Original Article

A clinical nomogram for predicting tumor regression grade in esophageal squamous-cell carcinoma treated with immune neoadjuvant immunotherapy

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Background: There are various treatment options for esophageal squamous cell cancer. including surgery, peri-operative chemotherapy, and radiation. More recently, neoadjuvant immunotherapy has also been shown improve outcomes. In this study, we addressed the question, "Can we predict which patients with esophageal squamous cell cancer will benefit from neoadjuvant immunotherapy?".

Methods: All patients with thoracic esophageal squamous-cell carcinoma (T2N+M0-T3-4N0/+M0) (according to the eighth edition of the National Comprehensive Cancer Network guidelines) who underwent immune neoadjuvant immunochemotherapy with programmed cell death protein 1 (PD-1) combined with paclitaxel plus cisplatin or nedaplatin in the Affiliated Cancer Hospital of Zhengzhou University, China, between November 2019 and August 2021 were included in this study. All patients underwent surgical resection. We developed a response [tumor regression grade (TRG)] prediction model using the least absolute shrinkage and selection operator (LASSO) regression incorporating factors associated with response. The accuracy of the prediction model was then validated.

Results: We included 79 patients who underwent neoadjuvant immunotherapy combined with chemotherapy, aged 48–78 years (62.05±6.67), including 21 males and 58 females. There were five cases of immune-related pneumonia, of which three cases were diagnosed as immune-related pneumonia during the perioperative period, and one case of immune-related thyroid dysfunction changes. After LASSO regression, the factors that were independently associated with TRG were clinical T stage before neoadjuvant therapy, clinical N stage before neoadjuvant therapy, albumin level difference from before to after neoadjuvant therapy, white blood cell (WBC) count before neoadjuvant therapy, and T stage before surgery. We constructed a prediction model, plotted the nomogram, and verified its accuracy. Its Brier score was 0.13, its calibration slope was 0.98, and its C-index was 0.90 (95% CI: 0.82–0.97).

Conclusions: Our prediction model can predict the likelihood of TRG in patients with esophageal squamous cell cancer after immunotherapy combined with neoadjuvant chemotherapy. Using this prediction model, we plan to conduct a subsequent neoadjuvant radiotherapy in patients with of TRG 2–3 patients with neoadjuvant radiotherapy.

Keywords: Esophageal squamous cell cancer; immunotherapy; pathological remission grading; prediction model

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Introduction

Risk factors for the development of esophageal squamous cell carcinoma include low socioeconomic status, consumption of tobacco, alcohol, hot beverages, and nitrosamines (1). There are different neoadjuvant treatment options for esophageal cancer, with a wide range of clinical studies such as NEOCRTEC5010 and CROSS have shown that for patients with locally advanced esophageal cancer, neoadjuvant chemoradiotherapy can improve the short term and long-term outcomes (2-6). However, the CROSS trial had an R0 resection rate in the surgery-only group of 69%, which was significantly lower than the 92% in the chemoradiotherapy + surgery group (P<0.001). Whether R0 resection was an important factor affecting the prognosis is not clear. The FFCD9901 study showed that neoadjuvant chemoradiotherapy not only did not increase the R0 resection rate but did increase the postoperative mortality rate, and the study was eventually discontinued (7). In a metanalysis in 2018 neoadjuvant chemoradiotherapy seemed to increase postoperative mortality (RR 1.46 and 1.58, respectively) (8). The Neoadjuvant Chemotherapy Versus Chemoradiotherapy for Cancer of the Esophagus or Cardia (NeoRes I) study, the study of Klevebro *et al.*, and a meta-analysis all showed that neoadjuvant chemoradiotherapy did not boost survival compared with neoadjuvant chemotherapy (9-11). The RTOG Trial 8911 showed that neoadjuvant chemotherapy did not improve the survival of patients (12). Other studies have shown that neoadjuvant chemotherapy can benefit patients in terms of survival compared to surgery alone (13,14), while neoadjuvant chemoradiotherapy may not necessarily benefit patients (15). While neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy alone can benefit patients, in this study we addressed the question, "Can emerging immunotherapy technologies also benefit the survival of esophageal squamous cell cancer patients?".

Programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors can activate T lymphocytes, inhibit tumor growth, and improve the prognosis of tumor patients. Many PD-1/PD-L1 inhibitors can treat melanoma, lung cancer, and renal cell cancer (16-18). There are many clinical studies on the use of PD-1/PD-L1 inhibitors in immunotherapies for esophageal cancer (19). A phase 2 trial, KEYNOTE-180, showed that the objective response rate (ORR) of pembrolizumab monotherapy was 14.3% (20). A phase 3 trial, KEYNOTE-181, showed that pembrolizumab for the treatment of advanced esophageal squamous-cell cancer patients with PD-L1 combined positive score ≥10 had a significantly longer median survival (8.2 vs 7.1 m, P=0.0095) and an ORR of 21.5% (20). PD-1/PD-L1 inhibitors have proven safety and efficacy in the treatment of esophageal squamous-cell carcinoma.

The better the tumor regression grade (TRG) after neoadjuvant therapy, the higher the 5-year survival rate (21-23). Patients with TRG 0–1 after neoadjuvant chemotherapy combined with immunotherapy could have a theoretically better prognosis than patients with TRG 2–3. We believe that for patients with TRG 2–3, neoadjuvant radiotherapy may also be added to increase the chance of better response. One study also investigated clinical factors and treatment which have prognostic evaluation of esophageal cancer (24), but not like us, if our study could screen out patients with TRG 2–3, radiation therapy was added next, it could benefit these patients in terms of survival, and ultimately all patients benefit from different treatment modes. To determine whether we could predict the benefit of neoadjuvant immunochemotherapy for esophageal cancer, we developed a prediction model for TRG.

We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-78/rc).

Methods

All patients with thoracic esophageal squamous-cell carcinoma (T2N+M0-T3-4N0/+M0) (according to the eighth edition of the National Comprehensive Cancer Network guidelines) who underwent neoadjuvant chemotherapy with PD-1 combined with paclitaxel plus cisplatin or nedaplatin at The Affiliated Cancer Hospital

of Zhengzhou University, China, between November 2019 and August 2021 were included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Affiliated Cancer Hospital of Zhengzhou University (ethics number 2019092702), and informed consent was taken from all individual participants. Prior to surgery, enhanced computed tomography (CT) or enhanced magnetic resonance imaging of the chest and upper abdomen, cardiac ultrasound, abdominal color Doppler ultrasound, upper gastrointestinal tract contrast, ultrasound gastroscopy, pulmonary function, and laboratory tests were performed. Before neoadjuvant therapy, PD-L1 expression was detected in esophagogastroscopic biopsy specimens by immunohistochemistry.

Prior to surgery, patients received two cycles of paclitaxel (135–175 mg/m^2), cisplatin (80–120 mg/m^2, D1 or D1–4), or nedaplatin (80–100 mg/m^2, D1 or D1–4), as well as PD-L1 inhibitor (200 mg/m^2). The surgical approaches included open or laparo-thoracoscopic McKeown surgery. PD-1 monoclonal antibodies for immunotherapy included tislelizumab, camrelizumab (Hengrui, Lianyungang, Jiangsu), toripalimab (Junshi Biotechnology, Pudong, Shanghai), Keytruda (Merck, New Jersey, USA), and sintilimab (Innovent Bio, Suzhou, Jiangsu).

