International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

A Diagnostic Nomogram for Predicting Hypercapnic Respiratory Failure in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Purpose: To develop and validate a nomogram for assessing the risk of developing hypercapnic respiratory failure (HRF) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Patients and Methods: From January 2019 to August 2023, a total of 334 AECOPD patients were enrolled in this research. We employed the Least Absolute Shrinkage and Selection Operator (LASSO) regression and multivariate logistic regression to determine independent predictors and develop a nomogram. This nomogram was appraised by the area under the receiver operating characteristic curve (AUC), calibration curve, Hosmer–Lemeshow goodness-of-fit test (HL test), decision curve analysis (DCA), and clinical impact curve (CIC). The enhanced bootstrap method was used for internal validation.

Results: Sex, prognostic nutritional index (PNI), hematocrit (HCT), and activities of daily living (ADL) were independent predictors of HRF in AECOPD patients. The developed nomogram based on the above predictors showed good performance. The AUCs for the training, internal, and external validation cohorts were 0.841, 0.884, and 0.852, respectively. The calibration curves and HL test showed excellent concordance. The DCA and CIC showed excellent clinical usefulness. Finally, a dynamic nomogram was developed (https://a18895635453.shinyapps.io/dynnomapp/).

Conclusion: This nomogram based on sex, PNI, HCT, and ADL demonstrated high accuracy and clinical value in predicting HRF. It is a less expensive and more accessible approach to assess the risk of developing HRF in AECOPD patients, which is more suitable for primary hospitals, especially in developing countries with high COPD-related morbidity and mortality.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, hypercapnic respiratory failure, nomogram, prediction model

Introduction

Chronic obstructive pulmonary disease (COPD) is a widespread chronic respiratory disorder that manifests as severe respiratory symptoms and irreversible airflow limitation.[1] Acute exacerbation of COPD (AECOPD) refers to the deterioration of respiratory symptoms in COPD patients within 14 days, and severe acute exacerbation is usually manifested as hypercapnia respiratory failure (HRF) resulting from prolonged hypercapnia.[1,2] The incidence of HRF in AECOPD patients is as high as 20%.[3] Lung ventilation function is further reduced in patients with HRF, because in severe COPD, hyperinflation causes the respiratory muscles to become fatigued.[4] During acute exacerbations, ventilatory

Received: 12 December 2023
Accepted: 7 May 2024
Published: 18 May 2024

failure may result from increased stresses on the respiratory muscles. Following hypercapnia, respiratory muscle activity is further impaired, which limits lung ventilation function.[5] A study on 1016 AECOPD patients with hypercapnia that reported death and readmission rates found that 11% patients died during hospitalization, with mortality rates at 60 days, 180 days, 1 year, and 2 years being 20%, 33%, 43%, and 49%, respectively. Within the following 6 months, 446 patients required readmission, indicating that hypercapnia is a reliable indicator of the probability of post-admission mortality in patients with AECOPD.[6] This was consistent with the results of Ahmadi et al's study.[7]

HRF is usually assessed by arterial blood PaO_2 and $PaCO_2$ levels. However, arterial blood gas analyzers are not widely available in many primary hospitals with limited medical resources, especially in developing countries with high COPD morbidity and mortality.[8] In addition, the arterial blood collection process is uncomfortable and difficult. Venous blood collection and questionnaire surveys are more economical and accessible than arterial blood collection.

To date, few studies have focused on and reported the indicators of respiratory failure in individuals with AECOPD and predictors of mortality risk. A meta-analysis including 13 articles revealed that the incidence of type II respiratory failure in AECOPD patients was negatively correlated with protein and uric acid values.[9] Zhao et al[10] found a negative correlation between the sarcopenia index (SI) and respiratory failure in AECOPD patients. Chen et al[11] determined seven predictors using the Least Absolute Shrinkage and Selection Operator (LASSO) regression and used these predictors to create a nomogram that could be utilized to predict the mortality risk in AECOPD patients with HRF. However, to our knowledge, no prediction model yet exists to predict the risk of HRF in AECOPD patients in the clinic. Hence, a clinical prediction tool to assess the possibility of HRF for individuals with AECOPD would be meaningful.

In this retrospective study, we collected and analyzed the clinical information of AECOPD patients, developed and verified a clinician-friendly nomogram according to the four easily obtained indicators, and explored its clinical value in assessing the possibility of HRF in AECOPD patients. Thus, we aimed to develop a nomogram to predict the risk of HRF in patients with AECOPD by easily obtained indicators and make it available to doctors in primary hospitals to facilitate risk stratification of patients and ensure timely referral of high-risk patients to specialist hospitals for further examination determining whether HRF occurs, enabling prompt initiation of NIV therapy for patients with HRF. At the same time, low-risk patients predicted by the nomogram can continue to be treated in local primary hospitals to avoid wasting medical resources.

Materials and Methods

Data Source

This was a retrospective study. The training cohort and internal validation cohort were consecutively enrolled from patients who were hospitalized in the Second People's Hospital of Hefei between January 2019 and January 2023. They were randomized into the training cohort (n=161) and internal validation cohort (n=69) in a 7:3 ratio. Patients hospitalized from January to August 2023 were consecutively enrolled as the external validation cohort (n=104).

Definition

The diagnosis of COPD is evaluated by respiratory specialists who combine the patient's history of risk factors (eg, smoking); respiratory symptoms (eg, dyspnea, cough, and sputum production); and spirometry findings in accordance with the "GOLD 2019" criteria.[1] Among these, irreversible airflow limitation (FEV1/FVC < 0.7 post-bronchodilation determined by forced spirometry) was a necessary condition for the diagnosis. The target population included in our study was patients with AECOPD, characterized with (1) a history of COPD and (2) baseline dyspnea, cough, and/or sputum that worsened within 14 days.[1,2] The 14 days here are counted from the time when respiratory symptoms of COPD patients begin to worsen because the original treatment regimen cannot control them.

