CONSTRUCTION AND EFFICACY OF A NOMOGRAM PREDICTION MODEL FOR HIGH RISK OF ACUTE PULMONARY EMBOLISM BASED ON CLINICAL AND BIOCHEMICAL INDEXES

Guixia Peng*, Zhixu Chen, Huagen Zhang
Department of Respiratory Intensive Care, Meizhou People's Hospital, Meizhou 514031, Guangdong Province, China

ABSTRACT

Objective: *To establish a nomogram model for predicting the high risk of acute pulmonary embolism (APE) based on clinical and biochemical indexes.*

Methods: *262 patients with acute exacerbation of chronic obstructive pulmonary disease in the respiratory department of our hospital from May 2017 to May 2020 were selected as the research subjects; 80 patients with acute pulmonary embolism formed the experimental group, and the remaining 182 patients formed the control group. The clinical data and laboratory examination indexes within 24 hours of admission were collected, and the risk factors of acute pulmonary embolism in patients with chronic obstructive pulmonary disease were analyzed by multivariate logistic regression analysis. The nomogram model for predicting acute pulmonary embolism in patients with chronic obstructive pulmonary disease was constructed with the RMS software package in R version 3.5.2, and an ROC curve analysis model was used to diagnose the critical value.*

Results: *There were no significant differences in gender, hypertension, chronic kidney disease, or WBC level between the two groups (P>.05). The experimental group contained a significantly greater proportion of patients ≥ 65 years old, smokers, and patients with diabetes and coronary heart disease than the control group (P<.05). The levels of Hb, RDW, NLR, PLR, CRP, SCR, D-D, IMA, HMGB1, and ACA in the experimental group were significantly lower than those in the control group (P<.05). Multivariate logistic regression analysis showed that age ≥65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5 μg/L were independent risk factors for acute pulmonary embolism in patients with chronic obstructive pulmonary disease (P<.05). These factors were used in the model as predictors of acute pulmonary embolism. ROC curve analysis showed that the area under the curve of the nomogram model was .861 (95% CI = .718-.925).*

Conclusion: *Age ≥65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5 μg/L are independent risk factors of acute pulmonary embolism in patients with chronic obstructive pulmonary disease.*

Keywords: *Clinical and biochemical indicators, acute pulmonary embolism, high risk, nomogram prediction model, efficacy.*

DOI: 10.19193/0393-6384_2022_1_56

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Acute pulmonary embolism (APE) is a pathological process in which a detached thrombus or other substance blocks the pulmonary artery or its branches. Pulmonary hemorrhage or necrosis is called pulmonary infarction. APE is a cardiovascular disease that poses a serious danger to human health, featuring high morbidity, high mortality, and high rates of missed diagnosis and misdiagnosis, with a morbidity surpassed only by coronary heart disease and hypertension, and a mortality surpassed only by tumor and myocardial infarction[1]. Patients with APE are prone to sudden right ventricular failure and sudden death. The mortality of untreated patients is 30% and can be reduced by about 2% to 8% with treatment. The prevention and treatment of APE have been generally neglected. Early identification of patients at a high risk of pulmonary embolism allows early intervention to improve the prognosis

and reduce the rates of mortality and disability[2, 3]. Blood biochemical markers for the current clinical diagnosis of APE include D-dimer (D-D), ischemia-modified albumin (IMA), high mobility group proteins (HMGB1), and anticardiolipin antibody (ACA). Blood biochemical marker analysis to predict APE is underutilized due to the lack of effective statistical methods[4]. A nomogram prediction model is an intuitive scoring system for the relationship between variables and outcome events that can optimize the accuracy of individual prediction. Such models have been developed for many cancer types for prognosis evaluation[5, 6]. At present, a nomogram prediction model for patients with a high risk of APE has not been constructed. This study presents a high-risk nomogram prediction model based on clinical and biochemical indexes for patients with APE and analyzes its efficacy as an effective and reliable risk assessment method.

