Original Article

Establishing a risk prediction model for residual pulmonary vascular obstruction after regular anticoagulant therapy for non-high-risk pulmonary embolism

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Background: The incidence of pulmonary embolism (PE) has been on the rise annually. Despite receiving regular sequential anticoagulation therapy, some patients with non-high-risk acute PE (APE) continue to experience residual pulmonary vascular obstruction (RPVO). This study sought to identify the risk factors for RPVO following 3 months of sequential anticoagulation therapy for non-high-risk PE. Machine learning techniques were utilized to construct a clinical prediction model for predicting the occurrence of RPVO.

Methods: A total of 254 acute non-high-risk PE patients were included in this study, all of whom were admitted to the Third People's Hospital of Yunnan Province between 2020 and 2023. After 3 months of regular anticoagulant treatment, computed tomography pulmonary angiography (CTPA) were reviewed to identify the presence of RPVO. Patients were then categorized into either the thrombolysis group or the thrombosis residue group. Throughout the study period, 49 patients were excluded due to missing data, irregular treatment, or loss to follow-up. Clinical symptoms, physical signs, and laboratory results of 205 PE patients were recorded. Correlation and collinearity analyses were conducted on relevant risk factors, and significance tests were performed. Heat maps illustrating the relationships between influencing factors were generated. Predictors were selected using least absolute shrinkage and selection operator (LASSO) regression, followed by multivariate logistic regression analysis to create a predictive model. Internal validation of the model was also carried out.

Results: By searching the literature to understand all the clinical indicators that may affect the efficacy of anticoagulation therapy. A total of 205 patients with non-high-risk acute pulmonary thromboembolism were evaluated for various risk factors. Five independent factors were identified by multivariable analysis—age, chronic obstructive pulmonary disease (COPD), acratia, pulmonary systolic blood pressure (PASP), and major arterial embolism—and their P value, odds ratio (OR) and confidence interval (CI) were as follows: (P=0.012, OR =1.123; 95% CI: 1.026–1.23), (P=0.002, OR =13.30; 95% CI: 2.673–66.188), (P=0.001, OR =14.009; 95% CI: 2.782–70.547), (P=0.003, OR =1.061; 95% CI: 1.020–1.103) and (P<0.001, OR =18.128; 95% CI: 3.853–85.293), which may indicate a poor prognosis after standard anticoagulant therapy. A nomogram was constructed using these variables and internally validated. The receiver operating characteristic (ROC) curves of the model demonstrated strong predictive accuracy, with an area under the curve (AUC) of 0.94 (95% CI: 0.89–0.96) for the training set and 0.93 (95% CI: 0.88–0.95) for the validation set. Calibration curves were utilized to assess the practicality of the nomogram.

Conclusions: A novel predictive model was developed based on a single-center retrospective study to identify patients with RPVO following anticoagulant therapy for acute non-high-risk PE. This model may aid in the early detection of patients, prompt adjustment of treatment, and ultimately lead to a decrease in adverse outcomes.

Keywords: Non-high-risk pulmonary thromboembolism; anticoagulant therapy; machine learning; nomogram; computed tomography pulmonary angiography (CTPA)

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Introduction

Venous thromboembolism (VTE) is a potentially fatal cardiovascular disease that affects approximately 1–3/1,000 of the population with significant morbidity and mortality. It consists of two related disorders: deep vein thrombosis (DVT) and pulmonary embolism (PE) (1). Acute PE (APE) ranks as the third most common acute cardiovascular syndrome globally, following myocardial infarction and stroke (2). Currently, CT pulmonary angiography (CTPA) is the preferred method for diagnosing PE due to its high sensitivity and specificity, as well as its non-invasive nature (3). Anticoagulant therapy for non-high-risk PE can involve monotherapy or sequential anticoagulant therapy (4). New oral anticoagulants like rivaroxaban, Edoxaban, dabigatran, and apixaban are increasingly used in treating non-high-risk PE. In addition, numerous studies have demonstrated the safety and efficacy of sequential anticoagulation for PE (4-8) and even the prevention of venous thrombosis (9,10).

Residual pulmonary vascular obstruction (RPVO) occurs when some thrombus remains in the pulmonary vessels after treatment for pulmonary thromboembolism, continuing to obstruct blood flow in the lungs (11). A study in Shanghai, China, found that rivaroxaban post-rivaroxaban sequential therapy had a positive therapeutic effect on acute pulmonary thrombosis, with 80.1% of patients resolving after 3 months of treatment (5). However, some patients still had residual thrombosis. Various factors such as body weight, liver and kidney function, age, and size of the embolism can impact the effectiveness of rivaroxaban therapy (12-15). According to one study (16), the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after APE treatment ranges from 0.1% to 9.1%. In recent years, predictive models have significantly contributed to predicting and evaluating the diagnosis and prognosis of diseases, aiding clinical work in early detection of potential diseases and assessing disease prognosis. Despite the advancements, there is currently a lack of a diagnostic predictive model for assessing the effectiveness of anticoagulation therapy for PE. To address this gap and understand the risk factors associated with prolonged anticoagulant therapy, chronic pulmonary thrombosis, and CTEPH, this study utilized existing diagnostic prediction models to explore the risk factors of RPVO following sequential treatment of APE. The primary objective of this research is to offer valuable insights to clinicians, enabling them to adjust anticoagulation therapy effectively, identify non-high-risk PE patients at risk of RPVO early on, and administer personalized anticoagulation therapy promptly to prevent poor prognosis or prolonged treatment duration. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1876/rc).

Highlight box

Key findings

- The risk factors of residual pulmonary vascular obstruction (RPVO) in non-high-risk patients with pulmonary embolism (PE) after regular anticoagulant therapy were identified by machine learning.

What is known and what is new?

- Not all pulmonary thrombus will dissolve and disappear after regular anticoagulant therapy for PE.
- The objective of this study was to predict the risk factors for RPVO after conventional anticoagulant therapy.

What is the implication, and what should change now?

- The clinical prediction model can provide a basis for clinicians to treat PE with anticoagulation therapy.

