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Nomogram to predict postoperative PR in patients undergoing CT-guided transthoracic lung biopsy

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Background: Pleural reaction (PR) frequently occurs following computed tomography-guided transthoracic needle biopsy (CT-TNB). The purpose of this study was to establish a predictive model for PR following CT-TNB.

Methods: In this study, a total of 436 patients who underwent CT-TNB between June 2016 and December 2017 at a tertiary hospital were consecutively included. Patient demographics, lesion features, laboratory tests, and biopsy parameters were collected. The least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression analyses were performed to establish a prediction model for post-CT-TNB PR, presented by a nomogram. Discrimination and calibration were assessed. For internal validation, a bootstrap resampling method was applied, and decision curve analysis (DCA) was used to evaluate its clinical utility.

Results: PR occurred in 7.8% (34/436) of patients. Four non-zero coefficient variables (gender, age, lesion location, and puncture position) were filtered by LASSO regression analysis and were used to establish a predictive model. The area under the curve in the derivation and validation was 0.840 (95% CI, 0.767–0.913) and 0.841 (95% CI, 0.769–0.912), respectively. The model was well-calibrated (P>0.05), and DCA indicated clinical efficacy.

Conclusions: In this study, we established a nomogram, including as parameters gender, age, lesion location, and puncture position, which may have great significance for individualized prediction of post-CT-TNB PR.

Keywords: Pulmonary; biopsy; pleural reaction; nomogram

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Introduction

Pleural reaction (PR) refers to a series of presentations, including a continuous cough, dizziness, dyspnea, chest pain, sweating, transient hypotension, and even syncope (1). PR is a common complication of pleural puncture, transthoracic needle biopsy, or thoracotomy tube (1,2). However, when compared to objective complications, such as pneumothorax and hemoptysis, PR is a more subjective complication that is often underestimated in computed tomography-guided transthoracic needle biopsy (CT-TNB) (1).

With the widespread use of low-dose CT for lung cancer screening and diagnosis (3,4), the incidence of pulmonary lesions, including asymptomatic pulmonary nodules and masses has significantly increased (5). In general, for pulmonary lesions larger than 10 mm or smaller lesions

with a high growth rate, clinicians will recommend further diagnostic procedures, such as transbronchoscopic lung biopsy, CT-TNB, or surgery (3,6). Among these, CT-TNB is the preferred biopsy method because of its minimal invasiveness, high diagnostic accuracy, and relatively low costs (6-8). CT-TNB-induced complications, including pneumothorax, hemoptysis, and intrapulmonary have been highlighted in several of studies (6,7,9). However, although the incidence is not low, PR following CT-TNB has received insufficient attention (1).

Nowadays, CT-TNB is commonly performed in an outpatient setting. The most important issue concerning outpatient management is not the occurrence of PR per se, but some PR requires immediate treatment. Therefore, it is essential to predict the occurrence of post-CT-TNB PR. To the best of our knowledge, no reported model for the prediction of post-CT-TNB PR is available to date. We hypothesized that variables of patient demographics, lesion features, and biopsy parameters may potentially predict PR. The purpose of this study was to establish a predictive model based on valuable predictors of post-CT-TNB PR.

Methods

Study population

In this study, we performed a retrospective cohort study, including a total of 436 consecutive patients who underwent CT-TNB at a tertiary hospital between June 2016 and December 2017. The study was approved by institutional ethics committee of Jinhua Hospital of Zhejiang University (No. 2018001008). Patient information was handled anonymously and therefore signed informed consent was waived. In patients, PR was defined as the occurrence of one or more presentations following CT-TNB, including puncture site pain [based on a scale of 0 to 10 (0= none, 10= severe)] (1), profuse sweating, dyspnea, continuous cough, dizziness, and hypotension [systolic blood pressure (SBP) decreases ≥20 mmHg, or diastolic blood pressure (DBP) decreases ≥10 mmHg].

