Original Article

Predictive model of postoperative pneumonia after neoadjuvant immunochemotherapy for esophageal cancer

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Background: Postoperative pneumonia (PP) is the most common pulmonary complication of esophagectomy. It is of great importance to identify any high-risk factors and prevent pulmonary complications to improve the prognosis of patients with esophageal cancer undergoing esophagectomy. Thus, we established a predictive model of PP in patients with neoadjuvant immunochemotherapy for resectable esophageal squamous cell carcinoma (ESCC), and provide suggestions for the best strategy for the perioperative period of the patients.

Method: We retrospectively analyzed 78 patients who underwent esophagectomy for squamous cell carcinoma after neoadjuvant immunochemotherapy between September 2019 and August 2021.We used the "glmnet" language package in R to perform least absolute shrinkage and selection operator (LASSO) regression to screen the best predictors of PP, and nomograms predicting PP were constructed utilizing screened factors. The performance of nomograms was internally validated by calibration curves, concordance index (C-index), and the Brier score for overall performance.

Results: Twenty-six patients (33.3%) had postoperative pneumonia. After LASSO regression, the factors that were independently associated with PP were diffusing capacity of the lungs for carbon monoxide (DLCO) (P=0.0002), white blood cell (WBC) difference before *vs.* after neoadjuvant immunochemotherapy (P=0.0133). We constructed a prediction model, plotted the nomogram, and verified its accuracy. Its Brier score was 0.147, its calibration slope was 0.98, and its C-index was 0.85 (95% CI: 0.75–0.95). Internal validation demonstrated a good discrimination power that the actual probability corresponds closely with the predicted probability.

Conclusions: Our prediction model can predict the possibility of PP in patients with neoadjuvant immunochemotherapy for resectable esophageal squamous cell carcinoma and may facilitate physicians' efforts to reduce the incidence of postoperative pneumonia.

Keywords: Postoperative pneumonia (PP); esophageal cancer; esophagectomy; neoadjuvant immunochemotherapy; predictive model

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Introduction

Esophageal squamous cell cancer (ESCC) is the 6th most common tumor in the world (1). Esophagectomy is still the most effective treatment option, although chemoradiotherapy or neoadjuvant chemotherapy may be effective in treating esophageal cancer treatment (2,3). In recent years, immune checkpoint inhibitors (ICIs) have shown promising results in the treatment of ESCC. Immunotherapy is added to neoadjuvant therapy in clinical trials, taking the neoadjuvant scheme of immunochemotherapy as a treatment strategy for ESCC (4,5). Research has shown that comparison of efficacy between immunotherapy combined with chemotherapy was significantly better than that of simple chemotherapy in neoadjuvant therapy for esophageal squamous cell carcinoma (6). Despite improvements in surgical techniques and postoperative care, however, neoadjuvant therapy may induce severe adverse effects that could increase postoperative morbidity (7,8). Risk management of patients with esophageal cancer therefore is an increasingly important component of treatment.

Postoperative pulmonary complications (PPCs) are the most common esophagectomy complications (8,9). Evidence indicates that the development of PPCs diminishes favorable surgical outcomes and impairs quality of life for patients (10). Postoperative pneumonia (PP) is the most common pulmonary complication by patients who undergo esophagectomy (11,12) ,up to 40% and prolong hospital stay, and could lead to death (7). PP was the most important parameter for predicting the overall survival (OS) of salvage esophagectomy (13). During the perioperative management of surgery for esophageal cancer with a high mortality, improved prevention and treatment of postoperative pneumonia are essential.

Factors that may lead to pneumonia after esophagectomy include smoking history, advanced age, chronic respiratory comorbidities, malnutrition, abnormal lung function (Pre FEV 1%, forced vital capacity in the first second expressed as a percent of predicted; PEF, peak expiratory flow), neoadjuvant therapy, thoracotomy, long operation time (8,14-17).

