



Construction and validation of risk prediction model for deep vein thrombosis in acute exacerbations of chronic obstructive pulmonary disease based on serum angiotensin 2 levels

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Background: This study aims to establish a predictive risk model for deep vein thrombosis (DVT) in patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD) based on serum angiotensin 2 (Ang-2) levels.

Methods: The research sample consisted of 650 patients with AECOPD admitted to the First Affiliated Hospital of Chengdu Medical College from January 2019 to January 2021, who were subsequently divided into a modeling group and a verification group. A univariate analysis was performed on the identified risk factors for DVT in AECOPD, and the significant factors were then incorporated into a multivariate logistic regression model to screen for the independent predictors of DVT. A nomogram was constructed, and a receiver operating characteristic curve (ROC), Hosmer-Lemeshow test, decision curve, and clinical impact curve in the modeling and validation cohort were used to analyze the discrimination power, calibration, and clinical validity of the predictive risk nomogram model of AECOPD with comorbid DVT.

Results: Univariate and multivariate logistic regression analyses showed that lower limb edema, BMI, diabetes, respiratory failure, D-dimer, and serum Ang-2 were risk factors for DVT in AECOPD. A nomogram model for predicting AECOPD with comorbid DVT was successfully established. The AUC values for the modeling group and the verification group were 0.844 (95% CI: 0.808–0.932) and 0.755 (95% CI: 0.679–0.861), respectively. According to the Hosmer-Lemeshow test, the P values of the nomogram in the modeling group and the verification group were 0.124 and 0.086, respectively. The decision curve and clinical impact curve suggested that most patients can benefit from this prediction model, and the predicted probability of the model was essentially the same as the actual clinical probability of DVT.

Conclusions: The predictive risk nomogram model of AECOPD with comorbid DVT based on serum Ang-2 levels has good discrimination power, calibration, and clinical influence. The model is a good fit and has a high predictive value, which helps clinicians identify AECOPD patients at high risk of DTV and formulate corresponding prevention and treatment measures.

Keywords: Acute exacerbation chronic obstructive pulmonary disease (AECOPD); deep venous thrombosis; angiotensin 2 (Ang-2); risk factors; nomogram

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease of the respiratory system mainly characterized by a continuous airflow limitation due to airways and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. COPD is associated with recurrent episodes, high morbidity, disability, and mortality (1). Most patients with COPD have persistent systemic inflammation, chronic hypoxia, and impaired pulmonary function over a long time. Therefore, COPD patients show decreased exercise tolerance and lower limb movement, often accompanied by lower limb vascular endothelial injury, thickened blood, and systemic congestion (2,3), which are all risk factors for thrombosis. An AECOPD is defined by a sustained worsening of symptoms, beyond normal day-to-day variation, which requires medical treatment (4). It is reported that the risk of DVT in AECOPD is 2.5 times that of the normal population, and the risk of pulmonary embolism is also doubled (5). Chen *et al.* (6) indicated that the overall incidence rate of DVT was 18.78 per 10,000 person-years in patients with COPD. A systematic review and meta-analysis showed that the incidence of deep vein thrombosis (DVT) in patients with AECOPD was 12.4% (7). Pulmonary embolism is one of the most serious complications of AECOPD, creating a substantial economic and social burden for families and society (8). An in-depth analysis of the risk factors for DVT in AECOPD patients will help to identify high-risk AECOPD patients at an early stage, thereby reducing the risk of DVT. However, there is currently no clear understanding of the relevant risk factors for DVT in AECOPD in clinical settings. Angiotensin 2 (Ang-2) is a newly discovered endothelial growth factor enriched in the Weibel-Palade bodies of vascular endothelial cells. Ang-2 is a 57-kDa glycoprotein that shares homology with a number of other angiopoietins and angiopoietin-like molecules. The gene encoding Ang-2 protein is located on chromosomes 8p23.111. Ang-2, a 496 amino acid-long protein, shares ~60% amino acid homology with Ang1 (9,10). It is released outside the cell when vascular endothelial cells are damaged. Ang-2 participates in the occurrence and development of vascular endothelial cell injury by binding to the Tie-2 receptor, and DVT in the lower limbs is closely related to venous vascular endothelial cell injury (11). Alqudah *et al.* showed that compared with healthy people, serum Ang-2 levels are significantly increased in patients with venous

thromboembolism of the lower limbs, a finding which helps diagnose DVT at an early stage (12). Ang-2 is also one of the inflammatory mediators. Increased levels of Ang-2 could destabilize the alveolar vasculature, which damages endothelial cells and leads to leakage, thereby resulting in pulmonary congestion and injury to the lung (13).

A disease risk prediction model is based on multiple causes of a disease. Through the establishment of a statistical model, it can predict the future probability of a disease in a population with specific characteristics (14). Constructing a risk prediction model for lower extremity DVT in patients with AECOPD can effectively aid medical staff in the early identification of people at risk of thrombosis and the implementation of individualized prevention strategies to reduce the occurrence of deep vein complications in the lower extremities. Hippisley-Cox *et al.* (15) constructed a prediction model for the occurrence of venous thrombosis in the overall population using a multicenter prospective research design. Their model quantified the absolute risk of venous thrombosis at 1 and 5 years to help identify patients with a high risk of venous thrombosis and perform prevention, but the patients included in their model did not specifically include those with AECOPD, and the predictive power of AECOPD with comorbid DVT in the lower extremities was not strong. Matsuo *et al.* (16) used D-dimer as an important diagnostic indicator for DVT in the lower extremities, but the specificity of D-dimer was only 13.3%. Cho *et al.* (13) also reported that serum Ang-2 levels were significantly higher in patients with acute exacerbations of COPD than in those with stable COPD or controls. However, the study just enrolled forty-nine patients with AECOPD, and did not investigate the association between serum Ang-2 levels and DVT.