Clinical characteristics

Patient clinical information and laboratory tests were retrospectively reviewed using our electronic medical record system. From each patient, the following variables were collected: age, gender, SBP, DBP, heart rate, pulse oximetry saturation (on room air), and coexisting chronic obstructive pulmonary disease (COPD) (yes or no), diagnosis of the lung lesion, lesion location classification I (left or right lung), lesion location classification II (hilum, upper lung, middle lung or lower lung), lesion diameter, lesion characteristics (ground-glass, solid, or cavitary), lesion differentiation (low, moderate, or high), lesion burr (yes or no), the closest distance between the lesion and a vessel (<10 mm, or ≥10 mm), CT value of lesion, puncture position (supine, prone or lateral), puncture distance (defined as the length between the center of the lung lesion and the pleura), procedure duration, biopsy times, and PR following procedure (yes or no). Laboratory tests were performed for blood glucose, C-reactive protein, prothrombin time, squamous cell carcinoma antigen, carcinoembryonic antigen, cytokerantin-19-fragment (CYFRA21-1), D-dimer, platelet counts, and triglyceride levels.

CT-TNB procedure

A clinician experienced in radiology and pneumology performed all biopsies. A coaxial 18-gauge needle (Lot Number, REXK0682; Bard Peripheral Vascular, Inc., Tempe, AZ) was used for all biopsies, and 2% lidocaine was used for local infiltration anesthesia prior to surgery. In general, two biopsies were taken and occasionally additional biopsies were obtained (8,10).

Patients were requested to maintain the supine position for at least 6 hours following CT-TNB, in which patient's symptoms were recorded. Generally, patients with mild PR spontaneously regained normally, and drug treatment (epinephrine or/and rehydration) was only administered when PR was severe.

Statistical analysis

We used descriptive statistics to summarize baseline characteristics. For continuous variables, the median (25–75% interquartile) was calculated, and categorical variables were displayed as numbers with percentages. Between-group comparisons, unpaired *t*-tests (normal distribution) or Mann-Whitney U test (non-normal distribution), Pearson Chi-squared tests or the Fisher's exact test were used, as appropriate. Variables with a P value of less than 0.05 in the univariate analysis were included in the multiple logistic regression. To account for missing data, multiple imputation was used (11). The least absolute shrinkage and selection operator (LASSO) regression method was employed to determine value predictors from collected variables.

The logistic regression analysis was used to establish the predictive model for post-CT-TNB PR, and a nomogram was constructed based on the model. The area under the curve (AUC) was calculated to assess the discrimination capacity of the model, and bootstrapping with 1000 iterations was performed for internal validation. Calibration was assessed by the unreliability test and calibration curve. Decision curve analysis (DCA) was performed to assess the clinical usefulness of the model by quantifying the net benefits at different threshold probabilities (12). R version 3.5.1 (https://www.r-project.org) with R packages (glmnet, rms) was used for statistical analyses. P<0.05 was considered statistically significant.

Results

Patient's clinical characteristics, lesion features, and biopsy parameters are shown in *Table 1*. Of the 436 patients, 34 (7.8%, 95% CI, 5.3–10.3%) patients experienced PR following CT-TNB, and 2 (5.9% of the PR) cases required treatment. With regard to the time window between CT-TNB and occurrence of the PR, 79.4% (27/34) patients experienced PR within half an hour, 11.8% (4/34) cases at 0.5–2 hours, and the remaining 3 cases at 2–6 hours post-CT-TNB. Univariable analysis showed that post-CT-TNB PR more frequently occurred in female patients, younger patients, patients with no coexisting COPD, higher preoperative pulse oxygen saturation, lower preoperative blood glucose levels, smaller lesion diameter, more puncture times, and longer procedure duration; while less frequent in the supine position, and in lesions in the hilus and the middle lung. However, only gender and age were independently associated with post-CT-TNB PR as assessed by multiple logistic regression (*Table 2*).

Based on non-zero coefficients in the LASSO regression analysis (*Figure 1*), 30 variables were reduced to the 4 most potential predictors (gender, age, lesion location, and puncture position). We constructed a risk prediction model for CT-TNB-induced PR based on the aforementioned 4 predictors. As shown in *Figure 2*, the AUC for the predictive model was 0.840 (95% CI, 0.767–0.913), whereas the AUC for the internal validation was 0.841 (95% CI, 0.769–0.912). The optimal cut-off value of the predictive model was –2.41, which was based on the value of the maximum Youden index. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 76.8%, 79.4%, 76.6%, 22.3%, and 97.8%, respectively.