Methods

Study design and data source

The flowchart in (*Figure 1*) illustrates the study design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Third People's Hospital of Yunnan Province (No. 2023KY041) and individual consent for this retrospective analysis was waived. A total of 254 patients with acute non-high-risk PE, admitted to

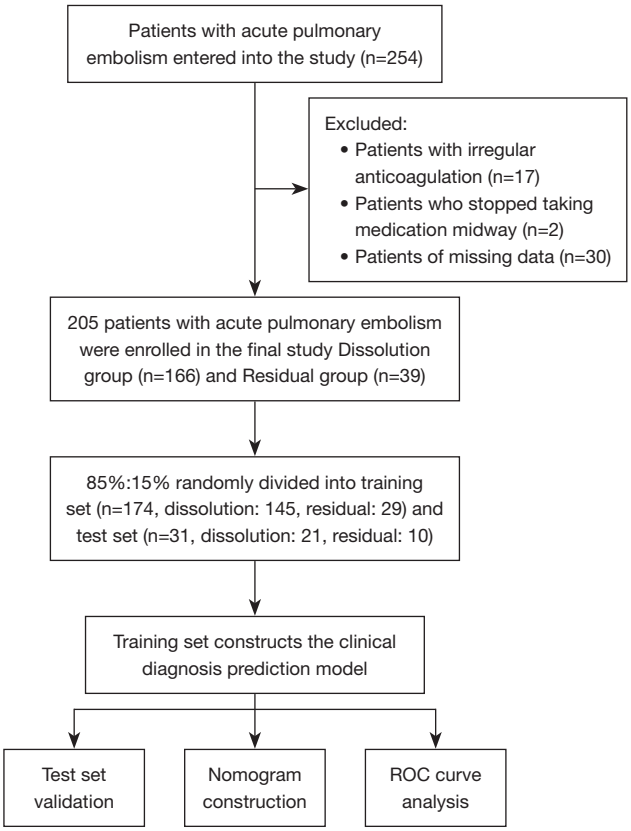

Figure 1 Flow diagram of the overall procedures. ROC, receiver operating characteristic.

the Respiratory Department of the Third People's Hospital of Yunnan Province from January 2020 to June 2023, were retrospectively collected. The inclusion criteria were as follows: (I) diagnosis of APE according to China's 2018 Guidelines for the Diagnosis, Treatment and Prevention of pulmonary embolism: clinical symptoms of APE (dyspnea, chest pain, syncope, lower limb edema, acratia, hemoptysis, etc.), elevated plasma D-dimer and computed tomography pulmonary angiography (CTPA); (II) categorization into low-risk, medium low-risk and medium high-risk groups based on the PE group; (III) administration of heparin subcutaneous injection followed by oral rivaroxaban anticoagulant therapy; (IV) CTPA examination was reviewed after 3 months of regular anticoagulant treatment. The exclusion criteria were: (I) age <18 years; (II) recurrent PE.

Data sources

The literature search results identified 48 potential risk factors from demographic characteristics, symptoms, physique, biochemical indicators, and examination results. Clinical records and laboratory data for each patient were collected using an electronic health system and completed by two respiratory physicians who were blinded to the study. Basic information such as sex, age, weight (kg), and medical history including hypertension, diabetes, coronary heart disease (CHD), renal insufficiency, hypohepatia, pneumonia, chronic obstructive pulmonary disease (COPD), tumor, gastric diseases, cerebral infarction, breathing difficulties, edema, acratia (Subjective feeling of acratia), chest pain, syncope, and hemoptysis were selected from the patient's electronic medical record. Laboratory findings at admission, including white blood cell count (WBC, $\times 10^9$/L), red blood cell (RBC, $\times 10^{12}$/L), hemoglobin (HB, g/L), blood platelet (PLT, $\times 10^9$/L), C-reactive protein (CRP, mg/L), alanine aminotransferase (ALT, U/L), aspartate transaminase (AST, U/L), albumin (ALB, g/L), globulin (g/L), blood urea nitrogen (BUN, mmol/L), creatinine (CR, μmoI/L), uric acid (UA, μmoI/L), prothrombin time (PT, S), international normalized ratio (INR), activated partial thromboplastin time (APTT, S), D-dimer (μg/mL), fibrin degradation products (FDP, μg/mL), triglyceride (TG, mmol/L), total cholesterol (TG, mmol/L), high-density lipoprotein (HDL, mmol/L), low-density lipoprotein (LDL, mmol/L), troponin T (TNT, μg/L), and N-terminal brain natriuretic peptide (NT-proBNP, pg/mL) were collected and evaluated. Pulmonary systolic blood pressure (PSAP, mmHg) was evaluated using cardiac ultrasound, while deep vein thrombosis (DVT) was assessed with color Doppler ultrasound. PE was indicated by the first CTPA examination, and the CTPA report describes the location of pulmonary thromboembolism and whether there is a thromboembolism in the left or right pulmonary artery, where it is defined as a major arterial embolism. CTPA results were reviewed by a specialist in thoracic radiology, who was unaware that the study was intended to evaluate PE after anticoagulation.

Clinical outcome

Based on the patient's symptoms, laboratory examination results and CTPA examination, a diagnosis of acute non-high-risk pulmonary thromboembolism was made, and anticoagulation therapy was initiated. The patient received subcutaneous injections of heparin drugs during hospitalization, followed by oral rivaroxaban 15 mg twice daily for 21 days, and then switched to oral rivaroxaban 20 mg once daily for continued anticoagulation treatment

after discharge. The patient will be informed in detail about the return visit time when discharged, and will be followed up 1–2 times irregularly within 3 months. Inform the patient to return to the hospital for re-examination of liver and kidney function, coagulation function and clinical symptoms (considering the side effects of contrast agent, economic cost and routine anticoagulation time of PE during the period, CTPA examination will not be re-examined). The CTPA examination will be reviewed within 1 week after 3 months. If the follow-up time is exceeded or the treatment time does not meet the standard, it will be excluded. If CTPA still indicates thrombus, RPVO is considered and meets the imaging diagnostic criteria. Clinically positive events (expert radiologist ruling out recurrent PE) were considered.

