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Construction and evaluation of nomogram for risk prediction of cognitive impairment in chronic obstructive pulmonary disease comorbidity

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Abstract

Objectives Chronic Obstructive Pulmonary Disease (COPD) remains a serious public health problem globally, and the mortality rate for older COPD patients with cognitive impairment is almost three times that of older patients with cognitive impairment or COPD. The aim of this study was to construct a nomogram prediction model for the risk of comorbid cognitive impairment in COPD patients and to evaluate its clinical application. It helps to detect cognitive impairment in COPD patients at an early stage and give them effective interventions in time, so as to delay the progression of COPD patients and improve their prognosis.

Methods In this study, patients with COPD hospitalized at the Affiliated Hospital of North China University of Science and Technology were evaluated for cognitive function using the Montreal Cognitive Assessment(MoCA) scale after stabilization of acute exacerbations. Participants were stratified into two groups: a case group (with cognitive impairment) and a control group (without cognitive impairment), based on predefined MoCA cutoff scores(< 26scores).

Based on the basic characteristics of the patients and the laboratory indexes after stabilization of acute exacerbations, we conducted statistical analyses, screened out the risk factors and established the Nomogram Prediction Model by using the R software, and finally, we evaluated the clinical value of the model through the calculation of ROC curves for sensitivity, specificity and kappa value. Finally, the sensitivity, specificity and Kappa value were calculated by ROC curve to evaluate the clinical value of the model.

Results After statistical analysis, C-reactive protein (CRP) and homocysteine (Hcy) were found to be the risk factors for combined cognitive impairment in COPD patients, and the Nomogram prediction model was constructed by combining CRP and Hcy and plotted the ROC curve, and it was found that its model finally screened the critical value of the total score of 62.55, and the area under the ROC curve of the model was 0.870, and the sensitivity was 84.7%, and the specificity was 80.4%, indicating that it has a high degree of consistency with the actual results,

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which indicated that the consistency between the prediction results and the actual results was better, and it had a higher clinical application value.

Conclusions CRP and Hcy are closely associated with comorbid cognitive impairment in COPD patients after stabilization of acute exacerbations, and increased levels of CRP and Hcy are associated with an increased risk of comorbid cognitive impairment in COPD patients. Combining both CRP and Hcy to create a nomogram model for predicting comorbid cognitive impairment in patients with COPD has good predictive ability.

Keywords Chronic obstructive pulmonary disease, Cognitive impairment, Nomogram

Background

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by persistent respiratory symptoms and irreversible airflow limitation due to airway and/or alveolar abnormalities caused by smoking and air pollution [1]. COPD remains a serious global public health problem, accounting for a large proportion of the world's chronic disease morbidity and mortality, and has become the third leading cause of death and the fifth leading cause of disability in humans [2]. Some data show that the prevalence of COPD has shown explosive growth since 2020, and COPD will cause more than 5.4 million deaths per year in the coming decades [3]. Although COPD has traditionally been recognized as a disease primarily affecting the lungs, it is often associated with many comorbidities outside the lungs, such as heart failure, osteoporosis, muscular dystrophy, and cognitive impairment [4]. These comorbidities are not necessarily attributable to COPD, as they may occur alone or as a result of shared risk factors. Patients with COPD are typically characterized by the co-existence of comorbidities; evidence suggests that 98% of COPD patients have single or multiple comorbidities [5]. It is worth noting that comorbidities increase the risk of death, and current evidence suggests that a higher proportion of COPD patients die from nonpulmonary causes compared with pulmonary causes [6]. With the development of research in recent years, cognitive impairment associated with COPD has attracted extensive attention from scholars. A large number of studies have confirmed [7, 8] that long-term smoking, hypoxia and hypercapnia, systemic inflammation, reduced physical activity, the number of exacerbations of the disease course, and respiratory complications such as sleep apnoea syndrome are all risk factors for cognitive impairment in COPD patients. Elderly COPD patients with cognitive impairment have almost three times the mortality rate of elderly patients with cognitive impairment or COPD[9]. The complication of cognitive impairment can exacerbate mortality and disability in patients with COPD and has implications for patient management, increasing the burden on the patient's family and society [10].

Cognition is a set of higher-level activities in the cerebral cortex that includes the perception, storage, retrieval, and use of information. Mild cognitive impairment (MCI) is a cognitive state intermediate between normal cognitive functioning and dementia and is characterized by the impact it can have on the patient's level of health and ability to function in daily life. Between 50 and 70% of patients will develop dementia within 5 to 7 years of the diagnosis of MCI [11]. Cognitive dysfunction is common in COPD patients. A recent meta-analysis incorporating 14 studies reported that an average of 32% of COPD patients are affected by cognitive impairment, and a quarter of COPD patients suffer from MCI [12], which affects cognitive functions such as attention, memory, learning ability, psychomotor speed, visuospatial and motor structures, executive functioning, and language ability in COPD patients, with memory, attention, and executive functioning are the most common areas of impairment [13]. Assessing cognitive status requires taking into account the influence of subjective and objective factors of the subject, which is difficult to summarise simply and accurately. The Montreal Cognitive Assessment (MoCA) scale is a screening tool that can detect MCI in a timely manner with high sensitivity and specificity [14]. The content of the scale covers 8 cognitive domains with a total of 30 points, with higher scores indicating more intact cognitive functioning. The MoCA scale has been translated into 83 versions in 51 countries and is available in a variety of English language forms to support repeated assessment of patients. Meanwhile, the MoCA scale has been shown to be valid and reliable in Chinese patients with MCI [15]. This outreach and diversity of delivery helps to ensure the accuracy and reliability of the assessment, which is essential for the prevention, treatment and intervention of MCI and helps to slow the progression of MCI to dementia.

In recent years, there has been an increasing number of studies on the relationship between cognitive impairment and the development of COPD, and many of them have shown that the inflammatory response plays an important role in the pathological process of cognitive dysfunction formation [16, 17]. A large number of scholars have become increasingly interested in CRP, WBC,

serum amyloid A (SAA), and other biomarkers that are both simple and clinically significant, and it has now been found that these simple and easy-to-obtain indicators are valuable in reflecting the development and prognosis of cognitive impairment.