Diffusing capacity of the lungs for carbon monoxide (DLCO) is an indicator used to measure the ability of the human body to transfer oxygen through the alveolar capillary membrane, and is the main indicator of the lung diffusion function (18,19). Only one literature report, a low DLCO has been identified as an important risk factor for complications after esophagectomy (20). However, there has not been any research on whether DLCO is an independent risk factor for PP with neoadjuvant immunochemotherapy for ESCC.

Thus, it is of great importance to identify any high-risk factors and prevent pulmonary complications to improve the prognosis of patients with esophageal cancer undergoing esophagectomy. We intended to explore a prediction model of PP in patients with ESCC undergoing operation following neoadjuvant immunochemotherapy. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-149/rc).

Methods

Patients

We retrospectively analyzed 78 patients who underwent esophageal squamous-cell carcinoma (according to the eighth edition of the National Comprehensive Cancer Network guidelines) surgery between September 2019 to August 2021 at the Affiliated Cancer Hospital of Zhengzhou University after receiving neoadjuvant immunochemotherapy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Affiliated Cancer Hospital of Zhengzhou University (No. 2019092702) and informed consent was taken from all the patients.

Before surgery, the patients underwent enhanced computed tomography (CT; General Electric Company 64 rows) or enhanced magnetic resonance imaging (MRI; Siemens 3.0T) of the chest and upper abdomen, cardiac ultrasound, abdominal color Doppler ultrasound, upper gastrointestinal angiography, ultrasound gastroscopy, lung function, and laboratory examinations. Before neoadjuvant therapy, the gastroscopic biopsy specimens were used for programmed death-ligand 1 (PD-L1) detection (immunocytochemistry method). The patients received 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), and PD-L1 inhibitor (200 mg/m^2) before surgery.

Pulmonary function test

All patients underwent spirometric testing at their preoperative. Pulmonary function test (PFT) including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), diffusing

capacity of the lung for carbon monoxide (DLCO) for measured using Master Screen PFT System (JAEGER. Germany). The values of the pulmonary function tests were related to the predicted values and expressed as percentage of the predicted value (% of predicted) by dividing the pulmonary function test values by the predicted values.

Surgery and perioperative management

All patients received respiratory tract treatment with ambroxol and doxofylline. Double-lumen endotracheal intubation was adopted in all the operations, and the surgical method was the McKeown esophagectomy or video-assisted thoracic surgery (VATS) with cervical anastomosis. After surgery, each patient was sent to the resuscitation room to wake up. Those who had complications, such as heart disease, or advanced age were sent to the intensive care unit (ICU) for continuous tracheal intubation ventilation, and were sent back to the general surgery ward after the tracheal intubation was removed on the morning of the first day after the operation when their condition became stable.

From the 2nd to 7th day after the operation in the general surgery ward, when the gastrointestinal angiography confirmed anastomotic patency, the patient orally drank water, and then gradually began to eat mushy and then solid food. All patients were discharged from the hospital after successfully ingesting solid food by mouth.

Definition of PP

All postoperative complications were clinically or radiologically diagnosed and classified according to the Clavien-Dindo Classification (CDC) classification grading system (21). PP was defined as an infection of 1 or both lungs and was diagnosed based on the following radiological criteria and clinical findings within 30 days postoperatively: (I) X-ray or CT scans confirming PP that required antibiotic treatment; (II) clinical symptoms, including a body temperature >38 or <35.5 ℃; (III) the emergence or increase of sputum production; (IV) a white blood cell (WBC) count $\leq 4\times10^9$/L or a WBC count $\geq 12\times10^9$/L. Pneumonia was confirmed if the imaging findings were positive, and any 1 of the 2 clinical symptoms was present in the patient.

