ORIGINAL RESEARCH

A Nomogram for Predicting the Risk of Pulmonary Hypertension for Patients with Chronic Obstructive Pulmonary Disease

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Background: Pulmonary hypertension (PH) is a life-threatening complication of chronic obstructive pulmonary disease (COPD). Timely diagnosis of PH in COPD patients is vital to achieve proper treatment; however, there is no algorithm to identify those at high risk. We aimed to develop a predictive model for PH in patients with COPD that provides individualized risk estimates.

Methods: A total of 527 patients with COPD who were admitted to our hospital between May 2019 and December 2020 were retrospectively enrolled in this study. Using echocardiographic results as a standard, patients were stratified into a moderate- or high-PH probability group and a low-PH probability group. They were randomly grouped into either the training set (n = 368 patients) or validation set (n = 159 patients) in a ratio of 7:3. We utilized the least absolute shrinkage and selection operator (LASSO) regression model to select the feature variables. The characteristic variables selected in the LASSO regression were analyzed using multivariable logistic regression to construct the predictive model. The predictive model was displayed using a nomogram. We used the receiver operating characteristic curve, calibration curve, and clinical decision curve analysis (DCA) to evaluate model performance, and internal validation was assessed.

Results: The predictive factors included in the prediction model were Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, emphysema, $PaCO_2$, NT-pro-BNP, red blood cell (RBC) distribution width-standard deviation (RDW-SD), and neutrophil/lymphocyte ratio (NLR). The predictive model yielded an area under the curve (AUC) of 0.770 (95% confidence interval [CI], 0.719–0.820); in the internal validation, the AUC was 0.741 (95% CI, 0.659–0.823). The predictive model was well calibrated, and the DCA showed that the proposed nomogram had strong clinical applicability.

Conclusion: This study showed that a simple nomogram could be used to calculate the risk of PH in patients with COPD which can be useful for the individualized clinical management of COPD patients who may be occur with PH. Further studies need to be confirmed by larger sample sizes and validated in the stable COPD population.

Keywords: chronic obstructive pulmonary disease, pulmonary hypertension, nomogram, LASSO regression

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease and currently the fourth leading cause of death worldwide; it is responsible for substantial morbidity and mortality.[1] The major pathophysiology of COPD is irreversible obstruction of the airway with progressive lung function decline.[2] Pulmonary hypertension (PH) is a frequent complication of COPD with insidious onset and non-specific symptoms. It is also associated with worse survival and increased risk of hospitalisation because of COPD exacerbation,[3] which belongs to the third group of PH associated with pulmonary disease and hypoxemia.[4] It has been reported that the prevalence of PH in patients suffering from COPD range between 20% and 91% based on right heart catheterism (RHC) or echocardiography, depending on the diagnostic criteria used to define it, COPD severity grades, and the methods by which the pulmonary pressure is measured.[5] PH

associated with COPD tends to be mostly mild to moderate in severity, however, a relatively small subset of patients who experience severe PH as a "pulmonary vascular phenotype" is increasingly noted.[6] Oswald-Mammosser et al found that the 5-year survival rate was only 36% in COPD patients with a mean pulmonary arterial pressure (mPAP) > 25 mmHg, compared with 62% in those with an mPAP < 25 mmHg.[7] Moreover, the clinical therapeutic strategies of COPD combined with PH differ from COPD patients. Given the prevalence of PH in COPD and its effect on outcomes there is value in screening for its presence. Early detection and timely treatment are particularly important in the disease progression in our clinical work.

Right heart catheterization (RHC) is the gold standard for the diagnosis and classification of PH. However, it is expensive, invasive, and associated with several complications,[8] Echocardiography is the most widely used and recommended non-invasive method for assessing PH.[9] Compared to RHC, echocardiography has been shown to be a reliable method in several studies.[10,11] In the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension, echocardiography is the preferred non-invasive test for PH screening and follow-up; the guidelines also recommend that it should be used to screen for PH in patients whose clinical data suggest an increased risk of PH.[12]

The current studies that introduced prognostic equations and scores for risk prediction have mostly focused on pulmonary arterial hypertension;[13] Thus far, few studies have attempted to derive a risk prediction score for PH in people with COPD, Gartman et al[14] have developed an easy-to-use scoring system that uses readily available parameters to define which COPD patients are at high risk for having elevated pulmonary artery pressure. We aimed to construct a non-invasive model that may be used to predict the individual probability of PH in patients with COPD, which, to the best of our knowledge, has not been reported in previous studies. Among the various models for predicting disease risk, nomograms are widely used by clinicians as they are more intuitive and easier to use.[15] The prediction results are more readable and have promising clinical applicability.

In this study, LASSO regression and multivariate logistic regression were used to determine the risk factors of PH in COPD patients (COPD-PH), define the degree of risk, construct a line graph prediction model, and visualize it with a nomogram. This model identifies potential predictors of COPD-PH, which can provide a new basis for early screening of high-risk populations, as well as provide a reference for the intervention of COPD progression and disease management.

