A Prediction Model for Intermediate- and High-risk Pulmonary Hypertension During the Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Research

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Abstract

Background: Pulmonary hypertension (PH) is a serious complication of COPD and is associated with poor prognosis. There are currently no established predictive models for PH during the acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Objective: To establish a prediction model for intermediate- and high-risk PH in AECOPD patients.

Methods: This study collected data from 203 AECOPD patients and divided the patients into a model group and an external validation group. The influence of each parameter on PH was analysed through univariate and multivariate analyses, and these data were used to build a prediction model. Finally, the discriminative ability, calibration ability and clinical efficacy of the model were tested.

Result: Age, RDW-CV and RDW-SD were related to PH, so these variables were used to establish a prediction model. In addition, the discriminative ability, calibration ability and clinical efficacy of the model were affirmed.

Conclusion: This study established a clinical prediction model for AECOPD patients with PH, and the prediction model has certain clinical value for assisting in the screening of intermediate- and high-risk patients with PH.

Introduction

Chronic obstructive pulmonary disease (COPD), which is characterized by incompletely reversible airflow limitation, is not only a chronic inflammatory disease involving the airway but also a systemic chronic inflammatory syndrome. The disease is the most common respiratory disease in the elderly population in both developing and developed countries and poses a major public health challenge [1]. The Global Burden of Disease study estimated that there were 174.5 million COPD patients worldwide in 2015 [2], and by 2030, COPD will become the third leading cause of death in the world [3].

PH is a serious complication of COPD and is associated with poor prognosis. Clinically, early diagnosis and timely treatment in the process of disease progression are particularly important. Invasive right heart catheterization (RHC) is currently the gold standard for diagnosing PH, but it has its own risks and complications [4,5]. Therefore, this approach is not commonly used in the clinic. In contrast, with the improvement of echocardiography technology, the sensitivity of echocardiography for achieving accurate diagnosis of lung diseases has increased, and it is considered to be a safe and easily available alternative to right heart catheterization. In the ESC guidelines [6,7], it is pointed out that the diagnosis of PH cannot rely on the pulmonary artery systolic pressure (PASP). Rather, the diagnosis of PH is based on the risk stratification of the tricuspid regurgitation velocity (TRI) combined with related PH signs. However, in some current studies regarding the prediction of PH, the standards for the inclusion of PH still relies on the PASP, and there are no established prediction models for PH in AECOPD patients. Therefore,

this study established a predictive model by classifying PH patients into low-, intermediate- and high-risk groups.

Materials And Methods

2.1. Participants

The data were collected from all patients with AECOPD who were admitted to the First Affiliated Hospital of Guangzhou University of Chinese Medicine from January 2019 to April 2021. The inclusion criteria were as follows: (1) the patient age was ≥ 40 years; (2) the patient had at least one historical pulmonary function test with a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) of < 0.70 , confirming the presence of persistent airflow limitation, and the patient had to be clinically stable for at least 3 months; (3) the patient had a primary diagnosis of AECOPD, defined as an acute worsening of respiratory symptoms that result in additional therapy[8]; (4) the patient had an echocardiography performed after admission; and (5) the patient was diagnosed with risk of PH according to the current ESC 2015 guidelines [6,7]. According to the peak TRV combined with the following related PH signs, the patients were divided into low-, intermediate-, and high-risk groups. Low-risk patients were defined as having a TRV of < 2.9 m/s (or not measurable) and not more than one additional echocardiography PH sign; intermediate risk was defined as having a TRV of < 2.9 m/s with two additional PH signs or having a TRV between 2.9–3.4 m/s and not more than one additional PH sign; high-risk patients were defined as having a TRV between 2.9–3.4 m/s with two additional PH signs or having a TRV of > 3.4 m/s. The relevant PH signs were: (1) pulmonary artery (PA) index, such as diameter or acceleration time (AcT), (2) inferior vena cava (IVC) and right atrium(RA) indexes, such as the diameter and the inspiratory collapse of the IVC and RA end-systolic area (RAA), and/or (3) ventricular index. It was important that all patients did not have flattening of the ventricular septum. The exclusion criteria were the following: (1) patients with idiopathic pulmonary arterial hypertension (IPAH) or pulmonary arterial hypertension (PAH) caused by other diseases, such as interstitial lung disease, congenital heart disease, heart valve disease, or autoimmune disease; (2) patients who had sleep apnoea syndrome, renal failure, asthma, left heart disease, blood system disease, thromboembolism disease, malignancy, or acute infectious diseases; and (3) patients who were recently given a blood transfusion.