In this study, we established a nomogram that was based on the predictive model to provide clinicians with a quantitative tool to predict the individual probability of post-CT-TNB PR (*Figure 3*). The calibration curve of the model for the probability of post-CT-TNB PR showed good agreement between prediction and observation of the model (*Figure 4*). The unreliability test yielded non-significant statistics (Emax =0.083, Eavg =0.013, P=0.966), which suggested that the model was a perfect fit.

The decision curve for the model is presented in *Figure 5*. The DCA showed that when the threshold probability of an individual was between 2–48%, application of this model to predict post-CT-TNB PR proved to be more beneficial than either the treat-all or treat-none strategies.

Discussion

Being able to anticipate post-CT-TNB PR may improve postoperative patient management. The reported predictive model is the first initiative of its kind to predict the occurrence of post-CT-TNB PR by combining patient's gender, age, lesion location, and puncture position, which were selected by LASSO regression and readily available. Furthermore, we developed a nomogram based on the aforementioned predictors for convenient prediction post-CT-TNB PR. The model showed good discrimination with an AUC of 0.840 (95% CI, 0.767–0.913), satisfactory calibration, and clinical usefulness.

Currently, CT-TNB is widely used for the diagnosis of pulmonary diseases (7,13). A number of studies focused on post-CT-TNB complications, including pneumothorax and hemoptysis (6,9). However, only few studies focused on PR in CT-TNB, thereby underestimating PR occurrence following CT-TNB (1). Reportedly, the incidence of PR in thoracocentesis is 5–46% (1,14-16). Mild PR causes patient discomfort whereas severe PR can lead to shock, and in some cases, may be life-threatening (17).

The underlying mechanism of PR is still unclear. Factors that may be associated with PR, include enhanced vagus reflex, patient's constitutional weakness or low pain threshold, preoperative anxiety, inexperienced operator, and inadequate pleural anesthesia (1). In the present study, we used an 18-gauge coaxial needle for transthoracic puncture, leading to an incidence of post-CT-TNB of 7.8%. Our study indicated a trend that PR occurred more frequently in female and younger patients, whose vagus reflex may be more enhanced following CT-TNB. No statistically significant difference was observed in the number of biopsies between the post-CT-TNB PR group