Methods

General materials

This study was examined and approved by the Medical Ethics Committee of our hospital. 262 patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) in the respiratory department of our hospital from May 2017 to May 2020 were selected as the research subjects. 80 patients with APE were included in the experimental group. Patients were included who met the diagnostic criteria of China Expert Consensus on Diagnosis and Treatment of APE of Chinese Society of Cardiology[7]; lacked inhibited liver, kidney, and other organ function or other basic lung diseases; had normal mental consciousness; and had complete clinical data. Patients were excluded who were less than 18 years old; had deceased or been lost; had malignant lung tumors, acute cerebral infarction, or acute myocardial infarction; had pulmonary embolism diagnosed before admission; had rheumatic immune system diseases and malignant tumors; or had damaged lung tissue due to tuberculosis or bronchiectasis. The remaining 182 patients were included in the control group. All patients provided complete clinical data and both patients and their families gave informed consent to participate in the study.

Methods

The clinical data and laboratory examination indexes within 24 hours of admission were collected. The clinical data included age, gender, smoking history (≥3 cigarettes per day for 1 year or more), and basic diseases (hypertension, diabetes, chronic kidney disease, and coronary heart disease). Laboratory indicators included white blood cell (WBC), hemoglobin (Hb), red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein (CRP), serum creatinine (Scr), D-D, IMA, HMGB1, and ACA.

Statistical methods

SPSS 21.0 statistical software was used to analyze the data in this study. The normally distributed measurement data were expressed by (). Independent sample t-tests were used for comparison between groups; ($\bar{x}\pm s$). The partially distributed measurement data were expressed by M (Q1, Q3), and the data between the two groups were tested with a nonparametric test. The counting data were represented by n (%), and χ^2 tests were used to test the relationship between the two groups.

Multivariate logistic regression analysis was used to assess the risk factors of APE in patients with COPD. The relative risk (OR) and 95% CI of each risk factor to pulmonary embolism were calculated. The nomogram model was constructed with the RMS software package in R version 3.5.2. The critical value of the model was analyzed with an ROC curve and P<.05 was regarded as statistically significant.

Results

Comparison of clinical data and laboratory examination indexes between two groups

There was no significant difference in gender, hypertension, chronic kidney disease, or WBC level between the two groups (P>.05). The experimental group contained a significantly greater proportion of patients aged ≥65 years old, smokers, and patients with diabetes and coronary heart disease than the control group (P<.05).

The levels of Hb in the experimental group were significantly lower than those in the control group and the levels of RDW, NLR, PLR, CRP, SCR, D-D, IMA, HMGB1, and ACA in the experimental group were significantly higher than those in the control group (P<.05). See Table 1.

Multivariate logistic regression analysis

The indexes with statistical significance in Table 1 were used as independent variables, and the occurrence of APE was considered the dependent

variable (see Table 2) for multivariate logistic regression analysis. The results show that the age ≥ 65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5μg/L are independent risk factors of APE in patients with COPD (P<.05). See Table 3.

Variable		Experimental group (n = 80)	Control group (n = 182)		
Age	< 55	25 (35.00)	100 (54.95)	10.948	.001
	≥ 65	52 (65.00)	82 (45.05)		
Gender	Male	51 (63.75)	108 (59.34)	.453	.501
	Female	29 (36.25)	74 (40.66)		
Smoking		48 (60.00)	76 (41.76)	7.418	.006
Basic disease	Hypertension	8 (10.00)	19 (40.44)	.112	.914
	Diabetes	22 (27.50)	25 (13.74)	7.152	.007
	Chronic renal failure	8 (10.00)	14 (7.69)	.385	.535
	Coronary heart disease	18 (22.5)	15 (9.89)	10.262	.001
WBC (×10⁹/L)		9.35±4.56	9.48±3.99	.232	.817
Hb (g/dl)		14.51±2.54	15.78±1.62	4.865	<.001
RDW (%)		18.75±3.58	17.62±3.43	2.423	.016
NLR		6.72±1.68	3.11±1.74	13.550	<.001
PLR		162.63±66.25	130.25±74.15	3.360	.001
CRP (mg/dl)		4.12±1.46	2.05±1.66	9.633	<.001
Scr (μmol/L)		125.63±54.28	70.16±25.49	11.265	<.001
D-D (mg/L)		2.53±.87	1.26±.25	18.104	<.001
IMA (μg/L)		45.75±8.06	25.03±7.50	20.127	<.001
HMGB1 (μg/L)		9.62±.65	2.34±.50	98.687	<.001
ACA (ng/L)		3.16±.83	1.23±.15	30.333	<.001