CRP is synthesized in the liver in response to activation of the interleukin-6 signalling pathway and is a systemic marker of inflammation, which has been linked to cognitive function [18]. COPD is a chronic lung disease due to persistent airflow limitation, and the hyperinflammatory response in vivo can result in extrapulmonary multiorgan involvement, and COPD participates in a wide range of inflammatory responses, such as neurally prominent metabolic, endocrine and other diverse activities. CRP as an acute inflammatory factor, CRP is considered an independent risk for future cardiovascular events, it has neurotoxic effects and induces vascular cognitive impairment by triggering, among other things, atherosclerosis [19]. Gorelick [20] found an inflammatory pathway of cognitive impairment confirmed by epidemiological studies and clinical trials. When inflammatory factors are consistently increased, inflammation can be involved in the development of neurodegenerative diseases through mechanisms such as activation of microglia, activation of the complement cascade, and disruption of the blood–brain barrier, which in turn impairs cognitive function [21, 22]. High levels of CRP in patients with COPD may be a useful biomarker for identifying individuals at increased risk of cognitive impairment and dementia. Secondly, monitoring CRP levels may have prognostic value once cognitive impairment is clinically evident in patients.

Hcy, a thiol-containing amino acid, is widely recognized as a risk factor for cognitive impairment and dementia [23]. Current studies suggest that Hcy toxicity is associated with neuronal and neurodegenerative diseases, and the possible pathways by which it induces cognitive impairment include increasing glutamate excitotoxicity, decreasing neuronal DNA repair capacity, accelerating oxidative stress, and β-amyloid (Amyloid-β, Aβ) formation, and disrupting hippocampal neuron function [24]. On the other hand, Hcy can induce vascular endothelial cell dysfunction, which may lead to cerebrovascular cognitive impairment. Studies have shown that Hcy can ultimately lead to fibrosis, vasospasm, and reduced compliance by stimulating vascular smooth muscle growth, interfering with lipid metabolism, and increasing foam cell formation [25, 26]. In addition, Hcy inhibits the production of nitric oxide, which promotes the production of peroxides and oxygen free radicals. These compounds cause damage to vascular endothelial cells, interfering with the normally regulated diastolic and contractile functions of blood vessels. The free radicals produced by oxidative reactions may also trigger hypoxia and ischemia in the brain and inhibit nerve conduction function, which in turn impairs cognitive function and leads to the development of neurological problems such as cognitive impairment or dementia [27, 28].

Nomograms are used as predictive models in medicine and have been widely used in clinical practice for the prediction of disease, especially in the assessment of survival related to some tumor patients. There is still a lack of reliable predictive models for the risk of comorbid cognitive impairment in COPD patients. Therefore, in this study, we screened the independent risk factors associated with COPD combined with cognitive impairment through unifactorial and multifactorial analyses and established a prediction model for the risk of COPD combined with cognitive impairment using the relevant factors. This will enable clinicians to identify COPD patients with potential cognitive impairment, intervene early to slow down the progression of the disease, improve the quality of life, and reduce the risk of death in COPD patients.

Objects and methods

In this study, a total of 304 patients with COPD hospitalized at the Affiliated Hospital of North China University of Science and Technology from July 2021 to September 2023 were evaluated for cognitive function using the Montreal Cognitive Assessment(MoCA) scale after stabilization of acute exacerbations. Participants were stratified into two groups: a case group (with cognitive impairment) and a control group (without cognitive impairment), based on predefined MoCA cutoff scores(< 26 scores). Finally, 85 COPD patients combined with cognitive impairment were selected as the case group after screening with inclusion and exclusion criteria as follows: (1) Diagnostic criteria: the diagnosis of COPD refers to the COPD Global Initiative Guidelines 2021 [29]: based on the history of smoking and other high-risk factors, clinical symptoms and signs and other information, COPD can be suspected clinically. Perfect pulmonary function tests, after inhalation of bronchodilators, the first–second forced expiratory volume of air (FEV1)/forceful lung volume (FVC) < 70% is to determine the existence of sustained The diagnosis of COPD is definitive if other known causes or diseases with characteristic pathological manifestations of airflow limitation are also excluded. (2) Inclusion criteria: meeting the above diagnostic criteria; a MoCA assessment score of < 26; good compliance to understand and complete the assessment; and voluntary participation in this study and signing of an informed consent form. (3) Exclusion criteria: those who have been diagnosed with cognitive impairment in the past due to diseases other than COPD, or those who suffer from psychiatric diseases, hearing

impairment, aphasia, etc., and are unable to complete the scale assessment; those who have a history of taking medications with clear cognitive impairment; those who have been abusing alcohol and narcotics and drugs for many years; those who have a low level of literacy, and do not have basic cognitive abilities (illiterate); those who have a combination of serious damage to other organs; those who are not able to provide a truthful and accurate medical history; those who cannot provide a true and accurate medical history. Those who are unable to provide a true and accurate medical history.

The control group (without cognitive impairment), based on predefined MoCA cutoff scores(< 26 scores) was selected from COPD patients who were hospitalized and diagnosed in our hospital from July 2021 to September 2023, and 219 COPD patients were screened as the control group after screening by inclusion and exclusion criteria as follows: (1) Diagnostic criteria: refer to the diagnostic criteria for COPD in the case group. (2) Exclusion criteria: those with comorbid cognitive impairment; refer to case group exclusion criteria. Basic information included gender, age, height measurement with shoes off, weight measurement with a single garment on, years of education; lifestyle habits: history of smoking (including years of smoking, daily smoking amount), history of alcohol consumption, etc., and body mass index (BMI) = weight (kg)/height2 (m2) was calculated at the same time, as well as smoking index: number of cigarettes smoked per day × number of years of smoking. This includes the presence of the following comorbidities such as hypertension, diabetes, and coronary heart disease. Clinically relevant laboratory indexes were examined including blood routine (WBC, RBC, HGB, NEU, LYM, MONO, PLT, HCT, MCV, MCH) which was perfected after stabilization of acute exacerbations, coagulation series (fibrinogen, D-dimer); CRP measurement; Hcy measurement; ESR measurement. All patients were required to perform MoCA assessment to calculate the score to evaluate their cognitive function, and a score less than 26 was diagnosed as cognitive impairment (for those with education less than 9 years, 1 point was added to the original score to correct the score).