Development of the prediction model

We referred to the Ryan scoring system to assign TRGs (25). The TRG 0–3 are these: 0: no viable cancer cells (complete response); 1: single cell or rare small groups of cancer cells (near complete response); 2: residual cancer with evident tumor regression but more than single cell or rare small groups of cancer cells (partial response); 3: extensive residual cancer with no evident tumor regression (poor or not response). Three pathologists were asked to reexamine the results of the pathological sections, and the final TRG grade had to be agreed upon by two or more pathologists. We divided the postoperative TRGs into two categories: grades 0 and 1 were combined into one category, and grades 2 and 3 were combined into another category. We abstracted and categorized the following demographic and tumor variables: age, sex, hypertension, diabetes, other comorbidities, smoking history, alcohol history, type of PD-1 pulmonary comorbidities, T stage before treatment, N stage, body mass index (BMI), nutritional score, white blood cell (WBC) count, hemoglobin, lymphocyte count, monocyte count, albumin, bilirubin, cholesterol, T stage after chemotherapy, changes in BMI, WBC count, hemoglobin, lymphocyte count, monocyte count, albumin, bilirubin, and cholesterol from before to after chemotherapy; and whether PD-1 was expressed.

The predictive accuracy of the model was assessed using three measures: (I) Brier score for overall performance; (II) calibration slope for calibration; and (III) concordance index (C-index) for discrimination. In addition to these numeric measures, we used the calibration plot and receiver operating characteristic curve to display the calibration and discrimination aspects of our final model. The closer the Brier score is to 0, the better the predictive ability, and the closer the standard slope is to 1, the closer the predicted value is to the result. A C-index closer to 1 indicated better discrimination. These measures were used together to evaluate the accuracy of the model's predictions. To this end, we conducted multiple repeated evaluation and took the model with the highest prediction accuracy as the final model.

Creation of the nomogram

The final results are presented as a nomogram. The nomogram contains a reference line on the top for scoring the points of each predictor from 0 to 100. The predictive variables are displayed below with bars that scale their effect size, visually demonstrating visually the relative weight of each variable and allowing for points to be assigned to each significant clinical characteristic (26). The overall score of each predictive factor and the corresponding probability of the occurrence of TRG 0–1 can be read on the second line from the bottom. We also plotted the decision curve and clinical impact curve to validate the prediction model.

Statistical analysis

All statistical analyses were performed using R 3.63 (https://www.r-project.org/). The best predictors of TRG were screened by the least absolute shrinkage and selection operator (LASSO) regression using the "glmnet" package in R. The "rms" package was used to incorporate the factors selected by LASSO regression into the multivariate logistic regression analysis to build a prediction model.

Results

Baseline clinical characteristics

We enrolled 79 patients who underwent neoadjuvant

Table 1 Patient and tumor characteristics of this study

Variables	Overall cohort (n=79)
Age (years)	62.05±6.67
Sex (males/females)	58 (73.4%)/21 (26.6%)
cT stage before INJT (1/2/3/4)	0/12/55/12
cN stage before INJT (–/+)	27 (34.2%)/52 (65.8%)
cT stage after INJT (1/2/3/4)	38/25/15/1
cN stage after INJT (–/+)	51 (64.6%)/28 (35.4%)
pT (0/1/2/3/4)	26/11/14/28/0
pN (0/1/2/3)	59/15/5/0
cTNM stage (I/II/III/IVa)	0/3/74/2
pTNM stage (I/II/III/IVa)	42/17/8/12
Hypertension (yes/no)	16 (20.3%)/63 (79.7%)
Diabetes (yes/no)	4 (5.1%)/75 (94.9%)
Smoking (yes/no)	50 (63.3%)/29 (36.7%)
Drinking (yes/no)	43 (54.4%)/36 (45.6%)
Location (u/m/l)	13/53/13
Surgery (open/VATS)	14 (17.7%)/65 (82.3%)
Tumor regression grade (0/1/2/3)	25/12/28/14
Tumor regression grade (0–1/2–3)	37 (46.8%)/42 (53.2%)
WBCs before INJT ($\times10^9$/L)	6.37±1.92
BMI before INJT (kg/m^2)	22.96±2.83
Hb before INJT (g/L)	136.24±17.49
Albumin before INJT (g/L)	41.61±3.31
Changes in albumin	0.77±4.34*
WBCs before surgery ($\times10^9$/L)	6.28±2.05
BMI before surgery (kg/m^2)	22.30±7.18
Hb before surgery (g/L)	122.16±14.42
Albumin before surgery (g/L)	40.81±2.99
Duration of surgery (min)	292.69±92.02
PD-1, n (%)	
Camrelizumab	14 (17.7)
Keytruda	1 (1.3)
Toripalimab	57 (72.2)
Sintilimab	5 (6.3)
Tislelizumab	2 (2.5)
Immune pneumonia (yes/no)	5 (6.3%)/74 (93.7%)
Changes in thyroid function (yes/no)	1 (1.3%)/78 (98.7%)