Materials and Methods
Study Population
In this retrospective cohort study, subjects were consecutive patients diagnosed with acute exacerbation COPD (AECOPD) and admitted to Hengshui People's Hospital of Hebei Province in China from May 2019 to December 2020. Demographic data (such as sex and age), laboratory indicators, lung function indicators, chest computed tomography (CT), and echocardiography findings were collected from the patients' medical records using a self-designed Microsoft Excel spreadsheet. Data from the first hospitalization or clinical visit were used for patients with multiple hospitalizations or multiple visits.This study was conducted in compliance with the Declaration of Helsinki.

Inclusion criteria were based on any of the following: all patients diagnosed with COPD exacerbations were considered potential patients, and the diagnosis of COPD according to the criteria of the 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Also, the patients with acute exacerbations were due to respiratory tract infection. The probability of PH was diagnosed according to the 2015 ESC/ERS guidelines.[12] The echocardiographic probability of pulmonary hypertension in patients with a suspicion of pulmonary hypertension was shown in Table S1. Patients were first stratified into low, intermediate, and high PH risk groups based on the echocardiographic assessment at the tricuspid regurgitation peak velocity (TRV) in conjunction with the presence of echocardiographic signs from at least two different categories: (1) pulmonary artery (PA) signs, such as PA diameter or acceleration time; (2) inferior vena cava (IVC) and right atrium (RA) signs, such as diameter and the inspiratory collapse of IVC and RA end-systolic area; and (3) ventricular signs. Patients were then allocated into two groups based on the probability of PH (intermediate or high-PH probability group and low-PH probability group). PH was diagnosed when echocardiography assessed PH with a moderate to high probability.

The exclusion criteria were as follows: incomplete clinical data, no results of cardiac color ultrasound examination and lung function examination, presence of diseases including class III or IV congestive heart failure (CHF), HIV, congenitalheart disease, cirrhosis, untreated obstructive sleep apnea, and systemic rheumatologic disease.

Data Collection

The following data were obtained from the electronic medical record system: demographics (age and sex), clinical data and laboratory tests, echocardiography data, lung function, and chest CT. The presence of emphysema was based on radiological reports or the team's review of imaging tests available to the patients. We collected the following information from the enrolled patients: age, sex, body mass index (BMI), smoking index, disease duration, presence of emphysema, and lung function grade. BMI is defined as a person's weight in kg divided by the square of the height in meters (kg/m^2). The smoking index was defined as the average root number per day multiplied by the number of years smoking. Several laboratory variables were considered. We divided NT-pro-BNP into two groups according to the 2015 ESC/ERS Guidelines with a cut-off value of 300 pg/mL; the proposed cut-off values are based on expert opinion.[12] All clinical and laboratory variables were recorded within 24 hours after admission.

Statistical Analysis

Statistical analyses were performed using R version 4.0.3 and IBM SPSS version 26.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range). Categorical variables are expressed as absolute values and percentages. The means of continuous variables were compared using independent group *t*-tests for normally distributed data and the Mann–Whitney test for non-normally distributed data. The χ^2 or Fisher's exact test was used to compare the proportions. A total of 527 patients were arbitrarily categorised into training and validation sets comprising 368 and 159 patients, respectively, according to a ratio of 7:3. The predictive nomogram was developed using the training set, and the performance was evaluated using the validation set.

We used the least absolute shrinkage and selection operator (LASSO) method to identify the optimal variables with non-zero coefficients as risk factors.[16] Thereafter, based on the results of LASSO regression analysis, a backward stepwise selection with the Akaike information criterion (AIC) was used to identify variables for the multivariate logistic regression models. Multivariable logistic regression analysis was used to establish a prediction model, and a nomogram was generated. The area under the curve (AUC) value of the model was calculated to predict the degree of discrimination of the prediction model, with higher AUCs indicating better discrimination and lower AIC values indicating superior model fitting. The calibration curve was drawn to evaluate the calibration of the nomogram by reviewing the predicted versus actual probabilities. In addition, a decision curve analysis (DCA) was conducted to evaluate the clinical usefulness of the nomogram.[17] All statistical analyses were two-tailed, and statistical significance was set at P < 0.05.

Results

Basic Characteristics of Patients

A total of 527 patients with COPD, including 170 women and 357 men who had been hospitalised, were retrospectively reviewed. Using echocardiographic results as a standard, patients were stratified into a moderate- or high-PH probability group and a low-PH probability group. There were 181 cases with a high-PH probability and 346 cases with a low-PH probability. There were no significant differences in age, sex, and course of disease between the two groups (P > 0.05), which could be compared. After random sampling in a ratio of 7:3, 368 and 159 COPD patients were included in the training and validation sets, respectively. There were no significant differences in the clinical and laboratory parameters between the training and validation sets (Table S2). The demographic and clinical characteristics of the patients are shown in Table 1. All patients completed the related examination, and the data of the patients in the two sets are presented in Table 2.