Table 1: Comparison of clinical data and laboratory examination indexes between experimental and control groups.

Code	Variable	Assignment
X1	Age	1 = ≥ 65, 0 = < 65
X2	Smoking	1 = yes, 0 = no
X3	Diabetes	1 = yes, 0 = no
X4	Coronary heart disease	1 = yes, 0 = no
X5	Hb	1 = ≥ 12 g/dl, 0 = < 12 g/dl
X6	RDW	1 = ≥ 19.7%, 0 = < 19.7%
X7	NLR	1 = ≥ 3.5, 2 = < 3.5
X8	PLR	1 = ≥ 146.9, 2 = < 146.9
X9	CRP	1 = ≥ 2.2 mg/dl, 2 = < 2.5 mg/dl
X10	Scr	1 = ≥ 91.72 μmol/L, 2 = < 91.72 μmol/L
X11	D-D	1 = ≥ 1.3 mg/L, 2 = < 1.3 mg/L
X12	IMA	1 = ≥ 26.4 μg/L, 2 = < 26.4 μg/L
X13	HMGB1	1 = ≥ 2.58 μg/L, 2 = < 2.58 μg/L
X14	ACA	1 = ≥ 1.5 μg/L, 2 = < 1.5 μg/L
Y	APE	1 = occurred, 2 = did not occur

Table 2: Variable assignment of influencing factors of APE in patients with COPD.

Variable	β	*SE*	Wald	*P*	*OR*	95% *CI*
Age ≥ 65	1.288	.376	10.825	.001	3.613	1.685-7.762
Smoking	1.262	.905	1.991	.149	1.579	0.610-9.652
Diabetes	2.115	.730	8.216	.064	2.221	1.962-9.261
Coronary heart disease	1.455	1.172	1.526	.201	1.221	0.416-8.263
Hb ≥ 12 g/dl	-.678	1.019	.442	.501	.512	0.075-3.624
RDW ≥ 19.7%	1.389	.982	1.957	.152	1.012	0.654-8.267
NLR ≥ 3.5	2.261	.670	11.389	.001	6.555	2.416-11.267
PLR ≥ 146.9	1.505	.673	4.909	.066	4.551	1.928-12.389
CRP ≥ 2.2 mg/dl	.431	.150	5.088	.003	3.556	1.152-6.082
Scr ≥ 91.72 μmol/L	1.772	1.062	2.711	.098	1.935	0.712-9.236
D-D ≥ 1.3 mg/L	1.739	.450	11.992	< .001	5.699	2.351-13.741
IMA ≥ 26.4 μg/L	2.330	.425	15.262	< .001	7.490	3.725-14.450
HMGB1 ≥ 2.58 μg/L	1.711	.375	19.662	< .001	5.524	2.541-11.785
ACA ≥ 1.5 μg/L	.991	.423	5.216	.002	2.681	1.142-6.304

Table 3: Multivariate logistic regression analysis of the influencing factors of APE in patients with COPD.

Nomogram model construction and prediction value

Age ≥65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5 μg/L were used as nomogram model predictors of APE (see Figure 1). ROC curve analysis showed that the area under the curve of the nomogram model predicting APE was .861 (95% CI=.718-.925). See Figure 2.