*, if the absolute value of the change is calculated, it should be 3.24±3.00. INJT, immune neoadjuvant therapy; u/m/l, upper/middle/lower; VATS, video-assisted thoracoscopic surgery; BMI, body mass index; WBC, white blood cell; PD-1, programmed cell death protein 1.

immunotherapy combined with chemotherapy. They were aged 48–78 years (62.05±6.67 years), and there were 58 males and 21 females. There were five cases of immune-related pneumonia, of which three cases were diagnosed as immune-related pneumonia during the perioperative period and two cases were diagnosed as immune-related pneumonia during continued immunotherapy after surgery. Immune-related thyroid function changes occurred in one case, which occurred during postoperative immune maintenance therapy. Patient demographic and tumor characteristics are listed in *Table 1*.

After LASSO regression analysis, the factors that were independently associated with the TRG included clinical T stage before neoadjuvant therapy, clinical N stage before neoadjuvant therapy, albumin difference before *vs.* after neoadjuvant therapy, WBC count before neoadjuvant therapy, and preoperative T stage (*Figure 1A*,*1B*, *Table 2*). The coefficient λ decreased with a greater number of variables. When λ was optimal, the coefficients of the excluded variables were compressed to 0, while the coefficients of the variables left in the model were nonzero. The results show that the optimal value of λ was 0.080700, and ln(λ) =–2.517017 (*Figure 1*). Through the LASSO analysis, the 38 clinically relevant factors that were initially inputted were reduced to five potential predictors (*Table 2*).

Since the P value of cN was less than 0.05, we created another regression model that excluded cN and then compared the Akaike's information criterion (AIC) values of the two regression models. The results showed that the AIC value of the regression equation was 86.5 with cN included *vs.* 87.7 after removing cN. Thus, we finally choose to include cN in the regression equation.

Finally, we present the prediction model as a nomogram (*Figure 2A*). We analyzed the degree of TRG variance associated with each factor, and the results showed that cT stage after immune neoadjuvant therapy (INJT) and change in albumin contributed the most to the TRG variance (*Figure 2B*).

The accuracy of this prediction model was then verified: The Brier score was 0.13, the calibration slope was 0.98, and the C-index was 0.90 (95% CI: 0.82–0.97). The calibration slope and the receiver operating characteristic curve were also plotted to graphically assess calibration and discrimination, respectively (*Figure 3A*). The calibration slope tests the concordance between predicted values and outcomes with a perfect slope equal to 1. The C-index tests the discrimination of the model, or the ability to tell which patients who have TRG 2–3 should be given neoadjuvant