Development of the predictive model

We abstracted and categorized the following demographic and tumor variables: age, sex, hypertension, diabetes, history of smoking, history of drinking, other comorbidities, chronic respiratory comorbidities duration of surgery, surgical approach; FVC, FEV1, FEV1/FVC, PEF, DLCO before surgery; T stage before treatment, N stage, body mass index (BMI), nutritional score, WBC count, hemoglobin, lymphocyte count, monocyte count, albumin, bilirubin, T stage after chemotherapy, changes in BMI, WBC count, hemoglobin, lymphocyte count, monocyte count, albumin and bilirubin from before to after chemotherapy.

The predictive accuracy of the model was assessed using the following 3 measures: (I) the Brier score for overall performance; (II) the calibration slope for calibration; (III) the concordance index (C-index) and receiver operating characteristics (ROC) curves. The closer the Brier score was to 0, the better the predictive ability of the model; the closer the standard slope was to 1, the closer the predicted value was to the result; the closer the C statistic was to 1, the better the discrimination. These results were used to judge the accuracy of the model's predictions. We carried out repeated verifications many times, and used the model with the highest prediction accuracy as the final model.

The final results are shown in the form of a nomogram. We also drew a decision curve and a clinical impact curve to validate the prediction model.

Statistical method

All the statistical analyses were performed using R 3.63 (https://www.r-project.org/). We used the "glmnet" language package in R to perform least absolute shrinkage and selection operator (LASSO) regression to screen the best predictors of PP, and the "rms" language package to incorporate the factors selected by the LASSO regression into the multivariate logistic regression analysis to establish the predictive model. $P<0.05$ was considered statistically significant.

Results

We performed a retrospective analysis of 78 patients who underwent neoadjuvant immunochemotherapy before undergoing esophagectomy. The patients were aged 48–78 (61.97±6.63) years, 58 male and 20 were female. On average, patients had a DLCO of 6.92 kPa and a FEV1 of 2.6 L. Fourteen patients (18%) underwent McKeown esophagectomy, and 64 patients (82%) underwent VATS. The average operation time was 295 minutes. There were 26 (33.3%) cases of PP, 8 (10.3%) cases of pleural effusion,

7 cases of anastomotic leakage. The average postoperative hospitalization time was 13 days. The basic characteristics of the research are shown in *Table 1*.

After LASSO regression analysis, the factors that were independently associated with PP included DLCO (P=0.0002), WBC difference before *vs.* after neoadjuvant therapy (P=0.0133) (*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 0.1208673, and ln(λ) =–2.113062 (*Figure 1B*). Through the LASSO analysis, the 47 clinically relevant factors that were initially inputted were reduced to two potential predictors (*Table 2*).

Finally, we present the prediction model as a nomogram (*Figure 2*). The accuracy of this prediction model was then verified: The Brier score was 0.147, the calibration slope was 0.98 (*Figure 3A*), and the C-index was 0.85 (95% CI: 0.75–0.95) (*Figure 3B*). The calibration slope tests the concordance between predicted values and outcomes with a perfect slope equal to 1. We also plotted the decision curve (*Figure 4A*) and the clinical impact curve (*Figure 4B*) to evaluate the prediction model.

Discussion

Our research revealed that DLCO, WBC difference before *vs.* after neoadjuvant therapy was an independent risk factor for PP, and the high-fitting model (Brier score 0.147, calibration slope 0.98, C-index 0.85) can effectively predict the PP after patients with ESCC undergoing operation following neoadjuvant immunochemotherapy

In this study, pulmonary complications was assessed based on the CDC classification, making the prediction of PP more accurate. Risk factors predicting pneumonia after esophagectomy vary across the literature. In our study, included 8 patients with COPD, but chronic respiratory comorbidities and thoracotomy were not independent risk factors. It has also been reported in some literature that peak expiratory flow PEF (15) and FEV1 (14) predict PP after esophagectomy. Theoretically, FEV1 and PEF are related. It has also been reported that in the acute exacerbation of COPD, the DLCO is more effective than FEV1 at predicting mortality, mechanical ventilation, and experience of ICU care (22). The DLCO can be used as an independent factor for predicting severe complications after lung cancer surgery (23,24), and an independent prognostic factor for the long-term survival of patients receiving lung cancer surgery (25,26). But currently not yet implemented in the preoperative prediction of major complications after patients with ESCC undergoing operation following neoadjuvant therapy. A decrease of DLCO is related to COPD (27,28). Research has shown that after neoadjuvant radiotherapy and NAC for lung cancer, the level of DLCO is significantly reduced, while the postoperative pulmonary complications are significantly increased (29). In addition, studies have reported in patients undergoing thoracic surgery, a DLCO <50–60% of the predicted value was found to be a risk factor for postoperative respiratory complications, a prolonged stay in the ICU, and death (30-32).