A total of 203 patients were enrolled in this study and were divided into two groups. The modelling group had 143 patients, and the external validation group had 60 patients. The data from the modelling group established a new model. The data from the external validation group tested the model. The two processes were carried out independently. According to whether or not a patient had pulmonary hypertension, the patients were divided into PH and non-PH groups.

The study was approved by the ethics committee of Guangdong Province of the First Affiliated Hospital of Guangzhou University of Chinese Medicine and complied with the guidelines of the Declaration of Helsinki. Due to the retrospective design of this study, it was not necessary for each patient to sign an informed consent form.

2.2. Data Collection.

By reviewing the patients' medical records, we obtained the following clinical data: age, sex, comorbidities and laboratory results during the first 24 hours after admission to the hospital. The inflammation markers were calculated as follows: NLR=neutrophil count/lymphocyte count, PLR=platelet count/lymphocyte count, SII=platelet count × neutrophil count/lymphocyte count, MLR=monocyte count/lymphocyte count.

2.3. Statistical Analysis

Statistical analyses were performed using STATA14.0 and Excel. Continuous variables are presented as the means with standard deviations or the interquartile ranges. The student's t-test or Wilcoxon rank-sum test were used as appropriate. Categorical variables are presented as percentages and were compared using the chi-square tests. Logistic regression analysis was used to conduct the multivariate analysis. Backward logistic regression analysis identified the variables to be included in the model. The receiver operating characteristic curve (ROC), the Hosmer-Lemeshow test results, calibration plot figures, and DCA were obtained using STATA14.0 and Microsoft Excel. All the statistical analyses were two-tailed, and a P value of < 0.05 was considered statistically significant.

Results

3.1. Characteristics of Study Population

In the modelling group, age and sex were statistically significant. The general characteristics of the modelling group and the external validation group were as follows: Table 1 and Table 2.

3.2. Univariate analysis of the modelling group

Univariate analysis was performed with the t-test and Wilcoxon rank-sum test. In Table 3, we found that RDW-CV, RDW-SD, PLt, PaCO₂ and D-dimer were statistically significant. When the p value was less than 0.05, the variable was included in the multivariate analysis.

3.3. Multivariate analysis of the modelling group

As shown in Table 4, age, male sex, RDW-CV, RDW-SD, PLt, PaCO₂ and D-dimer were included in the multivariate logistic regression analysis. Age, RDW-CV and RDW-SD were statistically significant.

3.4. Prediction model establishment

As shown in Table 5, after backward logistic regression analysis, the factors related to PH were age, RDW-CV and RDW-SD. The prediction model was established based on the results of multivariate analysis and was as follows: $\ln [P/(1 - P)] = -37.79 + 0.08 \times \text{age} + 0.64 \times \text{RDW-CV} + 0.51 \times \text{RDW-SD}$. Age, RDW-CV,

and RDW-SD were positively correlated with pulmonary hypertension. According to these factors, we established the nomogram, as shown in Figure 1.

3.5. Assessing the discriminating ability of the prediction model

By generating ROC curves, we obtained a sensitivity and specificity of 78.33% and 86.75%, respectively, an AUC of 0.8884, and a cut-off value of 0.4525 for this model, as shown in Figure 2. In addition, according to the prediction model, the AUC of the external validation group was 0.8145.

3.6. Assessing the calibration capability of the prediction model

The calibration ability of the prediction model was evaluated by the Hosmer-Lemeshow test. The p value was 0.407, which was greater than 0.05. A scatter plot was made using Excel. Figure 3 shows that the scatter points fluctuate on both sides of the reference line, indicating that the model group can accurately predict the occurrence of PH.

3.7. Assessing the clinical efficacy of the prediction model

DCA was used to evaluate the clinical efficacy of the model. The two groups of DCA are shown in Figure 4. The grey dotted line indicates that the model predicts that none of the COPD patients will have PH, and the clinical net benefit is 0. The black line represents the DCA of the model. It can be seen from the figure that the black line is higher than both the orange line and the grey dotted line, indicating that the model has clinical efficacy.