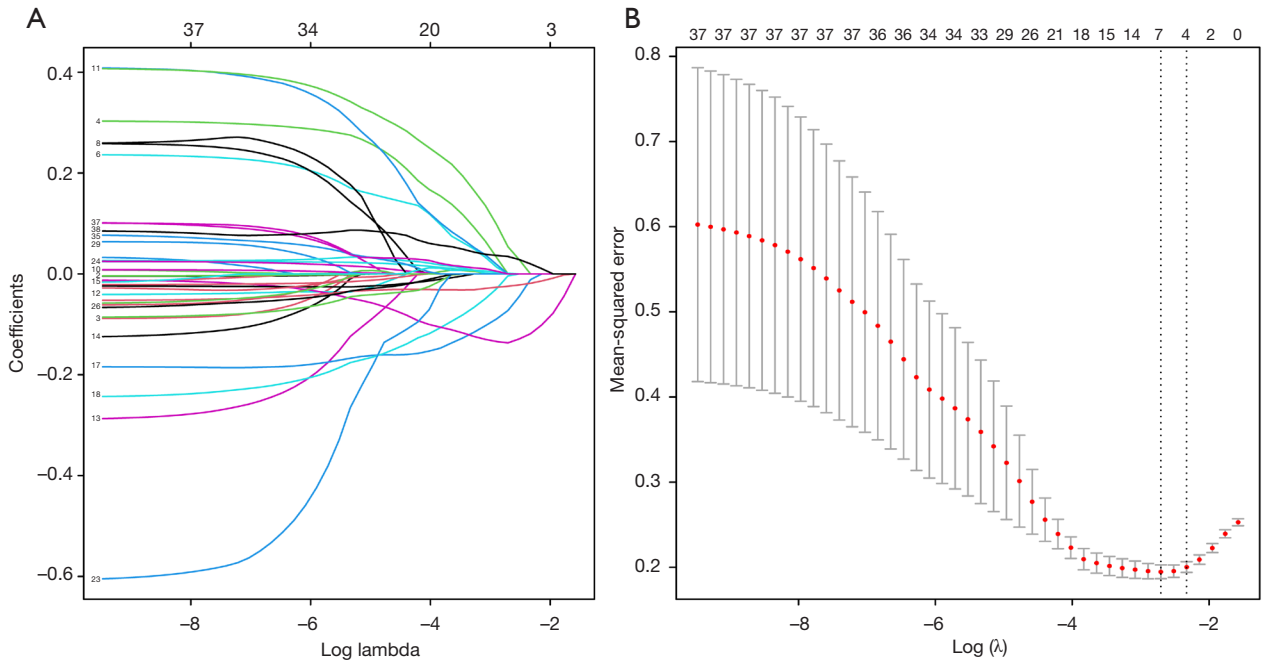

Figure 1 Screening of predictive factors. We used the LASSO regression method. (A) The LASSO regression method was used to choose predictive factors. (B) The penalty coefficient in the LASSO model was adjusted using cross-validation and minimum criteria. The vertical black line represented the optimal λ (i.e., the model provided the best fit to the data). The minimum λ was 0.080700, and ln(λ) =–2.517017. LASSO, the least absolute shrinkage and selection operator.

Table 2 Multivariate logistic regression analysis of the influencing factors screened by LASSO regression

Variable	P value
cT stage before INJT	0.0145
cN stage before INJT	0.0951
cT stage after INJT	0.0045
WBCs before INJT	0.0094
Change in albumin	0.0011

LASSO, the least absolute shrinkage and selection operator; cT, clinical T stage; INJT, immune neoadjuvant therapy; cN, clinical N stage; WBC, white blood cell.

immunotherapy. The receiver operating characteristic curve of this model is shown in *Figure 3B*. We also plotted the decision curve (*Figure 3C*) and the clinical impact curve (*Figure 3D*) for this model to evaluate the prediction model.

Discussion

In this study, we developed a prediction model to predict the likelihood of TRG 2–3 of esophageal cancer patients among those who underwent neoadjuvant chemotherapy combined with immunotherapy. Like other studies (27,28), the results showed that the prediction model could well predict the TRG, and the model fit was high (Brier score 0.13, calibration slope 0.99, and C-index 0.88).

Neoadjuvant immunotherapy could ethically enhance the function of T cells and achieve better anti-tumor efficacy. Meanwhile, there will also be immune-related side effects, such as immune pneumonia, abnormal thyroid function, etc.