Study process

The initial study involved 254 patients diagnosed with acute non-high-risk PE. Forty-nine patients were excluded for various reasons, such as significant data loss, irregular anticoagulant therapy, and mid-term discontinuation due to complications like gastrointestinal bleeding. Data with missing values less than 20% were supplemented using the univariate mean interpolation method. Ultimately, 205 patients were analyzed, with 166 showing thrombus dissolution and 39 having thrombosis residual thrombus. The study utilized receiver operating characteristic (ROC) curve analysis to determine the area under the curve (AUC) value, followed by correlation collinearity analysis and significance testing to create risk factor correlation heat maps. LASSO regression analyses were conducted to identify variables associated with the diagnosis of residual PE. The data were randomly divided into a training set and a test set at a ratio of 85%:15%. The training set was used to build a model, and the predictors related to PE were included in the multi-factor analysis, and the independent predictors were evaluated by logistic regression. A nomogram with five independent predictors of residual PE was established based on multiple logistic regression results. Internal validation was performed using the test set, with the AUC under the ROC curve used to assess diagnostic efficiency. An AUC of 0.5 indicated no discrimination, while an AUC of 1.0 indicated perfect discrimination. The Harrell consistency index (C-index) was employed to predict the model's ability to distinguish pulmonary thrombotic residual occurrence. In addition, a calibration plot was constructed to assess the alignment between the predicted probability of the decision rule and the observed RPVO. The calibration curve was utilized to evaluate the accuracy, calibration, bias, and overfitting of the model. A well-corrected curve should closely resemble the ideal diagonal line, indicating good agreement between model predictions and actual observations. Furthermore, ongoing follow-up and model validation of newly admitted patients with PE are being conducted based on the scoring indicators of the nomogram to assess the reliability of the model.

Statistical analysis

All figures were created using R software version 4.3.1. Use the 'CBCgrps' package for baseline data statistics (17), the 'ggplot2' and 'viridis' packages were used for difference analysis and heat mapping, and the 'glmnet' functions of 'glmnet' packages were used for LASSO and Logistic regression. Calculate the AUC of the model using the "riskRegression" R package. Build the nomogram using the logistic regression analysis of the "rms" package. R4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of 205 patients with acute non-high-risk PE were summarized in (*Table 1*). During data collection, only a few patients were missing TNT and NT-proBNP indicators, so it was not listed in detail. After 3 months of anticoagulant treatment, thrombus dissolution group was observed in 166 cases (166/205, 81%), while 39 cases (39/205, 19%) had thrombus residual group. Among the thrombus residual group, there were 25 males (25/39, 64.1%) and 14 females (25/39, 35.9%) with an average age of 77.33 years, significantly higher than the thrombus dissolution group (69.95 years). In included PE patients, hypertension was the most common complication in 115 patients (115/205, 56%), and breathing difficulties was the most common symptom in 155 patients (155/205, 75.6%). Single-factor difference analysis was performed on the included variables, and it was found that there was a difference in age between the two groups (P<0.001). The SPO_2 on admission in the thrombus residual group was lower than that in the thrombus dissolution group (84.54% *vs.* 89.37%, P<0.001). Among patients with PE, patients with CHD and COPD were more likely to have

Table 1 Study patient demographics, comorbidities, clinical symptoms, and experimental value indicators, represented by measurement data

Variables	Dissolution group (n=166)	Residual group (n=39)	P
Sex (male)	90 (54.2)	25 (64.1)	0.35
Age, years	69.95 (12.15)	77.33 (6.62)	<0.001
Weight, kg	63.81 (10.03)	66.03 (9.61)	0.21
SPO_2 (%)	89.37 (5.50)	84.54 (10.10)	<0.001
Pre-existing disease			
Hypertension	93 (56.0)	22 (56.4)	>0.99
Diabetes	32 (19.3)	11 (28.2)	0.31
CHD	24 (14.5)	12 (30.8)	0.03
Renal insufficiency	20 (12.0)	5 (12.8)	>0.99
Hypohepatia	22 (13.3)	5 (12.8)	>0.99
Pneumonia	121 (72.9)	29 (74.4)	>0.99
COPD	41 (24.7)	24 (61.5)	<0.001
Tumour	11 (6.6)	0 (0.0)	0.20
Gastric diseases	12 (7.2)	2 (5.1)	0.90
Cerebral infarction	14 (8.4)	5 (12.8)	0.58
Symptoms			
Breathing difficulties	117 (70.5)	38 (97.4)	0.001
Edema	61 (36.7)	25 (64.1)	0.003
Acratia	19 (11.4)	19 (48.7)	<0.001
Chest pain	52 (31.3)	6 (15.4)	0.07
Syncope	18 (10.8)	7 (17.9)	0.34
Hemoptysis	5 (3.0)	2 (5.1)	0.86
WBC, $\times10^9$/L	7.88 (3.13)	8.65 (2.92)	0.16
RBC, $\times10^{12}$/L	4.46 (0.86)	4.85 (0.78)	0.01
HB, g/L	132.57 (27.83)	148.33 (25.40)	0.001
PLT, $\times10^9$/L	204.70 (81.66)	191.92 (103.61)	0.40
CRP, mg/L	30.81 (48.74)	34.06 (49.02)	0.70
ALT, U/L	30.49 (44.87)	42.29 (62.32)	0.17
AST, U/L	35.38 (64.23)	48.49 (45.18)	0.22
ALB, g/L	37.16 (6.22)	37.23 (4.63)	0.95
Globulin, g/L	27.59 (4.90)	28.61 (4.95)	0.24
BUN, mmol/L	6.34 (3.54)	8.30 (4.35)	0.003
CR, μmol/L	88.32 (31.10)	107.51 (51.21)	0.003
UA, μmol/L	357.71 (137.94)	439.64 (181.29)	0.002
TG, mmol/L	1.79 (1.03)	1.88 (1.10)	0.64

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Dissolution group (n=166)	Residual group (n=39)	P
TC, mmol/L	4.11 (1.23)	4.15 (1.24)	0.87
HDL, mmol/L	1.37 (0.74)	1.51 (0.92)	0.29
LDL, mmol/L	2.77 (1.00)	2.83 (1.15)	0.72
TNT, μg/L	0.03 (0.04)	0.09 (0.17)	<0.001
NT-proBNP, pg/mL	1,563.90 (3,642.76)	3,774.26 (6,518.70)	0.005
AP, s	12.13 (2.42)	12.55 (1.88)	0.31
INR	1.70 (8.22)	1.12 (0.22)	0.66
APTT, s	29.19 (5.49)	29.52 (4.83)	0.72
TT, s	19.68 (5.95)	20.78 (9.78)	0.36
Fibrinogen, g/L	3.74 (1.49)	3.66 (1.46)	0.76
D-dimer, μg/mL	6.18 (6.46)	5.94 (6.29)	0.82
FDP, μg/mL	18.64 (15.81)	20.35 (17.19)	0.55
PASP, mmHg	39.20 (12.81)	60.44 (17.36)	<0.001
DVT	114 (68.7)	28 (71.8)	0.85
Major arterial embolism	38 (22.9)	30 (76.9)	<0.001