Discussion

This study established a clinical prediction model for PH in patients with AECOPD. The model incorporates 3 factors, namely, age, RDW-CV and RDW-SD, and this model has a higher predictive ability.

It can be seen from the above results that patients with PH are older patients. In the study by Ahmadou M. Jingi et al., 178 patients were evaluated, and this study indicated that age is a strong predictor of PH [9]. This result was similar to our research. Ageing can cause changes in the structure and function of blood vessels. This phenomenon is more pronounced in large arteries [10], which is related to the phenotypic changes in different cell types (such as endothelial cells, smooth muscle cells and pericytes) [11]. As we age, blood vessels undergo corresponding morphological changes, including blood vessel wall thickening, perivascular fibrosis and vasodilation. In the study by Gaballa et al. [12], it was found that ageing can increase the thickness of the culture medium, increase the collagen content and increase the collagen/elastin ratio by 12%, 21% and 38%, respectively. In contrast, with age, the density of elastin and the number of smooth muscle cell nuclei decreased by 20% and 31%, respectively. Due to the enhanced degradation of elastin, the deposition of collagen in the vascular media, intimal hyperplasia, and progressive endomysial thickening occur. Arterial thickening is the key reason that the ageing process promotes arterial stiffness in the vascular system [13]. In addition, the function of endothelium-dependent vasodilation in ageing blood vessels is impaired [14], resulting in an imbalance between vasoconstriction

and vascular relaxation [15]. Vascular impedance is mainly caused by arterial stiffness, which affects the cardiac ejection. In addition, ageing reduces aortic dilatability, resulting in a mismatch between the ventricular ejection and the aortic blood flow energy, leading to an increase in arterial pressure.

The current studies on patients with COPD with PH have mainly focused on RDW-CV and rarely involved RDW-SD. The results of backward logistic regression analysis showed that RDW-SD was also one of the risk factors for PH. Therefore, this study combines RDW-CV and RDW-SD and establishes a prediction model. RDW is a simple and inexpensive parameter that reflects the heterogeneity of red blood cells and is usually used in the diagnostic work up for anaemia. However, increasing evidence has shown that RDW is of great significance in human diseases, such as cardiovascular disease, venous thromboembolism, cancer, diabetes, community-acquired pneumonia, liver and kidney failure, and other acute or chronic diseases [16]. Seyhan EC et al. retrospectively analysed 270 patients with stable COPD and reported that increased RDW levels were associated with an increased mortality in COPD patients [17]. In another study on IPAH, 139 patients were followed up, and RDW was reported to be independently related to the disease severity [18]. However, the specific pathogenesis of RDW in COPD with PH remains unclear.

Inflammation is an important mechanism underlying the formation of PH[19]. Cigarette smoke, air pollution and the use of biomass fuels are the main risk factors for COPD. The exposure to tobacco smoke products reduced the release of vascular endothelial nitric oxide synthase, which in turn increased the activation of inflammatory cells and increased the expression of a variety of inflammatory factors. The continuous amplification of inflammation causes a decrease in endothelial function, resulting in the development of PH[20]. The production of IL-6, IL-8, TNF- α and other inflammatory factors significantly increases during the development of PH [21]. These inflammatory cytokines can affect iron metabolism and bone marrow function, thereby inhibiting erythropoiesis and causing larger, more immature red blood cells to enter the peripheral circulation, thus causing changes in RDW [22, 23]. In addition, RDW is associated with various inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate and platelet count [24,25], so chronic inflammation may promote the production of ineffective red blood cells, leading to an increase in RDW levels [26].

Relevant studies have shown that there is a correlation between the pathobiology of COPD and causes of PH in COPD patients, and hypoxia may play an important role in the progression of this disease [27]. The exposure to hypoxic conditions causes vascular remodelling, thickening of the fibromuscular intima, and an increase in smooth muscle in pulmonary arterioles and arterial media [28]. The pulmonary vasoconstriction and pulmonary vascular system occlusion caused by hypoxia were other important reasons for the increased pressure in the pulmonary artery in COPD patients. Hypoxia increases the production of peripheral red blood cells, which then can increase blood viscosity, leading to an increase in RDW, and this may be due to the strong response of endogenous erythropoietin to hypoxia [29]. In addition, oxidative stress was also considered to be an important influencing factor of the RDW value, and oxidative stress is related to cardiopulmonary thrombotic diseases [30], which may lead to pulmonary embolism and promote the formation of pulmonary hypertension.