Data were statistically analysed by applying SPSS 27.0 software, and $P < 0.05$ was considered a statistically significant difference (two-sided test). (1) Single-factor analysis: the count data were calculated as a ratio, and the chi-square test was used for comparison between groups. Measurement data were first tested for normality, and if they were normally distributed, they were expressed as "mean ± standard deviation", and the t-test for independent samples was used to compare the differences in means between two groups; non-normally distributed measurement data were expressed as "median (upper and lower quartile spacing)" [M (P25,P75)], and the non-parametric rank-sum test was used to compare the medians between groups. [M (P25,P75)], and the non-parametric rank sum test was used to compare the medians between groups. (2) Multi-factor analysis: Factors that were statistically significant in the univariate analysis were introduced into a binary logistic regression model to analyse and screen for risk factors for COPD combined with cognitive impairment. (3) Construction and evaluation of nomogram prediction model: Logistic regression preanalysis of meaningful indicators was jointly plotted into a nomogram prediction model using R 4.3.2 software, divide the data into a training set and a validation set in a 7:3 ratio and construct a nomogram model. By screening variables in single factor logistic regression and retaining variables with P values < 0.05, multiple factor logistic regression is performed to ensure the model is optimal. Stepwise regression is used to ensure the model reaches its optimum Validate on the training set and validation set using calibration curves and ROC curves, respectively,DCA curve further evaluates the stability of the model. ROC curves were used to evaluate the sensitivity and specificity of the prediction model and kappa value were used to evaluate the effectiveness of the model.

Results

Risk factors for comorbid cognitive impairment in patients with COPD

The basic characteristics between the two groups were analyzed by single factor analysis: Comparison between patients in the case group and the control group in terms of gender, age, body mass index, years of education, history of alcohol consumption, and comorbidities (hypertension, diabetes mellitus, and coronary artery disease) showed no statistically significant differences ($P > 0.05$); the differences in age and smoking index were statistically significant ($P < 0.05$), as shown in Table 1. Comparison of laboratory indicators between the two groups: the levels of CRP and Hcy of patients in the case group and the control group were compared, and the differences between the groups were statistically significant ($P < 0.05$); while the differences between the groups in the indicators WBC, RBC, HGB, NEU, LYM, MONO, PLT, HCT, MCV, MCH, FIB, DD, ESR were not statistically significant ($P > 0.05$). See Table 2.

The multi-factorial analysis used the indicators that were statistically significant between groups in the univariate analysis as independent variables (age, smoking index, CRP, Hcy), and the assigned values are shown in Table 3. Whether or not there was a combination of cognitive impairment was used as a dependent variable (yes = 1, no = 0), and multifactorial logistic regression

Table 1 Comparison of basic patient characteristics between the two groups

Analysis of factors	Form	Group		χ^2	*P*
		Case group($n=85$)	Control group ($n=219$)		
Gender	Male	53 (62.4)	156 (71.2)	2.247	0.134
	Female	32 (37.6)	63 (28.8)		
Drinking history	Yes	22 (25.9)	70 (32.0)	1.073	0.300
	No	63 (74.1)	149 (68.0)		
Hypertension	Yes	38 (44.7)	79 (36.1)	1.928	0.165
	No	47 (55.3)	140 (63.9)		
Diabetes	Yes	14 (16.5)	57 (26.0)	3.124	0.077
	No	71 (83.5)	162 (74.0)		
Coronary heart disease	Yes	13 (15.3)	55 (25.1)	3.400	0.065
	No	72 (84.7)	164 (74.9)		
Age (years)	-	73 (64.5 ~ 79.5)#	71 (64 ~ 76)#	−2.124*	0.034
Body mass index (kg/m^2)	-	23.42 (22.6 ~ 24.7)#	23.24 (21.4 ~ 24.7)#	−1.876*	0.661
Years of education (years)	-	6 (3.5 ~ 7.0)#	5 (3.0 ~ 7.0)#	−0.843*	0.399
Smoking index (years)	-	285 (186.5 ~ 495.0)#	241 (148.0 ~ 452.0)#	−2.380*	0.017

* Z-values for median-comparison rank-sum tests, data in ()# are interquartile spacing (P25,P75); other numbers in () are composition ratios (%)

Table 2 Comparison of laboratory indicators between the two groups of patients

Laboratory indicators	Case group (n = 85)	Control group (n = 219)	*Z*	*P*
WBC/(10^9 /L)	7.4 (6.20–9.70)	7.52 (6.00–9.90)	−0.390	0.697
RBC/(10^9 /L)	434 (4.00–4.78)	4.36 (3.99–4.79)	−0.468	0.640
HGB/(g/L)	140 (128.00 to 153.00)	140 (128.00–154.00)	−0.104	0.917
NEU/(10^9 /L)	6.02 (3.75–7.62)	6.1 (4.14–8.29)	−1.134	0.257
LYM/(10^9 /L)	1.52 (1.16–2.08)	1.63 (1.25–1.95)	−0.550	0.583
MONO/(10^9 /L)	0.4 (0.27–0.55)	0.36 (0.27– 0.47)	−0.937	0.349
PLT/(10^9 /L)	208 (144.00–275.00)	221 (167.00–275.00)	−1.171	0.242
HCT/(L/L)	0.419 (0.39– 0.45)	0.413 (0.37–0.45)	−0.918	0.359
MCV/(fL)	95 (92–99)	94 (91–98)	−1.670	0.095
MCH/(pg)	31.4 (30.60–32.20)	31.7 (30.50–33.10)	−1.712	0.087
FIB/(g/L)	4.08 (3.43–4.90)	3.93 (3.41–4.41)	−1.089	0.276
DD/(ng/mL)	552.4 (393.32–818.69)	510 (326.78–798.40)	−0.765	0.449
ESR/(mm/h)	21 (12.00–53.00)	20 (11.00–30.00)	−1.410	0.159
CRP/(μg/L)	40.2 (33.00–48.50)	30.4 (25.10–35.10)	−7.343	0.000
Hcy/(μmol/L)	17.65 (12.76–22.7)	7.35 (5.29–12.36)	−8.780	0.000

Data in () are interquartile spacing (P25,P75)

Table 3 Assignment of independent variables for multi-factor logistic regression analysis

Variable value	Assignment
Age	Measured value
Smoking index	Measured value
CRP	Measured value
Hcy	Measured value

analyses were performed. The results of the analyses showed that CRP and Hcy were risk factors affecting COPD patients with comorbid cognitive impairment ($P < 0.05$); age and smoking index had no effect on whether and comorbid cognitive impairment ($P > 0.05$), as shown in Table 4.