Considering that AECOPD patients are at a high risk of developing DVT in the lower extremities and that Ang-2 has not been included in the established models at home and abroad, the relationship between the levels of circulating Ang-2 and AECOPD with comorbid DVT in the lower extremities remains to be clarified. Therefore, this study adopted a prospective and observational research design by selecting 650 patients with AECOPD for a case-control study based on serum Ang-2 as a risk factor for DVT. In addition, we examined the association between serum Ang-2 levels and DVT in AECOPD patients. Furthermore, based on the TRIPOD statement (17), this study was targeted specifically at AECOPD patients to establish a serum Ang-2-based risk prediction model of DVT to assist clinicians in the early identification of individuals at risk

of lower extremity DVT and provide a theoretical and decision-making basis for early prevention of thrombosis. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1448>).

Methods

Research design

This study was a single-center, prospective, observational study.

Research subjects and inclusion and exclusion criteria

The convenience sampling method was used to recruit 650 AECOPD patients admitted to the Department of Pulmonary and Critical Care Medicine of the First Affiliated Hospital of Chengdu Medical College from January 2019 to January 2021. The random number table method was used to divide the enrolled patients into a modeling group (n=455) and a verification group (n=195) according to a 7:3 ratio. The diagnostic criteria of the 2019 GOLD guidelines (18) were used to confirm the diagnosis of chronic obstructive pulmonary disease; the diagnostic criteria of the 2017 edition of the Chinese Medical Association Surgery Branch “Deep Vein Thrombosis Diagnosis and Treatment Guidelines (Third Edition)” (19) were used to establish the diagnosis of lower extremity DVT, which was confirmed by Doppler ultrasound of the lower extremity blood vessels. The current gold standard for the clinical diagnosis of DVT is lower extremity venography. Nevertheless, venography is an invasive procedure, and Doppler ultrasound of the lower extremity blood vessels is a non-invasive procedure which effectively visualizes the thrombosis in veins. Non-invasive procedure is more acceptable to patients. Thus, we chose Doppler ultrasound of the lower extremity blood vessels as a means of detecting DVT. Exclusion criteria were as follows: (I) patients with a history of tumors; (II) patients who refused to participate in this study; (III) patients with neuropsychiatric diseases; and (IV) patients who could not complete the relevant examinations as requested by their treating doctor. Inclusion criteria were as follows: patients who were diagnosed, or patients suspected of being diagnosed, with pulmonary embolism in line with the “2019 ESC/ERS Acute Pulmonary Embolism Diagnosis and Management Guidelines” (20). This study was approved by the Ethics Committee of the First Affiliated Hospital of

Chengdu Medical College (2020CYFYIRB-BA-131). All procedures involving human participants complied with the Declaration of Helsinki (revised in 2013), and informed consent was obtained from all patients.

Variable selection

Risk factors were established following a literature review, small-scale expert consultation, and our previous experience in constructing a risk prediction model for DVT of the lower extremities and were screened as follows:

- (I) Basic information included gender, age, past history, smoking history, drinking history, and long-term antiplatelet data;
- (II) Clinical features consisted of initial mean arterial pressure, arrhythmia, lower extremity edema, living ability score, respiratory failure, and length of stay in hospital;
- (III) Detection of the general biological blood indicators consisted of initial results of white blood cell count; hemoglobin, hematocrit, and platelet levels; blood creatinine content; D-dimer; international normalized ratio (INR); and blood gas analysis following admission;
- (IV) Detection of Ang-2: an enzyme-linked immunosorbent assay was used to detect the blood Ang-2 levels of patients (Human Ang-2 ELISA kit, R&D System, Inc., MN, USA), according to the manufacturer's instructions. Signals were quantified by measuring the absorbance at 450 nm using a BioTek plate reader;
- (V) Auxiliary examination was conducted with a color Doppler ultrasound of the blood vessels of the lower extremities.

Outcome indicators

Patients in the modeling group were further subdivided into a thrombus group and a non-thrombus group according to the results of a lower extremity deep vein color Doppler ultrasonography after admission.