Table 1 Baseline Characteristics and Clinical Data of the Enrolled Subjects

Characteristics	Low PH Probability n=346	Intermediate or High-PH Probability, n = 181	t/z/χ^2	p value
Age (years)	73.00 [67.25, 78.00]	73.00 [68.00, 81.00]	−1.549	0.121

Gender (n, %)
  Male
  Female
	
	241 (69.7)
	105 (30.3)
		
		116 (64.1)
		65 (35.9)
			1.684	0.194

Duration of the disease (years)
  ≤10
  >10
	
	181 (52.3)
	165 (47.7)
		
		89 (49.2)
		92 (50.8)
			0.469	0.493

Hospital stay (day)	9 (7, 13)	10 (8, 14)	−2.852	0.004
BMI (kg/m^2) <18.5 ≥18.5	 59 (17.1) 287 (82.9)	 48 (26.5) 133 (73.5)	6.582	0.01

Smoking index (year root)
  ≤400
  >400
	
	248 (71.7)
	98 (28.3)
		
		123 (68)
		58 (32)
			0.789	0.374

GOLD Stage
  I
  II
  III
  IV
	
	97 (28.0)
	84 (24.3)
	59 (17.1)
	106 (30.6)
		
		41 (22.7)
		25 (13.8)
		25 (13.8)
		90 (49.7)
			20.032	<0.001

Emphysema (n,%)	234 (67.6)	138 (76.2)	4.246	0.039

Echocardiography index
  PAD (mm)
  TRV (m/s)
  LVD (mm)
  RVD (mm)
  LAD (mm)
	
	21 (20, 22)
	2.5 (2.3, 2.6)
	46 (43, 49)
	22 (20, 23)
	32 (29, 36)
		
		22 (20, 24)
		3.2 (3, 3.6)
		44 (40, 48)
		22 (20, 24)
		32 (28.5, 36.5)
			
			−5.320
			−16.262
			−4.778
			−8.497
			−0.185
				
				<0.001
				<0.001
				0.006
				<0.001
				0.268

Abbreviations: BMI, body mass index; PAD, pulmonary artery diameter; TRV, tricuspid regurgitation velocity; LVD, left ventricle diameter; RVD, right ventricle diameter; LAD, Left atrial diameter; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Selection of Independent Predictive Factors

Based on non-zero coefficients in the LASSO regression analysis (Figure 1), 27 variables were reduced to the nine most potential predictors, including emphysema, GOLD stage, absolute eosinophil count, red blood cell (RBC) distribution width-standard deviation (RDW-SD), platelet count (PLT), PaCO$_2$, N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), neutrophil/lymphocyte ratio (NLR), and albumin (ALB).

We further conducted a multivariable logistic regression analysis and generated a prediction model to obtain a deep insight into the relationship between PH and these risk factors. The results of the multiple logistic regression analyses are presented in Table 3. The nine variables screened by LASSO regression were incorporated into the multivariate logistic regression model to establish the prediction model, and the results showed that the six variables were statistically significant in predicting the risk of PH secondary to COPD. The results were as follows: GOLD stage (odds ratio [OR], 1.502; 95% confidence interval [CI], 0.895–2.521; P = 0.124), emphysema (OR, 2.012; 95% CI, 1.156–3.503; P=0.013), RDW-SD (OR, 1.054; 95% CI, 1.008–1.103; P=0.02), PaCO2 (OR, 2.167; 95% CI, 1.256–3.738; P=0.005), NT-pro-BNP

Table 2 Characteristics in the Training Set and the Validation Set

Variables	Training Set (n = 368)		P value	Validation Set (n = 159)		P value
	Low PH Probability n=241	Intermediate or High-PH Probability n=127		Low PH Probability n=105	Intermediate or High-PH Probability n=54	
WBCcount, ×10^9/L	7.58 (6.08, 10.20)	7.72 (6.15, 9.51)	0.834	7.52 (6.03, 11.19)	7.92 (6.09, 10.82)	0.857
Hemoglobin, g/L	133.60±19.60	132.31±23.27	0.024	133.00 (118.00, 144.50)	132.00 (121.25, 144.25)	0.907
RDW-SD (fl)	43.90 (41.85, 47.15)	46.70 (43.80, 51.00)	<0.001	45.00 (41.75, 47.75)	46.50 (43.40, 50.58)	0.017
MPV (fl)	9.90 (9.30, 10.50)	10.10 (9.60, 10.60)	0.076	10.00 (9.30, 10.70)	10.25 (9.50, 10.70)	0.343
PLT×10^9/L	232.00 (182.00, 284.50)	208.00 (167.00, 253.00)	0.003	234.00 (165.50, 291.50)	207.00 (159.75, 239.00)	0.110
NLR	5.40 (2.92, 10.06)	7.23 (4.68, 13.49)	<0.001	5.69 (2.99, 10.49)	6.63 (4.26, 14.95)	0.076
PaCO2 (n,%) <50mmHg ≥50mmHg	128 (53.1%) 113 (46.9%)	34 (26.8%) 93 (73.2%)	<0.001	48 (45.7%) 57 (54.3%)	19 (35.2%) 35 (64.8%)	0.203
NTproBNP ≤300pg/mL >300pg/mL	127 (52.7%) 114 (47.3%)	23 (18.1%) 104 (81.9%)	<0.001	52 (49.5%) 53 (50.5%)	8 (14.8%) 46 (85.2%)	<0.001
ALB (g/L)	38.51±5.34	36.41±5.15	0.466	38.77±4.84	35.55±4.51	0.790
PCT (ng/mL)	0.19 (0.12, 0.29)	0.21 (0.13, 0.41)	0.237	0.18 (0.12, 0.34)	0.20 (0.13, 0.54)	0.383
CRP (mg/L)	9.20 (1.00, 34.30)	19.40 (1.00, 49.00)	0.061	8.40 (1.00, 44.00)	13.05 (1.00, 56.43)	0.267
IL-8 (pg/mL)	8.50 (2.80, 51.05)	13.90 (3.00, 74.10)	0.226	8.00 (2.40, 55.50)	7.55 (3.03, 62.20)	0.692
IL-6 (pg/mL)	13.80 (6.60, 38.70)	14.50 (8.20, 45.50)	0.209	13.80 (5.50, 45.55)	20.60 (6.70, 42.35)	0.342
TNFα (pg/mL)	1.70 (0.90, 4.40)	1.70 (0.90, 4.40)	0.716	1.60 (0.90, 4.40)	1.50 (0.78, 4.40)	0.834
D. Dimer (ugDDU/mL)	0.84 (0.53, 1.32)	1.04 (0.66, 2.22)	0.002	0.86 (0.57, 1.77)	1.25 (0.71, 2.38)	0.009
UREA (mmol/L)	5.54 (4.40, 7.15)	5.86 (4.33, 7.61)	0.233	5.26 (4.19, 6.57)	5.59 (4.22, 7.80)	0.598
CREA (umol/L)	64.10 (51.10, 79.45)	63.20 (48.30, 79.80)	0.401	61.50 (50.2, 77.75)	59.10 (44.43, 74.40)	0.138
UAC (umol/L)	279.00 (219.00, 361.50)	292.00 (193.00, 371.00)	0.676	274.00 (220.50, 316.00)	267.50 (215.75, 353.25)	0.711
CK (U/L)	65.00 (44.00, 112.00)	62.00 (41.00, 111.00)	0.637	66.00 (45.00, 94.00)	58.50 (40.75, 163.50)	0.874
LDH (U/L)	174.00 (148.00, 215.00)	184.00 (150.00, 246.00)	0.108	170.00 (141.00, 192.50)	184.00 (158.00, 221.25)	0.019

