognosis of esophageal patients. In the independent cohort GSE53625, EC patients were divided into high-risk and low-risk groups based on the median CSRS in TCGA-ESCA as the cutoff value for further analysis to verify the generalizability of the CSRS score. The results of the univariate COX analysis in the TCGA cohort (Figure 3D) suggested that N stage, M stage, pathological stage and CSRS (HR = 2.903, 95%CI = 1.497–5.629, $p = 0.002$) were risk factors affecting the prognosis of esophageal cancer, which was similarly validated in the GSE53625 cohort (Figure 3E, risks score group: HR = 1.742, 95%CI = 1.129–2.686, $p = 0.012$). Further multivariate COX analysis at TCGA-ESCA (Figure 3F) and GSE53625 (Figure 3G) indicated the reliability of the prediction of prognosis in patients with EC by CSRS. CSRS can accurately distinguish esophageal cancer patients with different survival times, which means that a higher CSRS represents a worse prognosis as reflected by the results of the KM analysis (Figures 3H,I).

Integrating the above analysis, we constructed a nomogram model to predict the 1-,2- and 3-year survival of EC patients based on N stage, M stage, pathological stage and CSRS (Figure 3J). The fit is around the diagonal and the C-index value is 0.744, indicating good consistency of the model (Figure 3K). In addition, we evaluated the efficacy of the nomogram model. The DCA curve (Supplementary Figure S1A) results showed that the prediction of survival outcome in patients with EC using the CSRS was superior to that using American Joint Committee on Cancer (AJCC)

TABLE 2 The regression coefficients 7 CS-related prognostic genes.

Gene id	Coefficients
H3C1	0.29014853
IGFBP1	0.21577076
SLC30A10	0
FBXO5	0
SOX5	−0.11840431
MT1E	−0.1390272
CDHR4	−0.71213391

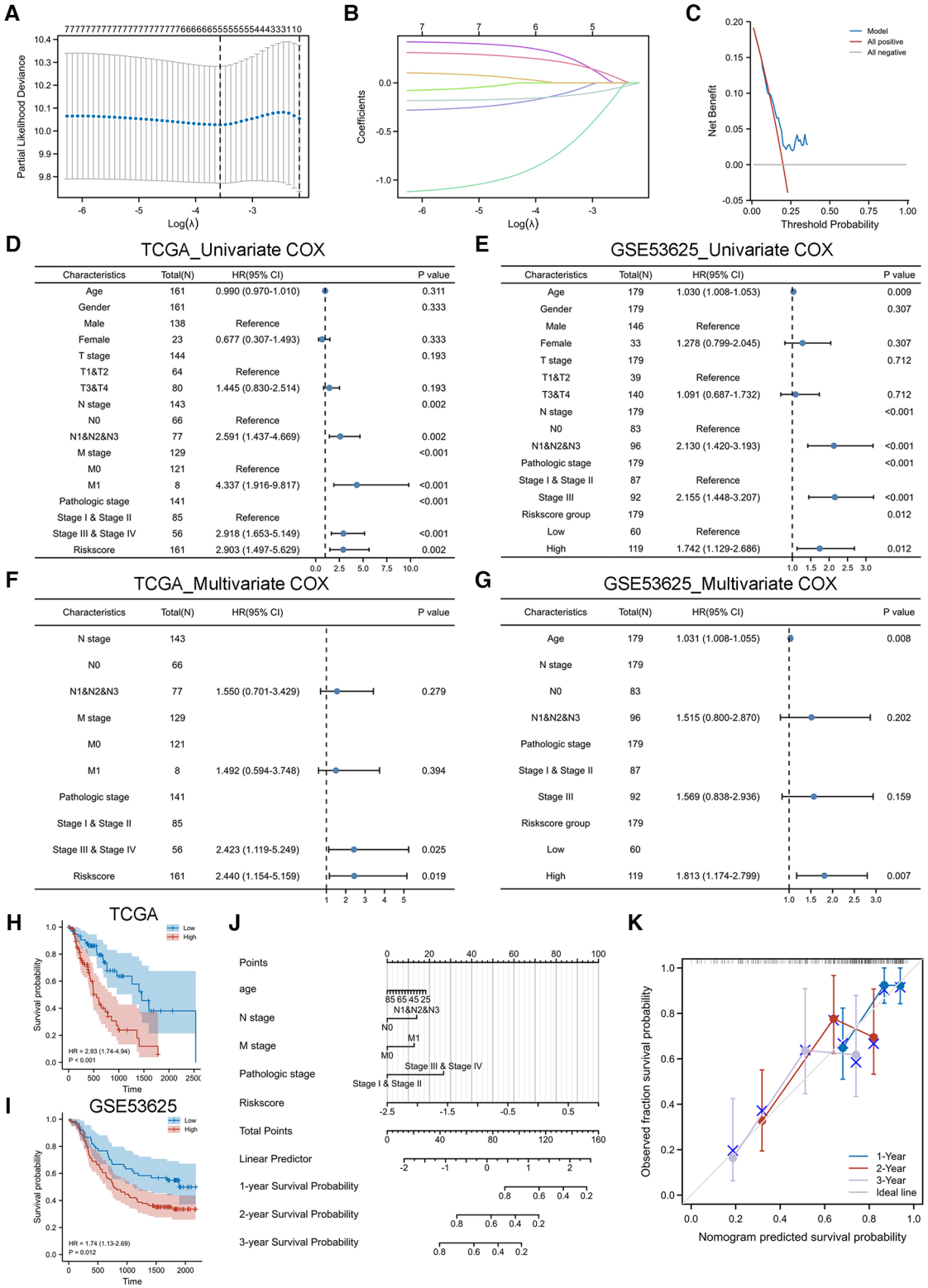

FIGURE 3
Construction and validation of CSRS nomogram model. (**A**,**B**) Five genes were identified as CS-related prognostic hub genes by lasso algorithm, including IGFBP1, H3C1, SOX5, CDHR4 and MT1E. (**C**) DCA chart confirmed the prognostic utility of CSRS. (**D**–**G**) Univariate and multivariate Cox regression analyses of OS in TCGA-ESCA. Validation is performed by GSE53625. (**H**–**I**) KM curves of OS in TCGA-ESCA and GSE53625. (**J**) Nomogram model to predict the 1-,2- and 3-year survival of EC patients. (**K**) Calibration curves for evaluating. The fit is around the diagonal and the C-index value is 0.744, indicating good consistency of the model.

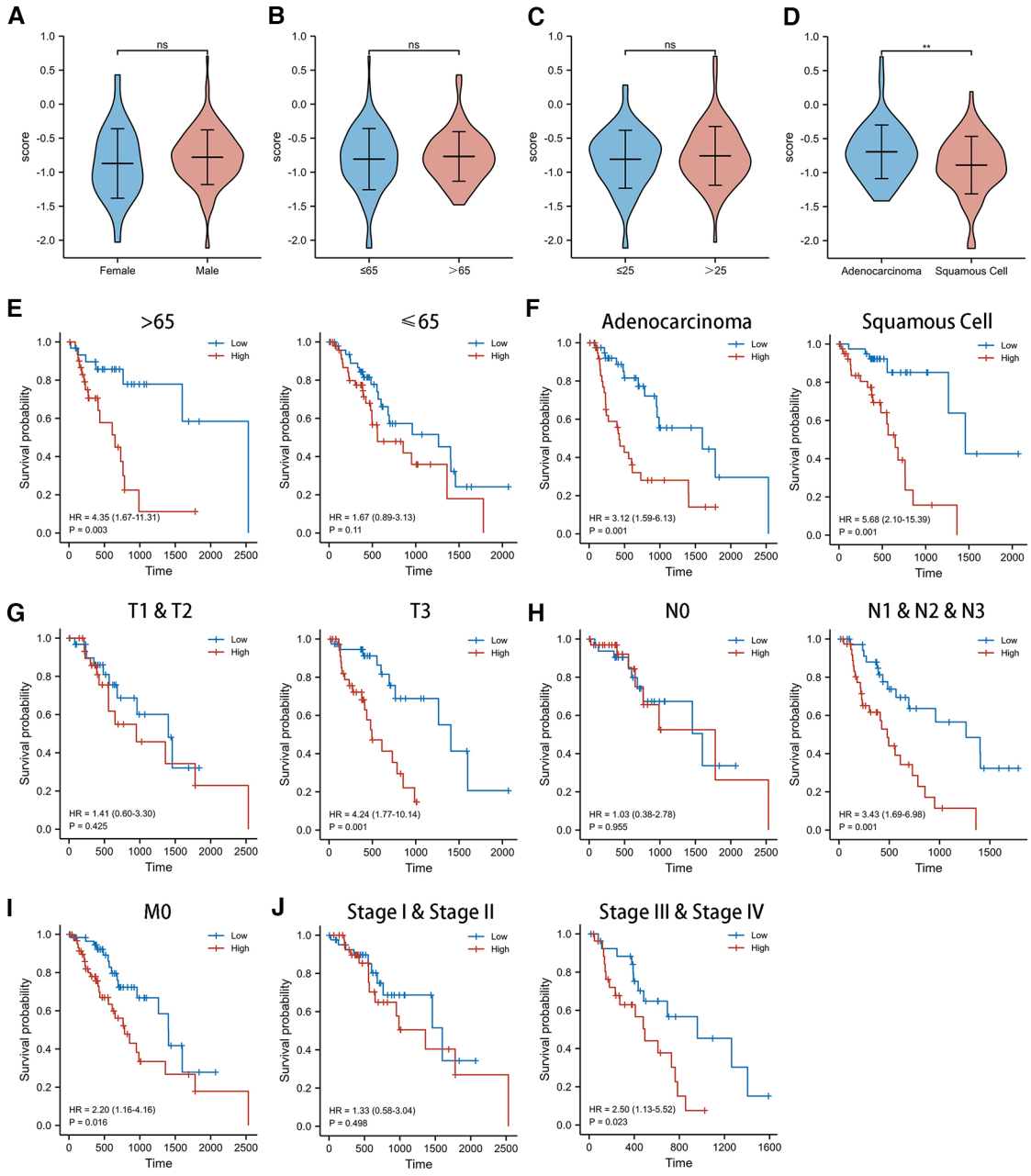

FIGURE 4
Clinicopathological characteristics and survival analysis of different CSRS groups. (**A**,**B**) CSRS distribution showed no significant differences in different gender (**A**), age (**B**) and BMI (**C**), while CSRS was higher in patients with EAC than ESCC (**D**). Subgroup survival analysis of age (**E**), pathological staging (**F**), T stage (**G**), N stage (**H**), M stage (**I**) and pathological stage (**J**) between high- and low-CSRS patients. EAC, Esophageal adenocarcinoma; ESCC, Esophageal squamous cell cancer; ns: No significance; $^{**}p < 0.01$.

staging. The benefit of prediction using our constructed nomogram model was greater than that of CSRS and AJCC. The KM curve (**Supplementary Figure S1B**) results showed that patients with high nomogram scores had a worse prognosis (HR = 5.35, 95% CI = 2.61–10.96, $p < 0.001$). The accuracy of the nomogram model in predicting the 1-(AUC = 0.781),3-(AUC = 0.754) and 5 (AUC = 0.946) years' prognosis of patients with EC was also assessed by time-dependent ROC analysis (**Supplementary Figure S1C**).

Clinicopathological characteristics and prognostic value in different CSRS groups

We observed no significant difference in the distribution of CSRS among EC groups by gender (**Figure 4A**), age (**Figure 4B**), and BMI (**Figure 4C**). However, in terms of pathological type (**Figure 4D**), CSRS was higher in patients with esophageal adenocarcinoma (EAC) than those with esophageal squamous cell cancer (ESCC).

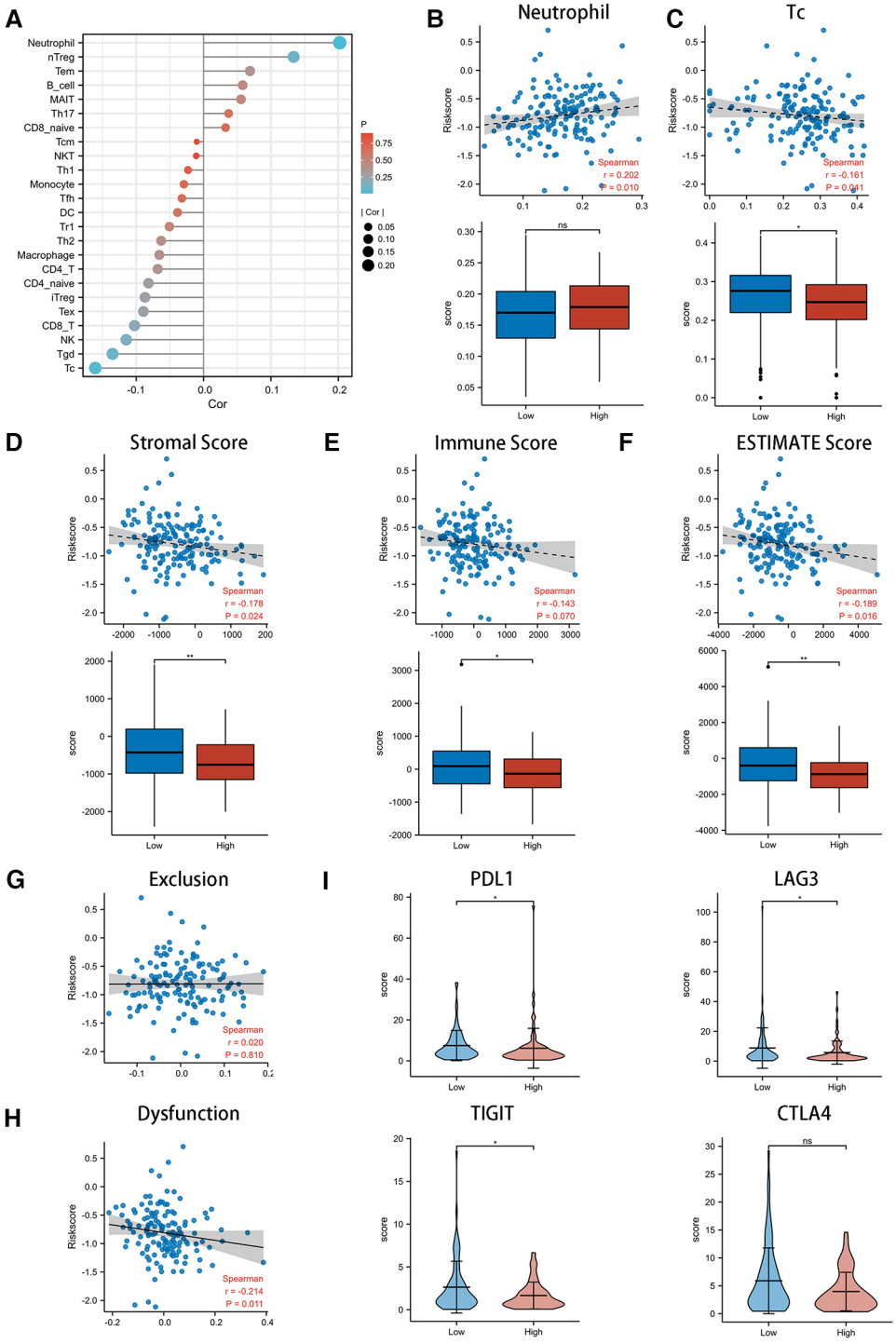

FIGURE 5
Exploring the role of CSRS in the immunotherapy of esophageal cancer. (A) Correlation of CSRS with immune cell infiltration was performed by ssGSEA analysis. High CSRS group were infiltrated by more neutrophil (B) and fewer Tc(C). Relationship between scores with CSRS, as well as comparison of scores between high- and low-CSRS group in stromal (D) score, immune (E) score and ESTIMATE (F) score. Relationship between exclusion (G) and dysfunction (H) scores with CSRS. (I) Comparison of checkpoint genes, including PDL1, LAG3, TIGIT and CTLA4, between high- and low-CSRS groups. ns: no significance; *: $p < 0.05$; **: $p < 0.01$.