The primary outcome was HRF, which is also known as type II respiratory failure. HRF was diagnosed in patients who met the following criteria: under normal atmospheric pressure at sea level, resting state, and inhalation of air, partial pressure of oxygen in arterial blood (PaO_2)<60 mmHg, accompanied by partial pressure of carbon dioxide in arterial blood ($PaCO_2$)>50 mmHg or oxygenation index<300 in the state of inhaling oxygen, accompanied by $PaCO_2$>50 mmHg.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) patients with confirmed AECOPD according to the "GOLD 2019" criteria; and (2) patients aged ≥45 years old. The exclusion criteria were: (1) patients with type I respiratory failure; (2) patients with other respiratory diseases such as bronchial asthma and obstructive sleep apnea hypopnea syndrome (OSAHS); (3) patients with other diseases that cause ventilation dysfunction; (4) patients with hematologic diseases, malignant tumors, severe liver and kidney diseases, hyperthyroidism, and diabetes; and (5) patients who did not complete arterial blood gas analysis, hematology, biochemistry examination, and ADL assessment within 24 h of admission. This study was approved by the Ethics Committee of the Second People's Hospital of Hefei (No. 2023-keyan-111) and adhered to the tenets of the Declaration of Helsinki. All individuals provided written informed consent after being fully briefed and advised about the study procedures.

Data Collection

Clinical information was gathered and documented from electronic medical records, including demographics and laboratory data. Arterial blood gas analysis, hematology, biochemistry, and ADL assessment were completed in all patients within 24 h of admission. This study included a total of 18 potential predictors, namely age, height, weight, body mass index (BMI), sex, smoking, white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), eosinophil (E), platelet count (PLT), hematocrit (HCT), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin (ALB), blood urea nitrogen (BUN), prognostic nutritional index (PNI), and activities of daily living (ADL). The PNI was computed by albumin and lymphocyte counts. The following formula was applied to calculate PNI: PNI = 10×serum albumin (g/dL) + 0.005×total lymphocyte count (per mm^3).[12]

Statistical Analysis

The mean±standard deviation ($\bar{x} \pm s$) was used to represent continuous variables that were normally distributed, and one-way ANOVA was used for analysis. The median (interquartile range, IQR) was used to compare continuous variables that were not normally distributed, and the Kruskal–Wallis test was used for analysis. Frequencies (percentages) were employed to represent categorical variables, and the chi-square test was used for analysis. To avoid deterioration in the efficacy and bias of the statistical analysis due to the direct removal of missing values, we used average value to compensate for the missing data of patients with a small number of missing covariates. The highest proportion of missing covariate was ALB (1.3%).

We used LASSO regression to recognize variables that affect HRF and then used multivariate logistic regression analysis to determine independent predictors.[13] LASSO regression was performed on potential risk factors in the training cohort, with the occurrence of HRF as the outcome variable (assigned values: occurrence=1, non-occurrence=0). The best lambada (λ) value was selected using 10-fold cross-validation. The two dashed lines in Figure 1A represent lambda. min and lambda. 1se, respectively. Lambda. min represents the λ of the minimum mean square error, which means the model best fits at that value of λ. Lambda.1se represents the λ of one standard error away from lambda. min, which means that the model incorporates the least number of variables at that value of λ and achieves good predictive performance. The number of variables included in the model decreases as λ increases. Multivariate logistic regression was used to analyze the variables with non-zero coefficients that the LASSO regression identified, and the variables with $P<0.05$ were considered independent predictors and subsequently utilized in developing the nomogram.

Three metrics were employed to assess the nomogram's performance—discrimination, calibration, and clinical usefulness. The area under the curve (AUC) was employed to measure the nomogram's discrimination. The calibration curve and HL test were applied to determine the nomogram calibration.[14] The slope of the calibration curve close to 1 and $P>0.05$ of the HL test indicated that the model is well calibrated. We performed 1000 bootstrap resampling on the training set to calculate the AUC, accuracy, and kappa value of the nomogram to evaluate the repeatability of the nomogram. Moreover, DCA and CIC were utilized to estimate the nomogram's clinical usefulness. The DCA suggests the net benefits of the nomogram at different threshold probabilities and could ascertain whether the nomogram benefits