Statistical analysis

Assessment of the sample size

According to small-scale expert consultation, a literature review (mainly a systematic review of the risk factors for COPD with comorbid DVT), and the experience with a

Table 1 Baseline characteristic data of the modeling group and the verification group

Variable	Modeling group (n=455)	Verification group (n=195)	t/χ^2	P
Male	255	95	2.948	0.086
Female	200	100	–	–
Age (years)	71.11±6.10	70.62±5.50	0.982	0.326
BMI (kg/m ²)	26.60±3.11	25.90±6.54	1.844	0.065
Hospital stay (days)	17.33±13.62	15.81±10.40	1.373	0.169
Smoking	189	70	1.812	0.178
Drinking	106	50	0.411	0.521
Antiplatelet therapy	114	48	0.014	0.905
Edema of lower extremity	205	95	0.737	0.391
Barthel index	51.90±16.71	52.20±23.73	–0.183	0.855
Mean arterial pressure/mmHg	100.94±12.30	100.02±15.43	0.786	0.431
Diabetes	148	70	0.695	0.404
Heart rate/min ⁻¹	95.70±17.12	94.61±18.40	0.734	0.463
Heart failure	35	20	1.158	0.282
Arrhythmia	116	63	3.175	0.075
Respiratory failure	211	98	0.825	0.364
WBC (×10 ⁹ ·L ⁻¹)	9.32±4.10	9.41±4.51	0.276	0.782
PLT (×10 ⁹ ·L ⁻¹)	208.90±53.72	212.52±50.30	0.798	0.425
INR	1.15±0.26	1.17±0.15	–1.001	0.315
D-dimer (mg·L ⁻¹)	1.78±1.21	1.66±1.49	1.073	0.283
Creatinine (μmol·L ⁻¹)	83.50±33.11	88.57±33.61	–1.756	0.079
Ang-2 (ng·mL ⁻¹)	3.01±0.53	2.88±1.26	1.852	0.644

BMI, body mass index; WBC, white blood cell; PLT, platelets; INR, international normalized ratio.

DVT analysis and prediction model constructed by our predecessors, 21 candidate factors were identified for DVT of the lower extremities. The names and values of the candidate factors are shown in *Table 1*. The sample size was calculated depending on number of independent variables in prediction model. The sample size was at least 10 times more than the number of independent variables (21). Assuming that each factor requires at least 10 cases for verification and the follow-up loss rate is 10%, the expected sample size should be at least 233 cases, with the formula: $21 \times 10 \div 0.9 = 233$. To increase the reliability of the predicted model, 650 cases were finally included in the study.

Processing of missing values

Only patients with complete data were included in the analysis.

Data were analyzed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA) and R 3.6.1 software (R Development Core Team, www.r-project.org). Count data are described by the number of cases (rate) and were analyzed by the χ^2 test. Normally distributed measurement data are represented by the mean \pm SD ($\bar{x} \pm s$) and were analyzed using independent t-tests for two-group comparisons. Binary logistic regression analysis was performed on variables reaching statistical significance to determine the independent risk factors for DVT. The independent risk factors were imported into R software

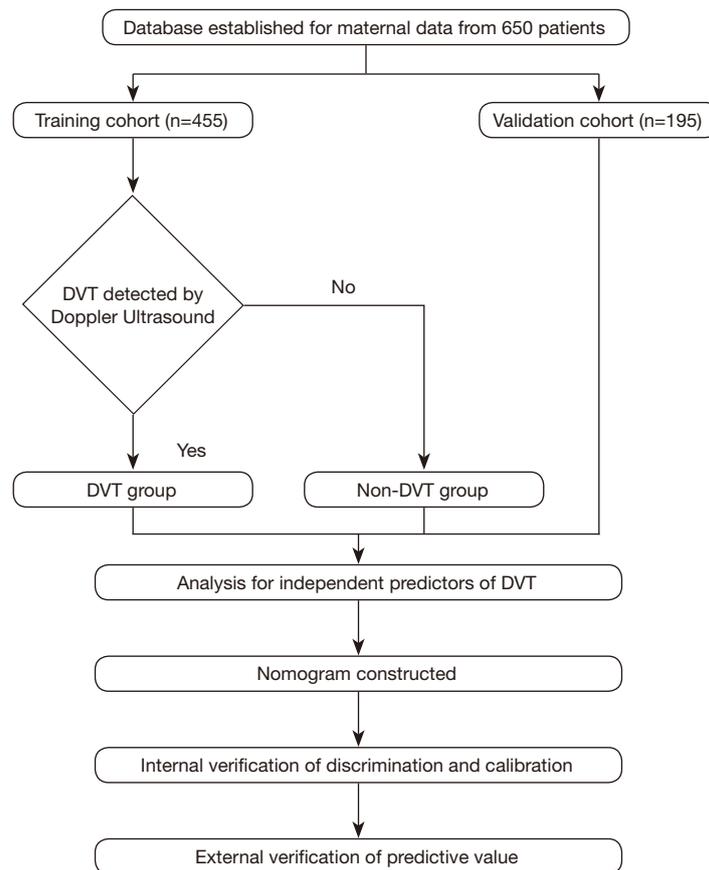


Figure 1 Flow chart describing the research method. DVT, deep vein thrombosis.

for further analysis, and the “rms” program package in R software was used to establish the nomogram and correction diagram of DVT occurrence. Discrimination, calibration, and clinical validity were verified in the modeling group and the verification group. The ROC curve was drawn based on the results of the nomogram model. The evaluation of the predictive power of the model for DVT in patients with AECOPD was performed by calculating the area under the curve (AUC), where $0.5 < \text{AUC} < 0.7$ indicates that the model’s distinguishing ability is low; $0.7 < \text{AUC} < 0.9$ indicates a moderate ability and $\text{AUC} > 0.9$ reflects a higher discrimination ability. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration of the prediction model: in this test, a P value > 0.05 suggests a small difference between the predicted value of the model and the actual observation, indicating the model calibration is good. A decision curve package was used to draw the decision curve, and a clinical impact curve was drawn to evaluate the net

clinical benefit and clinical impact of the model. Results with a P value < 0.05 indicated a statistically significant difference.