The results show that the WBC count difference before and after neoadjuvant therapy is also an independent predictor. WBC counts are related to a variety of factors (e.g., infection, tumors, and other diseases that trigger inflammatory reactions), and are an important indicator of the health of the human body (33). An increase in the WBC count before surgery will increase the incidence of PP after lung surgery (34), colorectal cancer surgery (35), craniotomy (36), and heart surgery (37). The preoperative WBC count is a strong predictor of pneumonia after lobectomy (38).

Numerous studies have shown that various factors related to pulmonary complications after esophagectomy can be treated before surgery to reduce their incidence. For example, preoperative inspiratory muscle training can improve lung function indicators and reduce the incidence of pulmonary complications after esophagectomy (39-42). PEF in pulmonary function tests has clinical value in predicting pneumonia after esophagectomy, and can be used as an indicator of preoperative pulmonary function training (15). Additionally, a pneumonia after esophagectomy can also be predicted by preoperative sarcopenia (43), which should be evaluated and treated before esophagectomy. It is necessary to introduce some rehabilitation strategies to reverse the state of sarcopenia in patients with preoperative sarcopenia. The incidence of PP in our research was 33.3%, which may be related to neoadjuvant therapy (29). Thus, nutritional interventions and exercise therapies during neoadjuvant therapy period can not only prevent PP, but also improve the survival of patients (43,44).

After esophagectomy, if the sputum is thick and not easy to cough up, antispasmodic drugs can be intravenously administered and inhaled, asthma relieved and phlegm

Table 1 Patient and tumor characteristics in this study

Variables	Overall cohort (n=78)
Age (year)	61.93±6.63
Sex (male/female)	58 (74.4%)/20 (25.6%)
Hypertension (yes/no)	16 (20.5%)/62 (79.5%)
Diabetes (yes/no)	4 (5.1%)/74 (94.9%)
Smoking (yes/no)	50 (64.1%)/28 (35.9%)
Chronic respiratory comorbidities (yes/no)	8 (10.3%)/70 (89.7%)
WBC before neoadjuvant therapy (10^9/L)	6.38±1.92
BMI before neoadjuvant therapy (kg/m^2)	22.97±2.83
Hb before neoadjuvant therapy (g/L)	136.35±17.47
Neutrophils before neoadjuvant therapy (10^9/L)	4.12±1.47
Total bilirubin before neoadjuvant therapy (μmol/L)	10.45±3.83
Albumin before neoadjuvant therapy (g/L)	41.63±3.3
WBC before surgery (10^9/L)	6.23±2
BMI before surgery (kg/m^2)	22.93±2.93
Hb before surgery (g/L)	122.36±14.32
Albumin before surgery (g/L)	40.87±2.98
Neutrophils before surgery (10^9/L)	4.18±1.94
Total bilirubin before surgery (μmol/L)	9.48±3.61
Changes in WBC	0.14±2.21
Preoperative PFT	
FVC (L)	3.17±0.77
FEV 1 (L)	2.63±0.7
Pre FEV 1%	98.53±17.92
FEV1/FVC (%)	100.8±8.35
PEF (L/min)	337.2±94.2
DLCO (mmol/min/kPa)	6.92±1.41
Pre DLCO %	85.91±14.26
Surgery (open/VATS)	14 (18%)/64 (82%)
Duration of surgery (min)	299.01±85.87
cT stage before neoadjuvant therapy (1/2/3/4)	0/11/55/12
cN stage before neoadjuvant therapy (–/+)	27 (34.6%)/51 (65.4%)
cT stage after neoadjuvant therapy (1/2/3/4)	38/24/15/1
cN stage after neoadjuvant therapy (–/+)	51 (65.4%)/27 (34.6%)
pT (0/1/2/3/4)	26/11/13/28/0
pN (0/1/2/3)	58/15/5/0