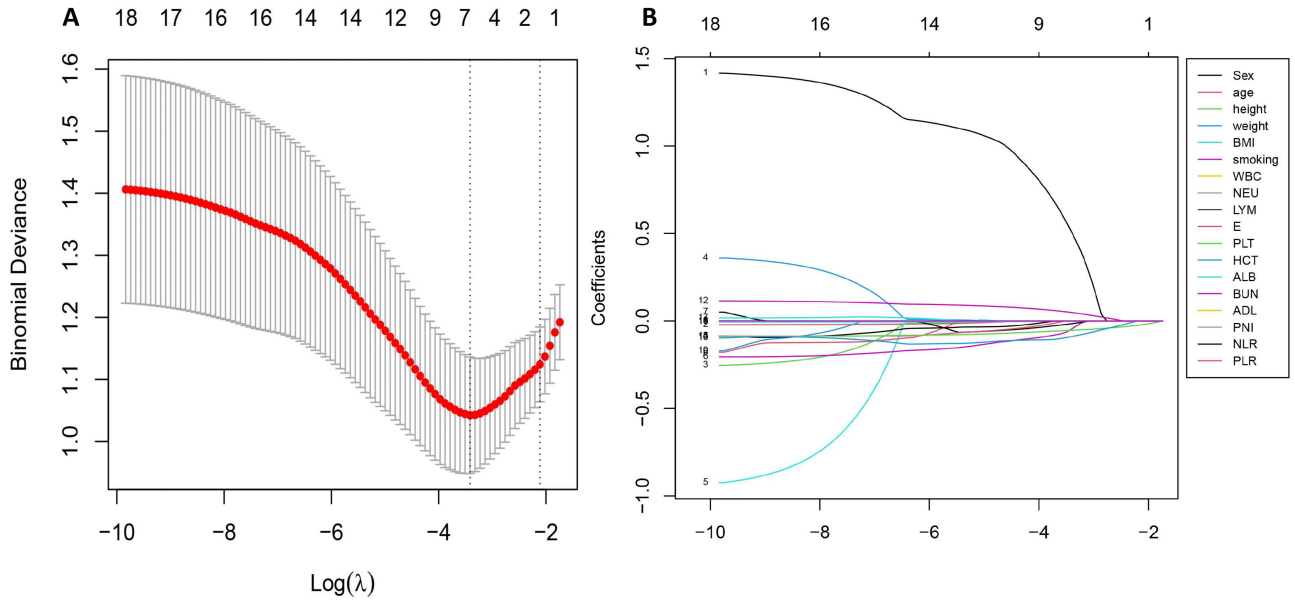

Figure 1 Risk factors selection by LASSO. (**A**) Determine the best lambda (λ) in the LASSO model using 10-fold cross-validation in the training cohort. (**B**) LASSO coefficient profiles (vertical axis) of the 18 variables in the training cohort. The upper horizontal axis represents the number of variables with non-zero coefficients in the model, while the lower horizontal axis represents log(λ).

from clinical applications. The CIC displays the actual and nomogram-predicted number of high-risk individuals at each threshold probability.

Both R (version 4.3.1) and SPSS (version 26.0; IBM Corporation, Armonk, NY, USA) software were used for statistical analyses. Statistical significance was considered when the two-tailed P value was <0.05.

Results

Patient Characteristics

From January 2019 to August 2023, a total of 334 AECOPD patients (267 [79.9%] male and 67 [20.1%] female) were enrolled in this research and were divided into a training cohort (n=161), an internal validation cohort (n=69), and an external validation cohort (n=104). A comparison of the baseline characteristics of the patients in the three cohorts is shown in Table 1. The average age of patients was 75.65±8.09 years. 199 (59.6%) were smokers, and 135 (40.4%) were

Table 1 Characteristics of AECOPD Patients in All Three Cohorts

Variables	Overall (n = 334)	Training Cohort (n = 161)	Internal Validation Cohort (n = 69)	External Validation Cohort (n = 104)	*P*
Age (years)	75.65 ± 8.09	75.48 ± 8.38	75.70 ± 7.52	75.88 ± 8.08	0.926
Height (cm)	163.95 ± 8.63	163.81 ± 8.44	165.30 ± 8.01	163.28 ± 9.28	0.306
Weight (kg)	59.43 ± 11.91	58.98 ± 11.12	61.17 ± 12.18	58.97 ± 12.88	0.396
BMI (kg/m2)	22.08 ± 3.95	21.98 ± 3.87	22.36 ± 4.03	22.04 ± 4.03	0.792
Female (n, %)	67 (20.1)	33 (20.5)	11 (15.9)	23 (22.1)	0.600
Smoking (n, %)	199 (59.6)	98 (60.9)	41 (59.4)	60 (57.7)	0.876
WBC (×109/L)	6.51 (5.15, 8.44)	6.68 (5.42, 8.80)	6.20 (5.06, 8.18)	6.81 (5.07, 8.40)	0.543
NEU (×109/L)	4.63 (3.60, 6.51)	4.80 (3.72, 6.76)	4.52 (3.42, 6.22)	4.60 (3.58, 6.47)	0.655
LYM (×109/L)	1.11 ± 0.62	1.13 ± 0.56	1.05 ± 0.50	1.13 ± 0.76	0.569
E (×109/L)	0.08 (0.02, 0.15)	0.08 (0.04, 0.16)	0.07 (0.02, 0.16)	0.07 (0.02, 0.14)	0.494
PLT (×109/L)	180.53 ± 60.66	187.53 ± 61.88	179.39 ± 53.47	170.46 ± 62.29	0.080
NLR (%)	4.55 (3.18, 7.84)	4.52 (3.16, 7.20)	4.55 (3.35, 8.48)	4.69 (3.09, 8.79)	0.812

(*Continued*)

Table 1 (Continued).

Variables	Overall (n = 334)	Training Cohort (n = 161)	Internal Validation Cohort (n = 69)	External Validation Cohort (n = 104)	*P*
PLR (%)	180.35 (122.86, 243.40)	179.14 (125.61, 243.16)	192.06 (129.74, 254.76)	117.10 (115.78, 235.80)	0.644
HCT (%)	41.91 ± 5.89	41.77 ± 6.41	42.15 ± 6.05	41.98 ± 4.91	0.898
ALB (g/L)	39.31 ± 4.14	38.78 ± 3.87	38.74 ± 3.83	40.50 ± 4.51	0.002
BUN (mmol/L)	7.09 ± 2.66	7.00 ± 2.67	7.23 ± 2.43	7.13 ± 2.81	0.810
PNI (%)	44.87 ± 5.59	44.42 ± 5.06	44.00 ± 4.96	46.14 ± 6.53	0.035
ADL (score)	77.74 ± 12.67	78.14 ± 12.47	77.10 ± 12.29	77.55 ± 13.31	0.837

Note: Data are given as frequencies (percentages), ($\bar{x} \pm s$), and median (interquartile range, IQR).
Abbreviations: BMI, body mass index; WBC, white blood cell count; NEU, neutrophil count; LYM, lymphocyte count; E, eosinophil; PLT, platelet count; HCT, hematocrit; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALB, albumin; BUN, blood urea nitrogen; PNI, prognostic nutritional indicators; ADL, activity of daily living. *P* represented the difference among the training cohort, internal validation cohort, and external validation cohort for baseline characteristics.

non-smokers. A total of 96 (28.7%) patients developed HRF. Besides, we divided 334 patients into HRF (+) and HRF (-) groups according to whether patients develop HRF or not and compared the baseline characteristics of patients in the two groups, which are shown in Table 1S.