Table 1 Clinical characteristics of study population

Variables	Post-CT-TNB pleural reaction		P
	No (n=402)	Yes (n=34)	
Baseline characteristics			
Gender, n (%)			<0.001
Female	143 (35.57)	23 (67.65)	
Male	259 (64.43)	11 (32.35)	
Age (year)	64 [56–71]	52 [36–59]	<0.001
SBP (mmHg)	129 [118–141]	122 [112–135]	0.121
DBP (mmHg)	78 [70–84]	76 [70–81]	0.255
HR (beat/min)	80 [71–88]	82 [75–88]	0.716
Pulse oximetry saturation (%)	97 [96–98]	98 [97–99]	0.004
COPD, n (%)			0.020
No	279 (69.40)	30 (88.24)	
Yes	123 (30.60)	4 (11.76)	
Blood test			
PT (s)	12.40 (11.60–13.30)	11.95 (11.20–13.02)	0.084
D-Dimer (mg/mL)	0.61 (0.34–1.29)	0.42 (0.22–0.94)	0.157
Platelets ($\times 10^9$/L)	231 [177–284]	233 [189–294]	0.848
CRP (mg/L)	4.85 (0.80–25.85)	1.75 (0.50– 4.00)	0.507
Blood glucose (mmol/L)	5.40 (4.75–6.80)	5.08 (4.58–5.60)	0.047
Triglyceride (mmol/L)	1.10 (0.84–1.49)	1.32 (1.05–1.95)	0.317
SCC (μg/L)	0.70 (0.50–1.20)	0.60 (0.40–1.00)	0.450
CYFRA21-1 (ng/mL)	2.60 (1.50–5.38)	1.90 (1.15–2.68)	0.271
CEA (ng/mL)	42.25 (1.14–6.83)	1.54 (0.62–9.32)	0.735
Lesions characteristics			
Diagnosis, n (%)			0.111
Benign	168 (41.79)	19 (55.88)	
Malignant	234 (58.21)	15 (44.12)	
Characteristics, n (%)			0.611
Ground-glass	14 (3.48)	1 (2.94)	
Solid	310 (77.11)	24 (70.59)	
Cavitary	78 (19.40)	9 (26.47)	
Location I, n (%)			0.956
Left lung	199 (49.50)	17 (50.00)	
Right lung	203 (50.50)	17 (50.00)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Post-CT-TNB pleural reaction		P
	No (n=402)	Yes (n=34)	
Location II, n (%)			0.006
Hilus of lung	21 (5.22)	0 (0.00)	
Upper lung	209 (51.99)	11 (32.35)	
Middle lung	19 (4.73)	0 (0.00)	
Lower lung	153 (38.06)	23 (67.65)	
Degree of differentiation, n (%)			0.412
Low	36 (8.96)	1 (2.94)	
Moderate	36 (8.96)	5 (14.71)	
High	5 (1.24)	0 (0.00)	
NA	325 (80.85)	28 (82.35)	
Burr, n (%)			0.494
No	236 (58.71)	22 (64.71)	
Yes	166 (41.29)	12 (35.29)	
Distance from the nearest vascular, n (%)			0.057
<10 mm	204 (50.75)	10 (29.41)	
≥10 mm	198 (49.25)	24 (70.59)	
CT value (HU)	35.0 (28.0–43.0)	32.5 (26.3–41.0)	0.870
Lesion diameter (mm)	30.0 (20.0–40.0)	20.0 (20.0–30.0)	0.003
Biopsy parameters			
Puncture distance (mm)	10.0 (0.0–20.0)	12.5 (0.0–20.0)	0.732
Procedure duration (min)	9.00 (8.00–11.75)	11.00 (8.25–12.00)	0.036
Puncture times, median (range)	1 [1–3]	1 [1–5]	0.039
Biopsy times, median (range)	2 [1–3]	2 [1–3]	0.098
Puncture position, n (%)			0.001
Supine	150 (37.31)	3 (8.82)	
Prone	184 (45.77)	26 (76.47)	
Lateral	68 (16.92)	5 (14.71)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; PT, prothrombin time; SCC, squamous cell carcinoma antigen; CYFRA21-1, cytokerantin-19-fragment; CEA, carcinoembryonic antigen; NA, not applicable.

and the non-PR group as assessed by univariable analysis. In this study cohort, 94.7% (413/436) patients received two biopsies. In several studies, it has been demonstrated that for most lesions, one or two biopsies can obtain sufficient specimen for pathological examination, yielding a stable and satisfactory diagnostic accuracy (10,18). When additional laboratory testing was needed (such as immunohistochemistry and analysis of tumor-markers) or when the first two biopsies failed, additional biopsies were considered. However, each biopsy can induce complications

Table 2 Multivariable analysis of potential predictive factors of post-CT-TNB pleural reaction

Parameters	Odds ratio	95% CI	P
Gender			
Female	Ref.		
Male	0.368	0.159–0.854	0.020
Age	0.944	0.916–0.974	0.000
Pulse oximetry saturation	1.325	0.956–1.835	0.091
COPD			
No	Ref.		
Yes	0.966	0.283–3.297	0.957
Blood glucose	0.753	0.531–1.068	0.112
Location II			
Lower lung	Ref.		
Hilus of lung	0.000	0.000–inf.	0.998
Upper lung	0.483	0.188–1.242	0.131
Middle lung	0.000	0.000–inf.	0.998
Lesion diameter	0.815	0.614–1.081	0.155
Procedure duration	1.019	0.856–1.215	0.829
Puncture times	1.470	0.652–3.315	0.353
Puncture position			
Supine	Ref.		
Prone	2.687	0.640–11.280	0.177
Lateral	1.872	0.362–9.674	0.454

COPD, chronic obstructive pulmonary disease.