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Overall cohort (n=78)
cTNM stage (I/II/III/IVa)	0/3/73/2
pTNM stage (I/II/III/IVa)	41/17/8/12
Location (u/m/l)	13/52/13
Tumor regression grade (0/1/2/3)	24/12/28/14
Postoperative pneumonia (yes/no)	26 (33.3%)/52 (66.7%)

WBC, white blood cell; BMI, body mass index; Hb, hemoglobin; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; Pre FEV 1%, forced vital capacity in the first second expressed as a percent of predicted; PEF, peak expiratory flow; DLCO, diffusing capacity of the lung for carbon monoxide. Pre DLCO %, the percent diffusing capacity of the lung for carbon monoxide; VATS, video-assisted thoracic surgery.

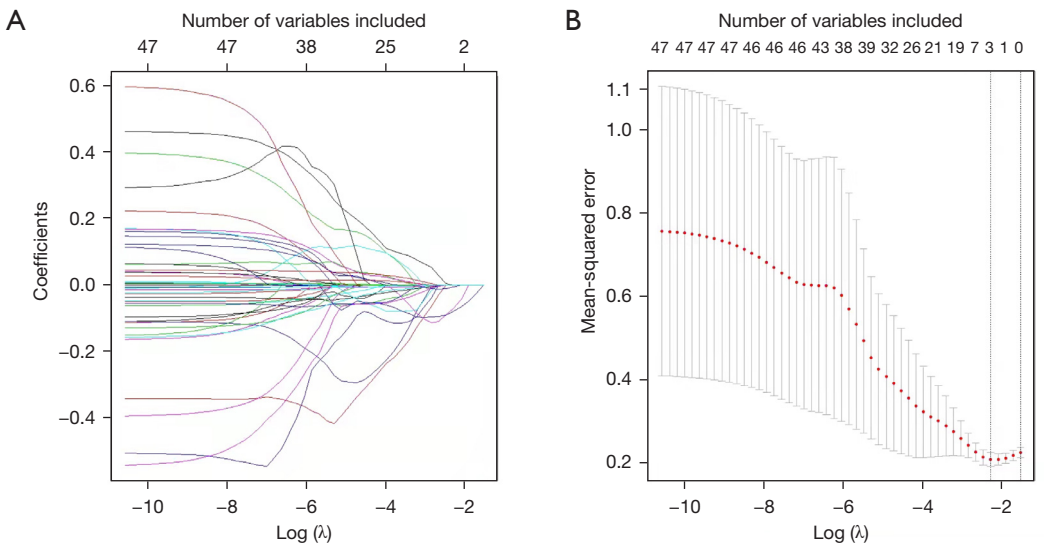

Figure 1 We used the LASSO regression method to screen the predictors. (A) Changes in 47 clinically relevant factors with the penalty parameter (λ). (B) 47 clinically relevant factors with the penalty parameter (λ) in the LASSO model was adjusted based on the cross-validation and minimum criteria. The vertical black line represents the best lambda (i.e., the model provides the best fit to the data). The minimum lambda is 0.1208673, and the logarithm log (λ) is –2.113062. LASSO, least absolute shrinkage and selection operator.

Table 2 Multivariate logistic regression analysis of the influencing factors selected through LASSO regression

Variables	P value
Change in WBC	0.0133
DLCO	0.0002

WBC, white blood cell; DLCO, diffusing capacity for carbon monoxide. LASSO, least absolute shrinkage and selection operator.

treated by drugs, and airway clearance techniques (45) and hand-assisted expectoration (46) used to assist excretion.