Results

General information

From January 2019 to January 2021, 700 cases of AECOPD were initially considered for the study. Of these, 25 patients with comorbid tumors were excluded, and 25 patients died before the screening was completed. A final 650 patients who met the criteria were included in the study, and the incidence of thrombosis in this sample was 25.8% (168/650). These cases were then divided into a modeling group (455 cases) and a verification group (195 cases), with details shown in *Table 1* and *Figure 1*. Differences in demographic data, clinical characteristics, auxiliary examinations, and other data between the two groups were not statistically significant ($P > 0.05$), indicating the two groups were comparable.

Table 2 Univariate analysis of patients in the modeling group

Variable	Thrombus group (n=118)	Non-thrombus group (n=337)	t/χ^2	P
Female	58	142	1.746	0.186
Male	60	195	–	–
Age (years)	72.83±4.80	71.92±6.50	1.377	0.168
BMI (kg/m ²)	28.96±3.12	25.80±2.73	10.34	<0.001
Hospital stay (days)	15.70±10.82	17.81±14.46	–1.448	0.148
Smoking	45	144	0.759	0.383
Drinking	28	78	0.016	0.897
Antiplatelet therapy	34	80	1.198	0.274
Edema of lower extremity	70	135	13.099	<0.001
Barthel index	48.40±26.43	53.24±24.52	–1.794	0.073
Mean arterial pressure/mmHg	108.62±12.02	98.30±11.42	8.331	<0.001
Diabetes	59	89	22.16	<0.001
Heart rate/min ⁻¹	96.41±18.34	95.51±16.80	0.489	0.625
Heart failure	10	25	0.137	0.711
Arrhythmia	35	81	1.456	0.228
Respiratory failure	71	140	12.19	<0.001
WBC (×10 ⁹ ·L ⁻¹)	9.22±4.50	9.31±3.91	0.23	0.818
PLT (×10 ⁹ ·L ⁻¹)	204.72±68.30	210.43±47.72	–0.994	0.321
INR	1.13±0.24	1.16±0.17	–1.471	0.141
D-dimer (mg·L ⁻¹)	3.18±1.53	1.29±0.49	19.971	<0.001
Creatinine (μmol·L ⁻¹)	87.82±37.90	82.53±31.24	1.498	0.135
Ang-2 (ng·mL ⁻¹)	3.39±0.58	2.88±0.45	9.791	<0.001

BMI, body mass index; WBC, white blood cell; PLT, platelets; INR, international normalized ratio.

Analysis of individual factors in the modeling group

In the modeling group, there was no statistical difference between the thrombus group and the non-thrombus group in terms of gender composition, age, drinking history, smoking history, hospital stay, long-term antiplatelet therapy, living ability score, heart rate, arrhythmia, or heart failure ($P>0.05$). In the thrombus group, average arterial pressure was higher than that in the non-thrombus group. The incidence of lower extremity edema, respiratory failure and diabetes was also higher in the thrombus group relative to the non-thrombus group.

Additionally, the BMI index of the thrombus group was significantly higher than the non-thrombus group ($P<0.05$, *Table 2*).

There was no significant difference in white blood cell count (WBC), platelet count, hematocrit, INR, or blood creatinine content between the two subgroups of patients ($P>0.05$). The concentration of D-dimer and serum Ang-2 in the thrombus group was significantly higher than that in the non-thrombus group ($P<0.05$, *Figure 2A*). When serum Ang-2 concentration alone was used as a diagnostic indicator, the sensitivity was 96.14%, the specificity was 67.99%, the cutoff value was 3.01 ng/mL, AUC =0.782, and the 95% CI: 0.742–0.819 (*Figure 2B*).

Logistic multivariate regression analysis of the modeling group

Logistic multivariate regression analysis was conducted by

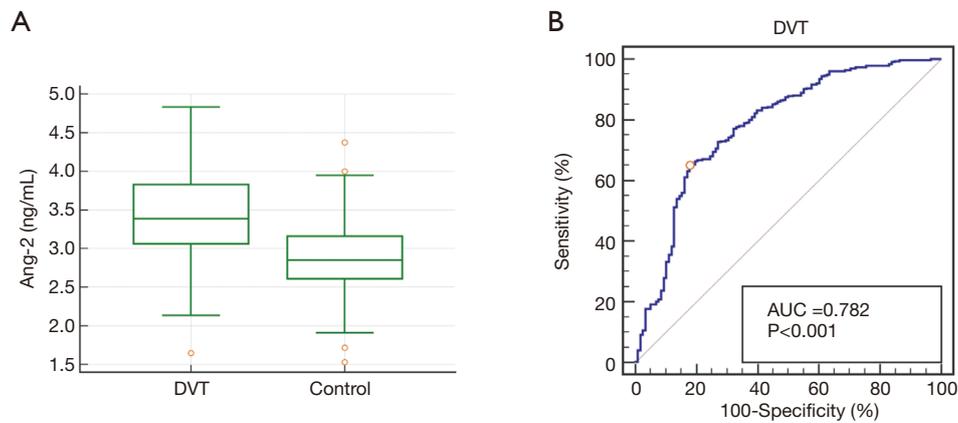


Figure 2 Laboratory and auxiliary examination results of the modeling group. (A) The differential expression of Ang-2 serum in the thrombus and non-thrombus subgroups of the modeling group; (B) the ROC curve of Ang-2 in AECOPD complicated with lower extremity DVT. ROC, receiver operating characteristic curve; AECOPD, acute exacerbation chronic obstructive pulmonary disease; DVT, deep vein thrombosis.

