Developing and Validating a Nomogram for Prediction Coronary Heart Disease in Patients With Chronic Obstructive Pulmonary Disease

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Abstract

Background: Previous studies indicate that there is an association between chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD). Herein, we established and further validated a novel nomogram for predicting CHD in patients with COPD.

Methods: In total, we assessed 421 patients with COPD admitted in the Second Affiliated Hospital of Nanchang University between January 2017 to August 2019. Univariate and multivariate analyses were used to develop a nomogram model containing variables which we screened, testing the discriminative ability and calibration of the nomogram by C-index, area under the curve (AUC) and calibration plots. Decision curve analysis was applied to evaluate the benefit of the screening model. Further, we conducted an internal validation by using the bootstrapping validation.

Results: Multivariate analysis shows that arterial thrombosis, prealbumin, albumin and estimated glomerular filtration rate are independent factors in predicting the risk of CHD. The prediction model exhibited discriminative ability with a C-index of 0.882 (95% CI: 0.848-0.916), and the AUC at 0.878 (95% CI: 0.843–0.913). The nomogram demonstrated efficient calibration and clinical applicability when deciding on interventions with a CHD possibility threshold of 7%. During the interval validation, it could still attain a C-index value of 0.869.

Conclusion: The nomogram can predict the risk of CHD in patients with COPD, with a high discriminative ability and potential clinical applicability.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease, characterized by airflow limitation, complicated by accelerated atherosclerosis and significantly increased risk of incident Coronary heart disease (CHD) [1–3]. Accumulated epidemiological evidence shows that COPD is linked to increased risk of CHD, which causes increased health burden in terms of prolonged hospitalization, costs, and mortality [3–5]. Coronary heart disease (CHD) is the leading cause of death worldwide, characterized by myocardial dysfunction and/or organic lesions due to insufficient blood and coronary artery stenosis [6–7]. Existing evidence indicates that coronary heart disease (CHD) may develop without typical symptoms for decades, early identification of vulnerable CHD will be very difficult, which makes it very critical to identify patients with high risk of CHD [8]. Whilst acknowledging Coronary angiography as the golden standard for coronary heart disease (CHD) diagnosis, patients have missed effective interventions due to its invasive and cannot be used as routine examinations, resulting in adverse clinical outcomes [6].

Recent studies have revealed that many clinical variables, as among them estimated glomerular filtration rate, Fibrinogen and SBP can serve as early diagnostic tools for coronary heart disease [9–11]. However, other findings argue that these variables were unable to accurately predict all patients with CHD.
Besides widely helping clinicians determine diagnosis and treatment strategies, a nomogram has been recommended in disease managing protocols. As an objective in our study, we developed a nomogram to assess the risk of CHD in patients with COPD, which would further help clinicians speedily diagnose high-risk patients, and administer treatment.

2. Materials And Methods

2.1 Patients

Our study conformed to the Helsinki Declaration, and obtained approval from the Ethics Committee of the Second Affiliated Hospital of Nanchang University. All researchers obtained certification of procedures for lancing the fingertip and blood drawing. 766 patients with COPD, diagnosed according to current Global Initiative for Chronic Obstructive Lung Disease guidelines based on clinical history and spirometric criteria (FEV1/FVC ratio < 0.7), were recruited by using research databases and hospital records between January 2017 and August 2019.

CHD was defined as death from CHD, myocardial infarction (by WHO MONICA criteria), or angiographic stenosis (involving at least 50% of a major coronary artery). Recruitment of COPD + CHD patients was based on the following inclusion criteria: (1) patients aged above 18 years, (2) patients who met both the standard diagnostic criteria for COPD and CHD. In addition, COPD patients without CHD met the following inclusion criteria: (1) had a minimum age of 18 years, (2) fulfilled the diagnostic criteria of COPD was confirmed for all patients. Exclusion criteria include: (1) absence of laboratory assessment data, (2) patients diagnosed with active lung diseases other than COPD, (3) patients previously diagnosed CHD or valvular heart disease, (4) patients taking any drug with antibiotic treatments (<3 months before study period) and corticosteroids or drugs that affect the cardiovascular system. Two authors extracted research data based on inclusion and exclusion criteria (L.L. Hu and L. Liu). Following the above criteria, we excluded 345 patients, therefore, our study constituted a total of 421 COPD patients.