Table 4 Results of multifactorial analysis of comorbid cognitive impairment in patients with COPD

Risk factor	*B*	*S.E*	*Wald*	*DF*	*P*	*OR*	95 per cent *CI*	
							Lower limit	Limit
Age	0.032	0.019	2.728	1	0.099	1.033	0.994	1.073
Smoking index	0.001	0.001	0.757	1	0.384	1.001	0.999	1.002
CRP	0.111	0.020	30.587	1	0.000	1.118	1.074	1.162
Hcy	0.154	0.024	41.032	1	0.000	1.167	1.113	1.223
constant	−9.328	1.648	32.056	1	0.000	0.000	-	-

Predictive model construction for COPD patients with comorbid cognitive impairment

Based on the results of the multi-factor analysis, the logistic regression prediction model was constructed for CRP and Hcy, and the nomogram was constructed in R 4.3.2 software. According to the values of CRP and Hcy of each patient, the corresponding scores (Points) and the total scores of the two scores (Total Points) can be obtained in the Nomogram, and the probability of combined cognitive impairment in COPD patients can be derived on Risk from the Total Points, as shown in Fig. 1. Through variable screening by single-factor logistic regression, variables with a P value less than 0.05 were retained for multi-factor logistic regression. In order to optimize the model, stepwise regression was used to ensure that the model reached the optimal level The calibration curve and ROC curve were used to validate the training set and validation set, respectively; The DCA curve further evaluates the stability of the model. Researchers and clinicians can access the online version of our nomogram at https://shiauwei.shinyapps.io/copd2/. By entering clinical data and reading the output data and tables generated by the web server, it is easy to obtain the predicted probability of COPD combined with cognitive impairment. Then we divided the data into a training set and a validation set in a 7:3 ratio and constructed the risk prediction model of the training set and the validation set.

The calibration curves of the validation set were internally validated using the Bootstrap method in R language for the column chart. The original data was sampled 1000 times and the calibration curves of the training and validation sets were plotted to further evaluate the accuracy and consistency of the new prediction model, as shown in Fig. 4. It can be seen that the calibration curve of the training set has a Mean absolute error of 0.011, indicating that the deviation between the line chart prediction model and the actual situation is small and shows good consistency (Fig. 2). The validation set has a Mean absolute error of 0.045, indicating that the average deviation between the model prediction probability and the actual frequency is 4.5% (Fig. 3). The DCA curve was performed on the training set, and the results showed that the line