Data are presented as mean (SD) or count data (%). P<0.05 indicates a statistical difference. SPO_2, blood oxygen saturation; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, serum albumin; BUN, blood urea nitrogen; CR, serum creatinine; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low-density lipoprotein; TNT, troponin T; NT-proBNP, N-terminal brain natriuretic peptide; AP, prothrombin time; INR, international normalized ratio; APTT, activated partial thrombin time; TT, coagulation time; FDP, fibrin degradation products; PASP, pulmonary arterial systolic pressure; DVT, deep venous thrombosis; Major arterial embolism, left or right pulmonary embolism; SD, standard deviation.

thrombus residual (30.8% *vs.* 14.5%, P=0.03 and 61.5% *vs.* 24.7%, P<0.001). PE patients with clinical manifestations of breathing difficulties (97.4% *vs.* 70.5%, P<0.001), edema (64.1% *vs.* 36.7%, P=0.003), and acratia (48.7% *vs.* 11.4%, P<0.001) were more likely to have residual thrombus than asymptomatic patients. It is worth noting that the thrombus residual is also related to the laboratory indicators RBC (P=0.01), HB (P=0.001), BUN (P=0.003), CR (P=0.003), UA (P=0.002) is related to TNT (P<0.001), and there is no difference in other indicators (P>0.05). In the pulmonary systolic blood pressure (PASP) calculated using cardiac ultrasound, patients in the thrombus residual group had a higher PASP than the thrombolysis group (60.44 *vs.* 39.20 mmHg, P<0.001), in addition, patients with PE who develop major arterial embolism are more likely to have residual thrombus (76.9% *vs.* 22.9%, P<0.001). The results are detailed in in (*Table 1*) and (*Figure 2A*). ROC curve analysis was conducted to determine the optimal AUC value, which was then ranked in descending order as depicted in (*Figure 2B*,*2C*).

Risk factor screening and modeling

Based on the literature search results, 48 potential risk factors were identified from demographic characteristics, symptoms, physical and biochemical indexes, and examination results. Through univariate difference analysis, 16 indicators showed significant differences between the two groups. Subsequently, univariate and multivariate logistic regression analyses were conducted on these 16 indicators, resulting in the identification of five significant indicators: age, COPD, acratia, PASP, and major arterial embolism. The P value, odds ratio (OR) and confidence interval (CI) of the results of multivariate analysis of these five variables were age (P=0.012, OR =1.123; 95% CI: 1.026–1.23), COPD (P=0.002, OR =13.30; 95% CI: 2.673–66.188),

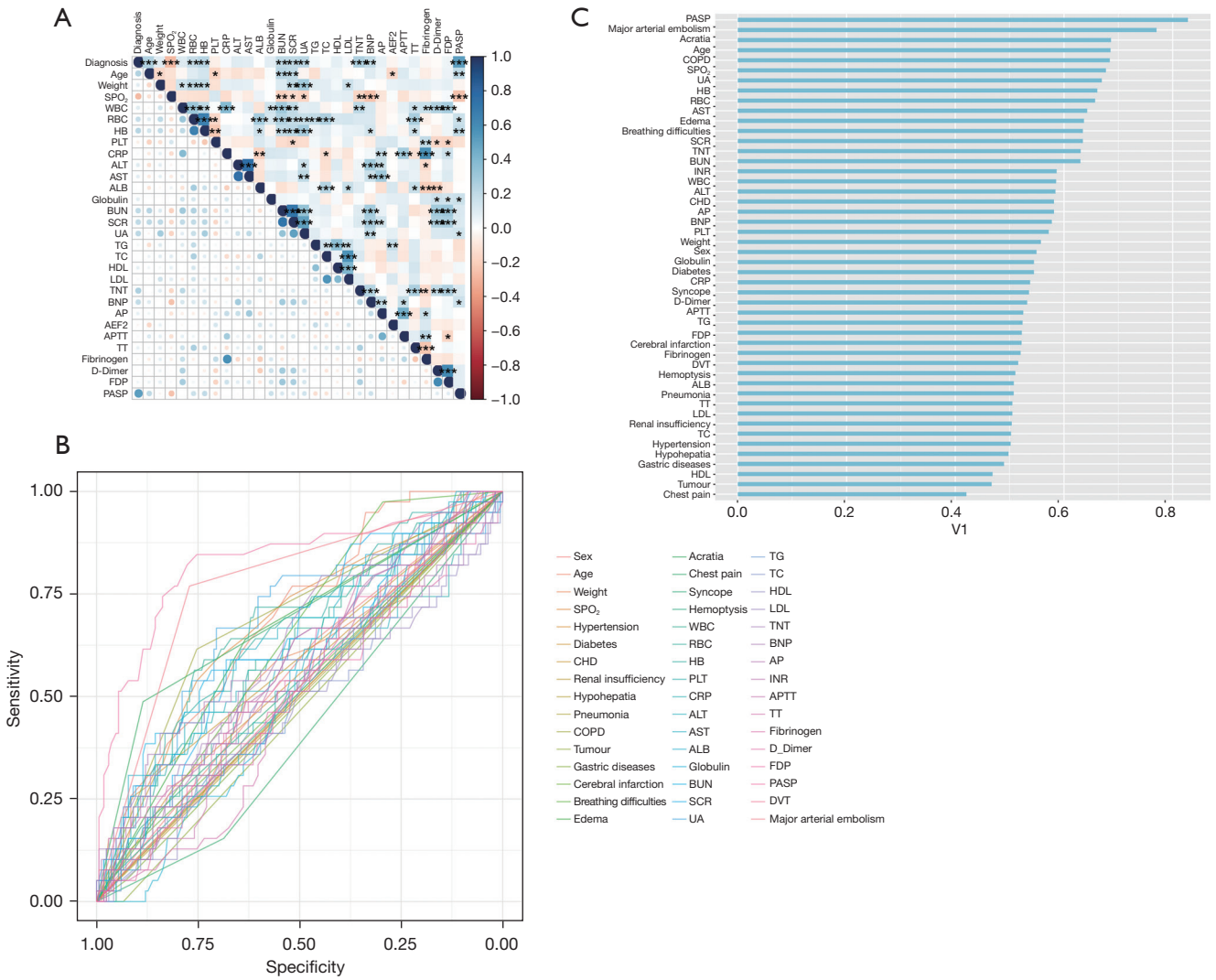

Figure 2 Difference analysis of different variables in anticoagulant treatment of acute pulmonary embolism patients. (A) Differential heat map analysis of continuous was carried out. *, P<0.05; **, P<0.01; ***, P<0.001. (B) ROC cure was drawn by difference analysis. (C) Sorted in descending order by AUC value size. SPO_2, blood oxygen saturation; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, serum albumin; BUN, blood urea nitrogen; CR, serum creatinine; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low-density lipoprotein; TNT, troponin T; NT-proBNP, N-terminal brain natriuretic peptide; AP, prothrombin time; INR, international normalized ratio; APTT, activated partial thrombin time; TT, coagulation time; FDP, fibrin degradation products; PASP, pulmonary arterial systolic pressure; DVT, deep venous thrombosis; Major arterial embolism, left or right pulmonary embolism; ROC, receiver operating characteristic; AUC, area under the curve.