After reviewing the postoperative pathological results of the patients, we found that the patients with complete tumor shrinkage did not all have TRG 0–1. There were 38 patients with complete clinical remission, but 18, 12, six, and two of them had TRGs of 0, 1, 2 and 3, respectively. For patients with TRG 0–1, neoadjuvant chemotherapy combined with immunotherapy was likely to benefit patients and obviate the need for neoadjuvant radiotherapy treatment. This important benefit, neoadjuvant chemoradiotherapy may increase mortality (7,8). However, for patients with TRG 2–3, neoadjuvant radiotherapy may be added to boost their survival. Therefore, we intend to screen these patients as candidates to receive neoadjuvant

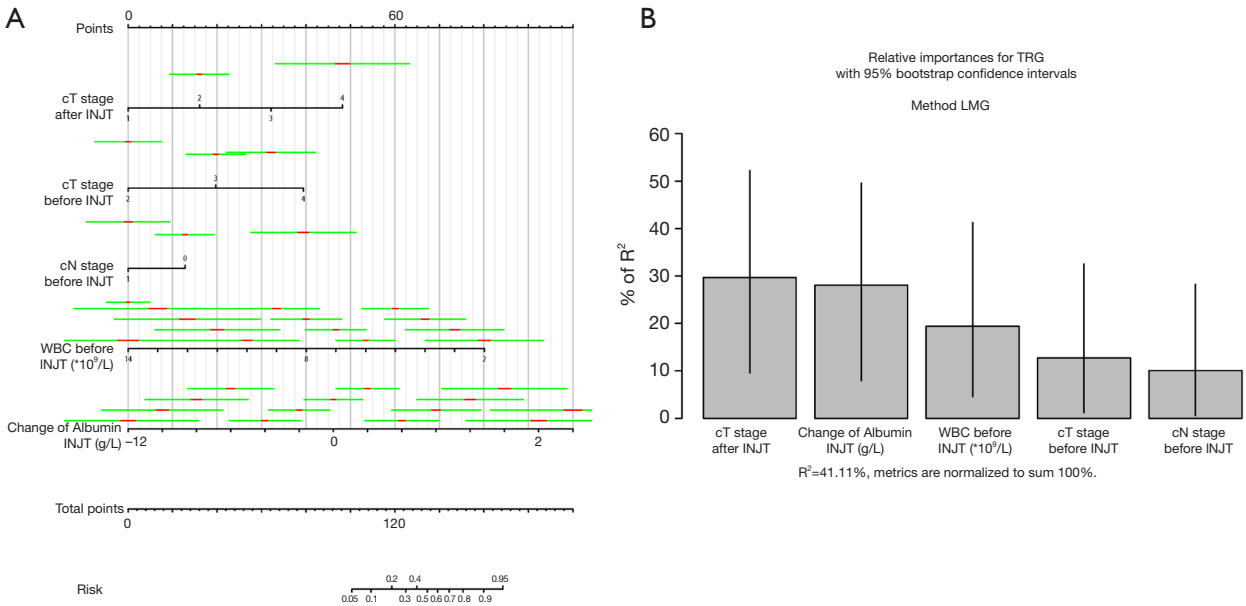

Figure 2 Nomogram plotted against various predictors and the importance of each predictor for TRG interpretation. (A) A nomogram for predicting the tumor regression grade of esophageal cancer patients treated with neoadjuvant immunotherapy. To use the nomogram, each factor has a score, and then the scores for each factor are added up to have a total score that corresponds to the likelihood of TRG 2–3 in the nomogram. (B) Degree of TRG variance explained by each influencing factor. INJT, immune neoadjuvant therapy; WBC, white blood cell; TRG, tumor regression grade; LMG, Lindeman, Merenda and Gold.

radiotherapy. However, it may not be accurate to rely solely on preoperative CT examination results to assess the need for combined radiotherapy. After all, in our study, 21.1% (8/38) of the patients with complete clinical remission had a TRG of 2 or 3. The prediction model we established can distinguish TRG 2–3 patients from TRG 0–1 patients well.