Table 3 Assignment table of independent predictors

Independent predictors	Assignment
Diabetes	0= no; 1= yes
BMI index	0= normal weight; 1= obesity
Lower extremity edema	0= no; 1= yes
D-dimer (mg/L)	0, <0.5 mg/L; 1, ≥0.5 mg/L
Ang-2 (ng/mL)	0, Ang-2 <3 ng/mL; 1, Ang-2 ≥3 ng/mL
Respiratory failure	0= no; 1= yes

Variables	OR(95% CI)	Pvalue
Diabetes	3.548(1.336–7.353)	0.004
BMI	1.066(1.004–1.198)	0.024
Lower Limb Edema	4.488(1.354–10.036)	0.001
D-dimer	10.129(2.913–25.468)	0.008
Ang-2	7.027(2.259–15.642)	0.005
Respiratory failure	5.522(2.349–12.246)	0.038

Figure 3 Logistic regression analysis of risk factors for AECOPD complicated with DVT in the modeling group. AECOPD, acute exacerbation chronic obstructive pulmonary disease; DVT, deep vein thrombosis.

taking DVT as the dependent variable and the statistically significant factors in the univariate analysis results (respiratory failure, lower extremity edema, BMI index,

diabetes, D-dimer, and serum Ang-2) as the independent variables. The variable assignment table is shown in detail in *Table 3*. The results suggested that lower extremity edema, BMI index, diabetes, respiratory failure, D-dimer, and serum Ang-2 were independent risk factors for COPD, while mean arterial pressure was not an independent risk factor for COPD complicated with DVT (*Figure 3*).

Establishing the risk nomogram model of AECOPD with comorbid DVT

The selected independent risk factors were entered into the R software, and the “lrm” function in the “rms” package was used to build the nomogram prediction model of AECOPD with comorbid DVT (*Figure 4*). The nomogram was constructed as follows: the score value corresponding to each predictive factor was obtained, and the sum of these score values was recorded as the total score. Finally, the predicted probability corresponding to the total score was the risk of DVT in AECOPD.

Verification of the prediction model

Distinguishing degree

The ROC curve of the two groups (see *Figure 5A*) shows that the modeling group had an AUC value of 0.844 (95% CI: 0.808–0.932) and a C index of 0.823. The verification group had an AUC value of 0.755 (95% CI: 0.679–0.861) and a C index of 0.764 (see *Figure 5B*), indicating that the

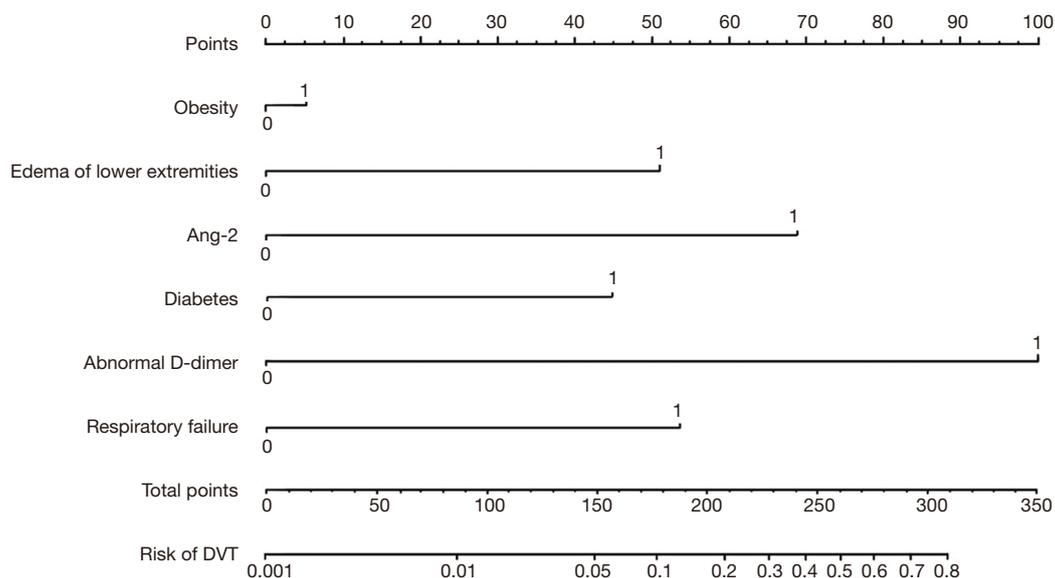


Figure 4 Risk nomogram model for predicting the occurrence of DVT in AECOPD patients. DVT, deep vein thrombosis; AECOPD, acute exacerbation chronic obstructive pulmonary disease.