The study evaluated the discriminative ability, calibration ability, and clinical efficacy of the new model. The AUC based on the ROC curve determined the discriminative ability of the model. The results showed that the model had a good discrimination ability. We analysed the model through the Hosmer-Lemeshow test and a calibration scatter plot and found that the P value of the model was higher than 0.05, and the scatter points fluctuated around the reference line without obvious deviation, indicating that the model had good calibration capability. DCA can be used to evaluate the clinical efficacy of the model [31, 32]. It can be seen from the research results that the DCA of the model was higher than the extreme value line, indicating that the new model had good clinical efficacy. Therefore, the new model can predict PH and has a certain clinical application value.

However, this study had limitations that cannot be ignored. As a single-centre retrospective observational study, this study had inherent bias. In addition, the sample size included in this study was small. Third, this study was unable to obtain data on the scores of the St. George's Respiratory Questionnaire (SGRQ), Modified British Medical Research Council (mMRC) Questionnaire, and COPD Assessment Test (CAT) and the patient's lung function data. Therefore, it is necessary to further evaluate the predictive abilities of the relevant questionnaires and lung function in patients who have COPD with PH.

Conclusion

This study established a clinical prediction model for AECOPD with PH. This model incorporates age, RDW-CV and RDW-SD and has a certain clinical value for assisting in the screening of intermediate- and high-risk patients with PH.

Declarations

Authors' contribution

Conceptualization: Xilian Feng and Liuliu Yang. Literature search: Xilian Feng, and Jiahua Liang. Data extraction and quality assessment: Jiamin Chen and Weiyan Chen. Software: Xilian Feng, and Jiahua Liang. Formal analysis: Yinuo Fan, Liuliu Yang, and Wei zhang. Validation: Liuliu Yang, and Wei zhang. Writing: Xilian Feng. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The institutional review board of the first affiliated hospital of Guangzhou University of Chinese Medicine approved this study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have to no conflict of interest.

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Tables

Table 1 Characteristics of Study Population in the modeling group

Parameter	All patients (n=143)	Low PH Risk (n=83)	Intermediate and High PH Risk (n=60)	<i>P</i> value
Age	73.52±9.16	71.55±9.02	76.23±8.72	0.002
Male (%)	124(86.71)	76(91.57)	48(80.00)	0.044
Hypertension (%)	64(44.76)	39(46.99)	25(41.67)	0.528
Diabetes (%)	15(10.49)	10(12.20)	5(8.20)	0.440
Coronary artery disease (%)	22(15.38)	14(16.87)	8(13.33)	0.563
Congestive heart failure (%)	5(3.50)	1(1.20)	4(6.67)	0.079

Table 2 Characteristics of Study Population in the external validation group

Parameter	All patients (n=60)	Low PH Risk (n=34)	Intermediate and High PH Risk (n=26)	<i>P</i> value
Age	73.48±9.95	70.15±10.17	77.85±7.89	0.002
Male (%)	55(91.67)	30(96.77)	25(96.15)	0.271
Hypertension (%)	32(53.33)	18(52.94)	14(53.85)	0.944
Diabetes (%)	12(20.00)	7(20.59)	5(19.23)	0.896
Coronary artery disease (%)	6(10.00)	5(14.71)	1(3.85)	0.165
Congestive heart failure (%)	3(5.00)	0(0.00)	3(11.54)	0.042