Abbreviations: RDW-SD, red blood cell distribution width-standard deviation; NLR, neutrophil-to lymphocyte ratio; ALB, albumin; MPV, mean platelet volume; PLT, platelet.
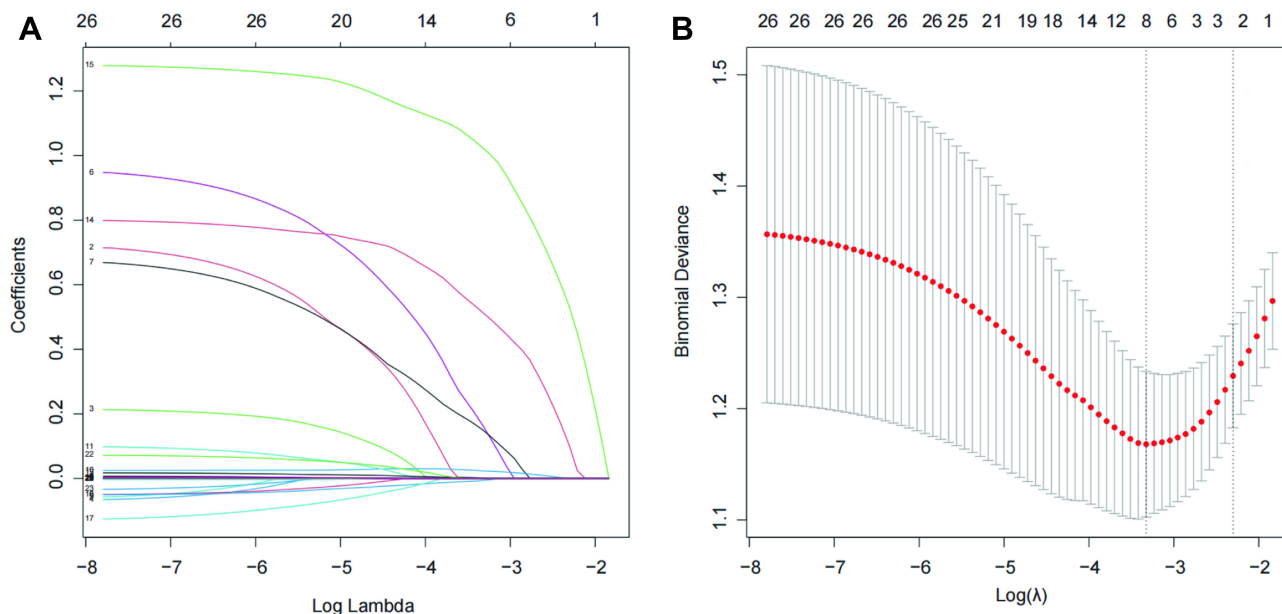
Figure 1 Characteristic variables selection using the least absolute shrinkage and selection operator (LASSO) logistic regression model. (**A**). LASSO coefficient profiles of 27 features. A coefficient profile plot was produced against the log (lambda) sequence. A vertical line was drawn at the value. (**B**) 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.

(OR, 4.056; 95% CI, 2.310–7.121; P<0.001), and NLR (OR, 1.014; 95% CI, 0.997–1.031; P=0.114). The AIC value was 408.7. Although GOLD stage and NLR had no significant correlation with PH risk in the multivariate analysis, the prediction model combined with the above six variables had a good fit according to the AIC criterion, and the nomogram did not focus on whether each factor was statistically significant. These six indices were incorporated into the nomogram.