Variable Selection

Firstly, LASSO regression was performed on potential risk factors in 161 AECOPD patients in the training cohort. Figure 1A and B present the LASSO coefficient profiles with non-zero coefficients that were found using the optimal lambda (λ). In this study, lambda. min was chosen, which was 0.033, at which point seven non-zero coefficient variables were included, namely sex, smoking, WBC, PLT, HCT, PNI, and ADL. Secondly, we performed multivariate logistic regression on the variables identified by LASSO regression to identify four independent variables (Table 2S). These four variables were the sex (OR=4.104, 95% CI=1.491–11.712); PNI (OR=0.760, 95% CI=0.766–0.934); HCT (OR=1.111, 95% CI=1.034–1.219); and ADL (OR=0.929, 95% CI=0.894–0.960) were independent variables for HRF in AECOPD patients (Table 2).

Development of a Diagnostic Nomogram

The model developed by multivariate logistic regression was logit (P)=8.575+1.412×sex-0.165×PNI+0.105×HCT-0.074×ADL. Figure 2 shows the traditional nomogram. The result indicated that women with a lower PNI value, higher HCT value, and lower ADL score have a higher risk of developing HRF in the AECOPD cohort. The variable with the most predictive was the variable with the highest score in the nomogram, namely HCT. The nomogram assigns a score to each predictor's value based on their impact on the outcome variable and then adds up the scores to obtain a total score. Finally, the probability of HRF in each patient is calculated on the basis of the total score. The higher the score, the higher the probability of the patient developing HRF.

Table 2 Independent Predictors Associated with Hypercapnic Respiratory Failure by Multivariate Analysis

Variables	β Coefficient	*SE*	OR (95% *CI*)	*P*
Gender	1.412	0.522	4.104 (1.491–11.712)	0.007*
PNI	−0.165	0.052	0.760 (0.766–0.934)	0.002*
HCT	0.105	0.043	1.111 (1.034–1.219)	0.015*
ADL	−0.074	0.018	0.929 (0.894–0.960)	<0.001*

Note: *P<0.05.
Abbreviations: PNI, prognostic nutritional indicators; HCT, hematocrit; ADL, activity of daily living; OR, Odds Ratio; *CI*, Confidence Interval.

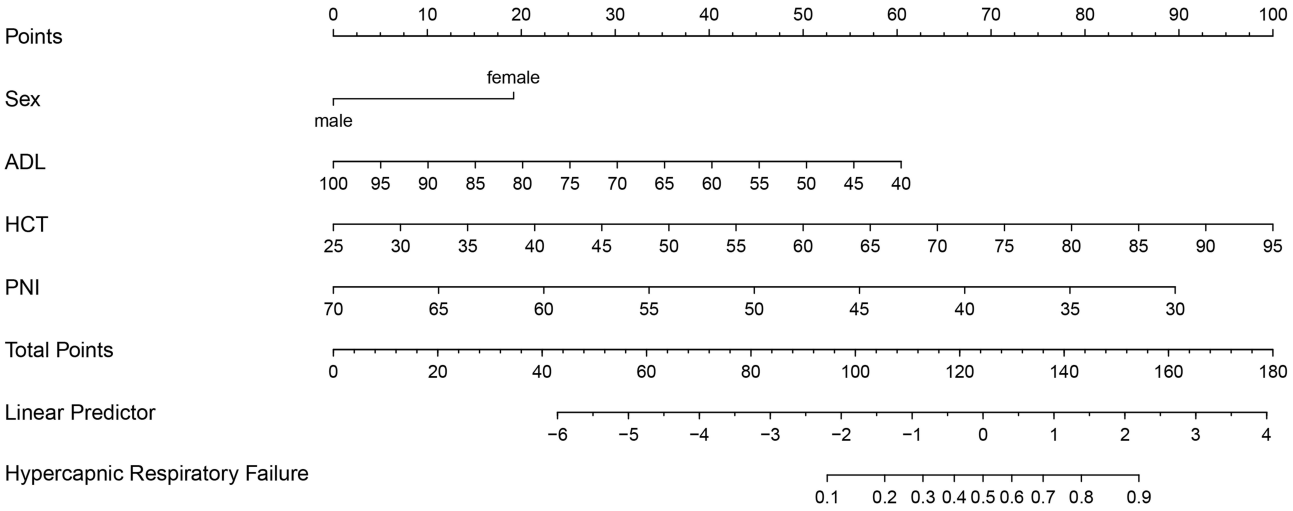

Figure 2 Nomogram forecasting hypercapnic respiratory failure in AECOPD patients.

Construction of a Dynamic Nomogram

We used the "shiny" and "rsconnect" packages of the R software to create a web-based dynamic nomogram. The dynamic nomogram can be viewed at https://a18895635453.shinyapps.io/dynnomapp/ (Figure 3). The probability of HRF in AECOPD patients can be assessed by inputting the patient's information into the dynamic nomogram.