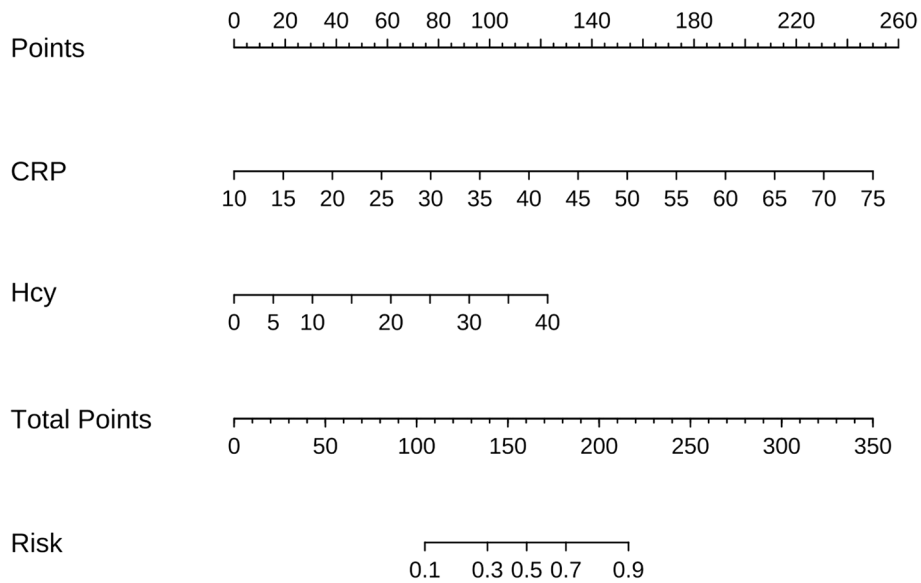

Fig. 1 Nomogram prediction model

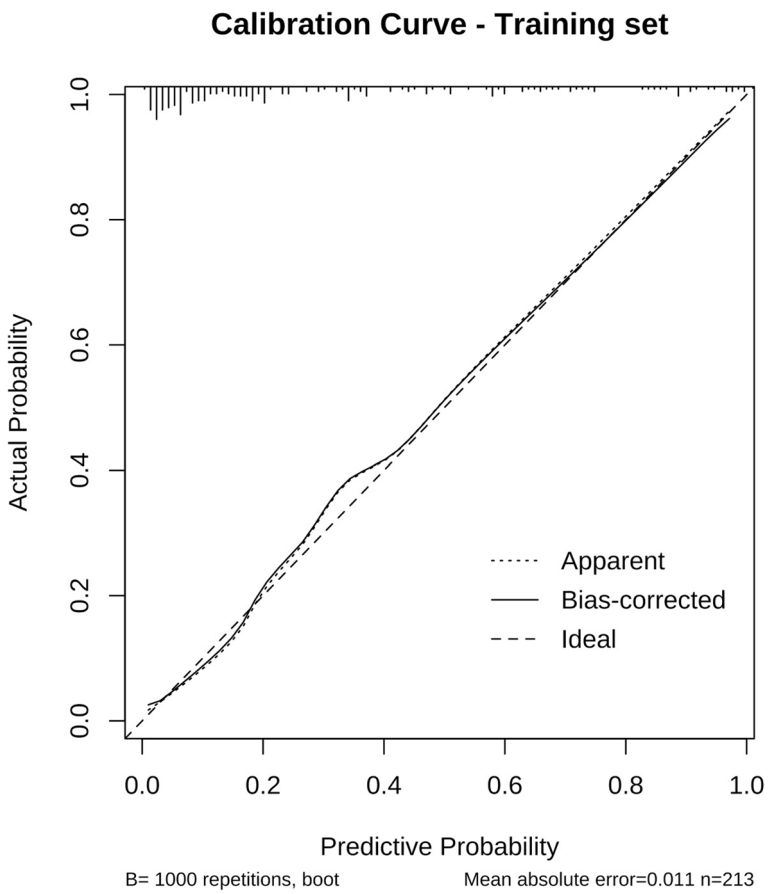

Fig. 2 Training set calibration curve

chart we plotted has good clinical applicability in predicting cognitive impairment in patients with chronic obstructive pulmonary disease (Fig. 4). The ROC curve for predicting combined cognitive impairment in COPD patients in the training set was plotted based on the total score of each patient, and the results showed that The sensitivity of the model diagnosis is 86.2%, the specificity is 78.7%, the area under the curve is 0.877 (0.862–0.935), and the Kappa value is 0.62. The ROC curve of the validation set shows that the sensitivity of the model diagnosis is 82.1%, the specificity is 62.5%, the area under the curve is 0.766 (0.646–0.885), and the Kappa value is 0.43. The calculated Hosmer Lemeshow test p-values for the training and validation sets are 0.094 and 0.2554, respectively, indicating that the predicted probabilities of the models in the training and validation sets are roughly consistent with the actual situation (Figs. 5, 6, Tables 5, 6).

Discussion

COPD is a respiratory disease mainly characterized by incomplete airflow limitation. The incidence of COPD is increasing day by day due to a combination of multiple risk factors such as smoking, environmental dust pollution, and population aging, is currently COPD as one of the three leading causes of death in the world, more than ninety percent of which occurs in low- and middle-income countries, and it is projected that by 2060, 5.4 million patients are expected to die from COPD and its complications [3].

COPD being a chronic disease, is often associated with many extrapulmonary comorbidities such as heart failure, osteoporosis, muscle wasting, and cognitive impairment in addition to its own respiratory symptoms [30]. MCI is a cognitive state intermediate between normal cognitive function and dementia.COPD is an independent risk factor for the development of cognitive impairment, and there is a strong correlation between the two. A cross-sectional study that included 940 patients with stable COPD showed that the prevalence of cognitive impairment was found to be 39% using the Mini-Mental State Examination (MMSE) [31], and the mortality rate of elderly COPD patients with cognitive impairment was nearly three times [9]. At present, the mechanism of COPD combined with cognitive impairment is still

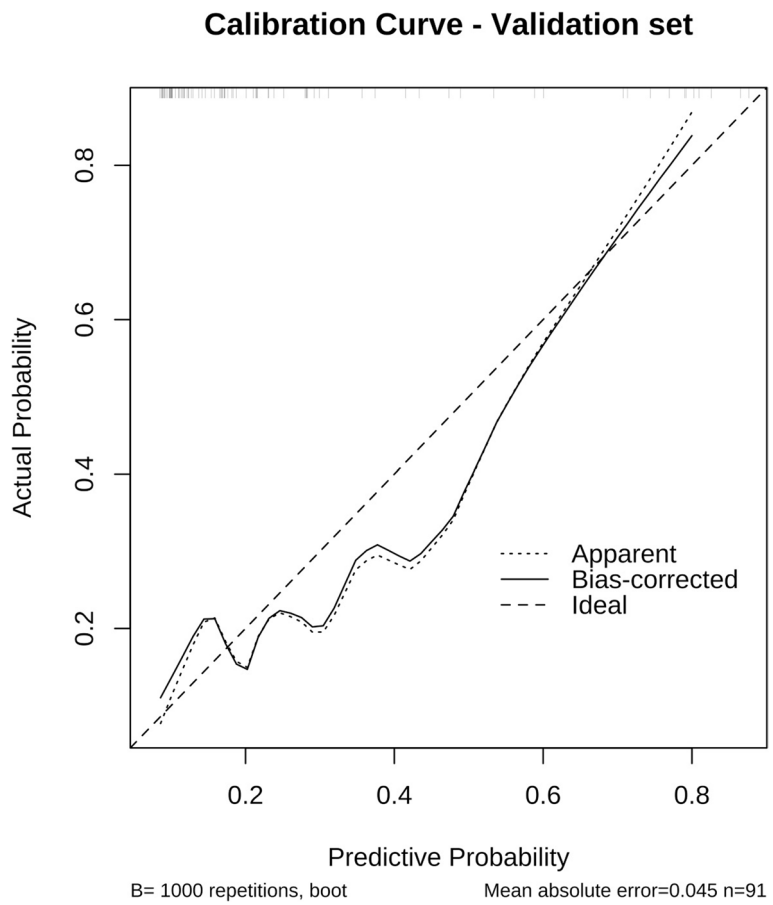

Fig. 3 Validation set calibration curve

unclear, which may be due to the fact that COPD patients are in hypoxia due to ventilation and ventilation dysfunction, leading to a decrease in cerebral blood perfusion, causing structural changes in the brain and affecting the cognitive function of the patients [32–34], as well as long-term inflammatory stimulation, which disrupts the balance of the damage repair mechanism and causes cerebral microcirculation disorders through direct neurotoxicity or endothelial damage, and eventually cognitive impairment occurs. And so on, and ultimately cognitive impairment [8, 35]. Currently, there is no consensus on the treatment options for COPD combined with cognitive impairment, and failure to effectively control the disease progression will not only affect the quality of life of patients but also increase the social healthcare and economic burden. Therefore, it is important to identify and intervene in cognitive dysfunction in COPD patients at an early stage, so that clinicians can correctly grasp the optimal time for treatment and give the optimal treatment plan.

In this study, 304 COPD patients were included, and a comprehensive analysis was carried out for a variety of factors affecting COPD patients, it was found that CRP and Hcy could be the risk factors for combined cognitive impairment in COPD patients, and a model for predicting the risk of combined cognitive impairment in COPD patients was established by combining the CRP and Hcy indexes, and validation demonstrated that it had a high-risk prediction ability and had a The validation shows that it has high-risk prediction ability and has good clinical application value. It can provide a favorable basis for clinicians to formulate treatment plans and improve the prognosis of patients with COPD combined with cognitive impairment.