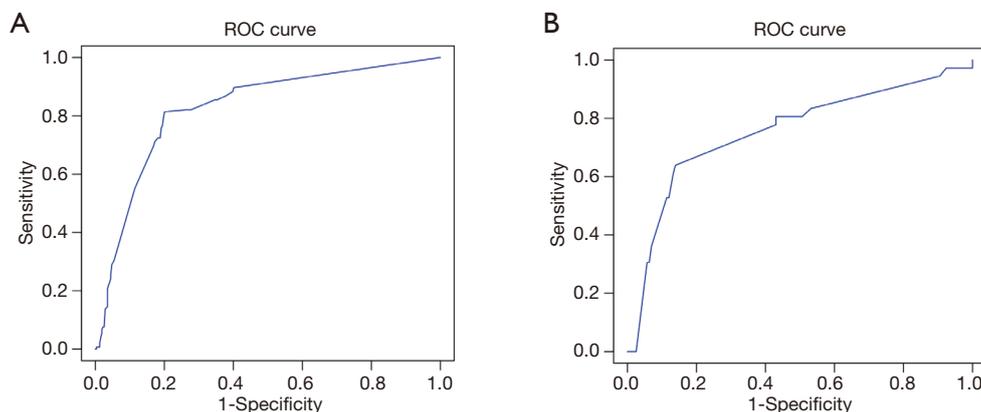


Figure 5 The ROC of the prediction model in the modeling group and the verification group. (A) AUC of the modeling group; (B) AUC of the verification group. ROC, receiver operating characteristic curve; AUC, area under the curve.

C index of the prediction model in both groups was greater than 0.75.

Calibration

Results of the Hosmer-Lemeshow test on the prediction model in the modeling group ($P=0.124$) and the verification group ($P=0.086$) showed that the P value in both groups was greater than 0.05, indicating that the difference was not statistically significant. The calibration chart showed that the predicted probability of the nomogram was highly

similar to the actual probability of the modeling group and the verification group (*Figure 6A,B*).

Clinical effectiveness

Decision curve analysis (DCA) was used to evaluate the availability and benefits of the prediction model, and the curve was drawn using the R software “rmda” package. The decision curve for the modeling group and the verification group is shown in *Figure 7A,B*. The abscissa represents the threshold probability, and the probability of

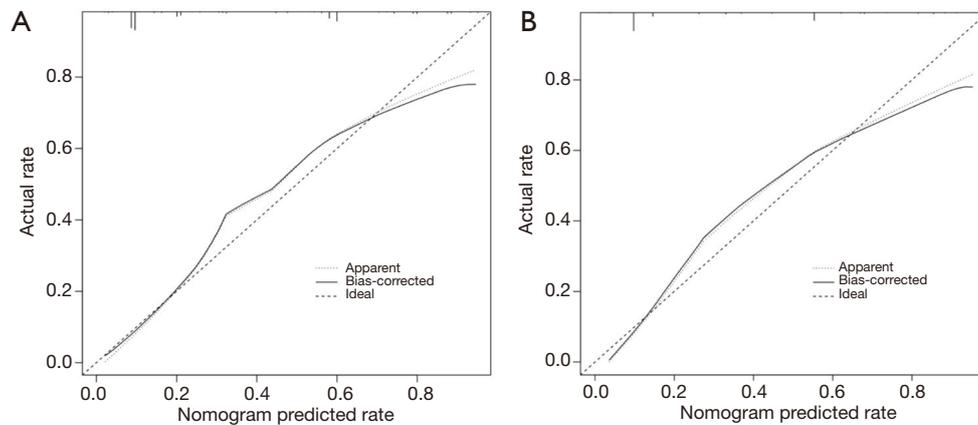


Figure 6 The calibration degree of the prediction model in the modeling group and the verification group. (A) The calibration degree of the modeling group; (B) the calibration degree of the verification group.