Evaluation of the Nomogram

The AUCs for the training, internal, and external validation cohorts were 0.841, 0.884, and 0.852, respectively (Table 3 and Figure 4), indicating that the nomogram has excellent discriminative ability. In all three cohorts, the calibration curves revealed good consistency between the predicted and actual probabilities (Figure 5). Additionally, the HL test across the three cohorts resulted in χ^2=8.677 (P=0.370 for the training cohort), χ^2=4.796 (P=0.779 for the internal validation cohort), and χ^2=9.854 (P=0.275 for the external validation cohort), showing that the nomogram was well calibrated. The DCA of the training cohort showed that the net benefit of using this nomogram to guide clinical decision-making was higher than the net benefit of "all treatment" or "no treatment" when the threshold probability was between 0.03 and 0.71 (Figure 6A). In this study, "treatment" represents a referral to specialist hospitals and further examination.

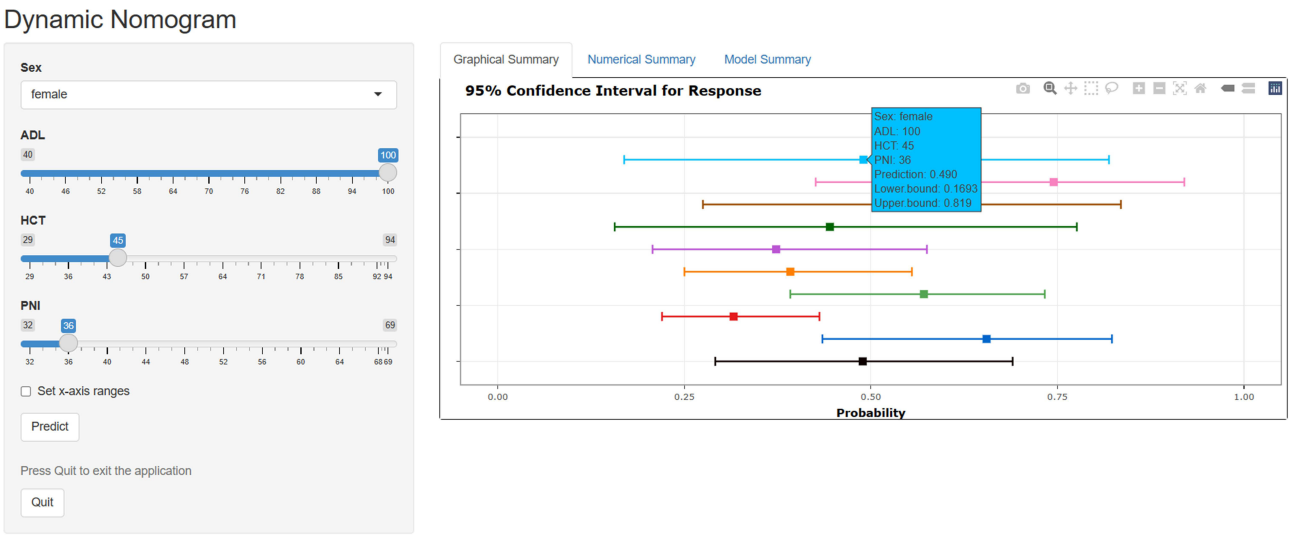

Figure 3 Dynamic Nomogram forecasting hypercapnic respiratory failure in AECOPD patients (https://a18895635453.shinyapps.io/dynnomapp/).

Table 3 Detailed Metrics in All Three Cohorts

Cohorts	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (95% *CI*)
Training cohort	0.711	0.862	0.667	0.885	0.820	0.841 (0.777–0.906)
Internal validation cohort	0.895	0.720	0.548	0.947	0.768	0.884 (0.800–0.969)
External validation cohort	0.875	0.778	0.636	0.933	0.808	0.852 (0.778–0.927)

Notes: Sensitivity=TP/(TP+FN); Specificity=TN/(TN+FP); PPV=TP/(TP+FP); NPV=TN/(TN+FN); Accuracy=(TP+FP)/N.
Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristics curve; *CI*, Confidence Interval; TP, True positive count; FP, False positive count; TN, True negative count; FN, False negative count; N, Total samples.

The DCA of the validation cohorts also showed the high clinical utility of the nomogram (Figure 6B and C). To fully evaluate the nomogram's clinical impact, we also displayed the CIC. The CIC of the training cohort showed that the nomogram consistently predicted more HRF than actually occurred within the threshold probability of 0.03–0.71, indicating that the nomogram can effectively identify patients with HRF within this threshold probability (Figure 6D), and the same results could be seen in the validation cohorts (Figure 6E and F). In short, the nomogram showed significant

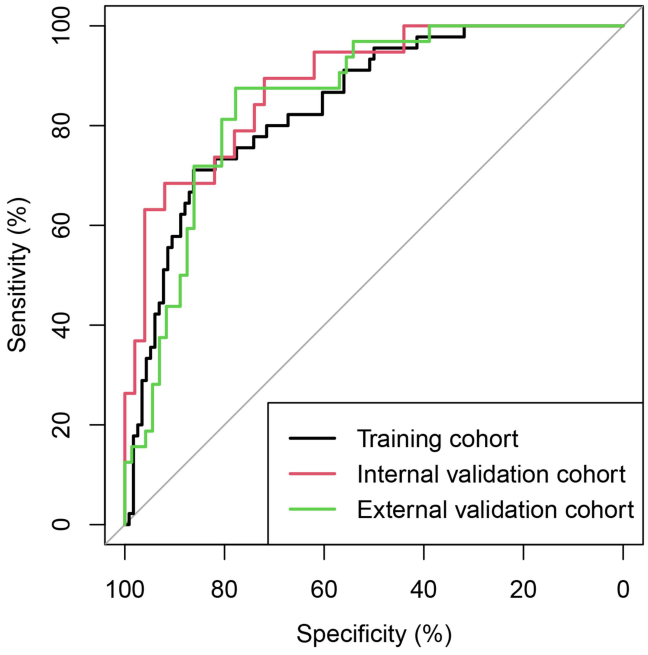

Figure 4 ROC curves in the training, internal validation, and external validation cohorts.