2.2 Data Collection

All the clinical and laboratory data of patients were obtained from electronic medical records, including age, gender, smoking and drinking status, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, body mass index. Laboratory variables included blood lipid testing, neutrophils, albumin, eGFR, creatinine, glycated hemoglobin, and fasting blood glucose.

2.3 Statistical Analysis

For data analysis, we used SPSS 22.0 (Chicago, IL, USA) and R statistical software (version 3.6.3, http://www.r-project.org). The chi-square or Fishers exact test was used to evaluate differences in categorical variables, while the Mann–Whitney U test or Students t-test was used for continuous variables. To identify the independent factors associated with COPD + CHD group, multiple logistic
regression analysis was performed. Using the above clinical predictors, we used R software to develop a nomogram predicting the risk of CHD in COPD patients.

For discriminative ability, we assessed the model using C-index and the area under the curve (AUC) of ROC curves. Calibration curves were analyzed by the predicted nomogram and the actual probability of the occurrence of CHD. The decision curve was used for analysis in the COPD group. Moreover, the clinical effectiveness of the CHD nomogram was determined by quantifying the net benefit at different threshold probabilities. We performed bootstrap verification (1,000 bootstrap resampling) on the CHD nomogram to calculate the relative corrected C-index. Two-sided p < 0.05 was generally considered statistically significant.

3. Results

All 421 eligible patients enrolled in the cohort were assigned into COPD and COPD + CHD groups (337 males; mean age 73.12 ± 8.55 years [range 40–97 years]). All data for the two groups including demographic, clinical, and laboratory test data are presented in Table 1.
| Characteristics of Patients in the COPD group and the COPD + CHD group. |
|---------------------------------------------------------------|
| **Demographic data**                                           |
| Age(year)                                                     | 74.51 ± 7.64 | 72.3 ± 8.95 | 0.01 |
| Gender,male,n(%)                                             | 131(84)      | 206(77.7)   | 0.122 |
| BMI                                                          | 22.35 ± 2.59 | 22.03 ± 2.38 | 0.193 |
| Smoke,n(%)                                                   | 132(84.6)    | 224(84.5)   | 0.981 |
| Alcohol,n(%)                                                 | 15(9.6)      | 16(6)       | 0.175 |
| Hypertension,n(%)                                            | 62(39.7)     | 73(27.5)    | 0.01 |
| AF,n(%)                                                      | 18(11.5)     | 20(7.5)     | 0.168 |
| Stroke,n(%)                                                  | 8(5.1)       | 9(3.4)      | 0.383 |
| ICH,n(%)                                                     | 2(1.3)       | 1(0.4)      | 0.558 |
| T2DM,n(%)                                                    | 3(1.9)       | 1(0.4)      | 0.146 |
| AT,n(%)                                                      | 103(66)      | 4(1.5)      | 0.001 |
| SBP(mmHg)                                                    | 134.55 ± 16.55 | 132.87 ± 12.14 | 0.234 |
| DBP(mmHg)                                                    | 76.52 ± 9.08  | 75.81 ± 6.14  | 0.343 |
| CKD,n(%)                                                     | 3(1.9)       | 4(1.5)      | 0.713 |
| PE,n(%)                                                      | 2(1.3)       | 0(0)        | 0.137 |
| Hyperlipidemia,n(%)                                          | 18(11.5)     | 18(6.8)     | 0.093 |
| **Serological test**                                         |
| NEUT#(10^9/L)                                                | 5.6 ± 3.19   | 6.91 ± 4.62 | 0.002 |
| Lym#(10^9/L)                                                 | 1.27 ± 0.48  | 1.10 ± 0.57 | 0.002 |
| RDW(FL)                                                      | 44.43 ± 10.74 | 42.58 ± 14.03 | 0.155 |
| PLT(10^9/L)                                                  | 178.13 ± 77.42 | 180.52 ± 76.08 | 0.758 |