acratia (P=0.001, OR =14.009; 95% CI: 2.782–70.547), PASP (P=0.003, OR =1.061; 95% CI: 1.020–1.103) and Major arterial embolism (P<0.001, OR =18.128; 95% CI: 3.853–85.293). Detailed results of univariate and multivariate analyses are shown (*Table 2*). LASSO regression screening variables were performed for risk factors (*Figure 3A,3B*). LASSO regression analysis obtained the common 5 non-zero coefficient characteristic variables: age, CODP, acratia, PASP and major arterial embolism. A model of 205 samples was constructed according to 85%:15% (Tables S1,S2), and the five variables screened by LASSO regression were analyzed by multivariate logistic

Table 2 Regression analysis of univariate and multivariate logistics

Variables	Univariate analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.081	1.034–1.131	0.001	1.123	1.026–1.23	0.01
SPO_2	0.914	0.868–0.963	0.001	1.002	0.917–1.095	0.95
CHD	2.63	1.175–5.887	0.01	1.539	0.380–6.229	0.54
COPD	4.878	2.338–10.176	<0.001	13.30	2.673–66.188	0.002
Breathing difficulties	5.915	2.125–19.18	0.007	3.429	0.267–43.990	0.34
Edema	3.074	1.487–6.355	0.002	1.002	0.278–3.611	0.99
Acratia	7.35	3.339–16.179	<0.001	14.009	2.782–70.547	0.001
RBC	1.662	1.118–2.471	0.01	1.511	0.522–4.373	0.44
HB	1.023	1.009–1.038	0.002	.986	0.956–1.016	0.35
BUN	1.128	1.036–1.229	0.005	1.000	1.000–1.000	0.45
CR	1.013	1.003–1.022	0.008	0.988	0.966–1.012	0.33
UA	1.004	1.001–1.006	0.003	1.002	0.997–1.007	0.51
TNT	2.113	1.14–4.323	0.007	1.324	0.91–1.034	0.06
NT-proBNP	1.14	1.004–1.745	0.01	1.0	1.0–1.0	0.45
PASP	1.089	1.06–1.119	<0.001	1.061	1.020–1.103	0.003
Major arterial embolism	11.228	4.905–25.704	<0.001	18.128	3.853–85.293	<0.001

OR, odds ratio; CI, confidence interval; SPO_2, blood oxygen saturation; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; RBC, red blood cell count; HB, hemoglobin; BUN, blood urea nitrogen; CR, serum creatinine; UA, uric acid; TNT, troponin T; NT-proBNP, N-terminal brain natriuretic peptide; PASP, pulmonary arterial systolic pressure; Major arterial embolism, left or right pulmonary embolism.

regression. These 5 variables were identified as independent risk factors for RPVO, and a nomogram was constructed, as shown in (*Figure 3C*). Prediction of residual thrombosis risk post regular anticoagulant therapy is based on a nomogram incorporating COPD, acratia, PASP, and major arterial embolism. By utilizing LASSO regression to fit the model, we can obtain the regression coefficient β, which indicates the impact of variables on the target prediction. The nomogram is constructed by selecting the variable with the highest coefficient β (PASP) as a reference point. Scores for each variable in the nomogram are then calculated based on the ratio of the regression coefficient of other variables to the reference coefficient, allowing for the prediction of residual PE probability. By determining the scores for each predictor, the corresponding probability can be derived by locating the predictor value on the nomogram. The cumulative sum of all predictor scores provides the probability of disease occurrence.

Internal verification

To validate the prediction model and evaluate the Nomogram diagnostic performance, we used an internal validation procedure based on random classification validation. The ROC curves of the model showed that the AUC of the training set and the test set were 0.94 (95% CI: 0.89–0.96) and 0.93 (95% CI: 0.88–0.95), respectively, as shown in (*Figure 4A*,*4B*), and C-index is 0.93, which indicated that the model had good consistency and reliability compared with observation results. The calibration curve shows a good agreement between the probability predicted by the Nomo chart and the actual probability (*Figure 4C*).

Discussion

Pulmonary thromboembolism is a critical cardiovascular condition that can lead to short-term mortality rates as