Relationship between C-reactive protein and COPD combined with cognitive impairment

CRP is a plasma protein synthesized by the liver, and CRP levels rise exponentially when an acute inflammatory response storm is generated in the body, making CRP a potent biomarker of inflammation in vivo [36]. Due to the short half-life of CRP in the blood, CRP levels decline rapidly once the acute injury is eliminated. However, in chronic diseases, CRP levels

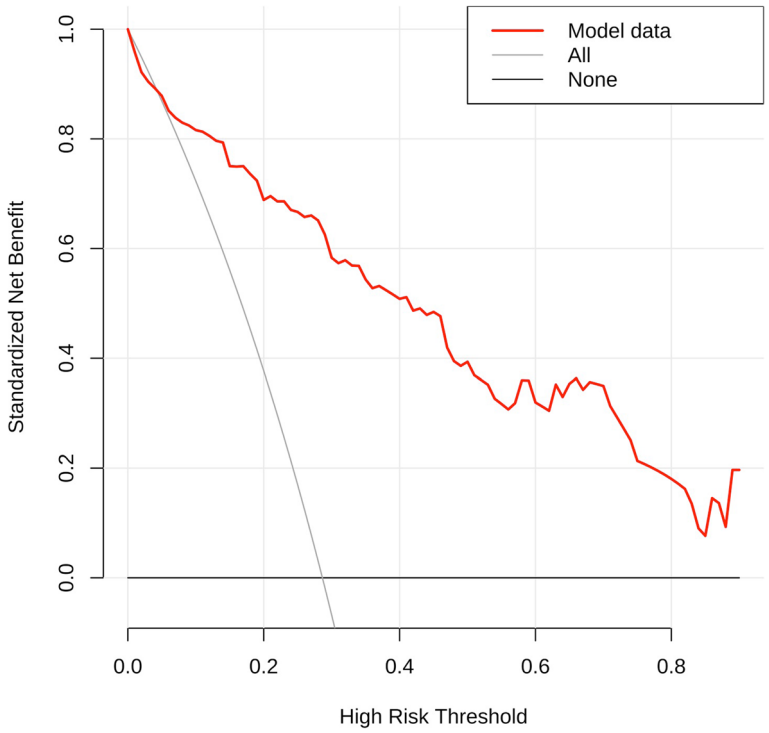

Fig. 4 DCA curve

remain elevated to a lesser extent [37, 38]. High levels of CRP have been reported to be a risk factor for Alzheimer's disease (AD), Parkinson's disease, and vascular dementia [39]. Elevated CRP levels have also been associated with more severe depressive symptoms [36, 40]. Inflammation may contribute to mood disorders and cognitive impairment through a number of mechanisms. One of these is the inflammatory cycle theory. Chronic inflammation can lead to the development of metabolic disorders, which can further elevate levels of inflammation in the body, ultimately leading to further disease progression [41]. Similarly, patients with a history of recurrent low-grade infections are more likely to develop mood disorders in later life [42].

COPD is considered to be a long-term chronic inflammatory disease, in this study inflammatory factor CRP level as a risk factor for COPD combined with cognitive impairment was significantly higher in the case group than in the control group, the findings of Yue Shuyu [43] were consistent with the results of this study, in addition to this scholar found that CRP level was negatively correlated with cognitive function. In a study by Crisan AF [44], it was found that patients with acute exacerbations of COPD with higher CRP levels also had relatively lower MoCA scores. The authors of another study suggested that relatively high levels of CRP could be used as an indicator of cognitive impairment [45].

Explanations for the impact of high levels of CRP on cognitive function may be as follows: firstly inflammation is involved in the development of neurodegenerative diseases through mechanisms such as activation of microglia, increased levels of pro-inflammatory cytokines, activation of the complement cascade, and disruption of the blood–brain barrier [21, 22]. It has been shown that inflammatory proteins (i.e., CRP) have been detected in brain plaques and neuroprogenitor fiber tangles in patients with AD [46], suggesting that inflammatory processes are involved in the etiology of AD. Clinically, CRP concentrations have been associated with age-related diseases and have been used as a marker of cardiovascular risk [47]. This can be supported by the results of a recent 10-year longitudinal study [48], in which elevated CRP levels were associated with future cognitive decline only in cognitively healthy older participants, whereas in patients with dementia elevated CRP was associated with a slower rate of future cognitive decline.

Another possible explanation involves reduced grey matter density in the brain, where increased CRP concentrations may lead to reduced grey matter volume in the frontal and cingulate cortex of the brain. A recent study reported that in older adults, higher baseline CRP is associated with reduced blood flow in frontal regions and anterior cingulate cortex, both of which are associated with executive functions [49]. In addition, structures