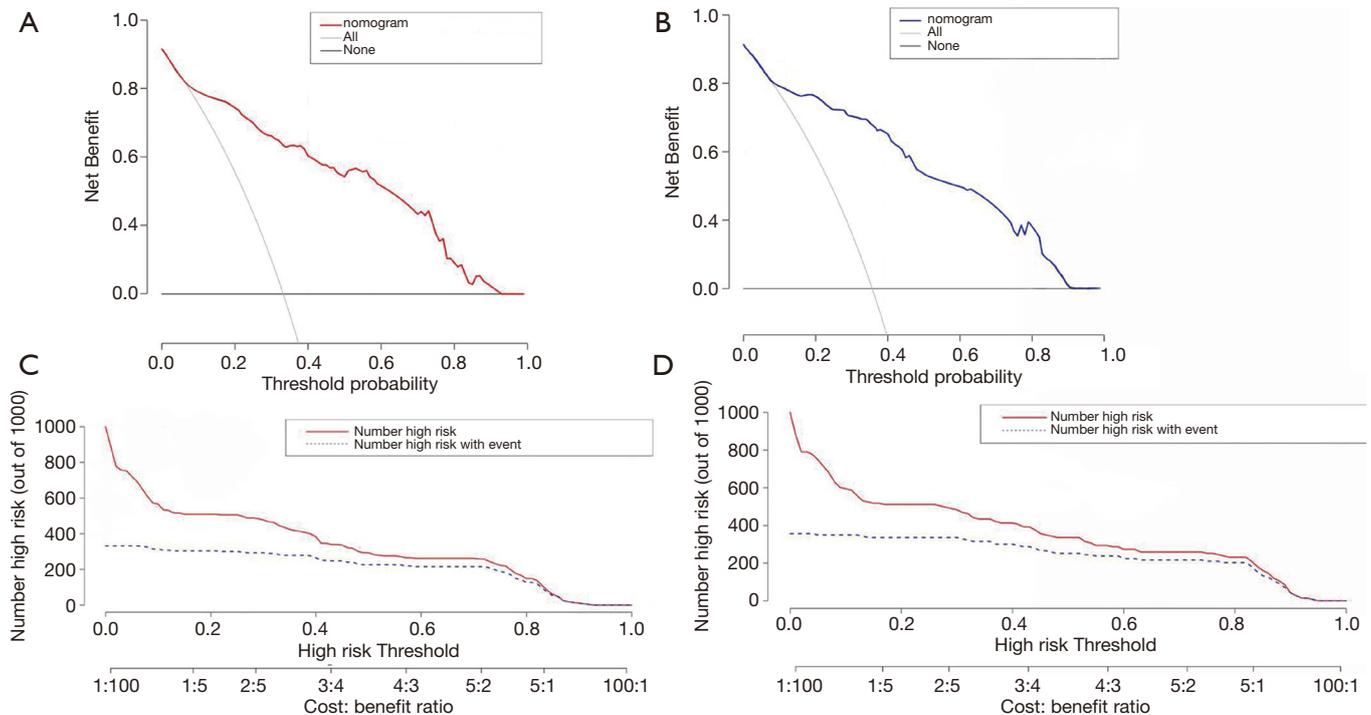


Figure 7 The decision curve and clinical influence curve of the prediction model in the modeling and verification groups. (A) The decision curve for the modeling group; (B) the decision curve for the verification group; (C) the clinical influence curve for the modeling group; (D) the clinical influence curve for the verification group.

DVT in AECOPD predicted by the model is represented as P_i . When P_i reaches a certain threshold (recorded as P_t), it is defined as positive and indicates that the model will benefit the patient (gain). However, there will also be losses in patients with DVT which are not predicted

(loss), and the net benefit (NB) is calculated by gain minus loss (22). The decision curve analysis illustrated in *Figure 7A,B* showed that the nomogram had highest NB across 10-92% threshold probabilities in the modeling group. Similar results were observed in the verification

group. In this study, the “plot clinical impact function” in R software was used to draw the clinical impact curve of the prediction model. The model was set up to predict risk stratification for 1,000 people, displaying the “loss” and “gain” axes and assigning 10 levels (Figure 7C,D). The red curve represents the number of people classified with DVT by the model under each threshold probability; the blue curve is the actual number of people with DVT at each threshold probability. The clinical impact curve suggests that the predicted probability of the model is essentially the same as the probability of DVT in the actual clinical setting.

Discussion

The incidence and mortality of COPD are increasing yearly, and it is currently the fourth cause of death worldwide (23). China has the main burden of COPD with a total of over 100 million patients suffering from COPD. Along with hypertension and diabetes, COPD is the most common chronic disease in China and causes substantial social and family economic burdens (24). COPD patients often suffer from chronic hypoxia, poor lung function, decreased activity endurance, and long-term bed rest in some cases, and these factors lead to slower blood flow and hypercoagulable blood that create the pathophysiological conditions for the formation of DVT. Studies have shown that more than 90% of pulmonary embolisms arise from DVT embolisms, the incidence of COPD with pulmonary embolism is approximately 15%, and the incidence of AECOPD with DVT is 19–29% (25,26). Yue *et al.* (27) have shown that the incidence of pulmonary embolism secondary to AECOPD is 23% higher than that of non-AECOPD patients, and the incidence of AECOPD with comorbid DVT was 19.61%. DVT has become a serious common comorbidity of AECOPD. The incidence of AECOPD with comorbid DVT in this study was 25.8%, which is consistent with the results of previous studies.

In this study, a univariate analysis of factors including gender, age, smoking and drinking history, length of hospitalization, antiplatelet therapy, living ability score, heart rate, and arrhythmia in the thrombus and non-thrombus subgroups of the modeling group showed no significant differences between the two groups, whereas lower limb edema, respiratory failure, and BMI index were significantly different between the two groups. Multivariate logistic regression analysis was subsequently performed on

the significant factors identified by the univariate analysis. Results indicated that lower limb edema and BMI index were independent risk factors for lower limb thrombosis, whereas mean arterial pressure was not an independent risk factor. Lung function injury of AECOPD, especially in the elderly, can substantially reduce lower limb exercise, leading to slowing the blood flow in the lower extremities and lower extremity edema. Slowing of blood may contribute to thrombosis development, which can result in swelling in lower extremities. Lower limb thrombosis and lower limb edema influence and promote each other. Determining exactly how these factors are causally related, therefore, warrants further study. At the same time, the nomogram also suggested that obese people have an increased risk of DVT. BMI is an important indicator for evaluating nutritional status, and it has been reported that people with a BMI greater than 30 kg/m² have a risk of DVT that is three times higher than that of normal-weight people (28). Because obesity is a state of chronic low-grade inflammation (29), it is more likely to induce vascular endothelial dysfunction and increase coagulation factor levels, both of which are pathophysiological factors associated with DVT of the lower extremities. It is worth noting that the predictive model of this study indicated that diabetes and respiratory failure are also independent risk factors for AECOPD with comorbid DVT. This may be due to the fact that long-term hyperglycemia can cause an increase in oxidative stress and damage the function and structural integrity of vascular endothelial cells, further increasing the incidence of thrombotic diseases. Studies have reported that DVT incidence in diabetic patients can be as high as 15–48% (30). In addition, hypoxia or carbon dioxide retention caused by respiratory failure can not only further damage the function of the vascular endothelium but may also lead to an increase in secondary red blood cells causing increased blood viscosity and blood stasis to form DVT in the lower extremities (31). The prediction model in this study was able to predict the risk of DVT in AECOPD with comorbid diabetes and respiratory failure in the clinical setting and thus allowed a timely investigation and intervention for DVT.