For this reason, we investigated the prognostic value of CSRS in different subgroups of patients with EC (Figure 4E–J). CSRS accurately determined prognosis in patients with either EAC (HR = 3.12, 95%CI = 1.59–6.13, $p = 0.001$) or ESCC (HR = 5.68, 95%CI = 2.10–15.39, $p = 0.001$), as well as in patients with EC aged more than 65 years (HR = 4.35, 95%CI = 1.67–11.31, $p = 0.003$) or T3 stage (HR = 4.24, 95%CI = 1.77–10.14, $p = 0.001$) or N1&N2&N3 stage (HR = 3.34, 95%CI = 1.69–6.98, $p = 0.001$) or M0 stage (HR = 2.20, 95%CI = 1.16–4.16, $p = 0.016$) or pathological stage III & IV (HR = 2.50, 95%CI = 1.13–5.52, $p = 0.023$). However,

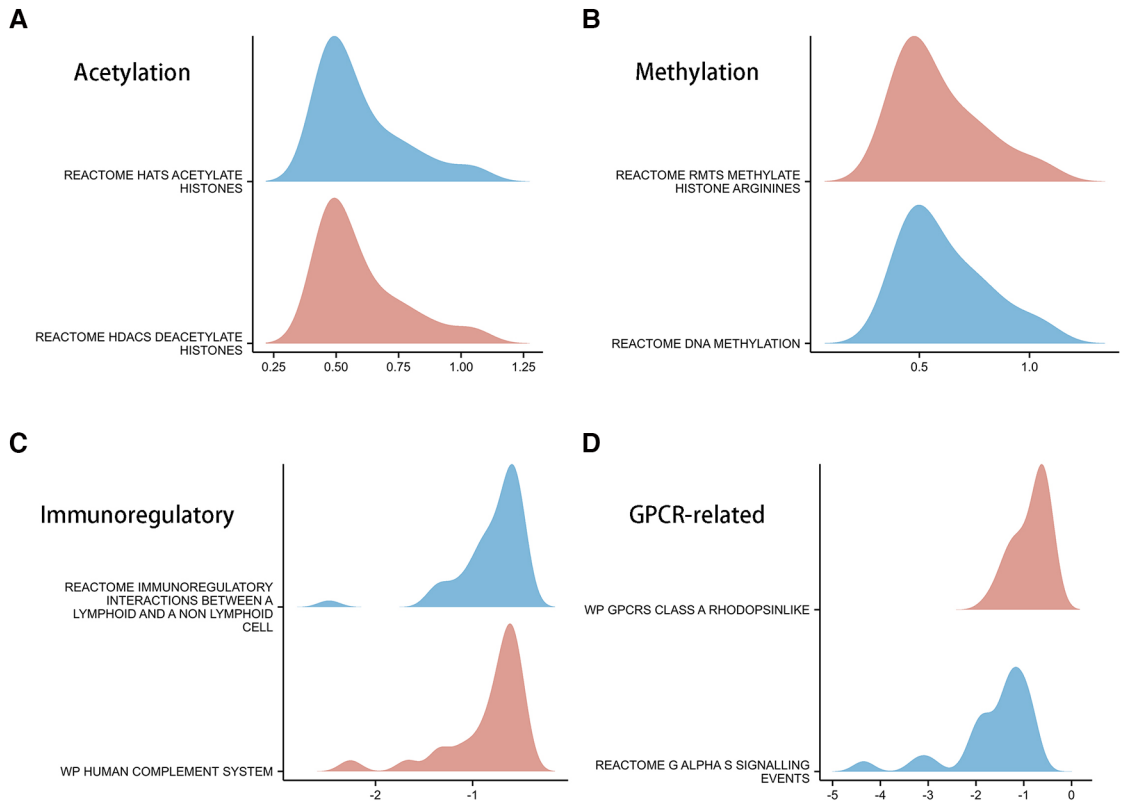

FIGURE 6
GSEA analysis in high- and low-CSRS group. (A) Acetylation-related pathways, including HATs acetylate histones and HDACs deacetylate histones. (B) Methylation-related pathways, including RMTs methylate histone arginine and DNA methylation. (C) Immunomodulatory-related pathways, including immunoregulatory interactions between a lymphoid and a non-lymphoid cell and human complement system. (D) GPCR-related pathways, including GPCRs class A rhodopsinlike and GαS signalling events.

for patients aged less than 65 years, T1 & T2 stages, N0 stages, and pathological stages I & II, CSRS scores were not good predictors of prognostic outcome.

Multidimensional immune infiltration analysis in different CSRS groups

We adopted three scoring systems to analyze tumor immune infiltration in EC patients with different CSRS groups, namely ssGSEA analysis (**Figures 5A–C**), ESTIMATE score (**Figures 5D–F**) and TIDE score (**Figures 5G,H**). EC patients in the high CSRS group were infiltrated by fewer Tc and Tgd cells, while there was a positive correlation with the infiltration of neutrophil cells. Stromal scores ($r = -0.178$, $p = 0.024$) and ESTIMATE scores ($r = -0.189$, $p = 0.016$) were observed to be negatively correlated with CSRS, whereas not immune scores. There were differences in all three scores between the high- and low-CSRS groups of esophageal cancer. The TIDE scoring system is commonly used to evaluate the efficacy of immunotherapy in oncology patients, including the exclusion score and dysfunction score of T cells. CSRS was negatively correlated with dysfunction scores ($r = -0.214$, $p = 0.011$), and no significant correlation was observed with exclusion scores. We subsequently compared the expression of immune checkpoint-related genes in different CSRS groups (**Figure 5I**). High expression of PDL1, LAG3 and TIGIT were observed in low-CSRS group ($p < 0.05$) than high-CSRS group.

Potential biological mechanisms in different CSRS groups

In order to explore the biological mechanisms leading to differences between high- and low- CSRS groups, GSEA analysis was performed. The results showed that the high-CSRS group was positively enriched in acetylation- (**Figure 6A**) and methylation-related (**Figure 6B**) pathways, and negatively enriched in immunomodulatory (**Figure 6C**) and GPCR-related pathways (**Figure 6D**).

Discussion

Cellular senescence (CS) is a cellular response to stress, including the activation of oncogenes, characterized by irreversible proliferation arrest (8). Cellular senescence was first discovered and described by Hayflick and Moorhead (19). They found that human cell cultured *in vitro* lost their ability to proliferate and entered a state of growth arrest after 50 to 70 generations of continuous culture. In recent years, as cellular senescence has been studied more

intensively, DNA damage response, endoplasmic reticulum stress and induction of antiapoptotic genes have been defined as the phenotypes of cellular senescence (20–24).

Some reports have suggested that the microenvironment of CS is associated with cancer progression, such as the SASP (25–27). SASP mediates chronic inflammation and stimulates the growth of cancer, while SASP also enhances cell cycle arrest, prompting immune cells to defend cancer (28, 29). There were limited studies on CS and esophageal cancer(EC), whereas identification of CS-related genes with clinical significance is crucial for immunotherapy studies of EC. Thus, we hypothesized that CS-related genes promote EC progression by affecting immune regulation.

In the present study, 241 CS-related DEGs were initially screened from TCGA-ESCA. The WGCNA network classified the CS-related DEGs into three different modules which were associated with the CS and apoptosis pathways. We finally identified five CS-associated prognostic genes in EC by COX analysis and the Lasso regression algorithm, including H3C1, IGFBP1, MT1E, SOX5 and CDHR4.

H3C1 is a member of histone family (30). Missense mutations in histone related genes promote tumor progression, a process known as oncohistones, which is a major challenge for tumor treatment (31, 32). Yi.H et al. revealed for the first time that high expression of histone deacetylase 7 (HDAC7) was closely associated with poor in EC, suggesting that HDAC7 is a potential cancer-promoting agent (33). IGFBP1 binds to insulin-like growth factors (IGFs) I and II in plasma, prolonging their half-life period (34). Elevated levels of IGF-1 and IGF-2 are related to various cancers (35–37), including EC (38, 39). The insulin-like growth factor (IGF) signaling pathway plays a key role in cell growth, differentiation, and apoptosis (38). IGFBP1 was identified as a promising biomarker for the diagnosis of early-stage esophageal cancer in a clinical study involving 2028 patients with esophageal cancer at three medical centers (40). However, there have been few biological studies on IGFBP-1 in esophageal cancer. CDHR4, which has been less studied, is a member of the cadherin related family. While cadherin, a key molecule for tumor entry into blood vessels and lymph, is associated with tumor infiltration and metastasis by mediating EMT (41, 42).Our study suggested that high expression of H3C1 and IGFBP1 predicted poor prognosis, while CDHR4 was a prognostic protective factor (**Figure 1H**), consistent with the results of the currently published studies. SOX5, a member of the SOX (SRY-related HMG-box) family involved in the determination of the cell fate. In a mouse model, SOX5 inhibits glioma formation by inducing acute cellular senescence (43). MT1E is an isoform of MT1, and it has been reported that MT1E expression is positively correlated with esophageal cancer malignancy (44).

We constructed a prognostic model based on CSRS by combining N stage, M stage, and pathological stage, which was validated well in an independent cohort (**Figure 3**). The DCA curve, KM curve and ROC curve demonstrated the validity of the nomogram model (**Supplementary Figure S1**). The nomogram model predicts better clinical benefit than AJCC staging for the prognosis of patients with esophageal cancer with a five-year AUC of 0.946. We observed differences in the distribution of CSRS in ESCC and EAC (**Figure 4D**). Therefore, further subgroup survival analysis was performed (**Figures 4E–J**). ESCC caused by smoking and alcohol consumption varies from the pathogenesis of EAC by Barrett's esophagus progression (45, 46). According to our analysis, the CSRS score to determine prognosis was not limited by pathological staging. However, CSRS was less effective in judging early-stage EC groups, as well as in younger subgroups. Regarding this observation, we believed that more clinical samples needed to be included for subsequent evaluation.

Immunotherapy has made brilliant achievements in the field of advanced EC treatment, rewriting the treatment paradigm of EC (47, 48). KEYNOTE-590 is the first global multicenter phase III clinical trial exploring the efficacy of immune combination chemotherapy in advanced EC (49). CheckMate −577 provides new high-level evidence for immunotherapy of locally advanced EC (50). We conducted an analysis between CSRS and tumor immune infiltration in EC to investigate whether CSRS contributes to the immunotherapy of EC (**Figure 5**). Results revealed that the high CSRS group had poor immunotherapy efficacy, while the low CSRS group may have better immunotherapy efficacy based on assessment of immune cell infiltration status, tumor microenvironment, T cell dysfunction and immune checkpoint-related genes.

To further validate the above findings, a GSEA analysis of DEGs in the high- and low- CSRS groups was performed (**Figure 6A**). The results showed that genes in the high CSRS group were positively enriched in acetylation and methylation related pathways. Negative enrichment was observed on immunomodulatory-related pathways. HDAC promotes tumorigenesis through biological mechanisms such as induction of cell proliferation and inhibition of apoptosis (51–53). Combining HDCA inhibitors with immunotherapy drugs for tumors significantly reverses immunotherapy resistance (54). Abnormal DNA methylation allows highly mutated tumors to evade immune responses through a rapid division mechanism, which is an important factor in tumor resistance to immune responses (55). The above analysis provides direction for higher immunotherapy benefit in patients with high CSRS, and further biological experimental validation will be needed further.

There are still some limitations to our study. Although CSRS was applied to different pathological types of esophageal cancer, it is generally effective in determining the prognosis of patients with early-stage esophageal cancer based on the current data. We believed that this may be due to the bias caused by the small number of cases of TCGA-ESCA, for example, there were only 16 patients with pathological stage I. Subsequently, we will expand the sample size or combine the data from our center to verify the generalizability of CSRS.

Conclusion

In the present study, we constructed a CS-related prognostic model for EC. Comprehensive analysis, combined with preliminary validation of independent cohort, suggested that CSRS is a prognostic risk factor for EC. Patients with high CSRS may have worse immunotherapy outcomes.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

SZ and NL were responsible for study design and writing. CY was involved in the study design and was responsible for scientific revision. SZ and NL contributed the same to this paper as the co-first author. QW and NL were responsible for data collection and analysis. SZ and HH contributed to the image painting. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1090700/full#supplementary-material.

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Development of nomograms predictive of anastomotic leakage in patients before minimally invasive McKeown esophagectomy

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Purpose: The present study aims to identify factors related to anastomotic leakage before esophagectomy and to construct a prediction model.
Methods: A retrospective analysis of 285 patients who underwent minimally invasive esophagectomy (MIE). An absolute shrinkage and selection operator was applied to screen the variables, and predictive models were developed using binary logistic regression.
Results: A total of 28 variables were collected in this study. LASSO regression analysis, combined with previous literature and clinical experience, finally screened out four variables, including aortic calcification, heart disease, BMI, and FEV1. A binary logistic regression was conducted on the four predictors, and a prediction model was established. The prediction model showed good discrimination and calibration, with a C-statistic of 0.67 (95% CI, 0.593–0.743), a calibration curve fitting a 45° slope, and a Brier score of 0.179. The DCA demonstrated that the prediction nomogram was clinically useful. In the internal validation, the C-statistic still reaches 0.66, and the calibration curve has a good effect.
Conclusions: When patients have aortic calcification, heart disease, obesity, and a low FEV1, the risk of anastomotic leakage is higher, and relevant surgical techniques can be used to prevent it. Therefore, the clinical prediction model is a practical tool to guide surgeons in the primary prevention of anastomotic leakage.

KEYWORDS
esophagectomy, anastomotic leakage, predictive model, nomogram, aortic calcification

Introduction

Esophageal carcinoma is one of the most common malignant tumors in the upper gastrointestinal tract. In 2020, the total number of new cases and deaths from esophageal cancer worldwide were 604,100 and 544,076, respectively, with its morbidity and mortality rates ranking 7th and 6th among all malignant tumors (1).

Anastomotic leakage (AL) after esophagectomy is what patients must consider a frequent and severe postoperative complication, which leads to a prolonged length of hospital stay (2, 3), increased physical and psychological distress, and even a delay in postoperative adjuvant therapy, resulting in an increased risk of distant metastasis of the tumor (4). With the development of surgical techniques and perioperative patient management, the incidence of anastomotic leakage is lower than before. However, according to a recent analysis of 6,022 patients from the Esodata dataset, who underwent esophageal resections at 39 centers representing 19 countries between January 2015 and December 2018, the frequency of leaks remains high, with an incidence rate of 12.5% (5). Therefore, early clinical observation and identification of anastomotic leakage are very important.