Building a Prediction Nomogram Model

Based on the six variables screened, we constructed a nomogram to predict the probability of PH in patients with COPD. The total number of points was calculated from the sum of the points assigned to each variable in the line graph. The higher the score, the higher the risk that a patient with COPD will develop PH (Figure 2).

Table 3 Parameters Used to Establish the COPD with Intermediate or High PH Probability Prediction Model in the Training Set

Parameter	OR	95% CI of Exp	P
GOLD stage	1.502	0.895–2.521	0.124
Emphysema	2.012	1.156–3.503	0.013
RDW-SD	1.054	1.008–1.103	0.020
PaCO2	2.167	1.256–3.738	0.005
NT-proBNP	4.056	2.310–7.121	<0.001
NLR	1.014	0.997–1.031	0.114

Abbreviations: OR, odds ratio; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; RDW-SD, red blood cell distribution width-standard deviation; NLR, neutrophil-to lymphocyte ratio.
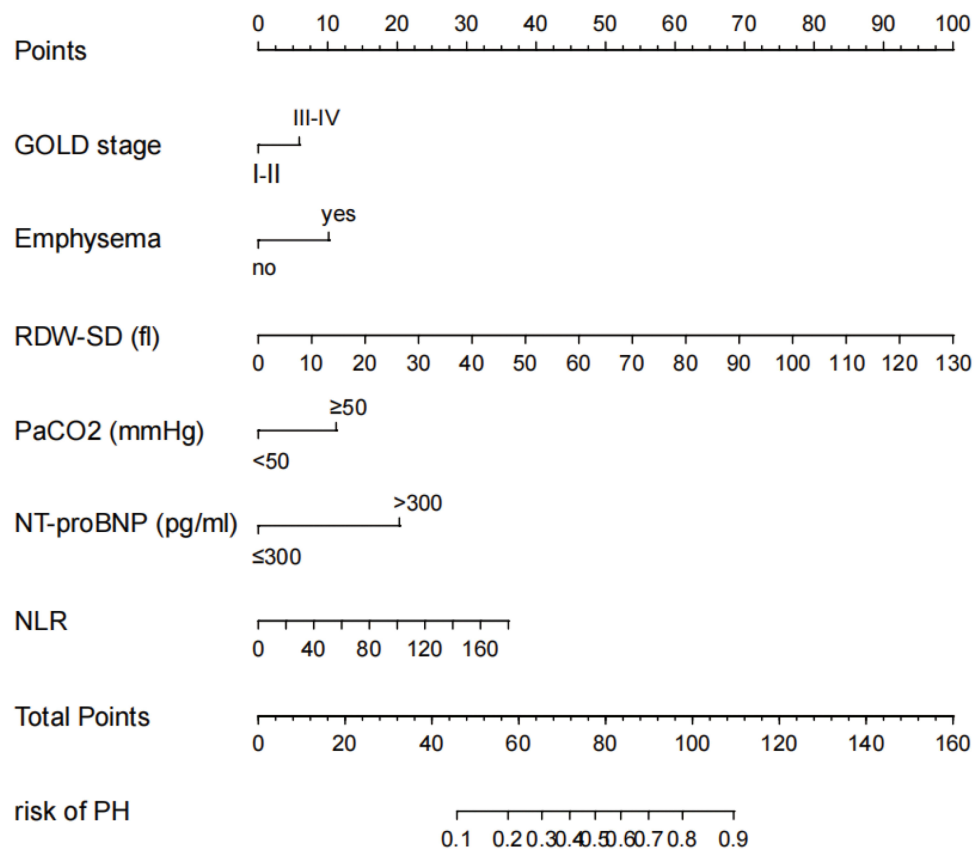
Figure 2 Nomogram to predict the risk of COPD-PH. The nomogram integrates the predictors selected by the least absolute shrinkage and selection operator (LASSO), including GOLD stage, emphysema, RDW-SD, PaCO$_2$, NT-pro-BNP, NLR.

Performance of the Predictive Model

The identification of the model is measured by the AUC, and the closer the AUC is to 1, the better the identification. In the predictive model, the pooled area under the receiver operating characteristic (ROC) curve of the nomogram was 0.77 in the training set and 0.741 in the validation set (Figure 3), which indicated moderately good performance.

To evaluate the calibration of the model, a calibration curve was drawn. The calibration curve describes the relationship between the PH risk predicted by the model and the PH risk observed in the training cohort. The calibration curve of the nomogram to predict the PH risk in COPD patients showed good agreement in both the training and validation datasets (Figure 4A and B). To summarize the results from the above validation, the nomogram of the model had a good prediction ability.

DCA was used to evaluate the clinical efficacy of the predictive model. The DCA curves were drawn using the predicted probability of PH for the model and validation groups, and the actual occurrence of PH probability. The DCA curves of the two groups are shown in Figure 5A and B. The DCA showed that when the threshold probability of an individual was between 5% and 75%, and in the validation set, it was between 14% and 55%, the application of this model to predict PH proved to be the greatest clinical benefit.