If the prognosis of patients is known early, a focus on high-risk patients could improve their prognosis. Before surgery, strengthening the optimization of respiratory function (47), the preventative use of antibiotics (48), preoperative oral care (49), and nutritional support (50) can reduce postoperative pulmonary complications of

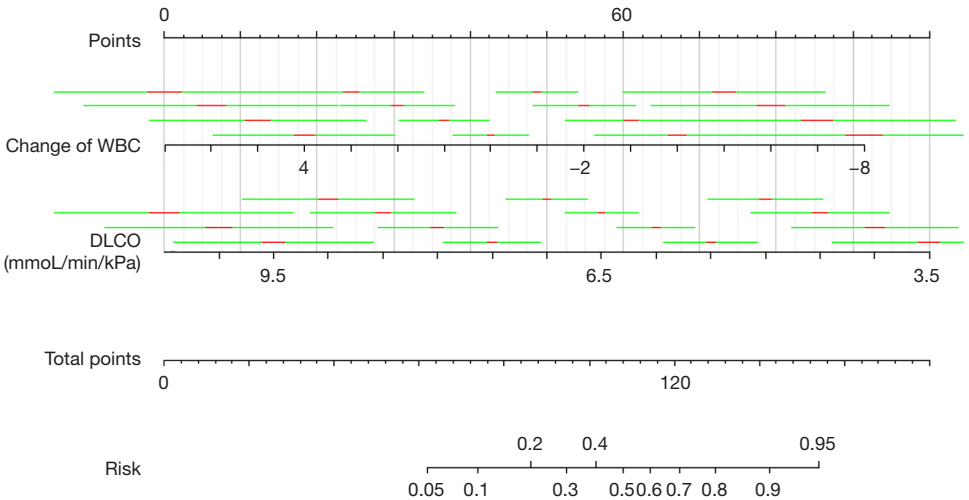

Figure 2 Nomogram predicted the incidence of PP in patients with neoadjuvant immunochemotherapy for resectable esophageal squamous cell carcinoma. Factors include DLCO, WBC difference before *vs.* after neoadjuvant immunochemotherapy. To use the nomogram, each factor has a score, and then the scores for each factor are added up to have a total score that corresponds to the likelihood of PP in the nomogram. DLCO, diffusing capacity for carbon monoxide; WBC, white blood cell; PP, postoperative pneumonia.