The current medical model has been transformed from traditional experience medicine to evidence-based medicine and gradually developed into precision medicine. As data are easier to obtain and predictive analysis becomes more convenient, the value of clinical data has received unprecedented attention, and individualized medicine has been mentioned more and more by clinicians (6). The clinical prediction model, as a quantification tool for assessing risks and benefits, can help doctors and patients make decisions before the outcome is available. The nomogram is a simple tool for predicting complications in clinical practice (7). It graphically compares known factors and makes individualized risk prediction more concise and intuitive.

Although many studies exist on the risk of anastomotic leakage after esophagectomy worldwide, there is still a lack of specific methods to evaluate the risk of anastomotic leakage before surgery, which can guide the significance of preoperative and intraoperative intervention for patients. This study aimed to establish a practical clinical prediction model for evaluating anastomotic leakage preoperatively in esophageal carcinoma patients. Patients with a potentially high risk of anastomotic leakage were screened according to their general physiological conditions and preoperative examinations, and individualized clinical intervention and surgical plan adjustment were given to reduce the incidence of postoperative anastomotic leakage.

Materials and methods

Patients

A retrospective analysis was carried out on 557 patients who were diagnosed with esophageal cancer by pathology or cytology and treated for radical esophagectomy between January 2015 and January 2020. The inclusion criteria were as follows: gastroscopy was performed preoperatively, patients were pathologically confirmed to have esophageal cancer, a minimally invasive McKeown esophagectomy with stapled anastomoses, including a three-field lymphadenectomy, was performed, and resection was performed with negative resection margins (pR0). Patients who had recurrent or metastatic cancer, palliative resection due to the discovery of T4b or M1 disease during surgery, an organ reconstruction other than gastric tube reconstruction, a route reconstruction other than posterior mediastinal route, and incomplete clinical data were excluded. A total of 285 patients were included in this study, and 272 patients were excluded, including 13 cases with data deletion, 45 cases with Ivor-Lewis or Sweet surgery, 5 cases with colon reconstruction or jejunal reconstruction, 99 cases with manual anastomosis, 88 cases with two-field lymphadenectomy, and 22 cases with the retrosternal route. The study design was approved by the institutional review board and ethics committee of Zhongshan Hospital at Xiamen University. Patient consent for inclusion was waived owing to the use of identified retrospective data.

Surgical procedures

Our standard procedures consisted of a three-field surgery (the modified McKeown procedure, with laparoscopy and right video-assisted thoracoscopic surgery) and reconstruction with a gastric tube through a posterior mediastinal route. An end-to-side esophagogastric anastomosis was performed in the neck using a circular stapled anastomotic technique. Lymph node dissection was based on a total three-field lymphadenectomy. The extent of the three-field LN dissection, including all nodes and periesophageal tissues below the level of the carina to the celiac trifurcation and all superior mediastinal nodes along the recurrent laryngeal nerve to the lower poles of the thyroid and lymph nodes in the supraclavicular fossa.

Potential predictor variables

The selection of candidate predictors was based on the reference literature and relevant clinical experience reported in **Table 1**. Intra-operative data and the pathological result were not included in the candidate predictors, although they were reported to be significant risk factors. In the clinic, preoperative evaluation for the incidence of anastomotic leakage is recommended, along with further interventional measures, including the selection of an appropriate surgical strategy and the extent of lymph node cleaning. Here, therefore, our patients included were given McKeown esophagectomy under thoracoscopy and laparoscopy plus a three-field lymph node dissection by two experienced thoracic surgeons, hoping to balance the effect of intra-operative variables on the incidence of anastomotic leakage. Because pathological reports can be obtained 5–7 days after surgery, the peak period of anastomotic leakage, they cannot be used for early leakage prediction. Given the condition, preoperative chest and abdominal CT imaging and gastroscopic puncture biopsy pathology are considered alternatives.

Definitions of anastomotic leakage

We defined anastomotic leakage as a full-thickness GI defect involving esophageal anastomosis, a staple line, or both, irrespective of presentation and method of identification (8). Anastomotic leakage, if early, can happen at the end or within 3 days of operation, mainly attributed to inappropriate anastomotic techniques or operating methods. If late, anastomotic leakage may develop 2 weeks or even 1 month post operation, commonly around 1 week post operation. It is established that anastomotic leakage has three levels: mild, medium, and severe. For mild cases, no particular clinical manifestations are presented, and they are often diagnosed during an examination, with no need for medical treatment and delayed oral feeding discontinuation as a curable option. For medium cases, symptoms of sepsis can be clearly seen in gastroscopy, radiography, and a CT image, and clinical interventions are required, including anti-infection therapy, bedside incision opening and gauze filling, drainage, stent implantation, etc. While for severe cases, clinical symptoms present to be critical, requiring surgical treatment. In the present study, all patients received cervical anastomosis. In these cases, the neck skin manifests red and swollen, tenderness, subcutaneous emphysema, putrid pus when pressed, saliva or gastric juice-like substance seen in the neck drainage tube, or even symptoms like increased body

TABLE 1 Demographics and clinical characteristics Among 285 patients with minimally invasive McKeown esophagectomy.

Characteristic	AL	Non-AL
Total number	77	208
Age (years)	61.0 ± 8.2	59.9 ± 8.2
Sex		
Female	12 (15.6%)	37 (17.8%)
Male	65 (84.4%)	171 (82.2%)
BMI (kg/m^2)	21.8 ± 3.1	21.4 ± 2.9
Smoking	48 (62.3%)	139 (66.8%)
Hypertension	24 (31.2%)	46 (22.1%)
Diabetes	6 (7.8%)	16 (7.7%)
Cardiac disease	6 (7.8%)	5 (2.4%)
Aortic calcification	33 (42.9%)	35 (16.8%)
nCRT	14 (18.2%)	49 (23.6%)
Pathology		
Squamous	74 (96.1%)	203 (97.6%)
Adenocarcinoma	1 (1.3%)	2 (1.0%)
Other	2 (2.6%)	3 (1.4%)
Location		
Upper	9 (11.7%)	38 (18.3%)
Middle	57 (74.0%)	128 (61.5%)
Lower	11 (14.3%)	42 (20.2%)
Long diameters (cm)	4.762 ± 3.546	4.58 ± 2.43
Total protein (g/L)	71.2 ± 5.3	70.5 ± 6.3
Albumin (g/L)	41.8 ± 3.5	41.8 ± 4.8
ALT (U/L)	18.3 ± 14.4	17.2 ± 11.1
AST (U/L)	20.7 ± 9.4	20.1 ± 9.1
Urea (mmol/L)	5.2 ± 1.8	5.4 ± 1.5
CREA (μmol/L)	76.3 ± 16.0	75.9 ± 15.6
Glu (mmol/L)	5.7 ± 1.8	5.5 ± 1.2
PLT (10^9/L)	248.4 ± 83.8	247.2 ± 72.5
Hb (g/L)	133.9 ± 14.8	134.1 ± 15.9
HCT (%)	39.8 ± 4.4	39.9 ± 4.7
FEV1 (L)	2.7 ± 0.6	2.8 ± 0.7
FEV1% Pred	100.6 ± 18.5	101.4 ± 17.2
FVC (L)	3.5 ± 0.7	3.6 ± 0.8
FVC1% Pred	104.2 ± 14.7	105.5 ± 15.5
FEV1/FVC (%)	76.6 ± 9.9	76.9 ± 8.8
Pulmonary function		
Normal	53 (68.8%)	158 (76.0%)
Mild dysfunction	19 (24.7%)	40 (19.2%)
Moderate dysfunction	4 (5.2%)	7 (3.4%)
Severe dysfunction	1 (1.3%)	3 (1.4%)

AL, anastomotic leakage; BMI, body mass index (kg/m^2); nCRT, Neoadjuvant chemoradiotherapy; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity.

temperature and heart rate, cervical anastomotic leakage is then suspected. Esophagus-chest enhanced CT can be implemented to identify the anastomotic leakage. If necessary, open the incision on the left neck to observe and conduct debridement for drainage. In circumstances where patients develop anastomotic leakage in routine DR 7 days after the operation with no local or systemic inflammatory responses, symptomatic treatment like fasting is given temporarily.

Statistical analysis

Continuous variables were presented with a mean and standard deviation. Frequencies and percentages were presented using categorical variables. Statistical analysis was conducted using the R software (Rx64 4.0.12). The last absolute shrinkage and selection operator is a scenario favored in variable screening by the statistician (9). It was able to find an optimal equilibrium point between accuracy estimation for models and the absolute values of the coefficients. This algorithm regulated the penalty coefficient so that errors could be minimized to achieve the screenings purposes and avoid the problem of overfitting. In addition to screening variables by statistical methods, artificial addition or deletion of variables is allowed after approval by clinical experts. Then, risk factors selected from the Lasso analysis were assessed using a binary logistic regression modeling technique; Besides, a nomogram that can visualize the prognostic strength of different risk factors in a single figure was established. The concordance index (c-index) and calibration curve were used to determine its predictive accuracy and discriminatory capacity. The Brier score was used for overall performance and captures aspects of both calibration and discrimination. Decision curve analysis was used to assess the clinical impact of the prediction model by quantifying the net benefits at different threshold probabilities. Last, the internal validation of the nomogram was conducted by bootstraps with 100 resamples.

Results

Patient characteristics

During the study period, 557 consecutive patients who had a malignant tumor of the esophagus based on preoperative imaging and bioptic-based histopathology underwent esophagectomy. Of these, 285 patients [236 males and 49 females; mean age 60 ± 8.2 years (range 36–87 years)] who met the inclusion were enrolled. The incidence of anastomotic

leakage after esophagectomy in this study was 27%, which was comparable and slightly higher than previous reports (rate of anastomotic leakage between 8% and 35%) (10, 11). Patients were divided into an AL group and a non-AL group. The demographic and clinical characteristics of the patients are summarized in Table 1.

In order to exclude the influence of intraoperative factors, the results of non-parametric test analysis and chi-square analysis showed no significant difference between the groups with and without anastomotic leakage after esophagectomy in terms of the surgeon, operative time, and intraoperative estimated blood loss (Table 2).

Development and evaluation of the predictive model

Lasso regression was performed on 285 cases with 28 clinical characteristics and demographic information using R software. Then, two predictors with non-zero coefficients were screened (Figures 1, 2), which were aortic sclerosis and heart disease, and aortic sclerosis ($P < 0.05$) was statistically significant. Based on the literature and previous clinical experience, we additionally added body mass index (kg/m^2) (BMI) and forced expiratory volume in the first second (FEV1) as predictors to the analyses. Anastomotic leakage was used as the dependent variable, and aortic sclerosis, heart disease, BMI, and FEV1 were included as independent variables in a binary logistic regression model. We used the following formulas for the logistic model to calculate the probability: probability $= 1/(1 + e^{-Y})$, e = base of the natural logarithm, $Y = -1.73791 + (0.04572 \times \text{BMI}) + (0.98899 \times \text{heart disease}) + (1.23872 \times \text{aortic sclerosis}) - (0.23648 \times \text{FEV1})$. Then, the nomogram to predict anastomotic leakage was plotted using R software for visualization purposes (Figure 3).

The predictive accuracy of the model was assessed using (1) C-index for discrimination, which measures how well the model discriminates between patients with and without AL. The predictive nomogram achieved a C-index of 0.67 (95% confidence interval [CI], 0.593–0.743) as outcome events are a dichotomous categorical variable, the same as in the area underthe ROC curve (AUC), And the receiver operating characteristic curve is displayed in Figure 4; (2) A calibration curve was based on the actual incidence and predicted incidence. The dotted line represents $y = x$ which means that the predicted and measured rates are exactly the same. The calibration curve of the nomogram to predict AL risk before oesophageal surgery demonstrated good agreement in this cohort (Figure 5), and (3) Brier score for overall performance, which ranges from 0 to 1, with a value closer to 0 indicating better predictive ability, and our model score of 0.179. The decision curve showed that if the threshold probability of a doctor is between 18% and 60%, using the nomogram to predict AL adds more benefit (Figure 6). Bootstrapping with 100 repetitions was used for model validation, and the bias-corrected measure of accuracy was c-index of 0.66. Together, the values we obtain for these measures indicate reasonably good predictive accuracy and are clinically useful.

TABLE 2 Intraoperative parameters of 285 patients with minimally invasive McKeown esophagectomy.

Variable	AL	Non-AL	*P*
Surgeon A	125 (60.10%)	48 (62.34%)	0.731
Surgeon B	83 (39.90%)	29 (37.66%)	
Surgery time (min)	381.2 ± 110.0	360.0 ± 101.9	0.107
Blood (ml)	170.8 ± 133.5	174.7 ± 142.1	0.689

AL, anastomotic leakage.

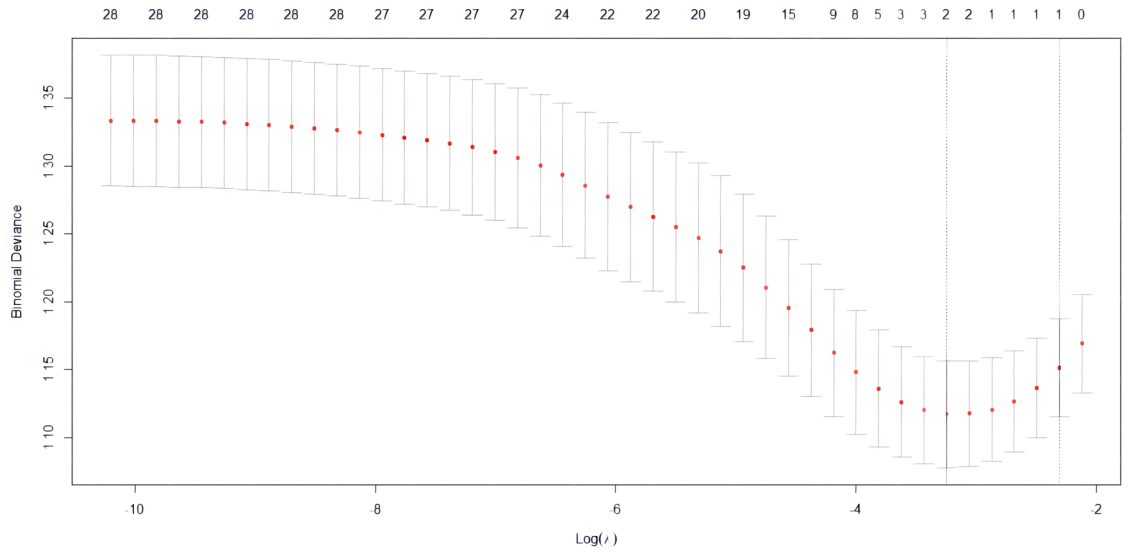

FIGURE 1
The LASSO regularization parameter lambda was selected by 10-fold cross-validation using the cv.glmnet function, and the optimal Lambda value was identified by the minimum cross-validated criterion and the minimum criterion within one standard error.