Discussion

The progression of COPD-PH is associated with an increased risk of exacerbations and increased mortality.[18] It is important to identify those COPD patients with PH, Kovacs et al[19] investigate the clinical variables and noninvasive diagnostic tools predict the presence of severe PH in COPD. Moreover, the predictors of death in patients with PH in COPD and risk stratification model associated with severe PH due to ILD have been documented in several studies,[20–22] these explorations are crucial in the selection
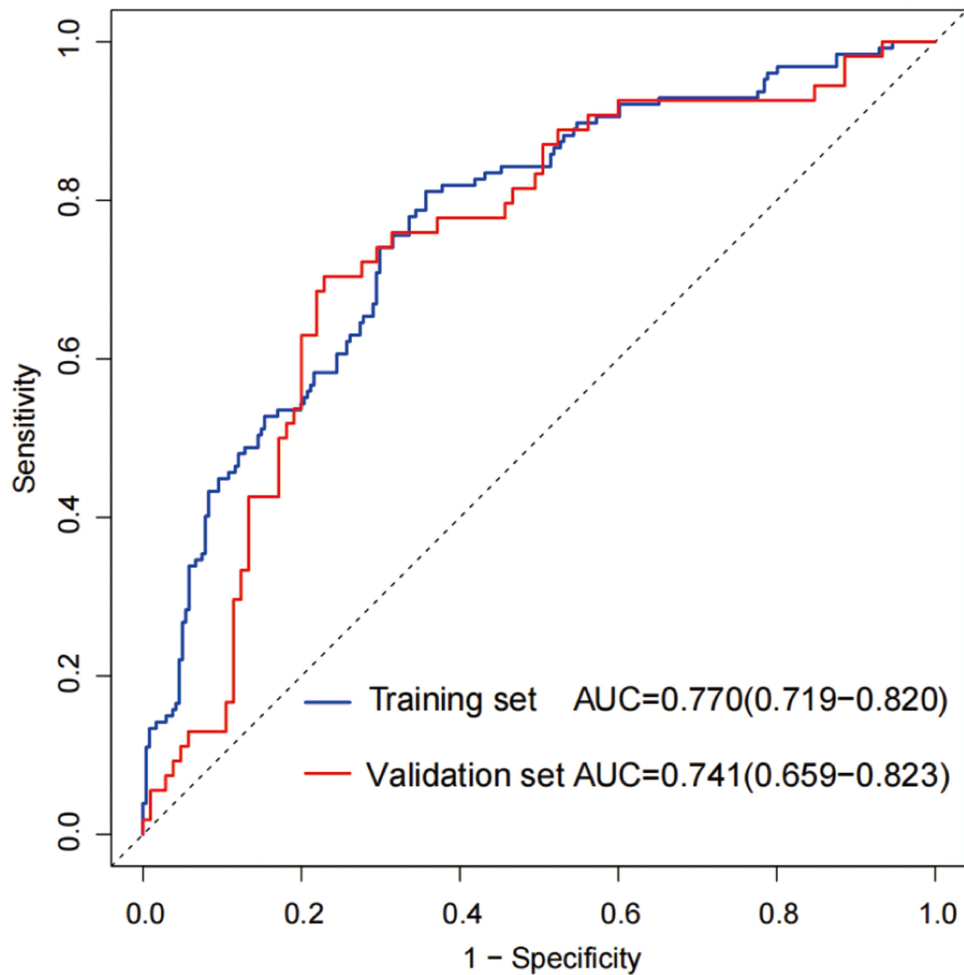
Figure 3 Receiver operating characteristic (ROC) curves of the training and validation sets. Blue AUC curve shows the discrimination of the model. Red AUC curve of the internal validation. The corresponding 95% confidence interval estimate is highlighted in black text.
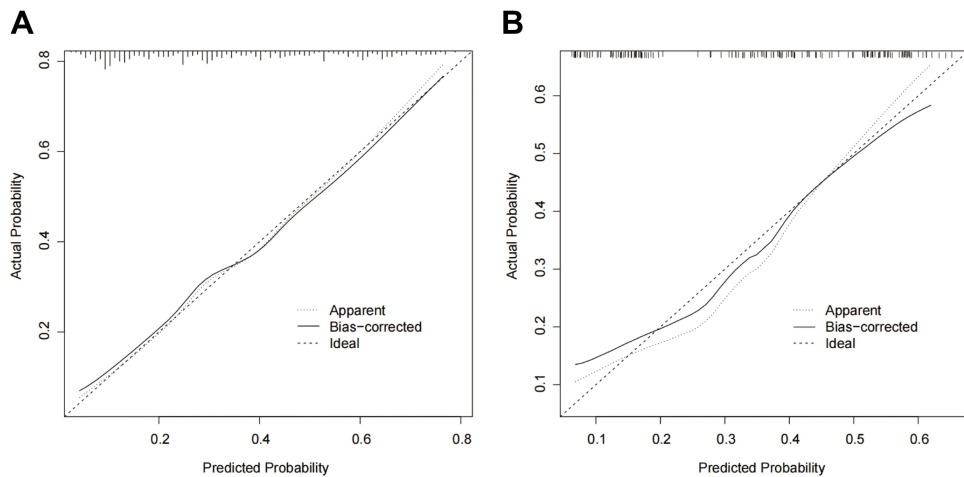**Abbreviation**: AUC, area under the curve.