Our prediction model showed that the difference between the pre-neoadjuvant and preoperative albumin levels was correlated with the score, i.e., the greater the increase in albumin level after chemotherapy, the more likely the TRG was to be 2–3. There are many studies on the relationship between albumin and the prognosis of solid tumors. (29-31). The albumin level is also associated with the prognosis of esophageal cancer (32,33). However, these were all studies on how the ratios of albumin to other indices was correlated with prognosis. It was also found that patients with higher serum albumin (>3.5 g/L) had a better prognosis (34). There are few reports on the correlation between the difference in albumin before *vs.* after neoadjuvant therapy and the prognosis or the TRG. In this study, we found that the changes in albumin from before to after chemotherapy were correlated with TRG, and the albumin difference explain much of the TRG variance (*Figure 2B*), indicating that the nutritional level may have a great impact on the response to this combined therapy on our patients. Highlighting that nutritional support therapy is a particularly important part of clinical treatment of patients with esophageal cancer.

In our results, the WBC count before neoadjuvant therapy was also an independent predictor. The higher the WBC count, the higher the score, and the more likely TRG was 0–1; otherwise, it tended to be TRG 2–3. The WBC count is related to a variety of factors (infection, tumor, systemic inflammatory response, etc.) and can provide predictive information for a variety of diseases, such as cardiovascular diseases and type 2 diabetes. It is an important marker of the health status of the human body (35). Circulating tumor cells (CTCs) in the peripheral blood of cancer patients can form CTC-WBC clusters with immune cells, such as WBCs, which can promote the proliferation and metastasis of CTCs. Patients with CTC-WBC clusters found in peripheral blood may have a poor prognosis (36,37). Since WBCs can form CTC-WBC clusters with tumor cells and these clusters are correlated with prognosis, our results, in which WBC count was a factor in the prediction model, are consistent with the above results.