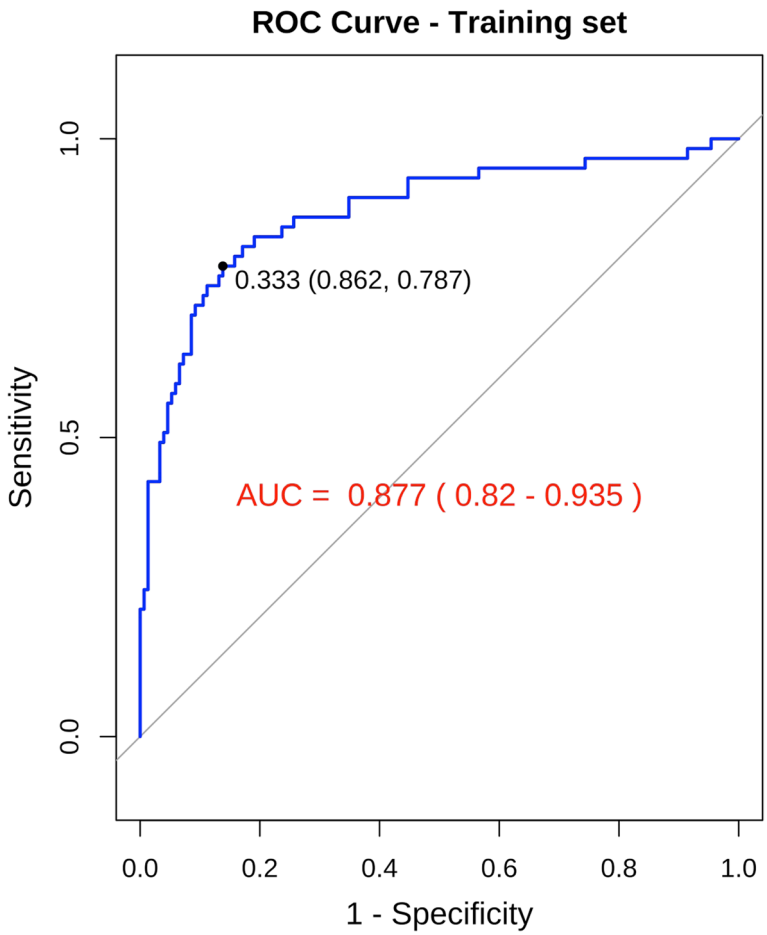

Fig. 5 Training set ROC curve

important for memory, such as the hippocampus, have high concentrations of pro-inflammatory cytokines and receptors and may be vulnerable to systemic inflammation [50]. Thus, inflammation may have different neural pathways affecting cognition.

In combination with the findings of this study, CRP levels were significantly higher in the COPD combined with the cognitive impairment group. We know that in patients with acute exacerbation of chronic obstructive pulmonary disease, infection can also lead to an increase in CRP. To avoid the impact of infection on CRP elevation, we chose to perform CRP testing in patients with chronic obstructive pulmonary disease after controlling acute infection symptoms, which will reduce the impact of infection on CRP elevation. In addition, from the data analysis in the article, we can also see that there is no significant difference in WBC between the two groups of patients, which proves that there is no significant correlation between the increase of CRP and infection in the cognitive impairment group of chronic obstructive pulmonary disease. From the results of our prediction model, it can be seen that CRP levels have some clinical value in determining whether COPD patients are combined with cognitive impairment.CRP is simple to detect, inexpensive to detect, and simple to interpret. Therefore, this can help clinicians better predict the risk of cognitive impairment in COPD patients and enable better early intervention to improve the quality of patient survival.

Relationship between Hcy and COPD combined with cognitive impairment

Hcy is produced in all cells and is a thiol-containing amino acid, the levels of which are influenced by the B vitamins cobalamin, vitamin B6, and folic acid, as they are cofactors for enzymes involved in the metabolism of methionine [51]. The oxidation reaction of Hcy produces free radicals and may also trigger hypoxia–ischemia in the brain and inhibit nerve conduction, which can impair cognitive function, leading to cognitive deficits or neurological problems, such as dementia, to problems occurring [27, 28]. Current studies suggest that Hcy toxicity is associated with neuronal and neurodegenerative diseases

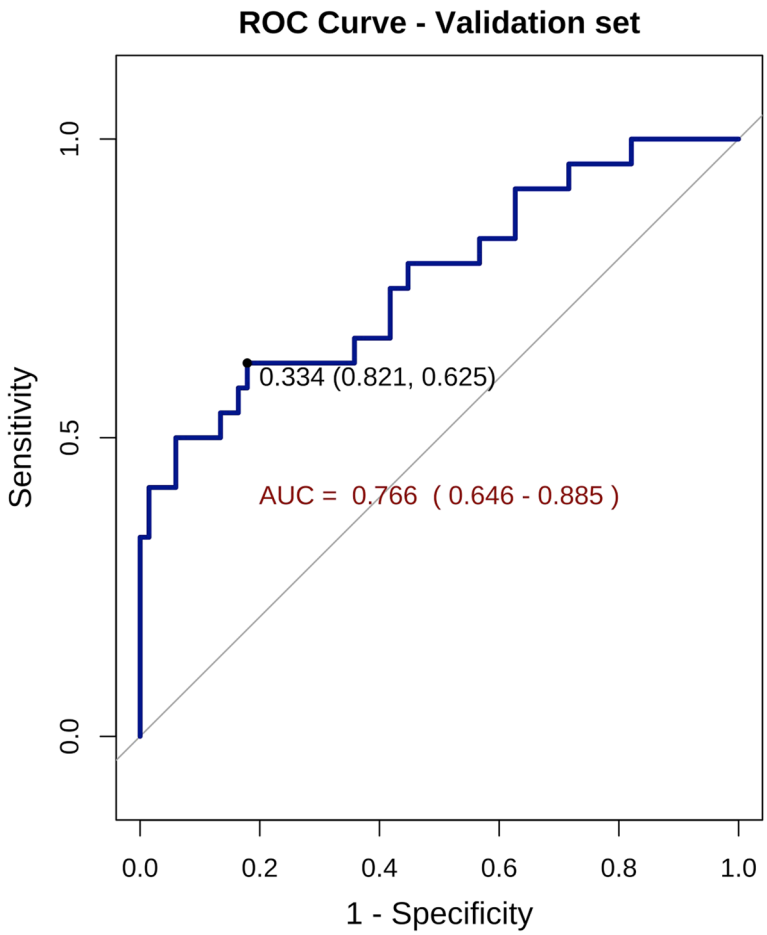

Fig. 6 Validation set ROC curve

Table 5 Evaluation of the effectiveness of Nomogram model in predicting COPD combined with cognitive impairment for train data set

Projected results	actual result		Sensitivity (%)	Specificity (%)	Jordon index	*Kappa* value
	Cognitive impairment	No cognitive impairment				
Cognitive impairment	131	13	86.2	78.7	64.9	0.62
No cognitive impairment	21	48				

Table 6 Evaluation of the effectiveness of Nomogram model in predicting COPD combined with cognitive impairment for valid data set

Projected results	actual result		Sensitivity (%)	Specificity (%)	Jordon index	*Kappa* value
	Cognitive impairment	No cognitive impairment				
Cognitive impairment	55	9	82.1	62.5	44.6	0.43
No cognitive impairment	12	15				

and is a risk factor for cognitive impairment and dementia [52].

Elevated Hcy is recognized as a risk factor for cardiovascular, renal, and cerebrovascular diseases [53–55]. Inflammatory processes in the vascular wall are critical in the initiation and continuation of pathology. High levels of Hcy may produce cytotoxicity and stimulate a proinflammatory response, leading to vascular endothelial dysfunction and lipid metabolism disorders, which can lead to thrombosis and atherosclerosis, indirectly contributing to vascular cognitive disorders, by stimulating the growth of vascular smooth muscle and increasing the formation of foam cells, among other pathways [56–58].