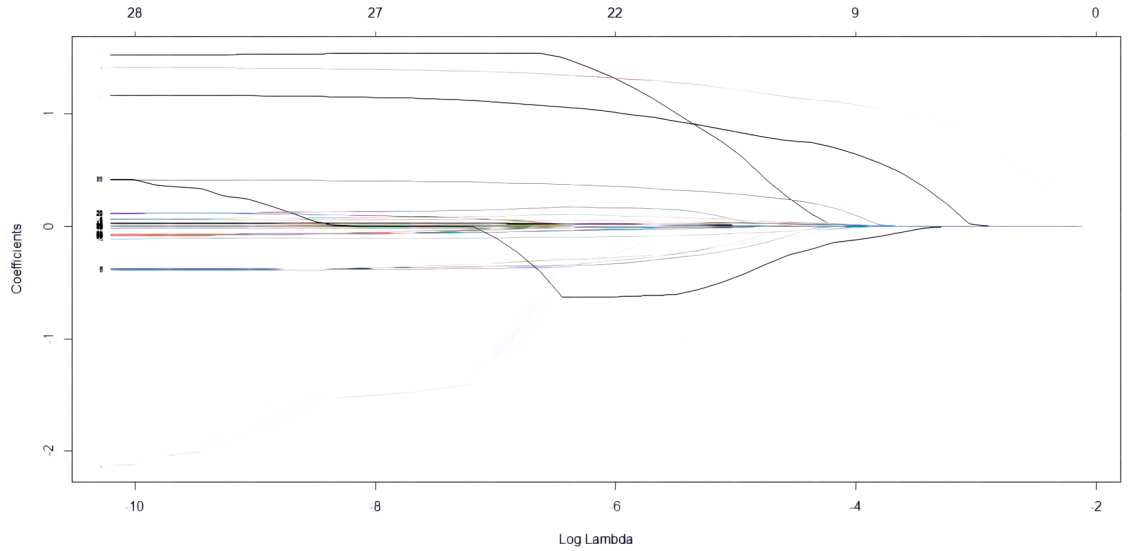

FIGURE 2
LASSO coefficient profiles of 28 predictive risk factors according to log(Lambda) sequence.

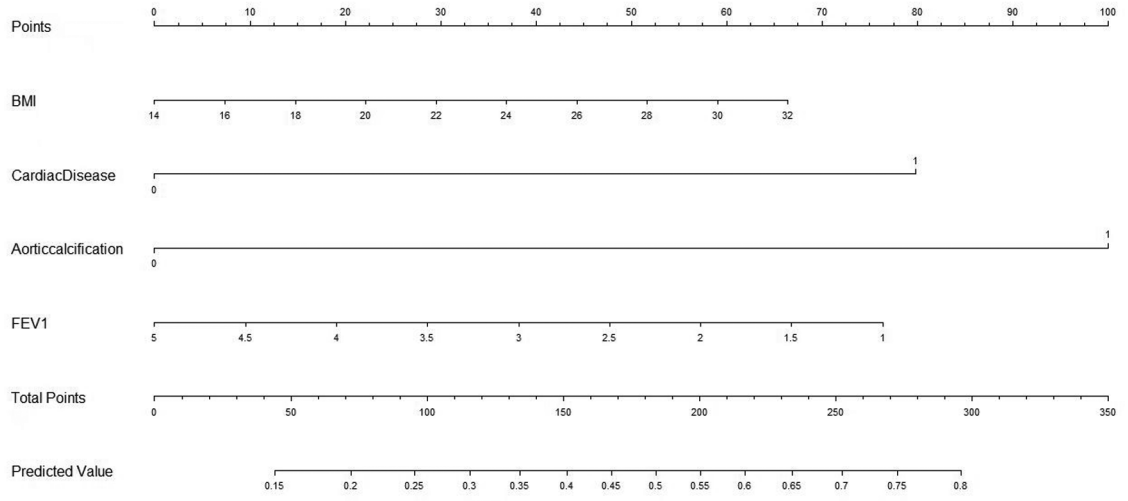

FIGURE 3
The developed AL risk nomogram with minimally invasive McKeown esophagectomy.

Use of the nomogram

The steps for using the nomogram are determining the patient's value for each predictive variable, adding the points from each predictor according to the top point reference line, and locating the sum of the points on the total points axis, which corresponds to the patient's likelihood of having AL.

The applicability of the nomogram can be illustrated through a clinical example: If a patient with a BMI of 22 kg/m^2, FEV1 of 4.5 L, aortic calcification, no previous history of heart disease, according to the nomogram, scores of each predictor were calculated to be 30, 77, 100, and 0, the total points would be 207, and the risk of AL would be 57%. The expected likelihood of AL for individual patients can be used for preoperative counseling and treatment planning.

Discussion

Esophageal cancer is a common malignant tumor of the digestive tract that occurs in the esophageal epithelium. Surgery is the main treatment option for esophageal cancer, and anastomotic leakage is one of the most serious complications after esophageal cancer resection. Therefore, patients with esophageal cancer may benefit from the early prevention and detection of AL.

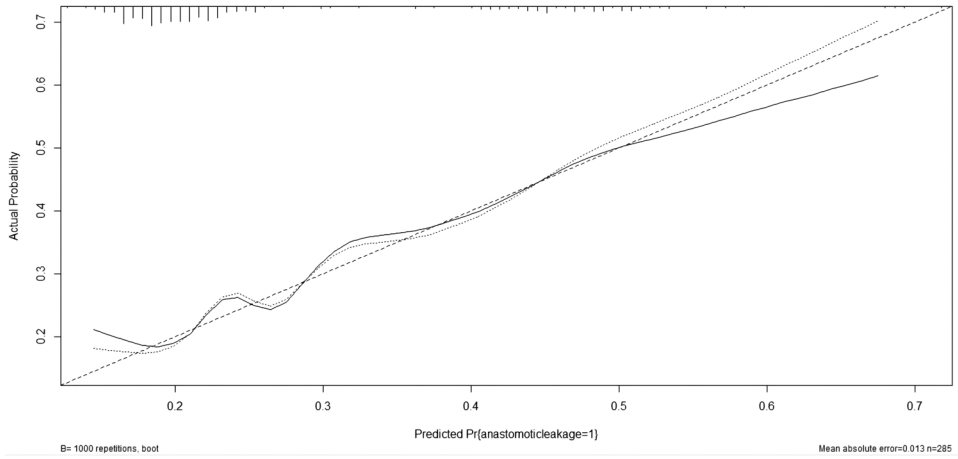

FIGURE 4
The accuracy of the model for identifying patients with AL was determined using AUC analysis.

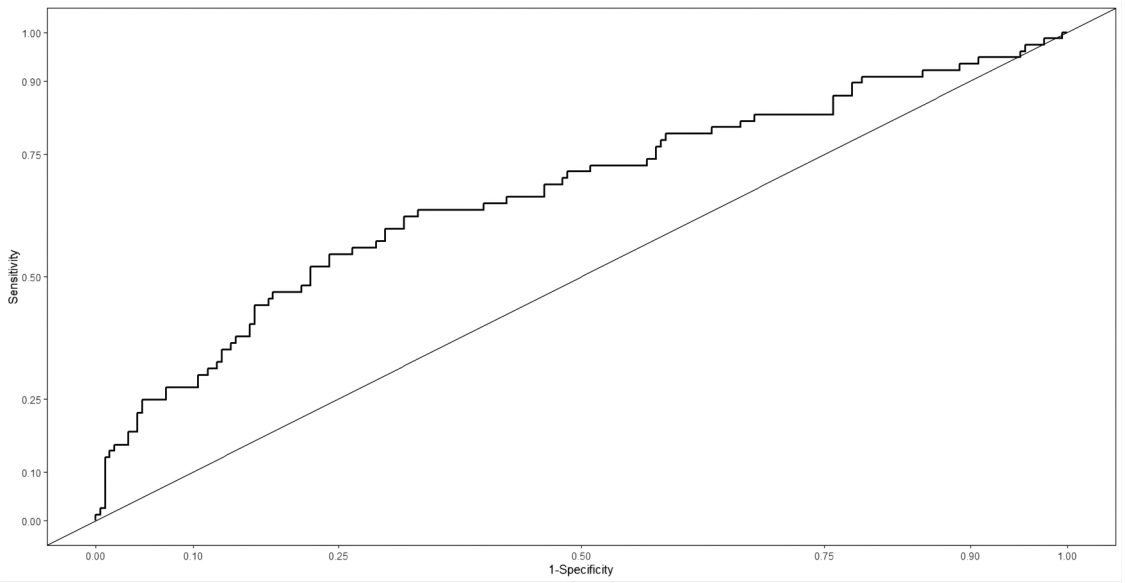

FIGURE 5
Calibration plots of the nomogram. The solid line represents the bias-corrected performance of the nomogram, where a closer fit to the diagonal dotted line represents a better prediction.

In recent years, with the popularization of statistical methods for clinical prediction models, more and more surgeons have applied them to the prediction of postoperative complications. Huang et al. and Sun et al. analyzed various indicators of the perioperative period, including the general state of patients, anastomosis site and method, postoperative blood inflammation index, and complications, to establish a risk prediction model for anastomotic leakage after esophagectomy, respectively (12, 13). In this case, the researcher systematically identified and rated their performance, a presentation we have not found in previous literature. This model provided a reference for doctors to diagnose anastomotic leakage in patients following esophagectomy. Unfortunately, due to the inclusion of intraoperative and postoperative indexes, these models simply apply to predict the incidence of anastomotic leakage after surgery and cannot advise for the prevention of anastomotic leakage preoperatively targeted at surgical methods, sites of anastomosis, and the extent of the lymph node dissection.

Previous studies have mainly focused on surgical factors and postoperative data, which is quite different from ours. We developed a novel tool to predict the healing ability of the anastomosis in the stomach conduit before esophageal surgery based on 5 years of data from indigenous Chinese patients. The main advantage of the current study is that our nomogram mainly applies to preoperative assessment, offers individualized surgical strategies, and achieves the goal of primary prevention. Four of the 28 clinical parameters were screened, and the weighting of each

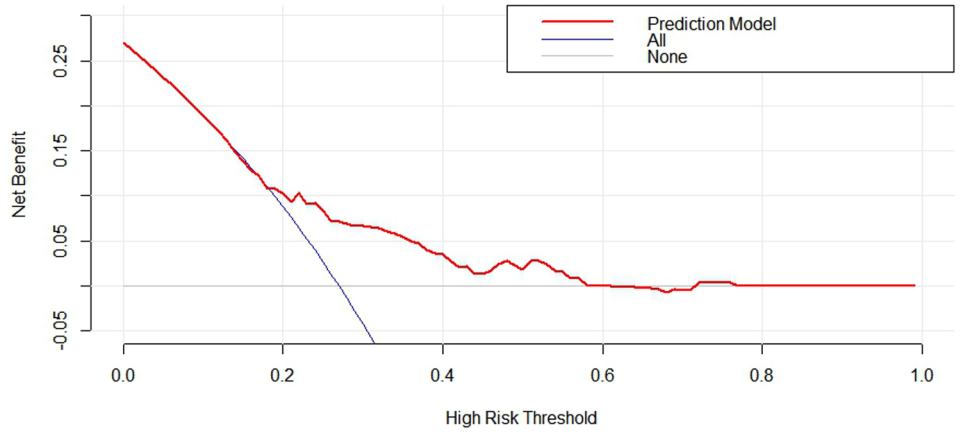

FIGURE 6
Decision curve for nomogram to predict the risk of anastomotic leakage before esophagectomy. The blue line assume all patients have AL. The gray line assume no patients have AL. The red curve represent clinical benefits of patients at different risk levels of AL.

parameter was significant in the nomogram, which could reflect the significant influence of these factors on the predicted value.

Atherosclerosis, now the recognized trigger for tissue ischemia, is inferred to have an impact on the anastomotic blood supply of the gastric tube (14). A previous study used the vascular calcification of arteries as an indicator for atherosclerosis to predict the risk of cardiovascular events (15). Inspired by this, van Rossum et al. proposed a semi-quantitative scoring system, which is practicable in evaluating the vascular calcification of gastric feeding arteries, based on preoperative chest and abdominal CT images of patients suffering esophageal carcinoma (16). The research displayed that the vascular calcification of gastric feeding arteries in preoperative routine chest and abdominal CT images was associated with the risk of cervical anastomotic leakage post radical treatment for esophageal carcinoma, and the calcification of aorta and common hepatic artery were identified as independent risk factors ($P < 0.05$). Such a finding is supported by anatomy and pathophysiology and is evidenced by the right gastroepiploic artery, which is derived from the branch of the common hepatic artery and serves as a supplier of gastric tube and anastomotic blood. By now, however, it is still a mystery whether the association of anastomotic leakage with arterial vascular calcification is only present in the limited blood flow of the gastric tube induced by local vascular disease or is also applicable in systemic vascular disease. In order to clarify the underlying relationship, Borggreve et al. conducted an analysis of the clinical information of 406 cases and then scored the arterial calcification from 10 positions throughout the body by CT imaging (17). As analyzed, the calcification of coronary arteries and aorta-arch superior thyroid arteries (brachiocephalic trunk, right common carotid artery, and right subclavian artery) were independent risk factors for anastomotic leakage. Such calcification may be a the predisposing factor or the outcome of diffuse arterial diseases. Hence, it can help identify patients who have a risk of anastomotic leakage. As such, there was a retrospective study by Goense et al. devoted to 167 esophageal carcinoma cases after the operation, indicating that the existence and severe degree of thoracic aorta calcification were associated with the risk of anastomotic leakage post-esophagectomy in an independent manner (18). This is in agreement with our findings. Here, only the right gastroepiploic arteries were retained following the McKeown esophagectomy, making the bottom of the gastric tube suffer from a relatively deficient blood supply, while vascular calcification might further aggravate the condition. Notably, vascular disease is tightly associated with multiple systemic and chronic lesions, such as diabetes, peripheral vascular disease, and renal insufficiency, which might be involved in the cure of cervical anastomosis via various pathways.

Heart-relevant diseases are defined as previous coronary atherosclerotic heart disease, continuous arrhythmia, a history of organic heart lesions, and abnormal diseases reflected in an improved electrocardiogram and echocardiography at admission. Additionally, the unstable hemodynamics during and post operation induced by heart-related diseases is as well a risk factor for anastomotic leakage. A meta-analysis by Schizas et al. revealed patients with atrial fibrillation had a significantly increased risk of anastomotic leakage relative to patients without atrial fibrillation (OR = 2.65, 95% CI, 1.53–4.59) (19). This might be attributed to the unstable hemodynamics caused by atrial fibrillation, leading to decreased anastomotic tissue blood, ultimately resulting in gastric tube ischemia and anastomotic leakage. The development of postoperative atrial fibrillation is partially due to the close range between the esophagus and left atrium in anatomy, and the free esophagus around the pericardium can increase the risk of left atrium associated complications during the operation. While coronary atherosclerosis and organic heart disease are recognized factors leading to atrial fibrillation.

Sufficient tissue oxygen delivery is another prerequisite for a smooth anastomotic cure (20). Compelling evidence by Gao et al. on 129 esophageal carcinoma cases who undertook minimally invasive McKeown operation indicated that the preoperative FEV1 <2.18 L and the lowest intra-operative ABG PaCO2 >45.5 mmHg were risk factors of anastomotic leakage post operation (21). The

research here demonstrated that the lower preoperative FEV1 reflected the higher incidence of postoperative anastomotic leakage. Studies in the past have noted that factors such as COPD, near-term smoking, and pneumonia, which are responsible for decreased pulmonary function, are also risk factors for cervical anastomotic leakage (22–24). This might be attributed to the low anastomotic tissue oxygenation associated with poor pulmonary function during and post operation. In view of the above, we should pay more attention to the association between pulmonary function and postoperative complications. In addition, active pulmonary function exercise, absolute smoking cessation for at least 2 weeks, atomization, reducing sputum, and other clinical interventional measures can help reduce the incidence of pneumonia and anastomotic leakage post operation.