AF, Atrial Fibrillation; ICH, intracerebral hemorrhae; T2DM, Type two Diabetes Mellitus; AT, Arterial Thrombosis; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CKD, Chronic Kidney Disease; PE, pulmonary embolism; NEUT#, neutrophil; Lym#, lymphocyte; RDW, Red blood cell distribution width; PLT, platelet; PA, Prealbumin; ALB, Albumin; ALP, Alkaline phosphatase; CR, Creatinine; eGFR: estimated glomerular filtration rate; UA, Uric acid; TC, total cholesterol; TG, triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; HbA1c, Hemoglobin A1c; FPG, Fasting plasma glucose; Apo(a), Apolipoprotein(a); Apo(b), Apolipoprotein(b); LP(a), Lipoprotein(a); Fib, Fibrinogen.
|                      | COPD + CHD (n = 156) | COPD (n = 265) | P   |
|----------------------|----------------------|----------------|-----|
| PA (mg/L)            | 158.08 ± 46.34       | 172.13 ± 60.13 | 0.012 |
| ALB (g/L)            | 35.05 ± 4.06         | 36.01 ± 4.05   | 0.019 |
| ALP (U/L)            | 88.87 ± 26.02        | 88.12 ± 56.27  | 0.876 |
| CR (umol/L)          | 96.25 ± 56.38        | 89.15 ± 70.6   | 0.285 |
| eGFR ml/(min · 1.73m²) | 78.99 ± 27.19       | 86.89 ± 29.23  | 0.007 |
| UA (umol/L)          | 374.59 ± 144.26      | 348.38 ± 141.31 | 0.069 |
| TC (mmol/L)          | 4.18 ± 0.98          | 4.07 ± 1       | 0.282 |
| TG (mmol/L)          | 1.13 ± 0.61          | 1 ± 0.61       | 0.042 |
| HDL-C (mmol/L)       | 1.18 ± 0.33          | 1.23 ± 0.44    | 0.199 |
| LDL-C (mmol/L)       | 2.44 ± 0.83          | 2.34 ± 0.8     | 0.234 |
| Hcy (umol/L)         | 17.5 ± 6.02          | 16.53 ± 5.06   | 0.078 |
| HbA1c (%)            | 6.13 ± 0.85          | 6.1 ± 0.74     | 0.703 |
| FPG (mmol/L)         | 5.59 ± 1.86          | 5.64 ± 2.2     | 0.782 |
| Apo(a) (g/L)         | 1.07 ± 0.28          | 1.07 ± 0.34    | 0.962 |
| Apo(b) (g/L)         | 0.76 ± 0.24          | 0.76 ± 0.29    | 0.819 |
| Fib (g/L)            | 3.43 ± 1.09          | 3.5 ± 1.67     | 0.676 |

AF, Atrial Fibrillation; ICH, intracerebral hemorrhae; T2DM, Type two Diabetes Mellitus; AT, Arterial Thrombosis; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; CKD, Chronic Kidney Disease; PE, pulmonary embolism; NEUT#, neutrophil; Lym#, lymphocyte; RDW, Red blood cell distribution width; PLT, platelet; PA, Prealbumin; ALB, Albumin; ALP, Alkaline phosphatase; CR, Creatinine; eGFR: estimated glomerular filtration rate; UA, Uric acid; TC, total cholesterol; TG, triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; HbA1c, Hemoglobin A1c; FPG, Fasting plasma glucose; Apo(a), Apolipoprotein(a); Apo(b), Apolipoprotein(b); LP(a), Lipoprotein(a); Fib, Fibrinogen.

In this cohort, the univariate analysis suggested that the occurrence of CHD is associated with age, hypertension, arterial thrombosis, neutrophil, lymphocyte, prealbumin, albumin, eGFR and TG (Table 1). All above factors were included in the regression model to identify the significant predictors of CHD. Results from multivariate logistic regression analysis results showed that four variables of COPD patients including arterial thrombosis, prealbumin, albumin and eGFR were independent predictors of CHD (Table 2).
The results from logistic regression analysis among the arterial thrombosis, prealbumin, and eGFR are shown in Table 2. We developed a nomogram that contained the above significant predictive factors (Fig. 1).

The area under the ROC curve showed a significant discriminatory power by the predictive nomogram (AUC = 0.878; 95% CI: 0.843–0.913) (Fig. 2). The prediction model demonstrated an effective accuracy for predicting CHD, with a C-index of 0.882 (95% CI: 0.848–0.916) in the cohort and 0.869 in the bootstrap validations.

The predictive nomogram demonstrated good calibration between prediction and observation in the cohort (Fig. 3).