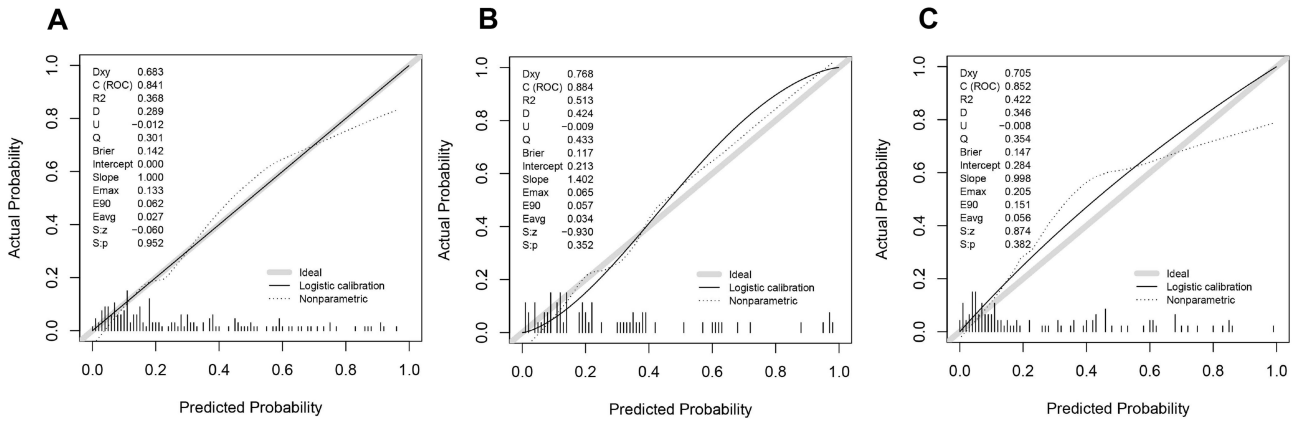

Figure 5 Calibration curves of the nomogram. The diagonal dashed line is the ideal calibration line, while the solid line is the actual line predicted by the nomogram. The closer the actual line is to the ideal line, the higher the calibration of the nomogram. (**A**) training cohort. (**B**) internal validation cohort. (**C**) external validation cohort.

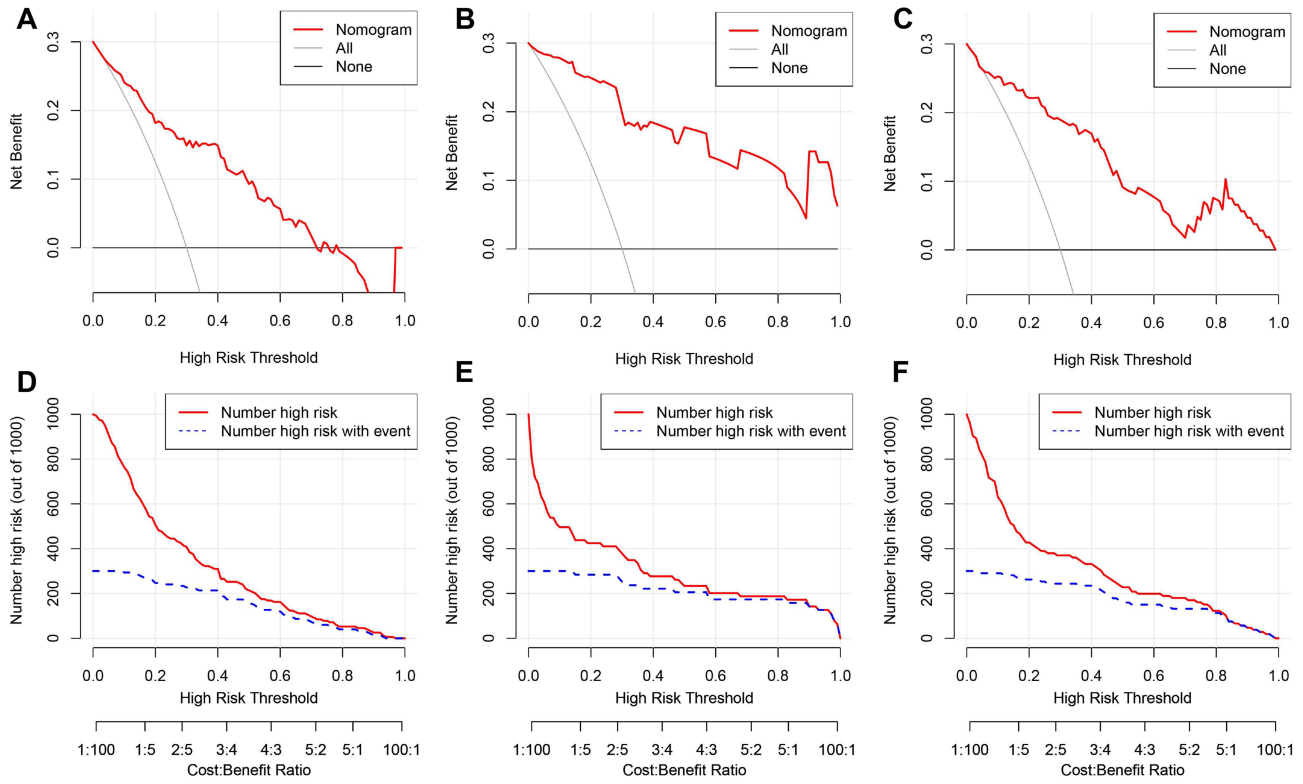

Figure 6 Clinical utility evaluation of the nomogram. DCA in the training cohort (**A**) internal validation cohort (**B**) and external validation cohort (**C**). CIC in the training cohort (**D**) internal validation cohort (**E**) and external validation cohort (**F**).

net benefits over an extensive range of threshold probabilities, as revealed by DCA and CIC, demonstrating its high clinical value and utility. After 1000 bootstrap resamplings of the training group, the nomogram's AUC was 0.823, accuracy was 0.784, and kappa value was 0.392, suggesting that the nomogram performs well and exhibited considerable generalizability.