Figure 4 Calibration curve for the risk prediction model of COPD-PH. (**A**) Calibration curves in the training set. (**B**) Calibration curves in the validation set. The x-axis depicts predicted PH risk; the y-axis, diagnosed PH. A slope of 45° indicates the best calibration, while a prediction line above or below 45° indicates an underestimate or overestimate of the actual patient risk.
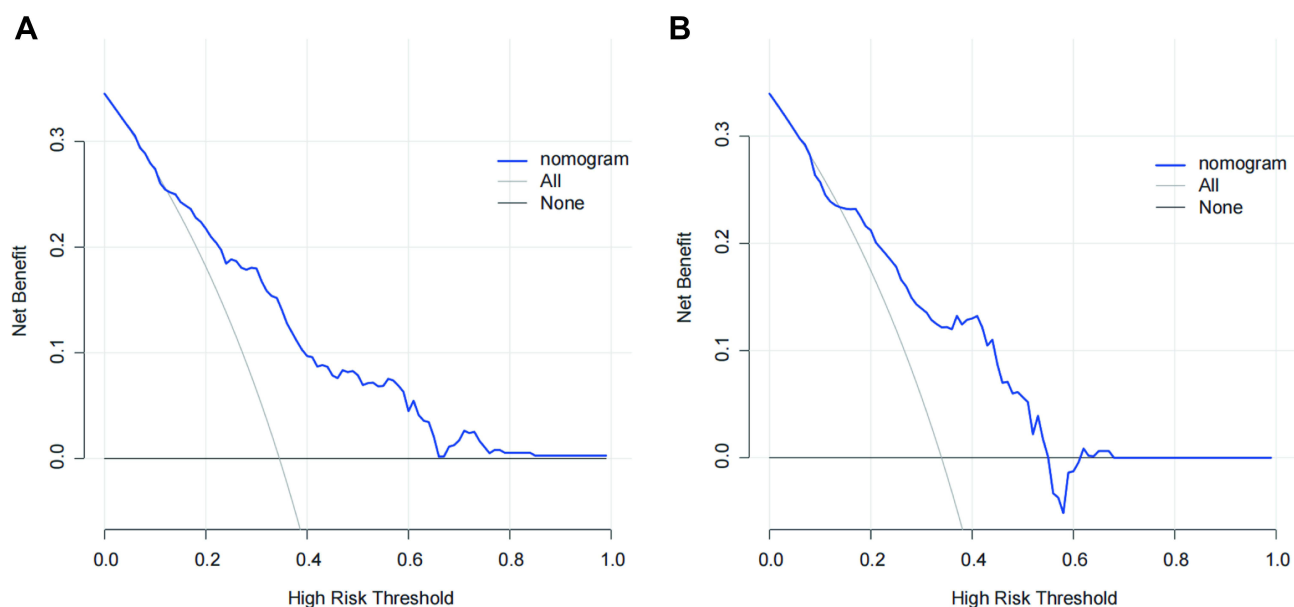
Figure 5 Decision curve analysis for the nomogram in the training cohort (**A**) and in the validation cohort (**B**). The blue solid line represents the nomogram.

of treatment options for PH and in the evaluation of prognosis. Improved and easily accessible identification of individuals at risk of COPD-PH is needed to select patients for RHC more accurately. We developed a validated clinical prediction model to predict the risk of PH in a retrospective cohort of patients with COPD. The analysis of risk factors has guiding significance for early recognition, clinical diagnosis and appropriate treatment. The results of this study suggest that emphysema, PCO2, NT-pro-BNP, RDW-SD, NLR, and GOLD stage are independent risk factors for PH in COPD patients. The selection of variables is the most important factor in developing a model. We carefully selected a list of candidate predictors based on the clinical and demographic characteristics of patients. We adopted the LASSO algorithm, which shrinks the coefficients of complex clinical variables and excludes relatively insignificant ones. Finally, a set of valid and concise variables was selected and synthetized. All six selected predictors were extracted from our data, and the model had good discriminability, calibration ability, and clinical application value.

In this study, NT-pro-BNP levels were found to be significantly higher in the COPD-PH group than in the COPD group, and regression analysis indicated that NT-pro-BNP was an independent risk factor for COPD-PH. The ESC/ERS guidelines recommend that BNP and NT-pro-BNP remain the only biomarkers that are widely used in the routine practice of PH centres as well as in clinical trials.[12] The results of this study showed that PaCO2 in COPD-PH patients was higher than that in patients without PH. Therefore, PaCO2 provides a convenient monitoring index for the early identification of PH in patients with COPD. PO2 was not selected because some patients took oxygen for a long time after admission, which interfered with the oxygen partial pressure level in blood gas analysis.

The necessity of aggressive screening for COPD-PH patients with emphysema should be emphasized. The presence of emphysema was closely related to PH, as assessed by echocardiography.[23] Severe PH can be seen in combined emphysema/fibrosis syndrome, where the prevalence of PH is high.[24] The mechanisms between PH and emphysema induced by cigarette smoking have been widely explored. In a rat model, apoptosis of alveolar cells and emphysema can be induced by blockading the vascular endothelial growth factor (VEGF) receptors[25] Moreover, the presence of emphysema causes destruction of the lung parenchyma, which further leads to a decline in lung function. It has been shown that the development of PH is associated with decreased pulmonary function. In a retrospective study, it was found that in patients with stable COPD, the incidence of PH was higher in patients with poorer pulmonary function, the degree of decline in pulmonary function was correlated with pulmonary artery pressure, and regression analysis showed that the degree of airflow limitation (FEV1%pred decline) was a risk factor for COPD-PH.[26] A more pronounced decline in FEV1%pred was also observed in COPD-PH patients in a three-year prospective study.[23] The present study is consistent with these findings, where FEV1%pred was significantly lower in COPD-PH patients than in the COPD group, and regression analysis showed that decreased lung function was an independent risk factor for COPD-PH.