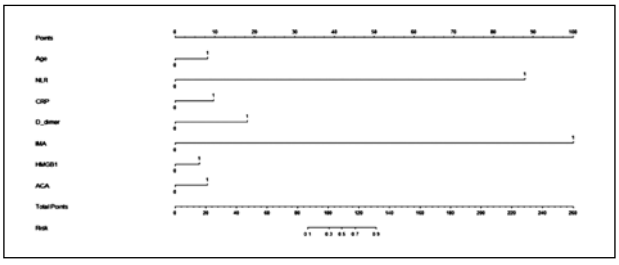

Figure 1: Construction of nomogram model of APE risk in patients with COPD.

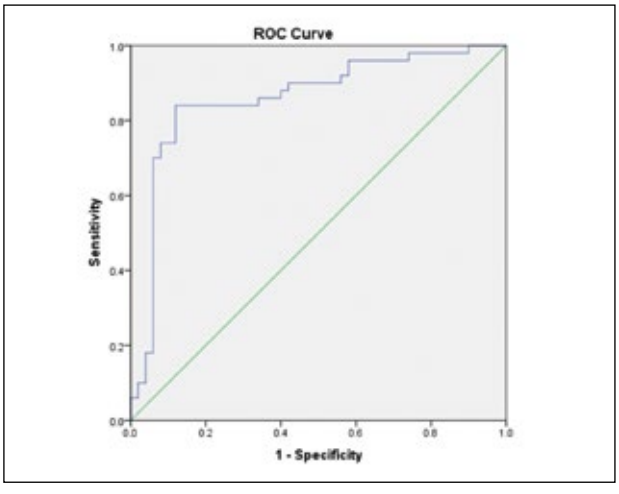

Figure 2: ROC curve of nomogram model for predicting the risk of APE in patients with COPD.

Discussion

APE (morbidity 1.12) is the third-most-common fatal cardiovascular disease, after coronary heart disease and hypertension, and mainly causes intravascular coagulation or shock by affecting pulmonary blood circulation and deteriorating blood perfusion in important organs. Because of its non-specific clinical manifestations, APE features urgent clinical onset and high rates of misdiagnosis and missed diagnosis[8, 9]. About 100,000 to 200,000 patients annually die from APE. Less than 10% of patients are diagnosed and treated and most patients are missed, seriously threatening their lives[10].

Various diagnostic technologies have gradually been developed with advances in science and technology, among which clinical biochemical indicators (such as D-D, IMA, HMGB1, and ACA) have been increasingly used in the clinical diagnosis of patients with APE. Some scholars have tried to improve the predictive value of clinical biochemical indicators for the risk of APE by improving the predictive tools used[11].

A nomogram model is a statistical model for individual prediction and analysis of clinical events that provides better individual prognosis risk assessment than other predictive statistical methods. A nomogram model predicting the risk of APE was successfully constructed based on clinical and biochemical indicators to screen patients at high risk of APE and provide a theoretical basis for optimizing the treatment plan. The study results show that age ≥65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5 μg/L are independent risk factors of APE in patients with COPD (P<.05). At present, NLR and CRP are simple and widely used as low-cost inflammatory response markers available in whole blood. NLR ≥3.5 and CRP ≥2.2 mg/dl are risk factors for APE, which indicates that the degree of inflammatory response is related to the risk of death. D-D is a specific degradation product of cross-linked fibrin under the action of the fibrinolytic system, which reflects the fibrinolytic function of blood clotting substances in vivo. In APE, its level is significantly increased. It is highly sensitive with a low specificity in the diagnosis of APE[12]. IMA is a non-specific ischemic marker formed after ischemia-reperfusion, with high sensitivity to myocardial ischemia. Studies have shown that serum IMA levels in APE patients are significantly higher than those in non-APE patients and the healthy population, with high specificity for the diagnosis of APE and positive predictors higher than D-D[13]. HMGB1 plays a regulatory transcription role in the nucleus in inflammation and immune responses[14]. ACA, as an autoantibody produced by negatively charged cardiolipin in the vascular intima, is significant in multiple thrombosis and plays an important role in the early diagnosis and disease monitoring of pulmonary embolism[15]. The above risk factors are included in the nomogram model. ROC curve analysis results show that the area under the curve of the nomogram model predicting APE was .861 (95% CI=.718-.925). Therefore, the nomogram model can objectively evaluate the risk of APE from the degree of the inflammatory response, nutrition, and metabolic conditions.