The occurrence and development of thrombotic diseases are not only related to abnormal blood coagulation and fibrinolysis processes but also to intravascular inflammation. Chung *et al.* (32) showed that thrombosis is also an inflammatory reaction process because there is a close

relationship between inflammatory reaction and thrombosis. The massive release of inflammatory mediators and the damage to the vascular endothelium during infection leads to platelet adhesion and aggregation. The *Ang-2* gene is located in the 8q23.1 chromosome and expressed in vascular endothelial cells. In the resting state, vascular endothelial cells express only a small amount of Ang-2, while the expression of Ang-2 increases significantly after being activated by external stimuli (33). In this study, the comparison of serum Ang-2 between the thrombus and non-thrombus groups showed that serum Ang-2 in the thrombus group was significantly higher than that in the non-thrombus group, and Ang-2 also had a higher sensitivity in diagnosing AECOPD complicated with DVT of the lower extremities. Gurnik *et al.* (34) reported that the main function of activated Ang-2 is to change the binding force of the Tie-2 receptor and depolymerize the Tie-2/Tie-1 receptor dimer. After depolymerization, Tie-2 can activate intracellular tyrosine kinase activity to activate downstream signaling pathways and realize related functions: by releasing the anchor chain effect on the intracellular skeletal protein, the structure of endothelial cells becomes relatively loose; and the interaction of Tie-2/Tie-1 between endothelial cells is changed, thereby increasing the gap between capillaries, and promoting the migration of peripheral white blood cells to the tissues. These changes will affect the flow of tissue fluid, aggravate the inflammatory response, and lead to edema, suggesting that lower extremity edema may also be related to increased Ang-2 expression and could be the reason why lower extremity edema and Ang-2 are independent risk factors for DVT. Sahni *et al.* (35) also reported that the serum level of Ang-2 is positively correlated with inflammatory mediators such as TNF- α and interleukin 6, and these two inflammatory factors have been proved to be risk factors for DVT in many studies. As a pro-inflammatory factor, Ang-2 plays an important role in the physiological activities of promoting inflammation and vascular leakage (32). D-dimer is not only the smallest fibrin degradation product but also a specific degradation product of the fibrous matrix of venous thrombosis. D-dimer will be abnormally elevated in the case of blood hypercoagulability or secondary hyperfibrinolysis and is a highly sensitive indicator of thrombosis and dissolution (36). This study also found that D-dimer concentration was significantly higher in patients with AECOPD complicated with DVT than those without thrombosis. However, most studies believe

that D-dimer has a lower specificity in diagnosing DVT. Therefore, this study combined D-dimer and other clinical features and indicators to establish a nomogram model, which combines the factors of lower extremity edema, BMI, diabetes, respiratory failure, D-dimer, and serum Ang-2. When the calculated score increases in the nomogram model, the corresponding risk of DVT also increases significantly. In this study, the Hosmer-Lemeshow test and ROC curve analysis were performed to verify the predictive performance of the nomogram, which indicated that the model fits well and has good predictive value in estimating the probability of DVT occurrence in AECOPD. Furthermore, by using the DCA and clinical impact curve to evaluate the availability and benefit of the model, it was found that the model can benefit 0.37–0.92 of patients, and the predicted probability of the model is consistent with the actual clinical probability of DVT. These results indicate that the model has an important impact on clinical benefit and helps clinicians with timely recognition and prevention of DVT in patients with AECOPD.

However, this study has some limitations. There have been many reports in the literature that bed rest or immobilization for more than 3 days are independent risk factors for DVT in patients with AECOPD and can lead to a significant increase in DVT incidence (37,38). But, in this study, none of the AECOPD patients were ICU patients, and their bed rest was no more than three days, so bed rest was not included as a risk factor. Secondly, there was no dynamic monitoring of serum Ang-2 levels undertaken in this study, so it was not possible to explore the correlation between the fluctuation of serum Ang-2 levels and the prognosis of AECOPD complicated with DVT; Finally, Due to the limited experimental conditions and other resources, this study is a single-center study, and the model has not been externally verified by other centers. Therefore, in future studies, the sample size should be expanded, and the predictive value of the nomogram model should be verified by a multi-center study.

Conclusions

In summary, our nomogram model for predicting the risk of DVT in AECOPD based on serum Ang-2 levels has good calibration, discrimination, and clinical impact. The model is a good fit and has a high predictive value. Due to the limitations of this study, multi-center follow-up studies

with larger samples will be needed to verify and add to the current findings.

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Footnote

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