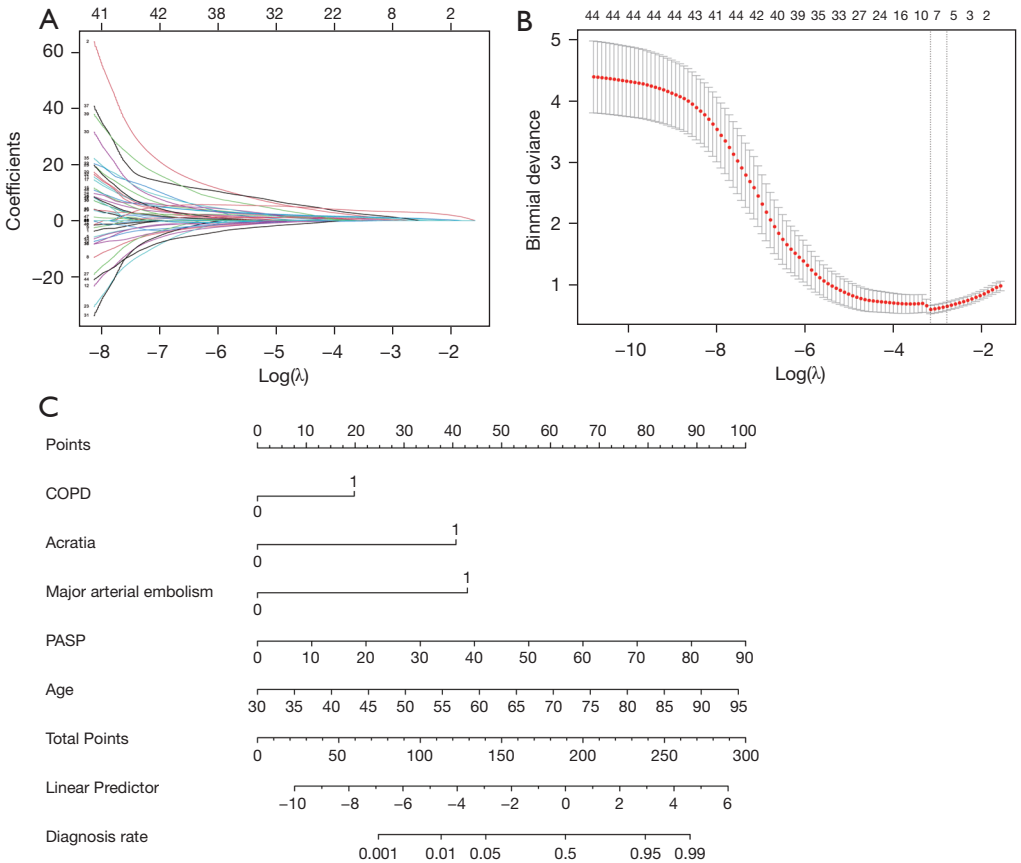

Figure 3 Predictor variables selection using the LASSO. (A) LASSO coefficient curves of 48 predictors were plotted according to log(λ) sequence. Vertical lines are drawn at values selected using ten-fold cross-validation, where the optimal 1 results in 5 nonzero coefficient. (B) After verifying the optimal λ, plot the partial likelihood deviation against log(λ) and plot the vertical dashed line according to the 1–SE criterion. (C) The probability of residual thrombus after anticoagulant treatment of acute pulmonary embolism is predicted by nomogram. COPD, chronic obstructive pulmonary disease; PASP, pulmonary systolic blood pressure; LASSO, least absolute shrinkage and selection operator; SE, standard error.

high as 30% (18) if left untreated. Advances in medical treatments have significantly reduced the mortality rate of acute non-high-risk PE to 3% (19). However, some patients may still experience RPVO even after three months of conventional anticoagulant therapy, necessitating prolonged treatment or surgical intervention for chronic thrombosis. This study aims to identify the factors influencing treatment outcomes by analyzing the medical history, clinical symptoms, physical signs, and laboratory findings of hospitalized patients with APE over the past three years. Through this analysis, we have identified five key risk factors that can accurately predict high-risk patients with residual pulmonary thrombosis. A nomogram scoring system has been developed based on these risk factors, which has demonstrated strong predictive power. This scoring system can help clinicians predict the risk of RPVO following sequential anticoagulation therapy in patients with acute pulmonary thromboembolism. By utilizing this score, healthcare professionals can tailor treatment plans more effectively, detect thrombus residue early in at-risk patients, and closely monitor changes in pulmonary thrombus formation.

In our nomogram, the most predictive factors were PASP and age, followed by major arterial embolism, acratia, and COPD. The area of pulmonary thromboembolism is known to influence the course and choice of anticoagulation therapy and is linked to clinical symptoms. Thrombolysis is recommended for cases of massive and submassive PE accompanied by hemodynamic instability (20). PASP is a key cardiovascular indicator, determined by the formula of tricuspid valve regurgitation velocity and right ventricular (RV) pressure through echocardiography, rather than the

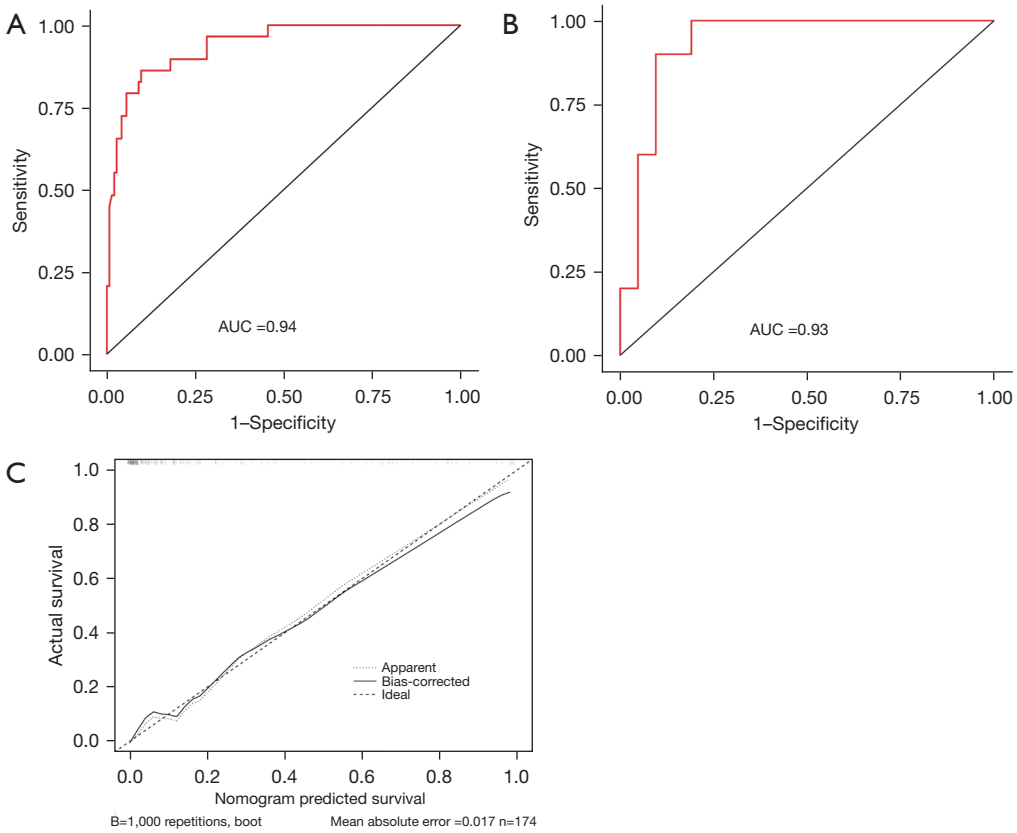

Figure 4 ROC curve and calibration curve verified model reliability and model prediction ability. Subject operation characteristic curve analysis in training set (A) and test set (B). The horizontal coordinate represents the false positive rate predicted by the model, and the vertical coordinate represents the true positive rate predicted by the model. (C) Calibration curves of the training set and validation set risk prediction models for thrombotic residual after anticoagulant therapy for acute pulmonary embolism. The X-axis represents the predicted risk of developing thrombotic residue, the Y-axis represents the actual diagnosis of thrombotic residue, and the dashed diagonal line represents the perfect prediction of the ideal model. Solid lines represent the performance of the model; the closer you get to the diagonal dotted line, the more accurate the model will be. ROC, receiver operating characteristic; AUC, area under the curve.