Discussion

COPD is a prevalent chronic condition jeopardizing human health and well-being. The Global Burden of Disease Survey reported that the third lethal factor globally in 2019 was COPD, and its prevalence was predicted to keep increasing over the coming decades. Besides increased morbidity and mortality, COPD also causes a heavy economic burden.[1] HRF is one of the most common comorbidities of COPD and is positively correlated with adverse prognosis and high mortality.[15] HRF is usually diagnosed by arterial blood gas analysis. However, the arterial blood collection process is painful and technically complex, and many primary hospitals, especially in developing countries with high COPD-related morbidity and mortality, lack arterial blood gas analyzers to perform analysis.[8] In primary hospitals, the choice of whether AECOPD patients need to be referred is commonly faced. Referral of all patients to specialist hospitals is often accompanied by a waste of medical resources, and no referral of all patients means danger to high-risk patients. Consequently, a nomogram that uses easily obtained indicators to assess the possibility of HRF in AECOPD patients should be developed and made available to primary hospital physicians.

According to the results of logistic regression analysis, sex, PNI, HCT, and ADL were all independently associated with HRF. We then used these four variables to construct and validate a nomogram. This nomogram demonstrated excellent discrimination and good calibration. The DCA and CIC both showed promising clinical application potential. This nomogram also demonstrated similarly good predictive performance in the external validation cohort. The precise probability of HRF might be spontaneously computed by inputting the numerical value of every parameter in the

nomogram. This greatly improved the practicality of the nomogram and assisted clinicians in making clinical management decisions.

The DCA (Figure 6) shows comparing with "all treatment" or "no treatment", using this nomogram to guide clinical decision-making might produce net benefit. The nomogram developed in this study is mainly used by doctors in primary hospitals on AECOPD patients who come to primary hospitals for treatment. Owing to the limitation of diagnosis, treatment, and medical equipment, it is difficult for primary hospitals to provide effective therapy for AECOPD patients with HRF, such as non-invasive ventilation (NIV). Therefore, "treatment" in this study denotes the referral of high-risk patients with HRF predicted by the nomogram from primary hospitals to specialist hospitals and further examination in specialist hospitals to determine whether HRF occurs, and timely NIV therapy for patients with HRF.[16]

Combining DCA and CIC in the training cohort, internal validation cohort, and external validation cohort of this study, it was found that compared with the "0–100 situation" of "all referrals" and "none referrals", using this nomogram to predict the risk of HRF in AECOPD patients and to decide whether the referral is not only necessary but also produced net benefit.

COPD used to be considered a disease predominantly affecting older men, but there is growing evidence regarding the significantly increased prevalence and importance of COPD in women.[17,18] This may be associated with increased smoking, greater sensitivity to tobacco smoke among women, and greater exposure to biomass smoke in women.[19] Female COPD patients had poorer lung function, more severe symptoms, and a worse prognosis than male patients.[20] Our research showed that sex was an independent predictor of HRF, and female AECOPD patients are more likely to experience HRF.

Our results showed that PNI independently predicted HRF in patients with AECOPD. When PNI was ≤38.58, AECOPD patients had a higher risk of HRF. Another cohort study consistent with ours, reported that 31.8 was the ideal cut-off value for PNI to predict mortality at 30 days in AECOPD patients hospitalized in the intensive care unit (ICU), with a sensitivity of 62.3% and specificity of 64.1%.[21] In Yuan et al's study, there was a 6% decrease in the probability of adverse inpatient outcomes for patients with AECOPD for each unit increase in PNI.[22]

PNI is an indicator that contemplates inflammation, the immune system, and nutrition.[23]

First, PNI was an objective indicator for evaluating nutrition. Initially, PNI was applied to evaluate the preoperative nutritional status and surgical risk of patients.[24] As research has progressed, PNI has demonstrated value in evaluating the prognosis of various malignant tumors.[25] In recent years, studies have also shown that PNI has significance in predicting the prognosis of respiratory diseases.[26,27] Baldemir and Cirik[28] indicated that PNI is an objective and practical nutritional marker for ICU-hospitalized COPD patients, with an optimal cut-off of 38.5. Studies have reported that COPD patients consume more energy and are more likely to become malnourished.[29] Malnutrition lowers muscle mass and impairs respiratory muscle function, which can exacerbate airflow limitation and increase the risk of respiratory failure in patients with AECOPD.[10]

Second, PNI calculation relies on circulating lymphocytes and is affected by viral infection and the immune function status during virus infection.[30] Several studies have found that individuals with infection-related disorders such as COPD,[30] sepsis,[31] and bacteremia[32] have a worse prognosis when their circulating lymphatic count is low. Studies exploring the correlation between PNI and the prognosis of individuals infected with viruses indicate that a higher PNI is associated with a protective effect.[33–35] Therefore, high PNI is a protective factor for HRF in COPD patients, possibly mediated in part by the effect of viral infection. Therefore, the role of virus infection and immune function should be considered in the protective effect of PNI on HRF.