Body mass index (BMI), calculated as weight in kilograms divided by height in square meters (kg/m^2), is a confirmed risk factor for anastomotic leakage. A meta-analysis by Mengardo et al. reports a higher incidence of AL in obese patients than in non-obese patients (25). Diabetes, dyspnea, and cardiac disease appeared significantly more prevalent among obese patients and increased in parallel with the extent of BMI. Notably, a BMI lower than 18.5 kg/m^2 and weight loss of 5% or more during the 3 months before surgery are strong indicators of malnutrition, which are reported to be associated with an increased risk of anastomotic leakage after esophagectomy. Therefore, underweight patients may benefit from preoperative nutritional assessments and nutritional supplementation due to their higher risk of malnutrition and cachexia. Overall, obese and underweight patients should receive extra attention for the early detection and prompt treatment of anastomotic leakage. In the present study, the nutritional risk score (NRS-2002) should be performed to screen for undernourished patients who would benefit from enhanced nutritional support preoperatively.

Studies have shown that neoadjuvant therapy affects the overall nutritional status of patients, their incredible immune function (26), increases the risk of postoperative infection, and ultimately has a negative impact on anastomotic healing. However, in the study, esophagectomy was performed in 285 patients, and 22.2% of patients with preoperative neoadjuvant therapy had AL. But 28.4% of patients without preoperative neoadjuvant therapy had AL ($P = 0.33$), and the results showed that neoadjuvant therapy was not associated with AL. However, some studies showed contrasting results (27, 28). Preoperative neoadjuvant therapy showed a correlation with AL. These studies suggest that patients receiving neoadjuvant therapy have more postoperative complications and a greater impact on cardiopulmonary function (29), which, in turn, reduces tissue perfusion and increases the risk of poor anastomotic healing. The differences in indications for neoadjuvant chemotherapy, choice of chemotherapy agents, and methods of operation may cause differences in the results.

With regard to these suggested causes, different attempts to optimize the conditions of anastomosis have been reported. A novel risk score for the prediction of anastomotic leakage may improve preoperative optimization, intraoperative strategy, and postoperative management. Prior to surgery, this nomogram offers a useful tool for clinicians to assess the risk of AL in individuals. Surgeons can then inform the patient and the referring physician of the predictive risk. Additionally, this new model plays instructive roles for surgical protocols in esophageal cancer patients. In the case of AL, some technical tips can be used prophylactically for high-risk patients. The use of pedicled omental transposition is a common surgery for the prevention of anastomotic leaks in carcinoma of the esophagus. The ability of the omentum to localize potentially dangerous inflammatory processes and induce neovascularization in the underlying tissues makes it a unique structure for preventing esophagogastric anastomotic leaks. In a previous study, Bhat et al. proved that the use of mobilized omentum wrapped around the anastomosis markedly decreased the incidence of anastomotic leakage, which has been evaluated in a prospective controlled trial (30). However, more accurate measurements and cutting is required before transposition. Surgery was difficult because some minor deviations may negatively affect the quality of pedicled omental. Song et al. adopted a novel approach using polymeric materials, requiring only proper tailoring during the operation. They reported excellent results, with a 2.4% incidence rate of anastomotic leaks and a 9.2% incidence rate using pedicled omental. Such results are attributed to the omental's inability to form the tight separation layer after fat liquefaction, which leads to an increased risk of anastomotic infection and leakage, while polymeric materials serve as an effective isolation layer to prevent anastomotic bleeding and inflammatory exudation.

There are some limitations that need to be mentioned in this study. First of all, this study was a retrospective study conducted in a single high-volume institution, so selection bias cannot be completely excluded, and external validation is required by more large-scale multicenter studies. Second, there are still some data that have not been collected in this study, so we cannot exclude some potential confounders that are not included in the analysis. Therefore, clinical predictive models needed an appropriate number of influential factors that were easy to collect and use to predict outcome variables. But with the development of science and technology, we will continue to explore big data, machine learning, artificial intelligence, and other technologies to apply them in clinical practice to achieve precision medicine.

Conclusion

In summary, when patients have aortic calcification, heart disease, obesity, and low FEV1, the risk of anastomotic leakage is higher. Identifying patients at risk of anastomotic leakage and providing relevant surgical techniques may help prevent postoperative complications. Therefore, the clinical prediction model in this study is a practical tool to guide surgeons in the primary prevention of anastomotic leakage in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conception and design: JC, JX, SK. Administrative support: JC, HD. Provision of study materials or patients: JC, JX. Collection and assembly of data: JC, JX. Data analysis and interpretation: JC, JX. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effect of preoperative radiotherapy on the prognosis of patients with stage cTxN0M0 esophageal squamous cell carcinoma: propensity score matching analysis based on SEER database

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Objective: The aim of this study was to investigate the effect of preoperative radiotherapy (RT) on overall survival (OS) in patients with stage cTxN0M0 esophageal squamous cell carcinoma (ESCC).
Methods: A total of 467 patients with ESCC diagnosed as cTxN0M0 and undergoing esophagectomy between 2004 and 2016 were downloaded from the Surveillance, Epidemiology, and End Results (SEER) database. According to the presence or absence of preoperative RT, the patients were divided into preoperative RT group and non-preoperative RT group. Propensity score matching (PSM) was performed to equalize baseline levels between groups. Univariate and multivariate Cox regression analyses were used to compare the survival differences between the two groups.
Results: Using PSM, 162 pairs of patients were selected. Preoperative RT was not a prognostic factor for OS in all patients with cTx stage. After PSM, for patients with cT1–2 stage, univariate Cox regression analysis showed that preoperative RT was an influencing factor of OS, and multivariate Cox regression analysis confirmed that preoperative RT was an independent predictor of OS. Compared with non-preoperative RT, preoperative RT significantly decreased OS (HR = 1.556, 95%CI 1.008–2.464, $p = 0.046$). For patients with cT3–4, univariate Cox regression analysis showed that preoperative RT was an influencing factor for OS, and multivariate Cox regression analysis determined that preoperative RT was independent predictors of survival. Compared with non-preoperative RT, preoperative RT significantly improved the OS (HR = 0.479, 95%CI 0.272–0.841, $p = 0.010$).
Conclusion: For ESCC, preoperative RT can improve the OS of patients with cT3-4N0M0. However, preoperative RT is not suitable for patients with cT1-2N0M0.

KEYWORDS
ESCC, cN0, PSM, OS, radiotherapy

Introduction

The incidence of esophageal cancer is increasing year by year (1). At present, the radical treatment of esophageal cancer mainly adopts surgical resection, radiotherapy and chemotherapy. Clinical studies have shown that single treatment can not achieve the ideal treatment effect (2, 3). How to take the comprehensive treatment plan for esophageal cancer is the focus of clinical researchers.

Preoperative neoadjuvant therapy is associated with tumor downstaging and can improve the resection rate and long-term survival rate of esophageal cancer, so it is usually used in patients with locally advanced stage. Several clinical trials have demonstrated the efficacy of preoperative neoadjuvant therapy (4–7). However, given the frequent presence of locally advanced disease and frequent lymph node metastases in these clinical trials, it is difficult to conclude that patients with early stage or non-metastatic lymph nodes would benefit from preoperative neoadjuvant therapy. For these patients, the efficacy of preoperative neoadjuvant therapy remains to be verified.

This study aimed to explore the effect of preoperative radiotherapy (RT) on the prognosis of patients with cTxN0M0 esophageal squamous cell carcinoma (ESCC) through a propensity score matching (PSM) study based on the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and methods

Study population

The SEER database is a publicly available database that includes data from 18 cancer registries in the United States, representing approximately 29% of the U.S. population (8). Patients diagnosed with ESCC between 2004 and 2016 were downloaded from the SEER database. Inclusion criteria: (1) Patients undergoing preoperative radiotherapy combined with surgery. (2) Patients with definite preoperative cTNM staging. (3) Stage cN0 was diagnosed without distant metastasis. (4) Report follow-up data and survival status. Exclusion criteria: (1) Patients without surgery. (2) Patients without preoperative radiotherapy. (3) Patients receiving postoperative radiotherapy.

Study variables

The characteristics analyzed in the current study included age at diagnosis (≤65, >65), sex (male, female), race (white, black and other/unkown), tumor site (upper, middle and lower third), tumor cT stage, histologic grade (high, moderate and poor), follow-up time, and survival status. OS was the end point of the study. OS was defined as the time from diagnosis to death from any reason.

Statistical analysis

The patients were divided into preoperative RT group and non-preoperative RT group according to the presence or absence of preoperative RT. Statistical analysis was performed using SPSS software. The chi-square test or Fisher exact test was used to compare categorical variables. PSM was used to balance baseline levels between groups (age, sex, race, tumor site, histologic grade) with a caliper value of 0.02. Univariate Cox regression analysis was used to screen the influencing factors of OS. Factors with $p < 0.1$ were included in multivariate Cox regression analysis to determine the independent predictors of OS. The hazard ratio (HR) and its 95% confidence intervals (95%CI) were calculated to assess the strength of association between different characteristics and OS. Subgroup analysis was performed by cT stage (cT1–2, cT3–4) to further determine the factors affecting OS. Kaplan-meier method was used to draw survival curves. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 2,161 patients diagnosed with ESCC who underwent surgery were downloaded from SEER database. 467 patients were enrolled in this study, including 206 patients who received preoperative RT and 261 patients who did not receive preoperative. The specific process of patient selection is shown in **Figure 1**. Baseline unadjusted comparisons of patient demographics and oncological outcomes by treatment group (preoperative RT vs. non-preoperative RT) are shown in **Table 1**. Among the patients with cT3–4, the patients with preoperative RT were more than those without preoperative RT. After PSM, 162 patients were enrolled in each group. The patient demographics and tumor outcomes comparisons between the two groups are shown in **Table 2**. Similarly, in patients with cT3–4, patients with preoperative RT are more than those without preoperative RT.

COX regression analysis

All patients

Preoperative RT was not a significant factor in OS for all patients, regardless of whether PSM was performed for covariates. **Table 3** shows the effects of pre-PSM and post-PSM covariates on postoperative OS.

cT1–2

After PSM, 205 patients were in cT1–2 stage, and 77 of them received preoperative RT. Baseline comparisons of patient demographics and oncological outcomes by treatment group are

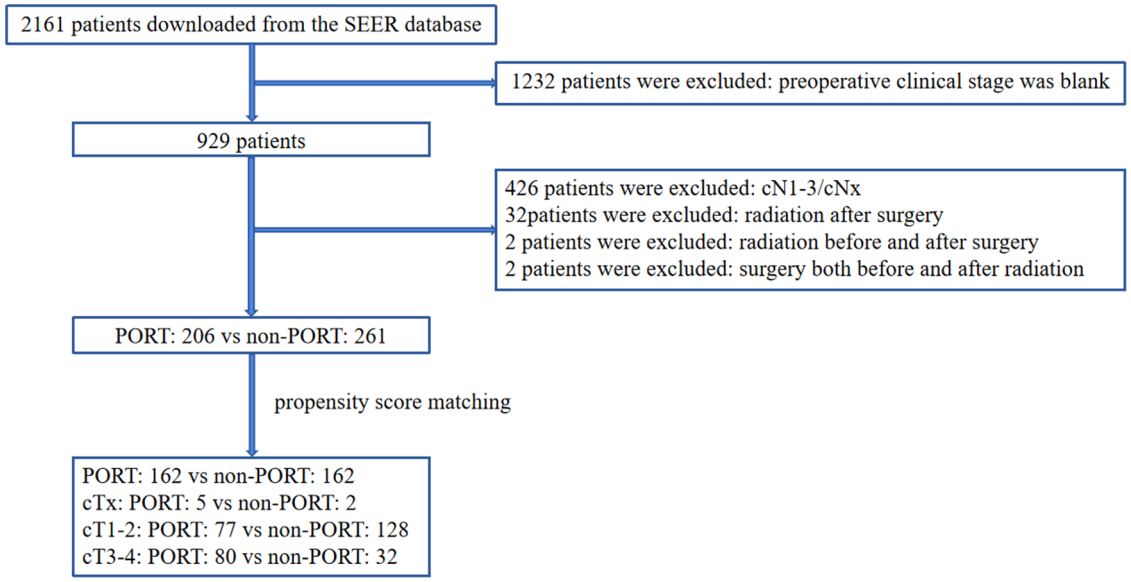

FIGURE 1
Flow chart of patient inclusion and exclusion.

TABLE 1 Comparison of patient demographics and tumor characteristics for the clinical node-negative patients before propensity score matching.

Characteristics	preoperative RT ($n = 206$)	Non-preoperative RT($n = 261$)	p
Race, n (%)			0.197
White	150	178	
Black	36	43	
Other/unkown	20	40	
Age, years, n (%)			0.000
≤65	139	118	
>65	67	143	
Sex, n (%)			0.259
Male	115	132	
Female	91	129	
Disease site, n (%)			0.919
Upper third	16	24	
Middle third	85	105	
Lower third	79	96	
Other/unkown	26	36	
Histologic grade, n (%)			0.099
High	12	32	
Moderate	109	137	
Poor	62	65	
Other/unkown	23	27	
cT stage, n (%)			0.000
cT1	54	165	
cT2	42	40	
cT3–4	105	53	
Other/unkown	5	3	
Survival status, n (%)			0.557
Alive	112	149	
Dead	94	112	

RT, radiotherapy.

TABLE 2 Comparison of patient demographics and tumor characteristics for the clinical node-negative patients after propensity score matching.

Characteristics	preoperative RT ($n = 162$)	Non-preoperative RT ($n = 162$)	p
Race, n (%)			0.590
White	114	107	
Black	29	30	
Other/unkown	19	25	
Age, years, n (%)			0.494
≤65	96	102	
>65	66	60	
Sex, n (%)			1
Male	81	81	
Female	81	81	
Disease site, n (%)			0.995
Upper third	13	14	
Middle third	60	59	
Lower third	66	65	
Other/unkown	23	24	
Histologic grade, n (%)			0.659
High	11	13	
Moderate	96	85	
Poor	40	45	
Other/unkown	15	19	
cT stage, n (%)			0.000
cT1	40	103	
cT2	37	25	
cT3–4	80	42	
Other/unkown	5	2	
Survival status, n (%)			0.500
Alive	90	96	
Dead	72	66	

RT, radiotherapy.

TABLE 3 Univariable cox analysis of the influence of each characteristic on overall survival.