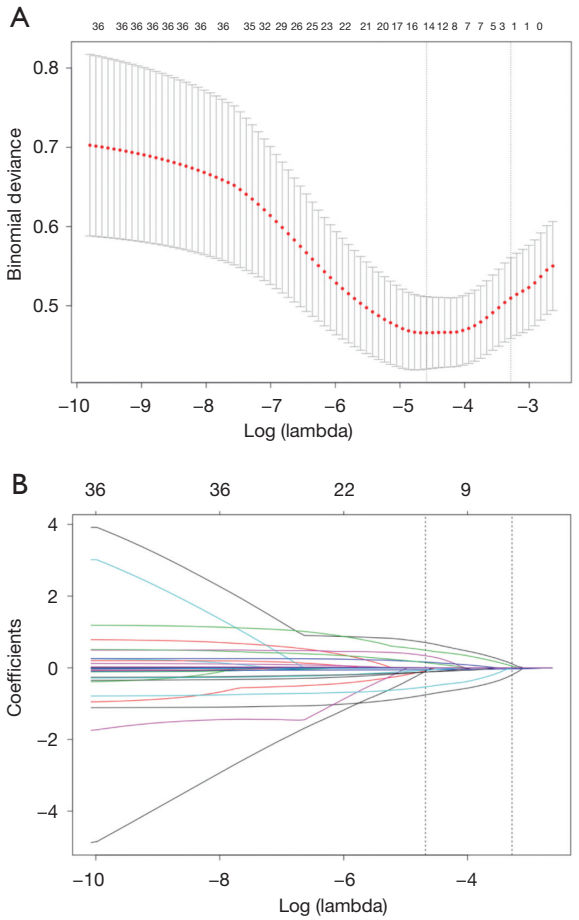

Figure 1 Predictors selection based on the least absolute shrinkage and selection operator (LASSO) regression method. (A) Tuning parameter (lambda) selection in the LASSO regression used 10-fold cross-validation. Binomial deviance was plotted versus log (lambda). The dotted vertical lines were drawn at the optimal values by using the 1-SE criteria; (B) LASSO regression coefficient profiles of variables. A coefficient profile plot was created against the log (lambda) sequence. Dotted vertical lines were drawn at the optimal values by using the 1-SE criteria. In the present study, predictors were chosen according to the 1-SE criteria, where optimal lambda resulted in four non-zero coefficients. SE, standard error.

(such as pneumothorax and hemoptysis) and therefore unnecessary additional biopsies should be avoided (8,19,20).

Not just inpatients, but also many outpatients commonly receive CT-TNB. The most important issue is not the occurrence of PR per se, but the management of these outpatients. Therefore, it is necessary to accurately predict the probability of PR post CT-TNB. In the present study, we established a nomogram based on four predictors (gender, age, lesion location, and puncture position) filtered by LASSO regression analysis. Regression shrinkage and variable selection based on the LASSO approach was first reported by Robert in 1996 (21), and this approach was considered to surpass the method of choosing predictors based on the strength of their univariable association with outcome, especially when many variables were present (21-23). In addition, all four predictors were readily accessible clinically.

Our prediction model showed both good discrimination ability and calibration. To evaluate its clinical usefulness, we performed DCA to assess whether the decisions made based on this predictive model would improve patient outcomes. This novel method was based on threshold probabilities