The decision curve implied that if the threshold probability of a patient and a doctor is 77 and 98%, then applying this nomogram to predict CHD risk is more effective than either treat-all-patients scheme or the treat-none scheme (Fig. 4).

4. Discussion

Cardiovascular comorbidities, CHD in particular, is prevalent in patients with COPD [12]. The presence of CHD in COPD negatively impacts on symptoms, hospitalizations and mortality [13]. Early identify patients at high risk of CHD to help COPD patients for clinical treatments or alternative management strategies. However, there is no existing model for early or accurate diagnosis of CHD from COPD patients.

In this work, multivariate logistic regression analysis suggested that arterial thrombosis, prealbumin, albumin and eGFR were associated with CHD in COPD patients. Arterial thrombosis is the most severe consequence of atherosclerosis, thrombotic cardiovascular diseases, including myocardial infarction and stroke, are the leading cause of death in developed countries [14–15]. Notably, endothelial injury is the initiating factor of atherosclerosis, accelerating atherosclerotic plaque formation, and contributes to plaque rupture and thrombosis [16–17]. Previous findings reported that endothelial dysfunction is a common phenomenon in patients with COPD and chronic coronary heart disease [18]. In our study,
patients with arterial thrombosis (lower-limb artery thrombosis and carotid thrombosis) accounted for 66% of cases with both COPD and CHD.

eGFR is a sensitive index for evaluating renal filtration function. First, kidney disease caused by reduced levels of eGFR may cause endothelial dysfunction, which is considered to be one of the initial mechanisms causing atherosclerosis [19–20]. Besides, inflammation and oxidative stress may further aggravate the progression of atherosclerosis [19, 21–22]. Previously, several studies indicated that low eGFR level is an independent risk factor in CVD patients [23–24]. Our findings corroborate with previous research, showing that eGFR significantly predicted the risk of CHD in patients with COPD.

Prealbumin (PA), a plasma protein involved in the transport of thyroxine and retinol, has been reported to vital in the clinical evaluation of liver function, inflammatory reaction, and nutritional status [25]. Previously, a few studies reported that PA levels in patients with CHD are reduced and independently related to the coronary stenosis severity in patients with Acute coronary syndrome [26–27]. Similar to PA, reducing of albumin led to a significant progression of atherosclerosis. A possible mechanism is albumin as an anti-inflammatory cytokin that it could selective-inhibits the production of TNF-α [28–29]. However, a follow-up study by Weigenberg et al. in 1997 showed that in men which over 64 years old, serum albumin levels were not significantly associated with the incidence of 5-year CHD [30]. Here, we found that PA and ALB is decreased in patients with CHD. Nevertheless, little information exists on the correlation of PA/ALB with CHD among the Chinese population, further prospective study is essential to elucidate this relationship.

As far as we are aware, this is the first study to develop and validate a nomogram for predicting the risk of CHD among COPD patients. We use real-world data, based on four feasible and easily available variables which aided in assessing the risk of CHD in patients with COPD. The predictive nomogram performed good discrimination with a C-index for 0.882 and AUC for 0.878. In the interval validation could still be reached 0.869 with high C-index. These results demonstrated that the nomogram exhibited a well-discriminated and satisfactory accuracy in estimating the risk of CHD amongst COPD patients.

**Limitations**

There were some limitations of the study, first, this was a single-center study, and thus, the cohort is not representative of all Chinese COPD patients. Future studies should note that it is important to increase the number of patients by enrolling from other Chinese hospitals. Besides, despite validating the nomogram using the same population, it must be validated externally with a wider range of patients.

**5. Conclusion**

The study developed a relatively accurate nomogram that can help clinicians assess the risk of CHD in patients with COPD, this will advance the practical clinical decisions made by the clinicians and further boost their management interventions.
Declarations

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Author Contributions

(I) Conception and design: Jing-song Xu; (II) Administrative support: Jing-song Xu; (III) Provision of study materials or patients: Long-long Hu, Liang Liu, Huan Liu; (IV) Collection and assembly of data: Yun YU; (V) Data analysis and interpretation: Yun YU, Jing-song Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Conflict of interest

The authors declare no conflict of interest.

Ethical approval

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 procedures of this study were approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University, and informed consents were obtained from all patients.

Consent for publication

All authors consent to the publication of this study.

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