Characteristics	Before PSM		p	After PSM		p
	HR	95%CI		HR	95%CI	
Race						
White	Ref			Ref		
Black	1.281	0.909–1.805	0.157	1.411	0.941–2.116	0.096
Other/unkown	1.240	0.820–1.875	0.307	1.364	0.830–2.243	0.221
Age, years						
≤65	Ref			Ref		
>65	1.079	0.821–1.418	0.587	1.041	0.741–1.463	0.817
Sex						
Male	Ref			Ref		
Female	0.837	0.636–1.103	0.207	0.978	0.700–1.365	0.894
Disease site						
Upper third	Ref			Ref		
Middle third	0.804	0.505–1.280	0.358	0.998	0.535–1.861	0.994
Lower third	0.526	0.323–0.856	0.010	0.733	0.389–1.382	0.337
Other/unkown	0.766	0.440–1.333	0.345	1.120	0.557–2.250	0.751
Histologic grade						
High	Ref			Ref		
Moderate	0.491	0.230–1.049	0.066	2.674	1.081–6.616	0.033
Poor	1.296	0.804–2.807	0.287	3.266	1.292–8.254	0.012
Other/unkown	1.560	0.945–2.573	0.082	2.158	0.769–6.057	0.144
cT stage						
cT1	Ref			Ref		
cT2	1.127	0.762–1.666	0.549	1.200	0.757–1.903	0.438
cT3–4	1.372	1.012–1.861	0.043	1.380	0.944–2.081	0.096
Other/unkown	1.990	0.729–5.430	0.179	2.369	0.856–6.556	0.097
Preoperative RT						
No	Ref			Ref		
Yes	1.111	0.845–1.462	0.450	1.105	0.791–1.543	0.558

RT, radiotherapy; Ref, reference.

shown in Supplementary Table S1. Baseline characteristics were not significantly unbalanced between the two groups. Univariate Cox regression analysis showed that preoperative RT and histologic grade were the influencing factors of OS, and preoperative RT was associated with increased risk of death (HR = 1.585, 95%CI 1.027–2.446, $p = 0.037$). Multivariate Cox regression analysis also showed that preoperative radiotherapy was an independent risk factor for OS in patients with stage cT1–2 ESCC (HR = 1.556, 95%CI 1.008–2.464, $p = 0.046$). The specific results of Cox analysis are shown in Table 4.

The survival curve drawn according to the Kaplan-Meier method is shown in Figure 2A. Preoperative RT increased the overall risk of death in patients with cT1–2. There was no significant difference in 1-year (76.62 vs. 86.72, chi-square = 3.461, $p = 0.063$) and 3-year (62.34 vs. 71.88, chi-square = 2.020, $p = 0.155$) survival between the two groups, but preoperative radiotherapy was associated with a significant reduction in 5-year survival (50.65 vs. 67.19%, chi-square = 5.526, $p = 0.019$).

cT3–4

After PSM, 112 patients were in cT3–4 stage, and 80 of them received preoperative RT. Baseline comparisons of patient

TABLE 4 Univariable and multivariable cox analysis of the influence of each characteristic on overall survival for cT1-2 patients after propensity score matching.

Characteristics	Univariable		p	Multivariable		p
Race						
White	Ref			–		
Black	1.381	0.842–2.264	0.201			
Other/unkown	1.108	0.544–2.257	0.777			
Age, years						
≤65	Ref			–		
>65	0.871	0.558–1.360	0.544			
Sex						
Male	Ref			–		
Female	1.067	0.692–1.647	0.768			
Disease site						
Upper third	Ref			–		
Middle third	0.958	0.398–2.309	0.924			
Lower third	0.962	0.400–2.313	0.931			
Other/unkown	1.679	0.662–4.261	0.276			
Histologic grade						
High	Ref			Ref		
Moderate	3.343	1.041–10.732	0.043	3.215	1.001–10.325	0.050
Poor	2.661	0.783–9.041	0.117	2.552	0.751–8.677	0.134
Other/unkown	2.686	0.739–9.765	0.134	2.479	0.680–9.032	0.169
Preoperative RT						
No	Ref					
Yes	1.585	1.027–2.446	0.037	1.556	1.008–2.404	0.046

RT, radiotherapy; Ref, reference.

demographics and oncological outcomes by treatment group are shown in Supplementary Table S2. Baseline characteristics were not significantly unbalanced between the two groups. Univariate Cox regression analysis showed that preoperative RT and race were the influencing factors of OS, and preoperative RT was associated with a reduced risk of death (HR = 0.477, 95%CI 0.274–0.832, $p = 0.009$). Multivariate Cox regression analysis also showed that preoperative RT was an independent predictor of OS in patients with cT3–4 ESCC, and preoperative RT significantly reduced the overall risk of death (HR = 0.479, 95%CI 0.272–0.841, $p = 0.010$). The specific results of Cox analysis are shown in Table 5.

The survival curve drawn according to the Kaplan-Meier method is shown in Figure 2B. Preoperative RT reduced the overall risk of death in patients with cT3–4. There was no significant difference in 1-year (82.50 vs. 75.00, chi-square = 0.815, $p = 0.367$) survival between the two groups, but preoperative radiotherapy was significantly associated with improved 3-year (65.00 vs. 37.50, chi-square = 7.058, $p = 0.008$) and 5-year (61.25 vs. 34.38, chi-square = 6.637, $p = 0.008$) survival.

Discussion

In this propensity score matching study, we found that preoperative RT was associated with OS in patients undergoing surgery for ESCC with preoperative diagnosis of stage cTxN0M0. Especially in patients with cT3–4 stage, preoperative RT

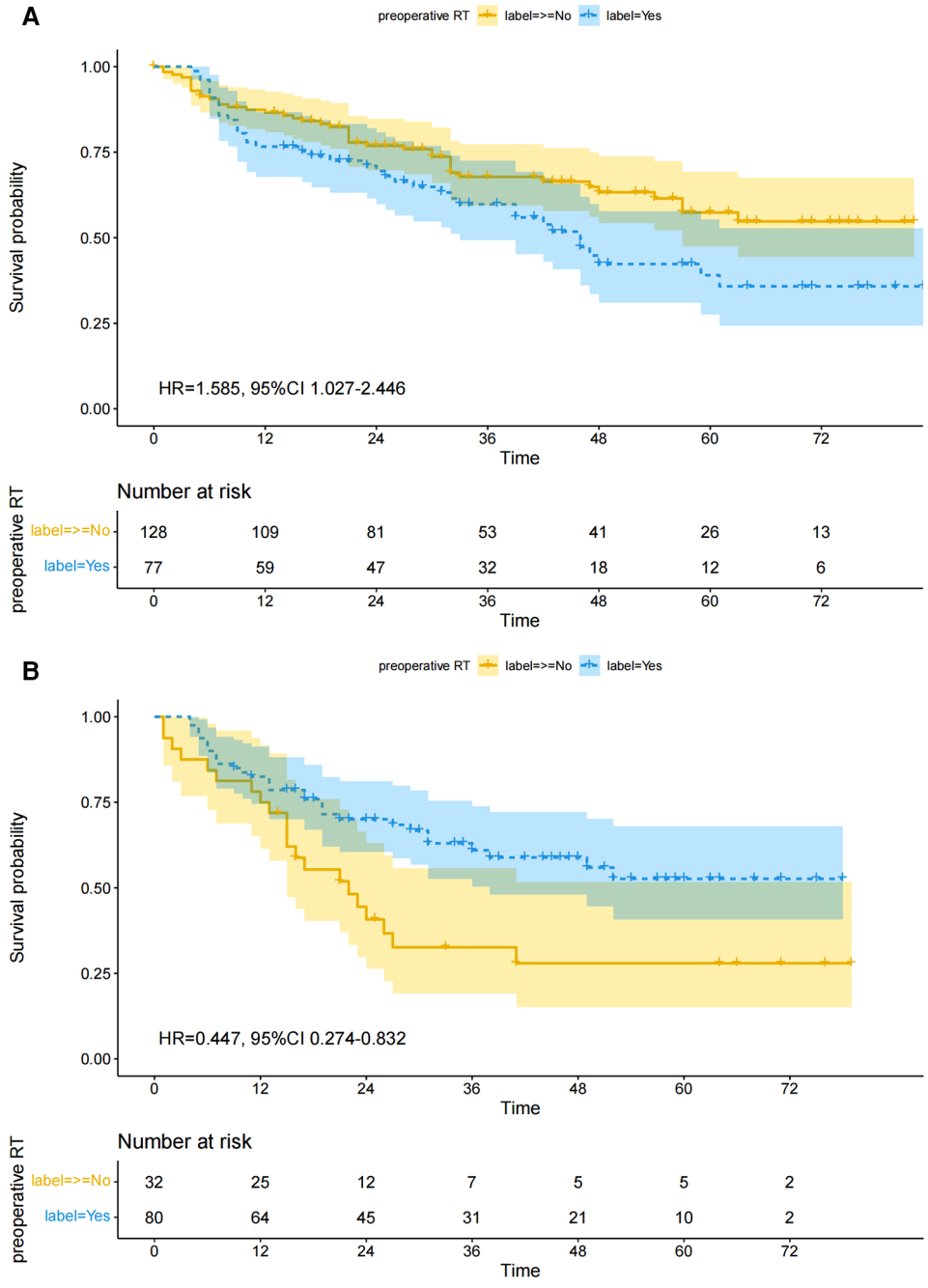

FIGURE 2
Overall survival between preoperative RT and non-preoperative RT groups after matching. (A) cT1–2, (B) cT3–4.

produced a significant effect. But for low stage patients (cT1–2), preoperative RT had a negative impact.

Preoperative neoadjuvant therapy has been widely used as a supplement to surgery for esophageal cancer (9, 10). The CROSS trial and the 5010 trial confirmed that preoperative chemoradiotherapy could significantly improve the long-term survival of patients with locally advanced esophageal cancer, and the 5010 trial alone targeted esophageal squamous cell carcinoma (4, 5). A study by the JCOG group in Japan has shown that preoperative chemotherapy also has a good survival effect (6).

For preoperative RT, there were also clinical studies reporting results. For example, the study by Dong et al. showed that preoperative RT improved long-term survival in locally advanced ESCC (11). However, the study of Gao et al. showed that preoperative radiotherapy is only suitable in certain populations (12). This difference means that preoperative radiotherapy is not suitable for all patients. In addition, most of the patients included in the previous clinical trials were locally advanced with lymph node metastasis. Therefore, for patients without lymph node metastasis, the effect of preoperative neoadjuvant therapy is

TABLE 5 Univariable and multivariable cox analysis of the influence of each characteristic on postoperative survival for cT3-4 patients after propensity score matching.

Characteristics	Univariable		p	Multivariable		p
Race						
White	Ref			Ref		
Black	1.904	0.910–3.981	0.087	1.727	0.823–3.627	0.149
Other/unkown	1.976	0.971–4.018	0.060	2.087	1.020–4.237	0.044
Age, years						
≤65	Ref			–		
>65	1.206	0.693–2.099	0.508			
Sex						
Male	Ref			–		
Female	0.848	0.489–1.471	0.557			
Disease site						
Upper third	Ref			–		
Middle third	1.214	0.464–3.175	0.693			
Lower third	0.574	0.209–1.575	0.281			
Other/unkown	0.810	0.247–2.659	0.729			
Histologic grade						
High	Ref			–		
Moderate	1.727	0.408–7.314	0.458			
Poor	3.330	0.786–14.114	0.103			
Other/unkown	0.956	0.134–6.798	0.964			
Preoperative RT						
No	Ref			Ref		
Yes	0.477	0.274–0.832	0.009	0.479	0.273–0.841	0.010

RT, radiotherapy; Ref, reference.

still unclear (13–15). We designed a propensity matching study specifically for patients with ESCC who were preoperatively diagnosed as stage cTxN0M0. Considering that the number of patients diagnosed with stage cN0M0 and receiving preoperative neoadjuvant therapy in a single medical center is small, it is difficult to formulate a valid analysis. Therefore, we downloaded the data of such patients from the SEER database. Due to its population-based nature, there are significant advantages to using the SEER database: the database collects data from 18 registries in 14 U.S. states, representing nearly 30% of the U.S. population, equivalent to a large multicenter database. In addition, treatment decisions for esophageal cancer must be made according to stage, so we also stratified patients according to cT stage to further study the efficacy of preoperative radiotherapy. Theoretically, preoperative treatment can help to shrink the tumor and shrink the lymph node, thereby increasing the radical resection rate and improving the long-term survival rate. However, in practice, comprehensive treatment is very complicated. Preoperative radiotherapy is associated with additional treatment-related adverse effects compared with surgery alone, adversely affecting quality of life in some patients, and potentially increasing postoperative mortality. Our study showed that preoperative RT was not appropriate for all patients with cTxN0M0. Preoperative RT was suitable for patients with stage cT3–4 ESCC, while patients with stage cT1–2 could not benefit from preoperative RT, and preoperative RT had a negative effect on patients with low cT stage. It's not hard to understand. For patients with cT1–2, the probability of occult lymph node metastasis and the depth of tumor invasion is low, and R0 resection is easy to be achieved by surgery. As a result, preoperative radiotherapy cannot bring significant survival effect, and the patients bear potential radiotherapy related adverse reactions. A meta-analysis showed that preoperative neoadjuvant therapy could reduce the tumor stage of cT2N0 stage esophageal cancer, but did not improve patient survival (16). Two multi-center retrospective studies in Taiwan and Europe showed that neoadjuvant therapy provided significant survival benefits for cT3N0 esophageal cancer (17, 18). Similarly, a large retrospective study by Gao et al. showed that although neoadjuvant therapy helped to improve postoperative survival in esophageal cancer patients with cN0 on the whole, neoadjuvant therapy was associated with decreased survival for early-staged true node-negative patients (12).

Of course, there are some limitations in this study. First, our results were based on a retrospective study. We grouped patients according to treatment mode and were therefore not random, which could lead to selection bias. Second, although propensity matching was used to avoid the imbalance between groups as much as possible, due to the limitations of the database itself, other data that might affect survival (such as comorbidities, physical status, etc.) were not available. Moreover, we do not have the exact treatment data of the patients, such as the specific dose and regimen of radiotherapy. Radiotherapy regimens and methods have been rapidly developed in the past decades, such as 3-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT), and their efficacy has been proven (19–21). In addition, due to limited access to the database, it was not possible to know whether patients receiving preoperative radiation therapy included some patients receiving salvage surgery after radiotherapy. Patient survival depends on the treatment techniques and regimens used, and further research is needed in this aspect. And, due to the limitation of the number of people diagnosed with cN0 stage in the SEER database from 2004 to 2016, the number of patients included in this article was not large. As the database data is constantly updated, we will dig deeper.

Conclusion

For ESCC, preoperative RT can improve the OS of patients with cT3-4N0M0, which is worthy of clinical application. However, preoperative RT is not suitable for patients with cT1-2N0M0. The role of preoperative RT should be further investigated in prospective studies.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

Because the SEER database is publicly accessible worldwide, therefore, we did not provide the approval of an institutional review board in the current study.

Author contributions

ZJ and BZ: had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: JS and BZ. Acquisition, analysis, or interpretation of data: ZJ, JS and JZ. Drafting of the manuscript: ZJ, JS and JZ. Critical revision of the manuscript for important intellectual content: ZJ, JS and BZ. Statistical analysis: ZJ, JS and JZ. Study supervision: JS and BZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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The application of radiomics in esophageal cancer: Predicting the response after neoadjuvant therapy

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Esophageal cancer (EC) is one of the fatal malignant neoplasms worldwide. Neoadjuvant therapy (NAT) combined with surgery has become the standard treatment for locally advanced EC. However, the treatment efficacy for patients with EC who received NAT varies from patient to patient. Currently, the evaluation of efficacy after NAT for EC lacks accurate and uniform criteria. Radiomics is a multi-parameter quantitative approach for developing medical imaging in the era of precision medicine and has provided a novel view of medical images. As a non-invasive image analysis method, radiomics is an inevitable trend in NAT efficacy prediction and prognosis classification of EC by analyzing the high-throughput imaging features of lesions extracted from medical images. In this literature review, we discuss the definition and workflow of radiomics, the advances in efficacy prediction after NAT, and the current application of radiomics for predicting efficacy after NAT.