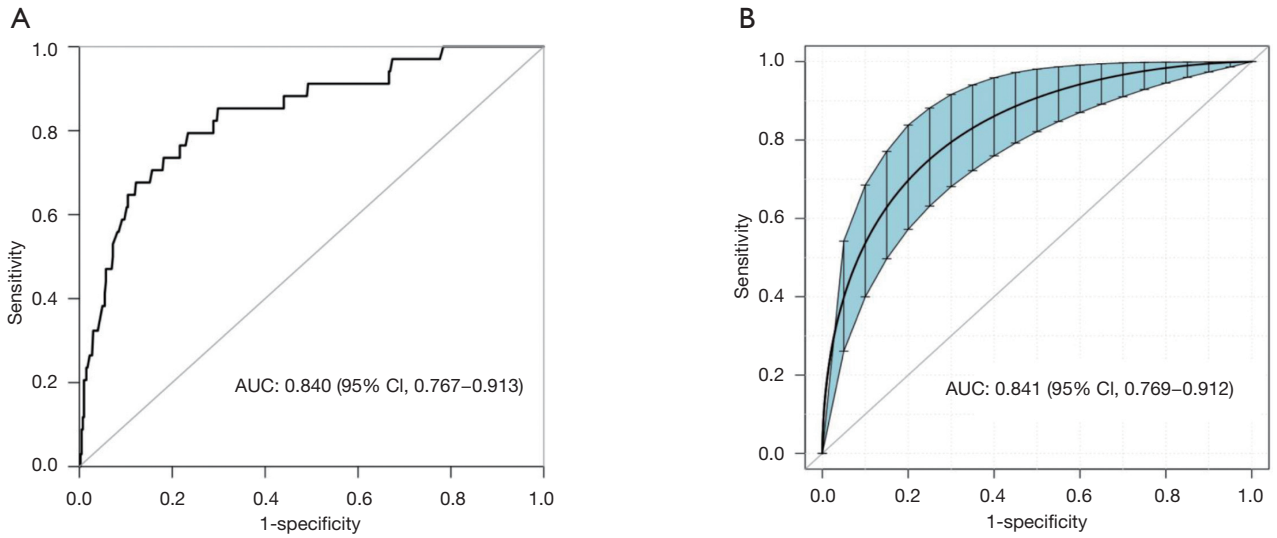

Figure 2 ROC of the predictive model and in the internal validation. AUC (A) shows the discrimination in the model, and AUC (B) of the internal validation. The dotted vertical lines represent 95% confidence interval. ROC, receiver operating characteristic; AUC, area under the curve.

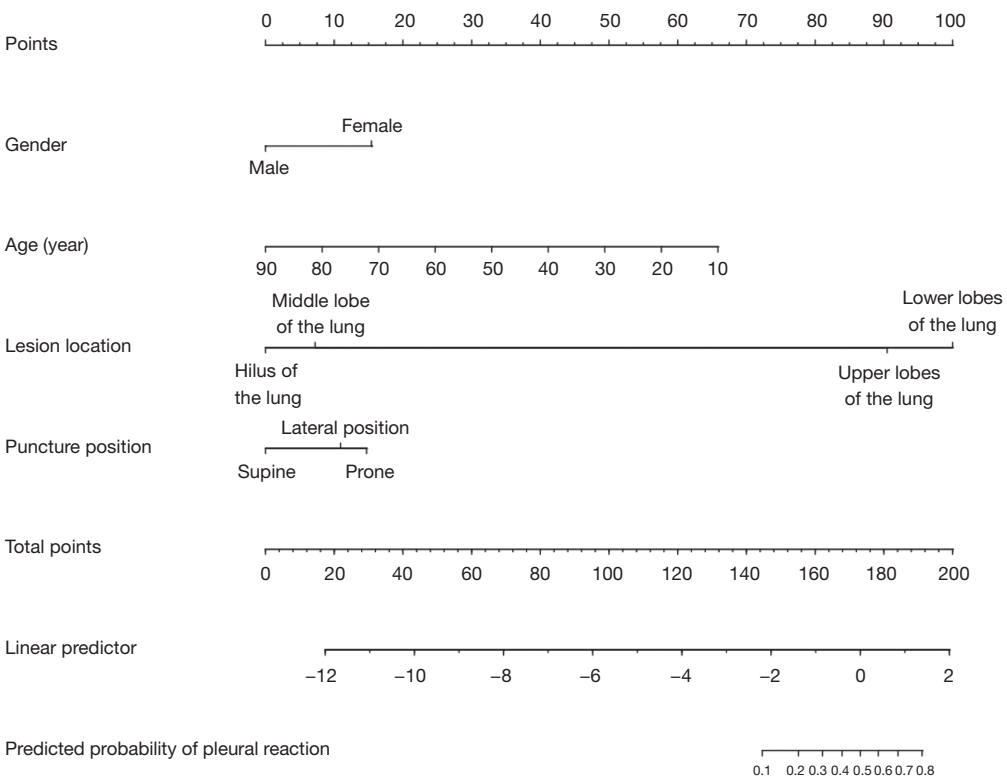

Figure 3 Nomogram for estimation of post-CT-TNB pleural reaction risk based on four predictors. Find score for each variable of an individual on the uppermost rule; add all scores together and find the sum of the scores on the "Total Points" rule, then the corresponding predicted probability of pleural reaction could be found on the lowest rule. CT-TNB, computed tomography-guided transthoracic needle biopsy.