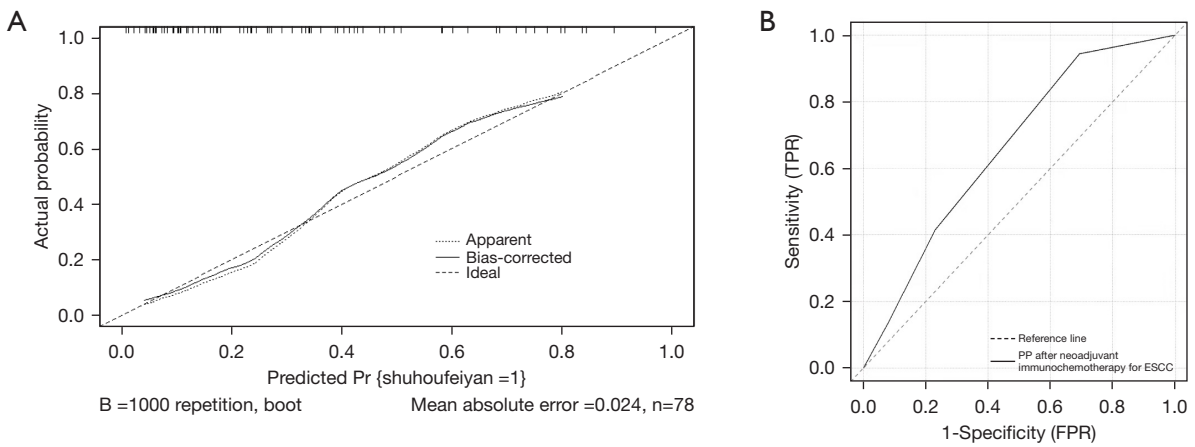

Figure 3 Our predictive model evaluation metrics include (A) calibrated slope and (B) ROC curve for LASSO regression. Its calibration slope of 0.98 and C-index of 0.85 (95% CI: 0.75–0.95). FPR, false positive rate; TPR, true positive rate; ROC, receiver operating characteristic; LASSO, least absolute shrinkage and selection operator; PP, postoperative pneumonia; ESCC, esophageal squamous cell cancer; CI, confidence interval.

esophageal cancer. Yu *et al.* (51) also published an expert consensus on the prevention and treatment of postoperative lung infection in patients with esophageal cancer, which should inform the management of the quality of life of patients with esophageal cancer and future research. In summary, strategies to reduce pulmonary complications after esophageal cancer surgery are essential to improve short- and long-term results.

We recognize that this study has limitations: because only a few medical institutions in China are studying neoadjuvant immunotherapy for ESCC, the sample size is too small, so our predictive model is only internally validated. In the next step, we will collect a large number of samples and make better predictions.

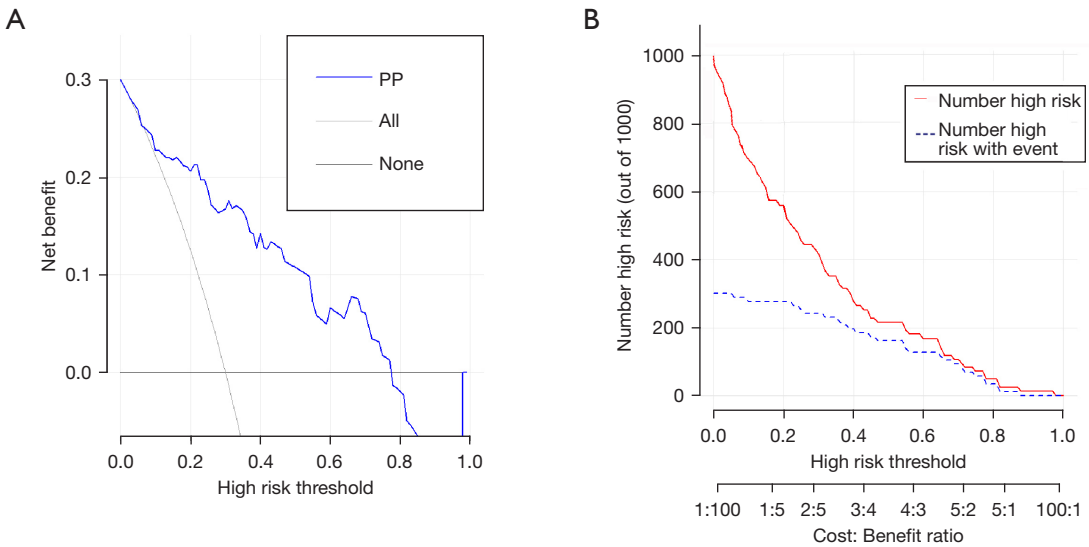

Figure 4 We plotted the decision curve (A) and the clinical impact curve (B) to evaluate the prediction model of PP. PP, postoperative pneumonia.

Conclusions

In conclusion, we show that readily determined DLCO, WBC difference before *vs.* after neoadjuvant therapy as a significant predictor of PP after patients with ESCC undergoing operation following neoadjuvant immunochemotherapy. This result may facilitate a physician's ability to make decisions to reduce the incidence of PP and interventions such as preoperative respiratory rehabilitation and oxygen therapy.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-149/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-149/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-149/coif). The 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). The study was approved by the Affiliated Cancer Hospital of Zhengzhou University (No. 2019092702) and informed consent was taken from all the patients.

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