Hematocrit (HCT) refers to the concentration of red blood cells, which reflects blood viscosity. The higher the HCT, the higher the blood viscosity.[36] AECOPD patients suffer from hypoxia, acidosis, and infection, leading to coagulation impairment and hypercoagulation.[37] When AECOPD develops blood hypercoagulability, it may raise the possibility of VET and aggravate ventilation-perfusion ratio (Va-Q) dysregulation. Blood hypercoagulability has been linked to exacerbations, vascular disorders, and a poor prognosis in AECOPD. The blood viscosity of COPD in the acute exacerbation phase was significantly higher than in the stable phase. Moreover, HCT and blood viscosity have been found to be considerably higher in AECOPD patients with respiratory failure than in patients without respiratory failure.[38,39] A database study conducted by Chambellan et al showed a positive correlation between HCT and $PaCO_2$ and a negative correlation with mortality.[40] The study's findings stated that HCT was a risk factor for HRF, and as the per-single unit of HCT increased, the probability of HRF in AECOPD patients increased by 11.1%.

Our study suggested that activities of daily living (ADL) were crucial for independent living and considered a beneficial factor in relation to HRF in AECOPD patients. ADL refers to the ability to complete activities of daily living, which is crucial to a person's independent life, including the completion of daily activities such as eating, dressing, washing, and walking. At present, the most commonly used scale for evaluating ADL is the Barthel Index, which is simple to operate, and the score is proportional to the independent functional ability.[41] ADL has been shown to be the strongest predictor of survival in older adults.[42] Ryg et al[43] found that the Barthel Index at admission could help identify and distinguish patients with high mortality risk and those with longevity. Research has shown that individuals suffering from COPD, especially those suffering from respiratory failure, could face challenges when performing daily activities.[44] Lung dysfunction and respiratory failure might even cause a patient to lose self-reliance. Previous studies on COPD patients have reported restrictions in completing ADL, and their ability to complete ADL typically decreases as the disease progresses.[45,46] This study found that AECOPD patients with HRF were limited in completing ADL. The ROC data indicated that when the ADL of AECOPD patients was ≤72.5, physicians should be vigilant to the occurrence of HRF.

By employing the nomogram, clinicians could assess each AECOPD patient's probability of developing HRF. This visualized tool may assist clinicians to quickly and easily identify high-risk individuals with HRF and intervene in a timely manner, which would help decrease the risk of death as well as more efficiently allocate healthcare resources.

Our research has several strengths: (1) This is the first study to create a nomogram to predict HRF in AECOPD patients. Although studies involving risk factors of respiratory failure for AECOPD patients were common, studies constructing the nomogram to predict HRF in AECOPD patients which guide doctors in primary hospitals to judge the necessity of referral remain insufficient. (2) In this study, a dynamic nomogram was developed, which is considerably more convenient than a normal one. Users only need to click on the dynamic nomogram's website and enter the variables' values, and then a predictive probability can be automatically generated to assess the likelihood of developing HRF in AECOPD patients, thereby helping doctors in primary hospitals to judge the risk of patients and refer high-risk patients to specialist hospitals in a timely manner.

Our study also has some limitations: (1) This study was a single-center study with a small sample size, needing more data validation from other center sources. This may prevent the nomogram from being extended to other populations. In the future, expanding the sample size and conducting multicenter research is essential. (2) Only four variables were included in this nomogram, and other factors such as patient comorbidities were not included. Future research should explore the influence of more relevant factors further. (3) Some COPD patients may present with the signs and symptoms of asthma, and it can be difficult to clearly distinguish COPD from asthma based on the current testing techniques.[47,48] Although the participants included in our study were conducted by respiratory specialists in strict accordance with the "GOLD 2019"criteria,[1] COPD patient whose main manifestation was asthma was excluded, which inevitably resulted in certain selective bias. Therefore, it is important to be cautious when generalizing our developed nomogram to all COPD patients. However, the results of internal and external verification show that our conclusions are reliable and robust.

Conclusion

We retrospectively collected and analyzed the clinical information of 334 individuals with AECOPD and developed a nomogram to evaluate the risk of HRF based on sex, PNI, HCT, and ADL. The sensitivity, specificity, and accuracy of the nomogram were 71.1%, 86.2%, and 82.0%. Furthermore, the nomogram also showed excellent clinical applicability. This nomogram, which does not require a blood gas analyzer, is a less expensive and more accessible way to assess the risk of developing HRF in AECOPD patients and is more suitable for primary hospitals, especially in developing countries with high COPD morbidity and mortality.

Abbreviations

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HRF, hypercapnic respiratory failure; OSAHA, obstructive sleep apnea hypopnea syndrome; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; LASSO, Least Absolute Shrinkage and Selection Operator; AUC, area under the receiver operating characteristics curve; DCA, decision curve analysis; CIC, clinical impact curve; SI, sarcopenia index; VET, venous thromboembolism; Va-Q, ventilation-perfusion ratio; BMI, body mass index; WBC, white blood cell count; NEU, neutrophil count; LYM, lymphocyte count; E, eosinophil;

PLT, platelet count; HCT, hematocrit; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALB, albumin; BUN, blood urea nitrogen; PNI, prognostic nutritional indicators; ADL, activity of daily living; OR, Odds Ratio; *CI*, Confidence Interval; PPV, positive predictive value; NPV, positive predictive value; ICU, intensive care unit.

Data Sharing Statement

The de-characterized data included in this study can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Ethical approval was gained from The Second People's Hospital of Hefei (No. 2023-keyan-111) and conformed to the Declaration of Helsinki.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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