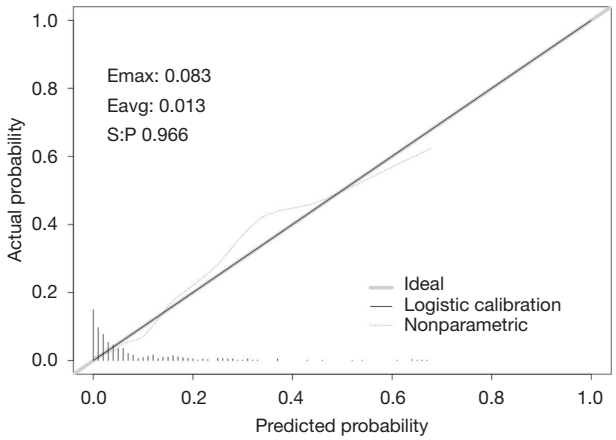

Figure 4 Calibration curve of the model. The calibration of the model in line with the agreement between predicted and observed outcomes of post-CT-TNB pleural reaction. The Y-axis represents the actual post-CT-TNB pleural reaction rate. The X-axis represents the predicted risk of post-CT-TNB pleural reaction. The shadowed line represents a perfect prediction by an ideal model. The dotted line represents the performance of the model, of which a closer fit to the shadow line represents a better prediction. CT-TNB, computed tomography-guided transthoracic needle biopsy.

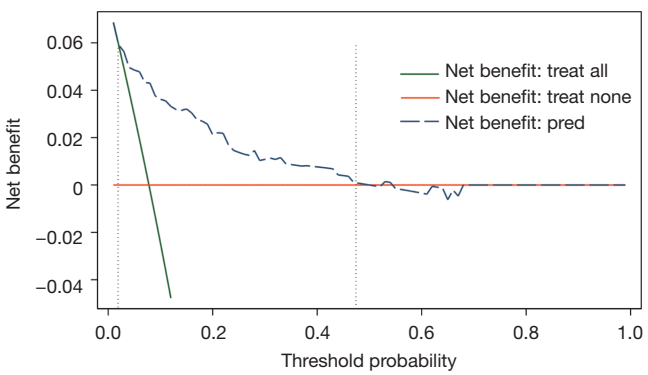

Figure 5 Decision curve analysis for the predictive model. The Y-axis measures the net benefit. The dashed line represents the model. The green line represents the assumption that all patients have post-CT-TNB pleural reaction, and the orange line represents the assumption that no patients have post-CT-TNB pleural reaction. The decision curve shows that when the threshold probability of an individual is between 2–48%, applying this model to predict post-CT-TNB pleural reaction adds more benefit than either the treat-all or the treat-none strategies.

to gain insight into clinical outcomes of a certain decision, and to weigh the net benefit (12,24,25). The decision curve based on this model was satisfactory and revealed that when the threshold probability of an individual was between 2–48%, applying our model to predict post-CT-TNB PR was more advantageous when compared to either treat-all or treat-none strategies.

There are several limitations to our study. First, it is a single-center and retrospective study therefore additional external verification is needed to confirm the usefulness of the proposed nomogram. Second, we did not further subdivide PR, and therefore this nomogram can only be used to predict the occurrence of post-CT-TNB PR, but not to distinguish PR severity.

Conclusions

Here, we established a nomogram for the prediction of post-CT-TNB PR based on 4 readily available clinical predictors, including gender, age, lesion location, and puncture position. The proposed predictive model showed sufficient discrimination ability and calibration, and demonstrated potential for clinical applications. Therefore, it may be of great value to facilitate the individualized prediction of post-CT-TNB PR to reduce the risk of PR-induced harm to patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics committee of Jinhua Hospital of Zhejiang University (No. 2018001008). The data were anonymous, and the requirement for informed consent was therefore waived.

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