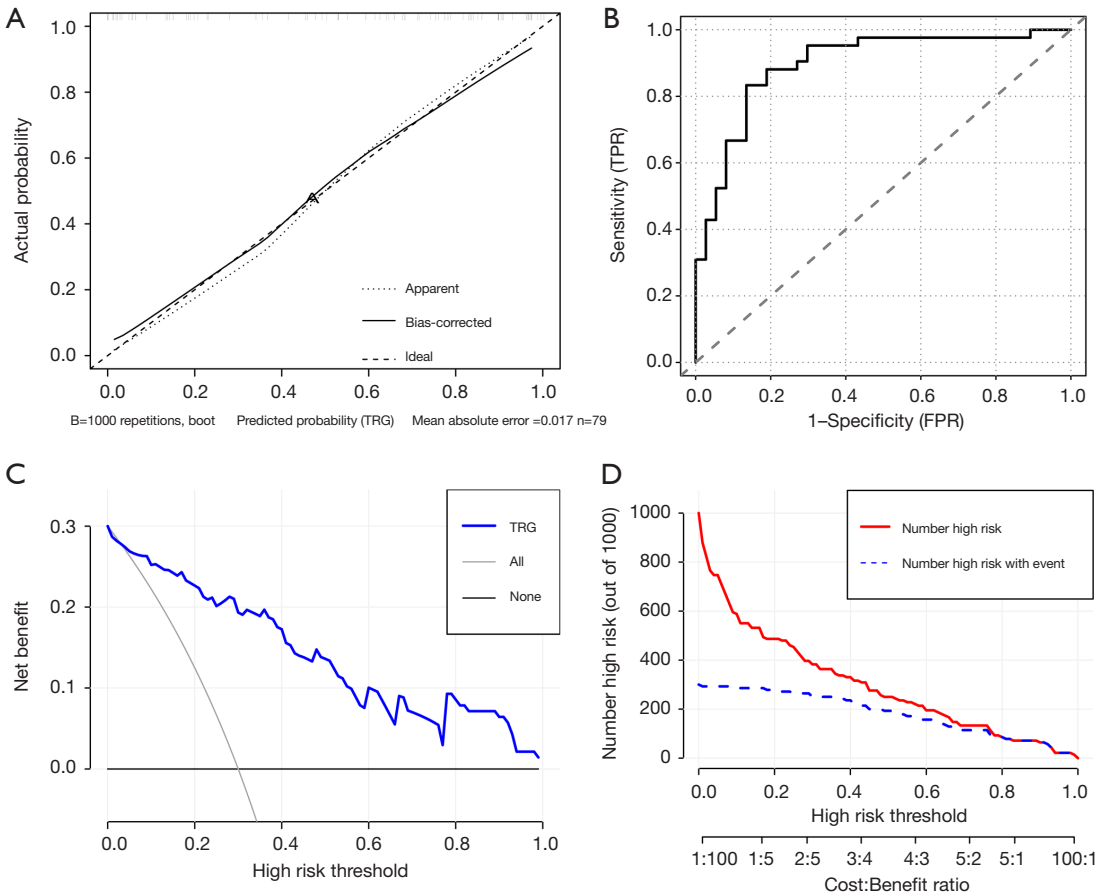

Figure 3 Various evaluation indicators of the prediction model (A) Calibration slope and (B) receiver operating characteristic curve of our model. Our model had a calibration slope of 0.98 and a C-index of 0.88. (C) Decision curve of the training cohort of the TRG 2–3 nomogram. (D) Clinical impact curve of the training cohort of the TRG 2–3 nomogram. TRG, tumor regression grade; FPR, false positive rate; TPR, true positive rate.

Among all patients, 39 of them underwent immunotherapy without PD-1 testing, and 40 patients underwent PD-1 testing, of whom 31 patients were positive. There are many studies on immunotherapy for esophageal cancer (19,20,38). For patients with positive PD-L1, the response rate was higher than those with negative PD-L1 (ORR: 15.5% *vs.* 6.4%). For patients with unclear PD-L1, the response rate was in between the two (11.6%) (39). Possibly because there was a high level of censored data (39/79, 49.4%), the PD-L1 status was not a factor associated with the TRG, so our prediction model did not include this factor. With the accumulation of more data, we plan to establish a predictive model for PD-L1-positive patients alone, and the results at that time may be more accurate and reliable for evaluating the effect of PD-L1 status on TRG in patients who have undergone neoadjuvant chemotherapy combined with immunotherapy.

Neoadjuvant immunotherapy could ethically enhance the function of T cells and achieve better anti-tumor efficacy. Meanwhile, there will also be immune-related side effects, such as immune pneumonia, abnormal thyroid function, etc. I think this Immune Neoadjuvant Immunotherapy could be used for other cancers, but some clinical researches need to be done.

We recognize that this study has limitations: (I) node positive patients with high scores before immune neoadjuvant therapy were more likely to have TRG 0–1. It is difficult to explain this finding based on current knowledge, but we plan to examine it in a future study. (II) The sample of 79 patients was small, and a larger sample would yield better predictive value. (III) We did not include PD-L1 expression as an influencing factor in this study due

to missing PD-L1 expression results. In the future, patients with PD-L1 test results will be included in the prediction model to determine the relationship between the efficacy of immunotherapy and PD-L1 expression in esophageal cancer.

Conclusions

Our prediction model may predict the likelihood of TRG 2–3 in patients with esophageal cancer after immunotherapy combined with neoadjuvant chemotherapy. We plan to conduct a study of TRG 2–3 patients undergoing neoadjuvant radiotherapy using this prediction model.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-78/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-78/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-78/coif). JMP reports leadership or fiduciary role in Florida Chapter American College of Surgeons and Scientific Board ADVOCARE. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Affiliated Cancer Hospital of Zhengzhou University (ethics number 2019092702), and informed consent was taken from all individual participants.

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