traditional invasive measurement of pulmonary artery pressure with right cardiac catheter. It is associated with RV overload, which can impact the prognosis of moderate and high-risk PE (21). Research has demonstrated a positive correlation between the area of PE and pulmonary artery systolic blood pressure. Specifically, when the embolization area surpasses 33%, the pulmonary artery systolic blood pressure exceeds 41mmHg, and if the embolization area goes beyond 40%, the pulmonary artery systolic blood pressure rises above 70 mmHg (15). Furthermore, the variations in PASP following acute pulmonary thromboembolism were found to be closely linked to the size of the embolization area (22,23). The findings of this research align with those of the current study. The average PASP of the group with residual PE thrombus was 60.44 mmHg in this study, significantly higher than that of the thrombolysis group (39.2 mmHg). In cases without severe left heart disease, PASP may provide insight into the extent of pulmonary thromboembolism and its correlation with residual pulmonary artery blockage after three months of anticoagulant therapy. It can affect the course and prognosis of anticoagulant treatment of acute pulmonary thromboembolism. Unfortunately, there are currently no imaging tools available to quantify the area of the clot, so it is not possible to directly measure the size of the clot to evaluate anticoagulant therapy. In this study, CTPA was used to examine the presence of left or right pulmonary arteries embolism in the early stage of PE. It was found that major arterial embolism also associated with predicting residual thrombus after symptomatic pulmonary

thromboembolism anticoagulation therapy, which is directly related to an increase in PASP.

A study of 647 patients who were first diagnosed with PE followed for up to 3 years found that older patients with PE were more likely to develop residual pulmonary artery obstruction (24). In addition, a prospective cohort study of 537 patients with acute pulmonary thromboembolism followed for 3 to 24 months found that patients older than 65 years were more likely to develop residual pulmonary obstruction (25). In this study, the average age of patients in the thrombus residual group was 77.33 years old, which was higher than that in the thrombolysis group of 36.95 years old, which was consistent with the above research results, indicating that older patients with pulmonary thromboembolism were more likely to affect the efficacy after anticoagulation, resulting in residual pulmonary artery obstruction. The reasons may be related to the following factors: first of all, with the growth of age, the physiological function of the body organs will undergo corresponding changes, and the digestion and absorption of the gastrointestinal tract of the elderly will be reduced, which reduces the blood concentration of oral rivaroxaban, thereby increasing the course of anticoagulant treatment. Second, a study on age and severity of PE found that advanced age is a risk factor for submassive PE (APE is associated with RV dysfunction, except for massive PE) (26). The proportion of patients with submassive PE, RV overload, and elevated PASP increased with age (15). Therefore, advanced age may influence the effectiveness of anticoagulant treatment to some extent. Consequently, as age increases, the risk of developing massive PE also rises, which in turn exacerbates the elevation of PASP, leading to excessive RV strain and hemodynamic instability. It is important to note that high-risk patients with PE were not included in this study, suggesting a potential area for future research.

In this study, we were surprised to find that acratia also has the ability to predict thrombi residual after symptomatic PE. Research have found (27) that the severity of PE is correlated with clinical symptoms to a certain extent. The more severe PE is, the greater the change in ventilaty-blood flow ratio and the decrease in blood oxygenation capacity will further lead to the emergence of clinical symptoms.

Shortcomings of this study, as this study is a retrospective single-center study rather than a population-based study or a national survey, there is inevitable selection bias, and further large-scale multi-center prospective studies are needed.

Conclusions

This study presents a 5-variable clinical prediction model that demonstrates strong accuracy in predicting the risk of RPVO in patients with acute symptomatic PE following anticoagulant therapy. Clinicians can utilize this model to monitor key research indicators during anticoagulant therapy and mitigate the likelihood of adverse outcomes.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1876/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1876/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1876/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Third People's Hospital of Yunnan Province (No. 2023KY041) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Difference of pulmonary thrombolysis group and residual group in training group

Variables	Dissolution group (N=145)	Residual group (N=29)	P
Sex (male)	79 (54.5)	19 (65.5)	0.37
Age, years	70.16 (12.49)	77.59 (6.61)	0.002
Weight, kg	63.73 (10.05)	65.59 (9.38)	0.36
SPO_2	89.32 (5.42)	84.14 (9.16)	<0.001
Pre-existing disease			
Hypertension	84 (57.9)	17 (58.6)	>0.99
Diabetes	29 (20.0)	10 (34.5)	0.14
CHD	21 (14.5)	9 (31.0)	0.059
Renal insufficiency	16 (11.0)	3 (10.3)	>0.99
Hypohepatia	21 (14.5)	5 (17.2)	0.92
Pneumonia	108 (74.5)	22 (75.9)	>0.99
COPD	36 (24.8)	16 (55.2)	0.002
Tumour	8 (5.5)	0 (0.0)	0.41
Gastric diseases	11 (7.6)	2 (6.9)	>0.99
Cerebral infarction	12 (8.3)	4 (13.8)	0.55
Symptoms			
Breathing difficulties	102 (70.3)	28 (96.6)	0.006
Edema	51 (35.2)	17 (58.6)	0.03
Acratia	18 (12.4)	15 (51.7)	<0.001
Chest pain	47 (32.4)	5 (17.2)	0.15
Syncope	16 (11.0)	4 (13.8)	0.91
Hemoptysis	3 (2.1)	2 (6.9)	0.41
WBC, $\times10^9$/L	7.97 (3.27)	8.79 (3.08)	0.21
RBC, $\times10^{12}$/L	4.51 (0.89)	4.88 (0.80)	0.03
HB, g/L	133.12 (28.99)	151.21 (26.16)	0.002
PLT, $\times10^9$/L	204.90 (83.22)	185.75 (111.50)	0.28
CRP, mg/L	32.46 (50.87)	43.11 (53.99)	0.31
ALT, U/L	29.01 (36.76)	45.01 (71.40)	0.07
AST, U/L	33.79 (55.19)	49.76 (48.60)	0.14
ALB, g/L	37.21 (6.13)	36.84 (4.59)	0.76
Globulin, g/L	27.72 (4.96)	27.82 (4.67)	0.92
BUN, mmol/L	6.33 (3.63)	8.77 (4.65)	0.002
CR, μmol/L	87.95 (30.66)	111.62 (57.76)	0.002
UA, μmol/L	352.94 (136.11)	430.31 (198.15)	0.011
TG, mmol/L	1.81 (1.07)	1.94 (1.15)	0.56
TC, mmol/L	4.09 (1.22)	4.16 (1.13)	0.79
HDL, mmol/L	1.38 (0.76)	1.41 (0.85)	0.84
LDL, mmol/L	2.76 (1.01)	2.71 (0.93)	0.81
TNT, ug/L	0.03 (0.04)	0.09 (0.17)	<0.001
NT-proBNP, pg/mL	1362.29 (2546.68)	4846.06 (7262.30)	<0.001
AP, s	12.21 (2.55)	12.74 (1.95)	0.29
INR	1.80 (8.80)	1.14 (0.24)	0.68
APTT, s	29.42 (5.61)	30.06 (4.41)	0.56
TT, s	19.92 (6.32)	20.37 (8.77)	0.74
Fibrinogen, g/L	3.79 (1.53)	3.84 (1.56)	0.86
D-Dimer, ug/mL	6.16 (6.60)	5.56 (6.20)	0.65
FDP, ug/mL	18.19 (15.87)	19.93 (16.60)	0.59
PASP, mmHg	39.15 (12.87)	60.03 (16.74)	<0.001
DVT	101 (69.7)	22 (75.9)	0.65
Major arterial embolism	32 (22.1)	22 (75.9)	<0.001