KEYWORDS

esophageal cancer, neoadjuvant therapy, radiomics, radiology, prediction model

1 Introduction

Esophageal cancer (EC) is one of the most common cancers worldwide, ranking seventh in incidence and sixth in its overall mortality rate (1). The prognosis after EC is unsatisfactory, with a 5-year survival rate of approximately 25% (2). Although surgery has been regarded as an effective treatment for EC, the higher postoperative mortality and

recurrence rate have prompted the investigation of multimodal treatments such as neoadjuvant therapy (NAT) (3). Currently, NAT combined with surgery has become the standard treatment for patients with locally advanced EC and is more effective in improving patient survival than surgery alone (4–7).

However, the prognosis of patients with NAT varies due to individual differences. For instance, the differences between esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), and inconsistencies in the standard therapy for NAT, such as the use of radiotherapy compared to chemotherapy, pose a significant obstacle to achieving good outcomes (8–10). In addition, ypTNM and tumor regression grade (TRG) are used to evaluate the efficacy of NAT in EC patients (11, 12). Though the methods described above are being studied and proven to have a good effect on evaluating the prognosis of EC, several limitations remain (13, 14). Numerous researchers contend that in EC patients receiving NAT, the ypTNM stage mainly loses its prognostic significance and may differ from nation to nation (15–17). Meanwhile, there is still debate about the optimal TRG system, which restricts its application (18). Therefore, accurate prediction of outcomes in patients with EC after NAT is still necessary, and breakthroughs are urgently needed. Most recently, investigators have focused on novel applications such as radiomics to improve the patient pathway.

Radiomics is a non-invasive technique that involves the extraction of quantitative features from medical images, the selection of features by using particular methods, and the analysis correlating with clinical data for classification or prediction (19, 20). Our earlier research used radiomics to predict pathological and survival outcomes in patients with thymic epithelial tumors and to detect lung allograft rejection in a rat lung transplantation model, both of which demonstrated the effectiveness of radiomics in the prognostic analysis of cancer or lung transplantation (21, 22). Other previous studies have shown that radiomics can play an active role in the clinical staging, outcome assessment, and prognostic analysis of cancer. A systematic review on the value of radiomics in predicting response to treatment in patients diagnosed with gastrointestinal tumors showed that radiomic models and individual radiomic features enabled better prediction (area under the curve (AUC) or accuracy > 0.75) in 37 studies (23). In EC, radiomics can predict adverse events after NAT, thus allowing physicians to judge other treatment strategies for their patients. It has been demonstrated that radiomics better predicts pathological responses such as pathological complete response (pCR), complications, recurrence, and survival (Table 1) (24, 34, 35, 39–43).

Nevertheless, there are still some problems with the prediction and practical application of radiomics to EC patients receiving NAT, such as the dilemma of individual precision therapy, the controversy of surgical removal versus organ preservation after NAT, and some other pitfalls. This article will review radiomics in predicting response after NAT in EC, aiming to assist physicians in their decision-making for treatment strategies. To the best of the authors' knowledge, this is the first literature review on applying radiomics in EC patients after NAT.

2 Radiomics

2.1 Brief introduction to radiomics

Radiomics is a high-throughput and non-invasive technique developed by Lambin et al. in 2012 to extract numerous imaging features from radiographic images that are hardly visible to radiologists. It further correlates these data with clinical outcomes like treatment efficacy, survival, or toxicity to develop identification or prediction models using objective methods (19, 20). It cannot be established without the development of medical imaging. Lambin et al. summarized the relationship between the development of medical imaging techniques and radiomics in the following four points: 1) innovations in medical devices (hardware), 2) innovations in imaging agents, 3) a standardized protocol allowing quantitative imaging, and 4) innovations in imaging analysis (19, 44). Radiomics can use high-dimensional data generated from medical imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and the combination of PET and CT (PET/CT), to provide mathematical quantification of tumor phenotypes through radiomic features, and establish identification or prediction models to correlate with tumor characteristics, clinical results and specific gene-expression patterns (23, 45, 46). It can capture the heterogeneity within the tumor, which is affected by many factors such as intracellular factors or cell microenvironment, and is the main obstacle to the practical and individualized treatment of tumors. Thus, it guides clinical diagnosis, such as continuing surgery or retaining organs (20, 47, 48). However, radiomics is still a very young and exploratory field. Most established models have not been used for routine clinical treatment, and there is a lack of sizeable external validation (49). The disciplines behind it may still seem immature because of the inconsistent standards, heterogeneous methods, and quality control, which often does not exist (50, 51). In summary, as an emerging field, radiomics has excellent potential to improve health care, mainly providing a solid foundation for clinicians or radiologists to develop cancer treatment strategies. However, its clinical application and value still need further research and exploration due to some limitations and problems.

2.2 The workflow of radiomics

Although there are many technical methods of radiomics, its workflow is roughly divided into the following five parts: data selection, segmentation, feature extraction, feature selection, as well as modeling and validation (20, 44, 46, 52).

The first step in radiomics is determining the imaging modalities, the tumor regions of interest (ROI), and a prediction target. Second, we manually, semi-automatically or automatically segment the delineated tumor ROIs in the original or processed images. 3D Slicer (www.slicer.org/), ITK-SNAP (www.itksnap.org/pmwiki/pmwiki.php), and MIM (www.mimsoftware.com/) are often used for segmentation of ROI (53). Third, we extract quantitative imaging

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TABLE 1 Predictive performances and application of radiomic models in esophageal cancer.

Outcomes	Imaging modalities	Number of patients	Prospective	Multi-center	Modeling methods	Predictive Performances*	Application	Reference
pCR								
	CT	55	No	No	LASSO	AUC, 0.86	Prediction of pCR in ESCC after nCRT	(24)
	CT	231	No	No	LR, SVM, KNN, NB, DC, RF, XGboost	AUC, 0.852	Prediction of pCR to nCRT in ESCC	(25)
	PET/CT	73	No	No	LASSO	AUC, 0.81	Prediction of response to nCRT in EC	(26)
	PET/CT	91	Yes	No	LASSO	AUC, 0.78	Prediction of response to nCRT in EC	(27)
	PET/CT	20	No	No	SVM, LR	AUC, 1.00	Modeling pathologic response of EC	(28)
	MRI	24	Yes	No	_	AUC, 0.914	Optimal timing for prediction of pCR to nCRT in EC	(29)
	MRI, PET/CT	54	No	No	LR	AUC, 0.914	Assessment of the response to nCRT in locally advanced ESCC	(30)
	PET/CT	96	No	No	LR	AUC, 0.857	Prediction of response to nCRT in EC	(31)
Recurrence								
	PET/CT	44	No	No	_	_	Prediction of recurrence and mortality of locally advanced EC patients	(32)
	PET/CT	44	No	No	_	_	Improvement of prognostic stratification in patients with ESCC treated with nCRT and surgery	(33)
	PET/CT	68	No	No	LR	AUC, 0.87 ± 0.06	Prediction of pCR and loco-regional control following nCRT in EC	(34)
	CT	206	No	No	LASSO	C-index, 0.746	Prediction of postoperative recurrence in patients with ESCC who achieved pCR after nCRT followed by surgery.	(35)
Survival								
	CT	239	No	Yes	RF	AUC, 0.69	Prediction of 3-year overall survival following chemoradiotherapy of EC	(36)
	CT	307	No	No	LASSO	C-index, 0.700	Improvement of survival prediction in ESCC	(37)
	PET/CT	65	No	No	RF	AUC, 0.822 ± 0.059	Prediction of treatment response and survival in EC patients treated with chemo-radiation therapy	(38)
	MRI, PET/CT	69	Yes	Yes	_	C- index, 0.82	Preoperative prediction of pathologic response to nCRT in patients with EC	(39)

*Only the best prediction outcomes were chosen for use with various modeling methods. pCR, pathological complete response; AUC, area under the curve; LASSO, least absolute shrinkage and selection operator; DC indicates decision tree; KNN, k-nearest neighbors; LR, linear regression; NB, naive bayes; RF, random forest; SVM, support vector machine; XGboost, extreme gradient boosting; ESCC, esophageal squamous cell carcinoma; nCRT, neoadjuvant chemoradiotherapy; EC, esophageal cancer.

features. Pyradiomics has now become a popular open-source Python package for extracting radiomic features from medical imaging (54). The primary categories of extracted radiomic features are shape-based features, histogram features (first-order features), texture features, and transform-based features. The shaped-based features describe the geometric properties of the tumor according to Shape-based (three-dimension) and Shape-based (two-dimension). In addition, first-order statistics describe the distribution of voxel intensities within the image region defined by the mask through commonly used and basic metrics. Texture features unfold the intra-tumoral heterogeneity. After resampling and filtering, transform-based features describe the frequency, spatial location, gray change, intensity, etc. Fourth, feature selection is performed on the extracted features using the filter, embedded or wrapper methods. Filter methods use statistics to rank and select the radiomic features, such as Pearson's Correlation, t-test, Mann-Whitney U test, etc.; Wrapper methods use the chosen multi-variate model to evaluate and find the optimal radiomic features, such as Recursive Feature Elimination, Las Vegas Wrapper, etc.; Embedded methods embed radiomic features during modeling, and optimal features are selected by observing each iteration of the model training phase, such as Least Absolute Shrinkage and Selection Operator (LASSO), Ridge Regression, etc. Radiomic features correlating with tumor stage or gene expression can also be selected to evaluate their value for better prediction. The ultimate goal is to construct the targeted radiomic models, such as regression models, support vector machine (SVM), etc., to provide accurate stratification and assess their prognostic ability. After modeling, validation is usually evaluated through discrimination and calibration (55). The former, discrimination, refers to the performance that the radiomic model differentiates patients having a specific event at a different level of risk, and the latter, calibration, refers to the accuracy of absolute risk estimates. For accuracy of the performance in the radiomic model, bootstrap, cross-validation or hold-out methods are often utilized during discrimination and calibration. Bootstrap (or bootstrapping) is a uniform sampling method from a given training set. As a resampling technique, cross-validation employs various data subsets to test and trains a model over different iterations. The hold-out method divides the data into multiple segments, using one part to train the model and the rest to validate and test it. Noticeably, an internal or external validation set in the hold-out method may increase the reliability of the validation results for estimating its real diagnostic performance (Figure 1).

3 Neoadjuvant treatment

NAT is now one of the most commonly used treatments for cancer and has a wide range of clinical applications in the areas of pancreatic cancer, breast cancer, gastric cancer, colorectal cancer, and cholangiocarcinoma (56–59). To improve clinical prognosis and outcomes, NAT has also been introduced to the treatment of EC, especially for patients with locally advanced EC. The primary neoadjuvant therapies (NATs) for EC are neoadjuvant chemotherapy (nCT), neoadjuvant chemoradiotherapy (nCRT), and NAT combined with immunotherapy (60–62).

The British Medical Research Council (OE02) trial was the first large-scale study to demonstrate the survival benefits of nCT for patients with EC (63). Also, several other studies made nCT one of the earliest standard treatments for locally advanced patients EC (64, 65). However, some studies indicated that perioperative chemotherapy regimens showed a survival benefit in distal esophageal and gastroesophageal junction adenocarcinoma, but only selected patients benefited from nCT vs. surgery alone for ESCC (66). The clinical application of nCT is still investigated in further trials.

According to several landmark trials, nCRT is superior to surgery alone in some aspects, including R0 resection, survival outcomes and recurrence, which provides excellent clinical utility (5, 67, 68). The AGITG DOCTOR trial also showed that offering second-line chemotherapy and radiation improved survival for patients who did not respond to initial chemotherapy (69). And the chemoradiotherapy for EC followed by surgery study (CROSS) trial demonstrated a survival benefit compared to surgery alone when using chemoradiation with the addition of paclitaxel (68).

NAT combined with immunotherapy has developed rapidly in recent years, achieving sound therapeutic effects in various cancer treatments. Previous studies have shown its potential therapeutic effect (70, 71). A meta-analysis enrolled 759 patients from 21 studies using the major pathologic response and pCR to evaluate the effectiveness of nCT combined with immunotherapy (72). Of the enrolled patients, major pathological remission was achieved in 52.0% (95% CI: 0.44-0.57) of patients on nCT combined with immunotherapy, and pCR was achieved in 29.5% (95% CI: 0.25-0.32) of patients.

Despite the widespread use of NAT in clinical practice, some drawbacks are hard to predict, including harmful toxic effects, outdated technology, and failure to address patients' and hospitals' actual requirements (25, 73). Its future development still depends on individual characteristics and hospital technology, such as physical condition, pCR or recurrence prediction, and more multidisciplinary combination therapy (61). Noticeably, based on accurate assessment and prediction, the application of radiomics may help to reduce these deficiencies and prevent further complications of NAT in EC.

4 The application of radiomics for predicting the efficacy after NAT

4.1 Pathological complete response

pCR is defined as the absence of disease in the resected specimen's esophagus and lymph nodes (T0N0). For patients with locally advanced EC, it has been correlated with a better outcome than non-pCR, which means there may be better survival and a lower local recurrence rate, providing a much better quality of life (74, 75). In this context, many techniques based on radiomics can be utilized to construct prediction models for pCR in EC patients after NAT, offering a bright prospect.

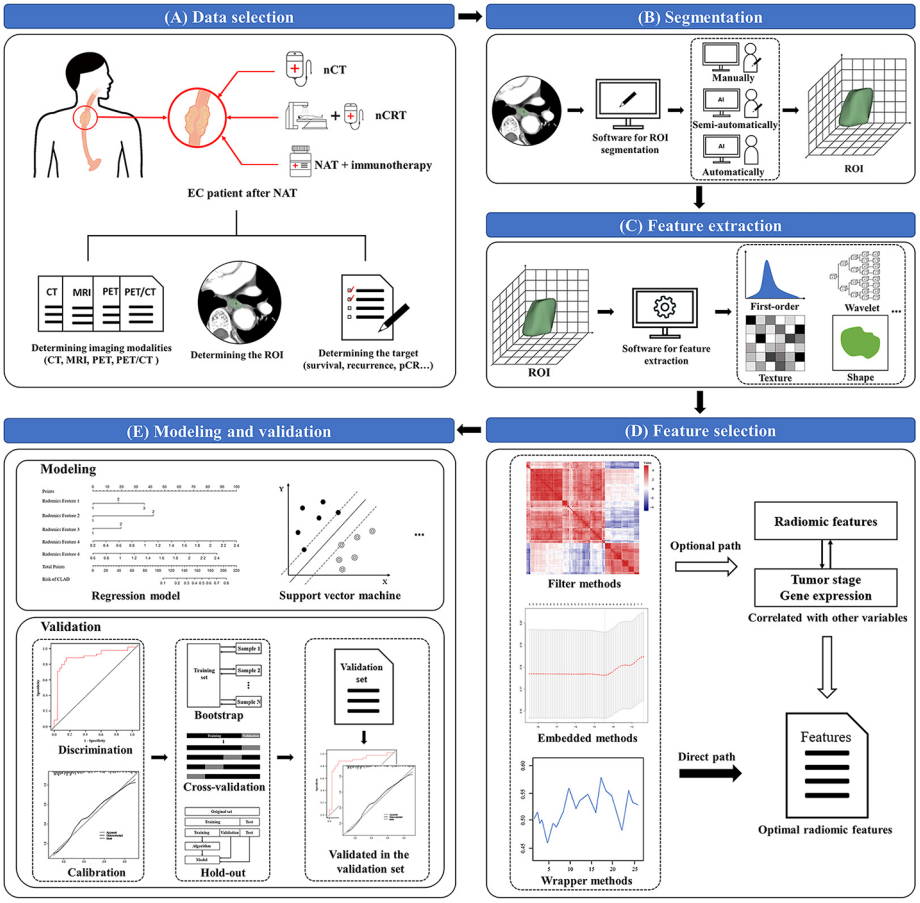

FIGURE 1
Workflow of radiomics. **(A)** Data selection: determines the imaging modalities, the tumor regions of interest (ROI), and a prediction target; **(B)** Segmentation: segments the delineated tumor ROIs in the original or processed images; **(C)** Feature extraction: extracts quantitative radiomic features through software or package from the tumor ROIs; **(D)** Feature selection: selects the extracted features by using the filter, embedded or wrapper methods; **(E)** Modeling and validation: models the selected radiomic features by specific methods, then discriminates and calibrates through bootstrap, cross-validation or hold-out methods. EC, esophageal cancer; NAT, neoadjuvant therapy; nCT, neoadjuvant chemotherapy; nCRT, neoadjuvant chemoradiotherapy; ROI, regions of interest; pCR, pathological complete response.