The neurotoxicity of Hcy and its direct effects on brain atrophy have been established [59, 60]. Current studies suggest that possible pathways by which Hcy induces cognitive impairment include increased glutamatergic excitotoxicity, reduced neuronal DNA repair capacity, accelerated oxidative stress and Aβ protein accumulation, disruption of hippocampal neuronal capacity, and exacerbation of hippocampal and cortical atrophy [24, 61]. A recent study showed that patients with higher Hcy levels had more severe cortical and hippocampal atrophy than those with lower Hcy levels [61]. In addition, a study concluded that the homocysteine-methionine cycle is a key metabolic sensor system mediating receptor-independent metabolism-related danger signal recognition and regulation of methylation in diseases such as metabolic disorders, autoimmune diseases, and cardiovascular diseases. High levels of Hcy's can directly affect functional brain performance by altering methylation processes [62]. An analysis of cognitive, neuropsychiatric, affective, and functional assessment of 929 elderly Caucasians found that Hcy levels were significantly higher in cognitively impaired patients than in non-cognitively impaired patients. They found that 10umol/L served as a threshold for Hcy, above which the risk of cognitive impairment was increased ($P=0.003$) [51], which was verified in the present study, in addition, a study has demonstrated that the Hcy levels were higher in the cognitively impaired group than in the non-cognitively impaired group in patients with COPD and that serum Hcy levels showed a negative trend in correlation with scores in specific cognitive domains on the MoCA scale [63]. The results of this study showed that Hcy was an independent risk factor for COPD combined with cognitive impairment. The study also found that higher Hcy levels increased the risk of cognitive impairment, suggesting that Hcy can be used as a reliable indicator to reflect whether COPD patients have combined cognitive impairment, which is helpful for clinicians to formulate intervention and treatment plans as early as possible, and to reduce the patients' physical and economic burdens.

Nomogram forecasting model

A Nomogram is a combination of several specific predictors that estimate the absolute probability and risk of an individual outcome and is commonly used to assess and predict the risk of disease occurrence and prognosis. It has the advantage of presenting complex regression equations in the form of graphs and rating scales, making it easy for healthcare professionals to interpret and evaluate the results. Currently, Nomograms have been applied in several research areas such as oncology, chronic diseases, gynecology, and so on [64]. However, there are fewer studies in predicting whether COPD patients are at risk of comorbid cognitive impairment models. Therefore, in this context, this study aimed to analyze the clinical data related to cognitive function in COPD patients, to find the risk indicators of COPD patients with comorbid cognitive impairment, and to establish the nomogram as a risk prediction model, which can provide a basis for clinical staff to assess and intervene in the risk of comorbid cognitive impairment in COPD patients.

The study results indicate that The ROC curve for predicting combined cognitive impairment in COPD patients in the training set was plotted based on the total score of each patient(Fig. 2), and the results showed that The sensitivity of the model diagnosis is 86.2%, the specificity is 78.7%, the area under the curve is 0.877 (0.862–0.935), and the Kappa value is 0.62. The ROC curve of the validation set shows that the sensitivity of the model diagnosis is 82.1%, the specificity is 62.5%, the area under the curve is 0.766 (0.646–0.885), and the Kappa value is 0.43. The calculated Hosmer Lemeshow test p-values for the training and validation sets are 0.094 and 0.2554, respectively, indicating that the predicted probabilities of the models in the training and validation sets are roughly consistent with the actual situation (Figs. 4, 5, Tables 5, 6).

It can be seen that the the nomogram model calibration curve of the training set has a Mean absolute error of 0.011, indicating that the deviation between the line chart prediction model and the actual situation is small and shows good consistency, and the results showed that The sensitivity of the model diagnosis is 86.2%, the specificity is 78.7%, the area under the curve is 0.877 (0.862–0.935), and the Kappa value is 0.62.

We also conducted internal validation of the model, and the results showed that the ROC curve of the validation set showed that the sensitivity of the model diagnosis was 82.1%, the specificity is 62.5%, the area under the curve is 0.766 (0.646–0.885), and the Kappa value is 0.43. The Kappa value and Mean absolute error of the validation set are not satisfactory, and the analysis may be related to the small amount of data in the validation set. The number of validation set members

will be increased for further validation in the future. Anyway, the nomogram model we established provides an effective method for quickly identifying cognitive impairment in COPD patients.

Our research still has some shortcomings. One limitation of our study is that the cognitive impairment group was restricted to individuals who were able to complete the MoCA. This criterion may have excluded those with severe cognitive impairment, potentially introducing a selection bias. Future studies should consider including a broader range of cognitive abilities to better represent the full spectrum of cognitive impairment. Another shortcoming of the article is that this study did not consider respiratory dysfunction and blood gas data. These are very important confounding factors when explaining the relationship between CRP and Hcy and cognitive impairment. In our study, the patients are in the controlled stage of acute exacerbation of the chronic obstructive pulmonary disease, and the majority of patients do not have blood gas analysis results, which indeed lacks the ability to rule out the impact of respiratory failure on cognitive impairment, Subsequently, we will conduct future studies to implore the relationship between blood gas analysis indicators and cognitive dysfunction.

In conclusion, our study demonstrates that CRP and Hcy may be valuable biomarkers for predicting cognitive impairment in COPD patients. The combination of CRP and Hcy showed significant predictive value, the nomogram model may be able to improve the early diagnosis and management of cognitive impairment in COPD patients, leading to better outcomes.

Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
MCI	Mild cognitive impairment
AD	Alzheimer's disease
CRP	C-reactive protein
Hcy	Homocysteine
MoCA	Montreal Cognitive Assessment
MMSE	Mini Mental State Examination

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Authors' contributions

W.Y and A.F contributed in carry out of the initial studies and design of the study. X.L and J.B administrated of the Search articles. T.L and H.J designed the data extract sheet and Quality assessment sheet. W.C and J.B collected the data and performed the statistical analysis. L.X, C.L, and G.M proofread the English expression and reviewed the manuscript. Y.G, W.L, and Y.L analyzed statistical data. J.L,Y.L and W.Y helped in writing of the final paper.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the North China University of Science and Technology Affiliated Hospital under approval number 20221108012.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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