Data are presented as mean (SD) or count data (%). SPO_2, blood oxygen saturation; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, serum albumin; BUN, urea nitrogen; CR, serum creatinine; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low-density lipoprotein; TNT, troponin T; NT-proBNP, N-terminal brain natriuretic peptide; AP, prothrombin time; INR, international normalized ratio; APTT, activated partial thrombin time; TT, coagulation time; FDP, fibrin degradation products; PASP, pulmonary arterial systolic pressure; DVT, deep venous thrombosis; Major arterial embolism, left or right pulmonary embolism. P<0.05 indicates a statistical difference.

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Table S2 Differences between training set and test set

Variables	Training set (N=174)	Test set (N=31)	P
Sex (male)	98 (56.3)	17 (54.8)	>0.99
Age, years	71.40 (12.03)	71.13 (9.52)	0.90
Weight, kg	64.04 (9.94)	65.29 (10.21)	0.52
SPO_2	88.46 (6.46)	88.42 (8.89)	0.97
Pre-existing disease			
Hypertension	101 (58.0)	14 (45.2)	0.25
Diabetes	39 (22.4)	4 (12.9)	0.33
CHD	30 (17.2)	6 (19.4)	0.97
Renal insufficiency	19 (10.9)	6 (19.4)	0.30
Hypohepatia	26 (14.9)	1 (3.2)	0.13
Pneumonia	130 (74.7)	20 (64.5)	0.33
COPD	52 (29.9)	13 (41.9)	0.26
Tumour	8 (4.6)	3 (9.7)	0.46
Gastric diseases	13 (7.5)	1 (3.2)	0.63
Cerebral infarction	16 (9.2)	3 (9.7)	>0.99
Symptoms			
Breathing difficulties	130 (74.7)	25 (80.6)	0.6
Edema	68 (39.1)	18 (58.1)	0.07
Acratia	33 (19.0)	5 (16.1)	0.90
Chest pain	52 (29.9)	6 (19.4)	0.32
Syncope	20 (11.5)	5 (16.1)	0.66
Hemoptysis	5 (2.9)	2 (6.5)	0.63
WBC, $\times10^9$/L	8.11 (3.24)	7.56 (2.12)	0.36
RBC, $\times10^{12}$/L	4.57 (0.88)	4.34 (0.64)	0.16
HB, g/L	136.14 (29.26)	132.39 (19.72)	0.49
PLT, $\times10^9$/L	201.71 (88.47)	205.42 (72.78)	0.82
CRP, mg/L	34.23 (51.39)	15.68 (24.22)	0.050
ALT, U/L	31.68 (44.56)	38.70 (68.18)	0.46
AST, U/L	36.45 (54.34)	45.89 (91.37)	0.43
ALB, g/L	37.15 (5.89)	37.32 (6.30)	0.88
Globulin, g/L	27.73 (4.90)	28.04 (5.06)	0.74
BUN, mmol/L	6.74 (3.91)	6.59 (2.97)	0.84
CR, μmol/L	91.90 (37.42)	92.39 (30.87)	0.94
UA, μmol/L	365.83 (150.37)	415.19 (144.30)	0.09
TG, mmol/L	1.84 (1.08)	1.67 (0.76)	0.40
TC, mmol/L	4.10 (1.20)	4.23 (1.35)	0.59
HDL, mmol/L	1.39 (0.78)	1.43 (0.78)	0.77
LDL, mmol/L	2.75 (1.00)	2.94 (1.21)	0.36
TNT, ug/L	0.04 (0.08)	0.05 (0.10)	0.63
NT-proBNP, pg/mL	1942.91 (3953.46)	2217.31 (6461.67)	0.75
AP, s	12.30 (2.46)	11.72 (1.28)	0.20
INR	1.69 (8.03)	1.04 (0.14)	0.65
APTT, s	29.53 (5.42)	27.71 (4.81)	0.08
TT, s	20.00 (6.76)	19.31 (7.29)	0.60
Fibrinogen, g/L	3.79 (1.53)	3.35 (1.11)	0.12
D-Dimer, ug/mL	6.06 (6.52)	6.59 (5.85)	0.67
FDP, ug/mL	18.48 (15.96)	21.71 (16.54)	0.30
PASP, mmHg	42.63 (15.63)	46.65 (18.35)	0.20
DVT	123 (70.7)	19 (61.3)	0.40
Major arterial embolism	54 (31.03)	14 (45.16)	0.12

Data are presented as mean (SD) or count data (%). SPO_2, blood oxygen saturation; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PLT, platelet; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, serum albumin; BUN, urea nitrogen; CR, serum creatinine; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low-density lipoprotein; TNT, troponin T; NT-proBNP, N-terminal brain natriuretic peptide; AP, prothrombin time; INR, international normalized ratio; APTT, activated partial thrombin time; TT, coagulation time; FDP, fibrin degradation products; PASP, pulmonary arterial systolic pressure; DVT, deep venous thrombosis; Major arterial embolism, left or right pulmonary embolism. $P<0.05$ indicates a statistical difference.

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