Increasing evidence suggests that inflammation plays a potential and decisive role in the progression of PH. The pathophysiology of pulmonary vascular remodelling in PH is not only the pathological damage of endothelial cell function but also the excessive perivascular infiltration of inflammatory cells[27] In our study, NLR was significantly higher in patients with PH than in those with PH. NLR, which is based on the neutrophil and lymphocyte counts, has been increasingly investigated for its use as a marker of systemic inflammation and infection, especially because it is a relatively inexpensive and widely available evaluation factor. Zuo et al reported that NLR could be used for the early prediction of patients with PH[28] This is the first study to demonstrate a significant increase in NLR in patients with PH compared to healthy volunteers. The authors found that the AUC of NLR for predicting the presence of PH was 0.767, the threshold was ≥1.65, sensitivity was 72%, and specificity was 69%, suggesting that NLR is a promising inflammatory marker for the presence of PH.[29] In our study, COPD patients with PH had higher RDW levels than those without PH. RDW may be a potential biomarker for the diagnosis of PH in COPD patients. However, the mechanism underlying the increased RDW levels in PH secondary to COPD is not well known.[30] Inflammation, dysfunctional erythropoiesis, iron deficiency, and oxidative stress are some of the possible mechanisms underlying elevated RDW, which is associated with poor outcomes in various cardiovascular disorders, pulmonary emboli, and PH.[29] RDW is related to several inflammatory markers, such as C-reactive protein (CRP) and ESR.[31] Ineffective erythropoiesis due to chronic inflammation may contribute to the increased RDW level in COPD patients with PH. Montagnana et al believed that the main factors contributing to the increase of RDW in patients with cardiopulmonary and vascular diseases were the involvement of inflammation and oxidative stress.[32] Therefore, it can be considered that a potential relationship between RDW and PH is inflammation, which is involved in the development of PH, and the RDW, as an indicator of the underlying inflammatory state of the body, can reflect the severity of PH.

If a patient's disease state can be predicted in advance, clinical decisions may be made differently in many cases.[33] We designed a visual nomogram for clinicians to provide a simple and practical reference. Our model integrates a set of parameters including clinical features, pulmonary function testing, chest imaging into a composite score that would assist the clinician to establish a pre-test probability of pulmonary hypertension before undertaking the invasive confirmation of PH with right heart catheterization. Our model can be applied in the following situations: first, this model can predict the patients at high PH risk in COPD by using common clinical variables and easily accessible laboratory tests which can help adjust and select treatment options. Individualized estimates of risk could help clinicians identify patients with the highest risk of PH and we recommend enhanced screening strategies for these patients. This model also plays an important role in follow-up and evaluation of patients with recurrent acute exacerbations of COPD, Second, it can be used as a decision support system for clinicians when the clinical features and imaging presentation of the patient are atypical.[34] We assert that these discoveries will contribute to a better comprehending of the relationship between PH and COPD, which in turn will provide new clinical research directions and more mechanisms for future studies. These benefits would be valuable and have a far-reaching influence on the prognosis of patients with COPD-PH.

This study has several considerable limitations. First, we did not diagnose PH with RHC, which is the gold standard for the diagnosis of PH. Second, the main population was patients with acute exacerbation of COPD, and there was a lack of studies on patients with stable COPD. The mechanisms driving acute PH during acute exacerbations may be different to mechanisms underlying chronic PH and therefore the predictors may be different in the prediction model. Additionally, our study was retrospective, and further prospective studies are needed to explore the future risk of PH in patients with COPD. Third, our study was conducted at a single center with a relatively small sample size, and multicenter prospective studies should be conducted to externally validate the results.

Conclusion

This study showed that a simple nomogram could be used to calculate the risk of PH in patients with COPD which can be useful for the individualized clinical management of COPD patients who may be occur with PH. Further studies need to be confirmed by larger sample sizes and validated in the stable COPD population.

Abbreviations

COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; RHC, right heart catheterization; ESC, European Society of Cardiology; ESR, European Respiratory Society; LASSO, least absolute shrinkage and selection operator; DCA, clinical decision curve analysis; GOLD, Chronic Obstructive Lung Disease; AUC, area under the curve;

COPD-PH, PH in COPD patients; CT, computed tomography; TRV, tricuspid regurgitation peak velocity; BMI, body mass index; SD, standard deviation; AIC, Akaike information criterion; RBC, red blood cell; RDW-SD, distribution width-standard deviation; PLT, platelet count; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NLR, neutrophil/lymphocyte ratio; ALB, albumin; ROC, receiver operating characteristic; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; RSVP, right ventricular systolic pressure; MPV, mean platelet volume.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Ethics Board of the Hengshui people's hospital and the Second Hospital of Hebei Medical University (Code: 2021-R236). Due to the nature of this retrospective study that used anonymized data, the requirements of obtaining informed consent from the patients were waived by the Institutional Ethics Board.

Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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