In conclusion, age ≥65 years old, NLR ≥3.5, CRP ≥2.2 mg/dl, D-D ≥1.3 mg/L, IMA ≥26.4 μg/L, HMGB1 ≥2.58 μg/L, and ACA ≥1.5 μg/L are independent risk factors of APE in patients with COPD. The construction of a nomogram model allows for a better prediction of the risk of acute pulmonary embolism. However, this study has some limitations. This study is a retrospective study with biased findings. This may reduce the prediction effect of the nomogram model due to the small sample size included; clinical biochemical indicators may also be affected by other diseases or drugs.

Although patients with pulmonary inflammatory diseases other than APE were excluded, inflammatory responses due to other causes may have been present.

References

1) Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost 2020; 26: 1076029620938149.

2) Akgedik R, Karamanli H, Aytekin İ, Kurt AB, Öztürk H, Dağlı CE. Swyer-James-Macleod syndrome mimicking an acute pulmonary embolism: a report of six adult cases and a retrospective analysis. Clin Respir J 2018; 12(2): 404-409.

3) Akyil F T, Akyil M, Topbas A. Is there Any Relationship Between Long-Term Mortality of Acute Pulmonary Embolism and Complete Blood Count Analysis? 2019.

4) Konstantinides SV, Barco S. Systemic Thrombolytic Therapy for Acute Pulmonary Embolism: Who Is a Candidate? Semin Respir Crit Care Med 2017; 38(1): 56-65.

5) Reissig A, Heyne JP, Kroegel C. Sonography of lung and pleura in pulmonary embolism: sonomorphologic characterization and comparison with spiral CT scanning. Chest 2001; 120(6): 1977-83.
6) Miller GA, Sutton GC, Kerr IH, Gibson RV, Honey M. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Med J. 1971; 2(5763): 681-4.
7) Section of Precision Medical of Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology, Myocarditis W G O A D. Chinese expert consensus statement on clinical diagnosis and treatment of fulminant myocarditis in adults. Zhonghua Xin Xue Guan Bing Za Zhi, 2017.
8) Browse NL, Clemenson G, Bateman NT, Gaunt JI, Croft DN. Effect of intravenous dextran 70 and pneumatic leg compression on incidence of postoperative pulmonary embolism. Br Med J 1976; 2(6047): 1281-4.
9) Turetz M, Sideris AT, Friedman OA, Triphathi N, Horowitz JM. Epidemiology, Pathophysiology, and Natural History of Pulmonary Embolism. Semin Intervent Radiol 2018; 35(2): 92-98.
10) Bikdeli B, Ziki MDA, Lip GYH. Erratum: Pulmonary Embolism and Atrial Fibrillation: Two Sides of the Same Coin? A Systematic Review. Semin Thromb Hemost 2017; 43(8): e1.
11) Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, et al. Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. J Am Coll Cardiol 2017: 1536-1544.
12) Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014; 311(11): 1117-24.
13) Yan L I, Liu L, Pei Y F. Application value of four blood coagulation combined with serum PCT, AT-III and D-D levels in the evaluation of patients with sepsis. Journal of Medical Forum, 2019.
14) Vermeer F, Bösl I, Meyer J, Bär F, Charbonnier B, et al. Saruplase is a safe and effective thrombolytic agent; observations in 1,698 patients: results of the PASS study. Practical Applications of Saruplase Study. J Thromb Thrombolysis 1999; 8(2): 143-50.
15) Rathbun S W, Whitsett T L, Vesely S K. Clinical utility of D-dimer in patients with suspected pulmonary embolism and nondiagnostic lung scans or negative CT finding. Chest, 2004, 125(3): 851-855.

Corresponding Author:
Guixia Peng
No. 63 Huangtang Road, Meijiang District, Meizhou City, Guangdong Province, China
Email: p24rvb@163.com
(China)