First, the CT-based radiomic model to predict pCR after NAT has a good prediction effect, especially in ESCC patients, with a high-performing level and good discrimination ability. Yang et al. (24) reported that three CT-based radiomic models could predict pCR in ESCC patients after nCRT in both the training (AUC, 0.84-0.86) and test cohorts (AUC, 0.71-0.79). In addition, peritumoral features can also serve as powerful prognostic indicators to construct radiomic models. Based on intratumoral and peritumoral features, Hu et al. (26) found that the combination of the two to establish a joint CT-based radiomic model had good identification performance and better prediction of pCR. There are also a small number of studies with general prediction results, which may be due to unestablished measurement errors, inconsistent standards, poor actual imaging quality, and small sample size (27). These aspects need to be explored further and improved in future research.

It is noteworthy that an increasing number of studies have also linked the radiomic features of PET alone or PET/CT to pCR. Previous studies have found that combining clinical factors and 18F-FDG PET-based radiomic features improves the ability to predict pCR (28). Meanwhile, CT can make up for the low anatomical spatial resolution of PET and provide more abundant radiomic features. Therefore, more PET/CT-based radiomic models are used to predict pCR after NAT in EC patients. PET/CT-based radiomic studies improved the predictive ability of pCR compared with PET alone and CT alone (AUCs for CT, PET, and PET/CT models were 0.73 ± 0.08, 0.66 ± 0.08, and 0.77 ± 0.07, respectively) (29). Beukinga et al. (30) constructed five different response prediction models based on eighteen clinical, geometric, and pre-processed texture features that were finally selected in PET and CT imaging. The predictive values were better than those of the models based on maximum standardized uptake values, demonstrating the advantages of PET/CT radiomic features over traditional parameters. SVM and logistic regression (LR) models can also be further constructed to predict the pathological response of tumors to nCRT. Lin et al. (75) reported that the SVM model obtained high accuracy (AUC, 1.00) and precision (no error classification), which was significantly better than traditional PET/CT measurements or clinical parameters. In general, using complementarity between

imaging techniques such as PET/CT can effectively supplement radiomic features, further establishing a more accurate prediction model.

Moreover, diffusion-weighted magnetic resonance imaging (DW-MRI) has proven its value in predicting pCR in EC after NAT. A study by Borggreve et al. (31) was conducted to determine the optimal timing of DW-MRI for predicting pCR to nCRT for EC. The relative change in tumor apparent diffusion coefficient (ΔADC (%)) during the first two weeks of nCRT is the most predictive for pCR to nCRT in EC patients. They found that a model including $\Delta ADC_{week\ 2}$ could discriminate between pathologic complete responders and non-pathologic complete responders in 87%. 18F-FDG PET/CT and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) have also been used to predict pCR after nCRT in patients with locally advanced ESCC. Integrating 18F-FDG PET/CT and DW-MRI parameters can more accurately identify the pathological response of ESCC primary tumors to nCRT, especially the related prediction of pCR (AUC, 0.914) (76).

In addition to clinical and metabolic parameters, radiomic features combined with biological expression products can also improve the accuracy of radiomic models. Biological expression products such as the cluster of differentiation 44 (CD44) and the hedgehog (HH) signaling pathway ligand Sonic Hedgehog (SHH), which are closely related to the prognosis of EC patients treated with nCRT, can be included in the comprehensive prediction model (77). Beukinga et al. (78) included human epidermal growth factor receptor 2 (HER2) and CD44 in the clinic-radiomic model, which improved the overall performance of the nCRT response in EC patients (AUC, 0.857), thus facilitating the differentiation of pCR.

Therefore, it is urgent to accurately predict the pCR of EC patients, especially for patients with different NATs (66). Some studies have also found that predicting pCR based on the pathological subtypes of patients can improve the performance of radiomic models, especially in ESCC patients relative to EAC patients. The potential mechanisms may be the difference in pCR rate and genomic characteristics (33, 79). In summary, radiomic studies for predicting pCR in patients with EC after NAT have broad prospects, and their clinical application is worthy of further exploration.

4.2 Recurrence

A previous study reported that preoperative use of NAT, such as nCRT, can reduce recurrence rates in EC patients (68). Although researchers have provided recent advances in prognostic stratification and modern multimodal treatment strategies, many EC patients still have a tumor recurrence and eventually die of the disease, mainly in the distance (32, 80–82). Therefore, developing a more accurate prediction model for recurrence in EC patients is necessary. As an emerging non-invasive method, the radiomics-based prediction model can be a helpful tool to accurately predict the recurrence in EC patients after NAT and has a similar effect to pCR.

The radiomic methods used to predict recurrence are mainly carried out through PET/CT. 18F-FDG PET/CT has been demonstrated to be an accurate and indispensable imaging technique in the diagnosis and staging of EC, and it is the most useful method for detecting asymptomatic recurrence in patients undergoing curative treatment for EC (36). During the follow-up of a study by Chang et al. (37), higher values of 18F-FDG PET/CT parameters were associated with poor recurrence-free survival (RFS). Radiomics-based prediction methods can predict RFS and other indicators and, thus, reflect the recurrence situation. In another study to predict the prognosis of EC patients after nCRT, all patients underwent 18F-FDG PET/CT before and after nCRT (32). Pretreatment radiomic features and changes in the PET-derived traditional parameters after nCRT were analyzed, and recurrence was also well predicted. Additionally, the composite radiomic features from pretreatment non-contrast CT and staging PET are highly accurate in predicting response in EC, especially recurrence (34). In short, the current studies have shown the value of methods based on radiomics in predicting recurrence in EC patients after NAT. In particular, the predicting model based on PET/CT radiomic research has excellent advantages.

In addition, few studies have investigated the prediction of recurrence in patients achieving pCR. In EC patients, pCR after nCRT is accompanied by a lower rate of recurrence and more prolonged survival than non-pCR (29). Hence, predicting the likelihood of recurrence in these patients is still important, ensuring that an appropriately tailored treatment strategy is implemented early in the cohort of patients with a high risk of recurrence (35). Studies based on radiomics to predict the risk of recurrence after NAT in EC patients who achieve pCR are underway. A radiomic nomogram incorporating radiomic features and clinical factors has been developed and can be used in postoperative assessments of the individual recurrence risk in patients achieving pCR (35). Comparing the radiomic signature ($P < 0.001$) and clinical nomogram ($P < 0.001$) in both the training (AUC, 0.746 vs. 0.685 vs. 0.614, respectively) and validation cohorts (AUC: 0.724 vs. 0.671 vs. 0.629, respectively), an improved ability to predict the postoperative recurrence risk in patients with ESCC who achieved pCR after nCRT followed by surgery has been shown. However, further research based on radiomics is required to predict recurrence in patients who eventually achieve pCR.

Therefore, the value of using radiomics to predict the recurrence of EC patients after NAT has been proven whether recurrence occurs after pCR. This promising and developing prediction method still needs to be further studied in the future to predict post-NAT recurrence in EC patients more accurately.

4.3 Survival

Survival of EC patients can generally be improved with NAT, but there is still the possibility of some risk factors that could seriously affect the survival prognosis. Thus, a predictive survival model in EC patients after NAT is necessary. In recent years, radiomic analysis has been proven effective in predicting tumor treatment response and patient survival (29, 38). Better survival can be implied if radiomics can anticipate the emergence of pCR following nCRT (75). Moreover, a radiomic model that primarily relies on PET, CT, and MRI data can be utilized to forecast the survival of EC patients after NAT.

As a suitable method, PET can help predict the survival of EC patients after NAT. The combination of traditional PET parameters and radiomic parameters is effective in predicting the survival of ESCC patients. Patients can be more effectively grouped into subgroups with different survival rates by combining the conventional and radiomic parameters of 18F-FDG PET with clinical analysis, which is beneficial for further treatment (32).

Another valuable tool for estimating EC patients' survival is the CT-based radiomics model. A study based on CT by Ruben et al. (83) developed and externally validated a random forest (RF) model using pretreatment CT radiomic features to predict 3-year overall survival (OS) in EC. The radiomic model had better predictive capability than the model using standard clinical variables (AUC, 0.69 vs. 0.63). The study by Lu et al. (84) found that, compared with the clinical nomogram, the radiomic-clinical nomogram improved the calibration and classification accuracy for OS prediction with a total net reclassification improvement of 26.9% (P = 0.008) and integrated discrimination improvement of 6.8% (P < 0.001). The results also concluded that based on CT, integrating the dual-region radiomic signature and clinicopathological factors improves OS prediction.

Additionally, researchers found that a combination of PET and CT was beneficial for predicting the survival of EC patients after NAT. The metabolic tumor volume (MTV) parameters measured by 18F-FDG PET/CT can also predict OS and RFS in patients with locally advanced EC (37). In addition, using an RF classifier based on 18F-FDG PET can also improve predictive and prognostic values, such as OS and RFS, compared to traditional survival analysis when applied to several tens of features in a limited database (85).

Furthermore, MRI is an excellent resource for creating predictive models. DCE-MRI and DW-MRI have been shown to have encouraging effects in predicting tumor response to nCRT and patient survival (86, 87). An MRI-based radiomic study also found that ADC skewness (AUC, 0.86) was the most useful ADC-derived parameter for predicting pCR and survival in ESCC patients receiving preoperative CRT therapy, which also confirms the feasibility of MRI-based radiomics in predicting survival (43). Notably, combining the individual and combined values of 18F-FDG PET/CT and DW-MRI during and after nCRT can validate the value of different radiomic approaches combined to predict survival (39).

Hence, some methods based on radiomics can predict the survival of EC patients after NAT, especially PET, CT and MRI. Future studies should focus on the continued optimization of predictive models, such as the relationship between pCR and survival. More informative radiomic features related to accurate survival prediction should be explored while better techniques such as artificial intelligence and deep learning can be utilized, which can be applied to optimize the screening of radiomic features (27, 88).

5 Discussion and suggestions

Radiomics has shown promising results when used to predict post-NAT responses in EC, particularly in predicting pCR, recurrence, and survival. However, the practical applications of radiomics still have some restrictions because of numerous factors (44). The primary sources of variability and pitfalls in radiomic research are study design, image acquisition and processing, and statistical analysis (89). In addition, some general defects in radiomic studies also impact their reliability and practical application. Thus, this article summarizes the following viewpoints to provide valuable solutions and possible directions for future research on radiomics in predicting the efficacy of patients with EC after NAT.

Radiomic analysis will be affected by the systematic errors of research design, resulting in its defects and deficiencies. Incorporation bias and spectrum bias can often be found (89). The outcome of using data from the analyzed images caused the incorporation bias. Defining the outcome from the analyzed image should be avoided. And spectrum bias is from models developed using only extreme cases, which means that researchers must ensure study data are generalizable to the population of interest.

Importantly, standards of radiomics must be established and further refined among different suppliers and institutions, promoting the standardization of radiomic research and improving its practical application (88, 90). Moreover, image acquisition and processing reasons include software and operator variability (89). Software variability means that hand-engineered features, calculated using a different software platform or version of the same software, may have different values despite adhering to accepted standards. The operator variability is caused by manual or semi-automatic delineation of ROI, so ROI should be scrutinized by experienced physicians or reduce and correct variability in ROI.

Additionally, there are still some improvements in the process before and during statistical analysis. First, imaging professionals should continue improving imaging quality and the method of delineating the ROI, because tumor segmentation could be challenging for small lesions (91), and the extracted radiomic features may raise the question of repeatability (29, 76). For instance, applying pre-processing before image analysis can optimize the performance of models, and proper feature selection methods can reduce the dimensionality of the generated data (92). Bias from overfitting, optimistic performance bias, and bias from the exclusion of indeterminate or missing feature data are often found in many radiomic research (89, 92). Researchers can evaluate the model on an independent external data set and use resampling methods, such as cross-validation, to decrease these biases as possible.

In many radiomic studies, some mutual deficiencies leading to unreliability and non-repeatability of their results should be solved. First, an increasing number of prospective, multicenter, large simple studies with external validation are needed. Currently, most of the studies were performed retrospectively, which means bias generated from the retrospective review could not be avoided (32, 37). Although limited resources restrict the development of multicenter prospective studies, their importance cannot be overemphasized. Borggreve et al. (39) conducted a multicenter prospective study to evaluate the individual and combined value of 18F-FDG PET/CT and DW-MRI. They found that changes in 18F-FDG PET/CT after nCRT and early changes in DW-MRI during nCRT contributed to the identification of nCRT by pCR in EC. Researchers also found that

18F-FDG PET/CT and DW-MRI may have complementary value in the evaluation of pCR, which is consistent with previous research results (76). Simultaneously, large sample sizes and rich external validation are also required to verify the accuracy of prediction models (27, 30, 39, 76). Second, the study of targeted radiomic prediction techniques is urgently needed for various NATs (66). Third, the links between radiomics and other disciplines deserve further strengthening; one example that has achieved good results in recent years is radio-genomics, in which it is assumed that imaging features are related to gene signatures (44). Multimodal technology has also proven its benefits, which combine multiple imaging techniques. PET/CT combined with MRI, is proven its benefits for predicting models (39, 76).

At present, the application of radiomics to predict the efficacy after NAT has become a popular and essential direction for patients with EC. In the future, applying radiomics in EC will be conducive to improving post-NAT efficacy prediction providing timely and accurate treatment strategies that truly benefit EC patients.

Author contributions

HG led the other two co-first authors, H-TT and W-LH, in manuscript preparation, reference literature review, and manuscript writing. J-JW, P-ZL, J-JY, HH, and H-JY were responsible for collection and sorting of literature. S-LH, Y-JZ, Z-QD, K-YJ, and X-YZ revised the manuscript. DT and H-NZ are responsible for the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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