Table 3 Univariate analysis of the modeling group

Parameter	All patients (n=143)	Low PH Risk (n=83)	Intermediate and High PH Risk (n=60)	P value
WBC($\times 10^9/L$)	7.95(6.29-10.25)	7.95(6.35-10.27)	8.02(6.03-10.22)	0.767
NEU($\times 10^9/L$)	5.29(4.26-7.90)	5.08(4.11-7.56)	5.45(4.31-7.98)	0.484
LYM($\times 10^9/L$)	1.47 $\pm$ 0.59	1.54 $\pm$ 0.59	1.36 $\pm$ 0.57	0.075
HGB(g/L)	131.78 $\pm$ 16.83	133.04 $\pm$ 15.68	130.05 $\pm$ 18.30	0.296
PLt($\times 10^9/L$)	226.00(179.00-268.00)	232.00(193.00-270.00)	200.00(162.50-257.00)	0.007
RDW-CV	13.71 $\pm$ 1.20	13.35 $\pm$ 1.03	14.22 $\pm$ 1.24	<0.001
RDW-SD	44.20 $\pm$ 3.90	42.23 $\pm$ 2.61	46.93 $\pm$ 3.74	<0.001
NLR	3.50(2.44-7.15)	3.22(2.21-6.42)	3.86(2.60-7.94)	0.070
PLR	145.49(111.25-221.05)	149.43(114.49-221.05)	142.70(110.90-219.76)	0.705
MLR	0.36(0.25-0.62)	0.36(0.27-0.58)	0.37(0.24-0.74)	0.846
SII	772.11(506.06-1527.44)	763.22(527.09-1527.44)	833.80(497.02-1734.14)	0.797
PaO ₂	84.70(74.90-95.40)	83.70(74.30-91.20)	86.85(75.15-104.10)	0.232
PaCO ₂	46.36 $\pm$ 10.17	44.57 $\pm$ 7.27	48.83 $\pm$ 12.85	0.013
Pondus Hydrogenii	7.391(7.365-7.421)	7.392(7.369-7.417)	7.386(7.355-7.423)	0.659
Lactic acid	1.52(1.22-1.82)	1.52(1.27-1.83)	1.43(1.18-1.89)	0.548
Lactate dehydrogenase	203.96 $\pm$ 67.30	203.41 $\pm$ 77.38	204.72 $\pm$ 50.79	0.909
Procalcitonin	0.05(0.05-0.07)	0.05(0.05-0.06)	0.05(0.05-0.09)	0.694
Serum osmolarity	290.02 $\pm$ 8.10	290.81 $\pm$ 7.19	288.93 $\pm$ 9.16	0.173
Albumin	38.97 $\pm$ 4.20	39.25 $\pm$ 4.02	38.59 $\pm$ 4.44	0.356
D-Dimer	0.50(0.31-1.02)	0.39(0.26-0.94)	0.63(0.38-1.29)	0.026
APTT	26.45 $\pm$ 5.03	25.84 $\pm$ 4.68	27.29 $\pm$ 5.42	0.090
PT	11.30(10.80-11.90)	11.30(10.80-11.70)	11.40(10.90-11.90)	0.507
TRV (%)				<0.001
<2.9m/s	98(68.53)	83(0.00)	15(10.49)	

2.9-3.4 m/s	27(18.88)	0(0.00%)	27(18.88)
>3.4 m/s	18(12.59)	0(0.00%)	18(12.59)

Abbreviations: WBC—white blood cell; NEU-neutrophils; LYM- lymphocytes; HGB –hemoglobin; PLt- platelets; RDW-red blood cell distribution width; PaO2- partial Pressure of Oxygen PaCO2—partial pressure of carbon dioxide; APTT-activated partial thromboplastin time; PT- prothrombin time.

Table 4 Multivariate analysis of the modeling group

Parameter	Low PH Risk (n=83)	Intermediate and High PH Risk (n=60)	<i>P</i> value
Age	71.55±9.02	76.23±8.72	0.048
Male(%)	76(91.57)	48(80.00)	0.117
PLt(×109/L)	232.00(193.00-270.00)	200.00(162.50-257.00)	0.204
RDW-CV	13.35±1.03	14.22±1.24	0.005
RDW-SD	42.23±2.61	46.93±3.74	<0.001
PaCO ₂	44.57±7.27	48.83±12.85	0.475
D-Dimer	0.39(0.26-0.94)	0.63(0.38-1.29)	0.391

Table 5 Parameters used to establish the non-invasive prediction model

Parameter	B	OR	<i>P</i> value	95%CI
Age	0.08	1.08	0.005	1.02-1.14
RDW-CV	0.64	1.90	0.009	1.27-3.08
RDW-SD	0.51	1.68	<0.001	1.37-2.04
Constant	-37.79	3.87 e-17	<0.001	

CI: Confidence interval

Figures

Figure 1

The nomogram of PH

Figure 2

a The ROC curves of modelling group b The ROC curves of external validation group

Figure 3

The calibration scatter plot of PH

Figure 4

a The DCA of modelling group b The DCA of external validation group